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Research Article

SYNTHESIS, CHARACTERISATION AND ANTICONVULSANT ACTIVITY OF 1-(ARYL)-3-(DIPHENYLMETHYL) UREA DERIVATIVES

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ABSTRACT

Some 1-(Aryl)-3-(diphenylmethyl)urea derivatives were synthesized using microwave irradiations. The structures of title compounds were confirmed by ^{1}HNMR, MS (EI), FT-IR. All synthesized compounds were evaluated for anticonvulsant activity by PTZ induced convulsions in mice and 1-(4-methoxyphenyl)-3-(diphenylmethyl)urea and 1-(4-chlorophenyl)-3-(diphenylmethyl)urea were found possess potent anticonvulsant activity. During these synthesis we have also noted that when urea is replaced by 1N-phenylurea or substituted 1N-phenylurea in a reaction with Benzil, it do not follow pinacol-pinacolone rearrangement to form hydanoin derivaives but forms 1-(Aryl)-3-(diphenylmethyl) urea derivatives.

Keywords: urea, microwave, hydantoin, PTZ, anticonvulsant.

INTRODUCTION

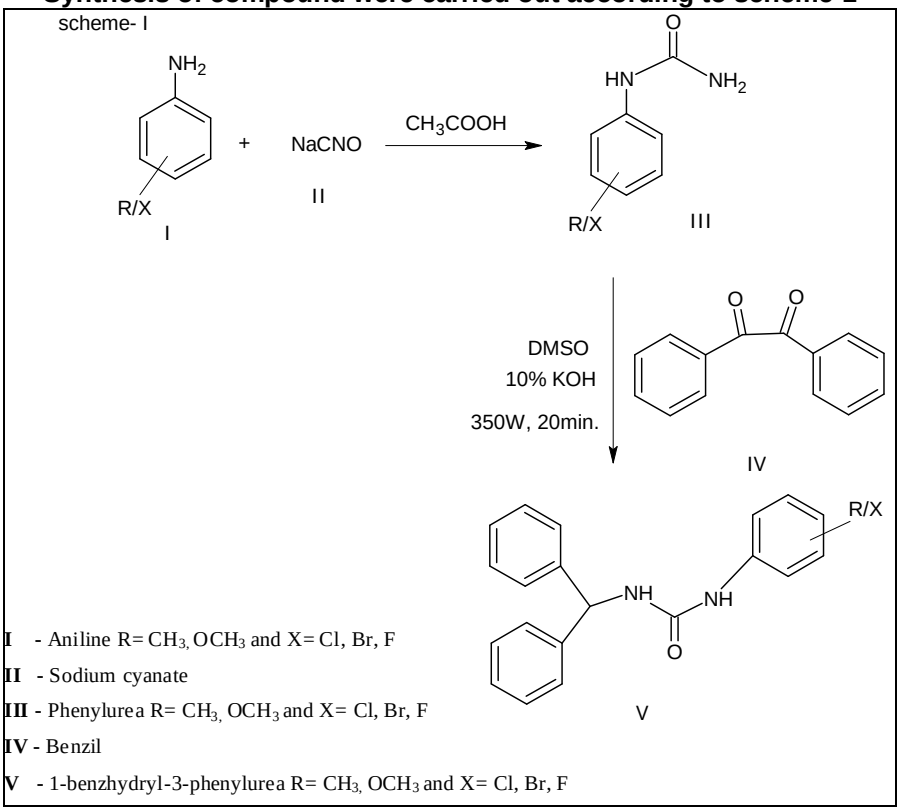
The urea derivatives such as N-nitrosoureas, benzoylureas, thioureas, and diarylsulphonylureas represent one of the most useful classes of anticancer agents, with a wide range of activities against leukemias and solid tumors.[1] Many urea-derived herbicides possess cytokinin-like activity (Krikorian, 1995). 1-benzhydryl-3-phenylureas, are reported as cannabinoid receptor 1 inverse agonist which lead to reduction in appetite and can be used as anti obesity agent.[3] It has been reported that various urea derivatives has antimicrobial,[1] hypoglycemic,[2] anticonvulsant activity. Ureas and monoacylurea derivatives also posses anticonvulsant activity (ex. Phenacemide).[4]

In present work, 1-(Aryl)-3-(diphenylmethyl)urea derivatives were synthesised using various 1N-arylurea and benzil in presence of 10% KOH and DMSO under microwave irradiation. Synthesised compounds were evaluated for anticonvulsant activity by PTZ induced convulsion in animal model.

MATERIAL AND METHODS

All the chemicals, solvents used for this work were obtained from S D fine-chem Ltd. (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



Synthesis of phenylurea derivatives

In a 250ml Beaker, aniline (0.1mol) was dissovled in 10 ml of glacial acetic acid, and diluted to 100ml with water. Solution of sodium cyanate (0.1mol) in 50ml of warm water was added to above mixture. It was allow standing for 30min. and then product was filtered.[5] Similarly some phenylurea derivatives listed in table no. 1 were prepared.

Synthesis of 1-(Aryl)-3-(diphenylmethyl)urea derivatives

Mixture of Benzil (7.14 mmol) and substituted phenylurea (14.3 mmol) was irradiated with microwave (350W for 20 min.) in presence of 10% aqueous KOH using DMSO as solvent and progress of reaction was monitored by TLC. On completion of the reaction, the mixture was cooled and poured into ice-cold water. Resulting solid was filtered, washed with water and recrystallised from ethanol. Similarly 1-(Aryl)-3-(diphenylmethyl)urea derivatives listed in table no.2 were prepared.

1-(diphenylmethyl)-3-phenylurea (PBU)

M.P. 202-204^{0}C, MS (EI): 302[M]$^+$. ^{1}HNMR (300MHz):6.2δppm(s,1H), 6.4δppm(s,1H) 7.3-7.6δppm (m,15H), 8.5δppm(s,1H). IR (KBr): 3348.54cm^{-1} (N-H stretch), 3039.91cm^{-1} (C-H aromatic stretch), 2908.75cm^{-1} (C-H stretch, Aliphatic) 1648.00 (C=O stretch), 1597.11cm^{-1} (C=C stretch, aromatic), 1242.20cm^{-1} (C-N stretch).

1-(4-methoxyphenyl)-3-(diphenylmethyl)urea (PABU)

M.P. 216-217^{0}C, MS (EI): 332M]$^+$. ^{1}HNMR (300MHz): 3.8δppm (s,3H), 6.2δppm (s, 1H), 6.0δppm (s, 1H), 6.9-7.3δppm (m, 14H), 8.3δppm(s, 1H). IR (KBr): 3319.60cm^{-1} (N-H stretch), 3041.84cm^{-1} (C-H, aromatic stretch), 2990.53cm^{-1} (C-H stretch, Aliphatic), 1681.98cm^{-1} (C=O stretch), 1620.26cm^{-1} (C=C stretch, aromatic), 1249.51cm^{-1} (C-N stretch), 1327.07cm^{-1} (C-O stretch).

1-(4-chlorophenyl)-3-(diphenylmethyl)urea (PCBU)

M.P. 212-213^{0}C. MS (EI): 336[M]$^+$. ^{1}HNMR (300MHz): 6.0δppm (s,1H), 6.3δppm (s,1H), 7.3-7.7δppm (m,14H), 8.2δppm(s,1H). IR (KBr): 3302.24cm^{-1} (N-H stretch), 3055.35cm^{-1} (C-H aromatic stretch), 2916.47cm-1 (C-H stretch, aliphatic), 1743.71cm^{-1} (C=O stretch), 1489.10cm^{-1} (C=C aromatic stretch), 1172.76cm^{-1}(C-N stretch), 671cm^{-1}(C-Cl stretch).

1-(4-methylphenyl)-3-(diphenylmethyl)urea (PMBU)

M.P. 206-207C, MS (EI): 316$[M]^+$. ^{1}HNMR (300MHz): 2.34δppm (s,3H), 6.1δppm (s, 1H), 6.3δppm (s,1H), 7.3-7.5δppm (m,14H), 8.27δppm (s,1H). IR (KBr): 3340.82cm^{-1} (N-H stretch), 3039.91cm^{-1} (C-H aromatic stretch), 2990.53cm^{-1} (C-H stretch, Aliphatic), 1647.00cm^{-1} (C=O stretch), 1597.11cm^{-1} (C=C stretch, aromatic), 1219.05cm^{-1}(C-N stretch).

1-(4-bromophenyl)-3-(diphenylmethyl)urea (PBBU)

M.P. 223-224^{0}C, MS (EI): 380$[M]^+$. 382$[M+1]^+$. ^{1}HNMR (300MHz): 6.1δppm (s,1H), 6.2δppm (s,1H), 7.2-7.7δppm (m,14H), 8.2δppm (s,1H). IR (KBr): 3354.48cm^{-1} (N-H stretch), 3178.79cm^{-1} (C-H aromatic stretch), 2901.04cm^{-1} (C-H stretch, Aliphatic), 1635.69cm^{-1} (C=O stretch), 1597.11cm^{-1} (C=C aromatic stretch), 1219.05cm^{-} (C-N stretch), 694cm^{-1}(C-Br stretch).

1-(4-flurophenyl)-3-(diphenylmethyl)urea (PFBU)

M.P. 223-224^{0}C, MS (EI): 320$[M]^+$. IR (KBr): 3316.41cm^{-1} (N-H stretch), 3162.81cm^{-1} (C-H aromatic stretch), 2943.53cm^{-1} (C-H stretch, Aliphatic), 1659.49cm^{-1} (C=O stretch), 1593.19cm^{-1} (C=C aromatic stretch), 1226.57cm^{-} (C-N stretch), 682cm^{-1}(C-F stretch).

Anticonvulsant activity

The Institutional Animal Ethics Committee approved the protocol adopted for the experimentation of 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 anticonvulsant activity at fixed dose 20mg/kg. Mice were divided into 9 groups containing five animals each.

PTZ induced convulsions animal model was used to evaluate anticonvulsant activity:

The 1-(Aryl)-3-(diphenylmethyl)urea derivatives (20mg/kg p.o.) were administered in test groups. PTZ (60mg/kg s.c.) was administered in control group. Diazepam (10mg/kg i.p.) was administered to in standard group. After 60 min (oral dose), pentylenetetrazole (60 mg/kg s.c.) was 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.[6] Data is represented in table no 3 and figure no.1

RESULT AND DISCUSSION

Substituted 1N-phenylurea were synthesised by using respective aniline with sodium cyanate and data is listed in table no 1. Using substituted 1N-phenylurea different 1-(Aryl)-3-(diphenylmethyl)urea derivatives were synthesised under microwave irradiation (350W for 30min.). The physicochemical data of synthesised compounds is listed in table no.2. Purity of all synthesised compounds was confirmed by melting point and TLC. All synthesised compounds were analysed by FT-IR, MS (EI), ^{1}HNMR. Anticonvulsant activity was evaluated using PTZ induced convulsion in mice using Diazepam as standard. Results obtained are listed in table no.3, figure no.1. In this all synthesised derivatives of 1-(Aryl)-3-(diphenylmethyl)urea possess anticonvulsant activity. Compounds PABU, PCBU are more potent anticonvulsant activity than PBU, PMBU and PBBU. During these synthesis we have also noted that when urea is replaced by 1N-phenylurea or substitued 1N-phenylurea in a reaction with Benzil, it do not follow pinacol-pinacolone rearrangement to form hydanoin derivaives but forms 1-(Aryl)-3-(diphenylmethyl)urea derivatives.

CONCLUSION

Simple convenient method for synthesis of 1-(Aryl)-3-(diphenylmethyl)urea was developed on microwave system. Synthesised compounds were confirmed by ^{1}HNMR, MS (EI), FT-IR. All synthesised derivatives of 1-(Aryl)-3-(diphenylmethyl)urea shows significant anticonvulsant activity. Electron donating substitutions on para position of 3-phenyl ring shows increase, while halogens such as fluorine, Bromine when substiued at para position of 3-phenyl ring shows decrease in anticonvulsant activity. More extensive study is needed to confirm the mode of action and to optimise the effectiveness of these compounds.

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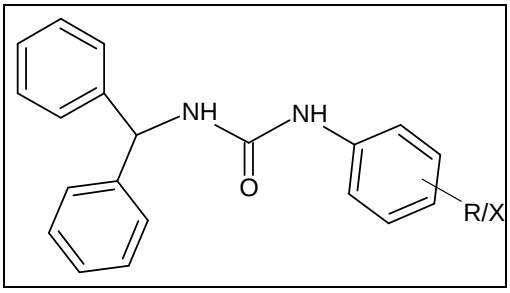
Table 1: physicochemical data of substituted 1-(aryl)urea

S. No.	compound	Molecular formula	Molecular weight	% yield	Melting point (^{0}C)	Rf value
1	1-phenylurea	$C_7H_8N_2O$	136	97	148-150	0.56
2	1-(4-methoxy)phenylurea	$C_8H_{10}N_2O_2$	166	93	165-167	0.60
3	1-(4-chloro)phenylurea	$C_7H_7ClN_2O$	170	96	140-142	0.48
4	1-(4-methyl)phenylurea	$C_8H_{10}N_2O$	150	98	183-185	0.52
5	1-(4-bromo)phenylurea	$C_7H_7BrN_2O$	214	92	158-160	0.63
6	1-(4-fluro)phenylurea	$C_7H_7FN_2O$	154	88	194-196	0.65

Mobile phase- ethyl acetate: n-Hexane (7:3)

Table 2: physicochemical data of 1-(Aryl)-3-(diphenylmethyl)urea derivatives



S. No.	Treatment groups	Straub Tail (sec)	Jerky M. (sec)	Clonic. C (sec)	Death (sec)
1	Normal	0	0	0	0
2	Control	45.6± 1.85	54± 2.08	73.33± 4.37	97.67± 3.84
3	DZP	0	0	0	0
4	PBU	88.67± 8.19	94.67± 4.66	140.7± 3.75	207.3± 103.0
5	PFBU	138.7± 8.11	124.7± 9.52	229.3± 6.53*	243.3± 122.0
6	PCBU	215.7± 18.75	933.7± 12.71*	881± 50.86*	0
7	PABU	299± 19.86	1052± 52.63*	994.7± 8.56*	0
8	PMBU	102.3± 12.4	249.7± 2.13	317.3± 17.34*	0
9	PBBU	120± 1.99	232.3± 3.71	551± 5.85*	170.7± 170.0

Mobile phase- ethyl acetate: n-Hexane (7:3)

Table 3: Anticonvulsant activity of 1-(Aryl)-3-(diphenylmethyl)urea derivatives by PTZ induced convulsions test in mice

S. No.	X/R	Molecular formula	Molecular weight	% Yield	Melting point (^{0}C)	Rf value
1	H	$C_{20}H_{18}N_2O$	302	88	202-204	0.52
2	P-OCH_3	$C_{21}H_{20}N_2O_2$	332	91	216-217	0.53
3	P-Cl	$C_{20}H_{17}ClN_2O$	336	84	212-214	0.50
4	P-methyl	$C_{21}H_{20}N_2O$	316	97	206-207	0.55
5	P-Br	$C_{20}H_{17}BrN_2O$	380	98	223-224	0.41
6	P-F	$C_{20}H_{17}FN_2O$	320	92	176-178	0.51

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.

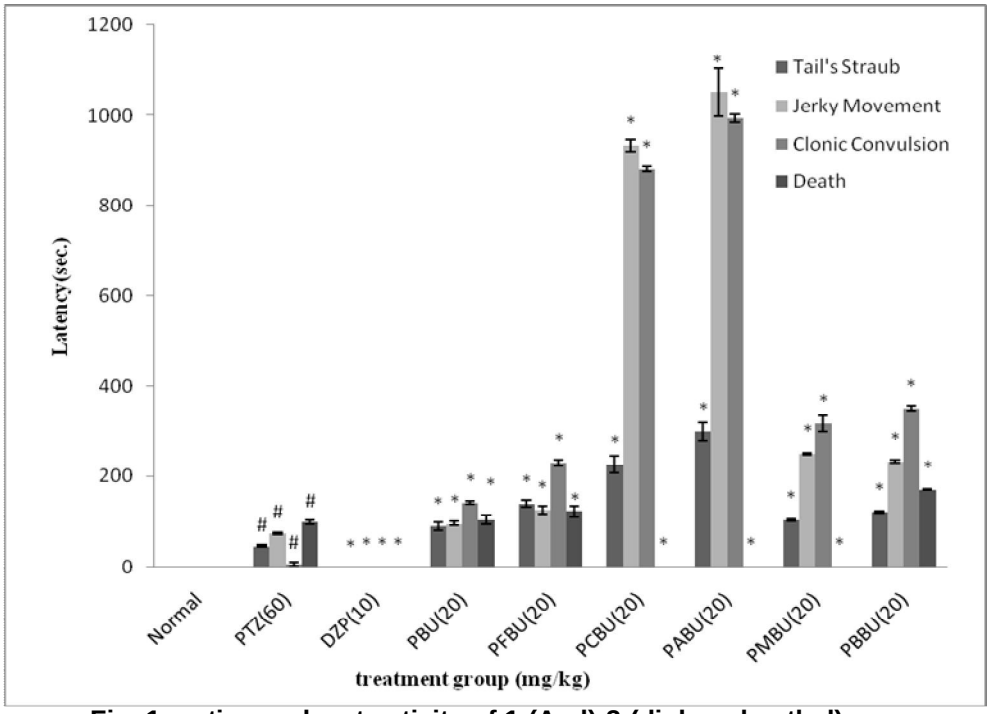


Fig. 1: anticonvulsant activity of 1-(Aryl)-3-(diphenylmethyl)urea derivatives for anticonvulsant activity by PTZ induced convulsions test in mice

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