بعض الوثائق الأصلية تالفة

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SYNTHESIS OF SOME SELECTED QUINOXALINE COMPOUNDS OF PHARMACEUTICAL INTEREST

THESIS
Presented by

Mostafa Hussein Mohammed
B.Pharm.Sci. (Cairo)

SUBMITTED FOR THE DEGREE OF MASTER
IN
PHARMACEUTICAL SCIENCES
(ORGANIC CHEMISTRY)

Under Supervision of

Prof. Dr. Mohga M. Badran
Professor of Organic Chemistry
Faculty of Pharmacy, Cairo University

Dr. Khaled A. M. Abouzid
Lecturer of Organic Chemistry
Faculty of Pharmacy, Ain-Shams University

Faculty of Pharmacy
Cairo University
2001

Approval Sheet

Committee in Charge

Approved:

Prof. Dr. **Mohga M. Badran**
Faculty of Pharmacy
Cairo University

Prof. Dr. **Nargues S. Habib**
Faculty of Pharmacy
Alexandria University

Prof. Dr. **Mervat M. El-Enany**
Faculty of Pharmacy
Cairo University

Acknowledgement

I would like to express my sincere thanks to **Prof. Dr. Mohga M. Badran**, Professor of Organic Chemistry, Faculty of Pharmacy, Cairo University, who suggested the idea of this research, for her great effort in supervision, sincere encouragement and unlimited continual help that she kindly offered throughout the development of this work.

I am profoundly grateful to **Dr. Khaled Abouzid M. Abouzid**, Lecturer of Organic Chemistry, Faculty of Pharmacy, Ain-Shams University for his kind supervision, valuable advice and indispensable help during the course of this work.

I would like to express my sincere thanks and gratitude to **Dr. Abdel-Hameed A. Abdel-Hameed**, Assistant Professor of Microbiology and Immunology, Faculty of Pharmacy, Cairo University for his sincere help and for the facilities provided during the performance of the antimicrobial screening.

To everyone who made this work possible, I am indeed very thankful.

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ABSTRACT

Abstract

TITLE OF THESIS

Synthesis of Some Selected Quinoxaline Compounds of Pharmaceutical Interest.

NAME OF CANDIDATE

Mostafa Hussein Mohammed

B. Pharm. Sci. (1997)

Faculty of Pharmacy, Cairo University

THESIS SUPERVISED BY:

Prof. Dr. Mohga M. Badran

Professor of Organic Chemistry, Faculty of Pharmacy, Cairo University

Dr. Khaled Abouzid M. Abouzid

Lecturer of Organic Chemistry, Faculty of Pharmacy, Ain-Shams University

A survey covering the methods used for the synthesis of quinoxalines in addition to their reactions is presented. A brief outline on their biological importance is also given.

The thesis involves the preparation of the starting quinoxaline derivatives needed for the preparation of the intermediates and/or final compounds. (Scheme of starting materials)

Treatment of 3-hydrazinoquinoxalin-2(1H)-one (II) with a number of aromatic aldehydes gave 3-(arylidenehydrazino)quinoxalin-2-(1H)-ones (V_{a-h}) which upon cyclization with bromine in acetic acid, afforded the corresponding 1-aryl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-ones (VI_{a-h}). Attempted alkylation of (VI) produced 1-aryl-5-substituted-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-ones (VII_{a-i}). Compound VI_a was treated with α-chloroanilide derivatives ($VIII_{a-h}$) to afford 5-(arylaminocarbonylmethyl)-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-ones (IX_{a-h}). The latter series was also prepared by condensation of 5-(ethoxycarbonylmethyl)-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one (VII_a) with the corresponding aromatic amine.

Furthermore, hydrazinolysis of ester (VII_a) furnished the desired hydrazide (X). Treatment of (X) with different aromatic aldehydes afforded arylidene derivatives (XI_{a-c}). Reaction of hydrazide (X) with 4-nitrobenzoic acid in excess phosphorus oxychloride afforded 5-[5-(4-nitrophenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1-phenyl-[1,2,4]-triazolo[4,3-a]quinoxalin-4(5H)-one (XII). Compound XII was also prepared via oxidative cyclization of the arylidene (XI_a).

Treatment of 2-chloro-3-hydrazinoquinoxaline (IV) with certain aromatic aldehydes gave 2-(arylidenehydrazino)-3-chloroquinoxalines ($XIII_{a-d}$) which upon cyclization with bromine in acetic acid, afforded the corresponding 1-aryl-4-chloro-[1,2,4]triazolo[4,3-a]quinoxalines (XIV_{a-d}). Reaction of (XIV_a) with the corresponding alkoxide furnished the respective 4-alkoxy-1-(3-nitrophenyl)-[1,2,4]triazolo[4,3-a] quinoxalines ($XV_{a,b}$). Amination of XIV_a with certain amines gave the respective 1-(3-nitrophenyl)-4-substituted-amino-[1,2,4]triazolo[4,3-a] quinoxalines (XVI_{a-h}). Reaction of XIV_a with thiourea furnished 1-(3-nitrophenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-thione (XVII). Attempted alkylation of XVII with chloroacetic acid afforded the corresponding mercaptoacetic acid derivative (XVIII). The latter compound was also prepared via reaction between XIV_a and thioglycolic acid. Reaction of XIV_a with ethyl thioglycolate afforded the ethyl ester (XVIV).

On the other hand, treatment of 3-hydrazinoquinoxalin-2(1H)-one (II) with different aromatic acids in phosphorus oxychloride followed by reaction with hydrazine hydrate afforded 1-aryl-4-hydrazino-[1,2,4]triazolo[4,3-a]quinoxalines ($XX_{a,b}$). XX_a was allowed to react with different aromatic aldehydes to afford 4-(arylidenehydrazino)-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxalines (XXI_{a-e}). Reaction of XX_b with certain esters or orthoesters furnished [1,2,4]ditriazolo[4,3-a:3`,4`-c]quinoxaline derivatives (XXII, XXIII and XXIV).

Moreover, acetylation of XX_b with acetic anhydride afforded the triacetyl derivative (XXV). Reaction of XX_b with succinic anhydride afforded 1-(4-nitrophenyl)-4-[(2,5-dioxopyrrolidin-1-yl)amino]-[1,2,4] triazolo[4,3-a]quinoxaline (XXVI). However, reaction with phthalic anhydride furnished the [1,2,4]ditriazolo[4,3-a:3`,4`-c]quinoxaline derivative (XXVII). Finally, reaction of XX_5 with acetylacetone afforded the respective pyrazolo derivative (XXVIII).

Accordingly, this work comprises the synthesis of the following unavailable starting materials and reported intermediates which were essential for the present study:

1) 1,4-Dihydroquinoxaline-2,3-dione (I)
2) 3-Hydrazinoquinoxalin-2(1H)-one (II)
3) 2,3-Dichloroquinoxaline (III)
4) 2-Chloro-3-hydrazinoquinoxaline (IV)
5) 3-(Benzylidenehydrazino)quinoxalin-2(1H)-one (V_a)
6) 1-Phenyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one (VI_a)
7) 5-Ethoxycarbonylmethyl-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one (VII_a)
8) N-Substituted-2-chloroacetamides ($VIII_{a-h}$)

In addition, this study comprises the synthesis of the following new series of compounds:

1) 3-(Arylidenehydrazino)quinoxalin-2(1H)-ones (V_{b-h})
2) 1-Aryl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-ones (VI_{b-h})
3) 1-Aryl-5-substituted-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-ones (VII_{b-i})

4) 5-(Arylaminocarbonylmethyl)-1-phenyl-[1,2,4]triazolo[4,3-a]-quinoxalin-4(5H)-ones (IX $_{a-h}$)

5) 5-(Hydrazinocarbonylmethyl)-1-phenyl-[1,2,4]triazolo[4,3-a]-quinoxalin-4(5H)-one (X)

6) 5-(Arylidenehydrazinocarbonylmethyl)-1-phenyl-[1,2,4]triazolo[4,3-a]- quinoxalin-4(5H)-ones (XI_{a-c})

7) 5-[5-(4-Nitrophenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1-phenyl-[1,2,4]-triazolo[4,3-a]quinoxalin-4(5H)-one (XII)

8) 2-(Arylidenehydrazino)-3-chloroquinoxalines ($XIII_{a-d}$)

9) 1-Aryl-4-chloro-[1,2,4]triazolo[4,3-a]quinoxalines (XIV_{a-d})

10) 4-Alkoxy-1-(3-nitrophenyl)-[1,2,4]triazolo[4,3-a]quinoxalines ($XV_{a,b}$)

11) 1-(3-Nitrophenyl)-4-substituted-amino-[1,2,4]triazolo[4,3-a]-quinoxalines (XVI_{a-h})

12) 1-(3-Nitrophenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-thione (XVII)

13) 4-Carboxymethylmercapto-1-(3-nitrophenyl)-[1,2,4]triazolo[4,3-a]quinoxaline (XVIII)

14) 4-Ethoxycarbonylmethylmercapto-1-(3-nitrophenyl)-[1,2,4]-triazolo[4,3-a]quinoxaline (XVIV)

15) 1-Aryl-4-hydrazino-[1,2,4]triazolo[4,3-a]quinoxalines ($XX_{a,b}$)

16) 4-(Arylidenehydrazino)-1-phenyl-[1,2,4]triazolo[4,3-a]-quinoxalines (XXI_{a-c})

17) 1-(4-Nitrophenyl)-[1,2,4]ditriazolo[4,3-a:3`,4`-c]quinoxaline (XXII)

18) 1-Ethoxycarbonyl-6-(4-nitrophenyl)-[1,2,4]ditriazolo[4,3-a:3`,4`-c] quinoxaline (XXIII)

19) 1-Ethoxycarbonylmethyl-6-(4-nitrophenyl)-[1,2,4]ditriazolo[4,3-a:3`,4`-c]quinoxaline (XXIV)

20) N,N`,N`-Triacetyl[4-hydrazino-1-(4-nitrophenyl)-[1,2,4]triazolo-[4,3-a]quinoxaline] (XXV)

21) 1-(4-Nitrophenyl)-4-[(2,5-dioxopyrrolidin-1-yl)amino]-[1,2,4]-triazolo[4,3-a]quinoxaline (XXVI)

22) 1-(2-Carboxyphenyl)-6-(4-nitrophenyl)-[1,2,4]ditriazolo[4,3-a:3`,4`-c]quinoxaline (XXVII)

23) 4-(3,5-Dimethylpyrazol-1-yl)-1-(4-nitrophenyl)-[1,2,4]triazolo-[4,3-a]quinoxaline (XXVIII)

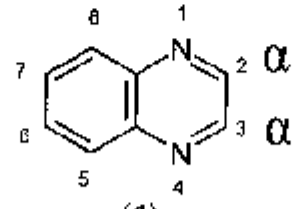
The identity of the new compounds was substantiated by elemental analysis as well as IR, NMR and Mass spectral data.

The results of preliminary microbiological evaluation of certain selected new compounds have been given and most of the tested compounds showed antibacterial and/or antifungal activity.

INTRODUCTION

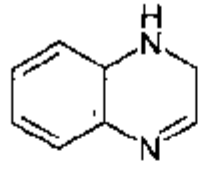
INTRODUCTION

Quinoxaline is benzo[b]pyrazine or 1,4-benzodiazine. The ring was early prepared by Hinsberg in 1884 through reaction of o-phenylenediamine and glyoxal [1]. The numbering of the quinoxaline ring system is shown in structure (1). The 2- and 3- positions are also designated as α-positions.



(1)

The reduced quinoxalines commonly encountered in the literature are the 1,2- (2), the 1,4-dihydro (3) and the 1,2,3,4-tetrahydroquinoxaline (4) [2].



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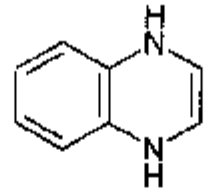

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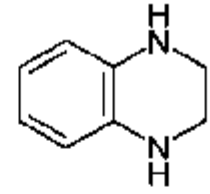

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