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SYNTHESIS, CHARACTERIZATION AND ANALGESIC ACTIVITY OF SEVERAL NEW N-SUBSTITUTED PHTHALIMIDE ANALOGUES

Omran Fhid*[1], Shaban E.A. Saad [2], Talal H. Zeglam[1], Asma Eswayah [1], Jamal Baki [1], Esra Alnnas [1], Yousra Haroon [1], Majda Zitouni [1] and Wafa Sdera [1]

Department of Pharmaceutical Chemistry [1], Department of Pharmacology [2], Faculty of Pharmacy, University of Tripoli- Libya

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Correspondence to Author:

Omran Fhid

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Tripoli- Libya

E-mail: ofhid@yahoo.com

ABSTRACT: The synthesis, characterization and spectroscopic studies of new N-substituted pthalimide analogues **2**–**7** with analgesic activity were described. The compounds were synthesized using phthalic anhydride with various appropriate amines (Triazolamine, Benzocaine, *p*-Nitro-aniline, pyrazinamide, Phenazone and glycine) in reflux synthesizer. The purity of the compounds was determined by TLC. With the physical and spectral data the structure of the new synthesized compounds were elucidated. The newly synthesized compounds were subjected for the screening of CNS activity by using standard experimental models. The analgesic activity of the selected compounds **2-7** were evaluated *in vivo* by *ip* carboxymethylcellulose (CMC) and acetic acid- induced 'writhing' test in mice. Compounds **2-7** were exhibited significant analgesic activity in hot-plate and acetic acid inducer screening test comparable to the control CMC (Carboxymethylcellulose) and aspirin.

INTRODUCTION: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for reducing pain and swellings associated with inflammation and represent an area in continuous and ever growing development. To control pain due to inflammation, analgesic drugs are administered, which can be classified as narcotic, when acting on the central nervous system, and non-narcotic or peripheral, when acting directly on the damaged tissue [1, 2]. Peripheral analgesics are drugs that, independent of their mode of action, show a therapeutic effect by suppressing the production of prostaglandins, which are lipids responsible for inflammation and pain.

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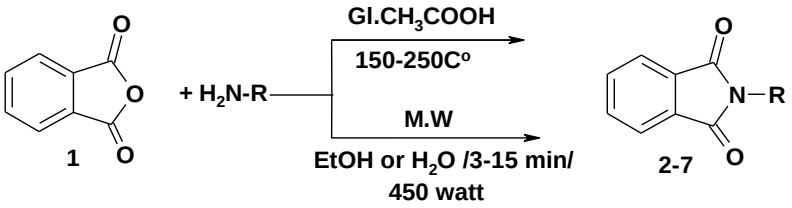
Non-steroidal anti-inflammatory drugs (NSAIDs) are examples of peripheral analgesics [2], since they block both isoforms COX-1 and COX-2 of the enzyme cyclooxygenase (COX).

Acetylsalicylic acid (aspirin), for instance, binds irreversibly to the COX enzyme via an acetylation reaction [3, 4], such that the production of pain-inducing mediators that act on nerve cells is halted. Other NSAIDs such as indomethacin or ibuprofen produce a reversible inhibition [5], competing with arachidonic acid for the active site of the enzyme. This pain-inducing mechanism has been actively studied and recently, it has been shown [6] that it is not a nerve signal but a signal transported in the bloodstream that triggers the central nervous system to produce molecules such as interleukin-1b and release them into the cerebrospinal fluid. Interleukin- 1b causes nerve cells to start producing COX, thereby initiating pain signal within the nervous system.

When NSAIDs are injected directly into the cerebrospinal fluid, they inhibit COX there and make the inflammation less painful. Accordingly, this class of painkillers had heretofore been thought to work exclusively outside the brain and should now be specifically designed to penetrate into the brain. Although many of the NSAIDs possess analgesic and anti-inflammatory properties, some of them have been used for the treatment of Alzheimer's disease [7] and also as anti-cancer agents [8, 9]. Given the importance of these drugs, that synthesizing new oxadiazole derivatives with analgesic and anti-inflammatory activities, for instance, 3-[3-(phenyl)-1, 2, 4-oxadiazol- 5-yl] propionic acid (POPA) has shown to possess both properties [10].

EXPERIMENTAL PROCEDURE: A series of N-substituted-pthalimides were synthesized for the purpose of determining the analgesic activity. The compounds were synthesized using phthalic anhydride and various appropriate amines in microwave and reflux synthesizer.



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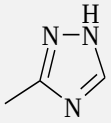	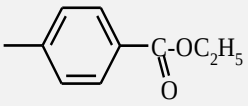	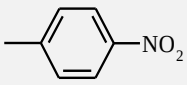	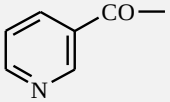	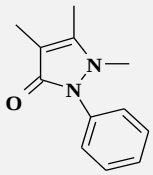	- CH_2COOH

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.

General procedure for synthesis of compounds 2-5: Phthalic anhydride **1** (3g; 20.4 mmol), selected amine (4.0 mmol), in 15-20 ml of glacial acetic acid medium, were refluxed for 2-3h. After cooling the precipitate was filtered off, washed with water and then recrystallized from appropriate solvent (**Table 1**).

General procedure for synthesis of compounds 6 and 7: Phthalic anhydride **1** (0.005 mole) was reacted with an equimolar amount of amino acid in distilled water in microwave synthesizer. The mixture was heated at 450 watt, for 3-15 minutes. The reaction was monitored using the technique of Thin layer Chromatography. The product was recrystallized from hot water (**Table 1**).

Pharmacology: N-substituted pthalimido analogues **2-7** were tested for analgesic properties and found to possess such activities. The results are shown in **Table 2** and **3**.

CNS Activity Screening Tests:

- **Analgesic activity:** The experiments were performed on male albino mice (15-18 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 of 4 animals. The tested compounds were administered intraperitoneally (*ip*) 30min before the test, in a solution of 1% carboxy methyl cellulose (CMC), in constant volume of(0.15-0.18) ml/kg . Controls received the same volume of the solvent. 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 pain and in hot-plate test **(Tables 2** and **3**).

TABLE 1: PHYSICAL AND ANALYTICAL ANALYSIS DATA OF PTHALIMIDE DERIVATIVES 2-7

Compounds	M. F. (M.Wt)	Re. Solvent	M.P C^{O}	Yield %	R.f cm	IR(KBr) cm^{-1}
2-(3H-1,2,4-Triazole-3-y)isoindoline-1,3-dione **2**	$C_{10}H_6O_2N$ (214)	EtOH	354-357	40 %	0.5	2850… N-H 1750…. C=O (imide) 1250-1350… C-N 1450-1550…. C=C
Ethyl-4 (1,3-dioxoisoindoline-2-yl) benzoate **3**	$C_{17}H_{13}O_4N$ (295)	EtOH	156-158	86%	0.8	3400… CH(ester). 1700… C=O 1350-1450… C=C 1600..C=O(COOH) 1300.. C-O,1250… C-N
2-(4-nitrophenyl) isoindoline-1,3 dione **4**	$C_{14}H_8O_4N_2$ (268)	EtOH	273-275	90%	0.8	1740… C=O(imide) 1350. N-C,1350… N-O
pyridine-3-yl carbonyl)-1H-isoindole-1,3- dione **5**	$C_{14}H_8O_3N_2$ (252)	Hexan	140-142	20%	0.3	1650… C=O 1770… C=O (imide) 1250-1490C-C-Ar 550-900… C-C-H,C-C=N,N-C-H.C-N-C(Ar)
2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-1H-isoindole-1,3(2H)-dione **6**	$C_{19}H_{18}O_3N$ (309.8)	EtOH	219 - 220	68.1	0.22	1650… C=O 1770…C=O (imide) 550-900 C-C-H,C-C=N,N-C-H.C-N-C(Ar)
(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl) acetic acid **7**	$C_{10}H_9O_4N$ (207.9)	H_2O	236-238	63.6	0.6	3100 O-H, 2600 C-H 1600 C=O, 1700 C=O

TABLE 2: ANALGESIC ACTIVITY OF PTHALIMIDE DERIVATIVES (2-7) BY HOT PLATE TEST

		Reaction time (sec)	
Compound	**Dose (250mg/kg)**	**Reaction time (sec)**	**Average reaction time**
Control	1% CMC	8 6 7 6	6.5
2		14 9 13 13	12.75*
3		11 9 10 12	12.75*
4		10 11 15 14	10.5*
5		10 11 15 14	12.5*

6		10 12 14 16	12
7		10 11 14 15	12.5*

Dose: 250 mg/ kg body wt. for standard and test compounds. * significantly different from control on hot plate test. The given compounds showed significant analgesic effect comparable with control and standard compounds.

TABLE 3: ANALGESIC ACTIVITY OF PTHALIMIDE DERIVATIVES (2-7) BY ACETIC ACID INDUCED PAIN

Compounds	Dose (250mg/kg)	No. of writhing reflux	Inhibition of writhing (%)
Control	=	50 52 90 50	- - - -
Aspirin	=	19 12 36	59.20 N S 74* 38.20 N S
2	=	5 8 12	90* 91.10* 76*
3	=	7 15 10	86* 83.34* 80*
4	=	6 4 5	88* 95.56* 90*
5	=	13 32 16	75* 64.67N S 68*
6	=	7 13 15	86* 75* 83.34*
7	=	8 10 16	91.10* 80* 68

N.S no significant; *significantly different from control

CONCLUSION: It is less likely that the present pthalimides have much effect on the central nervous system, further experiments using different models of analgesia are required to place the present compounds in their most appropriate category. A novel series of pthalimide derivatives incorporating active appropriate amine have been successfully synthesized and tested for analgesic activity. Compound **2-7** were found to be most active compared to the control. It may conclude, it was found that the compounds **2**, **4** and **7** displayed best activity in different models of analgesia than the control and the standard (aspirin).

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