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Synthesis And Anticonvulsant Activity Of Some N-Substituted-Phthalimide Analogs

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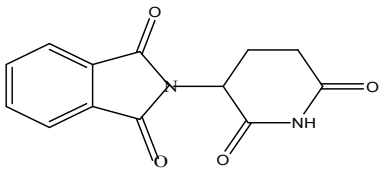
A series of N-substituted-phthalimides were synthesized for the purpose of determining the anticonvulsant activity of these compounds. The compounds were synthesized using Phthalic anhydride and various amines in microwave synthesizer. The structures of the synthesized derivatives were confirmed by means of IR, 1H-NMR.The anticonvulsant activity of all compounds were evaluated by subcutaneous pentylenetetrazole-induced seizure test .Compounds 1d, 1h and 1j were found to exhibit good activity.

Keyword: Phthalimides, Anticonvulsant Activity, Microwave.

INTRODUCTION: Epilepsy, a neurological disorder, has been found to affect around 1% of total world's population. Several new compounds such as zonisamide, vigabatrin, lamotrigine, gabapentin have emerged following the widely used classical antiepileptic drugs such as phenytoin, Phenobarbital, carbamazepine, valproic acid and various benzodiazepines. The need to synthesize newer molecules persists to treat those cases that have developed resistance to the available medication and to minimize the side effects to the lowest possible level.

The phthalimide pharmacophore was developed by Vameq et al. The isoindoline-1,3-dione ring system has been widely used to synthesize various derivatives having diverse pharmacological properties such as hypolipidemic,antimalarial,hypoglycaemic,antian drogenic,sedative hypnotic, antiangiogenic ,antiviral and antiepileptic. The anticonvulsant properties of isoindoline-1,3-dione ring system surfaced as a consequence of pioneering discovery of the anticonvulsant properties of Thalidomide. Thalidomide was first marketed in 1954 as an anticonvulsant.



Thalidomide

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MATERIALS AND METHOD

Chemistry

Reactions were carried out in CEM Microwave synthesizer. Melting points were determined in open glass capillary tubes using Lab India Visual Melting Point Apparatus and are uncorrected. IR Spectra were recorded as thin films in KBr pellets with a Nicolet spectrophotometer. Thin layer Chromatography was carried out using Silica Gel G as adsorbent and spots were detected under UV light. ^{1}H NMR was measured with a Jeol 400 spectrometer.

GENERAL METHOD

Phthalic anhydride (0.005 mole) was reacted with an equimolar amount of amine in microwave synthesizer. The mixture was heated at 150-250^{o}C for 3-10 minutes. The reaction was monitored using the technique of Thin layer Chromatography. The product was recrystallised using Ethanol. The different molecules synthesized are given in Table 1. The physical constants are listed in table 2.

SCHEME:

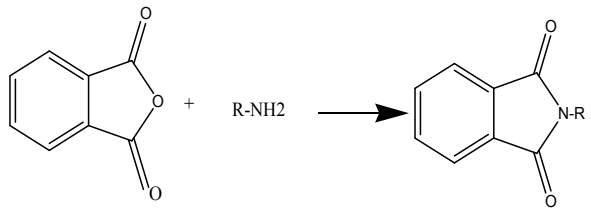


TABLE 1

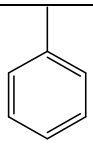
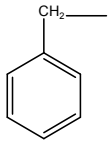
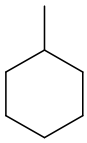
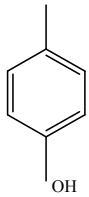
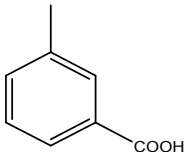
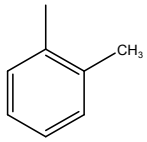
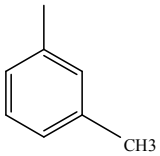
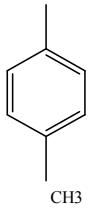
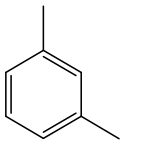
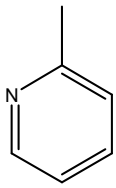
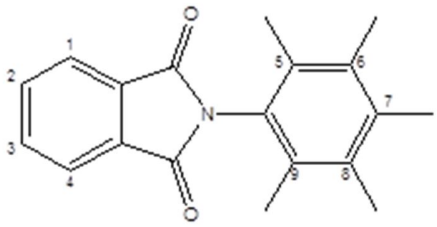
Compound	R R=	Compound	R=
1a		1b	
1c		1d	
1e		1f	
1g		1h	
1i		1j	

TABLE 2: LIST OF PHYSICAL CONSTANTS

COMPOUND	M.P(^{0}C)	YIELD(%)	MOLECULAR FORMULA	Mol wt.	R_f
1a	202-204	89	$C_{14}H_9NO_2$	223	0.43
1b	120-122	71	$C_{15}H_{11}NO_2$	237	0.51
1c	170-172	70	$C_{14}H_{15}NO_2$	229	0.46
1d	290-292	66	$C_{14}H_9NO_3$	239	0.57
1e	221-222	72	$C_{15}H_9NO_4$	267	0.62
1f	191-193	69	$C_{15}H_{11}NO_2$	237	0.48
1g	192-193	52	$C_{15}H_{11}NO_2$	237	0.54
1h	190-192	61	$C_{15}H_{11}NO_2$	237	0.65
1i	155-158	78	$C_{15}H_{11}NO_3$	253	0.57
1j	234-236	70	$C_{13}H_8N_20_2$	224	0.63



General Structure

N-Phenylphthalimide(2-pheny- isoindole-1,3-dione):IR:(KBr) cm^{-1} 1720,1690,1250 ; NMR: δ7.89(m,2H, 1,4 Aromatic protons), δ7.73(m,2H, 2,3 Aromatic protons), δ7.44(m,2H,6,8 Aromatic protons), δ 7.36(m,3H,5,7,9 Aromatic protons)

N-benzylphthalimide(2-benzyl-isoindole-1,3-dione):IR:(KBr)cm^{-1} 740,3050,1730,1230;NMR: δ4.78(s,2H), δ7.7(m,2H,1,4 Ar H), δ7.6(m,2H,2,3 Ar H), δ7.3(m,2H,6,8 Ar H), δ7.2(m,3H,5,7,9 Ar H)

N-cyclohexyl phthalimide (2-cyclohexyl-1,3-isoindole-1,3-dione): IR:(KBr) cm^{-1}2970,1690,1350; NMR: δ7.7(m,2H,1,4 Ar H), δ7.6(m,2H,2,3 ArH), δ4.0(m,1H,-N-CH), δ1-2(m,10H)

N-(4-hydroxyphenyl) phthalimide (2-(4-hydroxyphenyl)-isoindole-1,3-dione): IR: (KBr) cm^{-1} 3100,1720,1255;NMR: δ7.8(m,2H, 1,4 ArH), δ7.7(m,2H,2,3 ArH), δ7.4 (m,2H,6,8 ArH), δ7.3(m,2H,5,9 ArH) δ7.5 (s,1H, =C-OH)

N-(3-carboxyphenyl) phthalimide (2-(3-carboxyphenyl)-isoindole-1,3-dione):IR:(KBr) cm^{-1} 3217,2841,1658,1342; NMR: δ3.15(s,1H, -COOH), δ7.7(m,2H,1,4 Ar H), δ7.6(m,2H,2,3 ArH), δ8.02(m,1H,5 ArH), δ7.9(m,1H,7 ArH) ,δ7.47(m,1H,8 ArH), δ7.5(m,1H,9ArH)

N-(o-methylphenyl)-phthalimide (2-(2-methylphenyl)-isoindole-1,3-dione); IR: (KBr) cm^{-1} 1711,1219,3061,1492; NMR: δ2.1(s,3H,-CH_3), δ7.9(m,4H,1,2,3,4 ArH), δ7.3(m,4H,6,7,8,9 ArH).

N-(m-methylphenyl)-phthalimide (2-(3-methylphenyl)-isoindole-1, 3-dione): IR: (KBr) cm^{-1} 3062,1713,1602,1490,1236 ; NMR:

$^{\delta}$2.3(s,3H,-CH_3), $^{\delta}$7.9(m,4H,1,2,3,4 ArH), $^{\delta}$7.4(m,1H,5 ArH), $^{\delta}$7.2(m,3H,7,8,9 ArH)

N-(p-methylphenyl) phthalimide (2-(4-methylphenyl)-isoindole-1, 3-Dione): IR: (KBr)cm^{-1} 3042,1712,1512,1460,1214; NMR: $^{\delta}$2.5(s,3H.-CH_3) , $^{\delta}$7.9(m,2H,1,4 ArH), $^{\delta}$ 7.4 (m,2H,2,3 ArH), $^{\delta}$7.04(m,4H,5,6,8,9, ArH).

N-(3-methoxyphenyl)-phthalimide (2-(3-methoxyphenyl) isoindole-1,3-dione): IR: (KBr)cm^{-1} 2922,1770,1496,1380,1303,1257,1048,769; NMR: $^{\delta}$2.3(s,3H,-OCH_3), $^{\delta}$7.9(m,4H,1,2,3,4 ArH), $^{\delta}$7.3(m,4H,5,6,7,8,9 ArH)

N-(2-pyridyl)-phthalimide (2-(2-pyridyl)-isoindole-1,3-dione): IR: (KBr)cm^{-1} 1712,1581,1241,; NMR: $^{\delta}$7.95(m,2H, 1,4 ArH), $^{\delta}$7.5(2,3 2H, ArH), $^{\delta}$8.01(m,3H,6,7,8 ArH), $^{\delta}$8.66(m,1H,9 ArH).

Evaluation of the anticonvulsant activity (subcutaneous PTZ seizure threshold test)

Male and female albino mice weighing 25-35g were used as anticonvulsant animals and were maintained at a controlled temperature (25±2^{0}C). The animals were allowed free access to food and water except when removed from their cages for the experimental procedure. The Anticonvulsant activity was studied in 12 groups, each group consisting of 6 animals. First group served as a control group. Groups 2-11 served as test groups and Group 12 received the standard drug. Each compound was injected intraperitoneally (i.p.) at a dose of 50mg/kg(suspended in 1% CMC). Thirty minutes later PTZ was injected subcutaneously at a dose of 85 mg/kg dissolved in 0.9% Sodium chloride solution. The animals were then observed for 1h.

RESULTS AND DISCUSSION

Chemistry

N-substituted-1,3-isoindolinedione derivatives were synthesized according to the preferred synthetic route. These derivatives were prepared from phthalic anhydride and amine derivatives via direct fusion in microwave synthesizer at temperature 150-250^{0}C with a yield varying from 52-89%. The physical properties of the synthesized compounds are reported in Table 2. The purity of these compounds was determined by TLC and their structures were confirmed by IR, ^{1}H-NMR.

Anticonvulsant Screening

The anticonvulsant activity of the synthesized compounds was evaluated in mice using PTZ-induced convulsions. Phenytoin (40mg/kg) was used as a positive control and the test compounds were administered intraperitoneally at a dose of 50 mg/kg, half an hour after the administration of PTZ (85mg/kg). The results of these compounds are presented in Table 3. Compounds 1a, 1b and 1c have already been reported in the literature for anticonvulsant activity. Among the newly synthesized compounds , 1d,1h and 1j were found to show good anticonvulsant activity. The data obtained from the in vivo studies can be further evaluated for the side effects and mechanism of action so as to be introduced in the market for human use.

TABLE 3: ANTICONVULSANT ACTIVITY OF SYNTHESIZED COMPUNDS

Group	Compound	Onset time of convulsion (sec)
1	Control	35.7±0.2
2	1a	62±1.5
3	1b	67±2.4
4	1c	75±0.5
5	1d	81±5.7*
6	1e	39±1.8
7	1f	59±4.3
8	1g	62±5.5
9	1h	73±7.3*
10	1i	41.22±49
11	1j	98.22±16*
12	Standard	150.97±56

*P<0.05 as compared to control. Values are expressed as Mean±SEM.

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