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Research Article

SYNTHESIS, CHARACTERISATION AND ANTICONVULSANT ACTIVITY OF 3-SUBSTITUTED 2-THIOHYDANTOIN DERIVATIVES

Shirsath Pratibha Gangadhar*, Dandagvhal Kamlesh Ramesh and Sunil K Mahajan

Department of Pharmaceutical Chemistry, MGV'S Pharmacy college panchavati, Nashik-422 003, Maharashtra, India.

ABSTRACT

Some 3-sustitued 2-thiohydantoin derivatives were synthesised through Pinacol-Pinacolone rearrangement using microwave irradiations. Chemical structures of synthesised derivatives were identified by FT-IR, MS (EI), ^{1}HNMR. Synthesised derivatives were screen for anticonvulsant activity by PTZ induced convulsion in animal model. All synthesised 3-substituted 2-thiohydantoin derivatives shows significant anticonvulsant activity.

Keywords: 2-thiohydantoin, ^{1}HNMR, anticonvulsant, PTZ.

INTRODUCTION

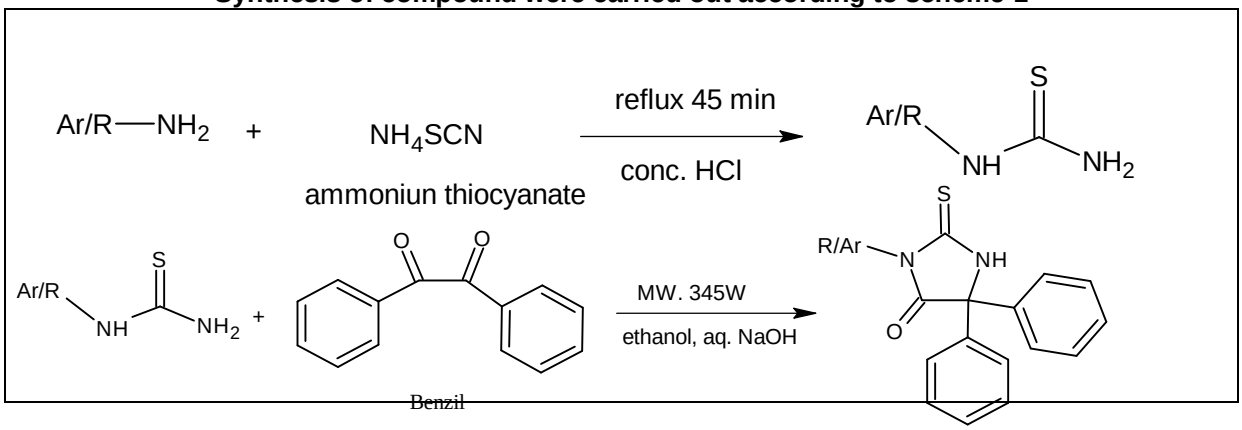
Thiohydatoins are sulfur analoges of hydantoins with one or both carbonyl groups replaced by thiocarbonyl groups.[1] Among the known thiohydantoins, 2-thiohydantoins are most notably known due to there wide application as hypolipidemic, anticarcinogenic, antimutagenic, antithyroidal, antiviral (against herpes simplex virus, HSV), human immunodeficiency virus, tuberculosis, antimicrobial (anti fungal,anti bacterial), anti-ulcer, and anti inflammatory[2] agent as well as pesticides.[3] Additionally 2-thiohydantois are used as reference standards for the development of C-Terminal protein sequencing, as reagent for development of dyes and in textile printing, metal catian complexetion and polymerization catalysis.[4, 5]

In present work we reported 3-sustituted 2-thiohydantoin were synthesised through Pinacol-pinacolone rearrangement reaction,[4] using various alkyl/aryl-thiourea and benzil in presence of 10% NaOH and ethanol under microwave irradiation. Synthesised compounds were evaluated for anticonvulsant activity by PTZ induced convulsion in animal model.[6]

MATERIAL AND METHODS

All the chemicals, solvents used for this work were obtained from s d fine-chem limited (SDFCL), MUMBAI. Reactions were carried on 'Catalyst systems Scientific microwave System'. Melting points of synthesised compounds were determined in open capillary tube using digital melting point apparatus VMP-D expressed in ^{0}C and were uncorrected. Silica gel chromatographic plates were used for TLC. IR spectra were recorded in KBr on FT-IR8400S SHIMADZU spectrometer. Mass spectra were recorded on GCMS QP2010 SHIMATZU instrument. ^{1}HNMR spectra were recorded on Mercury Plus 300 MHz model with TMS as an internal standard. Chemical shifts (δ) were expressed in parts per million (δ ppm).

Synthesis of compound were carried out according to scheme-1



3-substituted 2-thiohydantoin derivative

scheme- I

Synthesis of substituted N- thiourea

To appropriate amine (0.01mmol), concentrated hydrochloric acid (0.01mmol) was added and the solution was warmed. A saturated solution of Ammonium thiocyanate in water (15gm in 30mL) was added slowly in above solution. The mixture was reflux for 45 min. in 250 ml RBF then boil until the solution got turbid. The turbid solution was poured in cold water. The Separated precipitate as respective thiourea was filtered. Various substituted thiourea were prepared and listed in table no.1.

Synthesis of 3-alkyl/aryl-5,5-diphenyl-2-thioxoimidazolidine-4-one

To mixture of appropriate thiourea (o.o1mol), and benzil (0.01 mol), 40 ml ethanol and 30 ml 30% KOH was added at room temp. The mixture was stirred and transferred into 250 ml RBF, then it was refluxed in microwave for 25 min. at 345 W. after reflux mixture was cool and 80ml of water was added. Then filter the mixture, to filtrate amount of con. HCL was added drop wise with stirring to make acidic, it precipitate crude product, and was recrystallised from ethanol. Synthesized 3-alkyl/aryl-5,5-diphenyl-2-thioxoimidazolidine-4-one are listed in table no.2.

3,5,5-triphenyl-2-thioxoimidazolidin-4-one (PTP)

Mp: 190-194^{0}C, MS (EI): 344[M]$^+$, ^{1}HNMR (300MHz):7.3δppm (s,15H), 9.4δppm(s,1H). IR (KBr): 3302.24cm^{-1} (N-H stretch), 3055.35cm^{-1} (C-H aromatic stretch), 1743.71cm^{-1} (C=O stretch), 1489.10cm^{-1} (C=C aromatic stretch), 1234.48cm^{-1} (C=S stretch), 1172.76cm^{-1} (C-N stretch).

3-(4-methoxyphenyl)-5,5-diphenyl-2-thioxoimidazolidin-4-one (PATP)

Mp: 216-218^{0}C. MS (EI): 374[M]$^+$. ^{1}HNMR (300MHz): 3.8δppm (s, 3H), 7.1-7.7δppm (m, 14H), 9.7δppm (s,1H). IR (KBr): 3302.24cm^{-1} (N-H stretch), 3055.35cm^{-1} (C-H stretch, aromatic), 1743.71cm^{-1} (C=O stretch), 1234.48cm^{-1} (C=S stretch), 1172.76cm^{-1} (C-N stretch).

3-(4-chlorophenyl)-5,5-diphenyl-2-thioxoimidazolidin-4-one (PCTP)

Mp: 236-238^{0}C. MS (EI): 378[M]$^+$. ^{1}HNMR (300MHz):7-7.8δppm (m,14H), 9.7δppm (s,1H). IR (KBr): 3317.67cm^{-1} (N-H stretch), 3055.35cm^{-1} (C-H stretch, aromatic), 1743.71cm^{-1} (C=O stretch), 1481.38cm^{-1} (C=C stretch aromatic), 1226.77 cm^{-1} (C=S), 1172.76 cm^{-1} (C-N), 766.58 cm^{-1} (C-Cl stretch).

3-(4-fluorophenyl)-5,5-diphenyl-2-thioxoimidazolidin-4-one (PFTP)

Mp: 219-221^{0}C. MS (EI): 362[M]$^+$. ^{1}HNMR (300MHz): 7.1-7.6δppm (m, 14H), 9.6δppm (s, 1H). IR (KBr): 3326.39cm^{-1}(N-H stretch), 3063.06cm^{-1} (C-H stretch), 1489.10cm^{-1}(C=C stretch, aromatic), 1743.71cm^{-1} (C=O stretch), 1244.48cm^{-1}(C=S stretch), 1172.76cm^{-1}(C-N stretch), 779.27cm^{-1}(C-F stretch).

3-benzyl-5,5-diphenyl-2-thioxoimidazolidin-4-one (BTP)

Mp: 208-210^{0}C. MS (EI): 358[M]$^+$. ^{1}HNMR (300MHz): 2.4δppm (s, 2H), 7.3δppm (s, 15H). IR (KBr): 3317.67cm^{-1}(N-H stretch), 3047.63cm^{-1}(C-H stretch, aromatic), 2947.33cm^{-1} (C-H stretch, aliphatic), 1738.28cm^{-1}(C=O stretch), 1481.38cm^{-1}(C=C

stretch, aromatic), 1240.0cm^{-1}(C=S stretch), 1132.76cm^{-1}(C-N stretch).

Anticonvulsant activity

The Institutional Animal Ethics Committee approved the protocol adopted for the experimentation of animals. The animals, male Swiss Albino mice, weighing 18-25 gm were procured from Bharat Serums and Vaccines Ltd., Thane, Mumbai, India. All the animals were acclimatized for a week before use. All newly synthesized compounds were tested *in vitro* in order to evaluate their pharmacological activity. The dose of the compound was selected on trial and error method and evaluated for 30 mg, 50 mg, 100 mg, 150 mg and 200 mg per kg body wt. of mice initially. All the doses showed the strong activity so the least dose was selected. Now these compounds were screened for anticonvulsant profile at the dose of 20 mg/kg, exhibiting substantive anticonvulsant activity. The mice were divided into 8 groups containing five animals each.

Pentylenetetrazol (PTZ) induced convulsions in mice

The 3-(alkyl/aryl)-5,5-diphenyl-2 thioxoimidazolidine-4-one derivatives (20mg/kg p.o.) in test groups. PTZ (60mg/kg s.c.) were administered to control group and diazepam (10mg/kg i.p.) in standard group were administered to mice. To the mice after 60 min (oral dose), pentylenetetrazole (60 mg/kg s.c.) were administered and placed individual mice immediately in the centre of the flaxy glass chamber and observed for one hour. The latency period for each phase has recorded.

RESULT AND DISSUTION

Various thiourea were synthesised by using respective aromatic as well as aliphatic amine with ammonium thiocyanate and listed in table no 1 with their physicochemical data. Using various thiourea, 3-(alkyl/aryl)-5,5-diphenyl-2 thioxoimidazolidine-4-one derivatives were synthesised under microwave irradiation (350W for 20min.).The physicochemical data of synthesised compounds are listed in table no.2. Purity of all synthesised compounds was checked by melting point and TLC. All synthesised compounds were analysed by FT-IR, MS (EI), ^{1}HNMR. Anticonvulsant activity was performed by using PTZ induced convulsion in mice model. Diazepam is used as standard anticonvulsant. Results obtained are listed in table no.3, figure no. 1. Results shows that all synthesised derivatives of 2-thiohydantoin possess Significant anticonvulsant activity. Compounds PATP, PCTP, BTP show more potent anticonvulsant activity than PFTP, PTP.

CONCLUSION

Simple convenient method for synthesis of 2-hydantoins was developed on microwave system. Synthesised compounds were conformed by ^{1}HNMR, MS (EI), FT-IR. All synthesised derivatives of 2-thiohydantoin shows significant anticonvulsant activity. Electron donating groups on para position of 3-phenyl ring shows increase, while halogen group such as fluorine on para position of 3-phenyl ring shows decrease in anticonvulsant activity. More extensive study is needed to confirm the mode of action and studies to optimise the effectiveness of these compounds.

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Table 1: physicochemical data of substituted N-thiourea derivatives

S. No.	N-thiourea	Molecular formula	Molecular weight	% yield	Melting point (^{0}C)	Rf value
1	Phenylthiourea	$C_7H_8N_2O$	136	94	148.3	4.3
2	p-chlorophenylthiourea	$C_7H_7ClN_2O$	170	98	157.5	5.8
3	p-methoxyphenylthiourea	$C_8H_{10}N_2O_2$	166	99	170.1	5.4
4	p-flurophenylthiourea	$C_7H_7FN_2O$	154	84	186.9	3.5
5	benzylthiourea	$C_8H_{10}N_2O$	150	93	164.5	4.7

Mobile phase Ethylacetate: n-hexane (7:3)

Table 2: physicochemical data of 3-alkyl/aryl-5,5-diphenyl-2-thioxoimidazolidine-4-one derivatives

S.No.	compound	Molecular formula	Molecular weight	% Yield	Melting point (^{0}C)	Rf value
1	PTP	$C_{21}H_{16}N_2OS$	344	86	190-194	0.57
2	PATP	$C_{22}H_{18}N_2O_2S$	374	92	216-218	0.42
3	PCTP	$C_{21}H_{15}ClN_2OS$	378	87	236-238	0.48
4	PFTP	$C_{21}H_{15}FN_2OS$	362	93	219-221	0.59
5	BTP	$C_{22}H_{18}N_2O_2S$	358	79	208-210	0.64

Mobile phase- Ethylacetate: n-Hexane (7:3)

Table 3: Anticonvulsant activity of synthesized 3-substituted 2-thiohydantoin derivatives

S.No.	Treatment groups	Straub Tail (sec)	Jerky M. (sec)	Clonic. C (sec)	Death (sec)
1	Normal	00	00	00	00
2	Control	46.6±1.69	54.6±1.32	88.2±3.073	172.4±6.57
3	DZP	00	00	00	00
4	BTP	1375±11.59*	1422±13.41*	1092±67.74*	00
5	PTP	1760±16.52*	2729±31.14*	626.8±62.6*	00
6	PFTP	1022±91.96*	1493±21.42*	1066±44.39*	00
7	PCTP	1050±10.8*	1172±10.19*	1265±49.10*	00
8	PATP	1292±75.27*	1523±48.07*	1324±61.0*	00

All values are expressed as mean ± SEM, n=5, *p<0.05 compared with control. Statistical analysis was performed with One-way ANOVA followed by Dunnett's test.
p<0.05 was considered as statistically significant.

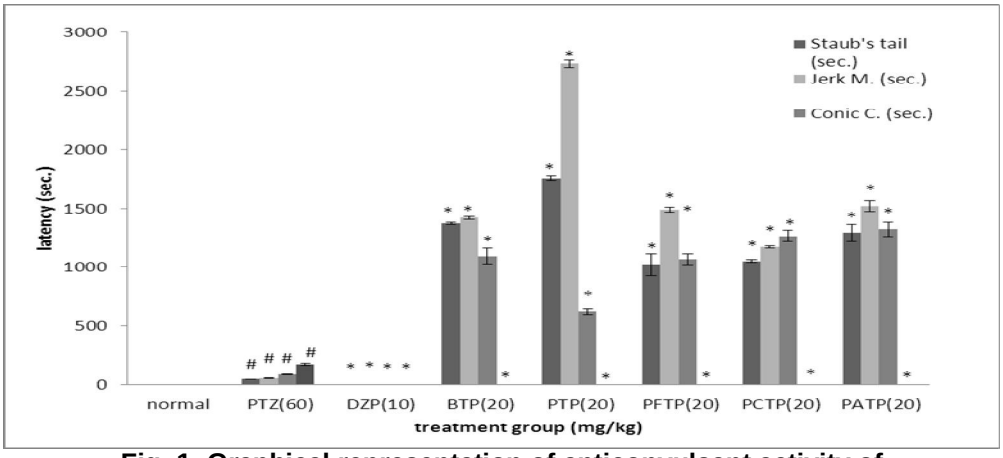

Fig. 1: Graphical representation of anticonvulsant activity of synthesized 3-substituted 2-thiohydantoin derivatives

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