SYNTHESIS OF SOME NEW QUINOXALINE DERIVATIVES FOR BIOLOGICAL EVALUATION

Thesis

Presented By

Shada Hassan Yassin
Assist. Lecturer of Medicinal Chemistry
Faculty of Pharmacy-Sana'a University

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Under the Supervision of

Prof. Dr.
Mohamed E. El-Sadek
Prof. of Medicinal Chemistry
Medicinal Chemistry Dept.
Faculty of Pharmacy
Zagazig University

Prof. Dr.
El-Sayed M. Lashine
Prof. of Medicinal Chemistry
Medicinal Chemistry Dept.
Faculty of Pharmacy
Zagazig University

Dr.
Osama I. El-Sabbagh
Ass. Prof. of Medicinal Chemistry
Medicinal Chemistry Dept.
Faculty of Pharmacy
Zagazig University

Faculty of Pharmacy
Zagazig University
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تشييد بعض مشتقات الكينوأوكسالين الجديدة لتقييمها بيولوجياً

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شذى حسن ياسين
المدرس المساعد بقسم الكيمياء الطبية
كلية الصيدلة – جامعة صنعاء
الجمهورية اليمنية

للحصول على

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(الكيمياء الطبية)

تحت إشراف

الأستاذ الدكتور
محمد الحسيني الصادق
أستاذ الكيمياء الطبية
كلية الصيدلة – جامعة الزقازيق

الأستاذ الدكتور
السيد محمد منصور لاشين
أستاذ الكيمياء الطبية
كلية الصيدلة – جامعة الزقازيق

الدكتور
أسامة إبراهيم الصباغ
أستاذ مساعد الكيمياء الطبية
كلية الصيدلة – جامعة الزقازيق

كلية الصيدلة
جامعة الزقازيق
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Dedication

This Thesis is Dedicated to:

The Soil of My Parents

My Husband Prof. Dr. Magdi Aqlan

My Daughter, Rasha and

My Son, Hassan,

All those who love me

Shada Hassan Yassin

ABSTRACT

In the present investigation, one known starting materials, five novel intermediates and thirty eight novel final compounds of 2(1H)-quinoxalinone derivatives were synthesized. Several new 2(1H)-quinoxalinone derivatives were prepared with the aim to have antibacterial and anti-inflammatory activities.

Accordingly, to obtain such derivatives, the following routes were adopted:

1- Cyclocondensation of equimolar amounts of 1,2-cyclohexandiamine with ethyl pyruvate or diethyl oxalacetate in ethanol containing catalytic amounts of glacial acetic acid afforded the desired synthon 3-methyl-4a,5,6,7,8,8a-hexahydro-2(1H) quinoxalinone **(I)** or its ethyl ester derivative **(III_b)**.Similarly, the reaction of 1,2-benzenediamine with diethyl oxaloacetate gave the coresponding unsaturated ethyl ester derivative **(III_a)**.

2- The novel 3-((2-(4-Substitutedphenyl)hydrazono) methyl) 4a,5,6,7,8,8a-hexahydroquinoxalin-2(1H)-ones **(II_{a-h})** were obtained in 70-90 **%** yields through coupling of the appropriate diazonium salt, of different aromatic amines (37% HCl and $NaNO_2$) with 3-methyl-4a,5,6,7,8,8a-hexahydro-2(1H)-quinoxalinone (I) in acetic acid buffered with sodium acetate at 0°C with intermittent stirring for 24 hrs.

3- Condensation of the ester **($III_{a,b}$)** with hydrazine hydrate in hot ethanol afforded the novel 2-(2-Oxo-1,2-dihydroquinoxalin-3-yl)acetohydrazide and its 1,2,4a,5, 6,7,8,8a-octahydro derivative**($IV_{a,b}$)**.

4- These hydrazides (**$IV_{a,b}$**) were condensed with succinic or phthalic anhydride in refluxing acetic acid to afford the new dioxopyrrolidine or

dioxoisoindoline **($V_{a,b}$)** and their octahydro derivatives **($VI_{a,b}$)**.

5- Moreover, the unsaturated acid hydrazide (**IV_a**) was stirred with the appropriate acid chloride in acetic acid/sodium acetate at room temperature for 12 hrs to afford the new 3-(4-substituted benzoylhydrazinocarbonylmethyl)-2(1H)-quinoxalinone **(VII_{a-c}).**

6- The reaction of the two acid hydrazides (**$IV_{a,b}$**) and the appropriate isothiocyante in refluxing ethanol for 2 hrs afforded the novel thiosemicarbazides (**$VIII_{a-c}$**) and their octahydro derivatives (**$VIII_{d-f}$**).

7- Cyclization of the thiosemicarbazides (**$VIII_{a-c}$**) was conducted in 2N NaOH by heating under reflux for 2 hrs to afford the novel 5-mercapto-4-substituted-4H-1,2,4-triazole derivatives (**IX_{a-c}**).

8- Furthermore, the playmaker acid hydrazide (**IV_a**) was condensed with different aromatic aldehydes in hot ethanol containing catalytic amounts of acetic acid to give the novel benzylidene derivatives (**X_{a-i}**).

9- This acid hydrazide (**IV_a**) could be reacted with carbon disulphide in the presence of potassium hydroxide either in hot ethanolic solution to give the novel oxadiazole (**XI**) or by cooling these reactants and stirring at room temperature for 14 hrs to afford the intermediate potassium salt of dithiocarbazate (**XII**).

10- This potassium salt intermediate could be cyclized using either hydrazine hydrate in refluxing ethanol to obtain the novel 4-amino-5-mercapto-4H-1,2,4-triazole **(XIII)** or substituted phenacyl bromides in situe and stirring reactants in dioxane at room temperature for 12 hrs to afford the novel thiazole derivatives (**XIV_{a-c}**).

The purity of the newly synthesized compounds was checked by TLC, and the structures of these compounds were confirmed by elemental

microanalyses and most of them were studied by different spectroscopic methods.

The rational behind the synthesis of these compounds, their methods of syntheses as well as their antibacterial and anti-inflammatory activities were discussed. In this thesis the following compounds were prepared:

Known starting materials:

1) 3-(Ethoxycarbonylmethyl)-2(1H)-quinoxalinone **(III_a)**

Novel intermediates:

1) 3-Methyl-4a,5,6,7,8,8a-hexahydro-2(1H)-quinoxalinone**(I)**
2) 3-(Ethoxycarbonylmethyl)- 1,2,,4a,5,6,7,8 , 8a-octahydro-2-quinoxalinone **(III_b)**
3) 2-(2-Oxo-1,2-dihydroquinoxalin-3-yl)acetohydrazide **(IV_a)**
4) 2-(2-Oxo-1,2,4a,5, 6,7,8,8a-octahydroquinoxalin-3-yl) acetohydrazide **(IV_b)**
5) Potassium,3-[2-(2-oxo-1,2-dihydroquinoxalin-3-yl) acetyl]dithiocarbazate **(XII)**

Novel final compounds:

1) 3-((2-(phenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one **(II_a)**
2) 3-((2-(4-Chlorophenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one **(II_b)**
3) 3-((2-(3-Chlorophenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one **(II_c)**

4) 3-((2-(4-Bromophenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one **(II_d)**

5) 3-((2-(3-Bromophenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one **(II_e)**

6) 3-((2-(4-Fluoro phenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one **(II_f)**

7) 3-((2-(2-Fluorophenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one **(II_g)**

8) 3-((2-(4-Methylphenyl)hydrazono)methyl)4a,5,6,7,8,8a-hexahydro quinoxalin-2(1H)-one**(II_h)**

9) 3-[(2,5-Dioxopyrrolidin-1-yl)aminocarbonylmethyl]-2(1H)-quinox alinone **(V_a)**

10) 3-[(1,3--Dioxoisoindolin-2-yl)aminocarbonylmethyl]-2(1H)-quinoxalinone **(V_b)**

11) 3-[(2,5-Dioxopyrrolidin-1-yl)aminocarbonylmethyl]-1,2,4a,5,6,7,8, 8a-octahydro-2-quinoxalinone (**VI_a**)

12) 3-[(1,3--Dioxoisoindolin-2-yl)aminocarbonylmethyl]-1,2,4a,5,6,7,8, 8a-octahydro-2-quinoxalinone (**VI_b**)

13) 3-(Benzoylhydrazinocarbonylmethyl)-2(1H)-quinoxalinone **(VII_a)**

14) 3-(4-Chlorobenzoylhydrazinocarbonylmethyl)-2(1H)-quinoxalinone **(VII_b)**

15) 3-(4-Methylbenzoylhydrazinocarbonylmethyl)-2(1H)-quinoxalin one **(VII_c)**

16) N^1-[(2-Oxo-1,2-dihydroquinoxalin-3-yl)methylcarbonyl]-N^4-phenylthiosemicarbazide **($VIII_a$)**

17) N^1-[(2-Oxo-1,2-dihydroquinoxalin-3-yl)methylcarbonyl]-N^4-ethyl thiosemicarbazide **($VIII_b$)**

18) N^1-[(2-Oxo-1,2-dihydroquinoxalin-3-yl)methylcarbonyl]-N^4-allyl thiosemicarbazide (**$VIII_c$**)

19) N^1-[(2-Oxo-1,2,4a,5,6,7,8,8a-octahydroquinoxalin-3-yl)methyl carbonyl]-N^4- phenylthiosemicarbazide (**$VIII_d$**)

20) N^1-[(2-Oxo-1,2,4a,5,6,7,8,8a-octahydroquinoxalin-3-yl)methyl carbonyl]-N^4- ethyl thiosemicarbazide **($VIII_e$)**

21) N^1-[(2-Oxo-1,2,4a,5,6,7,8,8a-octahydroquinoxalin-3-yl)methyl carbonyl]-N^4-allylthiosemicarbazide **($VIII_f$)**

22) 3-((5-Mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-2(1H)-quinoxalinone **(IX_a)**

23) 3-((5-Mercapto-4-ethyl-4H-1,2,4-triazol-3-yl)methyl)-2(1H)-quinoxalinone **(IX_b)**

24) 3-((5-Mercapto-4-allyl-4H-1,2,4-triazol-3-yl)methyl)-2(1H)-quinoxalinone **(IX_c)**

25) 3-(Benzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone**(X_a)**

26) 3-(4-Hydroxybenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone**(X_b)**

27) 3-(4-Bromobenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone **(X_c)**

28) 3-(4-Chlorobenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone **(X_d)**

29) 3-(4-Nitrobenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone **(X_e)**

30) 3-(4-Methoxybenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone **(X_f)**

31) 3-(2,4-Dichlorobenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone**(X_g)**

32) 3-(4-Methylbenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone**(X_h)**

33) 3-(4-Fluorobenzylidenehydrazinocarbonylmethyl)-2(1H)-quinoxalinone**(X_i)**

34) 3-((5-Mercapto-1,3,4-oxadiazol-2-yl)methyl)-2(1H)-quinoxalinone **(XI)**

35) 3-((4-Amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)-2(1H)-quinoxalinone **(XIII)**

36) 3-[N-(4-Phenyl-2-thioxo-2,3-dihydrothiazol-3-yl)aminocarb onylmethyl]-2(1H)-quinoxalinone(**XIV_a**)

37) 3-[N-(4-Chlorophenyl -2-thioxo-2,3-dihydrothiazol-3-yl)aminocarb onylmethyl]-2(1H)-quinoxalinone **XIV_b)**

38) 3-[N-(4-Methylphenyl-2-thioxo-2,3-dihydrothiazol-3-yl)aminocarb onylmethyl]-2(1H)-quinoxalinone **(XIV_c)**

Finally, some novel 2(1H)-quinoxalinone derivatives were subjected to biological evaluation to study their *in vitro* antimicrobial activity using cup-plate technique and also their *in vivo* anti-inflammatory activity was determined using the rat hind paw oedema method.

The preliminary antimicrobial activity for some new 2(1H)-quinoxalinone derivatives revealed that the hydrazono of hexahydro-2(1H)-quinoxalinones derivatives **($II_{b,f}$)** containing halogen showed a high activity

against Gram-positive both cocci and bacilli which were comparable to the reference drug (ciprofloxacin). Moreover, the saturated octahydro thiosemicarbazide derivatives **($VIII_{d,f}$)** showed a higher activity than their corresponding unsaturated ones **($VIII_{a,c}$)** whereas the octahydro thiosemicarbazide VIIId bearing a phenyl moiety has nearly the same activity as the reference drug ciprofloxacin against both Gram-positive and Gram-negative bacteria. All the tested compounds have no antifungal activity.

Some novel compounds **IX_a, IX_b, XI, XIII, XIV_a, XIV_b** and **XIV_c** were evaluated *in vivo* for their anti-inflammatory activities at a dose of 0.9mg/100gm body weight into mature male albino rats using the rat hind paw oedema method, in addition, their ulcerogenic activity was determined using celecoxib and indomethacin as references drugs. It was observed that the quinoxalinone derivatives bearing 4-chlorophenylthiazole **(XIV_b)** and the 4-phenyltriazole **(IX_a)** moieties showed a higher antiinflammatory activity than reference drug celecoxib with no ulcerogenic activity.

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Shada Hassan Yassin

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