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SYNTHESIS, REACTIVITY AND BIOLOGICAL ACTIVITY OF QUINOXALIN-2-ONE DERIVATIVES

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Abstract: Quinoxalines have a great interest in various fields and particularly in chemistry, biology and pharmacology. It enabled the researchers to develop many methods for their preparations and to seek new fields of application. In this review, we'll expose different methods of synthesis of the quinoxalin-2-one, its reactivity and finally we'll discuss the various biological activities of its derivatives.

Keywords: *quinoxalin-2-one, synthesis, reactivity, alkylation, cycloaddition, biological properties*

Résumé: L'importance des dérivés de la quinoxalinone dans différents domaines et, en particulier, en chimie, en biologie et en pharmacologie, a incité les chercheurs à développer de nombreuses méthodes de synthèse pour leurs préparations et à trouver de nouveaux domaines d'applications. Dans cette mise au point nous examinerons, d'abord, les méthodes de synthèse des dérivés de la quinoxalin-2-one, puis leurs réactivités et finalement nous discuterons les différentes activités biologiques de ses dérivés.

Mots clés: *quinoxalin-2-one, synthèse, réactivité, alkylation, cycloaddition, propriétés biologiques*

SUMMARY

INTRODUCTION

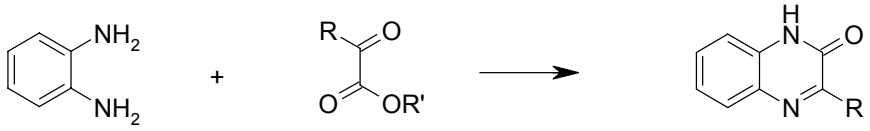
The quinoxalines are a class of heterocyclic compounds with different applications in various fields, whether pharmacology [1-5], agricultural chemistry [6, 7], or chemical industry [8, 11] where various patents were field. Thus, several new synthetic methods have been described in literature. We will show, in this development, the synthesis, reactivity and the biological properties of heterocyclic systems derived from quinoxaline

A. SYNTHESIS OF QUINOXALIN-2-ONE

The main synthesis methods proposed can be divided into two categories. The first one involves cyclocondensation reactions between *o*-phenylenediamines and aliphatic electrophile compounds, in conventional terms, or in the presence of metal salts in solution or solid support under microwaves. The pyrazine nucleus may also be formed using derivatives of *o*-substituted aniline.
Another class of reactions involves nitrogen heterocycles which has different links likely to opening reactions or rearrangements in different conditions, leading to opened intermediates that, later, cyclize to give the quinoxaline derivatives.

1. Condensation of *o*-phenylenediamine with α-ketocarboxylic acid and ketoesters

The 1,2-dihydroquinoxalin-2-ones and their derivatives substituted in position 3 were obtained by condensation of *o*-phenylenediamine **1** with α-ketocarboxylic acid and ketoesters or their correspondents in accordance with the method of Hinsberg [12-16] (Scheme 1).

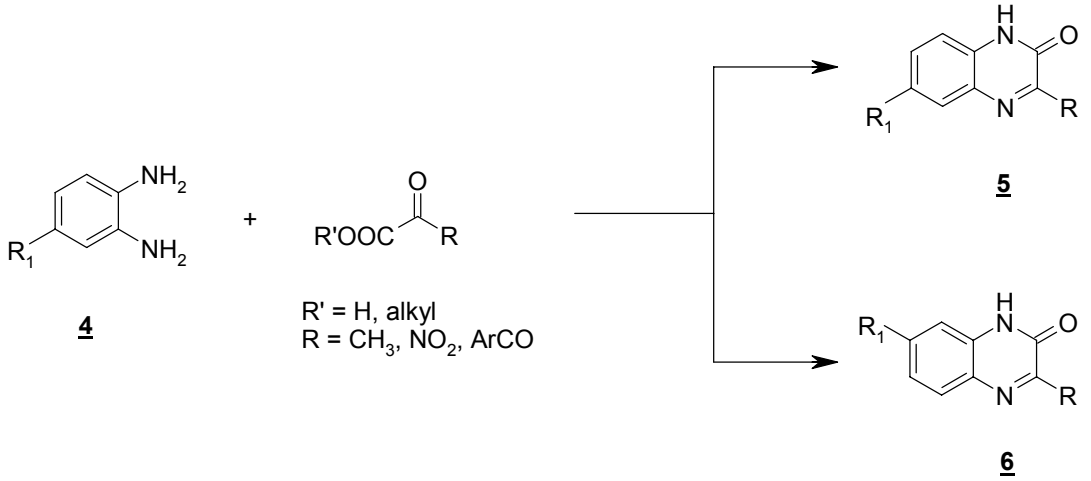


1 **2** **3**

R' = H, alkyl

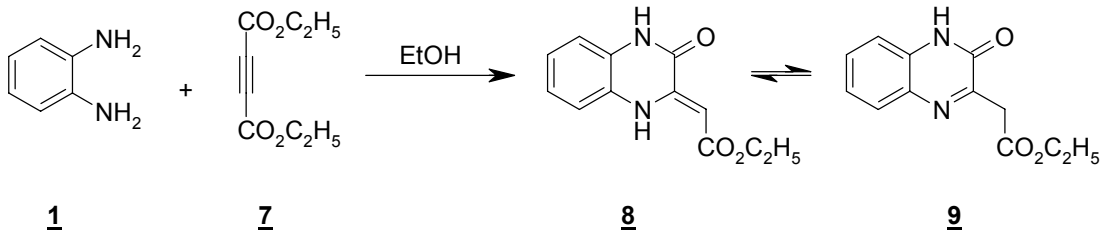
Scheme 1.

It should be noted that when the reaction involves the monosubstitued *o*-phenylendiamines, it was possible to obtain a mixture of two isomers **5** and **6** [17-24], (Scheme 2).



Scheme 2.

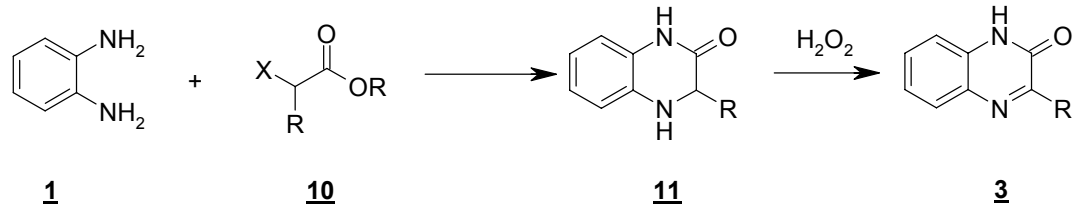
The condensation of *o*-phenylenediamine with diethyl acetylenedicarboxylate **7** in ethanol, used to prepare a compound with quinoxaline structure which exist in two tautomeric forms [25] (Scheme 3).



Scheme 3.

2. From quinoxaline intermediates

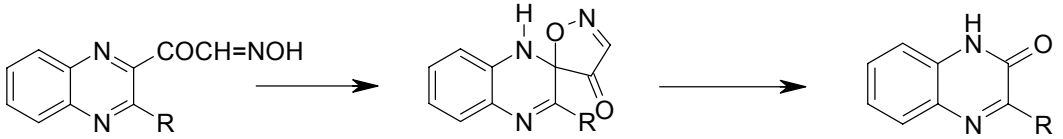
King *et al.* [26] have synthesized the quinoxaline **3** by condensing the α-halogenoesters **10** with *o*-phenylenediamine **1** and creating an oxidation by means of hydrogen peroxide (Scheme 4).



Scheme 4.

Several examples have been described in the literature on the hydrolysis of 2-aminoquinoxalines leading to quinoxalinones. Thus, the 2,3-diaminoquinoxaline is hydrolyzed by hydrochloric acid (2.5 M) at 100 °C, for 5 minutes to give 3-aminoquinoxalin-2-one [27]. In the same way, the treatment of 2-amino-3-phenylquinoxaline by nitric acid, give 3-phenylquinoxalin-2-one with an excellent performance [28].

By leading the oxime quinoxalinylglyoxal to reflux of dimethylaniline, it was possible to prepare the quinoxalinone **3** from a spiro intermediate **13** [29] (Scheme 5).



12
R = Me ou Ph

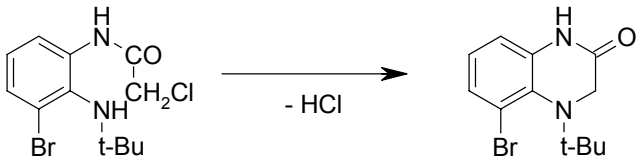
13

3

Scheme 5.

3. From derivatives of aniline

The 2-bromo-*N*-tert-butyl-6-(2-chloroacetamido) aniline **14** leads in reflux of acetonitrile for 24 hours to 5-bromo-4-tertbutyl-3,4-dihydro-2(1*H*)-quinoxalinone **15** with a yield of 79% (scheme 6) [30].

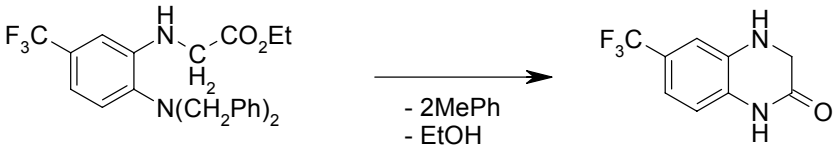


14

15

Scheme 6.

By subjecting the *N*,*N*-dibenzyl-2-(ethoxycarbonylmethyl)amino-4-(trifluoromethyl) aniline **16** to a reduction under a pressure of 3 atmospheres, which induces a spontaneous cyclization, giving the 6-trifluoromethyl-3,4-dihydro-2(1*H*)-quinoxalinone **17** with a yield of 97% (scheme 7) [31].



16

17

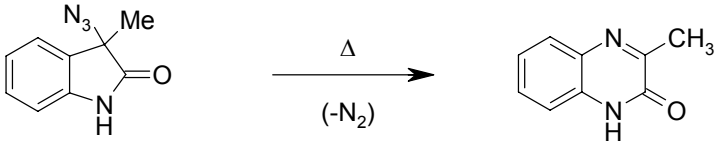
Scheme 7.

4. From heterocyclic systems

4.1. By cycle extension

4.1.1. From indolinone

The 3-methylquinoxalinone **18** may also be prepared by an extension of cycle [32]. Thus the 3-azido-3-methyl-2-indolinone **19** is transformed into quinoxalinone in xylene at reflux (scheme 8).

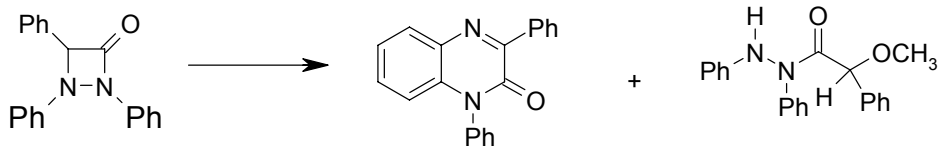


18 **19**

Scheme 8.

4.1.2. From diazetidone

The quinoxaline **21** was obtained with a yield of 34% by heating diazetidone **20** in reflux of methanol (Scheme 9) [33-34].

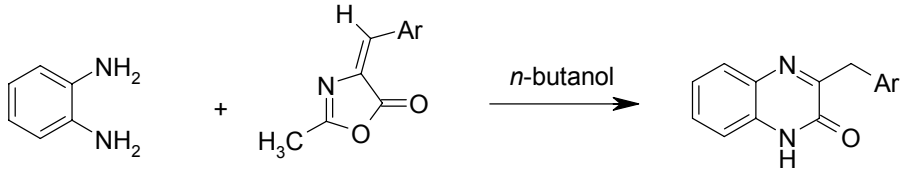


20 **21** **22**

Scheme 9.

4.1.3. From 4-arylidene-2-methyl-1,3-oxazolidin-5-one

Jellal *et al.* [35] carried out the condensation in *n*-butanol at reflux, *o*-phenylenediamine **1** and 2-arylidene-methyloxazolin-5-one **23**, for accessing the 3-arylmethylquinoxalin-2(1*H*)-one **24** (Scheme 10).



1 **23** **24**

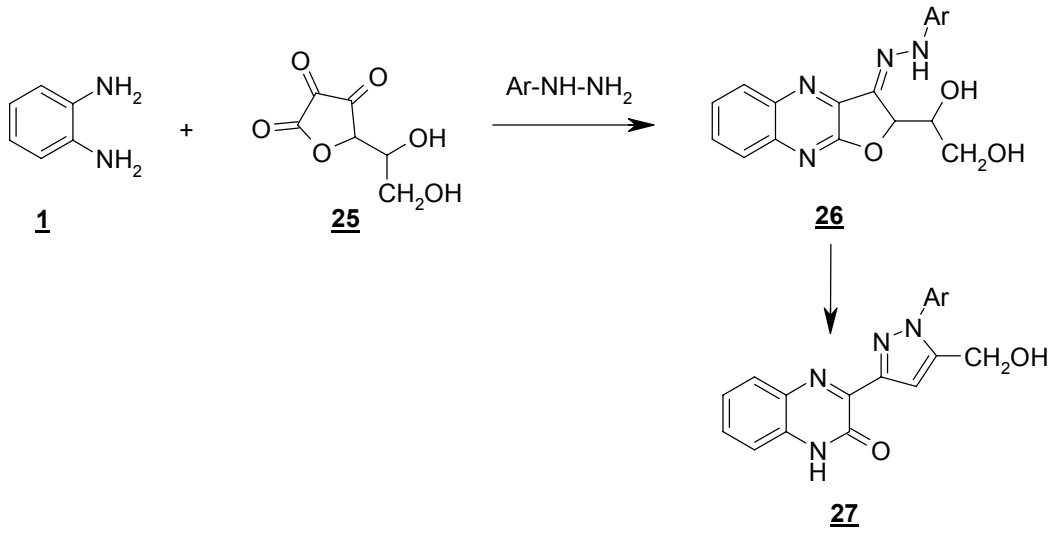
Scheme 10.

4.1.4. From dehydroascorbic acid

Similarly, the condensation of dehydroascorbic acid **25** with *o*-phenylenediamine **1**, led to compound **26** which turns into pyrazolylquinoxalinone **27** in the presence of arylhydrazines (Scheme 11) [36].

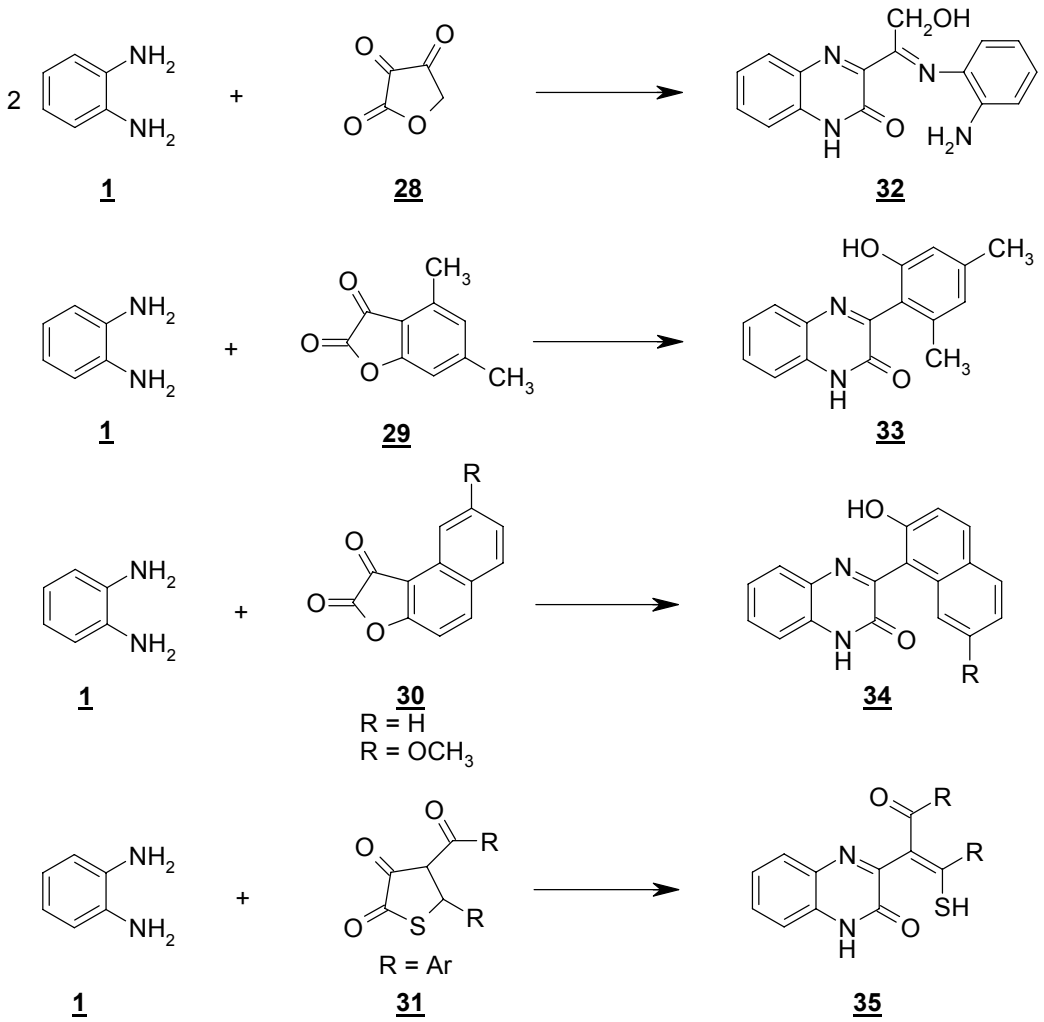
4.1.5. From dicarbonylated five-membered ring compounds

In a similar way, the authors [37-39] obtained quinoxalines **32** - **35** by condensing *o*-phenylenediamine with heterocyclic dicarbonyl compounds **28** - **31** (Scheme 12).



1 **25** **26** **27**

Scheme 11.



1 **28** **32**

1 **29** **33**

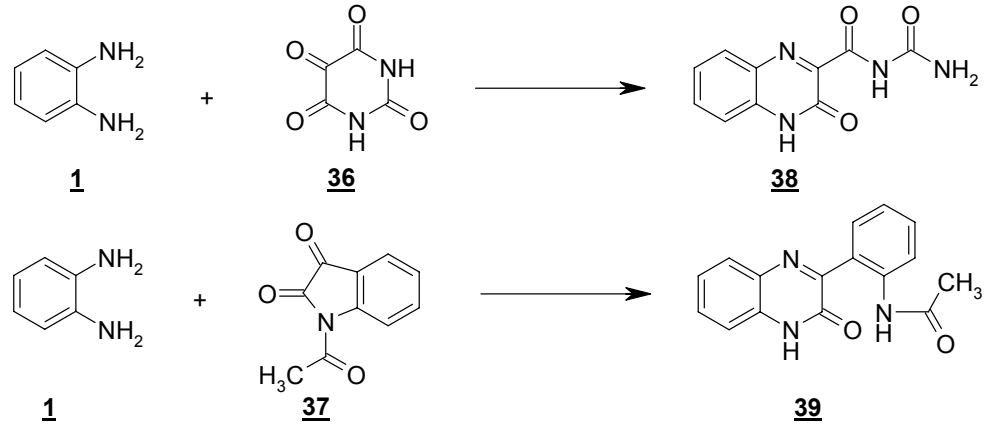
1 **30** **34**

1 **31** **35**

Scheme 12.

4.1.6. From nitrogenous polycarbonylated heterocycles

Other compounds containing function lactams **36** and **37** were also used as agents of cyclization for the preparation of quinoxalinones [40-43] **38** and **39** (Scheme 13).

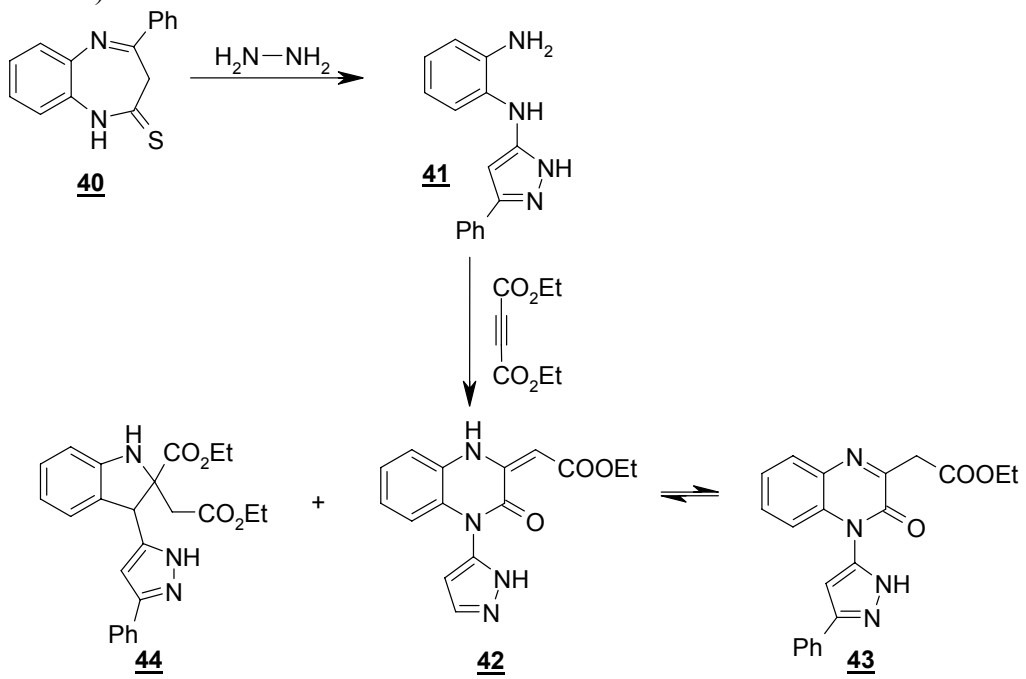


Scheme 13.

4.2. Through cycle contraction

4.2.1. From 1,5-benzodiazepin-2-one

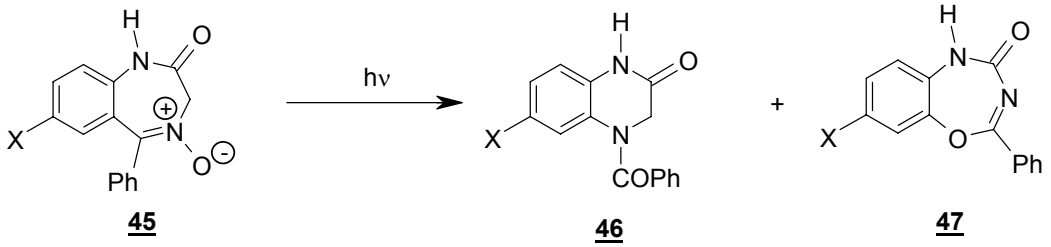
Ahabchane *et al.* [44] have been able to prepare the quinoxaline **42** from benzodiazepine-2-thione **40** in two steps. First, they made an opening round of the seven membered ring, by reacting hydrazine on benzodiazepine-2-thione, obtained by sulfuration of 1,5-benzodiazepin-2-one. The *o*-aminophenylaminopyrazole **41** obtained undergoes condensation with diethyl acetylenedicarboxylate, gave benzimidazoline **44**, beside of a new quinoxaline derivative which takes form in two tautomeric forms (Scheme 14).



Scheme 14.

4.2.2. From 1,4-benzodiazepin-2-one N-oxide

Irradiation of 1,4-benzodiazepine **45** gives quinoxaline **46** when (X = Cl). Conversely, we note the formation of oxadiazocine **47** [45], when (X = SMe) (Scheme 15).



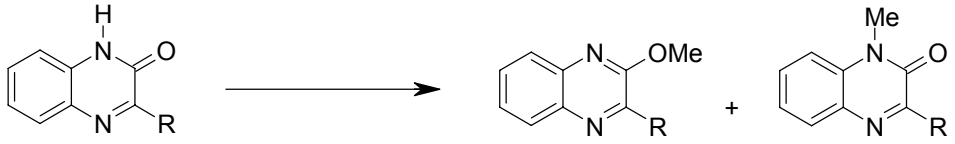
45 **46** **47**

Scheme 15.

B. REACTIVITY OF 1,2-DIHYDROQUINOXALIN-2-ONE

1. Alkylation

The alkylation reaction of quinoxalin-2-one gives a mixture of *O*-alkyl and *N*-alkyl derivatives. Thus the methylation of quinoxaline by diazomethane [46, 47] involved the two centers of the lactam function (Scheme 16).



3 **48** **49**

Scheme 16.

This reaction has been generalized to other alkylating agents, using phase transfer catalysis conditions, to lead to the *N* and *O* alkyl compounds.
The structures of the alkylated products were determined from the spectral data (^{1}H and ^{13}C NMR and mass spectroscopy) and confirmed by the X-ray diffraction (Fig. 1) [48].

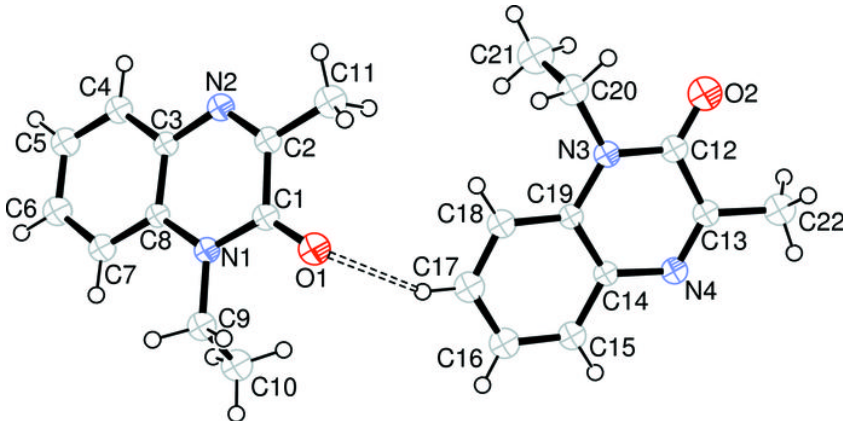
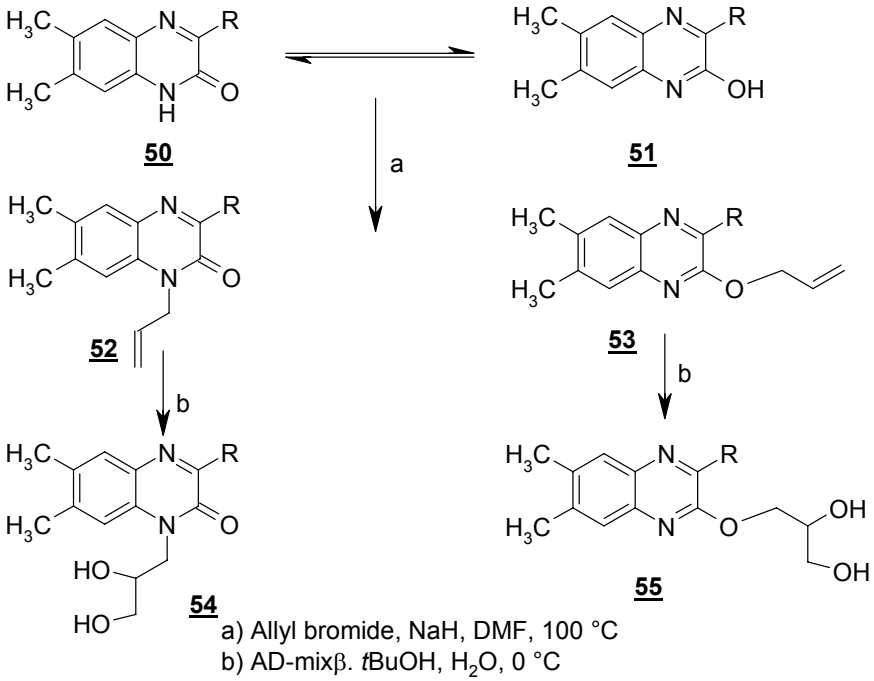


Figure 1. *Structure of the alkylated products*

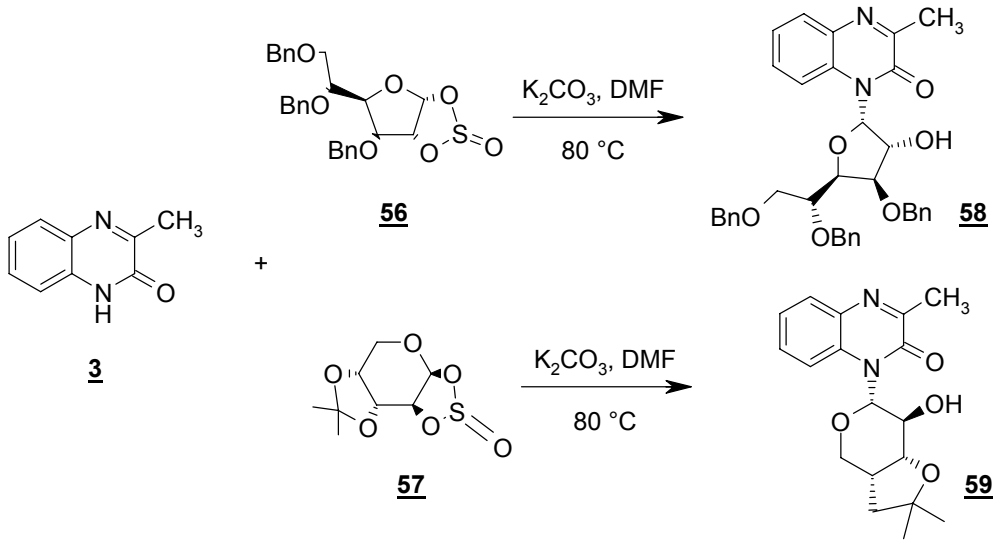
The alkylation reactions have been exploited to prepare quinoxalines differently functionalized in position 1 and 2.

Thus, Ali *et al.* [49], have adopted a protocol of using allyl bromide as an alkylating agent and sodium hydride in dimethylformamide at 100 °C. The dihydroxylation of *N* and *O* alkyl derivatives **54** and **55**, was performed with AD-mix β in a mixture *t*-butanol-water (Scheme 17).



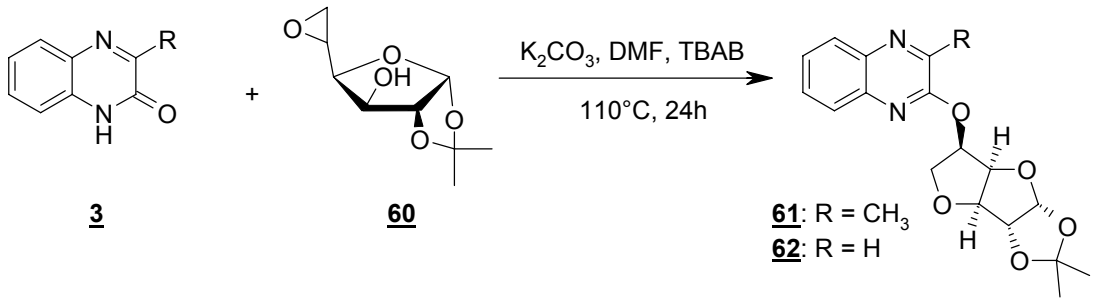
Scheme 17.

Benksim *et al.* [50] have developed an efficient synthesis method for obtaining nucleoside analogues **58** and **59**, from the quinoxalinone by reacting derivatives1,2-*O*-sulfonyl of gluco- **56** and arabino- **57** structure with 3-methylquinoxalin-2(1*H*)-one **3** in the presence of a weak base K_2CO_3 in DMF at 80 °C (Scheme 18).



Scheme 18.

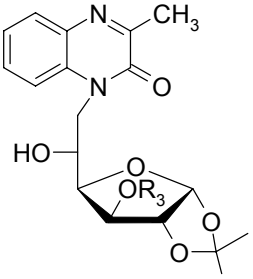
The condensation of quinoxalinone **3** with 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose **60**, leads to *O*-glucoquinoxalines **61** - **62**. In a reaction involving the rearrangement of the 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose to the corresponding 3,6-anhydro, which preferentially reacts with the oxygen atom of the lactam function of quinoxaline. The *O*-glucoquinoxalines **61** - **62** obtained were identified by spectroscopic data and confirmed by X-ray diffraction (Scheme 19) [51].



3 **60**

Scheme 19.

It should be noted that when the hydroxyl group of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose, is protected by an alkyl group, the same reaction is used to isolate the compound of *N*-alkylation beside the compound of *O*-alkylation (Scheme 20).

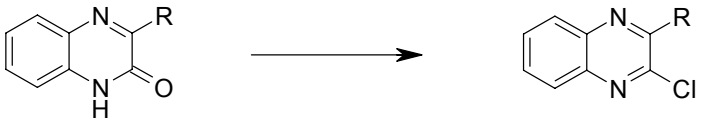


63: $R_3 = CH_3C_{19}H_{24}N_2O_6$
64: $R_3 = C_3H_5C_{21}H_{26}N_2O_6$
65: $R_3 = C_4H_9C_{22}H_{30}N_2O_6$
66: $R_3 = C_8H_{17}C_{26}H_{38}N_2O_6$
67: $R_3 = C_{10}H_{21}C_{28}H_{42}N_2O_6$
68: $R_3 = C_{12}H_{25}C_{30}H_{46}N_2O_6$

Scheme 20.

2. Nucleophilic substitution in position 2

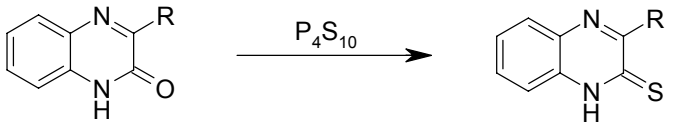
Nucleophilic substitution in position 2 of the 1,2-dihydroquinoxalin-2-one **3** has enabled the authors [52-54] to isolate the chlorinated products **69** by action of $POCl_3$ or PCl_5 (Scheme 21).



3 **69**

Scheme 21.

In the case where R = H [55], the chlorination reaction gives the 2,3-dichloroquinoxaline.
The reaction of thionation was achieved by the action of phosphorus pentasulfide in pyridine (Scheme 22) [56, 57].



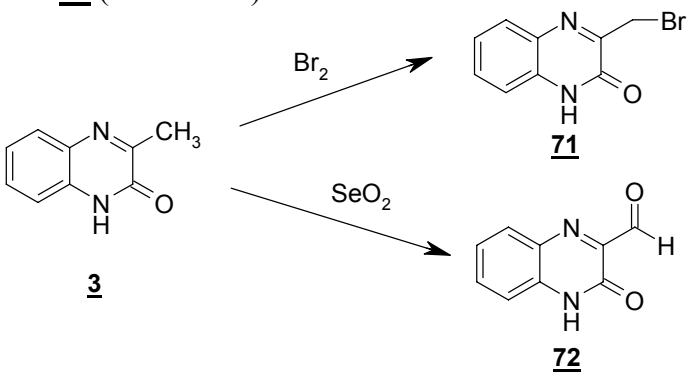
3 **70**

Scheme 22.

3. Reactivity of alkyl group in position 3

The alkyl group in position 3 of the quinoxalin-2-one is very reactive to some electrophil agents. Thus, Leese *et al.* [47] have easily made the bromination of 3-methylquinoxalin-2-one **3**.

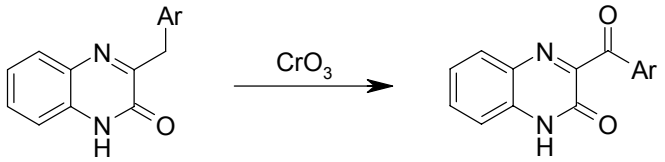
Baranov [58] has studied the oxidation of quinoxaline 3 by selenium oxide to obtain 3-formyl-quinoxaline **72** (Scheme 23).



3 **71** **72**

Scheme 23.

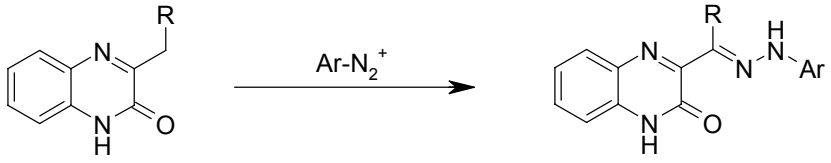
According to an oxidation reaction, Romanenko [59] has synthesized the 3-acyl-1,2-dihydroquinoxalin-2-one (Scheme 24).



73 **74**

Scheme 24.

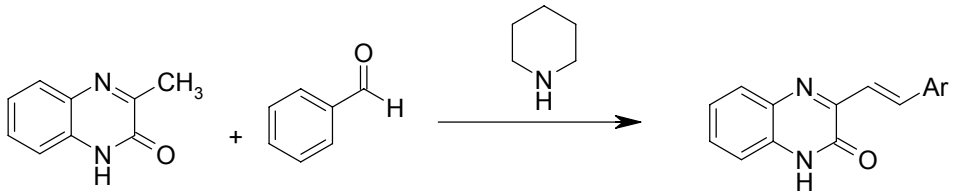
Kurasawa *et al.* [60] have performed the action of aryldiazonium salt with 3-methylquinoxalin-2-one **73** (Scheme 25).



73 **75**

Scheme 25.

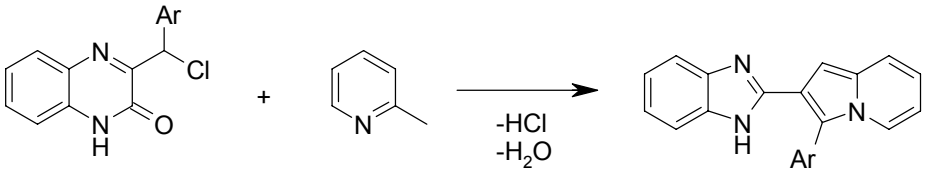
The condensation of 3-methylquinoxalin-2-one **3** with aromatic aldehydes gives the compound **76** (Scheme 26) [61].



3 **76**

Scheme 26.

Recently Vakhid *et al.* [62] prepared the 2-(indolizin-2-yl) bezimidazole **79**, by condensing 3-(arylchloromethyl-quinoxalin-2-one **77**, with α-picoline **78** (Scheme 27).



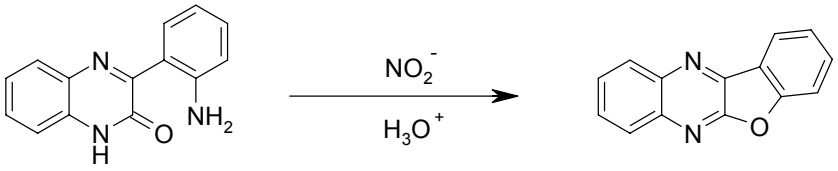
77 **78** **79**

Ar = 4-$NO_2C_6H_4$
Ph
2,4-$Cl_2C_6H_3$
3,5-$Cl_2C_6H_3$
CH_2Ph

Scheme 27.

4. Cyclization reactions involving positions 2 and 3 of the quinoxaline

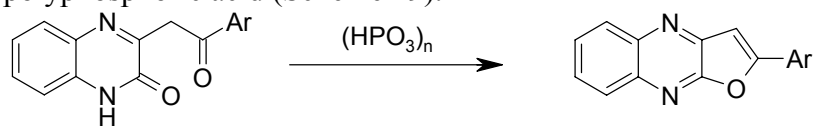
The cyclization reactions leading to oxygenated heterocyclic systems have been known for a long time and they can give an oxygen and sulfur heterocycles joined to quinoxaline. The Marchlewski and Sosnowski reaction, [63] conducted in the presence of hydrochloric acid, constitutes an oldest example (Scheme 28).



80 **81**

Scheme 28.

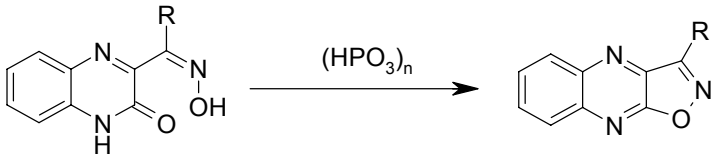
Andrejčikov *et al.* [64] carried out the cyclization of 3-aroylmethyl-1,2-dihydro-quinoxalin-2-one **82**, involving the carbonyl group of the lactam function in the presence of polyphosphoric acid (Scheme 29).



82 **83**

Scheme 29.

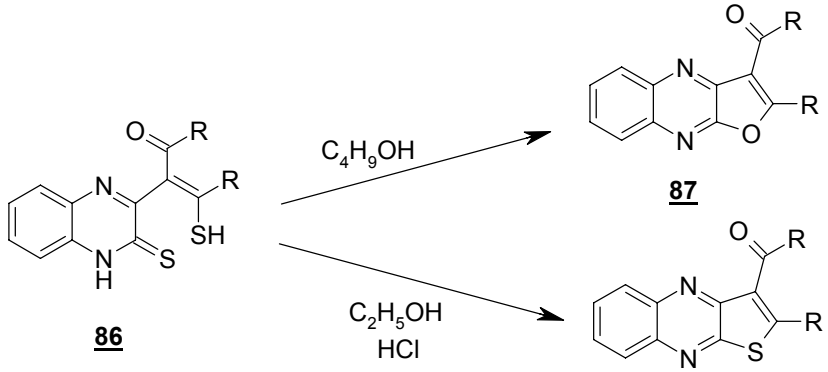
In the same conditions as before, the authors [65-68] performed the cyclization of oximes **84** (Scheme 30).



84 **85**

Scheme 30.

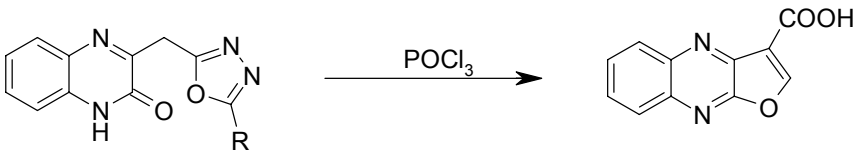
The cyclization of unsaturated sulfur-containing derivatives **86** can provide, according to the operating conditions, a furan ring **87** or thiophene ring **88** (Scheme 31) [69].



86 **87** **88**

Scheme 31.

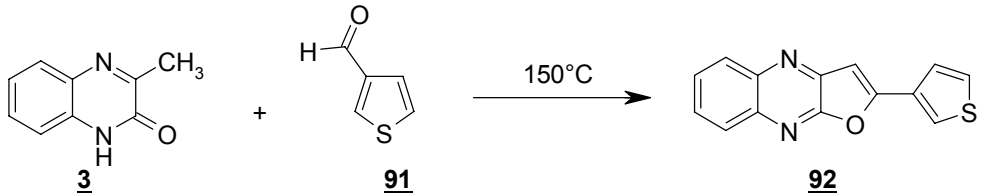
The heating of 3-(1,3,4-oxadiazol-2-yl)-methyl-1,2-dihydroquinoxalin-2-one **89**, in the presence of phosphorus oxychloride allows the preparation of the furoquinoxaline **90** [70] (Scheme 32).



89 **90**

Scheme 32.

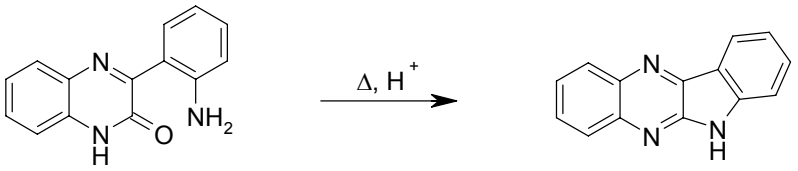
Essassi *et al.* have described the synthesis of 2-(3-thienyl)-2,3-dihydrofurano[2,3-b] quinoxaline **92** by condensing the 3-methylquinoxaline-2-one **3** with 3-formyl-thiophene **91**, at 150 °C (Scheme 33) [71].



3 **91** **92**

Scheme 33.

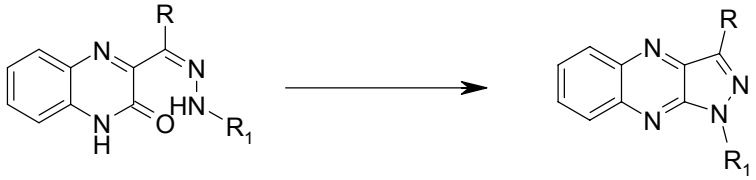
The literature reports other work on obtaining a contiguous quinoxaline nitrogen heterocycles such as indole and pyrazole. In fact, Schunk [72] and Wiendermanova [73], have been able to cyclize the 3-(*o*-aminophenyl)-1,2-dihydroquinoxalin-2-one **93** (Scheme 34), with the reflux of acetic acid or hydrochloride acid.



93 **94**

Scheme 34.

Other authors [74-76] have carried out the cyclization of hydrazone **95** to obtain the derivatives of pyrazolo[3,4-b]quinoxalines **96** called « Flavazoles » (Scheme 35).



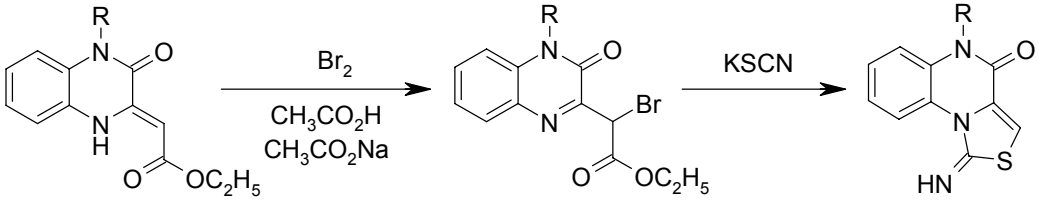
95 **96**

Scheme 35.

The cyclization occurs in an alkaline solution [77-78] or at reflux of acetic acid [79]. Several flavazoles were well prepared, when R = aryl or sugar. When R = H, the cyclization could not take place, neither in alkaline, or by heating in acid.

A tricyclic system containing the quinoxaline contiguous to the thiazole was obtained by exploiting the presence of β-enaminoester synthon.

Thus, the bromination of 3-ethoxycarbonylmethylidene-quinoxalin-2-one **97** by the bromine in acetic acid in the presence of sodium acetate leads to the bromo compound **98** which subsequently undergoes the action of potassium thiocyanate to give the thiazoloquinoxalin-2-one **99** (Scheme 36).



97 **98** **99**

Scheme 36.

The structure of compound **97** was confirmed by a crystallographic study, which highlights particularly the presence of a hydrogen bond between the NH group and the carbonyl group of the ester function (Figure 2) [80].

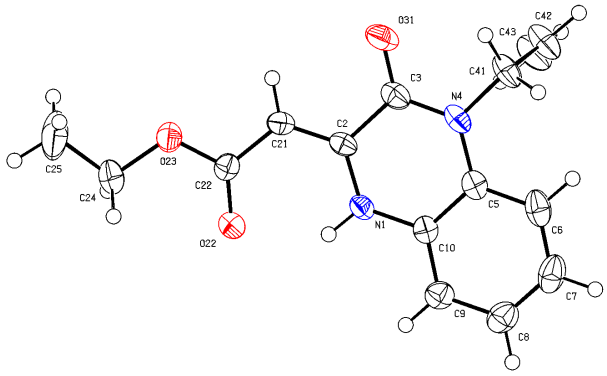
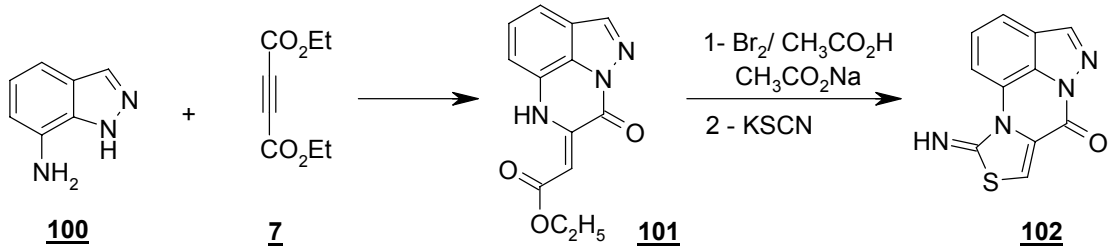


Figure 2. *Structure of 3-ethoxycarbonylmethylidene-quinoxalin-2-one*

Similar results were observed by condensing the 7-amino-indazole **100** with diethyl acetylenedicarboxylate **7**. The pyrazolo quinoxaline **101** obtained after reaction of bromination followed by action of potassium thiocyanate led to pyrazolothiazolo quinoxaline **102** (Scheme 37) [81].



100 **7** **101** **102**

Scheme 37.

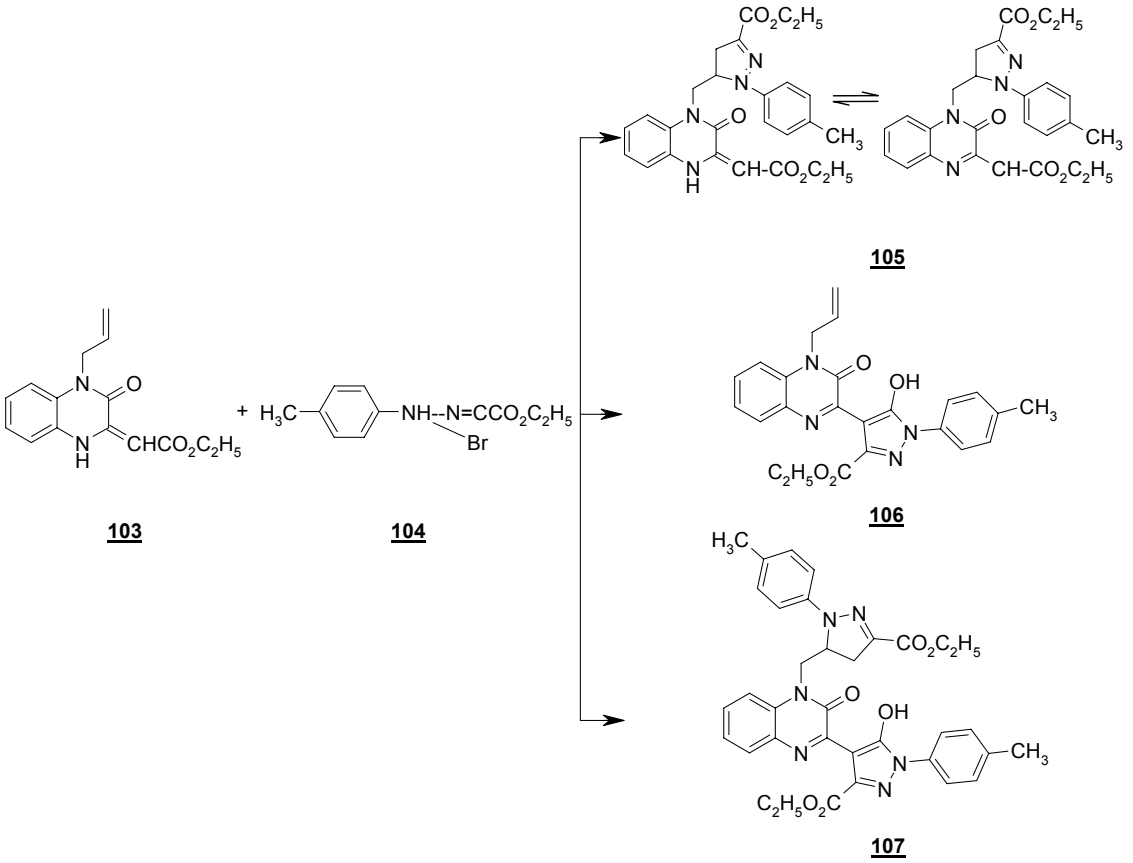
5. Reaction of 1,3 dipolar cycloaddition on quinoxalinone

The literature reports a few studies on the synthesis of heterocyclic systems containing the quinoxaline nucleus linked to various types of pentagonal pyrazole, isoxazole, imidazole and 1,2,3-triazole.

Ferfra *et al.* [82-85] studied the action of diethyl hydrazono-α-bromoglyoxylate **104** on quinoxaline **103** in the presence of triethylamine; the reaction of the 1,3-dipolar cycloaddition leading to a mixture of three products from two competitive reactions, a reaction of 1,3-dipolar cycloaddition involving the double bond of allyl group, leading to the pyrazoline; and a reaction of cyclocondensation involving the enaminoester synthon giving the pyrazole (Scheme 38).

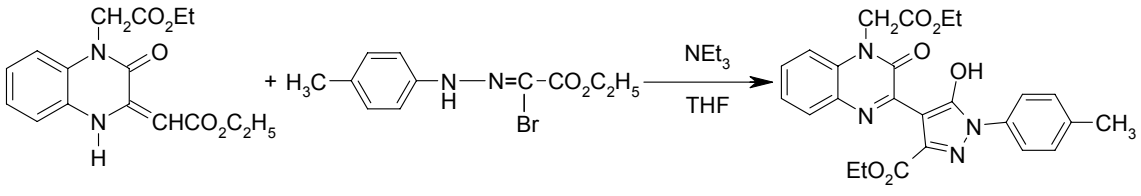
In the same operating conditions as before, the condensation of hydrazonoyle bromide **104** on the 1-ethoxycarbonylmethyl-3-(ethoxycarbonymethylene)-2-oxoquinoxaline **108**, leads exclusively to the 1-(ethoxycarboxymethyl)-5-hydroxypyrazolin-4'-yl)-2-oxoquinoxaline **109** (Scheme 39).

In the same series of reactions, the treatment of quinoxaline **103** by the α-chloro-phenyl phenylhydrazone **110** for 48 hours leads to a mixture of four products from the reaction of 1,3-dipolar cycloaddition and cyclocondensation, as well as from a reaction of alkylation of the nitrogen atom in position 4 of the quinoxaline ring (Scheme 40).



Scheme 38.

The authors also studied the action of chlorobenzaldoxime **115** of compound **103**, showing a similar behavior towards the dipolarophile sites, leading to a mixture of three products **116 - 118** (Scheme 41).

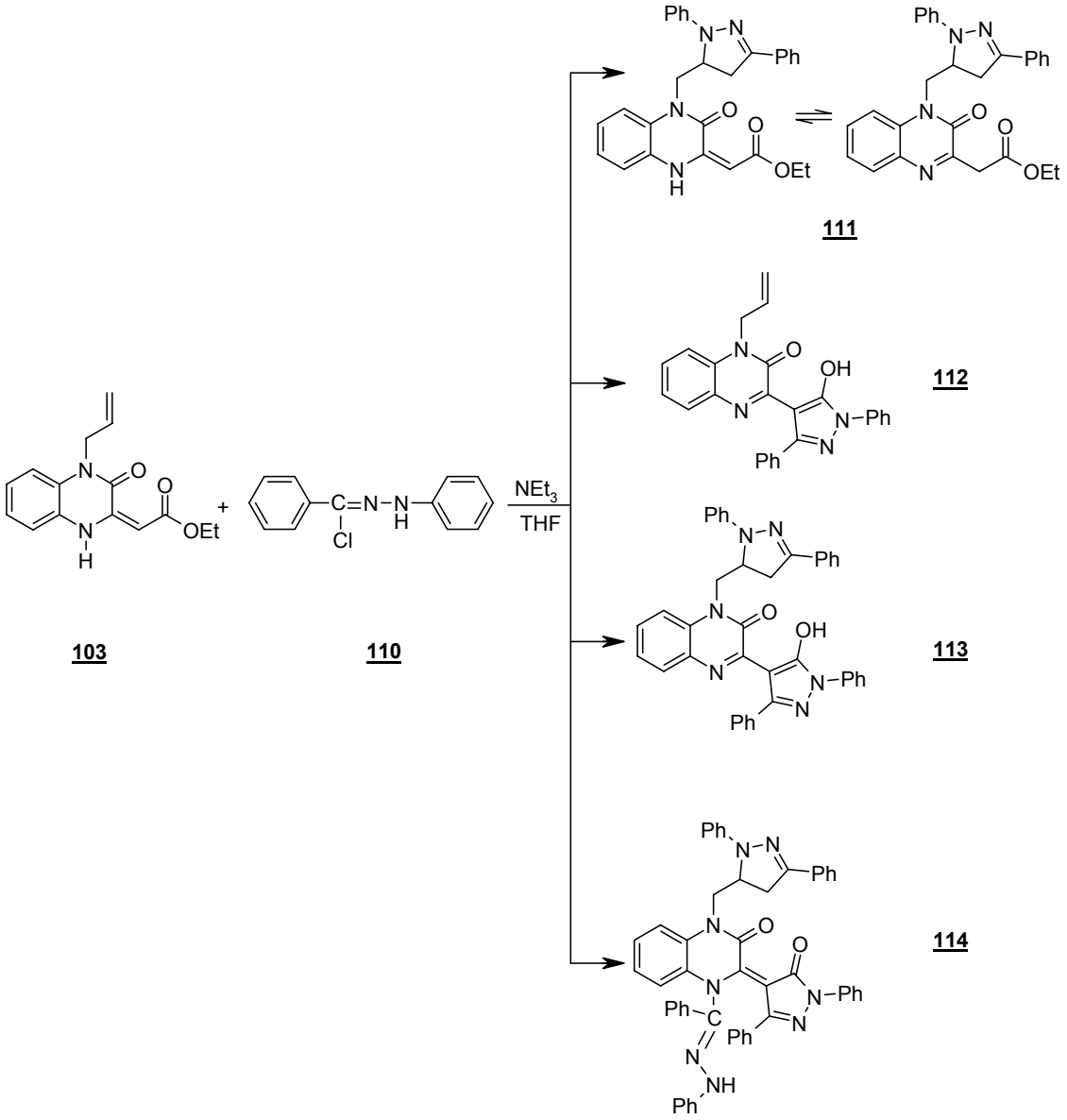


Scheme 39.

C. Biological properties of the quinoxalinone derivatives

In recent years, the quinoxalinone made a tremendous achievement in the biological and pharmacological fields.

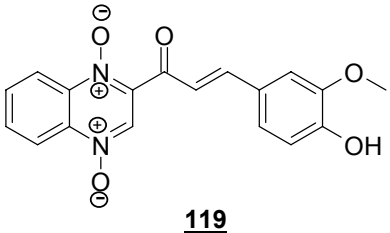
Burguete *et al.* [86] studied the anti-inflammatory and antioxidant activity of several quinoxalines. Compound **119** presented the most interesting activity.



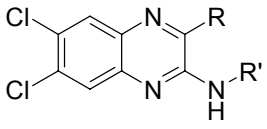
103 **110** **111** **112** **113** **114**

Scheme 40.

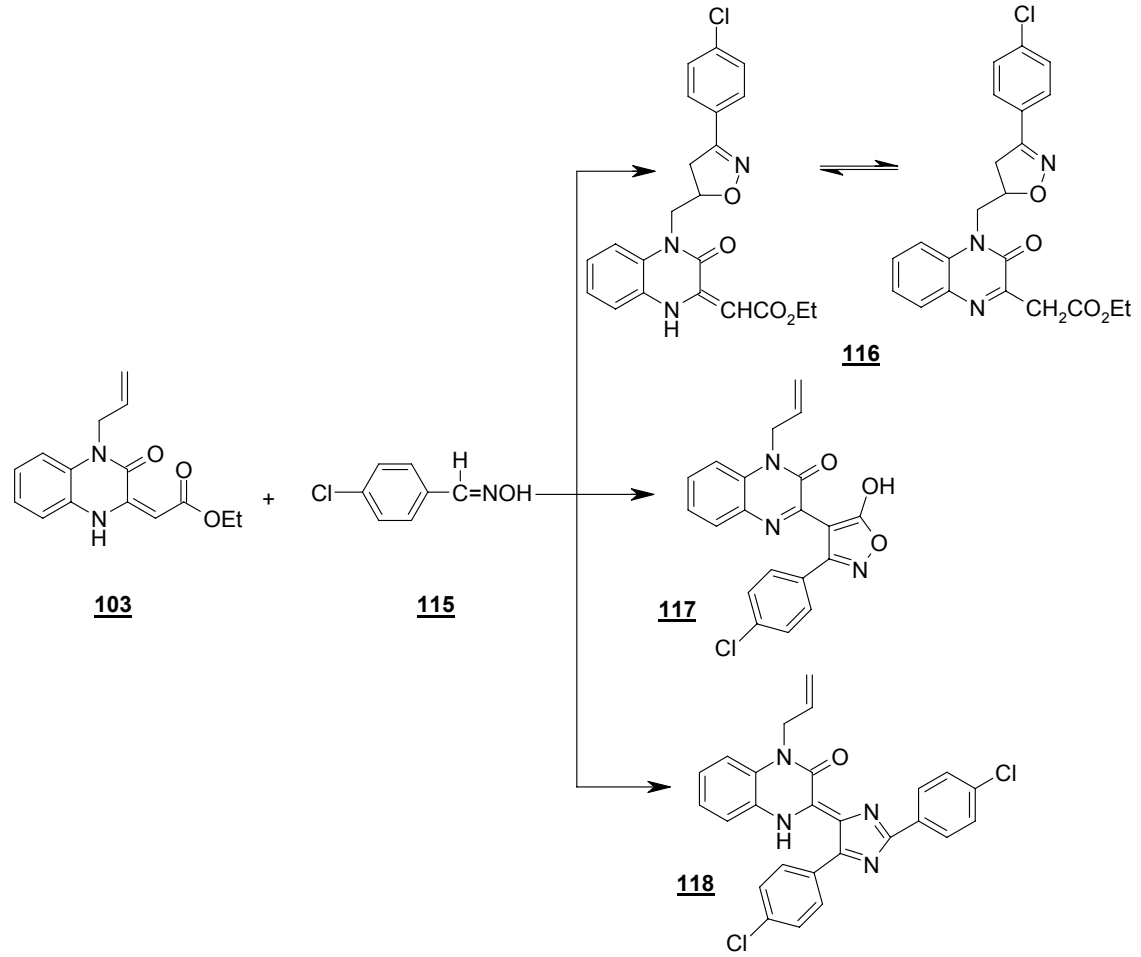
Similarly, in the study of the same anti-inflammatory activity, Li *et al.* [87] have evaluated the activity of the quinoxaline **B** by varying R and R substituents. Compounds B_1 and B_2 were found to be non-peptide antagonists of the interleukin-8 molecule receptor, which is involved in several inflammatory diseases and cancer [87].



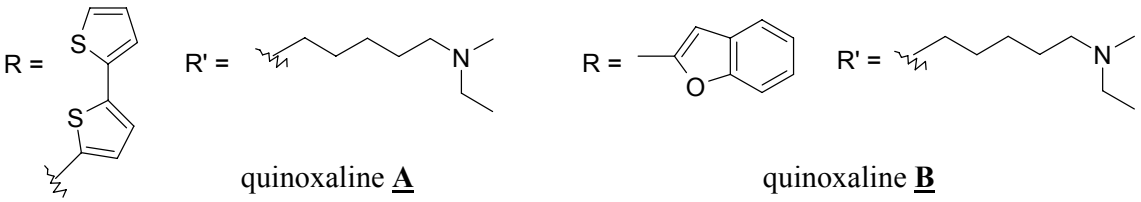
119



120

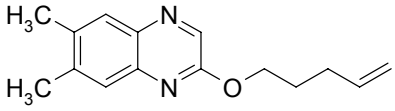


Scheme 41.

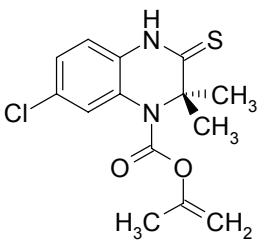


quinoxaline **A** quinoxaline **B**

Similarly, the quinoxalinone derivatives have antiviral properties [88, 89]. Many studies have shown the activity of a few quinoxaline compounds towards the human immunodeficiency virus (HIV-1), including the 6,7-dimethyl-2-(pent-4-enyloxy)quinoxaline **121**, [90] and S-2720 **122**, which not only inhibit HIV-1 RT, but prevent its replication at the cellular membrane [91].

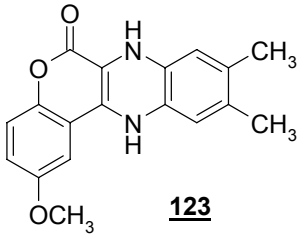


121

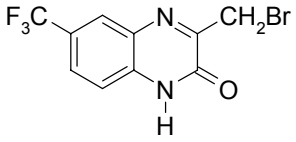


122

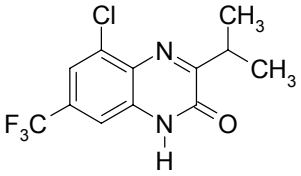
Another notable activity of quinoxalines is the anti-microbial one. In fact, Kotharkar *et al.* [92] have shown that 9,10-dimethyl-2-methoxy-6-oxo-7,12-dihydro–chromo-[3,4-b]quinoxaline **123** has both, antibacterial and antifungal activities. In another study [93], it has been shown that quinoxalines **124**, **125**, **126**, and **127** possess the same activities.



123



124



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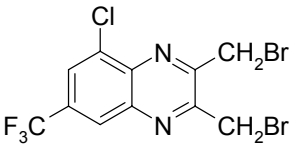
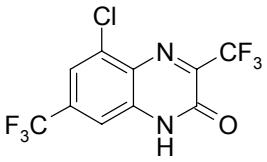
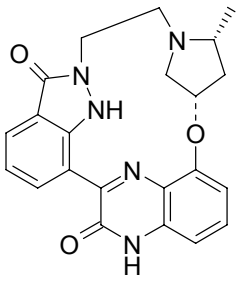


126

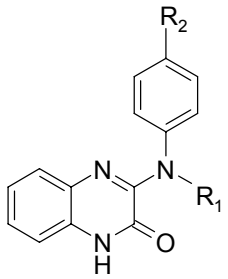


127

The compound **128** [94] is a new molecular macrocycle derived from the quinoxalin-2-one inhibitor of cyclin-dependent kinases CDK1, 2, 4 and 6. While the compound **129** [95] inhibiting glycogen phosphorylase is the enzyme responsible for the metabolism of glycogen to glucose since glucose is overproduced in patients suffering from diabetes.

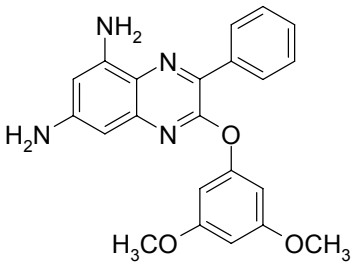


128

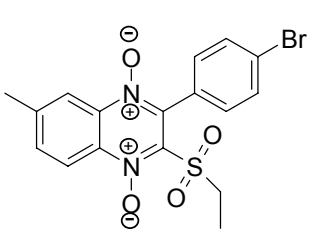


129

There are many quinoxaline derivatives which showed antitumor activity, Corona *et al.* [96] showed that 5,7-diamino-3-phenyl-2-[(3,5-dimethoxy)phenoxy]quinoxaline **130** has an antitumor activity in vitro, towards several types of tumors. Also the 3-(4-bromophenyl)-2-(ethylsulfonyl)-6-methylquinoxaline-1,4-dioxide **131**, has an activity against the tumor in the hypoxia stage, which is a phase where the tumor shows a resistance during chemotherapy and radiotherapy [97].

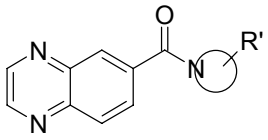


130



131

To conclude this part of biological activity, we will mention a few patents showing various activities of quinoxaline, as an inhibitor of the kinase protein [98], or as antagonists of bradykinin, which is a peptide responsible for the dilatation of blood vessels, thus leading to the lowering of blood pressure [99]. Finally, a series of new quinoxaline derivatives **132**, which could act as modulators of the AMPA receptor mediators of synaptic responses have been synthetized [100].



132

The circle containing nitrogen designates a heterocycle of 5 to 8 rings, the group R' may be a group 2- or 3-alkyl, cycloalkyl, hydroxy, alkoxy, alkoxy-alkyl, hydroxy-alkyl, or carbamoyl.

CONCLUSION

The derivatives of quinoxalinone occupy a significant place in several areas, particulary in pharmacology. Also, the modifications in the basic structure of the quinoxalin-2-one, have enabled the emergence of new derivatives with a wide spectrum of biological activity

The chemistry of the quinoxaline derivatives presents us with great opportunities due to the presence of different reactive sites: the lactam function involving the nitrogen atom and the carbonyl group; and is involved in alkylation reactions, amination, chlorination, and the sulfuration and in 1,3-dipolar cycloaddition.

Studies of these derivatives have shown that structural modification can improve its pharmacological profile conferring antibacterial, anticancer, anti-HIV, tranquilizers and sedative properties.

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