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Analgesic and anti-inflammatory activity of 3-methoxy-5-nitro-2-(1',3',4'-oxadiazolyl,1',3',4'-thiadiazolyl and 1',2',4'-triazolyl)benzofurans

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ABSTRACT

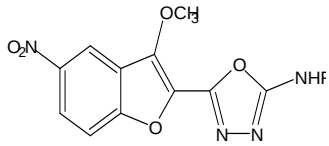
The analgesic and anti-inflammatory activity of title compounds was determined by thermal stimulus (tail flick) method and rat paw edema measurement using plethysmographic method respectively. Analgin and aspirin were used as standard drugs while testing analgesic activity and phenylbutazone was the standard drug used for the comparison of the potency of test compounds for their formalin induced anti-inflammatory activity. The title compounds have shown encouraging analgesic activity. Their analgesic potency has been found to be equal to that of a standard drug. The analgesic activity of remaining compounds is found to be moderate. The anti-inflammatory activity results indicate that some compounds are equally active and comparable with standard phenylbutazone. Other compounds have been found to be either moderately or poorly active. These experiments were carried with the permission of Institutional animal ethics registration No. 34800/2007/CPCSEC. 1-8-2001.

Keywords: Benzofuran, oxadiazole, thiadiazole, triazole, analgesic, anti-inflammatory.

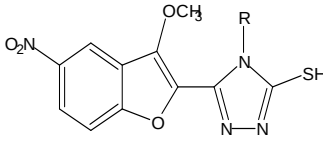
INTRODUCTION

Biheterocycles containing oxadiazole, thiadiazole and triazole are known to possess diverse biological property[1-4]. Such biheterocycles coupled with benzofuran ring have shown good anti-inflammatory and analgesic activity[5]. Some of the naphthofurans coupled with these heterocycles are reported to be bioactive compounds[6,7]. Natural benzofuran derivatives like codeine are known for their analgesic activity[9]. Benzofurans containing amynopyrazoles[9] ring,

benzofuran[2,3-c]pyridines[10,11] benzofuran containing alkylamino side-chain[12] have been found to possess analgesic activity and several benzofurocarboxamide derivatives have also been reported to possess analgesic activity[13]. Numerous synthetic benzofuran derivatives have been found to possess anti-inflammatory activity also. Some of the benzofuran derivatives reported from our laboratory have shown very good anti-inflammatory activity[14]. Encouraged by the results a new series of benzofuran derivatives have been synthesised[15] and tested for their analgesic and anti-inflammatory activity. The present report consists of Pharmaceutical activities of the new series.



1a-e



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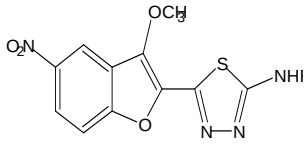

2a-e

Sl. No	Compound	Substituent 'R'
1	1a	C_6H_5
2	1b	C_6H_4. CH_3(p)
3	1c	C_6H_4. OCH_3(p)
4	1d	C_6H_4. Br(p)
5	1e	C_6H_4. Cl(p)
6	2a	C_6H_5
7	2b	C_6H_4. CH_3(p)
8	2c	C_6H_4. OCH_3(p)
9	2d	C_6H_4. Br(p)
10	2e	C_6H_4. Cl(p)
11	3a	C_6H_5
12	3b	C_6H_4. CH_3(p)
13	3c	C_6H_4. OCH_3(p)
14	3d	C_6H_4. Br(p)
15	3e	C_6H_4. Cl(p)

Analgesic Activity

The analgesic activity, in the present study was determined by tail-flick method and the results were compared with that of a standard drug. Suspensions of analgin and aspirin containing 10 mg/ml of drug were prepared in 2% gum acacia and used as standard drugs at a dose of 100 mg/kg body weight of test animal. The suspensions of test compounds were also prepared in 2% gum acacia at a concentration of 10 mg/ml and the dose administered was 100 mg/kg body weight of test animals.

Method of Testing

Albino mice of either sex were used for testing. The mice weighing between 20-25 grams, which show positive response were selected and divided into groups of four mice in each group. The first group served as control and received 2% gum acacia suspension. Second and third groups served as standards and received aspirin and analgin respectively at a dose of 100 mg/kg body weight orally. The remaining groups received compounds under investigation at a dose of 100 mg/kg body weight of mice orally. The tail of these treated mice was dipped (upto 5cm) in a water bath maintained at a constant temperature of 55 ^{o}C (± 0.7). the time taken to withdraw the

tail clearly out of water was considered as the reaction time with the cut off time being 10-12 seconds. The initial reading was taken immediately after drug administration and afterwards at the intervals of 30, 60 and 90 minutes. The results were recorded and are presented in the table-1.

Table-1: Results of Analgesic activity

Comp	Substituent 'R'	Dose Mg/kg	Average (+ SE) reaction time (Sec)after Drug treatment (min)			
			0	30	60	90
1a	C_6H_5	100	3.25 (±0.47)	4.00 (±0.25)	4.25 (±0.00)	4.25 (±0.00)
1b	C_6H_4. CH_3(p)	100	3.00 (±0.40)	4.00 (±0.70)	3.00 (±0.40)	3.00 (±0.40)
1c	C_6H_4. OCH_3(p)	100	3.25 (±0.40)	4.25 (±0.25)	7.25 (±0.25)	8.00 (±0.25)
1d	C_6H_4. Br(p)	100	2.75 (±0.25)	3.50 (±0.25)	4.25 (±0.25)	8.00 (±0.40)
1e	C_6H_4. Cl(p)	100	3.75 (±0.47)	5.75 (±0.25)	9.00 (±0.00)	8.75 (±0.40)
2a	C_6H_5	100	3.25 (±0.25)	2.50 (±0.00)	3.00 (±0.25)	4.25 (±0.40)
2b	C_6H_4. CH_3(p)	100	3.25 (±0.25)	3.25 (±0.40)	4.75 (±0.47)	5.25 (±0.47)
2c	C_6H_4. OCH_3(p)	100	2.75 (±0.25)	6.25 (±0.25)	9.50 (±0.40)	9.50 (±0.40)
2d	C_6H_4. Br(p)	100	3.25 (±0.40)	4.25 (±0.25)	7.25 (±0.25)	8.00 (±0.25)
2e	C_6H_4. Cl(p)	100	3.00 (±0.40)	3.25 (±0.25)	6.00 (±0.40)	6.25 (±0.25)
3a	C_6H_5	100	3.00 (±0.21)	3.25 (±0.25)	4.00 (±0.40)	6.25 (±0.25)
3b	C_6H_4. CH_3(p)	100	2.75 (±0.25)	3.25 (±0.25)	5.75 (±0.25)	4.00 (±0.00)
3c	C_6H_4. OCH_3(p)	100	3.25 (±0.40)	5.25 (±0.25)	7.25 (±0.40)	9.25 (±0.25)
3d	C_6H_4. Br(p)	100	3.00 (±0.40)	2.75 (±0.25)	3.00 (±0.00)	3.75 (±0.40)
3e	C_6H_4. Cl(p)	100	3.00 (±0.25)	3.25 (±0.05)	6.00 (±0.40)	7.00 (±0.25)
Control	2% gum Acacia	100	3.00 (±0.00)	3.00 (±0.00)	3.00 (±0.00)	3.00 (±0.00)
Analgin	Standard	100	3.00 (±0.22)	6.25 (±0.25)	10.5 (±0.40)	10.5 (±0.25)
Aspirin	Standard	100	3.00 (±0.00)	5.25 (±0.25)	8.25 (±0.40)	8.25 (±0.25)

Anti-inflammatory Activity

The anti-inflammatory activity was assessed by rat paw edema method wherein the procedure of plethysmographic measurement of edema produced by planter injection of 1% w/v formalin in the hind paw of the rat was followed. The method described by Wilhelm and Domenoz[16] as modified by Sisodia and Rao[17] was used for measuring the paw volume. Suspension of phenylbutazone containing 40 mg/ml of drug was prepared in 2% gum acacia and used as

standard drug. Suspensions of test compounds at a concentration of 40 mg/ml were also prepared in 2% gum acacia. The dose concentration of both standard drug and the test compounds was 100 mg/kg body weight. 1% w/v of formalin solution prepared and 0.1 ml of it in each case was injected in the planter region of left hind paw of albino rats.

Table-2: Results of Anti-inflammatory Activity

Comp	Constituent 'R'	Dose Mg/kg	Mean value (+S.E) of edema Volume at different intervals		Percentage of inhibition At Different intervals	
			2^{nd} Hour	4^{th} hour	2^{nd} Hour	4^{th} hour
1a	C_6H_5	100	1.35 (±0.002)	1.31 (±0.001)	12.67	20.60
1b	C_6H_4. CH_3(p)	100	1.46 (±0.015)	1.33 (±0.002)	16.66	19.33
1c	C_6H_4. CH_3(p)	100	1.14 (±0.001)	0.90 (±0.003)	34.95	45.45
1d	C_6H_4. Br(p)	100	1.52 (±0.032)	1.43 (±.0.003)	13.24	13.33
1e	C_6H_4. Cl(p)	100	1.61 (±0.015)	1.41 (±0.026)	18.10	14.54
2a	C_6H_5	100	1.65 (±0.601)	1.55 (±0.005)	15.82	16.60
2b	C_6H_4. CH_3(p)	100	1.41 (±0.002)	1.31 (±0.002)	19.46	20.46
2c	C_6H_4. CH_3(p)	100	1.11 (±0.001)	0.99 (±0.006)	36.64	40.00
2d	C_6H_4. Br(p)	100	1.31 (±0.003)	1.01 (±0.001)	25.22	38.78
2e	C_6H_4. Cl(p)	100	1.52 (±0.005)	1.40 (±0.004)	13.24	15.15
3a	C_6H_5	100	1.40 (±0.002)	1.38 (±0.002)	13.24	16.36
3b	C_6H_4. CH_3(p)	100	1.35 (±0.003)	1.25 (±0.005)	22.94	24.20
3c	C_6H_4. CH_3(p)	100	1.31 (±0.004)	1.11 (±0.001)	22.22	32.72
3d	C_6H_4. Br(p)	100	1.45 (±0.004)	1.3 (±0.002)	17.23	21.21
3e	C_6H_4. Cl(p)	100	1.60 (±0.032)	1.45 (±0.003)	18.67	12.12
Control	2% gum Acacia	100	1.752 (±0.0072)	1.65 (±0.0128)	--	--
Phenyl butazone	Standard	100	1.01 (±.001)	0.88 (±0.002)	42.35	46.60

Method of testing

Albino rats of either sex weighing 150-200 grams were used and divided into groups of six albino rats in each group. First group served as control, second group was used for standard drug phenylbutazone and the remaining groups served for compounds under investigation. An identification mark was made on both the hind paws just beyond tibiotorsal junction so that every time the paw was dipped in mercury column upto a fixed mark to ensure constant paw

volume. Immediately after 30 minutes of drug administration, 0.1 ml of 1% w/v formalin was injected in the planter region of left paw of the rats. The right paw was used as reference for non inflammated paw for comparision. The paw volume of all the test animals was measured after 2^{nd} and 4^{th} hours of drug administration. The percentage of increase in edema over the initial reading was also calculated. The increase in edema of animals treated with standard test compounds were compared with the increase in the edema of untreated control animal with the corresponding intervals of 2^{nd} and 4^{th} hours. Thus the percentage inhibition of edema at known intervals in treated animals was calculated as given below.

$$\text{Percentage inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

Where Vc = volume of paw edema in control animals
Vt = volume of paw edema in treated animals

The results were noted and are presented in the table-2

RESULTS

From the results of analgesic activity given in the table-1, it can be concluded that compounds 1c, 1d, 1e, 2c, 2d and 3c have shown challenging activity when compared with the standards. The compounds 2e and 3e have also shown very good analgesic property. The remaining compounds viz.,1a, 2b, 3a and 3b were moderately active and the remaining compounds were poorly active. The results of anti-inflammatory activity reveal that percentage inhibition of edema of compound 1c is equal to that of standard at the 4th hour after drug administration. The percentage inhibition of edema shown by 2c and 2d at 2^{nd} and 4^{th} hour after drug administration is also good. Compounds 1a, 3a, 3b, 2b, 3c and 3d were moderately active. The remaining compounds were poorly active as anti-inflammatory agents.

CONCLUSION

Based on the results summarized above it can be concluded that biheterocycles of benzofuran coupled with 1, 3, 4-oxadiazole, 1, 3, 4-thiadizole and 1, 2, 4-triazole are pharmacologically active molecules. The presence of methoxy group at 3^{rd} position and an electron withdrawing nitro group ($-NO_2$) present at the 5^{th} position of benzofuran moiety might have influenced the potency of molecule in general and it is quite clear that the presence of paramethoxy, parabromo, to that extent parachloro substituted R functions at 2^{nd} position of 1,3,4-oxadizole and 5^{th} positon of triazole moieties might be responsible for the enhanced activity in comparision of other compounds their category in particular. Most of the 1,3,4-thiadiazole were moderately active but only the p-methoxyaminophenyl substituted biheterocycle has shown good activity, both as analgesic and anti-inflammatory agent.

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