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Synthesis, Reactions and Biological Activity of Quinoxaline Derivatives

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Abstract The review deals with synthesis and reactions of quinoxaline derivatives as well as their diverse pharmacological and biological properties. Quinoxalines and fused ring systems show diverse pharmacological activities. Syntheses of quinoxaline derivatives *via* many different methods of synthetic strategies have been presented.

Keywords Quinoxalines, *o*-phenylenediamine, Oxidation, Nitration, Diazotization, Alkylation, Addition, Condensation, Cyclization, Substitutions reactions

1. Introduction

Quinoxaline derivatives have different pharamacological activities such as bacteriocides and insecticides [1], antibacterial [2-5], antifungal [2, 6], antitubercular [2, 7-9, 10], analgesic [4, 11] and anti-inflammatory [11, 12]. The importance of quinoxaline derivatives comes from its nitrogen contents (heterocyclic compounds).

A structure of ring fused with quinoxalines, display diverse pharmacological activities (antibacterial, anticancer and antiviral) [13, 14], antimalarial [15, 16] and anti-depressant activities [17]. Quinoxaline-diones derivatives use on treatment of epilepsy, pain and other neurodegenerative disorders [1, 18].

Quinoxalines were identified as antihypertensive agents and animal growth promoters [19, 20]. It was found that several highly mutagenic and carcinogenic quinoxalines have been identified in heated meat and fried fish [21]. Certain condensed quinoxalines exhibit antibacterial, analgesic, tuberculostatic, antileukemic activities [22]. Biologically active polypeptides such as levomycin and echinomycin have been shown to possess one or more quinoxalinyl residues [23].

1, 4-di-*N*-oxide quinoxaline derivatives are heterocycles that are often used in the synthesis of biologically active compounds, [24-51] as shown in (Figure 1).

2. Biological and Pharmacological Studies

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2.1. Antimicrobial Activity

Quinoxaline-1, 4-di-*N*-oxide derivatives, pyrazoloquinoxalines and 2-[4-arylidene hydrazinocarbonyl) aniline]-3-methyl quinoxalines (**274**, **275**, **276**, **277**, **278)** respectively have been identified as antibacterial, Antifungal agents and antimicrobial activity [2, 52, 53, 54, 55] as shown in (Figure 2).

2.2. Anti-Amoebic, Anti-Proliferative Activity

2-(5-substituted-3-phenyl-2-pyrazolinyl)-1, 3-thiazolino [5, 4-b] quinoxaline **279** was tested in vitro as anti-amoebic activity against strain of (*E. histolytica*) [56]. Recently; 6-arylamino-2, 3-bis (pyridin-2-yl)-7-choloroquinoxaline-5, 8- diones (**280)** have been as a potent anti-proliferative agent [57]; as shown in (Figure 3).

2.3. Hypoglycemic, Anti-Glaucoma Activity

(*N*-arylcarbamoyl and *N*- aryl thiocarbamoyl) hydrazinequinoxalin - 2 (1*H*) (**281)** have been informed as mild hypoglycaemic agents [58] and Brimonidin (**282)** (Alphagan) is a drug used for the treatment of open - angle glaucoma [59] shown in (Figure 4).

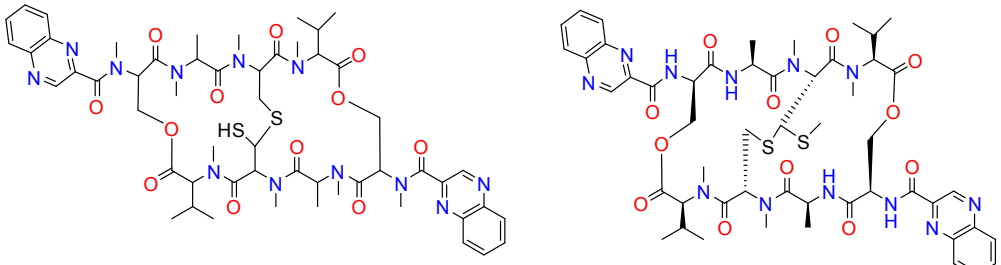
2.4. Antiviral Activity

2, 3-dimethyl-6-(dimethylaminoethyl)-6*H*-indolo-[2, 3-b] quinoxaline (**283)** shows highest activity against the herpes virus with biological activity due to DNA binding properties of these compounds [60]; shown in (Figure 5).

2.5. Cytotoxic with Anticancer, Antitumor Activity

A series of quinoxalines derivatives and substituted quinoxalines showed antitumor with remarkable cytotoxic effect against different Sarcoma type. For examples: 2,3,7-trichloro-6- methylsulfamoylquinoxaline (**284**) [61];

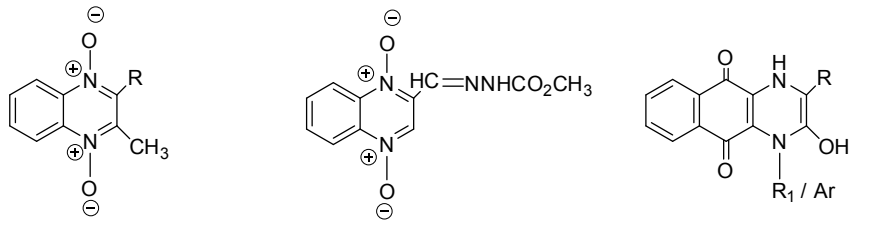
1*H*-quinoxalin-2-one (**285**), bromomethyl-5-chloro-3, 4-dihydro-1*H*-pyrido [2, 3-g] quinoxalin-2-one (**286**), 3-Phenoxymethyl-1*H*-quinoxalin-2-one (**287**)] [62, 63]; 2, 3-bis (bromo- methyl) -5,10- benzo[g]quinoxaline-dione (tricyclic quinone) derivative (**288**). Some substituted quinoxaline 1, 4-di-*N*-oxides (**289**) and tested for tumour inhibiting activity and highly active as a cytotoxic agent with highest hypoxic cytotoxicity [26, 64, 65] and pyridine-2-carboxylic acid *N*-(7-fluoro-pyrrolo[1,2-a] quinoxalin-4-yl) hydrazide (**290b**) derivatives (**290a**), in panel of cancer cell lines, a breast cancer cell and three colon cancer cells [66] was moderately active against colon cancer lines and highly active in all cells. The in vitro cytotoxic activities of 7-dialkylaminomethyl benzo*[g]* - quinoxaline -5, 10- dione derivatives (**291a-e**) was evaluated against panel of human cancer cell lines. These are ovarian carcinoma, colon cancer, breast cancer [67], shown in (Figure 6).



300 Levomycin

301 Echinomycin

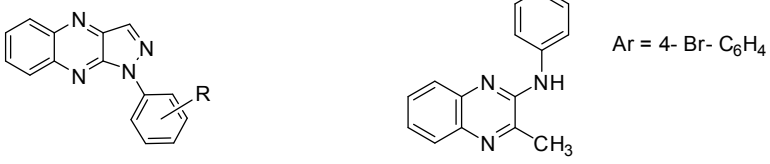
Figure 1. Levomycetin has a high level of activity and is only slightly toxic to man Echinomycin is a peptide anibintic



274 R=CH_2OH, R=CH_3

275

276 R=H, R_1=4-OH-C_6H_4.$C(CH_3)_3$



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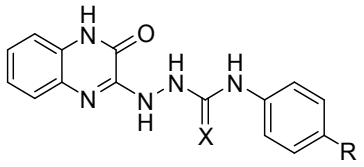
278 Ar = 4- Br- C_6H_4

Figure 2. Quinoxaline derivatives as examples of antibacterial, antifungal and antimicrobial activity

279 R =

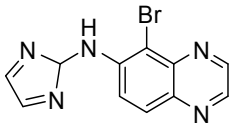
280 R_1=H,R_2=OH,R_3=H

Figure 3. Quinoxalines as examples of antiamoebic activity and antiproliferative



281

R = H, F
X = O, S



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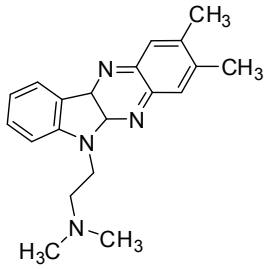

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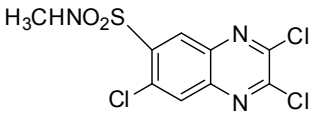
Figure 4. Quinoxalines as hypoglycaemic and antiglaucom activity

Figure 5. Quinoxalines as antiviral activity



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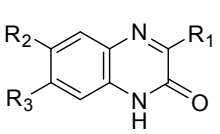

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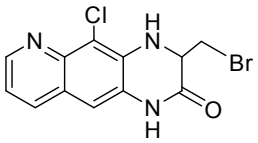
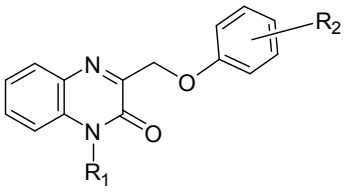


286

$R_1 = CH_2Br$; $R_2 = H$; $R_3 = CF_3$



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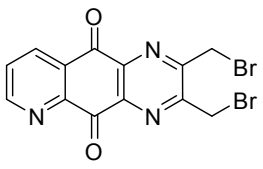

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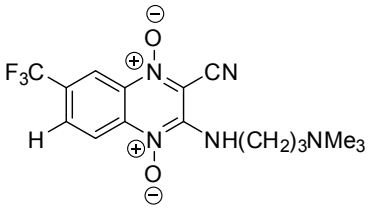

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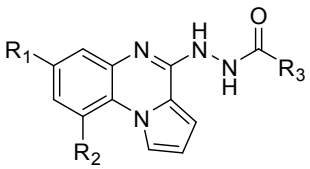
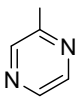
R_1= benzoyl ; R_2 = 2-C(O)NH-phenyl

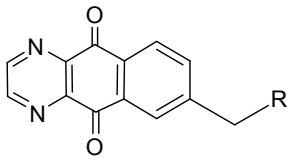


290

$R_1 = F$, $R_2 = H$, $R_3 =$

$R_1 = H$, $R_2 = F$, $R_3 =$





291

a;R=-$N(CH_3)_2$
b;R=-$N(CH_2CH_2OH)_2$
c;R=-$N(CH_2CH_2)_2$
d;R=-$N(CH_2CH_2)_2CH_2$
e;R=-$N(CH_2CH_2)_2O$

Figure 6. Quinoxalinone derivatives and substituted ans cytotoxic with anticancer, antitumor activity

2.6. Antithrombotic Activity

Quinoxalinone derivatives is a patented antithrombotic Activity [68] for examples (**292**); (**293**) and 3-{4-[5-(2, 6-dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3, 4-dihydro-quinoxalin-2-yl}-4-hydroxy-benzamidine (**294**) and 4-(4, 7-dimethyl- 3-oxo-3, 4-dihydroquinoxalin-2-ylmethyl)- benzamidine (**295**); shown in (Figure 7).

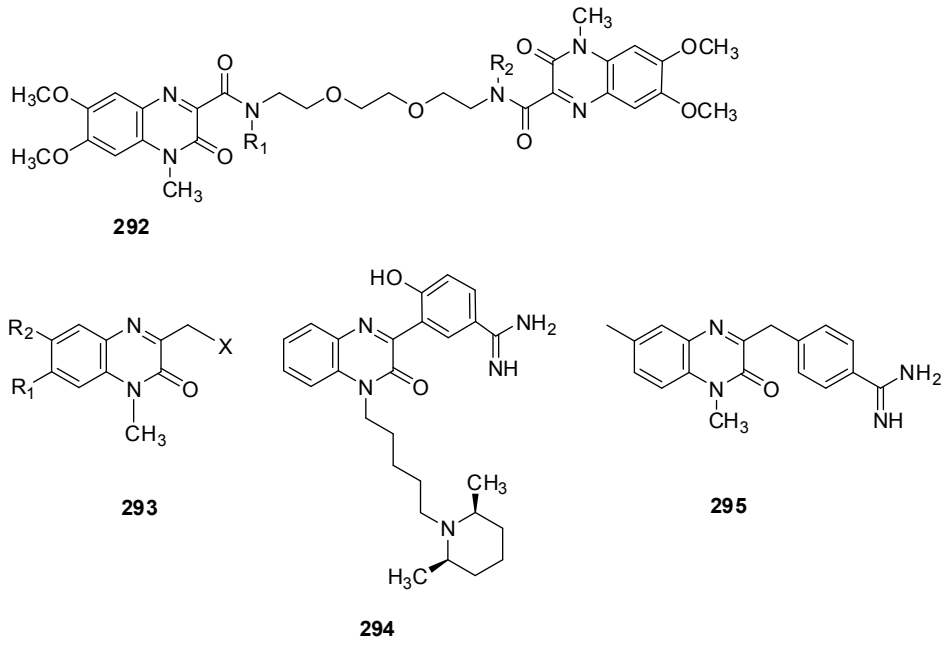


Figure 7. Quinoxalinone derivatives with antithrombotic activity

2.7. Anti-HIV Agents

Quinoxalinone derivatives for examples[7-Chloro-2,2-dimethyl-3-thioxo-3,4-dihydro-2*H*-quinoxa line-1-carboxylic acid isopropenyl ester (**296**), 7-methoxy-2-methylsulfanyl methyl-3-thioxo-3,4-dihydro-2*H*-quinoxaline-1-carboxylic acid iso- propyl ester (**297**), 2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2*H*-quinoxaline-1-carboxylic acid isopropyl ester (**298**), 3-cyclopropylethynyl-4,6-(sub)-3-trifluoro methyl-3,4-dihydro-1*H*-quinoxalin-2-one (**299**)] inhibitors of reverse transcriptase as potential anti-HIV Agents [69-71]; shown in (Figure 8).

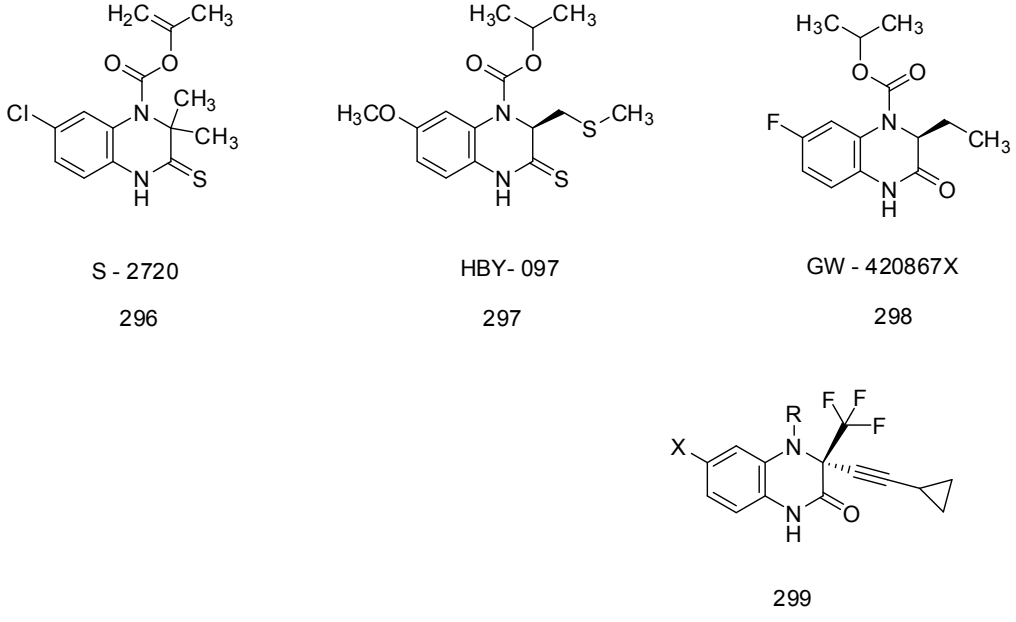


Figure 8. Quinoxalinone derivatives inhabitors of reverse transcriptase an potential anti-HIV Agents

2.8. Anti-Inflammatory and Analgesic Activity

Compounds quinoxaline derivatives (**200**, **202**, **206** and **211**) exhibited potent anti-inflammatory and analgesic activities [72]; shown in (Figure 9).

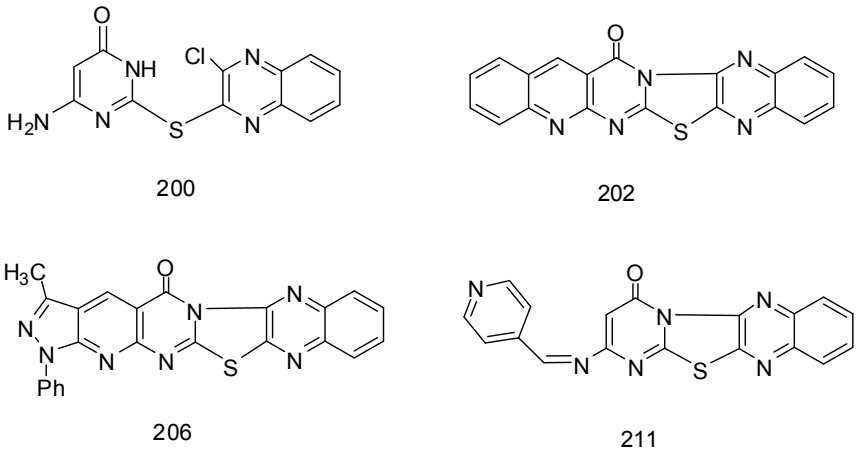


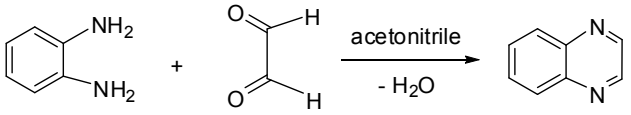
Figure 9. Quinoxalinone derive. As potential anti-inflammatory and analgesic activity

3. Synthesis of Quinoxaline derivatives *via* Different Methods

3.1. From Aromatic Diamines with Many of Organic Derivatives

3.1.1. Cyclocondensation of o-phenylenediamine with glyoxal

Quinoxaline **3** itself [73] is prepared via reaction of *o*-phenylenediamine **1a** and glyoxal **2** in acetonitrile; shown in (Scheme 1).

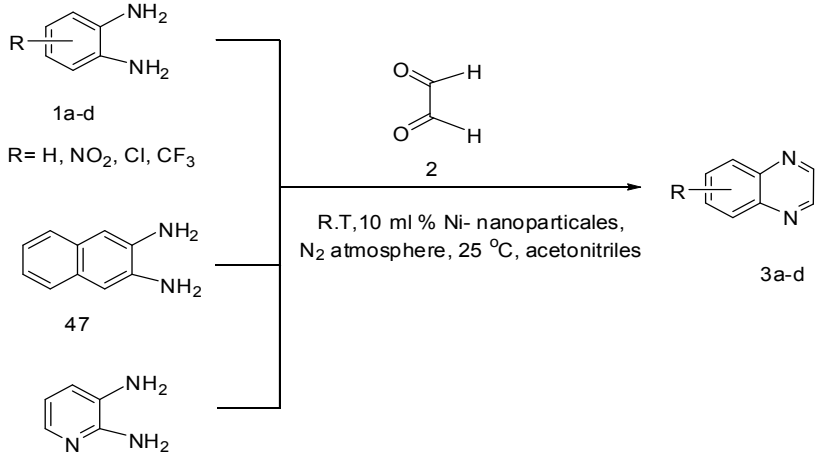


1a 2 3a

Scheme 1

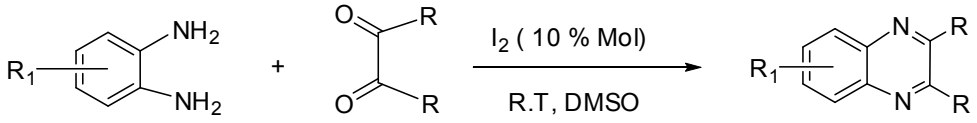
3.1.2. Use Different Methods of Catalyst Systems and Reaction Conditions

Quinoxalines derivatives **3a-d** was prepared via stirring of glyoxal **2** and *o*- phenylenediamine derivatives **1a-d** in acetonitrile in the presence of monodispersed and easily recyclable Ni-nanoparticles [**73**]. Shown in (Scheme 2).



Scheme 2

Furthermore, One -pot synthesis of quinoxaline derivatives were prepared via reacted *o*-phenylenediamine derivatives **1a, b, e** with 1, 2-dicarbonyl compounds [oxalaldehyde, biacetyl, oxalyl difluoride and dimethyl oxalate] respectively at room temperature by using different catalysts [**74-86]** as $CuSO_4.5H_2O$, IBX, lead oxide (PbO), ZrO_2, iodine, Palladium and Polyaniline sulphate, CuO nano particles, ZnO-β Zeolite, $HClO_4{\cdot}SiO_2$, and ruthenium-charcoal (Ru/C) were reported. The procedure presented is operationally simple, practical and green, shown in (Scheme 3).



1a,b,e 3a,e-g

R_1 = H, NO_2, CH_3 R= H, Me, F, OCH_3

Scheme 3

Some of different catalyst system (table 1) used for synthesis of quinoxaline derivatives and preparation of quinoxalines *via* microwave and room temperature (table 2) and some of these methods is one of the science of green chemistry.

Table 1. Synthesis of quinoxalines by different catalyst system

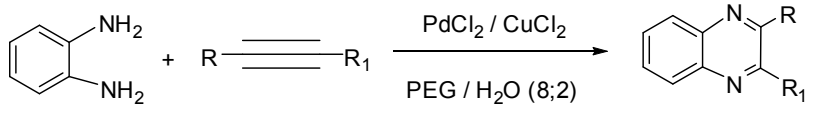
No. of References	Names of Scientists	Type of Catalyst used
[94-96]	More SV *et al*.; Wan JP *et al*.; Kumar BSPA *et al*.;	In Aqueous Media
		1. Using ceric ammonium nitrate (CAN) 2-Using trimethylsilyl chloride (TMSCl) 3. Using N-bromo succinimide

Table 2. Synthesis of quinoxalines via different reaction conditions

No. of References	Names of Scientists	Type of reaction conditions
[87-93]	Mohsenzadeh F et al.; Ashry El S H El et al.; Zhou JF et al.; Zhou J F et al.; Zhou JF et al.; Padmavathy K et al.; Zhang X Z et al.	Using microwave energy
[97-101]	Darabi HR et al.; Aghapoor K et al.; Meshram HM et al.; Hou JT et al.; Ghosh P et al.;	At room temperature

3.1.3. Oxidation of Aromatic Diamines with Many Organic Materials

Alkynes [102] **4** were oxidized efficiently using the catalytic amount of $PdCl_2$ and $CuCl_2$ in PEG-400 in the presence of H_2O with *o*-phenylenediamine **1a**.The optimized conditions were successfully utilized for the one-pot synthesis of 2,3-disubstituted quinoxaline derivatives, shown in (Scheme 4).

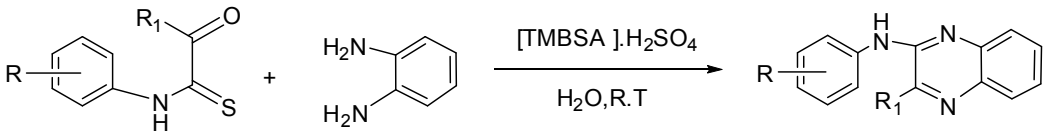


1a 4 3h-K

h; R = Ph R_1= 3-hydroxyphenyl
i; R = Ph R_1= P-tolyl
j; R = Ph R_1= 4-cyanophenyl
k; R = Ph R_1= 6-methoxy-2-naphthyl

Scheme 4

Furthermore, recyclable task-specific ionic liquid *N, N, N*-trimethyl -*N*- propane- sulfonic acid ammonium hydrogen sulfates [TMPSA]. H_2SO_4 was used as the catalyst [**103]** for the synthesis of quinoxaline **6**. Thus; treatment of *N*-substituted aniline**5** with *o*-phenylenediamine **1a** in water in the presence of [TMPSA]. HSO_4 afforded the 2, 3-disubstituted quinoxaline derivatives **6**. The reaction could be accomplished in water as well as organic solvent, and the satisfactory results were obtained under the mild conditions, shown in (Scheme 5).

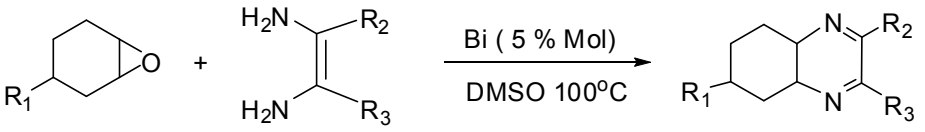


5 1a 6

R= H, NO_2, Cl, CF_3

Scheme 5

Moreover, tetrahydroquinoxaline derivatives **9** was achieved from epoxides **7** and ene-1, 2-diamines **8** by a Bi-catalyzed oxidative coupling by using Bi (5 mol %) as catalyst in presence of DMSO solvent **[104]**, shown in (Scheme 6).

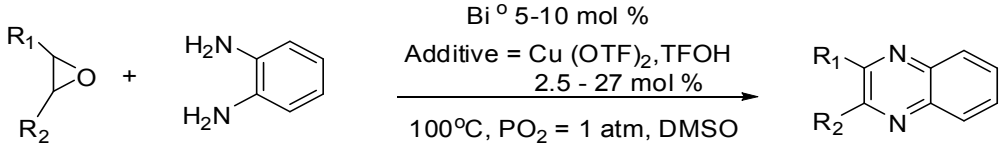


7 8 9

R_1,R_2,R_3= H

Scheme 6

Bi-catalyzed oxidative coupling of epoxides **[104] 10** and *o*-phenylenediamine **1a**-afforded 2, 3-susbstituted quinoxaline derivatives **3**, shown in (Scheme 7).

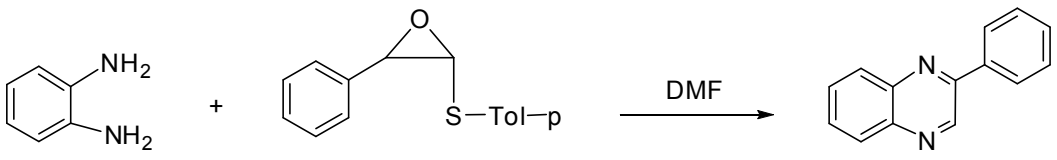


10 1a 3a

R_1, R_2 = H

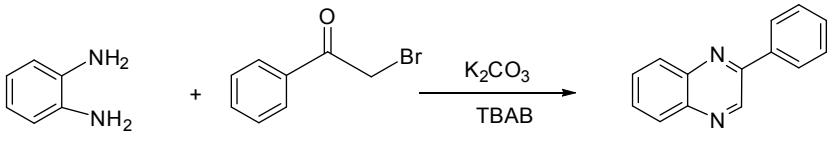
Scheme 7

Condensation of *p*- tolylsulfone **29**, **[104]** with *o*-phenylenediamine **1a** in DMF yields 2-phenyl - quinoxaline **30**, shown in (Scheme 8).



1a 29 30

Scheme 8

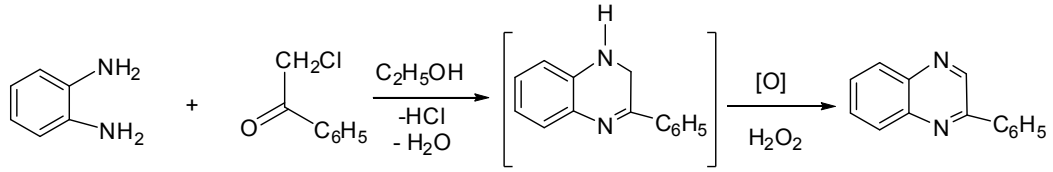


1a 31 30

Scheme 9

Moreover, reactions of α-bromo ketones (2-bromo-1-phenylethanone **31**) with *o*-phenylenediamine **1a** in presence of *tetra*-butyl ammonium bromide (TBAB) [117] in aqueous basic medium yield substituted quinoxalines **30**. This method proved to be easy, economic safe, and time consuming, shown in (Scheme 9).

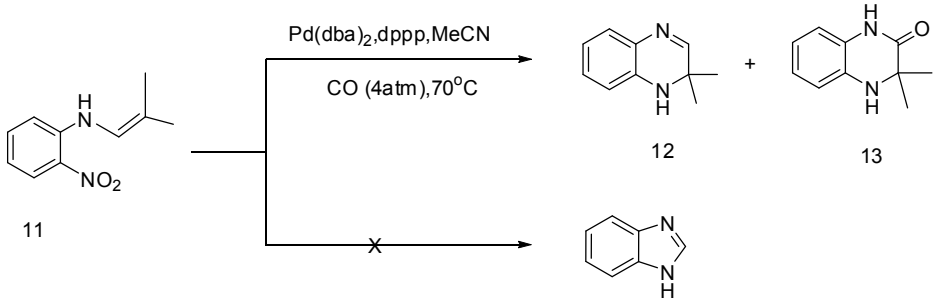
Furthermore, phenylquinoxaline **30** has been prepared through refluxing of phenacyl chloride **32** with *o*-phenylenediamine **1a** in ethanol followed by oxidation of the formed intermediate **33** [108, 118], shown in **(**Scheme 10).



1a 32 33 30

Scheme 10

The enamine **11** was subjected to the N-hetero-annulation conditions consisting of Pd $(dba)_2$ (0.07 mol %) and dppp (0.07 mol %) in DMF (w0.1 M) under 4 atm of carbon monoxide with the anticipation of a rapid enamine-imine tautomerization, followed by cyclization to give 1,2-dihydroquinoxaline **12** and 3,4-dihydroquinoxalin- one **13**, [105] were isolated in place of the expected benzimidazole **171**, shown in (Scheme 11).

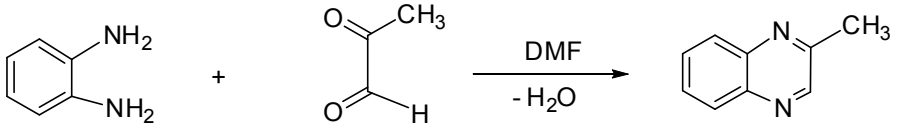


11 12 13 171

Scheme 11

3.1.4. Condensation of Aromatic Diamines and Dicarbonyl Derivatives.

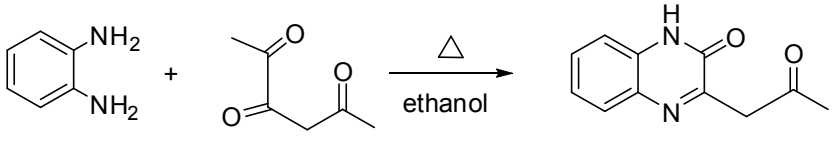
Condensation of aromatic diamine and α-dicarbonyl compound is a very facile and widely used method for the synthesis of quinoxalines and alkyl substituted quinoxalines [106-108]. Thus, 2-methyl-quinoxaline **3L** was prepared by the reaction *o*-phenylenediamine **1a** and 2-oxopropionaldehyde **2** in DMF; these compounds have been identified as antibacterial activity, shown in (Scheme 12).



1a 2-oxopropanal 3 L

Scheme 12

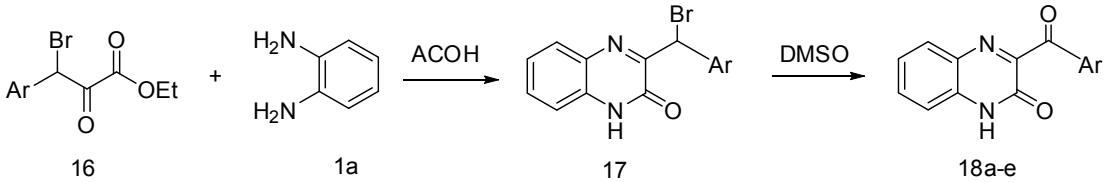
New derivatives of 3, 4-dihydroquinoxaline-2 (1*H*) -one **15** were synthesized and [109] characterized by reaction of *o*-phenylenediamine **1a** and hexane-2, 3, 5-trione **14** in ethanol, shown in (Scheme 13).



1a 14 15

Scheme 13

Reaction of 3-Bromo-2-oxo-3-phenyl-propionic acid ethyl ester derivatives **16** with *o*-phenylenediamine **1a** in acetic acid afforded the quinoxalin-2(1*H*)-ones derivatives **17** which oxidized in DMSO to give the quinoxalin-2(1*H*)-one derivatives **18** [110], shown in (Scheme 14).

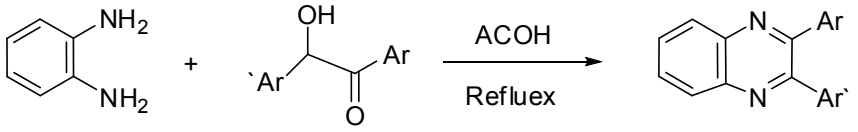


16 1a 17 18a-e

Ar, (a) = Ph
(b) = 4-BrC_6H_4
(c) = 2,4-$Cl_2C_6H_3$
(d) = 3-$O_2NC_6H_4$
(e) = 4-$O_2NC_6H_4$

Scheme 14

o-phenylenediamine **1a** and α-hydroxy ketones [111] in acetic acid *via* two methods: microwave irradiation and simple heating gave compounds **20a,b**, shown in (Scheme 15).

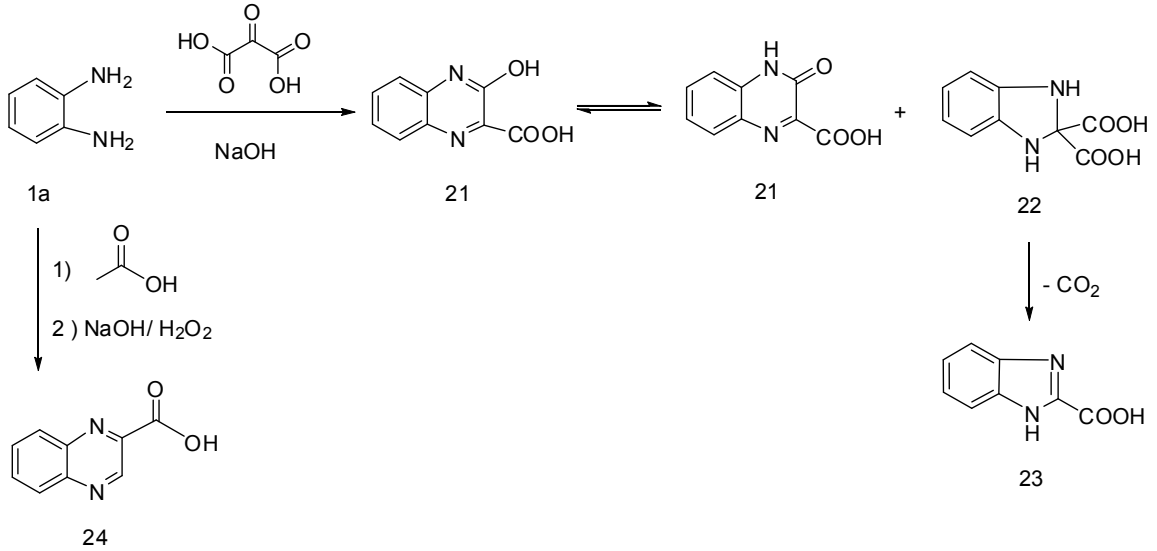


1a 19 20a,b

a ; Ar , Ar` = Ph
b: Ar = ph, Ar` = 4-$OMeC_6H_4$

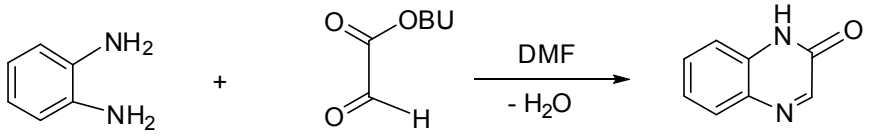
Scheme 15

Condensation of mesoxalic acid derivatives (2-oxomalonic acid) and *o*-phenylenediamine **1a** proceeds as expected whereas with sodium mesoxalate an anomalous reaction occurs [112] gave toutomerizem of 2-hydroxy quinoxaline-3-carboxylic acid or 3-oxo-3, 4-dihydro- quinoxaline-2-carboxylic acid **21**. Hydrogen transfer occurs even when a vigorous stream of oxygen is passed through the reaction mixture l, 2-dihydro benzimidazole- 2, 2-dicarboxylic acid **22** rather than its decarboxylation product **23** is thought to be the reducing agent. Condensation of *o*-phenyldiamine **1a** with acetic acid [113] and form 2-tetrahydroxy butyl quinoxaline which further react with hydrogen peroxide and solid sodium hydroxide form quinoxaline-2-carboxylic acid **24**. All compounds show highest biological activity, as in (Scheme 16).



Scheme: 16

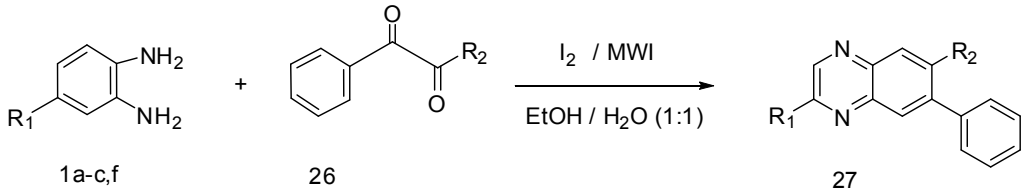
Quinoxaline-2-ones **25** were obtained in excellent yields by the condensation of *n*-butyl- oxo-acetate **2** and *o*-phenylenediamine **1a** in DMF [114], shown in (Scheme 17).



1a 2 25

Scheme:17

Condensation of *o*-phenylenediamine **1a-c, f** and 1, 2- dicarbonyl compounds **26** in the presence of a mild acidic reagent [115] lead to the synthesis of quinaxolines derivatives **27** in the presence of iodine as catalyst using microwave irradiation, shown in (Scheme 18).

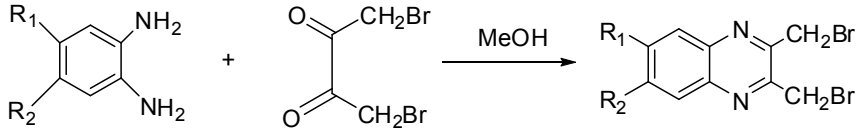


1a-c,f 26 27

R_1 = H,NO_2, Cl, OMe,
R_2 = H, CH_3,Ph

Scheme 18

Another approach for the synthesis of 2, 3-Bis (bromomethyl)quinoxaline derivatives **28** were synthesized by the condensation reaction of the corresponding *o*-phenylenediamine derivatives **1a** with 1,4-dibromo-2,3-butanedione **2** [13, 116], shown in (Scheme 19).

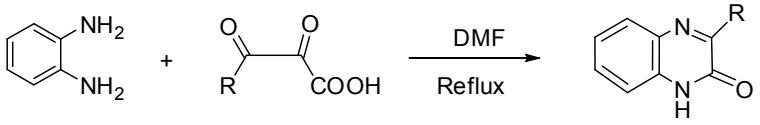


1a 2 28a,b

R_1 ; R_2 = H
R_1 = H R_2= CH_3

Scheme 19

Condensation of *o*-phenylenediamine **1a** with pyruvic acid **34** in DMF afforded 3- methyl quinoxaline- 2-one **35** [118], shown in (Scheme 20)



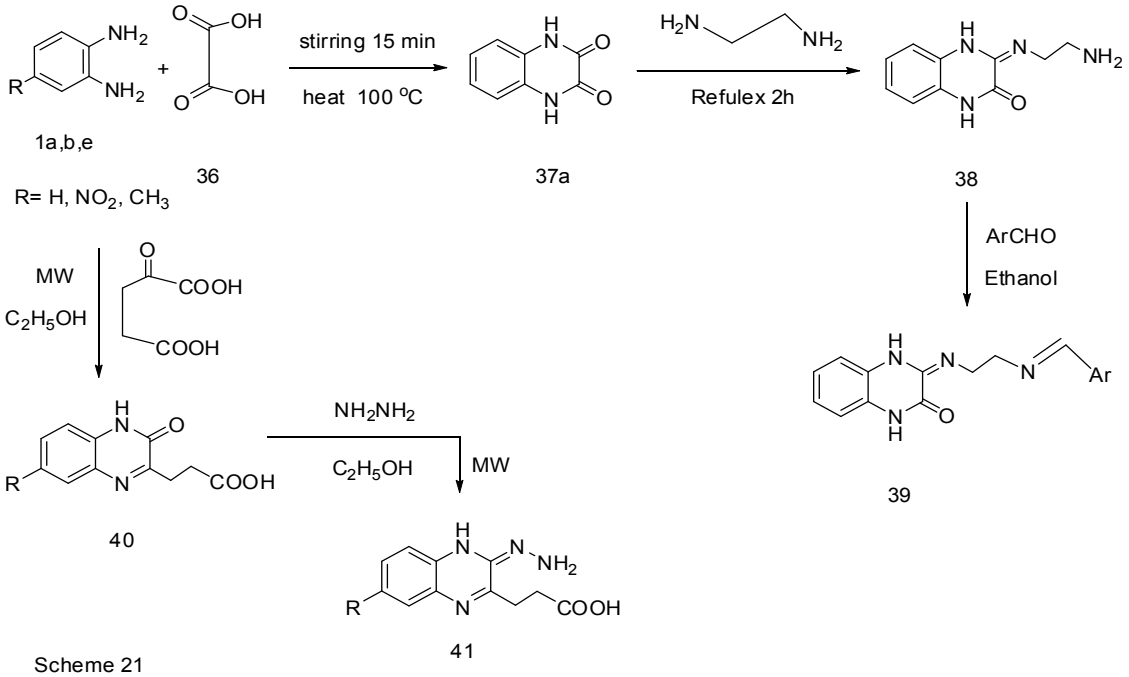
1a 34 35

R = CH_3

Scheme 20

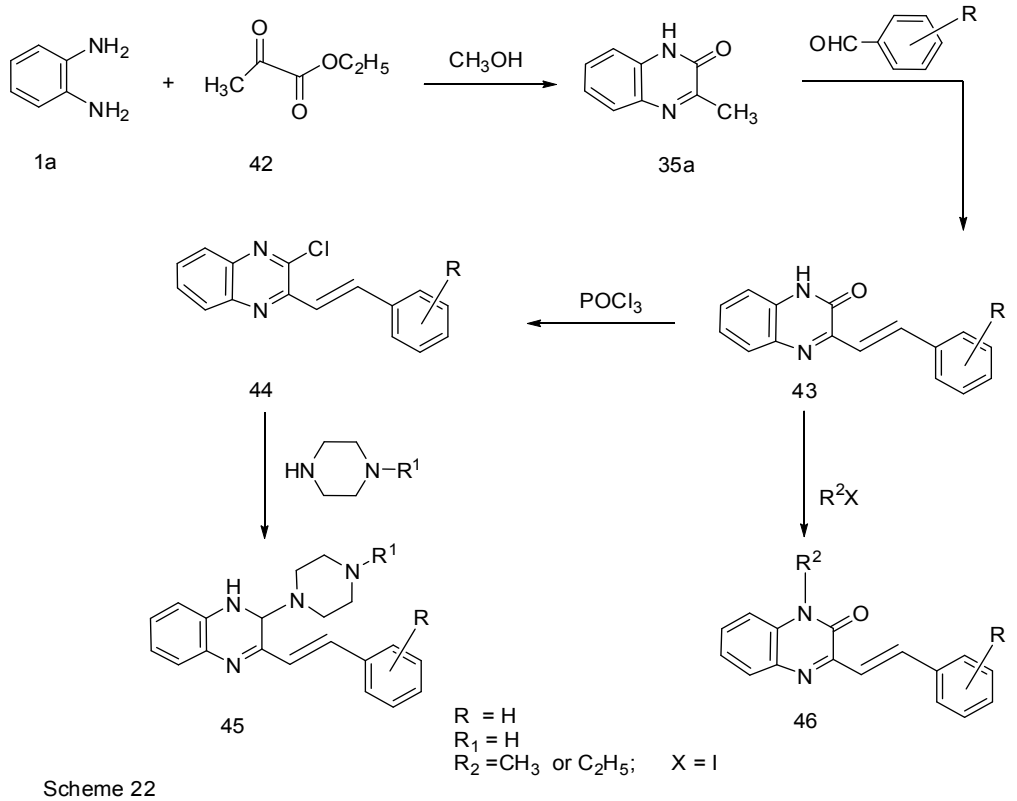
Synthesis of potential chemotherapic quinoxalinones via biocatalysis, thus, reaction of *o*-phenylenediamine **1a,b,e** and oxalic acid **36** [118-123] to give 1,4-dihydro quinoxaline-2,3-dione **37** which was reacted with ethane-1,2-diamine to yield 3-(2-amino-ethylimino)-3,4-dihydro-1*H*-quinoxalin-2-one **38**, the latter compound **38** was reacted with aryl aldehyde derivatives gave 3-[2-(benzylidene-amino) -ethyl- imino]- 3,4- dihydro-1*H*-quinoxalin-2-one derivatives **39**. Some of quinoxalinone derivatives was synthesized microwave assisted reaction between substituted aromatic diamine and α- keto-

glutric acid (2-oxopentanedioic acid) to yield 3-(3-oxo -3, 4-dihydro- quinoxalin-2-yl) propionic acid **40** and then treated with hydrazine hydrate to yield its hydrazones derivatives **41**, quinoxaline derivatives as potential anti-virus, shown in (Scheme 21).



Scheme 21

Condensation of **1a** with ethyl-2-oxo-propanoate **42** in methanol afforded quinoxalin-2(1*H*)-one **35,** which condensed with aromatic aldehyde to give 3-substituted styryl- quinoxalin-2(1*H*)-ones **43a-d**; [124] refluxing of **43a-d** with $POCl_3$ afforded the 2-chloro **44a-d**, which reacted with 4-substituted piprazine to give 2-piperazinyl derivatives **45a-g**. In addition, a series of 1-alkyl-3-substituted styryl- quinoxalin-2(1*H*)-ones **46a-d** was also prepared via reaction of **43a-d** with alkyl halide as show. These compounds have antimicrobial activity, shown in (Scheme 22).



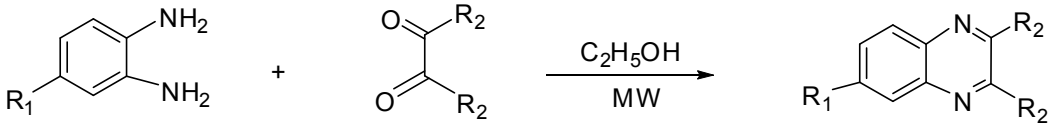
Scheme 22

Synthesis of quinoxalinone derivatives **48** via reacted of 2, 3- diamine- naphthalene **47** with a variety of α-ketoacids (2-oxopropanoic acid) through enzymatic catalysis or microwave irradiation [119], shown in (schemes 23).

47 48

Scheme 23 R = CH_3

Condensation reaction of *o*-phenylenediamine **1a, e** with α-dicarbonyl derivatives in ethanol under microwave irradiation afforded quinoxalines **3a, m** high yield [120], short reaction time; pure products without purification and using only ethanol instead of toxic and expensive solvents for isolation of the products are the advantages of this method, shown in (Scheme 24).

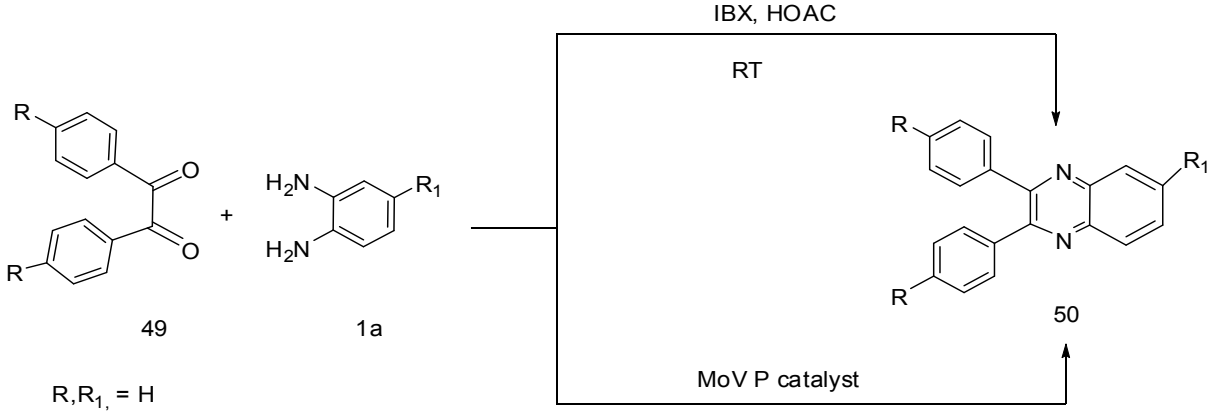


1a,e 3a,m

R_1 = H R_2 = H
R_1 = CH_3 R_2 = CH_3

Scheme 24

A readily available hypervalent iodine reagent was found to be highly effective in synthesis of quinoxaline derivatives **50**; [125-128] thus, stirring of 1, 2-diketones **49** and *o*-phenylenediamines **1a** at room temperature in acetic acid in presence of *o*-iodoxy benzoic acid (IBX) or in the presence of molybdophospho- vanadates (MOVP) as catalysts and toluene as solvent afforded **50**, shown in (Scheme 25).

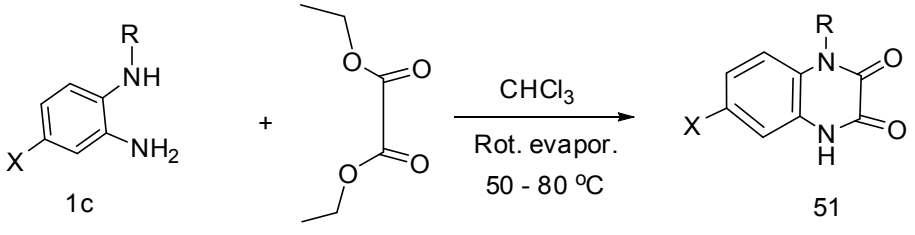


49 1a 50

R,$R_{1,}$ = H

Scheme: 25

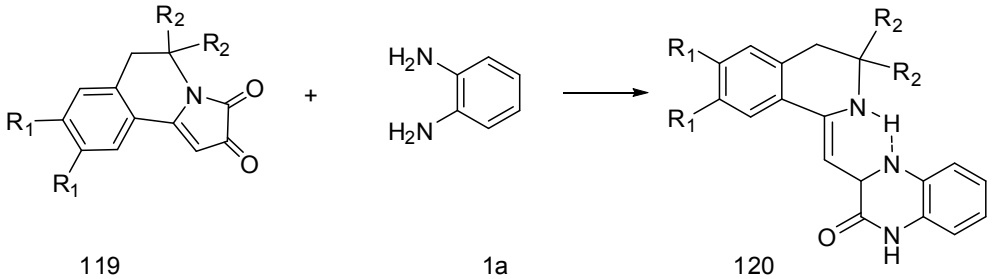
Various quinoxaline-2, 3-diones **51** [126] were synthesized by rotatory evaporation of 1, 2-diamino aromatic **1c** in diethyl oxalate in chloroform at 50-80℃; compound **51** as NMDA receptor antagonists, shown in (Scheme 26).



1c 51

Scheme 26 X = Cl , R = H

Reaction of *o*-phenylenediamine **1a** with 1, 2-dicarbonyl derivatives **119** in propan-1-ol in the presence of a catalytic amount of hydrochloric acid or *p*-toluene sulfonic acid [153] afforded quinoxalin-2-ones derivatives **120**, shown in (Scheme 27).

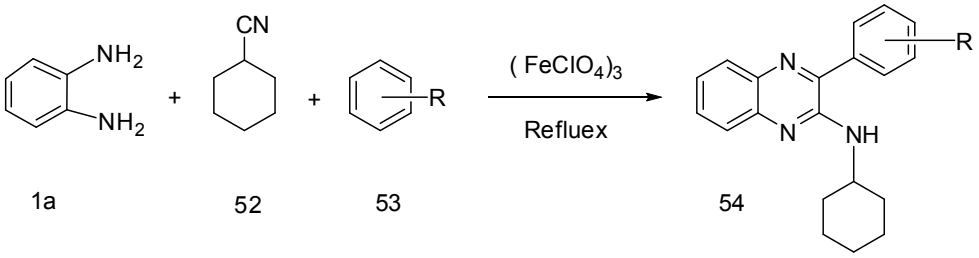


119 1a 120

R_1 = H

Scheme 27

Condensation of mixture *o*-phenylenediamine **1a**, cyclohexyl isocyanide **52** and aromatic aldehydes **53** in the presence of $(FeClO_4)_3$ as a catalyst afforded the corresponding *N*-cyclohexyl-3-aryl-quinoxaline-2-amines **54**, [129-131], shown in (Scheme 28).

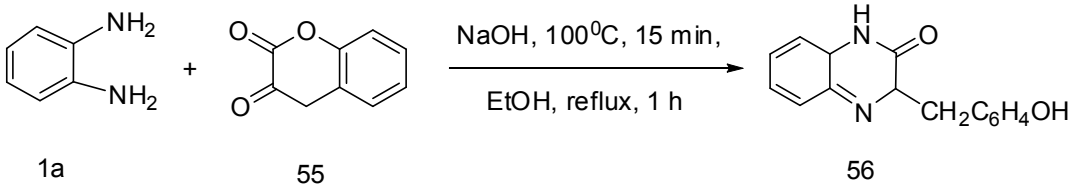


1a 52 53 54

R = H, 3- NO_2-C_6H_4, 4-Cl-C_6H_4 ,
4- NO_2- C_6H_4, 4-OCH_3-C_6H_4

Scheme 28

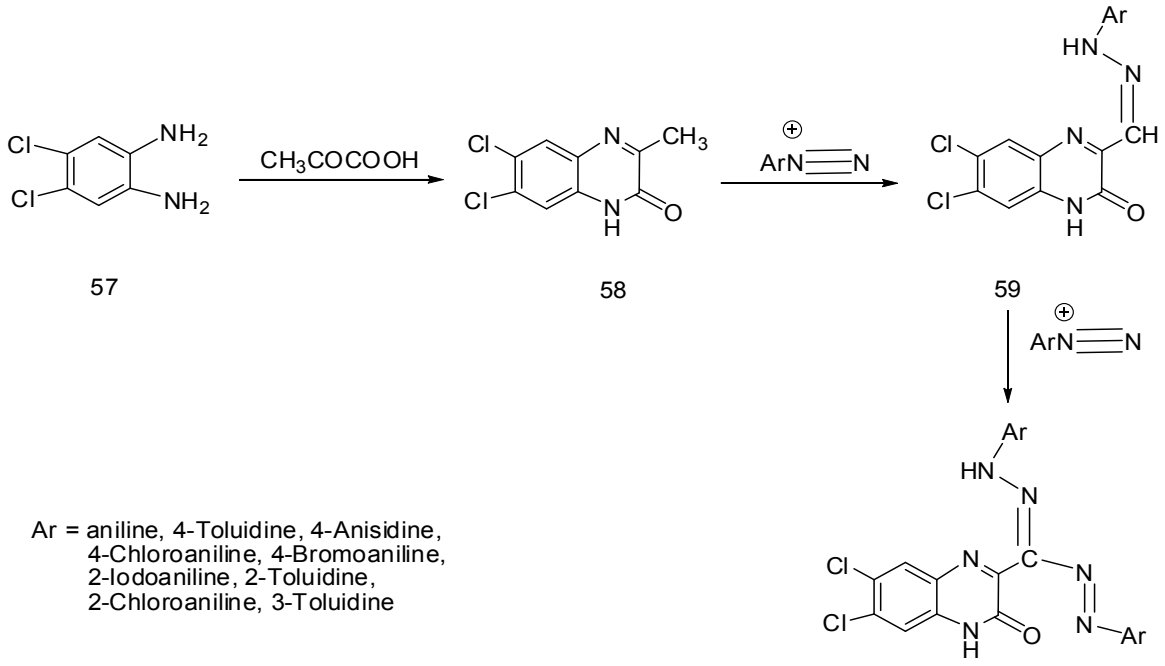
Reaction of *o*-phenylenediamine **1a** with 3, 4-dihydro-2*H*-1-benzopyran-2, 3-dione **55** gave 3-o-hydroxybenzyl-2(1*H*)-quinoxalinone **56**; [132], shown in (Scheme 29).



1a 55 56

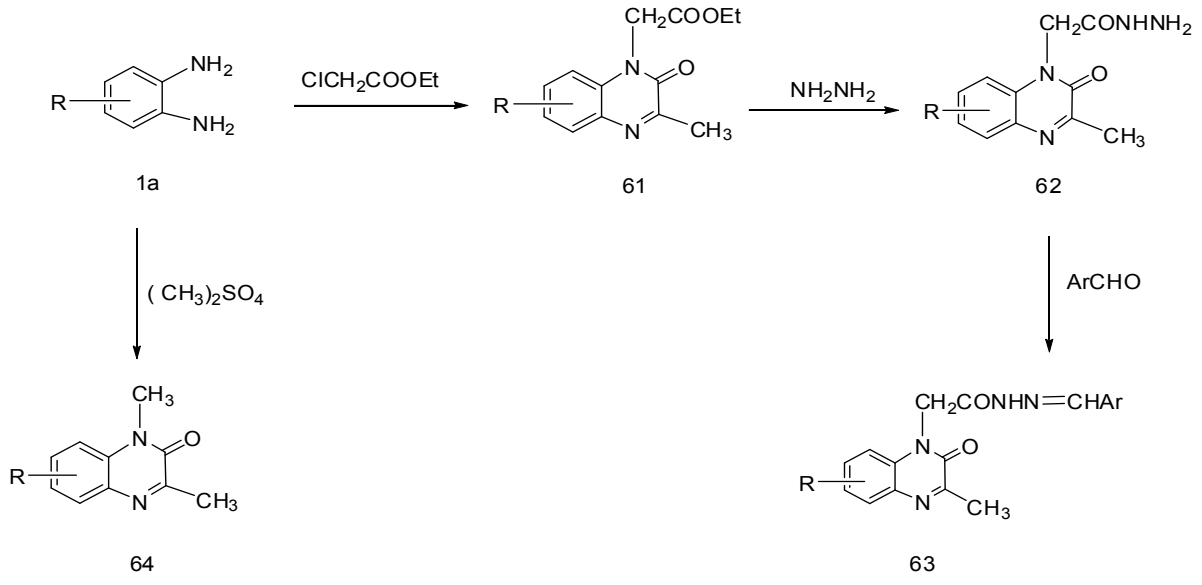
Scheme 29

Synthesis of aryl hydrazones, 2-oxo-6, 7-dichloro-1, 2-dihydro quinoxaline-3-carbaldehyde **60** occurred via refluxing [133] of dichlorophenylenediamine **57** with pyruvic acid followed by coupling with forming, as in (Scheme 30).



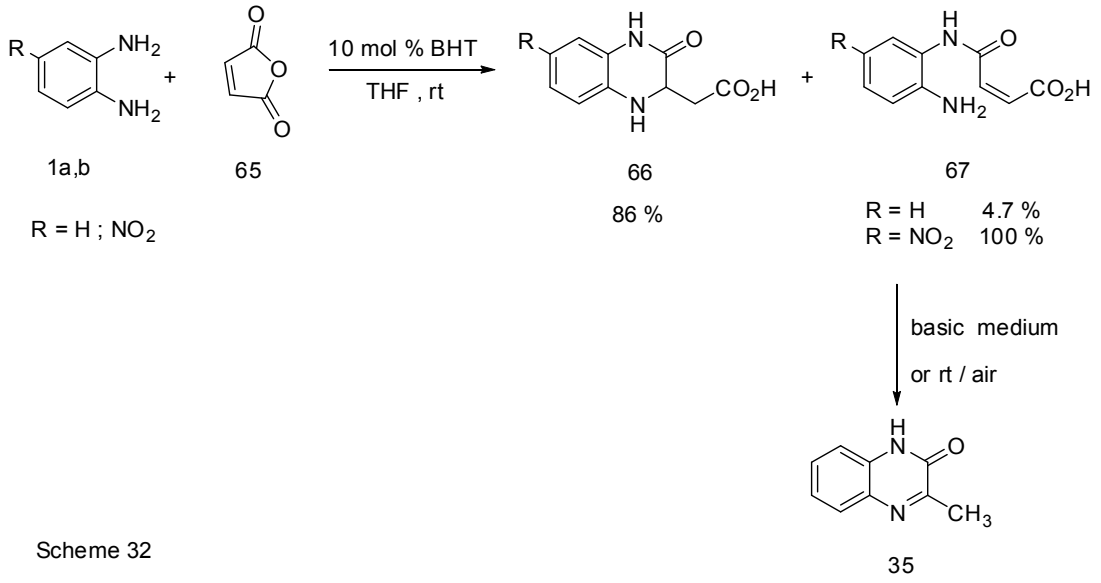
Scheme 30

Alkylation of *o*-phenylenediamine derivatives **1a** with dimethyl sulphate or ethyl chloroacetate produced [134] the quinoxalinone **61** and **64** respectively. Hydrazinolysis of the ester derivative **61** with hydrazine hydrate afforded the hydrazide derivative (3-methyl-2-oxo-2*H*-quinoxalin-1-yl) - acetic acid hydrazide **62**, which underwent condensation with aldehyde to give hydrazone derivative **63**; these compounds have antimicrobial activity, shown in (Scheme 31).



Scheme 31

Stirring of phenylenediamine **1a,b** with maleic anhydride **65** in THF [135] in the presence of 10 mol% of butylated hydroxyl toluene (BHT) afforded a mixture from 3-oxo -1, 2, 3, 4-tetrahydroquinoxalin-2-yl)-acetic acid **66** and 3-(2-amino-phenyl carbamoyl)-acrylic acid **67**. Decomposition of (3-oxo-1, 2, 3, 4-tetrahydro-quinoxalin-2-yl)-acetic acid) **66** and cyclized of **67** with basic medium afforded 3-methyl-1*H*-quinoxalin-2-one derivatives **35**, shown in (Scheme 32).



1a,b 65 66 67

R = H ; NO_2

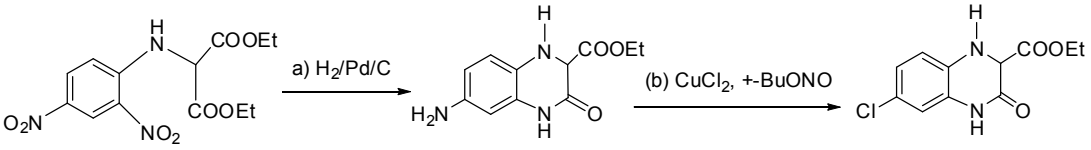
86 %

R = H 4.7 %
R = NO_2 100 %

35

Scheme 32

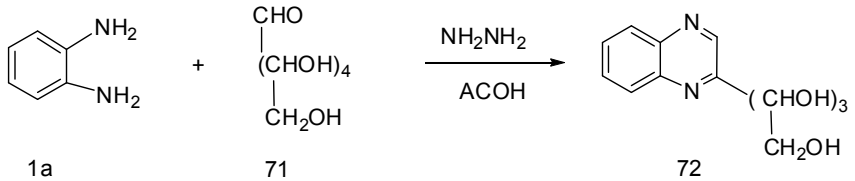
Synthesis of 6-chloro-3-oxo-1, 2, 3, 4-tetrahydroquinoxaline-2-carboxylic acid ethyl ester **70**, [136] via reduction and cyclization of 2-(2, 4-dinitro-phenylamino)-malonic acid diethyl ester **68** with (H_2/Pd/C). Compound **69** was reacted with ($CuCl_2$ + BuONO) to give **70**; these compounds as Glycine /NMDA receptor antagonist, shown in (Scheme 33).



68 69 70

Scheme: 33

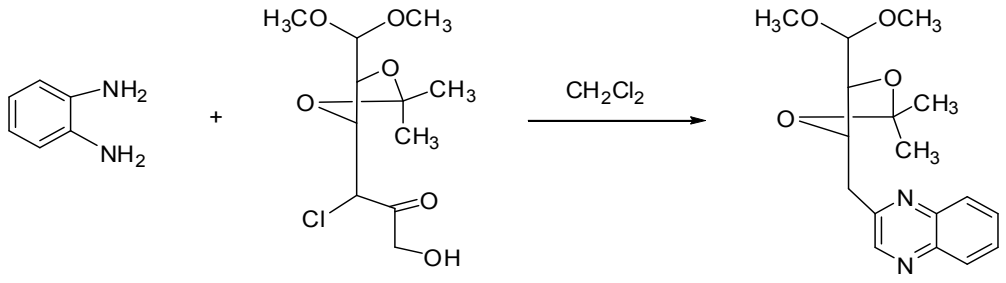
Quinoxaline derivative **72** was also prepared via condensation of glucose **71** with *o*-phenylenediamine **1a** [137, 138], shown in (Scheme 34).



1a 71 72

Scheme 34

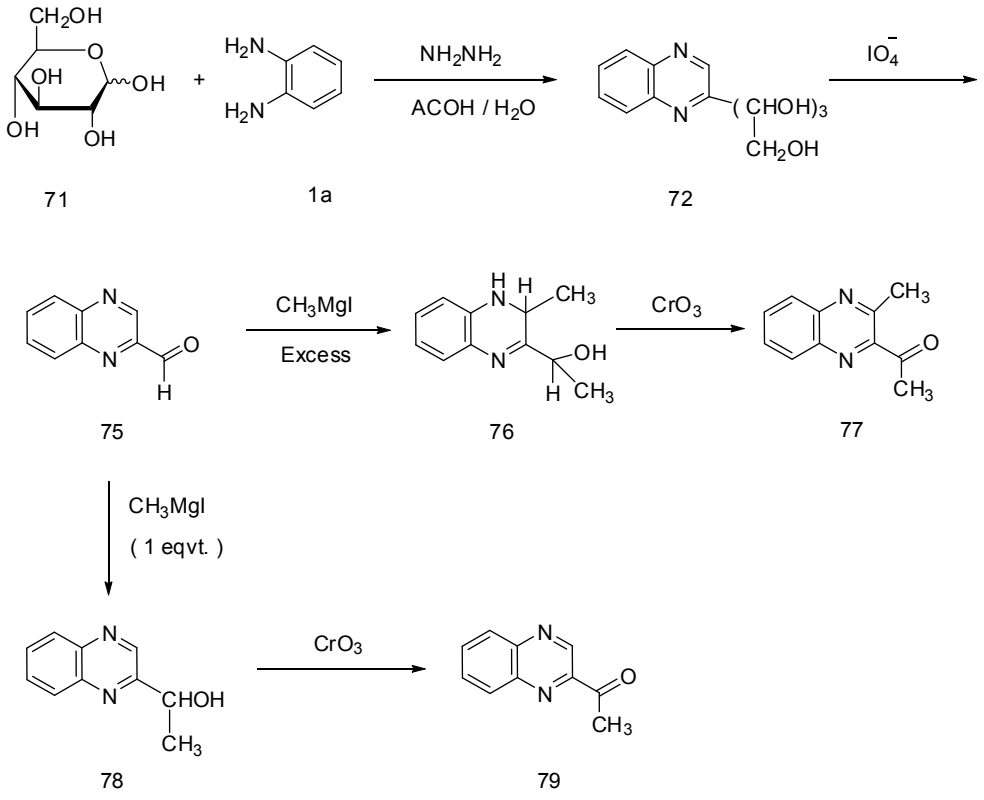
Reaction of hexulose **73** with *o*-phenylenediamines **1a** under neutral conditions in presences of dichloromethane [139] afforded the quinoxaline derivatives **74**; these compounds have cytotoxic activities, as in (Scheme 35).



1a 73 74

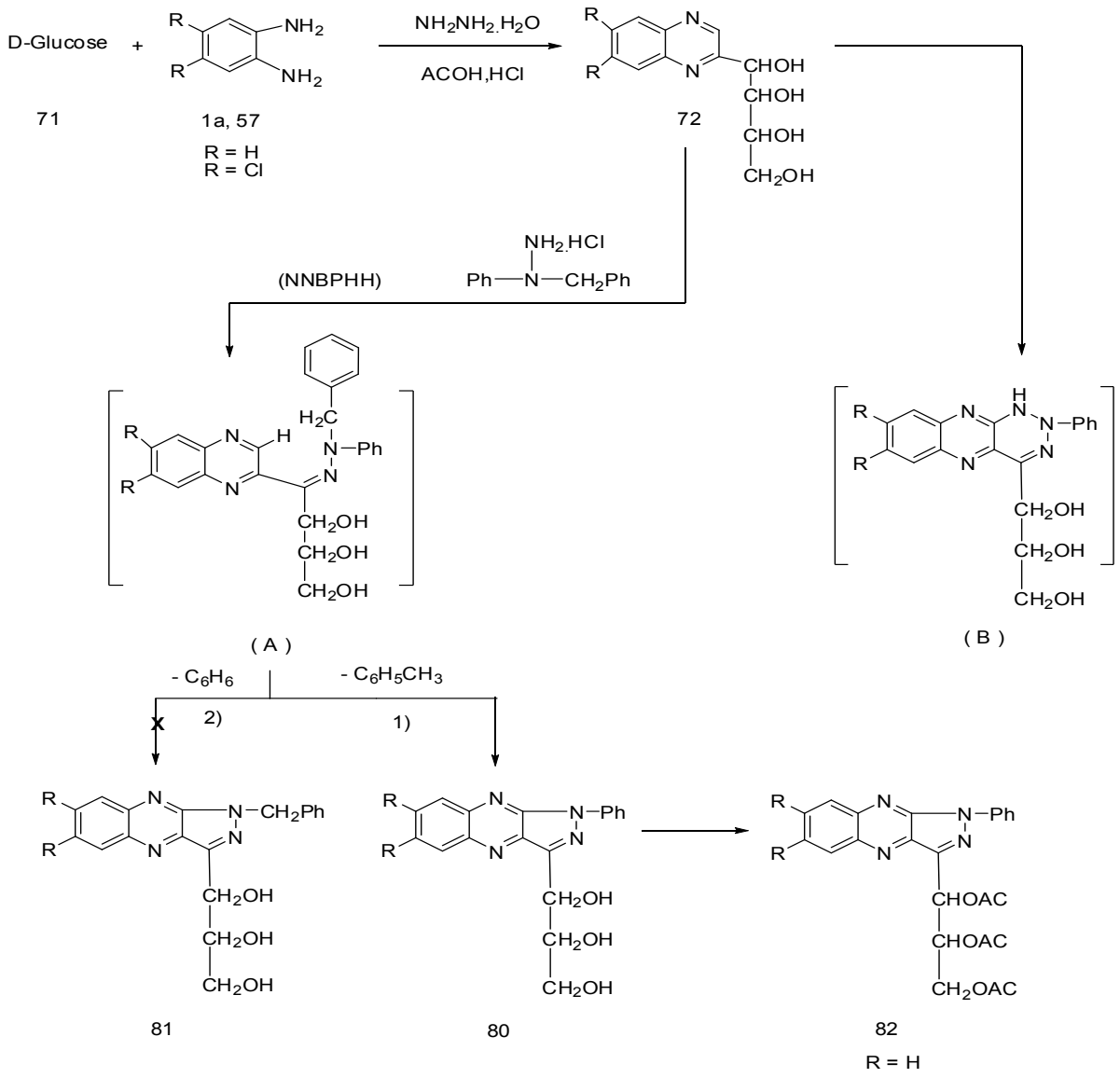
Scheme 35

Treatment of D-glucose **71** with *o*-phenylenediamine **1a** in the presence of hydrazine hydrate and acetic acid [137, 140-143] gave the tetrahydroxybutyl- quinoxaline derivative **72** which oxidized with iodate to give quinoxaline-2-carboxaldehyde **75**. Treatment of quinoxaline-2-carboxaldehyde **75** with excess of methyl magnesium iodide in ether gave 3-methyl-3, 4-dihydro-2- (hydroxyethyl) quinoxaline **76**. Oxidation of **76** with CrO_3 gave 12-acetyl-3 methylquinoxaline **77**. Alkylation of Quinoxaline-2-carbaldehyde **75** by methyl magnesium yielded 1-Quinoxalin-2-yl-ethanol **78** which was oxidation by CrO_3 to give 1-Quinoxalin-2-yl-ethanone **79**, as shown in (Scheme 36).



Scheme: 36

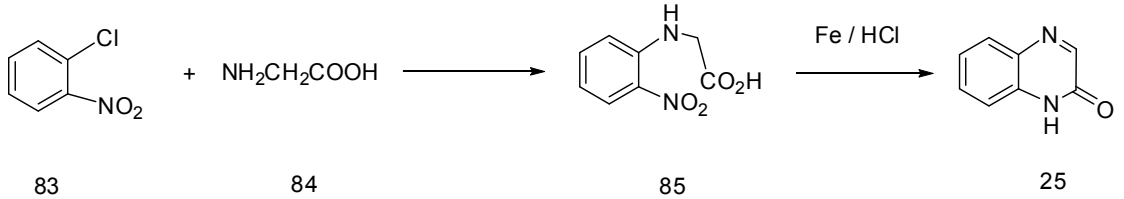
One-pot condensation of D-glucose **71**, *o*-phenylenediamine **1a or 57** with *N*,*N*-benzylphenylhydrazine hydrochloride in acidic medium [144] gave 3-(d-erythro-glycerol-1-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline **80**. Compound **80** was also obtained by condensation of 2-(D-*arabino*-tetritol-1-yl) quinoxaline **72** and NNBPHH in acidic medium. These results indicate that **72** is an intermediate during the formation of **80**, which reacts with NNBPHH in acidic medium to give *N*, *N*-benzyl- phenylhydrazone intermediate "A". The unisolated intermediate "A" is then cyclized by the excess NNBPHH with elimination of the benzyl group in toluene to give **80**. The cyclization of the intermediate "A" takes place by two possible routes 1) either by removal of the benzyl group. This compound **80** turns into product **82** via actylation, shown in (Scheme 37).



Scheme 37. Synthesis of 3-(D-erythro-glycerol-1-yl)-1-phenyl-1*H*-pyrazolo[3,4-b]quinoxaline (3) and 6,7-dichloro-3-(D-erythro- glycerol-1-yl)-1-phenyl-1*H*-pyrazolo[3,4-b]quinoxaline (B) by effect of phenylhydrazine hydrochloride and *N,N*-benzylphenyl- ydrazine hydrochloride.

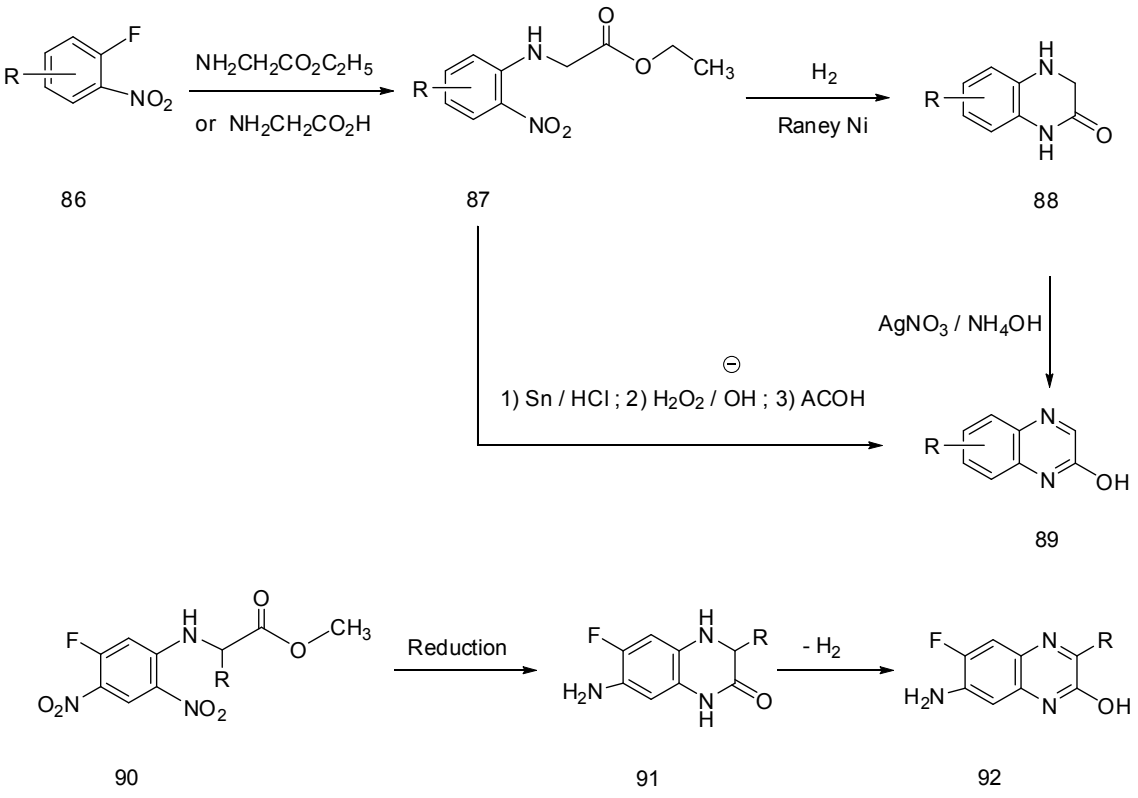
3.2. Intramolecular Cyclisation of N-Substituted Aromatic O-Diamines

Condensation of glycine **84** with *o*-Nitrohalogenobenzene **83** afforded 2-nitro-phenylamino)-acetic acid **89.** Reductive cyclisation of **85** with Fe/HCl gave quinoxaline-2-one **25** [145], shown in (Scheme 38).



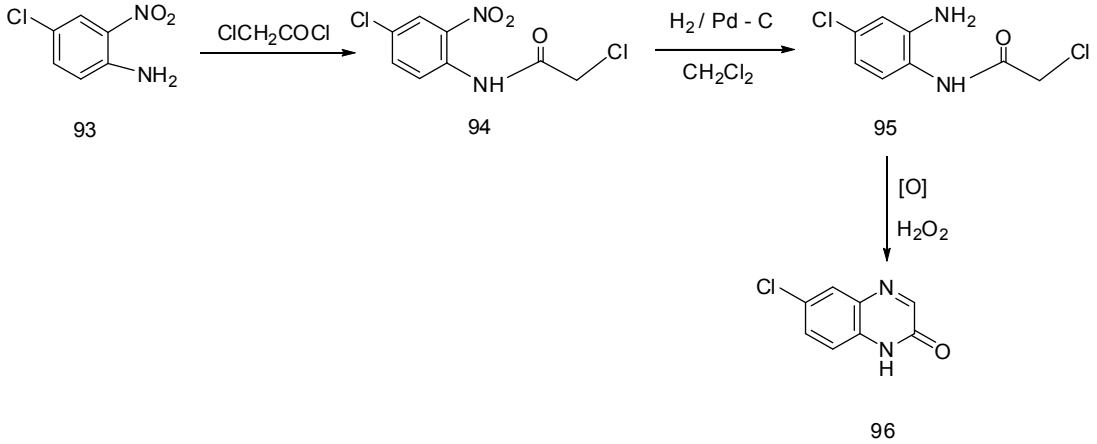
Scheme: 38

1, 5-difluoro-2,4-dinitrobenzene derivatives **86** reacted with amino acid or amino acid ester [146] to give the glycine derivatives **87**. Reductive cyclization of **87** with H_2 in Raney Ni afforded the quinoxalinones **88, 89** and products of **91, 92,** as shown in (Scheme 39).



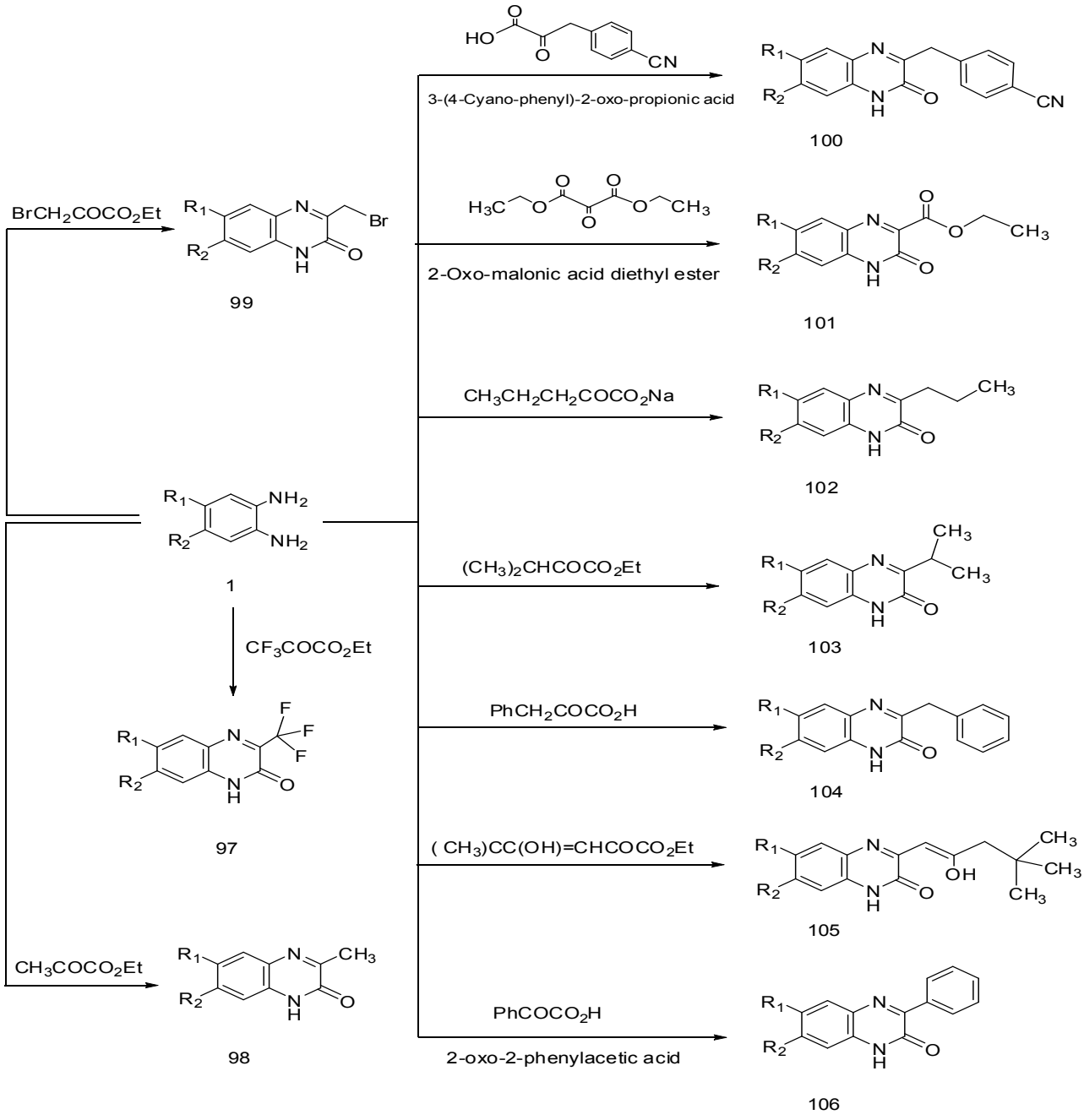
Scheme 39

6-chloro-1*H*-quinoxalin-2-one **99** was prepared by reaction of 5-chloro-2-nitro-phenylamine **93** with chloro acetyl chloride to yield 2-chloro-*N*-(4-chloro-2-nitro-phenyl)-acetamide **94**. Reduction of **94** which reduced with H_2/Pd-C to afford *N*-(2-amino-4-chloro-phenyl)-2-chloro acetamide **95** which further oxidized by H_2O_2 gave quinoxalin-2-one **96** [147], shown in (Scheme 40).



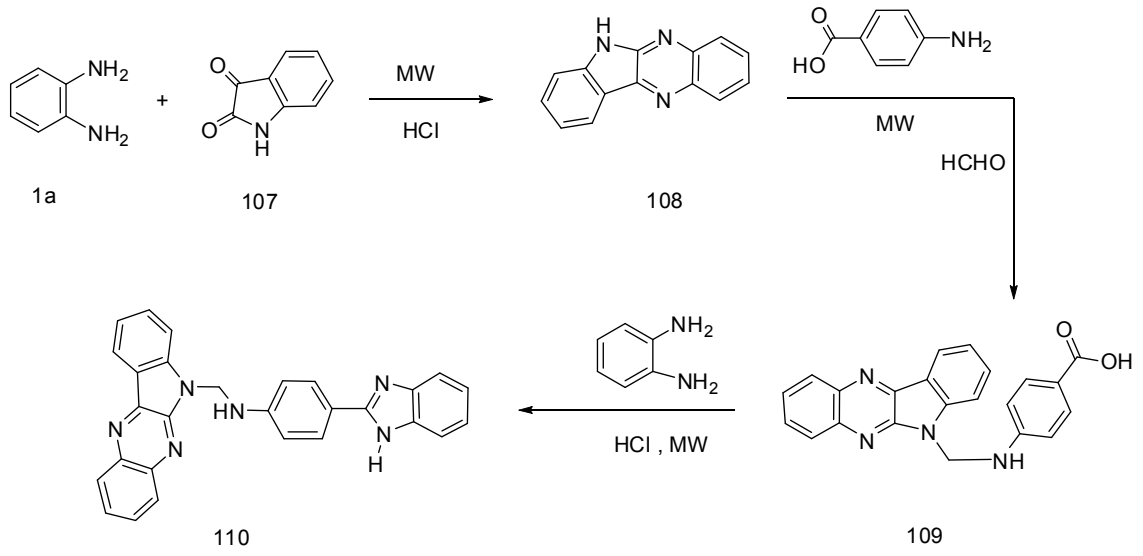
Scheme 40

A series of quinoxalinones derivatives (97-106) were prepared via reaction of o-phenalindiamine derivatives with many reagents [α - ketone acid (or aldehyde) ester] derivatives [148], all compounds have been identified as antibacterial, antifungal and anti-cancer agents, shown in (Scheme 41).



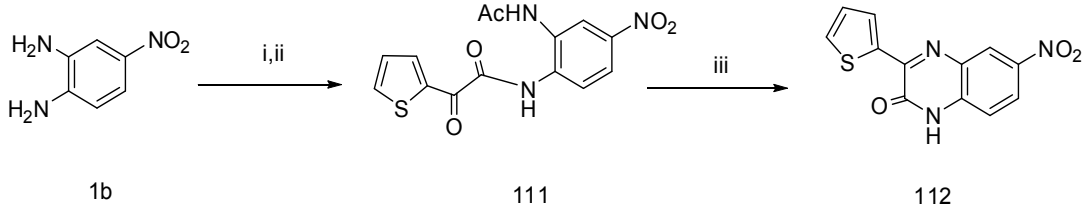
Scheme: 41 : Keto acid (or aldehyde) ester method for the synthesis of quinoxalinone derivatives

Reaction of isatine **107** [123,149] with *o*-phenylenediamine **1a** in the presence of hydro chloric acid give the quinoxaline derivatives **108** which was reacted with 4-amino-benzoic acid inter microwave to give 4-[(indolo[2,3-b]quinoxalin-6-ylmethyl)-amino]-benzoic acid **109**. Condensation of quinoaxaline of **109** with o-phenylene-diamine in the presence of hydrochloric acid gave [4-(1*H*-Benzoimidazol-2-yl)-phenyl]-indolo [2, 3-b] quinoxalin-6-ylmethyl-amine derivatives **110**, most of compounds have been identified as Potential Anti-Virus, shown in (Scheme 42).



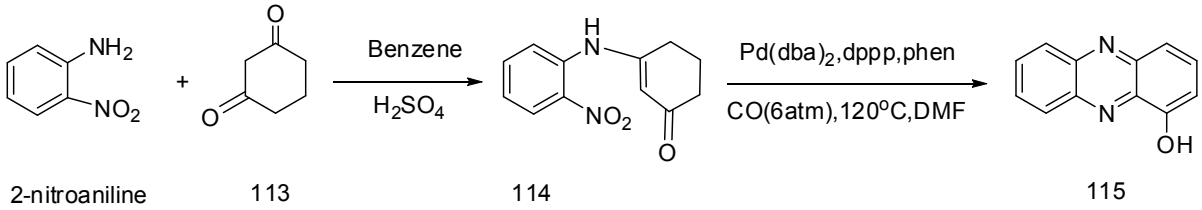
Scheme 42

Compound **1b** could be selectively reacted with acetic anhydride to provide the mono-acylated adduct in 95% yield and coupling with the α-keto acid as thiophene-2-glyoxylic acid gave *N*- (2-acetylamino- 4- nitro- phenyl) - 2- oxo -2 -thiophen-2-yl-acetamide **111**. Refluxing of compound **111** with methanol in presence hydrochloric acid to form 6-nitro-3-thiophen-2-yl-1*H*-quinoxalin-2-one **112** [150], shown in (Scheme 43).



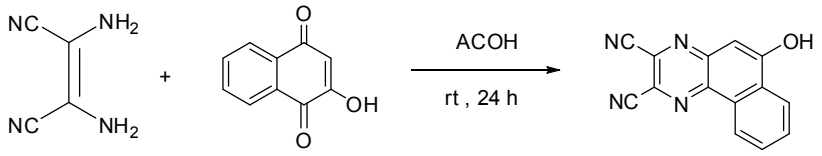
Scheme 43. Reagents and conditions: **(i)** Ac_2O, Et_3N, CH_2Cl_2, 0 ^oC to rt (95%); **(ii)** 2-thiophene-glyoxylic acid, EDCI, Et_3N, CH_2Cl_2, rt; **(iii)**1 M HCl, MeOH, reflux (70% over two steps).

Condensation of 1, 3-cyclohexanedione **113** with 2-nitroaniline gave 3-(2-nitro-phenylamino)-cyclohex-2-enone **114** which was cyclized by catalyst ($Pd(dba)_2$, dppp, phen) [105,151] in presences of DMF to produce phenazin-1-ol **115**, shown in (Scheme 44).



Scheme 44

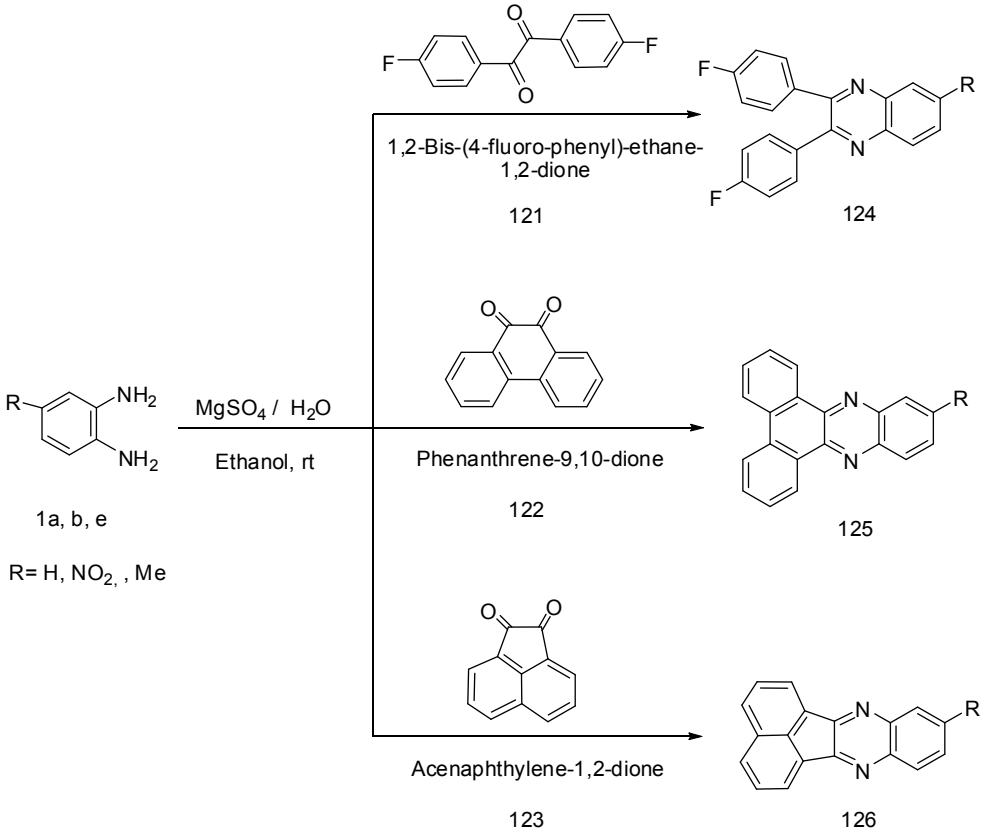
Reaction of diaminomaleonitrile **116** with 2-hydroxy-1, 4-naphthoquinone **117** in acetic acid at room temperature for 24 h [152] afforded 6-hydroxy-benzo*[f]* - quinoxaline-2, 3-dicarbonitrile **118**, shown in (Scheme 45).



116 117 118

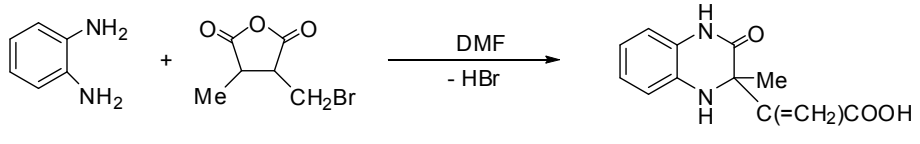
Scheme 45

Condensation of 1, 2-dicarbonyl derivatives **121** – **123** with *o*-phenylene- diamine **1a,b,e** at room temperature in the presence of magnesium sulfate heptahy- drate ($MgSO_4 \cdot 7H_2O$) afforded phenazine and quinoxaline derivatives **124**–**126**; **[**154-163] in excellent yields, shown in (Scheme 46).



Scheme 46. The synthesis of quinoxaline and phenazine derivatives using $MgSO4 \cdot 7H_2O$ as a catalyst.

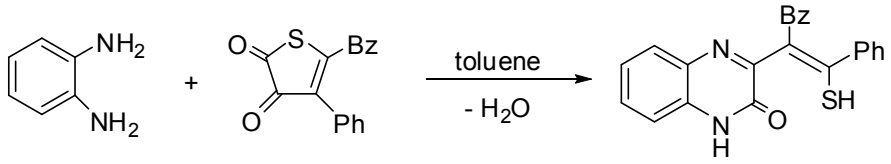
Condensation of *o*-phenylenediamine **1a** and 3-bromomethyl-4-methyl-2, 5-dihydro-2, 5-furandione (2-bromomethyl-3-methylmaleic anhydride) **127** in DMF gave 3-(1-carboxy vinyl) - 3-methyl-3, 4-dihydro-2(1*H*)-quinoxalinone **128** with loss of hydrogen bromide [**132], as in** (Scheme 47).



1a 127 128

Scheme 47

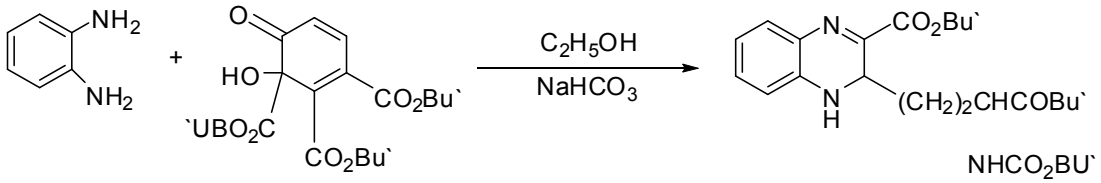
Reaction of o-phenylenediamine **1a** with 4-benzoyl-5-phenyl-2, 3-dihydro-2, 3-thiophenedione **129** in toluene [132] afforded 3-(α-benzoyl-β-mercaptostyryl)-2(1*H*)-quinoxalinone **130,** as shown in (Scheme 48).



1a 129 130

Scheme 48

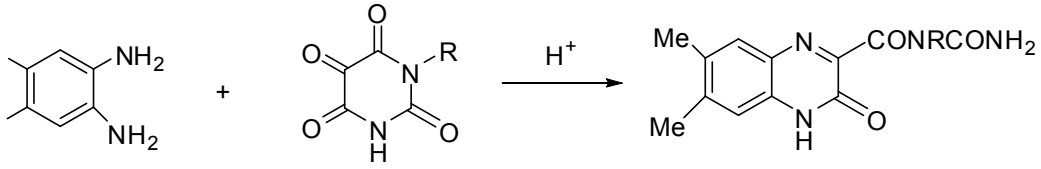
Condensation of o-phenylenediamine **1a** with 3-hydroxy-4-oxo-cyclohexa-1, 5-diene-1, 2, 3-tri-carboxylic acid tributyl ester **131** in hot aqueous ethanolic sodium hydrogen carbonate gave tert-butyl 3-[3-(tert-butoxycarbonyl)-3-(tert-butoxy carbonylamino) propyl]-2-quinoxaline carboxylate **132** [132], shown in (Scheme 49).



1a 131 132

Scheme 49

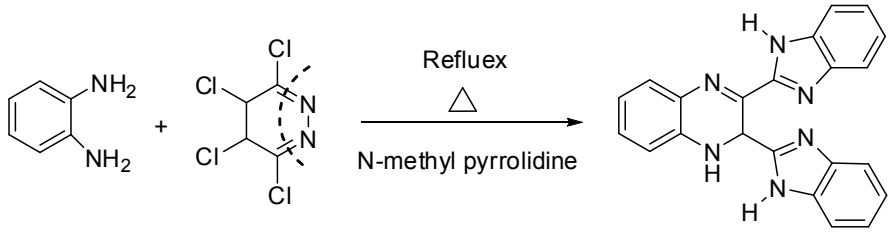
Reaction of 4, 5-dimethyl (*o*-phenylenediamine) with 1-Sub-pyrimidine-2, 4, 5, 6-tetraone **133** under acidic conditions [132] gave 6, 7-dimethyl-3-ureido carbonyl- 2(1*H*) - quinoxalinone **134**, shown in (Scheme 50).



133 134

Scheme 50

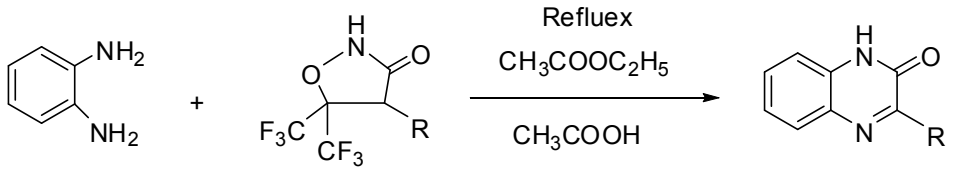
Treatment of *o*-phenylenediamine **1a** with 3, 4, 5, 6-tetrachloropyridazine **135 in** *N*-methyl pyrrolidine at 115℃ for 17 h gave a separable mixture of prouducts one of which was 2, 3-bis (benzimidazol-2-yl) quinoxaline **136**, [**132]** as shown in (Scheme 51).



1a 135 136

Scheme 51

Treatment of *o*-phenylenediamine **1a** with 3,3-bis(trifluoromethyl)-5-oxa- zolinone **[132] 137** in ethyl acetate containing a trace of acetic acid afforded 2(1*H*)-quinoxalinone **35**, shown in (Scheme 52).



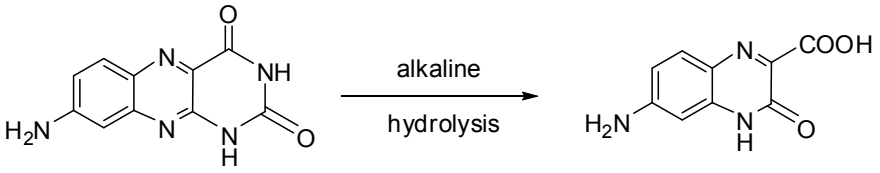
1a 137 35

R = CH_3

Scheme 52

3.3. Ring Transformation of Aryl Aromatic Compounds

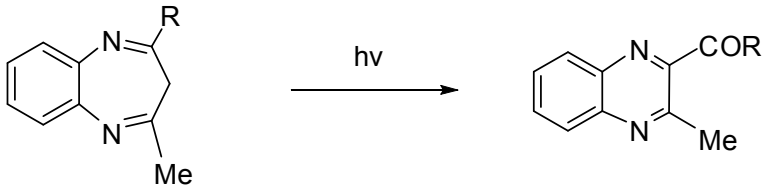
6-Amino-3-oxo-3, 4-dihydro-quinoxaline-2-carboxylic acid **139** is isolated from alkaline hydrolysis of a fused alloxazine (8-Amino-1*H*-benzo*[g]*pteridine-2, 4-dione) **138**[164], shown in (Scheme 53).



138 139

Scheme 53

UV irradiation of 1, 5-benzodiazepine (2-Methyl-3*H*-benzo*[b]* [1, 4] diazepine) derivatives **140** in benzene undergoes oxidative ring contraction to 2-benzoyl-3-methyl- quinoxaline **141**, [165] shown in (Scheme 54).

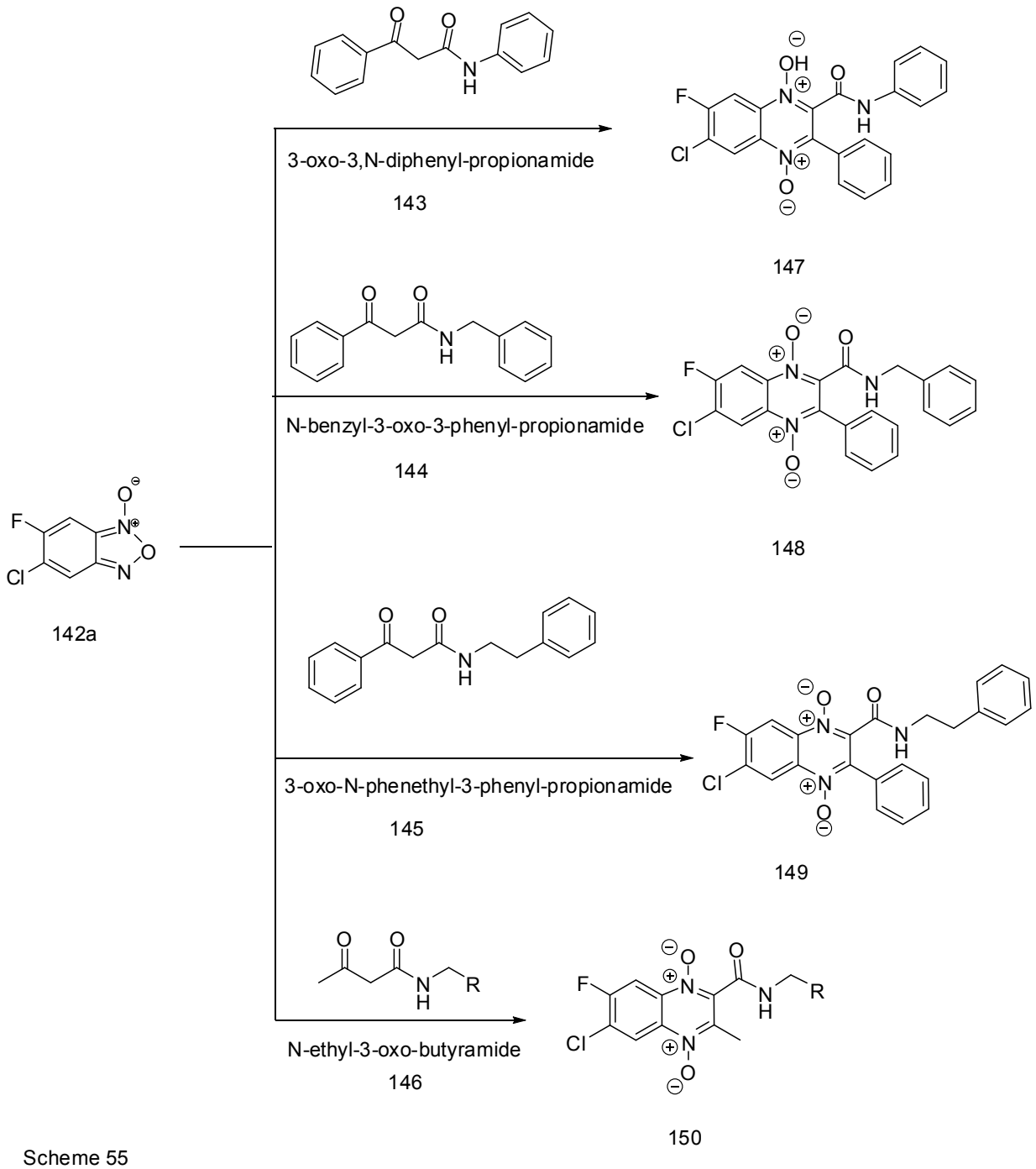


140 141

R= Ph, Me

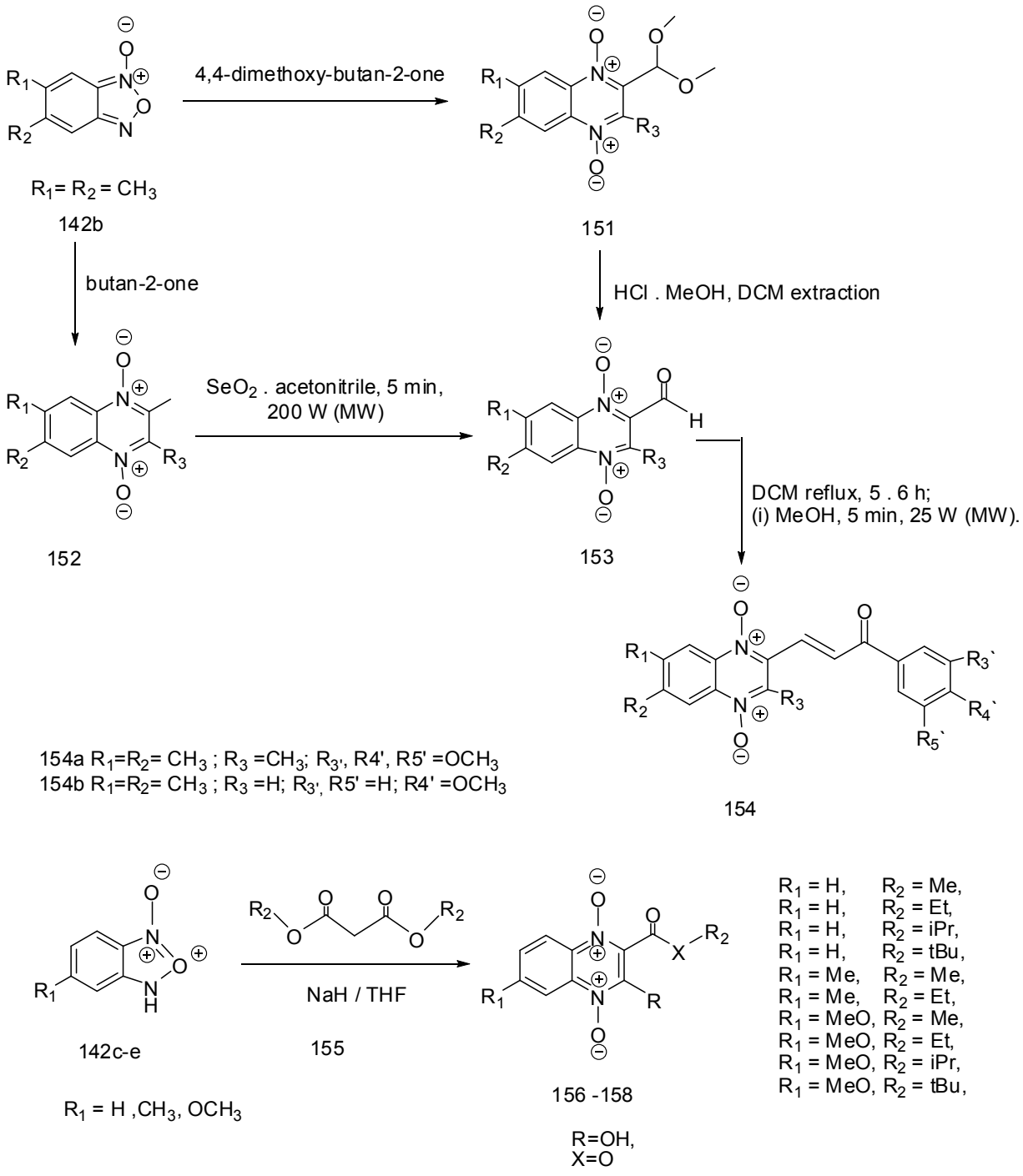
Scheme 54

Reaction of 5-chloro-6-fluoro-benzo[1,2,5]oxadiazole-1-oxide **142a** with 3 -oxo-3-*N*-diphenyl-propionamide **143,** *N*-benzyl-3-oxo-3-phenyl-propionamide **144,** 3 -oxo-*N*-phenethyl-3-phenyl-propionamide **145,** *N*-ethyl-3-oxo-butyramide **146** afforded 1,4-di-*N*-oxide-quinoxaline-2-carboxylic acid aryl amide derivatives **147-150**, thèse compounds have antimycobacterial activity [166], shown in (Scheme 55).

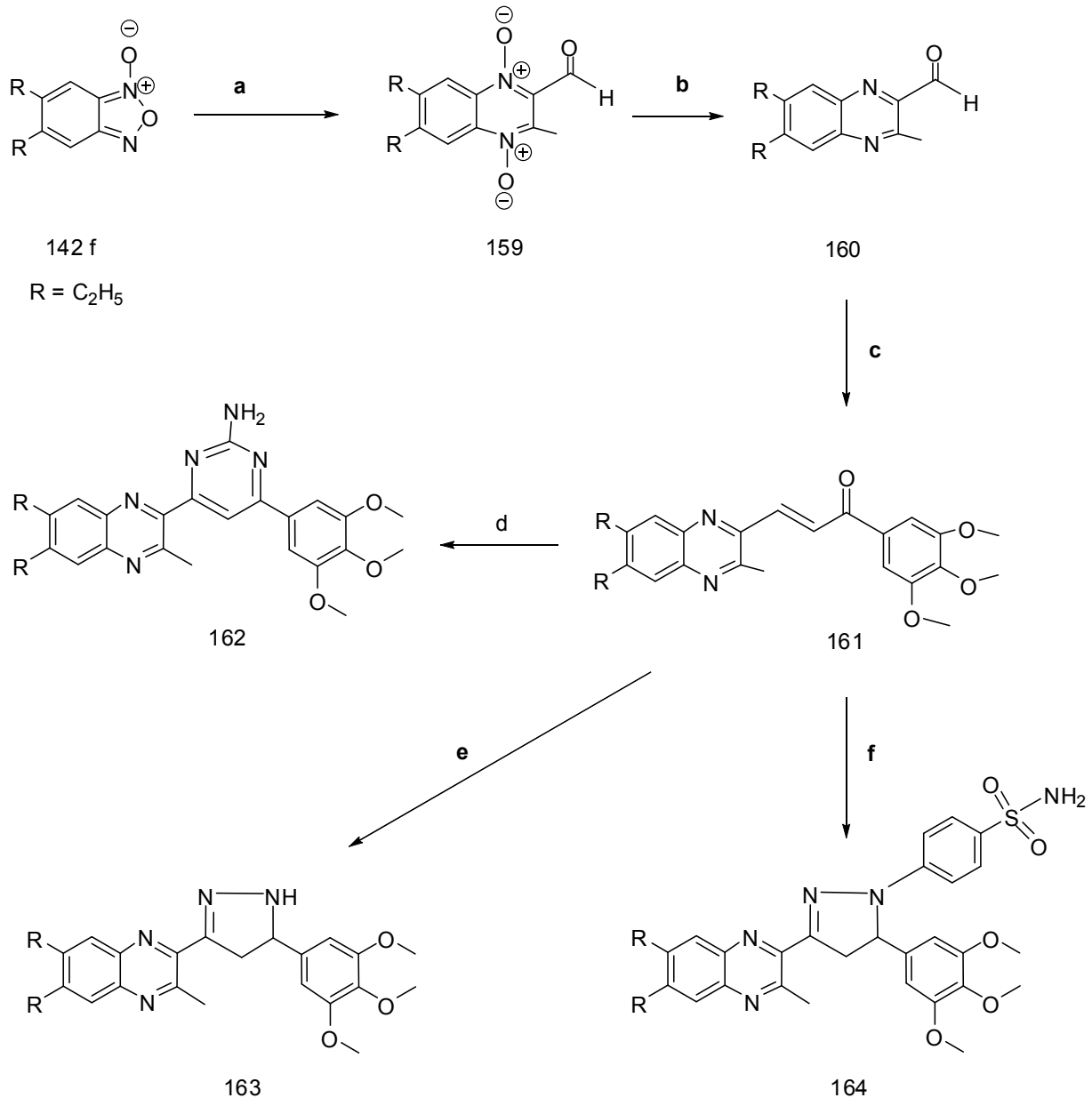


Scheme 55

Claisen-schmidt condensation [167] these reactions, which consist in a condensation between aldehyde derivatives, afford the corresponding α, β-unsaturated ketone system derivative. A series of quinoxaline 1, 4-di-*N*-oxide analogues [168 -170] **151 -164** were synthesized by the classic Beirut reaction **142b, c-e, f** with many reagents for examples β-diketone ester compounds, these compounds have been informed as antioxidant and anti-inflammatory agents, shown in (Schemes 56, 57).

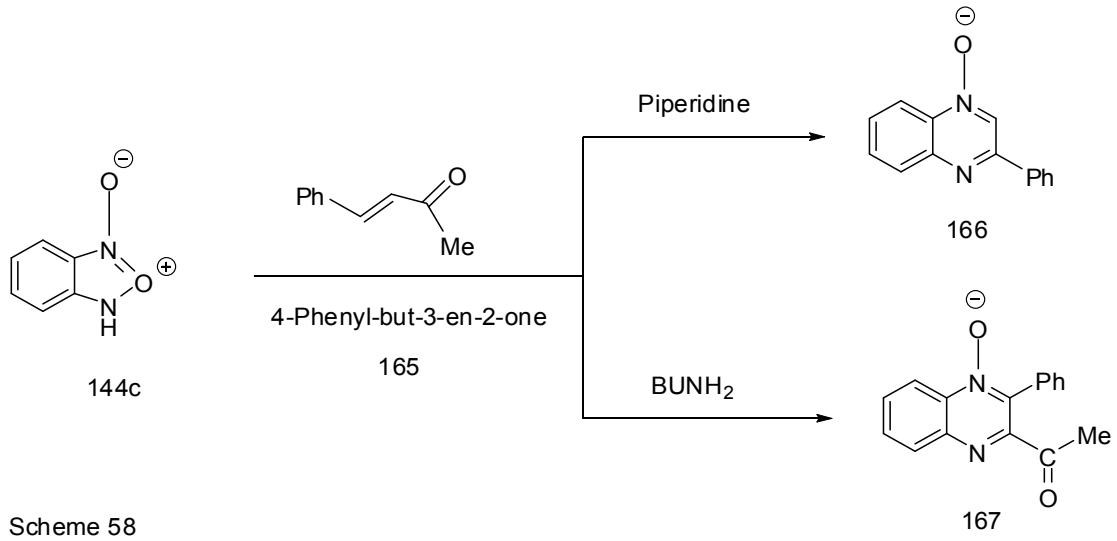


Scheme 56, Synthesis of quinoxaline 1,4-di-N-oxide analogues.



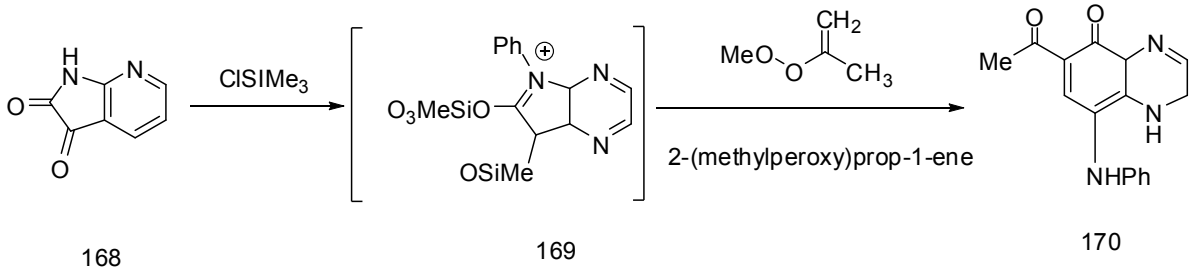
Scheme 57**:** Synthesis of 159 -164.
(**a**) Pentane-2,4-dione, triethylamine
(**b**) $Na_2S_2O_4$, methanol, 70 ^oC;
(**c**) 3,4,5-trimethoxybenzaldehyde, 3% NaOH . methanol, r.t;
(**d**) guanidine hydrochloride, 10% KOH . isopropanol reflux, 24 h;
(**e**) NH_2NH_2, ethanol, r.t.;
(**f**) 4-hydrazinobenzene-1-sulfonamide hydrochloride 97%, ethanol, 20 min, 50 W (MW).

On the other hand condensation of **142c** with 4-Phenyl-but-3-en-2-one **165** in the presence of piperidine or butylamine [132] afforded 2-phenylquinoxaline 4-oxide **166** and 2-acetyl-3-phenylquinoxaline-4-oxide **167**, shown in (Schemes 58).



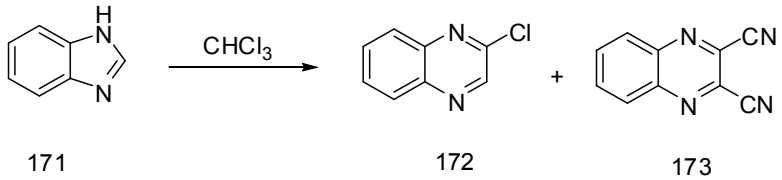
Scheme 58

Reaction of 6-Phenyl- 5*H*-5,7(6*H*)-pyrrolo[3,4-b]pyrazine **168** underwent electrolytic reduction in the presence of chlorotrimethylsilane, [132] to give the intermediate **169** which reacted with methyl acrylate to afford 6-acetyl-8-(phenyl amino)-*1,2*-dihydroquinoxalin-5(4a*H*)-one **170**, shown in (Scheme 59).



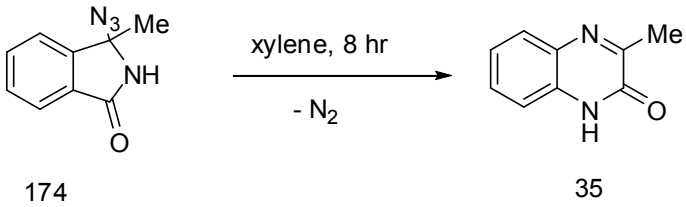
Scheme 59

Ring expansion[132] of benzimidazoles **171** with chloroform gave a separable 9:1 mixture of 2-chloro quinoxaline **172** and quinoxaline-2, 3-dicarbonitrile **173**, shown in (Scheme: 60).



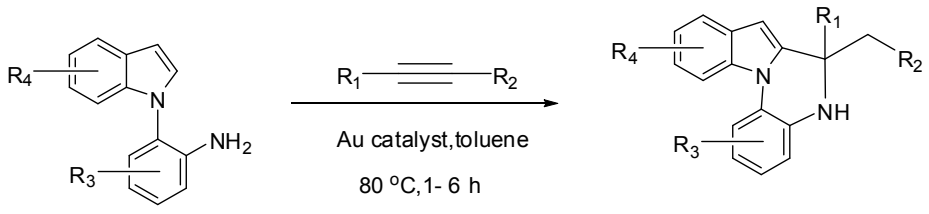
Scheme 60

Refluxing of 3-Azido-3-methyl-2-indolinone **174** in xylene [132] gave 3-methyl-2(1*H*)-quinoxalinone **35**, shown in (Scheme 61).



Scheme 61

Reaction of pyrrole-substituted anilines **175** and alkynes in presence of Au catalyst, toluene [171] afforded Substituted pyrrolo[1,2-*a*]quinoxalines **176**, shown in (Scheme 62).



175 176

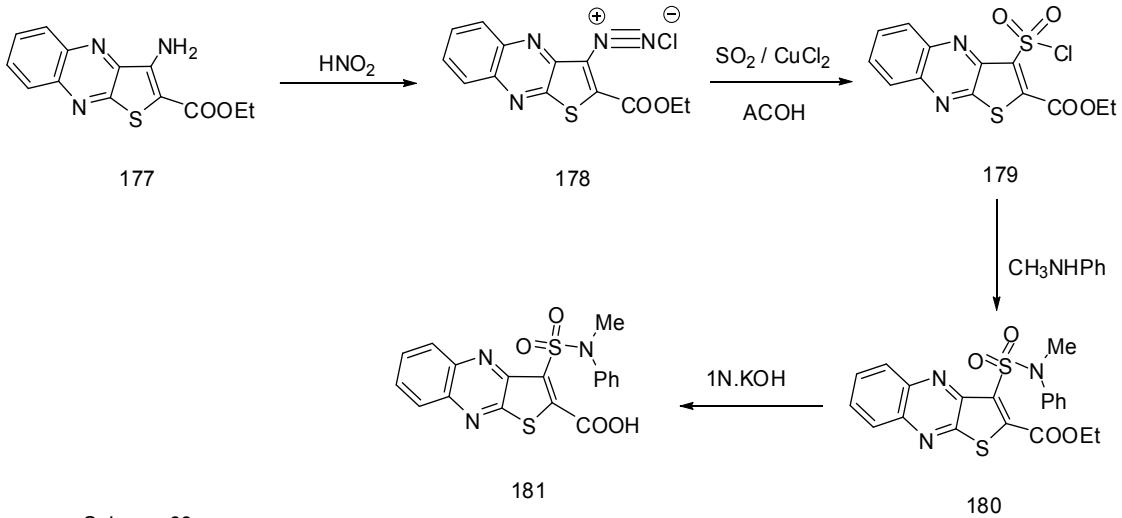
R_1= aryl, alkyl;
R_2= H, aryl, alkyl;
R_3= H, Me, OMe,CN;
R_4= H,Me,Et,OMe,CN,F

Scheme 62

4. Reactions of Quinoxalines

4.1. Diazotization Reactions

Diazotization [172] of 3-amino-2-ethoxycarbonylthieno[2,3-b]quinoxaline **177** gave the diazonium salt **178** which was reacted with SO_2 / CuCl in acetic acid to give the sulphonyl derivative **179** which reacted with *N*-methylaniline to give sulfamoyl quinoxaline derivative **180**. Hydrolysis of **180** with KOH afforded the corresponding acid **181**, shown in (Scheme 63).

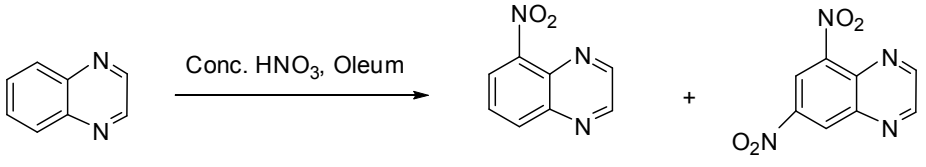


177 178 179 180 181

Scheme 63

4.2. Nitration Reactions

Nitration of quinoxaline **3a** occurs only under forcing conditions (Conc. HNO_3, Oleum, 90°C) [108] to give 5-nitroquinoxaline (1.5%) **182** and 5, 7- dinitro quinoxaline (24%) **183**, shown in (Scheme 64).



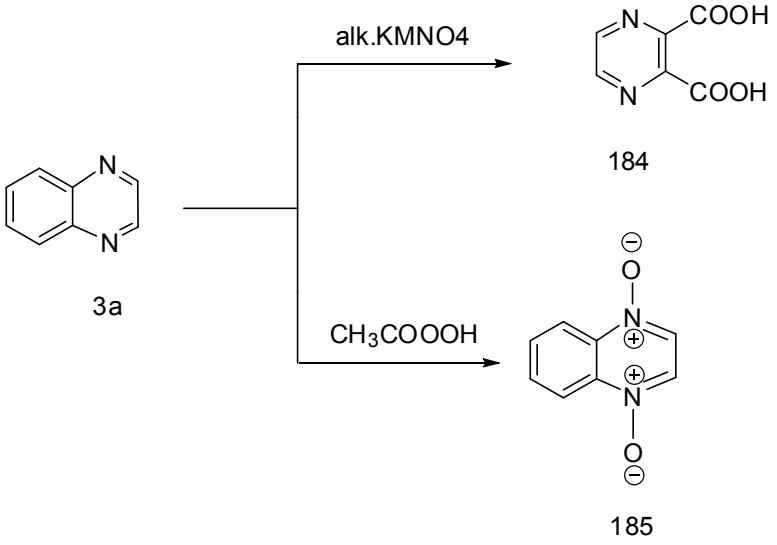
1.5 % 24%

3a 182 183

Scheme 64

4.3. Oxidation Reactions

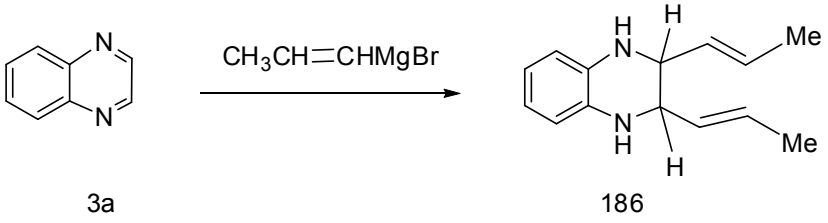
Oxidation of quinoxaline **3**.With alkaline potassium permanganate [108, 173 -176] gave pyrazine 2, 3-dicarboxylic acid **184**, while with peracid afforded the quinoxaline di-N-oxide **185**, shown in (Scheme 65).



Scheme 65

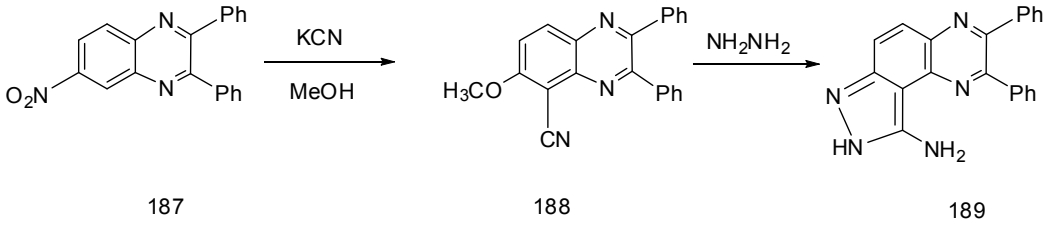
4.4. Substitutions Reactions

Quinoxalines **3** are easily attacked by nucleophiles, for e.g. two molecules of Grignard reagent can be added across quinoxaline molecule to give 2, 3-dipropenyl-1, 2, 3, 4-tetrahydro-quinoxaline **186**, [177] shown in (Scheme 66).



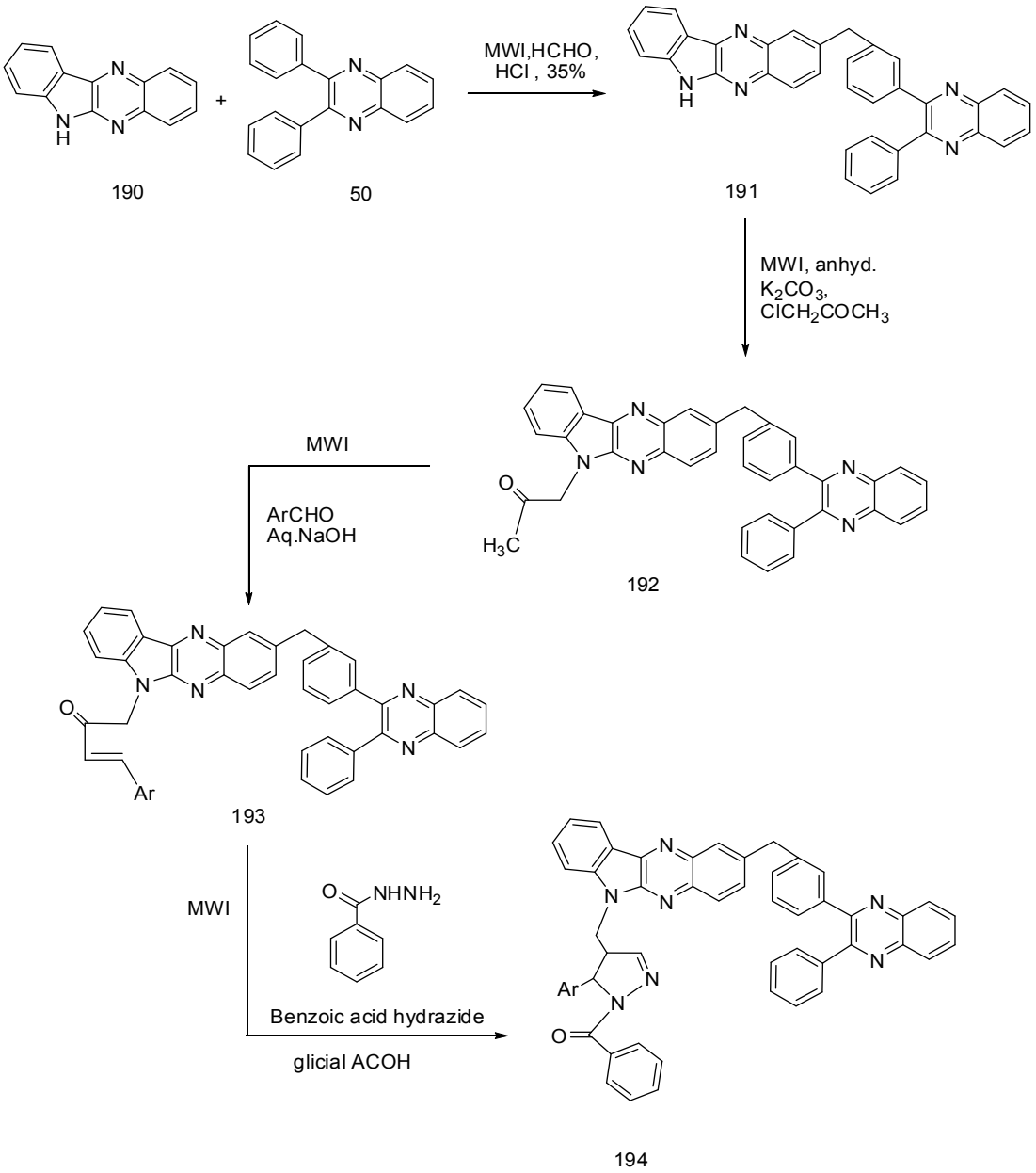
Scheme 66

2, 3-diphenyl-6-nitroquinoxaline **187** reacted with KCN in methanol [178] to gives 6-Methoxy-2, 3-diphenyl-quinoxaline-5-carbonitrile **188** which was reacted hydrazine hydrate to give **189**, shown in (Scheme 67).



Scheme 67

Indoloquinoxalines **190** reacted with 2, 3-diphenyl-quinoxaline **50** to give comp. **191**, [179] which condensed with methyl-chloroacetate in presence of K_2CO_3 to give **192**. Aldol condensation of **192** with aromatic aldehyde in acetic acid afforded the chalcons **193**, which condensed with benzoic acid hydrazide in acetic acid to give the pyrazol derivatives **194**; these compounds show highest antimicrobial activity, shown in (Scheme 68).

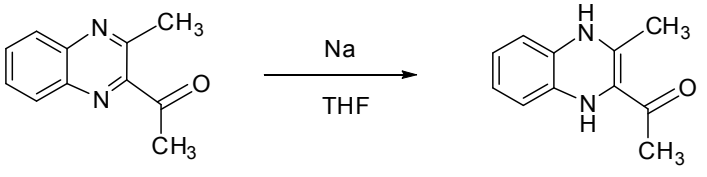


190 50 191 192 193 194

Scheme 68

5. Reduction of Quinoxaline Derivatives

Catalytic reduction of 2-acetyl-3-methylquinoxaline **195** with sodium in THF at 20°C yields the 1, 4-dihydroquinoxaline **196**, [180, 181] (Scheme 69).

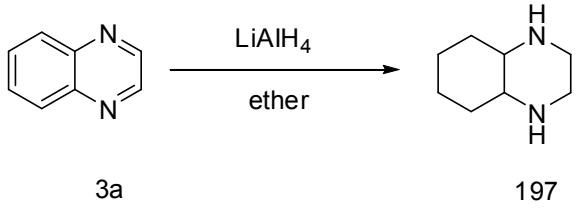


195 196

Scheme 69

Reduction of **3a** with $LiAlH_4$ in ether, afforded I, 2, 3, 4-*tetra*-hydro quinoxaline, while Sodium borohydride in acetic acid [182,183] and hydrogen in the presence of Pt [184] have been used to reduce 1, 2, 3, 4-*tetra*-hydro compounds.

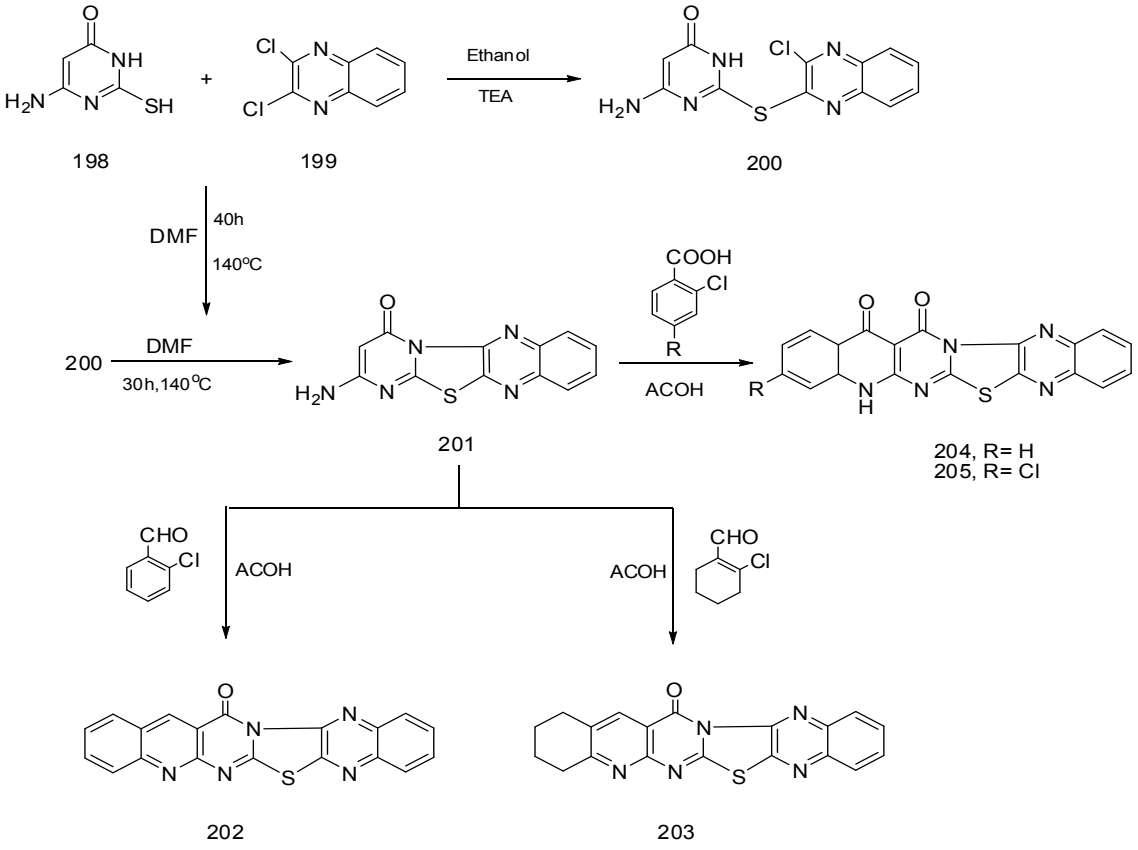
Hydrogenation of I, 2, 3, 4-*tetra*-hydroquinoxaline **197** over a 5% rhodium-onalumina catalyst at 100°C and 136 atmospheres pressure or over freshly prepared raney Ni gives meso (cis) - decahydro-quinoxaline **197**, [185] shown in (Scheme 70).



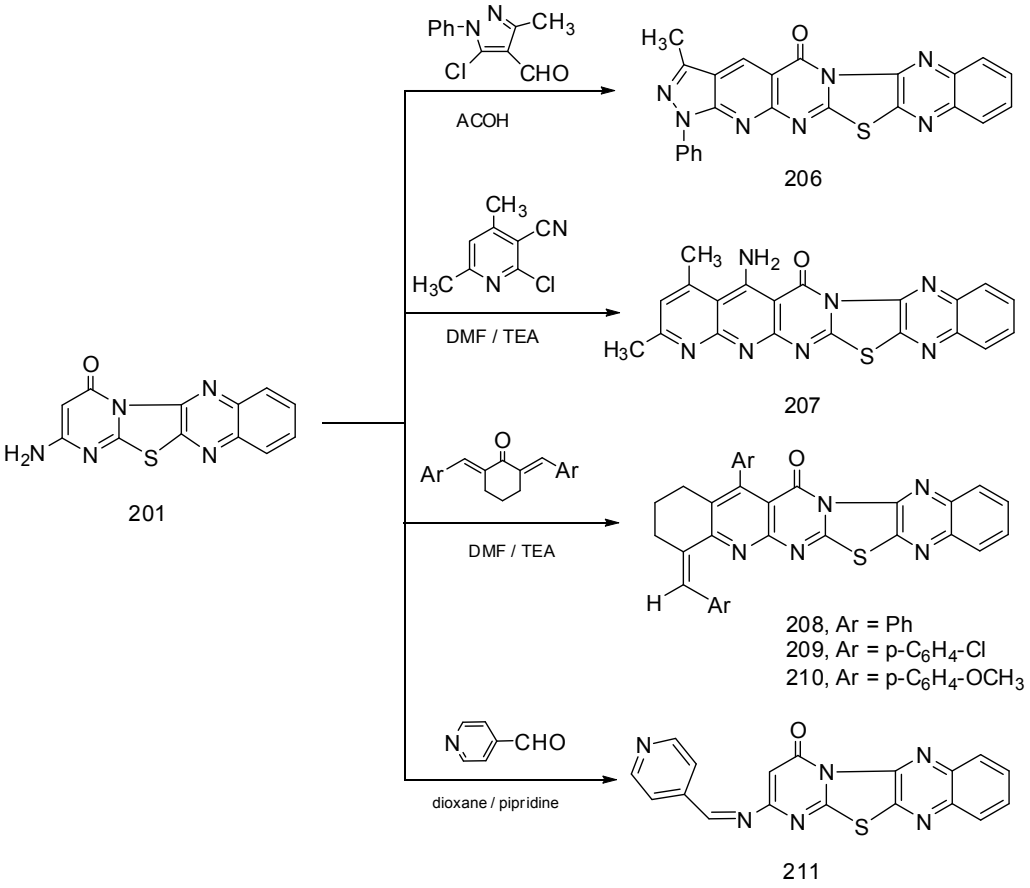
Scheme 70

6. Condensation and Cyclization Reactions

Reaction of 6-aminothiouracil **198** and 2, 3-dichloroquinoxaline **199** in ethanol/ TEA [72] yielded 6-amino-2- (3-chloroquinoxalin-2-ylthio) pyrimidin-4(3*H*)-one **200**, which was refluxed in dimethylformamide to give 2-aminopyrimidothiazolo [4, 5-b]- quinoxaline-4-one **201**. Compound **201** was utilized as a key intermediate for the synthesis of a new pyrimidothiazoloquinoxaline **202** – **211** derivatives by the reaction with 2-chlorobenzaldehyde, 2-chlorocyclohex-1-enecarbaldehyde, 2-chloro benzoic acid, 2,4- dichlorobenzoic acid, 5-chloro-3-methyl-1-phenyl-1*H*-Pyrazole-4-carbaldehyde,2-chloro-4,6-dimethylnicotinonitrile,α,β-unsaturated ketones and isonicotinaldehyde, respectively, shown in (Scheme 71, 72).

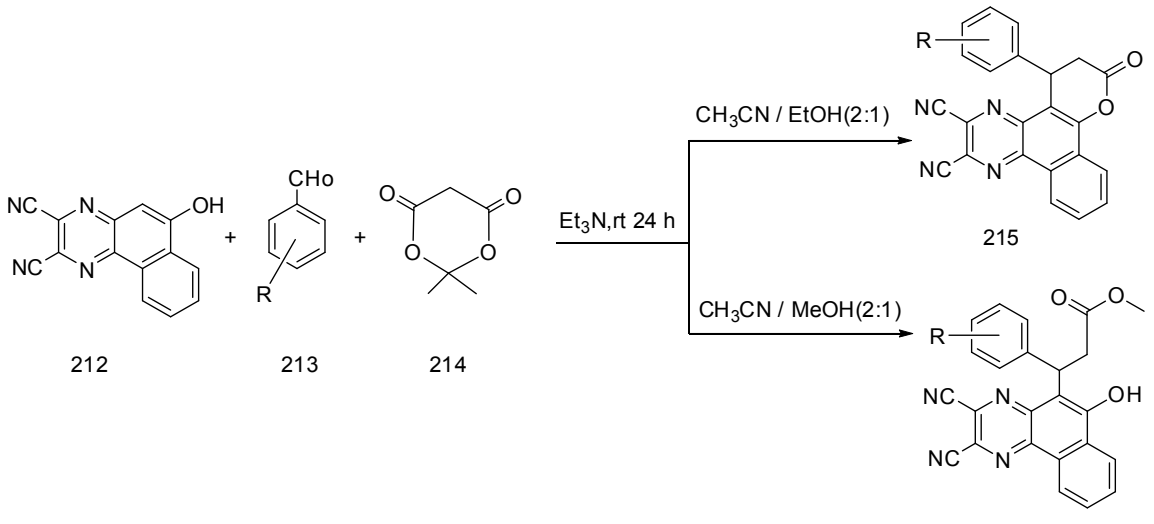


Scheme 71



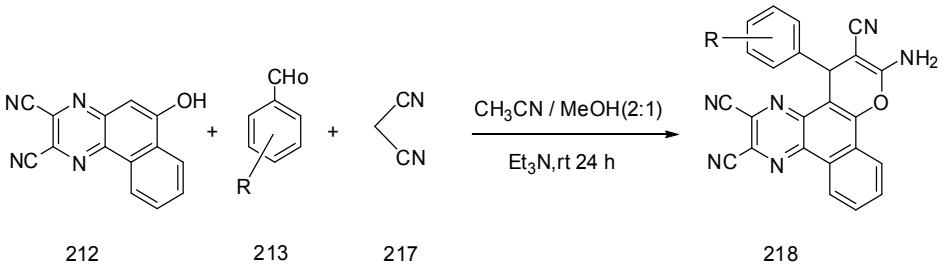
Scheme 72

Condensation between a 6-hydroxy-benzo*[f]* quinoxaline-2, 3-dicarbonitrile **212** with aromatic aldehyde **213**, and Meldrum's acid **214** in CH_3CN/EtOH (2:1) in the presence of a catalytic amount of triethylamine [152] leading to expected products **215** and **216**, shown in (Scheme 73).



Scheme 73

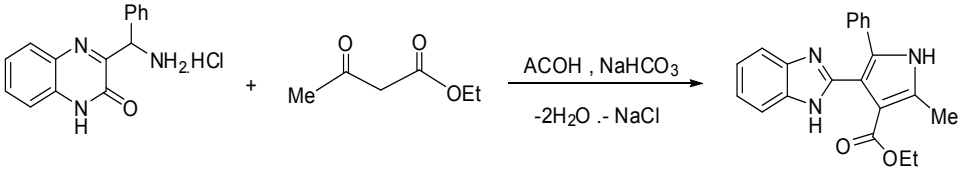
Furthermore, condensation between a 6-Hydroxy-benzo[f]quinoxaline-2, 3-dicarbonitrile **212**with aldehyde **213**, and malononitrile **217** in CH_3CN/EtOH (2:1) in the presence of a catalytic amount of triethylamine [152] leading to expected products **218**, shown in (Scheme 74).



212 213 217 218

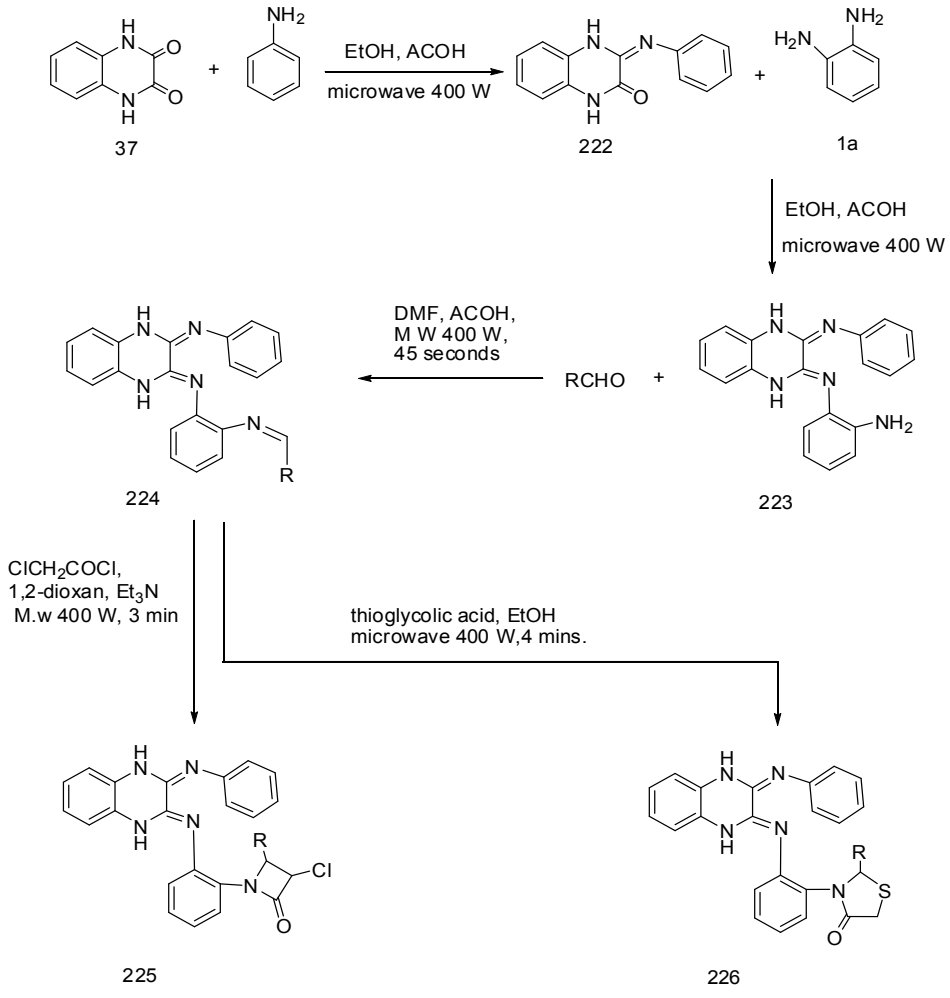
Scheme 74

Reaction of quinoxalin‑2(1*H*)‑one hydrochloride **219** with ethyl acetoacetate **220** in boiling acetic acid for 15 h gave 2‑(pyrrol‑3‑yl)benzimidazole **221** in 62% yield [186], shown in (Scheme 75).



219 220 221

Scheme 75



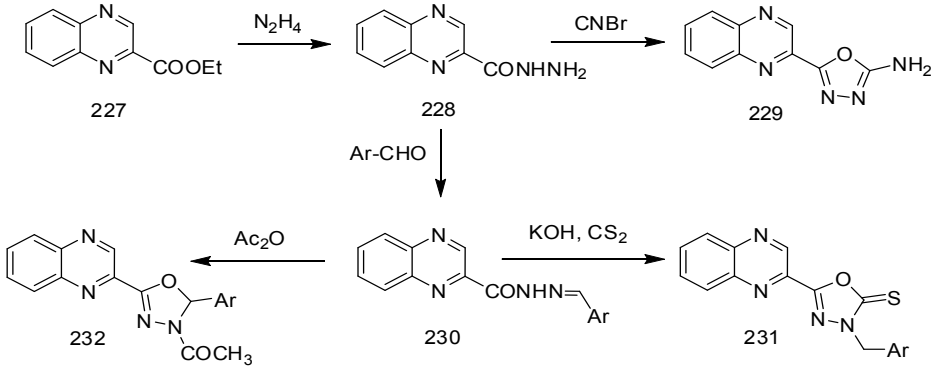
37 222 1a 224 223 225 226

Scheme 76

Compound **37** was added to a mixture of aniline and ethanol and few drops of glacial acetic acid stirred magnetically at

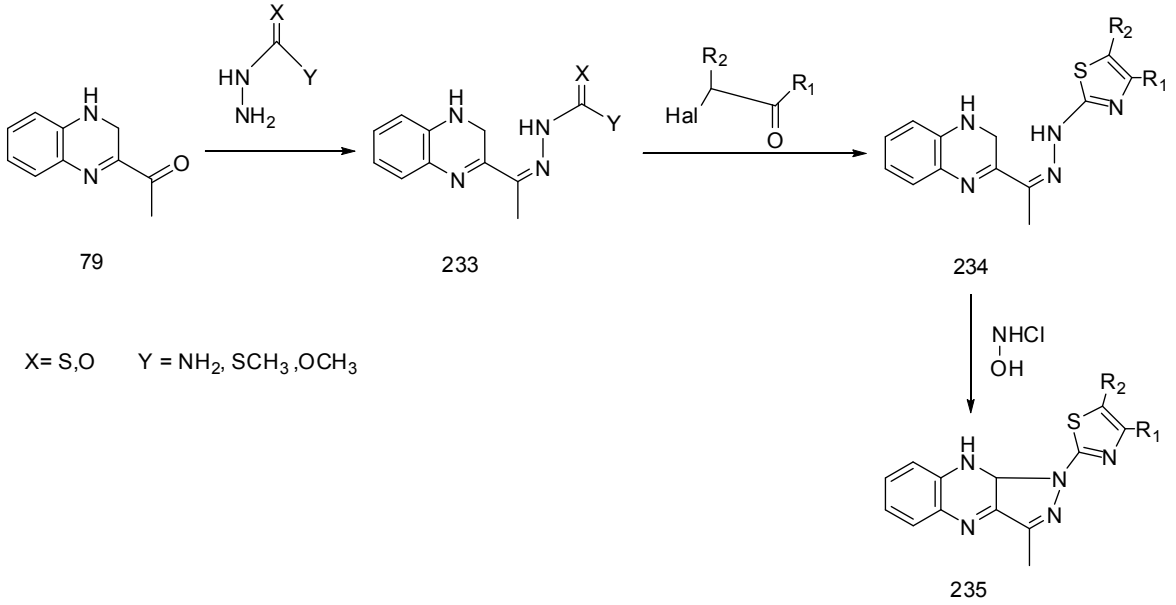
room temperature .Then, it was irradiated in microwave to yield of 3-((phenylimino)-3, 4-dihydro quinoxaline)-one **222**. [187] To a stirred solution of compound **222** and *o*-phenylenediamine **1a** in ethanol with few drops of glacial acetic acid. This mixture was irradiated with microwave to give *N*-((E)-3-(phenylimino) - 3, 4-dihydro- qunoxalin-2(1*H*)-ylidene) benzene-1, 2-diamine **223**. Compound **223** was dissolved in ethanol and aromatic aldehyde derivatives with few drops of glacial acetic acid to produce corresponding schiff bases **224**. The schiff base(s) **224** was dissolved in 1, 2-dioxan, followed by the addition of chloroacetyl- chloride and triethylamine. The reaction mixture was stirred for 1 h, and then, it was irradiated in a microwave to get **225**. The residue was purified by silica gel column to yield respective azetidinones. A mixture of schiff base (s), **224** thioglycolic acid and ethanol were irradiated in microwave to afford **226**, as in (Scheme 76).

Ethyl quinoxaline-2-carboxylate **227** reacts with hydrazine [188] to form quinoxaline -2-carbohydrazide **228**. This compound cyclised with CNBr to afforded 5-(quinoxalin- 3-yl) -1, 3, 4-oxadiazol-2-amine **229**. Compound **229** then converted to *N*'-arylidene quinoxaline-2-carbohydrazides **230** via condensation with aromatic aldehyde. The hydrzides **230** are cyclised to form 3-aryl-5-(quinoxalin-3-yl)-1,3,4-oxadiazole-2(3*H*)-thiones **231** and 1-(2-aryl-5-(quinoxalin-3-yl)-1, 3, 4-oxadiazol 3(2*H*)-yl) ethanones **232** by reacting with KOH/CS_2 and Ac_2O respectively, shown in (Scheme 77).



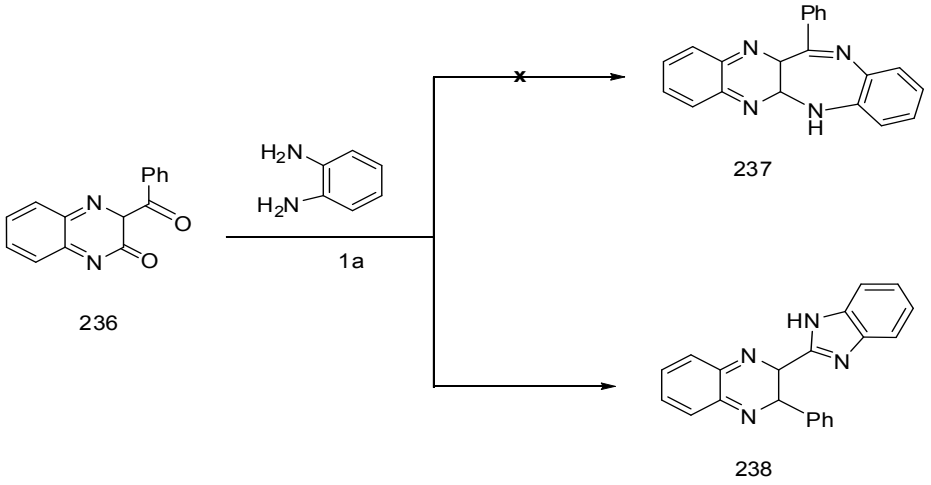
Scheme 77

Treatment of the 2-acetylquinoxaline thiosemicarbazone **233** with α-halogeno- ketones [189] gave the thiazoles **234** along thiazole synthesis. However, in the reaction mixture not only **234** was obtained, but along a redox process from the hydrazones **234** also the 1*H*-pyrazolo [3, 4-b]quinoxalines **235** could be obtained, shown in (Scheme 78).

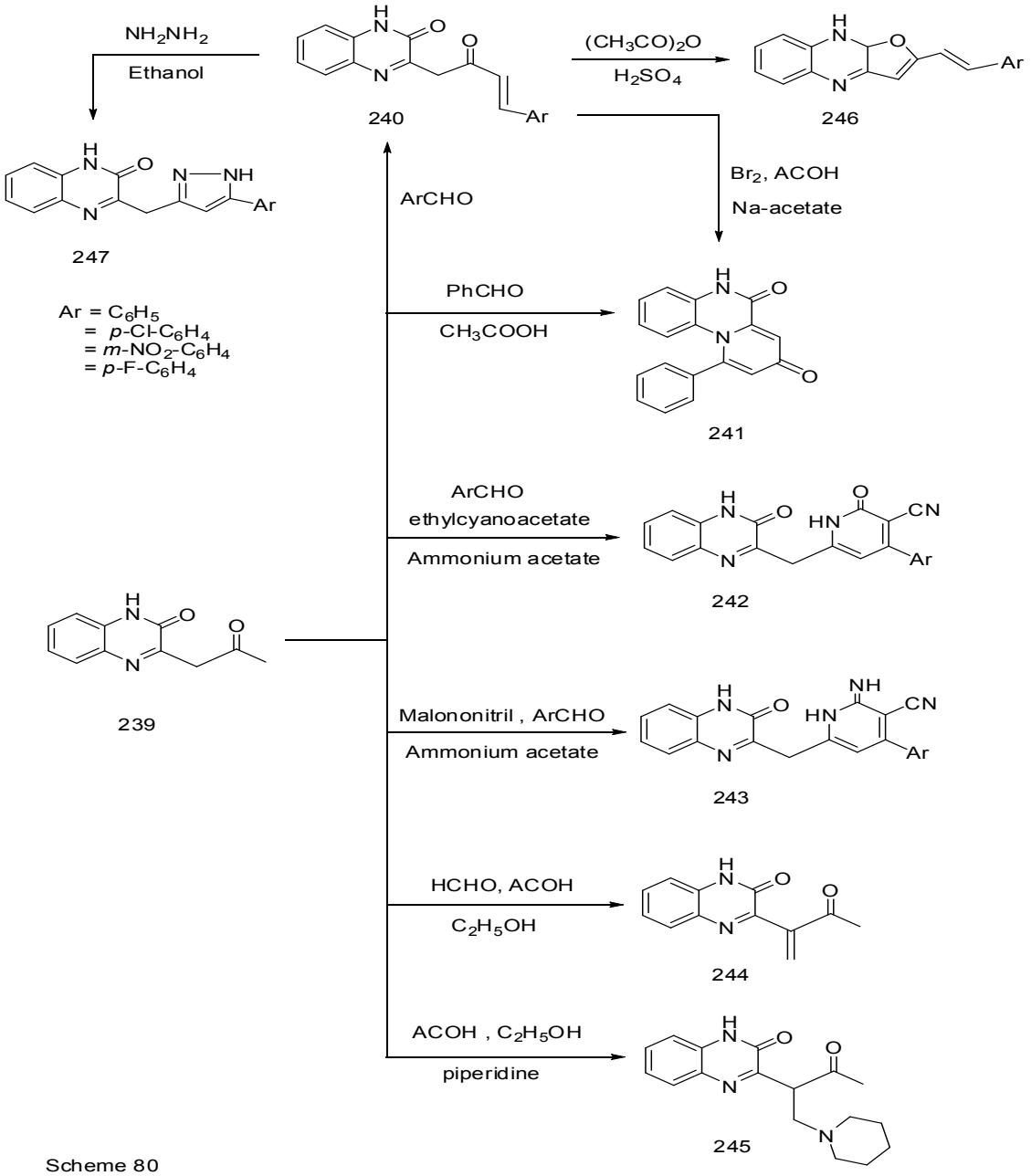


Scheme 78

Coupling *o*-phenylenediamine **1a** [190] with 3-benzoyl-1,2-dihydro-2-oxo- quinoxaline **236** in acetic acid give the phenyl-quinoxalinyl **238** and not to the expected quinoxalino benzodiazepine **237**, but to its isomer, 2-benzimidazolyl-3-phenyl quinoxaline **238**, shown in (Scheme 79).



Scheme 79



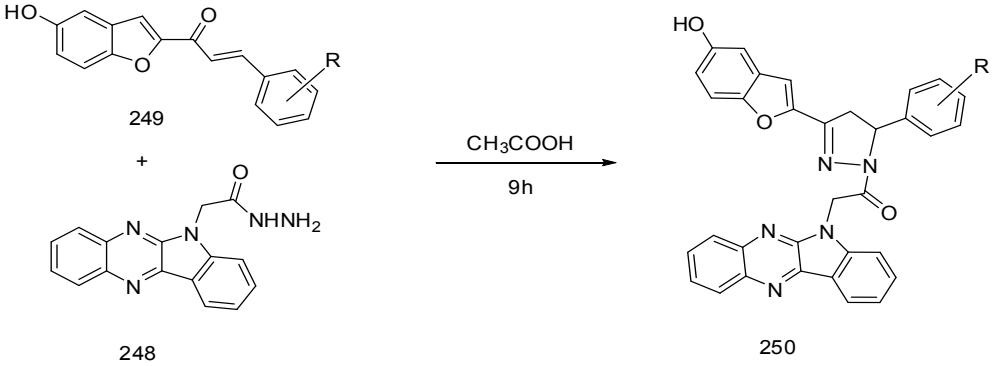
Scheme 80

7. Treatment of Quinoxalines with Many of Organic Reagents

7.1. Quinoxalines with Several of Organic Derivatives

Reaction of 3 - (2-oxo-propyl)-1*H*-quinoxalin-2-one **239** with several reagents for examples [aromatic aldehydes derivatives, ethylcyanoacetate, malononitril, bromine, acetic anhydride and hydrazine hydrate] gave products **240 – 247** respectively [109], shown in (Scheme 80).

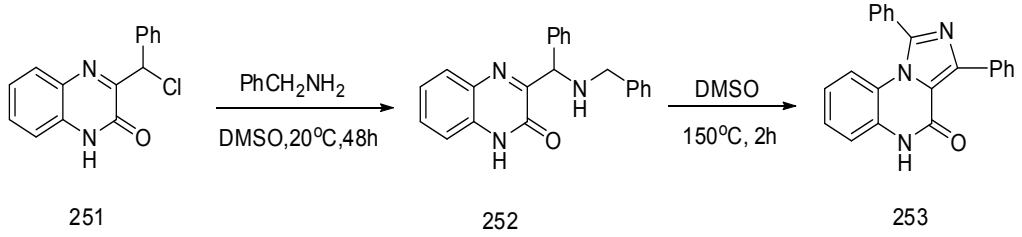
Reaction of 2-(5,8- dihydroquinoxalino[2, 3-b]indol-5- yl) acetohydrazide **248** With benzofuran chalcones **249** in acetic acid afforded 1-[3-(5-hydroxybenzo*[b]* furan-2- yl)-5-substituted phenyl-4, 5-dihydro-1*H*-1-pyrazolyl]-2- (5*H*-indolo[2, 3-b] quinoxalin-5-yl)-1-ethanone derivatives **250**, [191] shown in (Scheme 81).



Scheme 81

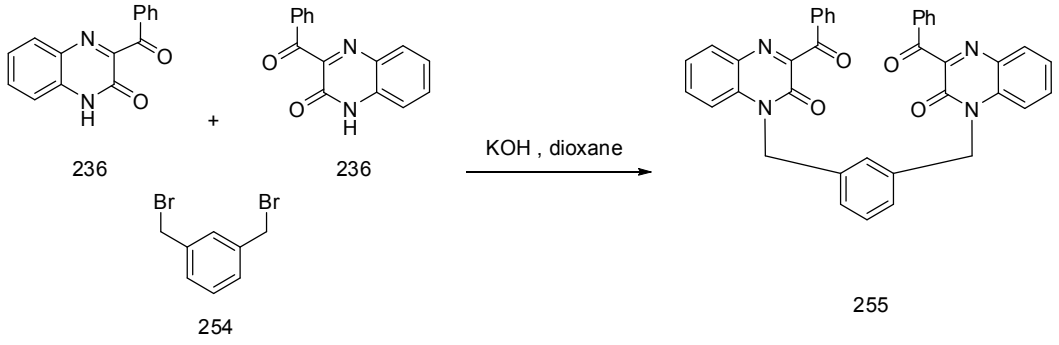
7.2. Alkylation Reactions

3-(α-chlorobenzyl)quinoxalin- 2-one **251** reacts with benzylamine in DMSO at room temperature to give 3-(α-benzylamino-benzyl) - quinoxalin-2-one **252** which undergoes intramolecular ring closure to 1,3-diphenylimidazo[1,5-a]quinoxalin-4(5*H*)-one **253**, [192] shown in (Scheme 82).



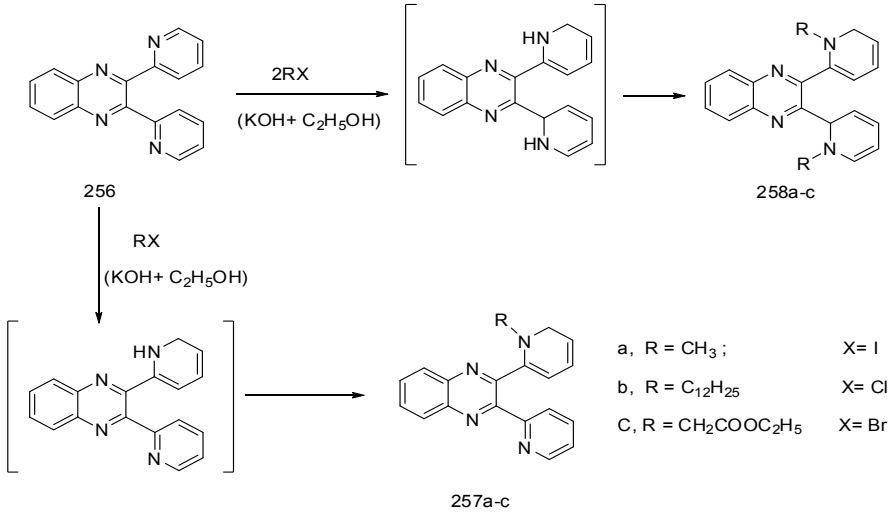
Scheme 82

1,3-bis(3-benzoyl-2-oxoquinoxalin-1-ylmethyl)- benzene **255**was achieved via alkylation of 3-Benzoyl-1*H*-quinoxalin-2-one **236** with 1,3-bis (dibromomethyl) benzene **254** in boiling dioxane in the presence of KOH [192], shown in (Scheme 83).



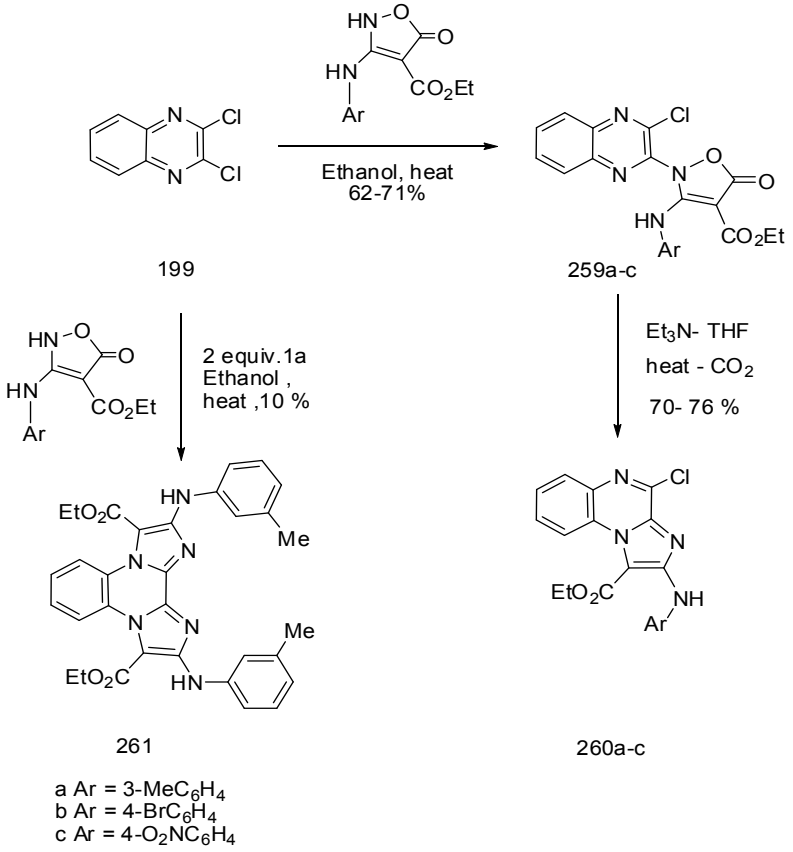
Scheme 83

The basicity of the quinoxaline N atoms in 2, 3-di (pyridine-2-yl) quinoxaline **256**, which is lower than that in pyridine, was responsible for quaternization [193] only in the pyridine part of the molecule. It should be noted that protons of benzene, pyridyl, and pyridine groups of **257a-c** and **258a-c** had the same resonances. This was indicative of the quaternization of the same N atom by methyliodide and dodecylbromide, these compounds show potential antimicrobial activity, as in (Scheme 84).



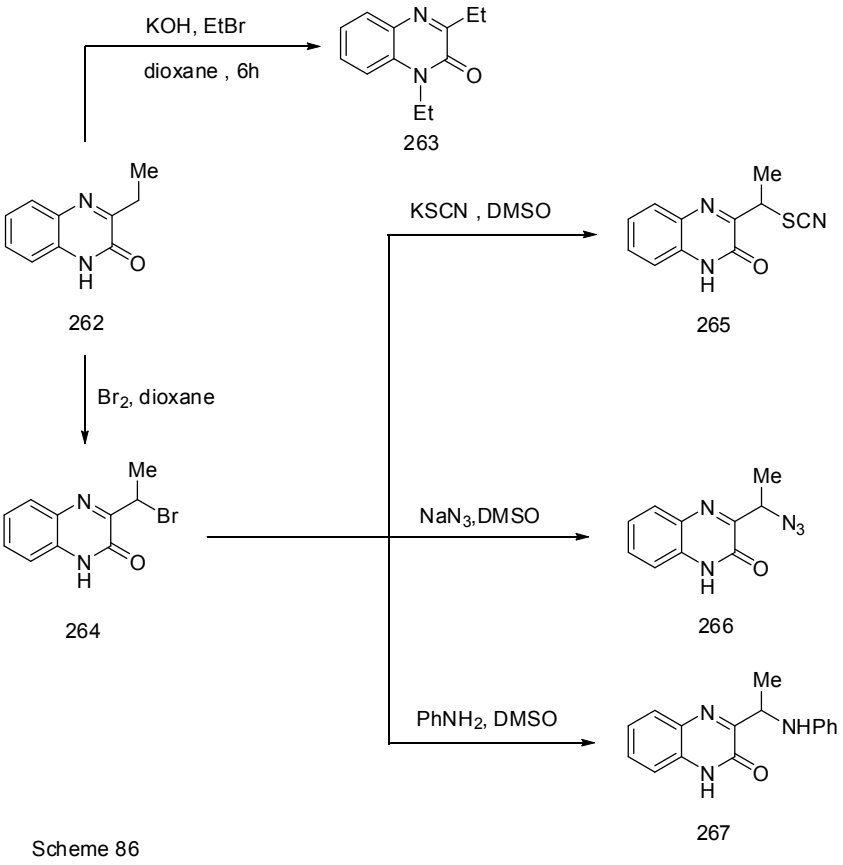
Scheme 84

The *N*-quinoxalinylisoxazolones **259a-c** was prepared by the reaction of the corresponding arylaminoisoxazolone with 2, 3-dichloroquinoxaline **199** in EtOH [194]. Products **259a-c** were rearranged to imidazo[1,2-*a*]quinoxaline derivatives **260a-c** by refluxing with triethylamine in THF, also when 2 equivalents of the isoxazolone were reacted with 2, 3-dichloroquinoxaline **199** under the above-described conditions in the absence of base, the rearranged bisimidazoquinoxaline product **261**, shown in (Scheme 85).



Scheme 85

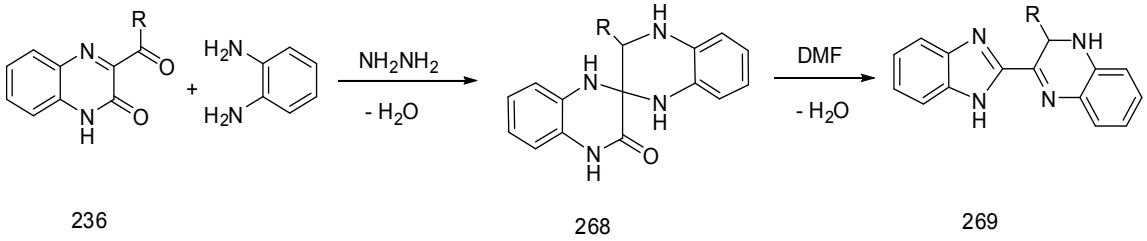
Alkylation of 3-ethylquinoxalin- 2(1*H*)-one **262** by using of ethyl bromide in refluxing dioxane with presence of KOH gave 1, 3-diethyl-1*H*-quinoxalin-2-one **263**. Bromination of compound **262 by** using of bromine afforded α-bromoethyl derivative **264.** Reaction of **264** with many reagent of nucleophiles as KSCN, NaN_3, and $PhNH_2$ in DMSO to give the corresponding 3-(α-x-ethyl) quinoxalines **265**-**267**, [195] shown in (Scheme 86).



Scheme 86

7.3. Addition Reactions (Spiro Compounds)

Reacted of 3-(2-aryl-2-oxoethylidene)- 3,4-dihydroquinoxalin-2(1*H*) - ones **236** with *o*-phenylenediamine **1a** and hydrazine hydrate (and phenylhydrazine), in refluxing acetic acid [196] undergo new acid catalyzed rearrangement with the contraction of pyrazine ring of the quinoxaline system **268** to give form 2-benzo imidazoloquinoxaline**s** derivatives **269**, shown in (Scheme 87).



236

R = Ph

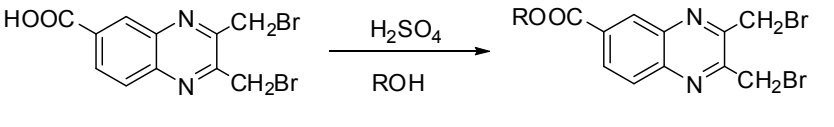
268

269

Scheme 87

7.4. Esterification Reactions

Esterification of 2, 3- Bis-bromomethyl-quinoxaline- 6-carboxylic acid **270** with methanol or ethanol in the presence of a catalytic amount of sulfuric acid [116], afforded the methyl ester and ethyl ester of quinoxaline derivatives **271**, as in (Scheme 88).



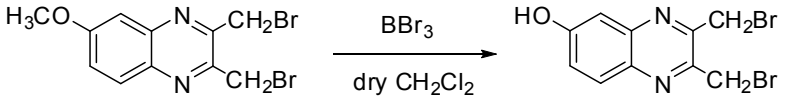
270 271

R = CH_3 (74%)
= CH_2CH_3 (90%)

Scheme 88

7.5. Demethylation Reaction

The 6-hydroxyquinoxaline **273** was synthesized by treating the methoxy compound [2, 3-Bis-bromomethyl-6-methoxy-quinoxaline] **272** with boron tri- bromide. The demethylation reaction [116] proceeded without any side reaction to produce an exceptional yield of 2, 3-Bis- bromomethyl-quinoxalin-6-ol **273**, as in (Scheme 89).



272 273

(94 %)

Scheme 89

8. Conclusions

The last twenty years have witnessed an important growth in research that have an enormous synthetic methodologies lead to the synthesis of quinoxalines derivatives due to its applications in various fields such as organic and medicinal chemistry and material sciences. However, the classical methods for the synthesis of quinoxaline derivatives are common, environmentally benign protocols have been developed with the goal of increasing the yields or reducing reaction times as well as chemical pollution. All the methods that have been used in preparing these quinoxaline derivatives are mentioned through organic chemistry and the green chemical science. Further design and development of greener methodologies for the synthesis of quinoxalines will ensure the rapid growth of an active and important area of research in heterocyclic chemistry for the construction of a wider spectrum of biologically important quinoxaline scaffolds. This review contains all the biological studies to the quinoxalines derivatives; it shows its biological importance as well. More than 190 references have been mentioned to show the importance of these quinoxaline derivatives. Through the study of these compounds it shows the presence of many quinoxaline derivatives that are used to cure so many diseases; they are considered ultimate drugs that found in pharmacies, for example: Levomycin, Echinomycin and Brimonidin (Alphagan).

REFERENCES

[1] Moloney, M. G. Nat. Prod. Rep.2002, 19, 597-616. DOI: 10.1039/B103777N, Review Article

[2] Tandon, V. K.; Yadav, D. B.; Maurya, H. K.; Chaturvedi, A. K.; Shukla, P. K. Med. Chem. 2006, 14, 6120-6126. DOI: 10.1016/j.bmc.2006.04.029

[3] Kotharkar, S. A.; Shinde, D.B. Bioorg. Med. Chem. Lett. 2006, 16, 6181-6184.

[4] Mashevskaya, I. V.; Makhmudov, R. R.; Aleksandrova, G. A.; Golovnira, O. V.; Duvalov, A. V.; Maslivets. A. N. Pharm. Chem. J. 2001, 35,196 -198.

[5] Vyas, D. A.; Chauhan, N. A.; Parikh, A. R. Indian J. Chem. 2007, 46B, 1699-1702.

[6] Carta, A.; Loriga, M.; Paglietti, G.; et al. Eur. J. Med. Chem. 2004, 39,195- 203.

[7] Seitz, L. E.; Suling, W. J.; Reynolds, R. C. J. Med. Chem. 2002, 45,5604-5606.

[8] Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A. Bioorg. Med. Chem. 2003, 11, 2149-2156.

[9] Jaso, A.; Zarranz, B.; Aldana, I.; Monge, A. J. Med. Chem. 2005, 48, 2019-2025.

[10] Jaso, A.; Zarranz, B.; Aldana, I.; Monge, A. Eur. J. Med. Chem. 2003, 38,791-800.

[11] Burguete, A. ; Pontiki, E.; Litina, D. H.; et al. Bioorg. Med. Chem. Lett. 2007, 17, 6439-6443.

[12] Wagle, S.; Adhikari, A. V.; Kumari, N. S. Indian J. Chem. 2008, 47B, 439-448.

[13] Ishikawa, H.; Sugiyama, T.; Kurita, K.; Yokoyama, A. Bioorg.Chem.2012, 41-42, 1-5.

[14] Loriga, M.; Piras, S.; Sanna, P.; Paglietti, G. Farmaco 1997, 52(3), 157-166.

[15] Crowther, A. F.; Curd, F.H.S.; Davey, D.G.; Stacey, G.J. J. Chem. Soc. 1949, 1260-1262.

[16] Rangisetty, J.B.; Gupta, C.N.V.H.B.; Prasad, A,L. Srinivas, P.; Sridhar, N.; Parimoo, P.; Veeranjaneyulu, A. J. Pharmacy, Pharmacology 2001, 53, 1409 -1413.

[17] Sarges, R.; Howard, H.R.; Browne, R.G.; Lebel, L.A.; Seymour, P.A.; Koe, B. k. J. Med. Chem. 1990, 33, 2240 -2254.

[18] (a) Jian, F. F.; Zhao, P.S. J. Mol. Struct. 2004,705, 133-139. (b) Cheon, H. G.; Lee, C. M.; Kimb, B.T.; Hwangb, K. J. Bioorg. Med. Chem. Lett 2004, 14, 2661. (c) Kaupp, G.; Naimi-Jamal, M. R. Eur. J. Org. Chem. 2002, 8, 1368-1373. (d) Wang, L.; Liu, J.; Tian, H.; Qian, C.Synth. Commun. 2004, 34, 1349-1358.

[19] Monge, A.; Palop, J.A.; Urbasos, I.; Fernández-Alvarez, E. J. Heterocyclic Chem.1989, 26(6), 1623-1626. DOI: 10.1002/jhet.5570260621

[20] Kurusawa, Y.; Muramatsu, M.; Okamoto, Y.; Takada, A. Heterocycl. Chem. 1986, 23, 637.

[21] Phadke, R. C.; Rangnekar, D.W. Bull. Chem. Soc. Japan 1986, 59, 1245-1247.

[22] Ramli, Y.; Moussaif, A.; Karrouchi, K; Essassi, E. J. Chem.2014, 2014, 1-21.

[23] Dell, A.; Williams, D. H.; Morris, H. R. J. Am. Chem. Soc. 1975, 97, 2497- 2502.

[24] Dirlam, J. P.; Presslitz, J. E. J. Med. Chem. 1978, 21, 483-485.

[25] Dirlam, J. P.; Czuba, L. J.; Dominy, B.W.; et al. J. Med. Chem. 1979, 22, 1118-1121.

[26] Monge, A.; Martinez-Crespo, F. J.; De Cerain, A. L.; et al. J. Med. Chem.1995, 38, 4488-4494.

[27] Monge, A.; Palop, J. A.; De Cerain, A. L.; et al. J. Med. Chem. 1995, 38, 1786-1792.

[28] Montoya, M. E.; Sainz, Y.; Ortega, M.A.; De Cerain, A. L.; Monge, A. Farmaco 1998, 53, 570-573.

[29] Ortega, M. A. ; Sainz, Y.; Montoya, M. E. ; De Cerain, A. L. ; Monge, A. Pharmazie 1999, 54, 24-25.

[30] Sainz, Y. ; Montoya, M. E. ; Martinez-Crespo, F. J.; Ortega, M. A. ; de Cerain, A. L.; Monge, A. Arzneim.-Forsch. 1999, 49, 55-59.

[31] Ortega, M. A.; Morancho, M. J.; Martinez-Crespo, F.J.; Sainz,Y.; Montoya, M. E.; de Cerain, A.L.; Monge, A. Eur. J. Med. Chem. 2000, 35, 21-30.

[32] Ortega, M. A.; Montoya, M. E.; Jaso, A.; Zarranz, B.; et al. Pharmazie 2001, 56, 205-207.

[33] Carta, A.; Paglietti, G.; Rahbar, N.M.E.; et al. Eur. J. Med Chem. 2002, 37, 355-366.

[34] Ortega, M. A.; Sainz, Y.; Montoya, M. E.; et al. Arzneim.-Forsch. 2002, 52, 113-119.

[35] Aldana, I.; Ortega, M. A.; Jaso, A.; et al. Pharmazie 2003, 58, 68-69.

[36] Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A. Bioorg. Med. Chem. 2003, 11, 2149-2156.

[37] Aguirre, G.; Cerecetto, H.; Di Maio, R.; et al. Bioorg. Med. Chem Lett. 2004, 14, 3835-3839.

[38] Kim, Y. B.;Kim, Y. H.; Park, J. Y.; Kim, S. K. Bioorg. Med. Chem. Lett. 2004, 14, 541-544.

[39] Perez-Melero, C.; Maya, A. B.; del Rey, B.; et al. Bioorg. Med. Chem. Lett. 2004, 14, 3771-3774.

[40] Singh, S. K.; Saibaba, V.; Ravikumar, V. Bioorg. Med. Chem. 2004, 12, 1881-1893.

[41] Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A.; et al. Bioorg. Med. Chem. 2004, 12, 3711-3721.

[42] Carta, A.; Corona, P.; Loriga, M. Curr. Med. Chem. 2005, 12, 2259-2272.

[43] Lima, L. M. ; Zarranz, B.; Marin, A. J. Heterocycl. Chem. 2005, 42,1381-1385.

[44] Zarranz, B.; Jaso, A.; Aldana, I.; et al. Arzneim.- Forsch. 2005, 55,754-761.

[45] Urquiola, C.;Vieites, M.; Aguirre, G. ;et al. Bioorg. Med. Chem. 2006, 14, 5503-5509.

[46] Zarranz, B.; Jaso, A.; Lima, L. M. Braz. J. Pharm. Sci. 2006, 42, 357-361.

[47] Burguete, A.; Pontiki, E.; Hadjipavlou-Litina, D.; et al. Bioorg. Med. Chem. Lett. 2007, 17, 6439-6443.

[48] Solano, B.; Junnotula, V.; Marín, A.; et al. J. Med. Chem. 2007, 50, 5485-5492.

[49] Marín, A. ; Lima, L. M. ; Solano, B. ; et al. Exp. Parasitol. 2008,118, 25-31.

[50] Vicente, E.; Charnaud, S.; Bongard, E. ; et al. Molecules 2008, 13, 69-77.

[51] Vicente, E.; Lima, L. M.; Bongard, E. Eur. J. Med. Chem. 2008, In Press. doi:10.1016/j.ejmech.2007.1011.1024.

[52] Francis, J.; Landquist, J.K.; levi, A.A.; Silk, J. A. ;Thorpe, J.M. J. Biochem. 1956, 63(3), 455-457.

[53] Dirlam, J.P.; Presslitz, J.E.;Williams, B.J. J. Med. Chem. 1983, 26(8),1122-1126.

[54] Vicente, E.; Villar, R.; Burguete, A.; et al. Antimicrob. Agents Chemother 2008, 52, 3321-3326.

[55] Hanan, R. M.; Ashraf, M. A.; Omneya, K. M. Arch Pharm Res.2004, 11, 1093-1098.

[56] Asha, B.; Abdul, B. R.; Amir, A. Eur. J. Med. Chem. 2009, 44,1317-1325.

[57] Jin-Hwa, C.; Ok, J.J.;Mi, C. J.; et al. Bioorg. Med. Chem. Lett. 2005, 15, 3380-3384.

[58] Yang, Y.; Zhang, S.; Wu B, et al. Chem.Med.Chem. 2012, 7(5), 823-835. Sastry, R.; Marwah, C.V.; Marwah, P.; A K.; Rao, G.S. Indian. J. Chem.1989, 28B, 885-891.

[59] Li, J.J. J.Org. Chem. 1999, 64, 8425-8427.

[60] Patel, N.; Bergman, J.; Graslund, A. Eur.J.Biochem.1991, 197, 597-604.

[61] Miyagi, T.; Yamamoto, H. Japanese Patent 1967, 17747.Chem. Abstr. 1968, 69, 10475.

[62] Cole, S.P.; Bhardwaj, G.; Gerlach, J.H.; et al. Science 1992, 258, 1650-1654.

[63] Lawrence, D. S.; Copper, J. E.; Smith, C.D. J. Med. Chem. 2001, 44(4), 594-601.

[64] Yoo, H.W.; Suh, M.E.; Park, S.W. J. Med. Chem. 1998, 41,4716 - 4722.

[65] Weng, Q.; Wang, D.; Guo, P.; et al. Eur. J. Pharmacology 2008, 581(3), 262-269.

[66] Fedora, G.; Francesca, A.; Osvaldo, G. D.; Antonella, B.; Antonio, G.; Nouri, N. Bioorg. Med.Chem.2007, 15, 288-294.

[67] Heesoon, L.; Sungmoon, C.; Kwon, N.; Jae-Kyung, J.K.; Jung, C. ;Sung, Y. I. Bioorg. Med. Chem 2004, 14, 1235-1237.

[68] Ries, U. J.; Priepke, H. W. M.; Hauel, N. H. Bioorg. Med. Chem. Lett. 2003, 13(14), 2297-2302.

[69] Balzarini, J.; Karlsson, A.; Meichsner, C. J. Virol 1994, 68(12), 7986-7992.

[70] Balzarini, J.; Pelemans, H. ; Riess, G. J. infect Dis 1997, 176(5), 1392-1397.

[71] Balzarini, J.; De clereg, E. ; Carbonez, A. AIDS Res Hum Retroviruses 2000, 16(6), 517-528.

[72] Abu-Hashem, A. A.; Gouda, M.A.; Badria, F. A. Eur. J. Med. Chem.2010, 45, 1976-1981. DOI:10.1016/j.ejmech.2010. 01.042

[73] Kumar A, kumar S, Saxena A, Mozumdar S. Catal. Commun. 2008, 9,778-784.

[74] Heravi, M. M.; Taheri, S.; Bakhtiari, K.; Oskooie, H. Catal.Commun.2007, 8, 211-214.

[75] Heravi, M. M.; Taheri, S.; Bakhtiari, K.; Oskooie, H.; Javadi, N.M. Arkivoc 2006, 16, 16-22.

[76] Kotharkar, S.A.; Shinde, D.B. J .Iranian Chem. Soc. 2006, 3, 267-271.

[77] Ajaikumar, S.; Pandurangan, A. Applied Catalysis A: General 2009, 357,184-192.

[78] Bandyopadhyay, D.; Mukherjee, S.; Rodriguez, R. R.; Banik, B. K. Molecules 2010, 15, 4207-4212.

[79] Wallace, J.M.; Bjorn, C.G.; Tamariz, J.; Akhmedov, N. G.; Hurley, M.T. Tetrahedron 2008, 64, 9675-9684.

[80] Rao, V. J.; Palaniappan, S. J. Mol. Catal. 2007, 265, 227-230.

[81] Lin, P.-Y.; Hou, R.-S.; Wang, H.-M.; Kang, I.-J.; Chen, L.-C. J. Chin Chem. Soc. 2009, 56, 683-687.

[82] Darabi, H. R.; Mohandessi, S.; Aghapoor, K.; Mohasenzadeh, F.A. Catal. Commun. 2007, 8, 389-392.

[83] Sadjadi, S.; Hekmatshoar, R.; Ahmadi, S. J.; Hosseinpour, M.; Outokesh, M. Synth Commun. 2010, 40, 607- 614.

[84] Meshram, G. A.; Deshpande, S. S. Eur. J. Chem. 2013, 4(4), 422 - 424.; Katkar, S. S.; Mohite, P. H.; Gadekar, L. S.; Arbad, B. R.; Lande, M. K. Cen. Eur. J. Chem. 2010,8,320.

[85] Das, B.; Venkateswarlu, K.; Suneel, K.; Majhi, A. Tetrahedron Lett. 2007, 48, 5371-5374.

[86] Kumar, A. V.; Reddy, V. P.; Rao, K. R. Synlett 2010, 17, 2571-2574.

[87] Mohsenzadeh, F.; Aghapoor, K.; Darabi, H. R. J. Braz. Chem. Soc. 2007, 18, 297-303.

[88] El- Ashry, S. H.; Atta, K. F.; Aboul-Ela, S.; Beldi, R. J. Carbohydrate Chem. 2007, 26, 1-16.

[89] Zhou, J.-F.; Gong, G.-X.; An, L.-T.; Liu, Y.; Zhu, F.-X.; Zhu, Y.-L.; Ji, S. J. Synlett 2008, 20, 3163-3166.

[90] Zhou, J.F.; Gong, G. X.; Shi, K.B.; Zhi, S. J. Chinese Chem. Lett. 2009, 20, 672-675.

[91] Zhou, J.-F.; Gong, G.-X.; Zhi, S.-J.; Duan, X.-L. Synth Commun. 2009, 39, 3743.

[92] Padmavathy, K.; Nagendrappa, G.; Geetha, K.V. Tetrahedron Lett. 2011, 52, 544-547.

[93] Zhang, X.-Z.; Wang, J.-X.; Bai, L. Synth Commun. 2011, 41, 2053-2063.

[94] More, S. V.; Sastry, M. N.V.; Yao, C.-F. Green Chem. 2006, 8, 91-95.

[95] Wan, J.-P.; Gan, S.-F.; Wu, J.-M.; Pan, Y. Green Chem. 2009, 11, 1633-1637.

[96] Kumar, B. S. P. A.; Madhav, B.; Reddy, K. H. V.; Nageswar, Y.V.D. Tetrahedron Lett. 2011, 52, 2862-2865.

[97] Darabi, H. R.; Tahoori, F.; Aghapoor, K.; Taala, F.; Mohsenzadeh, F. J. Braz. Chem. 2008, 19, 1646-1652.

[98] Aghapoor, K.; Darabi, H. R.; Mohsenzadeh, F.; Balavar, Y.; Daneshyar, H. Transition Met. Chem. 2010, 35, 49-53.

[99] Meshram, H. M.; Kumar, G. S.; Ramesh, P.; Reddy, B. C. Tetrahedron Lett. 2010, 51, 2580-2585.

[100] Hou, J.-T.; Liu, Y.-H.; Zhang, Z.-H. J. Heterocyclic Chem. 2010, 47, 703-706.

[101] Ghosh, P.; Mandal, A. Advances Applied Sci. Res. 2011, 2, 255-260.

[102] Chandrasekhar, S.; Reddy, N. Tetrahedron Letters 2010, 51, 3623-3625.

[103] Dong, F.; Kai, G.; Zhenghao, F.; Xinli, Z.; Zuliang, L. Catal. Commun.2008, 9, 317-320.

[104] Antoniottia, S.; Duach, E. Tetrahedron Letters 2002, 43, 3971-3973.

[105] Jeffery, M. W.; Bjo¨rn, C.G.; et al. Tetrahedron 2008, 64, 9675-9684.

[106] Raj, K.B. Heterocyclic chemistry .4th ed. New Delhi: New Age International publishers 2005, 535-538.

[107] Zmujdzin, l. b. A. Pol. Patent 1974, 69644. Chem. Abstr. 1974, 81, 77966.

[108] Noorulla, S.; Sreenivasulu, N. Inter. J. Res. Pharm. Biomed. Sci. 2011, 2 (3), 1100-1106.

[109] Shabaan, M.; Taher, T. A.; Osman, O. E. Eur. J. Chem.

2011, 2 (3), 365 - 371.

[110] Gorbunova, E. A.; Mamedov, V. A. Russian J. Organic Chem. 2006, 42(10), 1528-1531.

[111] Islami, R. M. ; Hassani, Z. Arkivoc 2008, (xv), 280-287.

[112] Taylor, E. C.; Thompson, M. J. J. Org. Chem.1961, 26, 3511. DOI: 10.1021/jo01067a604

[113] Kumar, N.; Sharma, P.; Kaur, N.; Pareek, A. J. Applicable Chem. 2013, 2 (2), 143-149.

[114] Atkinson, C. M.; Brown, C. W.; Simpson, J. C. E. J. Chem. Soc. 1956, 26-30.

[115] Bandyopadhyay, D.; Mukherjee, S.; Rodriguez, R. R.; Banik, B. K. Molecules 2010, 15, 4207-4212.

[116] Kleineweischede, A.; Mattay J. Eur. J. Org. Chem. 2006, 4, 947-957. DOI: 10.1002/ejoc.200500548

[117] Sherman, D.; Kawakami, J.; He, H.Y.; Dhun, F.; Weitao, P.; Labelle, X. Y. M. Tetrahedron Lett.2007, 48, 8943-8946.

[118] Thakuria, H.; Das, G. J. Chem. Sci. 2006, 118(5), 425-428.

[119] Gris, J.; Glisoni, R.; Fabian, L.; Fernandez, B.; Moglioni, A.G. Tetrahedron Lett. 2008, 49, 1053-1056.

[120] Rostamizadeh, S.; Jafari, S. Indian. J. Heterocyclic Chem. 2001, 10, 303-304.

[121] Ratnadeep, V.; Ghadage; Pramod, J. S. J. Chem. Pharm. Res. 2011, 3(5), 260-266.

[122] Khan, S.A.; Mullick, P.; Pandit, S.; Kaushik, D. Acta Poloniae Pharmaceutica - Drug Research 2009, 66(2), 169-172.

[123] Mahmoud, A. A.; Mohamed, M.Y. Der Pharma Chemica 2012, 4 (3), 1323-1329.

[124] Badran, M. M.; Moneer, A. A.; Refaat, M. H.; El-Malah, A. A. J. Chinese Chemical Society 2007, 54, 469-478.

[125] Heravi, M.M.; Bakhtiari, K.; Tehrani, M.H.; Javadi,N. M.; Oskooie, H.A. Arkivoc 2006, xvi, 16-22.

[126] Lin, S.K. Molecules 1996, 1, 37-40.

[127] Ruiz, M. D.; Autino, C. J.; Quaranta, N.; V´azquez, G. P.; Romanelli, P. G. The Scientific World J. 2012, 2012, Article ID 174784, 8.doi:10.1100/2012/174784.

[128] Cai, J.J.; Zou, J.P.; Pan, X.Q.; Zhang, W. Tetrahedron Lett. 2008, 49, 7386-7390.

[129] Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. Tetrahedron Lett. 2009, 50,767-769.

[130] Bhosale, R.S.; Sarda, S.R.; Ardhapure, S.S; et al. Tetrahedron Lett. 2005, 46, 6345- 6348.

[131] Khaksar, S.; Rostamnezhad, F. Bull. Korean Chem. Soc. 2012, 33, 2581-2584.

[132] Brown, D.J. The Chemistry of Heterocyclic Compounds, Quinoxalines: Supplement II, John Wiley & Sons, INC., New York 2004, 1-92.

[133] Iveta, W. Acta Universitatis Palackianae Olomucensis Facultas Rerum Naturalium 2002, 46, 771.

[134] Ali, M.M. Molecules 2000, 5, 864-873.

[135] Norma, F.; Santos-Sánchez; Salas-Coronado, R. Arkivoc 2008, v, 187-199.

[136] Varano, F. Eur. J. Med. Chem. 2001, 36, 203-209.

[137] Ohle, H.; Heilscher, M. Ber. Dtsch. Chem. Gas 1941, 74B, 13-19.

[138] Henseke, G.; Lemke, W. Chem. Ber. 1958, 91, 101.

[139] Yan, L.; Liu, F.; Dai, G.; Liu, H. Bioorg. Med. Chem. Lett. 2007, 17, 609-612.

[140] Leese, C. L.; Rydon, H.N. J.Chem.Soc. 1955,303-309.

[141] El Khadem, H. Advances in Carbohydrate Chemistry 1965, 20, 139-181. doi:10.1016/S0096-5332(08)60298-2.

[142] Bar1trop, J.A.; Richards, C.G.;Russell, D.M. J.Chern.Soc. 1959, 1423.

[143] Schellenberg, M. He1v.Chirn. Acta. 1970, 53, 1151.

[144] Mostafa, A.M.; Aboulela, L.S.; Sallam, E. A. M.; Louis, F. F.; Anthonsen, T. Green and Sustainable Chem. 2012, 2, 71-75.

[145] Toman, J.; Klicnar, J.; Macháček, V. Collect. Czech. Chem. Commun. 1978, 43, 2179-2189. Doi: 10.1135/cccc19782179.

[146] Wu, X.H.; Liu, G.; Zhang, J. Mol Divers 2004, 8(2),165-174.

[147] Gao, X.M.; Luo, W.P.; Shen, X.F. Pesticides 1998, 37(7), 12-13.

[148] Carta, A.; Sanna, P.; Gherardini, L. Il Farmaco, 2001, 56, 933 -938.

[149] Bajpai, S.; Singh, S.; srivastava, V. Inter. J. Innovative Res. Sci., Engineering and Technology 2013, 2(9), 2319-8753.

[150] Sherman, D.; Kawakami, J.; Hai-Ying, H.; et al. Tetrahedron Lett. 2007, 48, 8943-8946.

[151] Xie, F.; Zhang, M.; Jiang, H.; Chen, M.; Lv, W.; Zheng, A.; Jian, X. Green Chem. 2014, First published online 21 Aug 2014. DOI: 10.1039/C4GC01316F.

[152] Ghadari, R.; Hajishaabanha, F.; Aghaei, M.; Shaabani, A.; Weng, N.S. Mol Divers 2012, 16, 453-461.

[153] Surikova, O.V.; Aliev, Z. G.; Polygalova, N. N.; Mikhailovskii, A. G.; Vakhrin, M I. Russian J. Organic Chem. 2008, 44, 901-905.

[154] Karami, B.; Khodabakhshi, S. J. Serb. Chem. Soc.2011, 76 (9), 1191-1198.

[155] Karami, B.; Damavandi, J. A.; Bayat, M.; Montazerozohori, M. J. Serb. Chem. Soc. 2006, 71: 27.

[156] Karami, B.; Montazerozohori, M.; Habibi, M. H. Bull. Korean Chem. Soc. 2005, 26, 1125-1128.

[157] Karami, B.; Montazerozohori, M. ; Karimipour, G.; Habibi, M. H. Bull. Korean Chem. Soc. 2005, 26, 1431.

[158] Karami, B.; Montazerozohori, M. ; Habibi, M. H. ; Zolfigol, M. A. Heterocyclic Commun. 2005, 11, 513.

[159] Karami, B.; Montazerozohori, M.; Habibi, M. H. Phosphorus Sulfur Silicon Relat. Elem. 2006, 181, 2825-2831.

[160] Montazerozohori, M.; Karami, B. Helv. Chim. Acta 2006, 89, 2922- 2926.

[161] Montazerozohori, M.; Karami, B.; Aziz, M. Arkivoc 2007, (i), 99-104.

[162] 162.Karami, B.; Montazerozohori, M. Molecules 2006, 11, 720-725.

[163] Isikdag, İ.; Özkay, Y.; İncesu, Z. Turk J. Pharm. Sci. 2011, 8 (2), 179-188.

[164] Berezoviskii, V. M.; Polyakova, N. A.; Tulchinskaya, L. S.; Geterotsikl, K. Chem. Abstr. 1968, 68, 78254.

[165] Matsumoto, Y.; Matsumara, Y.; Lio, A.; omezwa, T.Y. Bull. Chem. Soc. Japan 1970, 43, 1496.

[166] Moreno, E.; Ancizu, S.; Pérez-Silanes, S. Eur. J. Med. Chem. 2010, 45, 4418- 4426.

[167] Burguete, A.; Pontiki, E.; Hadjipavlou-Litina, D. et al. Chem Biol Drug Des 2011, 77, 255-267.

[168] Yingjun, X.; Fanhong, W.u.; Zhiyi, Y.; Minmin, Z.; Sheng, J. Molecules 2011, 16, 6894-6901.

[169] Zarranz, B.; Jaso, A.; Lima, L. Brazilian J. Pharma. Sciences 2006, 42, 358-361.

[170] Ancizu, S.; Castrillo, N.; Pérez-Silanes, S ; et al. Molecules 2012, 17, 7737-7757.

[171] Liu, G.; Zhou, Y. u.; Lin, D.; Wang, J. ACS Comb. Sci. 2011, 13 (3), 209-213.

[172] Moustafa, O. S.; Badr, M.Z.A.; El-Emary, T.I. Bull. Korean Chem. Soc. 2002, 23, 567-570.

[173] Bansal, R.K. 3rd ed. New Age International Pvt. Ltd., Heterocyclic chemistry. 2005, 28, 464-472.

[174] Landquist, J. K. J. Chem. Soc. 1953, 2816-2821.

[175] Taranu, I. ; Popa, I.; Dragos, A. ; Vlatanescu, N. ; Buzatu, D. Chem. Bull. "Politehnica" Univ. (Timisoara) 2008, 53(67) ,1-2,192-195. ; Elina, A. S. ; OYu, M. Gen. Chem. (USSR) 1955, 25,145.

[176] Taranu, B.O.; Popa, I.; Dragos, A.; Taranu, I.; Dobrescu, M.C.; Vlatanescu, N.V. Chem. Bull. "Politehnica" Univ. (Timisoara) 2010, 55(69), 2,175-179.; Kimura T, Yakugaku Zasshi, 1957, 77,891.

[177] Maxer, A.; Salzmann, U.; Hofler, F. Helv. Chim. Acta.1971, 54, 2507.

[178] Takaski, H.; Otomasu, H. Chem. Pharm. Bull., 1970, 18, 22-25.

[179] Srinivas, M.; Tejasri, A.; Anjaneyulu, N.; Satyanarayana, K. Inter. J. Pharma Sciences 2013, 3, 142-146.

[180] Baritrop, J. A.; Richards, C.G.; Russel, D. M. J. Chem. Soc.1959, 1423.

[181] Hammer, J.; Halliday, R. E. J. Org. Chem. 1963, 28, 2488-2488.

[182] Ribel, W. J.; Blach, T. N. J. Org. Chem. 1959, 24, 205-207.

[183] Rao, K.V.; Jackman, D. J. Heterocycl. Chem. 1973, 10, 213-215.

[184] DeSelms, R. C.; Greaves, R. J.; Schleigh, W. R. J. Herterocycl. Chem. 1974, 11, 595.

[185] Smith, H.; Habib, M. S.; Iqbal, M.; Qureshi, M. I. J. Chem. Soc. 1964, 4053-4056.

[186] Mamedov, V.A.; Khafizova, E.A.; Gubaidullin, A. T.; et al. Russian Chemical Bulletin, International Edition 2011, 60, 368-372.

[187] Puratchikody, A.; Natarajan, R.; Jayapal, M.; Doble, M. Chem Biol Drug Des 2011, 78,988-998.

[188] Thirupathaiah, T.; kranthi k.; Laxminarayana, E.; Thirumala, C. M. Inter. J. Chem Tech Research, Coden (USA): IJCRGG, 2010, 2(4), 1987-1991.

[189] Sarodnick, G.; Heydenreich, M.; Linker, T.; Kleinpeter, E. Tetrahedron 2003, 59, 6311-6321.

[190] Yurii, A.; Sayapin, V. N. K.; Serguei, V. V.; et al. Arkivoc, 2009, iv, 46-56.

[191] Kuntal, M. Y. K. A. Med Chem Res 2011, 20, 300-306.

[192] Mamedov, V. A.; Kalinin, A. A.; Gorbunova, E. A.; Bauer, I.; Habicher, W. D. Russian J. Organic Chem. 2004, 40, 1041-1046.

[193] El'chishcheva, N.V.; Shklyaev, Yu. V.; Vnutskikh, Zh. A.; Chekryshkin, Yu. S.; Odegova, T. F. Pharmaceutical Chemistry J. 2012, 46,346-350.

[194] Wang, M.; Zhang, T.T.; Gao, J.J.; Liang, Y. Chem. Heterocyclic Comp. 2012, 48(6), 897-902.

[195] Mamedov, V.A.; Kalinin, A.A.; Gubaidullin, A.T.; Isaikina, O.G.; Litvinov, I. A. Russian J. Organic Chem. 2005, 41, 599-606.

[196] Mamedov, V.A.; Murtazina, A. M.; Gubaidullin, A.T. Russian Chemical Bulletin, International Edition 2010, 59, 1645-1655.