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Research Article

SYNTHESIS AND PHARMACOLOGICAL SCREENING OF NOVEL SUBSTITUTED BENZOXAZOLE DERIVATIVES AS AN ANTI-INFLAMMATORY AGENTS

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ABSTRACT

New series of derivatives of benzoxazole have been found to exhibit a wide variety of pharmacological activities. In the current research work, the title compounds were synthesized from 2-amino-5-substitutedphenolon cyclization with cyanogen bromide in methyl alcohol formed 2-amino benzoxazole derivatives.The identification and characterization of all the synthesized compounds were confirmed by melting point, thin layer chromatography, FT-IR, 1H NMR and mass spectral data. These newly synthesized compounds were evaluated for their anti-inflammatory activity by carrageenan-induced paw edema method. The results showed that, compounds IIIB and IIIA were significantly reduced the inflammation there by showed a promising anti-inflammatory activity whereas the compound IIID-IIIF moderately reduced the inflammation. Only the two compounds IIIC and IIIE showed very poor anti-inflammatory activity towards Carrageenan – induced paw edema rat.

Keywords: Benzoxazoles, Anti-inflammatory activity, Carrageenin-induced paw edema.

INTRODUCTION

A large number of substitutions have been incorporated in benzoxazole to produce therapeutically interesting drug candidates and these hybrid molecules exert remarkable biological and pharmacological potentials. The small and simple benzoxazole nucleus is present in compounds involved in research aimed at evaluating new products that possess biological activities, such as anticancer[7-10], antimicrobial[11], antifungal[12] and anti-inflammatory[13].

Anti-inflammatory drugs, presently available for the treatment of various inflammatory disorders, have one or more adverse and undesirable side-effects (Flower et al., 1980). Therefore, an attempt was made to search for synthetic-based anti-inflammatory products reputed to have beneficial effects for rheumatic disorders.

In the present work, we report the synthesis of new heterocyclic compound, 6-substituted-N-(4, 5-dihydro-1H-imidazol-2-yl)benzo[d]oxazol-2-amine and its derivatives. Anti-inflammatory activity of the compounds was evaluated and discussed.

MATERIALS AND METHODS

All the reagents and solvents used were of laboratory grade. All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded in potassium bromide pellets on FTIR8300 (Shimadzu) spectrometer; H-NMR spectra were recorded on AVANCE 300 MHz TMS as internal standard. Mass spectra were recorded on SHIMADZUQP2010 PLUS at IIT-Chennai. All the reactions were monitored by thin layer chromatography carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection (solvent system- toluene: ethylacetate: formic acid (5:4:1)).

Synthesis of6-substitude benzo[d]oxazol-2-amine (IA-F)

2-amino-5-substitutedphenol (0.01mol) wasdissolved in methanol (20 ml) and cooled the solution to 5ºC by adding chopped ice.A cold suspension of Cyanogenbromide (0.01mol) in methanol (20ml) was added over a period of 5min with rapid stirring. Continued the stirring for 2hrs at room temperature and neutralize with Sodium bicarbonate in small portions over a period of 30mins was added to bring the pH6.5 -7.0. Stirring was continued for another 1hour. The solid was separated by filtration, washed with cold water and on recrystallization from ethyl alcohol has resulted white solid, yield 70% m.p 238ºC. Which was purified by column chromatography on silica gel (toluene: ethyl acetate: formic acid) to give the required 6-substitude benzo[d]oxazol-2-amine.

Synthesis of dimethyl 6-substitudebenzo [d]oxazol-2-ylcarbonodithioimidate (IIA-F)

To a well stirred ice cold solution of IA-F (0.01mol) in Dimethyl formamide (DMF) 10ml, were added Carbon disulphide (0.01mole) and methyl iodide (0.01mole) in sequence at an interval of 30 min and stirring was continued for 3hrs. The mixture was then poured in ice cold water and the resulting solid was washed with water and recrystalised from ethanol.

Synthesis of 6-substitude-N-(4,5-dihydro-1H-imidazol-2-yl)benzo [d]oxazol-2-amine (IIIA-F)

To a solution of step –IIA-F (0.01mole) in dimethyl formamide (DMF) 15ml was added solution of ethylene diamine (0.01mole) in (DMF) 15ml with stirring at room temperature. The reaction mixture was refluxed for 8hrs. The mixture was poured on crushed ice. The resulting solid was dried and recrystalised from ethanol.

N-(4, 5-dihydro-1H-imidazol-2-yl)-6-fluorobenzo[d]oxazol-2-amine (IIIA)

Yield: 74%, m.p.214 ºC, IR (KBr): 751.18 (C-Fstr),3479 (NH str), 3084(Ar-CH str),1148 (C-N str), 1718 (cyclicC=O str).1H-NMR (DMSO)(δppm): 6.67-8.87 (m, 12H, Ar-CH), 2.2-3.5(s, 2H,CH), 3.5(2H, Methylene). EI-MSm/z: 427.

6-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)benzo[d]oxazol-2-amine (IIIB)

Yield: 70%, m.p.217 ºC, IR (KBr): 811 (C-Clstr),3430 (NH str), 3091(Ar-CH str),1206 (C-N str), 1624 (C=O str).1H-NMR (DMSO)(δppm): 6.67-8.87 (m, 12H, Ar-CH), 2.1-3.5(s, 2H,CH), 3.5(2H, Methylene). EI-MSm/z: 451.

6-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)benzo[d]oxazol-2-amine (IIIC)

Yield: 65%, m.p.218 ºC, IR (KBr): 609 (C-Brstr),3385 (NH str), 3079(Ar-CH str),1857 (C=O str).1H-NMR (DMSO)(δppm): 6.67-8.87 (m, 12H, Ar-CH), 2.1-3.5(s, 2H,CH), 3.5-5.6(2H, Methylene). EI-MSm/z: 518.

N-(4, 5-dihydro-1H-imidazol-2-yl)-6-methoxybenzo[d]oxazol-2-amine (IIID)

Yield: 78%, m.p.221 ºC, IR (KBr): 2852 (C-OCH3str),3084(Ar-CH str), 1718 (C=O str).1H-NMR (DMSO)(δppm): 7-8 (m, 12H, Ar-CH),2.1-3.5(s, 2H,Hetero-CH), 3.5-4.0 (m, C-OCH3), 2.5(2H,Methylene).EI-MSm/z: 417.

N-(4, 5-dihydro-1H-imidazol-2-yl)-6-nitrobenzo[d]oxazol-2-amine (IIIE)

Yield: 61%, m.p.218 ºC, IR (KBr): 2852 (C-OCH3str),3408, 3084(Ar-CH str),1718 (cyclicC=O str).1H-NMR (DMSO)(δppm):7-8 (m, 12H, Ar-CH),2.1-3.5(s, 2H,Hetero-CH), 3.5-4.0 (m, C-OCH3), 2.5(2H,Methylene). EI-MSm/z: 423.

N-(4,5-dihydro-1H-imidazol-2-yl)-6-methylbenzo[d]oxazol-2-amine (IIIF)

Yield: 53%, m.p.214 ºC, IR (KBr):1315 (C-NO2str),3080(Ar-CH str),1115 (C-N str), 1857 (C=O str).1H-NMR (DMSO)(δppm):6.67-8.0 (m, 11H, Ar-CH), 3.5-3.8 (s, 2H,CH), 2.5 (s, 1H,methylene). EI-MSm/z: 515.

RESULTS AND DISCUSSION

The target compounds were synthesized according to the Scheme-1. Further, the desired compounds (IIIA-F), 6-substitude-N-(4,5-dihydro-1H-imidazol-2-yl) benzo[d]oxazol-2-amine (IIIA-F) were obtained by reacting 6-substitude benzo[d]oxazol-2-amine (IA-F)with different reactants like carban disulphide, Dimethylformide, methyliodide and ethylene diamine. The yields, melting points and physical data of newly synthesized compounds are summarized in Table-1

The structure of this compound was assigned on the basis of analytical and spectral data [Mass: M+ at m/z 477; IR (KBr):1328 (C-S),3084(Ar-CH), 1148 (C-N), 1718 (C=O), 1H-NMR (DMSO):6.67-8.87 (m, 12H, Ar-CH), 2.1-3.5(s, 2H,CH), 3.5(2H, Methylene)].

Anti-inflammatory activity studies

All the synthesized compounds were (45, 90, 135 and 180 mg/kg) screened for anti-inflammatory activity by carrageenan-induced paw edema method.

The above acute model result was indicate that synthetic compounds at the dose levels of 45, 90, 135 and 180 mg/kg showed reduction in paw edema volume at all-time intervals as compared to carrageenan control but significant reduction in paw edema volume was noticed in 45 mg/kg at 1stand 4thhour observation 24.13 % and 23.71 % respectively.The groups treated with synthesized compounds atthe dose levels of 45, 90, 135 and 180 mg/kg showedreduction in paw edema volume at all-time intervals ascompared to carrageenan control but significantreduction in paw edema volume was noticed in 180 mg/kg body weight at 1st and 4thhour observation 08.25 % and 69.85 % respectively.

Fig. 1: Scheme of Bis-benzothiazole

Table 1: Physico – chemical properties of synthesized compounds

S. No.	Compounds name	Substituents ®	Molecular formula	Molecular weight	Melting point(ºC)	Rf(%)
1	IIIA	F	$C_{10}H_9FN_4O$	220.08	214	**0.68**
2	IIIB	Cl	$C_{10}H_9ClN_4O$	236.66	223	**0.66**
3	IIIC	Br	$C_{10}H_9BrN_4O$	281.11	243	**0.75**
4	IIID	OCH_3	$C_{11}H_{12}N_4O_2$	231.22	221	**0.74**
5	IIIE	NO_2	$C_{10}H_9N_5O_3$	247.21	233	**0.77**
6	IIIF	CH_3	$C_{11}H_{12}N_4O$	216.24	209	**0.71**

Table 2: Percentage inhibition of paw volume of synthesized compounds by carrageenan induced rat paw edema method

Compounds	Time			
	1hr	2hr	3hr	4hr
Carraggenan	NA	NA	NA	NA
Diclofenac sodium	58.18	60.18	72.53	80.11
IIIA	4.36	17.71	35.97	58.69
IIIB	8.75	21.83	41.14	69.23
IIIC	1.12	10.80	28.12	32.06
IIID	7.27	21.24	36.52	57.17
IIIE	16.79	27.17	33.33	38.09
IIIF	6.56	12.98	29.81	55.82

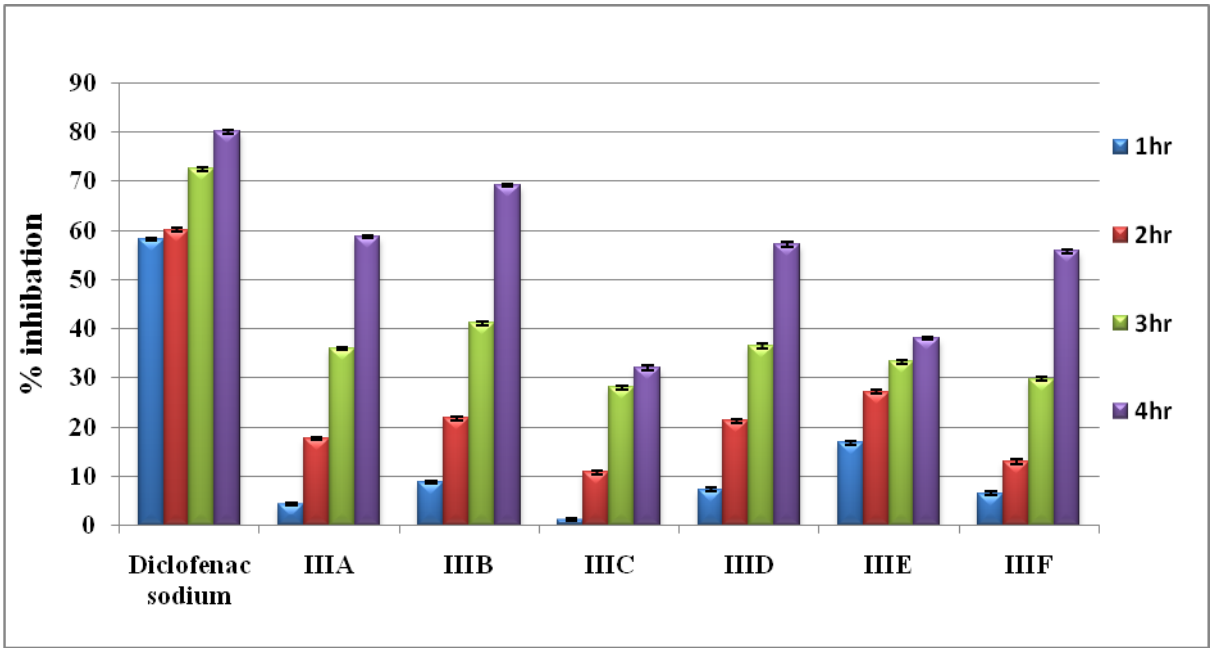

Fig. 2: Graphical representation of percentage inhibition of paw volume of synthesized compounds by carrageenan induced rat paw edema method.

CONCLUSION

All the newly synthesized compounds were screened for anti-inflammatory activity at a concentration of 45, 90, 135 and 180 mg/kg. All compounds showed good anti-inflammatory activity by carrageenan-induced paw edema method.

The results show that Compared to standard drug (Diclofenac sodium) Compound IIIB, IIIA and IIID were found to exhibit good anti-inflammatory activity.

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