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SYNTHESIS AND SCREENING OF METHYL-2-(2-(ARYLIDENEAMINO) OXAZOLE-5-YLAMINO) BENZOXAZOLE-5-CARBOXYLATE DERIVATIVES AS CYCLOOXYGENASE INHIBITORS

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ABSTRACT

We have synthesized a series of methyl-2-(2-(arylideneamino) Oxcazole-5-ylamino)benzoxazole-5-carboxylate derivatives and investigated their ability to inhibit human cyclooxygenase-2 enzyme (COX-2). The active compounds were screened for cyclooxygenase-1 (COX-1) inhibition. Compound VIId is 368-fold and VIIh is more than 454 fold selective towards COX-2 compared to COX-1. Thus, this class of compounds may serve as excellent candidates for selective COX-2 inhibition.

KEYWORDS

Benzaxozoles, synthesis, cyclooxygenase, evaluation, COX-2, COX-1

INTRODUCTION

Cyclooxygenase (COX; prostaglandin endoperoxide synthase) metabolizes arachidonic acid to prostaglandin (PG) H2, which serves as the precursor for the biosynthesis of various PGs, thromboxanes, and prostacyclin [1]. COX activity originates from two distinct and independently regulated isozymes, COX-1 and COX-2 [2]. COX-1 is a constitutive enzyme, whereas COX-2 is inducible and short-lived. COX-2 is the product of an immediate-early gene, and its expression is stimulated by a host of growth factors, cytokines, and mitogens[3]. COX-1 appears responsible for the biosynthesis of PGs in the gastric mucosa and in the kidney, whereas COX-2 appears responsible for biosynthesis in inflammatory cells and the central nervous system[4]. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the two isoforms to different extents, and this feature accounts for their shared therapeutic properties and side effects [5]. The differential tissue distribution of the COX isozymes has provided a rationale for the development of COX-2-selective inhibitors as nonulcerogenic, anti-inflammatory, and analgesic agents[6]. Most selective COX-2 inhibitors, including the recently approved drugs celecoxib[7] and rofecoxib[8] belong to the diarylheterocycle class of compounds[9-11]. Diarylheterocycles have been investigated extensively as COX-2 inhibitors since the description of the 2, 3-diaryloxazole, as a nonulcerogenic anti-inflammatory agent. In addition 2-Oxo-3H-benzoxazole derivatives exhibit a broad range of biological properties [13-16] including analgesic and anti-inflammatory activity [17-22]. Among them, especially 3-substituted-2-oxo-3H-benzoxazoles are known to exhibit analgesic and anti-inflammatory properties [23]. It has also been reported that mannich bases of 6-acyl-2-oxo-3H-benzoxazoles resulted in compounds with potent analgesic activity [20]. Additional studies with some 3-aminoalkyl-2-oxo-3H-benzoxazole derivatives also demonstrated potent analgesic and anti-inflammatory activity, and showed that

these compounds exerted their in vivo activity by inhibiting the synthesis of prostaglandin E72. (2-oxo-3H-benzoxazol-3-yl)propanamides also showed potent analgesic and anti inflammatory activity [24-27]. (6-acyl-2-oxo-3H-benzoxazol-3-yl)alkanoic acids possessed potent analgesic and anti-inflammatory activity with reduced gastric toxicity [28]. In general, most of the research on this class of compounds included substitutions on positions 3 and 6 of the 2-oxo-3H-benzoxazole nucleus. As a result, 2-oxo-3H-benzoxazoles bearing N-alkyl, N-acyl, N-diaminoalkyl and 6-acyl substituents were reported to have higher anti-inflammatory activity [29 - 30]. Berna et al described the synthesis of two novel 4-phenyl-and 4-(2-chlorophenyl)-6-(5-chloro-2-oxo-3H-benzoxazol-7-yl)-3(2H)-pyridazinone derivatives and showed potent anti-inflammatory activities without causing gastric lesions in the tested animals [31].

Hence these observations prompted us to synthesize a series of methyl-2-(2-(arylideneamino) oxazole-5-ylamino) benzoxazole-5-carboxylate derivatives (VI 1-VI15) and to evaluate their COX - 2 activity. The required starting material, methyl-3-amino-4-hydroxybenzoate (II) was synthesized in good yield (85%) according to reported procedure [33].The starting material (II) on cyclization with cyanogen bromide on rapid stirring at room temperature gave the product, methyl-2-aminobenzoxazole-5-carboxylate (III). The compound (III) on reaction with chloroacetyl chloride in dry benzene yields the compound, methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (IV). The compound (IV) on reaction with urea gave the compound methyl-2-(2-aminooxazol-5-ylamino) benzoxazole-5-carboxylate (V), finally which on reaction with various aromatic aldehydes conveniently converted into the targeted compounds methyl-2-(2-(arylideneamino) oxazole-5-ylamino) benzoxazole-5-carboxylate derivatives (VI).

The synthesized compounds were tested for their ability to inhibit human cyclooxgenase-2 (COX-2) enzyme and the more active compounds were tested for cyclooxgenase-1 (COX-1) inhibition in human whole blood assay [34]. Rofecoxib was used as active control in cyclooxygenase inhibition assay.

The compound which shown IC50 less than 10 mM concentration were tested for COX-1 inhibition. Interestingly two compounds, namely VIId and VIIh have exhibited good activity with high selectivity towards COX-2 inhibition when compared to rest of the compounds. Compound VIId is 368 times more selective towards COX-2 when compared to COX-1 (COX-1 IC50=373mM; COX-2 IC50=lmM). Surprisingly compound VIIh is 454 times more selective towards COX-2 inhibition than COX-1 (COX-1 IC50=500; COX-2 IC50=1.04 mM), interestingly 100 fold more selective than compound VII d. However they are more selective and less potent than rofecoxib in human whole blood assay. Although compounds VI b, VIc, VI e, VI f and VI g possess good selectivity, they have shown moderate activity towards COX-2. In conclusion, these classes of compounds may serve as excellent candidates for selective COX-2 inhibition.

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 XH NMR spectra were recorded on Varian-Gemini 200 MHz spectrometer in DMSO-d6 using TMS as an internal standard and mass spectras were recorded on Schimadzu QP 5050A spectrometer.

The targeted compounds were synthesized as shown in **Scheme-1**.

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

To a solution of aluminum nitrate (40g) in acetic acid- acetic anhydride [1:1] mixture (160ml), was added an appropriate phenol (I, 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°C [33].

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

4-carbomethoxy-2-nitrophenol (II, 10 g) 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°C.

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

1.3 mol of 4-carbomethoxy-2-aminophenol (III) was dissolved in Hit. Methyl alcohol and cooled the solution to 5°C by adding chopped ice. A cold suspension of 1.5 mol of cyanogenbromide in Hit of water was added over a period of 5min with rapid stirring. Continued the stirring for 0.75h at room temperature, 1.3 mol of solid sodium bicarbonate in small portions over a period of 1.5 h was added to bring the pH 6.5 -7.0. Stirring was continued for another lh. 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°C.

IV. Synthesis of methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (V)

A mixture of methyl-2-aminobenzoxazole-5-carboxylate (IV, 0.0lmol) and chloroacetyl chloride (0.0lmol) 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°C.

IV.Synthesis of methyl-2-(2-aminooxazol-5-ylamino) benzoxazole-5-carboxylate (VI)

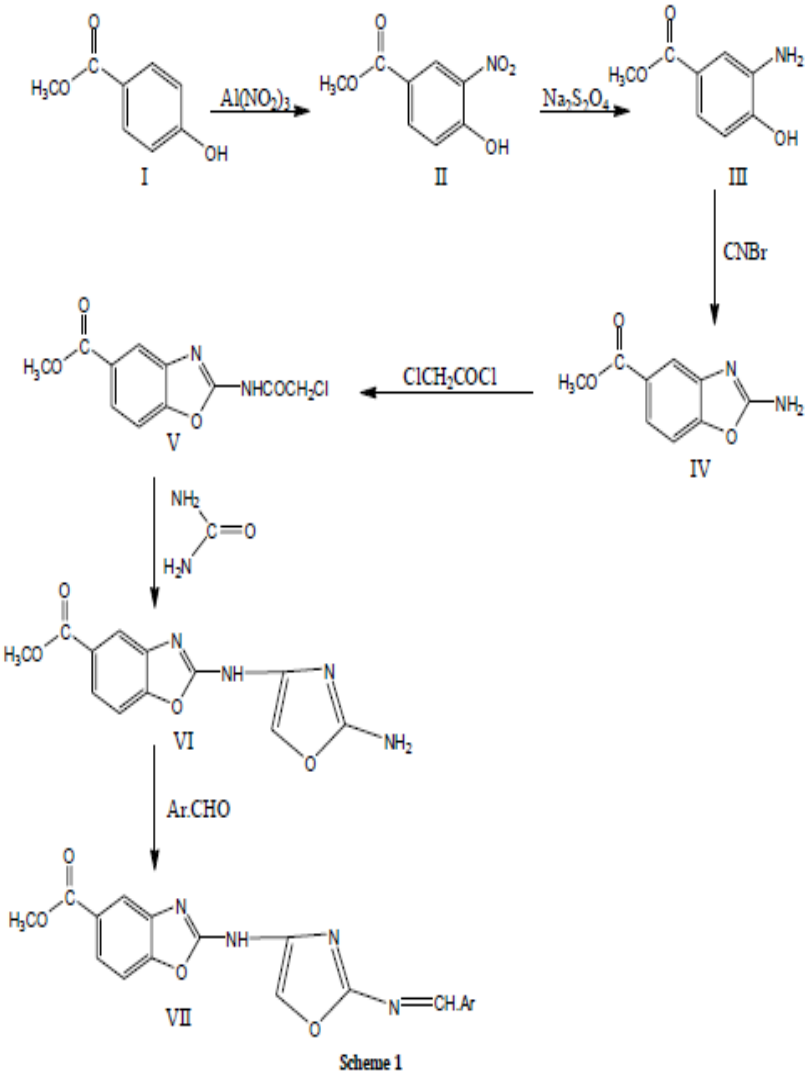
Methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (VI, 0.0lmol) and urea (0.0lmol) were dissolved in 10ml of absolute alcohol in conical flask. The conical flask was hanged with a funnel and was subjected to microwave irradiation at 480 Watts for 5min in LG-Microwave oven. The reaction was monitored 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% NaHC03 solution and purified by recrystallization from ethanol and water mixture found to be containing yield 97% and m.p 199°C.

V.Synthesis of methyl-2-(2-(arylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate (VII)

Methyl-2-(2-aminoxazol-5-ylamino) benzoxazole-5-carboxylate (XII, 0.01mol) and appropriate aromatic aldehydes, Benzaldehyde, salicyladehyde, p-hydroxybenzaldehyde, anisaldehyde, p-dimethylaminobenzaldehyde, p-

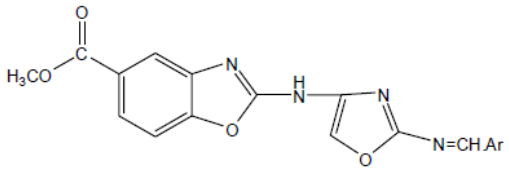
chlorobenzaldehyde, veratraldehyde, cinnam aldehyde and 3, 4, 5-trimethylbenaldehyde (0.015mol) were taken into a conical flask and were dissolved in 10ml of absolute alcohol. The conical flask was hanged with a funnel and was subjected to microwave irradiation at 480 Watts for 7min in LG-Microwave oven. The reaction was monitored by TLC. The reaction mixture was cooled and triturated with crushed ice; the separated solid was filtered, washed with 1% NaHC03 solution and purified by recrystallization from ethanol and water mixture. The compounds were characterized by spectral data. Physical data of all synthesized compounds given in

Table 1.



Scheme 1

Table 1: Physical data of methyl-2-(2-(arylideneamino) oxazol-4-ylamino) benzoxazole-5-carboxylates (VII)



SNo	Compd	Ar	Chemical formula	MeltingPoint (°C)	Yield (%)	Elemenyal analysis (C; N; H; O)
1	VIIa	4-dimethylaminophenyl	$C_{21}H_{19}N_5O_4$	228	94	62.22;4.72;17.27;15.79
2	VIIb	Phenyl	$C_{19}H_{14}N_4O_4$	211	95	62.98; 3.89; 15.46; 17.66
3	VIIc	2-hydroxyphenyl	$C_{19}H_{14}N_4O_5$	229	90	60.23; 3.73; 14.81; 21.14
4	VIId	4-chlorophenyl	$C_{19}H_{13}N_4O_4Cl$	204	91	57.51; 3.30; 14.12, 16.13, 8.94(Cl)
5	VIIe	4-methoxyphenyl	$C_{20}H_{16}N_4O_5$	235	96	61.22; 4.11; 14.28; 20.39
6	VIIf	4-hydroxyphenyl	$C_{19}H_{14}N_4O_5$	236	98	60.23; 3.73; 14.81; 21.14
7	VIIg	2-hydroxy-4-methoxyphenyl	$C_{20}H_{16}N_4O_6$	222	92	58.82; 3.95; 13.72; 23.51
8	VIIh	Cinnamalyl	$C_{21}H_{16}N_4O_4$	233	95	64.64; 4.15; 14.43; 16.48
9	VIIi	3,4,5-trimethylphenyl	$C_{22}H_{20}N_4O_4$	207	93	65.34; 4.98; 13.85; 15.82
7	VIIg	2-hydroxy-4-methoxyphenyl	$C_{20}H_{16}N_4O_6$	222	92	58.82; 3.95; 13.72; 23.51
8	VIIh	Cinnamalyl	$C_{21}H_{16}N_4O_4$	233	95	64.64; 4.15; 14.43; 16.48
9	VIIi	3,4,5-trimethylphenyl	$C_{22}H_{20}N_4O_4$	207	93	65.34; 4.98; 13.85; 15.82

CompoundVIIa: Methyl-(2-(4-(dimethylamino) benzylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate

IR (KBr, cm-1): 3133(NH), 1693 (C=N), 1610 (C=C), 1582 (C=N), 1249 (C-O-C);

^{1} H-NMR (DMSO-d6) 8: 8.8 (s, 1H, CH), 8.6 (s, 1H, Ar-H), 8.1(d, 1H, Ar-H), 8.0(d, 1H, Ar-H), 7.6(s, 1H, Ar-H oxazole ring), 7.5(d, 2H, Ar-H), 6.8(d, 2H, Ar-H) 5.3(s, 1H, NH), 3.8(s, 3H, OCH_3), 3.0(s, 6H, CH_3); MS *[m/z):* M+: 406.1

Compound VIIb: Methyl-2-(2 (benzylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate

IR (KBr, cm-1): 3138(NH), 1696 (C=N), 1602 (C=C), 1576 (C=N), 1233 (C-O-C).

1 H-NMR (DMSO-d6) 8: 8.6 (s, 1H, CH), 8.5 (s, 1H, Ar-H), 8.1(d, 1H, Ar-H), 8.0(d, 1H, Ar-H), 7.8 (d, 2H, ArH), 7.7 (s, 1H, Ar-H oxazole ring), 7.5(t, 3H, Ar-H), 6.8(d, 2H, Ar-H) 5.3(s, 1H, NH), 3.8(s, 3H, OCH3); MS *[m/z):* M+: 363.1

Compound VIIc: methyl-2-(2-(2-hydroxybenzylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate

IR [KBr, cm-1): 3137[NH), 1669 (C=N), 1620 (C=C), 1585 (C=N), 1241 [C-O-C).

^{1} H-NMR [DMSO-d6) 8: 11.2(s, 1H, OH), 8.8 [s, 1H, ArH), 8.3 [s, 1H, CH), 8.1[d, 1H, Ar-H), 8.0[d, 1H, Ar-H), 7.9 [s, 1H, ArH oxazole ring), 7.7 [d, 1H, Ar-H), 7.5[t, 1H, Ar-H), 7.1[t, 1H, Ar-H), 7.0[d, 1H, Ar-H), 5.5[s, 1H, NH), 3.9[s, 3H, OCH_3); MS *[m/z):* M+: 379.1

Compound VIId: Methyl-2-(2-(4-chlorobenzylideneamino) oxazol-5-ylamino) benzoxazole-5 carboxylate

IR [KBr, cm-1): 3112[NH), 1685 [C=N), 1609 [C=C), 1564 (C=N), 1223 [C-O-C).

^{1} H-NMR [DMSO-d6) 8: 8.6[s, 1H, ArH), 8.3 [s, 1H, CH), 8.2[d, 1H, Ar-H), 8.0[d, 1H, Ar-H), 7.9 [s, 1H, ArH oxazole ring), 7.8 [d, 2H, Ar-H), 7.5[d, 2H, Ar-H), 5.1[s, 1H, NH), 3.6[s, 3H, OCH3); MS *[m/z):* M+: 397.1

Compound VIIe: Methyl-2-(2-(4-methoxybenzylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate

IR [KBr, cm-1): 3114[NH), 1647 [C=N), 1615 [C=C), 1543 [C=N), 1212 [C-O-C).

1H-NMR [DMSO-d6) 8: 8.8[s, 1H, ArH), 8.5 [s, 1H, CH), 8.0[d, 1H, Ar-H), 7.8[d, 1H, Ar-H), 7.6 [s, 1H, ArH oxazole ring), 7.4 [d, 2H, Ar-H), 7.3[d, 2H, Ar-H), 5.4[s, 1H, NH), 3.9[s, 3H, OCH3), 3.6[s, 3H, OCH3); MS [m/z): M+: 393.1

Compound VIIf: Methyl-2-(2-(4-hydroxybenzylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate

IR [KBr, cm-1): 3133[NH), 1690 [C=N), 1602 [C=C), 1592 [C=N), 1259 [C-O-C).

[1] H-NMR [DMSO-d6) 8: 9.4[s, 1H, OH), 8.8[s, 1H, ArH), 8.6[s, 1H, CH), 8.1[d, 1H, Ar-H), 8.0[d, 1H, Ar-H), 7.9 [s, 1H, ArH oxazole ring), 7.8 [d, 2H, Ar-H), 6.8[d, 2H, Ar-H), 5.0[s, 1H, NH), 3.6 [s, 3H, OCH3); MS [m/z): M+: 379.1

Compound VIIg: methyl-2-(2-(2-hydroxy-4-methoxybenzy-lideneamino) oxazol-5 ylamino) benzoxazole-5-carboxylate

IR [KBr, cm-1): 3141[NH), 1659 [C=N), 1612 [C=C), 1568 [C=N), 1217 [C-O-C).

[1] H-NMR [DMSO-d6) 8: 11.5[s, 1H, OH), 8.8[s, 1H, ArH), 8.7[s, 1H, CH), 8.4[d, 1H, Ar-H), 8.3[d, 1H, Ar-H), 7.7 [s, 1H, ArH oxazole ring), 7.6 [d, 1H, Ar-H), 6.6[d, 1H, Ar-H), 6.4[s, 1H, ArH), 5.2[s, 1H, NH), 3.9[s, 3H, OCH3), 3.3[s, 3H, OCH3); MS [m/z): M+: 409.0

CompoundVIIh: methyl-2-(2-(3-cinnamylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate

IR [KBr, cm-1): 3103[NH), 1640 [C=N), 1600 [C=C), 1590 [C=N), 1219 [C-O-C).

[1] H-NMR [DMSO-d6) 8: 8.6 [s, 1H, ArH), 8.1 [d, 1H, Ar-H), 8.0[d, 1H, Ar-H), 7.7[s, 1H, Ar-H oxazole ring), 7.6[d, 2H, Ar-H),7.5 [s, 1H, CH), 7.4[t, 1H, Ar-H), 7.3[t, 1H, Ar-H), 7.0 [s, 1H, CH), 5.3 [s, 1H, CH), 4.6 [s, H, NH), 3.8[s, 3H, OCH3); MS [m/z): M+: 389.0

CompoundVIIi: methyl-2-(2-(3, 4, 5-trimethylbenzylideneamino) oxazol-5-ylamino) benzoxazole-5-carboxylate

IR [KBr, cm-1): 3201[NH), 1670 [C=N), 1628 [C=C), 1588 [C=N), 1219 [C-O-C).

[1] H-NMR [DMSO-d6) 8: 8.8 [s, 1H, ArH), 8.5 [d, 1H, CH), 8.1[d, 1H, Ar-H),8.0[s, 1H, ArH), 7.8[s, 1H, Ar-H oxazole ring), 7.3[s, 2H, Ar-H), 5.2 [s, 1H, CH), 5.3 [s, H, NH), 3.9[s, 3H, OCH3), 2.3[s, 6H, CH3), 2.13.9[s, 3H, CH3); MS [m/z): M+: 405.0

Biological Evaluation Cyclooxygenase Inhibitory Screening

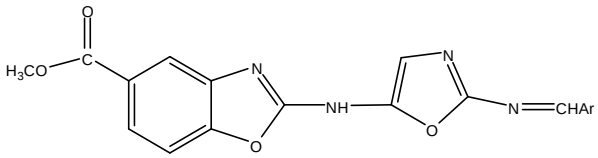
The compoundssynthesized were tested for cyclooxygenase-1 and cyclooxygenase-2 inhibitory activity. The method of Copeland et al. [34] was followed to determine the IC50 values. The enzyme activity is measured using chromogenic assay based on oxidation of N,N,N',N'-tetramethyl-p phenylenediamine (TMPD) during the reduction of prostaglandin G2 to prostaglandin H2 by COX-1 and COX-2 enzymes. COX-1 enzyme is from Ram seminal vesicles (microsomal fraction) and COX-2 is Recombinant human enzyme purified from SF9 cells (microsomal fraction) were used in the assay. The compounds were dissolved in DMSO and stock solution is diluted to required assay concentration. The assay mixture consists of Tris-HC1 buffer (pH 8.0, 100 mM), hematin (15 uM), EDTA (3 uM), enzyme (COX-1 or COX-2, l00mg) and test compound. The mixture was pre-incubated at 25°C for 15 min and then the reaction was initiated by the addition of arachidonic acid (l00uM) and TMPD (120uM) in total volume of 1.0 mL. The enzyme activity was measured by estimating the initial velocity of TMPD oxidation for the first 25 seconds of the reaction following the increase in absorbance at 603 nm. IC50 values are calculated from four parameter least squares non-linear regression analysis of the log dose vs. percentage inhibition plot.

RESULTS AND DISCUSSION

The target compounds were synthesized as outlined in **Scheme 1**. The required starting material, Methyl-3-amino-4-hydroxybenzoate (III) was prepared in good yield (85%) according to reported procedure [33].The Methyl-3-amino-4-hydroxybenzoate (III) on cyclization with cyanogen bromide on rapid stirring at room

temperature gave the product, Methyl 2-aminobenzoxazole-5-carboxylate (IV). The compound Methyl 2-aminobenzoxazole-5-carboxylate (IV) on reaction with chloroacetyl chloride in dry benzene yields the compound, Methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (V). The compound Methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (V) on reaction with urea gave the compound methyl-2-(2-aminooxazol-5-ylamino) benzoxazole-5-carboxylate (V), finally which on reaction with various aromatic aldehydes conveniently converted into the targeted compounds methyl-2-(2-(arylideneamino) oxazole-5-ylamino) benzoxazole-5-carboxylate derivatives (VII).

Table 2: Physical data of Methyl 2-(2-(arylideneamino) oxazol-5-ylamino)benzoxazole- 5-carboxylates (VII)



S.No	Compound	Ar	Chemical formula	COX-2[a]IC_{50}mM	COX-I[b]IC_{50}mM	COX-I/COX-2
1	VIIa	*p*-Dimethylamino	$C_{21}H_{19}N_5O_4$	>10	nt*	—
2	VIIb	Salicylyl	$C_{19}H_{14}N_4O_5$	>10	nt*	-
3	VIIc	Phenyl	$C_{19}H_{14}N_4O_4$	2.63	>500	>190
4	VIId	Anisalyl	$C_{20}H_{16}N_4O_5$	1.0	>368	>368
5	VIIe	Cinnamyl	$C_{21}H_{16}N_4O_4$	6.25	>500	>80
6	VIIf	3,4,5-Trimethylphenyl	$C_{22}H_{20}N_4O_4$	3.84	>500	>130
7	VIIg	*p*-Hydroxy phenyl	$C_{19}H_{14}N_4O_5$	2.27	>500	>220
8	VIIh	*p*-Chlorophenyl	$C_{19}H_{13}N_4O_4Cl$	1.06	>373	>454
9	VIIi	Veratralyl	$C_{20}H_{16}N_4O_6$	2.77	>500	>220

Whole blood as TXB2generation. IC50values were estimated from dose-response curve analysed by nonlinear regression using GraphPad software and values are average of three determinations, nt* samples those have IC50> 10 mM for COX-2 inhibition are not tested for COX-1 inhibition.

In the case of compound VIIc having a simple phenyl group and compound VII g having hydroxyl group on 4-position of phenyl ring showed moderate activity towards COX-2 inhibition. Compound VII h chloro group at 4-position of phenyl ring exhibited more inhibition (IC50=1.06 mM) when compare to compound VI c. In the case of compound VIIi, which bears veratryl group exhibited 2.5-fold less inhibition compared to compound VIIc.

Compound VII d possessing methoxy group on the phenyl ring exhibited highest activity (IC50=lmM) among tested compounds. Remaining compounds are less active with an IC50 more than 10 mM.The compound which

shown IC50less than 10 mM concentration were tested for COX-1 inhibition. Interestingly two compounds, namely VII d and VIIh shown good activity with high selectivity towards COX-2 inhibition when compared to rest of the compounds. Compound VIId is 368 times more selective towards COX-2 when compared to COX-1 (COX-1 IC50=3.84mM; COX-2 IC50=lmM). Surprisingly compound VIIh is 454 times more selective towards COX-2 inhibition than COX-1 (COX-1 IC50=>500; COX-2 IC50=1.06 mM), interestingly 100 fold more selective than compound VIId. However they are more selective and less potent than rofecoxib in human whole blood assay. Although compounds VIIc, VIIe, VIIg, VIIh and VIIi possess good selectivity, they have shown moderate activity towards COX-2 (results presented in Table-2). In conclusion, these classes of compounds may serve as excellent candidates for selective COX-2 inhibition.

CONCLUSION

This study reports the successful synthesis of the title compounds in good yields and moderate to potent COX-2 of these derivatives containing benzoxazole moiety which is comparable with standard drug. It has been observed that the increased COX-2 inhibitory activity is attributed to the presence of pharmacologically active substituents like 2-(dialkylamino) acetamido group.

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