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Der Chemica Sinica, 2010, 1 (3): 157-168

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and *in vivo* anti-inflammatory activity of a novel series of benzoxazole derivatives

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ABSTRACT

Novel series of benzoxazole derivatives were prepared by the condensation of methyl-2-(2-aminothiazol-5-ylamino) benzo[d]oxazole-5-carboxylate with various aromatic aldehydes. The structures of the synthesized compounds were VI_1-VI_{15} assigned on the basis of elemental analysis, IR, ^1H NMR and mass spectroscopy. These compounds were also screened for anti-inflammatory activity. The recorded percentage of inhibition showed a significant anti-inflammatory activity when compared to the reference anti-inflammatory drug diclofenac sodium.

Key words: Benzoxazole, Carrageenan - induced rat paw edema, 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 [1] activities. Anti-inflammatory activity of benzoxazole derivatives were also reported in the literature. Particularly, a series of synthesis of Schiff's bases (N'-benzylidene-2-alkylbenzoxazole-5-carbohydrazide) moiety have been reported to possess anti-inflammatory activity [10]. Derivatives of thiazole have antibacterial (Khalil et al, 2009), antitubercular [12], anticonvulsant activity [13] and anticancer activity [14] properties. Moreover, the thiazole nucleus is present in many compounds that have anti-inflammatory (Shivarama Holla et al, 2003). In the present study, the thiazole moiety was connected to the benzoxazole moiety 2-position, (VI_1-VI_{15}) (Table. I), to combine different pharmacophores on

one scaffold. Due to broad spectrum of activities reported in the literature so far, we herein report the synthesis of a novel series of methyl-2-(2-(benzylideneamino) thiazole-4-ylamino) benzoxazole-5-carboxylate derivatives (VI_1-VI_{15}) as the target compounds in order to examine their anti-inflammatory potential in comparison with control drug.

MATERIALS AND METHODS

All the melting points were determined by a digital melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin–Elmer 377 spectrophotometer, ^{1}H NMR spectra were measured on Bruker AV 400 MHz using DMSO as a solvent and TMS as an internal standard.

Synthesis of Methyl-3-nitro-4-hydroxybenzoate (I)

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

Synthesis of Methyl-3-amino-4-hydroxybenzoate (II)

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

Synthesis of methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (III)

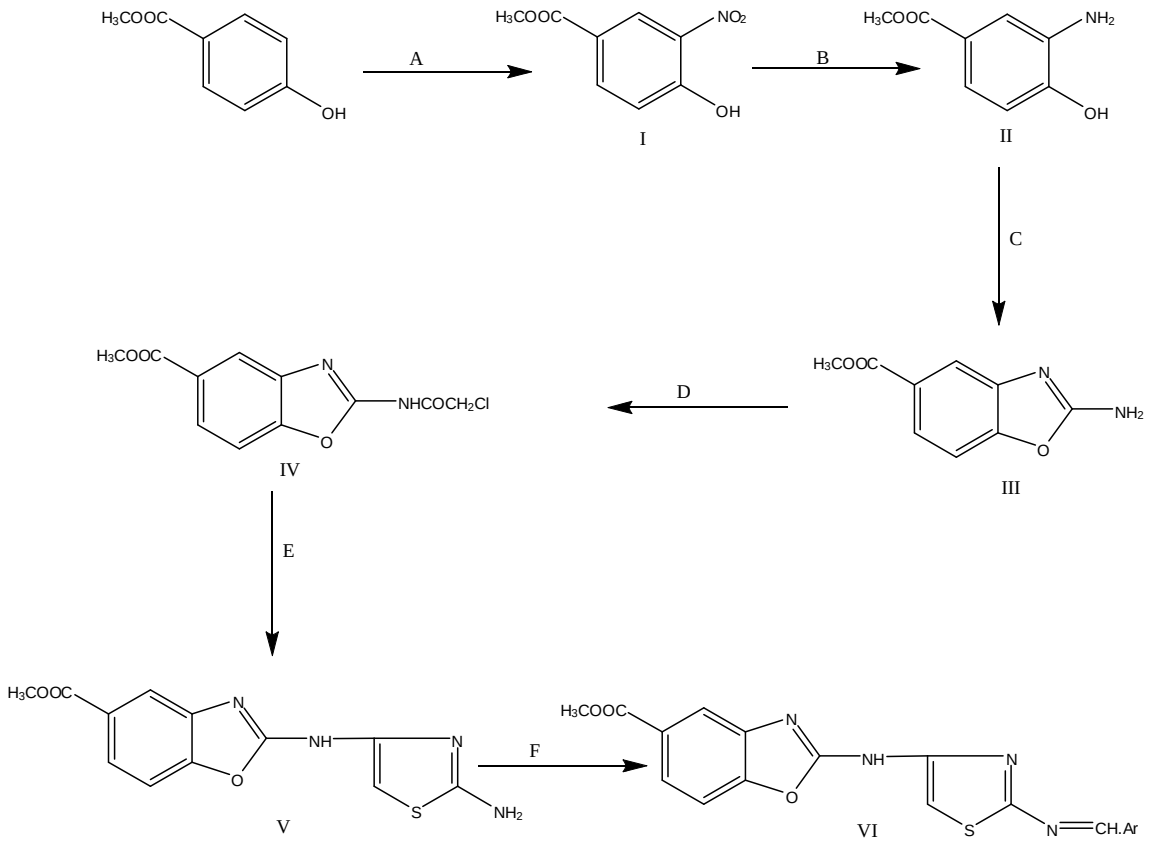
4-carbomethoxy-2-aminophenol (II, 1.3 mol) was dissolved in 1l. methyl alcohol and cooled the solution to 5^{O}C by adding chopped ice. A cold suspension of cyanogenbromide (1.5 mol) in 1l.of water was added over a period of 5min with rapid stirring. The reaction mixture was stirred for 0.75h at room temperature, solid sodium bicarbonate (1.3 mol) in small portions over a period of 1.5 h was added to bring the p^H 6.5 -7.0. Stirring was continued for another 1h. The solid was separated by filtration, washed with cold water and on recrystallization from ethyl alcohol has resulted white solid, yield 70% and m.p is 238^{O}C.

Synthesis of methyl 2-(2-chloroacetamido)benzo[d]oxazole-5-carboxylate (IV)

A mixture of methyl-2-aminobenzoxazole-5-carboxylate (III, 0.01mol) and chloroacetyl chloride (0.01mol) was taken in 20 ml of dry benzene and the reaction mixture was refluxed for 5h on a water bath. The solvent was evaporated and the residue was washed first with benzene and then with Petroleum ether. The compound was recrystallized from suitable solvent(s). The compound was found to be containing yield 72% and m.p is 177^{O}C.

Microwave synthesis of methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V)

Methyl-2-(2-chloroacetamido) benzo[d]oxazole-5-carboxylate (IV, 0.01mol) and thiourea (0.01mol) were dissolved in 10ml of absolute alcohol in conical flask. The conical flask was hanged with a funnel and was subjected to microwave irradiation at 480 Watts for 5min in LG-Microwave oven. The reaction was monitored by TLC. After the completion of the reaction the contents were cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture found to be containing yield 97% and m.p 199^{O}C. The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3450 (NH_2), 3146 (NH), 1672 (C=O), 1626(C=C), 1528 (C=N), 1342 (C-O-C), 1142(C=S). PMR spectrum (DMSO-d_6) of the compound has been found to exhibit proton signals (δ ppm) at: 8.3(s, 1H, Ar-H), 7.8 (d, 1H, Ar-H), 7.6 (d, 1H, Ar-H), 7.0 (s, 1H, CH, thiazole ring), 6.3 (s, 2H, NH_2), 5.5 (s, 1H, NH), 3.9 (s, 3H, CH_3).



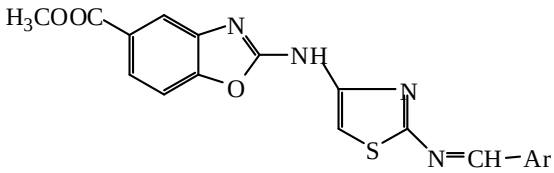
A= Ac_2O + AcOH/ Al_2NO_3
B= $Na_2S_2O_4$/ 50% MeOH
C= CMBr/ MeOH
D= $ClCH_2COCl$/ dry benzene
E= Thiourea/ EtOH
F= Ar.CHO/ EtOH + AcOH

Figure1: Scheme-1

Microwave synthesis of Methyl-2-(2-(aryylideneamino)thiazol-5-ylamino)benzo[d]oxazole-5-carboxylates (VI1-15)

Methyl-2-(2-aminothiazol-4-ylamino)benzoxazole-5-carboxylate (V,0.01mol) and appropriate aromatic aldehydes viz. 4-dimethylaminophenyl, *4-t*-butylphenyl, Anisyl, phenyl, 4-hydroxyphenyl,4-nitrophenyl, Veratryl, Cinnamyl, 3,4,5-trimethylphenyl, 4-tolyl, 2-hydroxyphenyl, 4-bromophenyl, 4-chlorophenyl, 2-naphthyl, 1-naphthyl (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction was monitored by TLC. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture. The compounds were characterized by spectral data (Physical Data Presented in Table-1).

Table1: Physical data of methyl 2-(2-(benzylideneamino) thiazol-4-ylamino) benzoxazole-5-carboxylates (VI)



Compd (VI)	Ar	Molecular Formula	Melting Point (^{O}c)	Yield (%)
1	4-dimethylamino phenyl	$C_{21}H_{19}N_5O_3S$	208	90
2	*4-t*-butylphenyl	$C_{23}H_{22}N_4O_3S$	301	93
3	4-methoxyphenyl	$C_{20}H_{16}N_4O_4S$	280	98
4	Phenyl	$C_{19}H_{14}N_4O_3S$	201	92
5	4-hydroxy phenyl	$C_{19}H_{14}N_4O_4S$	228	95
6	4-nitrophenyl	$C_{19}H_{13}N_5O_5S$	299	97
7	3,4 dimethoxyphenyl	$C_{19}H_{18}N_4O_5S$	226	96
8	Cinnamyl	$C_{21}H_{15}N_4O_3S$	240	94
9	3,4,5-trimethylphenyl	$C_{22}H_{20}N_4O_3S$	238	95
10	4-methylphenyl	$C_{20}H_{16}N_4O_3S$	303	91
11	2-hydroxyphenyl	$C_{19}H_{14}N_4O_4S$	234	91
12	4-bromophenyl	$C_{19}H_{13}BrN_4O_3S$	305	90
13	4-chlorophenyl	$C_{19}H_{13}ClN_4O_3S$	222	99
14	2-naphthyl	$C_{23}H_{16}N_4O_3S$	341	90
15	1-naphthyl	$C_{23}H_{16}N_4O_3S$	322	91

Compound VI 1: Methyl-2-(2-(4-(dimethylamino)benzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-dimethylaminophenyl (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.8 (s, 1H, ArH), 8.2(s, 1H, CH), 8.1 (d, 1H,ArH), 8.0 (d, 1H, ArH),7.5 (d, 2H, ArH), 6.8(d, 2H, ArH), 6.3 (s, 1H, ArH, thiazole ring), 5.2 (s, 1H, NH), 3.9 (s, 3H, CH_3), 3.0 (s, 6H, $(CH_2)_3$); IR (KBr) CM^{-1}: 3096 (NH), 1683 (C=O), 1640(C=C), 1576 (C=N), 1442(C-O-C), 1383(C=S), MS (*m/z):* M^+: 422.1, *Anal*. Calcd for $C_{21}H_{19}N_5O_3S$: C, 59.84; H, 4.54; N, 16.62; O, 11.39; S, 7.61.

Compound VI 2: methyl-2-(2-(4-tert-butylbenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-*t*-butylbenzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.7 (s, 1H, ArH), 8.2(s, 1H, CH), 8.1 (d, 1H,ArH), 8.0 (d, 1H, ArH),7.5 (d, 2H, ArH), 7.1(d, 2H, ArH), 6.0 (s, 1H, ArH, thiazole ring), 5.4 (s, 1H, NH), 3.9 (s, 3H, CH_3), 1.3(s, 9H, $(CH_3)_3$); IR (KBr) CM^{-1}: 3091 (NH), 1681 (C=O), 1642 (C=C), 1577 (C=N), 1443 (C-O-C), 1381 (C=S), MS (*m/z):* M^+: 435.1, *Anal*. Calcd for $C_{23}H_{22}N_4O_3S$: C, 63.58; H, 5.10; N, 12.89; O, 11.05; S, 7.38.

Compound VI 3: methyl-2-(2-(4-methoxybenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-methoxybutylbenzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.9 (s, 1H, CH), 8.7 (s, 1H, CH), 8.1 (d, 1H,ArH), 8.0(d, 1H, ArH),7.8 (d, 2H, ArH), 7.1 (d, 2H, ArH), 6.2 (s, 1H, ArH, thiazole ring), 5.0 (s, 1H, NH), 3.9 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3); IR (KBr) CM^{-1}: 3068 (NH), 1687 (C=O), 1645 (C=C), 1512 (C=N), 1432 (C-O-C), 1371 (C=S), MS (*m/z):* M^+: 409.0, *Anal*. Calcd for $C_{20}H_{16}N_4O_4S$: C, 58.81; H, 3.95; N, 13.72; O, 15.67; S, 7.85.

Compound VI 4: methyl-2-(2-(benzylideneamino)thiazol-5-ylamino)benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.6 (s, 1H, ArH), 8.1(s, 1H, CH), 8.0 (d, 1H,ArH), 7.9 (d, 1H, ArH),7.5 (d, 2H, ArH), 7.0(t, 3H, ArH), 6.1 (s, 1H, ArH, thiazole ring), 5.4 (s, 1H, NH), 3.8 (s, 3H, CH_3). IR (KBr) CM^{-1}: 3076 (NH), 1679 (C=O), 1646(C=C), 1580 (C=N), 1448(C-O-C), 1373 (C=S), MS (*m/z):* M^+: 379.0, *Anal.* Calcd for $C_{19}H_{14}N_4O_3S$: C, 60.31; H, 3.73; N, 14.81; O, 12.68; S, 8.47.

Compound VI 5: methyl-2-(2-(4-hydroxybenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-hydroxy benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ9.2 (S,1H,OH), 8.9 (s, 1H, ArH), 8.5 (s, 1H, CH), 8.1 (d, 1H,ArH), 8.0(d, 1H, ArH),7.7 (d, 2H, ArH), 6.8(d, 2H, ArH), 6.4 (s, 1H, ArH, thiazole ring), 4.6(s, 1H, NH), 3.7 (s, 3H, CH_3); IR (KBr) CM^{-1}: 3091 (NH), 1699 (C=O), 1676 (C=C), 1580 (C=N), 1455 (C-O-C), 1371 (C=S), MS (*m/z):* M^+: 395.0, *Anal.* Calcd for $C_{19}H_{14}N_4O_4S$: C, 57.86; H, 3.58; N, 14.21; O, 16.23; S, 8.13.

Compound VI 6: methyl-2-(2-(4-nitrobenzylideneamino)thiazol-5-ylamino)benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-nitro benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.6 (s, 1H, CH), 8.4 (s, 1H,ArH), 8.3 (d, 2H, ArH),8.1 (d, 1H, ArH), 7.9 (d, 1H, ArH), 7.8 (d, 2H, ArH), 6.5 (s, 1H, ArH, thiazole ring), 5.5 (s, 1H, NH), 3.8 (s, 3H, OCH_3); IR (KBr) CM^{-1}: 3091 (NH), 1692 (C=O), 1684 (C=C), 1582 (C=N), 1449 (C-O-C), 1373 (C=S), MS (*m/z):* M^+: 424.0, *Anal.* Calcd for $C_{19}H_{13}N_5O_5S$: C, 53.90; H, 3.09; N, 16.54; O, 18.89; S, 7.57.

Compound VI 7: methyl-2-(2-(3,4-dimethoxybenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 3, 4-dimethoxy benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.9 (s, 1H, ArH), 8.5 (s, 1H, CH), 8.1 (d, 1H,ArH), 8.0(d, 1H, ArH),7.6

(s, 1H, ArH), 7.4 (d, 1H, ArH), 6.9 (d, 1H, ArH), 6.5 (s, 1H, ArH, thiazole ring), 4.8 (s, 1H, NH), 3.8 (s, 9H, $3OCH_3$); IR (KBr) CM^{-1}: 3071 (NH), 1687 (C=O), 1663 (C=C), 1575 (C=N), 1451 (C-O-C), 1373 (C=S) , S (*m/z):* M^+: 439.0, *Anal.* Calcd for $C_{21}H_{18}N_4O_5S$: C, 57.53; H, 4.14; N, 12.78; O, 18.25; S, 7.31.

CompoundVI 8: methyl-2-(2-(3-phenylallylideneamino)thiazol-5-ylamino)benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and and cinnamaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1}H NMR (DMSO-d_6): δ 8.8 (s, 1H, ArH), 8.1 (d, 1H,ArH), 8.0(d, 1H, ArH),7.6 (t, 2H, ArH), 7.5 (s, 1H, CH), 7.4 (t, 2H, ArH), 7.3(t, 1H, ArH),7.0 (s, 1H, CH), 6.4 (s, 1H, ArH, thiazole ring), 5.6 (s, 1H, CH), 4.2 (s, 1H, NH), 3.7 (s, 3H, OCH_3); IR (KBr) CM^{-1}: 3088 (NH), 1681 (C=O), 1667 (C=C), 1573 (C=N), 1455 (C-O-C), 1371 (C=S), MS (*m/z):* M^+: 405.1, *Anal.* Calcd for $C_{21}H_{16}N_4O_3S$: C, 62.36; H, 3.99; N, 13.85; O, 11.87; S, 7.93.

Compound VI 9: methyl-2-(2-(3,4,5-trimethylbenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 3,4,5-trimethyl benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1}H NMR (DMSO-d_6): δ 8.7 (s, 1H, ArH), 8.6 (s, 1H,CH), 8.1 (d, 1H, ArH),8.0 (d, 1H, ArH), 7.3 (d, 2H, ArH), 6.1 (s, 1H, ArH, thiazole ring), 4.8 (s, 1H, NH), 3.8 (s, 3H, OCH_3), 2.3 (s, 6H, $2CH_3$), 2.1 (s, 1H, CH_3); IR (KBr) CM^{-1}: 3090 (NH), 1674 (C=O), 1660 (C=C), 1569 (C=N), 1449 (C-O-C), 1367 (C=S), MS (*m/z):* M^+: 421.1, *Anal.* Calcd for $C_{22}H_{20}N_4O_3S$: C, 62.84; H, 4.79; N, 13.32; O, 11.41; S, 7.63.

Compound VI 10: methyl-2-(2-(4-methylbenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-methyl benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1}H NMR (DMSO-d_6): δ 8.8 (s, 1H, CH), 8.6 (s, 1H,ArH), 8.1 (d, 1H, ArH),8.0 (d, 1H, ArH), 7.7 (d, 2H, ArH), 7.2 (d, 2H, ArH), 6.3 (s, 1H, ArH, thiazole ring), 5.1 (s, 1H, NH), 4.0(s, 3H, OCH_3

), 2.3 (s, 3H, CH_3); IR (KBr) CM^{-1}: 3092 (NH), 1695 (C=O), 1689 (C=C), 1589 (C=N), 1458 (C-O-C), 1371 (C=S), MS (*m/z):* M^+:393.1, *Anal.* Calcd for $C_{20}H_{16}N_4O_3S$: C, 61.21; H, 4.11; N, 14.28; O, 12.23; S, 8.17.

Compound VI 11: methyl-2-(2-(2-hydroxybenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 2-hydroxy benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 11.2 (S,1H,OH), 8.9 (s, 1H, ArH), 8.6 (s, 1H, CH), 8.1 (d, 1H,ArH), 8.0(d, 1H, ArH),7.6 (d, 1H, ArH), 7.5 (t, 1H, ArH), 7.2 (t, 1H, ArH), 7.0 (t, 1H, ArH), 6.3 (s, 1H, ArH, thiazole ring), 5.0 (s, 1H, NH), 3.9 (s,3H,CH_3); IR (KBr) CM^{-1}: 3088 (NH), 1697 (C=O), 1666 (C=C), 1578 (C=N), 1454 (C-O-C), 1375 (C=S), MS (*m/z):* M^+: 395.0, *Anal*. Calcd for $C_{19}H_{14}N_4O_4S$: C, 57.86; H, 3.58; N, 14.21; O, 16.23; S, 8.13.

Compound VI 12: methyl-2-(2-(4-bromobenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-bromo benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.7 (s, 1H, CH), 8.5 (s, 1H, CH), 8.0 (d, 1H,ArH), 7.9(d, 1H, ArH),7.6 (d, 1H, ArH), 7.5 (d, 2H, ArH), 7.3 (d, 2H, ArH), 5.9 (s, 1H, ArH, thiazole ring), 5.0 (s, 1H, NH), 3.9 (s, 3H, CH_3); IR (KBr) CM^{-1}: 3093 (NH), 1693 (C=O), 1679 (C=C), 1583 (C=N), 1446 (C-O-C), 1376 (C=S), MS (*m/z):* M^+: 458.1, *Anal.* Calcd for $C_{19}H_{13}BrN_4O_3S$: C, 49.90; H, 2.87; Br, 17.47; N, 12.25; O, 10.50; S, 7.01.

Compound VI 13: methyl-2-(2-(2-chlorobenzylideneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 4-chloro benzaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.8 (s, 1H, CH), 8.6 (s, 1H, CH), 8.1 (d, 1H,ArH), 8.0(d, 1H, ArH),7.7 (d, 1H, ArH), 7.5 (d, 1H, ArH), 7.4 (t, 1H, ArH), 7.3 (t, 1H, ArH), 6.4 (s, 1H, ArH, thiazole ring), 5.2 (s, 1H, NH), 3.6 (s, 3H, CH_3); IR (KBr) CM^{-1}: 3094 (NH), 1691 (C=O), 1680 (C=C),

1581 (C=N), 1447 (C-O-C), 1374 (C=S), MS (*m/z):* M^+: 413.0, *Anal*. Calcd for $C_{19}H_{13}ClN_4O_3S$: C, 55.28; H, 3.17; Cl, 8.59; N, 13.57; O, 11.63; S, 7.77.

Compound VI 14: methyl-2-(2-(naphthalen-2-ylmethyleneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 2-naphthaldehyde (0.015mol) were taken into 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 7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.7 (s, 1H, CH), 8.5 (s, 1H, CH), 8.4 (d, 1H,ArH), 8.3 (t, 1H, ArH),8.2 (d, 1H, ArH), 8.1(d, 1H, ArH), 8.0(d,1H, ArH),7.9(d, 1H, ArH),7.7(t, 1H, ArH), 7.4 (t, 1H, ArH), 6.3 (s, 1H, ArH, thiazole ring), 4.1 (s, 1H, NH), 3.9 (s, 3H, OCH_3); IR (KBr) CM^{-1}: 3090 (NH), 1692 (C=O), 1683 (C=C), 1585 (C=N), 1453 (C-O-C), 1370 (C=S), MS (*m/z):* M^+: 428.0, *Anal*. Calcd for $C_{23}H_{16}N_4O_3S$: C, 64.47; H, 3.76; N, 13.08; O, 11.20; S, 7.48.

Compound VI 15: methyl-2-(1-(naphthalen-2-ylmethyleneamino)thiazol-5-ylamino) benzo[d]oxazole-5-carboxylate

Methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (V,0.01mol) and 1-naphthaldehyde (0.015mol) were taken into 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 5-7min in LG-Microwave oven. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% $NaHCO_3$ solution and purified by recrystallization from ethanol and water mixture.

^{1} H NMR (DMSO-d_6): δ 8.8 (s, 1H, CH), 8.5 (s,1H, CH), 8.6 (d, 1H,ArH), 8.2 (t, 1H, ArH),8.0 (d, 1H, ArH),7.9(d,1H, ArH), 7.8(d,1H, ArH), 7.7 (d, 1H, ArH),7.6 (t, 1H, ArH), 7.5 (t, 1H, ArH), 6.1 (s, 1H, ArH, thiazole ring), 4.8 (s,1H, NH),3.4 (s, 3H, OCH_3); IR (KBr) CM^{-1}: 3093 (NH), 1689 (C=O), 1687 (C=C), 1581 (C=N), 1458 (C-O-C), 1365 (C=S), MS (*m/z):* M^+: 428.0, *Anal*. Calcd for $C_{23}H_{16}N_4O_3S$: C, 63.74; H, 5.17; N, 12.04; O, 12.20; S, 6.85.

Anti inflammatory activity

Carrageenan - induced rat paw edema method [16] was employed for evaluating the anti inflammatory activity of the synthesized compounds (VI_1-VI_{15}). Wister Albino rats of either sex weighing approx 200- 350 g, 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 **Chart-1**. The required starting material, methyl 3-amino-4-hydroxybenzoate **(II)** was prepared in good yield (85%). The starting material (**II)** on cyclization with cyanogen bromide in methyl alcohol on rapid stirring at room temperature gave the product, methyl 2-aminobenzo[d]oxazole-5-carboxylate**(III).**Methyl-2-aminobenzoxazole-5-carboxylate **(III) o**n reaction with chloro acetyl chloride in dry benzene yields the compound, methyl-2-(2-chloroacetamido) benzo[d]oxazole-5-carboxylate **(IV)**. methyl 2-(2-chloroacetamido)benzo[d]oxazole-5-carboxylate **(IV)** on cyclization with thiourea gave the compound methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate (**V**) which on reaction with various aromatic aldehydes viz, 4-dimethylaminophenyl, *4-t*-butylphenyl, Anisyl, phenyl, 4-hydroxyphenyl,4-nitrophenyl, Veratryl , Cinnamyl, 3,4,5-trimethylphenyl, 4-tolyl, 2-hydroxyphenyl, 4-bromophenyl, 4-chlorophenyl, 2-naphthyl, 1-naphthyl conveniently converted into the targeted compounds Methyl-2-(2-(aryylideneamino)thiazol-5-ylamino)benzo[d]oxazole-5-carboxylates **(VI).**

Table-2: Anti inflammatory activity of newly synthesized Compounds (VI_1-VI_{15})

Time	1.0hr	% red	2.0hr	% red	3.0hr	% red	4.0hr	% red
Carrageenan	2.82	NA	2.97	NA	3.24	NA	3.24	NA
DFS	1.0466	62.884	1.02	65.656	0.8666	73.25	0.5333	83.531
VI_1	1.5941	41.9125	1.46282	48.1502	1.6251	49.2563	1.3245	53.22*
VI_2	1.4	50.3546	0.96667	67.4523	0.76667	76.3374	0.43333	86.625***
VI_3	1.2301	39.256	1.2587	41.256	1.3548	50.8941	1.3598	71.61***
VI_4	1.4562	39.2254	1.66747	51.1637	1.30212	69.2159	1.4581	79.67***
VI_5	1.0351	37.856	1.6258	50.2143	1.3256	60.9991	1.5126	70.96***
VI_6	1.53333	45.6265	1.26667	57.3513	0.83333	74.2798	0.36667	88.6831***
VI_7	1.2658	29.0256	1.3258	32.0356	0.9584	38.2569	1.0256	49.67*
VI_8	1.5891	42.0351	1.2569	42.3691	1.3695	51.0365	1.0278	57.09*
VI_9	1.2544	40.8881	1.0236	48.0369	1.0265	52.01451	1.3654	60.64**
VI_{10}	1.16667	58.6288	0.93333	68.5746	0.76667	76.3374	0.46667	85.5967***
VI_{11}	1.53333	45.6265	1.26667	57.3513	0.83333	74.2798	0.5	83.5391***
VI_{12}	1.63333	42.0804	1.43333	51.7396	0.93333	71.1934	0.56667	82.5103***
VI_{13}	1.63333	42.0804	1.56667	47.2503	1.66667	48.5597	1.46667	54.7325*
VI_{14}	1.76667	37.3522	1.46667	50.6173	1.03333	68.107	0.63333	80.4527***
VI_{15}	1.53333	45.6265	1.26667	57.3513	0.83333	74.2798	0.5	83.5391***

****statistically significant (p<0.0001) difference in comparison to control, * statistically significant (p<0.05) difference in comparison to control Values are in Mean ±Standard Deviation NA = Not Applicable DFC = Diclofenac Sodium, n= six animals*

The yields, melting points and physical data of newly synthesized compounds are summarized in Table-1. In case of compound VI_4 with simple phenyl group the percentage reduction was 79.67% showed good inhibitory activity, where as in compound VI_1 with a dimethylamino group at 4-position of phenyl ring (53.22%), compound VI_3 a methoxy group at 4-position of the phenyl ring (71.61%), compound VI_5 a hydroxyl group at 4-position (70.96%) compound VI_8 unsaturation on the phenyl ring (57.09%) compound VI_9 three methyl groups at 3, 4, 5-positions of phenyl ring (60.64%), compound VI_{13} a bulkier chloro group on phenyl ring at 4-position (54.73%) showed moderate activity when comparing with the standard drug Diclofenac Sodium (83.53%).In case of compound VI_{11} a hydroxyl group on the phenyl ring at 2-position (83.53%),

compound VI_{12} a bromo group on phenyl ring at 4-position (82.51%) compound VI_{14} (80.452%) and VI_{15} (83.53%) showed almost equal to the standard drug. In case of the compound VI_7 two methoxy groups on phenyl ring at 3- and 4-positions showed very low inhibitory activity (49.67%).In case of compound VI_2 a *tert*-butyl group at 4-position on the phenyl ring (86.625%), compound VI_{10} a methyl group at 4-position of phenyl ring and compound VI_6 a nitro group at 4-possition on the phenyl ring (88.68%) showed anti-inflammatory activity more than the standard.

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. It has been observed that the increased anti-inflammatory activity is attributed to the presence of pharmacologically active thiazole ring on the benzoxazole moiety at 2-position.

Acknowledgements
The authors are thankful to the H.O.D, Deprt. of Pharmacology University College of Pharmaceutical Sciences, Kakatiya University. for providing proper facilities to carry out the anti-inflammatory work and IICT., Hyderabad, AP, India, for providing the ^{1}H NMR, IR and mass spectral analysis.

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