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Design, synthesis and biological evaluation of benzoxazole derivatives as new antiinflammatory agents

A. Srinivas*, J. Vidya Sagar, M. Sarangapani

Medicinal Chemistry Research Laboratories, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Andhra Pradesh, India.

Abstract

New series of methyl 2-(arylideneamino) benzoxazole -5-carboxylate derivatives were synthesized by the reaction of Schiff bases of methyl 2-aminobenzoxazole-5-carboxylate with appropriate aromatic aldehydes. The chemical structures of the synthesized compounds were confirmed by means of IR, 1HNMR, mass spectral analysis. Further, the synthesized compounds (SH1-SH9) were screened for antiinflammatory activity by using Carrageenan – induced paw edema rat model. The results showed that, compounds SH1-SH3 and SH6-SH8 were significantly ($p<0.0001$) reduced the inflammation there by showed a promising antiinflammatory activity; where as the compound SH5 moderately reduced the inflammation. Only the two compounds i.e SH4 and SH9 showed very poor anti-inflammatory activity towards Carrageenan – induced paw edema rat.

Keywords: Benzoxazole derivatives, IR, ^{1}H NMR and Mass spectroscopy, methyl 2-(arylideneamino) benzoxazole -5-carboxylate and anti inflammatory activity.

Introduction

Recent observations suggest that substituted benzoxazoles and related heterocycles, possess potential activity with lower toxicities in the chemotherapeutic approach in man[1,2] .Careful literature survey revealed that targets containing benzoxazole moiety, either isolated from plants or accessed by total synthesis, have remarkable biological activities.[3] For example, antimicrobial[4], antihistaminic[5], antiparasitics[6], herbicidal[7], antiviral[8], antiallergic[9]

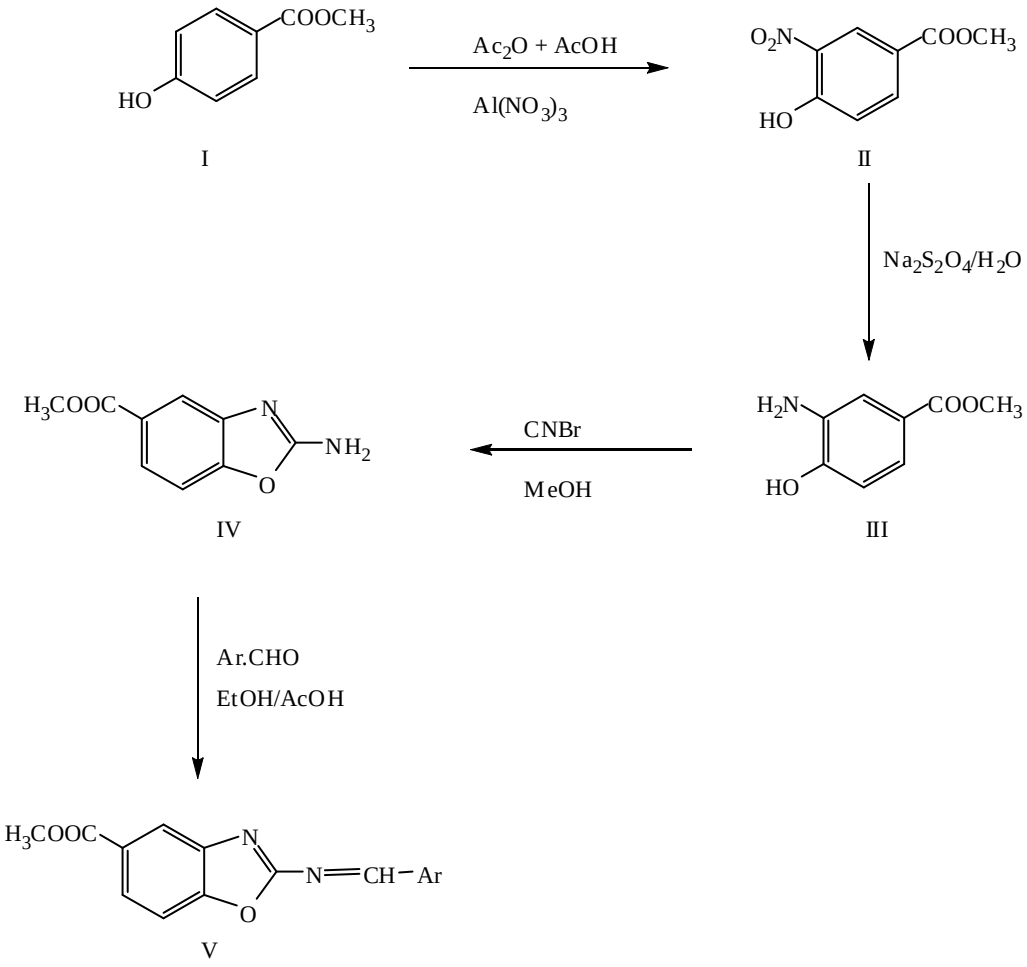
and antihelmintic activities[10]. Antiinflammatory activity of benzoxazole derivatives were also reported in the literature. The title compounds were synthesized by treating the methyl 2-aminobenzoxazole-5-carboxylate with appropriate aromatic aldehydes to get a new series of methyl 2- (arylideneamino) benzoxazole -5-carboxylate derivatives (SH1-AH9)

Materials and Methods

All melting points were taken in open capillaries on a veego VMP-1 apparatus and are uncorrected IR spectra were recorded as KBr pellets on a Perkin-Elmer FT IR 240-c spectrometer. The ^{1}H NMR spectra were recorded on Varian-Gemini 200 MHz spectrometer in DMSO-d_6 using TMS as an internal standard and mass spectras were recorded on Schimadzu QP 5050A spectrometer.

I. Synthesis of 4-Carbomethoxy-2-nitrophenol (II)

To a solution of aluminium nitrate (40gm) in acetic acid- acetic anhydride (1:1) mixture (160ml), was added an appropriate phenol (I, 40gm) in small portions, while cooling and shaking occasionally. The reaction mixture was left at room temperature for 1.5 hours while shaking the contents intermittently to complete the nitration.



Scheme-I

The resulting brown solution was diluted to complete the nitration. The resulting brown solution was diluted with ice-cold water and acidified with concentrated Nitric acid to get a bulky, yellow precipitate. It was filtered washed with small quantity of methanol and purified by recrystallization from alcohol to get a yellow crystalline solid (44g, 85%), m.p 73^{O}C[11].

II. Synthesis of 4-carbomethoxy-2-aminophenol (III)

4-carbomethoxy-2-nitrophenol (II, 10 gm) was dissolved in boiling alcohol (50%, 100ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colourless. Then the alcohol was reduced to one-third of its volume by distillation and the residual liquid was triturated with crushed ice. The resulting colourless, shiny product was filtered, washed with cold water and dried in the air. Its purification was effected by recrystallization from benzene to get colourless, shiny scales (5.1 g; 60%) m.p 143^{O}C[12].

II. Synthesis of methyl 2-aminobenzoxazole-5-carboxylate (IV)

1.3 moles of 4-carbomethoxy-2-aminophenol (III) was dissolved in 1lit. Methyl alcohol and cooled the solution to 5^{O}C by adding chopped ice. A cold suspension of 1.5 moles of Cyanogenbromide in 1lit.of water was added over a period of 5min with rapid stirring. Continued the stirring for 0.75hrs at room temperature, 1.3 moles of solid Sodium bicarbonate in small portions over a period of 1.5 hrs was added to bring the p^{H} 6.5 -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 238^{O}C.

IV. General Procedure for Microwave Synthesis of methyl 2-(arylideneamino) benzoxazole-5-carboxylate (V).

The methyl 2-aminobenzoxazole-5-carboxylate (IV) (0.01mol) and appropriate aromatic aldehydes (0.015mol) were taken in a conical flask and were dissolved in 10ml of absolute alcohol. The conical flask was hanged with a funnel and was subjected to microwave irradiation at 480 Watts for 5mins in LG-Microwave oven. After the completion of the reaction mixture was cooled and triturated with crushed ice, the separated solid was purified by suitable solvent to produce the compounds SH1-SH9. The physical data of these benzoxazole derivatives were given in table1.

Compound SHI

IR (KBr, cm-1): 3133(NH), 1693 (C=N), 1610 (C=C), 1582 (C=N), 1249 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 8.1 (s, 1H, CH), 7.0-7.7 (m, 5H, Ar-H), 6.8 (d, 2H, Ar-H), 3.0 (s, 6H, CH_3), 2.8 (s, 3H, CH_3); MS (*m/z):* M+ calculated 324.0, found 323.13.

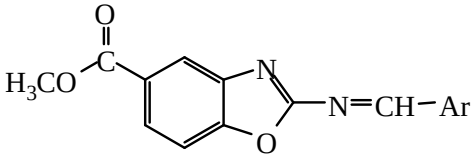
Compound SH2

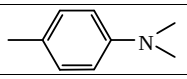
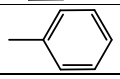
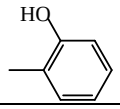
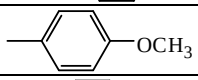
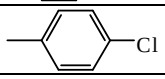
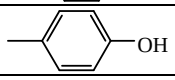
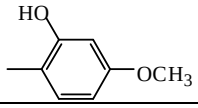
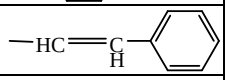
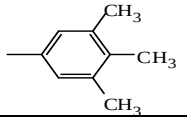
IR (KBr, cm-1): 3138(NH), 1696 (C=N), 1602 (C=C), 1576 (C=N), 1233 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 8.3 (s, 1H, CH), 7.0-7.8 (m, 8H, Ar-H), 2.2 (s, 3H, CH_3); MS (*m/z):* M+ calculated 281.0, found 280.08.

Compound SH3

IR (KBr, cm-1): 3137(NH), 1669 (C=N), 1620 (C=C), 1585 (C=N), 1241 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 12.4 (s, 1H, OH), 8.4 (s, 1H, CH), 7.0-7.6 (m, 7H, Ar-H), 3.9 (s, 3H, CH_3); MS (*m/z):* M+ calculated 297.0, found 296.08.

Table 1: Physical data of methyl 2-(arylideneamino)benzoxazole-5-carboxylate



S. No	Compound	Ar	Chemical formula	M. P. (^{O}C)	Yield (%)
1.	SH1		$C_{18}H_{17}N_3O_3$	208	95
2.	SH2		$C_{16}H_{12}N_2O_3$	212	90
3.	SH3		$C_{16}H_{12}N_2O_4$	222	91
4.	SH4		$C_{17}H_{14}N_2O_4$	202	95
5.	SH5		$C_{16}H_{12}N_2O_4$	226	99
6.	SH6		$C_{16}H_{11}ClN_2O_3$	232	99
7.	SH7		$C_{17}H_{14}N_2O_5$	224	98
8.	SH8		$C_{18}H_{14}N_2O_3$	238	95
9.	SH9		$C_{19}H_{18}N_2O_3$	230	97

Compound SH4

IR (KBr, cm-1): 3112(NH), 1685 (C=N), 1609 (C=C), 1564 (C=N), 1223 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 8.3 (s, 1H, CH), 7.0-7.7 (m, 7H, Ar-H), 3.8(s, 3H, OCH_3), 2.2 (s, 3H, CH_3); MS (*m/z):* M+ calculated 311.0, found 310.10.

Compound SH5

IR (KBr, cm-1): 3114(NH), 1647 (C=N), 1615 (C=C), 1543 (C=N), 1212 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 8.8 (s, 1H, CH), 7.2-8.0 (m, 7H, Ar-H), 3.9(s, 3H, CH_3); MS (*m/z):* M+ calculated 315.0, found 314.05.

Compound SH6

IR (KBr, cm^{-1}): 3133(NH), 1690 (C=N), 1602 (C=C), 1592 (C=N), 1259 (C-O-C); ^{1}H-NMR (DMSO-d_6) δ: 9.7 (s, 1H, OH), 8.4 (s, 1H, CH), 7.1-7.8 (m, 7H, Ar-H), 3.8 (s, 3H, CH_3); MS (*m/z):* M+ calculated 297.0, found 296.08.

Compound SH7
IR (KBr, cm-1): 3141(NH), 1659 (C=N), 1612 (C=C), 1568 (C=N), 1217 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 9.4 (s, 1H, OH), 8.5 (s, 1H, CH), 6.9-7.7 (m, 6H, Ar-H), 3.9 (s, 3H, CH_3), 3.2 (s, 3H, OCH_3); MS (*m/z):* M+ calculated 327.0, found 326.09

Compound SH8
IR (KBr, cm-1): 3201(NH), 1670 (C=N), 1628 (C=C), 1588 (C=N), 1219 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 7.9 (s, 1H, CH), 7.2 (s, 1H, CH) 7.0-7.6 (m, 8H, Ar-H), 6.8 (s, 1H, CH), 2.2 (s, 3H, CH_3); MS (*m/z):* M+ calculated 307.0, found 306.10.

Compound SH9
IR (KBr, cm-1): 3103(NH), 1640 (C=N), 1600 (C=C), 1590 (C=N), 1219 (C-O-C); ^{1}H-NMR (DMSO-d6) δ: 8.1 (s, 1H, CH), 7.2-7.7 (m, 5H, Ar-H), 3.9 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.0(s, 3H, CH_3); MS (*m/z):* M+ calculated 323.0, found 322.13

Anti inflammatory activity:
Carrageenan-induced rat paw edema method[13] was employed for evaluating the anti inflammatory activity of the synthesized compounds (SH1-SH9).

Wister Albino rats of either sex weighing approx 200-350 gm, were housed in clean polypropylene cages and kept under room temperature (25±2^{O}C), and relative humidity 40-50% in a 12 h light-dark cycle. Food was withdrawn 12 h before and during experimental hours. In this study, the animals were divided into groups as shown in the Table-2. Acute inflammation was produced by sub plantar injection of 0.1ml of 1% suspension of Carrageenan with 2% gum acacia in normal saline, in the right hind paw of the rats. After oral administration of the test compounds, the paw volume was measured Plethysmometrically at 1, 2, 3, and 4 h intervals. Diclofenac sodium 10mg/ml of 2% gum acacia in normal saline was used as standard drug.

Results and Discussion

The target compounds were synthesized according to the Scheme-1. The required starting material, Methyl-3-amino-4-hydroxybenzoate (III) was prepared in good yield (85%) according to reported procedure[11].The Methyl-3-amino-4-hydroxybenzoate (III) on cyclization with cyanogen bromide in methyl alcohol and water on rapid stirring at room temperature gave the product, Methyl-2-aminobenzoxazole-5-carboxylate (IV). Further, the desired compounds (SH1-SH9), methyl 2- (arylideneamino) benzoxazole -5-carboxylate were obtained by reacting Methyl-2-aminobenzoxazole-5-carboxylate (IV) with different Aromatic aldehydes. The yields, melting points and physical data of newly synthesized compounds are summarized in Table-1.

The formations of methyl 2- (arylideneamino) benzoxazole-5-carboxylates were confirmed by means of IR, 1HNMR, mass spectral analysis. The investigation of anti inflammatory acivity revealed that the tested compounds SH1-SH3 and SH6-SH8 were significantly ($p<0.0001$) reduced the inflammation there by showed a promising antiinflammatory activity, where as the compound SH5 moderately reduced the inflammation. Only the two compounds i.e SH4 and SH9 showed very poor anti-inflammatory activity towards Carrageenan – induced paw edema rat model when compared to the standard drug Diclofenac Sodium (10mg/ml).

Table 2a: Paw volume(Mean ± SD) of ((methyl 2-(arylideneamino)benzoxazole-5-carboxylates)) compounds by carrageenan induced rat paw edema method

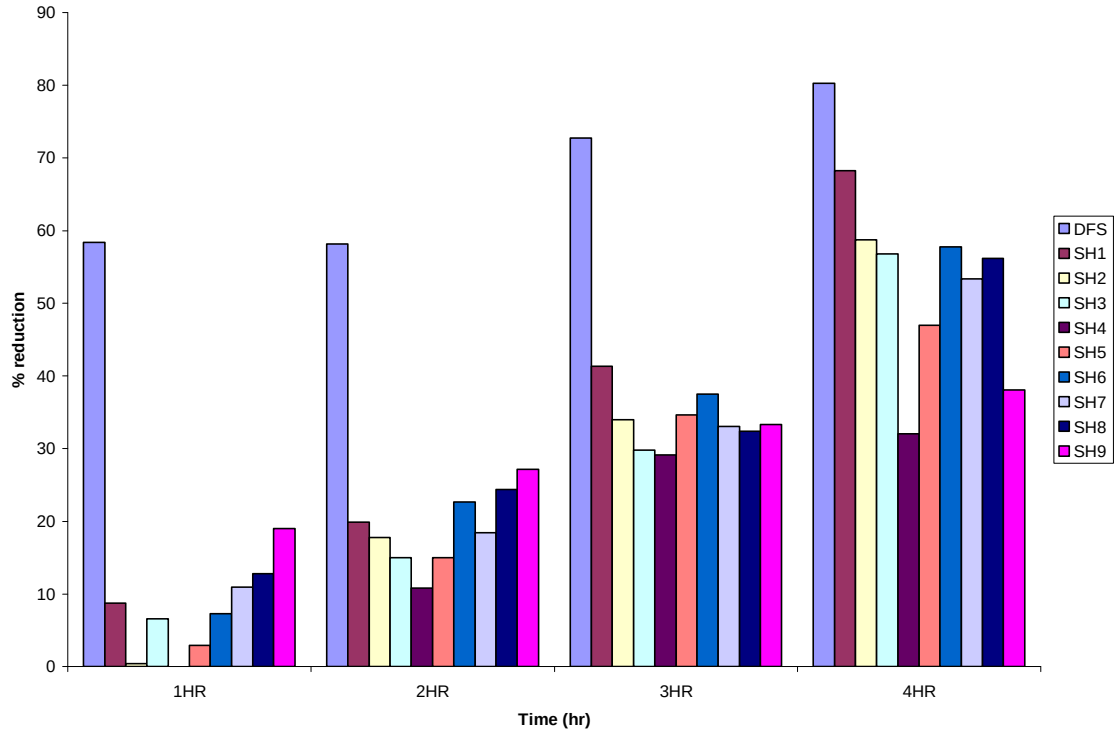
Time/ Compound	1.0hr	2.0hr	3.0hr	4.0hr
Carraggenan	2.74±0.213	2.87±0.254	3.12±0.218	3.15±0.284
DFS	1.14±0.236	1.2±0.236	0.85±0.274	0.62±0.265
SH1	2.5±0.258	2.3±0.281*	1.83±0.312***	1±0.294***
SH2	2.73±0.265	2.36±0.213	2.06±0.299***	1.3±0.325***
SH3	2.56±0.298	2.44±0.248	2.19±0.398***	1.36±0.398***
SH4	2.74±0.213	2.56±0.269	2.21±0.329***	2.14±0.214***
SH5	2.66±0.254	2.44±0.236	2.04±0.298***	1.67±0.248***
SH6	2.54±0.268	2.22±0.217*	1.95±0.387***	1.33±.297***
SH7	2.44±0.254	2.34±0.211	2.09±0.359***	1.47±0.287***
SH8	2.39±0.231	2.17±0.281**	2.11±0.280***	1.38±0.281***
SH9	2.22±0.258	2.09±0.269 **	2.08±0.291***	1.95±0.314***

(n = 6), *** = p<0.001, ** = p<0.01, * = p<0.05

Table 2b: Percentage inhibition of paw volume of ((methyl 2-(arylideneamino)benzoxa zole-5-carboxylates)) compounds by carrageenan induced rat paw edema method

Time	1hr %red	2 hr %red	3hr %red	4hr %red
Carraggenan	NA	NA	NA	NA
DFS	58.39	58.18	72.75	80.31
SH1	8.75	19.86	41.34	68.25
SH2	0.36	17.77	33.97	58.73
SH3	6.56	14.98	29.80	56.82
SH4	0	10.80	29.16	32.06
SH5	2.91	14.98	34.61	46.98
SH6	7.29	22.64	37.50	57.77
SH7	10.94	18.46	33.01	53.33
SH8	12.77	24.39	32.37	56.19
SH9	18.97	27.17	33.33	38.09

Figure 1: Graphical representation of percentage inhibition of paw volume of ((methyl 2-(arylideneamino)benzoxazole-5-carboxylate)) compounds by carrageenan induced rat paw edema method



Conclusion

This study reports the successful synthesis of the title compounds in good yields and moderate to potent anti inflammatory activity of these derivatives containing benzoxazole moiety which is comparable with standard drug.

References

[1] R.D. Haugwitz, R.G.Angel, G.A.Jacobs, B.V.Manner, V.L. Narayanan, L.R.Crothers and J. Szanto, *J. Med. Chem.*, 1982 (**25)** , 969.
[2] T. Hisano, M. Ichikawa, K. Tsumoto, M. Tasaki, *Chem. Pharm. Bull* 1982, **30**, 2996.
[3] Anita hari, Charles karan, Warren C. Rodrignes and Benjamin L. Miller, *J. Org. Chem.* 2001, **66 ,** 991.
[4] Sultan Nacak, Seyban Ersan, Rukiye Berkem and Tancel Ozden, *Arzneim-Forsch/ Drugs Res.*, 1997 **41**, 963
[5] Yousuke Katsura, Yoshikaz Inoue, Signetaka Nishino, Masaaki Tomoi, Harunobu Itoh and Hisashi Takasugi, *Chem. Pharm. Bull.*, 1992, **4(6)** , 1424 .
[6] Qian, Xuhong, Li, Zhibin, Sorg, Gonghua, Lizhorg, *J. Chem. Res. Synop.*, 2001, **4,** 138.
[7] Peter Paul Wilhelm, Wilhelm, Sittenthales, Hans Ulrich Bernhard and Torsten Rehm, *Ger. Offen* D.E. **3**, 638685 (Cl. A. 01 N57/08), (1980), *Chem. Abstr.*, 1989, **109**, 110657.
[8] Surendra Bahadhur and Pandey, *J. Indian Chem. Soc.*, 1981, **58** , 883 .
[9] *Chem. Abstr.* 1992, **117**, 69856K .

[10] B.Gopal Krishna, N. Raghunandan, J.V.Rao, S. Bari, B.Srinivas, A.Venkatesham and M.Sarangapani, *Indian Drugs* 2005, **42 (6)**.
[11] K. Rajmohan and N.V. Subba Rao, *Indian J. Chem.*, 1973, **11,** 1076.
[12] Finhorn and B.Ptyl, *Ann. Chem.,* 1900, **311,** 46.
[13] C.A. Winter, E.A. Risely and E.V. Nuss, *Pro. Soc. Exp. Biol. & Med.,* 1962, **111,** 544.