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Molecular Modeling and Synthesis of Certain Substituted Pyrrolidine Carboxylic acids with Anticonvulsant Potential

Thesis
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Content

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List of Abbreviations

Aº	: Angström
Ar	: Aryl
b.p.	: boiling point
br.	: broad
b.wt.	: body weight
ºC	: Degree Celsius
calc.	: Calculated
$CDCl_3$	: Deuterated chloroform
Co.	: Company
δ	: Chemical shift in parts per million downfield from tetramethylsilane (NMR)
s	: singlet
d	: doublet
t	: triplet
q	: quartet
DMSO	: Dimethylsulpoxide
ED_{50}	: Dose that is effective in 50% of the tested subjects
El	: Electron impact
Fig.	: Figure

gm : gram (s)

h : hour (s)

IC_{50} : Inhibitory concentration in 50% of the test subjects

IR : Infrared

Lit. : Literature

LD_{50} : Lethal dose in 50% of the test subjects

M^+ : Molecular ion

m : multiplet

min. : minutes

m.p. : melting point

MS : Mass spectrometry

FAB : Fast Atom Bombardment.

m/z : mass to charge ratio

NMR : Nuclear Magnetic Resonance

p : page

Pet. Ether : Petroleum ether

ppm : parts per million

alc :alcoholic

List of tables:

List of Figures:

Molecular Modeling and Synthesis of Certain Substituted Pyrrolidine Carboxylic acids with Anticonvulsant Potential

Thesis submitted by Mahmoud Mohamed Gamal Eldin, for the partial fulfillment of the degree of MSc. of Pharmaceutical Sciences (Pharmaceutical Chemistry), Ain Shams University (2010)

Abstract:

Molecular Modeling and synthesis of certain substituted pyrrolidine-3- carboxylic acids (***8a-e***, ***9a-e***, ***13a-e*** and ***14a-e***) have been accomplished. The aim of their preparation is to evaluate their anticonvulsant activity.

Reviews on different classes of antiepileptic and anticonvulsant agents, the mechanism of action of antiepileptic drugs have been discussed.

A detailed discussion on the molecular design strategy and the synthesis of the designed compounds ***8a-e***, ***9a-e***, ***13a-e*** and ***14a-e*** as well as the starting materials and intermediates have been described and illustrated in **Schemes *I, II*** and ***III***.

The starting materials, which have been synthesized throughout this work and reported in the literature are:

1- 2-(2-Cyanoethylamino)-3-phenylpropionic acid (***2a*****).**

2- 2-(2-Cyanoethylamino)-3-(4-hydroxyphenyl)propionic acid (***2b***)**.**

3- Ethyl 2-(3-ethoxy-3-oxopropylamino)-3-phenylpropanoate (***3a***)**.**

4- Ethyl 2-(3-ethoxy-3-oxopropylamino)-3-(4-hydroxyphenyl)-propanoate (***3b***)**.**

5- Ethyl 2-(N-(3-ethoxy-3-oxopropyl)acetamido)-3-phenyl propanoate **(*4a*).**

6- Ethyl 2-(N-(3-ethoxy-3-oxopropyl)acetamido)-3-(4-hydroxy-phenyl)propanoate **(*4b*).**

7- Ethyl 2-(N-(3-ethoxy-3-oxopropyl)acetamido)-3-(4-methoxyphenyl) propanoate (***5b*).**

8- Ethyl 3-(4-ethoxyphenyl)-2-(N-(3-ethoxy-3-oxopropyl)acetamido) propanoate (***5c*).**

9- Ethyl 2-(N-(3-ethoxy-3-oxopropyl)acetamido) -3-(4-propoxyphenyl)propanoate (***5d*).**

10- Ethyl 3-(4-butoxyphenyl)-2-(N-(3-ethoxy-3-oxopropyl)acetamido) propanoate (***5e*).**

11- Ethyl 1-acetyl-5-benzyl -4-oxopyrrolidine-3-carboxylate (***6a*).**

12- Ethyl 1-acetyl-5-(4-methoxybenzyl)-4-oxopyrrolidine-3-carboxylate (***6b*).**

13- Ethyl 1-acetyl-5-(4-ethoxybenzyl)-4-oxopyrrolidine-3-carboxylate (***6c*).**

14- Ethyl 1-acetyl-4-oxo-5-(4-propoxybenzyl)pyrrolidine-3-carboxylate (***6d*****).**

15- Ethyl 1-acetyl-5-(4-butoxybenzyl)-4-oxopyrrolidine-3-carboxylate (***6e*****).**

16- Ethyl 1-Acetyl-5-benzyl-4-hydroxypyrrolidine-3-carboxylate **(*7a*).**

17- Ethyl 1-Acetyl-4-hydroxy-5-(4-methoxybenzyl)pyrrolidine-3-carboxylate **(*7b*).**

18- Ethyl 1-Acetyl-5-(4-ethoxybenzyl)-4-hydroxypyrrolidine-3-carboxylate **(*7c*).**

19- Ethyl 1-Acetyl-4-hydroxy-5-(4-propoxybenzyl)pyrrolidine-3-carboxylate **(*7d*).**

20- Ethyl 1-Acetyl-5-(4-butoxybenzyl)-4-hydroxypyrrolidine-3-carboxylate **(*7e*).**

21- Ethyl 4-Acetoxy-1-acetyl-5-(4-methoxybenzyl)pyrrolidine-3-carboxylate **(*10b*).**

22- Ethyl 1-Acetyl-5-(4-methoxybenzyl)-2,5-dihydro-1H-pyrrole-3-carboxylate **(*11b*).**

23- Ethyl 1-Acetyl-5-(4-methoxybenzyl)pyrrolidine-3-carboxylate **(*12b*).**

Abstract

This study comprises the synthesis of the following new intermediates:

1- Ethyl 4-Acetoxy-1-acetyl-5-benzylpyrrolidine-3-carboxylate**(*10a*).**

2- Ethyl 4-Acetoxy-1-acetyl-5-(4-ethoxybenzyl)-pyrrolidine-3-carboxylate **(*10c*).**

3- Ethyl 4-Acetoxy-1-acetyl-5-(4-propoxybenzyl)-pyrrolidine-3-carboxylate **(*10d*).**

4- Ethyl 4-Acetoxy-1-acetyl-5-(4-butoxybenzyl)-pyrrolidine-3-carboxylate **(*10e*).**

5- Ethyl 1-Acetyl-5-benzyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **(*11a*).**

6- Ethyl 1-Acetyl-5-(4-ethoxybenzyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate **(*11c*).**

7- Ethyl 1-Acetyl-5-(4-propoxybenzyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate **(*11d*).**

8- Ethyl 1-Acetyl-5-(4-butoxybenzyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate **(*11e*).**

9- Ethyl 1-Acetyl-5-benzylpyrrolidine-3-carboxylate **(*12a*).**

10- Ethyl 1-Acetyl-5-(4-ethoxybenzyl)pyrrolidine-3-carboxylate **(*12c*).**

11- Ethyl 1-Acetyl-5-(4-propoxybenzyl)pyrrolidine-3-carboxylate **(*12d*).**

12- Ethyl 1-Acetyl-5-(4-butoxybenzyl)pyrrolidine-3-carboxylate **(*12e*).**

The synthesis of the target compounds, unsubstituted or substituted -5-aralkyl derivatives of 1-acetyl and deacetylated-4-hydroxy-5-benzyl and 5-(4-alkoxybenzyl)pyrrolidine-3-carboxylic acids (***8a-e)*** and (***9a-e)*** and 1-acetyl and deacetylated -5-benzyl and 5-(4-alkoxybenzyl) -pyrrolidine-3-carboxylic acids ***(13a-e)*** and (***14a-e),*** were successfully achieved.

These designed compounds gave compatible microanalytical data. Their IR and Mass spectral data were in accordance with the assigned structures. Further, the ^{1}H NMR of compounds ***8a-e***, ***9b-e, 13b-e*** and ***14c-e*** and ^{13}C NMR of compounds ***8c, 9d, 13e*** and ***14d***, taken as representative examples, have been recorded to confirm their structures.

The stereochemistry of compound ***7b,*** taken as a representative example, has been studied and discussed. This might speculate the possible stereochemical structure of the compounds in series ***7a-e***, ***8a-e***, ***9a-e***, ***12a-e***, ***13a-e*** and ***14a-e***.

The prepared target compounds are ***8a-e, 9a-e, 13a-e*** and ***14a-e***:

1- 1-Acetyl-5-benzyl- 4-hydroxypyrrolidine-3-carboxylic acid (***8a***).

2- 1-Acetyl-4-hydroxy-5-(4-methoxybenzyl)pyrrolidine-3-carboxylic acid (***8b***).

3- 1-Acetyl-5-(4-ethoxybenzyl)-4-hydroxypyrrolidine-3-carboxylic acid (***8c***).

4- 1-Acetyl-4-hydroxy-5-(4-propoxybenzyl)pyrrolidine-3-carboxylic acid (***8d***).

5- 1-Acetyl-5-(4-butoxybenzyl)-4-hydroxypyrrolidine-3-carboxylic acid (***8e***).

6- 5-Benzyl-4-hydroxypyrrolidine-3-carboxylic acid (***9a***).

7- 4-Hydroxy-5- (4- methoxybenzyl)pyrrolidine-3-carboxylic acid (***9b***).

8- 5-(4-Ethoxybenzyl)-4-hydroxypyrrolidine-3-carboxylic acid (***9c***).

9- 4-Hydroxy-5-(4- propoxybenzyl)pyrrolidine-3-carboxylic acid (***9d***).

10- 5-(4-Butoxybenzyl)-4-hydroxypyrrolidine-3-carboxylic acid (***9e***).

11- 1-Acetyl-5-benzylpyrrolidine-3-carboxylic acid (***13a***).

12- 1-Acetyl-5-(4-methoxybenzyl)pyrrolidine-3-carboxylic acid (***13b***).

13- 1-Acetyl-5-(4-ethoxybenzyl)pyrrolidine-3-carboxylic acid (***13c***).