Πανεπιστήμιο Κύπρου
University of Cyprus

DEPARTMENT OF CHEMISTRY

NEW CHEMISTRY OF *N*′-ARYLBENZAMIDINES

DOCTOR OF PHILOSOPHY DISSERTATION

STYLIANA IOANNIS MIRALLAI

2015

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NEW CHEMISTRY OF *N′*-ARYLBENZAMIDINES

STYLIANA IOANNIS MIRALLAI

A Dissertation Submitted to the University of Cyprus in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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VALIDATION PAGE

Doctoral Candidate: Styliana Ioannis Mirallai

Doctoral Thesis Title: New Chemistry of *N´*-Arylbenzamidines

The present Doctoral Dissertation was submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the ***Department of Chemistry*** *and was approved on the ……. by the members of the* ***Examination Committee***.

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EXPERIMENTAL PROCESSES ACCOMPLISHMENT

STATEMENT

The present doctoral dissertation was submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy of the University of Cyprus. The work described within this thesis has been carried out exclusively by Styliana I. Mirallai at the Organic Chemistry Research Laboratory, Department of Chemistry, University of Cyprus under the supervision of Dr. Panayiotis A. Koutentis (September 2009-June 2015).

The exceptions include: the elemental analysis of all compounds performed by Stephen Boyer at London Metropolitan University and the single crystal X-ray crystallography studies performed by Dr. Maria Manoli and Dr. Manolis J. Manos.

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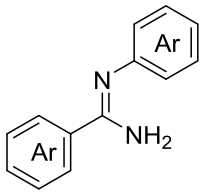
“Always choose the hard way”



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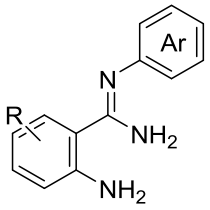

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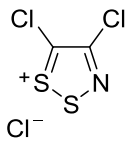

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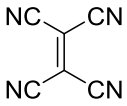

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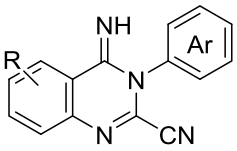

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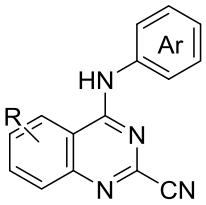

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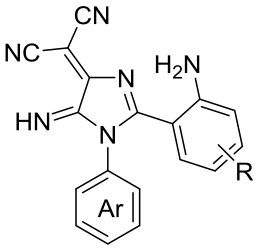

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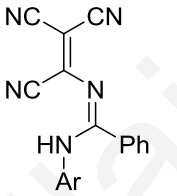

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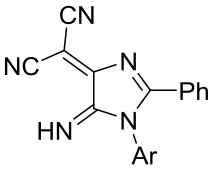

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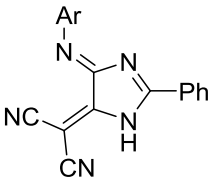

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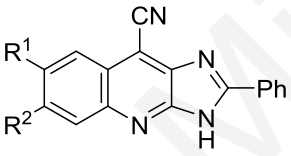

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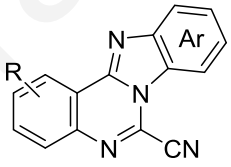

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ΠΕΡΙΛΗΨΗ

Η παρούσα διδακτορική διατριβή αρχίζει με μια σύντομη εισαγωγή (Κεφάλαιο 1) στην ετεροκυκλική χημεία, η οποία στη συνέχεια επικεντρώνεται στο άζωτο ως ετεροάτομο σε αρωματικά συστήματα, καθώς επίσης και στην χρήση των αμιδινών ως πρόδρομα μόρια για τη σύνθεση ιμιδαζολών και πυριμιδινών.

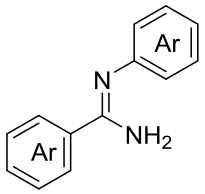
Στο Κεφάλαιο 2, γίνεται αρχικά διερεύνηση της κλασικής σύνθεσης των *N'*-αρυλοβενζαμιδινών **126**, χρησιμοποιώντας ως πρόδρομα μόρια ανιλίνες και βενζονιτρίλια υπό την παρουσία του $AlCl_3$. Ακολούθως, παρουσιάζεται μια βελτιωμένη σύνθεση των *N'*-αρυλοβενζαμιδινών **126**, η οποία απαιτεί τον σχηματισμό του συμπλόκου βενζονιτρίλιο-$AlCl_3$ πριν από την προσθήκη της ανιλίνης.

Έχοντας συνθέσει μια μικρή βιβλιοθήκη από 2-αμινοφαινυλο-*N'*-αρυλοβενζαμιδίνες **75** διερευνήσαμε την αντίδρασή τους με τα ηλεκτρονιόφιλα 4,5-διχλωρο-1,2,3-διθειαζολικό χλωρίδιο (**74**) (Appel salt) και τετρακυανοαιθένιο (TCNE): Η επεξεργασία των 2-αμινοφαινυλο-*N'*-αρυλοβενζαμιδινών **75** με το Appel salt **74** έδωσε τα καινούρια 3-αρυλ-4-ιμινο-3,4-διυδροκιναζολινο-2-καρβονιτρίλια **103** (Κεφάλαιο 3). Αντιθέτως, η επεξεργασία των 2-αμινοφαινυλ-*N'*-αρυλβενζαμιδινών **75** με το TCNE αναφέρεται ότι, οδηγεί στον σχηματισμό των ισομερών 4-αρυλοκιναζολινο-2-καρβονιτριλίων **76**. Στο Κεφάλαιο 4 παρουσιάζεται η επαναδιερεύνηση της αντίδρασης η οποία οδήγησε στην εύρεση τριών διαφορετικών συνθηκών οι οποίες δίνουν ως κύρια προϊόντα τα [4*H*-ιμιδαζολο-4-υλιδενο]μαλονονιτρίλια **106**, τα 4-αρυλοκιναζολινο-2-καρβονιτρίλια **76** ή τις ιμινοκιναζολίνες **103**, αντίστοιχα.

Στο Κεφάλαιο 5, η προαναφερθείσα αντίδραση με το TCNE απλουστεύθηκε για την αποφυγή του σχηματισμού των κιναζολινών **76** ή **103**. Επομένως, η αντικατάσταση των 2-αμινοφαινυλο-*N'*-αρυλοβενζαμιδινών **75** με τις *N'*-αρυλοβενζαμιδίνες **126** οδήγησε στον σχηματισμό των (1,2,2-τρικυανοβινυλο)βενζαμιδινών **156** σε καλές αποδόσεις, οι οποίες μπορούν να υποστούν κυκλοποίηση 5-exo-dig και να αποδόσουν τα ισομερή [1*H*-ιμιδαζολο-4(5*H*)-υλιδενο]μαλονονιτρίλια **157** σε ψηλές αποδόσεις. Τα μαλονονιτρίλια **157** με τη σειρά τους μπορούν να υποστούν αναδιάταξη Dimroth για να δώσουν τα [1*H*-ιμιδαζολο-5(4*H*)-υλιδενο]μαλονονιτρίλια **158** σε ψηλές αποδόσεις, ενώ η θερμόλυση των μαλονονιτριλίων **158** οδηγεί στον σχηματισμό των 2-φαινυλο-3*H*-ιμιδαζολο[4,5-

b]κινολινο-9-καρβονιτριλίων **159**. Στο Κεφάλαιο 6, παρουσιάζεται η επεξεργασία των άμεσα διαθέσιμων κιναζολιμινών και 4-ανιλινοκιναζολινών με μια πληθώρα από καταλύτες Pd και Cu η οποία δίνει πρόσβαση, μέσω οξειδωτικών και μη οξειδωτικών συζεύξεων, στα βενζο[4,5]ιμιδαζο[1,2-*c*]κιναζολινο-6-καρβονιτρίλια **215** σε ψηλές αποδόσεις.

Η διδακτορική διατριβή ολοκληρώνεται με την παρουσίαση των πειραματικών διαδικασιών και της βιβλιογραφίας.



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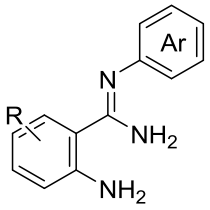

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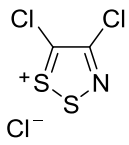

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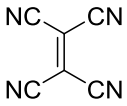
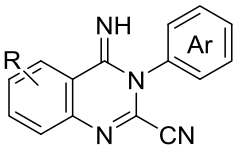


TCNE



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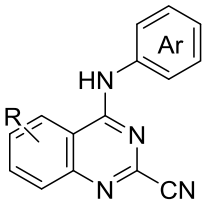

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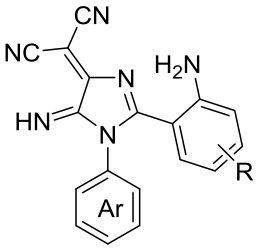

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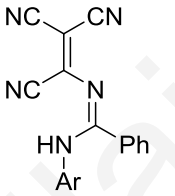

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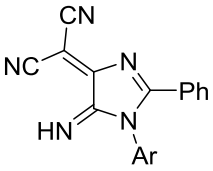

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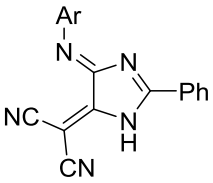

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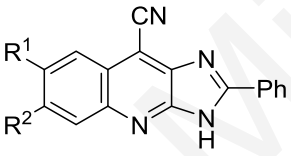

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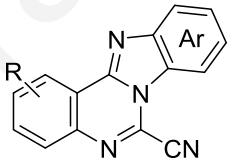

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ABSTRACT

The Thesis begins with a brief introduction (Chapter 1) on heterocyclic chemistry, which then focuses on nitrogen heteroaromatics and the use of amidines in the synthesis of imidazoles and pyrimidines.

In Chapter 2, the classical synthesis of *N'*-arylbenzamidines **126**, starting from anilines and benzonitriles in the presence of $AlCl_3$, is reinvestigated. Herein, an improved synthesis of *N'*-arylbenzamidines **126** is presented, that involves preforming the $AlCl_3$ complex of benzonitrile prior to the addition of the aniline.

Having in hand a small library of 2-aminophenyl-*N'*-arylbenzamidines **75** their reaction with electrophiles, 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (Appel salt) and tetracyanoethene (TCNE) was investigated: The treatment of 2-aminophenyl-*N'*-aryl-benzamidines **75** with Appel salt **74** gave novel 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles **103** (Chapter 3). In contrast, treatment of 2-aminophenyl-*N*-arylbenzamidines **75** with TCNE was reported to afford the isomeric 4-arylquinazoline-2-carbonitriles **76**. In Chapter 4 a reinvestigation of this reaction leads to three sets of conditions that give as major products the [4*H*-imidazol-4-ylidene]malononitriles **106**, the 4-arylquinazoline-2-carbonitriles **76** or the iminoquinazolines **103**, respectively.

In Chapter 5, the latter reaction with TCNE was simplified to avoid the formation of either quinazolines **76** or **103**. As such, by replacing 2-amino-*N'*-arylbenzamidines **75** with *N'*-arylbenzamidines **126** a series of (1,2,2-tricyanovinyl)benzamidines **156** prepared in good yields that can undergo a 5-exo-dig cyclization to yield the isomer [1*H*-imidazol-4(5*H*)-ylidene]malononitriles **157** in high yields. These can then Dimroth rearrange to give the [1*H*-imidazol-5(4*H*)-ylidene]malononitriles **158** in high yields, thermolysis of which formed the 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitriles **159**.

In Chapter 6, treatment of the readily available quinazolinimines and 4-anilinoquinazolines with a variety of Pd and Cu catalysts gave access, *via* oxidative and non oxidative coupling routes, to the biologically important benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitriles **215** in variable yields.

The Thesis finishes with a detailed Experimental section and a References section.

ACKNOWLEDGEMENTS

The years spent on my PhD were the most valuable and fruitful journey of my life. However, I could not travel and accomplish this journey without the tremendous support of my PhD supervisor, Dr. P. A. Koutentis. Thus, I thank him for providing me the opportunity to work on the projects described herein, for the knowledge I gained and for his help and support all these years.

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Within the team I thank Andreas Kalogirou, Maria Koyioni and Georgia Zissimou for their friendship, encouragement, support and knowledge exchange all these years. I would also like to thank a former member of the team, Hearklidia Ioannidou, for her friendship and support.

Finally, I would like to thank my family for their love, patience and support through the years of my PhD.

CONTENTS

Brief Contents

Detailed Contents

ABBREVIATIONS

Å	Ångström unit
Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
aka	also known as
Alk	alkyl
ANRORC	addition of nucleophile ring opening ring closure
aq	aqueous
Ar	argon atmosphere
Bn	benzyl
br	broad
Bu	butyl
Bz	benzoyl
c	cyclo
ca.	approximately (Latin: *circa*)
cat.	catalytic
cf.	compare (Latin: *confer*)
cm^{-1}	wavelength unit
concd.	concentrated
18-Crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
d	doublet (NMR) or days
δ	chemical shift
2D	two-dimensional
Da	Dalton unit (mass spectrometry)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double doublet
ddd	doublet of double doublets

DDQ	2,3-dichloro-5,6-dicyano-4-benzoquinone
decomp.	decomposition
DEPT	distortionless enhancement by polarization transfer
DIBOC	di-*tert*-butyl dicarbonate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
DSC	differential scanning calorimetry
E	electrophile
ε	extinction coefficient
e.g.	for example, (Latin: *exempli gratia*)
EI	electron ionization
equiv	equivalent
Et	ethyl
eV	electron volt unit
FTIR	Fourier transform infrared
g	gas
GCMS	gas chromatography mass spectrometry
gem	geminal
h	hour
Hal	halogen
HOMO	highest occupied molecular orbital
Hünig's base	*N*,*N*-diisopropylethylamine
hv	photolysis
Hz	Hertz unit
i	*iso*
I_A	Birds aromaticity index
i.e.	that is, (Latin: *id est*)
inf	inflection
In vacuo	under reduced pressure
i-Pr	isopropyl

IR	infrared
J	coupling constant (measured in Hz)
LDA	lithium diisopropylamide
LG	leaving group
liq.	liquid
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet (NMR) or medium (IR)
M^+	molecular ion
MALDI-TOF	matrix-assisted laser desorption/ionization-time of light
m/z	mass to charge ratio
Me	methyl
MHz	megahertz unit
min	minutes
mp	melting point
Ms	methanesulfonyl
MW	microwave
n	*normal*
v	frequency
NBS	*N*-bromosuccinimide
nd	no data
nm	nanometer unit
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
n-Pr	*n*-propyl
nr	no reaction
Nu	nucleophile
^oC	Celsius degrees
ox	oxidation
Ph	phenyl
PhCl	chlorobenzene
PhH	benzene

PIDA	iodobenzene diacetate
PIFA	[bis(trifluoroacetoxy)iodo]benzene
pK_b	negative log of the base dissociation constant, -logK_b
ppm	parts per million
psi	pounds per square inch (1 psi equals to 6894.76 Pa)
Py	pyridine
q	quartet
R_f	retention factor
rt	room temperature (20-25 ^oC, mean 22.5 ^oC)
rxn	reaction
s	singlet (NMR) or strong (IR)
sat.	saturated
sec	seconds
t	triplet
TCNE	tetracyanoethylene or tetracyanoethene
TCNEO	tetracyanoethylene oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Torr	Torricelli (unit of pressure equal to 1/760 atmosphere)
Ts	4-toluenesulfonyl
TsCl	4-toluenesulfonic chloride
TsOH	4-toluenesulfonic acid
TTF	tetrathiafulvalene
UV	ultraviolet
Vis	visible
W	Watt unit
w	weak (IR)
δ	chemical shift relative to a standard
Δ	heat (thermolysis < 400 ^oC)

λ_{max}	maximum wavelength
μL	microlitre unit

CHAPTER 1

Introduction

Sections

1.1 Heterocyclic chemistry

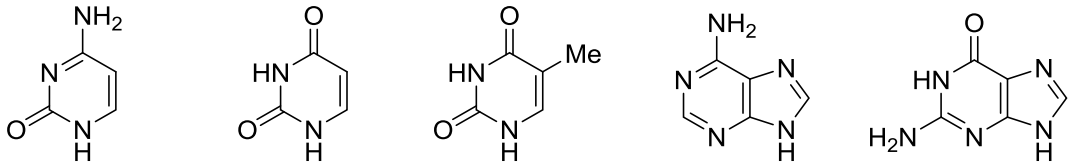
Heterocycles are molecules with cyclic structures whose skeletal rings contain at least one element from the periodic table other than carbon. The permutations available for constructing heterocycles, such as ring size, number and type of heteroatom, degree of saturation, are such that an infinite array of ring systems can be designed. Heterocycles that are conjugated, planar and obey Hückel's rule for aromaticity (*i.e.*, 4n + 2 π electrons) are described as being heteroaromatic and are referred to as heteroarenes or hetarenes.

Heterocyclic chemistry is the largest branch of organic chemistry in terms of the numbers of new compounds synthesized,[1] and heterocyclic compounds far outnumber aliphatic and carbocyclic compounds. It has been estimated that 85-90% of all publications today in organic chemistry utilize or are concerned in one way or another with heterocycles.[2]

Heterocycles are present in the majority of pharmaceuticals (*e.g.*, 90% of new drugs contain heterocycles) and agrochemicals, but also prevail in dyestuffs, reprography agents, and in a wide variety of additives.[3] Furthermore, heterocycles find uses as structural motifs for new materials, as protecting groups, as unique solvents and reagents, as latent functionalities in organic synthesis, as chemical entities that can be modified and substituted, but then destroyed to create new, non-heterocyclic or heterocyclic products and as such, constitute an integral part of modern synthetic methods.[2]

The main reason for the prevalence of heterocycles in the many varied applications outlined above is owed to the presence of the heteroatoms themselves, which, owing to their differing electron affinities, valences and chemistry, impart interesting properties to the molecules that cannot otherwise be obtained from purely carbocyclic or acyclic structures. Not surprisingly, nature has taken advantage of this and many natural products, such as alkaloids, DNA, vitamins, hormones and sugars, contain heterocycles,[2] and the active site of many receptors contain heteroaromatic amino acids as their key moieties.[4]

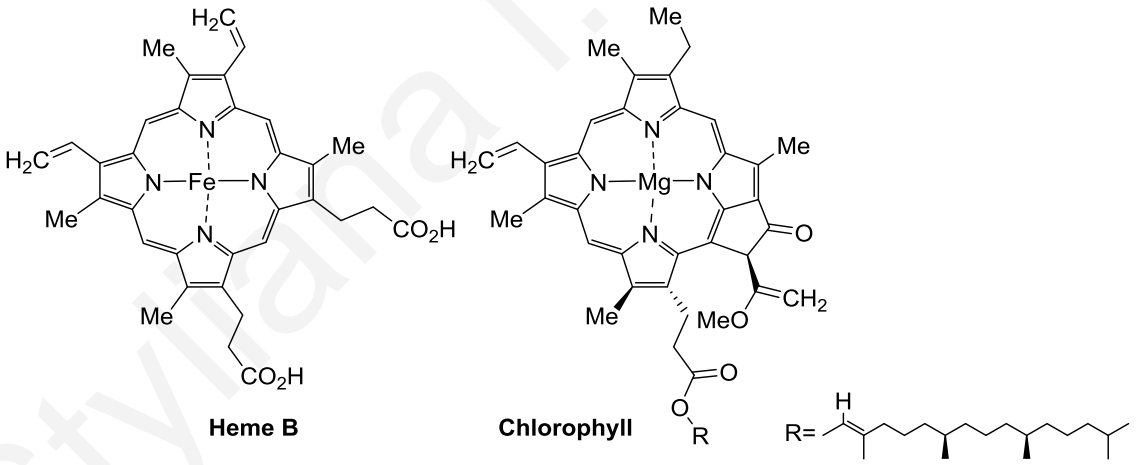
The importance of heterocyclic chemistry to life itself cannot be understated. The side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on pyrimidine (cytosine, uracil and thymine) and purine (adenine and guanine) bases.



Cytosine **Uracil** **Thymine** **Adenine** **Guanine**

The aromaticity, hydrogen-bonding interactions, and catalytic activity of the pyrimidine and purine bases of RNA may explain why they were formed in prebiotic conditions and gave rise to the "RNA world", which evolved into life on Earth.[5]

Other essential heterocycles are biosynthesized by animals or plants. For instance, Heme B, is one of the most important heterocycles biosynthesized by animals and it is responsible for oxygen transport in the red blood cells.[6] Hemes are most commonly recognized as components of hemoglobin, the red pigment in blood, but are also found in a number of other biologically important hemoproteins such as myoglobin, cytochrome, catalase, and endothelial nitric oxide synthase. Additionally chlorophyll, another related biomolecule that is biosynthesized by plants, is vital for photosynthesis, which allows plants to absorb energy from light.[7]



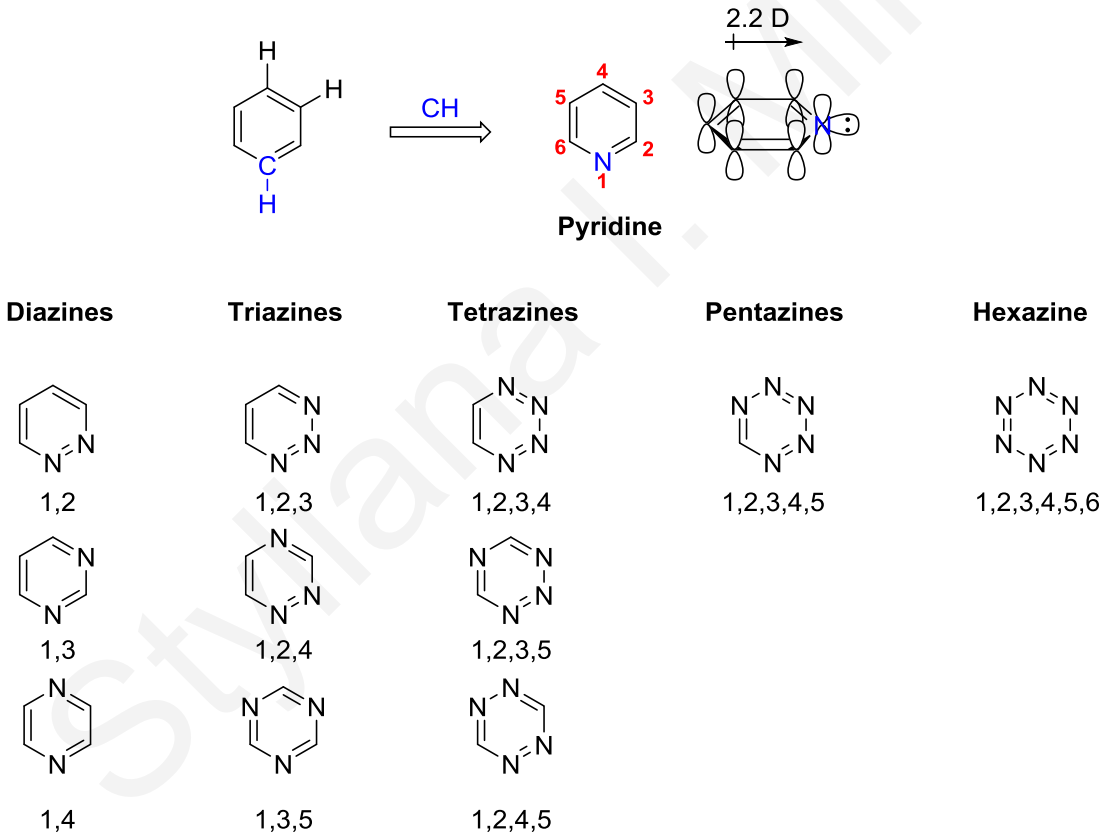
Heme B **Chlorophyll**

Not surprisingly, the study of heterocyclic chemistry, which is involved in many natural biochemical processes, has led to impressive advances in biological chemistry, genetic manipulation, enzymatic transformation and antibody recognition.[3]

Since many heterocyclic natural products are nitrogen heterocycles there is continued and considerable effort to develop the synthesis and chemistry of nitrogen heterocycles that exhibit a wide range of desirable properties which can improve the quality of life.

1.2 Nitrogen hetarenes

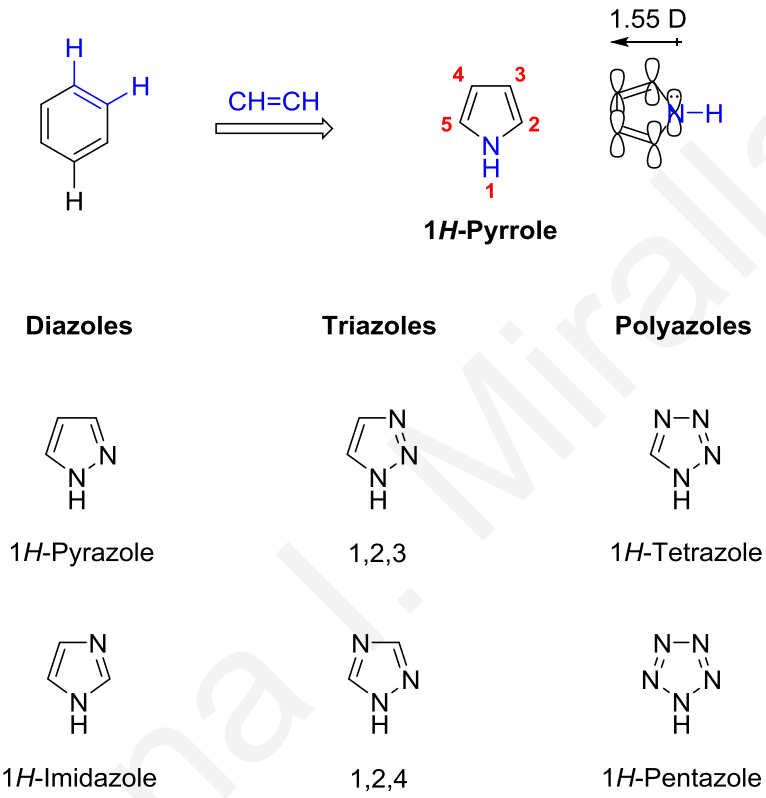
Pyridine (azabenzene), the simplest six-membered hetarene, is formally derived from benzene by replacing one CH (electronegativities C 2.5, H 2.2) with N (electronegativity N 3.1).[8] The introduction of the more electronegative N makes the carbon skeleton of the ring system less electron rich, deactivating the ring system to electrophilic substitution and activating it to nucleophilic substitution. The sp^2 N atom also bears a lone pair of electrons which resides in the plane of the ring system making pyridine basic (pK_b 8.8).[9] As such, the simple formal exchange of one CH for N leads to dramatic changes in the physical properties of benzene. Sequential replacement of other CH's by N leads to a range of azabenzenes (diazines, triazines, tetrazines, pentazines and hexazines), each with different physical and chemical properties (Scheme 1). Worthy of note is hexazine (N_6),[10] the all nitrogen analogue of benzene, which has yet to be synthesized.



Scheme 1

Analogously, the formal replacement of a CH=CH unit in benzene with NH gives the five membered heterocycle, pyrrole. In pyrrole, the nitrogen lone pair contributes to the aromatic sextet, which results in the electrons being less available for proton bonding. For

these reasons, pyrrole nitrogens are not strongly basic (pK_b 13.6),[11] and on protonation, the aromaticity is lost. Furthermore, the sequential replacement of CH's with N atoms in pyrrole, can give rise to a range of azaheteroles: pyrazoles, imidazoles, triazoles, tetrazoles and pentazoles (Scheme 2). Pentazoles are unstable and often highly explosive compounds. The first pentazole synthesized was phenylpentazole, where the pentazole ring is stabilized by conjugation with the phenyl ring.[12]



Scheme 2

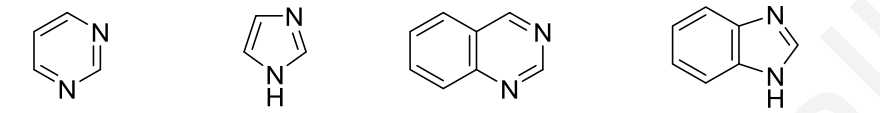
1.3 1,3-Dinitrogen hetarenes

Diazines and diazoles display similar reactivity to pyridine but to an exaggerated degree. Diazines, such as pyridazine, pyrimidine and pyrazine, have two nitrogens that are both pyridine like. This leads to a significant reduction in the electron density on carbon which strongly deactivates the molecules to electrophiles and increases their susceptibility to nucleophilic addition. Not surprisingly, the introduction of two electronegative N atoms makes diazines less basic (pK_b 10.8-13.5)[13] than pyridine (pK_b 8.8).[9]

Diazoles, such as pyrazole and imidazole, contain both pyridine- and pyrrole-like nitrogen atoms. As such, diazoles combine to various degrees the properties of both pyridines and

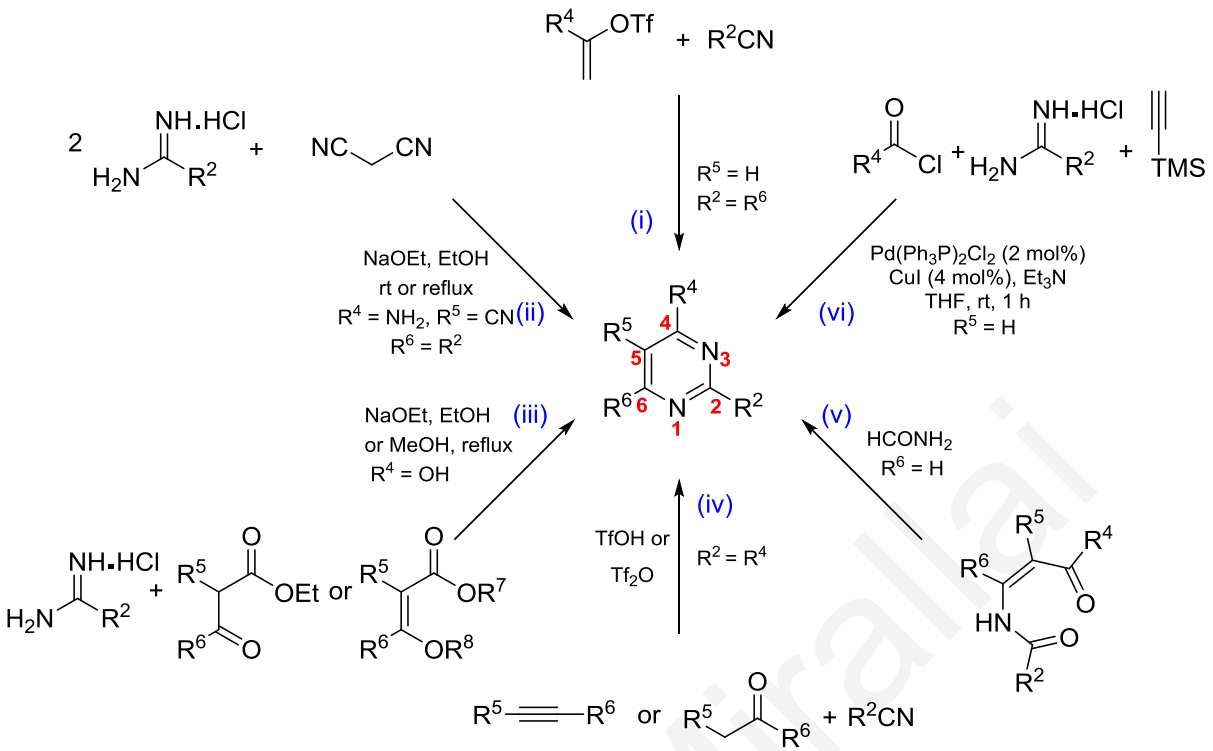
pyrroles. Diazoles are typically less reactive than pyrroles with respect to electrophilic aromatic substitution owing to the inductive electron-withdrawing effect of the second heteroatom. However, they are more reactive towards electrophiles than pyridine since diazoles still support 6π electrons over five atoms making them, by default, more electron rich that the azines.

An important class of diaza heteroarenes are the 1,3-dinitrogen heterocycles, pyrimidines and imidazoles. Their benzo-fused analogues are known as quinazolines and benzimidazoles.



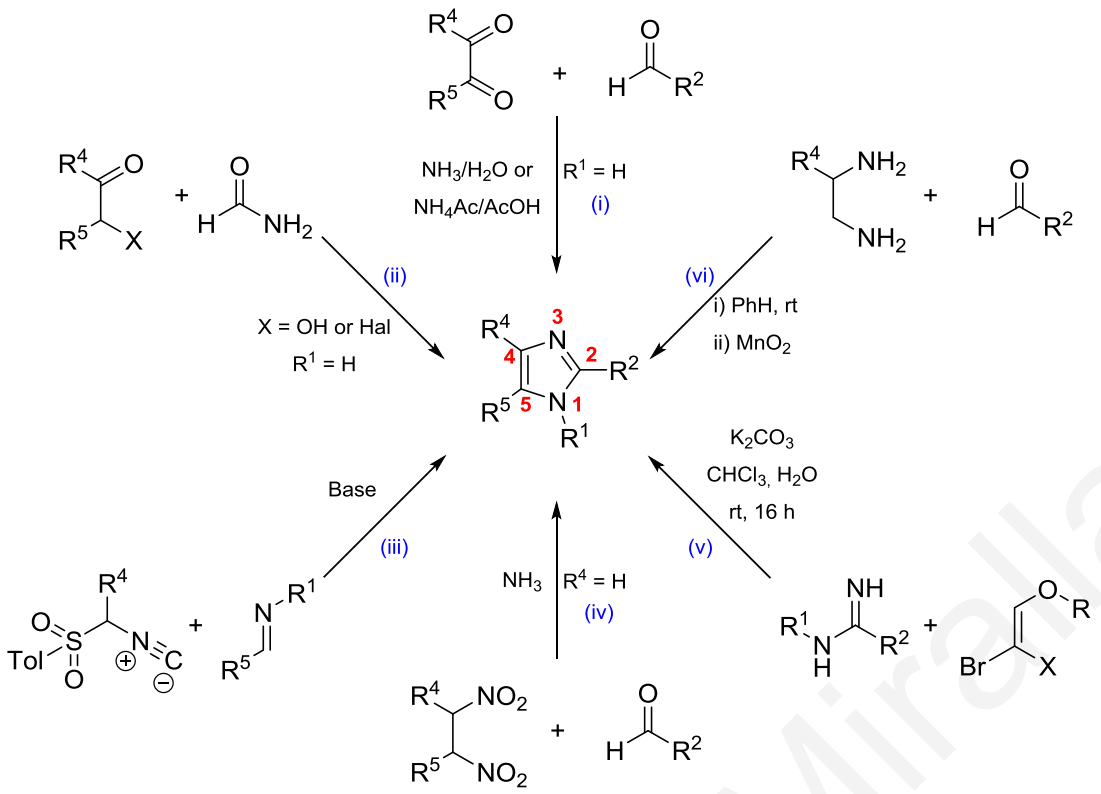
Pyrimidine **1*H*-Imidazole** **Quinazoline** **1*H*-Benzo[*d*]imidazole**

Pyrimidines are the most important diazines and essential for any form of life. Since their discovery in 1818,[14] there has been great interest in this heterocycle as it is a structural element of many biologically active substances, therapeutic agents and pesticides. Some general routes for pyrimidine synthesis involve: (i) the reaction of vinyl trifluoromethanesulfonates with nitriles;[15] (ii) the reaction of amidines with malononitrile;[16] (iii) the reaction of amidines with β-oxo esters or 3-alkoxyacrylates;[16] (iv) the reaction of alkynes[17] or activated ketones[18] with nitriles; (v) the reaction of (*Z*)-*N*-(3-oxoprop-1-en-1-yl)formamides with formamide;[19] and (vi) the reaction of acid chlorides with terminal alkynes under Sonogashira conditions (Scheme 3).[20,21]



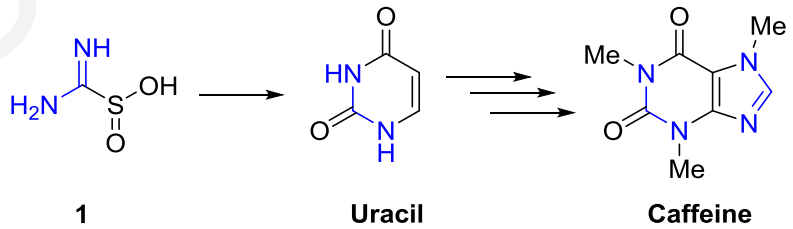
Scheme 3

The first reports on imidazoles were published in the 1840s and concerned 2,3,5-triphenyl-imidazoles.[22,23] In 1858, Debus[24] reported the reaction between glyoxal and ammonia and pioneered the synthesis of imidazoles. Owing to their prevalence in natural products and biologically active compounds, a remarkable number of syntheses have been developed for imidazoles. The most common routes involve the construction of: (i) 1,2- and 1,5-bonds from 1,2-dicarbonyl compounds (Radiszewski synthesis);[25] (ii) 1,5- and 3,4-bonds from *α*-halo or *α*-hydroxy ketones;[25] (iii) 1,2- and 4,5-bonds using cyanates (*e.g.*, tosylmethyl isocyanide) and *α*-aminocarbonyl compounds (Marckwald synthesis);[26] (iv) 1,2- and 2,3-bonds using *ortho*-dinitro analogues and aldehydes (Maquenne synthesis);[27] and (v) the use of amidines, guanidines, ureas and thioureas which are common N-C-N synthons;[26] and (vi) the dehydrogenation of tetrahydro-1,3-azoles which are simply derived from aldehyde ethylene glycol cyclic acetals (formed from the reaction of 1,2-diamines with aldehydes)[25] (Scheme 4).



Scheme 4

A common feature in the synthesis of both pyrimidines and imidazoles is the use of amidines which introduce the three atom fragment N-C-N into either ring system. Amidines therefore, represent useful versatile building blocks for a variety of monocyclic and fused pyrimidines and imidazoles. Moreover, they are found in nature. Caffeine for example, represents a diamidine heterocycle (imidazopyrimidine) which is biosynthesized in plants and acts as a natural pesticide that paralyzes and kills certain insects feeding on the plants, as well as enhancing the reward memory of pollinators.[28] In 2003, a novel six step total synthesis of caffeine was reported (Scheme 5),[29] starting from uracil which can be prepared from thiourea sulfone **1** (formamidine sulfinic acid).[30]

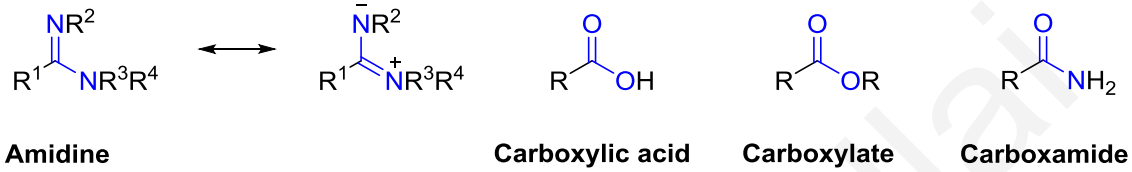


1 **Uracil** **Caffeine**

Scheme 5

1.4 Amidines

Amidines are the dinitrogen analogues of carboxylic acids, carboxylates (esters) and carboxamides.[31] They possess an amino nitrogen atom with a lone electron pair conjugated with the π electrons of a C=N imine bond. As such, amidines combine the properties of an azomethine-like C=N double bond with an amide-like C-N single bond with partial double bond character (Scheme 6).[32,33]



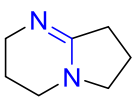
Scheme 6

Historically, IR spectroscopy has been used to aid the structural determination of amidines owing to their ν(N-H) and ν(C=N) absorptions at 3400–3300 and 1685–1580 cm^{-1}, respectively.[34] *N*,*N'*-Disubstituted amidines display ν(N-H) absorptions at 3300–3500 cm^{-1}, while their ^{1}H NMR N*H* signals appear at 5.40–6.70 ppm.[35-40] Amidines are considered as the strongest synthetically useful auxiliary bases (pK_b 6.5-20.0)[41] and some are classed as *organic superbases*.[42] Their high basicity is owed to their resonance-stabilized cations **2**. Specifically, amidine protonation occurs on the imino sp^2 nitrogen, rather than the sp^3 nitrogen which, having less *s* character, was expected to be more basic. This leads to the formation of a symmetrical amidinium cation that is resonance stabilized (*cf.* the isoelectronic carboxylate anion **3**) (Scheme 7).[31] Since the protonation occurs at the imino nitrogen atom, substitution at this site has the largest influence on their pK_b value followed by the substitution at the functional carbon.

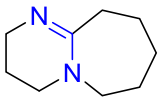
Scheme 7

The commercially available cyclic amidines 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) [pK_b (MeCN) = 23.8][43] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [pK_b (MeCN) = 24.3][43]

that are conformationally restricted to enhance this phenomenon, are commonly used super bases in organic synthesis.[44]

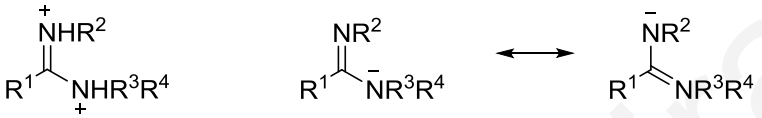


DBN [pK_b (MeCN) 23.8]



DBU [pK_b (MeCN) 24.3]

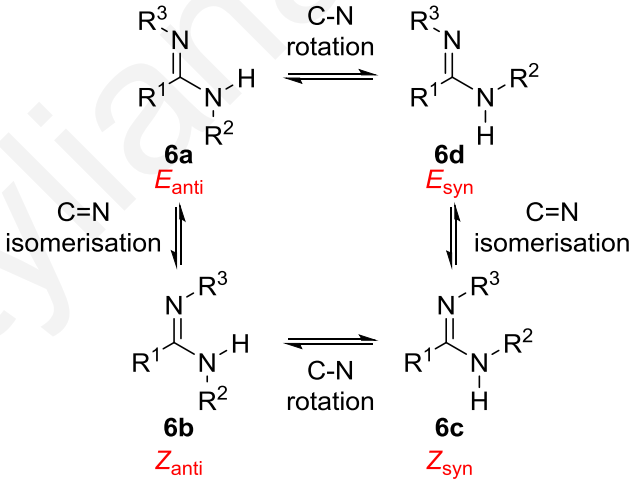
In strongly acidic media (see also Sect. 1.4.3), the dication **4** can be formed, which has a localized C=N double bond. While, in strong alkaline media, deprotonation affords the resonance stabilized anion **5** (Scheme 8).[33,45]



4 **5**

Scheme 8

Nomenclature of amidines. Monosubstituted, non-symmetric disubstituted, trisubstituted and tetrasubstituted amidines can exist as the different tautomers **6a-d** depending on the position of substituents relative to each other with respect to the double bond (Scheme 9).[31]



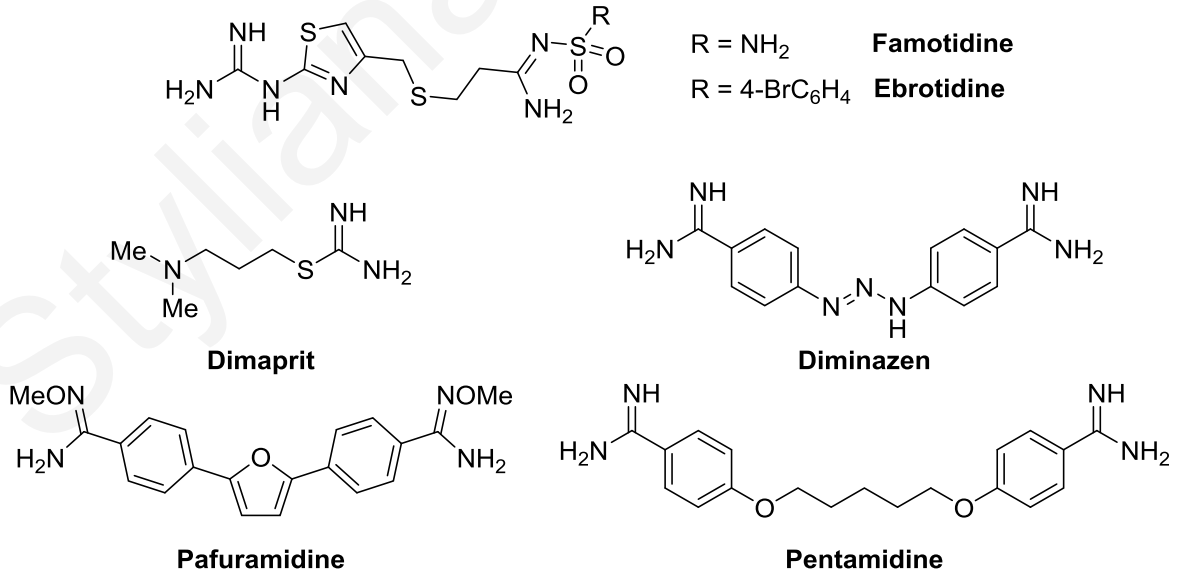
Scheme 9

The position of the tautomeric equilibrium can be quantified by ultraviolet spectroscopy and by comparing ionization constants of certain amidines and model compounds.[46,47] The

E,Z isomers are assigned with respect to priority groups around the C=N double bond and generally the *E* isomers are energetically more favored than the *Z* forms.[48] While the *syn* and *anti* assignments are governed by the priority groups around the C-N single bonds; *syn-anti* isomerisation in amidines can be studied by ^{1}H NMR spectroscopy.[49] Thus, investigation of the addition of secondary amines to isocyanates showed that *Z* formamidines are formed initially and being thermodynamically unstable, rearrange to the *E* isomers.[37,40] Despite this apparent general preference there are several exceptions where both *E* and *Z* forms are present.[31]

1.4.1 Applications of amidines

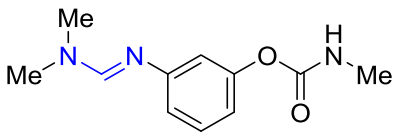
Amidines are important in the pharmaceutical industry owing to their wide range of biological activities.[50-53] Several amidines are commercially available drugs, wherein some are H_2 receptor antagonists[54] used for the treatment of peptic ulcer disease (*e.g.*, Famotidine),[55] erosive esophagitis (*e.g.*, Ebrotidine)[56] and gastroesophageal reflux disease (*e.g.*, Dimaprit).[57] Other amidine drugs have antiparasitic and antimicrobial properties[58] and are used for the treatment of Babesia inflection (*e.g.*, Diminazen),[59] treatment of pneumocystis pneumonia (*e.g.*, Pafuramidine),[60] and treatment of West African trypanosomiosis a.k.a. sleeping sickness (*e.g.*, Pentamidine).[61] Amidines are also considered as potential drugs for the treatment of malaria[62] and Chaga's disease.[63]



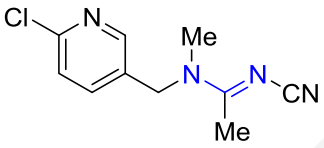
Amidines display anti-inflammatory,[64] analgesic (pain killers),[65] antibacterial[66] and antiseptic (*e.g.*, Hexamidine)[67] activities. Additionally, they represent promising

therapeutic targets for the symptomatic treatment of multiple central nervous system pathologies (*e.g.*, hyperactive neurological disorders,[68] Alzheimers's disease,[69] and epilepsy[70]) and treatment and prevention of secondary venous thromboembolism as anticoagulants.[71]

Many amidines are also commercially available agrochemicals *e.g.*, the acaricides and insecticides Formetanate[72] and Acetamiprid[73] (Assail®).

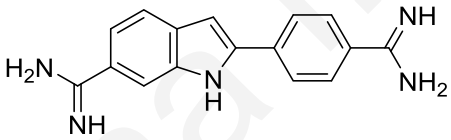


Formetanate



Acetamiprid

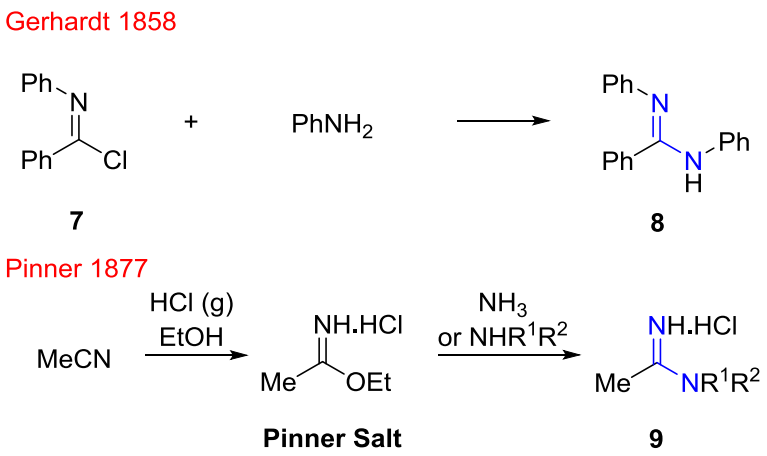
They also represent an important class of compounds with applications in the fields of catalyst design[74,75] and material science.[76] Moreover, they are considered as potential CO_2 trapping agents which can be used to minimize the greenhouse gas emissions from fossil fuel combustion.[77-79] While, other amidines find uses as fluorescent probes for DNA and RNA [*e.g.*, 4',6-diamidino-2-phenylindole (DAPI)] in fluorescence microscopy.[80]



DAPI

1.4.2 Synthesis of amidines

The first amidine, *N*,*N'*-diphenylbenzamidine **8**, was synthesized by Gerhardt in 1858[81] from the reaction of *N*-phenylbenzimidyl chloride **7** with aniline. In 1877,[82] Pinner developed a practical method for the synthesis of amidines **9** by dissolving or suspending nitriles in anhydrous alcohol that was then treated with an excess of dry hydrogen chloride, to afford the imino ether hydrochloride (Pinner salt), subsequent treatment of which with ammonia or primary or secondary amines gave amidines **9** (Scheme 10).

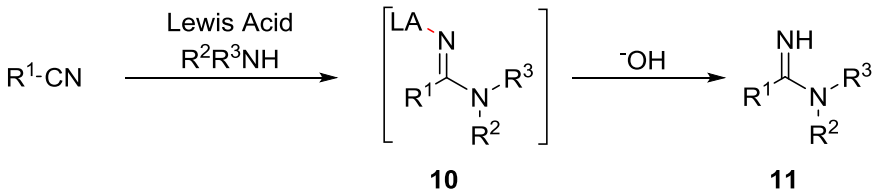


Scheme 10

Since the development of the Pinner amidation reaction many improvements were made to the early syntheses and new routes have been developed that utilize not only nitriles but carboxamides, thioamides, carboxylic acids and azides as starting materials.

From Nitriles. The direct synthesis of amidines from nitriles can be achieved if the nitriles are strongly activated, *i.e.* substituted by electron-withdrawing groups.[83] Alternatively, deprotonation "activation" of the arylamines using bases *e.g.*, BuLi,[84] sodamide,[85,86] or sodium hydride,[87] allowed the use of less activated nitriles.

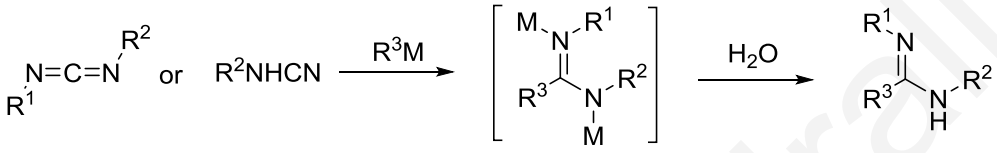
Unreactive nitriles can also be activated using a wide array of protic acids (*e.g.*, methanesulfonic[88] or toluenesulfonic acid[89]) and Lewis acids (Scheme 11) and lead to the formation of the intermediate **10**.[90-95] Common Lewis acids, such as $AlCl_3$, $ZnCl_2$ or stoichiometric amount of CuCl, can be used; however, these reactions required elevated temperatures of 150-200 °C and caustic work-ups (*e.g.*, 50% aq. NaOH) to release the amidines **11**.[90-96] More recently, Lewis acids of rare earth metals[97-101] have been used under milder conditions and often in a single step to provide amidines in good to excelled yields, however, these Lewis acids are not readily commercially available and their synthesis can be expensive. Alkyl- and aryl- nitriles can also be converted to unsubstituted amidines in the presence of alkylchloroaluminum amides, which were prepared by addition of ammonium chloride to commercially available trimethylaluminum.[102]



10 **11**

Scheme 11

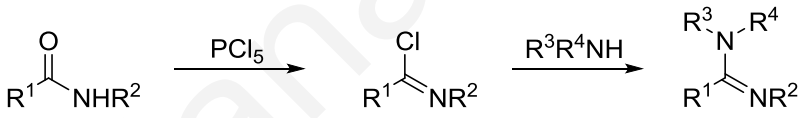
An interesting route to amidines **15** was achieved by adding Grignard, organolithium or organozinc reagents to carbodiimides **12** or cyanoamides **13** followed by hydrolysis of the resulting bismetallated intermediate **14** (Scheme 12).[103,104]



12 **13** **14** **15**

Scheme 12

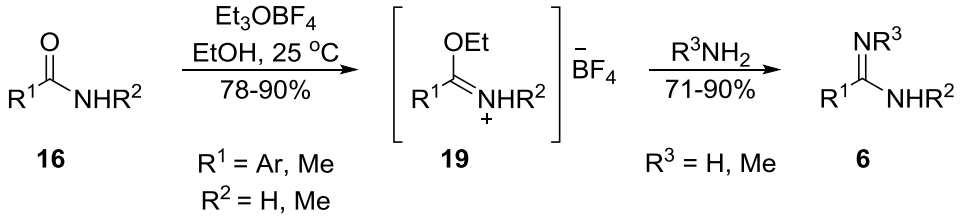
From carboxamides. Amides **16** can be converted to imidoyl chlorides **17** using phosphorous pentachloride. The formed imidoyl chlorides can then be condensed with primary or secondary amines to yield amidines **18** (Scheme 13).[105-108]



16 **17** **18**

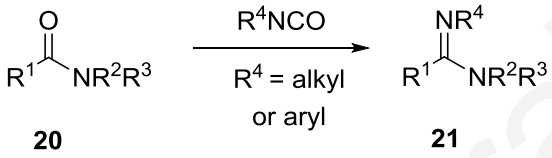
Scheme 13

This method is excellent for preparing di- and tri-substituted amidines. Other reagents such as phosphorous oxychloride or thionyl chloride can be used in the synthesis of imidoyl chlorides **17** but usually lower yields are obtained.[109] Furthermore, amides **16** can be *O*-alkylated with triethyloxonium fluoroborate at ambient temperature to yield the corresponding imidic ester fluoroborates **19**, which react with amines to yield the target amidines **6** (Scheme 14).[110,111]



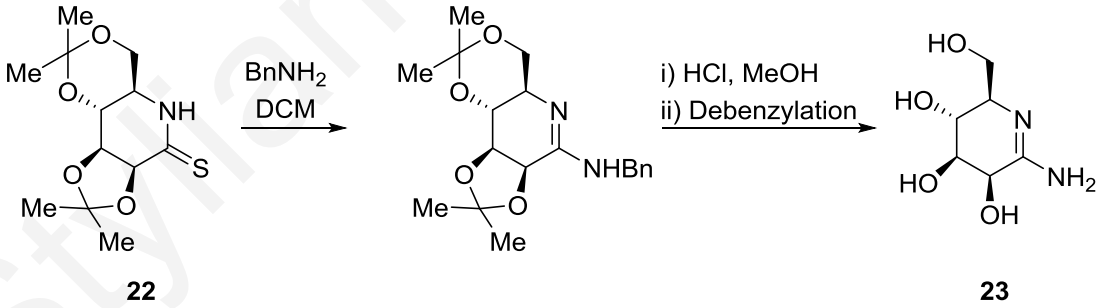
Scheme 14

In a different approach, aryl- and alkyl- isocyanates converted tertiary amides **20** into the amidines **21** in high yields (Scheme 15).[112]



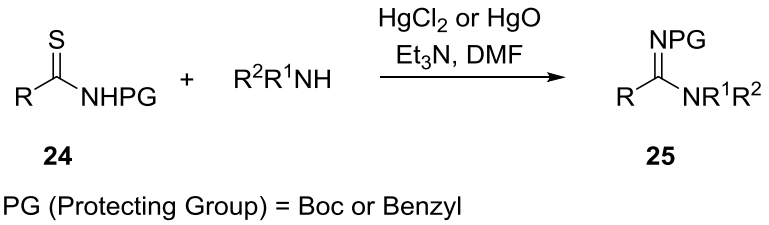
Scheme 15

From Thioamides. Thioamides are used as more reactive precursors than amides for amidine synthesis. Phosphorus sulfides (*e.g.*, phosphorus pentasulfide[113] and Lawesson's reagent[114]) are typically used for the conversion of amides to thioamides. One early example was the preparation of an amidine-type mannosidase inhibitor **23** from cyclic thioamide **22** (Scheme 16).[115]



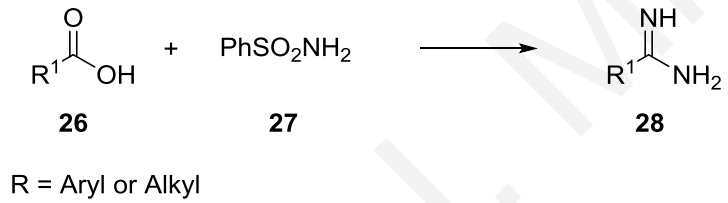
Scheme 16

Moreover, thioamides **24** gave access to a series of aryl and alkyl amidines **25** in the presence of mercury chloride or mercury oxide and ammonia in DMF (Scheme 17).[116,117] Recently, copper[118] and silver salts[119] were used for the conversion of thioamides to amidines in high to excellent yields.



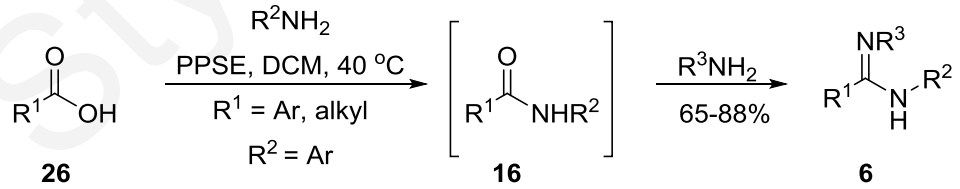
Scheme 17

From Carboxylic acids. In 1912, Roullier was the first who reported that aryl and alkyl carboxylic acids **26** in the presence of benzenesulfonamide **27** converted into amidines **28** (Scheme 18).[120] Furthermore, heating of secondary carboxylic acids with hexamethylphosphoramide (HMPA) gives rise to the formation of *N*-substituted *N'*,*N'*-dimethylamidines.[121,122]



Scheme 18

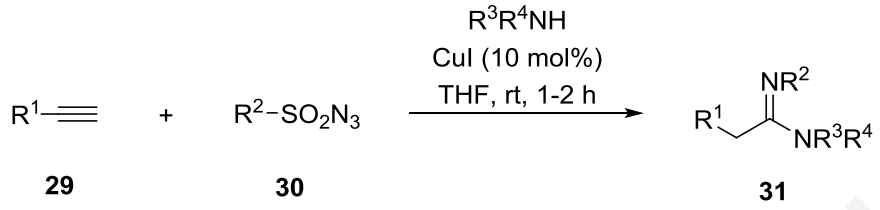
In addition, a direct synthesis of amidines **6** from carboxylic acids **26** and amines was achieved *via* intermediate amides **16** in the presence of polyphosphoric acid trimethylsilyl ester (PPSE), which was generated *in situ* from the reaction of phosphorous pentoxide with hexamethyldisiloxane as a condensing agent (Scheme 19).[123]



Scheme 19

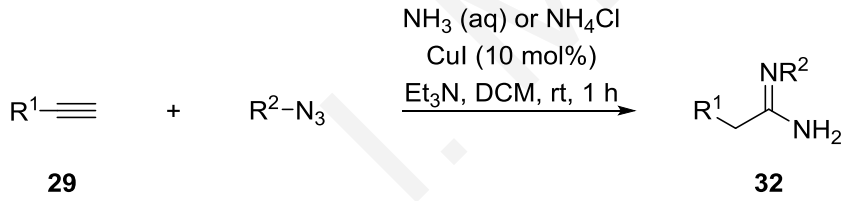
Additionally, amidines can also be synthesized by condensing anilines with carboxylic acids in the presence of $SOCl_2$.[124]

From azides. Bae *et al.*,[125] developed a multicomponent reaction involving the copper-catalyzed coupling of sulfonyl azides **30**, with a wide variety of alkynes **29** and primary or secondary amines yielding *N*,*N*-disubstituted amidines **31** (Scheme 20).



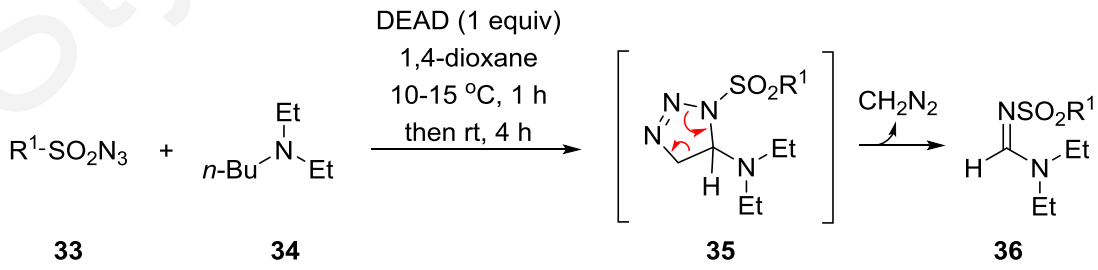
Scheme 20

This efficient reaction was carried out using catalytic amounts of copper in the presence of THF and tolerated a wide variety of electron-donating and electron-withdrawing, as well as, hetero alkyne substrates. In 2008, Chang *et al.*,[126] exchanged the amines with ammonium salts yielding *N*-monosubstituted amidines **32** (Scheme 21).



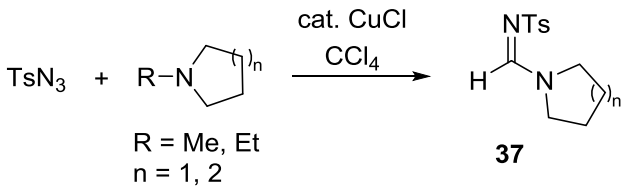
Scheme 21

Furthermore, Xu *et al.*,[127] showed that substituted amidines **36** can be released from the unstable triazoline intermediate **35** which is formed by using diethyl azodicarboxylate (DEAD), for the formation of an enamine, by activating the α and β hydrogens of a tertiary amine **34** followed by the addition of sulfonyl azide **33** (Scheme 22).



Scheme 22

In 2010, additional studies performed by Xu *et al.*,[128] demonstrated that highly substituted *N*-sulfonyl amidines **37** can be formed by using CuCl as a catalyst (Scheme 23).

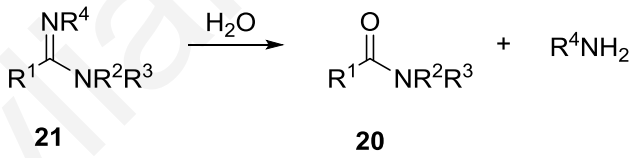


Scheme 23

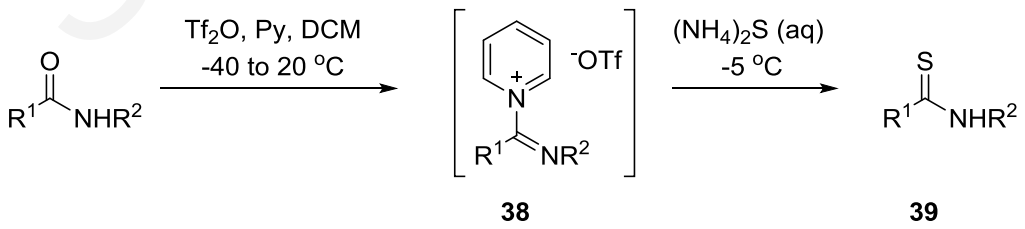
1.4.3 Chemistry of amidines

Amidines react with electrophiles and nucleophiles.[129] The simplest reaction of amidines with electrophiles is protonation (see Sect. 1.4). When amidines react with fairly strong acids, salts are formed *via* a first order reaction with respect to both compounds. Furthermore, alkylation,[130,131] acylation[132] and arylation[133] of amidines have also been reported.

The simplest reaction of amidines **21** or their salts with nucleophiles is hydrolysis, which gives the corresponding amides **20** and amines (Scheme 24).[134] Additionally, *N*-mono-substituted amidines **38** can undergo thiolysis to give the corresponding thioamides **39** while *N*,*N*-disubstituted amidines lead to the formation of tertiary thioamides (Scheme 25).[135]

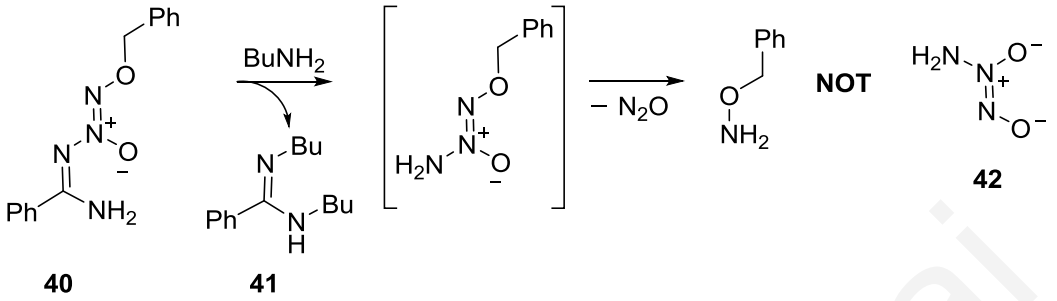


Scheme 24



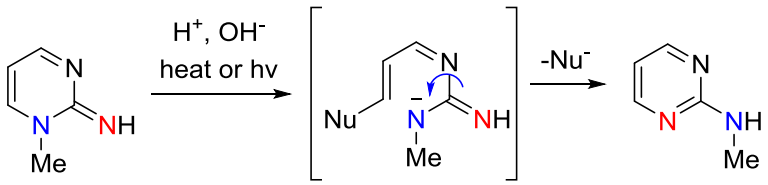
Scheme 25

Recently, the aminolysis of *N*-diazeniumdiolated amidine **40** into *N*,*N'*-dibutylbenzamidine **41** as a failed approach to the synthesis of diazeniumdiolated ammonia **42** was also reported (Scheme 26).[136]



Scheme 26

Furthermore, an important discovery in amidine chemistry was made in 1902 by Otto Dimroth,[137,138] who reported the "amidine rearrangement'' (aka Dimroth rearrangement). It is an isomerization whereby heteroatoms on a heterocycle are translocated; a representative example is given in Scheme 27.[139,140] In 1929[141] Chapman noted that amidines, when strongly heated below their decomposition point, can undergo a dynamic isomerism which involves mobile hydrocarbon radicals.

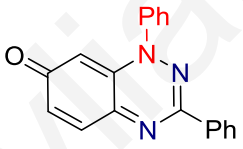


Scheme 27

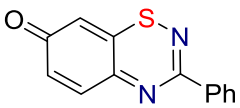
In addition, amidines are important scaffolds for the synthesis of a wide range of compounds such as amidrazones,[142,143] amidoximes[144] and heterocycles like diazirines,[145] azetidinones,[146] indoles,[147] oxazoles,[148] imidazoles,[24,149,150] C_{60}-fused imidazolines,[151] benzimidazoles,[124,152] imidazolobenzotriazinyls,[153] thiadiazoles,[154,155] thiazepines,[156] pyridines,[157] pyrimidines,[158] quinazolines,[159-162] 1,2,4-thiadiazines,[163,164] 1,2,4-benzothiadiazines,[89,165-167] benzothiazoles,[87] naphtho[1,8-*ef*][1,4]diazepines,[168] thieno[3,2,*d*]pyrimidines,[169] triazines,[170] tetrazines,[171] oxazines,[172] phenathridines[173] and furamidines.[87]

1.5 Origin of thesis

This thesis originated from an initial interest on the use of amidines as precursors to 1,2,4-benzothiadiazines **44**. Ongoing work in our team revealed that 1,2,4-benzotriazinones **43** displayed biological behavior against Aβ-amyloid aggregation inhibition and/or inhibition of AChE/BChE (Acetyl/Butyryl cholinesterases).[174] Replacing the triazine N-Ph group by sulfur[88] gives a more planar 1,2,4-benzothiadiazinone that studies indicated would improve the Aβ-amyloid aggregation inhibition activity compared to 1,2,4-benzotriazinones.

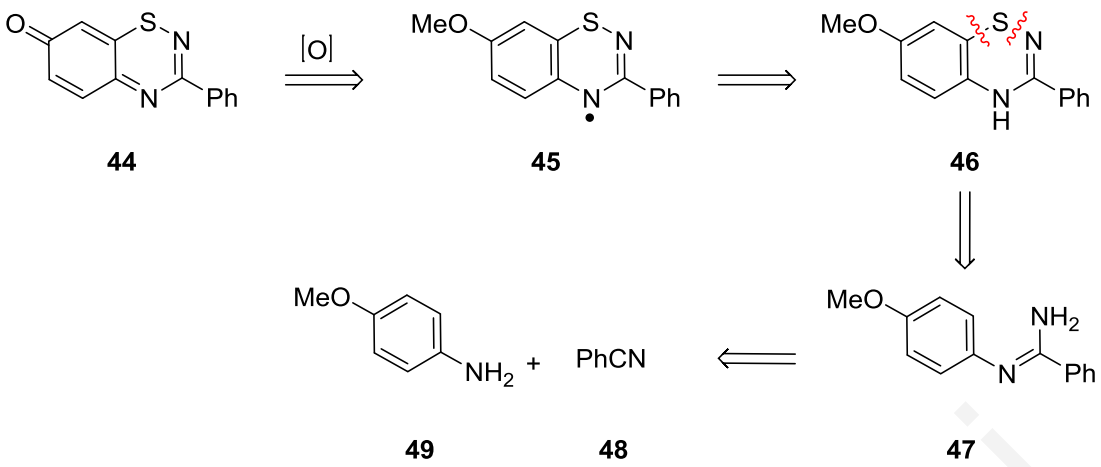


43



44

Retrosynthesis of 1,2,4-benzothiadiazinone **44**, identified the benzamidine **47** as a precursor (Scheme 28). Based on ongoing work within our team[175] the *p*-methoxy substituent on the benzamidine can facilitate the final oxidation step of the benzothiadiazinyl radical **45** to give the desired quinonimine **44**, which we considered necessary for competing against oxidation of the ring sulfur.



44 **45** **46** **49** **48** **47**

Scheme 28

At the time we initiated our study, there were only a few available literature procedures to 4-methoxyphenylbenzamidine **47** and they gave poor to moderate yields (14-40%).[176-179] Interestingly, during the course of this Thesis, we (see Chapter 2) and others[180,181] have now reported yields in excess of 90%.

Since it was essential to have access to the benzamidine **47** in large quantities we initially chose to reinvestigate the synthesis and chemistry of benzamidines in the hope of discovering improved syntheses and new chemistry. While the high yielding synthesis of the desired benzamidine **47** was achieved (Chapter 2), attempts to prepare the quinonimine **44** failed (not reported) and the work evolved in an orthogonal manner to investigate the use of these amidines in other cyclization reactions that led to the formation of quinazolines and imidazoles (Chapters 3-5).

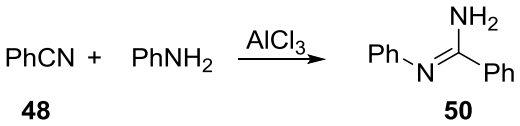
CHAPTER 2

Reinvestigating the synthesis of *N*-arylbenzamidines from benzonitriles and anilines in the presence of $AlCl_3$

Sections

2.1 Introduction

As mentioned earlier, (Chapter 1, Section 1.5), the study was initiated by a search for a high yielding synthesis of *N*-(4-methoxyphenyl)benzamidine **47** (Scheme 28). In the absence of a suitable literature procedure, the classic Lewis acid mediated addition of benzonitrile to anilines was re-optimised. Our chosen starting point was the reaction between $AlCl_3$, benzonitrile (**48**) and aniline which has been described in detail in the series *Organic Synthesis* (Scheme 29).[92]



Scheme 29

A search of the surrounding literature revealed some interesting information: 1) the reactions were typically carried out at high temperatures (180-200 ^oC); 2) the mode of addition was predominantly addition of the Lewis acid to a mixture of aniline and benzonitrile; 3) the work-ups involved the use of sometimes very caustic solutions of NaOH (50%); and 4) the presence of alkoxy or nitro groups was reported to be incompatible with the use of Lewis acids such as $AlCl_3$.[94]

A partial re-optimisation of the reaction conditions as reported herein provided useful results that included the $AlCl_3$ mediated synthesis of previously unobtainable 2-amino-4-methoxyphenylbenzamidine **51**.

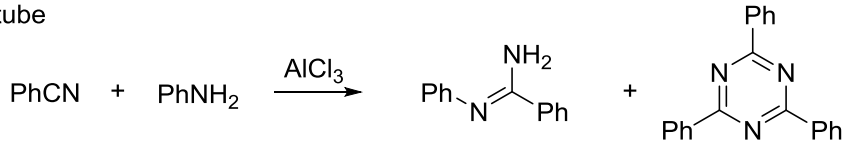
2.2 Investigation of the reaction of anilines with benzonitriles

Nucleophilic addition to unactivated nitriles was not considered to be facile and as such the reactions of anilines with benzonitriles was often conducted at elevated temperatures (180-200 ^oC). Surprisingly, the addition of Lewis acid catalysts to these reaction mixtures was typically carried out after the benzonitriles were mixed with anilines and heated to relatively high temperatures.[93,90] The alternative addition of Lewis acid catalyst to the benzonitrile prior to the addition of aniline has received considerably less attention.[95] It seemed rational to us that pre-forming the nitrile-Lewis acid complex[182-183] at near ambient temperatures prior to addition of the amine could allow these reactions to take place at

lower temperatures, *via* the now activated nitrile, which could lead to better recoveries of benzamidines.

As such we investigated the mode of addition for the classical preparation of *N*-phenylbenzamidine (**50**), described by Cooper and Partridge.[92] At first the original conditions [mixing of benzonitrile (**48**) with aniline, heating to 200 ^{o}C, followed by addition of $AlCl_3$] were reproduced to confirm the literature yields and to examine the effect of reaction time and temperature. Furthermore, we varied the concentrations of NaOH used in the work-up for decomposing the $AlCl_3$ reaction complexes. At best, with this mode of addition, the *N*-phenylbenzamidine (**50**) could be obtained in yields of *ca.* 70% (lit.,[92] 74%) when the reaction was heated to 200 ^{o}C prior to the addition of $AlCl_3$. The use of lower reaction temperatures (100 ^{o}C) and longer reaction times (6 h) gave reduced yields of the desired benzamidine **50**. The use of varying concentrations of NaOH during the reaction work-up did little to affect the product yields (Table 1). Switching the mode of addition gave interesting results. When powdered $AlCl_3$ was added to benzonitrile (**48**) at *ca.* 20 ^{o}C a solid complex rapidly formed that could not be stirred. Heating the reaction mixture to *ca.* 100 ^{o}C gave a uniform melt. Adding aniline to this melt at *ca.* 200 ^{o}C, led to poor recoveries of the desired *N*-phenylbenzamidine (**50**) and surprisingly higher recoveries of the benzonitrile trimer 2,4,6-triphenyl-1,3,5-triazine (**52**). As such the aniline was added to the melt at the lowest possible melt temperature *ca.* 100 ^{o}C and the reaction was left to heat for 4 h. Under these conditions the recovery of *N*-phenylbenzamidine (**50**) was increased to 83-84% (Table 1, entries 7 and 8). Adding the aniline at *ca.* 100 ^{o}C and then raising the reaction temperature to *ca.* 200 ^{o}C gave a reduced yield (Table 1, entry 5). Conversely adding the aniline prior to the melt temperature at *ca.* 50-70 ^{o}C and allowing the reaction to stand for 12 h also led to reduced recoveries of *N*-phenylbenzamidine (**50**) (Table 1, entries 9 and 10). Alternative combinations that were investigated including mixing all three reagents or mixing the $AlCl_3$ with the aniline at *ca.* 20 ^{o}C and then heating to *ca.* 100 ^{o}C failed to give superior yields of *N*-phenylbenzamidine (**50**) (Table 1).

Table 1. Investigation of the reaction between benzonitrile (**48**) (5.36 mmol), $AlCl_3$ (1 equiv) and aniline (**49**) (1 equiv) protected from moisture with a $CaCl_2$ drying tube



48 **49** **50** **52**

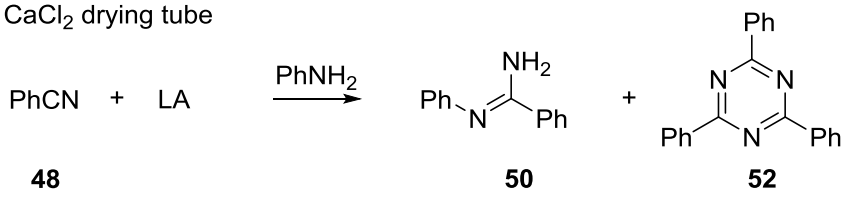
entry	reagents	time (h)	temp. (°C)	NaOH[a] (mol%)	yields (%) **50**	**52**
1	(PhCN + $PhNH_2$) + $AlCl_3$	1	200	50	70	trace
2	(PhCN + $PhNH_2$) + $AlCl_3$[b]	1	200	19	69	nd[d]
3	(PhCN + $PhNH_2$) + $AlCl_3$	1	200	12.5	66	trace
4	(PhCN + $PhNH_2$) + $AlCl_3$	6	100	12.5	60	3
5	(PhCN + $AlCl_3$) + $PhNH_2$	1	200	12.5	58	6
6	(PhCN + $AlCl_3$) + $PhNH_2$[c]	1	200	12.5	49	6
7	(PhCN + $AlCl_3$) + $PhNH_2$	4	100	12.5	83	3
8	(PhCN + $AlCl_3$) + $PhNH_2$	4	100	50	84	3
9	(PhCN + $AlCl_3$) + $PhNH_2$	12	70	12.5	72	trace
10	(PhCN + $AlCl_3$) + $PhNH_2$	12	50	12.5	66	trace
11	($AlCl_3$ + $PhNH_2$) + PhCN	6	100	12.5	55	1.5
12	(PhCN + $AlCl_3$ + $PhNH_2$)	6	100	12.5	53	1.5

[a] NaOH used during work up. [b] Cooper and Partridge *Org. Syn.* procedure (lit.,[92] 69-74% yield). [c] Aniline added at 100 °C then heated to 200 °C. [d] nd = no data.

2.3 Optimisation using different Lewis acids

While $AlCl_3$ appears to be the Lewis acid most commonly used for catalysing the nucleophilic addition of anilines to benzonitriles, other Lewis acids, including $ZnCl_2$,[90] $AlMe_3$,[184-185] and ytterbium amides[99] have also been used. We premixed benzonitrile with a range of commonly available Lewis acids that differ from each other by the hardness of the metal, and that are typically found in the synthetic laboratory, to examine their effect on the amidine synthesis (Table 2).

Table 2. Reaction of benzonitrile (**48**) (553 mg, 5.36 mmol) with Lewis acids (LA) (1 equiv) and aniline (1 equiv) protected from moisture with a $CaCl_2$ drying tube



48 **50** **52**

entry	LA	time (h)	temp. (°C)	yields (%) **50**	**52**
1	$AlCl_3$	4	100	83	3
2	$FeCl_3$	2	100	[b]	-
3	$TiCl_4$	5	135	68	36
4	$Ti(i\text{-}PrO)_4$	7	100	nr[c]	-
5	$SnCl_4$	5	100	6	-
6	$ZnCl_2$	5	100	6	-
7	SmI_2[a]	48	100	nr[c]	-

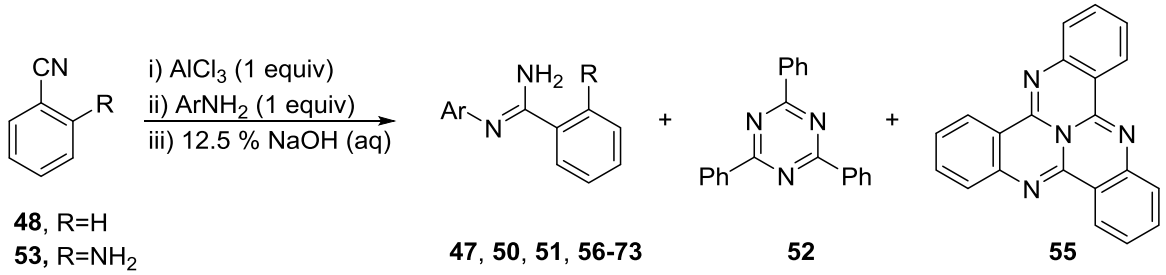
[a] In a solution of THF (1.0 M). [b] Complex mixture. [c] nr = No reaction.

In our hands, the softer Lewis acids [$ZnCl_2$, $SnCl_4$, $Ti(^iPrO)_4$] were ineffective leading to little or no reaction (Table 2, entries 5, 6 and 7). $TiCl_4$ did afford a respectable yield of *N*-phenylbenzamidine (**50**) (68%) but the complex formed between the benzonitrile (**48**) and the $TiCl_4$ required higher temperatures to generate a homogeneous melt and led to comparatively high recoveries of the 2,4,6-triphenyl-1,3,5-triazine (**52**) (36%) (Table 2, entry 3). $FeCl_3$ led to complex reaction mixtures that could not be resolved. In light of this study, we retained the use of $AlCl_3$ as Lewis acid for further studies.

2.4 Benzamidine formation in the presence of methoxy, nitro and halogen substituents

It was reported that the presence of alkoxy or nitro groups were incompatible with the use of Lewis acids such as $AlCl_3$, for the synthesis of benzamidines.[94] In light of this we examined our modified reaction conditions to the preparation of several more challenging targets (Table 3).

Table 3. Reaction of benzonitriles **48**, **53** or **54** (1 equiv) with anilines (500 mg) at *ca.* 100 °C protected from moisture with a $CaCl_2$ drying tube



48, R=H
53, R=NH_2
54, 4,5-$(MeO)_2$, R=NH_2

47, **50**, **51**, **56-73** **52** **55**

entry	Ar	Benzonitrile	time (h)	yields (%)	**52**	**55**
1	Ph	**48**	4	**50** (83)	3	-
2	4-$MeOC_6H_4$	**48**	4	**47** (93)	3	-
3	4-$NO_2C_6H_4$	**48**	4	**56** (16) (59)[a]	trace	-
4	4-$NO_2C_6H_4$	**48**	8	**56** (21)	trace	-
5	4-MeC_6H_4	**48**	6	**57** (93)	-	-
6	4-FC_6H_4	**48**	6	**58** (82)	-	-
7	4-ClC_6H_4	**48**	6	**59** (89)	-	-
8	4-BrC_6H_4	**48**	6	**60** (78)	-	-
9	4-IC_6H_4	**48**	6	**61** (85)[b]	-	-
10	3,4-$Cl_2C_6H_3$	**48**	6	**62** (91)	-	-
11	Ph	**53**	6	**63** (64)	-	-
12	4-MeC_6H_4	**53**	6	**64** (66)	-	12
13	4-$MeOC_6H_4$	**53**	8	**51** (49)	-	18
14	4-$MeOC_6H_4$	**53**	8	**51** (56)[c]	-	30
15	4-$NO_2C_6H_4$	**53**	12	**65** (0)[d]	-	-
16	4-FC_6H_4	**53**	6	**66** (58)	-	-
17	4-ClC_6H_4	**53**	6	**67** (48)	-	-
18	4-BrC_6H_4	**53**	6	**68** (43)	-	-
19	4-IC_6H_4	**53**	6	**69** (0)[d]	-	-
20	3,4-$Cl_2C_6H_3$	**53**	6	**70** (35)	-	-
21	3,4-$(MeO)_2C_6H_3$	**53**	12	**71** (60)	-	-
22	Ph	**54**	12	**72** (12)	-	-
23	4-$MeOC_6H_4$	**54**	12	**73** (12)	-	-

[a] 59% Based on recovered 4-nitroaniline. [b] Benzonitrile (2 equiv). [c] 2-Aminobenzonitrile (2 equiv). [d] Complex mixture.

Using our optimised reaction conditions, *N*-(4-methoxyphenyl)benzamidine **47** was obtained in 93% yield. This was notable since the reported base ($NaNH_2$) catalysed preparation of this benzamidine was low yielding (14%).[186] Disappointingly, the analogous preparation of *N*-(4-nitrophenyl)benzamidine (**56**) gave the product only in low yield (16-21%), although it was worth noting that after 4 h, based on recovered unreacted aniline the yield was a more respectable 59% (Table 3, entry 3). *N*-(4-Tolyl)- and *N*-(4-halophenyl)benzamidines **57**-**62** were readily prepared in high yields (78-93%) although

the 4-iodophenyl analogue did require additional benzonitrile (Table 3, entries 5-10). The previously reported attempt to synthesize both the 2-amino-*N*-(4-methoxyphenyl)benzamidine (**51**) and the 2-amino-*N*-(4-nitrophenyl)benzamidine (**65**) concluded that these two compounds could not be prepared using $AlCl_3$,[94] but in our hands 2-amino-*N*-(4-methoxyphenyl)benzamidine (**51**) was obtained in 56% yield when two equivalents of the benzonitrile were used; longer reaction times did not improve the yield. Unfortunately, 2-amino-*N*-(4-nitrophenyl)benzamidine (**65**) could not be isolated from the analogous reaction mixture. Generally, the reaction conditions were quite tolerant of halogen substituents providing the 4-fluoro-, chloro-, and bromophenyl analogues **66-68** (43-58%), however, in one case (**69**, Ar = 4-IC_6H_4, R = NH_2) the reaction gave a complex mixture (Table 3, entries 16-19). Both the 4-phenyl and 4-tolyl analogues could be isolated in comparatively good 64 and 66% yields, respectively. Interestingly, increasing the temperature of the anthranilonitrile **53** reactions to *ca.* 150 ^oC led to complex mixtures that could not be resolved. Furthermore, while the unsubstituted benzonitrile gave the expected triazine side product **52** in trace amounts, anthranilonitrile gave instead traces of tricycloquinazoline **55** (mp 322-323 ^oC)[187] on three individual occasions. The high temperature (290 ^oC) treatment of anthranilonitrile with $AlCl_3$ is known to give tricycloquinazoline **55** in 75% yield.[188]

2.5 Summary

By modifying the mode of addition (benzonitrile + Lewis acid, followed by aniline) and by moderating the reaction temperatures, the Lewis acid ($AlCl_3$) catalysed reaction of benzonitriles and anilines produced significantly improved yields of benzamidines. The reaction conditions are not compatible with nitro-substituted anilines, but do tolerate *p*-anisidine, allowing the preparation of the previously unobtainable 2-amino-*N*-(4-methoxyphenyl)benzamidine (**51**).

Since this study was completed, other methods have now been reported which require the activation of anilines (deprotonation) prior the addition of benzonitriles and allow the reaction to take place at lower temperatures (*ca*. 0-20 ^oC) and give access to a range of halo, alkyl, alkoxy substituted benzamidine analogues in moderate to high yields.[189-190]

CHAPTER 3

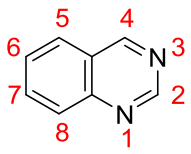
The one-step conversion of 2-amino-*N'*-arylbenzamidines into 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles using 4,5-dichloro-1,2,3-dithiazolium chloride

Sections

3.1 Introduction

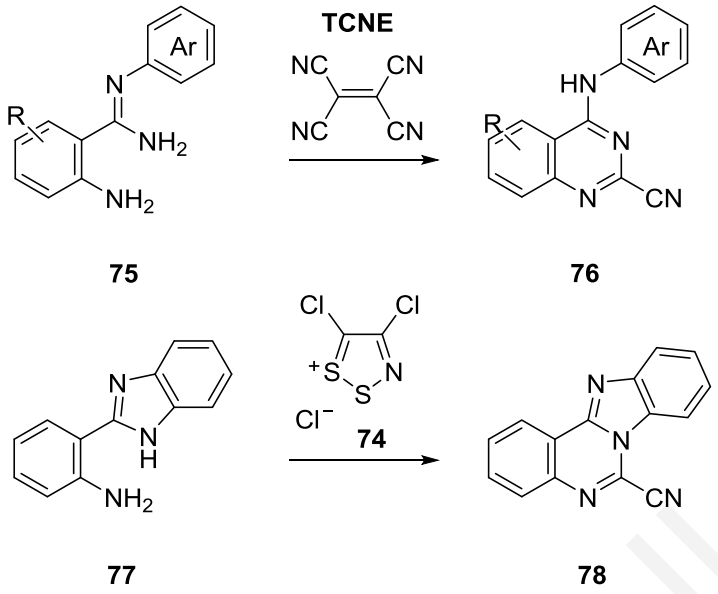
Having optimised a route to *N'*-arylbenzamidines (Chapter 2) and in particular the methoxy substituted analogues we then sought to use these compounds to prepare benzo[1,2,4]thiadiazinones, however, this chemistry was not fruitful. In light of this, we redirected our attention to the now readily available 2-amino-*N'*-arylbenzamidines **63-70**, **72-73**[191] which have been used to build the important quinazoline heterocycle.

Quinazoline (benzo[*a*]pyrimidine) is the parent heterocycle of an important group of compounds that find application as components in pharmaceuticals, agrochemicals, dyes, sensors, polymers, and in organic electronics. As such, there are extensive reviews on the synthesis, chemistry and properties of quinazolines.[192-195] The quinazoline skeleton is found in many natural products.[196]



Quinazoline

2-Amino-*N'*-arylbenzamidines **75**[191] are known to react with tetracyanoethylene (TCNE)[197,198] to give 4-anilinoquinazoline-2-carbonitriles **76** in moderate to good yields,[199] (Scheme 30), however, TCNE is a relatively expensive reagent and we considered replacing it with 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (Appel salt) which is easily prepared from chloroacetonitrile and disulfur dichloride.[200,201] The use of Appel salt **74** for the two step introduction of C-C≡N *via* the synthesis of neutral 1,2,3-dithiazoles (step 1) and their subsequent ring transformation to cyanoheteroarenes (step 2) has been well demonstrated,[202-211] and excellent reviews on the chemistry of 1,2,3-dithiazoles have appeared.[212-215] While the reaction of 2-cyano-(4-chloro-5*H*-1,2,3-dithiazolylidenamino)-benzenes with selected alkoxides gave 4-alkoxyquinazoline-2-carbonitriles,[216-219] there is only one report for an analogous two step preparation of 4-alkylaminopyrido[2,3-*d*]pyrimidine-2-carbonitriles from 2-aminopyridine-3-carbonitriles.[210] Furthermore, a similar reaction between Appel salt **74** and 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline **77** gave directly cyanobenzimidazoquinazoline **78** in 50% yield[220] (Scheme 30).



75 **76**

77 **78**

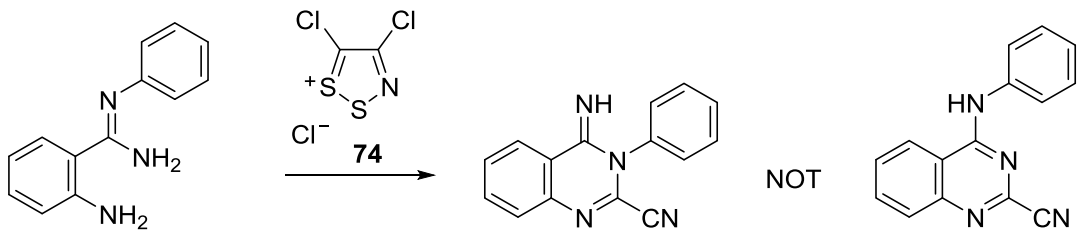
Scheme 30

Surprisingly, the reaction between 2-amino-*N′*-arylbenzamidines **63-70**, **72-73** and Appel salt **74** did not result in the expected 4-anilinoquinazoline-2-carbonitrile **79** but rather afforded the isomeric 3-phenyl-4-imino-3,4-dihydroquinazoline-2-carbonitrile **80** (Scheme 31). To the best of our knowledge this represented the first synthesis of a 2-cyano substituted quinazolin-4(3*H*)-imine, which was worthy of note since nitriles can readily be subsequently modified into a wide variety of other functionalities.[221,222] The results of our discovery are presented herein.

3.2 Treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (74) (Appel salt) with 2-amino-*N′*-phenylbenzamidine (63)

The reaction between anilines and 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) typically produce neutral (4-chloro-5*H*-1,2,3-dithiazolylideneamino)benzenes.[200,223] However, in a few cases where an *ortho* nucleophilic side chain is present on the arylamine, the product isolated arises as a result of an *in situ* ring transformation affording the more stable heteroarene.[220,224-234]

Thus, treating 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (Appel salt) with 2-amino-*N′*-phenylbenzamidine (**63**) proceeded to give 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) and not the expected 4-anilinoquinazoline-2-carbonitrile (**79**) (Scheme 31) directly as a one-pot process. Analysis of the reaction mixture by TLC failed to detect the presence of any intermediate.



63 **80** **79**

Scheme 31

4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) was isolated as colorless needles, mp 141-142 ^{o}C (from *c*-hexane) [mp (DSC) onset 143.9 ^{o}C, peak max. 146.2 ^{o}C] which differed considerably from that of 4-anilinoquinazoline-2-carbonitrile (**79**) mp (DSC) onset 211.7 ^{o}C, peak max 212.5 ^{o}C (from $CHCl_3$). Interestingly, our melting point for the anilinoquinazoline **79** was also significantly different from that reported in the literature (lit.,[199] mp 84-85 ^{o}C), despite matching closely with the reported ^{1}H, ^{13}C NMR and IR spectra. Furthermore, mass spectrometry of the iminoquinazoline **80** gave a parent ion at *m/z* (EI) 246 Da (M^+, 34%), which in combination with elemental analysis gave a molecular formula of $C_{15}H_{10}N_4$, supporting a compound that was isomeric with the anilinoquinazoline **79**. Further observed differences between the two isomers could be seen in the IR and NMR spectra: 4-anilinoquinazoline-2-carbonitrile (**79**) gave a nitrile stretching frequency of ν(C≡N) 2247 cm^{-1} while 4-imino-3-phenyl-3,4-dihydro-quinazoline-2-carbonitrile (**80**) gave a nitrile stretching frequency of ν(C≡N) 2239 cm^{-1}. The ^{13}C NMR spectrum showed 13 separate signals for both isomers, 7 of which were CH (by DEPT-135 NMR). However, the most down field and up field signals for the iminoquinazoline **80** appeared at 153.3 and 111.3 ppm, respectively while those for anilinoquinazoline **79** appeared at 157.5 and 115.1 ppm. Both compounds also had different R_f values of silica gel TLC plates R_f **80** (DCM/*t*-BuOMe, 90:10) 0.48 *vs* R_f **79** (DCM/*t*-BuOMe, 90:10) 0.52 indicating the iminoquinazoline **80** was the more polar of the two. Any ambiguity in the structural assignment was addressed by solving the single crystal X-ray structure for 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (Figure 1).

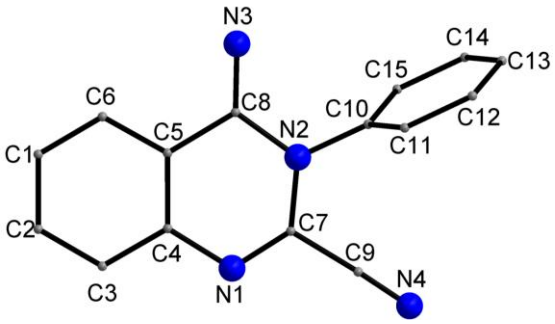
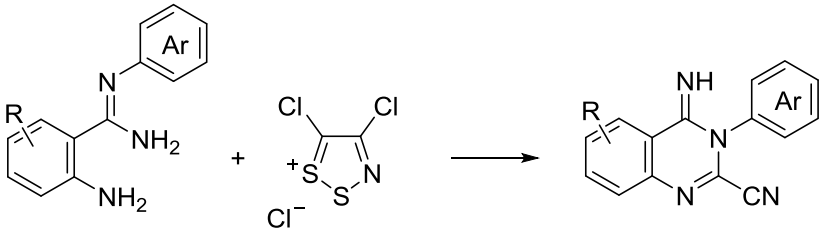


Figure 1. Ball and stick representation of the crystal structure of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) with atom labelling. The dihedral angle between the plane of the quinazoline and that of the phenyl ring is 68.94(4)^{o}. Hydrogen atoms were omitted for clarity.

3.3 Optimisation of iminoquinazoline 80 formation

By screening the type and equivalents of the organic base used the reaction of Appel salt **74** and 2-amino-*N'*-phenylbenzamidine (**63**) was partially optimised. Typically, 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) was treated with 2-amino-*N'*-phenylbenzamidine (**63**) (51 mg, 0.24 mmol) in DCM (4 mL) at *ca.* 20 ^{o}C for 4 h followed by the addition of base at *ca.* 20 ^{o}C and an additional 2 h stirring, protected from moisture with $CaCl_2$ drying tube. When pyridine (2-4 equiv) was used as base only traces of the iminoquinazoline **80** were obtained, while more basic trialkylamines such as Et_3N (2-4 equiv) or Hünig's base (*i*-Pr_2NEt) (2-4 equiv) gave 55-61 and 72-75% yields, respectively. Interestingly, increasing the base strength further by using the bicyclic amidine DBU (2-3 equiv) led to low product yields (32-36%). With these data in mind we reacted 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) with various substituted 2-amino-*N'*-arylbenzamidines **63-70**, **72-73** in the presence of Hünig's base (2 equiv) and obtained the iminoquinazolines **80-88**, respectively (Table 4).

Table 4. Reaction of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (0.24 mmol) with 2-amino-*N*′-arylbenzamidines **63-70, 72-73** (1 equiv) in DCM (4 mL) at *ca.* 20 °C for 4 h followed by the addition of *i*-Pr_2NEt (2 equiv) at *ca.* 20 °C and an additional 2 h stirring, protected from moisture with a $CaCl_2$ drying tube



63-70, 72-73 **74** **80-88**

entry	Ar	R	yields (%)
1	Ph	H	**80** (75)
2	4-MeC_6H_4	H	**81** (81)
3	4-$MeOC_6H_4$	H	**82** (74)
4	4-FC_6H_4	H	**83** (57)
5	4-ClC_6H_4	H	**84** (65)
6	4-BrC_6H_4	H	**85** (63)
7	3,4-$Cl_2C_6H_3$	H	**86** (65)
8	Ph	4,5-$(MeO)_2$	**87** (53)
9	4-$MeOC_6H_4$	4,5-$(MeO)_2$	**88** (61)

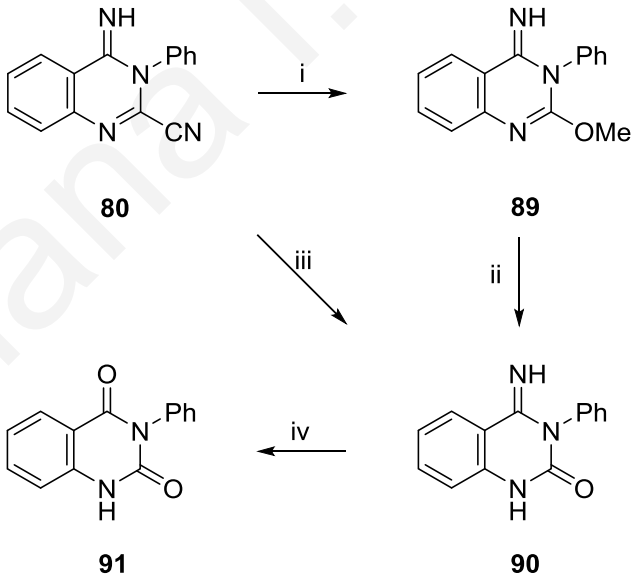
As can be seen from Table 4 the reaction yields range between 53 and 81%. For the unsubstituted benzamidines (R = H) the yields were affected by the nature of the *N*-aryl group; neutral or electron rich Ar groups (Ar = Ph, 4-Tol, and 4-$MeOC_6H_4$, Table 4, entries 1-3) gave higher yields (74-81%), however, where the Ar group was less electron rich (Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, and 3,4-$Cl_2C_6H_3$, Table 4, entries 4-7) the yields dropped (57-65%). The reaction also tolerated electron rich dimethoxy substituted benzamidines which gave the expected iminoquinazolines **87** and **88** in moderate yields, 53 and 61%, respectively (Table 4, entries 8 and 9).

3.4 Some chemistry of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (80)

On close inspection, the two quinazoline isomers **79** and **80** can in theory be isomerised into each other *via* a Dimroth rearrangement,[235] furthermore, the base (NaOH) treatment of 3-alkyl- or 3-benzyl-4-imino-3,4-dihydroquinazolines was known to afford the Dimroth rearranged 4-alkylamino and 4-benzylaminoquinazoline isomers.[236] The isomerisation of

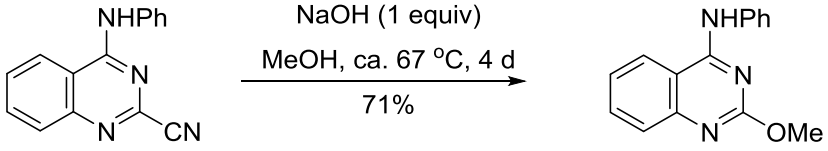
the iminoquinazoline **80** into the 4-anilinoquinazoline **79** *via* acid or base catalysis was therefore investigated.

Initially, solutions of the iminoquinazoline **80** in either dry toluene, toluene in the presence of Hünig's base, or in neat Hünig's base heated to *ca.* 110 ^{o}C indicated that the iminoquinazoline **80** was stable to these conditions. However, the reaction of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) in the presence of NaOH (1 equiv) in MeOH at *ca.* 67 ^{o}C for 3 h, gave 2-methoxy-3-phenylquinazolin-4(3*H*)-imine (**89**) in quantitative yield (99%). The use of milder bases such as, K_2CO_3 and Na_2CO_3 led to lower yields (70%), while the use of amine bases such as, Hünig's base, pyridine or DMAP in MeOH gave complex reaction mixtures. Interestingly, further treatment of 2-methoxy-3-phenylquinazolin-4(3*H*)-imine (**89**) with HCl (10%) at *ca.* 67 ^{o}C for 30 min led to the quantitative formation of 4-imino-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (**90**)[237] (99%). Furthermore, the quantitative conversion of the iminoquinazoline **79** into 4-imino-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (**90**) could also be achieved in one pot. Finally, hydrolysis of the iminoquinazolinone **90** with 1N NaOH at *ca.* 20 ^{o}C for 7 d gave the known 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**91**)[238] in 90% yield (Scheme 32).



Scheme 32 *Reagents and Conditions:* i) NaOH (1 equiv), MeOH, *ca.* 67 ^{o}C, 3 h, 99%; ii) 10% HCl, *ca.* 67 ^{o}C, 30 min, 99%; iii) NaOH (1 equiv), MeOH, *ca.* 67 ^{o}C, 3 h, then 10% HCl, *ca.* 60 ^{o}C, 20 min, 99%; iv) 1N NaOH, *ca.* 20 ^{o}C, 7 d, 90%.

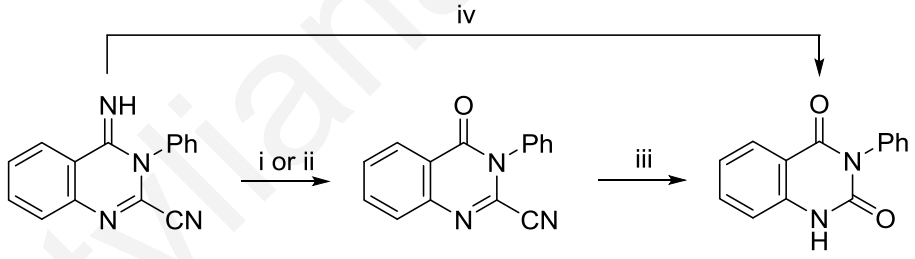
Interestingly, similar treatment of 4-anilinoquinazoline-2-carbonitrile (**79**) with NaOH (1 equiv) in MeOH at *ca.* 67 °C for 4 d led to substitution of the nitrile to afford the known 4-anilino-2-methoxyquinazoline (**92**)[239] in good yield (71%) (Scheme 33).



79 **92**

Scheme 33

On the other hand direct acid treatment of the iminoquinazoline **80** with either TFA (1 equiv) in DMSO, DMF or DMA at *ca.* 20 °C or at *ca.* 100 °C or in the presence of HCl (1 equiv) in THF/water (1:1) also failed to give the Dimroth rearranged product but did afford the known 4-oxo-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**93**)[240] in high yield, while when 2 or more equivalents of HCl were used 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**91**) was obtained in 92-99% yields. Interestingly, heating the dihydroquinazolinone **93** in the presence of HCl (1 equiv) in THF/water (1:1) at *ca.* 65 °C gave no reaction but with HCl (2 equiv) after 3 d at *ca.* 65 °C 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**91**)[238] was formed in 96% yield (Scheme 34).

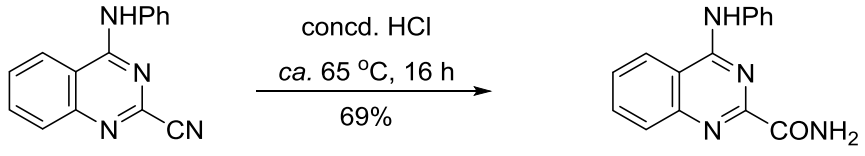


80 **93** **91**

Scheme 34 *Reagents and Conditions:* i) TFA (1 equiv), DMSO, *ca.* 20-100 °C, 2 d, 99%; ii) HCl (1 equiv), THF/H_2O (1:1), *ca.* 65 °C, 1 d, 87%; iii) HCl (2 equiv), THF/H_2O (1:1), *ca.* 65 °C, 3 d, 96%; iv) HCl (4 equiv), THF/H_2O (1:1), *ca.* 65 °C, 1.5 d, 99%.

In contrast to the above, similar treatment of the isomer anilinoquinazoline **79** with HCl (1 equiv) in THF/water (1:1) at *ca.* 65 °C for 24 h gave no hydration, hydrolysis or isomerization and the compound was recovered unchanged. Nevertheless, in the presence

of neat concd. HCl at *ca.* 65 °C for 16 h gave 4-anilinoquinazoline-2-carboxamide (**94**) in 69% yield (Scheme 35). These studies supported that the iminoquinazoline **80** and the anilinoquinazoline **79** did not interconvert under acid conditions.

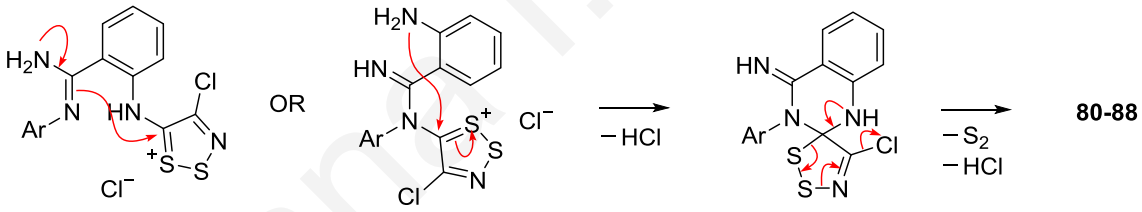


79 **94**

Scheme 35

3.5 Mechanistic rationale for the formation of the iminoquinazolines 80-88

There are two possible routes to the iminoquinazolines **80-88**: Appel salt **74** condenses with 2-amino-*N'*-arylbenzamidines at the primary aniline to give adduct **95** or alternatively at the amidino secondary amine to give adduct **96**. These can then undergo intramolecular cyclizations to give a common spirocyclic intermediate **97** which can cleave to give the observed iminoquinazolines **80-88** (Scheme 36).



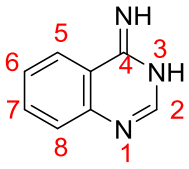
95 **96** **97**

Scheme 36

Unfortunately, we were unable to isolate any intermediates that could support either proposal, we note however, that amidines typically alkylate to give the more basic amine which is typically the secondary amine[241] and this may explain why none of the 4-anilinoquinazoline-2-carbonitrile (**79**) was observed. Further studies to understand this transformation are now underway in our laboratory.

3.6 Summary

An interesting quinazoline subclass is quinazolin-4(3*H*)-imine, the structure of which is featured in biologically active compounds that behave as cholinesterase inhibitors,[242-246] cMET kinase inhibitors,[247] modulators of chemokine CCR3 activity,[248] or exhibit antiproliferative[249] or cardiotonic activities.[250,251]



Quinazolin-4(3*H*)-imine

Recent methods for the preparation of quinazolin-4(3*H*)-imines include the palladium-catalyzed three component reaction of carbodiimide, isocyanide and a nucleophile,[252,253] the three-step synthesis of 3-aryl-2-halo-4(3*H*)-quinazoliniminium halides from readily accessible heteroenyne-allenes,[254] the reaction of anthranilonitrile with triethylortho-formate,[255] the single step synthesis from simple carbonyl compounds, primary amines or amino acid methyl esters and 2-azido-5-nitrobenzonitrile,[236] and a one-pot cyclization of 2-(dichloroisocyanido)benzonitrile with α-aminoketones.[256]

Treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) with 2-amino-*N'*-arylbenz-amidines **63-70**, **72-73** affords 4-imino-3-aryl-3,4-dihydro-quinazoline-2-carbonitriles **80-88** directly in moderate to good yields (53-81%). The reaction provides a route to C-2 cyano substituted quinazolin-4(3*H*)-imines.

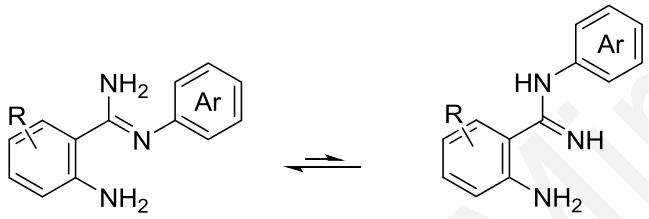
CHAPTER 4

The reaction of 2-amino-*N'*-arylbenzamidines with tetracyanoethylene reinvestigated: Routes to imidazoles, quinazolines and quinolino[2',3':4,5]imidazo[1,2-*c*]quinazoline-8-carbonitrile

Sections

4.1 Introduction

As mentioned earlier (see Chapter 1, Section 1.4, Scheme 9), 2-amino-*N'*-arylbenzamidines **75** exist in equilibrium with several proto- and rota-tautomeric forms such as 2-amino-*N*-arylbenzamidine **75b** (Scheme 37) and they are synthetically useful building blocks and selected analogues target tyrosine kinases which is important in cancer drug discovery and development.[257-259] The benzamidines **75** can be readily prepared from: a) anthranilonitriles and anilines in the presence of $AlCl_3$;[94,191,199] b) reduction of *N*-aryl-2-nitrobenzamidines using $SnCl_2$ in concd. HCl;[260] c) reductive cleavage of 1,2,3-benzotriazines with hydrazine and Raney nickel;[261] or from d) HCl mediated hydrolytic cleavage of *N*-aryl-2,2-dimethyl-1,2-dihydroquinazolin-4-amines.[94,199]

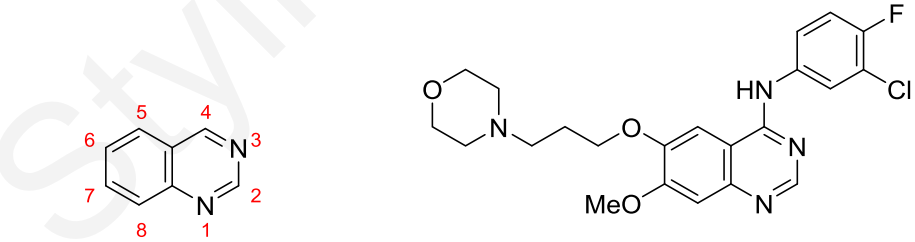


75a **75b**

($\Delta E_{\mathbf{75a\text{-}75b}}$ = -2.7 kcal mol^{-1})[5]

Scheme 37

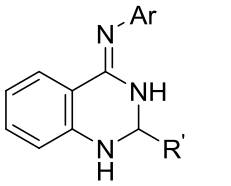
2-Amino-*N'*-arylbenzamidines **75** are particularly useful for the synthesis of 4-(arylamino)quinazolines, a subclass of quinazolines,[192-194] that also act as kinase inhibitors.[166,167,262,263] Several derivatives, *e.g.*, Gefitnib (Iressa®),[264,265] have been approved and marketed for the treatment of cancer.



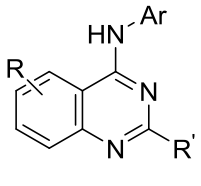
Quinazoline **Gefitnib (Iressa®)**

Treatment of 2-amino-*N'*-arylbenzamidines **75** with formic acid gives the 4-(arylamino)quinazolines **98**,[266] while reaction with alkyl- or aryl-aldehydes with or without iodine affords 2-(alkyl/aryl)-*N*-aryl-2,3-dihydroquinazolin-4(1*H*)-imines **99**,[94,267] which can be oxidized to the aromatic 2-(alkyl/aryl)-4-anilinoquinazolines **100**.[94,267] Treating

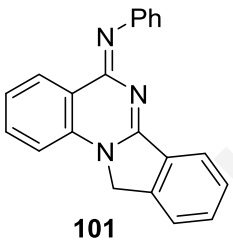
amidines **75** with TCNE gave 4-(arylamino)quinazoline-2-carbonitriles **76** as the sole products.[199] Interestingly, treating 2-amino-*N'*-phenylbenzamidine (**63**) with phthalaldehyde afforded the polycyclic (*Z*)-*N*-phenylisoindolo[2,1-*a*]quinazolin-5(11*H*)-imine (**101**),[268] while treatment with tetracyanoquinodimethane (TCNQ) gave (Z)-2-{4-[4-(phenylimino)-3,4-dihydroquinazolin-2(1*H*)-ylidene]cyclohexa-2,5-dien-1-ylidene}malononitrile (**102**);[269] a similar substitution of both geminal nitriles was also observed with 2-(1,3-dioxo-1,3-dihydro-2*H*-inden-2-ylidene)malononitrile.[270]



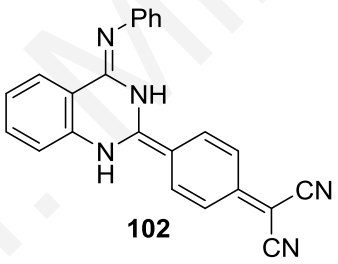
99 (R' = Ar/Alk)



98 (R'= H)
100 (R' = Ar/Alk)
76 (R' = CN)

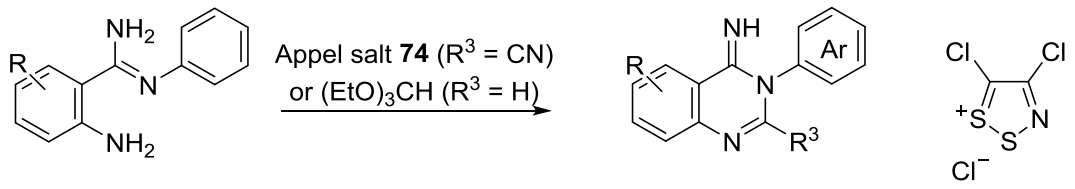


101



102

Earlier, we reported (see Chapter 2) the reaction of 2-amino-*N'*-arylbenzamidines **75** with 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (Appel salt) to give 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles **103** (Scheme 38).[271] Interestingly, Szczepankiewicz *et al.*,[272] developed a solvent free synthesis of 3-arylquinazolin-4(3*H*)-imines **104** from 2-amino-*N'*-arylbenzamidines **75** and triethyl orthoformate (Scheme 38). The same group also proposed the intermediacy of 3-arylquinazolin-4(3*H*)-imines in the reaction of butane-2,3-diones with 2-amino-*N'*-arylbenzamidines to give 2-acetyl-3-aryl-2-methyl-2,3-dihydroquinazolin-4(1*H*)-ones and suggested the formation of the quinazolin-4(3*H*)-imine was kinetically controlled.[273]



75 **103** (R^3 = CN) **104** (R^3 = H) **74**

Scheme 38

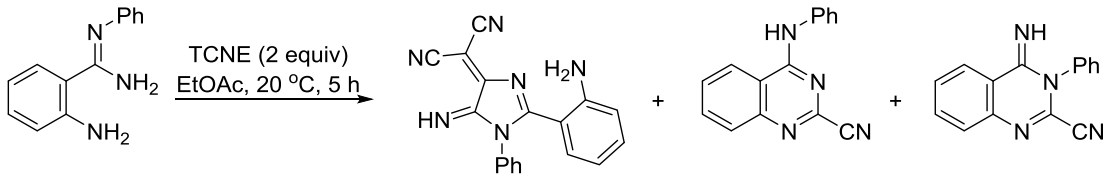
The transformation of 2-amino-*N'*-arylbenzamidines **75** into quinazolin-4(3*H*)-imines is important since this heterocycle features in biologically active compounds that behave as cholinesterase inhibitors,[242-246] cMET kinase inhibitors,[247] modulators of chemokine CCR3 activity,[248] or exhibit antiproliferative[249] or cardiotonic activities.[250,251] Understanding the cyclization modes of 2-amino-*N'*-arylbenzamidines **75** can help develop improved syntheses of these and other heterocycles.

The recent results from the Szczepankiewicz team[272,273] prompted a reinvestigation of the reaction of 2-amino-*N'*-phenylbenzamidine (**63**) with TCNE. In our hands, the reaction mixture was complex, affording not one but three products that can be isolated by column chromatography (Scheme 38). Reaction conditions were developed that enabled each of the compounds to be isolated as the major product. The results support Szczepankiewicz's kinetic ring closure arguments.[273] Finally, some cyclization chemistry of the obtained products are reported.

4.2 Reinvestigating the reaction of TCNE and 2-amino-*N'*-phenylbenzamidine (63)

In our hands, repeating the literature reaction,[199] *i.e.* adding a solution of 2-amino-*N'*-phenylbenzamidine (**63**) (1 equiv) into a stirred solution of TCNE (2 equiv) in dry EtOAc, at *ca.* 20 °C failed after 5 h to give the expected precipitation of 4-(phenylamino)quinazoline-2-carbonitrile (**79**) in the reported 71% yield. TLC analysis of the reaction mixture supported the presence of three products that were isolated by chromatography and identified as 2-[2-(2-aminophenyl)-5-imino-1-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**105**) (12%), 4-(phenylamino)quinazoline-2-carbonitrile (**79**) (37%) and 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (2%) (Scheme 39). The isolated yields of products **79**, **80** and **105** were reproducible on both 0.1 and 1.0 mmol

reaction scales and the possibility that the products readily interconverted under the reaction conditions was excluded.



63 **105** (12%) **79** (37%) **80** (2%)

Scheme 39

The structure of the 4,5-dihydroimidazole **105** was elucidated by single crystal X-ray crystallography (Figure 2), while the structures of the quinazolines **79** and **80** were supported by comparison of their known spectroscopic data. Nevertheless, owing to a mismatch in the reported melting point data of the quinazoline **79** (mp 84-85 °C)[199] and that obtained from our sample (mp 211.5-212.5 °C) we also solved its structure by single crystal X-ray crystallography (Figure 3).

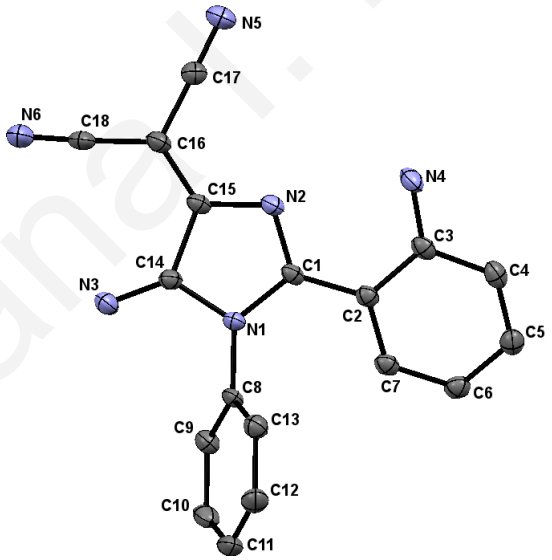


Figure 2. The crystal structure of 2-[2-(2-aminophenyl)-5-imino-1-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**105**) (50% probability ellipsoids and hydrogen atoms omitted for clarity).

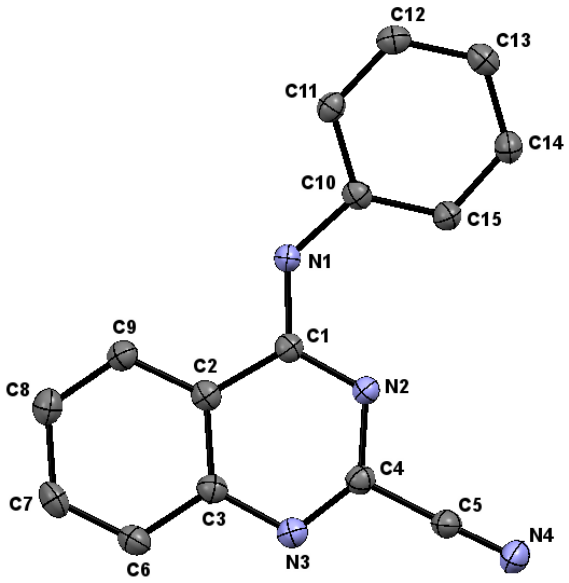


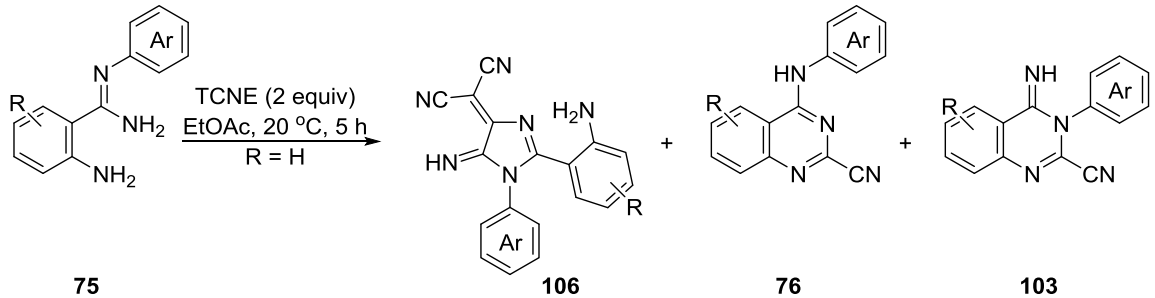
Figure 3. The crystal structure of 4-(phenylamino)quinazoline-2-carbonitrile (**79**) (50% probability ellipsoids and hydrogen atoms omitted for clarity).

In light of our interest in the chemistry of benzamidines and TCNE[274] we reoptimized this reaction by examining the mode of addition, reagent equivalents, choice of solvent, reaction temperature and use of acid or base additives.

Reversing the mode of addition, *i.e.* adding a solution of TCNE to a solution of benzamidine **63** led to higher yields of the 4-(phenylamino)quinazoline **79** and to clarify the need of excess TCNE we ran both modes of additions using equimolar ratios of benzamidine **63**/TCNE (1:1) and obtained the products in very similar yields to the respective reactions ran with benzamidine **63**/TCNE ratio of 1:2. Investigating further, we added EtOAc solutions of TCNE (1 equiv) to EtOAc solutions of the benzamidine **63** (1 equiv) cooled to 0-5 ^{o}C and also heated to *ca.* 77 ^{o}C. At 0-5 ^{o}C the reaction after 3 days gave only two products, the quinazolines **79** and **80** in 92 and 1% yields, respectively, but at *ca.* 77 ^{o}C all three products formed and notably the yield of the imidazole **105** was relatively high (25%). While the low temperature reaction gave a surprisingly good yield of the phenylaminoquinazoline **79** (92%) it was difficult to maintain the temperature of the reaction mixture at *ca.* 5 ^{o}C for 3 days, as such, we investigated the effect of additives (acids and bases) in the hope that these could improve the reaction conditions or affect a change in the product distributions. Regardless of the mode of addition, when a 1:1 ratio of benzamidine **63** to TCNE was reacted in EtOAc at *ca.* 20 ^{o}C, the introduction of strong bases (0.25-1.5 equiv) such as NaOH, DBU or *i*-Pr_2NEt led to very low product yields and

predominantly formation of intractable precipitates, while the addition of weaker bases such as pyridine or NaOAc gave product distributions and yields similar to reactions that were ran without additives. The introduction of strong acids such as concd. HCl, $TsOH \cdot H_2O$, H_2SO_4 and TFA, led to the formation of benzamidine salts, which precipitated from the reaction mixture, and very little reaction was observed with the TCNE even after heating the reaction mixtures at reflux. The addition of milder acids, however, significantly affected the yields and product distributions: When TCNE (1 equiv) was added to a mixture of benzamidine **63** (1 equiv) and AcOH (pK_a 4.76) (0.5 to 2.0 equiv) in EtOAc at *ca.* 20 ^oC then the yields of the phenylaminoquinazoline **79** improved; the highest yield (87%) was obtained using AcOH (1.5 equiv). Replacing AcOH with either formic acid (pK_a 3.77) or *t*-$BuCO_2H$ (pK_a 5.02) gave lower overall yields. Interestingly, when the mode of addition was reversed and benzamidine **63** (1 equiv) was added to a mixture of TCNE (1 equiv) and AcOH (0.5-1.0 equiv) a very different product distribution was obtained, with the imidazole **105** (32%) and the phenylaminoquinazoline **79** (33%) forming in near equal amounts. In this case, replacing the AcOH with formic acid led to the imidazole **105** becoming the major product (up to 43% using 0.5 equiv of HCO_2H), while products **79** and **80** were observed as traces. The use of formic acid (0.5 equiv) to improve the yield of the imidazole **105** was not applicable when the reaction solvent was replaced by THF, DCM, acetone or MeCN. Our best reaction conditions for preparing the 4,5-dihydroimidazole **105** were when a solution of the benzamidine **63** (1 equiv) in EtOAc was added dropwise to a hot (*ca.* 77 ^oC) solution of TCNE (1 equiv) and formic acid (0.5 equiv) in EtOAc followed by heating at *ca.* 77 ^oC for 2 h (*Conditions A*) which gave the imidazole **105** in 45% yield. Using these conditions several analogues **106** were prepared in 41-51% yields (Table 5, entries 1-7).

Table 5. Reactions of 2-amino-*N'*-arylbenzamidines **75** with TCNE under Conditions A, B and C, respectively[a]



75 **106** **76** **103**

entry	Ar	Conditions		yields (%)	
1	Ph	A	**105** (45)	**79** (6)	**80** (trace)
2	4-Tol	A	**107** (41)	**113** (6)	**81** (trace)
3	4-$MeOC_6H_4$	A	**108** (48)	**114** (7)	**82** (trace)
4	4-FC_6H_4	A	**109** (51)	**115** (6)	**83** (trace)
5	4-ClC_6H_4	A	**110** (43)	**116** (7)	**84** (trace)
6	4-BrC_6H_4	A	**111** (42)	**117** (5)	**85** (trace)
7	3,4-$(MeO)_2C_6H_3$	A	**112** (44)	**118** (6)	**119** (trace)
8	Ph	B	0	**79** (97)	**80** (1)
9	4-Tol	B	0	**113** (98)	**81** (1)
10	4-$MeOC_6H_4$	B	0	**114** (97)	**82** (1)
11	4-FC_6H_4	B	0	**115** (98)	**83** (1)
12	4-ClC_6H_4	B	0	**116** (95)	**84** (2)
13	4-BrC_6H_4	B	0	**117** (97)	**85** (1)
14	3,4-$(MeO)_2C_6H_3$	B	0	**118** (93)	**119** (1)
15	Ph	C	0	**79** (29)	**80** (69)
16	4-Tol	C	0	**113** (30)	**81** (62)
17	4-$MeOC_6H_4$	C	0	**114** (29)	**82** (62)
18	4-FC_6H_4	C	0	**115** (30)	**83** (65)
19	4-ClC_6H_4	C	0	**116** (31)	**84** (69)
20	4-BrC_6H_4	C	0	**117** (27)	**85** (65)
21	3,4-$(MeO)_2C_6H_3$	C	0	**118** (28)	**119** (64)

[a] **Conditions A**: a solution of the benzamidine **75** (1 equiv) in EtOAc was added dropwise to a hot (*ca.* 77 °C) solution of TCNE (1 equiv) and formic acid (0.5 equiv) in EtOAc followed by heating at *ca.* 77 °C for 2 h; **Conditions B**: a solution of TCNE (1 equiv) in MeCN was added to a solution of the benzamidine **75** (1 equiv) and AcOH (1 equiv) in MeCN at *ca.* 20 °C and left to stir for 7-8 h; **Conditions C**: a solution of the benzamidine **75** (1 equiv) in MeCN was added dropwise to a solution of TCNE (2 equiv) in MeCN at *ca.* -20 °C and left to stir at this temperature for 1 d.

Since the addition of TCNE (1 equiv) to a mixture of benzamidine **63** (1 equiv) and AcOH (1.5 equiv) in EtOAc at *ca.* 20 °C led to phenylaminoquinazoline **79** in 87% yield, we then examined replacement of the solvent in the hope that this reaction could be improved further. When the solvent was replaced by either THF, $MeNO_2$ or DCM the phenylaminoquinazoline **79** was isolated in good yields (64-80%) while in EtOH and PhH the yields were very low (8-17%). When MeCN used as the solvent the yield of the phenylaminoquinazoline **79** (89%) was similar to that obtained with EtOAc (87%) but, there was no trace of the imidazole **105**.

As such, the reaction in MeCN was investigated further and when the quantity of AcOH added was reduced from 1.5 to 1 equiv the phenylaminoquinazoline **79** yield improved to

97% and identified our best conditions (*Conditions B*) for the preparation of the 4-arylaminoquinazolines **76**. Interestingly, removal of the AcOH also led to high yields (94%) of the quinazoline **79** but under these conditions the yields dropped for benzamidine analogues that hosted electron withdrawing halogen substituents on the aniline moiety. In these cases introducing the AcOH (1 equiv) additive to the reaction mixtures helped return product yields to greater than 93% (Table 5, entries 8-14).

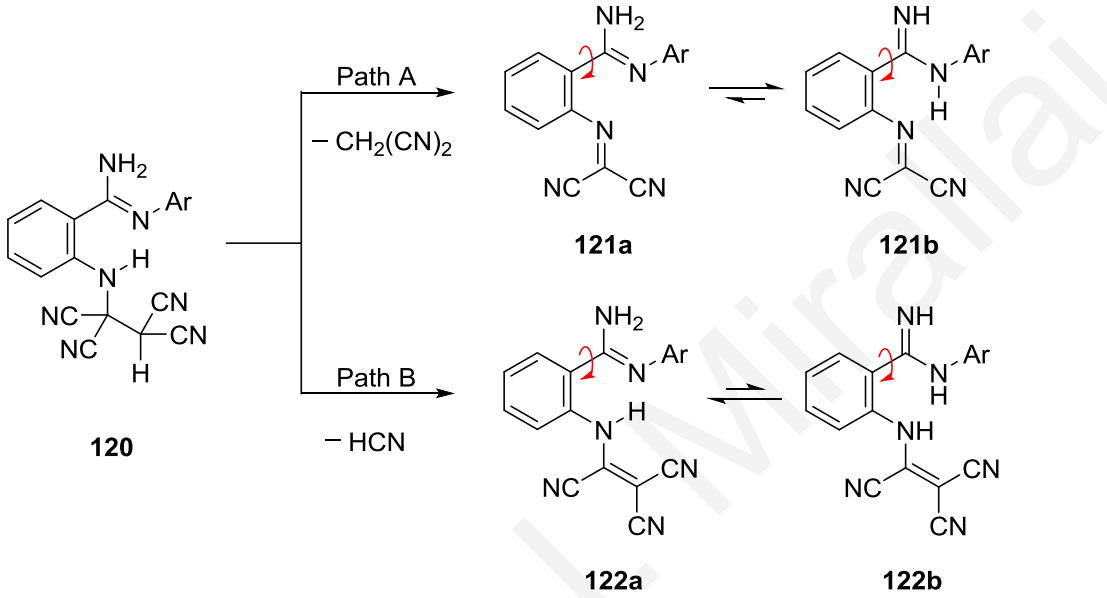
During an initial screen of reaction temperature we also noted that lower reaction temperatures (*ca.* -20 ^{o}C) led to higher yields of both the imidazole **105** (34%) and the iminoquinazoline **80** (14%). A subsequent solvent screen identified that in DMF, DCM, $MeNO_2$ and MeCN no imidazole **105** formed and that in MeCN the yield of the iminoquinazoline **80** reached 69%. In MeCN the equivalents of TCNE could be reduced from 2 to 1 without a significant loss in product yield (69 to 64%) but these reactions required at least 4 days to consume all the starting benzamidine **63**. Under these partially optimized conditions reversing the mode of addition *i.e.* adding TCNE (1 equiv) to a *ca.* -20 ^{o}C cooled MeCN solution of the benzamidine **63** (1 equiv) led to a ~50/50 mixture of both quinazolines, but interestingly the same mode of addition using EtOAc led to a good yield of the phenylaminoquinazoline **79** (77%) and only a trace (1%) of the iminoquinazoline **80**. In light of the lengthy reaction times (4 days) when a 1:1 ratio of reagents we chose our best conditions for the formation of the iminoquinazoline **80** as the addition of the benzamidine **63** (1 equiv) to a *ca.* -20 ^{o}C cooled MeCN solution of TCNE (2 equiv) (*Conditions C*). Using these conditions we prepared several analogues **80-85, 119** in 62-69% yields (Table 5, entries 15-21).

4.3 Mechanistic rationale for the formation of products 76, 103 and 106

*4.3.1. Formation of 4-arylaminoquinazoline-2-carbonitriles **76** and 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles **103***

2-Amino-*N'*-phenylbenzamidine (**63**) hosts three different nitrogen atoms: the primary amine of the aniline, which is the more nucleophilic, and two amidine nitrogens which are more basic, preferentially protonating on the imine nitrogen (C=N-Ph) to give the more

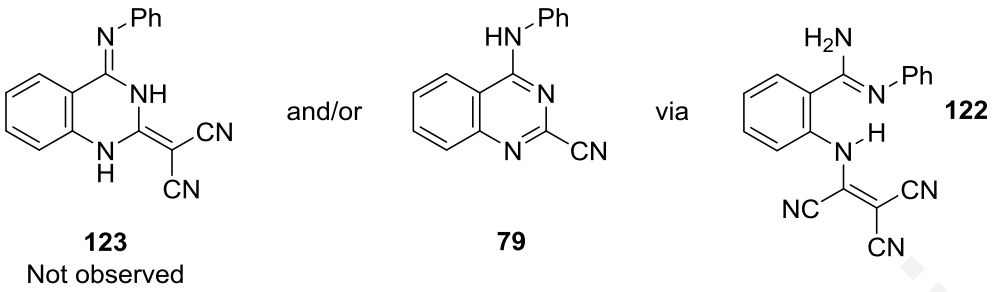
delocalized cation.[275] Since primary anilines can react with TCNE to give *N*-aryltricyano-vinylamines in good yields,[276] and in rare cases carbonimidoyl dicyanides,[277] we assume that the reaction between the 2-amino-*N'*-arylbenzamidines and TCNE yields an adduct **120** that converts to either the dicyanide **121** *via* loss of malononitrile (Path A) or the tricyanovinylamine **122** *via* loss of HCN (Path B) both of which can exist in equilibrium with various proto- and rota- tautomeric isomers (*e.g.*, isomers, **121a** and **122a**, respectively) (Scheme 40).



Scheme 40

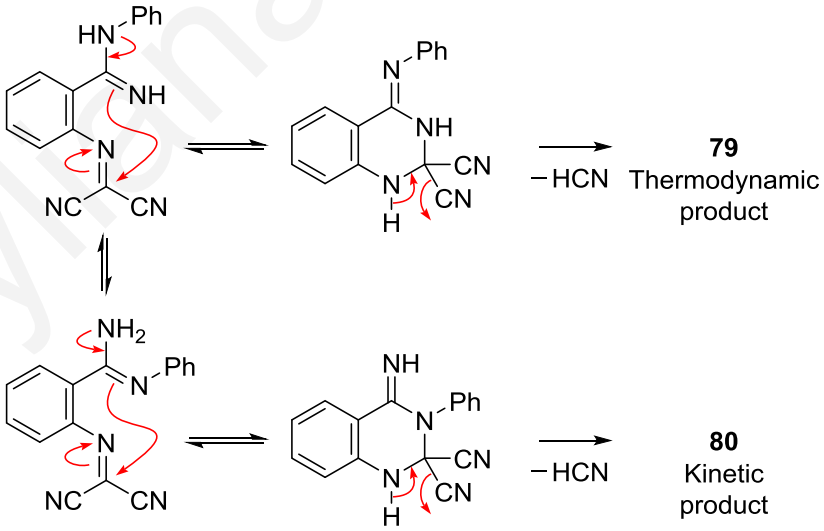
Disappointingly, none of these possible intermediates were observed in the reaction mixtures, presumably owing to a subsequent rapid intramolecular cyclization onto the neighboring amidine moiety to give the observed quinazolines **76** and **103**. There was some tentative support, however, that the intermediate was the carbonimidoyl dicyanide **121** rather than the tricyanovinylamine **122**: Firstly, the initial TCNE adduct **120** was expected to have the aniline NH group H-bonded to the amidine enhancing its acidity and therefore more likely to facilitate the subsequent elimination of malononitrile; secondly, had the tricyanovinylamine **122** been the intermediate then this could have reacted in a similar manner to TCNQ and led to the formation of the ylidenemalononitrile **123** (Scheme 41) (*c.f.* compound **102**); thirdly, the carbonimidoyl dicyanide **121** was expected to be the more reactive (electrophilic) of the two and thus could explain why the subsequent cyclizations occurred so quickly that intermediates were not isolable. The above suppositions are intuitively derived and a clear picture can only come from further studies,

nevertheless, for the purpose of the subsequent discussions we assume the carbonimidoyl dicyanide **121** to be the intermediate.



Scheme 41

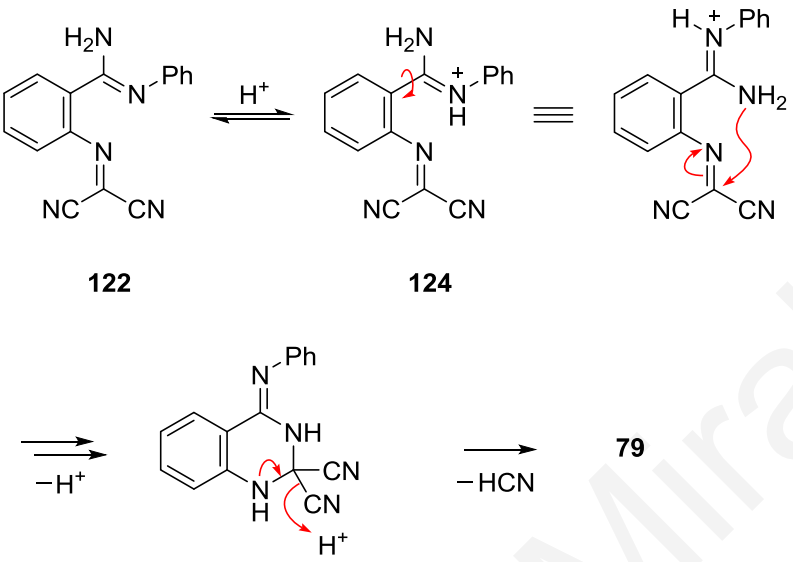
Computational studies by Szczepankiewicz *et al.*,[273] on the reaction of 2-amino-*N'*-phenylbenzamidine (**63**) with butane-2,3-dione suggested that in our case the 4-imino-3-phenylquinazoline **80** was the kinetic product and the phenylaminoquinazoline **79** the thermodynamic product. Fortunately, when benzamidine **63** and TCNE reacted in MeCN the relative formation of quinazolines **79** and **80** was satisfactorily controlled by moderating the reaction temperature and mode of addition. In the absence of additives the reaction mechanism presumably follows that shown in Scheme 42.



Scheme 42

When preparing the arylaminoquinazolines **76**, it was noted that electron withdrawing halogens on the aniline moiety led to lower yields, necessitating the addition of AcOH (1

equiv) to the benzamidine solution. We assume that the role of the weak acid is to protonate the more basic amidine imine nitrogen (C=N-Ph) making it less nucleophilic, to afford the intermediate **124** that then undergoes a subsequent cyclization *via* the amidine amide-like nitrogen (=C-NH_2) (Scheme 43).

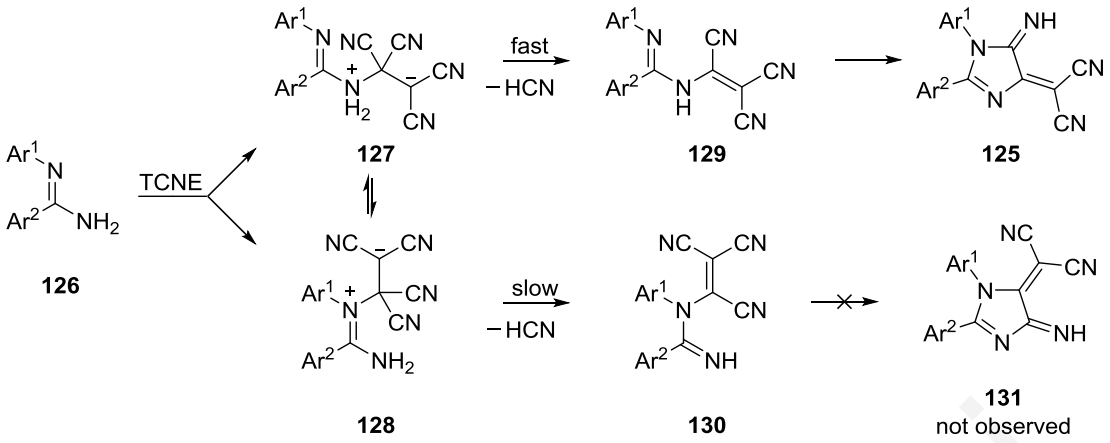


Scheme 43

Worthy of note is that most of the reported cyclizations of 2-amino-*N'*-phenylbenzamidine (**63**) that lead to the formation of 4-anilino or 4-arylimino quinazolines have been performed with heating and thus the isolation in these cases of the thermodynamic and not the kinetic product is unsurprising.

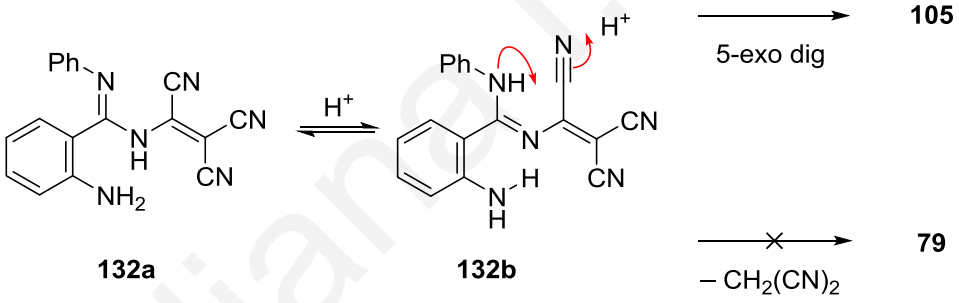
*4.3.2. Formation of 2-[2-(2-aminophenyl)-1-aryl-5-imino-1*H*-imidazol-4(5*H*)-ylidene]malononitriles **106***

The mechanistic rationale for the formation of the red colored [1*H*-imidazol-4(5*H*)-ylidene]malononitriles **106** was more complex. From our related work (see Chapter 5), we know that 2-[2-aryl-5-imino-1-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitriles **125** can be prepared from the reaction of *N'*-arylbenzamidines **126** with TCNE.[274] This addition of TCNE to the amidine amide-like nitrogen (=C-NH_2) (pK_a 8.2)[278] was unexpected. Presumably, the initial TCNE adducts **127** or **128** are in equilibrium but adduct **127** proceeds more rapidly to the isolable tricyanovinylamidine **129** that then undergoes the 5-exo-dig cycloaddition to the observed imidazole **125** (Scheme 44).



Scheme 44

In the reaction between TCNE and 2-amino-*N'*-phenylbenzamidine (**63**), which hosts a more nucleophilic phenylamine, the formation of the imidazole **105** was surprising. Tentatively, the formic acid in the reaction mixture assists the formation of the imidazole **105** in two distinct ways: firstly, by protonating the more basic amidine imine nitrogen (C=N-Ph) which enables TCNE to react with the remaining amide-like nitrogen (=C-NH_2), and secondly, by facilitating an acid catalyzed 5-exo dig cycloaddition[279-281] (Scheme 45).



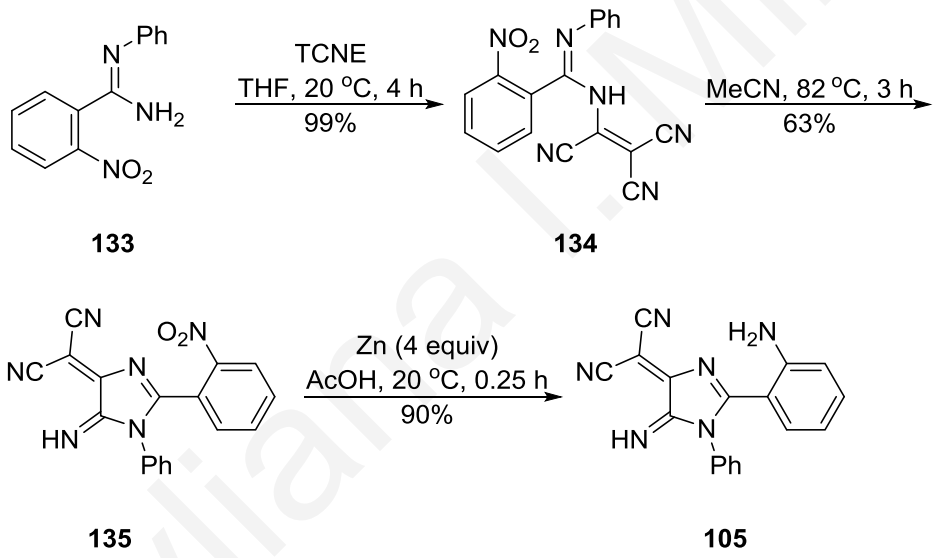
Scheme 45

Furthermore, this formic acid catalyzed cyclization must be sufficiently fast to limit the alternative cyclization involving the tricyanovinylamidine **132** to give again the quinazoline **79**. Worthy of note was that a highly probable internal H-bond in the tricyanovinylamidine **132** would hinder the latter cyclization. That the yield for the imidazole **105** could not be improved above 45% suggests that the reaction is more complex that we describe. At least half of the reaction products remain as intractable polar materials and further work is needed to clarify the reactions mechanisms. We note that 2-amino-*N'*-arylbenzamidines **75** in neat 85% formic acid heated at *ca.* 95 ^{o}C for 2 h afford

the 4-arylaminoquinazolines **76** in 70-92% yields,[266] however, no trace of these products were observed in the reaction with TCNE.

4.4 Independent synthesis and chemistry of 2-[2-(2-aminophenyl)-5-imino-1-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (105)

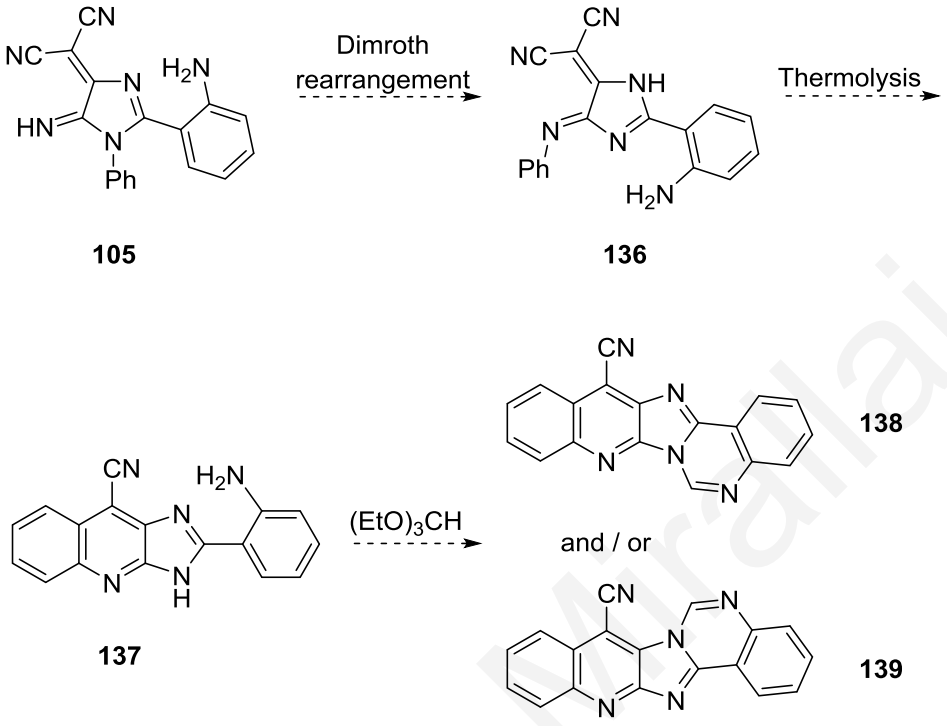
Previously, we reported an efficient route to [1*H*-imidazol-4(5*H*)-ylidene]malononitriles **125** *via* the reaction of TCNE with *N′*-arylbenzamidines **126** (Scheme 43).[274] In a similar manner the [1*H*-imidazol-4-ylidene]malononitrile **105** can be independently prepared by reacting TCNE with (*Z*)-2-nitro-*N′*-phenylbenzamidine (**133**) to give (*Z*)-2-nitro-*N′*-phenyl-*N*-(1,2,2-tricyanovinyl)benzamidine (**134**) which on warming in MeCN gave 2-[5-imino-2-(2-nitrophenyl)-1-phenyl-1,5-dihydro-4*H*-imidazol-4-ylidene]malononitrile (**135**), mild reduction of which using Zn powder in AcOH gave the desired (imidazolylidene)malononitrile **105** in four steps with a 43% overall yield (Scheme 46).



Scheme 46

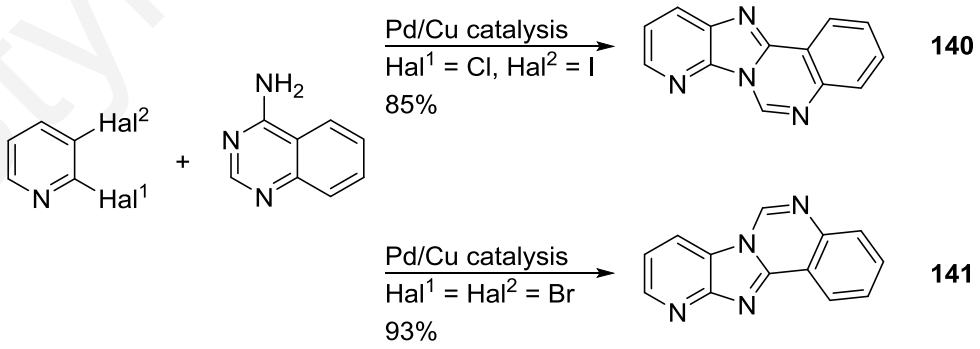
Furthermore, [1*H*-imidazol-4(5*H*)-ylidene]malononitriles **125** can undergo a Dimroth rearrangement in either DCM/DBU or in MeOH/NaOH to give 2-(2-phenyl-5-aryl-3,5-dihydro-4*H*-imidazol-4-ylidene)malononitriles, thermolysis of which afforded imidazolo-[4,5-*b*]quinolines.[274] The analogous Dimroth rearrangement of the (4*H*-imidazol-4-ylidene)malononitrile **105**, and subsequent thermolysis of the obtained isomer **136**, could give 2-(2-aminophenyl)-1*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**137**), which on treatment with triethyl orthoformate should give either quinolino[3',2':4,5]imidazo[1,2-

c]quinazoline-13-carbonitrile (**138**) or quinolino[2',3':4,5]imidazo[1,2-*c*]quinazoline-8-carbonitrile (**139**) or both (Scheme 47).



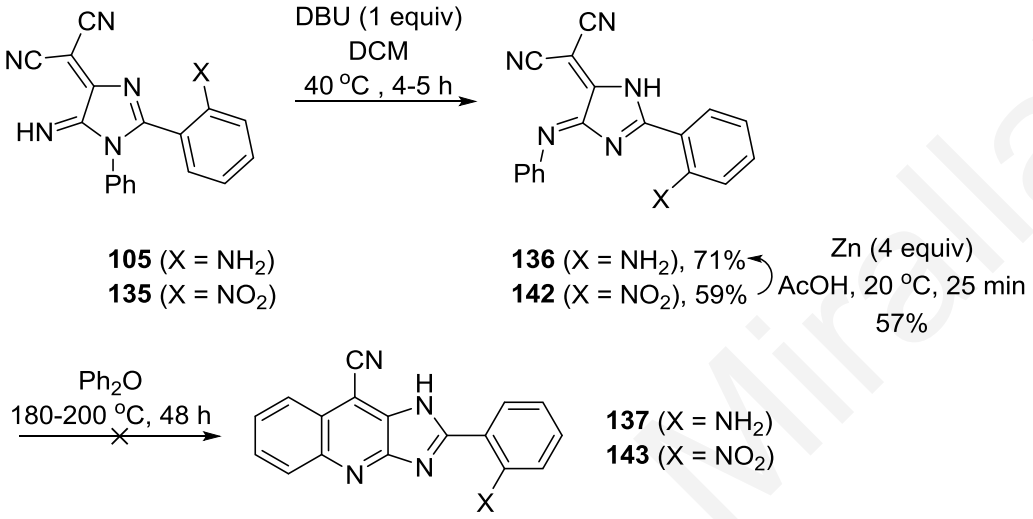
Scheme 47

Accessing either of these two pentacyclic heteroarenes looked attractive owing to their potential biological and/or material properties. Interestingly the closely related pyrido-[3',2':4,5]imidazo[1,2-*c*]quinazoline (**140**) and pyrido[2',3'-4,5]imidazo[1,2-*c*]quinazoline (**141**) have been prepared by Maes using an altogether different transition metal catalyzed synthesis (Scheme 48).[282]



Scheme 48[282]

As such, treating the 4,5-dihydroimidazole **105** with DBU (1 equiv) in DCM at *ca.* 40 ^{o}C for 3 h gave the Dimroth rearrangement product 2-[2-(2-aminophenyl)-5-(phenylimino)-3*H*-imidazol-4(5*H*)-ylidene]malononitrile (**136**) in 71% yield; interestingly, in MeOH/NaOH the Dimroth reaction failed. Unfortunately, thermolysis of the imidazole **136** in diphenyl ether at *ca.* 180 ^{o}C led to a complex reaction mixture with no major product (Scheme 49).

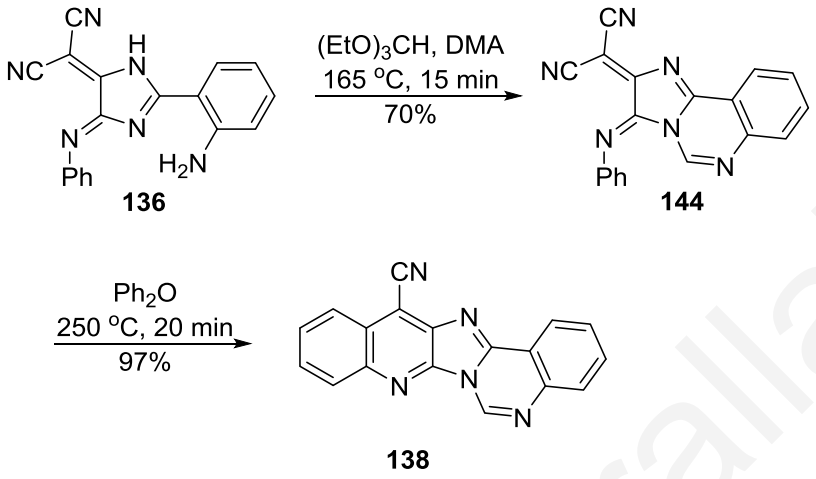


Scheme 49

In light of this, a semi-independent synthesis of the desired imidazo[4,5-*b*]quinoline **137** was attempted: the Dimroth rearrangement of the available 2-nitrophenyl-substituted imidazole **135** using DBU/DCM gave the isomeric 2-nitrophenylimidazole **142** in 59% yield; similar to the amino analogue above, the attempted rearrangement in MeOH/MeONa failed. Furthermore, the thermolysis of the 2-nitrophenylimidazole **142** in diphenyl ether at *ca.* 200 ^{o}C time 48 h, led to a complex reaction mixture and intractable solids. Any doubts regarding the structure of the 2-nitrophenyl Dimroth product **142** was probed by reduction of the nitro group in the presence of Zn powder (4 equiv) in AcOH, to give the amino analogue **136** in 57% yield identical to that described above (Scheme 49).

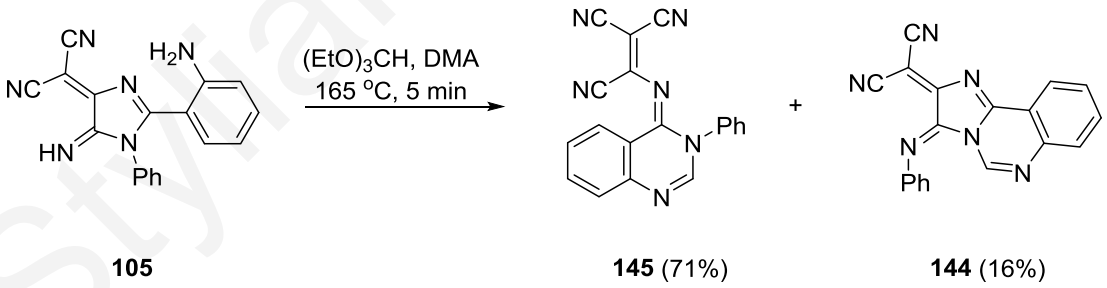
To overcome the above, the [3*H*-imidazol-4(5*H*)-ylidene]malononitrile **136** was treated with triethyl orthoformate in DMA at *ca.* 165 ^{o}C for 15 min to give the orange colored (*Z*)-2-[3-(phenylimino)imidazo[1,2-*c*]quinazolin-2(3*H*)-ylidene]malononitrile (**144**) in 70% yield, the structure of which was supported by single crystal X-ray crystallography (Figure 4). DSC studies of the imidazoquinazoline **144** indicated a decomposition onset point at

234.6 °C and gratifyingly, heating the compound in diphenyl ether at 250 °C for 20 min gave the desired quinolino[3',2':4,5]imidazo[1,2-*c*]quinazoline-13-carbonitrile (**138**) in 97% yield (Scheme 50).



Scheme 50

Interestingly, attempts to prepare the other isomer, by treating the [1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**105**) with ethyl orthoformate gave two unexpected products, the yellow colored 2-{[3-phenylquinazolin-4(3*H*)-ylidene]amino}ethene-1,1,2-tricarbonitrile (**145**) in 71% and the imidazo[1,2-*c*]quinazoline **144** (Scheme 51) in 16% yield. The structure of the tricarbonitrile **145** was supported by single crystal X-ray crystallography (Figure 5).



Scheme 51

DSC of 2-[(3-phenylquinazolin-4(3*H*)-ylidene)amino]ethene-1,1,2-tricarbonitrile (**145**) displayed a decomposition with an onset temperature at 278.7 °C and a peak max. at 300.4 °C; however, **145** was thermally stable after heating in diphenyl ether at *ca*. 300 °C for 24 h, indicating that it was not an intermediate to the formation of the imidazo-

quinazoline **144**. Presumably, under the reaction conditions the (imidazolylidene)-malononitrile **105** can ring open in two distinctly different ways, the first to regenerate a tricyanovinyl intermediate (either before or after the quinazoline is formed) that leads to the formation of the major product **145** and the second must be a Dimroth related ring opening that leads to the formation of the minor product **144**.

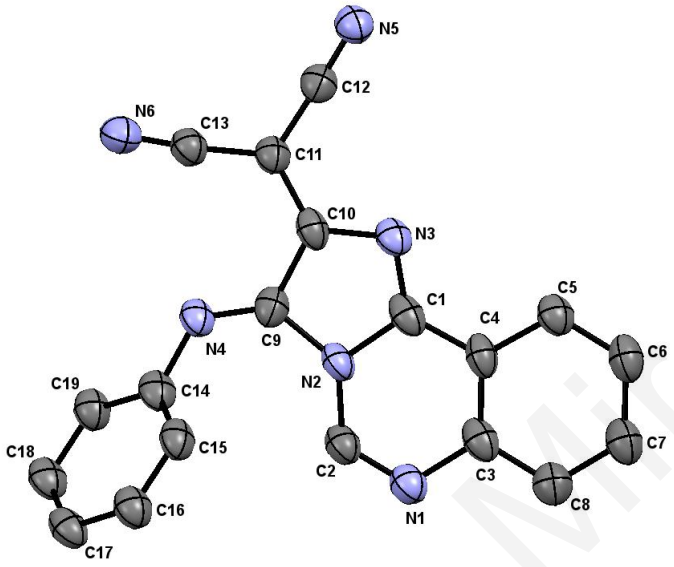


Figure 4. The crystal structure of (*Z*)-2-[3-(phenylimino)imidazo[1,2-*c*]quinazolin-2(3*H*)-ylidene]malononitrile (**144**) (50% probability ellipsoids and hydrogen atoms omitted for clarity).

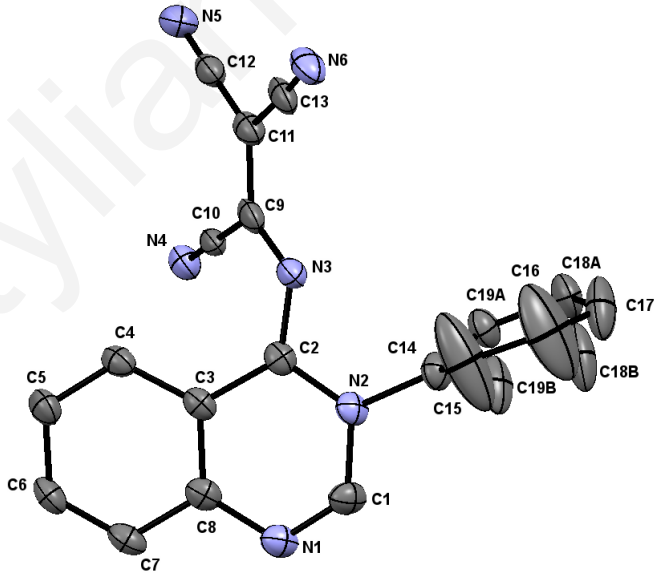


Figure 5. The crystal structure of 2-[(3-phenylquinazolin-4(3*H*)-ylidene)amino]ethene-1,1,2-tricarbonitrile (**145**) (50% probability ellipsoids and hydrogen atoms omitted for clarity).

4.5 Summary

The reaction of 2-amino-*N'*-arylbenzamidines **75** and TCNE is more complex than originally reported affording three products **76**, **103** and **106** which, depending on the reaction conditions can be isolated as the main reaction products. By adding the benzamidines **51**, **63-64**, **66-68** and **71** to a hot EtOAc solution of TCNE in the presence of HCO_2H the [1*H*-imidazol-4(5*H*)-ylidene]malononitriles **106** can be prepared in 41-51% yields. By adding TCNE to a solution of the benzamidines **51**, **63-64**, **66-68** and **71** and AcOH in MeCN at *ca.* 20 ^oC the 4-(arylamino)quinazoline-2-carbonitriles **79, 113-118** can be prepared in 93-98% yields. While adding the benzamidines **51**, **63-64**, **66-68** and **71** to a cooled (*ca.* -20 ^oC) MeCN solution of TCNE afforded the isomeric 3-aryl-4-iminoquinazoline-2-carbonitriles **80-85** and **119** in 62-69% yields. Mechanistic rationale suggests that the latter quinazolines **103** are the kinetic products and the 4-(arylamino)quinazolines **76** the thermodynamic products. Furthermore, the use of mild acids such as AcOH and HCO_2H was beneficial in enhancing the yields of the 4-(arylamino)quinazolines **76** and the [1*H*-imidazol-4(5*H*)-ylidene]malononitriles **106**. The imidazole **105**, which undergoes a Dimroth rearrangement in the presence of DBU was also a useful precursor to a new pentacyclic system quinolino[3',2':4,5]imidazo[1,2-*c*]quinazoline-13-carbonitrile (**138**). The mechanistic rationale provided for the above transformations remains tentative pending further studies, nevertheless we believe the chemistry demonstrates that 2-amino-*N'*-arylbenzamidines **75** are valuable building blocks for heterocyclic synthesis and warrant further study.

CHAPTER 5

Reactions of tetracyanoethylene with *N′*-arylbenzamidines: A short route to 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitriles

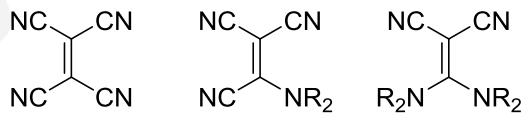
Sections

5.1 Introduction

Previously, the complex reaction of 2-amino-*N*′-arylbenzamidines **125** and TCNE was reported, which, depending on the reaction conditions, afforded three possible main products **76**, **103** and **104** (Chapter 4, Scheme 39). To understand better the formation of the unexpected red imidazole **106** the reaction was simplified by replacing 2-amino-*N*′-arylbenzamidines **75** with *N*′-arylbenzamidines **126** (Scheme 54). The absence of the 2-amino moiety in the latter benzamidines should avoid the formation of the quinazolines **76** and **103** and potentially lead to higher yields of the imidazoles.

Tetracyanoethylene (TCNE)[197,283] a cyanocarbon,[284] is the simplest of the percyano alkenes. It is highly electron-deficient and strongly electrophilic. Not surprisingly, TCNE can act as a powerful electron acceptor forming charge transfer complexes with various donors,[285,286] or it can participate in pericyclic chemistry as an electron deficient dienophile in Diels-Alder reactions[285] or enophile in [2+2] cycloadditions.[287,288] Furthermore, it can act as an umpolung source of dicyanomethylene.[289-291] Its most common reaction is that of addition to its double bond and subsequent loss of the cyanide (tricyanovinylation). Direct addition to the nitrile can also occur but is less common.[292,293] The chemistry of TCNE has been extensively reviewed.[288,294-300]

With primary or secondary aliphatic amines and with most primary and secondary aromatic amines, the reaction with TCNE gives *N*-tricyanovinylamines **146**, although with an excess of amine 1,1-diamino-2,2-dicyanoethylenes **147**[276,294,301] or 1,2-diamino-1,2-dicyanoethylenes **148**[302] are formed. TCNE does not react with tertiary aliphatic amines, but it readily reacts with both tertiary and secondary aromatic amines, attacking the arene to give 4-tricyanovinylarylamines **149** *via* the initial formation of a 1:1 π complex.[276]

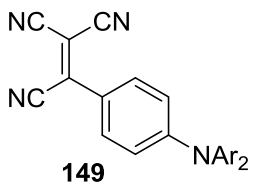


TCNE

146

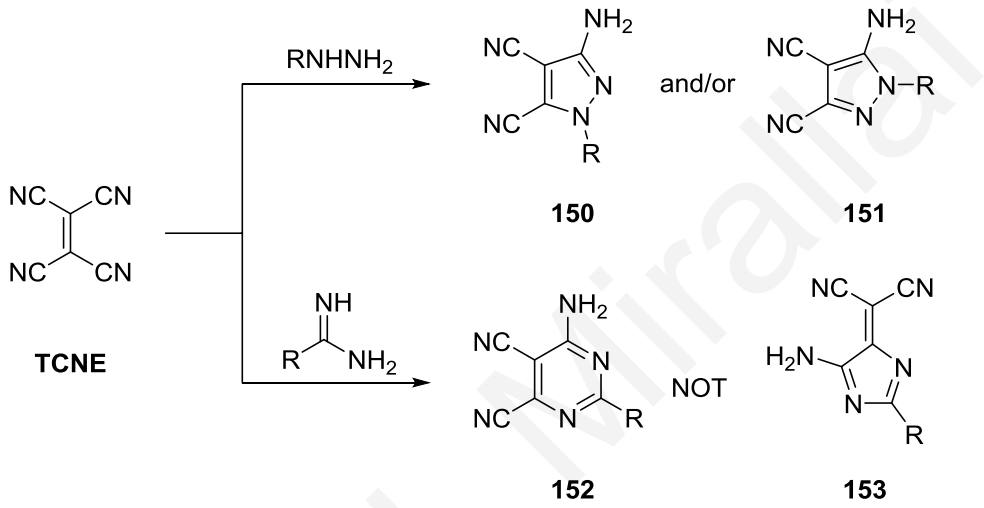
147

148



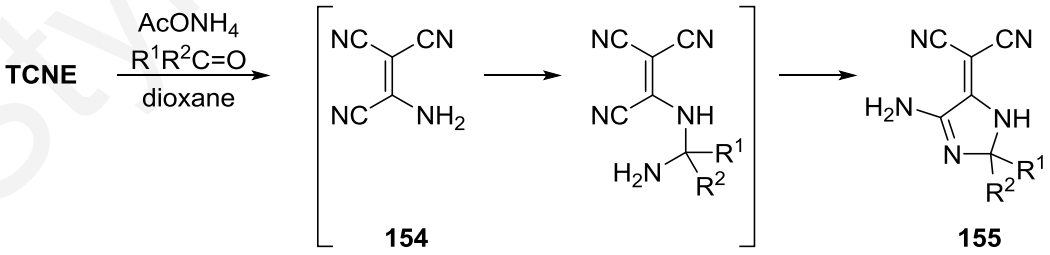
149

TCNE also reacts with a variety of bis-amino nucleophiles to give, after the initial addition to the double bond, intramolecular cyclizations typically on the vicinal nitrile that lead to various heterocyclic systems. For example, TCNE reacts with substituted hydrazines to give pyrazoles **150** and/or **151**,[292,293,303] or with 2-amidines to give 2-substituted 6-amino-pyrimidine-4,5-dicarbonitriles **152**. The latter 6-exo-dig cyclization is somewhat surprising since a 5-exo-dig cyclization could in theory occur on the geminal nitrile to yield five membered imidazoles of type **153** (Scheme 52).



Scheme 52

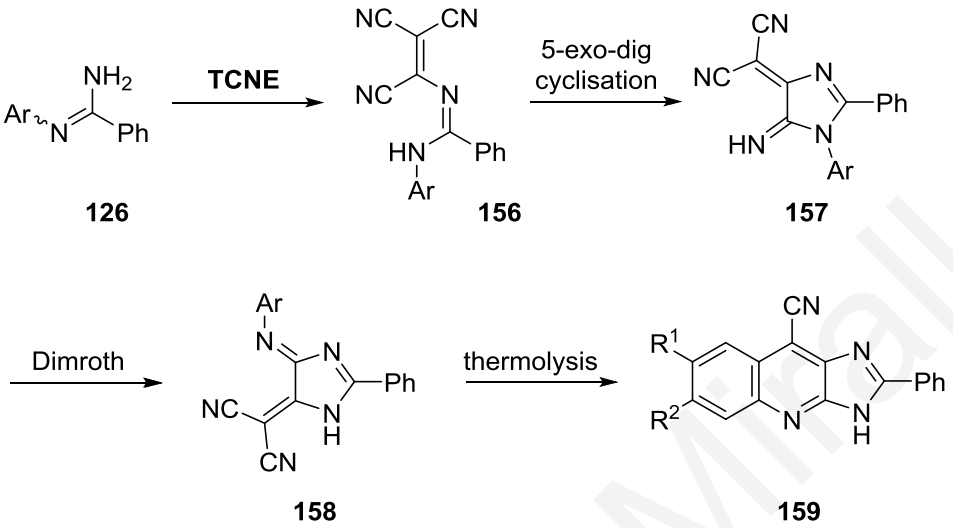
To the best of our knowledge, only one report on the preparation of imidazolines from TCNE has appeared whereby N-methylamino functionalization of the intermediate tricyanovinylamine **154** led to a geminal (5-exo-dig) heterocyclization to give 2-(5-amino-2,3-dihydro-4*H*-imidazol-4-ylidene)malononitriles **155** (Scheme 53).[304]



Scheme 53

In light of this and our interest in preparing cyano substituted heteroarenes,[206,207,209-211,291,305-310] we report below our complementary study on the reaction of TCNE with

readily available *N′*-arylbenzamidines **126**,[191] which affords *(Z)*-*N*-aryl-*N′*-(1,2,2-tricyanovinyl)benzamidines **156** that readily undergo a 5-exo-dig cyclization to the (imidazolylidene)malononitriles **157**, that in two steps, *via* the Dimroth rearrangement product **158**, can be converted into 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitriles **159** (Scheme 54).



126 **156** **157**

158 **159**

Scheme 54

Previous syntheses of imidazo[4,5-*b*]quinolines include the one-pot Beckmann rearrangement of 3-acyl-2-(alkylamino)quinolin-4-(1*H*)-ones,[311] the reductive cyclization of 5-(2-nitrobenzylidene)-3,5-dihydroimidazol-4-ones,[312,313] from lithiated 3-aminoquinolines with nitriles,[314] and from 2,3-diaminoquinolines.[315] Derivatives have a variety of uses as NO synthase inhibitors[315] and as analogues of antiviral polyhalogenated benzimidazole ribonucleosides,[316] furthermore, fused 3*H*-imidazo[4,5-*b*]quinoline-9-carbonitriles have been investigated as fluorescent dyes.[317]

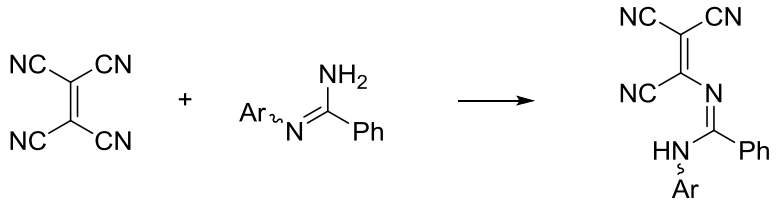
5.2 Investigation of the reaction of *N′*-phenylbenzamidine 50 with TCNE

The reaction of *N′*-phenylbenzamidine **50** with TCNE was investigated in a variety of solvents and temperatures and in almost all cases three products were observed in varying ratios by TLC: a colorless [R_f 0.51 (DCM/Et_2O, 95:05); λ_{max} 241 nm, log ε 4.29 (DCM)], a yellow [R_f 0.48 (DCM); λ_{max} 440 nm, log ε 4.31 (DCM)] and an orange product [R_f 0.71 (DCM/Et_2O, 95:05); λ_{max} 452 nm, log ε 4.26 (DCM)] **160**, **169** and **178**, respectively. The order of formation was determined (by TLC) to be first the colorless, then the yellow and finally the orange colored compound. It was noted that the colorless product **160** converted

rapidly into the yellow product **169** during a 2D TLC study, furthermore, polar protic solvents such as MeOH or EtOH strongly promoted the formation of the orange product **178**. Both mass spectrometry and elemental analysis of these three products showed they were isomers with a molecular formula of $C_{18}H_{11}N_5$ indicating that an addition between TCNE and *N′*-phenylbenzamidine **50** followed by loss of HCN had occurred.

Since silica promoted the conversion of the colorless compound into the isomeric yellow we pursued a non chromatographic work up to isolate a clean sample of the colorless compound **160**: Treating *N′*-phenylbenzamidine **50** (1 mmol) with TCNE (1 mmol) in dry THF at *ca.* 20 ^{o}C led to the exclusive formation of the colorless compound **160** (by TLC). By carefully evaporating the THF, redissolving the residue in a small quantity of Et_2O and diluting with *n*-pentane we were able to precipitate a microanalytically pure sample of the colorless product **160** in 97% yield. IR spectroscopy suggested the presence of amino [ν(NH) 3258 cm^{-1}] and nitrile [ν(C≡N) 2201 cm^{-1}] functional groups and this was supported by NMR studies. In particular, the ^{1}H NMR supported the presence of the NH with a D_2O exchangeable signal at 8.04 ppm and the ^{13}C NMR supported the presence of a tricyanovinylamine with three nitrile signals at 112.5, 108.4 and 108.0 ppm together with an upfield signal for the dicyanomethylene carbon at 66.9 ppm that was typical of a tricyanovinylamine.[318] The data tentatively suggested the product to be *N*-phenyl-*N′*-(1,2,2-tricyanovinyl)benzamidine (**160**), which could originate from simple substitution of one nitrile by the least sterically hindered *N′*-arylbenzamidine amino group. The reaction was general and in total nine analogues were prepared (Table 6). Interestingly, where the benzamidines contained *N′*-aryl substituents with either chloro, bromo, iodo or nitro substituents (Table 6, entries 5-9) the reactions required a slight excess (1.2 equiv) of TCNE to come to completion.

Table 6. Reaction of TCNE with *N′*-arylbenzamidines **47, 50-51, 56-62** (1 mmol) in dry THF (10 mL) at *ca.* 20 °C for 2 h



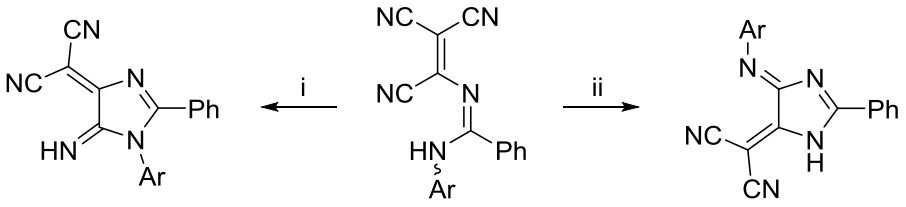
TCNE **155** **156**

entry	TCNE (mmol)	Ar	yields **156** (%)
1	1.0	Ph	**160** (97)
2	1.0	4-$MeOC_6H_4$	**161** (98)
3	1.0	4-MeC_6H_4	**162** (99)
4	1.0	4-FC_6H_4	**163** (95)
5	1.2	4-ClC_6H_4	**164** (93)
6	1.2	3,4-$Cl_2C_6H_3$	**165** (91)
7	1.2	4-BrC_6H_4	**166** (92)
8	1.2	4-IC_6H_4	**167** (87)
9	1.2	4-$O_2NC_6H_4$	**168** (88)

5.3 Reactions of *N′*-aryl-*N*-(1,2,2-tricyanovinyl)benzamidines 156

Solutions of the tricyanovinylbenzamidine **160** in DMF or DMSO at *ca.* 20 °C or heated to reflux in a range of solvents such as DCM, PhMe or THF led to mixtures of both yellow and orange products **169** and **178**, respectively. Furthermore, treatment with either base (Hünig's base or DBU) or acid catalysts ($TsOH \cdot H_2O$, H_2SO_4 or Lewis acids like $AlCl_3$, $FeCl_3$, $ZnCl_2$) gave more complex mixtures. Fortunately, simply heating a solution of the tricyanovinylbenzamidine **160** in dry acetonitrile led to the formation of the yellow isomer **169** in 88% yield while in MeOH the orange isomer **178** was formed in 92% yield. These conversions were generally high yielding for all nine analogues (Table 7).

Table 7. Reactions of *N′*-aryl-*N*-(1,2,2-tricyanovinyl)benzamidines **160-168** (0.1 mmol) in either i) dry MeCN (1 mL) at *ca.* 82 °C for 3 h or ii) MeOH (1 mL) at *ca.* 65 °C for 1 h



157 **156** **158**

entry	Ar	yields (%) **157**	**158**
1	Ph	**169** (88)	**178** (92)
2	4-$MeOC_6H_4$	**170** (89)	**179** (91)
3	4-MeC_6H_4	**171** (89)	**180** (94)
4	4-FC_6H_4	**172** (89)	**181** (88)
5	4-ClC_6H_4	**173** (87)	**182** (86)
6	3,4-$Cl_2C_6H_3$	**174** (87)	**183** (90)
7	4-BrC_6H_4	**175** (85)	**184** (87)
8	4-IC_6H_4	**176** (84)	**185** (85)
9	4-$O_2NC_6H_4$	**177** (92)	**186** (93)

The ^{13}C NMR spectroscopic data for both the yellow and orange isomers **169** and **178**, respectively suggested one less nitrile group which indicated a cyclization had occurred. As mentioned above, cyclizations to give either six membered pyrimidines (*via* a 6-exo-dig cyclization) or five membered imidazoles (*via* a 5-exo-dig) were possible (Scheme 51), however, a study of the available spectroscopic data was inconclusive. To identify these isomers we collected single crystal X-ray data, which supported the yellow isomer to be 2-[5-imino-1,2-diphenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**169**) (Figure 6) and the orange isomer to be (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]-malononitrile (**178**) (Figure 7).

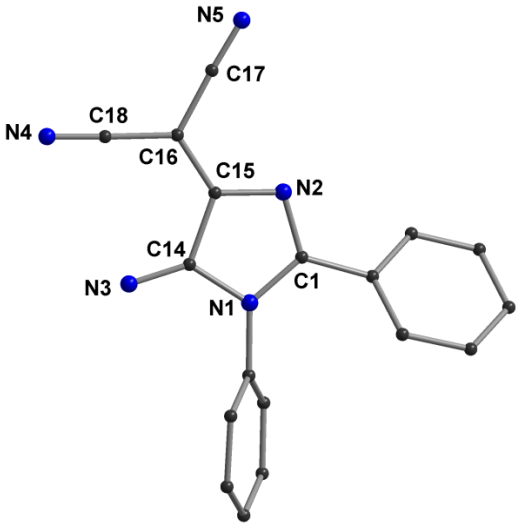


Figure 6. Ball and stick representation of the crystal structure of 2-[5-imino-1,2-diphenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**169**) with crystallographic atom labelling. Hydrogen atoms were omitted for clarity.

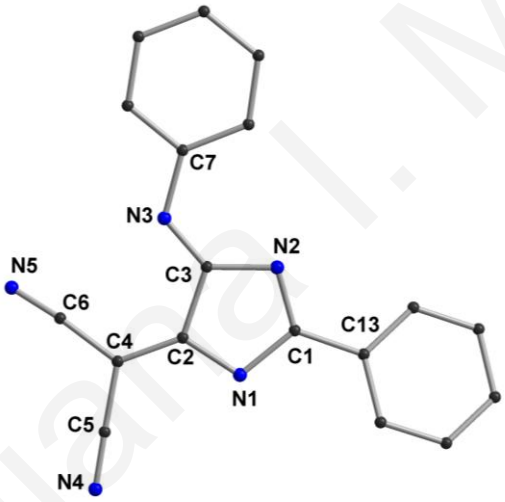


Figure 7. Ball and stick representation of the crystal structure of (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**178**) with crystallographic atom labelling. Hydrogen atoms were omitted for clarity.

Interestingly, ^{1}H NMR spectra of the imidazoles **157** in $CDCl_3$ were complicated, showing what appeared to be *E/Z* isomers. ^{1}H NMR spectroscopy of imidazole **169** in $CDCl_3$ indicated twenty ArH and two NH resonances, while ^{13}C NMR spectroscopy gave 16 quaternary C of which four were potentially from nitriles [δ_C(*C*≡N) 113.0, 112.5, 112.3 and 111.7 ppm] and twelve CH signals. While the spectra were simplified by switching the deuterated solvent from $CDCl_3$ to DMSO-d_6, we serendipitously discovered that excellent

^{1}H NMR spectra could be obtained with $CDCl_3$ which was saturated with gaseous HCl. The imidazole **169** could be recovered unchanged from $CDCl_3$/HCl confirming that, other than protonation, presumably on the exocyclic imine, no chemical transformation had occurred during the collection of the NMR data. A close analysis of the single crystal X-ray data of the imidazole **169** revealed a 50/50 *E/Z* distribution of the (disordered) hydrogen electron density on the exocyclic imine nitrogen in agreement with the NMR data. On the other hand, ^{1}H and ^{13}C NMR spectra of isomers **158** were complicated by prototautomerisation[319,320] and this was also partly supported by UV/vis spectroscopy. ^{1}H NMR spectroscopy of isomer **178** indicated an NH at 12.62 ppm and 10 aromatic protons for the major tautomer, while ^{13}C NMR spectra were poorly resolved, revealing the presence of only four quaternary C signals of which two were potentially from nitriles [δ_C(*C*≡N), 114.6 and 114.1 ppm] and four aromatic CH signals instead of the expected six quaternary C and six aromatic CH signals. Attempts to improve the resolution of these spectra by using a range of deuterated solvents and concentrations (acetone-d_6, $CDCl_3$, DMSO-d_6, TFA-*d*) or by collecting over 20000 scans at 125 MHz and increasing the relaxation delay D1 from 2 to 6 sec., or with the use of $Cr(acac)_3$ or hexamethylphosphorous triamide (HMPT) as relaxation reagents, and also attempting VT NMR (DMSO-d_6 heated at *ca.* 50 ^{o}C or acetone-d_6 cooled to *ca.* 0 ^{o}C) studies failed to improve the spectra. UV/vis spectra collected for the imidazole **178** were markedly different depending on the choice of solvent. Solutions of the imidazole **178** in polar aprotic solvents such as pyridine, acetone, DMF or DMSO were distinctly reddish-pink in color and the spectra had well defined long wavelength absorptions while in solvents such DCM, $CHCl_3$ and ethers or in protic solvents such as MeOH or AcOH the solutions were orange and the long wavelength peaks were lost (Figure 8).

Tentatively, we attributed this spectroscopic phenomena to prototautomerization, which presumably arises because the imidazole NH in compound **178** is strongly activated (*i.e.*, acidic and therefore mobile) by the exocyclic ylidene malononitrile, as well as the endocyclic and exocyclic imine bonds.

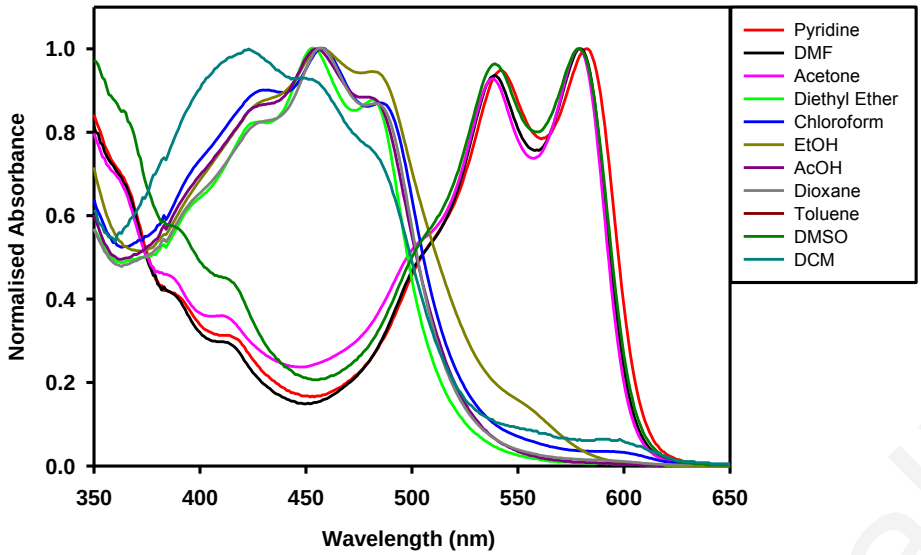
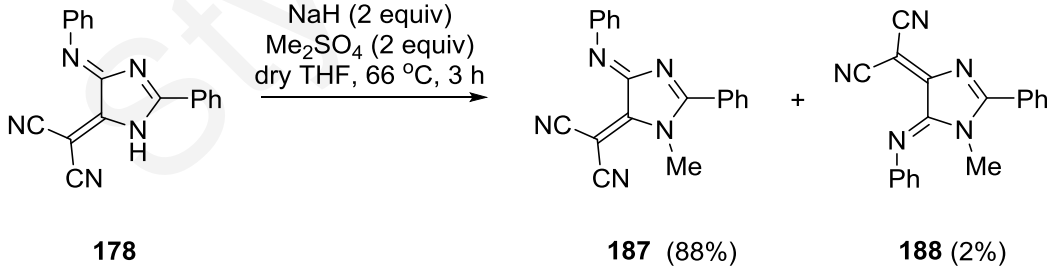


Figure 8. Comprarison of UV/vis spectra of (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**178**) in various solvents. Maximum intensity absorptions have been normalized.

5.4 Chemistry of (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]-malononitrile (178)

To study the chemistry of the imidazole **178** further, an N-methylation study was performed using methyl sulfate in dry THF. The products obtained were (*Z*)-2-[1-methyl-2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**187**) and (*Z*)-2-[1-methyl-2-phenyl-5-(phenylimino)-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**188**) in 88 and 2% yields, respectively (Scheme 55).



Scheme 55

Unlike the non-methylated imidazole **178** the ^{1}H and ^{13}C NMR spectra of both methylated isomers were well resolved, showing the expected eight quaternary, six CH and one CH_3

carbon signals. The assigned regioselectivity of the methylations was supported by 2D-NOESY 1H-NMR and also for the major isomer **187** by single crystal X-ray spectroscopy (Figure 9).

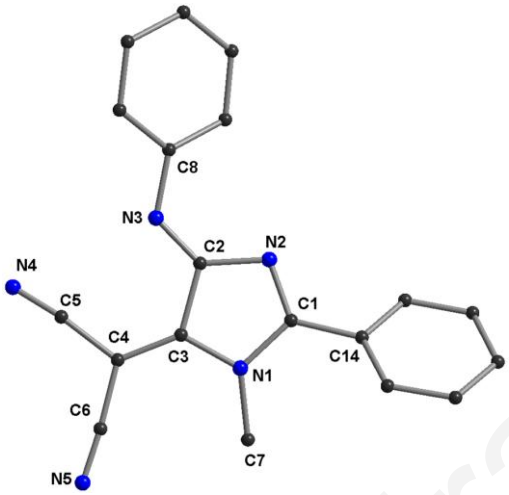
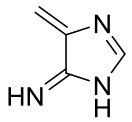
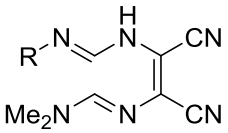


Figure 9. Ball and stick representation of the crystal structure of (*Z*)-2-[1-methyl-2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**187**) with crystallo-graphic atom labelling. Hydrogen atoms were omitted for clarity.

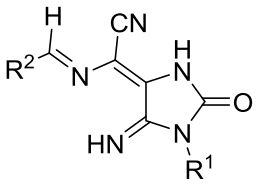
Both the above imidazoles are examples of *ortho* quinone methide imines (QMI's) which typically are reactive species and not readily isolated.[321] Not surprisingly, very few examples of this ring system have been reported: 4-methylene-1*H*-imidazol-5(4*H*)-imines **189** have been proposed as possible intermediates in the conversion of (*Z*)-N^1-{1,2-dicyano-2-[(*N*,*N*-dimethylamino)methylamino]vinyl}formamidines **190** into purines or imino-pyrroles,[322] and as intermediates in the preparation of purine-N^9-acetic acids from HCN and glycine.[323] More recently, a series of prototautomerically closely related 4-imino-5-methyleneimidazolidin-2-ones **191** have been isolated and characterized.[324,325] Interestingly, the ^{1}H NMR in DMSO-d_6 indicated the imine NH was present as two broad singlets (δ_H 9.1-8.8 ppm) in a 1:1 ratio, which was attributed to *E/Z* isomers of the exocyclic methylene (*cf.* the ^{1}H NMR of imidazole **169**). To date, to the best of our knowledge only one X-ray structure has been reported, that of (*E*)-4-[5-imino-1-phenyl-1*H*-imidazol-4(5*H*)-ylidene]-2,2-dimethyl-oxazolidin-5-imine (**192**).[326]



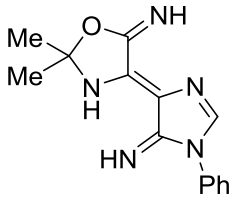
189



190



191

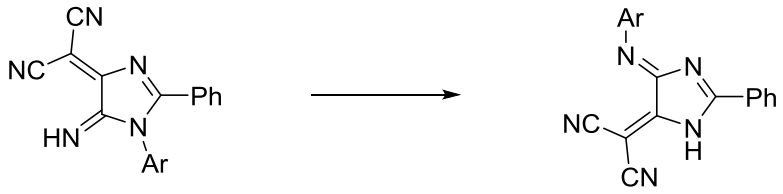


192

5.5 Dimroth rearrangement of imidazole 169 into imidazole 178

A close analysis of the two imidazoles **169** and **178** indicated that the latter was probably the product of a Dimroth rearrangement of the former. Dimroth rearrangements are typically thermally induced or initiated by acids or bases.[235] Nevertheless, a pure sample of the imidazole **169** dissolved in MeOH and left to stir at *ca.* 20 ^{o}C for 38 h was converted into the imidazole **178** in high yield. The reaction time could be considerably shortened to 1 h by heating the reaction mixture to *ca.* 67 ^{o}C. Furthermore, in a non-protic non nucleophilic solvent such as DCM heated to *ca.* 40 ^{o}C the conversion of imidazole **169** into imidazole **178** required the addition of base with DBU (1 equiv) giving the best results (Table 8). When DBU was replaced by pyridine, DMAP or lutidine or DABCO (1 equiv) the Dimroth rearrangement could not be driven to completion, while the use of trialkylamines, such as Et_3N (2-4 equiv) or Hünig's base (*i*-Pr_2NEt) led to no reaction. The reaction with DBU could also be carried out at *ca*. 20 ^{o}C but the reaction time increased to 22 h while the yield decreased to 84-86%. Finally, reducing the equivalents of DBU led to incomplete reactions (Table 8, entry 1) while no significant advantage was observed in using more than one equivalent (Table 8, entry 3). Interestingly, the use of sterically hindered Barton's base also gave **178** in 91% (Table 8, entry 4).

Table 8. Dimroth rearrangement of 2-(1-aryl-5-imino-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene)malononitriles **157** (0.1 mmol) into (*Z*)-2-[4-(arylimino)-2-phenyl-4-1*H*-imidazol-5(4*H*)-ylidene]malononitriles **158**. *Conditions* ***A****:* MeOH (1 mL), *ca.* 67 °C, 1 h. *Conditions* ***B****:* R_3N base in DCM (2 mL) heated to *ca.* 40 °C

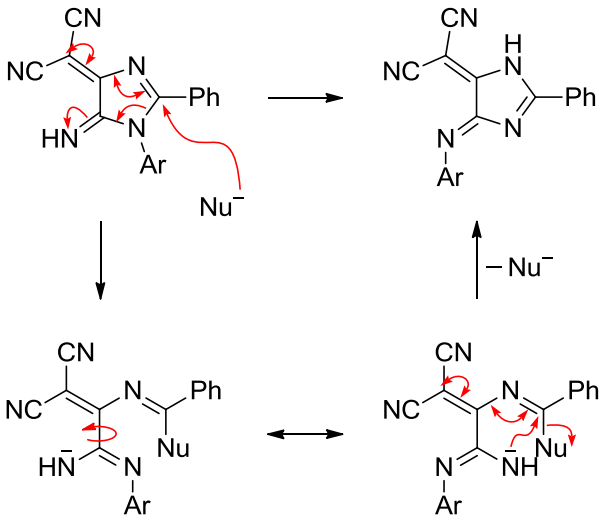


157 **158**

entry	Ar	cond. B base (equiv), time (h)	yields **158** (%) cond. A	cond. B
1	Ph	DBU (0.5), 48	-	ir[a]
2	Ph	DBU (1), 4	-	**178** (97)
3	Ph	DBU (2), 3	-	**178** (96)
4	Ph	Barton's base (1),[b] 10	**178** (99.6)	**178** (91)
5	4-$MeOC_6H_4$	DBU (1), 4	**179** (99)	**179** (90)
6	4-MeC_6H_4	DBU (1), 4	**180** (94)	**180** (91)
7	4-FC_6H_4	DBU (1), 6	**181** (98)	**181** (92)
8	4-ClC_6H_4	DBU (1), 6	**182** (98)	**182** (92)
9	3,4-$Cl_2C_6H_3$	DBU (1), 6	**183** (96)	**183** (93)
10	4-BrC_6H_4	DBU (1), 6	**184** (94)	**184** (88)
11	4-IC_6H_4	DBU (1), 6	**185** (95)	**185** (91)
12	4-$O_2NC_6H_4$	DBU (1), 6	**186** (95)	**186** (95)

[a] ir = incomplete reaction; [b] 2-*tert*-butyl-1,1,3,3-tetramethylguanidine.

The rearrangement was irreversible since treating (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**178**) with either NaOH (0.5 mol%) in MeOH at *ca.* 67 °C or with DBU (1 equiv) in dry DCM at *ca*. 40 °C for 24 h led to no reaction. The reaction presumably is initiated by nucleophilic attack by either methanol/methoxide or even DBU, which can act as a nucleophile,[327] at the imidazole C-2 position which is strongly electrophilic, activated by both the exocyclic ylidenemalononitrile and the imidazole imine which have constructively aligned dipoles. Subsequent ring opening *via* cleavage of the imidazole N(1)–C(2) bond affords a ring opened species that can rotate and undergo ring closure to afford the new imidazole **158** (Scheme 56).



Scheme 56

5.6 Thermolysis studies of imidazoles 169 and 178

The thermolysis of both imidazoles **169** and **178** was also investigated: Differential scanning calorimetry (DSC) studies under an argon atmosphere showed that the imidazole **169** immediately decomposed after melting (mp: onset 195.6 ^{o}C, peak 201.3 ^{o}C; decomp: onset 205.2 ^{o}C peak 207.9 ^{o}C). On heating a bulk sample under argon atmosphere at *ca.* 220 ^{o}C for 20 min a reaction mixture was obtained from which the imidazole **178** was isolated in low yield (33%) together with two new products **193** (11%) and traces of compound **194**.

Compound **193** was isolated as yellow prisms [mp (DSC) onset 237.4 ^{o}C, peak max. 238.3 ^{o}C, onset 297.4 ^{o}C, decomp. 297.5 ^{o}C; (from *c*-hexane/DCE, 80:20)]. Elemental analysis and electron impact mass spectrometry supported the molecular formula $C_{18}H_{11}N_5$. IR spectroscopy indicated the presence of an amino stretch [ν(NH) 3298 cm^{-1}] and a cyano stretch [ν(C≡N) 2226 cm^{-1}]. ^{1}H NMR spectroscopy indicated an NH at 7.45 ppm and 10 aromatic protons resonances, while ^{13}C NMR spectroscopy, revealed the presence of eight quaternary carbons of which two appeared to belong to nitriles [δ_C(*C*≡N) 113.6 and 112.5 ppm] together with six aromatic CH resonances. As before, single crystals were grown by slow vapor diffusion of *n*-pentane into a benzene solution at room temperature, and single crystal X-ray diffraction studies revealed the structure to be 2-phenyl-6-(phenylamino)pyrimidine-4,5-dicarbonitrile (**193**) (Figure 10).

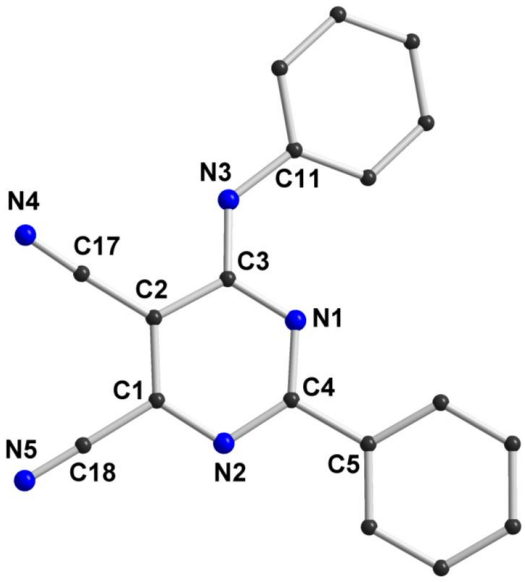
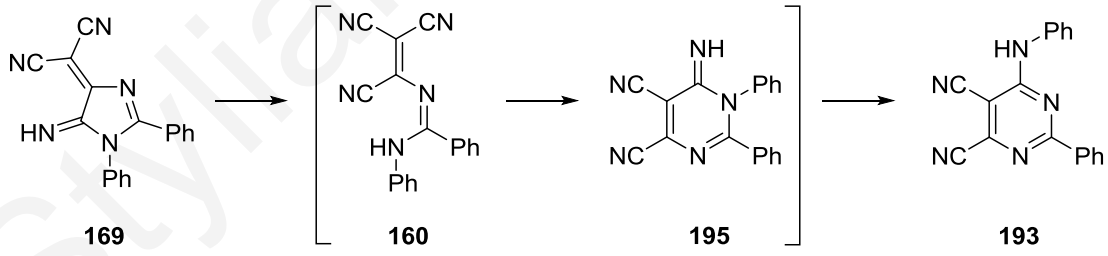


Figure 10. Ball and stick representation of the crystal structure of 2-phenyl-6-(phenyl-amino)pyrimidine-4,5-dicarbonitrile (**193**) with crystallographic atom labelling. The hydrogen atoms were omitted for clarity.

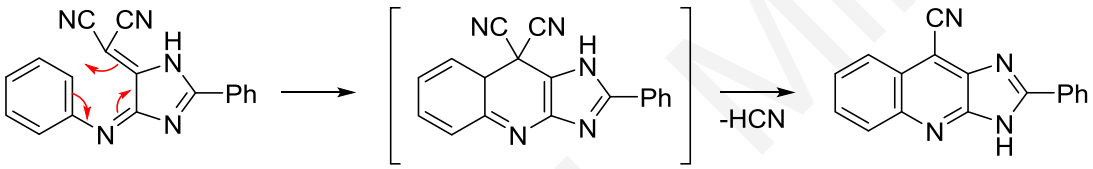
Tentatively, pyrimidine **193** can form from imidazole **169** in three steps: Firstly imidazole **169** ring opens to give the tricyanovinylamidine intermediate **160** which subsequently undergoes a 6-exo-dig heterocyclization on the vicinal nitrile to give 6-imino-1,2-diphenyl-1,6-dihydropyrimidine-4,5-dicarbonitrile (**195**), that under the reaction conditions Dimroth rearranges to the observed pyrimidine **193** (Scheme 57). Unfortunately, no trace of the pyrimidine **195** could be identified and isolated from the reaction mixture.



Scheme 57

Surprisingly, complex reaction mixtures were also obtained when the thermolysis was carried out using inert solvents such as toluene, xylene, chlorobenzene or diphenyl ether at reflux, while in benzene heated to reflux the yellow imidazole **169** was stable.

Compound **194** was isolated as colorless fibres [mp (DSC) decomp. onset 304.7 °C, peak max. 305.1 °C; (from *n*-pentane/THF, 90:10)]. Elemental analysis and electron impact mass spectrometry supported the molecular formula $C_{17}H_{10}N_4$. IR spectroscopy indicated the presence of a cyano stretch [ν(C≡N) 2230 cm^{-1}]. Owing to the poor solubility of the compound NMR spectroscopy was performed in deuterated trifluoroacetic acid. ^{1}H NMR spectroscopy indicated nine aromatic protons resonances with a splitting pattern that suggested one mono substituted phenyl and one *ortho* disubstituted benzene ring. ^{13}C NMR spectroscopy, revealed the presence of eight quaternary carbons one of which supported the presence of a nitrile δ_C(*C*≡N) 112.6 ppm and seven aromatic CH resonances. Based on these data we tentatively suggest that the product was 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**194**), which based on the carbon nitrogen connectivity could have formed from imidazole **178** *via* an electrocyclic ring closure and subsequent loss of HCN (Scheme 58).

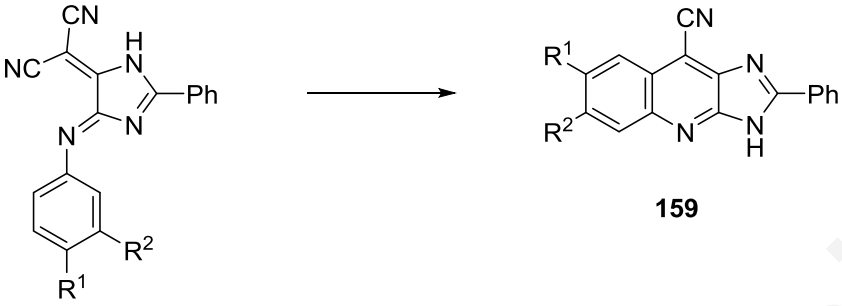


178 **194**

Scheme 58

In light of this, we carried out a DSC study of a pure sample of the imidazole **178** that showed only an exothermic transition (onset 255.8 °C peak 256.7 °C). On cooling to *ca.* 20 °C, a TLC analysis of the contents of this DSC pan revealed only one product, compound **194**. Subsequent thermolysis of the imidazole **178** in diphenyl ether at *ca.* 280 °C, for 4 h protected from moisture with $CaCl_2$ drying tube, gave compound **194** quantitatively. The reaction temperature could be lowered to *ca.* 215 °C without affecting the product yield, although this led to longer reaction times (26 h). In boiling benzene or toluene no 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**194**) was obtained, while chloro-benzene led to an incomplete reaction even after 2 days. The reaction was general and all the imidazoles **178-186** could be converted into their corresponding 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitriles **194**, **196-203** (Table 9).

Table 9. Thermolysis of (*Z*)-2-[4-(arylimino)-2-phenyl-4-1*H*-imidazol-5(4*H*)-ylidene]malononitriles **158** (0.05 mmol) in Ph_2O (1 mL) protected by a $CaCl_2$ drying tube to give 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitriles **159**



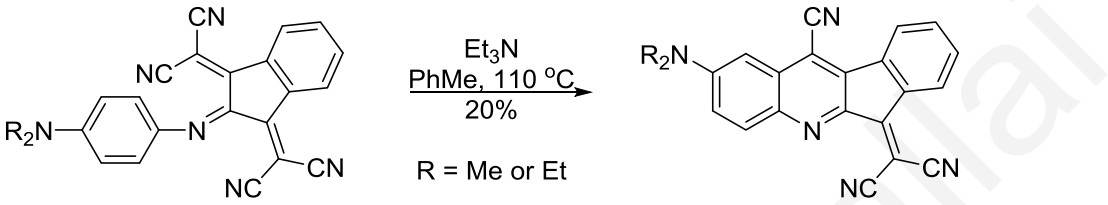
158 **159**

entry	R^1	R^2	temp. (^oC)	time (h)	yields **159** (%)
1	H	H	280	4	**194** (98)
2	H	H	260	6	**194** (99)
3	H	H	240	18	**194** (99.5)
4	H	H	215	26	**194** (99)
5	MeO	H	280	2	**196** (99)
6	Me	H	280	2	**197** (99)
7	F	H	280	6	**198** (99)
8	Cl	H	280	6	**199** (98)
9	Cl	Cl	280	6	**200** (84)[a]
10	Br	H	280	4	**202** (98)
11	I	H	280	4	**203** (98)
12	O_2N	H	280	6	[b]

[a] 7,8-Dichloro-2-phenyl-1*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**201**) was also isolated as a side product (12%). [b] A complex and unresolvable reaction mixture was observed.

Worthy of note was that the imidazoles **158** supporting electron donating substituents on the arylimino group (Table 9, entries 5 & 6) reacted faster than analogs supporting electron withdrawing groups (Table 9, entries 7 & 8). Furthermore, the thermolysis of the unsymmetrically substituted dichlorophenylimidazole **183** (Table 9, entry 9) gave as expected the two possible isomeric products: 6,7-dichloro-2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**200**) and 7,8-dichloro-2-phenyl-1*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**201**) in 84 and 12% yields, respectively where the product ratio presumably reflects the steric demands for the respective cyclizations. Disappointingly, thermolysis of the nitrophenyl analogue (Table 9, entry 12) led to a very complex reaction mixture (by TLC) which could not be resolved.

While there are many examples of the preparation of quinolines *via* electrocyclic ring closures followed by elimination of a leaving group to regain aromaticity,[328-334] there are very few examples which afford quinolines fused to five[335,336] and six membered rings,[337,338] and only one example involving an ylidenemalononitrile; cyclization of 2,2'-(2-{[4-(dialkylamino)phenyl]imino}-1*H*-indene-1,3(2*H*)-diylidene)dimalononitriles **204** affords 2-[2-(dialkylamino)-11-cyano-6*H*-indeno[2,1-*b*]quinolin-6-ylidene)malononitriles **205** in low yields (Scheme 59).[339]

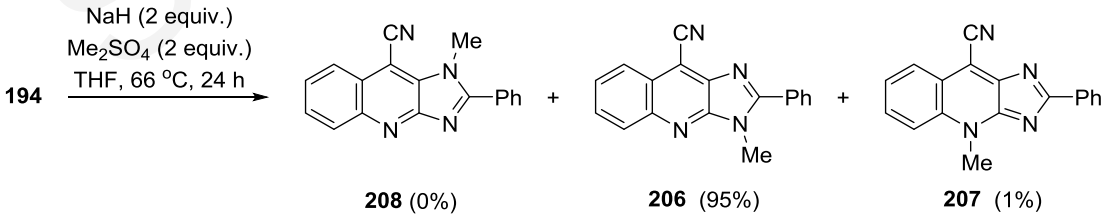


204 **205**

Scheme 59

5.7 Preparation of *N*-methylated 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitriles

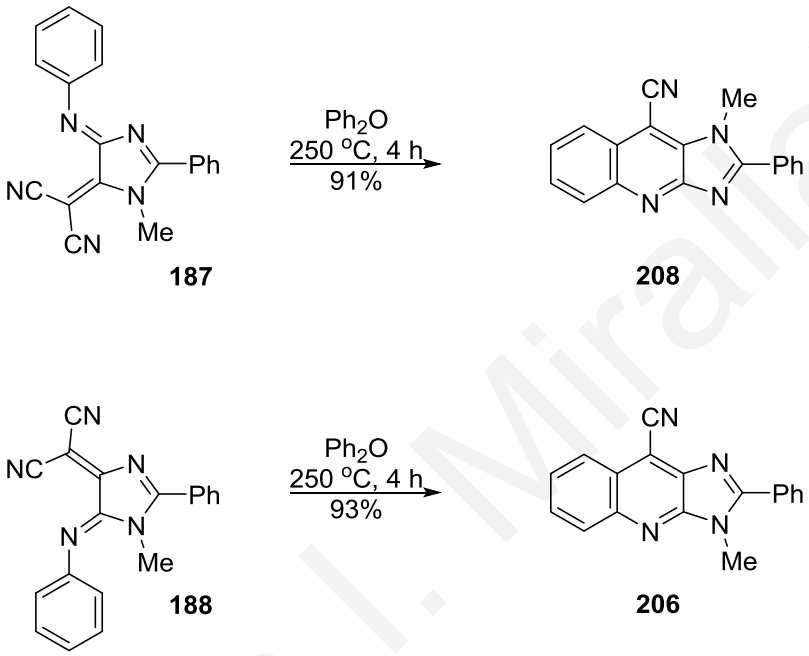
The regioselectivity of 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**194**) towards N-methylation was investigated. As such, methylation of 2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**194**) using NaH (2 equiv) and dimethyl sulfate (2 equiv) in dry THF at *ca.* 66 °C gave two products: 3-methyl-2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**206**) and 4-methyl-2-phenyl-4*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**207**) in 95 and 1% yields, respectively (Scheme 60). No trace of 1-methyl-2-phenyl-1*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**208**) was observed. The regioselectivity of the methylations was supported by 2D-NOESY ^{1}H NMR experiments.



208 (0%) **206** (95%) **207** (1%)

Scheme 60

Since both the methylated imidazoles (*Z*)-2-[1-methyl-2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**187**) and (Z)-2-[1-methyl-2-phenyl-5-(phenyl-imino)-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**188**) were in our possession these were also independently thermolyzed to give 1-methyl-2-phenyl-1*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**208**) and 3-methyl-2-phenyl-3*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**206**) in high yields, respectively (Scheme 61).



187 208

188 206

Scheme 61

5.8 Summary

The reaction of TCNE and *N'*-arylbenzamidines affords a densely functionalized adduct which on standing or gentle heating undergoes a 5-exo-dig cyclization to give the novel imidazoles **157**. These in turn in neat refluxing MeOH or in DCM with DBU as catalyst suffer Dimroth rearrangements to give imidazoles **158**. The latter compounds readily undergo thermal mediated electrocyclic ring closures to give 3*H*-imidazo[4,5-*b*]quinolines **159** in almost quantitatively yields. As such, the synthetic route outlined above affords a new 4-step but high yielding route to this useful ring system *via* readily available TCNE and *N'*-arylbenzamidines.

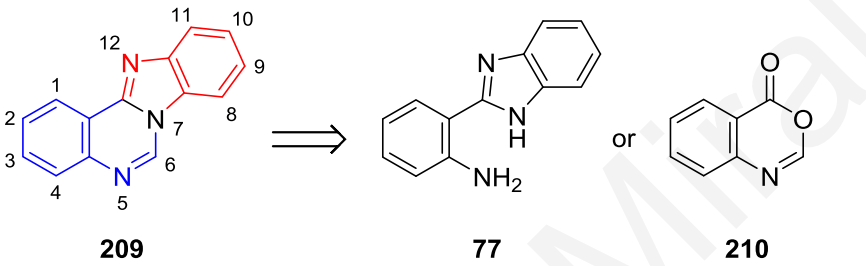
CHAPTER 6

The conversion of 4-anilinoquinazoline- and 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles into benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitriles *via* oxidative and non-oxidative C-N couplings

Sections

6.1 Introduction

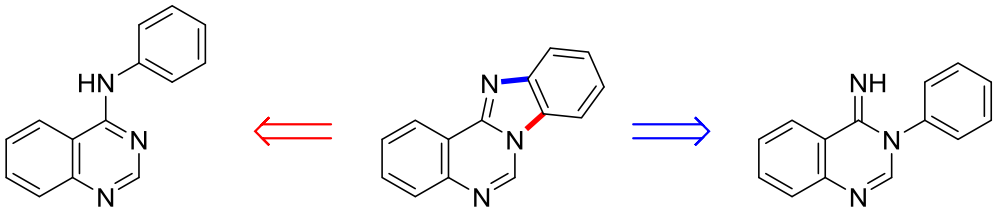
Benzo[4,5]imidazo[1,2-*c*]quinazoline (**209**) is a planar trinitrogen heteroacene that hosts both benzimidazole and quinazoline structures fused together *via* a shared bond (Scheme 62).[340] Not surprisingly, benzo[4,5]imidazo[1,2-*c*]quinazolines display a wide array of biological activities. Some act as DNA interchelators and show antitumor,[341-343] anticancer,[220,344] antiviral,[345,346] and antimicrobial[347-351] activities, while others act as anticonvulsant agents,[352] or as bronchodilators.[353,354] Metal chelates with ruthenium(II),[355] tin[356] and lead[356] have also been studied. Benzo[4,5]imidazo[1,2-*c*]quinazolines also have hole transporting properties.[357]



209 **77** **210**

Scheme 62

Most syntheses of benzo[4,5]imidazo[1,2-*c*]quinazolines focus on building the pyrimidine ring starting from 2-(2-aminophenyl)benzimidazoles **77**[340,220,346,352,358-365] or *via* structurally related precursors *e.g.*, 2-(2-nitrophenyl)benzimidazoles,[366,367] *N*-[2-(benzimidazol-2-yl)-phenyl]phosphanimines,[368,369] 2-(2-azidophenyl)benzimidazoles,[370] *N*-[2-(benzimidazol-2-yl)phenyl]methanimines,[349,350,371] and 2-(2-halophenyl)benzimidazoles.[372-374] A second major synthetic route of benzo[4,5]imidazo[1,2-*c*]quinazolines is *via* construction of the imidazole ring which has been limited to treatment of 4*H*-benzo[*d*][1,3]oxazin-4-ones **210** with benzene-1,2-diamines either directly[347,348,351,354,358,375-379] or *via* the isolable intermediate 3-(2-aminophenyl)-3*H*-quinazolin-4-ones,[354,380] or structurally related benzo-[1,3]thiazin-4-ones (Scheme 62).[381] Interestingly, a structural analysis of both 4-anilino-quinazoline (**211**) and 3-phenylquinazolin-4(3*H*)-imine (**212**), revealed that their structures are just one C-N bond short of the benzo[4,5]imidazo[1,2-*c*]quinazoline skeleton (Scheme 63).



211 **209** **212**

Scheme 63

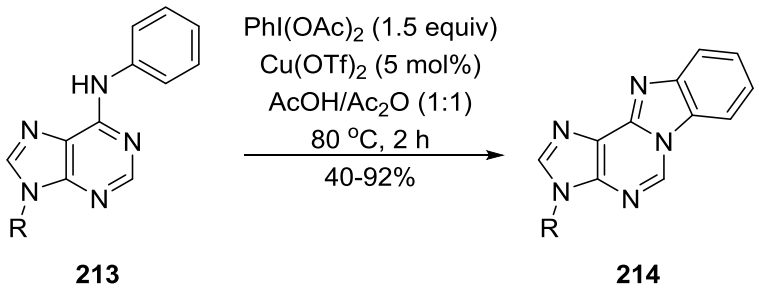
Our ongoing studies on the synthesis and chemistry of 2-amino-*N'*-arylbenzamidines[191] provided us with a small library of 4-anilinoquinazoline- and 3-aryl-4-imino-3,4-dihydro-quinazoline-2-carbonitriles.[271,382] In light of the limited number of routes to the benzo[4,5]-imidazo[1,2-*c*]quinazoline skeleton *via* construction of the imidazole ring we investigated both oxidative and non-oxidative methods for converting these readily available quinazoline-2-carbonitriles into benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitriles. The development of synthetic routes that hosted nitriles in the final products are worthwhile since these can readily be converted into a wide range of other functionalities.[221,222] Furthermore, the presence of a cyano group in this tetracycle reportedly improved the cytotoxicity in comparison to the parent compound.[220]

6.2. Oxidative and non-oxidative cyclization chemistry of 4-anilinoquinazoline-2-carbonitriles

The 4-anilinoquinazolines **211** host a *N*,*N'*-disubstituted benzamidine motif within their structures, cyclization of which affords the desired benzo[4,5]imidazo[1,2-*c*]quinazolines. The literature on the preparation of benzo- or hetareno-fused imidazoles from amidines *via* oxidative C-N coupling highlighted the use of electro-oxidation[383,384] and the use of a variety of oxidants including H_2O_2,[385] cerium ammonium nitrate (CAN),[383] NaOCl,[386] NCS,[387] MnO_2,[388] $Pb(OAc)_4$[383,389-391] and hypervalent iodine(III) reagents.[152,392] In our hands, cyclization efforts using either H_2O_2, CAN, NCS, MnO_2 or $Pb(OAc)_4$ failed but succeeded with hypervalent iodine(III) reagents.

$PhI(OAc)_2$ (PIDA or DAIB) and $PhI(OTf)_2$ (PIFA or BFIB) either alone in equimolar or greater quantities,[390,393-398] or catalytically in the presence of co-oxidants,[399,400] are typically used for such cyclizations. Variations where the hypervalent iodine(III) reagent is generated *in situ* have also been reported.[401,402]

The closest reported reaction to our targeted cyclization was the oxidative ring closure of the structurally related 6-anilinopurines **213** to give the benzo[4,5]imidazo[2,1-*i*]purines **214**, using PIDA (1.5 equiv), $Cu(OTf)_2$ (5 mol%) in a solvent mixture of $AcOH/Ac_2O$ (1:1) heated at reflux (Scheme 64).[400]



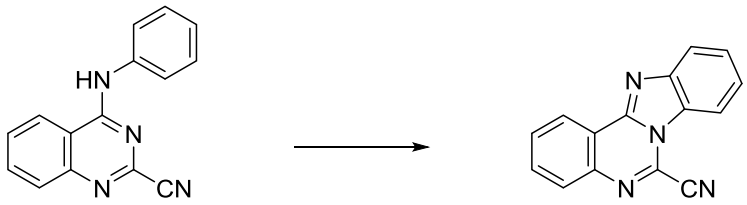
213 **214**

Scheme 64[400]

In our hands these conditions worked well for converting 4-anilinoquinazoline-2-carbonitrile (**79**) into benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile (**78**) which was isolated in 81% yield together with a small quantity of an unidentified side product (Table 10, entry 1). Side products have also been observed by Chu *et al.*,[394] who noted that their formation could be avoided by using PIFA in place of PIDA.

As such, by replacing PIDA with PIFA and using neat trifluoroacetic acid (TFA) as solvent heated at *ca.* 80 °C for 30 min the desired product **78** was obtained exclusively in 86% yield (Table 11, entry 4). With this result in hand, and in light of the excess PIFA being used, we then examined if the oxidative cyclization would work in the absence of the $Cu(OTf)_2$ cooxidant and gratifyingly, the reaction worked equally well to give after 30 min at 80 °C the target in 85% yield (Table 10, entry 5). Surprisingly, the reaction also worked when performed with PIFA (1.1 equiv) in neat TFA without heating, affording after just 30 min the desired product in 92% yield (Table 10, entry 7 and Table 2, entry 1). Furthermore, repeating the reaction using PIDA (1.1 equiv) or PIFA (1.1 equiv) in neat AcOH failed to consume the starting material (Table 10, entries 9 & 10) and supported the need for the more acidic solvent [$pK_a^{(TFA)}$ 0.23 $pK_a^{(AcOH)}$ 4.76], whereas the use of PIDA (1.1 equiv) in neat TFA at 20 °C led to complete consumption of the starting material in 2 h to give the desired product in only 75% (Table 10, entry 11). If the TFA solvent was replaced by DCM or MeCN, which are also good solvents for these oxidative cyclizations,[393-397] then the reactions required heating and took longer to come to completion affording the desired product in only moderate (40-52%) yields (Table 10, entries 12 & 13).

Table 10. Optimisation of the oxidative cyclization of 4-anilinoquinazoline-2-carbonitrile (**79**) (0.20 mmol) to give benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile (**78**)



79 **78**

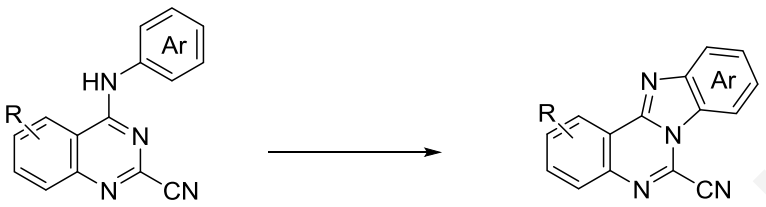
entry	oxidant (equiv)	additive (mol%)	solvent (mL)	temp. (^{o}C)	time (h)	yields (%)
1	$PhI(OAc)_2$ (1.5)	$Cu(OTf)_2$ (5)	$AcOH/Ac_2O$ (0.25:0.25)	80	2	81[a,b]
2	$PhI(OAc)_2$ (1.5)	$Cu(OTf)_2$ (5)	PhMe (0.5)	80	2	-[c]
3	$PhI(OTf)_2$ (1.5)	$Cu(OTf)_2$ (5)	$AcOH/Ac_2O$ (0.25:0.25)	80	1.5	73[b]
4	$PhI(OTf)_2$ (1.5)	$Cu(OTf)_2$ (5)	TFA (0.5)	80	0.5	90
5	$PhI(OTf)_2$ (1.5)	-	TFA (0.5)	80	0.5	85
6	$PhI(OTf)_2$ (1.1)	-	TFA (0.5)	80	0.5	82
7	$PhI(OTf)_2$ (1.1)	-	TFA (0.5)	20	0.5	92
8	$PhI(OTf)_2$ (0.05)	-	TFA (0.5)	20	17	nr[d]
9	$PhI(OTf)_2$ (1.1)	-	AcOH (0.5)	20	20	ir[e,b]
10	$PhI(OAc)_2$ (1.1)	-	AcOH (0.5)	20	22	ir[e,b]
11	$PhI(OAc)_2$ (1.1)	-	TFA (0.5)	20	2	75[b]
12	$PhI(OTf)_2$ (1.5)	-	DCM (0.5)	40	14	40[f]
13	$PhI(OTf)_2$ (1.5)	-	MeCN (0.5)	20	14	52[g]

[a] Literature conditions (ref. 400). [b] A trace of an unidentified side product was isolated. [c] Complex reaction mixture (by TLC). [d] nr = no reaction, recovered starting material. [e] ir = incomplete reaction, mainly starting material. [f] 15% recovered starting material. [g] 5% recovered starting material.

Having partially optimized this oxidative ring closure the mildest conditions, PIFA (1.1 equiv) in neat TFA at room temperature, were then applied to a range of 4-anilino-quinazoline-2-carbonitriles **76**, (Table 11). These metal free conditions worked well for the parent, the 4-Me and the 4-MeO substituted analogues (Table 11, entries 1-3), however, the reactions with 4-anilinoquinazolines that hosted inductively electron withdrawing halogen substituents on the aniline moiety (Table 11, entries 6-17) required prolonged reaction times. As such, we re-optimized the reaction conditions for 4-(4-fluoroanilino)-quinazoline-2-carbonitrile (**115**) (Table 11, entries 6-9): Increasing the equivalents of PIFA (from 1.1 to 2 equiv) or raising the reaction temperatures (from 20 to 80 ^{o}C) did not significantly improve the reaction (data not shown). Fortunately, a shorter reaction time (1.5 h) was achieved by re-introducing $Cu(OTf)_2$ (5 mol%), increasing the amount of PIFA (1.5 equiv) and raising the reaction temperature to *ca.* 80 ^{o}C (Table 11, entry 9). Worthy of note was that with the reagents in this stoichiometry the reaction worked well even at *ca.*

20 ^{o}C to give the product **223** in 85% yield although the reaction required more time (6 h) to consume the starting material (Table 11, entry 8). These Cu catalyzed conditions worked equally well for the remaining halogen bearing analogues (Table 11, entries 11,13,15 and 17).

Table 11. Reactions of 4-anilinoquinazoline-2-carbonitriles **79**, **113-118**, **216-218** (0.20 mmol) with PIFA (1.1-1.5 equiv) and $Cu(OTf)_2$ (0-5 mol%) in neat TFA to give benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitriles **78**, **219-229**

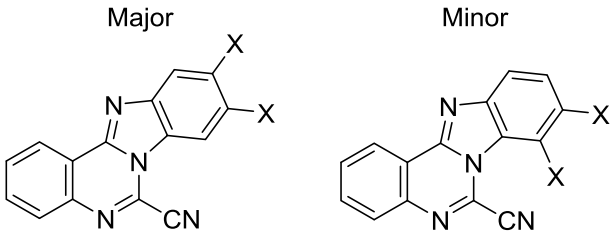


76 **215**

entry[a]	R	Ar	PIFA (equiv)	$Cu(OTf)_2$ (mol%)	temp. (^{o}C)	time (h)	yields **215** (%)
1	H	H	1.1	-	20	0.5	**78** (92)
2	H	9-Me	1.1	-	20	1	**219** (80)
3	H	9-MeO	1.1	-	20	1	**220** (82)
4	H	9,10-$(MeO)_2$	1.1	-	20	26	**221/222** (85)[b]
5	H	9,10-$(MeO)_2$	1.5	5	80	3	**221/222** (82)[b]
6	H	9-F	1.1	-	20	7 d	**223** (81)[c]
7	H	9-F	1.1	5	80	25	**223** (86)
8	H	9-F	1.5	5	20	6	**223** (85)
9	H	9-F	1.5	5	80	1.50	**223** (89)
10	H	9-Cl	1.1	-	20	32	**224** (86)
11	H	9-Cl	1.5	5	80	4	**224** (88)
12	H	9,10-$(Cl)_2$	1.1	-	20	4 d	**225/226** (41)[d,e]
13	H	9,10-$(Cl)_2$	1.5	5	80	2	**225/226** (77)[d]
14	H	11-Br	1.1	-	20	7 d	**227** (77)[f]
15	H	11-Br	1.5	5	80	0.75	**227** (82)
16	H	9-Br	1.1	-	20	32	**228** (87)
17	H	9-Br	1.5	5	80	4	**228** (87)
18	2,3-$(MeO)_2$	H	1.1	-	20	16	**229** (83)
19	2,3-$(MeO)_2$	H	1.5	5	80	8	**229** (85)

[a] Substituent numbering based on major product. [b] Two inseparable products **221**/**222** (2.6:1) by ^{1}H NMR of crude. [c] Incomplete reaction: 4% of starting material recovered (note at 24 h there was 53% of product). [d] Two inseparable products **225**/**226** (2.6:1) by ^{1}H NMR of crude. [e] Incomplete reaction: 35% of starting material recovered. [f] Incomplete reaction: 2% of starting material recovered (note at 24 h there was 45% of product).

Not surprisingly, the reactions of 4-anilinoquinazolines that hosted unsymmetrically substituted anilines **118** [Ar= 3,4-$(MeO)_2$] and **216** [Ar = 3,4-$(Cl)_2$] gave mixtures of two cyclization products a major and minor the ratio of *ca.* 2.6:1, which tentatively reflected steric phenomena.

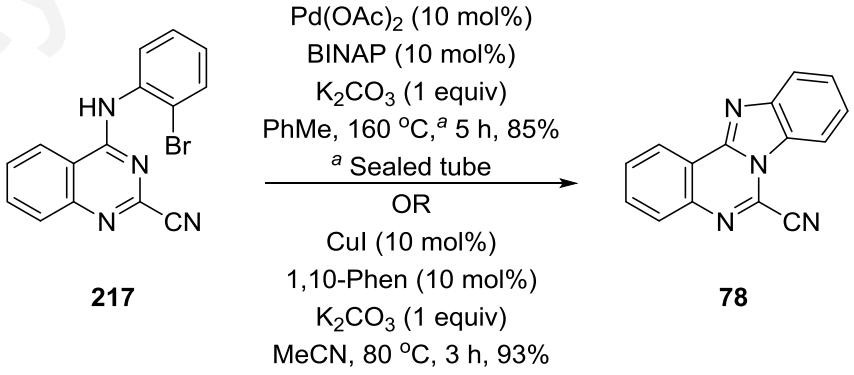


221 (X = MeO)
225 (X = Cl)

222 (X = MeO)
226 (X = Cl)

With 4-(2-bromoanilino)quinazoline-2-carbonitrile (**217**) in hand, we considered a regio-controlled transition metal-catalyzed non-oxidative coupling. A number of non oxidative cyclization protocols are known for the transformation of *N*-alkyl or aryl-substituted *N'*-(2-halophenyl)benzamidines to give 1-alkyl- or 1-aryl-substituted 2-aryl-1*H*-benzimidazoles; some involve transition metal catalysis (*e.g.*, Pd,[403-407] Cu,[406,409-415] or Co[416]), while others invoke base mediated aryne intermediates[410,417-419] or simply intramolecular nucleophilic aromatic substitution.[314,410,420]

After screening several Pd catalysts [$Pd(OAc)_2$, $Pd(dppf)Cl_2.CH_2Cl_2$, $Pd(MeCN)_2$, $Pd(PhCN)_2$, $PdCl_2(Ph_3P)_2$ and $Pd(Ar_3P)_3$ where Ar = 3,5-$(F_3C)_2C_6H_3$ (aka Superstable Pd(0) Catalyst®)], ligands [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,10-phenanthroline (1,10-Phen), 1,1'-bis(diphenylphosphino)ferrocene (DPPF) and *N*,*N'*-dimethylethylenediamine (DMEDA)], bases [$KHCO_3$, K_3PO_4, M_2CO_3 (M = Na, K, Cs), KOH and DBU] and solvents (PhMe, MeCN, 1,4-dioxane, THF, DMSO, DMF, DMA and EtOH) we identified the following conditions: $Pd(OAc)_2$ (10 mol%), BINAP (10 mol%), K_2CO_3 (1 equiv), PhMe at *ca.* 160 °C (sealed tube – Wood's metal bath temperature) that after 5 h completely consumed the starting material and gave the target **78** in a 85% yield (Scheme 65).

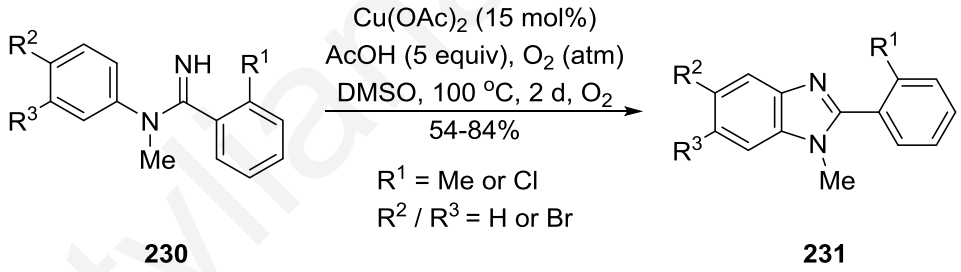


Scheme 65

Worthy of note was the need for high reaction temperatures (*ca.* 160 ^{o}C): lower temperatures (*ca.* 110 ^{o}C) led to long reaction times (> 2 d) and incomplete consumption of the starting material (up to 12% recovered). Attempts to lower the reaction temperatures or reduce the Pd catalyst loading were unsuccessful, however, the alternative use of CuI (10 mol%) with 1,10-Phen (10 mol%) as ligand using K_2CO_3 (1 equiv) as base in MeCN heated at reflux enabled the cyclization at significantly lower reaction temperature (*ca.* 80 ^{o}C) in 3 h to give the desired tetracycle **78** in an improved 93% yield (Scheme 65). The use of less CuI (5 mol%), alternative ligands (BINAP or DMEDA) failed to drive the reaction to completion while the use of "ligand free" reaction conditions (CuI, DBU and DMSO)[413] led to no reaction. Interestingly, most reported reactions of this type invoked the need for 2 equiv of base, however, this led to a lower yield (80%).

6.3. Oxidative and non-oxidative cyclization chemistry of 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles 103

Unlike the above *N*,*N'*-disubstituted benzamidines and to the best of our knowledge, there is only one report on the oxidative coupling of *N*,*N*-disubstituted benzamidines: the O_2/$Cu(OAc)_2$ mediated oxidative cyclization of three *N*-aryl-*N*-methylbenzamidines **230** to 1-methyl-2-arylbenzimidazoles **231** in 54-84% yields (Scheme 66)[421] and there are no reports of non-oxidative couplings.

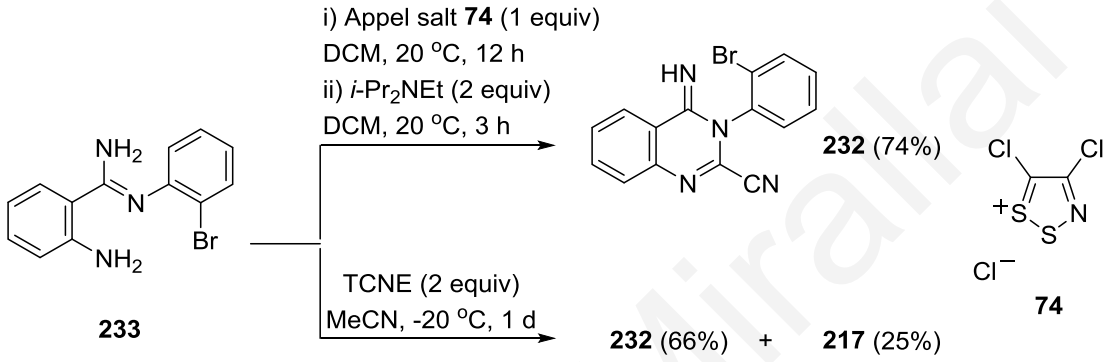


230 **231**

Scheme 66[421]

Attempted oxidative couplings of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) using either Buchwald's conditions (Scheme 65), alternative oxidants such as H_2O_2, NCS, MnO_2, $Pb(OAc)_4$, DDQ, benzoquinone and CAN, or the $Cu(OTf)_2$/PIFA conditions described above (Table 11) failed to give any reaction or led to complex reaction mixtures (by TLC).

As such, we then investigated the alternative non-oxidative coupling. The desired 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**232**) was prepared *via* two routes: Firstly, by reaction of 2-amino-*N'*-(2-bromophenyl)benzamidine (**233**) with 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (Conditions A)[271] which gave the product **232** in 74% yield and secondly by reaction of 2-amino-*N'*-(2-bromophenyl)benzamidine (**233**) with TCNE at *ca.* -20 ^{o}C (Conditions B)[382] which gave the product **232** in 66% yield together with the isomeric 4-(2-bromoanilino)quinazoline **217** in 25% yield (Scheme 67).

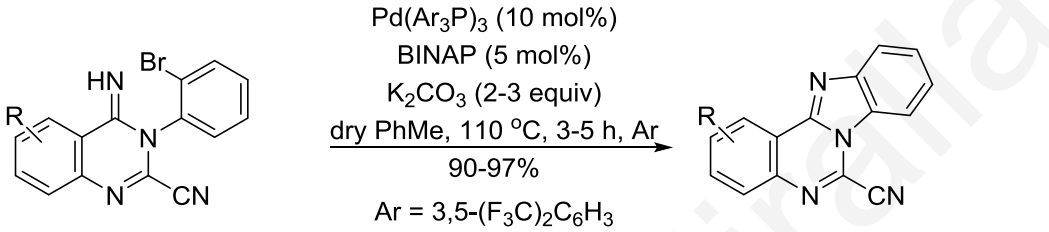


Scheme 67[382]

Initially, Cu mediated non-oxidative C-N coupling reactions of 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**232**) were attempted, however, our best conditions for the 4-anilino analogue **79** *ie* CuI (10 mol%) 1,10-Phen (10 mol%), K_2CO_3 (1 equiv) in MeCN heated at reflux failed to give the desired cyclization. In light of this we switched back to the Pd catalyzed conditions and identified the following semi-optimized conditions: $Pd(OAc)_2$ (10 mol%), BINAP (10 mol%), Cs_2CO_3 (1 equiv) in dry PhMe heated at reflux for 17 h under an argon atmosphere which led to complete consumption of the starting material and gave the target tetracycle **78** in 78% yield. By switching the Pd catalyst to Superstable Pd(0) Catalyst® (10 mol%) and using K_2CO_3 (2 equiv) as base we were able to lower the quantity of BINAP (5 mol%) and shorten the reaction time to only 5 h improving the product yield to a satisfactory 93%. Interestingly, traces of moisture or air led to significantly reduced product yields (62-65%) and longer reaction times, while the reaction with Superstable Pd(0) Catalyst® also worked in the absence of BINAP to give benzimidazo[1,2-*c*]quinazoline-2-carbonitrile (**78**) in near quantitative yield (98%) but this reaction needed 3 days to come to completion. These conditions were also suitable for preparing the 2,3-dimethoxy-substitiuted benzimidazo[1,2-*c*]quinazoline **229** (Table 12, entry 5) but were unsuitable for preparing the 2-Cl, 2-Br, 3-Cl, 1-Me and 3-MeO

analogues: after 24 h the reactions failed to come to completion (data not shown). Attempts to run these reactions at higher temperatures (140-160 ^{o}C) using either microwave irradiation or by immersing the sealed reactions mixtures into preheated Wood's metal baths led to complex reaction mixtures and low to moderate yields of the desired product (data not shown). Fortunately, in these cases, increasing the quantity of K_2CO_3 to 3 equiv led to total consumption of the starting material within 6 h (Table 12).

Table 12. Non-oxidative cyclization of 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitriles **234-239** (0.2 mmol) to give benzimidazo[1,2-*c*]quinazoline-2-carbonitriles **78**, **229, 240-244**



232, **234-238** **78, 229, 240-244**

entry	R[a]	K_2CO_3 (equiv)	time (h)	yields (%)
1	H	2	5	**78** (93)
2	H	3	5	**78** (95)
3	1-Me	3	3	**240** (97)
4	3-MeO	3	6	**241** (91)
5	2,3-$(MeO)_2$	2	5	**229** (94)
6	2,3-$(MeO)_2$	3	5	**229** (96)
7	2-Cl	3	6	**242** (92)
8	3-Cl	3	5	**243** (94)
9	2-Br	3	6	**244** (90)

[a] Substituent numbering based on product.

Interestingly, the more sterically hindered 1-Me analogue **240** reacted the fastest (3 h) (Table 12, entry 3), suggesting that steric compression at the reaction site may promote the reaction. Furthermore, repeating the reaction of the unsubstituted analogue **78** with 3 equiv of K_2CO_3 did not shorten the reaction time and gave the cyclized product in an identical yield compared to the analogous reaction using 2 equiv of K_2CO_3. With these improved conditions we attempted to reoptimize the reactions by switching back to a stronger base Cs_2CO_3 (2 and 3 equiv) or to reduce the Pd catalyst to 5 mol%, however, in both cases the reactions failed to come to completion. Switching the Pd catalyst also led to a slower consumption of the starting materials. Tentatively, we believe that increasing the equivalents of K_2CO_3, which was heterogeneous in the reaction mixture, from 2 to 3 assists

the reaction simply by increasing the surface area. We note that our inorganic bases are typically powdered and vacuum dried at 80-90 ^{o}C before use to improve the available surface area.[422] This may also explain the need for dry PhMe since traces of moisture in the solvent can affect the dispersion of the anhydrous base. Attempts to overcome this by using a biphasic reaction mixture or by using phase transfer catalysts (18-crown-6, $BnEt_3NCl$),[4224] failed.

6.4 Summary

A $Cu(OTf)_2$ catalyzed PIFA mediated oxidative cyclization of 4-anilinoquinazoline-2-carbonitriles **76** affords thirteen substituted benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitriles **215** hosting electron releasing Me and MeO substituents or electron withdrawing halogen substituents in good to excellent yields. Interestingly, in at least two cases (the unsubstituted and the dimethoxy substituted analogues) the reactions work equally well in the absence of the copper catalyst. Where the anilino moiety is unsymmetrical the oxidative cyclization suffers from regioselectivity, however, this can be overcome by switching to a non-oxidative strategy: $Pd(OAc)_2$ and CuI catalyzed protocols were developed that successfully cyclized 4-(2-bromoanilino)quinazoline-2-carbonitrile (**217**) to benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile (**78**) in high yields. An alternative Pd(0) catalyzed non-oxidative C-N coupling was also developed that enabled the cyclization of seven 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitriles **232**, **234-238** again in high yields (90-97%). These methods expand the synthetic routes of benzo[4,5]-imidazo[1,2-*c*]quinazolines **215** and potentially can find application in the synthesis of structurally related heterocycles.

CHAPTER 7

Experimental Section

Sections

7.1 General procedures and methods

Anhydrous Na_2SO_4 was used for drying organic extracts and all volatiles were removed under reduced pressure. The inorganic bases used in heterogeneous reaction mixtures were typically powdered and vacuum dried at 80-90 ^oC prior to use to improve the available surface area. [422] All chemicals were commercially available except those whose synthesis is described. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography[423.] was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm). A CEM Discover Microwave Reactor was used for microwave experiments. Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler-Hotstage Microscope apparatus. Decomposition points (decomp.) were determined using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere, using heating rates of 5 $^oC/min^{-1}$ (DSC mp listed by *onset* and *peak max* values). Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin-Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation "inf". IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with a Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz, respectively) or on a 500 machine (at 500 and 125 MHz, respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. DEPT135 or APT NMR studies identified quaternary and tertiary carbons, which are indicated by (s), (d) and (q) notations, respectively. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe. MALDI-TOF mass spectra were recorded on a Bruker Autoflex III Smartbeam instrument. 4,5-Dichloro-1,2,3-dithiazolium chloride (**74**)[200,201] and tetracyanoethene (TCNE)[198] were prepared according to literature procedures.

7.2 Compounds related to Chapter 2

*7.2.1 (Z)-N'-Phenylbenzamidine (**50**) (typical procedure).* To stirred benzonitrile (**48**) (550 μL, 5.36 mmol) at *ca.* 20 ^{o}C was added portionwise powdered anhydrous $AlCl_3$ (706 mg, 5.36 mmol). The reaction mixture was then heated (*ca.* 100 ^{o}C) until a homogeneous melt formed. To this was added aniline (489 μL, 5.36 mmol) and the mixture was heated for 4 h and then allowed to cool to *ca.* 20 ^{o}C. The resultant solid mass was then crushed and slurried in 12.5% NaOH (40 mL). The resulting mixture was extracted (DCM), washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles followed by chromatography of the residue gave 2,4,6-triphenyl-1,3,5-triazine (**52**) (16.4 mg, 3%) as light yellow needles, mp 231-232 ^{o}C (lit.,[424] 231-232 ^{o}C) (PhH); R_f 0.36 (*n*-hexane/DCM, 90:10); (Found: C, 81.42; H, 4.77; N, 13.61. $C_{21}H_{15}N_3$ requires C, 81.53; H, 4.89; N, 13.58%); λ_{max} (DCM)/nm 271 (log ε 1.84); ν_{max}/cm^{-1} 1589m, 1517s, 1447m, 1368s, 1300w, 1175w, 1146w, 1069w, 1028m, 841m, 743s; δ_H(300 MHz; $CDCl_3$) 8.79 (6H, d, *J* 7.5, Ar *H*), 7.63-7.56 (9H, m, Ar *H*), 5.30 (2H, s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 171.6 (s), 136.2 (s), 132.5 (d), 129.0 (d), 128.6 (d); *m/z* (EI) 309 (M$^+$, 37%), 103 (100), 76 (19), 44 (59). Further elution (*t*-BuOMe) gave *the title compound* **50** (871 mg, 83%) as colorless plates, mp 115.5-116 ^{o}C (lit.,[90] 116 ^{o}C) (PhH); R_f 0.71 (*t*-BuOMe); λ_{max}(DCM)/nm 269 (log ε 3.12); ν_{max}/cm^{-1} 3468w and 3350w (NH_2), 3039w (aryl C-H), 1616s, 1589m, 1570s, 1496m, 1489m, 1448m, 1379m, 1296w, 1238m, 1170m, 1076m, 1024m, 975w, 948w, 929w, 914w, 837m, 777m, 750m; δ_H(300 MHz; $CDCl_3$) 7.87 (2H, d, *J* 6.6, Ar *H*), 7.51-7.41 (3H, m, Ar *H*), 7.38-7.33 (2H, m, Ar *H*), 7.06 (1H, dd, *J* 7.4, 7.4, Ar *H*), 6.99 (2H, d, *J* 7.2, Ar *H*), 4.87 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 155.0 (s), 149.7 (s), 135.8 (s), 130.5 (d), 129.5 (d), 128.5 (d), 126.8 (d), 122.9 (d), 121.6 (d); *m/z* (EI) 196 (M$^+$, 100%), 193 (56), 180 (35), 178 (13), 152 (4), 119 (9), 104 (38), 93 (76), 77 (98), 66 (10), 51 (39).

*7.2.2 (Z)-N'-(4-Methoxyphenyl)benzamidine (**47**).* Similar treatment of benzonitrile (**48**) (417 μL, 4.06 mmol) with $AlCl_3$ (536 mg, 4.06 mmol) and *p*-anisidine (500 mg, 4.06 mmol) heated at *ca.* 100 ^{o}C for 4 h gave the *title compound* **47** (853 mg, 93%) as colorless plates, mp 114 ^{o}C (lit.,[176] 115.5 ^{o}C) (*c*-hexane/EtOH, 95:05); R_f 0.36 (*t*-BuOMe); λ_{max}(DCM)/nm 276 (log ε 3.92); ν_{max}/cm^{-1} 3439m, and 3294w (NH_2), 3125w, 3003w (aryl C-H), 2833w, 1638m, 1601m, 1566m, 1502s, 1466m, 1439m, 1381m, 1288m, 1242m, 1223m, 1182m, 1169w, 1128w, 1103m, 1088w, 1036m, 1001w, 978w, 930w, 862m, 847w, 829w, 814w, 789m, 754m, 718m; δ_H(300 MHz; $CDCl_3$) 7.87 (2H, d, *J* 5.4, Ar *H*),

7.49-7.41 (3H, m, Ar *H*), 6.92 (4H, br s, Ar *H*), 4.86 (2H, br s, NH_2), 3.80 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 155.5 (s), 155.0 (s), 142.6 (s), 135.9 (s), 130.4 (d), 128.4 (d), 126.7 (d), 122.4 (d), 114.8 (d), 55.4 (q, O*C*H$_3$); *m/z* (EI) 226 (M^+, 91%), 211 (26), 182 (2), 167 (4), 123 (40), 108 (98), 104 (100), 92 (8), 80 (15), 77 (38), 64 (11), 51 (13).

*7.2.3 (Z)-N'-(4-Nitrophenyl)benzamidine (**56**).* Similar treatment of benzonitrile (**48**) (371 μL, 3.62 mmol) with $AlCl_3$ (477 mg, 3.62 mmol) and 4-nitroaniline (500 mg, 3.62 mmol) heated at *ca.* 100 ^oC for 8 h gave the *title compound* **56** (180 mg, 21%) as yellow needles, mp 164.5-165 ^oC (lit.,[425] 167-168 ^oC) (PhH); (Found: C, 64.82; H, 4.51; N, 17.38. $C_{13}H_{11}N_3O_2$ requires C, 64.72; H, 4.60; N, 17.42%); R_f 0.74 (*t*-BuOMe); λ_{max}(DCM)/nm 334 (log ε 5.36); ν_{max}/cm^{-1} 3477m and 3363m (NH_2), 1643m, 1607m, 1574m, 1491m, 1447w, 1373m, 1335s, 1317m, 1301m, 1258m, 1173m, 1109m, 1078w, 1059w, 1030w, 1001w, 926w, 870m, 858m, 808w, 791m, 783m, 748m; δ_H(300 MHz; $CDCl_3$) 8.20 (2H, d, *J* 8.4, Ar *H*), 7.84 (2H, br s, Ar *H*), 7.54-7.43 (3H, m, Ar *H*), 7.06 (2H, d, *J* 7.8, Ar *H*), 4.98 (2H, br s, NH_2); δ_C(75 MHz; $CDCl_3$) 156.8 (s), 154.8 (s), 143.2 (s), 134.7 (s), 131.2 (d), 128.7 (d), 126.8 (d), 125.5 (d), 122.1 (d); *m/z* (EI) 241 (M^++1, 100%), 240 (53), 225 (10), 194 (20), 179 (18), 167 (4), 151 (5), 138 (14), 118 (6), 108 (27), 104 (100), 92 (13), 76 (45), 65 (22), 50 (19).

*7.2.4 (Z)-N'-(4-Methylphenyl)benzamidine (**57**).* Similar treatment of benzonitrile (**48**) (479 μL, 4.66 mmol) with $AlCl_3$ (615 mg, 4.66 mmol) and *p*-toluidine (500 mg, 4.66 mmol) heated at *ca.* 100 ^oC for 6 h gave the *title compound* **57** (906 mg, 93%) as colorless needles, mp 102-103 ^oC (lit.,[426] 103-105 ^oC) (*c*-hexane); R_f 0.86 (*t*-BuOMe); λ_{max}(DCM)/nm 278 (log ε 3.92); ν_{max}/cm^{-1} 3449w (NH_2), 3292w, 3123w, 3055w, 2918w, 2860w, 1633s, 1601m, 1568m, 1504m, 1447w, 1383m, 1234m, 1105w, 1024w, 926w, 866m, 793m, 777m, 758w, 714m; δ_H(300 MHz; $CDCl_3$) 7.83 (2H, d, *J* 6.6, Ar *H*), 7.51-7.40 (3H, m, Ar *H*), 7.15 (2H, d, *J* 8.1, Ar *H*), 6.89 (2H, d, *J* 8.1, Ar *H*), 4.81 (2H, br s, NH_2), 2.33 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 155.1 (s), 146.7 (s), 135.8 (s), 132.2 (s), 130.4 (d), 130.0 (d), 128.4 (d), 126.7 (d), 121.4 (d), 20.8 (q, *C*H$_3$); *m/z* (EI) 211 (M^++1, 13%), 210 (M^+, 85), 194 (24), 165 (3), 133 (5), 107 (100), 103 (66), 91 (43), 77 (38), 65 (25), 51 (28).

*7.2.5 (Z)-N'-(4-Fluorophenyl)benzamidine (**58**).* Similar treatment of benzonitrile (**48**) (462 μL, 4.50 mmol) with $AlCl_3$ (593 mg, 4.50 mmol) and 4-fluoroaniline (432 μL, 4.50 mmol) heated at *ca.* 100 ^oC for 6 h gave the *title compound* **58** (794 mg, 82%) as colorless

needles, mp 124.5-125 °C (lit.,[99] 126-128 °C) (*c*-hexane/EtOH, 95:05); R_f 0.57 (*t*-BuOMe); λ_{max}(DCM)/nm 278 (log ε 3.83); ν_{max}/cm^{-1} 3470w and 3344w (NH_2), 3202w (aryl C-H), 1614s, 1570m, 1499s, 1473w, 1445w, 1410w, 1379m, 1238w, 1213s, 1092w, 1076w, 1028w, 1011w, 979w, 928w, 862w, 851w, 802w, 779m, 762s, 706s; δ_H(300 MHz; $CDCl_3$) 7.84 (2H, d, *J* 6.6, Ar *H*), 7.48-7.40 (3H, m, Ar *H*), 7.07-7.01 (2H, m, Ar *H*), 6.94-6.89 (2H, m, Ar *H*), 4.88 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 159.0 (d, $^1J_{CF}$ 240.8, *C*F), 155.2 (s), 145.6 (s), 135.6 (d), 130.6 (d), 128.5 (d), 126.7 (d), 122.7 (d, $^3J_{CF}$ 7.6, *C*H), 116.1 (d, $^2J_{CF}$ 22.7, *C*H); *m/z* (EI) 214 (M^+, 55%), 198 (21), 169 (93), 156 (78), 147 (51), 129 (26), 119 (31), 111 (77), 104 (40), 95 (41), 77 (40), 69 (100), 57 (70), 51 (28).

*7.2.6 (Z)-N'-(4-Chlorophenyl)benzamidine (**59**).* Similar treatment of benzonitrile (**48**) (406 μL, 3.92 mmol) with $AlCl_3$ (517 mg, 3.92 mmol) and 4-chloroaniline (500 mg, 3.92 mmol) heated at *ca.* 100 °C for 6 h gave the *title compound* **59** (807 mg, 89%) as colorless needles, mp 116.5 °C (lit.,[176] 115.5 °C) (*c*-hexane/EtOH, 95:05); R_f 0.86 (*t*-BuOMe); λ_{max}(DCM)/nm 241 (log ε 4.34), 284 (3.94); ν_{max}/cm^{-1} 3470w and 3346w (NH_2), 1612s, 1568s, 1485m, 1447w, 1404w, 1379m, 1238w, 1171w, 1097m, 1011m, 858m, 779m, 723w, 708s; δ_H(300 MHz; $CDCl_3$) 7.81 (2H, d, *J* 6.9, Ar *H*), 7.51-7.40 (3H, m, Ar *H*), 7.30 (2H, d, *J* 8.7, Ar *H*), 6.90 (2H, d, *J* 8.7, Ar C*H*), 4.79 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 155.4 (s), 148.0 (s), 135.3 (s), 130.7 (d), 129.5 (d), 128.6 (d), 128.1 (s), 126.8 (s), 123.0 (d); *m/z* (EI) 232 (M^++2, 28%), 230 (M^+, 85), 216 (7), 214 (31), 169 (14), 149 (7), 147 (9), 129 (27), 127 (61), 113 (11), 111 (29), 104 (68), 97 (15), 77 (33), 69 (11), 51 (13).

*7.2.7 (Z)-N'-(4-Bromophenyl)benzamidine (**60**).* Similar treatment of benzonitrile (**48**) (298 μL, 2.91 mmol) with $AlCl_3$ (386 mg, 2.91 mmol) and 4-bromoaniline (500 mg, 2.91 mmol) heated at *ca.* 100 °C for 6 h gave the *title compound* **60** (624.5 mg, 78%) as colorless needles, mp 122-123 °C (lit.,[427] 124 °C) (*c*-hexane/EtOH, 95:05); R_f 0.71 (*t*-BuOMe); λ_{max}(DCM)/nm 246 (log ε 4.38); ν_{max}/cm^{-1} 3470w and 3345w (NH_2), 1614s, 1568m, 1497w, 1481m, 1447w, 1400w, 1379m, 1298w, 1238m, 1172w, 1099w, 1072m, 1007m, 858m, 779m, 719w, 706s; δ_H(300 MHz; $CDCl_3$) 7.81 (2H, d, *J* 6.9, Ar *H*), 7.51-7.40 (5H, m, Ar *H*), 6.86 (2H, d, *J* 8.7, Ar *H*), 4.72 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 155.3 (s), 148.5 (s), 135.3 (s), 132.5 (d), 130.8 (d), 128.6 (d), 126.8 (d), 123.5 (d), 115.8 (s); *m/z* (EI) 276 (M^++2, 65%), 274 (M^+, 73), 260 (15), 258 (19), 194 (7), 173 (50), 171 (53), 157 (15), 155 (17), 104 (100), 97 (28), 92 (15), 84 (11), 77 (58), 65 (11), 51 (28).

*7.2.8 (Z)-N'-(4-Iodophenyl)benzamidine (**61**).* Similar treatment of benzonitrile (**48**) (468 μL, 4.56 mmol) with $AlCl_3$ (301 mg, 2.28 mmol) and 4-iodoaniline (500 mg, 2.28 mmol) heated at *ca.* 100 ^oC for 6 h gave the *title compound* **61** (622.5 mg, 85%) as colorless needles, mp 137 ^oC (lit.,[427] 139 ^oC) (*c*-hexane/EtOH, 95:05); R_f 0.86 (*t*-BuOMe); λ_{max}(DCM)/nm 246 (log ε 5.03), 280 inf (4.70); ν_{max}/cm^{-1} 3470w and 3345w (NH_2), 3071 (aryl C-H), 1612s, 1568s, 1481w, 1470w, 1447w, 1396w, 1375m, 1298w, 1238m, 1177w, 1101w, 1076w, 1063w, 1001m, 858m, 777m, 717m, 704s; δ_H(300 MHz; $CDCl_3$) 7.83-7.78 (3H, m, Ar *H*), 7.63 (2H, d, *J* 8.1, Ar *H*), 7.48-7.39 (2H, m, Ar *H*), 6.73 (2H, d, *J* 8.1, Ar *H*), 4.89 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 155.0 (s), 149.5 (s), 138.4 (d), 135.4 (s), 130.7 (d), 128.5 (d), 126.7 (d), 124.0 (d), 86.3 (s); *m/z* (EI) 323 (M^++1, 13%), 322 (M^+, 100), 306 (15), 245 (4), 219 (76), 194 (6), 179 (6), 104 (80), 98 (27), 92 (33), 76 (48), 65 (12), 51 (10).

*7.2.9 (Z)-N'-(3,4-Dichlorophenyl)benzamidine (**62**).* Similar treatment of benzonitrile (**48**) (317 μL, 3.09 mmol) with $AlCl_3$ (407 mg, 3.09 mmol) and 3,4-dichloroaniline (500 mg, 3.09 mmol) heated at *ca.* 100 ^oC for 6 h gave the *title compound* **62** (746 mg, 91%) as colorless plates, mp 108-109 ^oC (lit.,[93] 110-111 ^oC) (*c*-hexane/EtOH, 95:05); R_f 0.79 (*t*-BuOMe); λ_{max}(DCM)/nm 246 (log ε 4.43), 285 (4.13); ν_{max}/cm^{-1} 3449w and 3326w (NH_2), 1614s, 1568s, 1470m, 1458m, 1387m, 1371m, 1227w, 1128m, 1024m, 930w, 897m, 879m, 847w, 831w, 797m, 777s, 725m, 712m; δ_H(300 MHz; $CDCl_3$) 7.79 (2H, d, *J* 6.9, Ar *H*), 7.52-7.37 (4H, m, Ar *H*), 7.08 (1H, d, *J* 2.1, Ar *H*), 6.81 (1H, dd, *J* 8.4, 2.1, Ar *H*), 4.77 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 155.6 (s), 149.2 (s), 135.0 (s), 133.0 (s), 131.0 (d), 130.9 (d), 128.6 (d), 126.8 (d), 126.3 (s), 123.6 (d), 121.5 (d); *m/z* (EI) 268 (M^++4, 8%), 266 (M^++2, 51), 264 (M^+, 78), 250 (13), 248 (23), 163 (38), 161 (57), 147 (12), 145 (18), 109 (20), 104 (100), 97 (10), 77 (54), 52 (23).

*7.2.10 (Z)-2-Amino-(N'-phenyl)benzamidine (**63**).* Similar treatment of anthranilonitrile (**53**) (634 mg, 5.37 mmol) with $AlCl_3$ (708 mg, 5.37 mmol) and aniline (489 μl, 5.37 mmol) heated at *ca.* 100 ^oC for 6 h gave the *title compound* **63** (722 mg, 64%) as colorless plates, mp 146-147 ^oC (lit.,[94] 146-147 ^oC) (PhH); R_f 0.62 (*t*-BuOMe); λ_{max}(DCM)/nm 327 (log ε 2.92); ν_{max}/cm^{-1} 3493w and 3433m (NH_2), 3385w, 3205w, 1600s (aryl C-H), 1579m, 1568m, 1539m, 1483m, 1446m, 1375m, 1325m, 1271m, 1238m, 1149m, 1072m, 1022m, 908m, 839m, 781m, 740s, 700m; δ_H(300 MHz; $CDCl_3$) 7.43-7.35 (3H, m, Ar *H*), 7.22-7.17 (1H, m, Ar *H*), 7.12-7.06 (1H, m, Ar *H*), 7.02-6.99 (2H, m, Ar *H*), 6.74-6.67 (2H, m, Ar

H), 5.99 (2H, s, N*H*$_2$), 4.81 (2H, s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) one C (s) resonance missing 155.8 (s), 148.8 (s), 147.8 (s), 131.1 (d), 129.5 (d), 127.3 (d), 123.1 (d), 121.8 (d), 117.1 (d), 116.6 (d); *m/z* (EI) 211 (M^++1, 63%), 210 (25), 196 (27), 167 (4), 119 (40), 105 (4), 93 (100), 92 (24), 77 (19), 65 (22), 51 (16).

*7.2.11 (Z)-2-Amino-N'-(4-methylphenyl)benzamidine (**64**).* Similar treatment of anthranilonitrile (**53**) (551 mg, 4.66 mmol) with $AlCl_3$ (615 mg, 4.66 mmol) and *p*-toluidine (500 mg, 4.66 mmol) heated at *ca.* 100 ^oC for 6 h gave first tricycloquinazoline **55** (60 mg, 12%) as yellow cotton like fibers, mp 322-323 ^oC (lit.,[187] 322-323 ^oC); R_f 0.51 (DCM); ν_{max}/cm^{-1} 3480w, 3360m (NH), 1630m, 1597m, 1587m, 1506w, 1470m, 1445w, 1294s, 1182m, 1111s, 841m, 754m; δ_H(300 MHz; $CDCl_3$) 8.50 (3H, d, *J* 8.1, Ar *H*), 7.63 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.55 (1H, d, *J* 8.1, Ar *H*), 7.37 (1H, dd, *J* 7.5, 7.5, Ar *H*); *m/z* (EI) 320 (M^+, 18%), 311 (27), 293 (78), 167 (41), 149 (13), 127 (89), 118 (11), 97 (56), 91 (27), 77 (19), 71 (25). Further elution (*t*-BuOMe) gave the *title compound* **64** (688.5 mg, 66%) as colorless plates, mp 150-151 ^oC (lit.,[94] 152-153 ^oC) (*c*-hexane/EtOH, 95:05); R_f 0.33 (*t*-BuOMe); λ_{max}(DCM)/nm 285 (log ε 3.84), 326 (3.91); ν_{max}/cm^{-1} 3493w, 3433w and 3387w (NH_2), 3179w, 1609s, 1572m, 1537m, 1504m, 1448w, 1375m, 1325m, 1271w, 1238m, 1157m, 1105w, 1053w, 1034w, 1015w, 868w, 849w, 825m, 779w, 741s, 712w; δ_H(300 MHz; $CDCl_3$) 7.41 (1H, dd, *J* 7.8, 1.2, Ar *H*), 7.22-7.15 (3H, m, Ar *H*), 6.90 (2H, *J* 8.1, Ar *H*), 6.74-6.66 (2H, m, Ar *H*), 5.81 (2H, br s, N*H*$_2$), 4.86 (2H, br s, N*H*$_2$), 2.35 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 156.1 (s), 147.7 (s), 146.0 (s), 132.5 (s), 131.0 (d), 130.1 (d), 127.3 (d), 121.7 (d), 117.1 (d), 116.6 (s), 116.6 (d), 20.8 (q, *C*H$_3$); *m/z* (EI) 226 (M^++1, 10%), 225 (M^+, 99), 208 (16), 119 (22), 107 (100), 106 (94), 92 (27), 77 (11), 65 (28).

*7.2.12 (Z)-2-Amino-N'-(4-methoxyphenyl)benzamidine (**51**).* Similar treatment of anthranilonitrile (**53**) (959 mg, 8.12 mmol) with $AlCl_3$ (535 mg, 4.06 mmol) and *p*-anisidine (500 mg, 4.06 mmol) heated at *ca.* 100 ^oC for 8 h gave first tricycloquinazoline **55** (260 mg, 30%) as yellow cotton like fibers, mp 322-323 ^oC (lit.,[187] 322-323 ^oC); identical to that described above. Further elution (*t*-BuOMe) gave the *title compound* **51** (545 mg, 56%) as cream colored plates, mp 148-149 ^oC (PhH); R_f 0.41 (*t*-BuOMe); (Found: C, 69.66; H, 6.30; N, 17.37. $C_{14}H_{15}N_3O$ requires C, 69.69; H, 6.27; N, 17.41%); λ_{max}(DCM)/nm 296 (log ε 4.70), 327 (4.67); ν_{max}/cm^{-1} 3482w, 3441w and 3383w (NH_2), 3192w (aryl C-H), 2962w, 2926w and 2835w (alkyl C-H), 1606s, 1574m, 1537m, 1500s, 1470m, 1456w, 1414w, 1373m, 1327m, 1285m, 1234s, 1182m, 1169m, 1155m, 1099m,

1032m, 932m, 901m, 870m, 849m, 827m, 783m, 737s, 714m; δ_H(300 MHz; $CDCl_3$) 7.41 (1H, dd, *J* 8.0, 1.1, Ar *H*), 7.18 (1H, ddd, *J* 7.7, 7.7, 1.5, Ar *H*), 6.92 (4H, br s, Ar *H*), 6.73-6.66 (2H, m, Ar *H*), 5.99 (2H, br s, NH_2), 4.86 (2H, br s, NH_2), 3.81 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 156.4 (s), 155.7 (s), 147.8 (s), 141.7 (s), 131.0 (s) (d), 127.3 (d), 122.7 (d), 117.1 (d), 116.6 (s), 116.5 (d), 114.8 (d), 55.5 (q, OCH_3); *m/z* (EI) 241 (M^+, 71%), 224 (10), 209 (7), 181 (3), 154 (2), 123 (66), 119 (40), 108 (100), 92 (27), 80 (12), 65 (19), 52 (6).

*7.2.13 (Z)-2-Amino-N'-(4-fluorophenyl)benzamidine (**66**).* Similar treatment of anthranilonitrile (**53**) (531 mg, 4.50 mmol) with $AlCl_3$ (593 mg, 4.50 mmol) and 4-fluoroaniline (432 μL, 4.50 mmol) heated at *ca.* 100 ^oC for 6 h gave the *title compound* **66** (593.5 mg, 58%) as colorless plates, mp 143.4-145 ^oC (*c*-hexane/EtOH, 95:05); R_f 0.67 (*t*-BuOMe); (Found: C, 68.18; H, 5.35; N, 18.21. $C_{13}H_{12}FN_3$ requires C, 68.11; H, 5.28; N, 18.33%); λ_{max}(DCM)/nm 283 (log ε 3.82), 330 (3.71); ν_{max}/cm^{-1} 3495w, 3435w and 3377w (NH_2), 3204w, 1610s, 1572m, 1537m, 1495s, 1450w, 1406w, 1375m, 1327m, 1267w, 1234w, 1211s, 1159m, 1088w, 1009w, 872w, 839m, 789m, 744s, 710w; δ_H(300 MHz; $CDCl_3$) 7.39 (1H, d, *J* 7.5, Ar *H*), 7.22-7.17 (1H, m, Ar *H*), 7.08-7.02 (2H, m, Ar *H*), 6.95-6.90 (2H, m, Ar *H*), 6.73-6.66 (2H, m, Ar *H*), 5.78 (2H, br s, NH_2), 4.91 (2H, br s, NH_2); δ_C(75 MHz; $CDCl_3$) 159.1 (d, $^1J_{CF}$ 241.6, *C*F), 156.5 (s), 147.7 (s), 144.5 (s), 131.2 (d), 127.3 (d), 123.0 (d, $^3J_{CF}$ 7.6, *C*H), 117.1 (d), 116.6 (d), 116.3 (s), 116.2 (d, $^2J_{CF}$ 21.9, *C*H); *m/z* (EI) 229 (M^+, 52%), 212 (19), 185 (3), 119 (61), 111 (100), 92 (31), 84 (9), 75 (15), 65 (27), 57 (5).

*7.2.14 (Z)-2-Amino-N'-(4-chlorophenyl)benzamidine (**67**).* Similar treatment of anthranilonitrile (**53**) (463 mg, 3.92 mmol) with $AlCl_3$ (517 mg, 3.92 mmol) and 4-chloroaniline (500 mg, 3.92 mmol) heated at *ca.* 100 ^oC for 6 h gave the *title compound* **67** (461 mg, 48%) as colorless plates, mp 162-163 ^oC (lit.,[94] 161-162 ^oC) (*c*-hexane/EtOH, 95:05); R_f 0.78 (*t*-BuOMe); λ_{max}(DCM)/nm 242 (log ε 4.21), 272 (3.69); ν_{max}/cm^{-1} 3495w, 3435w and 3381w (NH_2), 3206w (aryl C-H), 1611s, 1580m, 1566m, 1537m, 1481m, 1400w, 1375m, 1327w, 1265w, 1240m, 1159m, 1088m, 1009m, 868w, 847w, 824w, 766w, 746m; δ_H(300 MHz; $CDCl_3$) 7.39 (1H, dd, *J* 7.8, 0.9, Ar *H*), 7.31 (2H, d, *J* 8.7, Ar *H*), 7.20 (1H, dd, *J* 7.7, 1.5, Ar *H*), 6.93 (2H, d, *J* 8.7, Ar *H*), 6.74-6.66 (2H, m, Ar *H*), 5.82 (2H, br s, NH_2), 4.79 (2H, br s, NH_2); δ_C(75 MHz; $CDCl_3$) 156.3 (s), 147.7 (s), 147.2 (s), 131.4 (d), 129.6 (d), 128.4 (s), 127.3 (d), 123.3 (d), 117.2 (d), 116.7 (d), 116.2 (s); *m/z* (EI)

247 (M^++2, 15%), 245 (M^+, 51), 230 (9), 228 (27), 209 (3), 192 (3), 166 (3), 136 (24), 129 (29), 127 (100), 119 (97), 105 (14), 92 (53), 75 (15), 65 (33).

*7.2.15 (Z)-2-Amino-N'-(4-bromophenyl)benzamidine (**68**).* Similar treatment of anthranilonitrile (**53**) (344 mg, 2.91 mmol) with $AlCl_3$ (3.84 mg, 2.91 mmol) and 4-bromoaniline (500 mg, 2.91 mmol) heated at *ca.* 100 °C for 6 h gave the *title compound* **68** (358 mg, 43%) as colorless plates, mp 167-168 °C (lit.,[94] 167-168 °C) (*c*-hexane/EtOH, 95:05); R_f 0.76 (*t*-BuOMe); λ_{max}(DCM)/nm 241 (log ε 4.46), 280 (4.13), 331 (3.88); ν_{max}/cm^{-1} 3495w, 3433w and 3383w (NH_2), 3211w (aryl C-H), 1609s, 1574m, 1566m, 1537m, 1479m, 1396w, 1375m, 1327w, 1242m, 1159m, 1095w, 1070m, 1005m, 868w, 847w, 822w, 766w, 746s, 710w; δ_H(300 MHz; $CDCl_3$) 7.46 (2H, d, *J* 8.4, Ar *H*), 7.39 (1H, d, *J* 7.8, Ar *H*), 7.23-7.16 (1H, m, Ar *H*), 6.87 (2H, d, *J* 8.4, Ar *H*), 6.74-6.66 (2H, m, Ar *H*), 5.80 (2H, br s, N*H*$_2$), 4.80 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) one C (s) resonance missing 156.3 (s), 147.8 (s), 132.6 (d), 131.4 (d), 127.4 (d), 123.8 (d), 117.2 (d), 116.8 (d), 116.2 (s), 116.1 (s); *m/z* (EI) 291 (M^++2, 34%), 289 (M^+, 35), 274 (14), 272 (14), 236 (17), 209 (4), 193 (5), 173 (54), 171 (56), 119 (100), 105 (18), 92 (57), 76 (16), 65 (52), 52 (10).

*7.2.16 (Z)-2-Amino-N'-(3,4-dichlorophenyl)benzamidine (**70**).* Similar treatment of anthranilonitrile (**53**) (364 mg, 3.09 mmol) with $AlCl_3$ (407 mg, 3.09 mmol) and 3,4-dichloroaniline (500 mg, 3.09 mmol) heated at *ca.* 100 °C for 6 h gave the *title compound* **70** (305.5 mg, 35%) as colorless plates, mp (hotstage) 129-130 °C (lit.,[94] 130-131 °C) (*c*-hexane/EtOH, 95:05); R_f 0.90 (*t*-BuOMe); (Found: C, 55.64; H, 3.98; N, 14.98. $C_{13}H_{11}Cl_2N_3$ requires C, 55.73; H, 3.96; N, 15.00%); λ_{max}(DCM)/nm 242 (log ε 4.27), 287 (3.75); ν_{max}/cm^{-1} 3495m, 3453w and 3395m (NH_2), 3277w, 1632s, 1576m, 1574m, 1547m, 1495w, 1468m, 1450m, 1387s, 1375m, 1321m, 1261w, 1252m, 1223w, 1157w, 1119m, 1020w, 889s, 852m, 835m, 771m, 750s, 717w; δ_H(300 MHz; $CDCl_3$) 7.42-7.35 (2H, m, Ar *H*), 7.21 (1H, dd, *J* 7.8, 1.2, Ar *H*), 7.10 (1H, d, *J* 1.8, Ar *H*), 6.83 (1H, dd, *J* 8.4, 1.8, Ar *H*), 6.73-6.67 (2H, m, Ar *H*), 5.65 (2H, br s, N*H*$_2$), 4.88 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 156.6 (s), 148.3 (s), 147.7 (s), 133.0 (s), 131.6 (d), 131.1 (d), 127.3 (d), 126.4 (s), 123.8 (d), 121.7 (d), 117.2 (d), 116.8 (d), 115.8 (s); *m/z* (EI) 283 (M^++2, 4%), 281 (M^++1, 13), 279 (M^+, 35), 264 (9), 262 (11), 236 (17), 208 (2), 192 (3), 163 (28), 161 (49), 119 (100), 92 (29), 75 (5), 65 (22).

*7.2.17 2-Amino-N'-(3,4-dimethoxyphenyl)benzamidine (**71**).* Similar treatment of anthranilonitrile (**53**) (550 μL, 5.36 mmol) with $AlCl_3$ (706 mg, 5.36 mmol) and 3,4-

dimethoxyaniline (489 μL, 5.36 mmol) heated at *ca.* 100 ^{o}C) for 12 h gave the *title compound* **71** (873 mg, 60%) as colorless needles, mp (hotstage) 144-145 ^{o}C (*c*-hexane/DCM, 90:10); R_f 0.45 (*t*-BuOMe/EtOH, 95:05); (found: C, 66.45; H, 6.45; N, 15.41. $C_{15}H_{17}N_3O_2$ requires C, 66.40; H, 6.32; N, 15.49%); λ_{max}(DCM)/nm 251 inf (log ε 4.20), 297 (3.91), 328 (3.91); ν_{max}/cm^{-1} 3493w, 3431w, 3366w and 3204w (NH_2), 3007w (aryl C-H), 2968w and 2959w (alkyl C-H), 1626s, 1582m, 1574w, 1537w, 1504s, 1464w, 1451w, 1439w, 1410w, 1375w, 1325w, 1279w, 1260w, 1231s, 1198m, 1161w, 1152w, 1132m, 1026m, 941m, 868w, 842w, 818w, 773m, 762m, 748s, 719w; δ_H(500 MHz; $CDCl_3$) 7.42 (1H, d, *J* 7.5, Ar *H*), 7.19 (1H, ddd, *J* 7.5, 7.5, 1.0, Ar *H*), 6.87 (1H, d, *J* 8.5, Ar *H*), 6.74-6.68 (2H, m, Ar *H*), 6.58 (1H, d, *J* 2.0, Ar *H*), 6.54 (1H, dd, *J* 8.3, 2.3, Ar *H*), 6.00 (2H, br s, N*H*$_2$), 4.85 (2H, br s, N*H*$_2$), 3.87 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 156.6 (s), 149.9 (s), 147.8 (s), 145.1 (s), 142.1 (s), 131.1 (d), 127.3 (d), 117.2 (d), 116.7 (d), 116.5 (s), 112.8 (d), 112.2 (d), 106.2 (d), 56.2 (q, O*C*H$_3$), 55.8 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 273 (MH$^+$+1, 5%), 272 (MH$^+$, 100).

*7.2.18 (Z)-2-Amino-4,5-dimethoxy-N'-phenylbenzamidine (**72**).* Similar treatment of 4,5-dimethoxyanthranilonitrile (**54**) (957 mg, 5.36 mmol) with $AlCl_3$ (706 mg, 5.36 mmol) and aniline (489 μL, 5.36 mmol) 4 h gave the *title compound* **72** (178 mg, 12%) as colorless needles, mp (hotstage) 172-173 ^{o}C; (from *c*-hexane/EtOH, 90:10); (found: C, 66.51; H, 6.26; N, 15.40. $C_{15}H_{17}N_3O_2$ requires C, 66.40; H, 6.32; N, 15.49%); R_f 0.40 (*t*-BuOMe/EtOH, 90:10); λ_{max}(DCM)/nm 267 (log ε 4.30), 337 (4.04); ν_{max}/cm^{-1} 3435w and 3343w (NH_2), 3279w, 3117w, 3009w, 2961w, 2934w, 2911w and 2905w (aryl C-H), 2858w and 2830w (alkyl C-H), 1632m, 1587w, 1562m, 1514m, 1483m, 1458w, 1446w, 1412w, 1391m, 1285w, 1265w, 1223s, 1174w, 1113w, 1069w, 1024w, 1001w, 964w, 912w, 876w, 843m, 777w; δ_H(300 MHz; $CDCl_3$) 7.36 (2H, dd, *J* 7.7, 7.7 Ar *H*), 7.07 (1H, dd, *J* 7.5, 7.5 Ar *H*), 7.00-6.95 (3H, m, Ar *H*), 6.26 (1H, s, Ar *H*), 5.81 (2H, br s, N*H*$_2$), 4.70 (2H, br s, N*H*$_2$), 3.87 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 155.7 (s), 152.1 (s), 148.9 (s), 143.6 (s), 140.7 (s), 129.5 (d), 122.9 (d), 121.9 (d), 111.6 (d), 107.9 (s), 100.7 (d), 57.0 (q, O*C*H$_3$), 55.7 (q, O*C*H$_3$); *m/z* (EI) 271 (M$^+$, 100%), 254 (37), 239 (50), 211 (6), 193 (7), 179 (41), 163 (36), 147 (6), 135 (14), 120 (7), 93 (30), 77 (33), 65 (9), 51 (11).

*7.2.19 (Z)-2-Amino-4,5-dimethoxy-N'-(4-methoxyphenyl)benzamidine (**73**).* Similar treatment of 4,5-dimethoxyanthranilonitrile (**54**) (723 mg, 4.06 mmol) with powdered

anhydrous $AlCl_3$ (535 mg, 4.06 mmol) and *p*-anisidine (500 mg, 4.06 mmol) for 4 h gave the *title compound* **73** (151 mg, 12%) as colorless plates, mp (hotstage) 174-175 ^{o}C; (from EtOH); (found: C, 63.82; H, 6.35; N, 13.86. $C_{16}H_{19}N_3O_3$ requires C, 63.77; H, 6.36; N, 13.94%); R_f 0.47 (*t*-BuOMe/EtOH, 60:40); λ_{max}(DCM)/nm 266 (log ε 4.21), 336 (3.99); ν_{max}/cm^{-1} 3458w, 3433w and 3348w (NH_2), 3308w, 3011w (aryl C-H), 2994w, 2957w, 2936w and 2837w (alkyl C-H), 1635s, 1603m, 1587m, 1558m, 1518m, 1501s, 1466m, 1447m, 1414w, 1385m, 1346w, 1271m, 1215s, 1184m, 1171m, 1103m, 1067w, 1038w, 1018m, 999m, 964w, 854m, 835m, 814w, 777m; δ_H(300 MHz; $CDCl_3$) 6.95 (1H, s, Ar *H*), 6.92 (4H, m, Ar *H*), 6.26 (1H, s, Ar *H*), 5.82 (2H, br s, N*H*$_2$), 4.74 (2H, br s, N*H*$_2$), 3.86 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 156.2 (s), 155.6 (s), 152.0 (s), 143.5 (s), 141.8 (s), 140.7 (s), 122.8 (d), 114.8 (d), 111.6 (d), 108.1 (s), 100.7 (d), 57.0 (q, O*C*H$_3$), 55.7 (q, O*C*H$_3$), 55.5 (q, O*C*H$_3$); *m/z* (EI) 301 (M$^+$, 83%), 284 (19), 269 (18), 241 (3), 226 (3), 179 (38), 163 (13), 148 (5), 135 (10), 123 (100), 108 (63), 92 (7), 80 (9), 77 (6), 64 (4), 52 (5).

7.3 Compounds related to Chapter 3

*7.3.1 Preparation of 4-imino-3-aryl-3,4-dihydroquinazoline-2-carbonitriles **80-88** (see Table 4 , entries 1-9)*

*7.3.1.1 4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (typical procedure).* To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) in DCM (4 mL) at *ca.* 20 °C was added 2-amino-*N'*-phenylbenzamidine (**63**) (51 mg, 0.24 mmol). After 4 h, to the reaction mixture was added Hünig's base (83.5 μL, 0.48 mmol) and left to stir at *ca.* 20 °C for an additional 2 h. The reaction mixture was then adsorbed onto silica and chromatography (*n*-hexane) gave traces of S_8, followed (*n*-hexane/DCM, 80:20) by 4-chloro-5*H*-1,2,3-dithiazol-5-one (8 mg, 20%). Further elution (DCM/*t*-BuOMe, 90:10) gave the *title compound* **80** (43 mg, 75%) as colorless needles, mp (hotstage) 141-142 °C (from *c*-hexane), mp (DSC) onset 143.9 °C, peak max. 146.2 °C (from *c*-hexane); (found: C, 73.02; H, 3.95; N, 22.67. $C_{15}H_{10}N_4$ requires C, 73.16; H, 4.09; N, 22.75%); R_f 0.48 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 237 inf (log ε 4.25), 245 inf (4.18), 255 (4.13), 265 (4.19), 274 (4.11), 298 inf (3.77), 311 (3.94), 324 (3.99), 340 inf (3.85); ν_{max}/cm^{-1} 3341w, 3308w (NH), 3071w (aryl C-H), 2239w (C≡N), 1643m, 1605w, 1574w, 1560m, 1491w, 1472w, 1462m, 1348m, 1302m, 1283m, 1227w, 1217w, 1167m, 1138m, 1030w, 1007w, 997w, 876w, 827w, 800w, 760s; δ_H(300 MHz; $CDCl_3$) 8.25 (1H, d, *J* 6.9, Ar *H*), 7.69-7.63 (5H, m, Ar *H*), 7.54 (1H, ddd, *J* 7.4, 7.4, 1.8, Ar *H*), 7.44-7.40 (2H, m, Ar *H*), 6.71 (1H, br s, N*H*); δ_C(125 MHz; $CDCl_3$) 153.3 (s), 143.2 (s), 135.0 (s), 133.4 (d), 131.3 (d), 131.2 (s), 131.0 (d), 129.9 (d), 129.0 (d), 128.4 (d), 125.6 (d), 122.5 (s), 111.3 (s, *C*≡N); *m/z* (EI) 246 (M^+, 34%), 245 (M^+-H, 100), 236 (7), 219 (17), 192 (11), 160 (8), 141 (7), 129 (7), 118 (12), 113 (11), 111 (12), 102 (25), 97 (17), 91 (20), 85 (19), 83 (17), 77 (64), 71 (25), 69 (26), 64 (46), 57 (48).

*7.3.1.2 4-Imino-3-p-tolyl-3,4-dihydroquinazoline-2-carbonitrile (**81**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with (*Z*)-2-amino-*N'*-*p*-tolylbenzamidine (**64**) (54 mg, 0.24 mmol) at *ca.* 20 °C gave the *title compound* **81** (51 mg, 81%) as beige needles, mp (hotstage) 155-156 °C (from *n*-hexane/DCM), mp (DSC) onset 158.6 °C, peak max. 160.9 °C (from *n*-hexane/DCM); (found: C, 73.69; H, 4.54; N, 21.58. $C_{16}H_{12}N_4$ requires C, 73.83; H, 4.65; N, 21.52%); R_f 0.60 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 255 (log ε 4.08), 264 (4.14), 274 (4.07), 298 inf (3.72), 310 (3.89), 323 (3.94), 342 inf (3.79); ν_{max}/cm^{-1} 3292w (NH), 3040w, 3009w (aryl C-H), 2924w, 2907w,

2887w and 2874w (alkyl C-H), 2243w (C≡N), 1641s, 1603w, 1578m, 1566w, 1510m, 1464m, 1352m, 1323s, 1308m, 1292w, 1240w, 1225w, 1186m, 1180m, 1146m, 1111w, 1026w, 1002w, 956w, 839m, 814w, 789m, 768s; δ_H(300 MHz; $CDCl_3$) 8.26 (1H, d, *J* 8.1 Ar *H*), 7.70–7.6 (2H, m, Ar *H*), 7.52 (1H, ddd, *J* 7.4, 7.4, 1.8 Ar *H*), 7.44 (2H, d, *J* 8.1 Ar *H*), 7.28 (2H, d, *J* 8.4 Ar *H*), 6.34 (1H, br s, N*H*), 2.47 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 153.5 (s), 143.3 (s), 141.7 (s), 133.4 (d), 132.2 (s), 131.7 (d), 131.3 (s), 129.8 (d), 128.6 (d), 128.3 (d), 125.7 (d), 122.4 (s), 111.3 (s, *C*≡N), 21.4 (q, *C*H_3); *m/z* (EI) 260 (M^+, 12%), 259 (M^+-H, 49), 239 (9), 224 (8), 207 (31), 179 (8), 169 (11), 163 (44), 149 (12), 133 (25), 119 (10), 113 (28), 106 (20), 97 (29), 91 (67), 77 (22), 69 (37), 65 (31), 57 (30).

*7.3.1.3 4-Imino-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2-carbonitrile (**82**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with 2-amino-*N'*-(4-methoxyphenyl)benzamidine (**51**) (58 mg, 0.24 mmol) at *ca.* 20 °C gave the *title compound* **82** (49 mg, 74%) as orange needles, mp (hotstage) 140-141 °C (from *n*-hexane/DCM), mp (DSC) onset 142.8 °C, peak max. 144.3 °C (from *n*-hexane/DCM, 90:10); (found: C, 69.61; H, 4.28; N, 20.14. $C_{16}H_{12}N_4O$ requires C, 69.55; H, 4.38; N, 20.28%); R_f 0.42 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 255 (log ε 4.09), 265 (4.14), 273 (4.07), 298 inf (3.73), 310 (3.90), 324 (3.95), 342 inf (3.80); ν_{max}/cm^{-1} 3312w, 3281w, 3262w (NH), 3075w, 3057w, 3011w (aryl C-H), 2963w, 2934w, 2909w, 2835w, 2243w (C≡N), 1634s, 1607m, 1587m, 1576w, 1560m, 1510s, 1472m, 1462m, 1437w, 1354m, 1344w, 1321s, 1306s, 1283m, 1250s, 1234s, 1182s, 1167m, 1148m, 1136w, 1115w, 1057w, 1032m, 999w, 968w, 951w, 891w, 879w, 858m, 841s, 824m, 779m, 770s; δ_H(300 MHz; $CDCl_3$) 8.27 (1H, d, *J* 7.8 Ar *H*), 7.72-7.62 (2H, m, Ar *H*), 7.52 (1H, ddd, *J* 7.4, 7.4, 1.7 Ar *H*), 7.32 (2H, d, *J* 9.0 Ar *H*), 7.14 (2H, d, *J* 9.0 Ar *H*), 6.89 (1H, br s, N*H*), 3.91 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 161.3 (s), 153.5 (s), 143.2 (s), 133.3 (d), 131.6 (s), 130.1 (d), 129.7 (d), 128.6 (d), 128.2 (d) 127.0 (s), 125.6 (d), 122.5 (s), 116.1 (d), 111.4 (s, *C*≡N), 55.6 (q, O*C*H_3); *m/z* (EI) 276 (M^+, 92%), 275 (M^+-H, 100), 261 (54), 259 (43), 250 (7), 234 (11), 210 (24), 181 (9), 159 (12), 154 (28), 149 (13), 129 (14), 122 (16), 102 (52), 97 (26), 95 (30), 91 (21), 83 (27), 77 (31), 71 (28), 69 (39), 64 (22), 59 (33), 57 (57).

*7.3.1.4 3-(4-Fluorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**83**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with 2-amino-*N'*-(4-fluorophenyl)benzamidine (**66**) (55 mg, 0.24 mmol) at *ca.* 20 °C gave the *title compound* **83** (36 mg, 57%) as beige needles, mp 163-163.5 °C (from *n*-hexane/DCM,

90:10), mp (DSC) onset 167.9 °C, peak max. 169.2 °C (from *n*-hexane/DCM, 90:10); (found: C, 68.29; H, 3.30; N, 21.12. $C_{15}H_9FN_4$ requires C, 68.18; H, 3.43; N, 21.20%); R_f 0.52 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 235 inf (log ε 4.19), 255 (4.09), 263 (4.14), 273 (4.08), 299 inf (3.75), 310 (3.90), 323 (3.95), 339 inf (3.81); ν_{max}/cm^{-1} 3304w, 3285w (NH), 3075w, 3048w, 3009w (aryl CH), 2241w (C≡N), 1638s, 1599m, 1578m, 1564w, 1508s, 1462m, 1418w, 1372w, 1346m, 1317s, 1288m, 1244w, 1227m, 1177m, 1150m, 1096w, 1026w, 1003w, 881w, 851m, 839m, 831m, 822m, 789w, 764s; δ_H(300 MHz; $CDCl_3$) 8.21 (1H, d, *J* 7.5 Ar *H*), 7.74-7.64 (2H, m, Ar *H*), 7.55 (1H, ddd, *J* 7.4, 7.4, 1.5 Ar *H*), 7.45-7.32 (4H, m, Ar *H*); δ_C(75 MHz; $CDCl_3$) 165.4 (s), 162.0 (d, $^1J_{CF}$ 252.9), 153.8 (s), 143.0 (s), 133.5 (d), 131.1 (d, $^3J_{CF}$ 9.1), 130.0 (d), 128.5 (d), 125.4 (d), 122.2 (s), 118.2 (d, $^2J_{CF}$ 22.7), 111.2 (s, *C*≡N); *m/z* (EI) 264 (M^+, 26%), 263 (M^+-H, 100), 245 (12), 236 (3), 209 (1), 154 (6), 147 (7), 132 (3), 102 (27), 95 (32), 90 (7), 75 (29), 63 (7).

*7.3.1.5 3-(4-Chlorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**84**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with 2-amino-*N'*-(4-chlorophenyl)benzamidine (**67**) (59 mg, 0.24 mmol) at *ca.* 20 °C gave the *title compound* **84** (44 mg, 65%) as colorless needles, mp (hotstage) 209-210 °C (from *n*-hexane/DCM, 90:10), mp (DSC) onset 198.9 °C, peak max. 200.6 °C (from *n*-hexane/DCM, 90:10); (found: C, 64.34; H, 3.10; N, 19.92. $C_{15}H_9ClN_4$ requires C, 64.18; H, 3.2; N, 19.96%); R_f 0.61 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 253 inf (log ε 4.17), 264 (4.18), 273 (4.11), 298 inf (3.79), 310 (3.94), 323 (3.99), 340 inf (3.85); ν_{max}/cm^{-1} 3304w (NH), 3053w (aryl C-H), 2241w (C≡N), 1643s, 1597w, 1574w, 1566w, 1493m, 1466m, 1406w, 1350m, 1315s, 1292m, 1246w, 1223w, 1172m, 1155w, 1090m, 1067w, 1049w, 1022w, 1001w, 970w, 948w, 879w, 841m, 812w, 785w, 775s; δ_H(300 MHz; $CDCl_3$) 8.21 (1H, d, *J* 8.1 Ar *H*), 7.71–7.64 (2H, m, Ar *H*), 7.65 (2H, d, *J* 8.4 Ar *H*), 7.56 (1H, ddd, *J* 7.4, 7.4, 1.4 Ar *H*), 7.38 (2H, d, *J* 8.7 Ar *H*), 5.70 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 153.8 (s), 143.0 (s), 137.5 (s), 133.7 (s), 133.6 (d), 131.3 (d), 130.9 (s), 130.4 (d), 130.1 (d), 128.6 (d), 125.4 (d), 122.1 (s), 111.2 (s, *C*≡N); *m/z* (EI) 282 (M^++2, 10%), 281 (M^++1, 36), 280 (M^+, 31), 279 (M^+-H, 100), 244 (12), 154 (8), 149 (4), 113 (7), 111 (21), 102 (30), 90 (10), 75 (26), 63 (8).

*7.3.1.6 3-(4-Bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**85**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with 2-amino-*N'*-(4-bromophenyl)benzamidine (**68**) (69 mg, 0.24 mmol) at *ca.* 20 °C gave the *title*

compound **85** (49 mg, 63%) as orange needles, mp (hotstage) 191-192 °C (from *n*-hexane/DCM, 90:10), mp (DSC) onset 191.7 °C, peak max. 193.6 °C (from *n*-hexane/DCM, 90:10); (found: C, 55.41; H, 2.70; N, 17.15. $C_{15}H_9BrN_4$ requires C, 55.41; H, 2.79; N, 17.23%); R_f 0.75 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 253 inf (log ε 4.25), 263 (4.23), 273 (4.15), 299 inf (3.85), 311 (4.00), 323 (4.06), 339 inf (3.94); ν_{max}/cm^{-1} 3298w (NH), 3086w, 3049w, 3028w, 3011w (Ar CH), 2243w (C≡N), 1688w, 1641s, 1593m, 1564m, 1489m, 1400w, 1348m, 1319m, 1290m, 1244w, 1223w, 1175m, 1155w, 1070w, 1018m, 1001m, 970w, 880w, 839m, 808m, 785m, 775s; δ_H(300 MHz; $CDCl_3$) 8.18 (1H, d, *J* 7.8 Ar *H*), 7.79 (2H, d, *J* 8.7 Ar *H*), 7.70-7.64 (2H, m, Ar *H*), 7.55 (1H, ddd, *J* 7.4, 7.4, 1.8 Ar *H*), 7.31 (2H, d, *J* 8.7 Ar *H*), 6.86 (1H, br s, N*H*); δ_C(125 MHz; $CDCl_3$) 153.7 (s), 143.0 (s), 134.3 (d), 133.6 (d), 130.8 (s), 130.6 (d), 130.1 (d), 128.6 (d), 125.6 (s), 125. (d), 122.1 (s), 111.2 (s, *C*≡N); *m/z* (EI) 326 (M^++2, 29%), 325 (M^++1, 98), 324 (M^+, 30), 323 (M^+-H, 100), 259 (3), 244 (32), 209 (5), 207 (5), 192 (5), 155 (14), 122 (18), 102 (42), 90 (23), 76 (33), 63 (16), 50 (17).

*7.3.1.7 3-(3,4-Dichlorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**86**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with 2-amino-*N'*-(3,4-dichlorophenyl)benzamidine (**70**) (67 mg, 0.24 mmol) at *ca.* 20 °C gave the *title compound* **86** (49 mg, 65%) as beige plates, mp (hotstage) 175-176 °C (from *n*-pentane/DCM, 90:10), mp (DSC) onset 176.6 °C, peak max. 180.5 °C (from *n*-pentane/DCM, 90:10); (found: C, 57.24; H, 2.5; N, 17.69. $C_{15}H_8Cl_2N_4$ requires C, 57.17; H, 2.56; N, 17.78%); R_f 0.77 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 252 inf (log ε 4.19), 264 (4.17), 273 (4.08), 299 inf (3.79), 310 (3.93), 323 (3.97), 339 inf (3.85); ν_{max}/cm^{-1} 3265w (N*H*), 3092w, 3044w, 3019w, 3007w (aryl C-H), 2953w, 2924w, 2853w, 2241w (C≡N), 1620s, 1601m, 1574m, 1562m, 1472m, 1462m, 1389w, 1354m, 1337m, 1256w, 1231m, 1182w, 1132m, 1119w, 1055m, 1034m, 1022w, 970w, 928w, 876m, 854w, 827m, 770s; δ_H(300 MHz; $CDCl_3$) 8.12 (1H, d, *J* 7.2 Ar *H*), 7.73 (1H, d, *J* 8.7 Ar *H*), 7.70-7.65 (2H, m, Ar *H*), 7.60-7.54 (2H, m, Ar *H*), 7.30 (1H, dd, *J* 8.4, 2.4 Ar *H*); δ_C(125 MHz; $CDCl_3$) 154.1 (s), 142.8 (s), 135.9 (s), 133.9 (s), 134.8 (s) 133.7 (d), 132.5 (s), 131.1 (d), 130.5 (s), 130.2 (d), 128.8 (d), 128. (d), 125.1 (d), 121.7 (s), 111.1 (s, *C*≡N); *m/z* (EI) 317 (M^++2, 43%), 315 (M^+, 100), 313 (M^+-2, 21), 304 (6), 285 (18), 280 (43), 272 (10), 270 (10), 260 (25), 258 (56), 244 (8), 230 (14), 223 (28), 216 (85), 186 (29), 136 (19), 109 (26), 103 (64), 96 (27), 90 (20), 76 (40), 64 (81), 57 (38).

*7.3.1.8 4-Imino-6,7-dimethoxy-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**87**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with 2-amino-4,5-dimethoxy-*N'*-(phenyl)benzamidine (**72**) (64 mg, 0.24 mmol) at *ca.* 20 °C gave the *title compound* **87** (38 mg, 53%) as colorless needles, mp (hotstage) 230 °C (sub.) (from acetone), mp (DSC) onset 260.8 °C, peak max. 263.2 °C (from acetone); (found: C, 66.55; H, 4.42; N, 18.38. $C_{17}H_{14}N_4O_2$ requires C, 66.66; H, 4.61; N, 18.29%); R_f (*t*-BuOMe/EtOH, 60:40) 0.59; λ_{max}(DCM)/nm 249 inf (log ε 4.56), 257 inf (4.61), 266 (4.66), 275 inf (4.62), 314 (3.98), 329 (4.05), 355 (4.05), 372 inf (4.00), 393 inf (3.67); ν_{max}/cm^{-1} 3304w, 3287w (NH), 3100w, 3073w, 3013w (aryl CH), 2976w, 2940w, 2870w and 2830w (alkyl C-H), 2237w (C≡N), 1628m, 1609s, 1570m, 1512s, 1493m, 1470m, 1454m, 1433w, 1381m, 1348m, 1304m, 1277m, 1229m, 1204m, 1182w, 1125m, 1055m, 1038w, 1003m, 995m, 934w, 876w, 856m, 841m, 822m, 793m, 781m, 765m; δ_H(300 MHz; $CDCl_3$) 7.72-7.66 (4H, m, Ar *H*), 7.44–7.41 (2H, m, Ar *H*), 7.08 (1H, s, Ar *H*), 6.34 (1H, br s, N*H*), 4.01 (3H, s, OCH_3), 4.00 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 153.6 (s), 152.7 (s), 151.1 (s), 138.7 (s), 134.9 (s), 131.3 (d), 131.1 (d), 129.5 (s), 129.1 (d), 116.2 (s), 111.5 (s, *C*≡N), 109.0 (d), 105.6 (d), 56.5 (q, O*C*H$_3$), 56.3 (q, O*C*H$_3$); *m/z* (EI) 306 (M^+, 31%), 305 (83), 289 (11), 261 (5), 236 (3), 193 (2), 149 (8), 129 (10), 111 (7), 97 (13), 83 (13), 77 (37), 71 (15), 69 (27), 57 (26), 51 (10).

*7.3.1.9 4-Imino-6,7-dimethoxy-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2-carbonitrile (**88**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (50 mg, 0.24 mmol) with 2-amino-4,5-dimethoxy-*N'*-(4-methoxyphenyl)benzamidine (**73**) (71 mg, 0.24 mmol) at *ca.* 20 °C gave the *title compound* **88** (49 mg, 61%) as pale yellow needles, mp (hotstage) 234-235 °C (from acetone), mp (DSC) onset 254.5 °C, peak max. 255.4 °C (from acetone); (found: C, 64.44; H, 4.84; N, 16.60. $C_{18}H_{16}N_4O_3$ requires C, 64.28; H, 4.79; N, 16.66%); R_f 0.73 (*t*-BuOMe/EtOH, 90:10); λ_{max}(DCM)/nm 248 (log ε 4.62), 255 inf (4.61), 268 (4.61), 276 inf (4.55), 316 (4.01), 330 (4.10), 358 (4.10), 392 (3.73); ν_{max}/cm^{-1} 3289w (NH), 3100w, 3055w, 3024w and 3015w (aryl C-H), 2984w, 2963w, 2943w, 2914w, 2866w and 2827w (alkyl C-H), 2237w (C≡N), 1640m, 1632m, 1607m, 1587w, 1578w, 1512s, 1458m, 1429w, 1414w, 1377m, 1339w, 1318w, 1308w, 1298m, 1275s, 1252s, 1221w, 1198m, 1186w, 1167m, 1121s, 1107m, 1063w, 1032m, 1017w, 995m, 953w, 882m, 868m, 837s; δ_H(300 MHz; $CDCl_3$) 7.66 (1H, s, Ar *H*), 7.32 (2H, d, *J* 8.7 Ar *H*), 7.13 (2H, d, *J* 8.7 Ar *H*), 7.05 (1H, s, Ar *H*), 6.51 (1H, br s, N*H*), 4.00 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 3.91 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 161.5 (s),

153.7 (s), 153.1 (s), 151.2 (s), 138.8 (s), 130.3 (d), 130.2 (s), 127.2 (s), 116.3 (s), 116.3 (d), 111.7 (s, *C*≡N), 109.1 (d), 105.8 (d), 56.5 (q, O*C*H_3), 56.3 (q, O*C*H_3), 55.7 (q, O*C*H_3); *m/z* (EI) 336 (M^+, 89%), 335 (100), 321 (41), 305 (8), 245 (42), 159 (14), 122 (5), 107 (15), 92 (14), 77 (32), 64 (12), 51 (10).

*7.3.2 Base hydrolysis of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (Scheme 32)*

*7.3.2.1 2-Methoxy-3-phenylquinazolin-4(3H)-imine (**89**)* (*from the iminoquinazoline **80** (reaction conditions i, Scheme 32).* To solution of 4-imino-3-phenyl-3,4-dihydro-quinazoline-2-carbonitrile (**80**) (24.6 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of NaOH (4 mg, 0.1 mmol) in MeOH (0.5 mL) and the stirred mixture was heated at *ca*. 67 °C for 3 h and then allowed to cool to *ca.* 20 °C. The reaction mixture was then diluted (H_2O), neutralised (10% HCl) and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the *title compound* **89** (25 mg, 99%) as pale yellow plates, mp (DSC) onset 126.3 °C, peak max. 128.4 °C (from DCM/*n*-pentane, 60:40); (found: C, 71.63; H, 5.27; N, 16.82. $C_{15}H_{13}N_3O$ requires C, 71.70; H, 5.21; N, 16.72%); R_f 0.40 (*t*-BuOMe/DCM, 20:80); λ_{max}(DCM)/nm 240 inf (log ε 4.32), 247 inf (4.22), 265 inf (3.94), 275 (3.98), 284 inf (3.91), 305 inf (3.69), 316 (3.81), 329 (3.69); ν_{max}/cm^{-1} 3310w, 3277w (NH), 3260w, 3061w, 2951w, 2924w, 2853w, 1643s, 1634m, 1605s, 1582s, 1481m, 1472m, 1454w, 1437m, 1371m, 1360m, 1323s, 1308m, 1298m, 1261w, 1242w, 1233w, 1184m, 1171m, 1144m, 1119w, 1074w, 1049m, 1030m, 976m, 962m, 905w, 870w, 833w, 806m, 764s; δ_H(500 MHz; $CDCl_3$) 8.20 (1H, d, *J* 7.5 Ar *H*), 7.61-7.57 (3H, m, Ar *H*), 7.54-7.51 (1H, m, Ar *H*), 7.44 (1H, dd, *J* 0.5, 0.5 Ar *H*), 7.30-7.27 (3H, m, Ar *H*), 3.92 (3H, s, OC*H*$_3$); δ_C(125 MHz; $CDCl_3$) 156.6 (s), 152.0 (s), 144.7 (s), 135.1 (s), 132.9 (d), 130.1 (d), 129.3 (d), 129.0 (d), 125.7 (d), 125.4 (d), 124.5 (d), 119.5 (s), 55.1 (q, O*C*H_3); *m/z* (EI) 251 (M^+, 22%), 250 (100), 235 (11), 119 (6), 91 (6), 77 (8).

*7.3.2.2 4-Imino-3-phenyl-3,4-dihydroquinazolin-2(1H)-one (**90**) from the quinazolini-mine 89 (reaction conditions ii, Scheme 32).* To solution of 2-methoxy-3-phenyl-quinazolin-4(3*H*)-imine (**80**) (25.1 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of 10% HCl (0.5 mL) and the stirred mixture was heated at *ca*. 67 °C for 30 min and then

allowed to cool to *ca.* 20 °C. The reaction mixture was then neutralised (10% K_2CO_3) and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **90** (23.5 mg, 99%) as colorless plates, mp (DSC) onset 218.4 °C, peak max. 223.7 °C (from MeOH) (lit.,[237] 214-218 °C); (found: C, 70.93; H, 4.54; N, 17.61. $C_{14}H_{11}N_3O$ requires C, 70.87; H, 4.67; N, 17.71%); R_f 0.32 (DCM/*t*-BuOMe, 70:30); λ_{max}(DCM)/nm 246 inf (log ε 4.37), 294 inf (3.88), 306 (4.07), 318 (4.01); ν_{max}/cm^{-1} 3294w, 3206w, 3152w and (NH), 3090w and 3065w (aryl C-H), 2997w, 2934w, 2891w and 2852w (alkyl C-H), 1688s (C=O), 1614s, 1491m, 1447m, 1406m, 1294s, 1267m, 1171m, 1157m, 1142m, 1117w, 1069w, 1042w, 962w, 907w, 864w, 839w, 829w, 791s, 775m, 756s; δ_H(500 MHz; CD_2Cl_2) 9.00 (1H, br s, Ar *H*), 8.15 (1H, br s, Ar *H*), 7.60 (2H, dd, *J* 6.8, 6.8 Ar *H*), 7.54 (1H, dd, *J* 7.3, 7.3 Ar *H*), 7.46 (1H, dd, *J* 7.6, 7.6 Ar *H*), 7.32 (2H, d, *J* 7.5 Ar *H*), 7.16 (1H, dd, *J* 7.5, 7.5 Ar *H*), 6.87 (1H, d, *J* 8.0 Ar *H*), 6.78 (1H, br s, N*H*); δ_C(125 MHz; CD_2Cl_2) one C (s) missing 150.9 (s), 137.4 (s), 135.5 (s), 133.5 (d), 130.5 (d), 129.9 (d), 129.6 (d), 127.3 (d), 123.4 (d), 116.0 (s), 115.2 (d); *m/z* (EI) 238 (3), 237 (M^+, 20%), 236 (100), 195 (1), 145 (1), 118 (14), 104 (2), 91 (14), 77 (6), 65 (6).

*7.3.2.3 4-Imino-3-phenyl-3,4-dihydroquinazolin-2(1H)-one (**90**) from the quinazolin-imine **80** (reaction conditions iii, Scheme 32).*To solution of 4-imino-3-phenyl-3,4-dihydro-quinazoline-2-carbonitrile (**80**) (24.6 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of NaOH (4 mg, 0.1 mmol) in MeOH (0.5 mL) and the stirred mixture was heated at *ca*. 67 °C for 3 h and then allowed to cool to *ca.* 20 °C. The reaction mixture was then acidified (10% HCl) and the volatiles evaporated under reduced pressure. The remaining solid was then dissolved (H_2O), neutralised (10% K_2CO_3) and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **90** (23.4 mg, 99%) as colorless plates, mp (DSC) onset 218.4 °C, peak max. 223.7 °C (from MeOH) (lit.,[237] 214-218 °C) identical to the sample described above.

*7.3.2.4 3-Phenylquinazoline-2,4(1H,3H)-dione (**91**) from the quinazolinimine **90** (reaction conditions iv, Scheme 32).*To 4-imino-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (**90**) (23.7 mg, 0.1 mmol) was added a solution of 1N NaOH (1 mL) and the reaction mixture left to stir at *ca*. 20 °C for 7 d. The reaction mixture was then neutralised (10% HCl) and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried

(Na_2SO_4). Removal of the volatiles gave the title compound **91** (21.5 mg, 90%) as colorless plates, mp (DSC) onset 281.2 °C, peak max. 281.8 °C (lit.,[238] 281-282 °C) (from *c*-hexane/EtOH, 50:50); R_f 0.52 (DCM/*t*-BuOMe, 80:20); λ_{max}(DCM)/nm 242 inf (log ε 3.97), 309 (3.47), 3.19 (3.39); ν_{max}/cm^{-1} 3213w, 3198w, 3122w, 3080w, 3057w, 3020w, 3003w (aryl C-H), 2941w, 2899w and 2808w (alkyl C-H), 1726m (C=O), 1697w, 1659s (C=O), 1626m, 1611m, 1591m, 1518w, 1493m, 1445m, 1400m, 1341w, 1327w, 1288m, 1273w, 1240w, 1150m, 1072w, 1026w, 1017w, 876w, 866w, 817w, 783w, 752s; δ_H(300 MHz; $CDCl_3$) 9.52 (1H, s, Ar *H*), 8.15 (1H, dd, *J* 1.5, 1.5 Ar *H*), 7.60-7.49 (4H, m, Ar *H*), 7.34-7.30 (2H, m, Ar *H*), 6.94 (1H, d, *J* 8.1, Ar *H*); δ_C(75 MHz; $CDCl_3$) one C (s) missing 162.5 (s), 151.4 (s), 138.6 (s), 135.4 (d), 134.8 (s), 129.5 (d), 128.9 (d), 128.8 (d), 128.5 (d), 123.6 (d), 115.1 (d), 114.8 (s); *m/z* (EI) 238 (M^+, 100%), 237 (31), 146 (51), 119 (100), 93 (48), 90 (17), 77 (8), 64 (22).

*7.3.3. Base hydrolysis of 4-anilinoquinazoline-2-carbonitrile (**79**) (Scheme 33)*

*7.3.3.1 4-Anilino-2-methoxyquinazoline (**92**).* To a solution of 4-anilinoquinazoline-2-carbonitrile (**79**) (24.6 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of NaOH (4 mg, 0.1 mmol) in MeOH (0.5 mL) and the stirred mixture was heated at *ca*. 67 °C for 4 d and then allowed to cool to *ca.* 20 °C. The reaction mixture was then diluted (H_2O), neutralised (10% HCl) and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **92** (17.8 mg, 71%) as pale yellow plates, mp (DSC) onset 198.4 °C, peak max. 200.9 °C, decomp. onset 206.1 °C, peak. max. 208.9 °C (lit.,[239] 198-200 °C) (from DCM/*n*-pentane, 60:40); R_f 0.45 (DCM/*t*-BuOMe, 80:20); λ_{max}(DCM)/nm 278 (4.17), 295 inf (4.02), 322 inf (4.06), 335 (4.71), 349 inf (4.08); ν_{max}/cm^{-1} 3161w, 3051w (aryl C-H), 2986w, 1620m, 1599m, 1568s, 1530m, 1497s, 1470m, 1445s, 1416m, 1373s, 1323s, 1292w, 1259m, 1190w, 1177w, 1138w, 1103w, 1072m, 1030w, 991w, 912w, 879w, 871w, 853w, 841w, 800w, 766m, 754m; δ_H(500 MHz; $CDCl_3$) 7.80-7.76 (3H, m, Ar *H*), 7.74-7.69 (2H, m, Ar *H*), 7.46 (1H, br s, N*H*), 7.41 (2H, dd, *J* 7.5, 7.5 Ar *H*), 7.37 (1H, ddd, *J* 7.3, 7.3, 2.0 Ar *H*), 7.16 (1H, dd, *J* 7.5, 7.5 Ar *H*), 4.07 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 162.6 (s), 159.5 (s), 152.1 (s), 138.1 (s), 133.2 (d), 129.1 (d), 127.5 (d), 124.4 (d), 123.8 (d), 121.5 (d), 120.5 (d), 112.3 (s, *C*≡N), 54.5 (q, O*C*H$_3$); *m/z* (EI) 251 (M^+, 46%), 250 (M^+-1, 100), 235 (11), 220 (26), 207 (7), 144 (6), 116 (9), 110 (6), 90 (9), 77 (20), 65 (14), 51 (11).

*7.3.4 Acid hydrolysis of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (Scheme 34)*

*7.3.4.1 4-Oxo-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**93**) (reaction conditions i, Scheme 34).* To a stirred solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (24.6 mg, 0.1 mmol) in DMSO (1 mL) was added TFA (7.7 μL, 0.1 mmol). The reaction mixture was heated at *ca.* 100 ^{o}C for 2 d and monitored by TLC. When no starting quinazoline remained (by TLC) the reaction mixture was allowed to cool to *ca.* 20 ^{o}C and then neutralised with 10% K_2CO_3, diluted in H_2O (3 mL) and extracted (*t*-BuOMe, 2 × 30 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica and chromatographed to give the title compound **93** (23.5 mg, 99%), as colorless needles, mp (hotstage) 193-194 ^{o}C (lit.,[240] 196-197 ^{o}C) (from *c*-hexane/EtOH, 90:10); R_f 0.55 (DCM/*t*-BuOMe, 95:05); λ_{max}(DCM)/nm 249 inf (log ε 3.70), 260 inf (3.54), 291 inf (3.71), 303 (3.79), 312 inf (3.73), 327 (3.59); ν_{max}/cm^{-1} 3076w, 3052w (aryl C-H), 2239w (C≡N), 1692s (C=O), 1605m, 1599m, 1584m, 1560m, 1491m, 1466m, 1462m, 1342s, 1323m, 1279s, 1236w, 1211w, 1159w, 1117w, 1107w, 1088w, 1076w, 1022w, 1009w, 972w, 893w, 885w, 847w, 799w, 777s, 768s; δ_H(500 MHz; $CDCl_3$) 8.37 (1H, d, *J* 5.0 Ar *H*), 7.92-7.86 (2H, m, Ar *H*), 7.69 (1H, dd, *J* 7.5, 7.5 Ar *H*), 7.63-7.60 (3H, m, Ar *H*), 7.43-7.41 (2H, m, Ar *H*); δ_C(75 MHz; $CDCl_3$) 160.1 (s), 146.5 (s), 135.4 (d), 135.2 (s), 131.5 (s), 130.7 (d), 130.3 (d), 130.1 (d), 128.7 (d), 128.2 (d), 127.5 (d), 123.0 (s), 111.0 (s, *C*≡N); *m/z* (EI) 247 (M$^+$, 100%), 219 (51), 192 (7), 166 (6), 129 (6), 119 (48), 102 (13), 90 (12), 77 (71), 63 (8), 51 (32).

*7.3.4.2 4-Oxo-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**93**) (reaction conditions ii, Scheme 34).* To a stirred solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (24.6 mg, 0.1 mmol) in THF/H_2O (50:50) (1 mL) was added conc. HCl (9 μL, 0.1 mmol). The reaction mixture was heated at *ca.* 65 ^{o}C for 24 h and monitored by TLC. When no starting quinazoline remained (by TLC) the reaction mixture was allowed to cool to *ca.* 20 ^{o}C and then neutralised with 10% K_2CO_3 and extracted (*t*-BuOMe, 2 × 30 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica and chromatographed to give the title compound **93** (21.5 mg, 87%), as colorless needles, mp 193-194 ^{o}C (lit.,[240] 196-197 ^{o}C) identical to that described above.

*7.3.4.3 3-Phenylquinazoline-2,4(1H,3H)-dione (**91**) [from the quinazolinone **93** (reaction conditions iii, Scheme 34]*. To a stirred solution of 4-oxo-3-phenyl-3,4-dihydro-

quinazoline-2-carbonitrile (**93**) (23.7 mg, 0.1 mmol) in THF/H_2O (50:50) (1 mL) was added conc. HCl (18 μL, 0.2 mmol). The reaction mixture was heated at *ca.* 65 ^oC for 3 d and monitored by TLC. When no starting quinazoline remained (by TLC) the reaction mixture was allowed to cool to *ca.* 20 ^oC and then neutralised with 10% K_2CO_3 and extracted (*t*-BuOMe, 60 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica and chromatographed to give the title compound **91** (22.8 mg, 96%), as colorless plates, mp (DSC) onset 281.2 ^oC, peak max. 281.8 ^oC (lit.,[238] 281-282 ^oC) identical to authentic sample.

*7.3.4.4 3-Phenylquinazoline-2,4(1H,3H)-dione (**91**) from the quinazolinimine **80** (reaction conditions iv, Scheme 34)*. To a stirred solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (24.6 mg, 0.1 mmol) in THF/H_2O (50:50) (1 mL) was added concd. HCl (56 μL, 0.4 mmol). The reaction mixture was heated at *ca.* 65 ^oC for 1.5 d and monitored by TLC. When no starting quinazoline remained (by TLC) the reaction mixture was allowed to cool to *ca.* 20 ^oC and then neutralised with 10% K_2CO_3 and extracted (*t*-BuOMe, 60 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica and chromatographed to give the title compound **91** (23.6 mg, 99%), as colorless plates, mp (DSC) onset 281.2 ^oC, peak max. 281.8 ^oC (lit.,[238] 281-282 ^oC) (from *c*-hexane/EtOH, 50:50) identical to an authentic sample.

*7.3.5 Hydration of 4-anilinoquinazoline-2-carbonitrile (**79**)*

*7.3.5.1 4-Anilinoquinazoline-2-carboxamide (**94**)*. To 4-anilinoquinazoline-2-carbonitrile (**79**) (24.6 mg, 0.10 mmol) was added concd. HCl (0.5 mL). The reaction mixture was heated at *ca.* 65 ^oC for 16 h and monitored by TLC. When no starting material remained the reaction mixture was allowed to cool to *ca.* 20 ^oC and neutralised with 6M NaOH followed by precipitation and filtration of the *title compound* **94** (18.2 mg, 69%), as colorless needles, mp (DSC) onset 229.6 ^oC, peak max. 230.1 ^oC (from THF/*n*-pentane, 60:40); (found: C, 68.26; H, 4.69; N, 20.92. $C_{15}H_{12}N_4O$ requires C, 68.17; H, 4.58; N, 21.20%); R_f 0.48 (THF/DCM, 50:50); λ_{max}(DCM)/nm 339 (log ε 4.22); ν_{max}/cm^{-1} 3505w, 3414w, 3289w and 3186w (NH), 1680w, 1638m, 1626m, 1609w, 1566s, 1531m, 1493m, 1487s, 1447m, 1416s, 1368m, 1315w, 1302w, 1292w, 1256w, 1213w, 1157w, 1134w, 1096w, 1078w, 1030w, 989w, 910w, 883w, 870w, 847w, 796w, 768m, 758s; δ_H(500 MHz; $CDCl_3$) 9.98 (1H, s, Ar *H*), 8.61 (1H, d, *J* 10.0 Ar *H*), 7.97-7.90 (4H, m, Ar *H*), 7.88 (1H, br s, N*H*), 7.70 (1H, dd, *J* 7.5, 7.5 Ar *H*), 7.68 (1H, br s, N*H*), 7.43 (2H, dd, *J* 7.5, 7.5 Ar

H), 7.17 (1H, dd, *J* 7.5, 7.5 Ar *H*); δ_C(75 MHz; $CDCl_3$) 165.7 (s), 158.4 (s), 154.5 (s), 149.5 (s), 139.0 (s), 133.7 (d), 128.7 (d), 128.6 (d), 127.6 (d), 124.1 (d), 123.2 (d), 122.4 (d), 114.9 (s); *m/z* (EI) 264 (M^+, 92%), 219 (100), 192 (5), 129 (5), 110 (14), 92 (13), 77 (35), 65 (8), 51 (16).

7.4 Compounds related to chapter 4

*7.4.1 The reaction of TCNE with 2-amino-N'-phenylbenzamidine (**63**) according to the reported literature*[199]

To a stirred solution of TCNE (256 mg, 2.00 mmol) in dry EtOAc (10 mL) at *ca*. 20 °C was added a solution of 2-amino-*N'*-phenylbenzamidine (**63**) (211 mg, 1.00 mmol) in dry EtOAc (10 mL) and left to stir for 5 h at *ca*. 20 °C. The reaction mixture was then adsorbed onto silica and chromatographed (DCM/*t*-BuOMe, 90:05) to give *2-[2-(2-aminophenyl)-5-imino-1-phenyl-1,5-dihydro-4*H*-imidazol-4-ylidene]malononitrile* (**105**) (38.2 mg, 12%) as red needles, mp (DSC) decomp. onset 197.9 °C, peak max. 201.2 °C (from *n*-pentane/THF, 90:10); R_f 0.47 (DCM/Et_2O, 98:02); (found: C, 69.20; H, 3.72; N, 26.83. $C_{18}H_{12}N_6$ requires C, 69.22; H, 3.87; N, 26.91%); λ_{max}(DCM)/nm 256 inf (log ε 4.36), 296 inf (4.21), 336 (4.34), 407 (4.37), 431 (4.49), 510 (4.48); ν_{max}/cm^{-1} 3404w (NH_2), 3327w, 3285w and 3231w (NH), 2226w and 2207w (C≡N), 1622m, 1578w, 1551w, 1495s, 1477s, 1422s, 1396s, 1341m, 1318m, 1267m, 1248s, 1229m, 1198w, 1169m, 1113w, 1077w, 1067w, 1026w, 989w, 943w, 877w, 847w, 833w, 812w, 785w, 774w, 744s, 721w; δ_H(500 MHz; DMSO-d_6) 9.93 (1H, s, N*H*), 7.75 (2H, br s, NH_2), 7.61-7.59 (3H, m, Ar *H*), 7.40 (2H, d, *J* 6.5, Ar *H*), 7.18 (1H, dd, *J* 7.8, 7.8, Ar *H*), 6.81 (1H, d, *J* 9.0, Ar *H*), 6.59 (1H, d, *J* 8.5, Ar *H*), 6.17 (1H, dd, *J* 8.3, 8.3, Ar *H*); δ_C(125 MHz; DMSO-d_6) one C (d) resonance missing, 169.1 (s), 166.7 (s), 155.2 (s), 154.5 (s), 135.6 (d), 134.0 (s), 130.7 (d), 130.1 (d), 128.8 (d), 117.7 (d), 115.0 (d), 114.3 (s, *C*≡N), 113.4 (s, *C*≡N), 104.2 (s), 63.2 [s, *C*$(CN)_2$]; *m/z* (EI) 312 (M^+, 100%), 284 (7), 245 (8), 220 (11), 194 (22), 167 (8), 118 (35), 104 (22), 92 (14), 77 (46), 65 (10), 51 (18). Further elution (DCM/*t*-BuOMe, 90:20) gave 4-(phenylamino)quinazoline-2-carbonitrile (**79**) (92.6 mg, 37%) as colorless needles, mp (hotstage) 210-211 °C (from $CHCl_3$), mp (DSC) onset 211.7 °C, peak max. 212.5 °C (lit.,[199] 84-85 °C) (from $CHCl_3$); R_f 0.58 (DCM/*t*-BuOMe, 95:05); (found: C, 73.29; H, 3.97; N, 22.60. $C_{15}H_{10}N_4$ requires C, 73.16; H, 4.09; N, 22.75%); λ_{max}(DCM)/nm 245 (log ε 3.66), 259 (4.75), 280 (3.28), 336 (4.27); ν_{max}/cm^{-1} 3402w, 3373w and 3346w (NH), 3061w and 3011w (aryl C-H), 2247w (C≡N), 1614m, 1607m, 1568s, 1530m, 1522m, 1495s, 1487s, 1449m, 1422m, 1412m, 1369m, 1361m, 1317m, 1304w, 1292w, 1258w, 1217w, 1175w, 1161w, 1125w, 1107w, 1094w, 1078w, 1032w, 993w, 903w, 864w, 795w, 789w; δ_H(500 MHz; $CDCl_3$) 7.99 (1H, d, *J* 8.0, Ar *H*), 7.94 (1H, d, *J* 8.0, Ar *H*), 7.91 (1H, d, *J* 7.5, Ar *H*), 7.78 (2H, d, *J* 8.0, Ar *H*), 7.73 (1H, dd, *J* 7.8, 7.8 Ar *H*), 7.63 (1H, br s,

N*H*), 7.46 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.24 (1H, dd, *J* 7.5, 7.5, Ar *H*); δ_H(500 MHz; DMSO-d_6) 10.31 (1H, br s, N*H*), 8.62 (1H, d, *J* 8.0, Ar *H*), 7.98 (1H, dd, *J* 8.0, 8.0, Ar *H*), 7.88 (1H, d, *J* 8.0, Ar *H*), 7.81 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.75 (2H, d, *J* 7.3, Ar *H*), 7.46 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.23 (1H, dd, *J* 7.5, 7.5, Ar *H*); δ_C(75 MHz; DMSO-d_6) 158.5 (s), 149.0 (s), 140.1 (s), 138.1 (s), 134.5 (d), 129.1 (d), 128.8 (d), 128.2 (d), 125.2 (d), 123.45 (d), 123.4 (d), 117.0 (s), 115.6 (s); *m/z* (EI) 246 (M^+, 42%), 245 (M^+-1, 100), 219 (2), 192 (4), 169 (8), 123 (6), 102 (10), 97 (7), 77 (14). Further elution (DCM/*t*-BuOMe, 90:20) gave 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (4.7 mg, 2%) as colorless needles, mp (hotstage) 141-142 °C (lit.,[271] 141-142 °C) (from *c*-hexane), mp (DSC) onset 143.9 °C, peak max. 146.2 °C (from *c*-hexane); R_f 0.48 (DCM/*t*-BuOMe, 90:10); λ_{max}(DCM)/nm 245 inf (4.18), 255 (4.13), 265 (4.19), 274 (4.11), 298 inf (3.77), 311 (3.94), 324 (3.99), 340 inf (3.85); ν_{max}/cm^{-1} 3341w, 3308w (NH), 3071w (Ar CH), 2239w (C≡N), 1643m, 1605w, 1574w, 1560m, 1491w, 1472w, 1462m, 1348m, 1302m, 1283m, 1227w, 1217w, 1167m, 1138m, 1030w, 1007w, 997w, 876w, 827w, 800w, 760s; δ_H(300 MHz; $CDCl_3$) 8.25 (1H, d, *J* 6.9, Ar *H*), 7.69-7.63 (5H, m, Ar *H*), 7.54 (1H, ddd, *J* 7.4, 7.4, 1.8, Ar *H*), 7.44-7.40 (2H, m, Ar *H*), 6.71 (1H, br s, N*H*); δ_C(125 MHz; $CDCl_3$) 153.4 (s), 143.2 (s), 135.0 (s), 133.4 (d), 131.3 (d), 131.2 (s), 131.0 (d), 129.9 (d), 129.0 (d), 128.4 (d), 125.6 (d), 122.5 (s), 111.3 (s, *C*≡N); *m/z* (EI) 246 (M^+, 34%), 245 (M^+-H, 100), 236 (7), 219 (17), 192 (11), 160 (8), 141 (7), 129 (7), 118 (12), 113 (11), 111 (12), 102 (25), 97 (17), 91 (20), 85 (19), 83 (17), 77 (64), identical to an authentic sample.

*7.4.2 Preparation of 2-[2-(2-aminophenyl)-1-aryl-5-imino-1,5-dihydro-4H-imidazol-4-ylidene]malononitriles **105-112** (see Table 5, entries 1-7, Conditions A)*

*7.4.2.1 2-[2-(2-Aminophenyl)-5-imino-1-phenyl-1,5-dihydro-4H-imidazol-4-ylidene]-malononitrile (**105**) (typical procedure).* To a stirred solution of TCNE (128 mg, 1.00 mmol) in dry EtOAc (10 mL) at *ca*. 20 °C was added 85% formic acid (18.9 μL, 0.5 equiv) and the mixture was then heated to *ca*. 77 °C. To this mixture, a solution of 2-amino-*N*′-phenylbenzamidine (**63**) (211 mg, 1.00 mmol) in dry EtOAc (10 mL) was added dropwise (10 min) and left to stir for 2 h at *ca*. 77 °C. On cooling to *ca*. 20 °C, the reaction mixture was adsorbed onto silca and chromatographed (DCM/*t*-BuOMe, 90:05) to give the title compound **105** (141.2 mg, 45%) as red needles, mp (DSC) decomp. onset 197.9 °C, peak max. 201.2 °C (from *n*-pentane/THF, 90:10); R_f 0.47 (DCM/Et_2O, 98:02); identical to that described above. Further elution (DCM/*t*-BuOMe, 95:05) gave 4-(phenylamino)-

quinazoline-2-carbonitrile (**79**) (14.2 mg, 6%) as colorless needles, mp (hotstage) 210-211 °C (lit.,[199] 84-85 °C) (from $CHCl_3$); R_f 0.58 (DCM/*t*-BuOMe, 95:05), identical to that described above. Further elution (DCM/*t*-BuOMe, 95:10) gave a trace of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) as colorless needles, mp (hotstage) 141-142 °C (lit.,[271] 141-142 °C) (from *c*-hexane); R_f 0.48 (DCM/*t*-BuOMe, 90:10), identical to that described above.

*7.4.2.2 2-[2-(2-Aminophenyl)-5-imino-1-(p-tolyl)-1,5-dihydro-4H-imidazol-4-ylidene]-malononitrile (**107**).* Similar treatment of 2-amino-*N*'-(*p*-tolyl)benzamidine (**64**) (225 mg, 1.0 mmol) gave the *title compound* **107** (134.2 mg, 41%) as red needles, mp (DSC) decomp. onset 175.3 °C, peak max. 188.6 °C (from *n*-pentane/THF, 90:10); R_f 0.53 (DCM/Et_2O, 98:02); (found: C, 69.87; H, 4.43; N, 25.68. $C_{19}H_{14}N_6$ requires C, 69.92; H, 4.32; N, 25.75%); λ_{max}(DCM)/nm 255 inf (log ε 4.34), 297 (4.23), 335 (4.23), 406 inf (4.27), 432 (4.40), 507 (4.40); ν_{max}/cm^{-1} 3433w (NH_2), 3364w, 3314w and 3265w (NH), 2220 (C≡N), 1656w, 1630m, 1609w, 1578w, 1574w, 1551w, 1510w, 1493s, 1477s, 1425m, 1396s, 1354m, 1317m, 1310m, 1273m, 1254s, 1234m, 1201w, 1169m, 1153w, 1120w, 1070w, 1018w, 993w, 982w, 943w, 934w, 860m, 835w, 826m, 764m, 719s; δ_H(500 MHz; DMSO-d_6) 9.87 (1H, br s, N*H*), 7.74 (2H, br s, NH_2), 7.40 (2H, d, *J* 7.5, Ar *H*), 7.27 (2H, d, *J* 8.0, Ar *H*), 7.19 (1H, dd, *J* 7.8, 7.8, Ar *H*), 6.81 (1H, d, *J* 8.5, Ar *H*), 6.66 (1H, d, *J* 8.5, Ar *H*), 6.20 (1H, dd, *J* 7.5, 7.5, Ar *H*), 2.40 (3H, s, CH_3); δ_C(125 MHz; DMSO-d_6) 169.2 (s), 166.7 (s), 155.4 (s), 154.5 (s), 139.8 (s), 135.6 (d), 131.3 (s), 131.2 (d), 130.1 (d), 128.5 (d), 117.7 (d), 115.0 (d), 114.3 (s, *C*≡N), 113.5 (s, *C*≡N), 104.3 (s), 63.1 [s, *C*$(CN)_2$], 20.9 (q, *C*H_3); *m*/*z* (MALDI-TOF) 328 (MH^++1, 100%), 274 (23), 261 (30), 242 (60), 209 (28), 153 (6), 130 (7).

7.4.2.3 2-[2-(2-Aminophenyl)-5-imino-1-(4-methoxyphenyl)-1,5-dihydro-4*H*-imidazol-4-ylidene]malononitrile (**108**). Similar treatment of 2-amino-*N*'-(4-methoxyphenyl)-benzamidine (**51**) (mg, 1.0 mmol) gave the *title compound* **108** (163.2 mg, 48%) as red needles, mp (DSC) decomp. onset 207.0 °C, peak max. 208.6 °C (from *n*-pentane/THF, 90:10); R_f 0.50 (DCM/Et_2O, 98:02); (found: C, 66.65; H, 4.04; N, 24.48. $C_{19}H_{14}N_6O$ requires C, 66.66; H, 4.12; N, 24.55%); λ_{max}(DCM)/nm 256 inf (log ε 4.22), 275 inf (4.10), 283 (4.10), 302 (4.10), 326 inf (4.04), 379 inf (3.96), 408 inf (4.07), 433 (4.19), 509 (4.21); ν_{max}/cm^{-1} 3424w (NH_2), 3281w and 3262w (NH), 2228w (C≡N), 1659w, 1622w, 1605w, 1582w, 1549w, 1512m, 1493s, 1479s, 1441w, 1422m, 1418m, 1391s, 1350s, 1315m,

1300m, 1273s, 1254s, 1221s, 1204w, 1190w, 1175w, 1165m, 1109w, 1105w, 1069w, 1015w, 937w, 881m, 843m, 833w, 825w, 804w, 777w, 768w, 750s; δ_H(500 MHz; DMSO-d_6) 9.87 (1H, br s, N*H*), 7.77 (2H, br s, NH_2), 7.34 (2H, d, *J* 8.5, Ar *H*), 7.19 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.14 (2H, d, *J* 8.5, Ar *H*), 6.81 (1H, d, *J* 8.5, Ar *H*), 6.69 (1H, d, *J* 8.5, Ar *H*), 6.22 (1H, dd, *J* 6.5, 6.5, Ar *H*), 3.83 (3H, s, OCH_3); δ_C(125 MHz; DMSO-d_6) 169.1 (s), 166.7 (s), 160.1 (s), 155.7 (s), 154.6 (s), 135.6 (d), 130.15 (d), 130.1 (d), 126.2 (s), 117.7 (d), 115.8 (d), 115.1 (d), 114.4 (s, *C*≡N), 113.5 (s, *C*≡N), 104.3 (s), 62.9 [s, *C*$(CN)_2$], 55.6 (q, O*C*H_3); *m*/*z* (MALDI-TOF) 344 (MH^++1, 18%), 343 (MH^+, 100), 342 (M^+, 7), 226 (5), 225 (65).

*7.4.2.4 2-[2-(2-Aminophenyl)-1-(4-fluorophenyl)-5-imino-1,5-dihydro-4H-imidazol-4-ylidene]malononitrile (**109**).* Similar treatment of 2-amino-*N*'-(4-fluorophenyl)benzamidine (**66**) (229 mg, 1.0 mmol) gave the *title compound* **109** (168. mg, 51%) as red needles, mp (DSC) decomp. onset 195.7 ^oC, peak max. 201.2 ^oC (from *n*-pentane/THF, 90:10); R_f 0.56 (DCM/Et_2O, 98:02); (found: C, 65.32; H, 3.25; N, 25.29. $C_{18}H_{11}FN_6$ requires C, 65.45; H, 3.36; N, 25.44%); λ_{max}(DCM)/nm 256 inf (log ε 4.02), 302 inf (3.93), 336 (4.07), 404 inf (4.10), 429 (4.23), 510 (4.22); ν_{max}/cm^{-1} 3428w (NH_2), 3246w (NH), 3034w (aryl C-H), 2224w (C≡N), 1661w, 1622w, 1607w, 1599w, 1574w, 1549w, 1506m, 1489s, 1481s, 1422m, 1393s, 1350s, 1319w, 1273m, 1253w, 1236w, 1219s, 1200m, 1171m, 1157w, 1096w, 1069w, 984w, 889m, 847m, 833w, 824w, 812w, 771w, 745s, 729w; δ_H(500 MHz; DMSO-d_6) 10.1 (1H, br s, N*H*), 7.71 (2H, br s, NH_2), 7.50-7.43 (4H, m, Ar *H*), 7.20 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 6.81 (1H, d, *J* 8.5, Ar *H*), 6.63 (1H, d, *J* 8.0, Ar *H*), 6.24 (1H, dd, *J* 7.8, 7.8, Ar *H*); δ_C(125 MHz; DMSO-d_6) 169.1 (s), 166.8 (s), 162.5 (d, $^1J_{CF}$ 245.9 Hz), 155.0 (s), 154.4 (s), 135.6 (d), 131.4 (d, $^3J_{CF}$ 9.0 Hz), 130.3 (s), 130.0 (d), 117.7 (d), 117.5 (d, $^2J_{CF}$ 23.0 Hz), 115.1 (d), 114.3 (s, *C*≡N), 113.4 (s, *C*≡N), 104.3 (s), 63.1 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 332 (MH^++1, 38%), 331 (MH^+, 100), 330 (M^+, 7), 242 (5), 214 (2), 213 (30).

*7.4.2.5 2-[2-(2-Aminophenyl)-1-(4-chlorophenyl)-5-imino-1,5-dihydro-4H-imidazol-4-ylidene]malononitrile (**110**).* Similar treatment of 2-amino-*N*'-(4-chlorophenyl)benzamidine (**67**) (246 mg, 1.0 mmol) gave the *title compound* **110** (149.0 mg, 43%) as red needles, mp (DSC) decomp. onset 171.1 ^oC, peak max. 183.5 ^oC (from *n*-pentane/THF, 90:10); R_f 0.44 (DCM/Et_2O, 98:02); (found: C, 62.44; H, 3.18; N, 24.16. $C_{18}H_{11}ClN_6$ requires C, 62.34; H, 3.20; N, 24.24%); λ_{max}(DCM)/nm 259 inf (log ε 4.08), 301 inf (4.96), 337 (4.07),

405 inf (4.02), 429 (4.13), 510 (4.12); ν_{max}/cm^{-1} 3406w (NH_2), 3310w and 3281w (NH), 2224w and 2208w (C≡N), 1643w, 1624m, 1574w, 1553w, 1493s, 1477s, 1421s, 1396s, 1341m, 1317m, 1265m, 1248s, 1204w, 1169m, 1117w, 1092m, 1065m, 1018w, 993w, 986w, 937w, 849w, 831m, 766w, 747s, 718m; δ_H(500 MHz; DMSO-d_6) 10.19 (1H, br s, N*H*), 7.66 (2H, d, *J* 8.5, Ar *H*), 7.64 (2H, br s, NH_2), 7.44 (2H, d, *J* 8.5, Ar *H*), 7.20 (1H, dd, *J* 7.5, 7.5 Ar *H*), 6.80 (1H, d, *J* 8.5, Ar *H*), 6.63 (1H, d, *J* 8.0, Ar *H*), 6.26 (1H, dd, *J* 7.5, 7.5 Ar *H*); δ_C(125 MHz; DMSO-d_6) 169.1 (s), 166.8 (s), 154.7 (s), 154.2 (s), 135.5 (d), 134.6 (s), 133.0 (s), 130.8 (d), 130.1 (d), 128.7 (d), 117.7 (d), 115.1 (d), 114.3 (s, *C*≡N), 113.4 (s, *C*≡N), 104.4 (s), 63.3 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 349 (MH^++2, 25%), 348 (MH^++1, 20), 347 (MH^+, 100), 281 (45), 229 (46).

*7.4.2.6 2-[2-(2-Aminophenyl)-1-(4-bromophenyl)-5-imino-1,5-dihydro-4H-imidazol-4-ylidene]malononitrile (**111**).* Similar treatment of 2-amino-*N*'-(4-bromophenyl)benzamidine (**68**) (290 mg, 1.0 mmol) gave the *title compound* **111** (165.1 mg, 42%) as red needles, mp (DSC) decomp. onset 184.7 °C, peak max. 190.4 °C (from *n*-pentane/THF, 90:10); R_f 0.50 (DCM/Et_2O, 98:02); (found: C, 55.36; H, 2.83; N, 21.36. $C_{18}H_{11}BrN_6$ requires C, 55.26; H, 2.83; N, 21.48%); λ_{max}(DCM)/nm 263 inf (log ε 4.11), 301 inf (4.00), 338 (4.13), 405 inf (3.99), 430 (4.10), 512 (4.07); ν_{max}/cm^{-1} 3389w (NH_2), 3302w and 3269w (NH), 2229w and 2212w (C≡N), 1639w, 1624m, 1612w, 1574w, 1549w, 1491s, 1477s, 1418s, 1396s, 1368w, 1342m, 1315w, 1277m, 1252s, 1209w, 1171w, 1119w, 1070m, 1063m, 1016w, 988w, 937m, 847m, 829m, 766m, 752s, 716m; δ_H(500 MHz; DMSO-d_6) 10.20 (1H, br s, N*H*), 7.66 (1H, d, *J* 8.5, Ar *H*), 7.64 (2H, br s, NH_2), 7.37 (2H, d, *J* 8.5, Ar *H*), 7.21 (1H, dd, *J* 7.5, 7.5, Ar *H*), 6.81 (1H, d, *J* 8.5, Ar *H*), 6.64 (1H, d, *J* 9.0, Ar *H*), 6.27 (1H, dd, *J* 7.8, 7.8, Ar *H*); δ_C(125 MHz; DMSO-d_6) 169.1 (s), 166.8 (s), 158.3 (s), 154.6 (s), 154.1 (s), 135.5 (d), 133.4 (s), 131.0 (d), 130.1 (d), 129.2 (d), 117.7 (d), 115.1 (d), 114.3 (s, *C*≡N), 113.4 (s, *C*≡N), 104.4 (s), 63.3 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 394 (MH^++2, 13%), 392 (MH^++1, 30), 391 (MH^+, 71), 327 (29), 325 (13), 275 (68), 273 (55), 257 (100), 138 (21), 134 (19).

*7.4.2.7 2-[2-(2-Aminophenyl)-1-(3,4-dimethoxyphenyl)-5-imino-1,5-dihydro-4H-imidazol-4-ylidene]malononitrile (**112**).* Similar treatment of 2-amino-*N*'-(3,4-dimethoxyphenyl)benzamidine (**71**) (271 mg, 1.0 mmol) gave the *title compound* **112** (158.0 mg, 44%) as maroon needles, mp (DSC) decomp. onset 153.9 °C, peak max. 156.7 °C (from *n*-pentane/THF, 90:10); R_f 0.41 (DCM/Et_2O, 95:05); (found: C, 64.39; H, 4.25; N, 22.48.

$C_{20}H_{16}N_6O_2$ requires C, 64.51; H, 4.33; N, 22.57%); λ_{max}(DCM)/nm 247 (log ε 4.30), 282 inf (4.09), 290 inf (4.13), 305 inf (4.17), 328 (4.21), 405 inf (4.17), 432 (4.20), 509 (4.23); ν_{max}/cm^{-1} 3435w and 3391w (NH_2), 3239w and 3198w (NH), 3086w (aryl C-H), 2932w and 2837w (alkyl C-H), 2220w (C≡N), 1624m, 1605w, 1578w, 1574w, 1553w, 1512s, 1493s, 1482s, 1425m, 1422m, 1414s, 1396s, 1344m, 1315w, 1290w, 1267s, 1252s, 1233s, 1167m, 1136w, 1090w, 1024w, 999w, 951w, 887w, 868w, 856w, 831w, 812w, 768m, 760m, 750w; δ_H(500 MHz; DMSO-d_6) 9.94 (1H, br s, N*H*), 7.84 (2H, br s, NH_2), 7.20 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.12 (1H, d, *J* 8.5, Ar *H*), 7.09 (1H, d, *J* 1.5, Ar *H*), 6.91 (1H, dd, *J* 8.3, 2.3, Ar *H*), 6.81 (1H, d, *J* 8.5, Ar *H*), 6.76 (1H, d, *J* 8.5, Ar *H*), 6.24 (1H, dd, *J* 7.8, 7.8 Ar *H*), 3.83 (3H, s, OCH_3). 3.72 (3H, s, OCH_3); δ_C(125 MHz; DMSO-d_6) 168.9 (s), 166.7 (s), 155.6 (s), 154.8 (s), 149.9 (s), 149.8 (s), 135.7 (d), 130.1 (d), 126.2 (s), 121.1 (d), 117.8 (d), 115.1 (d), 114.4 (s, *C*≡N), 113.5 (s, *C*≡N), 112.5 (d), 112.2 (d), 104.2 (s), 62.7 [s, *C*$(CN)_2$], 55.8 (q, O*C*H_3), 55.7 (q, O*C*H_3); *m*/*z* (MALDI-TOF) 373 (MH^+, 16%), 372 (M^+, 100), 242 (9).

*7.4.3 Preparation of 4-(arylamino)quinazoline-2-carbonitriles **79**, **113-118** (see Table 5, entries 8-14, Conditions B)*

*7.4.3.1 4-(Phenylamino)quinazoline-2-carbonitrile (**79**) (typical procedure).* To a stirred solution of 2-amino-*N'*-phenylbenzamidine (**63**) (211 mg, 1.00 mmol) in MeCN (10 mL) at *ca*. 20 °C was added glacial AcOH (57.0 μL, 1.00 mmol). To that mixture, was added dropwise a solution of TCNE (128 mg, 1.00 mmol) in MeCN (10 mL) at *ca*. 20 °C and left to stir for 7 h. The reaction mixture was then adsorbed onto silca and chromatographed (DCM/*t*-BuOMe, 95:05) to give the title compound **79** (238.1 mg, 97%) as colorless needles, mp (hotstage) 210-211 °C (lit.,[199] 84-85 °C) (from $CHCl_3$); R_f 0.58 (DCM/*t*-BuOMe, 95:05), identical to that described above. Further elution (DCM/*t*-BuOMe, 95:10) gave 4-imino-3-phenyl-3,4-dihydro-quinazoline-2-carbonitrile (**80**) (2.1 mg, 1%) as colorless needles, mp (hotstage) 141-142 °C (lit.,[271] 141-142 °C) (from *c*-hexane), R_f 0.48 (DCM/*t*-BuOMe, 90:10), identical to that described above.

*7.4.3.2 4-(p-Tolylamino)quinazoline-2-carbonitrile (**113**).* Similar treatment of 2-amino-*N*'-(*p*-tolyl)benzamidine (**64**) (225 mg, 1.0 mmol) gave the *title compound* **113** (255.0 mg, 98%) as colorless needles, mp (hotstage) 208-209 °C (lit.,[199] 130-131 °C) (from $CHCl_3$),

mp (DSC) onset 208.8 °C, peak max. 209.3 °C (from $CHCl_3$); R_f 0.78 (DCM/*t*-BuOMe, 95:05); ν_{max}/cm^{-1} 3389w (NH), 3048w (aryl C-H), 2953w, 2918w and 2855w (alkyl C-H), 2243w (C≡N), 1618s, 1607s, 1574s, 1566s, 1530s, 1495s, 1454w, 1423m, 1369s, 1319w, 1304w, 1267w, 1258w, 1234w, 1223w, 1217w, 1134w, 1090w, 997w, 864w, 810m, 799m, 790m, 768s; δ_H(500 MHz; DMSO-d_6) 10.25 (1H, br s, N*H*), 8.60 (1H, d, *J* 8.0, Ar *H*), 7.97 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.86 (1H, d, *J* 8.0, Ar *H*), 7.79 (1H, ddd, *J* 7.5, 7.5, 1.0, Ar *H*), 7.60 (2H, d, *J* 8.5, Ar *H*), 7.25 (2H, d, *J* 8.5, Ar *H*), 2.33 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 158.6 (s), 148.9 (s), 140.2 (s), 135.4 (s), 134.5 (s), 134.4 (d), 129.0 (d), 128.2 (d), 128.0 (d) 123.6 (d), 123.5 (d), 117.0 (s), 115.6 (s), 20.6 (q, *C*H_3); *m*/*z* (MALDI-TOF) 262 (MH^++1, 19%), 261 (MH^+, 100), 236 (2).

*7.4.3.3 4-[(4-Methoxyphenyl)amino]quinazoline-2-carbonitrile (**114**).* Similar treatment of 2-amino-*N*'-(4-methoxyphenyl)benzamidine (**51**) (241 mg, 1.0 mmol) gave the *title compound* **114** (268.4 mg, 97%) as pale yellow needles, mp (hotstage) 198-199 °C (lit.,[199] 90-91 °C) (from $CHCl_3$); mp (DSC) onset 197.4 °C, peak max. 199.1 °C (from $CHCl_3$); R_f 0.62 (DCM/*t*-BuOMe, 95:05); ν_{max}/cm^{-1} 3350m (NH), 3075w and 3049w (aryl C-H), 2953w (alkyl C-H), 2249w (C≡N), 1612w, 1600m, 1582s, 1564w, 1558w, 1514s, 1489m, 1456w, 1429w, 1408w, 1373m, 1358w, 1314m, 1296m, 1261m, 1253m, 1236m, 1225w, 1186w, 1171m, 1128w, 1111w, 1094w, 1038m, 995w, 868w, 860w, 820w, 799w, 787w, 768s, 758m; δ_H(500 MHz; DMSO-d_6) 10.25 (1H, br s, N*H*), 8.57 (1H, d, *J* 8.5, Ar *H*), 7.96 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.86 (1H, d, *J* 8.0, Ar *H*), 7.78 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.61 (2H, d, *J* 7.8, Ar *H*), 7.03 (2H, d, *J* 7.5, Ar *H*), 3.79 (3H, s, OCH_3); δ_C(125 MHz; DMSO-d_6) 158.6 (s), 156.9 (s), 148.8 (s), 140.3 (s), 134.4 (d), 130.7 (s), 129.0 (d), 128.1 (d), 125.3 (d), 123.4 (d), 117.1 (s), 115.6 (s), 114.0 (d), 55.4 (q, O*C*H_3); *m/z* (EI) 278 (MH^++1, 17%), 277 (MH^+, 100), 252 (2), 215 (1).

*7.4.3.4 4-[(4-Fluorophenyl)amino]quinazoline-2-carbonitrile (**115**).* Similar treatment of 2-amino-*N*'-(4-fluorophenyl)benzamidine (**66**) (229 mg, 1.0 mmol) gave the *title compound* **115** (258.8 mg, 98%) as pale yellow needles, mp (hotstage) 209-211 °C (from $CHCl_3$), mp (DSC) onset 210.8 °C, peak max. 212.2 °C (from $CHCl_3$); R_f 0.77 (DCM/*t*-BuOMe, 95:05); (found: C, 68.30; H, 3.30; N, 21.12. $C_{15}H_9FN_4$ requires C, 68.18; H, 3.43; N, 21.20%); λ_{max}(DCM)/nm 258 inf (log ε 4.22), 268 inf (4.20), 282 inf (4.15), 332 (4.35); ν_{max}/cm^{-1} 3385w (NH), 3059w and 3034w (aryl C-H), 2247w (C≡N), 1616m, 1607m, 1570s, 1558m, 1533m, 1506w, 1495s, 1456w, 1449w, 1425w, 1369m, 1321w, 1256w,

1246w, 1234w, 1217w, 1161w, 1130w, 1105w, 1034w, 976w, 955w, 897w, 864w, 831w, 795w, 789w, 766s, 745s; δ_H(500 MHz; DMSO-d_6) 10.34 (1H, br s, N*H*), 8.59 (1H, d, *J* 8.5, Ar *H*), 7.99 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.89 (1H, d, *J* 8.5, Ar *H*), 7.81 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.79-7.74 (2H, m, Ar *H*), 7.33-7.28 (2H, m, Ar *H*); δ_C(125 MHz; DMSO-d_6) 159.3 (d, $^1J_{CF}$ 241.3), 158.5 (s), 148.8 (s), 140.0 (s), 134.4 (d), 134.2 (s), 129.0 (d), 128.1 (d), 125.4 (d, $^3J_{CF}$ 8.3), 123.4 (d), 116.9 (s), 115.41 (d, $^2J_{CF}$ 22.3), 115.44 (s); *m/z* (EI) 265 (MH^+, 15%), 248 (55), 247 (100), 236 (7).

*7.4.3.5 4-[(4-Chlorophenyl)amino]quinazoline-2-carbonitrile (**116**).* Similar treatment of 2-amino-*N*'-(4-chlorophenyl)benzamidine (**67**) (246 mg, 1.0 mmol) gave the *title compound* **116** (264.8 mg, 95%) as colorless needles, mp (hotstage) 230-231 °C (lit.,[199] 208-201 °C) (from $CHCl_3$); mp (DSC) onset 230.1 °C, peak max. 230.7 °C (from $CHCl_3$); R_f 0.73 (DCM/*t*-BuOMe, 95:05); ν_{max}/cm^{-1} 3348w (NH), 3063w (aryl C-H), 2251w (C≡N), 1614m, 1601m, 1574s, 1564m, 1526s, 1497m, 1487s, 1456w, 1425m, 1400w, 1368m, 1359w, 1314w, 1258w, 1223w, 1179w, 1126w, 1098w, 1092w, 1016w, 993w, 864w, 854w, 816m, 787m, 766s, 752w; δ_H(500 MHz; DMSO-d_6) 10.37 (1H, br s, N*H*), 8.60 (1H, d, *J* 8.0, Ar *H*), 7.99 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.89 (1H, d, *J* 8.0, Ar *H*), 7.84-7.79 (3H, m, Ar *H*), 7.51 (2H, d, *J* 7.5, Ar H); δ_C(125 MHz; DMSO-d_6) 158.4 (s), 149.0 (s), 139.9 (s), 137.2 (s), 134.6 (d), 129.2 (d), 128.8 (s), 128.7 (d), 128.2 (d), 124.9 (d), 123.5 (d), 117.0 (s), 115.7 (s); *m/z* (MALDI-TOF) 283 (MH^++2, 25%), 282 (MH^++1, 9), 281 (MH^+, 100), 153 (7), 130 (3).

*7.4.3.6 4-[(4-Bromophenyl)amino]quinazoline-2-carbonitrile (**117**).* Similar treatment of 2-amino-*N*'-(4-bromophenyl)benzamidine (**68**) (290 mg, 1.0 mmol) gave the *title compound* **117** (314.7 mg, 97%) as pale yellow needles, mp (hotstage) 234.5-235 °C (lit.,[199] 176-177 °C) (from $CHCl_3$), mp (DSC) onset 233.0 °C, peak max. 233.6 °C, (from $CHCl_3$); R_f 0.77 (DCM/*t*-BuOMe, 95:05); ν_{max}/cm^{-1} 3352w (NH), 3063w (aryl C-H), 2255w (C≡N), 1616m, 1603m, 1570s, 1562m, 1522s, 1487s, 1456w, 1422m, 1398w, 1368m, 1354w, 1315m, 1296w, 1258w, 1236w, 1217w, 1182w, 1128w, 1076m, 1009w, 993m, 951w, 937w, 870w, 845w, 820s, 791m, 764s; δ_H(500 MHz; DMSO-d_6) 10.35 (1H, br s, Ar *H*), 8.60 (1H, d, *J* 8.0, Ar *H*), 8.00 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.90 (1H, d, *J* 8.5, Ar *H*), 7.82 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.75 (2H, d, *J* 8.5, Ar *H*), 7.64 (2H, d, *J* 7.5, Ar H); δ_C(125 MHz; DMSO-d_6) 158.4 (s), 149.0 (s), 139.9 (s), 137.6 (s), 134.6 (d), 131.7 (d),

129.3 (d), 128.3 (d), 125.2 (d), 123.5 (d), 117.0 (s), 115.7 (s); *m*/*z* (MALDI-TOF) 327 (MH^++2, 28%), 325 (MH^+, 33), 309 (4), 308 (19), 307 (100), 282 (3), 153 (30).

*7.4.3.7 4-[(3,4-Dimethoxyphenyl)amino]quinazoline-2-carbonitrile (**118**).* Similar treatment of 2-amino-*N*'-(3,4-dimethoxyphenyl)benzamidine (**71**) (271 mg, 1.0 mmol) gave the *title compound* **118** (286.0 mg, 93%) as pale yellow plates, mp (hotstage) 202-203 °C (from $CHCl_3$); mp (DSC) onset 202.1 °C, peak max. 203.9 °C (from $CHCl_3$); R_f 0.34 (DCM/*t*-BuOMe, 95:05); (found: C, 66.71; H, 4.52; N, 18.18. $C_{17}H_{14}N_4O_2$ requires C, 66.66; H, 4.61; N, 18.29%); λ_{max}(DCM)/nm 283 inf (3.76), 344 (3.67); ν_{max}/cm^{-1} 3375w (NH), 3017w (aryl C-H), 2937w and 2837w (alkyl C-H), 2247w (C≡N), 1622m, 1609w, 1574s, 1530m, 1518m, 1499s, 1464m, 1429w, 1414w, 1373m, 1323w, 1307w, 1265w, 1279w, 1236w, 1223s, 1202m, 1175w, 1165w, 1144m, 1090w, 1042w, 1028s, 999w, 955w, 870w, 843w, 800m, 792s, 772m, 761s, 746s; δ_H(500 MHz; DMSO-d_6) 10.23 (1H, br s, N*H*), 8.60 (1H, d, *J* 8.0, Ar *H*), 7.97 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.87 (1H, d, *J* 7.5, Ar *H*), 7.80 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.38 (1H, d, *J* 2.5, Ar *H*), 7.31 (1H, dd, *J* 9.0, 2.3, Ar *H*), 7.04 (1H, d, *J* 8.5, Ar *H*), 3.79 (6H, s, 2 × OC*H*$_3$); δ_C(125 MHz; DMSO-d_6) 158.5 (s), 148.9 (s), 148.6 (s), 146.5 (s), 140.2 (s), 134.4 (d), 131.1 (s), 129.0 (d), 128.2 (d), 123.4 (d), 117.0 (s), 115.8 (d), 115.6 (s), 111.8 (d), 108.5 (d), 55.8 (q, O*C*H$_3$), 55.7 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 308 (MH^++1, 13%), 307 (MH^+, 100), 306 (M^+, 8).

*7.4.4 Preparation of 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles **80-85**, **119** (see Table 1, entries 15-21, Conditions C)*

*7.4.4.1 4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**80**) (typical procedure).* To a stirred solution of TCNE (256 mg, 2.00 mmol) in dry MeCN (10 mL) cooled to *ca*. -20 °C was added dropwise a solution of 2-amino-*N*'-phenylbenzamidine (**63**) (211 mg, 1.00 mmol) in dry MeCN (10 mL). The reaction mixture was then and left to stir at *ca*. -20 °C for 1 d, after which time it was adsorbed onto silica and chromatographed (DCM/*t*-BuOMe, 95:05) to give 4-(phenylamino)quinazoline-2-carbonitrile (**79**) (71.0 mg, 29%) as colorless needles, mp (hotstage) 210-211 °C (lit.,[199] 84-85 °C) (from $CHCl_3$); R_f 0.58 (DCM/*t*-BuOMe, 95:05), identical to that described above. Further elution (DCM/*t*-BuOMe, 95:10) gave the title compound **80** (169.6 mg, 69%) as colorless needles, mp

(hotstage) 141-142 °C (lit.,[271] 141-142 °C) (from *c*-hexane); R_f 0.48 (DCM/*t*-BuOMe, 90:10); identical to that described above.

*7.4.4.2 4-Imino-3-p-tolyl-3,4-dihydroquinazoline-2-carbonitrile (**81**).* Similar treatment of 2-amino-*N*'-(*p*-tolyl)benzamidine (**64**) (225 mg, 1.0 mmol) gave the *title compound* **81** (160.3 mg, 62%) as colorless needles, mp (hotstage) 155-156 °C (lit.,[271] 155-156 °C) (from *n*-hexane/DCM, 90:10); R_f 0.60 (DCM/*t*-BuOMe, 90:10); δ_H(300 MHz; $CDCl_3$) 8.26 (1H, d, *J* 8.1, Ar *H*), 7.70–7.60 (2H, m, Ar *H*), 7.52 (1H, ddd, *J* 7.4, 7.4, 1.8, Ar *H*), 7.44 (2H, d, *J* 8.1, Ar *H*), 7.28 (2H, d, *J* 8.4, Ar *H*), 6.34 (1H, br s, N*H*), 2.47 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 153.5 (s), 143.3 (s), 141.7 (s), 133.4 (d), 132.2 (s), 131.7 (d), 131.3 (s), 129.8 (d), 128.6 (d), 128.3 (d), 125.7 (d), 122.4 (s), 111.3 (s, *C*≡N), 21.4 (q, *C*H_3); *m*/*z* (MALDI-TOF) 262 (MH^++1, 19%), 261 (MH^+, 100), 246 (24), 153 (2), identical to an authentic sample.

7.4.4.3 *4-Imino-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2-carbonitrile (**82**).* Similar treatment of 2-amino-*N*'-(4-methoxyphenyl)benzamidine (**51**) (241 mg, 1.0 mmol) gave the *title compound* **82** (172.0 mg, 62%) as colorless needles, mp (hotstage) 140-141 °C (lit.,[271.]140-141 °C) (from *n*-hexane/DCM, 90:10); R_f 0.42 (DCM/*t*-BuOMe, 90:10); δ_H(300 MHz; $CDCl_3$) 8.27 (1H, d, *J* 7.8, Ar *H*), 7.72–7.62 (2H, m, Ar *H*), 7.52 (1H, ddd, *J* 7.4, 7.4, 1.7, Ar *H*), 7.32 (2H, d, *J* 9.0, Ar *H*), 7.14 (2H, d, *J* 9.0, Ar *H*), 6.89 (1H, br s, N*H*), 3.91 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 161.3 (s), 153.5 (s), 143.2 (s), 133.3 (d), 131.6 (s), 130.1 (d), 129.7 (d), 128.2 (d), 127.0 (s), 125.6 (d), 122.5 (s), 116.1 (d), 111.4 (s), 55.6 (q); *m*/*z* (MALDI-TOF) 278 (MH^++1, 3%), 277 (MH^+, 100), 153 (2), 130 (13), identical to an authentic sample.

*7.4.4.4 3-(4-Fluorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**83**).* Similar treatment of 2-amino-*N*'-(4-fluorophenyl)benzamidine (**66**) (229 mg, 1.0 mmol) gave the *title compound* **83** (171.0 mg, 65%) as colorless needles, mp (hotstage) 163-163.5 °C (lit.,[271] 163-163.5 °C) (from *n*-hexane/DCM, 90:10); R_f 0.52 (DCM/*t*-BuOMe, 90:10); δ_H(300 MHz; $CDCl_3$) N*H* deuterium exchanged, 8.21 (1H, d, *J* 7.5, Ar *H*), 7.74-7.64 (2H, m, Ar *H*), 7.55 (1H, ddd, *J* 7.4, 7.4, 1.5, Ar *H*), 7.45-7.32 (4H, m, Ar *H*); δ_C(75 MHz; $CDCl_3$) 165.4 (s), 162.0 (d, $^1J_{CF}$ 252.9), 153.8 (s), 143.0 (s), 133.5 (d), 131.1 (d, $^3J_{CF}$ 9.1), 130.0 (d), 128.5 (d), 125.4 (d), 122.2 (s), 118.2 (d, $^2J_{CF}$ 22.7), 111.2 (s); *m*/*z* (MALDI-TOF) 265 (MH^+, 39%), 167 (32), 153 (100), 130 (9), identical to an authentic sample.

*7.4.4.5 3-(4-Chlorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**84**).* Similar treatment of 2-amino-*N*'-(4-chlorophenyl)benzamidine (**67**) (246 mg, 1.0 mmol) gave the *title compound* **84** (193.1 mg, 69%) as colorless needles, mp (hotstage) 209-210 ^{o}C (lit.,[271] 209-210 ^{o}C) (from *n*-hexane/DCM, 90:10); R_f 0.61 (DCM/*t*-BuOMe, 90:10); δ_H(300 MHz; $CDCl_3$) 8.21 (1H, d, *J* 8.1, Ar *H*), 7.71-7.64 (2H, m, Ar *H*), 7.65 (2H, d, *J* 8.4, Ar *H*), 7.56 (1H, ddd, *J* 7.4, 7.4, 1.4, Ar *H*), 7.38 (2H, d, *J* 8.7, Ar *H*), 5.70 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 153.8 (s), 143.0 (s), 137.5 (s), 133.7 (s), 133.6 (d), 131.3 (d), 130.9 (s), 130.4 (d), 130.1 (d), 128.6 (d), 125.4 (d), 122.1 (s), 111.2 (s); *m*/*z* (MALDI-TOF) 283 (MH^++2, 72%), 282 (MH^++1, 31), 281 (MH^+, 100), 246 (31), 188 (3), 153 (12), 130 (2), 116 (3), 100 (4), identical to an authentic sample.

*7.4.4.6 3-(4-Bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**85**).* Similar treatment of 2-amino-*N*'-(4-bromophenyl)benzamidine (**68**) (290 mg, 1.0 mmol) gave the *title compound* **85** (210 mg, 65%) as colorless needles, mp (hotstage) 191-192 ^{o}C (lit.,[271] 191-192 ^{o}C) (from *n*-hexane/DCM, 90:10); R_f 0.75 (DCM/*t*-BuOMe, 90:10); δ_H(300 MHz; $CDCl_3$) 8.18 (1H, d, *J* 7.8, Ar *H*), 7.79 (2H, d, *J* 8.7, Ar *H*), 7.70-7.64 (2H, m, Ar *H*), 7.55 (1H, ddd, *J* 7.4, 7.4, 1.8, Ar *H*), 7.31 (2H, d, *J* 8.7, Ar *H*), 6.86 (1H, br s, N*H*); δ_C(125 MHz; $CDCl_3$) 153.7 (s), 143.0 (s), 134.3 (d), 133.6 (d), 130.8 (s), 130.6 (d), 130.1 (d), 128.6 (d), 125.6 (s), 125.3 (d), 122.1 (s), 111.2 (s); *m*/*z* (MALDI-TOF) 328 (MH^++3, 50%), 327 (MH^++2, 100), 326 (MH^++1, 44), 325 (MH^+, 96), 300 (46), 298 (41), 245 (95), 219 (10), 144 (10), identical to an authentic sample.

*7.4.4.7 3-(3,4-Dimethoxyphenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**119**).* Similar treatment of 2-amino-*N*'-(3,4-dimethoxyphenyl)benzamidine (**71**) (271 mg, 1.0 mmol) gave the *title compound* **119** (194.8 mg, 64%) as colorless needles, mp (hotstage) 192-193 ^{o}C (from *c*-hexane/DCM, 90:10); mp (DSC) onset 193.1 ^{o}C, peak max. 193.9 ^{o}C (from *c*-hexane/DCM, 90:10); R_f 0.35 (DCM/Et_2O, 90:10); (found: C, 66.77; H, 4.49; N, 18.17. $C_{17}H_{14}N_4O_2$ requires C, 66.66; H, 4.61; N, 18.29%); λ_{max}(DCM)/nm 254 inf (4.26), 264 (4.26), 274 (4.22), 298 inf (3.96), 310 (4.05), 323 (4.06), 341 inf (3.92), 362 inf (3.68); ν_{max}/cm^{-1} 3277w (NH), 3044w and 3007w (aryl C-H), 2965w (alkyl C-H), 2239w (C≡N), 1634s, 1603w, 1597w, 1574w, 1562w, 1512s, 1468m, 1441w, 1422w, 1362w, 1335w, 1321m, 1310m, 1262s, 1240s, 1213w, 1180m, 1171s, 1152s, 1146s, 1107w, 1072w, 1036m, 1026m, 1016m, 970w, 905m, 889w, 860s, 826m, 779m, 770s, 746w, 731w; δ_H(500 MHz; $CDCl_3$) 8.28 (1H, br s, Ar *H*), 7.70 (1H, dd, *J* 8.0, 8.0, Ar *H*), 7.64 (1H, d, *J*

8.0, Ar *H*), 7.53 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.07 (1H, d, *J* 8.5, Ar *H*), 7.00 (1H, dd, *J* 8.5, 2.5, Ar *H*), 6.84 (1H, d, *J* 2.5, Ar *H*), 3.98 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$); δ_C(125 MHz; $CDCl_3$) 153.4 (s), 151.1 (s), 150.7 (s), 143.3 (s), 133.4 (d), 131.6 (s), 129.9 (d), 128.3 (d), 127.1 (s), 125.7 (d), 122.6 (s), 121.6 (d), 112.1 (d), 111.4 (s, *C*≡N), 111.2 (d), 56.2 (q, O*C*H$_3$), 56.1 (q, O*C*H$_3$); *m/z* (EI) 327 (MH^+, 15%), 326 (M^+, 100), 307 (11).

*7.4.5 Independent synthesis of 2-[2-(2-aminophenyl)-5-imino-1-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**105**)*

*7.4.5.1 (Z)-2-Nitro-N'-phenylbenzamidine (**133**).* To stirred 2-nitrobenzonitrile (398 mg, 2.68 mmol) at *ca.* 20 °C was added in one portion powdered anhydrous $AlCl_3$ (358 mg, 2.68 mmol). The reaction mixture was then heated (*ca.* 100 °C) until a homogeneous melt formed. To this hot melt was then added aniline (245 μL, 2.68 mmol) and the mixture was heated (*ca.* 100 °C) for 8 h and then allowed to cool to *ca.* 20 °C. The resultant solid mass was then crushed and slurried in 10% NaOH (40 mL), extracted with DCM (4 × 40 mL), washed with H_2O (1 × 40 mL) and the organic phase dried (Na_2SO_4), adsorbed onto silica and chromatographed (*t*-BuOMe) to give the *title compound* **133** (465 mg, 72%) as yellow plates, mp (hotstage) 81.5-83 °C (from *c*-hexane), mp (DSC) onset 79.4 °C, peak max. 84.8 °C (from *c*-hexane); R_f 0.38 (DCM/*t*-BuOMe, 90:10); (found: C, 64.70; H, 4.49; N, 17.39. $C_{13}H_{11}N_3O_2$ requires C, 64.72; H, 4.60; N, 17.42%); λ_{max}(DCM)/nm 259 inf (log ε 4.05); ν_{max}/cm^{-1} 3464w and 3333w (NH_2), 3059w (Ar CH), 1616s, 1585m, 1574m, 1522s, 1483m, 1449w, 1383m, 1362s, 1304w, 1275w, 1236w, 1177w, 1157w, 1074w, 1024w, 995w, 962w, 918w, 889w, 856w, 837m, 804w, 783s, 766s; δ_H(500 MHz; DMSO-d_6) 7.96 (1H, d, *J* 8.5, Ar *H*), 7.78-7.75 (2H, m, Ar *H*), 7.66 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.31 (2H, dd, *J* 7.5, 7.5 Ar *H*), 6.99 (1H, dd, *J* 7.5, 7.5, Ar *H*), 6.82 (1H, d, *J* 8.0, Ar *H*), 6.69 (1H, br s, Ar *H*), 6.49 (2H, br s, N*H*$_2$); δ_C(125 MHz; DMSO-d_6 at 55 °C) 152.5 (s), 149.6 (s), 148.7 (s), 132.6 (s), 132.4 (d), 129.9 (d), 129.7 (d), 129.0 (d), 123.6 (d), 122.0 (d), 121.0 (d); *m*/*z* (MALDI-TOF) 243 (MH^++1, 15%), 242 (MH^+, 100).

*7.4.5.2 2-Nitro-N'-phenyl-N-(1,2,2-tricyanovinyl)benzamidine (**134**).* To a stirred solution of TCNE (256 mg, 2.00 mmol) in dry THF (5 mL) at *ca.* 20 °C was added in one portion a solution of 2-nitro-*N'*-phenylbenzamidine (**133**) (241 mg, 1.00 mmol) in dry THF (5 mL). The mixture was then left to stir at *ca.* 20 °C for 4 h, after which time the reaction was complete (by TLC), and the volatiles were removed under reduced pressure (at < 25 °C). The residue was then dissolved in Et_2O (2 mL) and after cooling to 0 °C, *n*-

pentane (40 mL) was added and triturated to precipitate the *title compound* **134** (338.2 mg, 99%) as colorless plates, mp (hotstage) 130-131 °C (from *n*-pentane/THF, 90:10); R_f 0.50 (DCM/Et_2O, 95:05); (found: C, 62.97; H, 2.87; N, 24.63. $C_{18}H_{10}N_6O_2$ requires C, 63.16; H, 2.94; N, 24.55%); λ_{max}(DCM)/nm 258 (log ε 4.18); ν_{max}/cm^{-1} 3244m (NH), 3096w (aryl C-H), 2261w and 2228w (C≡N), 1697s, 1630w, 1591s, 1574w, 1537s, 1530s, 1495m, 1456w, 1393m, 1346s, 1325m, 1308m, 1269w, 1221w, 1152w, 1132m, 1074w, 1071m, 1041w, 1032w, 968w, 943w, 939w, 916w, 891w, 854m, 810w, 797m, 770w, 760w; δ_H(500 MHz; $CDCl_3$) 8.10 (1H, d, *J* 8.5 Ar *H*), 8.01 (1H, br s, N*H*), 7.78 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.71-7.66 (2H, m, Ar *H*), 7.39-7.38 (3H, br s, Ar *H*), 7.05 (2H, br s, Ar *H*); δ_C(125 MHz; $CDCl_3$) 168.2 (s), 160.2 (s), 146.6 (s), 134.5 (d), 132.7 (d), 131.5 (d), 130.73 (d), 130.69 (d), 130.6 (s), 127.8 (d), 125.0 (d), 123.4 (s), 111.7 (s, *C*≡N), 108.3 (s, *C*≡N), 108.1 (s, *C*≡N), 66.9 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 343 (MH^+, 26%), 334 (46), 333 (100), 311 (9), 283 (8), 130 (59), 102 (8), 100 (27).

*7.4.5.3 2-[5-Imino-2-(2-nitrophenyl)-1-phenyl-1,5-dihydro-4H-imidazol-4-ylidene]-malononitrile (**135**).* A stirred solution of 2-nitro-*N'*-phenyl-*N*-(1,2,2-tricyanovinyl)-benzamidine (**134**) (34.2 mg, 0.10 mmol) in dry MeCN (1 mL) was heated at *ca*. 82 °C for 3 h. On cooling to *ca.* 20 °C the reaction mixture was adsorbed onto silica and chromatographed (DCM) to give the *title compound* **135** (21.5 mg, 63%) as yellow hexagonal plates, mp (DSC) decomp. onset 258.8 °C peak max. 262.4 °C (from *n*-pentane/THF, 90:10); R_f 0.56 (DCM/Et_2O, 95:05); (found: C, 63.03; H, 2.84; N, 24.44. $C_{18}H_{10}N_6O_2$ requires C, 63.16; H, 2.94; N, 24.55%); λ_{max}(DCM)/nm 256 inf (log ε 4.21), 388 (3.72); ν_{max}/cm^{-1} 3304w (NH), 3078 (aryl C-H), 2234w (C≡N), 1647w, 1632w, 1593w, 1576w, 1559w, 1530s, 1510s, 1483m, 1456w, 1445w, 1391w, 1364m, 1346s, 1321w, 1260w, 1227w, 1186w, 1157w, 1146w, 1074w, 1065w, 1026w, 1009w, 999w, 966w, 920w, 868w, 855m, 799s, 790m, 768m, 748m; δ_H(300 MHz; CD_3CN) N*H* deuterium exchanged, 8.00 (1H, d, *J* 9.0, Ar *H*), 7.68 (1H, ddd, *J* 7.5, 7.5, 1.0, Ar *H*), 7.59-7.52 (2H, m, Ar *H*), 7.38-7.36 (3H, m, Ar *H*), 7.19 (2H, dd, *J* 6.0, 3.0, Ar *H*); (75 MHz; CD_3CN) four C (s) resonances missing, 152.3 (s), 138.1 (s), 135.5 (d), 132.7 (d), 131.5 (d), 131.4 (d), 129.6 (s), 128.8 (d), 126.3 (d), 125.7 (d), 114.8 (s, *C*≡N), 113.4 (s, *C*≡N); *m*/*z* (MALDI-TOF) 344 (MH^++1, 13%), 343 (MH^+, 100), 242 (3), 100 (5).

*7.4.5.4 2-[2-(2-Aminophenyl)-5-imino-1-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**105**).* To a solution of 2-[5-imino-2-(2-nitrophenyl)-1-phenyl-1,5-dihydro-4*H*-

imidazol-4-ylidene]malononitrile (**135**) (17.1 mg, 0.05 mmol) in glacial AcOH (0.5 mL) at *ca.* 20 °C was added Zn powder (13.0 mg, 0.200 mmol) and left to stir at *ca.* 20 °C for 15 min. After the reaction was complete (by TLC) the mixture was filtered, diluted with Et_2O (5 mL), washed with H_2O (2 × 5 mL) and dried (Na_2SO_4). The organic phase was adsorbed onto silica and chromatographed (DCM/Et_2O, 95:05) to give the title compound **105** (14.1 mg, 90%) as red needles, mp (DSC) decomp. onset 197.9 °C, peak max. 201.2 °C (from *n*-pentane/THF, 90:10); R_f 0.47 (DCM/Et_2O, 98:02); δ_H(500 MHz; DMSO-d_6) 9.93 (1H, s, N*H*), 7.77 (2H, s, NH_2), 7.61-7.59 (3H, m, Ar *H*), 7.40 (2H, d, *J* 6.5, Ar *H*), 7.18 (1H, dd, *J* 7.8, 7.8, Ar *H*), 6.81 (1H, d, *J* 9.0, Ar *H*), 6.59 (1H, d, *J* 8.5, Ar *H*), 6.17 (1H, dd, *J* 8.3, 8.3, Ar *H*); identical that described above.

*7.4.6 Chemistry of 2-[2-(2-aminophenyl)-5-imino-1-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**105**)*

*7.4.6.1 2-[2-(2-Aminophenyl)-5-(phenylimino)-3H-imidazol-4(5H)-ylidene]malononitrile (**136**)*. To a stirred solution of 2-[2-(2-aminophenyl)-5-imino-1-phenyl-1,5-dihydro-4*H*-imidazol-4-ylidene]malononitrile (**105**) (31.2 mg, 0.100 mmol) in dry DCM (1 mL) at *ca*. 20 °C was added DBU (14.9 μL, 0.100 mmol). The reaction mixture was then heated at *ca*. 40 °C for 4 h, allowed to come to *ca.* 20 °C and then extracted with 5% HCl (1 mL), washed with H_2O (1 × 1 mL) and the organic fraction dried (Na_2SO_4). Removal of the volatiles followed by addition of MeOH (0.5 mL), H_2O (3 mL), and filtration of the precipitate, gave the *title compound* **136** (22.4 mg, 71%) as maroon needles, mp (DSC) decomp. onset 203.5 °C, peak max. 214.8 °C (from *n*-pentane/THF, 50:50); R_f 0.40 (DCM/Et_2O, 98:02); (found: C, 69.13; H, 3.74; N, 26.80. $C_{18}H_{12}N_6$ requires C, 69.22; H, 3.87; N, 26.91%); λ_{max}(DCM)/nm 248 (log ε 4.02), 269 (3.88), 295 (3.88), 329 (3.78), 376 inf (3.80), 397 (3.91), 417 inf (3.90), 463 inf (3.90), 503 (3.98), 566 inf (3.71), 632 inf (3.38); ν_{max}/cm^{-1} 3422w and 3401w (NH_2), 3294w and 3242w (NH), 3063w (aryl C-H), 2224w (C≡N), 1643m, 16281m, 1601m, 1574w, 1559w, 1530s, 1501m, 1452m, 1414w, 1383w, 1327w, 1306m, 1260s, 1229m, 1202w, 1171m, 1072w, 1042w, 1024w, 1001w, 972w, 924w, 851w, 835w, 773w, 758m, 743s; δ_H(500 MHz; DMSO-d_6) two H resonances missing owing to prototautomerism, 9.32 (2H, br s, NH_2), 7.91 (1H, br s, Ar *H*), 7.46 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.35 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.26 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.21 (1H, br s, N*H*), 6.84 (1H, d, *J* 9.0, Ar *H*), 6.60 (1H, dd, *J* 7.0, 7.0, Ar *H*); δ_C(125 MHz; DMSO-d_6) three C (s) resonances missing owing to prototautomerism, 153.6 (s), 146.5 (s),

135.9 (d), 130.4 (d), 128.9 (d), 125.9 (d), 122.7 (d), 117.0 (d), 115.3 (d), 114.3 (s, *C*≡N), 113.6 (s, *C*≡N), 104.5 (s), 66.8 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 313 (MH^+, 80%), 311 (M^+-1, 97%), 190 (100), 167 (90).

*7.4.6.2 2-[2-(2-Nitrophenyl)-5-(phenylimino)-3H-imidazol-4(5H)-ylidene]malononitrile (**142**).* To a stirred solution of 2-[5-imino-2-(2-nitrophenyl)-1-phenyl-1,5-dihydro-4*H*-imidazol-4-ylidene]malononitrile (**135**) (24.1 mg, 0.100 mmol) in dry DCM (1 mL) at *ca.* 20 °C was added DBU (14.9 μL, 0.100 mmol). The reaction mixture was then heated at *ca.* 40 °C for 5 h, allowed to come to *ca.* 20 °C and then extracted with 5% HCl (1 mL), washed with H_2O (1 × 1 mL) and the organic fraction dried (Na_2SO_4). Adsorption of the organic phase on silica and chromatography (DCM/Et_2O, 95:05) gave the *title compound* **142** (14.2 mg, 59%) as maroon needles, mp (DSC) decomp. onset 180.2 °C, peak max. 186.5 °C (from *n*-pentane/THF, 50:50); R_f 0.65 (DCM/Et_2O, 95:05); (found: C, 63.03; H, 2.86; N, 24.40. $C_{18}H_{10}N_6O_2$ requires C, 63.16; H, 2.94; N, 24.55%); λ_{max}(DCM)/nm 256 (log ε 3.90), 294 inf (3.76), 409 (3.70), 440 (3.69), 467 inf (3.69), 561 inf (2.94), 606 (2.84); ν_{max}/cm^{-1} 2210w (C≡N), 1748w, 1734w, 1719w, 1645w, 1634w, 1597w, 1574w, 1530s, 1526s, 1506m, 1497m, 1489w, 1472w, 1456w, 1418w, 1346m, 1315w, 1301w, 1258w, 1191w, 1163w, 1148w, 1123w, 1072w, 1053w, 1026w, 1002w, 966w, 910w, 883w, 854w, 843w, 831w, 820w, 789w, 785w, 756w, 734w; δ_H(500 MHz; CD_3CN) N*H* deuterium exchanged, 8.17 (1H, dd, *J* 7.8, 1.8, Ar *H*), 7.91-7.87 (2H, m, Ar *H*), 7.84 (1H, dd, *J* 6.8, 2.5, Ar *H*), 7.46 (2H, dd, *J* 8.3, 8.3 Ar *H*), 7.32-7.29 (3H, m, Ar *H*); δ_C(125 MHz; CD_3CN) three C (s) resonances missing owing to prototautomerism, 149.2 (s), 147.5 (s), 134.8 (d), 132.3 (d), 130.5 (d), 129.9 (d), 129.7 (d), 128.5 (d), 126.0 (d), 123.3 (s), 114.0 (s, *C*≡N), 113.5 (s, *C*≡N), 66.3 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 344 (MH^+, 21%), 343 (MH^+, 100), 219 (10), 153 (86), 133 (51), 130 (49), 104 (2).

*7.4.6.3 Zinc reduction of 2-[2-(2-nitrophenyl)-5-(phenylimino)-3H-imidazol-4(5H)-ylidene]malononitrile (**142**).* To a solution of 2-[2-(2-nitrophenyl)-5-(phenylimino)-3*H*-imidazol-4(5*H*)-ylidene]malononitrile (**142**) (17.1 mg, 0.050 mmol) in glacial AcOH (0.5 mL) at *ca.* 20 °C was added Zn powder (13.0 mg, 0.200 mmol) and left to stir at *ca.* 20 °C for 15 min. After the reaction was complete (by TLC) the mixture was filtrated, diluted in Et_2O (5 mL), washed with H_2O (2 × 5 mL), dried (Na_2SO_4), adsorbed onto silica and chromatographed (DCM/Et_2O, 95:05) to give 2-[2-(2-aminophenyl)-5-(phenylimino)-3*H*-imidazol-4(5*H*)-ylidene]malononitrile (**136**) (8.9 mg, 57%) as maroon needles, mp (DSC)

decomp. onset 203.5 °C, peak max. 214.8 °C; R_f 0.40 (DCM/Et_2O, 98:02); identical to that described above.

*7.4.6.4 (Z)-2-[3-(Phenylimino)imidazo[1,2-c]quinazolin-2(3H)-ylidene]malononitrile (**144**)*. To a stirred solution of (*Z*)-2-[2-(2-aminophenyl)-5-(phenylimino)-3,5-dihydro-4*H*-imidazol-4-ylidene]malononitrile (**136**) (32.2 mg, 0.100 mmol) in DMA (100 μL) at *ca*. 20 °C was added triethyl orthoformate (100 μL) and the reaction mixture was immersed into a preheated (*ca*. 170 °C) Wood's metal bath and left to stir for 15 min, after which time the reaction mixture was removed from the Wood's metal bath, allowed to cool to *ca*. 20 °C, diluted in DCM (5 mL), washed with H_2O (2 × 5 mL), dried (Na_2SO_4), adsorbed onto silica and chromatographed (DCM) to give the title compound **144** (22.4 mg, 70%) as orange needles, mp (hotstage) 234-235 °C (from *c*-hexane/THF, 90:10), mp (DSC) decomp. onset 234.6 °C, peak max. 235.8 °C (from *c*-hexane/THF, 90:10); R_f 0.47 (DCM); (found: C, 70.69; H, 2.94; N, 25.97. $C_{19}H_{10}N_6$ requires C, 70.80; H, 3.13; N, 26.07%); λ_{max}(DCM)/nm 247 inf (log ε 4.48), 252 (4.49), 281 inf (4.48), 290 (4.56), 310 inf (4.45), 323 inf (4.28), 348 (4.05), 367 (3.99), 451 inf (4.32), 480 (4.48), 513 (4.43); ν_{max}/cm^{-1} 3080w (aryl C-H), 2220m (C≡N), 1628m, 1589w, 1574m, 1493s, 1485s, 1471m, 1452s, 1391w, 1346m, 1331m, 1312m, 1275w, 1250w, 1220w, 1190w, 1171w, 1132s, 1101w, 1088m, 1022w, 999w, 986w, 912w, 876w, 847w, 820w, 793w, 775s, 752s, 702m; δ_H(500 MHz; $CDCl_3$) 8.53 (1H, dd, *J* 8.0, 1.0, Ar *H*), 7.94 (1H, ddd, *J* 7.8, 7.8, 1.5, Ar *H*), 7.82 (1H, br s, C*H*), 7.74 (1H, d, *J* 8.0, Ar *H*), 7.69 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.51 (2H, d, *J* 7.8, 7.8, Ar *H*), 7.33 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.06 (2H, d, *J* 7.5, Ar *H*); δ_C(125 MHz; $CDCl_3$) 163.1 (s), 161.5 (s), 146.2 (s), 144.7 (s), 140.5 (s), 138.1 (d), 136.8 (s) 130.4 (d), 130.0 (d), 128.8 (d), 127.6 (d), 127.0 (d), 118.1 (d), 117.0 (s), 112.8 (s, *C*≡N), 112.2 (s, *C*≡N), 71.1 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 324 (MH^++1, 9%), 323 (MH^+, 100), 296 (6), 270 (9), 248 (3), 220 (15), 129 (2), 104 (2).

*7.4.6.5 Quinolino[3',2':4,5]imidazo[1,2-c]quinazoline-13-carbonitrile (**138**)*. A stirred solution of 2-[3-(phenylimino)imidazo[1,2-*c*]quinazolin-2(3*H*)-ylidene]malononitrile (**144**) (32.2 mg, 0.100 mmol) in diphenyl ether (1 mL) was immersed into a preheated (*ca*. 250 °C) Wood's metal bath and left to stir for 20 min, after which time the reaction mixture was removed from the Wood's metal bath, allowed to cool to *ca*. 20 °C, and triturated with *n*-pentane (4 mL). Filtration gave the *title compound* **138** (28.6 mg, 97%) as yellow fibres, mp (hotstage) 305-306 °C (from *c*-hexane/THF, 90:10), mp (DSC) onset

306.3 °C, peak max. 306.8 °C (from *c*-hexane/THF, 90:10); R_f 0.63 (DCM/Et_2O, 95:15); (found: C, 73.29; H, 2.98; N, 23.61. $C_{18}H_9N_5$ requires C, 73.21; H, 3.07; N, 23.72%); λ_{max}(DCM)/nm 269 inf (log ε 4.46), 279 (4.67), 288 (4.78), 303 (4.55), 325 (3.97), 349 inf (4.18), 368 (4.42), 392 (4.31), 414 (4.33); ν_{max}/cm^{-1} 3061 (aryl C-H), 2228w (C≡N), 1632m, 1601m, 1584w, 1520m, 1503w, 1466m, 1450m, 1406w, 1395m, 1379m, 1368w, 1323w, 1306w, 1296w, 1271w, 1252w, 1233m, 1198w, 1140m, 1094w, 1036w, 1020w, 1011w, 963w, 953w, 923w, 889m, 876w, 793w, 777s, 762s, 725s, 702s; δ_H(500 MHz; $CDCl_3$) 9.51 (1H, s, C*H*), 8.83 (1H, d, *J* 8.0, Ar *H*), 8.45 (1H, d, *J* 8.0, Ar *H*), 8.34 (1H, d, *J* 8.5, Ar *H*), 8.07 (1H, d, *J* 8.5, Ar *H*), 7.95 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.90 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.84-7.79 (2H, m, Ar *H*); δ_C(125 MHz; $CDCl_3$) 152.4 (s), 144.5 (s), 144.0 (s), 143.9 (s), 137.7 (s), 135.4 (d), 134.5 (d), 129.6 (d), 129.4 (d), 129.35 (d), 129.0 (d), 128.2 (d), 126.4 (s), 125.6 (d), 125.4 (d), 118.3 (s), 114.0 (s, *C*≡N), 105.5 (s); *m*/*z* (MALDI-TOF) 296 (MH^+, 53%), 295 (M^+, 13), 242 (100), 142 (3), 129 (2).

*7.4.6.6 2-[(3-Phenylquinazolin-4(3H)-ylidene)amino]ethene-1,1,2-tricarbonitrile (**145**).* To a stirred solution of 2-[2-(2-aminophenyl)-5-imino-1-phenyl-1,5-dihydro-4*H*-imidazol-4-ylidene]malononitrile (**105**) (31.2 mg, 0.100 mmol) in DMA (100 μL) at *ca*. 20 °C was added triethyl orthoformate (100 μL). The reaction mixture was then immersed into a preheated (*ca*. 170 °C) Wood's metal bath and left to stir for 5 min, after which time the reaction mixture was removed from the Wood's metal bath, allowed to cool to *ca*. 20 °C, diluted in DCM (5 mL), washed with H_2O (2 × 5 mL) and dried (Na_2SO_4). Removal of the volatiles and chromatography (DCM) of the residue gave the *title compound* **145** (23.0 mg, 71%) as yellow plates, mp (hotstage) 191-192 °C (from *c*-hexane/THF, 90:10), mp (DSC) onset 191.2 °C, peak max. 192.8 °C, decomp. onset 278.7 °C, peak max. 300.4 °C (from *c*-hexane/THF, 90:10); R_f 0.63 (DCM); (found: C, 70.60; H, 3.01; N, 25.99. $C_{19}H_{10}N_6$ requires C, 70.80; H, 3.13; N, 26.07%); λ_{max}(DCM)/nm 272 inf (log ε 4.10), 318 (3.92), 405 (4.24); ν_{max}/cm^{-1} 3080w (aryl C-H), 2212w and 2199w (C≡N), 1607m, 1591m, 1562w, 1520s, 1497s, 1487s, 1464m, 1452s, 1360w, 1331m, 1281m, 1265w, 1227w, 1211w, 1200w, 1167w, 1157w, 1150w, 1111w, 1078w, 1069w, 1032w, 1003w, 986w, 964w, 926w, 914w, 876w, 856w, 804w, 770m, 758w, 711w; δ_H(500 MHz; $CDCl_3$) 8.28 (1H, s, C*H*), 8.13 (1H, d, *J* 8.5, Ar *H*), 8.05 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 8.00 (1H, d, *J* 7.5, Ar *H*), 7.79 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.70-7.64 (3H, m, Ar *H*), 7.47 (2H, d, *J* 8.0, Ar *H*); δ_C(125 MHz; $CDCl_3$) 154.5 (s), 147.5 (s), 144.4 (d), 143.0 (s), 137.2 (s), 137.1 (d), 131.1 (d), 130.7 (d), 130.0 (d), 129.1 (d), 127.8 (d), 127.1 (d), 118.3 (s), 112.3 (s), 111.9 (s,

C≡N), 111.2 (s, *C*≡N), 71.9 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 324 (MH^++1, 24%), 323 (MH^+, 100), 296 (10), 285 (12), 283 (20), 262 (10), 232 (14), 226 (26), 222 (25), 153 (83), 134 (7), 130 (6). Further elution (DCM) gave (*Z*)-2-[3-(phenylimino)imidazo[1,2-c]quinazolin-2(3*H*)-ylidene]malononitrile (**144**) (3.8 mg, 16%) as orange needles, mp (DSC) decomp. onset 234.6 ^oC, peak max. 235.8 ^oC (from *c*-hexane/THF, 90:10); R_f 0.47 (DCM); identical to that described above.

7.5 Compounds related to chapter 5

7.5.1 Reaction of N'-arylbenzamidines with tetracyanoethylene (TCNE)

*7.5.1.1 N'-Phenyl-N-(1,2,2-tricyanovinyl)benzamidine (**160**) (Typical Procedure, see Table 6).* To a stirred solution of tetracyanoethylene (128 mg, 1 mmol) in dry THF (5 mL), at *ca.* 20 ^{o}C and protected with $CaCl_2$ drying tube was added a solution of *N'*-phenylbenzamidine (**50**) (196 mg, 1.0 mmol) in dry THF (5 mL). The mixture was then left to stir at *ca*. 20 ^{o}C for 2 h, after which time the reaction was complete (by TLC), and the solvent was evaporated under reduced pressure (at < 25 ^{o}C). The residue was then dissolved in Et_2O (2 mL) and after cooling to 0 ^{o}C, *n*-pentane (40 mL) was added and triturated to form the precipitated *title compound* **160** (288.7 mg, 97%) as colorless plates, mp (DSC) onset 135.7 ^{o}C, peak max. 139.1 ^{o}C, decomp. onset 140.8 ^{o}C peak max. 141.0 ^{o}C (from *n*-pentane/THF, 90:10); (found: C, 72.61; H, 3.66; N, 23.45. $C_{18}H_{11}N_5$ requires C, 72.72; H, 3.73; N, 23.56%); R_f 0.51 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 241 (log ε 4.29), 280 inf (3.74); ν_{max}/cm^{-1} 3258m (NH), 3064w (aryl C-H), 2826w, 2201w (C≡N), 1692s, 1670w, 1651w, 1603m, 1593m, 1562s, 1557s, 1493m, 1454w, 1445m, 1375m, 1323m, 1315m, 1310m, 1285m, 1263m, 1184w, 1159w, 1126s, 1071m, 1039w, 1030m, 1007m, 1001w, 941w, 935w, 918m, 910m, 881m, 847w, 814w, 783s, 729m; δ_H(500 MHz; $CDCl_3$) 8.04 (1H, br s, N*H*), 7.54-7.50 (3H, m, Ar *H*), 7.49-7.46 (3H, m, Ar *H*), 7.32 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.17 (2H, br s, Ar *H*); δ_C(125 MHz; $CDCl_3$) 168.5 (s), 161.8 (s), 132.84 (s), 132.81 (d), 130.8 (d), 130.4 (d), 129.3 (d), 128.6 (d), 127.8 (d), 126.4 (s), 112.5 (s, *C*≡N), 108.4 (s, *C*≡N), 108.0 (s, *C*≡N), 66.9 [s, *C*$(CN)_2$]; *m/z* (MALDI-TOF) 299 (MH^++1, 1%), 298 (MH^+, 8), 295, (3), 282 (100), 261 (3), 260 (7), 259 (8), 180 (18).

*7.5.1.2 N'-(4-Methoxyphenyl)-N-(1,2,2-tricyanovinyl)benzamidine (**161**).* Similar treatment of TCNE (128 mg, 1.0 mmol) with *N'*-(4-methoxyphenyl)benzamidine (**47**) (226 mg, 1.0 mmol) gave the *title compound* **161** (319.3 mg, 98%) as colorless plates, mp (hotstage) 68.8–69.5 ^{o}C (from *n*-pentane/THF, 90:10); (found: C, 69.62; H, 4.18; N, 21.40. $C_{19}H_{13}N_5O$ requires C, 69.71; H, 4.00; N, 21.39%); R_f 0.56 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 275 inf (3.96); ν_{max}/cm^{-1} 3269m (NH), 3063w (aryl C-H), 2899w and 2843w (alkyl C-H), 2226w (C≡N), 1695w, 1684w, 1653w, 1636w, 1607w, 1593w, 1568w, 1539w, 1512s, 1466w, 1447w, 1420w, 1387w, 1321m, 1312m, 1302m, 1254s, 1180w, 1171w, 1125m, 1065w, 1028w, 910w, 841m, 812w, 799w, 775w, 746w; δ_H(500 MHz; $CDCl_3$) NH resonance missing, 7.50-7.48 (3H, m, Ar *H*), 7.33 (2H, dd, *J* 8.0, 8.0, Ar *H*),

7.08 (2H, br s, Ar *H*), 6.99 (2H, d, *J* 8.0, Ar *H*), 3.85 (3H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) 168.7 (s), 162.4 (s), 160.7 (s), 132.7 (d), 129.3 (d), 129.2 (d), 128.6 (d), 126.5 (s), 125.0 (s), 116.0 (d), 112.5 (s, *C*≡N), 108.5 (s, *C*≡N), 108.0 (s, *C*≡N), 66.7 [s, *C*$(CN)_2$], 55.6 (q, O*C*H_3); *m*/*z* (MALDI-TOF) 331 (MH^++2, 17%), 331 (MH^++1, 3), 328 (MH^+, 2), 312 (8), 227 (29), 211 (12), 210 (100), 181 (13), 71 (8).

*7.5.1.3 N'-(p-Tolyl)-N-(1,2,2-tricyanovinyl)benzamidine (**162**)*. Similar treatment of TCNE (128 mg, 1.0 mmol) with *N'*-(*p*-tolyl)benzamidine (**57**) (210 mg, 1.0 mmol) gave the *title compound* **162** (309.3 mg, 99%) as colorless plates, mp (DSC) onset 149.4 °C, peak max. 151.0 °C, decomp. onset 152.2 °C peak max. 153.6 °C (from *n*-pentane/THF, 90:10); (found: C, 73.33; H, 4.25; N, 22.58. $C_{19}H_{13}N_5$ requires C, 73.30; H, 4.21; N, 22.49%); R_f 0.59 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 277 inf (3.80); ν_{max}/cm^{-1} 3252m (NH), 2808w (alkyl C-H), 2517w, 2199w (C≡N), 1694m, 1682m, 1601m, 1591m, 1560s, 1510m, 1497w, 1470w, 1447m, 1385m, 1379m, 1323s, 1315m, 1296s, 1265m, 1213w, 1179w, 1128s, 1072m, 1065m, 1040w, 1030m, 1022w, 1007m, 980w, 966w, 945w, 933w, 912m, 880m, 845w, 830m, 810m, 806w, 798w, 781m, 746m; δ_H(500 MHz; $CDCl_3$) 8.00 (1H, s, N*H*), 7.50-7.46 (3H, m, Ar *H*), 7.34-7.29 (4H, m, Ar *H*), 7.03 (2H, br s, Ar *H*), 2.42 (3H, s, CH_3); δ_C(125 MHz; $CDCl_3$) 168.5 (s), 162.1 (s), 140.8 (s), 132.8 (d), 131.4 (d), 130.1 (s), 129.3 (d), 128.6 (d), 127.5 (d), 126.5 (s), 112.5 (s, *C*≡N), 108.4 (s, *C*≡N), 108.0 (s, *C*≡N), 66.8 [s, *C*$(CN)_2$], 21.3 (q, *C*H_3); *m*/*z* (MALDI-TOF) 312 (MH^+, 4%), 296 (7), 275 (3), 247 (4), 194 (100), 105 (3), 91 (9).

*7.5.1.4 N'-(4-Fluorophenyl)-N-(1,2,2-tricyanovinyl)benzamidine (**163**)*. Similar treatment of TCNE (128 mg, 1.0 mmol) with *N'*-(4-fluorophenyl)benzamidine (**58**) (214 mg, 1.0 mmol) gave the *title compound* **163** (299.6 mg, 95%) as colorless plates, mp (DSC) onset 146.0°C, peak max. 148.2 °C, decomp. onset 149.1 °C peak max. 150.4 °C (from *n*-pentane/THF, 90:10); (found: C, 69.36; H, 3.33; N, 22.19. $C_{18}H_{10}FN_5$ requires C, 68.57; H, 3.20; N, 22.21%); R_f 0.49 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 244 (log ε 4.23), 276 inf (3.76); ν_{max}/cm^{-1} 3258m (NH), 2814w (alkyl C-H), 2521w, 2203w (C≡N), 1697m, 1686m, 1605m, 1593m, 1562m, 1508s, 1447m, 1418w, 1379m, 1323m, 1314m, 1292m, 1287m, 1265w, 1238m, 1223m, 1184w, 1155m, 1126s, 1096w, 1071m, 1042w, 1030m, 1008m, 982w, 943w, 933w, 916m, 883m, 849m, 841m, 822w, 802w, 783m, 750m; δ_H(500 MHz; $CDCl_3$) 8.02 (1H, br s, N*H*), 7.51 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.46 (2H, d, *J* 8.5, Ar *H*), 7.35 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.21-7.19 (4H, m, Ar *H*); δ_C(125 MHz; $CDCl_3$) 168.5 (s), 163.1

(s, $^{1}J_{CF}$ 251.5, *C*F), 161.8 (s), 133.0 (d), 129.9 (d, $^{3}J_{CF}$ 8.9, *C*HCHCF), 129.2 (d), 128.8 (d), 126.2 (s), 118.1 (d, $^{2}J_{CF}$ 22.4, *C*HCF), 112.3 (s, *C*≡N), 108.3 (s, *C*≡N), 108.0 (s, *C*≡N), 68.0 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 316 (MH^+, 3%), 300 (5), 198 (100), 105 (4).

*7.5.1.5 N'-(4-Chlorophenyl)-N-(1,2,2-tricyanovinyl)benzamidine (**164**).* Similar treatment of TCNE (154 mg, 1.2 mmol) with *N'*-(4-chlorophenyl)benzamidine (**59**) (231 mg, 1.0 mmol) gave the *title compound* **164** (314.6 mg, 95%) as colorless plates, mp (DSC) onset 146.8 °C, peak max. 148.4 °C, decomp. onset 150.3 °C peak max. 151.9 °C (from *n*-pentane/THF, 90:10); (found: C, 64.97; H, 2.93; N, 21.17. $C_{18}H_{10}ClN_5$ requires C, 65.17; H, 3.04; N, 21.11%); R_f 0.41 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 242 (log ε 4.33), 277 inf (3.81); ν_{max}/cm^{-1} 3254w (NH), 2525w, 2201w (C≡N), 1692m, 1603m, 1593m, 1562m, 1493s, 1447m, 1408w, 1383w, 1323m, 1304m, 1294m, 1277w, 1265w, 1188w, 1128m, 1094m, 1071w, 1030w, 1016m, 945w, 939w, 930w, 912m, 880w, 837m, 822w, 806w, 781m, 760w, 739w; δ_H(500 MHz; $CDCl_3$) 8.05 (1H, s, N*H*), 7.54-7.49 (3H, m, Ar *H*), 7.46 (2H, d, *J* 8.5, Ar *H*), 7.36 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.11 (2H, br s, Ar *H*); δ_C(125 MHz; $CDCl_3$) 168.3 (s), 161.5 (s), 136.6 (s), 133.0 (d), 131.3 (s), 131.1 (d), 129.2 (d), 129.1 (d), 128.8 (d), 126.1 (s), 112.3 (s, *C*≡N), 108.3 (s, *C*≡N), 107.9 (s, *C*≡N), 66.9 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 334 (MH^++2, 3%), 332 (MH^+, 1), 318 (12), 316 (55), 294 (34), 231 (30), 216 (29), 214 (100).

*7.5.1.6 N'-(3,4-Dichlorophenyl)-N-(1,2,2-tricyanovinyl)benzamidine (**165**).* Similar treatment of TCNE (154 mg, 1.2 mmol) with *N'*-(3,4-dichlorophenyl)benzamidine (**62**) (265 mg, 1.0 mmol) gave the *title compound* **165** (335.1 mg, 93%) as colorless plates, mp (DSC) onset 151.5 °C, peak max. 155.5 °C, decomp. onset 157.0 °C peak max. 158.1 °C (from *n*-pentane/THF, 90:10); (found: C, 58.83; H, 2.59; N, 19.21. $C_{18}H_9Cl_2N_5$ requires C, 59.04; H, 2.48; N, 19.12%); R_f 0.46 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 244 (log ε 4.67), 278 inf (4.13); ν_{max}/cm^{-1} 3254m (NH), 2795w, 2533w, 2259w and 2197w (C≡N), 1703w, 1688s, 1605m, 1593m, 1564m, 1497w, 1474s, 1447w, 1406w, 1393w, 1370w, 1327m, 1304s, 1277m, 1242w, 1128s, 1086w, 1076w, 1065m, 1036m, 1011w, 982w, 957w, 932w, 912m, 887w, 874m, 847w, 829m, 818w, 797m, 781s, 745m; δ_H(500 MHz; $CDCl_3$) 8.12 (1H, br s, N*H*), 7.58 (1H, d, *J* 8.5 Ar *H*), 7.55 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.47 (2H, d, *J* 7.5, Ar *H*), 7.38 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.33 (1H, br s, Ar *H*), 6.99 (1H, br s, Ar *H*); δ_C(125 MHz; $CDCl_3$) 167.8 (s), 160.8 (s), 135.4 (s), 135.2 (s), 133.2 (d), 132.6 (d), 132.0 (s), 129.5 (d), 129.2 (d), 129.0 (d), 127.1 (d), 125.8 (s), 112.1 (s, *C*≡N), 108.2 (s, *C*≡N), 107.9

(s, *C*≡N), 67.2 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 368 (MH^++2, 3%), 366 (MH^+, 2), 350 (8), 329 (4), 303 (2), 250 (65), 248 (100), 207 (8), 199 (9), 181 (7), 127 (8), 111 (22), 109 (4), 105 (15), 97 (5), 88 (13), 77 (2).

*7.5.1.7 N'-(4-Bromophenyl)-N-(1,2,2-tricyanovinyl)benzamidine (**166**)*. Similar treatment of TCNE (154 mg, 1.2 mmol) with *N'*-(4-bromophenyl)benzamidine (**60**) (275 mg, 1.0 mmol) gave the *title compound* **166** (346.0 mg, 91%) as colorless plates, mp 85–86 °C (from *n*-pentane/THF, 90:10); (found: C, 57.39; H, 2.72; N, 18.62. $C_{18}H_{10}BrN_5$ requires C, 57.47; H, 2.68; N, 18.62%); R_f 0.54 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 242 (log ε 4.48), 279 inf (3.87); ν_{max}/cm^{-1} 3277w (NH), 3099w and 3063w (aryl C-H), 2974w and 2899w (alkyl C-H), 2255w and 2201w (C≡N), 1692m, 1653w, 1609m, 1595m, 1568m, 1489s, 1449m, 1402w, 1379m, 1311s, 1296m, 1273w, 1249w, 1202w, 1182w, 1125s, 1072s, 1030w, 1013s, 937w, 910m, 837s, 808w, 794w, 777s, 750m; δ_H(500 MHz; $CDCl_3$) 8.05 (1H, br s, N*H*), 7.64 (2H, d, *J* 8.0 Ar *H*), 7.52 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.46 (2H, d, *J* 8.5, Ar *H*), 7.36 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.04 (2H, d, *J* 5.5, Ar *H*); δ_C(125 MHz; $CDCl_3$) 168.3 (s), 161.4 (s), 134.1 (d), 133.0 (d), 131.8 (s), 129.3 (d), 129.2 (d), 128.8 (d), 126.1 (s), 124.6 (s), 112.3 (s, *C*≡N), 108.3 (s, *C*≡N), 107.9 (s, *C*≡N), 66.9 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 378 (MH^++2, 2%), 376 (MH^+, 1), 362 (4), 360 (5), 312 (2), 260 (90), 258 (100), 181 (26), 111 (3), 71 (27).

*7.5.1.8 N'-(4-Iodophenyl)-N-(1,2,2-tricyanovinyl)benzamidine (**167**)*. Similar treatment of TCNE (154 mg, 1.2 mmol) with *N'*-(4-iodophenyl)benzamidine (**61**) (322 mg, 1.0 mmol) gave the *title compound* **167** (366.0 mg, 87%) as colorless plates, mp (hotstage) 89.5–91 °C (from *n*-pentane/THF, 90:10); (found: C, 51.22; H, 2.31; N, 16.68. $C_{18}H_{10}IN_5$ requires C, 51.08; H, 2.38; N, 16.55%); R_f 0.59 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 246 (log ε 4.51), 278 inf (3.94); ν_{max}/cm^{-1} 3273w (NH), 3067w (aryl C-H), 2964w and 2903w (alkyl C-H), 2255w and 2201w (C≡N), 1692m, 1609m, 1593m, 1566m, 1493m, 1487s, 1449m, 1398w, 1375m, 1319s, 1312s, 1250w, 1182w, 1125s, 1067m, 1028w, 1009s, 937w, 910m, 849m, 835m, 777m, 748m; δ_H(500 MHz; $CDCl_3$) 8.06 (1H, br s, N*H*), 7.84 (2H, d, *J* 8.0, Ar *H*), 7.52 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.46 (2H, d, *J* 8.5, Ar *H*), 7.36 (2H, dd, *J* 7.8, 7.8, Ar *H*), 6.90 (2H, d, *J* 5.5, Ar *H*); δ_C(125 MHz; $CDCl_3$) 168.3 (s), 161.4 (s), 140.1 (d), 133.0 (d), 132.6 (s), 129.4 (d), 129.2 (d), 128.8 (d), 126.1 (s), 112.3 (s, *C*≡N), 108.3 (s, *C*≡N), 107.9 (s, *C*≡N), 96.3 (s), 66.9 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 426 (MH^++2, 1%), 424 (MH^+, 2), 408 (2), 387 (2), 386 (2), 323 (55), 307 (10), 306 (100), 180 (30), 179 (11), 105 (9).

*7.5.1.9 N'-(4-Nitrophenyl)-N-(1,2,2-tricyanovinyl)benzamidine (**168**).* Similar treatment of TCNE (154 mg, 1.2 mmol) with *N'*-(4-nitrophenyl)benzamidine (**56**) (241 mg, 1.0 mmol) gave the *title compound* **168** (301.0 mg, 88%) as colorless plates, mp (DSC) onset 149.9 °C, peak max. 152.9 °C, decomp. onset 155.1 °C peak max. 156.1 °C (from *n*-pentane/THF, 90:10); (found: C, 62.97; H, 2.84; N, 24.55. $C_{18}H_{10}N_6O_2$ requires C, 63.16; H, 2.94; N, 24.55%); R_f 0.64 (DCM/Et_2O, 95:05); λ_{max}(DCM)/nm 248 (log ε 4.29), 282 inf (4.03); ν_{max}/cm^{-1} 3296w (NH), 3119w and 3082w (aryl C-H), 2808w, 2627w, 2260w and 2201w (C≡N), 1757w, 1692m, 1612m, 1593m, 1574m, 1524s, 1497m, 1474w, 1449w, 1420w, 1387m, 1348s, 1321m, 1312m, 1292w, 1234w, 1184w, 1176w, 1144m, 1132m, 1109w, 1074w, 1028w, 1011w, 1001w, 939w, 926w, 912m, 856m, 837m, 822w, 771m, 754m, 741w; δ_H(500 MHz; $CDCl_3$) NH resonance missing, 8.35 (2H, d, *J* 8.5, Ar *H*), 7.55 (1H, dd, *J* 7.3, 7.3 Ar *H*), 7.43 (2H, d, *J* 8.5, Ar *H*), 7.39-7.35 (4H, m, Ar *H*); δ_C(125 MHz; $CDCl_3$) one C (s) resonance missingresonance missing 149.0 (s), 148.1 (s), 138.5 (s), 133.3 (d), 129.1 (d), 129.0 (d), 128.7 (d), 125.9 (d), 125.8 (s), 112.0 (s, *C*≡N), 108.1 (s, *C*≡N), 107.8 (s, *C*≡N), 68.0 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 344 (MH^++1, 1%), 343 (MH^+, 2), 340 (5), 327 (100), 304 (41), 242 (11), 225 (99), 179 (48).

*7.5.2 Conversion of N-Aryl-N-(1,2,2-tricyanovinyl)benzamidines **156** into 2-[5-imino-1-aryl-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitriles **157***

*7.5.2.1 2-[5-Imino-1,2-diphenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**169**) (Typical Procedure, see Table 7).* A stirred solution of *N'*-phenyl-*N*-(1,2,2-tricyanovinyl)benzamidine (**160**) (29.7 mg, 0.1 mmol) in dry acetonitrile (1 mL) was heated at *ca*. 82 °C for 3 h and chromatography (DCM) of the residue gave the *title compound* **169** (26.2 mg, 88%) as yellow prisms, mp (DSC) onset 195.6 °C, peak max. 201.3 °C, decomp. onset 205.2 °C peak max. 207.9 °C (from *n*-pentane/THF, 90:10); (found: C, 72.61; H, 3.66; N, 23.45. $C_{18}H_{11}N_5$ requires C, 72.72; H, 3.73; N, 23.56%); R_f 0.48 (DCM); λ_{max}(DCM)/nm 265 (3.36), 331 (4.24), 440 (4.31); ν_{max}/cm^{-1} 3237w (NH), 3063w and 3051w (aryl C-H), 2234w and 2214w (C≡N), 1655w, 1609w, 1597w, 1578w, 1503m, 1493m, 1466s, 1441m, 1416s, 1331s, 1317m, 1275m, 1221m, 1196w, 1182w, 1163w, 1121m, 1072w, 1032w, 1000w, 980w, 941w, 872m, 843w, 781m; δ_H(500 MHz; $CDCl_3$) 10.39 (1H, s, N*H*), 9.26 (1H, s, N*H*), 7.71 (2H, d, *J* 7.5, Ar *H*), 7.67 (2H, d, *J* 7.5, Ar *H*), 7.64-7.62 (3H, m, Ar *H*), 7.60-7.56 (2H, m, Ar *H*), 7.54-7.52 (3H, m, Ar *H*), 7.38-7.34 (4H, m, Ar *H*), 7.25-7.23 (2H, m, Ar *H*), 7.20-7.18 (2H, m, Ar *H*); δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance

missing, 7.69 (2H, d, *J* 8.5, Ar *H*), 7.59-7.56 (4H, m, Ar *H*), 7.36 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.23-7.21 (2H, m, Ar *H*); δ_H(500 MHz; DMSO-d_6) 10.47 (1H, s, N*H*), 7.63-7.54 (6H, m, Ar *H*), 7.45-7.42 (4H, m, Ar *H*); δ_C(125 MHz; $CDCl_3$) 171.4 (s), 168.7 (s), 165.0 (s), 160.8 (s), 158.4 (s), 157.3 (s), 134.8 (d), 134.6 (d), 133.9 (s), 132.5 (s), 131.23 (d), 131.20 (d), 131.0 (d), 130.9 (d), 130.1 (d), 130.0 (d), 128.89 (d), 128.85 (d), 128.1 (d), 128.0 (d), 125.8 (s), 125.6 (s), 113.0 (s, *C*≡N), 112.5 (s, *C*≡N), 112.3 (s, *C*≡N), 111.7 (s, *C*≡N), 72.1 [s, *C*$(CN)_2$], 70.5 [s, *C*$(CN)_2$]; δ_C(125 MHz; DMSO-d_6) 170.0 (s), 167.0 (s), 155.6 (s), 134.1 (d), 132.5 (s), 130.4 (d), 130.3 (d), 130.2 (d), 128.72 (d), 128.69 (d), 126.1 (s), 113.6 (s, *C*≡N), 112.9 (s, *C*≡N), 67.1 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 299 (MH^++1, 25%), 298 (MH^+, 100), 242 (2), 180 (4), 153 (70); *m*/*z* (EI) 297 (M^+, 58%), 296 (100), 271 (7), 244 (3), 194 (22), 180 (12), 167 (6), 153 (3), 118 (12), 104 (17), 91 (5), 77 (73), 65 (3), 51 (32).

*7.5.2.2 2-[5-Imino-1-(4-methoxyphenyl)-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**170**).* Similar treatment of *N'*-(4-methoxyphenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**161**) (32.7 mg, 0.1 mmol) gave the *title compound* **170** (29.1 mg, 89%) as orange prisms, mp (DSC) onset 187.1 °C, peak max. 191.1 °C, decomp. onset 195.4 °C, peak max. 203.0 °C (from *c*-hexane/DCE, 50:50); (found: C, 69.62; H, 3.90; N, 21.27. $C_{13}H_{13}N_5O$ requires C, 69.71; H, 4.00; N, 21.39%); R_f 0.38 (DCM); λ_{max}(DCM)/nm 267 (log ε 3.85), 276 inf (3.84), 283 inf (3.87), 319 (4.16), 378 inf (3.98), 447 (4.22); ν_{max}/cm^{-1} 3265w and 3232w (NH), 3069w (aryl C-H), 2976 (alkyl C-H), 2224w and 2208w (C≡N), 1653w, 1605w, 1595w, 1578w, 1514m, 1504w, 1468s, 1445m, 1423m, 1410m, 1337m, 1304w, 1273m, 1256m, 1217m, 1182w, 1171w, 1123m, 1076w, 1020w, 1001w, 982w, 912w, 854w, 845m, 810w, 781w, 766w; δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance missing, 7.73 (2H, dd, *J* 8.5, 1.0, Ar *H*), 7.58 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.37 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.13 (2H, d, *J* 9.0, Ar *H*), 7.05 (2H, d, *J* 9.0, Ar *H*), 3.89 (3H, s, O*C*H_3); δ_H(500 MHz; DMSO-d_6) 10.41 (1H, s, N*H*), 7.64-7.59 (3H, m, Ar *H*), 7.45 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.36 (2H, d, *J* 9.0, Ar *H*), 7.12 (2H, d, *J* 8.5, Ar *H*), 3.82 (3H, s, O*C*H_3); δ_C(125 MHz; DMSO-d_6) 170.2 (s), 167.1 (s), 160.2 (s), 156.3 (s), 134.1 (d), 130.5 (d), 130.2 (d), 128.8 (d), 126.3 (s), 124.8 (s), 115.6 (d), 113.7 (s, *C*≡N), 113.1 (s, *C*≡N), 66.4 [s, *C*$(CN)_2$], 55.5 (q, O*C*H_3); *m*/*z* (MALDI-TOF) 329 (MH^++1, 24%), 328 (MH^+, 100), 252 (17), 210 (8), 153 (2).

*7.5.2.3 2-[5-Imino-2-phenyl-1-p-tolyl-1H-imidazol-4(5H)-ylidene]malononitrile (**171**).* Similar treatment of *N'*-(*p*-tolyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**162**) (31.1 mg, 0.1

mmol) gave the *title compound* **171** (27.7 mg, 89%) as yellow needles, mp (DSC) onset 173.9 °C, peak max. 179.9 °C, decomp. onset 192.5 °C peak max. 202.7 °C (from *n*-pentane/THF, 90:10); (found: C, 73.16; H, 4.15; N, 22.33. $C_{19}H_{13}N_5$ requires C, 73.30; H, 4.21; N, 22.49%); R_f 0.57 (DCM); λ_{max}(DCM)/nm 267 (3.89), 327 (4.22), 445 (4.29); ν_{max}/cm^{-1} 3227m (NH), 3065w and 3042w (aryl C-H), 2230w and 2214w (C≡N), 1651w, 1607w, 1591w, 1578w, 1518m, 1503w, 1466s, 1439m, 1418s, 1331s, 1318w, 1300w, 1277m, 1221m, 1194w, 1182w, 1159w, 1121m, 1082w, 1070w, 1034w, 979w, 947w, 905w, 885m, 820m, 785m, 760w; δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance missing, 7.72 (2H, d, *J* 7.5, Ar *H*), 7.58 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.38-7.35 (4H, m, Ar *H*), 7.09 (2H, d, *J* 8.0, Ar *H*), 2.46 (3H, s, C*H*$_3$); δ_H(500 MHz; DMSO-d_6) 10.41 (1*H*, s, N*H*), 7.62 (1*H*, dd, *J* 7.5, 7.5, Ar *H*), 7.58 (2H, d, *J* 8.0, Ar *H*), 7.44 (2H, dd, *J* 8.0, 7.5, Ar *H*), 7.39 (2H, d, *J* 8.0, Ar *H*), 7.30 (2H, d, *J* 8.0, Ar *H*), 2.40 (3H, s, C*H*$_3$); δ_C(125 MHz; DMSO-d_6) 170.1 (s), 167.0 (s), 155.9 (s), 139.9 (s), 134.1 (d), 130.9 (d), 130.4 (d), 129.8 (s), 128.7 (d), 128.5 (d), 126.2 (s), 113.7 (s, *C*≡N), 113.0 (s, *C*≡N), 66.7 [s, $C(CN)_2$], 20.8 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 313 (MH$^+$+1, 11%), 312 (MH$^+$, 100).

*7.5.2.3 2-[1-(4-Fluorophenyl)-5-imino-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**172**).* Similar treatment of *N'*-(4-fluorophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**163**) (31.5 mg, 0.1 mmol) gave the *title compound* **172** (28.0 mg, 89%) as yellow needles, mp (DSC) onset 192.7 °C, peak max. 197.6 °C, decomp. onset 201.1 °C peak max. 210.1 °C (from *n*-pentane/THF, 90:10); (found: C, 68.46; H, 3.33; N, 22.16. $C_{18}H_{10}FN_5$ requires C, 68.57; H, 3.20; N, 22.21%); R_f 0.50 (DCM); λ_{max}(DCM)/nm 265 (2.70), 331 (4.18), 440 (4.25); ν_{max}/cm^{-1} 3235m (NH), 3073w (aryl C-H), 2232w and 2216w (C≡N), 1653w, 1609w, 1580w, 1512s, 1466s, 1445s, 1418s, 1331s, 1315w, 1300w, 1277m, 1236m, 1221s, 1194w, 1184w, 1167w, 1155w, 1121m, 1099w, 1080w, 1074w, 1032w, 1001w, 984m, 964w, 945w, 874m, 841m, 820w, 814w, 779m, 756w; δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance missing, 7.69 (2H, d, *J* 8.0, Ar *H*), 7.60 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.39 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.27-7.21 (4H, m, Ar *H*); δ_H(500 MHz; DMSO-d_6) 11.02 (1H, s, N*H*), 8.05 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.98 (2H, d, *J* 8.0, Ar *H*), 7.94-97 (2H, m, Ar *H*), 7.89-7.84 (4H, m, Ar *H*); δ_C(125 MHz; DMSO-d_6) 170.0 (s), 167.0 (s), 162.6 (s, $^1J_{CF}$ 245.0, *C*F), 155.6 (s), 134.1 (d), 131.4 (d, $^3J_{CF}$ 8.8, *C*HCHCF), 130.4 (d), 128.84 (s), 128.77 (d), 126.1 (s), 117.3 (d, $^2J_{CF}$ 23.8, *C*HCF), 113.6 (s, *C*≡N), 112.9 (s, *C*≡N), 66.7 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 317 (MH$^+$+1, 13%), 316 (MH$^+$, 100), 252 (2), 198 (3), 105 (2).

*7.5.2.4 2-[1-(4-Chlorophenyl)-5-imino-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**173**).* Similar treatment of *N'*-(4-chlorophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**164**) (33.2 mg, 0.1 mmol) gave the *title compound* **173** (28.9 mg, 87%) as yellow needles, mp (DSC) onset 188.6 °C, peak max. 193.5 °C, decomp. onset 198.2 °C peak max. 201.5 °C (from *n*-pentane/THF, 50:50); (found: C, 65.16; H, 2.99; N, 20.94. $C_{18}H_{10}ClN_5$ requires C, 65.17; H, 3.04; N, 21.11%); R_f 0.55 (DCM); λ_{max}(DCM)/nm 267 (log ε 3.69), 332 (4.12), 440 (4.23); ν_{max}/cm^{-1} 3231m (NH), 3061w (aryl C-H), 2230w and 2218w (C≡N), 1651w, 1609w, 1591w, 1578w, 1503m, 1495s, 1466s, 1443s, 1414s, 1329s, 1315w, 1302w, 1277m, 1223s, 1194w, 1182w, 1123m, 1094m, 1082w, 1074w, 1032w, 1020w, 980w, 947w, 878m, 835m, 822w, 781m, 754w; δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance missing, 7.69 (2H, d, *J* 7.5, Ar *H*), 7.61 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.53 (2H, d, *J* 7.5, Ar *H*), 7.40 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.17 (2H, d, *J* 8.5, Ar *H*); δ_H(500 MHz; DMSO-d_6) 10.67 (1H, s, N*H*), 7.67-7.62 (3H, m, Ar *H*), 7.56 (2H, d, *J* 8.0, Ar *H*), 7.48-7.46 (4H, m, Ar *H*); δ_C(125 MHz; DMSO-d_6) 169.9 (s), 167.0 (s), 155.2 (s), 134.8 (s), 134.1 (d), 131.5 (s), 130.8 (d), 130.4 (d), 130.3 (d), 128.8 (d), 126.0 (s), 113.5 (s, *C*≡N), 112.9 (s, *C*≡N), 66.8 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 334 (MH^++2, 25%), 333 (MH^++1, 9), 332 (MH^+, 100), 214 (3), 153 (2).

*7.5.2.5 2-[1-(3,4-Dichlorophenyl)-5-imino-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**174**).* Similar treatment of *N'*-(3,4-dichlorophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**165**) (36.6 mg, 0.1 mmol) gave the *title compound* **174** (31.7 mg, 87%) as orange needles, mp (DSC) onset 114.5 °C, peak max. 115.5 °C (from *n*-pentane/THF, 50:50); (found: C, 50.51; H, 2.53; N, 15.51. $C_{18}H_9Cl_2N_5.CH_2Cl_2$ requires C, 50.58; H, 2.46; N, 15.52%); R_f 0.60 (DCM); λ_{max}(DCM)/nm 242 inf (log ε 4.00), 267 inf (3.68), 333 (4.12), 436 (4.24); ν_{max}/cm^{-1} 3316w (NH), 3096w and 3076w (aryl C-H), 2224w (C≡N), 1647w, 1589w, 1578w, 1566w, 1497m, 1477s, 1464s, 1435s, 1414s, 1385m, 1335m, 1315w, 1298w, 1278m, 1271m, 1250w, 1234w, 1229w, 1219w, 1196w, 1182w, 1161w, 1134m, 1113w, 1101w, 1057m, 1036w, 1001w, 991w, 949w, 885w, 851m, 826m, 808w, 783m, 766m; δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance missing, 7.71 (2H, d, *J* 7.0, Ar *H*), 7.64 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.60 (1H, br s, Ar *H*), 7.44 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.40 (1H, br s, Ar *H*), 7.06 (1H, dd, *J* 8.5, 2.0, Ar *H*); δ_H(500 MHz; DMSO-d_6) 10.87 (1H, s, N*H*), 7.87-7.85 (2H, m, Ar *H*), 7.65 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.59 (2H, d, *J* 7.5, Ar *H*), 7.49 (2H, dd, 7.8, 7.8, Ar *H*), 7.45 (1H, dd, *J* 8.5, 2.0, Ar *H*), 5.75 (2H, s, C*H*$_2$Cl$_2$); δ_C(125 MHz; DMSO-d_6) 169.7 (s), 166.8 (s), 154.7 (s), 134.2 (d), 133.1 (s), 132.6 (s), 132.5 (s),

132.1 (d), 131.2 (d), 130.3 (d), 129.5 (d), 128.9 (d), 125.9 (s), 113.4 (s, *C*≡N), 112.8 (s, *C*≡N), 67.0 [s, *C*(CN)$_2$], 54.8 (*C*H$_2$Cl$_2$); *m*/*z* (MALDI TOF) 370 (MH$^+$+4, 5%), 369 (MH$^+$+3, 11), 368 (MH$^+$+2, 52), 367 (MH$^+$+1, 16), 366 (MH$^+$, 100), 316 (16), 252 (4), 242 (7).

*7.5.2.6 2-[1-(4-Bromophenyl)-5-imino-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**175**).* Similar treatment of *N'*-(4-bromophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**166**) (37.6 mg, 0.1 mmol) gave the *title compound* **175** (32.0 mg, 85%) as yellow needles, mp (DSC) onset 166.1 °C, peak max. 170.5 °C, decomp. onset 172.7 °C peak max. 173.0 °C (from *n*-pentane/THF, 90:10); (found: C, 57.31; H, 2.64; N, 18.55. $C_{18}H_{10}BrN_5$ requires C, 57.47; H, 2.68; N, 18.62%); R_f 0.56 (DCM); λ_{max}(DCM)/nm 267 inf (log ε 3.81), 332 (4.17), 440 (4.28); ν_{max}/cm^{-1} 3233m (NH), 3063w (aryl C-H), 2228w and 2218w (C≡N), 1649w, 1607w, 1591w, 1578w, 1493s, 1466s, 1439s, 1414s, 1404s, 1329s, 1314m, 1300m, 1277m, 1223m, 1192w, 1180m, 1121m, 1103w, 1080w, 1069w, 1032w, 1016w, 980w, 947w, 878m, 833m, 822w, 783m, 760w; δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance missing, 7.69 (4H, d, *J* 7.5, Ar *H*), 7.61 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.41 (2H, dd, 8.0, 8.0, Ar *H*), 7.10 (2H, d, *J* 8.0, Ar *H*); δ_H(500 MHz; DMSO-d_6) 10.67 (1H, s, N*H*), 7.80 (2H, d, *J* 8.0, Ar *H*), 7.68 (1H, dd, *J* 7.0, 7.0, Ar *H*), 7.56 (2H, d, *J* 7.5, Ar *H*), 7.47 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.39 (2H, d, *J* 8.5, Ar *H*); δ_C(125 MHz; DMSO-d_6) 170.0 (s), 167.0 (s), 155.2 (s), 134.1 (d), 133.4 (d), 132.0 (s), 131.1 (d), 130.4 (d), 128.9 (d), 126.1 (s), 123.6 (s), 113.6 (s, *C*≡N), 113.0 (s, *C*≡N), 66.8 [s, *C*(CN)$_2$]; *m*/*z* (MALDI TOF) 379 (MH$^+$+3, 13%), 378 (MH$^+$+2, 90), 377 (MH$^+$+1, 8), 376 (MH$^+$, 100), 260 (12), 252 (18).

*7.5.2.7 2-[1-(4-Iodophenyl)-5-imino-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**176**).* Similar treatment of *N'*-(4-iodophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**167**) (42.3 mg, 0.1 mmol) gave the *title compound* **176** (35.6 mg, 84%) as orange plates, mp (DSC) onset 172 °C, peak max. 176 °C, onset 185 °C decomp. 207 °C (from *n*-pentane/THF, 90:10); (found: C, 50.92; H, 2.34; N, 16.49. $C_{18}H_{10}IN_5$ requires C, 51.08; H, 2.38; N, 16.55%); R_f 0.59 (DCM); λ_{max}(DCM)/nm 243 (log ε 4.65), 324 (4.43), 441 (4.54); ν_{max}/cm^{-1} 3316w (NH), 3084w and 3032w (aryl C-H), 2222w (C≡N), 1641w, 1607w, 1589w, 1576w, 1501m, 1491m, 1468s, 1441s, 1416s, 1398m, 1335m, 1312w, 1298w, 1267m, 1244w, 1225w, 1196w, 1180w, 1161w, 1130m, 1103w, 1067m, 1055w, 1028w, 1011w, 1001w, 989w, 979w, 941w, 831m, 824m, 783w, 764m; δ_H[500 MHz; $CDCl_3$/HCl (g)] NH resonance missing, 7.88 (2H, d, *J* 8.5, Ar *H*), 7.70 (2H, d, *J* 7.5, Ar *H*), 7.61 (1H,

dd, *J* 7.5, 7.5, Ar *H*), 7.41 (2H, dd, *J* 8.0, 8.0, Ar *H*), 6.96 (2H, d, *J* 8.5, Ar *H*); δ_H(500 MHz; DMSO-d_6) 10.66 (1H, s, N*H*), 7.95 (2H, d, *J* 8.5, Ar *H*), 7.63 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.56 (2H, d, *J* 7.5, Ar *H*), 7.47 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.22 (2H, d, *J* 8.5, Ar *H*); δ_C(125 MHz; DMSO-d_6) 169.9 (s), 167.0 (s), 155.1 (s), 139.2 (d), 134.1 (d), 131.9 (s), 130.9 (d), 130.3 (d), 128.8 (d), 126.1 (s), 113.6 (s, *C*≡N), 112.9 (s, *C*≡N), 97.2 (s), 66.8 [s, *C*$(CN)_2$]; *m*/*z* (MALDI TOF) 425 (MH^++1, 15%), 424 (MH^+, 100), 153 (4).

*7.5.2.8 2-[5-Imino-1-(4-nitrophenyl)-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**177**)*. Similar treatment of *N'*-(4-nitrophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**168**) (34.2 mg, 0.1 mmol) gave the *title compound* **177** (31.5 mg, 92%) as yellow plates, mp (DSC) onset 209 °C, peak max. 214 °C, decomp. onset 219.4 °C, peak max. 224.2 °C (from *n*-pentane/DCE, 90:10); (found: C, 63.03; H, 2.99; N, 24.51. $C_{18}H_{10}N_6O_2$ requires C, 63.16; H, 2.94; N, 24.55%); R_f 0.35 (DCM); λ_{max}(DCM)/nm 264 (log ε 4.09), 325 (4.23), 433 (4.25); ν_{max}/cm^{-1} 3285w (NH), 3115w and 3084w (aryl C-H), 2224w and 2216w (C≡N), 1663w, 1611w, 1591w, 1574w, 1520m, 1497m, 1468s, 1439m, 1416w, 1391m, 1348s, 1331w, 1315w, 1298w, 1275w, 1209m, 1186w, 1177w, 1113w, 1103w, 1061m, 1024w, 1013w, 1001w, 980w, 934w, 864m, 853m, 835m, 789m, 773w; δ_H[500 MHz; $CDCl_3$/HCl (g)] 8.43-8.37 (2H, m, Ar *H*), 7.69-7.61 (3H, m, Ar *H*), 7.46-7.43 (4H, d, *J* 7.5, Ar *H*); δ_H(500 MHz; DMSO-d_6) 10.80 (1H, s, N*H*), 8.43 (2H, d, *J* 8.0, Ar *H*), 7.70 (2H, d, *J* 8.5 Ar *H*), 7.64 (1H, dd, *J* 6.8, 6.8, Ar *H*), 7.55 (2H, d, *J* 6.5, Ar *H*), 7.46 (2H, dd, *J* 7.3, 7.3, Ar *H*); δ_C(125 MHz; DMSO-d_6) 169.8 (s), 166.9 (s), 154.4 (s), 147.9 (s), 138.4 (s), 134.1 (d), 130.44 (d), 130.38 (d), 129.1 (d), 128.9 (d), 125.8 (s), 125.5 (d), 113.4 (s, *C*≡N), 112.8 (s, *C*≡N), 66.9 [s, *C*$(CN)_2$]; *m*/*z* (MALDI TOF) 344 (MH^++1, 27%), 343 (MH^+, 100), 252 (90), 225 (18), 153 (8), 105 (53).

*7.5.3 Conversion of N-Aryl-N-(1,2,2-tricyanovinyl)benzamidines **156** into (Z)-2-[2-phenyl-4-(arylimino)-1H-imidazol-5(4H)-ylidene]malononitriles **158***

*7.5.3.1 (Z)-2-[2-Phenyl-4-(phenylimino)-1H-imidazol-5(4H)-ylidene]malononitrile (**178**)*. A solution of *N'*-phenyl-*N*-(1,2,2-tricyanovinyl)benzamidine (**160**) (29.7 mg, 0.1 mmol) in MeOH (1 mL) left to stir at *ca*. 65 °C for 1 h and chromatography of the residue (DCM/Et_2O, 95:05) gave the *title compound* **178** (27.5 mg, 92%), as orange fibres, mp (DSC) decomp. onset 254.9 °C, peak max. 256.7 °C (from *c*-hexane/DCE, 50:50); (found: C, 72.82; H, 3.54; N, 23.43. $C_{18}H_{11}N_5$ requires C, 72.72; H, 3.73; N, 23.56%); R_f 0.71 (DCM/Et_2O, 95:05); λ_{max}(pyridine)/nm 345 (4.28), 365 inf (4.16), 390 inf (3.96), 414 inf

(3.88), 505 inf (4.05), 542 (4.28), 582 (4.30) λ_{max}(DCM)/nm 259 inf (log ε 4.01), 267 inf (4.04), 286 inf (4.12), 323 (4.26), 424 (4.28), 452 (4.26), 483 inf (4.17), 556 inf (3.17), 598 inf (3.03); λ_{max}(acetone)/nm 333 (log ε 4.27), 426 inf (4.20), 456 (4.24), 484 inf (4.18), 539 inf (3.67), 580 (3.58); λ_{max}(DMF)/nm 271 inf (log ε 4.30), 282 (4.33), 292 inf (4.32), 308 inf (4.24), 331 (4.28), 344 (4.31), 365 inf (4.21), 387 inf (4.00), 414 inf (3.86), 501 inf (4.06), 539 (4.33), 579 (4.37); λ_{max}(DMSO)/nm 272 inf (log ε 4.29), 283 (4.31), 293 inf (4.30), 308 inf (4.23), 332 inf (4.28), 346 (4.31), 365 inf (4.02), 389 inf (4.02), 415 inf (3.91), 503 inf (4.08), 538 (4.33), 578 (4.34); ν_{max}/cm^{-1} 3196w (NH), 3047w (aryl C-H), 2230m and 2220w (C≡N), 1641m, 1601m, 1582m, 1570m, 1530s, 1491w, 1458m, 1418w, 1335w, 1319m, 1308m, 1294m, 1285s, 1225m, 1204m, 1180m, 1171m, 1155w, 1078w, 1065m, 1024w, 999w, 966m, 932w, 922m, 849m, 785m, 773s; δ_H(500 MHz; DMSO-d_6) 12.62 (1H, s, N*H*), 8.32 (2H, d, *J* 7.5, Ar *H*), 7.77 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.63 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.49 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.45 (2H, br s, Ar *H*), 7.31 (1H, d, *J* 7.3, Ar *H*); δ_C(125 MHz; DMSO-d_6) five carbon resonances missing possibly owing to prototautomerism 146.7 (s), 135.5 (d), 130.5 (d), 129.7.9 (d), 129.6 (d), 126.6 (d), 126.6 (s), 114.6 (s, *C*≡N), 114.1 (s, *C*≡N); *m/z* (EI) 297 (M^+, 100%), 296 (62), 271 (22), 194 (48), 180 (5), 167 (12), 135 (5), 118 (25), 104 (71), 103 (67), 91 (7), 77 (78), 63 (6), 51 (26); *m*/*z* (MALDI-TOF) 299 (MH^++1, 17%), 298 (MH^+, 100%), 153 (1).

*7.5.3.2 (Z)-2-{4-[(4-Methoxyphenyl)imino]-2-phenyl-1H-imidazol-5(4H)ylidene}malo-nonitrile (**179**).* Similar treatment of *N'*-(4-methoxyphenyl)-*N*-(1,2,2-tricyanovinyl)benz-amidine (**161**) (32.7 mg, 0.1 mmol) gave the *title compound* **179** (30.0 mg, 91%), as red fibres, mp (DSC) decomp. onset 258.5 °C, peak max. 260.3 °C (from *c*-hexane/DCE, 50:50); (found: C, 69.72; H, 3.95; N, 21.30. $C_{19}H_{13}N_5O$ requires C, 69.71; H, 4.00; N, 21.39%); R_f 0.63 (DCM/Et_2O, 95:05); λ_{max}(DMF)/nm 281 inf (log ε 4.28), 290 (4.27), 300 (4.27), 341 inf (4.15), 403 (4.06), 427 (4.04), 481 inf (3.92), 503 inf (4.11), 540 (4.34), 583 (4.39); ν_{max}/cm^{-1} 3202w (NH), 2843w (alkyl C-H), 2224m and 2212w (C≡N), 1641m, 1611w, 1599m, 1582m,1566s, 1520s, 1491m, 1454m, 1443w, 1427w, 1333w, 1312m, 1300m, 1290m, 1254s, 1242m, 1196w, 1182w, 1167m, 1159s, 1148s, 1061w, 1024s, 970w, 922s, 843s, 806w, 785m, 764w; δ_H(500 MHz; DMSO-d_6) 13.04 (1H, br s, N*H*), 8.32 (2H, d, *J* 7.5, Ar *H*), 7.76-7.73 (3H, m, Ar *H*), 7.62 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.06 (2H, d, *J* 8.5, Ar *H*), 3.83 (3H, s, OCH_3); δ_C(125 MHz; DMSO-d_6) five carbon resonances missing possibly owing to prototautomerism 159.7 (s), 139.1 (s), 134.4 (d), 129.5 (d), 129.0 (d),

126.2 (s), 114.6 (d), 114.2 (s, *C*≡N), 113.8 (s, *C*≡N), 55.4 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 329 (MH$^+$+1, 23%), 328 (MH$^+$, 100), 327 (M$^+$, 16).

*7.5.3.3 (Z)-2-[2-Phenyl-4-(p-tolylimino)-1H-imidazol-5(4H)-ylidene]malononitrile (**180**).* Similar treatment of *N'*-(*p*-tolyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**162**) (31.1 mg, 0.1 mmol) gave the *title compound* **180** (29.1 mg, 94%), as orange fibres, mp (DSC) decomp. onset 271.4 ^{o}C, peak max. 272.0 ^{o}C (from *c*-hexane/DCE, 50:50); (found: C, 73.28; H, 4.17; N, 22.58. $C_{19}H_{13}N_5$ requires C, 73.30; H, 4.21; N, 22.49%); R_f 0.76 (DCM/Et$_2$O, 95:05); λ_{max}(DMF)/nm 275 inf (log ε 4.45), 286 (4.47), 295 inf (4.47), 311 inf (4.42), 338 (4.420), 369 inf (4.28), 394 (4.20), 420 (4.18), 469 inf (4.12), 504 (4.31), 538 (4.44), 581 (4.47); ν_{max}/cm^{-1} 3211w (NH), 3055w and 3030w (aryl C-H), 2226m and 2216w (C≡N), 1643s, 1612m, 1601m, 1584s, 1572s, 1526s, 1489m, 1456s, 1416w, 1331w, 1312s, 1296s, 1284s, 1231m, 1194m, 1173s, 1101w, 1076w, 1061w, 1032w, 1014w, 1001w, 970w, 955w, 922m, 856w, 827s, 806w, 785s, 766w; δ_H(500 MHz; DMSO-d_6) 12.88 (1H, s, N*H*), 8.32 (2H, d, *J* 7.0, Ar *H*), 7.77 (1H, d, *J* 7.5, 7.5, Ar *H*), 7.63 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.45 (2H, br s, Ar *H*), 7.30 (2H, d, *J* 8.5, Ar *H*), 2.37 (3H, s, C*H*$_3$); δ_C(125 MHz; DMSO-d_6) six carbon resonances missing possibly owing to prototautomerism 143.5 (s), 134.8 (d), 129.8 (d), 129.7 (d), 129.0 (d), 126.0 (s), 114.1 (s, *C*≡N), 113.5 (s, *C*≡N), 20.8 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 313 (MH$^+$+1, 25%), 312 (MH$^+$, 100), 153 (2).

*7.5.3.4 (Z)-2-{4-[(4-Fluorophenyl)imino]-2-phenyl-1H-imidazol-5(4H)-ylidene}malononitrile (**181**).* Similar treatment of *N'*-(4-fluorophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**163**) (31.5 mg, 0.1 mmol) gave the *title compound* **181** (27.8 mg, 88%), as orange fibres, mp (DSC) onset 267.4 ^{o}C, peak max. 267.7 ^{o}C, decomp. onset 268.7 ^{o}C, peak max. 271.2 ^{o}C (from *c*-hexane/DCE, 50:50); (found: C, 68.56; H, 3.27; N, 22.15. $C_{18}H_{10}FN_5$ requires C, 68.57; H, 3.20; N, 22.21%); R_f 0.65 (DCM/Et$_2$O, 95:05); λ_{max}(DMF)/nm 275 inf (log ε 4.44), 282 (4.46), 292 inf (4.44), 307 inf (4.37), 339 (4.40), 363 inf (4.33), 387 inf (4.18), 412 inf (4.09), 465 inf (3.96), 501 inf (4.19), 537 (4.41), 578 (4.47); ν_{max}/cm^{-1} 3229w (NH), 3053w (aryl C-H), 2226m and 2210w (C≡N), 1647m, 1601m, 1570s, 1530s, 1487m, 1456m, 1414w, 1335w, 1314m, 1298m, 1287s, 1233s, 1213m, 1194m, 1167w, 1159m, 1146m, 1096w, 1061m, 1028w, 1010w, 1001w, 982w, 968w, 951m, 933w, 920m, 903w, 860w, 843s, 814m, 785m, 777m; δ_H(500 MHz; DMSO-d_6) 12.87 (1H, br s, N*H*), 8.32 (2H, d, *J* 7.5, Ar *H*), 7.78 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.64 (3H, dd, *J* 7.5, 7.5, Ar *H*), 7.52 (1H, br s, Ar *H*), 7.32 (2H, dd, *J* 8.5, 8.5, Ar *H*); δ_C(125 MHz; DMSO-d_6) five carbon

resonances missing possibly owing to prototautomerism 163.3 (d, $^{1}J_{CF}$ 84.6, *C*F), 161.0 (d, $^{2}J_{CF}$ 246.3, *C*F), 142.5 (s), 134.9 (d), 129.8 (d), 129.0 (d), 125.9 (s), 116.0 (d, $^{3}J_{CF}$ 22.5, *C*HCF), 113.9 (s, *C*≡N), 113.4 (s, *C*≡N); *m*/*z* (MALDI-TOF) 317 (MH^++1, 27%), 316 (MH^+, 100), 153 (3).

*7.5.3.5 (Z)-2-{4-[(4-Chlorophenyl)imino]-2-phenyl-1H-imidazol-5(4H)-ylidene}malononitrile (**182**).* Similar treatment of *N'*-(4-chlorophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**164**) (33.2 mg, 0.1 mmol) gave the *title compound* **182** (28.6 mg, 86%), as orange fibres, mp (DSC) onset 269.0 °C, peak max 269.5 °C, decomp. onset 270.1 °C, peak max. 271.9 °C (from *c*-hexane/DCE, 50:50); (found: C, 65.24; H, 3.15; N, 21.01. $C_{18}H_{10}ClN_5$ requires C, 65.17; H, 3.04; N, 21.11%); R_f 0.71 (DCM/Et_2O, 95:05); λ_{max}(DMF)/nm 277 inf (log ε 4.43), 286 inf (4.46), 296 (4.46), 310 inf (4.42), 339 (4.42), 366 inf (4.32), 393 (4.18), 418 (4.12), 471 inf (4.01), 507 inf (4.23), 544 (4.43), 585 (4.46); ν_{max}/cm^{-1} 3208w (NH), 3048w (aryl C-H), 2228m and 2218w (C≡N), 1641m, 1607m, 1595m, 1582m, 1568s, 1526s, 1493w, 1477m, 1456m, 1416w, 1312s, 1300s, 1290s, 1275w, 1236m, 1205w, 1190m, 1169m, 1092s, 1061w, 1030w, 1009m, 1001w, 972m, 955w, 922m, 839s, 802w, 785s, 756w; δ_H(500 MHz; DMSO-d_6) 12.69 (1H, br s, N*H*), 8.32 (2H, d, *J* 7.5, Ar *H*), 7.79 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.65 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.55 (2H, d, *J* 8.0, Ar *H*), 7.46 (2H, br s, Ar *H*); δ_C(125 MHz; DMSO-d_6) six carbon resonances missing possibly owing to prototautomerism 145.1 (s), 135.0 (d), 129.9 (d), 129.1 (d), 129.01 (d), 126.5 (s), 114.0 (s, *C*≡N), 113.4 (s, *C*≡N); *m*/*z* (MALDI-TOF) 335 (MH^++3, 7%), 334 (MH^++2, 39), 333 (MH^++1, 20), 332 (MH^+, 100).

*7.5.3.6 (Z)-2-{4-[(3,4-Dichlorophenyl)imino]-2-phenyl-1H-imidazol-5(4H)ylidene}malononitrile (**183**).* Similar treatment of *N'*-(3,4-dichlorophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**165**) (36.6 mg, 0.1 mmol) gave the *title compound* **183** (32.9 mg, 90%), as red fibres, mp (DSC) onset 267.2 °C, peak max 269.1 °C, decomp. onset 270.5 °C, peak max. 274.8 °C (from *c*-hexane/DCE, 50:50); (found: C, 59.19; H, 2.50; N, 19.20. $C_{18}H_9Cl_2N_5$ requires C, 59.04; H, 2.48; N, 19.12%); R_f 0.67 (DCM/Et_2O, 95:05); λ_{max}(DMF)/nm 285 inf (log ε 4.38), 296 (4.39), 310 (4.34), 348 (4.32), 369 inf (4.25), 393 (4.11), 419 inf (3.99), 476 inf (3.82), 510 inf (4.37), 548 (4.37), 591 (4.41); ν_{max}/cm^{-1} 3198w (NH), 3049w (aryl C-H), 2234m and 2218w (C≡N), 1647m, 1605m, 1564s, 1528s, 1493m, 1454s, 1416w, 1383w, 1333w, 1312s, 1296s, 1271w, 1254w, 1219s, 1192m, 1161w, 1124m, 1063w, 1024s, 1001w, 970m, 924s, 901m, 891s, 829m, 816w, 779m; δ_H(500 MHz;

DMSO-d_6) 12.72 (1H, br s, N*H*), 8.29 (3H, d, *J* 7.5, Ar *H*), 7.79 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.72 (1H, d, Ar *H*), 7.65 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.34 (2H, br s, Ar *H*); δ_C(125 MHz; DMSO-d_6) seven peaks missing possibly owing to prototautomerism 171.7 (s), 146.4 (s), 135.2 (d), 131.5 (s), 131.0 (d), 129.9 (d), 129.1 (d), 126.0 (s), 113.8 (s, *C*≡N), 113.2 (s, *C*≡N); *m*/*z* (MALDI-TOF) 370 (MH^++4, 1%), 369 (MH^++3, 1), 368 (MH^++2, 12), 367 (MH^++1, 3), 366 (MH^+, 23), 271 (2), 153 (100).

*7.5.3.7 (Z)-2-{4-[(4-Bromophenyl)imino]-2-phenyl-1H-imidazol-5(4H)-ylidene}malononitrile (**184**)*. Similar treatment of *N'*-(4-bromophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**166**) (37.6 mg, 0.1 mmol) gave the *title compound* **184** (32.8 mg, 87%), as orange fibres, mp (DSC) onset 278.1 °C, peak max 278.4 °C, decomp. onset 279.0 °C, peak max. 281.7 °C (from *c*-hexane/DCE, 50:50); (found: C, 57.40; H, 2.73; N, 18.75. $C_{18}H_{10}BrN_5$ requires C, 57.47; H, 2.68; N, 18.62%); R_f 0.72 (DCM/Et_2O, 95:05); λ_{max}(DMF)/nm 287 inf (log ε 4.39), 296 (4.40), 310 (4.35), 347 (4.34), 366 inf (4.26), 394 inf (4.10), 417 inf (3.98), 476 inf (3.80), 508 inf (4.15), 545 (4.41), 586 (4.44); ν_{max}/cm^{-1} 3208w (NH), 3044w (aryl C-H), 2228m and 2218w (C≡N), 1643m, 1605m, 1593m, 1581w, 1566s, 1526s, 1493w, 1474m, 1456m, 1416w, 1312s, 1300s, 1290s, 1271w, 1234m, 1200w, 1169s, 1028w, 1007m, 970w, 922m, 835s, 785s, 756w; δ_H(500 MHz; DMSO-d_6) 12.68 (1H, br s, N*H*), 8.31 (2H, d, *J* 7.5 Ar *H*), 7.78 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.68-7.63 (4H, m, Ar *H*), 7.35 (2H, br s, Ar *H*); δ_C(125 MHz; DMSO-d_6) six carbon resonances missing possibly owing to prototautomerism 145.5 (s), 135.1 (d), 132.1 (d), 129.9 (d), 129.1 (d), 126.0 (s), 113.9 (s, *C*≡N), 113.4 (s, *C*≡N); *m*/z (MALDI-TOF) 379 (MH^++3, 9%), 378 (MH^++2, 58), 377 (MH^++1, 10), 376 (MH^+, 100), 260 (47), 258 (90), 153 (30), 105 (17).

*7.5.3.8 (Z)-2-{4-[(4-Iodophenyl)imino]-2-phenyl-1H-imidazol-5(4H)-ylidene}malononitrile (**185**)*. Similar treatment of *N'*-(4-iodophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**167**) (37.6 mg, 0.1 mmol) gave the *title compound* **185** (35.9 mg, 85%), as orange fibres, mp (DSC) onset 281.4 °C, peak max 282.5 °C, decomp. onset 283.2 °C, peak max. 284.8 °C (from *c*-hexane/DCE, 50:50); (found: C, 51.17; H, 2.46; N, 16.46. $C_{18}H_{10}IN_5$ requires C, 51.08; H, 2.38; N, 16.55%); R_f 0.74 (DCM/Et_2O, 95:05); λ_{max}(DMF)/nm 290 (log ε 4.39), 312 (3.35), 344 (4.33), 395 inf (4.07), 421 inf (3.95), 482 inf (3.80), 509 inf (4.12), 546 (4.39), 587 (4.42); ν_{max}/cm^{-1} 3202w (NH), 3046w (aryl C-H), 2230m and 2220w (C≡N), 1643m, 1607m, 1593m, 1582w, 1562s, 1526s, 1493m, 1474m, 1455s, 1416w, 1335w, 1312s, 1300s, 1290s, 1269w, 1234m, 1221w, 1200m, 1171m, 1055m,

1028w, 1003s, 970m, 920m, 849w, 831s, 800w, 787s; δ_H(500 MHz; DMSO-d_6) 12.59 (1H, br s, N*H*), 8.31 (2H, d, *J* 7.5, Ar *H*), 7.83 (2H, d, *J* 8.5, Ar *H*), 7.78 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.64 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.20 (2H, br s, Ar *H*); δ_C(125 MHz; DMSO-d_6) six carbon resonances missing possibly owing to prototautomerism 145.9 (s), 137.9 (d), 135.1 (d), 129.9 (d), 129.1 (d), 125.9 (s), 113.9 (s, *C*≡N), 113.4 (s, *C*≡N), *m*/*z* (MALDI-TOF) 426 (MH^++2, 3%), 425 (MH^++1, 18), 424 (MH^+, 100), 252 (3).

*7.5.3.9 (Z)-2-{4-[(4-Nitrophenyl)imino]-2-phenyl-1H-imidazol-5(4H)-ylidene}malononitrile (**186**).* Similar treatment of *N'*-(4-nitrophenyl)-*N*-(1,2,2-tricyanovinyl)benzamidine (**168**) (34.2 mg, 0.1 mmol) gave the *title compound* **186** (31.9 mg, 93%), as red fibres, mp (DSC) onset 299.3 °C, peak max 299.9 °C, decomp. onset 300.5 °C, peak max. 303.4 °C (from *n*-pentane/DCE, 50:50); (found: C, 63.26; H, 3.04; N, 24.54. $C_{18}H_{10}N_6O_2$ requires C, 63.16; H, 2.94; N, 24.55%); R_f 0.40 (DCM/Et_2O, 95:05); λ_{max}(DMF)/nm 353 (log ε 4.92), 524 inf (4.27), 567 (4.50), 612 (4.44); ν_{max}/cm^{-1} 3244w (NH), 3103w (aryl C-H), 2232w and 2222w (C≡N), 1649w, 1609w, 1599w, 1589w, 1535s, 1514m, 1493w, 1481w, 1456m, 1414w, 1344s, 1333m, 1319m, 1298m, 1288s, 1236w, 1202w, 1188w, 1157w, 1107w, 1061w, 1026w, 1001w, 972w, 922w, 862s, 835w, 800w, 785w, 762w; δ_H(500 MHz; DMSO-d_6) 12.56 (1H, br s, N*H*), 8.33 (2H, d, *J* 8.5, Ar *H*), 8.29 (2H, d, *J* 7.5, Ar *H*), 7.79 (1H, dd, *J* 7.0, 7.0, Ar H), 7.64 (2H, dd, *J* 7.0, 7.0, Ar H), 7.47 (2H, br s, Ar *H*); δ_C(125 MHz; DMSO-d_6) five carbon resonances missing possibly owing to prototautomerism 152.8 (s), 144.7 (s), 135.4 (d), 130.0 (d), 129.2 (d), 125.9 (s), 124.9 (d), 113.7 (s, *C*≡N), 113.2 (s, *C*≡N), 67.0 [s, *C*$(CN)_2$]; *m*/*z* (MALDI-TOF) 344 (MH^++1, 16%), 343 (MH^+, 52), 226 (6), 172 (6), 153 (100), 116 (5).

*7.5.4 Methylation of (Z)-2-[2-phenyl-4-(phenylimino)-1H-imidazol-5(4H)-ylidene]malononitrile (**178**).* To a stirred solution of (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**178**) (29.7 mg, 0.1 mmol) in dry THF (1 mL) at *ca.* 20 °C was added NaH (4.8 mg, 0.2 mmol) and dimethyl sulfate (19 μL, 0.2 mmol). The mixture was heated at *ca*. 66 °C for 3 h and then allowed to cool to *ca.* 20 °C. Removal of the volatiles followed by chromatography (DCM/*n*-hexane, 70:30) of the residue gave *(Z)-2-[1-methyl-2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile* (**187**) (27.3 mg, 88%) as orange needles, mp (DSC) onset 216.1 °C, peak max. 216.8 °C, decomp. onset 241.8 °C, peak max. 259.1 °C (from *c*-hexane/DCE, 80:20); (found: C, 73.17; H, 4.22; N, 22.36. $C_{19}H_{13}N_5$ requires C, 73.30; H, 4.21; N, 22.49%); R_f 0.47 (DCM/*n*-hexane,

70:30); λ_{max}(pyridine)/nm 325 (log ε 4.10), 404 inf (3.90), 431 inf (4.06), 461 (4.20), 488 (4.21); λ_{max}(DCM)/nm 281 (log ε 4.18), 319 (4.11), 401 inf (3.99), 427 (4.14), 457 (4.27), 483 (4.28); λ_{max}(acetone)/nm 332 (log ε 4.06), 401 inf (3.96), 427 inf (4.14), 454 (4.27), 480 (4.21); λ_{max}(DMF)/nm 277 (log ε 4.14), 322 (4.12), 404 inf (3.95), 431 inf (4.13), 460 (4.27), 485 (4.26); λ_{max}(DMSO)/nm 278 (log ε 4.13), 327 (4.11), 405 inf (3.92), 433 inf (4.09), 463 (4.22), 490 (4.22), 580 (2.94); ν_{max}/cm^{-1} 3074w (aryl C-H), 2949w (alkyl C-H), 2218w (C≡N), 1636w, 1595m, 1580w, 1570m, 1524s, 1489m, 1460w, 1445m, 1437w, 1369w, 1325s, 1306s, 1290m, 1232m, 1198w, 1182m, 1161w, 1074w, 1061s, 1041w, 1024w, 1001w, 966w, 932w, 924w, 866w, 847m, 841m, 812w, 779s, 771s; δ_H(500 MHz; DMSO-d_6) 7.86 (2H, d, *J* 7.5, Ar *H*), 7.75-7.70 (3H, m, Ar *H*), 7.65 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.48 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.34 (1H, dd, *J* 7.3, 7.3, Ar *H*), 3.65 (3H, s, C*H*$_3$); δ_C(125 MHz; DMSO-d_6) 171.4 (s), 158.5 (s), 156.6 (s), 145.5 (s), 132.9 (d), 129.7 (d), 129.0 (d), 128.9 (d), 128.5 (d), 126.2 (d), 126.1 (s), 113.9 (s, *C*≡N), 113.5 (s, *C*≡N), 58.1 [s, *C*(CN)$_2$], 34.5 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 312 (MH$^+$, 7%), 153 (100). Further elution (DCM) gave *(Z)-2-[1-methyl-2-phenyl-5-(phenylimino)-1*H*-imidazol-4(5*H*)-ylidene]malononitrile* (**188**) (0.8 mg, 2%) as orange plates, mp (DSC) decomp. onset 213.2 °C, peak max. 215.4 °C (from *n*-pentane/DCM, 80:20); (found: C, 73.13; H, 4.16; N, 22.21. $C_{19}H_{13}N_5$ requires C, 73.30; H, 4.21; N, 22.49%); R_f 0.52 (DCM); λ_{max}(pyridine)/nm 332 (log ε 4.12), 445 (4.10), 488 inf (4.06), 527 inf (3.83); λ_{max}(DCM)/nm 267 (log ε 4.05), 322 (4.26), 336 inf (4.16), 436 (4.19), 496 inf (4.01); λ_{max}(acetone)/nm 333 (log ε 4.13), 447 (4.18), 482 inf (4.11); λ_{max}(DMF)/nm 267 (log ε 4.22), 324 (4.24), 340 inf (4.14), 449 (4.12), 486 inf (4.06); λ_{max}(DMSO)/nm 268 (log ε 4.16), 327 (4.24), 451 (4.00), 500 inf (3.99), 535 inf (3.89), 580 (3.68); ν_{max}/cm^{-1} 3082w and 3061w (aryl C-H), 2830w (alkyl C-H), 2218w (C≡N), 1659w, 1649w, 1607w, 1589w, 1576w, 1506m, 1470s, 1437s, 1387s, 1339m, 1296w, 1229m, 1196w, 1180w, 1097w, 1070w, 1051m, 1022w, 999w, 937w, 922m, 843m, 804w, 783w, 756m; δ_H(500 MHz; $CDCl_3$) 7.89 (2H, d, *J* 7.7, Ar *H*), 7.68 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.57 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.41 (2H, dd, *J* 8.0, 8.0, Ar *H*), 7.21 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.06 (1H, d, *J* 7.8, Ar *H*), 3.03 (3H, s, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) one quaternary C (s) resonance missing 174.5 (s), 147.5 (s), 145.2 (s), 134.2 (d), 130.2 (d), 129.3 (d), 129.1 (d), 126.4 (s), 126.0 (d), 120.7 (d), 113.0 (s, *C*≡N), 112.5 (s, *C*≡N), 71.8 [s, *C*(CN)$_2$], 35.9 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 312 (MH$^+$, 22%), 290 (12), 289 (100), 205 (19), 178 (11), 118 (7).

*7.5.5 Dimroth rearrangement of 2-[1-aryl-5-imino-2-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**157**) into (Z)-2-[4-(arylimino)-2-phenyl-1H-imidazol-5(4H)-ylidene]malononitrile (**158**)*

*7.5.5.1 (Z)-2-[2-Phenyl-4-(phenylimino)-1H-imidazol-5(4H)-ylidene]malononitrile (**178**) (typical procedure, see Table 8)*

Method A: A stirred solution of 2-[5-imino-1,2-diphenyl-1*H*-imidazol-4(5*H*)-ylidene]-malononitrile (**169**) (1 g, 3.37 mmol) in MeOH (15 mL) was heated at *ca*. 67 ^{o}C for 1 h and then allowed to cool to *ca.* 20 ^{o}C. Addition of H_2O (30 mL) and filtration of the precipitate, gave the title compound **178** (989.5 mg, 99%), as orange fibres, mp (DSC) onset 254.9 ^{o}C, decomp. 256.7 ^{o}C (from *c*-hexane/DCE, 50:50), identical to that described above.

Method B*:* To a stirred solution of 2-[5-imino-1,2-diphenyl-1*H*-imidazol-4(5*H*)-ylidene]-malononitrile (**169**) (1 g, 3.37 mmol) in dry DCM (15 mL) at *ca*. 20 ^{o}C, DBU (502 μL, 3.37 mmol) was added. The reaction mixture was then heated at *ca*. 40 ^{o}C for 4 h, protected from moisture with $CaCl_2$ drying tube. The reaction mixture was then extracted (5% HCl), washed (H_2O) and the organic fraction dried (Na_2SO_4). Removal of the volatiles followed by addition of MeOH (10 mL), H_2O (30 mL), and filtration of the precipitant, gave the title compound **178** (912.4 mg, 91%) as orange fibres, mp (DSC) onset 254.9 ^{o}C, decomp. 256.7 ^{o}C (from *c*-hexane/DCE, 50:50), identical to that described above.

*7.5.6 Thermolysis of 2-[5-imino-1,2-diphenyl-1H-imidazol-4(5H)-ylidene]malononitrile (**169**)*

Thermolysis of 2-[5-imino-1,2-diphenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**169**) at *ca*. 220 ^{o}C (Wood's metal bath) for 20 min under argon atmosphere followed by chromatography (DCM) gave *2-phenyl-6-(phenylamino)pyrimidine-4,5-dicarbonitrile* (**193**) (3.4 mg, 11%) as yellow fibres, mp (DSC) onset 237.4 ^{o}C, peak max. 238.3 ^{o}C (from *c*-hexane/DCE, 80:20); (found: C, 72.85; H, 3.67; N, 23.39. $C_{18}H_{11}N_5$ requires C, 72.72; H, 3.73; N, 23.56%); R_f 0.42 (DCM); λ_{max}(DCM)/nm 273 inf (log ε 4.59), 292 (4.64), 363 inf (3.76); ν_{max}/cm^{-1} 3298w (NH), 3163w, 3127w, 3065w (aryl C-H), 2226w (C≡N), 1611m, 1574m, 1555s, 1495w, 1481w, 1460w, 1429m, 1385m, 1350w, 1290w, 1244w, 1196w, 1173w, 1155w, 1092w, 1070w, 1036w, 1028w, 1018w, 1001w, 937w, 908w, 841w, 806w, 766m; δ_H(500 MHz; $CDCl_3$), 8.37 (2H, d, *J* 7.5, Ar *H*), 7.65 (2H, d, *J* 8.0, Ar *H*), 7.58 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.50 (4H, dd, *J* 7.8, 7.8, Ar *H*), 7.45 (1H, br s, N*H*), 7.33 (1H, dd, *J*

7.5, 7.5, Ar *H*); δ_C(125 MHz; $CDCl_3$) 166.7 (s), 159.5 (s), 144.4 (s), 135.8 (s), 134.9 (s), 133.2 (d), 129.5 (d), 129.3 (d), 128.9 (d), 126.5 (d), 122.5 (d), 113.6 (*C*≡N), 112.5 (*C*≡N), 93.3 (s); *m*/*z* (MALDI-TOF) 299 (MH^++1, 21%), 298 (MH^+, 100%). Further elution (DCM/Et_2O, 95:05) gave (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]-malononitrile (**178**) (10.1 mg, 34%) as orange fibres, mp (DSC) decomp. onset 254.9 °C, peak. 256.7 °C (from *c*-hexane/DCE, 50:50), identical to that described above, followed by traces of 2-phenyl-1*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**194**) as colorless fibres, mp (DSC) decomp. onset 304.7 °C, peak max. 305.1 °C (from *c*-hexane/DCE, 50:50); identical to that described above.

*7.5.7 Thermolysis of (Z)-2-[2-phenyl-4-(arylimino)-1H-imidazol-5(4H)-ylidene]malononitrile (**158**)*

*7.5.7.1 2-Phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**194**) (typical procedure, see Table 9).* An intimate mixture of (*Z*)-2-[2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**178**) (14.6 mg, 0.05 mmol) and diphenyl ether (1 mL) was heated at *ca*. 280 °C for 4 h. Chromatography (*n*-hexane/DCM, 50:50) of the reaction mixture gave recovered diphenyl ether (1 mL) and further elution (DCM/Et_2O, 90:10) gave the *title compound* **194** (13.4 mg, 98%) as colorless fibres, mp (DSC) decomp. onset 304.7 °C, peak max. 305.1 °C; (from *n*-pentane/THF, 90:10); (found: C, 75.53; H, 3.62; N, 20.80. $C_{17}H_{10}N_4$ requires C, 75.54; H, 3.73; N, 20.73%); R_f 0.23 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 216 (log ε 4.77), 265 (4.68), 281 inf (4.39), 371 (4.71); ν_{max}/cm^{-1} 3073br&w and 3015br&w (aryl C-H & NH), 2887w, 2710w, 2230w (C≡N), 1628m, 1616w, 1593w, 1526m, 1514w, 1481m, 1472m, 1460s, 1402s, 1333s, 1288m, 1240m, 1186w, 1163m, 1138w, 1072w, 1028w, 1001w, 939m, 928w, 880w, 862w, 843w, 787s, 762s; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.42 (1H, d, *J* 8.5, Ar *H*), 8.22-8.20 (3H, m, Ar *H*), 8.11 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.97 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.78 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.63 (2H, dd, *J* 8.0, 8.0, Ar *H*); δ_C(125 MHz; TFA-*d*) 166.6 (s), 150.9 (s), 139.6 (s), 139.3 (d), 137.4 (d), 132.9 (d), 132.50 (d), 132.46 (s), 131.4 (d), 127.9 (d), 126.2 (s), 124.5 (s), 124.2 (d), 112.6 (s, *C*≡N), 109.2 (s); *m*/*z* (MALDI-TOF) 272 (MH^++1, 18%), 271 (MH^+, 100), 270 (M^+, 15).

*7.5.7.2 7-Methoxy-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**196**).* Similar treatment of (*Z*)-2-[4-(4-methoxyphenylimino)-2-phenyl-1*H*-imidazol-5(4*H*)-ylidene]-malononitrile (**179**) (16.4 mg, 0.05 mmol) gave the *title compound* **196** (14.9 mg, 99%) as

pale yellow plates, mp (DSC) decomp. onset 309.3 °C, peak max. 309.5 °C; (from *n*-pentane/THF, 90:10); (found: C, 71.87; H, 3.97; N, 18.66. $C_{18}H_{12}N_4O$ requires C, 71.99; H, 4.03; N, 18.66%); R_f 0.23 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 226 (log ε 4.68), 253 inf (4.69), 271 (4.83), 372 (4.52), 402 inf (4.27); ν_{max}/cm^{-1} 3069br&w (aryl C-H & NH), 2963w, 2920w and 2855w (alkyl C-H), 2224w (C≡N), 1630m, 1601w, 1514m, 1472m, 1460s, 1433w, 1402w, 1336s, 1288w, 1261m, 1242s, 1211m, 1179m, 1148w, 1128w, 1070w, 1041m, 1028w, 997w, 986w, 939m, 849w, 822m, 804w, 783w, 766w; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.27 (2H, d, *J* 8.0, Ar *H*), 8.19 (1H, d, *J* 9.5, Ar *H*), 7.89-7.84 (2H, m, Ar *H*), 7.76-7.72 (3H, m, Ar *H*), 4.11 (3H, s, OC*H*$_3$); δ_C(125 MHz; TFA-*d*) one quaternary C (s) resonance missing 163.7 (s), 162.8 (s), 146.7 (s), 138.7 (d), 137.5 (s), 132.1 (d), 130.8 (s), 130.58 (d), 130.56 (d), 129.0 (s), 126.5 (d), 123.3 (s), 105.6 (s), 104.3 (d), 57.2 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 302 (MH^++1, 12%), 301 (MH^+, 100), 300 (M^+, 37), 242 (16), 153 (34).

*7.5.7.3 7-Methyl-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**197**).* Similar treatment of (*Z*)-2-[2-phenyl-4-(*p*-tolylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**180**) (15.6 mg, 0.05 mmol) gave the *title compound* **197** (14.8 mg, 99%) as pale yellow plates, mp (DSC) decomp. onset 322.8 °C, peak 323.8 °C; (from *n*-pentane/THF, 90:10); (found: C, 75.94; H, 4.26; N, 19.68. $C_{18}H_{12}N_4$ requires C, 76.04; H, 4.25; N, 19.71%); R_f 0.26 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 220 (log ε 4.68), 267 (4.58), 282 inf (4.30), 369 (4.60); ν_{max}/cm^{-1} 3063br&w and 3028br&w (aryl C-H & NH), 2967w and 2912w (alkyl C-H), 2758w, 2224w (C≡N), 1632w, 1618w, 1591w, 1524w, 1514m, 1479s, 1460s, 1404m, 1396m, 1333s, 1288m, 1233m, 1213m, 1202w, 1184w, 1157w, 1148w, 1101w, 1069w, 1034w, 1022w, 974w, 934s, 893w, 868w, 826s, 808m, 779w, 768w; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.23-8.20 (3H, m, Ar *H*), 8.14-8.09 (1H, m, Ar *H*), 8.01-7.96 (1H, m, Ar *H*), 7.80-7.6 (1H, m, Ar *H*), 7.66-7.63 (2H, m, Ar *H*), 2.64 (3H, t, *J* 9.0, C*H*$_3$); δ_C(125 MHz; TFA-*d*) 165.5 (s), 149.5 (s), 145.3 (s), 139.5 (d), 138.7 (d), 137.8 (s), 132.0 (d), 131.8 (s), 130.8 (d), 126.2 (s), 126.0 (d), 124.1 (s), 123.3 (d), 112.3 (s, *C*≡N), 107.8 (s), 21.8 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 286 (MH^++1, 14%), 285 (MH^+, 100), 284 (M^+, 30).

*7.5.7.4 7-Fluoro-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**198**).* Similar treatment of (*Z*)-2-[5-(4-fluorophenylimino)-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**181**) (15.8 mg, 0.05 mmol) gave the *title compound* **198** (14.3 mg, 99%) as pale yellow plates, mp (DSC) decomp. onset 338.5 °C, peak max. 339.1 °C; (from *n*-

pentane/THF, 90:10); (found: C, 70.82; H, 3.10; N, 19.38. $C_{17}H_9FN_4$ requires C, 70.83; H, 3.15; N, 19.43%); R_f 0.34 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 218 (log ε 4.76), 266 (4.62), 279 inf (4.38), 366 (4.69); ν_{max}/cm^{-1} 3067br&w and 3010br&w (aryl C-H & NH), 2903w, 2228w (C≡N), 1637m, 1597w, 1524m, 1477m, 1458s, 1406s, 1398m, 1333s, 1302w, 1281w, 1236s, 1207w, 1188w, 1157w, 1128w, 1097w, 1088w, 1070w, 1038w, 1028w, 1007w, 974w, 939m, 852m, 824w, 818w, 783m; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.28 (1H, dd, $^3J_{HH}$ 9.5, $^4J_{HF}$ 4.5, Ar *H*), 8.25 (2H, d, *J* 7.5, Ar *H*), 8.05 (1H, dd, $^3J_{HF}$ 7.8, $^4J_{HH}$ 2.3, Ar *H*), 7.89-7.84 (2H, m, Ar *H*), 7.71 (2H, dd, *J* 8.0, 8.0, Ar *H*); δ_C(125 MHz; TFA-*d*) 165.9 (s), 163.6 (s, $^1J_{CF}$ 232.5, *C*F), 148.1 (s), 139.4 (s), 139.3 (d), 132.2 (d), 130.8 (d), 130.6 (s), 128.9 (d, $^3J_{CF}$ 10.0, *C*HCHCF), 127.9 (s, $^3J_{CF}$ 10.0, *C*CHCF), 126.7 (d, $^2J_{CF}$ 27.5, *C*HCF), 122.6 (s), 112.1 (s, *C*≡N), 111.1 (d, $^2J_{CF}$ 25.0, *C*HCF), 106.5 (s, $^3J_{CF}$ 6.3, *C*CHCF); *m*/*z* (MALDI-TOF) 290 (MH^++1, 12%), 289 (MH^+, 100), 288 (M^+, 21), 153 (4).

*7.5.7.5 7-Chloro-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**199**).* Similar treatment of (*Z*)-2-[5-(4-chlorophenylimino)-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**182**) (16.7 mg, 0.05 mmol) gave the *title compound* **199** (15 mg, 98%) as pale yellow plates, mp (DSC) decomp. onset 356.4 °C, peak max. 357.8 °C; (from *n*-pentane/THF, 90:10); (found: C, 68.93; H, 2.98; N, 18.26. $C_{17}H_9ClN_4$ requires C, 67.00; H, 2.98; N, 18.39%); R_f 0.38 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 206 (log ε 4.55), 226 (4.82), 235 inf (4.78), 272 (4.79), 283 inf (4.68), 369 (4.79), 385 inf (4.62), 414 inf (4.21); ν_{max}/cm^{-1} 3194br&w, 3156br&w and 3069br&w (aryl C-H & NH), 2903w, 2708w, 2241w (C≡N), 1628m, 1603w, 1589w, 1529m, 1499m, 1476s, 1458s, 1443w, 1406s, 1391s, 1333s, 1317m, 1294m, 1277w, 1231m, 1202m, 1188m, 1157w, 1134w, 1125w, 1082w, 1026w, 1003w, 980w, 949m, 935w, 878w, 864w, 829s, 785m; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.44 (1H, d, *J* 1.5, Ar *H*), 8.29 (2H, d, *J* 7.5, Ar *H*), 8.22 (1H, d, *J* 9.0, Ar *H*), 8.07 (1H, dd, *J* 9.0, 2.0 Ar *H*), 7.89 (1H, dd, *J* 7.5, 7.5 Ar *H*), 7.74 (2H, dd, *J* 8.0, 8.0 Ar *H*); δ_C(125 MHz; TFA-*d*) 164.0 (s), 148.8 (s), 140.4 (s), 140.2 (s), 139.4 (d), 137.3 (d), 132.2 (d), 130.97 (s), 130.94 (d), 127.1 (d), 126.9 (s), 125.9 (d), 122.9 (s), 112.0 (s, *C*≡N), 106.4 (s); *m*/*z* (MALDI-TOF) 307 (MH^++2, 33%), 306 (MH^++1, 18), 305 (MH^+, 100), 304 (M^+, 11).

*7.5.7.6 6,7-Dichloro-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**200**) and 7,8-dichloro-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**201**).* Similar treatment of

(*Z*)-2-[5-(3,4-dichlorophenylimino)-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**183**) (18.3 mg, 0.05 mmol) gave *6,7-dichloro-2-phenyl-1*H-*imidazo[4,5*-b*]quinoline-9-carbonitrile* (**200**) (14.2 mg, 84%) as colorless needles mp (DSC) decomp. onset 323.6 ^{o}C, peak max. 324.4 ^{o}C; (from *n*-pentane/THF, 90:10); (found: C, 60.09; H, 2.29; N, 16.46. $C_{17}H_8Cl_2N_4$ requires C, 60.20; H, 2.38; N, 16.52%); R_f 0.63 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 205 (log ε 4.59), 231 inf (4.79), 244 (4.85), 277 (4.87), 290 inf (5.02), 367 inf (4.76), 376 (4.79), 389 inf (4.62), 422 inf (4.18); ν_{max}/cm^{-1} 3096br&w (aryl C-H & NH), 2978w, 2879w, 2228w (C≡N), 1628m, 1587w, 1528m, 1474m, 1460s, 1439w, 1408m, 1389s, 1335m, 1313w, 1288m, 1242m, 1223m, 1204m, 1183w, 1119m, 1101w, 1070w, 1047s, 1028w, 986m, 941m, 928w, 876s, 841w, 816w, 787m, 764w; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.51 (1H, s, Ar *H*), 8.38 (1H, s, Ar *H*), 8.25 (2H, d, *J* 7.5, Ar *H*), 7.88 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.72 (2H, dd, *J* 8.0, 8.0, Ar *H*); δ_C(125 MHz; TFA-*d*) 161.2 (s), 146.7 (s), 140.7 (s), 140.0 (s), 137.8 (d), 137.4 (s), 130.5 (d), 129.1 (d), 128.0 (s), 125.8 (d), 125.5 (d), 123.6 (s), 120.4 (s), 110.1 (s, *C*≡N), 104.0 (s); *m*/*z* (MALDI-TOF) 343 (MH^++4, 3%), 342 (MH^++3, 7), 341 (MH^++2, 54), 340 (MH^++1, 13), 339 (MH^+, 100), 338 (12), 219 (56). Further elution (DCM/Et_2O, 90:10) gave *7,8-dichloro-2-phenyl-1*H-*imidazo[4,5*-b*]quinoline-9-carbonitrile* (**201**) (2.1 mg, 12 %) as colorless plates mp (DSC) decomp. onset 358.3 ^{o}C, peak max. 362.1 ^{o}C; (from *n*-pentane/THF, 90:10); (found: C, 60.28; H, 2.42; N, 16.34. $C_{17}H_8Cl_2N_4$ requires C, 60.20; H, 2.38; N, 16.52%); R_f 0.50 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 209 (log ε 4.87), 225 inf (4.73), 277 (4.39), 365 (3.94), 378 (3.94); ν_{max}/cm^{-1} 3173br&w (aryl C-H & NH), 2234w (C≡N), 1624w, 1609w, 1574w, 1526m, 1479s, 1456s, 1435w, 1393s, 1375s, 1317m, 1300m, 1285w, 1194s, 1153m, 1103w, 1049w, 1038w, 1024w, 1001w, 986w, 947w, 924m, 881w, 824s, 814s, 781m, 752w; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.41 (2H, d, *J* 8.0, Ar *H*), 8.19 (1H, d, *J* 9.0, Ar *H*), 8.12 (1H, d, *J* 9.5, Ar .*H*), 7.95 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.78 (2H, dd, *J* 7.8, 7.8, Ar *H*); δ_C(125 MHz; TFA-*d*) one quaternary C (s) resonance missing 163.2 (s), 147.2 (s), 145.1 (s), 140.1 (d), 139.8 (s), 136.8 (d), 133.3 (s), 132.6 (d), 131.5 (d), 130.8 (s), 128.0 (d), 125.0 (s), 122.1 (s), 104.6 (s); *m*/*z* (MALDI-TOF) 343 (MH^++4, 3%), 342 (MH^++3, 5), 341 (MH^++2, 64), 340 (MH^++1, 24), 339 (MH^+, 100), 338 (12), 219 (13).

*7.5.7.7 7-Bromo-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**202**).* Similar treatment of (*Z*)-2-[5-(4-bromophenylimino)-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**184**) (18.8 mg, 0.05 mmol) gave the *title compound* **202** (17.1 mg, 98%) as

colorless plates, mp (DSC) decomp. onset 337.6 °C, peak max. 338.6 °C; (from *n*-pentane/THF, 90:10); (found: C, 58.35; H, 2.67; N, 15.96. $C_{17}H_9BrN_4$ requires C, 58.47; H, 2.60; N, 16.05%); R_f 0.43 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 229 inf (log ε 4.73), 235 (4.74), 273 (4.75), 283 inf (4.64), 369 (4.77), 412 inf (3.94); ν_{max}/cm^{-1} 3069br&w (Ar CH & NH), 2878w, 2735w, 2222w (C≡N), 1628m, 1599w, 1589w, 1529m, 1495m, 1476s, 1464s, 1406s, 1393s, 1333s, 1296m, 1234m, 1202m, 1188m, 1165w, 1132w, 1126w, 1105w, 1070w, 1040s, 972w, 935m, 918w, 874s, 858m, 818s, 781m; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.61 (1H, s, Ar *H*), 8.27 (2H, d, *J* 8.0, Ar *H*), 8.18 (1H, d, *J* 9.5, Ar *H*), 8.11 (1H, d, *J* 9.0, Ar *H*), 7.87 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.72 (2H, dd, *J* 7.8, 7.8, Ar *H*); δ_C(125 MHz; TFA-*d*) one quaternary C (s) resonance missing 162.7 (s), 148.9 (s), 140.4 (s), 139.9 (d), 139.3 (d), 132.2 (d), 130.94 (s), 130.89 (d), 129.3 (d), 127.7 (s), 127.1 (s), 126.7 (d), 122.9 (s), 112.0 (s, *C*≡N), 106.3 (s); *m*/*z* (MALDI-TOF) 351 (MH^++2, 49%), 350 (MH^++1, 14), 349 (MH^+, 100), 312 (25), 270 (30), 246 (8), 219 (37), 105 (6).

*7.5.7.8 7-Iodo-2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**203**).* Similar treatment of (*Z*)-2-[5-(4-iodophenylimino)-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene]malononitrile (**185**) (15.8 mg, 0.05 mmol) gave the *title compound* **203** (14.3 mg, 99%) as pale colorless needles, mp (DSC) decomp. onset 342.2 °C, peak max. max. 342.8 °C; (from *n*-pentane/THF, 90:10); (found: C, 51.50; H, 2.23; N, 14.05. $C_{17}H_9IN_4$ requires C, 51.54; H, 2.29; N, 14.14%); R_f 0.30 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 207 (log ε 4.62), 227 (4.84), 249 inf (4.67), 272 (4.82), 285 inf (4.64), 374 (4.81), 386 (4.64); ν_{max}/cm^{-1} 3098br&w (aryl C-H & NH), 2911w, 2737w, 2224w (C≡N), 1697m, 1630m, 1597w, 1528m, 1490m, 1477s, 1460s, 1404s, 1391s, 1333s, 1315m, 1294m, 1233m, 1204m, 1194w, 1136w, 1103w, 1067w, 1028w, 1001w, 966w, 937s, 872m, 824s, 785s, 760m; δ_H(500 MHz; TFA-*d*) N*H* deuterium exchanged, 8.92 (1H, s, Ar *H*), 8.44 (1H, d, *J* 9.0, Ar *H*), 8.34 (2H, d, *J* 8.0, Ar *H*), 8.03 (1H, d, *J* 9.0, Ar *H*), 7.95 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.79 (2H, dd, *J* 7.8, 7.8, Ar *H*); δ_C(125 MHz; TFA-*d*) 164.6 (s), 149.1 (s), 145.5 (d), 140.4 (s), 139.3 (d), 136.0 (d), 132.2 (d), 131.0 (s), 130.9 (d), 127.2 (s), 125.9 (d), 123.1 (s), 112.1 (s, *C*≡N), 106.2 (s), 98.1 (s); *m*/*z* (MALDI-TOF) 398 (MH^++1, 8%), 397 (MH^+, 100), 270 (63), 246 (3), 219 (43), 105 (4).

*7.5.8 N-Methylation of 2-phenyl-1H-imidazo[4,5-b]quinoline-9-carbonitrile (**194**)*

To a stirred solution of 2-phenyl-1*H*-imidazo[4,5-*b*]quinoline-9-carbonitrile (**194**) (13.5 mg, 0.05 mmol) in dry THF (1 mL) at *ca.* 20 °C was added NaH (2.4 mg, 0.1 mmol) and

dimethyl sulfate (9.5 μL, 0.1 mmol). The mixture was heated at *ca*. 66 ^{o}C for 26 h and then allowed to cool to *ca.* 20 ^{o}C. Removal of the volatiles followed by chromatography (DCM/Et_2O, 90:10) of the residue gave *3-methyl-2-phenyl-3*H-*imidazo[4,5*-b*]quinoline-9-carbonitrile* (**206**) (13.5 mg, 95%) as colorless needles, mp (DSC) onset 204.0 ^{o}C, peak max. 204.4 ^{o}C (from *n*-pentane/DCE, 70:30); (found: C, 75.90; H, 4.36; N, 19.69. $C_{18}H_{12}N_4$ requires C, 76.04; H, 4.25; N, 19.71%); R_f 0.68 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 217 (log ε 4.90), 263 (4.80), 357 (4.76); ν_{max}/cm^{-1} 3063w (aryl C-H), 2995w, 2953w, 2922w and 2851w (alkyl C-H), 2228w (C≡N), 1612w, 1584w, 1516w, 1484m, 1466s, 1447m, 1435m, 1396m, 1335s, 1286m, 1258w, 1232w, 1204w, 1182w, 1169m, 1157w, 1107w, 1076w, 1053w, 1022w, 945w, 930w, 860w, 849w, 795w, 779m, 764s; δ_H(500 MHz; TFA-*d*) 8.44 (1H, d, *J* 8.5, Ar *H*), 8.39 (1H, d, *J* 8.0, Ar *H*), 8.06 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.99-7.96 (3H, m, Ar *H*), 7.90 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.77 (2H, dd, *J* 8.0, 8.0, Ar *H*), 4.35 (3H, s, C*H*$_3$); δ_C(125 MHz; TFA-*d*) one quaternary C (s) resonance missing 158.6 (s), 146.6 (s), 144.4 (s), 136.1 (d), 132.9 (d), 131.1 (d), 130.4 (d), 129.7 (d), 129.5 (d), 125.8 (s), 124.6 (d), 123.6 (s), 120.1 (s), 102.5 (s), 31.4 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 286 (MH$^+$+1, 11%), 285 (MH$^+$, 100), 284 (M$^+$, 93). Further elution (DCM/Et_2O, 90:10) gave *4-methyl-2-phenyl-4*H-*imidazo[4,5*-b*]quinoline-9-carbonitrile* (**207**) (1.1 mg, 1%) as yellow plates, mp (DSC) onset 254.9 ^{o}C, peak max. 255.6 ^{o}C (from *n*-pentane/DCE, 70:30); (found: C, 75.88; H, 4.29; N, 19.62. $C_{18}H_{12}N_4$ requires C, 76.04; H, 4.25; N, 19.71%); R_f 0.54 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 228 (log ε 4.71), 248 inf (4.42), 264 inf (4.31), 381 (4.67), 389 inf (4.59); ν_{max}/cm^{-1} 3069w (aryl C-H), 2951w and 2922w (alkyl C-H), 2222w (C≡N), 1624w, 1593m, 1578w, 1483m, 1454s, 1431s, 1412m, 1393w, 1369m, 1335m, 1308w, 1285m, 1256s, 1217m, 1171m, 1136w, 1105w, 1074m, 1066m, 1022w, 1011w, 935m, 856w, 797w, 760m; δ_H(500 MHz; TFA-*d*) 8.54 (1H, d, *J* 8.5, Ar *H*), 8.46 (2H, d, *J* 7.5, Ar *H*), 8.37 (1H, d, *J* 9.0, Ar *H*), 8.25 (1H, ddd, *J* 8.0, 8.0, 1.0, Ar *H*), 8.06 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.79 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.66 (2H, dd, *J* 7.8, 7.8, Ar *H*), 4.85 (3H, s, C*H*$_3$); δ_C(125 MHz; TFA-*d*) 169.3 (s), 156.0 (s), 138.4 (d), 138.0 (s), 137.2 (d), 134.7 (s), 131.8 (d), 131.7 (d), 131.6 (d), 128.8 (d), 126.7 (s), 125.2 (s), 119.2 (d), 112.8 (s, *C*≡N), 107.4 (s), 37.7 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 286 (MH$^+$+1, 13%), 285 (MH$^+$, 100), 284 (M$^+$, 9).

*7.5.9 Thermolysis of (Z)-2-[1-methyl-2-phenyl-4-(phenylimino)-1H-imidazol-5(4H)-ylidene]malononitrile (**187**)*

An intimate mixture of (*Z*)-2-[1-methyl-2-phenyl-4-(phenylimino)-1*H*-imidazol-5(4*H*)-ylidene]malononitrile (**187**) (14.2 mg, 0.05 mmol) and diphenyl ether (1 mL) was heated at *ca*. 250 ^{o}C for 4 h. Chromatography (*n*-hexane/DCM, 50:50) of the reaction mixture gave recovered diphenyl ether (1 mL) and further elution (DCM/Et_2O, 90:10) gave *1-methyl-2-phenyl-1*H-*imidazo[4,5*-b*]quinoline-9-carbonitrile* (**208**) (12.9 mg, 91%) as colorless prisms, mp (DSC) onset 226.4 ^{o}C, peak max. 227.3 ^{o}C; (from *n*-pentane/THF, 90:10); (found: C, 75.92; H, 4.35; N, 19.68. $C_{18}H_{12}N_4$ requires C, 76.04; H, 4.25; N, 19.71%); R_f 0.34 (DCM/Et_2O, 90:10); λ_{max}(EtOH)/nm 218 (log ε 4.92), 263 (4.83), 358 (4.77); ν_{max}/cm^{-1} 3086w (aryl C-H), 2951w (alkyl C-H), 2220w (C≡N), 1605w, 1524m, 1479m, 1462m, 1443m, 1400m, 1366s, 1337s, 1292m, 1246m, 1238m, 1211w, 1184w, 1163w, 1136w, 1078m, 1055w, 1047w, 1022w, 1015w, 984w, 962w, 943w, 932w, 881w, 870w, 860w, 798w, 793w, 785s, 773s; δ_H(500 MHz; TFA-*d*) 8.66 (1H, d, *J* 8.5, Ar *H*), 8.39 (1H, d, *J* 8.5, Ar *H*), 8.28 (1H, dd, *J* 7.9, 7.9, Ar *H*), 8.15 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.99 (2H, d, *J* 7.0, Ar *H*), 7.93 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.82 (2H, dd, *J* 8.0, 8.0, Ar *H*), 4.59 (3H, s, C*H*$_3$); δ_C(125 MHz; TFA-*d*) 167.3 (s), 148.7 (s), 141.2 (s), 137.7 (d), 137.5 (d), 133.1 (d), 132.2 (d), 132.0 (d), 131.8 (s), 127.7 (d), 126.9 (s), 125.1 (d), 123.9 (s), 112.3 (s, *C*≡N), 109.5 (s), 36.2 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 286 (MH^++1, 18%), 285 (MH^+, 100), 284 (M^+, 24), 283 (13), 118 (7), 105 (6).

*7.5.10 Thermolysis of (Z)-2-(1-methyl-2-phenyl-5-(phenylimino)-1H-imidazol-4(5H)-ylidene)malononitrile (**188**)*

An intimate mixture of (*Z*)-2-(1-methyl-2-phenyl-5-(phenylimino)-1*H*-imidazol-4(5*H*)-ylidene)malononitrile (**188**) (14.2 mg, 0.05 mmol) and diphenyl ether (1 mL) was heated at *ca*. 280 ^{o}C for 1 h. Chromatography (*n*-hexane/DCM, 50:50) of the reaction mixture gave recovered diphenyl ether (1 mL) and further elution (DCM/Et_2O, 90:10) gave *1-methyl-2-phenyl-1*H-*imidazo[4,5*-b*]quinoline-9-carbo-nitrile* (**206**) (14.4 mg, 93%) as colorless prisms, mp (DSC) onset 204.0 ^{o}C, peak max. 204.4 ^{o}C (from *n*-pentane/DCE, 70:30) identical to that described above.

7.6 Compounds related to chapter 6

7.6.1 Preparation of N-arylbenzamidines

*7.6.1.1 2-Amino-N'-(2-bromophenyl)benzamidine (**233**) (typical procedure).* To stirred anthranilonitrile (343 mg, 2.91 mmol) at *ca.* 20 °C was added powdered anhydrous $AlCl_3$ (387 mg, 2.91 mmol). The reaction mixture was then heated (*ca.* 100 °C) until a homogeneous melt formed. To this was added 2-bromoaniline (500 mg, 2.91 mmol) and the mixture was heated for 6 h and then allowed to cool to *ca.* 20 °C. The resultant solid mass was then crushed and slurried in 12.5% NaOH (40 mL). The resulting mixture was extracted (DCM, 3 × 50 mL), washed (H_2O, 1 × 50 mL) and dried (Na_2SO_4). The organic phase adsorbed onto silica and chromatographed (*t*-BuOMe) to give the title compound **233** (306 mg, 36%) as colorless needles, mp (hotstage) 126-127 °C (lit.,[94] 127-129 °C) (from *c*-hexane/EtOH, 90:10); R_f 0.74 (*t*-BuOMe); λ_{max}(DCM)/nm 250 (log ε 4.45), 304 (3.78), 352 (3.76); ν_{max}/cm^{-1} 3478w, 3451w and 3370w (NH), 3169w and 3046w (aryl C-H), 1630s, 1614s, 1580m, 1562m, 1545m, 1493w, 1464m, 1433w, 1387m, 1319w, 1310w, 1271w, 1258w, 1233w, 1161w, 1121w, 1040w, 1024m, 868w, 835m, 785w, 748m; δ_H(500 MHz; $CDCl_3$) 7.64 (1H, d, *J* 8.0, Ar *H*), 7.43 (1H, d, *J* 8.0, Ar *H*), 7.30 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.20 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.04 (1H, d, *J* 7.5, Ar *H*), 6.95 (1H, dd, *J* 7.8, 7.8, Ar *H*), 6.74 (1H, d, *J* 8.0, Ar *H*), 6.69 (1H, dd, *J* 7.5, 7.5, Ar *H*), 5.96 (2H, br s, N*H*$_2$), 4.77 (2H, br s, N*H*$_2$); δ_C(125 MHz; $CDCl_3$) 156.1 (s), 147.9 (s), 147.4 (s), 133.3 (d), 131.4 (d), 128.5 (d), 127.5 (d), 124.5 (d), 123.2 (d), 117.2 (d), 116.6 (s), 116.5 (d), 116.4 (s); *m/z* (EI) 291 (M^++2, 38%), 289 (M^+, 39), 274 (13), 272 (14), 210 (100), 193 (23), 173 (69), 171 (71), 119 (92), 105 (34), 92 (63), 76 (16), 65 (57).

*7.6.1.2 2-Amino-N'-(2-bromophenyl)-6-methylbenzamidine (**245**).* Similar treatment of 6-methylanthranilonitrile (384 mg, 2.91 mmol) with anhydrous $AlCl_3$ (387 mg, 2.91 mmol) and 2-bromoaniline (500 mg, 2.91 mmol) gave the *title compound* **245** (1.33 g, 43%) as colorless plates, mp (hotstage) 153-154 °C (from *c*-hexane/DCM, 90:10); R_f 0.76 (*t*-BuOMe); (found: C, 55.40; H, 4.57; N, 13.62. $C_{14}H_{14}BrN_3$ requires C, 55.28; H, 4.64; N, 13.81%); λ_{max}(DCM)/nm 287 (log ε 3.71); ν_{max}/cm^{-1} 3429w, 3350w and 3269w (NH), 3123w (aryl C-H), 1626s, 1599s, 1578s, 1466m, 1433w, 1379w, 1302w, 1285w, 1169w, 1101w, 1070w, 1041w, 1026m, 968w, 935w, 862w, 851w, 783m, 754s; δ_H(500 MHz; CD_3CN) 7.63 (1H, d, *J* 8.0, Ar *H*), 7.34 (1H, dd, *J* 7.0, 7.0, Ar *H*), 7.02 (2H, dd, *J* 9.0, 9.0, Ar *H*), 6.97 (1H, dd, *J* 7.0, 7.0, Ar *H*), 6.57 (2H, dd, *J* 7.8, 7.8, Ar *H*), 5.35 (2H, br s,

NH_2), 4.64 (2H, br s, NH_2), 2.40 (3H, s, CH_3); δ_C(125 MHz; DMSO-d_6) 155.7 (s), 148.6 (s), 145.9 (s), 135.6 (s), 132.9 (d), 128.8 (d), 128.6 (d), 123.7 (d), 123.0 (s), 122.5 (d), 118.0 (d), 116.5 (s), 112.8 (d), 19.9 (q, *C*H_3); *m*/*z* (MALDI-TOF) 306 (MH^++2, 100%), 304 (MH^+, 88), 289 (34), 287 (35), 224 (27), 209 (13), 173 (8), 133 (26).

*7.6.1.3 2-Amino-N'-(2-bromophenyl)-4-methoxybenzamidine (**246**)*. Similar treatment of 4-methoxyanthranilonitrile (431 mg, 2.91 mmol) with anhydrous $AlCl_3$ (387 mg, 2.91 mmol) and 2-bromoaniline (500 mg, 2.91 mmol) gave the *title compound* **246** (1.62 g, 51%) as colorless plates, mp (hotstage) 122-123 ^oC (from *c*-hexane/DCM, 90:10); R_f 0.58 (*t*-BuOMe); (found: C, 52.43; H, 4.35; N, 13.02. $C_{14}H_{14}BrN_3O$ requires C, 52.52; H, 4.41; N, 13.12%); λ_{max}(DCM)/nm 266 (log ε 4.15), 286 inf (3.89), 321 (3.94); ν_{max}/cm^{-1} 3466w and 3350w (NH), 2999w (aryl C-H), 2965w and 2895w (alkyl C-H), 1618s, 1614s, 1593m, 1572m, 1553m, 1508m, 1466w, 1441w, 1427w, 1377s, 1306w, 1256m, 1231m, 1215s, 1164m, 1157w, 1092w, 1067w, 1034w, 1024m, 966w, 833s, 795m, 758s; δ_H(500 MHz; $CDCl_3$) 7.63 (1H, d, *J* 8.0, Ar *H*), 7.35 (1H, d, *J* 8.5, Ar *H*), 7.28 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.03 (1H, d, *J* 7.5, Ar *H*), 6.94 (1H, dd, *J* 8.0, 8.0, Ar *H*), 6.27 (1H, dd, *J* 6.0, 2.5, Ar *H*), 6.22 (1H, d, *J* 2.5, Ar *H*), 6.15 (2H, br s, NH_2), 4.70 (2H, br s, NH_2), 3.79 (3H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) 162.2 (s), 156.0 (s), 149.9 (s), 147.4 (s), 133.3 (d), 129.0 (d), 128.4 (d), 124.4 (d), 123.4 (d), 116.9 (s), 109.4 (s), 103.7 (d), 100.8 (d), 55.1 (q, O*C*H_3); *m*/*z* (MALDI-TOF) 322 (M^++2, 100%), 320 (MH^+, 100), 305 (21), 303 (22), 242 (1), 149 (4).

*7.6.1.4 2-Amino-N'-(2-bromophenyl)-4,5-dimethoxybenzamidine (**247**)*. Similar treatment of 4,5-dimethoxyanthranilonitrile (**54**) (518 mg, 2.91 mmol) with anhydrous $AlCl_3$ (387 mg, 2.91 mmol) and 2-bromoaniline (500 mg, 2.91 mmol) gave the *title compound* **247** (0.71 g, 20%) as colorless needles, mp (hotstage) 151-152 ^oC (from *c*-hexane/DCM, 80:20); R_f 0.44 (*t*-BuOMe); (found: C, 51.35; H, 4.54; N, 12.17. $C_{15}H_{16}BrN_3O_2$ requires C, 51.44; H, 4.61; N, 12.00%); λ_{max}(DCM)/nm 275 inf (log ε 4.05), 337 (3.94); ν_{max}/cm^{-1} 3468w, 3370w and 3291w (NH), 3138w and 3065w (aryl C-H), 2934w and 2833w (alkyl C-H), 1626s, 1558w, 1522m, 1468w, 1440w, 1387m, 1350w, 1277w, 1246m, 1229s, 1213s, 1192w, 1179w, 1159w, 1031w, 1022w, 997w, 854m, 829w, 768m, 743s; δ_H(500 MHz; $CDCl_3$) 7.63 (1H, d, *J* 8.0, Ar *H*), 7.29 (1H, dd, *J* 7.3, 7.3, Ar *H*), 7.04 (1H, d, *J* 8.0, Ar *H*), 6.96 (1H, br s, Ar *H*), 6.94 (1H, dd, *J* 8.0, 8.0, Ar *H*), 6.27 (1H, s, Ar *H*), 5.82 (2H, br s, NH_2), 4.68 (2H, br s, NH_2), 3.87 (3H, s, OCH_3), 3.83 (3H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) 155.9 (s), 152.5 (s), 147.4 (s), 143.9 (s), 140.8 (s), 133.3 (d), 128.4 (d), 124.4 (d),

123.3 (d), 116.8 (s), 111.8 (d), 107.6 (s), 100.9 (d), 57.1 (q, O*C*H_3), 55.8 (q, O*C*H3); *m*/*z* (MALDI-TOF) 352 (MH^++2, 97%), 350 (MH^+, 100), 349 (M^+, 12), 339 (6), 337 (6), 335 (4), 333 (3), 272 (3).

*7.6.1.5 2-Amino-N'-(2-bromophenyl)-5-chlorobenzamidine (**248**).* Similar treatment of 5-chloroanthranilonitrile (442 mg, 2.91 mmol) with anhydrous $AlCl_3$ (387 mg, 2.91 mmol) and 2-bromoaniline (500 mg, 2.91 mmol) gave the *title compound* **248** (1.70 g, 52%) as colorless needles, mp (hotstage) 147-147.5 °C (from *c*-hexane/DCM, 90:10); R_f 0.65 (*t*-BuOMe); (found: C, 48.03; H, 3.36; N, 12.87. $C_{13}H_{11}BrClN_3$ requires C, 48.10; H, 3.42; N, 12.95%); λ_{max}(DCM)/nm 243 inf (log ε 4.56), 286 inf (3.94), 343 (3.92); ν_{max}/cm^{-1} 3428w, 3397w, 3312w and 3198w (NH), 3065w (aryl C-H), 1630m, 1614m, 1585m, 1572w, 1541w, 1487w, 1464m, 1435w, 1375m, 1301w, 1254w, 1236w, 1161w, 1115w, 1083w, 1038w, 1024w, 880w, 860w, 839w, 819s, 789w, 747s; δ_H(500 MHz; $CDCl_3$) 7.64 (1H, d, *J* 8.0, Ar *H*), 7.41 (1H, br s, Ar *H*), 7.30 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.15 (1H, dd, *J* 9.0, 2.5, Ar *H*), 7.02 (1H, d, *J* 8.0, Ar *H*), 6.97 (1H, ddd, *J* 7.8, 7.8, 1.5, Ar *H*), 6.67 (1H, d, *J* 9.0, Ar *H*), 5.96 (2H, br s, NH_2), 4.78 (2H, br s, NH_2); δ_C(125 MHz; $CDCl_3$) 155.2 (s), 146.9 (s), 146.5 (s), 133.4 (d), 131.3 (d), 128.5 (d), 127.2 (d), 124.8 (d), 123.0 (d), 120.9 (s), 118.4 (d), 117.3 (s), 116.5 (s); *m*/*z* (MALDI-TOF) 328 (MH^++4, 24%), 326 (MH^++2, 100), 324 (MH^+, 76), 312 (5), 310 (4).

*7.6.1.6 2-Amino-N'-(2-bromophenyl)-4-chlorobenzamidine (**249**).* Similar treatment of 4-chloroanthranilonitrile (442 mg, 2.91 mmol) with anhydrous $AlCl_3$ (387 mg, 2.91 mmol) and 2-bromoaniline (500 mg, 2.91 mmol) gave the *title compound* **249** (1.84 g, 57%) as colorless needles, mp (hotstage) 130-131 °C (from *c*-hexane/DCM, 90:10); R_f 0.62 (*t*-BuOMe); (found: C, 47.97; H, 3.40; N, 12.83. $C_{13}H_{11}BrClN_3$ requires C, 48.10; H, 3.42; N, 12.95%); λ_{max}(DCM)/nm 261 inf (log ε 4.09), 286 inf (3.82), 330 (3.81); ν_{max}/cm^{-1} 3476w, 3375w and 3283w (NH), 3188w and 3067w (aryl C-H), 1624s, 1578m, 1549m, 1491m, 1470m, 1435w, 1420w, 1375m, 1321w, 1258w, 1234w, 1113w, 1053w, 1024m, 914s, 854m, 835m, 806w, 787w, 748s; δ_H(500 MHz; $CDCl_3$) 7.64 (1H, dd, *J* 8.0, 1.0, Ar *H*), 7.35 (1H, d, *J* 8.5, Ar *H*), 7.30 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.22 (1H, d, *J* 7.5, Ar *H*), 6.96 (1H, ddd, *J* 8.0, 8.0, 1.0, Ar *H*), 6.72 (1H, d, *J* 2.0, Ar *H*), 6.64 (1H, d, *J* 9.0, 2.0, Ar *H*), 6.12 (2H, br s, NH_2), 4.75 (2H, br s, NH_2); δ_C(125 MHz; $CDCl_3$) 155.5 (s), 149.0 (s), 146.9 (s), 137.1 (s), 133.4 (d), 128.8 (d), 128.5 (d), 124.7 (d), 123.1 (d), 116.6 (s), 116.5

(d), 116.4 (d), 114.6 (s); *m*/*z* (MALDI-TOF) 328 (MH^++4, 26%), 326 (MH^++2, 100), 324 (MH^+, 76), 312 (12), 310 (9), 309 (12), 307 (7).

*7.6.1.7 2-Amino-5-bromo-N'-(2-bromophenyl)benzamidine (**250**).* Similar treatment of 5-bromoanthranilonitrile (571 mg, 2.91 mmol) with anhydrous $AlCl_3$ (387 mg, 2.91 mmol) and 2-bromoaniline (500 mg, 2.91 mmol) gave the *title compound* **250** (2.15 g, 58%) as colorless plates, mp (hotstage) 136.5-138 °C (from *c*-hexane/DCM, 90:10); R_f 0.60 (*t*-BuOMe); (found: C, 42.19; H, 2.92; N, 11.26. $C_{13}H_{11}Br_2N_3$ requires C, 42.31; H, 3.00; N, 11.39%); λ_{max}(DCM)/nm 244 inf (log ε 4.38), 265 inf (4.21), 343 (3.70); ν_{max}/cm^{-1} 3428w, 3393w, 3318w and 3196w (NH), 3067w (aryl C-H), 1632s, 1611s, 1582m, 1568m, 1537m, 1485m, 1462s, 1435w, 1375s, 1304w, 1254m, 1234w, 1163m, 1119w, 1115w, 1051w, 1022w, 872w, 839m, 833w, 818s, 787w, 745s; δ_H(500 MHz; $CDCl_3$) 7.64 (1H, d, *J* 8.0, Ar *H*), 7.55 (1H, br s, Ar *H*), 7.31 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.27 (1H, dd, *J* 7.5, 2.0, Ar *H*), 7.02 (1H, d, *J* 8.0, Ar *H*), 6.97 (1H, dd, *J* 7.5, 7.5, Ar *H*), 6.63 (1H, d, *J* 9.0, Ar *H*), 5.99 (2H, br s, NH_2), 4.76 (2H, br s, NH_2); δ_C(125 MHz; $CDCl_3$) one C (s) resonance missing, 155.1 (s), 146.9 (s), 134.0 (d), 133.4 (d), 130.1 (d), 128.5 (d), 124.8 (d), 123.0 (d), 118.7 (d), 117.9 (s), 116.5 (s), 107.6 (s); *m*/*z* (MALDI-TOF) 372 (MH^++4, 76%), 370 (MH^++2, 100), 368 (MH^+, 74), 358 (18), 356 (36), 351 (25), 306 (7), 304 (8), 290 (7), 174 (5), 172 (5).

*7.6.2 Preparation of 4-(arylamino)quinazoline-2-carbonitriles **218**, **216** and **217***

*7.6.2.1 6,7-Dimethoxy-4-(phenylamino)quinazoline-2-carbonitrile (**218**) (typical procedure).* To a stirred solution of 2-amino-*N'*-(3,4-dimethoxyphenyl)benzamidine (**71**) (271 mg, 1.00 mmol) in MeCN (10 mL) at *ca*. 20 °C was added glacial AcOH (57.0 μL, 1.00 mmol). To that mixture, at *ca*. 20 °C was added dropwise a solution of TCNE (128 mg, 1.00 mmol) in MeCN (10 mL) and left to stir for 7 h. The reaction mixture was then adsorbed onto silica and chromatographed (DCM/*t*-BuOMe, 95:05) to give the *title compound* **218** (104.8 mg, 34%) as yellow needles, mp (hotstage) 286-287 °C (*c*-hexane/THF, 80:20), mp (DSC) onset 286.6 °C, peak max. 287.1 °C; R_f 0.55 (DCM/*t*-BuOMe, 95:05); (found: C, 66.60; H, 4.47; N, 18.13. $C_{17}H_{14}N_4O_2$ requires C, 66.66; H, 4.61; N, 18.29%); λ_{max}(DCM)/nm 258 inf (log ε 4.16), 268 inf (4.14), 281 inf (4.09), 332 (4.29); ν_{max}/cm^{-1} 3401w (NH), 3015w (aryl C-H), 2928w and 2855w (alkyl C-H), 2239w (C≡N), 1611m, 1578m, 1514s, 1460s, 1425m, 1396w, 1360w, 1294w, 1273m, 1242m, 1205m, 1161m, 1074w, 1036w, 1001m, 889w, 864w, 841m, 777w, 737s; δ_H(500 MHz;

DMSO-d_6) 9.93 (1H, br s, N*H*), 7.91 (1H, s, Ar *H*), 7.69 (2H, d, *J* 7.5, Ar *H*), 7.45 (2H, dd, *J* 7.8, 7.8, Ar *H*), 7.30 (1H, s, Ar *H*), 7.21 (1H, dd, *J* 7.5, 7.5, Ar *H*), 3.98 (3H, s, OCH_3), 3.95 (3H, s, OCH_3); δ_C(125 MHz; DMSO-d_6) 156.9 (s), 155.1 (s), 151.0 (s), 146.1 (s), 138.4 (s), 138.1 (s), 128.8 (d), 124.8 (d), 123.3 (d), 117.3 (s), 109.7 (s), 107.6 (d), 102.2 (d), 56.6 (q, O*C*H$_3$), 56.3 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 308 (MH^++1, 12%), 307 (MH^+, 100), 100 (5). Further elution (DCM/*t*-BuOMe, 60:40) gave 4-imino-6,7-dimethoxy-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**87**) (2.1 mg, 1%) as colorless needles, mp (hotstage) 230 °C (sub.) [lit.,[271] 230 °C (sub.)] (from acetone); R_f 0.59 (*t*-BuOMe/EtOH, 60:40); δ_H(300 MHz; $CDCl_3$) 7.72-7.66 (4H, m, Ar *H*), 7.44–7.41 (2H, m, Ar *H*), 7.08 (1H, s, Ar *H*), 6.34 (1H, br s, N*H*), 4.01 (3H, s, OCH_3), 4.00 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 153.6 (s), 152.7 (s), 151.1 (s), 138.7 (s), 134.9 (s), 131.3 (d), 131.1 (d), 129.5 (s), 129.1 (d), 116.2 (s), 111.5 (s, C≡N), 109.0 (d), 105.6 (d), 56.5 (q, O*C*H$_3$), 56.3 (q, O*C*H$_3$), identical to an authentic sample.

*7.6.2.2 4-[(3,4-Dichlorophenyl)amino]quinazoline-2-carbonitrile (**216**).* Similar treatment of 2-amino-*N'*-(3,4-dichlorophenyl)benzamidine (**70**) with TCNE gave the *title compound* **216** (138 mg, 44%) as colorless needles, mp (hotstage) 258-259 °C (*c*-hexane/THF, 80:20), mp (DSC) onset 258.6 °C, peak max. 259.2 °C; R_f 0.62 (DCM/*t*-BuOMe, 95:05); (found: C, 57.02; H, 2.53; N, 17.66. $C_{15}H_8Cl_2N_4$ requires C, 57.17; H, 2.56; N, 17.78%); λ_{max}(DCM)/nm 248 inf (log ε 4.23), 268 (4.07), 282 inf (3.99), 336 (4.23), 396 (3.11), 424 (3.02); ν_{max}/cm^{-1} 3366w (NH), 3129w and 3032w (aryl C-H), 2251w (C≡N), 1618w, 1602w, 1570m, 1555w, 1522s, 1499w, 1474m, 1425m, 1366m, 1314w, 1219w, 1132w, 1092w, 1030w, 997w, 955w, 914w, 862w, 806m, 793m, 760s; δ_H(500 MHz; DMSO-d_6) 10.39 (1H, br s, N*H*), 8.59 (1H, d, *J* 8.0, Ar *H*), 8.14 (1H, d, *J* 2.5, Ar *H*), 8.01 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.91 (1H, d, *J* 8.0, Ar *H*), 7.85-7.82 (2H, m, Ar *H*), 7.70 (1H, d, *J* 8.5, Ar *H*); δ_C(125 MHz; DMSO-d_6) 158.2 (s), 149.0 (s), 139.6 (s), 138.5 (s), 134.8 (d), 130.9 (s), 130.6 (d), 129.4 (d), 128.3 (d), 126.4 (s), 124.2 (d), 123.5 (d), 122.9 (d), 116.8 (s), 115.6 (s); *m*/*z* (MALDI-TOF) 317 (MH^++2, 9%), 315 (MH^+, 22), 266 (14), 215 (39), 153 (100), 130 (5). Further elution (DCM/*t*-BuOMe, 90:20) gave 3-(3,4-dichlorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**86**) (5.4 mg, 2%) as beige plates, mp (hotstage) 175-176 °C (lit.,[271] 175-176 °C) (from *n*-pentane/DCM, 90:10); R_f 0.77 (DCM/*t*-BuOMe, 90:10); δ_H(300 MHz; $CDCl_3$) 8.12 (1H, d, *J* 7.2, Ar *H*), 7.73 (1H, d, *J* 8.7, Ar *H*), 7.70-7.65 (2H, m, Ar *H*), 7.60-7.54 (2H, m, Ar *H*), 7.30 (1H, dd, *J* 8.4, 2.4, Ar *H*); δ_C(125 MHz; $CDCl_3$) 154.1 (s), 142.8 (s), 135.9 (s), 133.9 (s), 134.8 (s) 133.7 (d),

132.5 (s), 131.1 (d), 130.5 (s), 130.2 (d), 128.8 (d), 128. (d), 125.1 (d), 121.7 (s), 111.1 (s, C≡N), identical to an authentic sample.

*7.6.2.3 4-[(2-Bromophenyl)amino]quinazoline-2-carbonitrile (**217**).* Similar treatment of 2-amino-*N'*-(2-bromophenyl)benzamidine (**231**) with TCNE gave the *title compound* **217** (290 mg, 89%) as colorless plates, mp (hotstage) 181-182 °C (*c*-hexane/THF, 90:10), mp (DSC) onset 181.8 °C, peak max. 182.6 °C; R_f 0.76 (DCM/*t*-BuOMe, 95:05); (found: C, 55.33; H, 2.70; N, 17.00. $C_{15}H_9BrN_4$ requires C, 55.41; H, 2.79; N, 17.23%); λ_{max}(DCM)/nm 258 inf (log ε 3.97), 270 inf (3.93), 283 inf (3.85), 297 inf (3.79), 337 (4.14); ν_{max}/cm^{-1} 3395w (NH), 3062w (aryl C-H), 2245w (C≡N), 1614m, 1595m, 1584m, 1570m, 1558m, 1530s, 1495m, 1460m, 1441m, 1420m, 1369w, 1356m, 1319m, 1236w, 1217w, 1171w, 1130w, 1092w, 1022m, 1018m, 991m, 868w, 760s, 752s, 746s; δ_H(500 MHz; $CDCl_3$) 8.78 (1H, d, *J* 8.5, Ar *H*), 8.35 (1H, br s, N*H*), 8.02 (2H, dd, *J* 9.3, 9.3, Ar *H*), 7.95 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.78 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.66 (1H, d, *J* 8.0, Ar *H*), 7.45 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.10 (1H, dd, *J* 7.8, 7.8, Ar *H*); δ_C(125 MHz; $CDCl_3$) 157.1 (s), 149.6 (s), 140.4 (s), 135.1 (s), 134.3 (d), 132.4 (d), 129.8 (d), 129.7 (d), 128.8 (d), 125.8 (d), 122.9 (d), 120.4 (d), 116.5 (s), 115.6 (s), 114.8 (s); *m*/*z* (MALDI-TOF) 327 (MH^++2, 100%), 325 (MH^+, 64), 245 (19). Further elution (DCM/*t*-BuOMe, 90:10) gave *3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile* (**232**) (3.3 mg, 1%) as colorless needles, mp (hotstage) 184-186 °C (from *c*-hexane/DCM, 90:10), mp (DSC) onset 183.7 °C, peak max. 186.2 °C; R_f 0.54 (DCM/*t*-BuOMe, 90:10); (found: C, 55.56; H, 2.64; N, 17.26. $C_{15}H_9BrN_4$ requires C, 55.41; H, 2.79; N, 17.23%); λ_{max}(DCM)/nm 274 (log ε 4.16), 283 (4.22), 293 (4.15), 318 inf (3.81), 330 (3.94), 343 (3.97), 360 inf (3.80); ν_{max}/cm^{-1} 3323w (NH), 3013w (aryl C-H), 2239 (C≡N), 1641s, 1605w, 1589m, 1564m, 1472m, 1462m, 1354s, 1337w, 1321w, 1302w, 1231w, 1182w, 1161w, 1121m, 1065m, 1024w, 1003m, 880m, 816s, 779s, 762s; δ_H(500 MHz; $CDCl_3$) 8.21 (1H, br s, Ar *H*), 7.89 (1H, d, *J* 8.0, Ar *H*), 7.73-7.68 (2H, m, Ar *H*), 7.61 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.56 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.52 (2H, dd, *J* 8.0, 8.0, Ar *H*), 6.72 (1H, br s, N*H*); δ_C(125 MHz; $CDCl_3$) one C (d) resonance missing, 152.6 (s), 143.1 (s), 134.8 (d), 134.6 (s), 133.5 (d), 132.7 (d), 131.0 (d), 130.0 (d), 129.8 (d), 128.7 (d), 125.5 (s), 123.9 (s), 122.5 (s), 111.1 (s); *m*/*z* (MALDI-TOF) 326 (MH^++1, 6%), 325 (MH^+, 68), 324 (M^+, 24), 323 (100).

*7.6.3 Preparation of 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitriles **232**, **234-239***

*7.6.3.1 3-(2-Bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**232**).*

Method A *via TCNE (typical procedure).* To a stirred solution of TCNE (256 mg, 2.00 mmol) in dry MeCN (10 mL) at *ca*. -20 °C was added a solution of 2-amino-*N'*-(2-bromophenyl)benzamidine (**233**) (289 mg, 1.00 mmol) in dry MeCN (10 mL). The reaction mixture was then left to stir at *ca*. -20 °C for 1 d, after which time it was adsorbed onto silica and chromatographed (DCM/*t*-BuOMe, 95:05) to give the title compound **232** (215 mg, 66%) as colorless plates, mp (hotstage) 184-186°C (from *c*-hexane); R_f 0.54 (DCM/*t*-BuOMe, 90:10); identical to that described above.

Method B *via Appel salt **74** (typical procedure).* To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (826 mg, 3.97 mmol) in DCM (40 mL) at *ca.* 20 °C was added 2-amino-*N'*-(2-bromophenyl)benzamidine (**233**) (1.15 g, 3.97 mmol) and the mixture was then left to stir at *ca.* 20 °C for 12 h. Then, to the reaction mixture was added Hünig's base (1.36 μL, 7.92 mmol) and left to stir at *ca.* 20 °C for an additional 3 h. The reaction mixture was then adsorbed onto silica and chromatographed (*n*-hexane) to give traces of S_8, followed by (*n*-hexane/DCM, 80:20) 4-chloro-5*H*-1,2,3-dithiazol-5-one (65 mg, 11%). Further elution (DCM/*t*-BuOMe, 90:10) gave the title compound **232** (856 mg, 74%) as colorless plates, mp (hotstage) 184-186 °C (from *c*-hexane); R_f 0.54 (DCM/*t*-BuOMe, 90:10); identical to that described above.

*7.6.3.2 3-(2-Bromophenyl)-4-imino-5-methyl-3,4-dihydroquinazoline-2-carbonitrile (**234**) (Method B).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (826 mg, 3.97 mmol) with 2-amino-*N'*-(2-bromophenyl)-6-methylbenzamidine (**245**) (1.207 g, 3.97 mmol) gave the *title compound* **234** (338.1 mg, 74%) as colorless plates, mp (hotstage) 123-124.5 °C (from *c*-hexane/DCM, 90:10); mp (DSC) onset 123.2 °C, peak max. 129.0 °C (from *c*-hexane/DCM, 90:10); R_f 0.73 (DCM/*t*-BuOMe, 90:10); (found: C, 56.19; H, 3.36; N, 16.51. $C_{16}H_{11}BrN_4$ requires C, 56.66; H, 3.27; N, 16.52%); λ_{max}(DCM)/nm 245 inf (log ε 4.09), 260 inf (3.91), 269 (3.93), 279 (3.85), 315 inf (3.78), 328 (3.84), 342 (3.80), 360 inf (3.59); ν_{max}/cm^{-1} 3408w (NH), 3055w (aryl C-H), 2237 (C≡N), 1626s, 1591m, 1560m, 1516w, 1470m, 1435w, 1360s, 1325w, 1305w, 1290w, 1217w, 1173w, 1156w, 1086w, 1065w, 1047w, 1024w, 1005s, 966w, 870w, 847w, 802s, 760s, 725m; δ_H(500 MHz;

$CDCl_3$) N*H* deuterium exchanged, 7.88 (1H, dd, *J* 7.8, 1.0, Ar *H*), 7.61 (1H, ddd, *J* 7.8, 7.8, 1.3, Ar *H*), 7.55-7.48 (4H, m, Ar *H*), 7.33 (1H, dd, *J* 7.0, 1.3, Ar *H*), 2.83 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) two C (s) resonances missing, 145.0 (s), 139.7 (s), 134.9 (d), 133.3 (d), 132.6 (d), 132.3 (d), 131.4 (d), 129.8 (d), 128.6 (s), 126.9 (d), 124.4 (s), 121.3 (s), 111.2 (s), 31.0 (q, CH_3); *m*/*z* (MALDI-TOF) 341 (MH^++2, 97%), 339 (MH^+, 100).

*7.6.3.3 3-(2-Bromophenyl)-4-imino-7-methoxy-3,4-dihydroquinazoline-2-carbonitrile (**235**) (Method B).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (826 mg, 3.97 mmol) with 2-amino-*N'*-(2-bromophenyl)-4-methoxybenzamidine (**246**) (1.270 g, 3.97 mmol) gave the *title compound* **235** (275.4 mg, 77%) as colorless plates, mp (hotstage) 159-161 °C (from *c*-hexane/DCM, 90:10), mp (DSC) onset 160.3 °C, peak max. 162.6 °C (from *c*-hexane/DCM, 90:10); R_f 0.47 (DCM/*t*-BuOMe, 90:10); (found: C, 54.28; H, 2.98; N, 15.70. $C_{16}H_{11}BrN_4O$ requires C, 54.10; H, 3.12; N, 15.77%); λ_{max}(DCM)/nm 247 inf (log ε 4.29), 256 (4.36), 265 (4.39), 275 (4.30), 300 inf (3.61), 313 (3.70), 327 (3.68), 354 inf (3.49); ν_{max}/cm^{-1} 3298w (NH), 3009w (aryl C-H), 2967w, 2940w and 2839w (alkyl C-H), 2237 (C≡N), 1634s, 1613s, 1592s, 1574w, 1562w, 1491s, 1472m, 1437w, 1352m, 1308s, 1283m, 1224w, 1200w, 1167s, 1130w, 1069w, 1026s, 1001w, 893w, 839m, 826w, 797m, 783w, 764s, 754s, 727m; δ_H(500 MHz; $CDCl_3$) N*H* deuterium exchanged, 8.10 (1H, br s, Ar *H*), 7.88 (1H, d, *J* 8.3, Ar *H*), 7.61 (1H, ddd, *J* 7.5, 7.5, 1.5, Ar *H*), 7.53-7.49 (2H, m, Ar *H*), 7.13-7.11 (2H, m, Ar *H*), 3.93 (3H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) one C (s) resonance missing, 163.8 (s), 144.9 (s), 134.8 (d), 132.6 (d), 131.5 (s), 131.0 (d), 129.7 (d), 127.0 (d), 124.0 (s), 118.8 (d), 115.4 (s), 111.1 (s, C≡N), 110.3 (d), 55.8 (q); *m*/*z* (MALDI-TOF) 357 (MH^++2, 100%), 355 (MH^+, 89).

*7.6.3.4 3-(2-Bromophenyl)-4-imino-6,7-dimethoxy-3,4-dihydroquinazoline-2-carbonitrile (**236**) (Method B).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (826 mg, 3.97 mmol) with 2-amino-*N'*-(2-bromophenyl)-4,5-dimethoxybenzamidine (**247**) (1.390 g, 3.97 mmol) gave the *title compound* **236** (256.3 mg, 66%) as colorless plates, mp (hotstage) 226-227 °C (from *c*-hexane/DCM, 90:10); mp (DSC) onset 226.7 °C, peak max. 227.4 °C, decomp. onset 232.6 °C, peak max 239.5 °C (from *c*-hexane/DCM, 90:10); R_f 0.32 (DCM/*t*-BuOMe, 90:10); (found: C, 53.10; H, 3.27; N, 14.63. $C_{17}H_{13}BrN_4O_2$ requires C, 53.01; H, 3.40; N, 15.54%); λ_{max}(DCM)/nm 258 inf (log ε 4.33), 268 (4.39), 277 inf (4.33), 304 inf (3.60), 316 (3.78), 330 (3.88), 355 (3.87), 374 inf (3.77), 396 inf (3.40); ν_{max}/cm^{-1} 3291w (NH), 3092w, 3067w and 3009w (aryl C-H), 2965w, 2938w and 2837w

(alkyl C-H), 2237w (C≡N), 1636s, 1609s, 1504s, 1472m, 1452m, 1442m, 1423w, 1379m, 1346w, 1304s, 1283m, 1265m, 1250m, 1207m, 1182w, 1126s, 1119s, 1076w, 1049w, 1024m, 997m, 885m, 864s, 851m, 831m, 775m, 760s; δ_H(500 MHz; $CDCl_3$) 7.90 (1H, d, *J* 8.0, Ar *H*), 7.67 (1H, br s, Ar *H*), 7.63 (1H, dd, *J* 8.0, 8.0, Ar *H*), 7.54 (1H, dd, *J* 8.0, 8.0, Ar *H*), 7.51 (1H, dd, *J* 7.8, 1.8, Ar *H*), 7.11 (1H, s, Ar *H*), 6.28 (1H, br s, N*H*), 4.02 (3H, s, OCH_3), 4.00 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 153.8 (s), 151.2 (s), 138.6 (s), 134.9 (d), 134.4 (s), 132.8 (d), 131.1 (d), 129.9 (d), 129.2 (s), 124.2 (s), 116.1 (s), 111.3 (s, C≡N), 109.3 (d), 105.7 (d), 56.5 (q, OCH_3), 56.4 (q, OCH_3); *m*/*z* (MALDI-TOF) 387 (MH^++2, 83%), 385 (MH^+, 100), 305 (10).

*7.6.3.5 3-(2-Bromophenyl)-6-chloro-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**237**) (Method B).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (826 mg, 3.97 mmol) with 2-amino-*N'*-(2-bromophenyl)-5-chlorobenzamidine (**248**) (1.290 g, 3.97 mmol) gave the *title compound* **237** (290.1 mg, 81%) as colorless plates, mp (hotstage) 226.5-228 °C (from *c*-hexane/DCM, 90:10); mp (DSC) onset 227.0 °C, peak max. 228.7 °C (from *c*-hexane/DCM, 90:10); R_f 0.70 (DCM/*t*-BuOMe, 90:10); (found: C, 49.96; H, 2.18; N, 15.47. $C_{15}H_8BrClN_4$ requires C, 50.10; H, 2.24; N, 15.58%); λ_{max}(DCM)/nm 242 inf (log ε 4.05), 250 (4.04), 256 inf (4.02), 266 (4.05), 276 (3.95), 304 inf (3.74), 316 (3.91), 329 (3.96), 343 inf (3.85), 359 inf (3.68), 379 inf (3.20); ν_{max}/cm^{-1} 3298w (NH), 3055w (aryl C-H), 2243w (C≡N), 1643m, 1630m, 1601w, 1587w, 1570w, 1557w, 1464w, 1424m, 1344m, 1312s, 1296m, 1165m, 1121w, 1080w, 1047w, 1030w, 1003w, 975w, 941w, 903w, 837s, 771s, 729m, 721m; δ_H(500 MHz; $CDCl_3$) 8.28 (1H, br s, Ar *H*), 7.90 (1H, d, *J* 8.0, Ar *H*), 7.66 (2H, dd, *J* 8.5, 2.0, Ar *H*), 7.62 (2H, dd, *J* 6.5, 6.5, Ar *H*), 7.54 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.49 (1H, dd, *J* 8.0, 1.5, Ar *H*), 6.67 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) three C (s) and one C (d) resonances missing, 141.6 (s), 136.1 (s), 135.0 (d), 133.9 (d), 133.0 (d), 131.0 (d), 130.0 (d), 125.5 (d), 124.0 (s), 111.0 (s, C≡N); *m*/*z* (MALDI-TOF) 363 (MH^++4, 13%), 361 (MH^++2, 100), 359 (MH^+, 55), 130 (2).

*7.6.3.6 3-(2-Bromophenyl)-7-chloro-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**238**) (Method B).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (826 mg, 3.97 mmol) with 2-amino-*N'*-(2-bromophenyl)-4-chlorobenzamidine (**249**) (1.290 g, 3.97 mmol) gave the *title compound* **238** (284.5 mg, 79%) as colorless plates, mp (hotstage) 146-148 °C (from *c*-hexane/DCM, 90:10); mp (DSC) onset 146.1 °C, peak max. 150.7 °C (from *c*-hexane/DCM, 90:10); R_f 0.67 (DCM/*t*-BuOMe, 90:10) ; (found: C, 49.99; H, 2.17;

N, 15.46. $C_{15}H_8BrClN_4$ requires C, 50.10; H, 2.24; N, 15.58%); λ_{max}(DCM)/nm 245 (log ε 4.23), 254 (4.23), 264 (4.25), 274 (4.14), 302 inf (3.63), 313 (3.76), 326 (3.80), 344 inf (3.63), 362 inf (3.41), 383 inf (2.89); ν_{max}/cm^{-1} 3298w and 3273w (N-H), 3069w (aryl C-H), 2241w (C≡N), 1640s, 1585m, 1571m, 1557w, 1472w, 1462m, 1416m, 1346m, 1298s, 1155s, 1115w, 1080m, 1028w, 1003w, 920m, 867w, 869w, 851w, 835m, 824m, 760m, 727m, 718m; δ_H(500 MHz; $CDCl_3$) N*H* deuterium exchanged, 8.29 (1H, br s, Ar *H*), 7.91 (1H, d, *J* 8.0, Ar *H*), 7.67 (1H, d, *J* 1.5, Ar *H*), 7.63 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.55-7.49 (3H, m, Ar *H*); δ_C(125 MHz; $CDCl_3$) four C (s) and one C (d) resonances missing, 144.1 (s), 139.7 (s), 135.0 (d), 133.0 (d), 131.0 (d), 130.2 (d), 130.0 (d), 128.1 (d), 124.0 (s), 110.9 (s, C≡N); *m*/*z* (MALDI-TOF) 363 (MH^++4, 17%), 361 (MH^++2, 100), 359 (MH^+, 96), 340 (7), 338 (45), 336 (35).

*7.6.3.7 6-Bromo-3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**239**) (Method B).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**74**) (826 mg, 3.97 mmol) with 2-amino-5-bromo-*N'*-(2-bromophenyl)benzamidine (**250**) (1.465 g, 3.97 mmol) gave the *title compound* **239** (306.6 mg, 76%) as colorless plates, mp (hotstage) 240-245.0 ^oC (from *c*-hexane/DCM, 90:10); mp (DSC) onset 244.4 ^oC, peak max. 246.9 ^oC (from *c*-hexane/DCM, 90:10); R_f 0.63 (DCM/*t*-BuOMe, 90:10); (found: C, 44.42; H, 1.99; N, 13.83. $C_{15}H_8Br_2N_4$ requires C, 44.59; H, 2.00; N, 13.87%); λ_{max}(DCM)/nm 243 (log ε 4.06), 251 (4.04), 267 (4.05), 277 (3.95), 304 inf (3.74), 317 inf (3.91), 329 (3.98), 343 inf (3.88), 360 inf (3.70), 379 inf (3.23); ν_{max}/cm^{-1} 3294w (NH), 3053w and 3030w (aryl C-H), 2243w (C≡N), 1643m, 1630m, 1585m, 1570m, 1462m, 1418w, 1346m, 1310s, 1296m, 1277w, 1163m, 1067w, 1047w, 1030w, 1001w, 976w, 941w, 891w, 835s, 813s, 770s, 727m, 714m; δ_H(500 MHz; $CDCl_3$) 8.48 (1H, br s, Ar *H*), 7.90 (1H, d, *J* 8.0, Ar *H*), 7.80 (1H, dd, *J* 8.8, 2.3, Ar *H*), 7.63 (1H, dd, *J* 7.5, 7.5, Ar *H*), 7.55 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.49 (1H, dd, *J* 9.0, 1.5, Ar *H*), 6.66 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) four C (s) resonances missing, 142.0 (s), 136.8 (d), 135.0 (d), 133.0 (d), 131.0 (d), 130.1 (d), 130.0 (d), 128.6 (d), 124.1 (s), 124.0 (s), 111.0 (s, C≡N); *m*/*z* (MALDI-TOF) 407 (MH^++4, 20%), 405 (MH^++2, 29), 403 (MH^+, 15), 130 (100), 128 (51).

*7.6.4 Preparation of Benzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitriles **78**, **219-229**, **240-244***

*7.6.4.1 Benzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**78**):* **Method A***: via the PIFA only mediated oxidative cyclization of 4-(phenylamino)quinazoline-2-carbonitrile (**79**) (typical procedure).* To a stirred solution of 4-(phenylamino)quinazoline-2-carbonitrile (**79**) (49.2 mg, 0.20 mmol) in trifluoroacetic acid (TFA) (1 mL) was added phenyliodine bis(trifluoroacetate) (PIFA) (94.6 mg, 0.22 mmol) at *ca.* 20 °C and left to stir for 30 min. The reaction mixture was then diluted (water, 5 mL), extracted (DCM, 3× 5 mL) and dried (Na_2SO_4). The organic phase was then adsorbed onto silica and chromatographed (DCM) to give benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile (**78**) (45.1 mg, 92%) as pale yellow fibres, mp (hotstage) 258-259 °C (lit.,[220] 252-254 °C) (*n*-pentane/THF, 80:20), mp (DSC) onset 259.0 °C, peak max. 259.5 °C; R_f 0.65 (DCM); (found: C, 73.61; H, 3.42; N, 22.79. $C_{15}H_8N_4$ requires C, 73.76; H, 3.30; N, 22.94%); λ_{max}(DCM)/nm 276 inf (4.46), 286 (4.60), 296 (4.59), 317 (3.87), 331 (3.82), 346 (3.59), 390 (3.03); ν_{max}/cm^{-1} 3048w (aryl C-H), 2243w (C≡N), 1620w, 1587w, 1526w, 1468w, 1449m, 1383m, 1327w, 1312w, 1261w, 1252w, 1223w, 1204w, 1159w, 1119w, 1013w, 976w, 935w, 918w, 876w, 851w, 820w, 793m, 775w, 758m, 746s; δ_H(500 MHz; $CDCl_3$) 8.73 (1H, dd, *J* 7.5, 1.5, Ar *H*), 8.58 (1H, d, *J* 8.5, Ar *H*), 8.06 (2H, dd, *J* 7.0, 7.0, Ar *H*), 7.88 (1H, ddd, *J* 7.5, 7.5, 1.5, Ar *H*), 7.84 (1H, ddd, *J* 7.5, 7.5, 1.0, Ar *H*), 7.67 (1H, ddd, *J* 7.5, 7.5, 1.0, Ar *H*), 7.60 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*); δ_C(125 MHz; DMSO-d_6) 146.0 (s), 144.1 (s), 141.2 (s), 132.4 (d), 131.3 (d), 129.3 (d), 127.4 (s), 127.1 (d), 124.44 (d), 124.38 (d), 122.2 (s), 120.6 (d), 120.0 (s), 112.4 (d), 112.2 (s, C≡N); *m*/*z* (MALDI-TOF) 246 (MH^++1, 23%), 245 (MH^+, 100), 244 (M^+, 29).

Method B*: via the PIFA and Cu(OTf)$_2$ mediated oxidative cyclization of 4-(phenyl-amino)quinazoline-2-carbonitrile (**79**) (typical procedure).* To a stirred solution of 4-(phenylamino)quinazoline-2-carbonitrile (**79**) (49.2 mg, 0.20 mmol) in TFA (1 mL) was added phenyliodine bis(trifluoroacetate) (PIFA) (129.0 mg, 0.30 mmol) and Cu(OTf)$_2$ (3.6 mg, 5 mol%) at *ca.* 20 °C. The reaction mixture was then immersed in a preheated oil bath at *ca.* 80 °C and left to stir for 30 min. The reaction mixture was then diluted (water, 5 mL), extracted (DCM, 3× 5 mL) and dried (Na_2SO_4). The organic phase was then adsorbed onto silica and chromatographed (DCM) to give benzo[4,5]imidazo[1,2-*c*]quinazoline-6-

carbonitrile (**78**) (44.1 mg, 90%) as pale yellow fibres, mp (hotstage) 258-259 °C (lit.,[220] 252-254 °C) (*n*-pentane/THF, 80:20); R_f 0.65 (DCM); identical to that described above.

Method C*: via the Pd(OAc)$_2$ mediated non-oxidative cyclization of 4-[(2-bromo-phenyl)amino]quinazoline-2-carbonitrile (**217**) (typical procedure).* A mixture of 4-[(2-bromophenyl)amino]quinazoline-2-carbonitrile (**217**) (32.5 mg, 0.10 mmol), Pd(OAc)$_2$ (2.2 mg, 10 mol%), BINAP (6.2 mg, 10 mol%) and powdered dry K_2CO_3 (13.8 mg, 0.10 mmol) was placed in a sealed tube, deaerated with argon and dissolved in dry PhMe (1 mL) at *ca.* 20 °C. The reaction mixture was then immersed into a preheated Wood's metal bath at *ca*. 160 °C and left to stir for 5 h. The reaction mixture was then cooled to *ca.* 20 °C and adsorbed onto silica and chromatographed (DCM) to give benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile (**78**) (20.8 mg, 85%) as pale yellow fibres, mp (hotstage) 258-259 °C (lit.,[220] 252-254 °C) (*n*-pentane/THF, 80:20); R_f 0.65 (DCM); identical to that described above.

Method D*: via the CuI mediated non-oxidative cyclization of 4-[(2-bromo-phenyl)-amino]quinazoline-2-carbonitrile (**217**) (typical procedure).* A mixture of 4-[(2-bromo-phenyl)amino]quinazoline-2-carbonitrile (**217**) (32.5 mg, 0.10 mmol), CuI (1.9 mg, 10 mol%), 1,10-phenanthroline (2.0 mg, 10 mol%) and powdered dry K_2CO_3 (13.8 mg, 0.10 mmol) dissolved in dry MeCN (1 mL) at *ca.* 20 °C and the stirred reaction mixture was heated at reflux (*ca*. 80 °C) for 3 h, then cooled to *ca.* 20 °C, adsorbed onto silica and chromatographed (DCM) to give benzo[4,5]imidazo[1,2-*c*]-quinazoline-6-carbonitrile (**78**) (22.6 mg, 93%) as pale yellow fibres, mp (hotstage) 258-259 °C (lit.,[3b] 252-254 °C) (*n*-pentane/THF, 80:20); R_f 0.65 (DCM); identical to that described above.

Method E*: via the Pd(OAc)$_2$ mediated non-oxidative cyclization of 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**232**) (typical procedure).* A mixture of 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**232**) (32.5 mg, 0.10 mmol), Pd(OAc)$_2$ (2.2 mg, 10 mol%), BINAP (6.2 mg, 10 mol%) and Cs_2CO_3 (32.6 mg, 0.10 mmol) was deaerated with argon and dissolved in dry PhMe (1 mL) at *ca.* 20 °C. The stirred reaction mixture was then heated at reflux (*ca*. 110 °C) for 17 h, then cooled to *ca.* 20 °C, adsorbed onto silica and chromatographed (DCM) to give benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile (**78**) (19.0 mg, 78%) as pale yellow fibres, mp (hotstage) 258-259 °C (lit.,[220] 252-254 °C) (*n*-pentane/THF, 80:20); R_f 0.65 (DCM); identical to that described above.

Method F*: via the Pd[3,5-(F$_3$C)$_2$C$_6$H$_3$]$_3$ mediated non-oxidative cyclization of 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**232**) (typical procedure).* A mixture of 3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**232**) (65.0 mg, 0.20 mmol), Pd[3,5-(F$_3$C)$_2$C$_6$H$_3$]$_3$ (42.4 mg, 10 mol%), BINAP (6.2 mg, 5 mol%) and powdered dry K_2CO_3 (82.8 mg, 0.60 mmol) was deaerated with argon and dissolved in dry PhMe (2 mL) at *ca.* 20 ^{o}C. The stirred reaction mixture was then heated at reflux (*ca*. 110 ^{o}C) for 5 h, then cooled to *ca.* 20 ^{o}C, adsorbed onto silica and chromatographed (DCM) to give benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile (**78**) (46.6 mg, 95%) as pale yellow fibres, mp (hotstage) 258-259 ^{o}C (lit.,[220] 252-254 ^{o}C) (*n*-pentane/THF, 80:20); R_f 0.65 (DCM); identical to that described above.

*7.6.4.2 9-Methylbenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**219**) (Method A).* Similar treatment of 4-(*p*-tolylamino)quinazoline-2-carbonitrile (**113**) (52.0 mg, 0.20 mmol) with PIFA (94.6 mg, 0.22 mmol) in TFA gave the *title compound* **219** (41.1 mg, 80%) as pale yellow fibres, mp (hotstage) 252-253 ^{o}C (*n*-pentane/THF, 80:20), mp (DSC) onset 253.2 ^{o}C, peak max. 253.4 ^{o}C; R_f 0.63 (DCM); (found: C, 73.32; H, 3.87; N, 21.57. $C_{16}H_{10}N_4$ requires C, 74.40; H, 3.90; N, 21.69%); λ_{max}(DCM)/nm 279 inf (4.62), 291 (4.78), 303 (4.77), 320 (4.16), 335 (4.06), 352 inf (3.67), 396 (3.22); ν_{max}/cm^{-1} 3028w (aryl C-H), 2922w (alkyl C-H), 2243w (C≡N), 1622w, 1589w, 1582w, 1526w, 1487w, 1466m, 1433w, 1387m, 1334w, 1294w, 1263w, 1254w, 1223w, 1217m, 1171m, 999w, 968w, 949w, 877w, 856w, 823w, 808s, 772s; δ_H(500 MHz; $CDCl_3$) 8.69 (1H, dd, *J* 7.8, 1.8, Ar *H*), 8.32 (1H, br s, Ar *H*), 8.04 (1H, d, *J* 8.0, Ar *H*), 7.90 (1H, d, *J* 8.0, Ar *H*), 7.84 (1H, ddd, *J* 7.6, 7.6, 1.8, Ar *H*), 7.81 (1H, ddd, *J* 7.5, 7.5, 1.5, Ar *H*), 7.47 (1H, d, *J* 8.5, Ar *H*), 2.64 (3H, s, C*H*$_3$); δ_C(125 MHz; DMSO-d_6) 145.5 (s), 142.1 (s), 141.0 (s), 134.9 (s), 132.1 (d), 131.2 (d), 129.2 (d), 128.8 (d), 127.6 (s), 124.3 (d), 122.2 (s), 120.05 (s), 120.01 (d), 112.2 (s, C≡N), 112.1 (d), 22.1 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 260 (MH$^+$+1, 53%), 259 (MH$^+$, 100), 258 (M$^+$, 11).

*7.6.4.3 9-Methoxybenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**220**) (Method A).* Similar treatment of 4-[(4-methoxyphenyl)amino]quinazoline-2-carbonitrile (**114**) (55.3 mg, 0.20 mmol) with PIFA (94.6 mg, 0.22 mmol) in TFA gave the *title compound* **220** (44.6 mg, 82%) as pale yellow plates, mp (hotstage) 210.5-212 ^{o}C (*n*-pentane/DCM, 80:20), mp (DSC) onset 211.1 ^{o}C, peak max. 211.8 ^{o}C; R_f 0.43 (DCM); (found: C, 69.95; H, 3.62; N, 20.31. $C_{16}H_{10}N_4O$ requires C, 70.06; H, 3.68; N, 20.43%); λ_{max}(DCM)/nm 254

inf (4.19), 284 inf (4.41), 295 (4.61), 306 (4.69), 324 inf (4.17), 340 (4.02), 402 (2.14); ν_{max}/cm^{-1} 3046w (aryl C-H), 2995w and 2839w (alkyl C-H), 2237w (C≡N), 1624m, 1595w, 1556w, 1526w, 1491m, 1466m, 1433m, 1387m, 1337w, 1290m, 1273w, 1254w, 1221s, 1205m, 1178w, 1125w, 1032m, 955w, 880w, 831m, 818m, 768s; δ_H(500 MHz; $CDCl_3$) 8.64 (1H, dd, *J* 6.8, 1.5, Ar *H*), 8.03-8.01 (2H, m, Ar *H*), 7.91 (1H, d, *J* 9.0, Ar *H*), 7.84-7.79 (2H, m, Ar *H*), 7.27 (1H, dd, 9.0, 2.5, Ar *H*), 3.98 (3H, s, OC*H*$_3$); δ_C(125 MHz; $CDCl_3$) 157.4 (s), 145.0 (s), 140.7 (s), 138.3 (s), 131.8 (d), 131.2 (d), 129.2 (d), 127.8 (s), 124.0 (d), 122.0 (s), 121.1 (d), 120.2 (s), 117.0 (d), 112.2 (s), 95.3 (d), 56.0 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 275 (MH$^+$, 15%), 274 (M$^+$, 100), 153 (2).

*7.6.4.4 Mixture of 9,10-dimethoxybenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**221**) and 8,9-dimethoxybenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**222**) (Method B).* Similar treatment of 4-[(3,4-dimethoxyphenyl)amino]quinazoline-2-carbonitrile (**216**) (61.2 mg, 0.20 mmol) with PIFA (129.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (3.6 mg, 5 mol%) in TFA gave a mixture of the *title compounds* **221** and **222** (50.2 mg, 82%) as pale yellow plates, mp (hotstage) 234-236 ^{o}C (*n*-pentane/DCM, 80:20), mp (DSC) onset 235.5 ^{o}C, peak max. 235.7 ^{o}C, onset 235.5 ^{o}C, peak max. 236.2 ^{o}C; R_f 0.50 (DCM); (found: C, 66.93; H, 3.90; N, 18.36. $C_{17}H_{12}N_4O_2$ requires C, 67.10; H, 3.97; N, 18.41%); λ_{max}(DCM)/nm 250 (log ε 4.23), 285 inf (4.41), 306 (4.54), 315 inf (4.54), 348 inf (3.98), 428 inf (3.17); ν_{max}/cm^{-1} 3092w and 3032w (aryl C-H), 2997w, 2936w and 2839w (alkyl C-H), 2236w (C≡N), 1593w, 1524w, 1489s, 1468w, 1460w, 1439m, 1391w, 1348w, 1333w, 1300m, 1271w, 1248m, 1224m, 1204s, 1163w, 1148s, 1028w, 1018w, 988w, 917w, 826s, 814m, 762s; δ_H(500 MHz; $CDCl_3$) ratio based on (^{1}H NMR is **221**/**222** 2.6:1) 8.65-8.63 (3.6H, m, Ar *H*), 8.05-8.03 (4.6H, m, Ar *H*), 7.85-7.78 (7.4H, m, Ar *H*), 7.48 (1H, s, Ar *H*), 7.08 (2.6H, s, Ar *H*), 4.08 (3H, s, OC*H*$_3$), 4.04 (3H, s, OC*H*$_3$), 4.010 and 4.006 (15.3H, 2 × s, OC*H*$_3$); δ_C(125 MHz; DMSO-d_6) one C (d) resonance missing, 153.4 (s), 149.6 (s), 147.2 (s), 146.4 (s), 144.4 (s), 140.7 (s), 140.3 (s), 139.2 (s), 137.9 (s), 133.9 (s), 131.9 (d), 131.7 (d), 131.0 (d), 130.7 (d), 128.7 (d), 128.2 (d), 124.0 (d), 123.6 (d), 123.3 (d), 122.8 (s), 120.7 (s), 119.6 (s), 119.59 (s), 119.2 (s), 113.6 (s), 112.9 (s), 112.6 (s), 101.6 (d), 94.9 (d), 92.5 (d), 61.0 (q, O*C*H$_3$), 56.5 (q, O*C*H$_3$), 56.0 (q, O*C*H$_3$), 56.0 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 305 (MH$^+$, 100%), 304 (M$^+$, 62).

*7.6.4.5 9-Fluorobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**223**) (Method B).* Similar treatment of 4-[(4-fluorophenyl)amino]quinazoline-2-carbonitrile (**115**) (52.8 mg, 0.20 mmol) with PIFA (129.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (3.6 mg, 5 mol%) in TFA gave the *title compound* **223** (46.8 mg, 89%) as pale yellow fibres, mp (hotstage) 240-242 °C (*n*-pentane/THF, 80:20), mp (DSC) onset 241.6 °C, peak max. 242.3 °C; R_f 0.71 (DCM); (found: C, 68.72; H, 2.67; N, 21.22. $C_{15}H_7FN_4$ requires C, 68.70; H, 2.69; N, 21.36%); λ_{max}(DCM)/nm 247 inf (log ε 4.18), 275 inf (4.58), 286 (4.76), 296 (4.81), 315 (4.12), 330 (4.06), 342 (3.82), 395 inf (3.25); ν_{max}/cm^{-1} 3026w (aryl C-H), 2243w (C≡N), 1626m, 1593m, 1485s, 1468m, 1439m, 1379m, 1342w, 1283m, 1252w, 1203m, 1184m, 1179m, 1161m, 1121w, 964w, 880w, 843s, 833w, 812s, 771s; δ_H(500 MHz; $CDCl_3$) 8.68 (1H, dd, *J* 7.8, 1.8, Ar *H*), 8.27 (1H, dd, *J* 8.5, 2.5, Ar *H*), 8.05 (1H, dd, *J* 8.0, 1.0, Ar *H*), 7.99 (1H, dd, *J* 9.0, 4.5, Ar *H*), 7.88 (1H, ddd, *J* 7.5, 7.5, 1.5, Ar *H*), 7.84 (1H, ddd, *J* 7.5, 7.5, 1.5, Ar *H*), 7.43 (1H, ddd, *J* 9.0, 9.0, 2.0, Ar *H*); δ_C(125 MHz; $CDCl_3$) 159.7 (d, $^1J_{CF}$ 243.8), 146.5 (d, $^4J_{CF}$ 2.5), 141.0 (s), 140.4 (s), 132.5 (d), 131.5 (d), 129.4 (d), 127.3 (d, $^3J_{CF}$ 12.9), 124.3 (d), 121.8 (s), 121.5 (d, $^3J_{CF}$ 9.8), 119.9 (s), 115.8 (d, $^2J_{CF}$ 25.1), 111.2 (s), 99.7 (d, $^2J_{CF}$ 30.0); *m*/*z* (MALDI-TOF) 264 (MH^++1, 11%), 263 (MH^+, 83), 262 (M^+, 100).

*7.6.4.6 9-Chlorobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**224**) (Method B).* Similar treatment of 4-[(4-chlorophenyl)amino]quinazoline-2-carbonitrile (**116**) (56.0 mg, 0.20 mmol) with PIFA (129.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (3.6 mg, 5 mol%) in TFA gave the *title compound* **224** (48.7 mg, 88%) as pale yellow fibres, mp (hotstage) 217.5-219 °C (*n*-pentane/DCM, 80:20), mp (DSC) onset 218.5 °C, peak max. 219.1 °C; R_f 0.78 (DCM); (found: C, 64.57; H, 2.51; N, 20.21. $C_{15}H_7ClN_4$ requires C, 64.65; H, 2.53; N, 20.10%); λ_{max}(DCM)/nm 247 inf (4.16), 278 inf (4.55), 288 (4.72), 298 (4.79), 317 (4.12), 333 (4.02), 344 inf (3.68), 385 (3.17); ν_{max}/cm^{-1} 3076w (aryl C-H), 2241w (C≡N), 1620m, 1589w, 1571w, 1460m, 1377m, 1329w, 1281m, 1261w, 1246w, 1221w, 1200m, 1117w, 1078w, 939w, 878w, 837w, 827m, 767s; δ_H(500 MHz; $CDCl_3$) 8.69 (1H, dd, *J* 8.0, 1.5, Ar *H*), 8.54 (1H, d, *J* 1.5, Ar *H*), 8.07 (1H, d, *J* 7.5, Ar *H*), 7.95 (1H, d, *J* 8.5, Ar *H*), 7.89 (1H, ddd, *J* 7.8, 7.8, 1.3, Ar *H*), 7.84 (1H, ddd, *J* 8.0, 8.0, 1.0, Ar *H*), 7.62 (1H, dd, *J* 7.0, 2.0, Ar *H*); δ_C(125 MHz; $CDCl_3$) 146.5 (s), 142.6 (s), 141.1 (s), 132.7 (d), 131.6 (d), 130.2 (s), 129.4 (d), 128.0 (d), 127.8 (s), 124.5 (d), 121.8 (s), 121.4 (d), 119.8 (s), 112.6 (d), 111.9 (s, C≡N); *m*/*z* (MALDI-TOF) 280 (M^++2, 41%), 278 (M^+, 100).

*7.6.4.7 Mixture of 9,10-dichlorobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbo-nitrile (**225**) and 8,9-dichlorobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**226**) (Method B).* Similar treatment of 4-[(3,4-dichlorophenyl)amino]quinazoline-2-carbonitrile (**118**) (63.0 mg, 0.20 mmol) with PIFA (129.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (3.6 mg, 5 mol%) in TFA gave a mixture of the *title compounds* **225** and **226** (48.3 mg, 77%) as pale yellow plates, mp (hotstage) 205-208 ^oC (*n*-pentane/DCM, 80:20), mp (DSC) onset 206.5 ^oC, peak max. 210.0 ^oC; R_f 0.75 (DCM/*t*-BuOMe, 95:05); (found: C, 57.28; H, 1.82; N, 17.69. $C_{15}H_6Cl_2N_4$ requires C, 57.53; H, 1.93; N, 17.89%); λ_{max}(DCM)/nm 265 inf (log ε 4.27), 276 inf (4.52), 287 inf (4.67), 292 (4.70), 302 (4.73), 320 inf (4.13), 334 (4.02), 348 inf (3.70), 389 (3.16); ν_{max}/cm^{-1} 3092w and 3057w (aryl C-H), 2241w (C≡N), 1622w, 1585w, 1557w, 1468w, 1450w, 1438s, 1404m, 1377m, 1354w, 1327w, 1290w, 1233w, 1254w, 1225w, 1196m, 1171w, 1163w, 1128w, 1107m, 1099m, 1028w, 1018w, 962w, 920w, 897w, 870m, 843w, 826w, 789m, 773s; δ_H(500 MHz; $CDCl_3$) ratio based on (^{1}H NMR is **225**/**226** 2.6:1) 8.69 (3.8H, m, Ar *H*), 8.14 (1H, s, Ar *H*), 8.09 (2.6H, dd, *J* 7.8, 7.8, Ar *H*), 7.94-7.85 (7H, m, Ar *H*), 7.76 (1H, d, *J* 8.5, Ar *H*); δ_C(125 MHz; $CDCl_3$) three C (s) resonances missing, 148.4 (s), 147.5 (s), 144.3 (s), 143.3 (s), 141.3 (s), 140.7 (s), 133.1 (d), 131.8 (d), 131.75 (s), 131.6 (d), 130.9 (d), 130.1 (s), 129.5 (d), 129.0 (d), 128.9 (d), 128.8 (d), 128.7 (s), 126.4 (s), 124.7 (d), 124.65 (d), 121.5 (s), 119.5 (s), 119.4 (s), 119.2 (d), 113.8 (d), 113.3 (s), 111.7 (s, C≡N); *m*/*z* (MALDI-TOF) 317 (MH^++4, 1%), 315 (MH^++2, 32), 313 (MH^+, 100), 242 (15).

*7.6.4.8 11-Bromobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**227**) (Method B).* Similar treatment of 4-[(2-bromophenyl)amino]quinazoline-2-carbonitrile (**217**) (65.0 mg, 0.20 mmol) with PIFA (129.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (3.6 mg, 5 mol%) in TFA gave the *title compound* **227** (53.2 mg, 82%) as pale yellow plates, mp (hotstage) 258-259 ^oC (*n*-pentane/DCM, 80:20), mp (DSC) onset 258.9 ^oC, peak max. 259.3 ^oC; R_f 0.86 (DCM); (found: C, 55.63; H, 2.09; N, 17.26. $C_{15}H_7BrN_4$ requires C, 55.75; H, 2.18; N, 17.34%); λ_{max}(DCM)/nm 242 (4.44), 280 inf (4.48), 289 (4.60), 299 (4.55), 319 (3.93), 334 (3.84), 346 inf (3.60), 389 (3.11); ν_{max}/cm^{-1} 3086w and 3030w (aryl C-H), 2239w (C≡N), 1622w, 1607w, 1585m, 1466m, 1420s, 1377m, 1340w, 1327w, 1283m, 1261m, 1219w, 1182m, 1150w, 1128w, 1055w, 930m, 878w, 841w, 787w, 773s, 743s; δ_H(500 MHz; $CDCl_3$) 8.88 (1H, dd, *J* 8.0, 1.5, Ar *H*), 8.56 (1H, d, *J* 8.0, Ar *H*), 8.08 (1H, d, *J* 8.0, Ar *H*), 7.91 (1H, ddd, *J* 8.0, 8.0, 2.0, Ar *H*), 7.89-7.85 (2H, m, Ar *H*), 7.46 (2H, dd, *J* 8.0, 8.0, Ar *H*); δ_C(125 MHz; $CDCl_3$) 146.4 (s), 142.9 (s), 141.3 (s), 132.9 (d), 131.5 (d), 130.1 (d),

129.3 (d), 128.0 (s), 125.1 (d), 125.0 (d), 122.0 (s), 119.7 (s), 114.2 (s), 112.0 (s, C≡N), 111.6 (d); *m*/*z* (MALDI-TOF) 325 (MH^++2, 69%), 323 (MH^+, 100), 322 (M^+, 37), 244 (4).

*7.6.4.9 9-Bromobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**228**) (Method B).* Similar treatment of 4-[(4-bromophenyl)amino]quinazoline-2-carbonitrile (**117**) (65.0 mg, 0.20 mmol) with PIFA (129.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (3.6 mg, 5 mol%) in TFA gave the *title compound* **228** (56.1 mg, 87%) as pale yellow plates, mp (hotstage) 237-238 °C (*n*-pentane/DCM, 80:20), mp (DSC) onset 238.4 °C, peak max. 238.8 °C; R_f 0.82 (DCM); (found: C, 55.75; H, 2.15; N, 17.21. $C_{15}H_7BrN_4$ requires C, 55.75; H, 2.18; N, 17.34%); λ_{max}(DCM)/nm 248 inf (3.99), 278 inf (4.37), 288 (4.55), 300 (4.64), 318 (3.97), 333 (3.86), 345 inf (3.49), 387 inf (2.98); ν_{max}/cm^{-1} 3071w (aryl C-H), 2245w (C≡N), 1620w, 1585m, 1452s, 1423w, 1379s, 1329w, 1281m, 1260w, 1246w, 1219m, 1202m, 1136w, 1115w, 1061w, 1013w, 928w, 876w, 833m, 819s, 768s, 735m; δ_H(500 MHz; $CDCl_3$) 8.70-8.68 (2H, m, Ar *H*), 8.07 (1H, dd, *J* 8.3, 0.8, Ar *H*), 7.91-7.88 (1H, m, Ar *H*), 7.85 (1H, ddd, *J* 7.5, 7.5, 1.0, Ar *H*), 7.76 (1H, dd, *J* 8.8, 1.3, Ar *H*); δ_C(125 MHz; $CDCl_3$) 146.4 (s), 143.0 (s), 141.1 (s), 132.7 (d), 131.6 (d), 130.7 (d), 129.4 (d), 128.3 (s), 124.5 (d), 121.8 (s), 121.7 (d), 119.7 (s), 117.5 (s), 115.5 (d), 111.9 (s, C≡N); *m*/*z* (MALDI-TOF) 325 (MH^++2, 64%), 323 (MH^+, 100), 283 (3), 244 (2).

*7.6.4.10 2,3-Dimethoxybenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**229**) (Method B).* Similar treatment of 6,7-dimethoxy-4-(phenylamino)quinazoline-2-carbonitrile (**218**) (61.2 mg, 0.20 mmol) with PIFA (129.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (3.6 mg, 5 mol%) in TFA gave the *title compound* **229** (51.8 mg, 85%) as yellow fibres, mp (hotstage) 284-285 °C (*n*-pentane/DCM, 80:20), mp (DSC) onset 284.4 °C, peak max. 285.8 °C, decomp. onset 328.0 °C, peak max. 343.9 °C; R_f 0.20 (DCM); (found: C, 66.97; H, 3.85; N, 18.41. $C_{17}H_{12}N_4O_2$ requires C, 67.10; H, 3.97; N, 18.41%); λ_{max}(DCM)/nm 246 (log ε 4.30), 280 inf (3.54), 292 (4.66), 304 (4.74), 323 (4.07), 338 (4.04), 351 (3.76), 391 (3.57); ν_{max}/cm^{-1} 3024w (aryl C-H), 2978w and 2835w (alkyl C-H), 2239w (C≡N), 1628w, 1609w, 1587w, 1494s, 1470m, 1452m, 1437m, 1389m, 1315w, 1283w, 1256w, 1233s, 1209w, 1157w, 1123w, 1092m, 1026w, 1016w, 995m, 862m, 851m, 789w, 762s, 750s; δ_H(500 MHz; $CDCl_3$) 8.55 (1H, d, *J* 8.5, Ar *H*), 8.01 (1H, d, *J* 8.5, Ar *H*), 7.99 (1H, s, Ar *H*), 7.65 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.54 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.42 (1H, s, Ar *H*), 4.14 (3H, s, OCH_3), 4.06 (3H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) 153.4 (s), 152.6 (s), 145.9 (s), 144.2 (s), 137.1 (s), 127.4 (s), 127.1 (d), 123.7 (d), 120.3 (s), 120.1 (d), 114.2 (s), 112.5 (s),

112.4 (d), 109.5 (d), 103.6 (d), 56.8 (q, O*C*H$_3$), 56.5 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 306 (MH$^+$+1, 7%), 305 (MH$^+$, 100), 304 (M$^+$, 99).

*7.6.4.11 2,3-Dimethoxybenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**229**) (Method F).* Similar treatment of 3-(2-bromophenyl)-4-imino-6,7-dimethoxy-3,4-dihydroquinazoline-2-carbonitrile (**236**) (76.8 mg, 0.20 mmol) with Pd[3,5-(F$_3$C)$_2$C$_6$H$_3$]$_3$ (42.4 mg, 10 mol%), BINAP (6.2 mg, 5 mol%) and K$_2$CO$_3$ (82.8 mg, 0.60 mmol) in dry PhMe gave the *title compound* **229** (58.6 mg, 96%) as yellow fibres, mp (hotstage) 284-285 ^{o}C (*n*-pentane/DCM, 80:20), R_f 0.20 (DCM); identical to that described above.

*7.6.4.12 1-Methylbenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**240**) (Method F).* Similar treatment of 3-(2-bromophenyl)-4-imino-5-methyl-3,4-dihydroquinazoline-2-carbonitrile (**234**) (67.8 mg, 0.20 mmol) with Pd[3,5-(F$_3$C)$_2$C$_6$H$_3$]$_3$ (42.4 mg, 10 mol%), BINAP (6.2 mg, 5 mol%) and K$_2$CO$_3$ (82.8 mg, 0.60 mmol) in dry PhMe gave the *title compound* **240** (50 mg, 97%) as yellow plates, mp (hotstage) 251-251.5 ^{o}C (*n*-pentane/DCM, 80:20), mp (DSC) onset 251.5 ^{o}C, peak max. 252.5 ^{o}C; R_f 0.79 (DCM); (found: C, 74.41; H, 3.84; N, 21.55. C$_{16}$H$_{10}$N$_4$ requires C, 74.40; H, 3.90; N, 21.69%); λ_{max}(DCM)/nm 246 inf (log ε 3.75), 276 inf (4.19), 286 (4.38), 297 (4.39), 322 inf (3.55), 335 (3.55), 353 (3.49), 399 (2.82); ν_{max}/cm^{-1} 3073w (aryl C-H), 2920w and 2851w (alkyl C-H), 2241w (C≡N), 1616w, 1591w, 1516w, 1446w, 1451m, 1389w, 1383w, 1358w, 1314w, 1278m, 1231w, 1211m, 1188w, 1132m, 1038w, 1018w, 966w, 935w, 812s, 768w, 737s; δ_H(500 MHz; CDCl$_3$) 8.59 (1H, d, *J* 8.0, Ar *H*), 8.08 (1H, d, *J* 8.0, Ar *H*), 7.90 (1H, d, *J* 8.0, Ar *H*), 7.72 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.67-7.62 (2H, m, Ar *H*), 7.58 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 3.23 (3H, s, C*H*$_3$); δ_C(125 MHz; CDCl$_3$) 146.4 (s), 144.2 (s), 142.3 (s), 138.8 (s), 133.3 (d), 131.3 (d), 127.1 (d), 126.7 (d), 126.5 (s), 124.3 (d), 122.2 (s), 120.8 (d), 118.9 (s), 112.3 (s, C≡N), 112.2 (d), 23.5 (q, *C*H$_3$); *m*/*z* (MALDI-TOF) 260 (MH$^+$+1, 7%), 259 (MH$^+$, 100), 258 (M$^+$, 48).

*7.6.4.13 3-Methoxybenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**241**) (Method F).* Similar treatment of 3-(2-bromophenyl)-4-imino-7-methoxy-3,4-dihydroquinazoline-2-carbonitrile (**235**) (71.0 mg, 0.20 mmol) with Pd[3,5-(F$_3$C)$_2$C$_6$H$_3$]$_3$ (42.4 mg, 10 mol%), BINAP (6.2 mg, 5 mol%) and K$_2$CO$_3$ (82.8 mg, 0.60 mmol) in dry PhMe gave the *title compound* **241** (49.8 mg, 91%) as yellow plates, mp (hotstage) 221-222 ^{o}C (*n*-pentane/DCM, 80:20), mp (DSC) onset 221.3 ^{o}C, peak max. 222.3 ^{o}C; R_f 0.38 (DCM); (found: C, 69.93; H, 3.66; N, 20.37. C$_{16}$H$_{10}$N$_4$O requires C, 70.06; H, 3.68; N, 20.43%);

λ_{max}(DCM)/nm 242 (log ε 4.42), 279 inf (4.66), 290 (4.77), 300 (4.77), 320 (4.04), 333 (3.93), 351 (3.58), 404 (3.28); ν_{max}/cm^{-1} 3057w (aryl C-H), 2241w (C≡N), 1628m, 1611m, 1587m, 1558w, 1521w, 1483s, 1452s, 1429w, 1385s, 1352w, 1318m, 1271m, 1227s, 1203w, 1163m, 1128w, 1098m, 1020m, 1011w, 955m, 843s, 837m, 829m, 764s, 746s; δ_H(500 MHz; $CDCl_3$) 8.58 (1H, d, *J* 8.5, Ar *H*), 8.52 (1H, d, *J* 8.5, Ar *H*), 7.99 (1H, d, *J* 8.5, Ar *H*), 7.63 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.55 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.43 (1H, d, *J* 2.0, Ar *H*), 7.40 (1H, *J* 7.0, 2.0, Ar H), 3.99 (3H, s, OC*H*$_3$); δ_C(125 MHz; $CDCl_3$) 162.9 (s), 146.2 (s), 144.2 (s), 143.1 (s), 127.3 (s), 127.1 (d), 125.7 (d), 123.8 (d), 122.6 (s), 121.3 (d), 120.2 (d), 113.3 (s), 112.3 (d), 112.1 (s, C≡N), 110.1 (d), 55.9 (q, O*C*H$_3$); *m*/*z* (MALDI-TOF) 275 (MH$^+$, 22%), 274 (M$^+$, 100).

*7.6.4.14 2-Chlorobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**242**) (Method F).* Similar treatment of 3-(2-bromophenyl)-6-chloro-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**238**) (72.0 mg, 0.20 mmol) with Pd[3,5-$(F_3C)_2C_6H_3]_3$ (42.4 mg, 10 mol%), BINAP (6.2 mg, 5 mol%) and K_2CO_3 (82.8 mg, 0.60 mmol) in dry PhMe gave the *title compound* **242** (52.5 mg, 94%) as yellow plates, mp (hotstage) 246-248 ^oC (*n*-pentane/DCM, 80:20), mp (DSC) onset 246.6 ^oC, peak max. 251.0 ^oC; R_f 0.62 (DCM); (found: C, 64.63; H, 2.46; N, 19.99. $C_{15}H_7ClN_4$ requires C, 64.65; H, 2.53; N, 20.10%); λ_{max}(DCM)/nm 240 inf (log ε 4.42), 281 inf (4.57), 291 (4.68), 302 (4.68), 321 (4.03), 335 (4.00), 350 (3.82), 393 inf (3.33); ν_{max}/cm^{-1} 3063w (aryl C-H), 2237w (C≡N), 1622w, 1607w, 1585m, 1547w, 1466w, 1450m, 1427m, 1383m, 1323w, 1308w, 1277w, 1246m, 1225w, 1207w, 1136w, 1109m, 1076w, 1013w, 934w, 883w, 878w, 843m, 827m, 767m, 758m, 743s, 731s; δ_H(500 MHz; $CDCl_3$) 8.71 (1H, d, *J* 2.0, Ar *H*), 8.57 (1H, d, *J* 8.5, Ar *H*), 8.06 (1H, d, *J* 8.0, Ar *H*), 8.00 (1H, d, *J* 8.5, Ar *H*), 7.80 (1H, dd, *J* 8.5, 2.3, Ar *H*), 7.69 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.62 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*); δ_C(125 MHz; $CDCl_3$) one C (s) resonance missing, 144.8 (s), 144.0 (s), 139.5 (s), 137.6 (s), 132.9 (d), 130.7 (d), 127.4 (d), 124.8 (d), 124.0 (d), 122.2 (s), 121.0 (s), 120.8 (d), 112.5 (d), 112.0 (s, C≡N); *m*/*z* (MALDI-TOF) 281 (MH$^+$+2, 23%), 280 (MH$^+$+1, 47), 279 (MH$^+$, 100), 278 (M$^+$, 93).

*7.6.4.15 3-Chlorobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**243**) (Method F).* Similar treatment of 3-(2-bromophenyl)-7-chloro-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**237**) (72.0 mg, 0.20 mmol) with Pd[3,5-$(F_3C)_2C_6H_3]_3$ (42.4 mg, 10 mol%), BINAP (6.2 mg, 5 mol%) and K_2CO_3 (82.8 mg, 0.60 mmol) in dry PhMe gave the *title compound* **243** (51.0 mg, 92%) as yellow plates, mp (hotstage) 240.5-242 ^oC

(*n*-pentane/DCM, 80:20), mp (DSC) onset 241.3 °C, peak max. 242.3 °C; R_f 0.52 (DCM); (found: C, 64.57; H, 2.43; N, 19.99. $C_{15}H_7ClN_4$ requires C, 64.65; H, 2.53; N, 20.10%); λ_{max}(DCM)/nm 249 inf (4.14), 279 inf (4.55), 289 (4.66), 300 (4.66), 320 (4.01), 335 (3.90), 352 inf (3.54), 395 (3.16); ν_{max}/cm^{-1} 3034w (aryl C-H), 2243w (C≡N), 1620w, 1585m, 1521w, 1449s, 1427m, 1389m, 1315m, 1278w, 1259w, 1238w, 1211m, 1205m, 1132m, 1124w, 1072m, 1018w, 1015w, 928m, 850w, 829m, 765s, 762s, 742s, 718m; δ_H(500 MHz; $CDCl_3$) 8.64 (1H, d, *J* 8.5, Ar *H*), 8.55 (1H, d, *J* 8.5, Ar *H*), 8.05-8.04 (1H, m, Ar *H*), 8.02 (1H, br s, Ar *H*), 7.78 (1H, dd, *J* 8.5, 2.0, Ar *H*), 7.68 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.60 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*); δ_C(125 MHz; $CDCl_3$) 145.4 (s), 144.1 (s), 141.8 (s), 138.5 (s), 131.7 (d), 128.7 (d), 127.4 (d), 127.3 (s), 125.6 (d), 124.7 (d), 123.2 (s), 120.7 (d), 118.3 (s), 112.4 (d), 111.9 (s, C≡N); *m*/*z* (MALDI-TOF) 280 (MH^++1, 24%), 279 (MH^+, 100), 278 (M^+, 59), 130 (20).

*7.6.4.16 2-Bromobenzo[4,5]imidazo[1,2-c]quinazoline-6-carbonitrile (**244**) (Method F).* Similar treatment of 6-bromo-3-(2-bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**239**) (80.8 mg, 0.20 mmol) with Pd[3,5-$(F_3C)_2C_6H_3]_3$ (42.4 mg, 10 mol%), BINAP (6.2 mg, 5 mol%) and K_2CO_3 (82.8 mg, 0.60 mmol) in dry PhMe gave the *title compound* **244** (58.1 mg, 90%) as yellow plates, mp (hotstage) 262-264 °C (*n*-pentane/DCM, 80:20), mp (DSC) onset 263.1 °C, peak max. 264.6 °C; R_f 0.66 (DCM); (found: C, 55.64; H, 2.11; N, 17.22. $C_{15}H_7BrN_4$ requires C, 55.75; H, 2.18; N, 17.34%); λ_{max}(DCM)/nm 241 inf (log ε 4.22), 283 inf (4.36), 292 (4.48), 303 (4.47), 321 inf (3.85), 336 (3.80), 351 (3.63), 401 (3.00); ν_{max}/cm^{-1} 3084w (aryl C-H), 2245w (C≡N), 1622w, 1603w, 1582m, 1541w, 1481w, 1462w, 1445s, 1423m, 1331m, 1319w, 1304w, 1279w, 1244w, 1202m, 1134w, 1103w, 1067m, 1017w, 930w, 893w, 879w, 835s, 827m, 766s, 760s, 745s, 739s; δ_H(500 MHz; $CDCl_3$) 8.89 (1H, d, *J* 2.0, Ar *H*), 8.58 (1H, d, *J* 8.5, Ar *H*), 8.06 (1H, d, *J* 8.5, Ar *H*), 7.96 (1H, dd, *J* 8.8, 2.3, Ar *H*), 7.92 (1H, d, *J* 8.5, Ar *H*), 7.70 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*), 7.62 (1H, ddd, *J* 7.8, 7.8, 1.0, Ar *H*); δ_C(125 MHz; $CDCl_3$) one C (s) resonance missing, 144.6 (s), 144.0 (s), 139.8 (s), 135.7 (d), 130.7 (d), 127.4 (d), 127.1 (d), 125.8 (s), 124.8 (d), 122.3 (s), 121.1 (s), 120.8 (d), 112.5 (d), 112.0 (s, C≡N); *m*/*z* (MALDI-TOF) 325 (MH^++2, 100%), 323 (MH^+, 100), 244 (4).

7.7 X-Ray crystallographic studies

7.7.1 General Procedure and Instrumentation. Data were collected on an Oxford-Diffraction Supernova diffractometer, equipped with a CCD area detector utilizing either Cu Kα radiation (λ = 1.5418 Å) for compounds **79**, **105**, **144**, **169**, **178** and **187** or Mo Kα radiation (λ = 0.71073 Å) for compound **80**, **145** and **193**. A suitable crystal was attached to glass fibers using paratone-N oil and transferred to a goniostat where they were cooled for data collection. Unit cell dimensions were determined and refined by using 6074 ($3.02 \leq \theta \leq 28.90^{\circ}$), 6948 ($5.71 \leq \theta \leq 72.76°$), 2290 ($3.39 \leq \theta \leq 66.98°$), 3262 ($8.50 \leq \theta \leq 66.87°$), 2301 ($3.12 \leq \theta \leq 28.88°$), 2161 ($3.45 \leq \theta \leq 66.97^{\circ}$), 2247 ($3.33 \leq \theta \leq 71.89^{\circ}$), 2367 ($4.97 \leq \theta \leq 66.97^{\circ}$) and 2113 ($2.98 \leq \theta \leq 2\ 8.90^{\circ}$) reflections for compounds **80**, **79**, **105**, **144**, **145**, **169**, **178**, **187** and **193** respectively. Empirical absorption corrections (multi-scan based on symmetry-related measurements) were applied using CrysAlis RED software.[428] The structure was solved by direct methods using SIR92[429] and refined on F^2 using full-matrix least squares using SHELXL97.[430] Software packages used: CrysAlis CCD[428] for data collection, CrysAlis RED[428] for cell refinement and data reduction, WINGX for geometric calculations,[431] and DIAMOND[432] for molecular graphics. The non-H atoms were treated anisotropically. The hydrogen atom attached to N3 was located on a difference Fourier map, whereas all other hydrogen atoms were placed in calculated, ideal positions and refined as riding on their respective carbon atoms.

7.7.2 Crystal Refinement Data

*7.7.2.1 4-Imino-3-phenyl-3,4-dihydroquinazo-line-2-carbonitrile (**80**)*: $C_{15}H_{10}N_4$, M = 246.27, orthorhombic, space group *Pbca*, a = 16.3251(4), b = 6.7320(2), c = 21.6139(5) Å, V = 2375.4(2) Å^3, Z = 8, T = 100(2) K, ρ_{calcd} = 1.377 g cm^{-3}, $2\theta_{max}$ = 53. Refinement of 176

parameters on 2460 independent reflections out of 10391 measured reflections (R_{int} = 0.0236) led to R_1 = 0.0363 [I>2s(I)], wR_2 = 0.1119 (all data), and S = 1.080 with the largest difference peak and hole of 0.193 and -0.206 e^{-3}, respectively.

7.7.2.2 2-[2-(2-Aminophenyl)-5-imino-1-phenyl-1H-imidazol-4(5H)-ylidene]malononitrile ***(105)***: $C_{18}H_{12}N_6$, M = 312.34, Monoclinic, space group *P 2/n*, a = 10.3562(5) Å, b = 5.6532(3) Å, c = 26.1430(13) Å, α = 90°, β = 94.754(4)°, γ = 90°, V = 1525.29(13) $Å^3$, Z = 4, T = 100(2) K, ρ_{calcd} = 1.360 g cm^{-3}, $2\theta_{max}$ = 67. Refinement of 230 parameters on 2705 independent reflections out of 5184 measured reflections (R_{int} = 0.0374) led to R_1 = 0.0509 [I > 2s(I)], wR_2 = 0.1480 (all data), and S = 1.013 with the largest difference peak and hole of 0.294 and -0.328 e^{-3}, respectively.

7.7.2.3 4-(Phenylamino)quinazoline-2-carbonitrile ***(79)***: $C_{15}H_9N_4$, M = 245.26, Monoclinic, space group *P* $2_1/c$, a = 7.1177(2) Å, b = 21.5777(5) Å, c = 30.8365(7) Å, α = 90°, β = 92.281(2)°, γ = 90°, V = 4732.2(2) $Å^3$, Z = 16, T = 100(2) K, ρ_{calcd} = 1.377 g cm^{-3}, $2\theta_{max}$ = 67. Refinement of 685 parameters on 8433 independent reflections out of 16808 measured reflections (R_{int} = 0.0249) led to R_1 = 0.0450 [I > 2s(I)], wR_2 = 0.1445 (all data), and S = 1.083 with the largest difference peak and hole of 0.704 and -0.283 e^{-3}, respectively.

7.7.2.4 (Z)-2-[3-(Phenylimino)imidazo[1,2-c]quinazolin-2(3H)-ylidene]malononitrile ***(144)***: $C_{19}H_{10}N_6$, M = 322.33, Triclinic, space group *P -1*, a = 8.2982(8) Å, b = 12.5334(11) Å, c = 15.6588(15) Å, α = 93.241(8)°, β = 98.358(8)°, γ = 105.279(8)°, V = 1546.7(3) $Å^3$, Z = 4, T = 100(2) K, ρ_{calcd}= 1.384 g cm^{-3}, $2\theta_{max}$ = 67. Refinement of 452 parameters on 5338 independent reflections out of 9122 measured reflections (R_{int} = 0.0648) led to R_1 = 0.0937 [I > 2s(I)], wR_2 = 0.3269 (all data), and S = 0.817 with the largest difference peak and hole of 0.479 and -0.691 e^{-3}, respectively.

7.7.2.5 (2-[(3-Phenylquinazolin-4(3H)-ylidene)amino]ethene-1,1,2-tricarbonitrile ***(145)***: $C_{19}H_{10}N_6$, *M* = 322.33, Monoclinic, space group *P 21/c*, *a* = 17.5482(9) Å, *b* = 8.6967(4) Å, *c* = 10.4977(7) Å, α = 90°, β = 104.070(6)°, γ = 90°, *V* = 1554.01(15) Å^3, *Z* = 4, T = 100(2) K, ρ_{calcd} = 1.377 g cm^{-3}, $2\theta_{max}$ = 25. Refinement of 262 parameters on 2737 independent reflections out of 10007 measured reflections (R_{int} = 0.0300) led to R_1 = 0.0740 [I > 2s(I)], wR_2 = 0.1889 (all data), and *S* = 1.077 with the largest difference peak and hole of 0.943 and -0.891 e^{-3}, respectively.

7.7.2.6 2-[5-Imino-1,2-diphenyl-1H-imidazol-4(5H)-ylidene]malononitrile ***(169)***: $C_{18}H_{11}N_5$, *M* = 297.32, *orthorhombic*, space group *P b c a*, *a* = 6.7212(5) Å, *b* = 16.922(2) Å, c = 25.652(3) Å, α = 90°, β = 90°, γ = 90°, *V* = 2917.5(5) Å^3, *Z* = 8, T = 100(2) K, ρ_{calcd} = 1.354 g cm^{-3}, $2\theta_{max}$ = 67. Refinement of 215 parameters on 2584 independent reflections out of 6039 measured reflections (R_{int} = 0.0374) led to R_1 = 0.0541 (I>2s(I)), wR_2 = 0.1703 (all data), and *S* = 1.082 with the largest difference peak and hole of 0.324 and -0.263 e^{-3}, respectively.

7.7.2.7 (Z)-2-[2-Phenyl-4-(phenylimino)-1H-imidazol-5(4H)-ylidene]malononitrile ***(178)***: $C_{18}H_{11}N_5$, *M* = 297.32, *orthorhombic*, space group *P b c n*, *a* = 23.5138(7) Å, *b* = 13.2286(4) Å, c = 9.4729(3) Å, α = 90°, β = 90°, γ = 90°, *V* = 2946.59(16) Å^3, *Z* = 8, T = 100(2) K, ρ_{calcd} = 1.340 g cm^{-3}, $2\theta_{max}$ = 67. Refinement of 212 parameters on 2632 independent reflections out of 6161 measured reflections (R_{int}=0.0222) led to R_1 = 0.0359 (I>2s(I)), wR_2 = 0.0977 (all data), and *S* = 1.099 with the largest difference peak and hole of 0.211 and -0.186 e^{-3}, respectively.

7.7.2.8 (Z)-2-[1-Methyl-2-phenyl-4-(phenylimino)-1H-imidazol-5(4H)-ylidene]malononitrile ***(187)***: $C_{19}H_{13}N_5$, *M* = 311.34, *monoclinic*, space group *P 2/c*, *a* = 18.0008(18) Å, *b* = 12.1839(12) Å, c = 14.6705(19) Å, α = 90°, β = 108.737(12)°, γ = 90°, *V* = 3047.0(6) Å^3, *Z* = 8, T = 100(2) K, ρ_{calcd} = 1.357 g cm^{-3}, $2\theta_{max}$ = 67. Refinement of 217 parameters on 2688 independent reflections out of 5111 measured reflections (R_{int} = 0.0180) led to R_1 = 0.0538

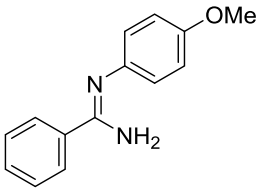
(I>2s(I)), wR_2 = 0.1536 (all data), and S = 1.041 with the largest difference peak and hole of 0.394 and -0.296 e^{-3}, respectively.

7.7.2.9 2-Phenyl-6-(phenylamino)pyrimidine-4,5-dicarbonitrile ***(193):*** $C_{18}H_{11}N_5$, M = 297.32, *monoclinic*, space group $P\ 2_1/c$, a = 8.5353(6) Å, b = 14.8828(10) Å, c = 11.7854 (8) Å, α = 90°, β = 104.911(7)°, γ = 90°, V = 1446.68(17) $Å^3$, Z = 4, T = 100(2) K, ρ_{calcd} = 1.365 g cm^{-3}, $2\theta_{max}$ = 25. Refinement of 211 parameters on 2540 independent reflections out of 5481 measured reflections (R_{int} = 0.0290) led to R_1 = 0.0432 (I>2s(I)), wR_2 = 0.1153 (all data), and S = 1.066 with the largest difference peak and hole of 0.197 and -0.209 e^{-3}, respectively.

Crystallographic data for compounds **80**, **79**, **105**, **144**, **145**, **169**, **178**, **187** and **193** have been deposited with the Cambridge Crystallographic Data Centre with deposit numbers CCDC-952956, CCDC-1402622, CCDC-1061767, CCDC-1061766, CCDC-1061768, CCDC-943799, CCDC-943800, CCDC-943801 and CCDC-943798 respectively. This data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +441223336033; or e-mail: deposit@ccdc.cam.ac.uk).

LIST OF COMPOUNDS PREPARED

Compound number in bold followed by page number where compound appears in Chapter 7 (Experimental Section).



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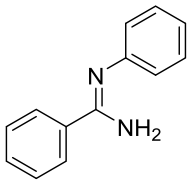

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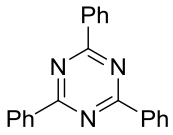

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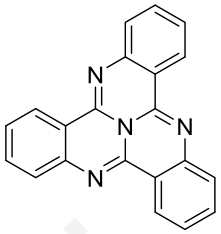

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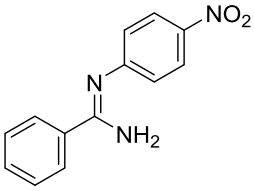

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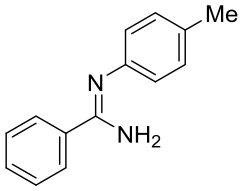

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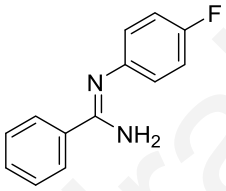

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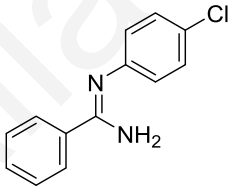

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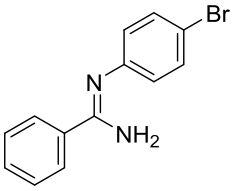

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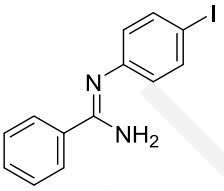

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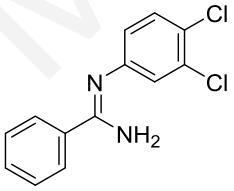

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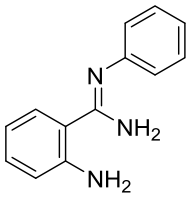

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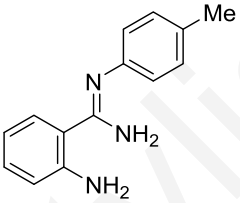

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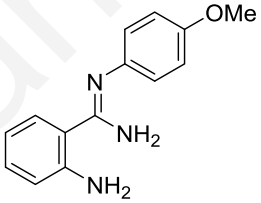

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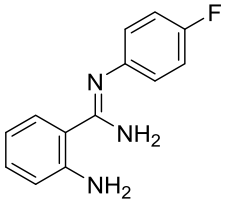

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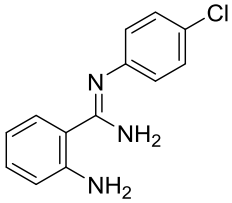

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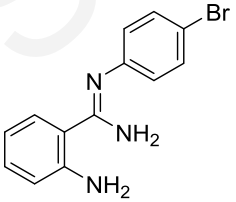

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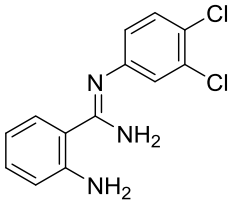

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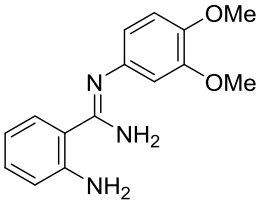

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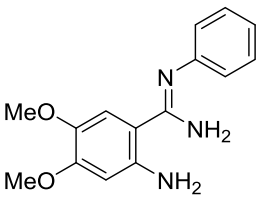

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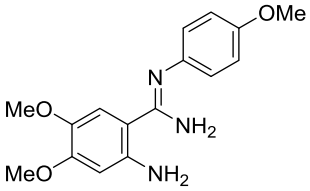

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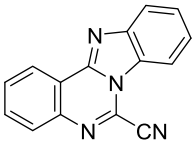

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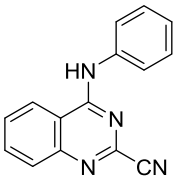

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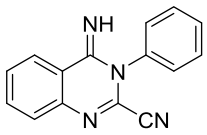

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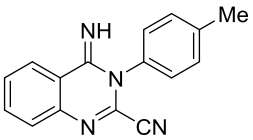

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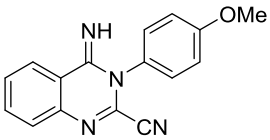

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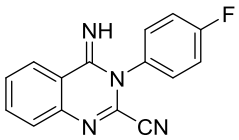

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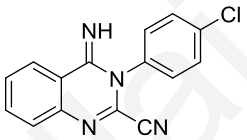

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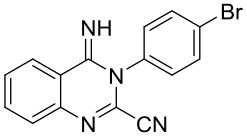

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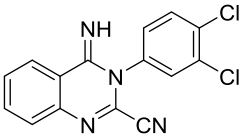

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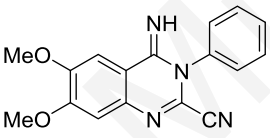

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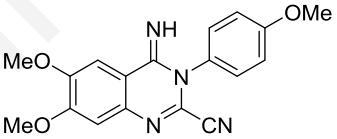

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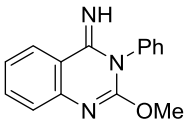

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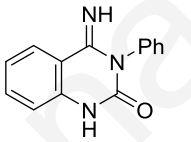

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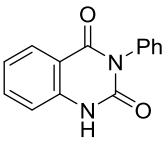

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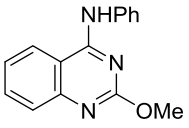

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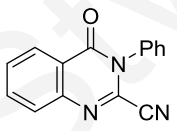

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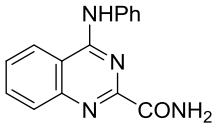

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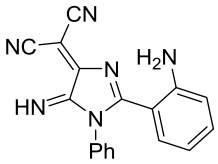

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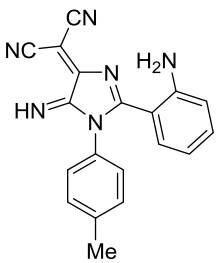

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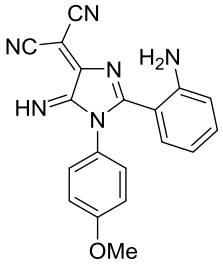

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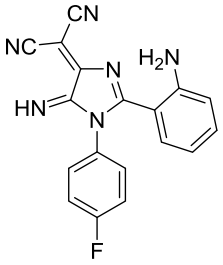

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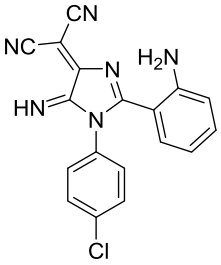

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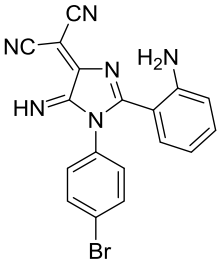

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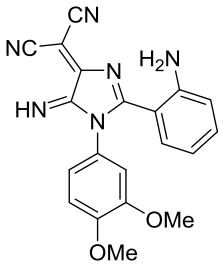

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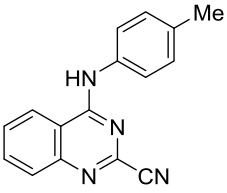

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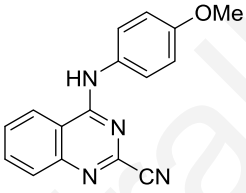

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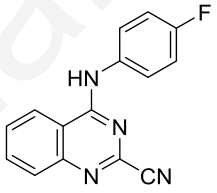

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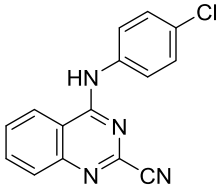

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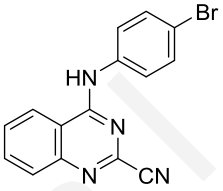

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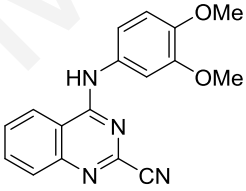

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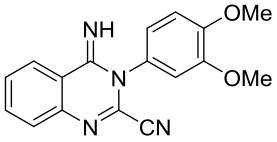

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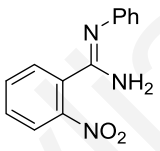

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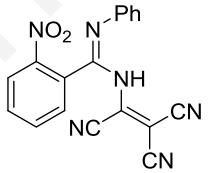

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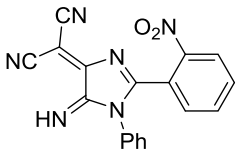

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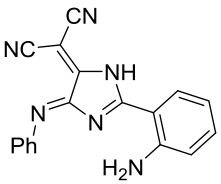

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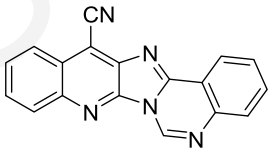

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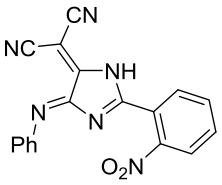

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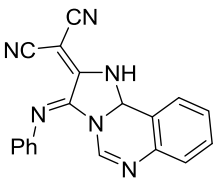

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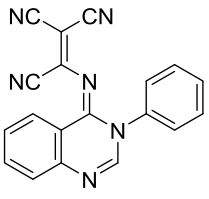

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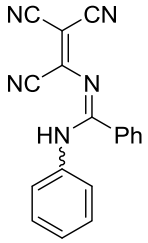

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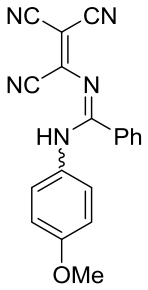

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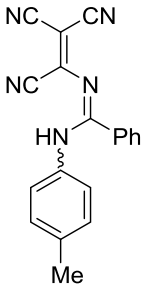

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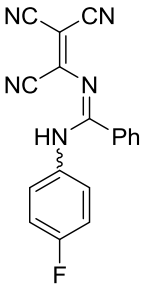

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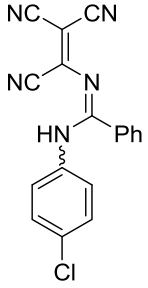

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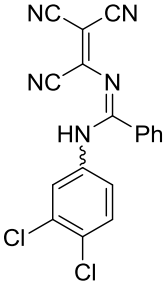

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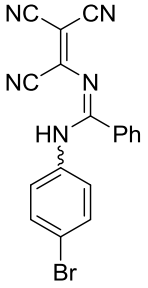

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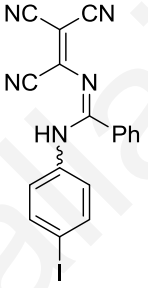

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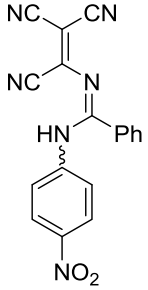

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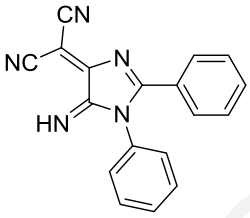

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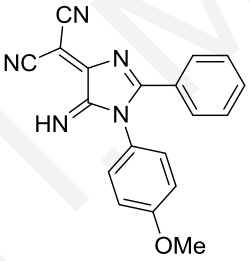

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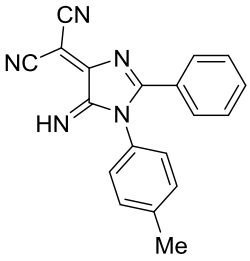

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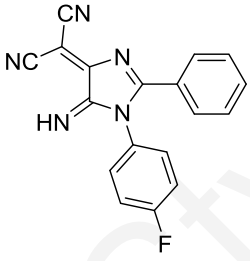

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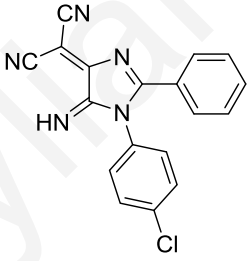

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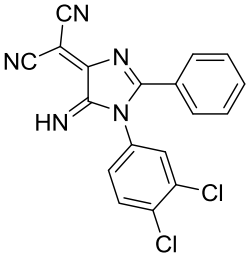

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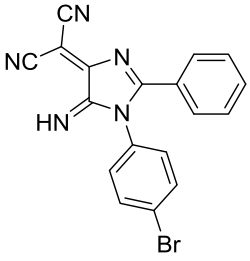

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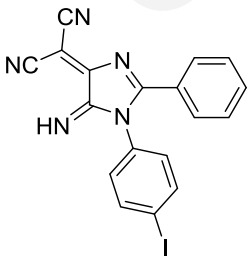

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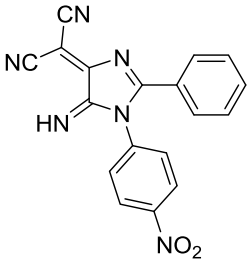

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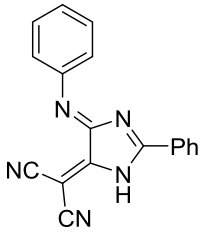

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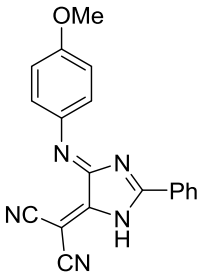

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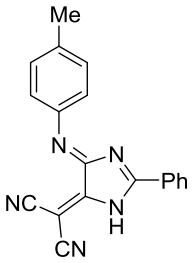

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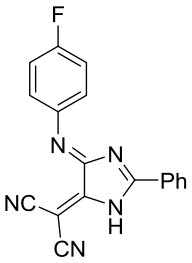

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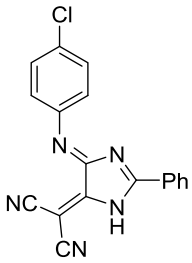

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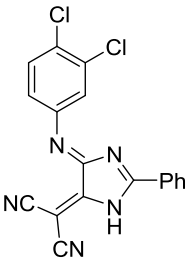

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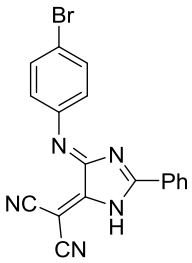

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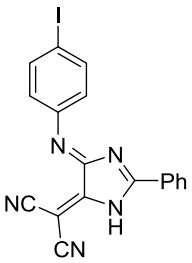

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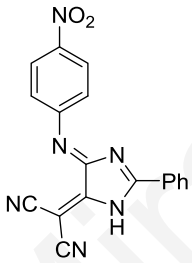

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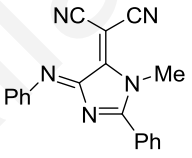

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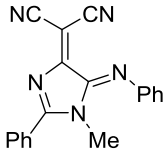

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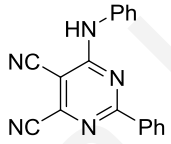

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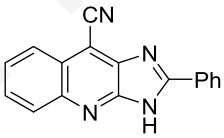

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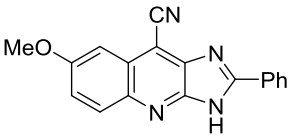

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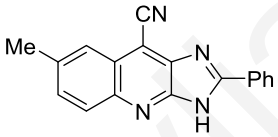

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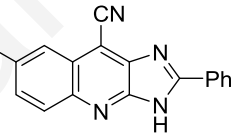

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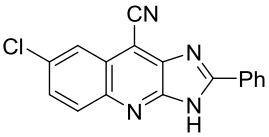

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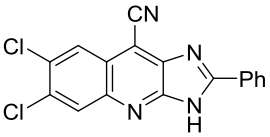

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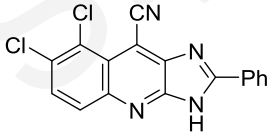

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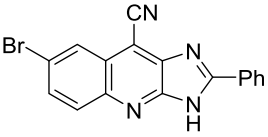

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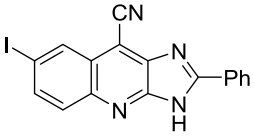

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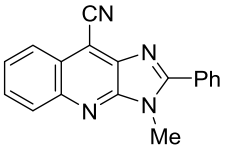

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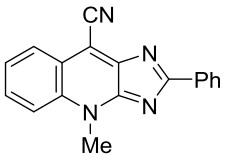

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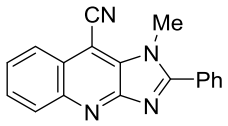

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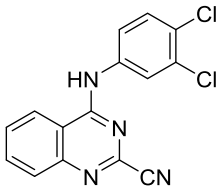

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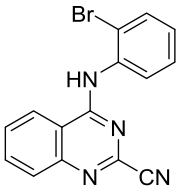

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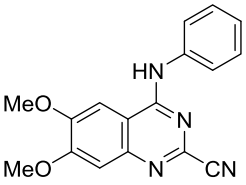

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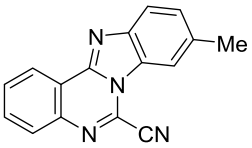

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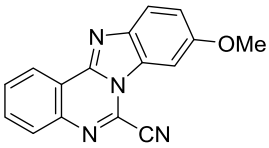

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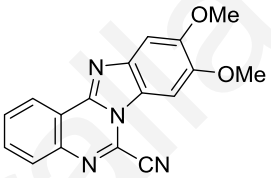

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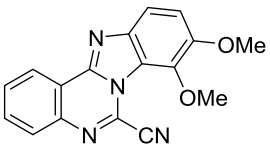

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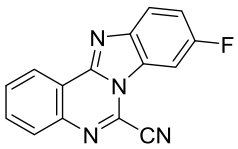

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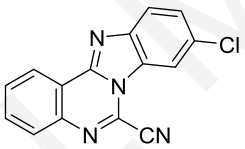

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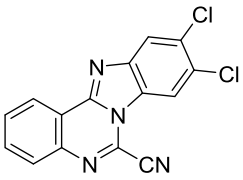

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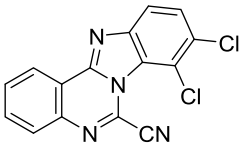

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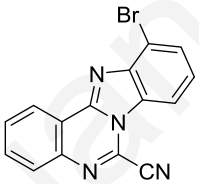

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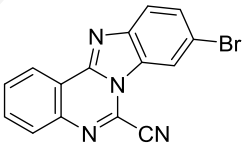

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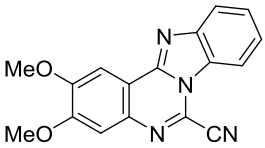

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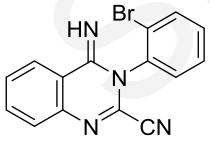

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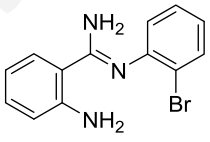

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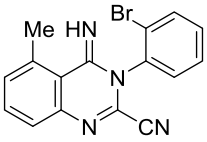

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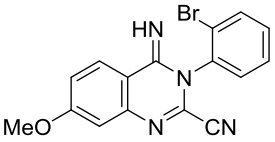

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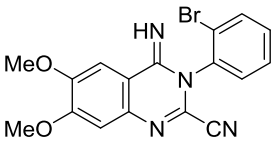

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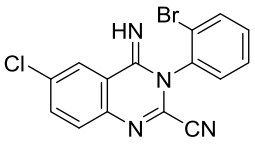

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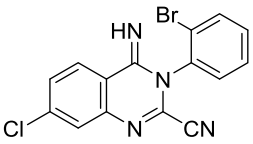

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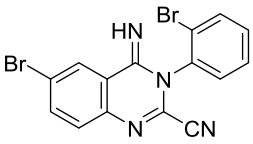

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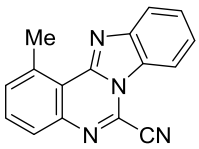

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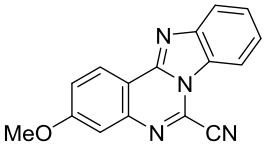

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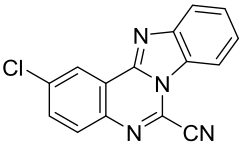

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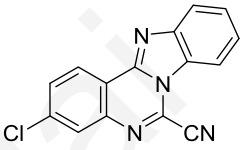

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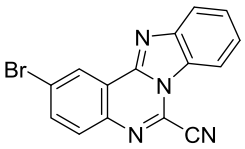

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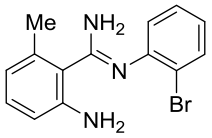

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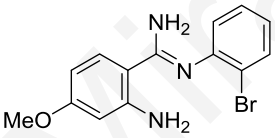

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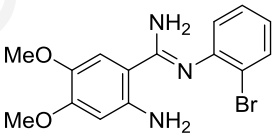

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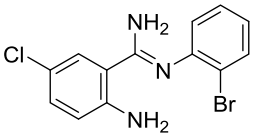

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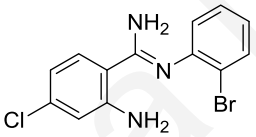

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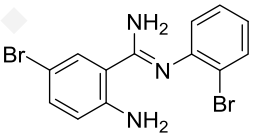

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