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Synthesis, Reactions, Mechanisms and Structure

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Foreword

Heterocycles form a fundamental basis for the development of pharmaceutical and agricultural products with wide applications. In this book the author describes the synthesis, and the chemical properties of an important class of heterocyclic chemistry, the quinoxalines.

Chapter 1 describes some properties of the Quinoxaline–As a Parent Heterocycle.

Chapter 2 covers recent advances in the Synthesis of Quinoxalines involving the methods based on the (a) condensation of 1,2-diaminobenzenes and derivatives with various two-carbon unit suppliers, (b) condensation of *o*-benzoquinone diimines and diimides with various two-carbon unit suppliers, (c) condensation of *N,N*-dimethyl(dibenzyl)ethylenediamine with 1,2- and 1,4-dihydroxybenzenes, (d) synthesis of quinoxalines from aniline and its derivatives, (e) synthesis of quinoxalines from heterocyclic systems and (f) synthesis of quinoxalines based on the carbocyclic system.

From the data presented in this chapter many original and interesting methods recently appeared for the synthesis of quinoxalines, which are difficult to obtain or in general are unobtainable. These new methods by Kaufmann, Tanimori, Kalinski and Shaabani are based on the reactions of a wide variety of compounds that deserve further attention.

Chapter 3 describes two methods of the Synthesis of Pyrrolo[l,2-*a*]quinoxalines based both on quinoxalines and pyrroles. Chapter 4 captures the Synthesis of Imidazo[1,5-*a*]- and Imidazo[1,2-*a*]quinoxalines. Chapter 5 discusses the Synthesis of Quinoxaline Macrocycles through (a) introduction of the quinoxaline system into macrocycles, (b) the closing of 1,n-bis(quinoxalin-1-yl)alkanes and (c) from both resorcin[4]arenes and quinoxalines. Chapter 6 demonstrates all known Rearrangements of Quinoxalin(on)es in the Synthesis of Benzimidazol(on)es and the interesting new rearrangements discovered by Mamedov, the author of this book, comprising (a) the acid catalysed conversion of "any of the spiro-derivatives of 1,2,3,4-tetrahydrtinquinoxalin-3-one with at least one mobile hydrogen atom in their spiro-forming component into benzimidazole derivative with the spiro-forming

component at position 2" and (b) the acid catalyzed rearrangement of "any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one without any mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazolone derivative with the spiro-forming component at position 1".

Henk van der Plas

Preface

The book gives equal weight to each of the fundamental aspects of quinoxaline chemistry: synthesis, reactions, mechanisms, structure, properties, and uses. The first four chapters present a survey of the developments in quinoxaline chemistry since the publication of the monograph on "Condensed Pyrazines" by Cheeseman and Cookson in 1979. These chapters give a comprehensive coverage of the important quinoxaline-containing ring systems such as thiazolo[3,4-*a*]-, pyrrolo [1,2-*a*]-, imidazo[1,5-*a*]-, pyrano[2,3-*b*]quinoxalines, etc. Chapter five describes many new methods for the construction of quinoxaline macrocycles, which are important because of their application to optical devices and materials. The remaining sixth chapter gives a review of all the previously known rearrangements of heterocyclic systems that lead to benzimidazole derivatives. A critical analysis of these transformations reveals novel acid-catalyzed rearrangements of quinoxalinones giving 2-heteroaryl benzimidazoles and 1-heteroaryl benzimidazolones in the presence of nucleophilic reactants. The Appendix gives X-ray crystallographic data for a number of quinoxaline derivatives (41 samples) synthesized in the Laboratory of the Chemistry of Heterocyclic Compounds of the A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences. The literature has been covered up to the end of 2013, with some additional data from publications in 2014 and 2015.

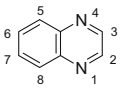
This book is the result of a collective effort. I find it necessary to acknowledge the assistance rendered by the compilers of this book Dr. Nataliya A. Zhukova, who contributed to the final version of the manuscript and also Dr. Elena A. Hafizova, Dr. Liliya V. Mustakimova and the authors of the dissertations Dr. A.A. Kalinin (in Chap. 6), Dr. D.F. Saifina (in Chap. 6), Ph.D. O.G. Isaykina (in Chap. 6), Ph.D. A. M. Murtazina (in Chap. 6) and Ph.D. V.R. Galimullina (in Chap. 6) as well as all my co-workers whose names appear in the references. My profound thanks are due to Ida H. Rapoport for her invaluable assistance in reading the first English version of the manuscript. Special acknowledgments are due to Prof. Aidar T. Gubaidullin for X-ray structural analyses of all the compounds and the X-ray structural analyses data in the Appendix. I take this opportunity to express my special thanks to the

administration and mainly to the director of the A.E. Arbuzov Institute of Organic and Physical Chemistry of the Kazan Research Center of the Russian Academy of Sciences Prof. Oleg G. Sinyashin for his interest in our research and to the Russian Foundation for Basic Research for funding (Grants No. 07-03-00613-a, 10-03-00413-a, 13-03-00123-a). The completion of this endeavor would have never been possible without the consent of Prof. Bert U.W. Maes from the University of Antwerp, whom I am extremely grateful to. And last, but no means least, I consider myself indebted to Profs. Yakov A. Levin and Ildus A. Nuretdinov of the A.E. Arbuzov Institute, Eugene A. Berdnikov of the Kazan University and Sadao Tsuboi of the Okayama University (Japan). Their dedication and skill taught me how to teach. I thank them.

Finally, I should like to thank Prof. John A. Joule from the University of Manchester, who has constantly provided me with helpful advice and criticism as regards the grammatical and editing aspects while the manuscript was in preparation. I am particularly grateful to my wife Dr. Vera L. Mamedova and my son Javid and daughter Sevil. They endured with patience and understanding the many days and nights of my staying at the Institute and the endless hours on the computer. They helped me in so many ways that are too numerous to mention.

Contents

Chapter 1
Quinoxaline–As a Parent Heterocycle



Quinoxaline

Quinoxalines are products of the spontaneous condensation of 1,2-diaminobenzene (1,2-DAB) with 1,2-dicarbonyl compounds (Scheme 1.1). The reaction was independently discovered many years ago by Hinsberg (1884) and Körner (1884).

Hinsberg suggested calling this series of compounds quinoxalines to point out their relationship with quinolines and the glyoxal—the dicarbonyl compound, from which the first representative of the series was obtained. Quinoxaline: [*Quin* (oline) + (gly)*oxal* + *ine*] (Hinsberg 1884).

Quinoxaline is a bicyclic heterocycle consisting of a benzene ring fused to a pyrazine, hence a quinoxaline is also called Benzo[*a*]pyrazine, Benzopyrazine, Benzoparadiazine, 1,4-Benzodiazine, Phenopiazine, Phenpiazine, Quinazine, and Chinoxalin. It is isomeric with quinazoline, phthalazine, and cinnoline.

quinazoline

phthalazine

cinnoline

At least five methods are currently used for the synthesis of quinoxaline **3** (R = H). The first and the principal method is based on the condensation of 1,2-DAB with two-carbon suppliers, such as glyoxal (Mirjalili and Akbari 2011; Rahmatpour 2012; Chandra Shekhar et al. 2014) (Scheme 1.2, Eq. 1), ethane-1,2-diol (Climent et al. 2012; Tang et al. 2015) (Scheme 1.2, Eq. 2), 2-aminoethanol (Tang et al. 2015) (Scheme 1.2, Eq. 3), 1,4-dioxane-2,3-diol (Venuti 1982) (Scheme 1.2, Eq. 4). The second method is based on the reaction of

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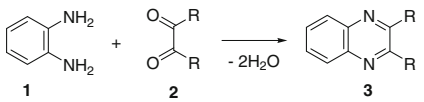
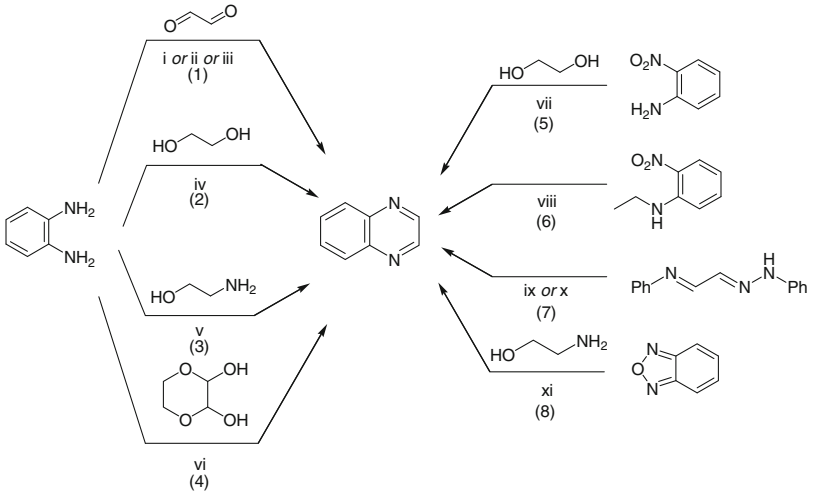


Scheme 1.1 Hinsberg and Körner synthesis of quinoxalines

2-nitroaniline with ethane-1,2-diol (Nguyen et al. 2015) (Scheme 1.2, Eq. 5). The third is the self-condensation of aniline derivatives, such as *N*-ethyl-2-nitroaniline (Walczak et al. 2015) (Scheme 1.2, Eq. 6) and *N*-[2-(2-phenylhydrazono)ethylidene]aniline (McNab 1980; Duffy et al. 2004) (Scheme 1.2, Eq. 7). The fourth method is based on the condensation of benzofurazan (benzo[*c*][1,2,5]oxadiazole) with 2-aminoethanol (Samsonov 2007) (Scheme 1.2, Eq. 8), and the fifth method is based on the redox processes of various quinoxaline derivatives (Hirasawa et al. 2008; Karki et al. 2013; Chelucci and Figus 2014; Cui et al. 2015; Jeong et al. 2015) (Scheme 1.3).

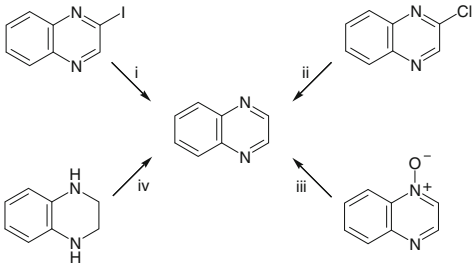
Quinoxaline **3** (R = H) is a light yellow to brown crystalline, water-soluble powder, with the molecular formula $C_8H_6N_2$ and the molar mass 130.15 g/mol. The



i = aq. HF, rt (98%)
ii = PS/$AlCl_3$ (10 mol%), EtOH, reflux (95%)
iii = nano-TiO_2, rt (88%)
iv = Au/CeO_2 (cat), diglime (91%)
v = $CsOH{\cdot}H_2O$, MS, 120 °C, 23 h, O_2 atmosphere (81%)
vi = EtOH, rt, 30 min (95%)
vii = $FeCl_3{\cdot}6H_2O$, $Na_2S{\cdot}nH_2O$, 180 °C, 24 h (67%)
viii = DMAC, toluene, K_2CO_3, 165 °C (5%)
ix = 600 °C, 0.01 Torr (35%)
x = 475 °C, 0.007 mbar, 35 min (78%)
xi = *p*-TsOH, 150-170 °C, 4 h (87%)
PS/$AlCl_3$ = Polystyrene-supported aluminium chloride
DMAC = *N,N*-Dimethylacetamide

Scheme 1.2 Current methods for the quinoxaline ring synthesis

Scheme 1.3 The use of quinoxaline derivatives in quinoxaline synthesis



i = In, water, reflux, 5.5 h (44%)
ii = $Pd(OAc)_2$, PPh_3, $NaBH_4$, TMEDA, THF (72%)
iii = $Cu(OTf)_2$, 1,2-DCE, MS 4Å, 60 °C, 12 h (81%)
iv = FeO*x*@NGr-C (cat), heptane, 15 bar air, 100 °C, 12 h (93%)
TMEDA = *N,N,N′,N′*-Tetramethylethylenediamine;
1,2-DCE = 1,2-Dichloroethane;
FeOx@NGr-C=Iron oxides surrounded by nitrogen-doped-graphene sh immobilized on carbon support

pK_a (Albert 1963) of quinoxaline in water at 20 °C is 0.60: it is therefore considerably a weaker base than the isomer diazanaphthalenes namely, cinnoline (pK_a 2.42), phtalazine (pK_a 3.47), and quinazoline (pK_a 1.95). Quinoxaline has the following physical properties: mp 29–32 °C, bp 220–223 °C, density 1.124 g/mL at 25 °C and flash point 209 °F TCC (98.33 °C) and is used mainly in organic synthesis.

The ^{1}H NMR spectrum of quinoxaline **3** (R = H) has been measured in DMSO-d_6. The signal for H(2) and H(3) of quinoxaline appears as an AA′BB′ system. The low-field half of the AA′BB′ multiplet is assigned to the protons H(5) and H(8) and the high-field half to the protons H(6) and H(7). Some broadening of the signals from protons 5 and 7 is attributed to long-range coupling with protons 2 and 3. The chemical shifts for protons 2 and 3, 5 and 8, and 6 and 7 are 8.97, 8.13–8.09, and 7.90–7.86 ppm (our result), respectively. As compared with the 8.85 (s, 2H), 8.17–8.05 (m, 2H), 7.84–7.72 (m, 2H) in $CDCl_3$ (Cui et al. 2015) and 8.83 (s, 2H), 8.10 (dd, J = 4.2, 2.3 Hz, 2H), 7.76 (dd, J = 4.2, 2.3 Hz, 2H) in $CDCl_3$ (Tang et al. 2015).

For a general introduction to quinoxaline chemistry as a parent heterocycle see Chap. II in "Condensed Pyrazines" by Cheeseman and Cookson (1979).

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Chapter 2
Synthesis of Quinoxalines

2.1 Introduction

The synthesis of quinoxalines has been intensively studied in the past, especially because of the diverse biological activities ascribed to many representatives of this class of compounds. Consequently, a large variety of synthetic methods for the synthesis of functionalized quinoxalines has been reported in literature. The first reports were published more than a century ago (Hinsberg 1884; Körner 1884), but even today chemists endeavor to create new and improved routes to these versatile compounds.

The synthesis and chemistry of quinoxalines have attracted considerable attention in the past 10 years (Porter 1984; Horton et al. 2003; Sherman et al. 2007; Patidar et al. 2011). The quinoxaline moiety is present in a large variety of physiologically active compounds, with applications varying from medicinal to agricultural. Various quinoxalines exhibit biological activities including antiviral (Westphal et al. 1977; Fonseca et al. 2004), in particular, against retroviruses such as HIV (Loriga et al. 1997; Balzarini et al. 2000; Rosner et al. 1998; Patel et al. 2000), antibacterial (Griffith et al. 1992; El-Sabbagh et al. 2009), antimicrobial (Sanna et al. 1999; Ali et al. 2000; Carta et al. 2001; Seitz et al. 2002; Badran et al. 2003; Singh et al. 2010), anti-inflammatory (Wagle et al. 2008; El-Sabbagh et al. 2009), antiprotozoal (Hui et al. 2006), anticancer (Monge et al. 1995a; Loriga et al. 1997; Lindsley et al. 2005; Carta et al. 2006), (colon cancer therapies) (LaBarbera and Skibo 2005), antidepressant (Sarges et al. 1990), antifungal (Loriga et al. 1997; El-Hawash et al. 1999; Carta et al. 2001), antituberculosis (Waring et al. 2002; Jaso et al. 2003; Ancizu et al. 2010), antimalarial (Rangisetty et al. 2001; Guillon et al. 2004), antihelmintic (Sakata et al. 1988), antidiabetic (Gupta et al. 2005), and as kinase inhibitors (Levitzki 2003; Lindsley et al. 2005). Additionally, they are used in the agricultural field as fungicides, herbicides, and insecticides (Sakata et al. 1988). Quinoxaline moieties are also present in the structure of various antibiotics such as echinomycin, levomycin, and actinoleutin, which are known to inhibit the

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growth of gram-positive bacteria and are active against various transplantable tumors (Dell et al. 1975; Kim et al. 2004). In addition, quinoxaline derivatives have found applications as dyes (Katoh et al. 2000; Sonawane and Rangnekar 2002; Jaung 2006), efficient electroluminescent materials (Thomas et al. 2005), in organic light-emitting devices (Fukuda et al. 1996; O'Brien et al. 1996; Wang et al. 2002; Kulkarni et al. 2005; Thomas et al. 2005), as fluorescent materials (Ahmad et al. 1996; Hirayama et al. 2005; Tsami et al. 2007), organic semiconductors (O'Brien et al. 1996; Dailey et al. 2001), chemically controllable switches (Crossley and Johnston 2002), building blocks for the synthesis of anion receptors (Sessler et al. 2002), cavitands (Castro et al. 2004), dehydroannulenes (Sascha and Rudiger 2004), and DNA-cleaving agents (Yamaguchi et al. 1998; Kazunobu et al. 2002; Hegedus et al. 2003; Patra et al. 2005). They also serve as useful rigid subunits in macrocyclic receptors in molecular recognition (Elwahy 2000; Mizuno et al. 2002; Kumar et al. 2008).

Besides these, quinoxalines have been identified as platforms for diversity-oriented synthesis on a solid phase (Lee et al. 1997; Zaragoza and Stephensen 1999), and they are established as inhibitors of aldose reductase (Sarges and Lyga 1988), agonists of the γ-aminobutyric acid A ($GABA_A$)/benzodiazepine receptor complex (TenBrink et al. 1994; Jacobsen et al. 1996), antagonists of the AMPA and angiotensin II receptors (Kim et al. 1993), antagonists of the selective human A3 adenosine receptor (Catarzi et al. 2005), antagonists of 5-HT3 receptors (Monge et al. 1993), growth inhibitors of *Trypanosoma cruzi* (Aguirre et al. 2004), in the growth inhibition of *Escherichia coli* (Takeda et al. 2005), in cyclooxygenase (COX-2) inhibitory activity (Singh et al. 2004), and as inhibitors of cholesteryl ester transfer protein (Jones et al. 2005; Eary et al. 2007).

A number of selected examples of biologically active quinoxalines chosen from an impressive list (Negwer and Scharnow 2001) are depicted in Fig. 2.1. Note: 'R' indicates the salt form of the drug; 'S' indicates the synonyms under which the drug is known; 'U' indicates its medicinal use; and 'P' indicates the page in reference (Negwer and Scharnow 2001).

As can be seen from the below data (Fig. 2.1) quinoxalines belong to a class of excellent heterocyclic scaffolds owing to their wide biological properties and diverse therapeutic applications in medicinal research. They are complementary in shapes and charges to numerous biomolecules they interact with, thereby resulting in increased binding affinity. The pharmacokinetic properties of drugs bearing quinoxaline cores have shown them to be relatively easy to administer either as intramuscular solutions, oral capsules, or rectal suppositories. Below (Figs. 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17 and 2.18) the recent advances in the synthesis (see papers referred to under the structures) and pharmacological diversities of quinoxaline motifs which might pave ways for novel drugs development are given.

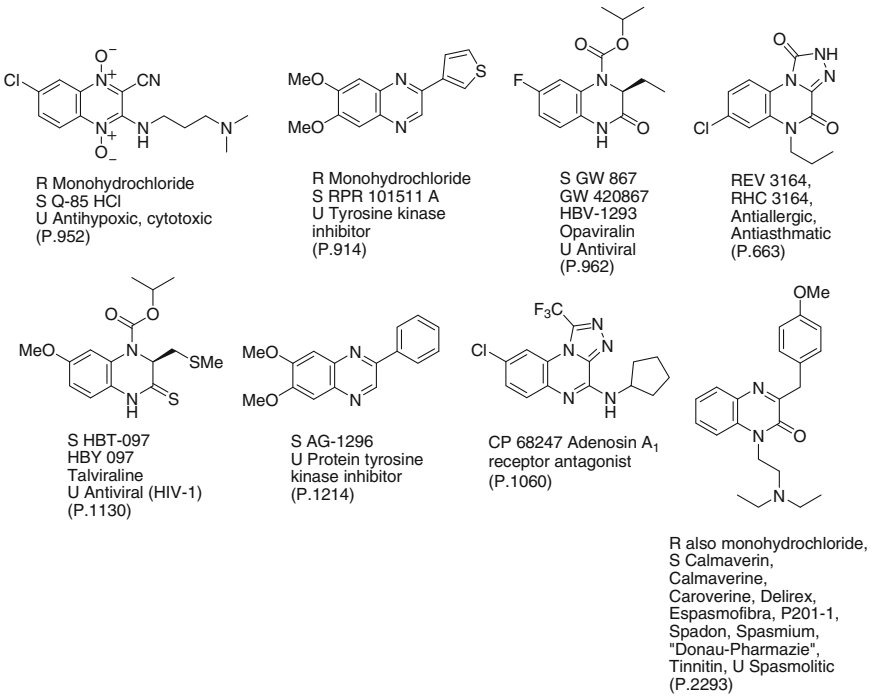
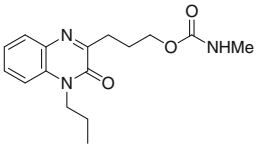
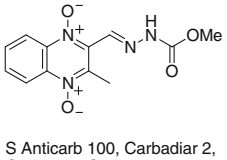


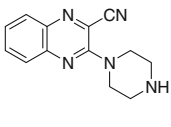
Fig. 2.1 Quinoxaline containing drugs and their synonyms



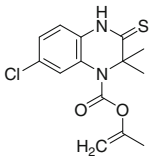
S Bamaquimast, L 004
U Anti-asthmatic
(P.1303)



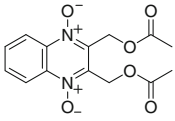
S Anticarb 100, Carbadiar 2,
Carbadox, Carbamix,
Enterodox, Enterosuis,
Fortigro, Getroxel,
GS-6244, Mecadox
U Antibacterial
(P.546)



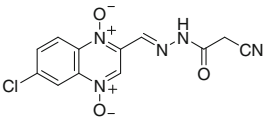
S VC 501
U Anti-emetic
(P.806)



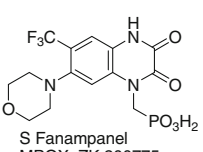
S 2720
U Antiviral
(P.942)



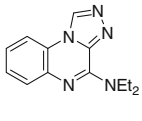
S Chinoxidin,
Chinoxydin,
Quinoxidin
U Antibacterial
(P.935)



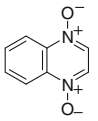
S Ciadox, Cyadox,
VUFB-11502
U Antibacterial
growth promotor
(veterinary)
(P.655)



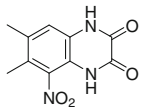
S Fanampanel
MPQX, ZK 200775
U Neuroprotectant
(AMPA receptor antagonist)
(P.944)



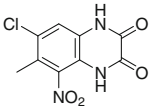
CP 41475
Antidepressant
CNS stimulant



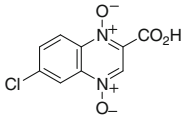
S Grofas ICI8173,
Quindoxin,
RD2579
U Growth promotor
(veterinary)
(P.237)



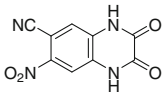
S ACEA 1328
U NMDA / glycine site
antagonist
(P.427)



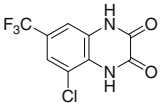
S ACEA 1416
U NMDA / glycine site
antagonist
(P.319)



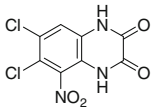
S MCD-819
U Antibiotic from
Streptomyces ambofaciens
MA2870 (P.317)
R Sodium salt (22587-19-5)



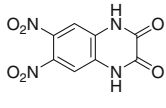
S CNQX, FG 9065
U Glutamate receptor
antagonist
(P.315)



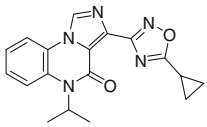
S ACEA 1011
U Glycine receptor
antagonist
(neuroprotective)
(P.315)



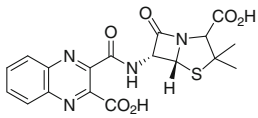
S ACEA 1021, Glystatine,
Licostinel
U NMDA receptor
antagonist
(neuroprotective) (P.233)



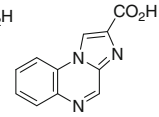
S DNQX, FG 9065
U non-DMDA receptor
antagonist
(P.234)



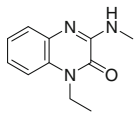
S FG 10571 NNC 14-0571
Panadiplon,
U 78875 anxiolytic
benzodiazepin receptor
partial agonist
(P.1545)



S Chinacillina, Quinacillin
R.D. 13962
U Antibiotic
(P.1535)

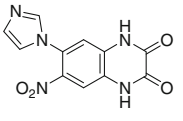


S Dazoquinast P.
Anti-allergic
(P.533)

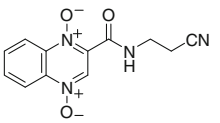


S Ataquimast,
Tinamast
U Tumor
necrosis factor
antagonist
(P.581)

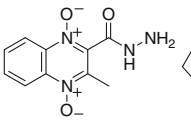
Fig. 2.1 (continued)



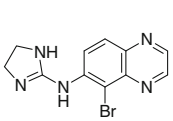
R Monohydrochloride
S YM-90K, YM-900
U Neuroprotective
(AMPA antagonist)
(P.533)



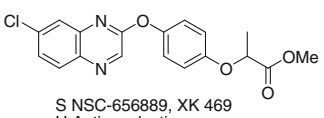
S CGA 56766 Cinoquidox
U Antibacterial
growth promotor (veterinary)
(P.800)



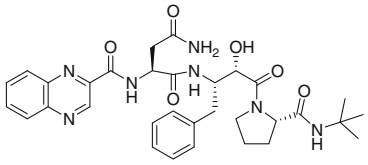
S Drazidox
U Antiseptic
(P.437)



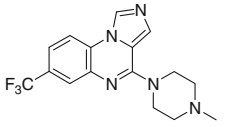
R D-Tartrate (1:2)
S AGN 190342-LF
Alphagan
Brimonidine tartratr
UK-14304-18
U Antihypertensive
Antiglaucoma agent
(α_2-adrenoceptor agonist)
(P.542)



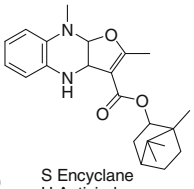
S NSC-656889, XK 469
U Antineoplastic
(P.1526)



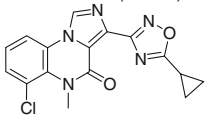
S R 87366
U Antiviral
(P.2999)



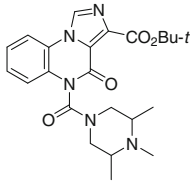
R Maleate(1:2)
S CGB 12066B
U (Serotonin-1B agonist)
(P.1393)



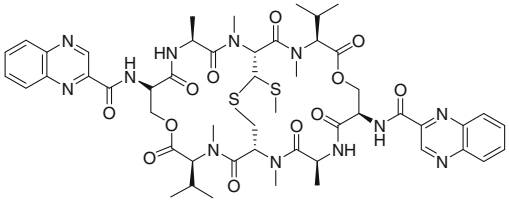
S Encyclane
U Antiviral
(P.2446)



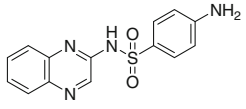
S U-80447
U Antidepressant
Anxiolytic
(P.1191)



S U 97775
U Anxiolytic
($GABA_A$ receptor ligand)
(P.2442)

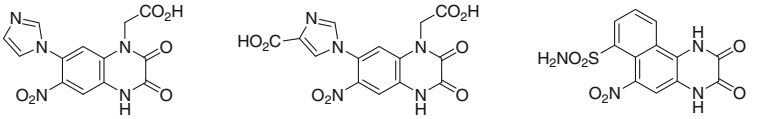


S Ehinomycin, NSC-526417, Quinomycin A
U Antineoplastic antibiotic
(P.3218)



R also monosodium salt,
S Anticox, Apokina, Avicocid,
Aviochina, Benachinossalina,
Biococcid, Biocrin S, Chinovit L,
Chinoxal, Coccidione,
Coccidioxal, Coccistop,
Coccisulfa, Compound 3-120,
Coxine 200, Deidrochin L,
Embazin, Italquina, Izochinossal,
Kinocond, Kokozigal S, Liquicox,
Med-Solvimix, Nococcin, Oxalin 100,
Quinoxal, Quinoxipra-C,
Solaquin Un Comm. Lombarda,
Solucoccid, SQX,
Sulfabenzpyrazinium,
Sulfachinossalina,
Sulfachinoxalin, Sulfox,
Sulfoxin, Sulfaquinoxaline,
Sul-Q-Nox, Sulquin,
Ursokoxalin, U Coccidiostatic
(P.916)

Fig. 2.1 (continued)

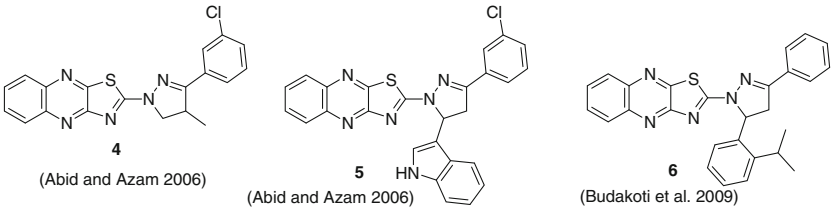


1 (YM872)
(Mattes et al. 2010)

2 (LU112313)
(Olayiwola et al. 2007)

3 (NBQX)
(Löscher et al. 1999; Olayiwola et al. 2007)

Fig. 2.2 Antibiotic and AMPA receptor antagonists containing quinoxaline core structures



4
(Abid and Azam 2006)

5
(Abid and Azam 2006)

6
(Budakoti et al. 2009)

7
(Duque-Montano et al. 2013)

8
(Lopez-Vallejo et al. 2011)

9
(Lopez-Vallejo et al. 2011)

Fig. 2.3 Some quinoxaline motifs with antiamoebic activity

Thus quinoxaline derivatives are crucial structural scaffolds found in diverse library of compounds which are therapeutically useful agents in medicinal chemistry research. A constant analysis into chemistry and biodiversity relevance of quinoxaline is inevitable for its pharmacological influence. Above data unveiled numerous biological applications of quinoxaline-based scaffolds offering excellent pathways to new biomolecular targets which qualify them to be excellent precursors in drug design and future candidates in therapeutic research. It also demonstrated that a continuous explorative study into the world of quinoxaline cannot be overemphasized, if mankind wants to stay healthy and live free of infection. This is because it provides resourceful tool of information for synthetic modifications of old existing quinoxaline-based drugs in order to tackle drug resistance bottlenecks in therapeutic medicine.

This diversity of useful synthetic quinoxaline derivatives accounts for the appearance of modifications of the classical synthetic methods and for the search for new methods ensuring the availability of the corresponding functionalized quinoxalines.

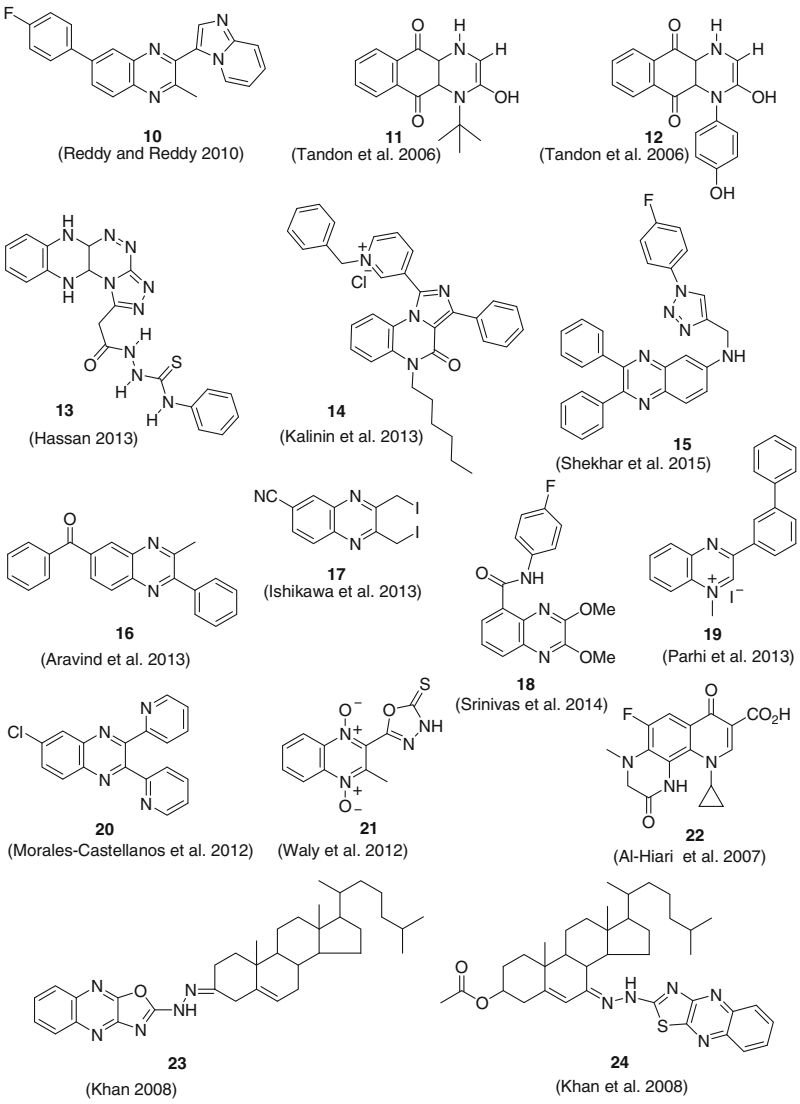


Fig. 2.4 Some quinoxaline motifs with antibacterial activity

In this chapter, a comprehensive overview of the different synthetic methodologies leading to functionalized quinoxalines and their di-, tetra-, and hexahydro derivatives will be given. These methodologies are based on the five main approaches to the synthesis of quinoxalines: condensation of 1,2-diaminobenzenes (1,2-DABs) with various two-carbon unit donors, cyclization of aniline derivatives,

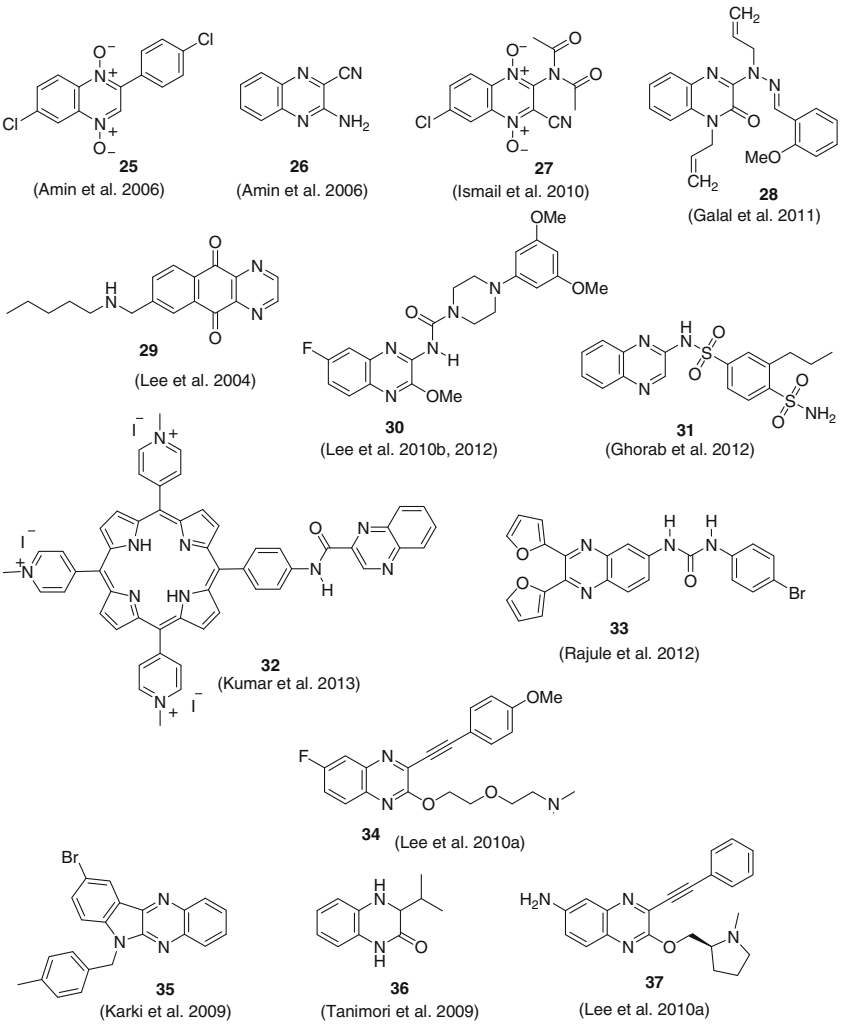


Fig. 2.5 Some quinoxaline motifs with anticancer activity

and reactions of various heterocyclic systems devoid of a pyrazine fragment and with heterocyclic systems containing a pyrazine fragment.

The synthesis of fused and polycyclic derivatives of quinoxalines will not be dealt with in this chapter, except those cases where the formation of these systems occurs in one pot. This implies either the condensed parent compounds or the compounds capable, besides constructing a quinoxaline system, to annulate separate rings on various sides under the reaction conditions.

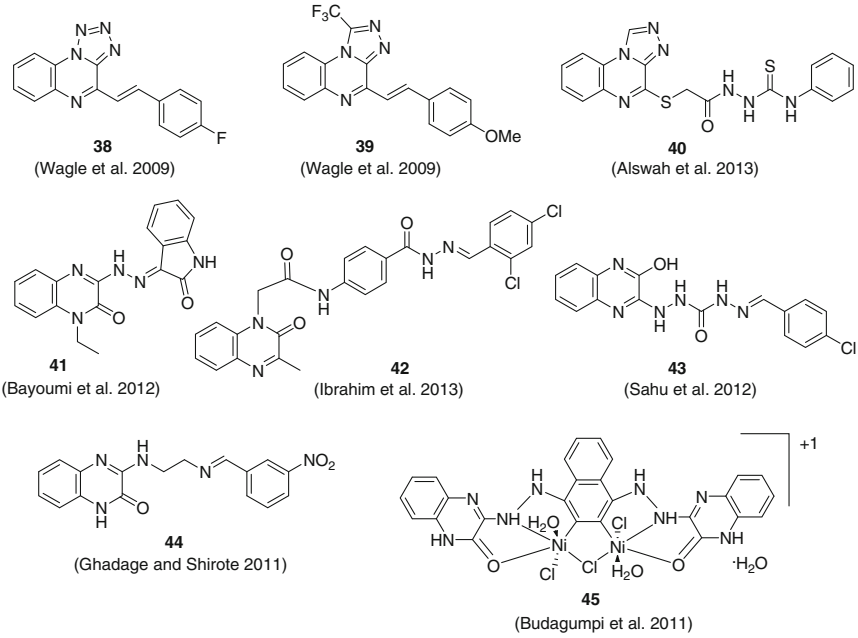


Fig. 2.6 Some quinoxaline motifs with anticonvulsant activity

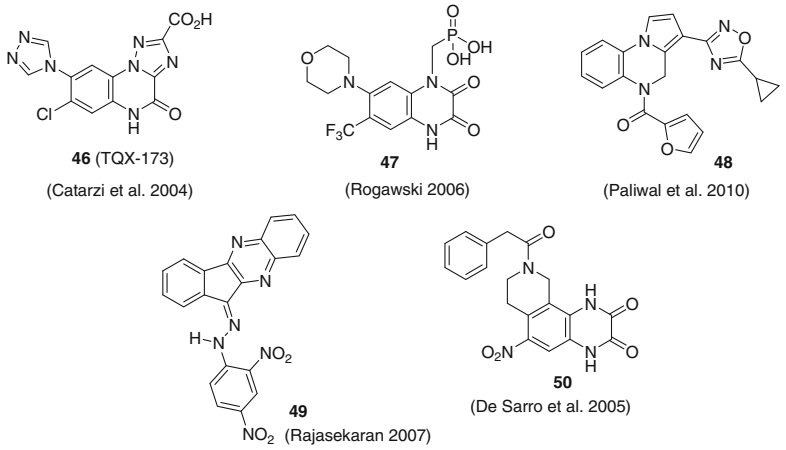


Fig. 2.7 Some quinoxaline motifs with antiepileptic activity

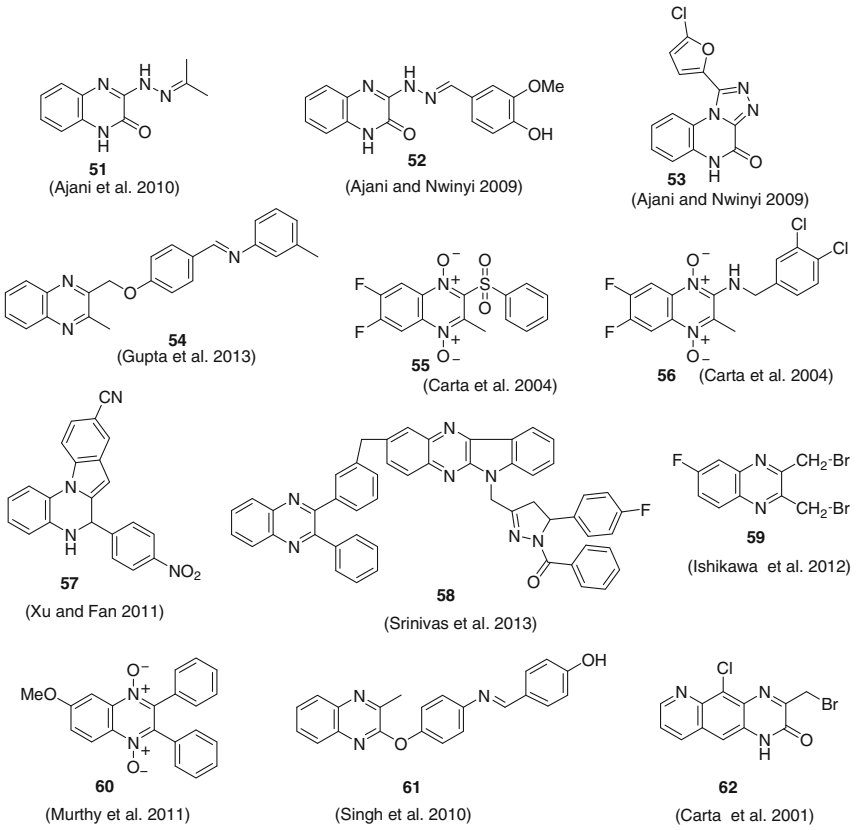


Fig. 2.8 Some quinoxaline motifs with antifungal activity

2.2 Condensation of 1,2-Diaminobenzenes (1,2-DABs; *Ortho*-Phenylenediamines) and Derivatives with Various Two-Carbon Unit Suppliers

2.2.1 With Pyruvates (2-Oxopropanoates)

The reaction of pyruvates with 1,2-DABs, first discovered by Hinsberg (1884, 1887) and Körner (1884) many years ago, independently of one another, is still the most appropriate method for the synthesis of 3-substituted quinoxalin-2(1*H*)-ones (Abasolo et al. 1987; Piras et al. 2006; Eller et al. 2007; El-Sabbagh et al. 2009; Yuan et al. 2009; Singh et al. 2010). A kinetic study of the Hinsberg reaction involved reacting unsymmetrical 1,2-DABs with pyruvates and the formation of

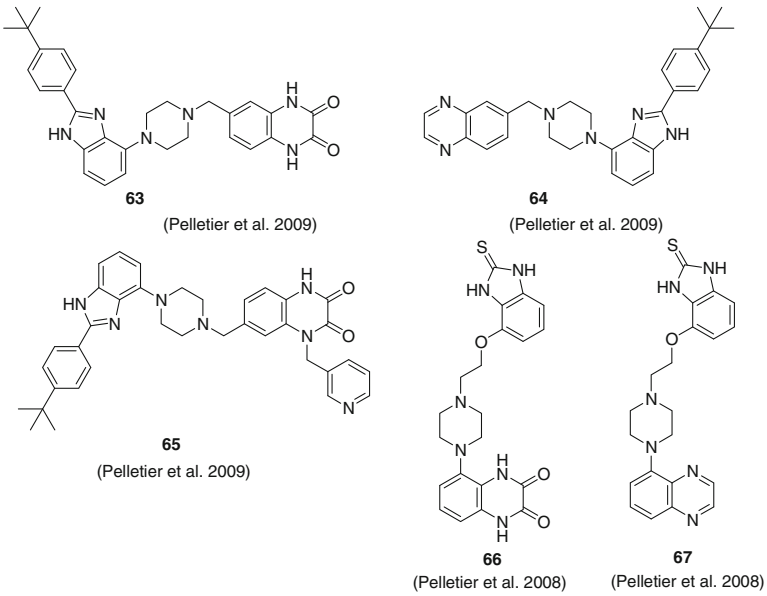


Fig. 2.9 Some quinoxaline motifs with GnRH antagonist activity

isomeric quinoxalin-2(1*H*)-ones (Abasolo et al. 1987). Some related compounds were synthesized in acetic acid to improve the regioselectivity (Lumma et al. 1981). The reaction of *N*-methyl-1,2-DAB with pyruvic acid, unlike the reactions of unsymmetrical 1,2-DABs, proceeds with the formation of 1,3-dimethylquinoxalin-2(1*H*)-ones as the sole products (Lawrence et al. 2001). Recently, a one-pot synthesis of polyfunctionalized dihydroquinoxalinone derivatives via the anti-Michael reaction has been developed (Ballini et al. 2009). Six quinoxalinone and three benzoquinoxalinone derivatives were obtained by using *S. cerevisiae* as a biocatalyst and also by means of microwave-assisted approaches (Gris et al. 2008). In general, most of these methods involve the use of toxic/volatile organic solvents with long reaction times, poor yields, and tedious product isolation procedures.

Nageswar and coworkers developed a facile and expeditious synthesis of 3-substituted quinoxalin-2(1*H*)-ones in water under catalyst-free conditions (Murthy et al. 2010). 3-Substituted quinoxalin-2(1*H*)-ones **158** are obtained when the pyruvic esters **156** or the phenylglyoxylate **157** are used in reaction with 1,2-DABs **155a–c** (Scheme 2.1) (Murthy et al. 2010).

While ethyl glyoxalate **159** and terminal alkynes **160** were used instead of pyruvic esters **156**, or phenyloxalate **157,** a novel and efficient protocol for the copper(II) catalyzed synthesis of furoquinoxalines **161–163** from readily available 1,2-DABs **155a–h** has been developed (Naresh et al. 2014) (Scheme 2.2).

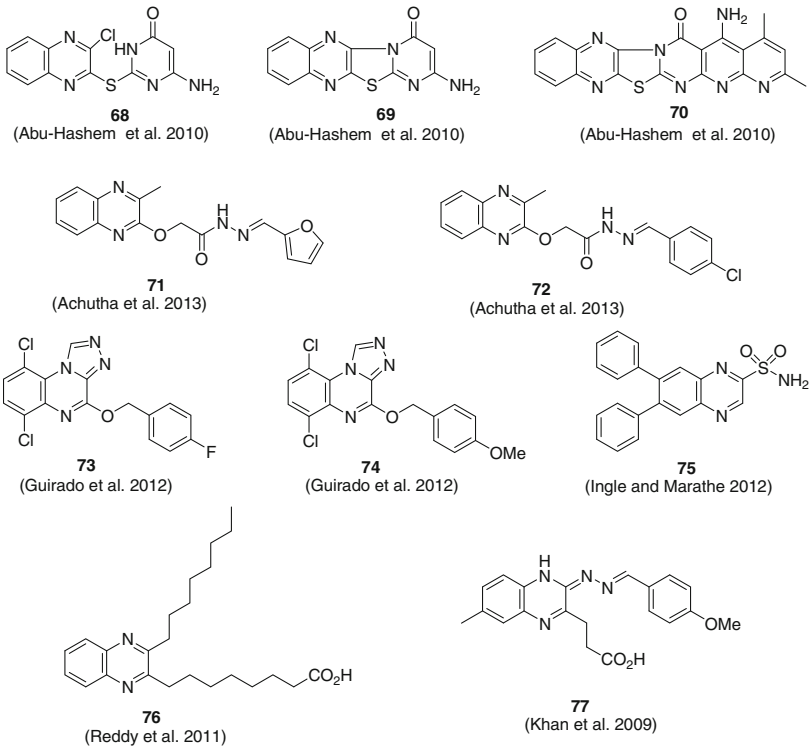


Fig. 2.10 Some quinoxaline motifs with anti-inflammatory and analgesic activities

A possible reaction mechanism for the formation of furoquinoxalines appears to be the tandem C–C bond formation followed by a *5-endo-dig* cyclization reaction as outlined in Scheme 2.3. Generally, in A3-coupling reactions, the amine **155a** reacts with aldehyde **159** and forms the imine which is further transformed to iminium ion **A**; at the same time the in situ generated copper acetylide **B** from terminal alkyne and copper(II) trifluoromethanesulfonate attacks the intermediate **A** to produce the propargylamine **C** (Peshkov et al. 2012). The resulting propargylamine **C** further attacks the ester functionality intramolecularly, leading to the generation of intermediate **D**. Since intermediate **D** is easily enolizable in an acidic medium, it provides the cyclized intermediate 3-(alkynyl)-3,4-dihydroquinoxalin-2(1*H*)-one **E** and a further cleavage of the metal π-complex occurs followed by oxidation furnishing the target furoquinoxaline.

This novel method involves the formation of four new bonds (2C–C, C–N, and C–O) in a cascade pathway.

A new and effective procedure was developed for the synthesis of 3-ethylquinoxalin-2(1*H*)-one from 1,2-DAB **155a** and ethyl 2-oxobutanoate

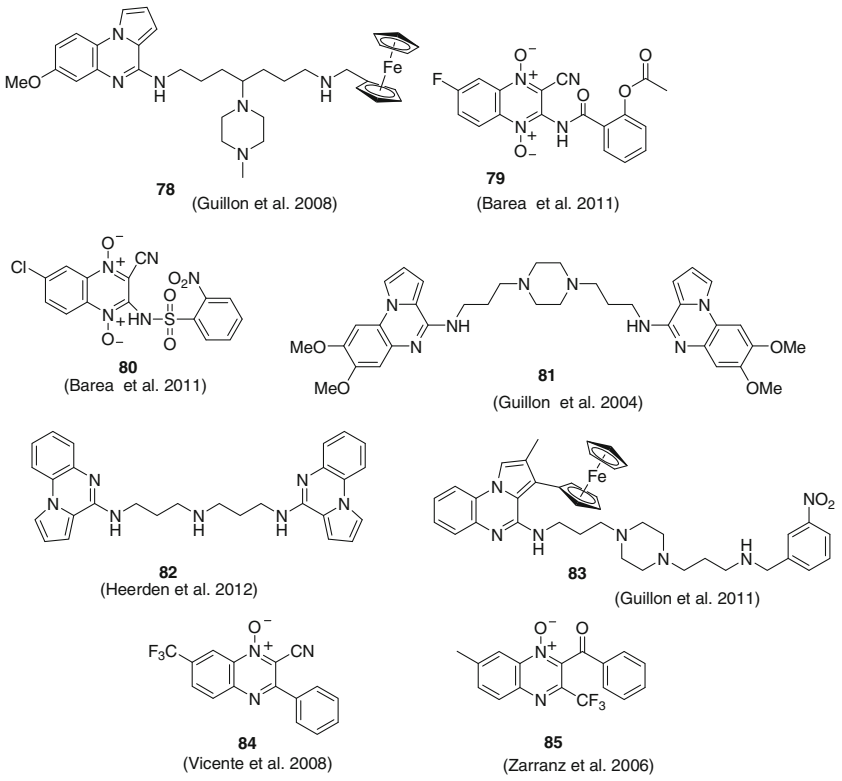


Fig. 2.11 Some quinoxaline motifs with antimalarial activity

(Mamedov et al. 2005). The latter was prepared by the Grignard reaction of diethyl oxalate with ethylmagnesium bromide or iodide. 3-Functionally substituted quinoxalin-2(1*H*)-ones can also be synthesized by the functionalization of an alkyl group at C(3) of quinoxalin-2(1*H*)-ones. For example, the functionalization of quinoxalinone **165** was performed via the substitution of the bromine atom in α-bromoethyl derivative **166** when acted upon by various nucleophiles (Scheme 2.4) (Mamedov et al. 2005). Compound **166** is readily obtained by the treatment of a suspension of **165** in 1,4-dioxane with bromine at 12–15 °C. The bromine atom in **166** is readily replaced by such nucleophiles as KSCN, $PhNH_2$, and NaN_3 in DMSO to give the corresponding 3-(α-ethyl)quinoxalines **167–169**. Both the treatment of 3-(α-azidoethyl)quinoxaline **169** with a 70 % aqueous acetic acid and the direct oxidation of quinoxalinone **165** with chromic anhydride in 95 % acetic acid proceed with the formation of ketone **170** as the major product (Scheme 2.4) (Mamedov et al. 2005).

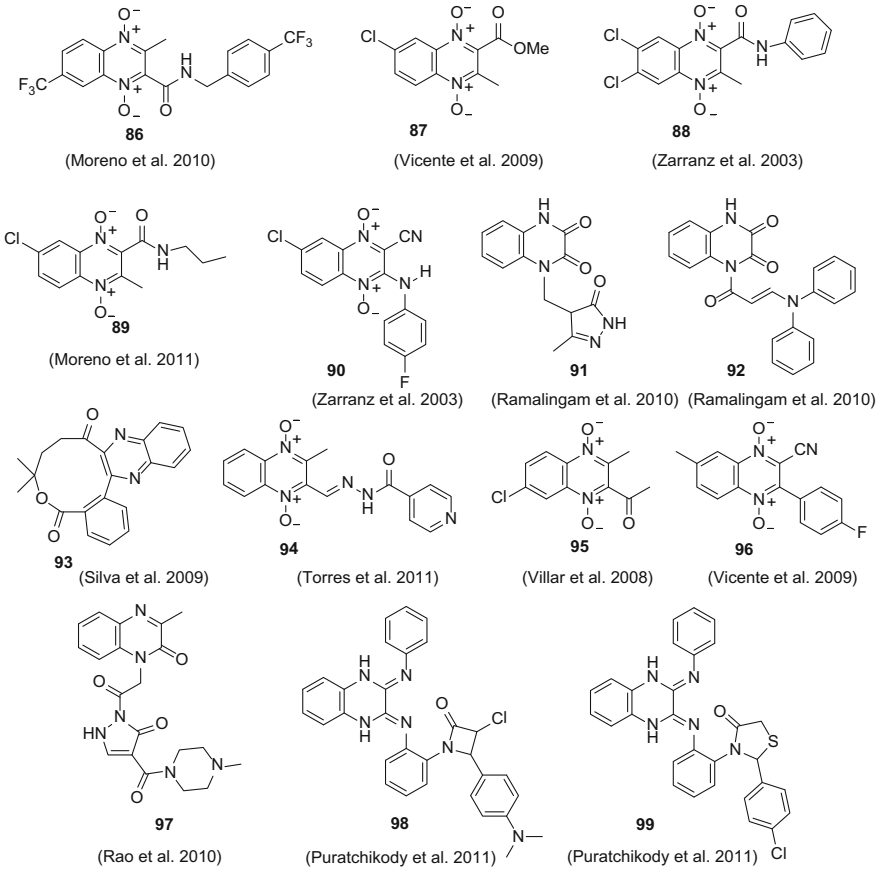


Fig. 2.12 Some quinoxaline motifs with antitubercular activity

Later the same strategy, using Cr_2O_3 in AcOH, was applied for oxidizing the methylene group of three 3-benzylquinoxalin-2(1*H*)-ones (Piras et al. 2006).

The cyclocondensation of equimolar amounts of 1,2-cyclohexanediamine (1,2-DACH) **171a** and ethyl pyruvate **156a** in a hot EtOH solution containing a catalytic amount of AcOH proceeds with the formation of 3-methyl-4*a*,5,6,7,8,8*a*-hexahydro-2(1*H*)-quinoxalinone **172** (Scheme 2.5) (El-Sabbagh et al. 2009). The coupling of the latter with an equimolar amount of diazonium salts **173** at 0 °C in AcOH, buffered with NaOAc, provided the novel hydrazones **174**. A good yield of ester **175** was obtained through the reaction of 1,2-DACH **171a** with diethyl oxaloacetate **156d** in EtOH containing AcOH at 80 °C and then at room temperature.

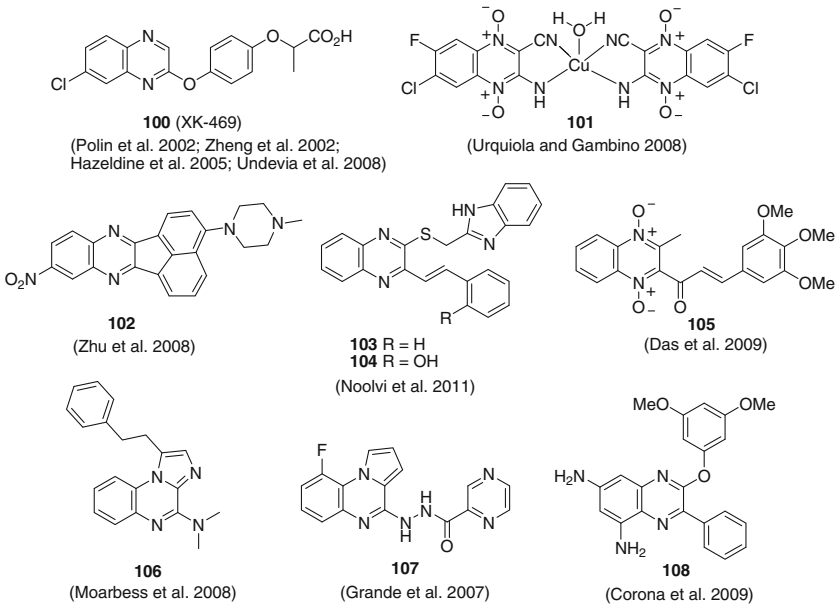


Fig. 2.13 Some quinoxaline motifs with antitumor activity

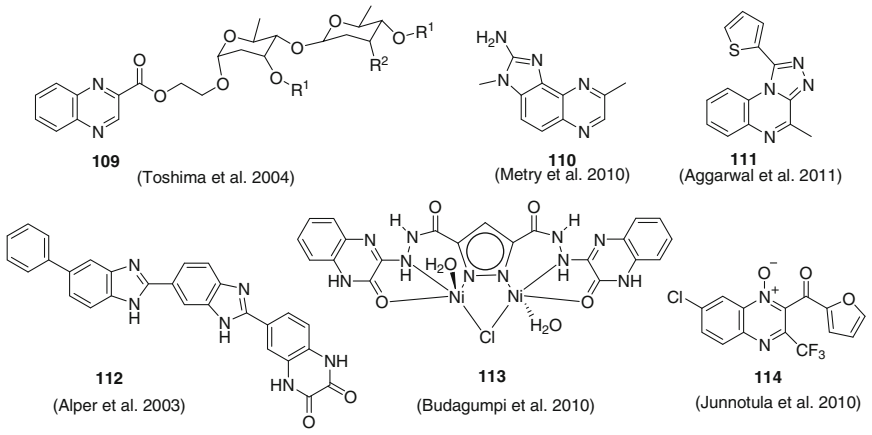


Fig. 2.14 Some quinoxaline motifs with DNA-cleavage properties

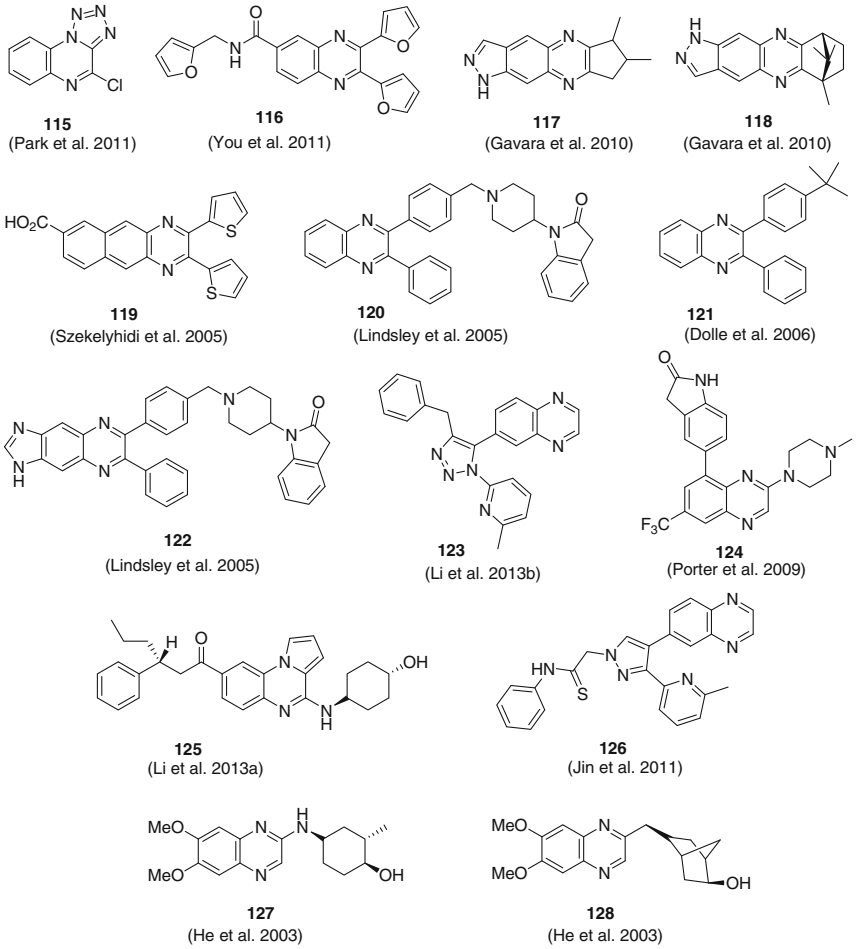


Fig. 2.15 Some quinoxaline motifs with kinase inhibitory activity

The hydrazide **176** was obtained through condensation of the ester **175** with hydrazine hydrate by heating the reactants in EtOH at reflux. Hydrazide **176** was used for synthesizing other functionalized derivatives of hexahydroquinoxalin-2 (1*H*)-one **175** (El-Sabbagh et al. 2009).

Diethyl ketomalonate (diethyl mesoxalate) **177** reacts with 1,2-DAB **155a** in the same way as do pyruvates to provide 3-ethoxycarbonyl quinoxalin-2(1*H*)-one **178** (Scheme 2.6) (Mahesh et al. 2011).

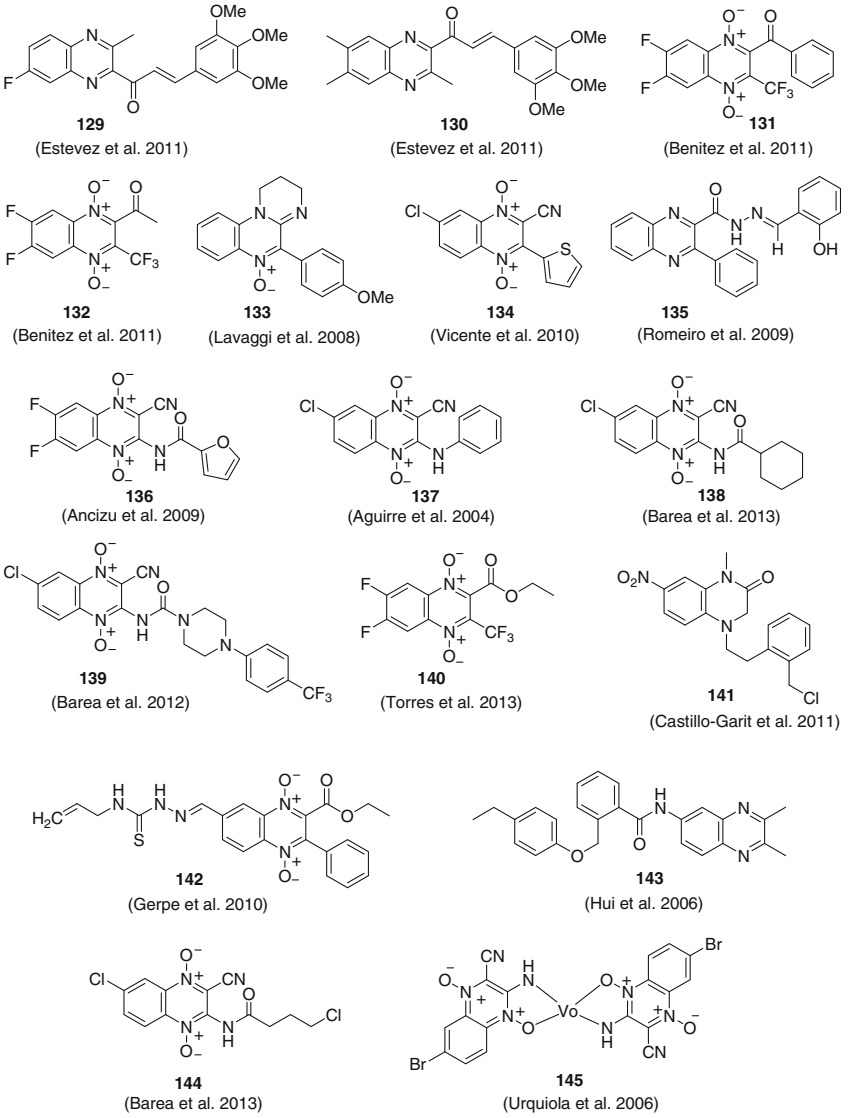


Fig. 2.16 Some quinoxaline motifs with trypanocidal properties

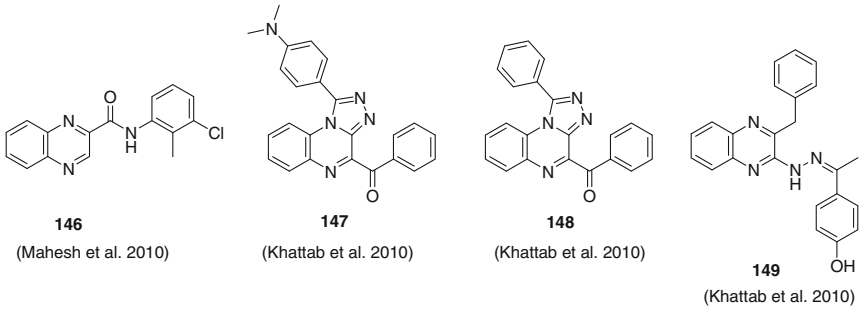


Fig. 2.17 Some quinoxaline motifs with antidepressant activity

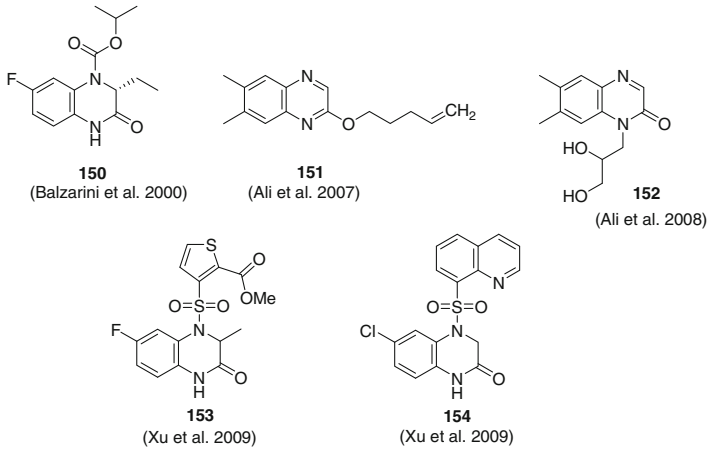
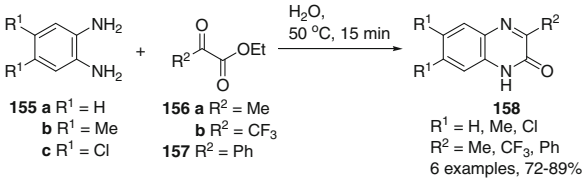


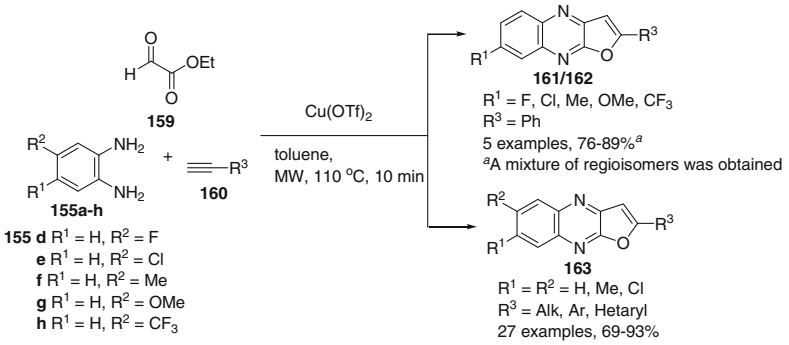
Fig. 2.18 Some quinoxaline motifs with anti-HIV activity

Scheme 2.1 Synthesis of 3-substituted quinoxalin-2 (1*H*)-ones **158** in H_2O under mild conditions

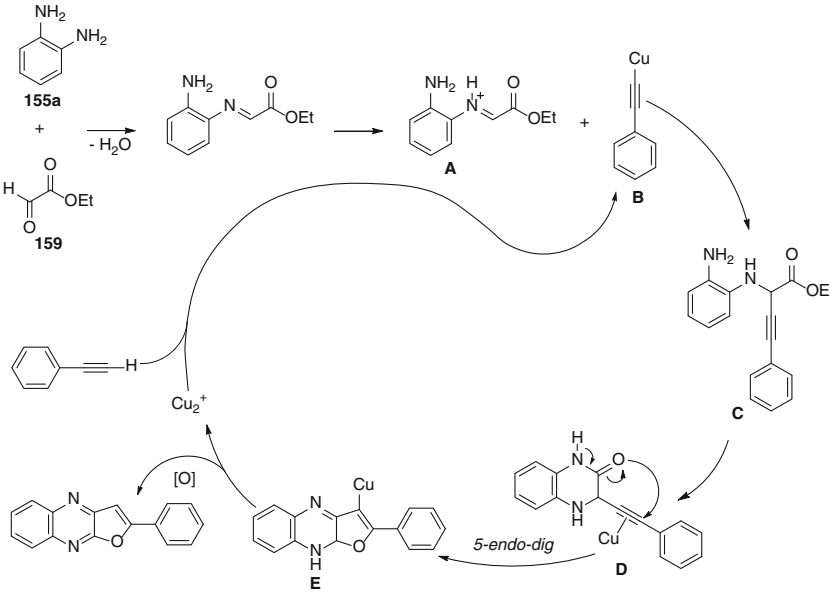


2.2.2 *With α-Diketones (1,2-Diketones)*

There are many examples of quinoxalines being prepared from α-diketones (1,2-diketones) usually involving the reaction of 1,2-DABs in refluxing ethanol or acetic acid (Carta et al. 2003; Fonseca et al. 2004; Hui et al. 2006; Wang et al. 2006;

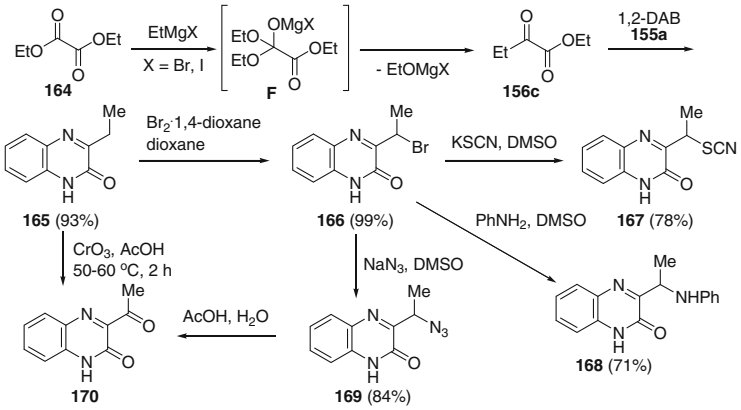


Scheme 2.2 Substrate scope for the synthesis of furoquinoxalines **161–163** with terminal alkynes under optimized conditions

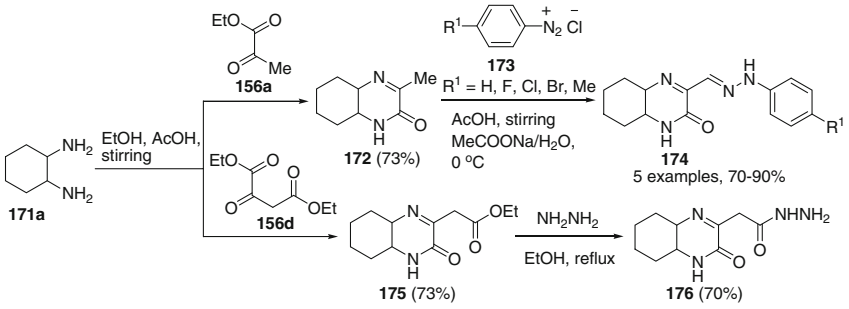


Scheme 2.3 Possible reaction mechanism for the tandem A3-coupling and 5-*endo-dig* cyclization

Tingo li et al. 2011; Xu et al. 2011a; You et al. 2011). Various catalysts, such as graphite (Kadam et al. 2013), bismuth(III) triflate (Yadav et al. 2008), metal hydrogen sulfates (Niknam et al. 2008), gallium(III) triflate (Cai et al. 2008), molecular iodine (Bhosale et al. 2005; More et al. 2005), cerium(IV) ammonium nitrate (More et al. 2006), stannous chloride (Shi et al. 2008), manganese(II) chloride (Heravi et al. 2008), zirconium tetrakis(dodecylsulfate) (Hasaninejad et al.

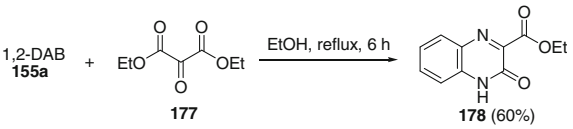


Scheme 2.4 The synthesis and side-chain functionalization of 3-ethylquinoxalin-2(1*H*)-one **165**



Scheme 2.5 Synthesis of hexahydro-2(1*H*)-quinoxalinones **172**, **174**, **175,** and **176**

Scheme 2.6 Synthesis of 3-ethoxycarbonyl quinoxalin-2(1*H*)-one **178**



2009), zirconium(IV) chloride (Aghapoor et al. 2010), niobium(V) chloride (Hou et al. 2010), silica-supported antimony(III) chloride ($SbCl_3/SiO_2$) (Darabi et al. 2009), silica-bonded *S*-sulfonic acid (SBSSA) (Niknam et al. 2009), silica sulfuric acid (SSA) (Shaabani and Maleki 2007), cellulose sulfuric acid (CSA) (Shaabani et al. 2009), amidosulfonic acid (Li et al. 2008), *p*-TsOH (Shi and Dou 2008), montmorillonite K-10 (Huang et al. 2008), zinc chloride-exchanged K10-montmorillonite (Zn^{2+}-K10-clay) (clayzic) (Dhakshinamoorthy et al. 2011), binary metal oxides supported on Si-MCM-41 mesoporous molecular sieves (Ajaikumar and Pandurangan 2009), polyaniline-sulfate salt (Srinivas et al. 2007, 2008), Wells–Dawso-type heteropolyacid ($H_6P_2W_{18}O_{62}\cdot 24H_2O$) (Heravi et al.

2007), Keggin-type heteropolyacid ($H_4SiW_{12}O_{40}$) (Huang et al. 2009), ionic liquid 1-*n*-butylimidazolium tetrafluoroborate (Potewar et al. 2008), Brönsted acid ionic liquid [$(CH_2)_4SO_3HMIM$][HSO_4] (Beheshtiha et al. 2010), nano-TiO_2 (Mirjalili and Akbari 2011), TiO_2–P25–SO_4^{2-} (Krishnakumar and Swaminathan 2010), TiO_2–SO_4^{2-} (Krishnakumar et al. 2010), acidic Al_2O_3 (Jafarpour et al. 2011), ZnO-beta zeolite (Katkar et al. 2010), LiBr (Hasaninejad et al. 2010), NH_4Br (Raju et al. 2009), Amberlyst-15/H_2O (Liu et al. 2010), PEG-400 (Zhang et al. 2010), and $KHSO_4$ (Oskooie et al. 2007), have all been used to promote this transformation.

A facile and simple catalyst-free protocol has been developed for the condensation of 1,2-diketones with 1,2-DABs in polyethylene glycol (PEG), providing quinoxaline derivatives in good yields (Huang et al. 2013). The important features of the methodology are broad substrates scope, simple workup, catalyst free, environmentally benign, and no requirement for metal catalysts. It is noteworthy that the cyclization reaction of 1,2-diketones with aliphatic 1,2-diamines is also conducted smoothly to afford pyrazines in good yields under the standard conditions (Huang et al. 2013). In addition, PEG could be recovered easily and was reused without evident loss in activity.

In order to reduce the reaction time and increase the yields of the quinoxalines, microwave irradiation methods have recently been extensively used (Zhao et al. 2004; Zhou et al. 2009; Bandyopadhyay et al. 2010; Zare et al. 2010).

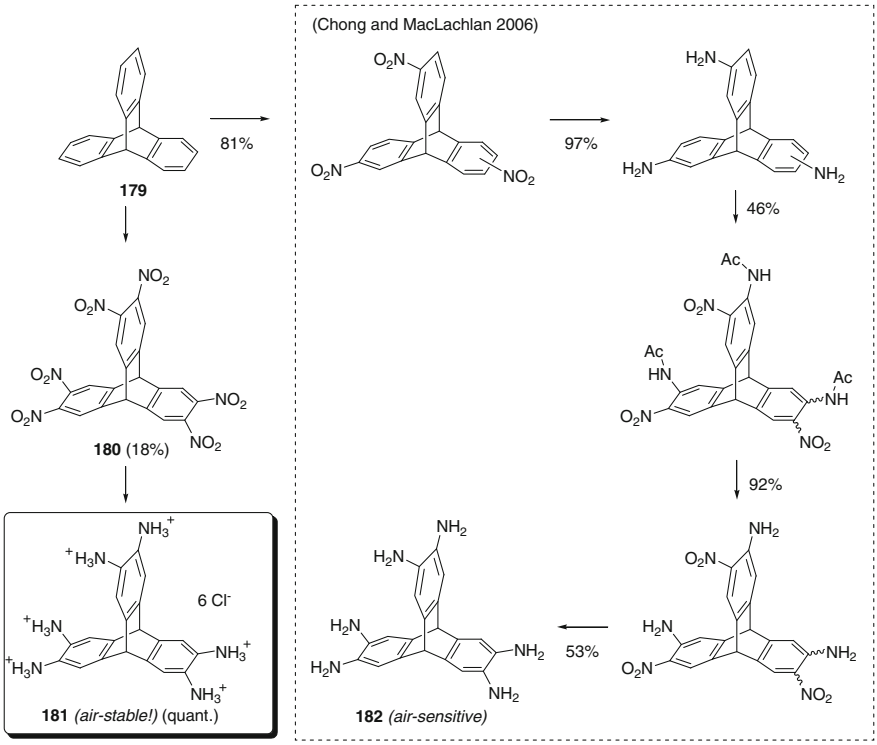
When symmetric α-diketones and symmetric 1,2-DAB derivatives and unsymmetric α-diketones and symmetric 1,2-DAB derivatives, and vice versa, have been used, the symmetric α-diketones and unsymmetric 1,2-DAB derivatives always exclusively produce one regioisomer (Carta et al. 2003; Zhao et al. 2004; Bhosale et al. 2005; More et al. 2005; Hui et al. 2006; Wang et al. 2006; Heravi et al. 2007, 2008; Oskooie 2007; Huang et al. 2008, 2009; Cai et al. 2008; Li et al. 2008, 2011; Shi and Dou 2008; Srinivas et al. 2008; Darabi et al. 2009; Niknam et al. 2009; Raju et al. 2009; Shaabani et al. 2009; Ajaikumar and Pandurangan 2009; Aghapoor et al. 2010; Bandyopadhyay et al. 2010; Beheshtiha et al. 2010; Hasaninejad et al. 2010; Liu et al. 2010; Katkar et al. 2010; Hou et al. 2010; Krishnakumar and Swaminathan 2010; Krishnakumar et al. 2010; Zare et al. 2010; Zhang et al. 2010; Jafarpour et al. 2011; Mirjalili and Akbari 2011; Tingoli et al. 2011; You et al. 2011). A similar situation was observed with unsymmetric diketones and unsymmetric 1,2-DAB derivatives. In this case the reactions proceed with the formation of mainly one (Hui et al. 2006; Bandyopadhyay et al. 2010; Mirjalili and Akbari 2011) and occasionally two products (Klein et al. 2001), although one could expect the formation of four possible regioisomeric quinoxalines. This selectivity is due to activation and deactivation of the nucleophilic ability of the amino group, and of the electrophilicity of that carbonyl carbon atom, which are involved in the first step of the condensations (Hui et al. 2006; Bandyopadhyay et al. 2010).

Instead of the simple α-dicarbonyl compounds and 1,2-DAB derivatives for the synthesis of quinoxalines (or compounds containing quinoxaline fragments), one can envisage that (a) fused compounds containing the α-dicarbonyl moiety with simple 1,2-DABs, (b) fused compounds containing a 1,2-diamino moiety and

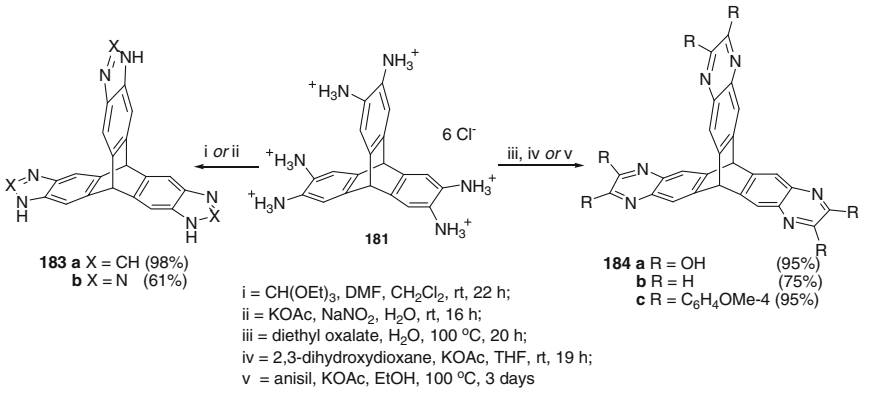
normal α-dicarbonyl compounds, and (c) fused compounds containing α-dicarbonyl and fused compounds containing 1,2-diamino groups can be used. All these combinations lead to condensed quinoxalines derivatives. In these cases the reaction conditions can be different, e.g., heating the reactants in refluxing EtOH solution (Michon et al. 2002; Elmes et al. 2011), refluxing in EtOH in the presence of catalytic amounts of *p*-TsOH (Unver et al. 2010), HCl (Kollenz and Theuer 2001), heating in AcOH solution at reflux (Shibinskaya et al. 2011), in an ionic liquid ([bmim] Br/MW) (Zare et al. 2010), stirring in EtOH solution at room temperature in the presence of catalytic amounts of TiO_2–P25–SO_4^{2-} (Krishnakumar and Swaminathan 2010), TiO_2–SO_4^{2-} (Krishnakumar et al. 2010), $NbCl_5$ (Hou et al. 2010), stirring in EtOH/H_2O solution at room temperature in the presence of catalytic amounts of silica-bonded S-sulfonic acid (Niknam et al. 2009) stirring in MeCN/H_2O solution at room temperature in the presence of catalytic amounts of Zn^{2+}-K10-clay (clayzic) (Dhakshinamoorthy et al. 2011), and stirring a CH_2Cl_2 solution at room temperature in the presence of catalytic amounts of ethereal HCl (Kollenz and Theuer 2001), in boiling pyridine (Kulisic et al. 2011) or toluene (Michon et al. 2002) solutions.

Not only the usual 1,2-DABs, but also 2,3,6,7,14,15-hexaammoniumtriptycene hexachloride **181**–compound containing three 1,2–DABs fragments–can contribute to the construction of quinoxaline systems (Mastalerz et al. 2011). The two-step synthesis of the ammonium salt **181** starts (Scheme 2.7) with a sixfold nitration of triptycene **179** (Shalaev and Skvarchenko 1974). Triptycene **179** was dissolved in fuming nitric acid and heated at 80–85 °C for 4 h giving after workup a pale yellow solid as crude product. From ^{1}H NMR spectroscopy it can be estimated that the desired hexanitrotriptycene **180** was formed as the main product in approximately a 38 % yield. By recrystallization from hot DMF it was possible to separate **180** as yellow needles from the crude mixture in yields between 16 and 18 % of sufficient purity (approximately 97 % of the desired regioisomer as quantified by ^{1}H NMR spectroscopy).

The reduction using tin(II) chloride in aqueous hydrochloride/ethanol solution was carried out for the subsequent sixfold transformation of the hexanitrotriptycene **180** to the corresponding hexaammonium hexachloride **181**. This resulted in the pale yellow ammonium salt **181** as a heptahydrate, which was determined by elemental analysis, in quantitative yield. This was found (Mastalerz et al. 2011) to be superior to methods using Pd/C and H_2 or Raney-Ni/hydrazine. The reaction was performed in air, and no precautions were found to be necessary. More important to us than the high yield is the stability of **181** toward oxidation, which was known before for similar structures (Far et al. 2002) containing electron-rich 1,2-DAB units. This stability makes the handling for further transformations easier, which is exemplified in some selected condensation reactions (Scheme 2.8). For example, with triethyl orthoformate the benzimidazole analog of triptycene **183a** is accessible in almost quantitative yield (98 %) (Far et al. 2002) by directly using the ammonium salt **181** as a reactant in water as solvent. Similarly, a benzotriazole analog **183b** is accessible in a 61 % yield by reacting **181** with sodium nitrite and potassium acetate at room temperature (Damshoder and Peterson 1940). Quinoxaline



Scheme 2.7 Two-step synthesis of air-stable hexaammoniumtriptycene hexachloride **181** as a synthetic analog of hexaminotriptycene **182**

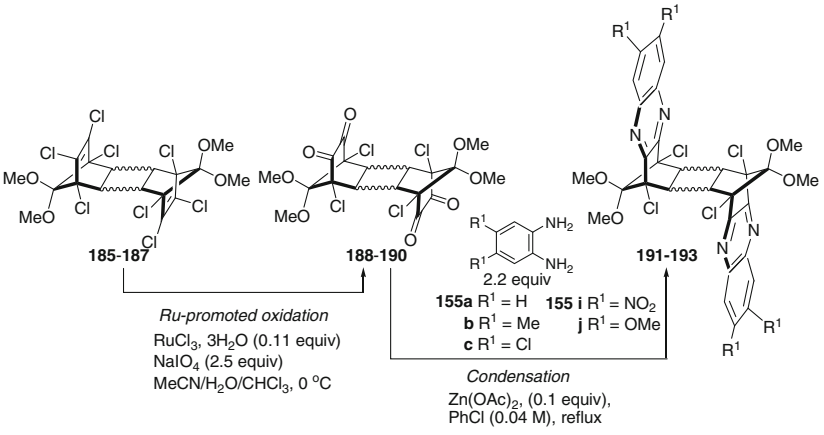


Scheme 2.8 Reactions of hexaammonium salt **181** in condensation reactions

derivative–2,3,6,7,12,13-hexahydroxy-2,6,12-trihydrotripty[2,3-d:6,7-d′:12,13-d″] tripyrazyl **184a** can be prepared by the reaction of the hexaammonium salt **181** with diethyloxalate in water at 100 °C, giving the product as a pale yellow solid in high yield (95 %). For the reaction of **181** with dihydroxydioxane or anisil to the corresponding quinoxalines 2,6,12-trihydrotripty[2,3-d:6,7-d′:12,13-d″]tripyrazyl **184b** and 2,3,6,7,12,13-hexa(4′-methoxyphenyl)-2,6,12-trihydrotripty-[2,3-d:6,7-d ′:12,13-d″]tripyrazyl **184c** the addition of a stoichiometric amounts of potassium acetate is crucial. Treatment under similar conditions without potassium acetate gave no reactions while with potassium acetate quinoxaline **184b** was accessible in 75 % and quinoxaline **184c** in almost quantitative yield (95 %).

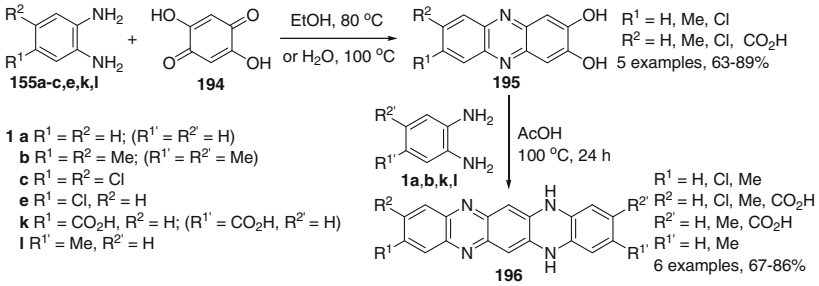
Compounds containing a two α-dicarbonyl fragments can act as a provider of two two-carbon fragments, e.g., reacting compounds **188–190** with 1,2-DAB derivatives **155a–c**, **i**, **g** gives Z-shaped quadruple-bridged orthocyclophanes **191–193** in one step (Scheme 2.9) (Chou and Liao 2011). Similarly, reaction of 2,5-dihydroxy-*p*-benzoquinone **194** in two stages makes it possible to synthesize unsymmetrically substituted 5,14-dihydro-5,7,12,14-tetraazapentacenes **196** (Scheme 2.10) (Seillan et al. 2008).

A three-step synthesis of nineteen Z-shaped quadruple-bridged [6,6] and [6,4] orthocyclophanes comprising two quinoxaline-based sidewalls has been described (Chou and Liao 2011). The synthesis began with the *bis*-Diels–Alder adducts



	Yields, %		
		188-190	**191-193**
	188,191	84	89-94
	189,192	95	92-94
	190,193	98	91-99

Scheme 2.9 Synthesis of quinoxaline-annelated Z-shaped quadruple-bridged orthocyclophanes **191–193**



Scheme 2.10 Synthesis of substituted 5,14-dihydro-5,7,12,14-tetraazapentacenes **196**

185–187 transformed by ruthenium-promoted oxidation into the *bis*-α-diketones **188–190**, which were then condensed with various 1,2-DABs **155a–e** to construct sidewalls (phane parts) of Z-shaped quadruple-bridged orthocyclophanes **191–193** (Scheme 2.9).

The commercially available 2,5-dihydroxy-*p*-benzoquinone **194** reacted with 1.1 equivalents of various substituted 1,2-DABs **155** to afford high yields of substituted 2,3-dihydroxyphenazines **195** (Yosioka and Otomasu 1954; Römer et al. 1979; Pozzo et al. 1998; Seillan et al. 2008). These could be reacted further over 24 h with an excess of substituted 1,2-DABs **155a**, **b**, **k**, **l** (10 equivalents) in the presence of glacial AcOH yielding pentacyclic derivatives **196** (Scheme 2.10) (Seillan et al. 2008).

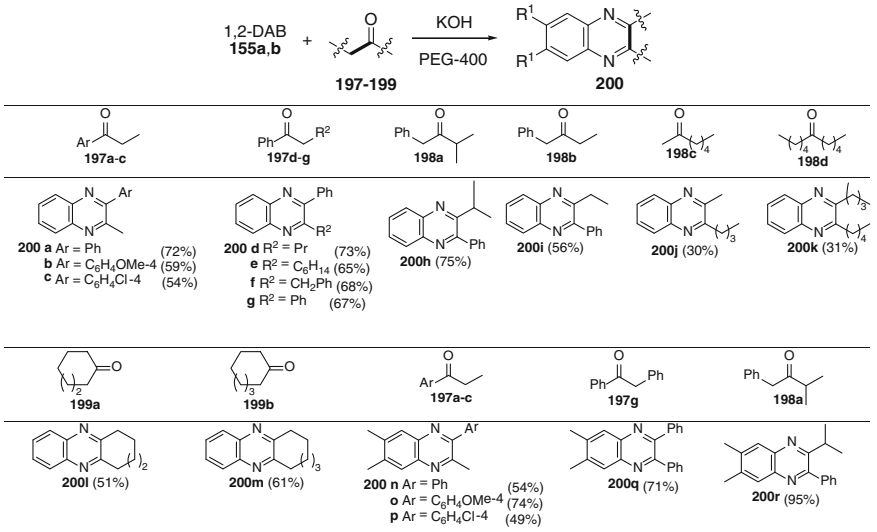
An efficient and practical route to a novel fluorescent benzo[*a*]pyrano[2,3-*c*] phenazine framework has been developed by a one-pot, four-component reaction of 2-hydroxynaphthalene-1,4-dione, 1,2-DABs, aromatic aldehydes, and Meldrum's acid in glacial acetic acid at 70 °C (Saluja et al. 2014).

Many of the dicarbonyl compounds required for this approach to quinoxalines are best obtained by oxidation of α-haloketones, α-ketoalcohols, or α-nitrosation or α-diazocoupling of ketones followed by the hydrolysis of the resulting monooximes or diazoketones. Therefore, under certain conditions, ketones such as α-haloketones, α-ketoalcohols, ketooximes, and diazoketones can be used directly for the synthesis of quinoxalines as suppliers of the two-carbon fragment.

2.2.3 With Ketones

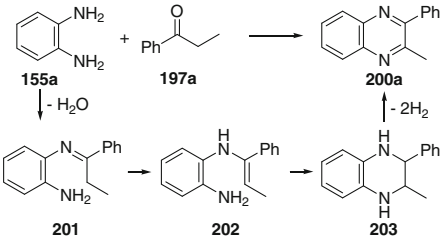
In air, 1,2-DABs **155a**, **b** react with an array of ketones **197–199** in PEG-400 at 60 °C in the presence of KOH to afford the corresponding quinoxalines **200** in good yields (Scheme 2.11) (Cho et al. 2007).

Although not fully understood as yet, a reaction pathway that is consistent with the product formed could proceed by the condensation ketone and diamine with the initial formation of a ketimine **201**. This in turn could tautomerize to form enamine **202**; KOH may play some role in facilitating this change. Subsequent steps may



Scheme 2.11 Ketones as two-carbon suppliers for quinoxaline synthesis

Scheme 2.12 A plausible reaction pathway for quinoxaline formation from a ketone and 1,2-DAB



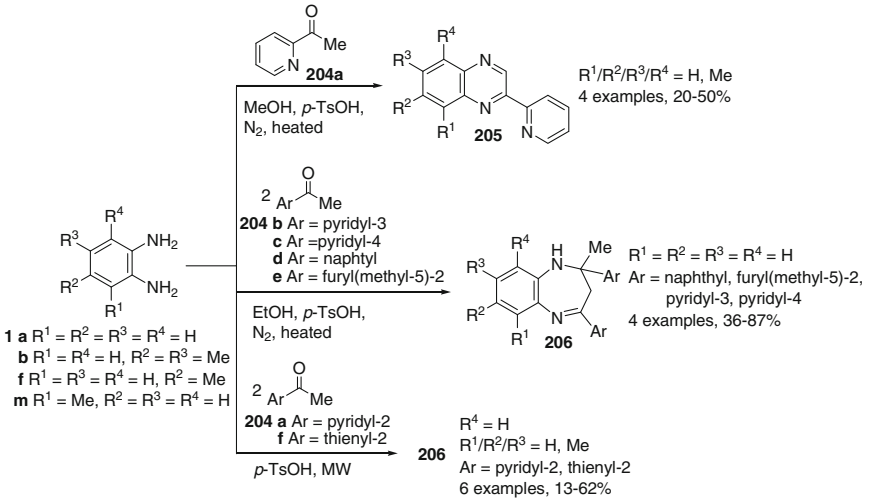
involve intramolecular hydroamination giving a 1,2,3,4-tetrahydroquinoxaline **203**, and then dehydrogenated to give **200a** (Scheme 2.12).

The reactions of **155a** with 1-arylpropan-1-ones **197b** and **197c**, which have either an electron-donating or an electron-withdrawing substituent on the aromatic ring, also proceed to give the corresponding 2-aryl-3-methylquinoxalines, **200b** and **200c**. Alkyl aryl ketones **197d–g** were also reacted with **155a** to give the corresponding 2-alkyl-3-arylquinoxalines **200d–g** in a yield range of 65–73 %. The reaction proceeds likewise with alkyl benzyl ketone **198a** to produce 2-isopropyl-3-phenylquinoxaline **200h**. However, the reaction did not proceed satisfactorily using acetophenone, with 2-phenylquinoxaline being formed in only a 20 % yield. In the reaction of **155a** with 1-phenylbutan-2-one **198b**, 2-ethyl-3-phenylquinoxaline **200i** was obtained in a 56 % yield with no formation of the regioisomer, 2-benzyl-3-methylquinoxaline. As shown in Scheme 2.12, the preferential formation of a 2-aryl-3-alkylquinoxaline seems to be due to the relative stability of the intermediate enamine. A lower reaction rate and yield were observed with nonactivated dialkyl ketones **198c** and **198d**. Here again, no regioisomeric

quinoxaline was observed with **198c**. Cyclic ketones such as cycloheptanone **199a** and cyclooctanone **199b** also reacted with **155a** to give 7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoxaline **200l** and 6,7,8,9,10,11-hexahydrocycloocta[*b*]quinoxaline **200m** in 51 and 61 % yields, respectively. A similar treatment of **155b** with alkyl(aryl) ketones **197a–c** and **197g** afforded corresponding quinoxalines **200n–q** in the 49–74 % yield range. The cyclization of **155b** with **198a** resulted in a quantitative yield of quinoxaline **200r**.

It should be pointed out that in the presence of *p*-TsOH as a catalyst the reaction of 1,2-DABs **155a**, **b**, **f**, **m** with acetylarenes **204** in hot EtOH and under microwave irradiation conditions proceeds with the formation of 2,3-dihydro-1,5-benzodiazepine derivatives **206** in moderate yields (Scheme 2.13) (Yong et al. 2005). Unexpectedly, it was found that quinoxalines **205** are formed in the reaction of 1,2-DABs **155a**, **b**, **h**, **j** with 2-acetylpyridine **204a** in MeOH in contrast to 3- and 4-acetylpyridines **204b**, **c** and other acetylarenes **204d–f** derivatives (Scheme 2.13).

The alternative formation of quinoxalines **205** and benzodiazepines **206** can be understood with the help of the proposed reaction mechanism (Scheme 2.14). 1,2-DABs **155a**, **b**, **f**, **m** react with ketone **204** to form an imino-intermediate, which by *N*-protonation and C-deprotonation may form a zwitterion. In the case of the 2-substituted pyridine in MeOH solution, it is proposed that this intermediate cyclizes and is dehydrogenated to form quinoxaline derivatives **205**. The formation of quinoxaline derivatives is limited to those reactions in which the aryl group is 2-pyridyl and there still remains a question over the oxidation to the final product. When the zwitterionic intermediate reacts at carbon with another equivalent of the ketone, a new intermediate could be formed which could undergo further cyclisation to give benzodiazepine derivatives **206**.



Scheme 2.13 The synthesis of quinoxalines from methyl aryl/hetaryl ketones and 1,2-DABs