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Antiinflammatory and analgesic potentiation effects of some Imidazolyl-l-(aryl/substituted aryl) esters

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Imidazolyl-l-(aryl/substituted aryl) ester have been synthesised and evaluated for biological activity. The tri-substituted products of this series have been found to be potent analgesics as compared to other compounds. In anti-inflammatory activity screening, some compounds showed pronounced activity.

THE purine ring system is undoubtedly among the most ubiquitous of all the heterocyclic compounds [1,2]. Profound analgesia was shown by various heterocycles. Recent literature is enriched with findings about the synthesis and pharmacological screening of fused heterocycles. The 1H-Imidazole nucleus is associated with diverse pharmacological activities such as antiinflammatory, analgesic and tranquilizing effect[3-6]. Further more, several other reports have also pointed out that a slight variation in substitution pattern of phenol, propionic and acetic acid nuclei causes a measurable difference in activity.[7,8]

These findings focused particular interest to incorporate imidazole, propionic/acetic acids and phenols in one framework with the hope to make the available for biological activity. The structure of resulting products, Imidazolyl-l-(aryl/substituted aryl) propionates/acetates was assigned by microanalytical and spectral evidances.

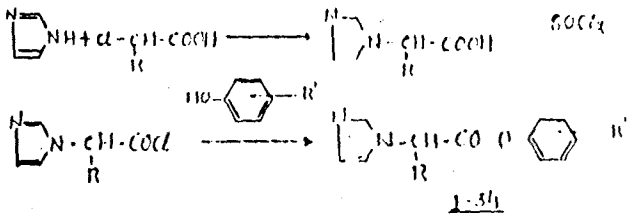
MATERIAL AND METHODS

Animals: Albino Rats (100-130g) of either sex supplied by a local breeder were used. The rats were kept under standard conditions. The food and water were withdrawn 24 hrs before the start of the experiments.

Standard Drugs : The standard drugs used for comparing with the test compounds were acetyl salicylic acid and phenylbutazone for analgesic and Antiinflammatory activities respectively. These drugs were given, i.p., as solutions in distilled water.

A series of imidazolyl-l-(aryl/substituted aryl) propionates and acetates were synthesised starting with imidazole and α-chloropropionic/acetic acids (0.558 mole), followed by $SOCl_2$ treatment to yield requisite imidazolyl-l-propionyl/acetyl chlorides.[9] Finally these chlorides were condensed with different substituted phenols to afford the final products (1-34). The Ir spectra recorded in KBr (cm^{-1}) on an Acculab-10 spectrophotometer. ^{1}H-nmr spectra in DMSO- d_6 on a varian CFT-20 instrument using trimethyl silane (TMS) as an internal standard. The purity of compounds was monitored by TLC. Physical and spectral data of the compounds (1- 34) are given in **Table-1**.

The Scheme-I outlines the synthetic part of the present work -



*For Correspondence

Table - 1: Pharmacological Activity of imidazolyl-l-(aryl/substituted aryl) propionates and acetates

Compound No.	R	R'	PA4 Analgesic activity	% Inhibition of paw volume
1.	CH_3	2,4,6-NO_2	158.29	9.67
2.	H	2,4,6-NO_2	165.90	26.30
3.	CH_3	2-NO_2	115.57	11.32
4.	H	2-NO_2	140.32	10.63
5.	CH_3	3-NO_2	140.82	10.52
6.	H	3-NO_2	110.35	12.13
7.	CH_3	4-NO_2	111.35	10.03
8.	H	4-NO_2	113.42	13.23
9.	CH_3	2,4,6-Cl	155.76	30.57
10.	H	2,4,6-Cl	168.38	10.03
11.	CH_3	2,4-Cl	110.32	25.09
12.	H	2,4-Cl	130.83	20.97
13.	CH_3	2-Cl	135.35	10.35
14.	H	2-Cl	140.52	19.83
15.	CH_3	3-Cl	109.39	12.09
16.	H	3-Cl	120.86	10.25
17.	CH_3	4-Cl	115.58	9.99
18.	H	4-Cl	125.37	16.02
19.	CH_3	2,4,6-Br	137.58	30.20
20.	H	2,4,6-Br	187.55	35.68
21.	CH_3	2-Br	125.57	9.20
22.	H	2-Br	140.83	20.52
23.	CH_3	3-Br	127.27	17.70
24.	H	3-Br	150.03	25.02
25.	CH_3	4-Br	104.78	17.09
26.	H	4-Br	120.53	32.05

Compound No.	R	R'	PA4 Analgesic activity	% Inhibition of paw volume
27.	CH_3	2-Me	103.40	15.92
28.	H	2-Me	109.93	12.07
29.	CH_3	3-Me	105.86	20.59
30.	H	3-Me	104.36	10.32
31.	CH_3	4-Me	109.78	6.39
32.	H	4-Me	103.93	10.02
33.	CH_3	—	109.83	9.20
34.	H	—	115.90	11.90
Standard	—	—	204.61	45.45

The melting points were taken in a melting point apparatus (Toshniwal, Indian) and are uncorrected.

Microanalytical results obtained for C, H and N were within ± 0.04-0.06% of the theoretical values.

Analgesic Activity

Test for analgesic activity was performed by using the hot plate technique[10,11]. Albino rats (100-130 g) were divided into three groups, each of four rats. A group of rats were treated intrapertioneally (i.p.) with 50 mg/kg body weight of the aqueous suspension (with few drops of Tween-80) of the test compounds. Another group was administered i.p. 30 mg/kg body weight of acetyl salicylic acid (ASA) and the third group (control group) was fed with the same volume of distilled water. The rats were placed on a hot plate maintained at the temperature of 55 ± 0.5°. The time between placing the rat on the hot plate and beginning of licking the paw was considered as reaction time. The reaction time was recorded at 15 min intervals upto 45 minutes. The percent analgesic activity (PAA) was calculated using the following formula;

$$PAS = \frac{T_2}{T_1} x100$$

Where, T_1 = Reaction time (sec) before test compound's administration.

T_2 = Reaction time (sec) after test compound's administration.

Antiinflammatory Activity

Antiinflammatory activity was measured using the carrageenan- induced paw odema test in rats[12]. Albino rats (100-130 g) were divided into three groups each consisting of four rats. A group of rats was treated i.p. with 50 mg/kg body weight of the aqueous suspension of the test compounds. Another group was administered i.p. 30 mg/kg body weight of aqueous suspension of phenylbutazone and the third group was fed with the same volume of distilled water. After one hr. the animals were injected with 0.05 ml suspension of carrageenan (1.0 percent in 0.9 percent saline) in the right hind paw planter apponeurosis. The measurements of the paw volume were made using the mercury displacement technique with the help of a plethysmometer immediately before and 1,2,3,4,5 h., after the carrageenan injection. The percent inhibition of inflammation after 5 h was calculated by the method of Newbould[13], using the following formula;

$$\text{Percent Inhibition I} = 100\left[1-\frac{a-x}{b-y}\right]$$

Where,

x = Mean paw volume of rats before the administration of carrageenan injection in the test and the standard groups.

a = Mean paw volume of rats after the administration of carrageenan and test compound or standard compound.

y = Mean paw volume of rats before the administration of carrageenan injection in the control group.

b = Mean paw volume of rats after the administration of carrageenan injection in the control group.

RESULTS AND DISCUSSION

The results are presented in Table-1. The results show that the substitution of tribromo, trichloro and trinitro in the aromatic ring of the products 20, 10 and 2 is responsible for analgesic activity. The propionyl series of the nitro and trichloro were less active, whereas, the tribromo propionyl exhibited further reduction in analgesic potential.

Tribromo acetyl derivative 20 showed better anti-inflammatory activity, whereas, trichloro, tribromo propionyl, 9 and 10 and p-bromo acetyl, 26 produced nearly similar action. It appears that all bromo substituted products exhibit, letter analgesic and anti-inflammatory activities, compared to other substituted products. However, the fact remains that none of the compounds made in the present investigation have showed analgesic and Antiinflammatory activities comparable to those of Acetylsalicylic Acid and phenylbutazone.

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REFERENCES

1. Hansten PD, **Drug Interaction**, Philadelphia Lea and Febiger 1971, 635.
2. Washington DC, **Evaluation of Drug Interaction**, 2nd edition American Pharmaceutical Association 1976 325.
3. Joshi K.C., Mishra R.A. & Sharma K. **J. Hetrocycl Chem**, 1989, 26, 409.
4. Naithani PK, Bhalla M, Palit G, Srivastava VK & Shankar K, **Ind J Heterocyclic Chem**, 1991, 1, 65.
5. Shealy YE, Montogomery JA & Loster WR, **J. Biochem Pharmacol**, 1962, 11, 674.
6. Yamanka H, Sakamoto Y, Shiozawa A & Adochi K, J. Pn Kokaikoho; 1979, 696, **Chem Abstr**, 1979, 91, 175325r.
7. Khuchandai ML & Srivastava SK, **Curr Sci**, 1987, 56, 264.
8. Nakanishi M, Saheki S & Tsuda A, **JPN Patent, Chem Abstr**, 1970, 73, 66336c.
9. Tatsuo H & Armold J, **J. Org. Chem**, 1975, 40, 3037.
10. Eddy NB & Leimbach D, **J. Pharm and Expt Thera**, 1953, 107, 385.
11. Cruzon G, Hutson PH & Tricklebank MD, **Br J Pharm**, 1980, 70, 44.
12. Winter CA, Risley EA and Nuss GW, **Proc Soc Expt Biol Med** 1962.
13. Newbould BB, **Br J Pharmacol**, 1963, 21, 157.