SYNTHESIS OF CERTAIN 1,1-DISUBSTITUTED CYCLOALKANES AND THEIR BIOLOGICAL PROFILE

Thesis
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Mohamed Samir Mohamed

Contents

List of abbreviations

AEDs	Antiepileptic drugs
ACC	Acetyl Co A carboxylase
BB	Bombesin receptor
CI/MS	Chemical ionization mass spectroscopy
CNS	Central nervous system
DCC	N,N\-dicyclohexylcarbodiimide
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
ED_{50}	Effective dose 50%
EI/MS	Electron ionization mass spectroscopy
GABA	γ- Aminobutyric acid
GIT	Gastrointestinal tract
H	Hour / Hours
IC_{50}	Inhibitory concentration 50%
i.m.	Intramuscular
i.p.	Intraperitoneal
Ir	Infrared
i.v.	Intravenous
LD_{50}	Lethal dose 50%
LTB_4	Leukotriene B_4
M_1 receptor	Muscarinic receptor type 1
M^+	Molecular ion peak
m.p.	Melting point
MES	Maximal electric shock
MEST	Maximal electric shock seizure threshold
mg	Milligram
ml	Mliliter
mmol	Millimole
MSC	Methansulphonyl chloride

NMR	Nuclear magnetic resonance
NMDA	N-Methyl-D-aspartate
PCP	Phencyclidine (phenyl cyclohexyl - piperidine)
p.o.	Per Os (orally)
PTZ	Pentylenetetrazole
r.t	Room temperature
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran

List of tables and figures

Abstract

Synthesis of certain1,1-disubstituted cycloalkanes and their biological profiles

Abstract

Thesis submitted by **Mohammed Samir Mohammed Abd el Maksoud** for the partial fulfillment for the degree of master of Pharmaceutical Sciences (Pharmaceutical Chemistry), Cairo University.

In this work the synthesis of N-benzyl and substituted benzyl-N-(1-((cyclohexylamino)methyl)cyclohexyl)benzenamines**,** ***7a-h;*** N-(1-(cyclohexyl carbamoyl) cyclohexyl)-N-phenylarylamides**,** ***8a-h***; 3-cyclohexyl-1,2-diphenyl and 2-(substituted phenyl) -1,3-diazaspiro[4.5]decane**,** ***9a-h*** and N-(1-((cyclohexylamino) methyl)cyclohexyl)-N-phenyl substituted benzamides, ***11a-h*** has been accomplished aiming to evaluate their anticonvulsant and antinoceciptive properties.

The thesis divided into the following sections :

I- Introduction:

This part includes a review on the biological profile and pharmacodynamics of 1,1-disubstituted cyclohexanes and related compounds.

II- Basis of the present investigation:

This part gives the pharmacological basis on which the synthesized compounds were chosen in addition to the schemes followed in their synthesis.

III- Theoretical discussion:

This part shows the reactions followed in the synthesis of the new target compounds in addition to the intermediates needed in their preparation as well as the spectral analyses of the synthesized compounds. The strategy followed for the synthesis of the designed compounds, starting materials and intermediates has been described in **Schemes I-VII**.

IV- Experimental part:

This includes the detailed procedures for the synthesis of the new compounds and intermediates in addition to their physical characters.

i) Published intermediates :

- 1-(Phenylamino)cyclohexanecarbonitrile ***(1)*** .
- 1-(Phenylamino)cyclohexanecarboxamide ***(2)*** .
- 1-(Phenylamino)cyclohexanecarboxylic acid ***(3)*** .
- 1-(N-Phenylbenzamido)cyclohexanecarboxylic acid ***(4a)*** .
- 1-(4-Chloro-N-phenylbenzamido)cyclohexanecarboxylic acid ***(4b)*** .
- 1-(4-Methoxy-N-phenylbenzamido)cyclohexanecarboxylic acid ***(4c)***.
- Methyl1-(N-phenylbenzamido)cyclohexanecarboxylate ***(5a)***.
- Methyl1-(4-chloro-N-phenylbenzamido)cyclohexanecarboxylate ***(5b)***.
- Methyl1-(4-methoxy-N-phenylbenzamido)cyclohexanecarboxylate ***(5c)***.
- (1-(Benzyl(phenyl)amino)cyclohexyl)methanol ***(6a)***.
- (1-((4-Chlorobenzyl)(phenyl)amino)cyclohexyl)methanol ***(6b)***.

- (1-((4-Methoxybenzyl)(phenyl)amino)cyclohexyl)methanol ***(6c)***.
- Methyl 7-methoxybenzo[d][1,3]dioxole-5-carboxylate ***(16)***.

ii) New intermediates:

- 1-(4-Nitro-N-phenylbenzamido)cyclohexanecarboxylic acid ***(4d)***.
- 1-(3,4,5-Trimethoxy-N-phenylbenzamido)cyclohexanecarboxylic acid ***(4e)***.
- 1-(7-Methoxy-N-phenylbenzo[d][1,3]dioxole-5-carboxamido) cyclohexane carboxylic acid ***(4f)*** .
- 1-(8-Methoxy-N-phenyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamido) cyclohexane carboxylic acid ***(4g)*** .
- Methyl 1-(4-nitro-N-phenylbenzamido)cyclohexanecarboxylate ***(5d)***.
- Methyl 1-(3,4,5-trimethoxy-N-phenylbenzamido) cyclohexane carboxylate ***(5e)***.
- Methyl 1-(7-methoxy-N-phenylbenzo[d][1,3]dioxole-5-carboxamido) cyclohexanecarboxylate ***(5f)***.
- Methyl 1-(8-methoxy-N-phenyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamido) cyclohexanecarboxylate ***(5g)*** .
- (1-((4-Nitrobenzyl)(phenyl)amino)cyclohexyl)methanol ***(6d)***.
- (1-(Phenyl(3,4,5-trimethoxybenzyl)amino)cyclohexyl)methanol ***(6e)***.
- (1-(((7-Methoxybenzo[d][1,3]dioxol-5-yl)methyl)(phenyl)amino) cyclohexyl) methanol ***(6f)***.

- (1-(((8-Methoxy-2,3-dihydrobenzo[b][1,4]dioxin-6- yl) methyl)(phenyl)amino)cyclohexyl)methanol ***(6g)***.
- N-(1-(Hydroxymethyl)cyclohexyl)-N-phenylbenzamide ***(10a)***.
- 4-Chloro-N-(1-(hydroxymethyl)cyclohexyl)-N-phenylbenzamide ***(10b)***.
- N-(1-(Hydroxymethyl)cyclohexyl)-4-methoxy-N-phenylbenzamide ***(10c)***.
- N-(1-(Hydroxymethyl)cyclohexyl)-4-nitro-N-phenylbenzamide ***(10d)***.
- N-(1-(Hydroxymethyl)cyclohexyl)-3,4,5-trimethoxy-N-phenyl benzamide ***(10e)***.
- N-(1-(Hydroxymethyl)cyclohexyl)-7-methoxy-N-phenylbenzo [d][1,3] dioxole-5-carboxamide ***(10f)***.
- N-(1-(Hydroxymethyl)cyclohexyl)-8-methoxy-N-phenyl-2,3- dihydrobenzo [b][1,4]dioxine-6-carboxamide ***(10g)*** .
- Methyl 8-methoxy-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate ***(17)***.
- 7-Methoxybenzo[d][1,3]dioxole-5-carboxylic acid ***(18)***.
- 8-Methoxy-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid ***(19)***.

iii) Target compounds *7a-h, 8a-h, 9a-h* and ***11a-h***:

- N-Benzyl-N-(1-((cyclohexylamino)methyl)cyclohexyl)benzenamine ***(7a)***.

- N-(4-Chlorobenzyl)-N-(1-((cyclohexylamino)methyl) cyclohexyl) benzenamine ***(7b)*** .
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-N-(4-methoxybenzyl) benzenamine ***(7c)***
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-N-(4-nitrobenzyl) benzenamine ***(7d)***.
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-N-(3,4,5-trimethoxybenzyl) Benzenamine ***(7e)*** .
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-N-((7-methoxybenzo [d][1,3] dioxol-5-yl) methyl)benzenamine ***(7f)*** .
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-N-((8-methoxy-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)benzenamine ***(7g)***.
- N-(4-Aminobenzyl)-N-(1-((cyclohexylamino)methyl)cyclohexyl) benzenamine ***(7h)***.
- N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-N-phenylbenzamide ***(8a)***.
- 4-Chloro-N-(1-(cyclohexylcarbamoyl)cyclohexyl)-N-phenylbenzamide ***(8b)***.
- N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-4-methoxy-N-phenylbenzamide ***(8c)***.
- N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-4-nitro-N-phenylbenzamide ***(8d)***.
- N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-3,4,5-trimethoxy-N-

phenylbenzamide ***(8e)***.

- N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-7-methoxy-N-phenylbenzo [d][1,3] dioxole-5-carboxamide ***(8f)***.
- N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-8-methoxy-N-phenyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide ***(8g)***.
- 4-Amino-N-(1-(cyclohexylcarbamoyl)cyclohexyl)-N-phenylbenzamide ***(8h)*** .
- 3-Cyclohexyl-1,2-diphenyl-1,3-diazaspiro[4.5]decane ***(9a)***.
- 2-(4-Chlorophenyl)-3-cyclohexyl-1-phenyl-1,3-diazaspiro[4.5]decane ***(9b)***.
- 3-Cyclohexyl-2-(4-methoxyphenyl)-1-phenyl-1,3-diazaspiro[4.5]decane ***(9c)***.
- 3-Cyclohexyl-2-(4-nitrophenyl)-1-phenyl-1,3-diazaspiro[4.5]decane ***(9d)***.
- 3-Cyclohexyl-1-phenyl-2-(3,4,5-trimethoxyphenyl)-1,3-diazaspiro [4.5] decane ***(9e)***.
- 3-Cyclohexyl-2-(7-methoxybenzo[d][1,3]dioxol-5-yl)-1-phenyl-1,3-diazaspiro[4.5]decane (***9f)***.
- 3-Cyclohexyl-2-(8-methoxy-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-phenyl-1,3-diazaspiro[4.5]decane ***(9g)***.
- 4-(3-Cyclohexyl-1-phenyl-1,3-diazaspiro[4.5]decan-2-yl)aniline ***(9h)***.
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-N-phenylbenzamide ***(11a)***

- 4-Chloro-N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-phenylbenzamide ***(11b).***
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-4-methoxy-N-phenyl benzamide ***(11c)***.
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-4-nitro-N-phenylbenzamide ***(11d)***.
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-3,4,5-trimethoxy-N-phenylbenzamide ***(11e)***.
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-7-methoxy-N-phenyl benzo[d][1,3]dioxole-5-carboxamide ***(11f)***.
- N-(1-((Cyclohexylamino)methyl)cyclohexyl)-8-methoxy-N-phenyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide ***(11g)***.
- 4-Amino-N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-henylbenzamide ***(11h)***.

V- Biological evaluation:

The above mentioned newly synthesized compounds were tested for their anticonvulsant and antinoceciptive activities. The achieved biological results and structure activity relationship of studied compounds were discussed.

The maximal pentylenetetrazole seizures test was used for determination of the anticonvulsant activity using diphenylhydantoin and valproic acid as reference standards. The hot-plate technique was used for determination of the antinoceciptive profile using tramadol hydrochloride as reference standard.