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Synthesis, characterization and pharmacological activity of some new phthalimide derivatives

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ABASTRCT

*Some novel appropriate amines linked to phthalimide moiety have been synthesized via microwave and reflux synthesizer. The phthalic anhydride was treated with various aliphatic amines (aminoethanol , aminopropanol, amino ethyl morphline, and some amino acids), the purity of the synthesized products were monitored by using TLC in an appropriate developing system. The structures of the new synthesized compounds were confirmed by using physical and spectral analysis. All the synthesized compounds were evaluated in vivo for analgesic activity by using standard experimental models. Compounds **2, 4** and **6** showed significant analgesic effect with hot plate and acetic acid inducer writhing tests in mice compared to the control group.*

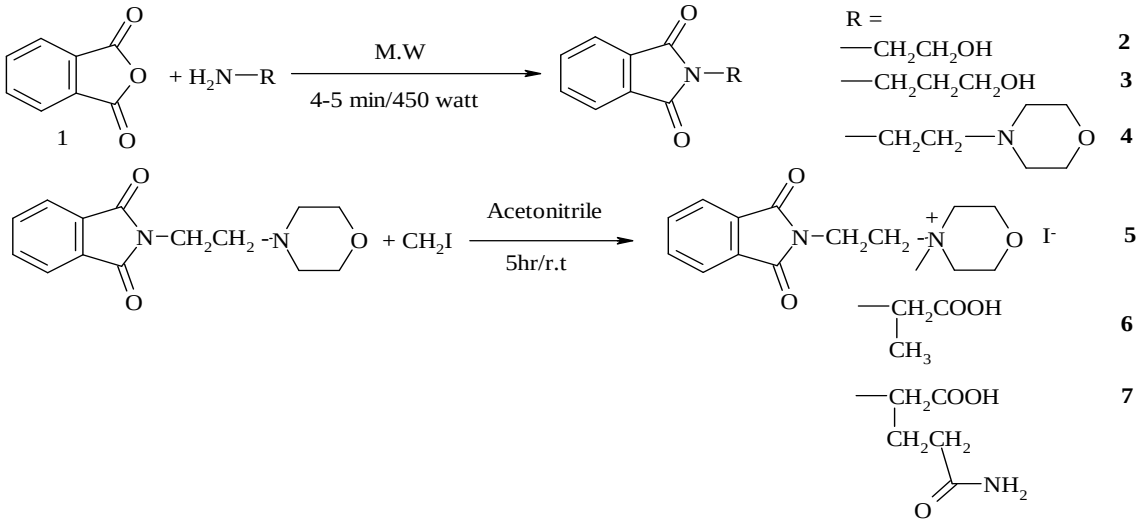
Keywords: Phthalic anhydride, N-substituted phthalimide, analgesic activity.

INTRODUCTION

Phthalimide possess a structural features –CO-N(R)-CO- and an imide ring which help them to be biologically active and pharmaceutically useful [1]. Phthalimid have received attention due to their antibacterial, antifungal, analgesic [2], antitumor [3,4], anxiolytic [5].

Recently, phthalimide and some of its derivatives have proved to have important biological effects similar or even higher than known pharmacological molecules and so their biological activity is being a subject of biomedical research [6-9].

As a result, we have synthesized and evaluated the analgesic activity of several new N-substituted-phthalimides (**Schemes 1**) and interestingly, some of them have shown significant analgesic activity.



Scheme .1. Synthesis of phthalimide derivatives 2-7

MATERIALS AND METHODS

All chemicals and solvents, reagents used in the present study were of analytical grade purchased from Sigma**,** Fischer. All the solvents were used after distillation. The melting points were determined by open capillary method and were uncorrected. The purity of compounds was confirmed by thin layer chromatography using Silica coated aluminium sheets(silica gel 60 F_{254}). IR spectra were recorded using KBr on FTIR Shimadzu.

Table.1. physicochemical properties of the new synthesized compounds 2-7

Compounds.	Rec. Solvent	M.P C^O	Yield %	R.f cm^{-1}	IR(KBr) cm^{-1}
2-(hydroxyethyl) isoindoline-1,3-dione **2** $C_{10}H_{11}O_3N$ (194.1)	Petr. ether : chloroform (1:1)	138-140	63.6	0.33	3400 O-H 2900 C-H 1700 C=O 1050 C-N
2-(3-hydroxypropyl) isoindoline-1,3-dione **3** $C_{11}H_{18}O_3N$ (213.8)	Petr. ether: Ethyl. acetate (2:1)	77-79	87.8	0.31	3400 O-H 2900 C-H 1700 C=O 1050 C-N
2-(2-morpholinoethyl) isoindoline-1,3-dione **4** $C_{14}H_{18}O_3N_2$ (263.8)	Petr. ether	139-140	61.53	0.28	2800 C-H 1700 C=O 1050 C-N 1150 C-O 1030 C-N 1400 C-N
4-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-4-methyl morpholin-4-ium iodide **5** $C_{15}H_{21}O_3N_2I_1$ (390.8)	Acetonitrile	294-296	53.8	0.3	=
2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoic acid **6** $C_{11}H_{11}O_4N$	Water	229-231	57.6	0.66	3100 O-H 2600 C-H 1600 C=O 1700 C=O imides
5-amino-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-oxopentanoic acid **7** $C_{13}H_{14}O_5N_2$	Water	242-243	71.1	0.25	3100 N-H 2900 O-H 1600 C=O 1700 C=O

General procedure for synthesis of compounds 2-4, 6, 7

Phthalic anhydride **1** (0.005 mole) was reacted with an equimolar amount of amine in microwave synthesizer. The mixture was heated at 450 watt, for 4-5 minutes. The reaction was monitored using the technique of Thin layer

Chromatography. After cooling the precipitate was filtered off, washed with water and then recrystallized from appropriate solvent (**Scheme.1. Table 1**).

Synthesis of morphline-ethyl-phthalimide iodide 5

To a solution of 2-(2-morpholinoethyl) isoindoline-1,3-dione **4** (1.0 mmol) in 5 ml of dry acetonitrile was added an equivalent amount of methyl iodide (1.0 mmol), and stirred at room temperature for 5h. The resulting precipitate was filtered off, and recrystallized from acetonitrile (**Scheme. 1. Table. 1)**

PHARMACOLOGY:

New Phthilimide derivatives **2-7**, were tested for analgesic effect and found to possess such activity. The results are shown in Table **2** and **3**.

- **Analgesic activity:**

The experiments were performed on male albino mice (15-30 g). The animals were kept at constant temperature facilities exposed to 12:12 h light: dark cycle. A standard pellet diet and tap water was given *adlibitum*. Each experimental group consisted 4 animals. The tested compounds were administered intraperitoneal (*ip*) 30min before the test, in a solution of 1% carboxy methyl cellulose (CMC), in dose 50mg/kg and volume of 1ml/100g. The animals were placed on hot plate after 30 minutes of injection test drug or CMC. The temperature is controlled from (55-56 ℃). Record the time when the animal licks its fore limbs or jumps out of the plate as therapeutic end point [10].

The investigated compounds were assessed on the behavioral animal tests:

- **Reactivity to pain stimulus**

A. hot plate method. **B.** Pain inducer by acetic acid.

All the synthesized compounds **2-7** were investigated with regard to their CNS activity in animal *in vivo* tests, All tested compounds displayed best activity in the acetic acid induced writhing and in hot-plate tests.

Table.2. Analgesic Activity of new phthalimide derivatives 2-7 by acetic acid inducer pain

No. of. mice	Control	2	3	4	5	6	7
1	54	23	32	27	11	26	6
2	49	19	38	24	14	23	9
3	52	20	31	29	12	24	7
4	57	21	36	31	16	21	5
Mean	53	20.75	34.25	27.75	13.25	23.5	6.75
STDEV	3.366502	1.707825	3.304038	2.986079	2.217356	2.081666	1.707825
p value	<0.0000025	<0.000002	<0.00021	<0.00000029	<0.00000011	<0.000005.7	<0.0000024

Each group consisted of 4 animals. $^{*}p < 0.01$

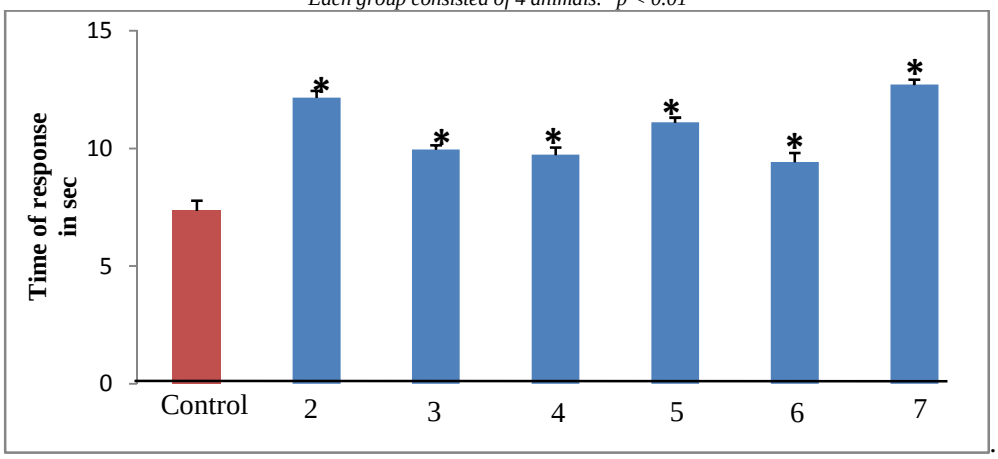


Figure..2. Analgesic Activity of new phthalimide derivatives 2-7 by acetic acid inducer pain

Table.3. Analgesic Activity of new phthalimide derivatives 2-7 by hot plate method

No. of. mice	Control	2	3	4	5	6	7
1	7.04	11.86	10	9.36	11.26	10	12.76
2	7.3	12	9.67	10.11	11.31	9.13	12.6
3	7.1	12.56	10.13	9.87	10.84	9.23	13
4	8	12.2	10.02	9.58	11	9.34	12.46
Mean	7.36	12.155	9.955	9.73	11.1025	9.24	12.705
STDEV	0.44.9.8	0.303919	0.19841	0.328329	0.221566	0.39281	0.231733
p value	-	<0.0000019	<0.000003.8	<0.00013	<0.0000051	<0.0004	<0.000006

Each group consisted of 4 animals. $^{*}p < 0.01$

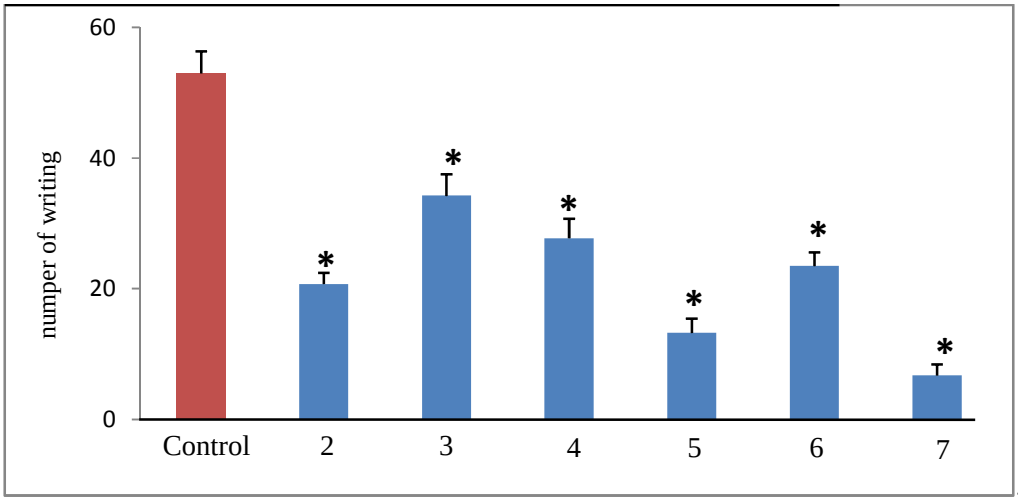


Figure.2. Analgesic Activity of new phthalimide derivatives 2-7 by hot plate method

RESULTS AND DISCUSSION

Chemistry:
N-substituted-phthalimide derivatives were synthesized according to the preferred synthetic route. These derivatives were prepared from phthalic anhydride and appropriate aliphatic amines via direct fusion, with a yield varying from 61-87%. The purity of these compounds was determined by TLC and their structures were confirmed by IR. The physicochemical properties of the synthesized compounds are reported in **Table 1**.

Pharmacology:
All described, new phthilimido derivatives **2-7,** were evaluated *in vivo* for analgesic activity by using standard experimental models. The evaluation of analgesic activity was done by acetic acid inducer pain and hot plate methods, the reaction time is noted as therapeutic end point. From the **fig.1**and **2**, among all the synthesized compounds **2-7** at dose of 50 mg/kg showed central analgesic activity by increasing the reaction time and peripheral analgesic activity by decreasing number of writhing. This suggested that the best analgesic activity was observed for the compound 2-(hydroxyethyl) isoindoline-1,3-dione **2 ,** 4-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-4-methyl morpholin-4-ium iodide **5** and 5-amino-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-oxopentanoic acid **7** compared with control group. **Table. 2** and **3, fig.1** and **2.**

CONCLUSION

Thus, we concluded that novel N-substituted Phthilimide produce significant analgesic activity. But it should be suggested that further exact mechanism of action is necessary.

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