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Synthesis and pharmacological screening of some noval benzoxazole derivatives

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ABSTRACT

Benzoxazole is used primarily in industry and research, and has no household use. Benzoxazole is an aromatic organic compound with a molecular formula C_7H_5NO, a benzene-fused oxazole ring structure, and an odor similar to pyridine. Being a heterocyclic compound, benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. It is found within the chemical structures of pharmaceutical drugs such as flunoxaprofen. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for fictionalizations. In this research paper we have studied about the activities such as Anti-inflammatory activity, Analgesic activity, Microbiological screening, Anti-inflammatory activity, Analgesic activity, Microbiological screening and Anti-inflammatory activity.

Keywords: Benzoxazole, Anti-inflammatory activity, Analgesic activity, Microbiological screening, Anti-inflammatory activity, Analgesic activity etc.

INTRODUCTION

Pharmacology means study of drugs involve the understanding of its action, movement in the body, therapeutic uses, possible side effects and toxicity [1]. To produce its characteristic effects, a drug must be present in appropriate concentrations at its site of action. Although obviously a function of the amount of drug administered, the concentration of active, unbound (free) drug attained also depend upon the extent and rate of its absorption, distribution (which mainly reflects relative binding to plasma and tissue protein), metabolism (biotransformation), and excretion [2]. The pharmacological responses shown by any drug are subjected to qualitative and quantitative evaluation viz. a drug on oral administrative showed it to be a hypotensive. The activity may be due to on any one of the following sites: (1) Central nervous system, (2) Post ganglionic nerve ending, (3) Ganglia, (4) Arterioles or others. Pharmacology establishes the effect of the drug on particular site, i.e., the mode of action. It is assumed that pharmacological activity is a function of physical properties if it is a structurally non-specific drug and chemical properties well if it is a structurally specific drug. The structure is then modified in the following manner to affect the properties, (1) shifts are made in the position of functional groups, (2) valance bond are saturated, (3) acidity or basicity is modified and variations of configuration about asymmetric centers are made. A correlation between the pharmacological action and structure in a series of compounds is its structure activity relationship (SAR). A slight alteration in the structure might increase or abolish a particular effect observed in the parent molecule. [3] For all the studies on albino mice (25-30gm) of either sex were used. The drug was administered orally using suspension of drug in corboxymethyl cellulose (CMC).

All experiments were carried out with the consent of Institutional Animal Ethical Committee of Integral University (approved by CPCSEA Regd. No.- IU/Pharm/M. Pharm/CPCSEA/10/32) . In the effort of establish the effect of the synthesized compounds, the following pharmacological screening was carried out.

Anti-inflammatory activity
Analgesic activity
Microbiological screening
Anti-inflammatory activity
Analgesic activity
Microbiological screening
Anti-inflammatory activity

MATERIALS AND METHODS

Anti-inflammatory activity
Paw edema- Male or female Wistar rats with a body weight between 100 and 150 g are used. The animals are starved overnight. To insure uniform hydration, the rats receive 5 ml of water by stomach tube (controls) or the test drug dissolved or suspended in the same volume. Thirty minutes later, the rats are challenged by a subcutaneous injection of 0.05 ml of 1% solution of carrageenan into the plantar side of the left hind paw. The paw is marked with ink at the level of the lateral malleolus and immersed in mercury up to this mark. The paw volume is measured plethysmographically immediately after injection, again 3 and 6 h, and eventually 24 h after challenge. [4]

Analgesic activity
Writhing tests- Mice of either sex with a weight between 20 and 25 g are used. Phenylquinone in a concentration of 0.02% is suspended in a 1% suspension of carboxymethylcellulose. An aliquot of 0.25 ml of this suspension is injected intraperitoneally. Groups of 6 animals are used for controls and treated mice. Preferably, two groups of 6 mice are used as controls. Test animals are administered the drug or the standard at various pretreatment times prior to phenylquinone administration. The mice are placed individually into glass beakers and five min are allowed to elapse. The mice are then observed for a period of ten min and the number of writhes is recorded for each animal. For scoring purposes, a writhe is indicated by stretching of the abdomen with simultaneous stretching of at least one hind limb. The formula for computing percent inhibition is: average writhes in the control group minus writhes in the drug group divided by writhes in the control group times 100%. The time period with the greatest percent of inhibition is considered the peak time. A dose range is reserved for interesting compounds or those which inhibit writhing more than 70%. Compounds with less than 70% inhibition are considered to have minimal activity. [5]

Microbiological screening
For both antibacterial and assay compounds were dissolved in absolute ethanol (0.8 mg/ml). Further dilutions of the compounds and standard drugs in the test medium have concentrations of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 mg/ml. The minimum inhibitory concentrations (MIC) were determined using the method of two-fold serial dilution. In order to ensure that the solvent *'per se'* had no effect on bacterial growth, a control test was also performed containing inoculated broth supplemented with only ethanol at the same dilutions used in our experiments and found inactive in culture medium.

Antibacterial assay-
The cultures were obtained in Nutrient agar broth (Difco) for all the bacteria after 24 h of incubation at 37$\pm$1°C. Testing was carried out in Nutrient agar broth at pH 7.4 and the two-fold serial dilution technique was applied. The final inoculums size was 10^5 CFU/ml. A set of tubes containing only inoculated broth was kept as controls. Norfloxacine was taken as standard. After incubation for 24 h at 37$\pm$1°C, the last tube with no growth of microorganism was recorded to represent MIC expressed in mg/ml .[6]

RESULTS AND DISCUSSION

Anti-inflammatory activity-
Out of all compound studied only compound SHF-2, SHF-6, SHF-8 and SHF-9 showed appreciable anti-inflammatory activity as compared to diclofenac sodium. Compound SHF-1 and SHF-7 showed significant anti-inflammatory activity. Other compound did not produce significant anti-inflammatory activity.

Analgesic activity-
Out of all compound studied only SHF-3 and SHF-8 showed significant analgesic activity. Other compound did not produce significant analgesic activity.

Microbiological screening-
No anti-bacterial activity was found in the synthesized compound.

ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS

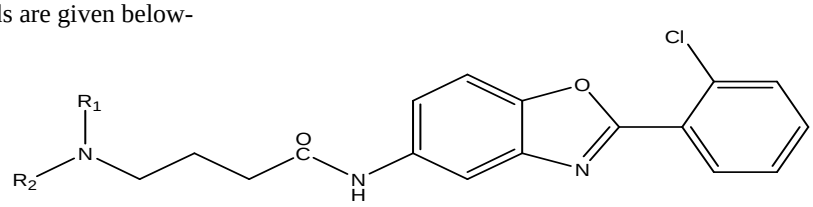
S.N.	Code No.	Dose (mg/ kg)	No. of rats	Volume in ml.				% inhibition	t- value	p- value
				(at o hour) V1	(after 3 hr) V2	change in paw vol. ΔV	Mean Increase in paw vol.±sem			
1	Control	-	1	0.70	1.15	0.45	0.400±0.020			
			2	0.85	1.25	0.40				
			3	0.70	1.10	0.40				
			4	0.65	1.0	0.35				
2	Diclo.	30	1	0.60	0.70	0.10	0.125±0.014	68.75	11.00	0.001
			2	0.65	0.75	0.10				
			3	0.55	0.70	0.15				
			4	0.60	0.75	0.15				
3	SHF-1	50	1	0.80	0.90	0.10	0.112±0.01	72	12.01	0.001
			2	0.60	0.75	0.15				
			3	0.80	0.90	0.10				
			4	0.60	0.70	0.10				
4	SHF-2	50	1	0.60	0.80	0.20	0.212±0.12	47	7.83	0.001
			2	0.50	0.75	0.25				
			3	0.65	0.85	0.20				
			4	0.70	0.80	0.20				
5	SHF-3	50	1	0.70	0.80	0.10	0.187±0.03	53.25	5.67	0.001
			2	0.65	0.75	0.20				
			3	0.75	0.95	0.20				
			4	0.55	0.80	0.25				
6	SHF-4	50	1	0.60	0.90	0.30	0.350±0.05	t- test failed		
			2	0.70	1.20	0.50				
			3	0.60	0.90	0.30				
			4	0.60	0.90	0.30				
7	SHF-5	50	1	0.60	0.70	0.10	0.125±0.014	68.75		
			2	0.65	0.75	0.15				
			3	0.55	0.70	0.15				
			4	0.60	0.75	0.15				
8	SHF-6	50	1	0.70	0.85	0.15	0.150±0.02	62.5	8.66	0.001
			2	0.80	1.0	0.20				
			3	0.65	0.75	0.10				
			4	0.70	0.85	0.15				
9	SHF-7	50	1	0.60	0.75	0.15	0.112±0.012	72	12.01	0.001
			2	0.65	0.75	0.10				
			3	0.55	0.65	0.10				
			4	0.65	0.75	0.10				
10	SHF-8	50	1	0.50	0.65	0.15	0.137±0.02	65.75	8.34	0.001
			2	0.45	0.65	0.20				
			3	0.65	0.75	0.10				
			4	0.65	0.75	0.10				
11	SHF-9	50	1	0.60	0.05	0.10	0.062±0.012	84.5	14.00	0.001
			2	0.75	0.05	0.15				
			3	0.60	0.05	0.15				
			4	0.75	0.10	0.15				

Analgesic activity of synthesized compounds

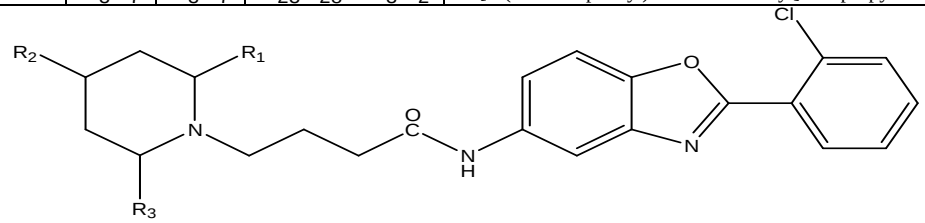
S.N.	Code No.	Dose (mg/ kg)	No. of mice	No. of writhing in mice (after 20 min.)	Mean Writhing	% inhibition	t- value	p- value
1	Control	-	1	16	15	-		
			2	15				
			3	15				
			4	14				
2	Aspirin	30	1	6	5.50	63.33	19.00	0.0001
			2	5				
			3	6				
			4	5				
3	SHF-1	50	1	10	10	33.33	8.66	0.0001
			2	11				
			3	9				
			4	10				
4	SHF-2	50	1	6	6	60	15.59	0.0001
			2	7				
			3	5				
			4	6				
5	SHF-3	50	1	12	11	26.66	6.92	0.0004
			2	11				
			3	11				
			4	10				
6	SHF-4	50	1	13	12	20	5.1962	0.002
			2	11				
			3	12				
			4	12				
7	SHF-5	50	1	15	14.75	1.66	.3333	.7502
			2	15				
			3	16				
			4	13				
8	SHF-6	50	1	12	11.75	21.66	5.165	0.0021
			2	11				
			3	11				
			4	13				
9	SHF-7	50	1	7	6.5	56.66	17	0.0001
			2	6				
			3	7				
			4	6				
10	SHF-8	50	1	14	14	6.66	1.7321	.1340
			2	15				
			3	14				
			4	13				
11	SHF-9	50	1	8	8.25	45	10.72	0.0001
			2	7				
			3	9				
			4	9				

CONCLUSION

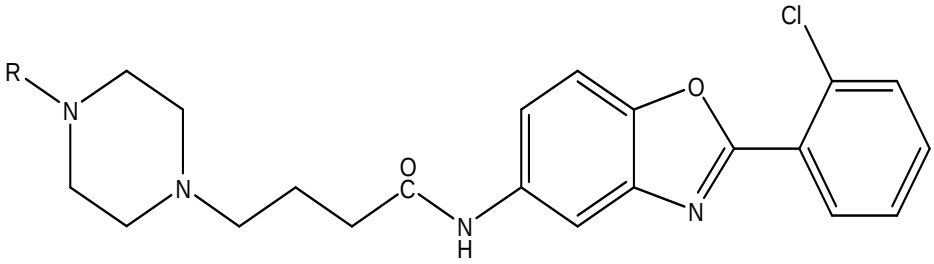
In an approach to synthesize some potent benzoxazole derivatives, some compounds were synthesized. The details of these compounds are given below-

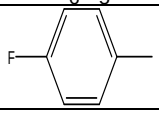


S.N.	CODE NO.	R_1	R_2	MOLECULAR FORMULA	CHEMICAL NAME
1	SHF-8	C_3H_7	C_3H_7	$C_{23}H_{28}ClN_3O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4-dipropylamino-butyramide



S.N.	CODE NO.	R_1	R_2	R_3	MOLECULAR FORMULA	CHEMICAL NAME
2	SHF-1	H	CH_3	H	$C_{23}H_{26}ClN_3O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4(4-methyl piperidine-1-yl)-butyramide
3	SHF-2	CH_3	H	H	$C_{23}H_{26}ClN_3O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4(2-methyl piperidine-1-yl)-butyramide
4	SHF-3	H	H	H	$C_{22}H_{24}ClN_3O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4-piperidine-1-yl-butyramide
5	SHF-4	CH_3	H	CH_3	$C_{24}H_{28}ClN_3O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4(2,6-dimethyl piperidine-1-yl)-butyramide



S.N.	CODE NO.	R	MOLECULAR FORMULA	CHEMICAL NAME
6	SHF-5	C_2H_5	$C_{23}H_{27}ClN_4O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4(4-ethyl piperazine-1-yl)-butyramide
7	SHF-6	CH_3	$C_{22}H_{25}ClN_4O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4(4-methyl piperazine-1-yl)-butyramide
8	SHF-7	C_6H_5	$C_{27}H_{27}ClN_4O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4(4-phenyl piperazine-1-yl)-butyramide
9	SHF-9		$C_{27}H_{26}ClFN_4O_2$	N-[2-(2-Chlorophenyl)-benzoxazole-5yl]-4-[4-(4-fluoro phenyl] piperazine-1-yl)-butyramide

The structures were confirmed using IR and NMR spectroscopy. The potency of synthesized compounds were established using following pharmacological screening-

Analgesic activity

Paw edema- Male or female Wistar rats with a body weight between 100 and 150 g are used. The animals are starved overnight. To insure uniform hydration, the rats receive 5 ml of water by stomach tube (controls) or the test drug dissolved or suspended in the same volume. Thirty minutes later, the rats are challenged by a subcutaneous injection of 0.05 ml of 1% solution of carrageenan into the plantar side of the left hind paw. The paw is marked with ink at the level of the lateral malleolus and immersed in mercury up to this mark. The paw volume is measured plethysmographically immediately after injection, again 3 and 6 h, and eventually 24 h after challenge. [3]

Analgesic activity

Writhing tests- Mice of either sex with a weight between 20 and 25 g are used. Acetic acid in a concentration of 1% (1ml/kg) is used to produce writhing. An aliquot of 0.025 ml of this suspension is injected intraperitoneally. Groups of 6 animals are used for controls and treated mice. Preferably, two groups of 6 mice are used as controls. Test animals are administered the drug or the standard at various pretreatment times prior to Acetic acid administration. The mice are placed individually into glass beakers and five min are allowed to elapse. The mice are then observed for a period of ten min and the number of writhes is recorded for each animal. For scoring purposes, a writhe is indicated by stretching of the abdomen with simultaneous stretching of at least one hind limb. The formula for

computing percent inhibition is: average writhes in the control group minus writhes in the drug group divided by writhes in the control group times 100%. The time period with the greatest percent of inhibition is considered the peak time. A dose range is reserved for interesting compounds or those which inhibit writhing more than 70%. Compounds with less than 70% inhibition are considered to have minimal activity. [4]

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