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SYNTHESIS AND DEVELOPMENT OF 1,2,4-TRIAZOLYL-BENZOXAZOLE DERIVATIVES AS NOVEL COX-2 INHIBITORS

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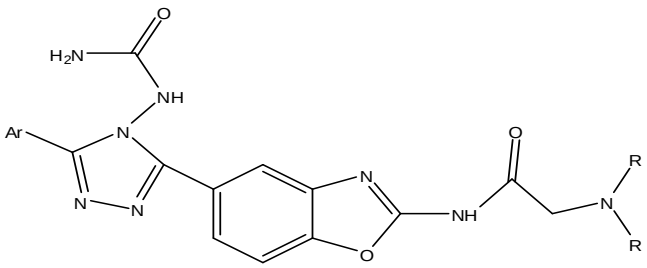
ABSTRACT

In the present research investigations we have synthesized a series of 2-(dialkylamino)-N-(5-(5-aryl-4-ureido-4H-1,2,4-triazol-3-yl)benzoxazol-2-yl)acetamides (Xa1-16).The newly synthesised derivatives were characterized by using the data of IR, ^{1} H NMR and Mass Spectral analysis. Thus synthesized and characterized targeted compounds were further screened for their *in vitro* COX-2 inhibition activity by using TMPD Assay method. The IC_{50} values of Compounds **Xa 13, 14, 15** and **16** were found to be more potent COX-2 inhibitors comparable to that of standard refecoxib, remaining compounds were shown mild to moderate COX-2 inhibitory activity. Thus, this class of compounds apart from the ease of synthesis and higher yield may serve as excellent candidates for selective COX-2 inhibition analysis.

KEYWORDS: Novel benzoxazoles, COX-2 inhibitory activity, ^{1}H NMR, Mass.

INTRODUCTION

Recent observations suggest that substituted benzoxazoles and related heterocycles, possess potential activity with lower toxicities in the chemotherapeutic approach in man [1].Careful literature survey revealed that targets containing benzoxazole moiety, either isolated from plants or accessed by total synthesis, have remarkable biological activities [2] viz. antimicrobial [3], anti histaminic [4], anti parasitics [5], herbicidal [6], antiviral [7], anti-allergic [8], anti [9] and anti-inflammatory [10] activities. Cyclooxygenase (COX) is the key enzyme which catalyses the conversion of arachidonic acid to prostaglandins and thromboxanes[11]. There are two types of cyclooxygenase enzymes, COX-1 and COX-2. COX-1 is a constitutive enzyme, produced in many tissues such as the kidney and the gastrointestinal tract, while COX-2 is inducible and is expressed during inflammation at a site of injury [12-14]. Treatment of inflammation with steroids (i.e., glucocorticoids) is associated with severe side effects leading, at times, to heart, liver, and kidney damages [15]. Presently, non steroidal anti-inflammatory drugs (NSAID) are the preferred agents for the treatment of pain and inflammation, particularly arthritis. Due to broad spectrum of activities reported in the literature so far, we herein report the synthesis of a novel series 2-(dialkylamino)-N-(5-(5-aryl-4-ureido-4H-1,2,4-triazol-3-yl)benzoxazol-2-yl)acetamides (Xa1-16) and 2-(dialkylamino)-N-(5-(5-aryl-4-thioureido-4H-1,2,4-triazol-3-yl)benzoxazol-2-yl)acetamides (X b1-16) as the target compounds in order to examine their Cyclo Oxygenase inhibitory potential in comparison with control drug.



MATERIALS AND METHODS

Melting points of all synthesized compounds were determined by open capillary tubes and are uncorrected. The IR spectra (KBr pellets) were recorded on Spectrum BX series model spectrometer for Compounds **B1** and **B8**. 1H NMR spectra were recorded for compound **B1** on AV 300 MHz NMR Spectrometer, using TMS as internal standard. The mass spectra were recorded on –LCQ ion Mass spectrometer. The purity of the compounds were checked by Thin Layer Chromatography (TLC) on Merck Silica gel 60 F254 pre coated sheet using Chloroform and Ethyl acetate in 1:1 v/v.

General Procedure for the synthesis of 4-carbomethoxy-2-nitrophenl (II)

To a solution of aluminium nitrate (40grms) in acetic acid- acetic anhydride (1:1) mixture (160ml), was added an appropriate phenol (I,40grms) 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. 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).[16]

General Procedure for the synthesis of 4-carbomethoxy-2-amino phenol (III)

4-carbomethoxy-2-nitrophenol (II, 10 grams) 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 (lit [17]. m.p 143^{O}C).

General Procedure for the synthesis of methyl-2-aminobenozoxazole-5-carboxylate (IV)

4-carbomethoxy-2-aminophenol (III, 1.3 moles) was dissolved in 1lit. methyl alcohol and cooled the solution to 5^{O}C by adding chopped ice. A cold suspension of cyanogenbromide (1.5 moles) in 1lit.of water was added over a period of 5min with rapid stirring.

The reaction mixture was stirred for 0.75hrs at room temperature, solid sodium bicarbonate (1.3 moles) 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% and m.p is 238^{O}C.

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3364(NH_2), 1783 (C=O), 1576 (C=N), 1085 (C-O-C).

PMR spectrum (DMSO-d_6) of the compound has been found to exhibit proton signals (δ ppm) at: 7.4(d, 1H, Ar-H), 7.3(d, 1H, Ar-H), 7.2 (s, 1H, Ar-H) 4.7(s, 2H, NH_2), 3.4(s, 3H, CH_3).

On the basis of the above spectral data, the compound obtained could be characterized as methyl- 2-aminobenzoxazole-5-carboxylate (IV).

General Procedure for the synthesis of methyl-2-(2-chloroacetamido benzoxazole-5-carboxylate (VI)

A mixture of methyl-2-aminobenzoxazole-5-carboxylate (IV, 0.01mol) and chloroacetyl chloride (0.01mol) was taken in 20 ml of dry benzene and the reaction mixture was refluxed for 5hrs 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.

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 1775(C=O), 1682 (C=O), 1575 (C=N), 1560(C=C), 1085 (C-O-C).

^{1}H NMR Spectrum (DMSO-d_6) has been found to exhibit characteristic proton signals (δ, ppm) at: 8.3 (s, 1H, Ar-H), 7.9-8.0 (dd, 2H, Ar-H), 7.8 (s,1H, NH), 4.4 (s,2H, CH_2), 3.8 (s, 3H, CH_3).

On the basis of the above spectral data, the compound obtained could be characterized as methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (VI).

General Procedure for the synthesis of methyl-2-{(2-(dialylamino) Acetamido)}-benzoxazole-5-carboxylates (VI)

To a solution of Methyl 2-(2-chloroacetamido) benzoxazole-5-carboxylate (V, 0.01mol) in 20 ml of dry Acetone, N, N-dialkylamine (0.01mol) was added and the reaction mixture was refluxed for 5hrs on a water bath. The colorless products formed were recrystallized by suitable solvents. The compounds were characterized as the methyl 2-{(2-dialkylamino)acetamido)}-benzoxazole-5-carboxylates (VI) by their spectral data.

For instance, to a solution of Methyl 2-(2-chloroacetamido) benzoxazole-5-carboxylate (V, 0.01mol) in 20ml of dry Acetone, dimethylamine (0.01mol) was added and the reaction mixture was refluxed for 5hrs, the colorless product formed has been purified by recrystallization from alcohol resulted white solid, yield 65% m.p 164^{O}C.

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 1683 (C=O), 1588 (C=N), 1284 (C-O-C), 1126 (C-N).

^{1}H NMR Spectrum (DMSO-d_6) has been found to exhibit characteristic proton signals (δ, ppm) at: 8.6(s,1H,Ar-H), 8.1 (dd, 2H, Ar-H), 7.8(dd, 2H, Ar-H), 7.7 (s,1H, NH), 3.9 (s, 3H, CH_3), 3.2(s,2H, CH_2), 2.3 (s, 3H, $(CH_3)_2$).

On the basis of the above spectral data, the compound obtained could be characterized as methyl 2-{(2-dimethylamino)acetamido)}-benzoxazole-5-carboxylates (VIb).

General procedure for the synthesis of 2-(dialkylamino)-N-(5-(hydrazinecarbonyl)benzoxazol-2-yl)acetamide (VII)

Methyl-2-{(2-dialkylamino)acetamido)}-benzoxazole-5-carboxylates (VI) (0.01 mol) was dissolved in ethanol and added hydrazinehydrate (99%) (0.03 mol) and the reaction mixture was refluxed for 2 h, cooled in ice bath, The obtained product was filtered, dried and recrystallised by using ethyl alcohol.[18]

General Procedure for the synthesis of N-(5-(2-arylidenehydrazinecarbonyl)benzoxazol-2-yl)-2-(dialkylamino)acetamide (VIII)

2-(dialkylamino)-N-(5-(hydrazinecarbonyl)benzoxazol-2-yl)acetamide (VII) (0.01mol) and appropriate aromatic aldehydes (0.015mol) in alcohol(20ml) with 2 to 3 drops of acetic acid, heated under reflux on a water bath for one hour. The solvent was removed to possible extent by distillation under reduced pressure. The product thus obtained was filtered, washed with water dried and purified by recrystallization from ethyl alcohol.[19]

General Procedure for the synthesis of 2-(dialkylamino)-N-(5-(5-aryl-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)acetamide (IX)

A mixture of N-(5-(2-arylidenehydrazinecarbonyl)benzoxazol-2-yl)-2-(dialkylamino)acetamide (VIII) (0.01mol) and sodium acetate (0.02mol) were dissolved in 30 ml of glacial acetic acid with stirring. Which was added with bromine (0.7 ml in 5ml of glacial acetic acid) slowly while stirring until the colour of bromine exists. Then the reaction mixture was poured into crushed ice and collected the precipitate and washed with water, then dried. The resulting compound was purified by recrystallization from appropriate portion of DMF and water.

General Procedure for the synthesis of 2-(dialkylamino)-N-(5-(5-aryl-4-ureido-4H-1,2,4-triazol-3-yl)benzoxazol-2-yl)acetamides (Xa)

Compound 2-(dialkylamino)-N-(5-(5-aryl-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)acetamide (IX) (0.001 mol) was dissolved in glacial acetic acid and added with semicarbazide hydrochloride(0.0015 mol) and pinch of sodium acetate . The contents of the flask were refluxed for 8 h, poured into crushed ice. The product obtained was filtered, washed with cold alcohol, dried and recrystallised from methyl alcohol.

Adopting this procedure totally we have synthesized sixteen derivatives. The yields, melting points and physical data of newly synthesized compounds were summarized in table-1.

Cyclooxygenase -2 inhibitory Screening[20]

The compounds prepared were tested for cyclooxygenase – 2 inhibitory activity. The method of Graph Pad Prism was followed to determine the IC_{50} values. The enzyme activity is measured using chromogenic assay based on oxidation of of N,N,N′,N′-tetramethyl-p-phenylenediamine (TMPD) during the reduction of prostaglandin G2 to prostaglandin H2 by COX–2 enzymes. 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-HCl buffer (pH 8.0, 100 mM), hematin (15 μM), EDTA (3 μM), enzyme (COX-1 or COX-2, 100μg) 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 (100μM) and TMPD (120μM) 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. IC_50 values calculated from four parameter least squares non-linear regression analysis of the log dose v/s percentage inhibition plot. The results were given in table-2.

SPECTRAL DATA

Compound Xa1:

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3450 (NH2), 3146 (NH), 1672 (C=O), 1626(C=C), 1528 (C=N), 1342 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at:8.2 (d, 2H, Ar-H), 8.0 (s,1H,ArH), 7.9(s, 1H, NH), 7.8(d, 2H, ArH), 7.5(d,2H,ArH), 7.4 (t, 1H, ArH), 6.2(s, 2H,NH_2), 6.0(s, 1H, NH), 4.0(s, 2H, CH_2), 2.7(s, 6H, $(CH_3)_2$)
MS (m/z%): 420.17 (theoretically), MS (m/Z %) : 421.0 (Practical)

Compound Xa2:

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3453 (NH2), 3143 (NH), 1675 (C=O), 1623(C=C), 1531 (C=N), 1345 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at:8.0 (s, 1H, Ar-H), 7.9 (s,1H,NH), 7.8(d, 2H, ArH), 7.6(d, 2H, ArH), 7.0(d,2H,ArH), 6.4 (s, 2H, NH_2), 6.1(s, 1H,NH), 4.2(s, 1H, CH_2), 3.0(s, 6H, $(CH_3)_2$), 2.8(s, 6H, $(CH_3)_2$)
MS (m/z%): 463.2 (theoretically), MS (m/Z %) : 463.0 (Practical)

Compound Xa3:

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3458 (NH2), 3148 (NH), 1680 (C=O), 1628(C=C), 1539 (C=N), 1349 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at:9.6 (s, 1H, OH), 8.1 (s,1H,ArH), 8.0(s, 1H, NH), 7.8(d, 2H, ArH), 7.6(d,1H, ArH), 7.4 (t,1H, ArH), 7.1(t, 2H,ArH), 6.3(s, 2H,NH_2),6.1 (s, 1H, NH), 4.0(s, 2H, CH_2), 2.9(s, 6H, $(CH_3)_2$)
MS (m/z%): 436.16 (theoretically), MS (m/Z %) : 434.0 (Practical)

Compound Xa4:

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**

3452 (NH2), 3154 (NH), 1674 (C=O), 1634(C=C), 1533 (C=N), 1355 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.2(s,1H,ArH), 8.1(s, 1H, NH), 7.9(d, 2H, ArH), 7.8(d,2H, ArH), 7.5 (d,2H, ArH), 6.4(s, 2H,NH_2), 5.9(s, 1H,NH), 4.3(s, 2H, CH_2), 3.8(s,3H,)CH_3), 2.8(s,6H, $(CH_3)_2$)
MS (m/z%): 450.18 (theoretically), MS (m/Z %) : 451.0 (Practical)

Compound Xa5:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3453 (NH2), 3158 (NH), 1679 (C=O), 1640(C=C), 1540 (C=N), 1363 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.3(d,2H,ArH), 8.0(s,1H, ArH), 7.9(s, 1H, NH), 7.8(d,2H, ArH), 7.5 (t,2H, ArH), 7.4(t,1H, ArH), 6.2(s,2H,NH_2), 6.0(s, 1H,NH), 3.2(s, 2H, CH_2), 2.8(d,4H, $(CH_2)_2$), 1.0(s, 6H, $(CH_3)_2$).
MS (m/z%): 448.20 (theoretically), MS (m/Z %) : 449.0 (Practical)

Compound Xa6:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3463 (NH2), 3167 (NH), 1687 (C=O), 1647(C=C), 1546 (C=N), 1368 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.1(s,1H,ArH), 8.0(s,1H,NH), 7.9(d,2H,ArH), 7.8(d,2H,ArH), 6.8(d,2H,ArH), 6.2(s,2H,NH_2), 5.7(s, 1H,NH), 3.3(s, 2H, CH_2), 3.1(s, 6H, $(CH_3)_2$), 2.6(d,4H, $(CH_2)_2$), 1.1(s, 6H, $(CH_3)_2$).
MS (m/z%): 491.20 (theoretically), MS (m/Z %) : 492.0 (Practical)

Compound Xa7:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3454 (NH2), 3167 (NH), 1693 (C=O), 1640(C=C), 1541 (C=N), 1377 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 9.5(s,1H, OH), 8.1(s,1H,ArH), 8.0(s,1H,NH),7.8(d,2H,ArH),7.6(d,1H,ArH),
7.2(t,1H,ArH), 7.1 (d, 2H, ArH), 6.2(s,2H,NH_2), 5.5(s, 1H,NH), 3.3(s, 2H, CH_2), 2.7(d,4H, $(CH_2)_2$), 1.0(s, 6H, $(CH_3)_2$).
MS (m/z%): 464.19 (theoretically), MS (m/Z %) : 465.0 (Practical)

Compound Xa8:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3468 (NH2), 3163 (NH), 1693 (C=O), 1642(C=C), 1553 (C=N), 1362 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.1(s,1H,ArH), 7.9(s,1H,NH), 7.8(d,2H,ArH), 7.1(d,2H,ArH), 6.1(s,2H,NH_2), 5.9(s, 1H,NH), 3.9(s, 3H, OCH_3), 3.4 (s, 2H, CH_2), 2.4(d,4H, $(CH_2)_2$), 1.1(s, 6H, $(CH_3)_2$).
MS (m/z%): 478.21 (theoretically), MS (m/Z %) : 479.0 (Practical)

Compound Xa9:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3474 (NH2), 3163 (NH), 1699 (C=O), 1651(C=C), 1543 (C=N), 1361 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.3(d,2H,ArH), 8.1(s,1H,ArH), 8.0(s,1H,ArH), 7.8(d,2H,ArH), 7.5(t, 2H, ArH), 7.4 (t, 1H, ArH), 6.2(s,2H,NH_2), 5.8(s, 1H,NH), 3.4 (s, 2H, CH_2), 2.4(d,4H, $(CH_2)_2$ piperidine), 1.5(m, 6H, $(CH_2)_3$ piperidine).
MS (m/z%): 460.21 (theoretically), MS (m/Z %) : 461.0 (Practical)

Compound Xa10:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3467 (NH2), 3170 (NH), 1692 (C=O), 1658(C=C), 1536 (C=N), 1368 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.1(s,1H,ArH), 8.0(d,2H,ArH), 7.9(d,2H,ArH), 6.9(d, 2H, ArH), 6.2 (s,2H,NH_2), 6.0(s, 1H,NH), 3.3 (s, 2H, CH_2), 3.1 (s, 6H, $(CH_3)_2$, 2.5(d,4H,$(CH_2)_2$piperidine), 1.5(m, 6H, $(CH_2)_3$ piperidine).
MS (m/z%): 503.24 (theoretically), MS (m/Z %) : 504.0 (Practical)

Compound Xa11:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3455 (NH2), 3162 (NH), 1684 (C=O), 1650(C=C), 1544 (C=N), 1360 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 9.6 (s,1H, OH), 8.1(s,1H,ArH), 8.0(s,1H,NH), 7.8(d,2H,ArH), 7.6(s, 1H, ArH), 7.2 (t,1H,ArH), 7.1 (t, 2H,ArH), 6.2 (s, 2H, NH_2), 6.0(s, 1H,NH), 3.2 (s, 2H, CH_2), 2.5(d,4H,$(CH_2)_2$piperidine), 1.6(m, 6H, $(CH_2)_3$ piperidine).
MS (m/z%): 476.19 (theoretically), MS (m/Z %) : 477.0 (Practical)

Compound Xa12:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3464 (NH2), 3172 (NH), 1695 (C=O), 1612(C=C), 1557 (C=N), 1374 (C-O-C).

PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.1(s,1H,ArH), 8.0(s,1H,NH), 7.9(d,2H,ArH), 7.8(d, 2H, ArH), 7.1 (d,2H,ArH), 6.3 (s, 2H, NH_2), 5.7(s, 1H,NH), 3.8 (s, 3H, OCH_3), 3.3 (s, 2H, CH_2), 3.5(d,4H,$(CH_2)_2$piperidine), 1.5(m, 6H, $(CH_2)_3$ piperidine).
MS (m/z%): 490.21 (theoretically), MS (m/Z %) : 491.0 (Practical)

Compound Xa13:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3467 (NH2), 3169 (NH), 1691 (C=O), 1616(C=C), 1552 (C=N), 1379 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.2 (d, 2H, ArH), 8.0(s,1H,ArH), 7.9(s,1H,NH), 7.8(d,2H,ArH), 7.5(d, 2H, ArH), 7.4 (t,1H,ArH), 6.1 (s, 2H, NH_2), 5.9(s, 1H,NH), 3.6(d, 4H, $(CH_2)_2$ morpholine), 3.3 (s, 2H, CH_2), 2.5(d,4H,$(CH_2)_2$ morpholine).
MS (m/z%): 462.28 (theoretically), MS (m/Z %) : 463.0 (Practical)

Compound Xa14:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3468 (NH2), 3171 (NH), 1694 (C=O), 1620(C=C), 1557 (C=N), 1385 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.1 (s,1H,ArH), 8.0(s,1H,NH), 7.9(d,2H,ArH), 7.8(d, 2H, ArH), 6.8 (d,2H,ArH), 6.2 (s, 2H, NH_2), 6.0(s, 1H,NH), 3.6(d, 4H, $(CH_2)_2$ morpholine), 3.1 (s, 2H, CH_2), 3.0(s, 6H, $(CH_3)_2$), 2.6(d,4H,$(CH_2)_2$ morpholine).
MS (m/z%): 505.22 (theoretically), MS (m/Z %) : 507.0 (Practical)

Compound Xa15:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3477 (NH2), 3163 (NH), 1687 (C=O), 1614(C=C), 1551 (C=N), 1380 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 9.4 (S, 1H, oH), 8.1 (s,1H,ArH), 7.9(s,1H,NH), 7.8(d,2H,ArH), 7.6(d, 2H, ArH), 7.2 (t, 1H,ArH), 7.0(d, 2HArH), 6.2 (s, 2H, NH_2), 6.0(s, 1H,NH), 3.5(d, 4H, $(CH_2)_2$ morpholine), 3.1 (s, 2H, CH_2), 2.5(d,4H,$(CH_2)_2$ morpholine).
MS (m/z%): 478.12 (theoretically), MS (m/Z %) : 479.0 (Practical)

Compound Xa16:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands at: **(cm^{-1}):**
3481(NH2), 3184 (NH), 1690 (C=O), 1630(C=C), 1562 (C=N), 1396 (C-O-C).
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□
ppm) at: 8.0 (s,1H,ArH), 7.9(s,1H,NH), 7.8(d,2H,ArH), 7.7(d, 2H, ArH), 7.1 (d,2H,ArH), 6.3 (s, 2H, NH_2), 6.0(s, 1H,NH), 3.8 (s, 3H, OCH_3), 3.7(d, 4H, $(CH_2)_2$ morpholine), 3.2(s, 2H, CH_2), 2.6(d,4H,$(CH_2)_2$ morpholine).
MS (m/z%): 492.19 (theoretically), MS (m/Z %) : 493.0 (Practical)

RESULTS AND DISCUSSION

The targeted compounds were synthesized by nitration of appropriate phenol followed by reduction treated with cyanogen bromide cyclized to with benzoxazole. Which on treatment with clhoroacetyl chloride in dry benzene followed by treatment with 2^0 amines in dry acetone. The resulting compound was treated with hydrazine hydrate followed by treatment with various aromatic aldehydes. The resultant A mixture and sodium acetate were dissolved in glacial acetic acid with stirring. Which was added with bromine (0.7 ml in 5ml of glacial acetic acid) slowly while stirring until the colour of bromine exists. Finally the compounds were treated with semicarbazide and thiosemicarbazide. The yields were found to be 60 to 78 percentages. The structures of the synthesized compounds were characterized by IR, ^{1}HNMR, mass spectral analysis. All the derivatives synthesized were shown good to moderate activity when comparing with the IC_{50} value of Refecoxib (standard) i.e. 12.790.

Among all the synthesized compounds, compounds with simple aliphatic secondary amines i.e dimethyl amine and di ethyl amine shown mild to moderate cyclo oxygenase-2 inhibitory activity where as compounds with heterocyclic secondary amines i.e pyperdine and morpholine shown good cyclo oxygenase-2 inhibitory activity comparatively.

The compounds Xa1, Xa2, Xa3, Xa 4, Xa5, Xa6, Xa7 and Xa8 were shown very poor cyclo oxygenase-2 inhibitory activity compare to the standard drug.

Compound Xa9, Xa10, Xa11 and Xa12 were shown moderate activity with the IC_{50} values of 10.21, 10.387, 11.031 and 10.210 respectively. Interestingly Compound Xa13, Xa14 and Xa15 were showed very potent COX-2 inhibitory activity when comparing with the standard with the IC_{50} values of 08.241,8.210, 07.101 and 09.198 respectively. Interestingly all these four compounds were showed good activity with high selectivity towards COX-2 inhibition when compared to rest of the compounds. In conclusion, these classes of compounds may serve as excellent candidates for selective COX-2 inhibition (Table2).

Scheme

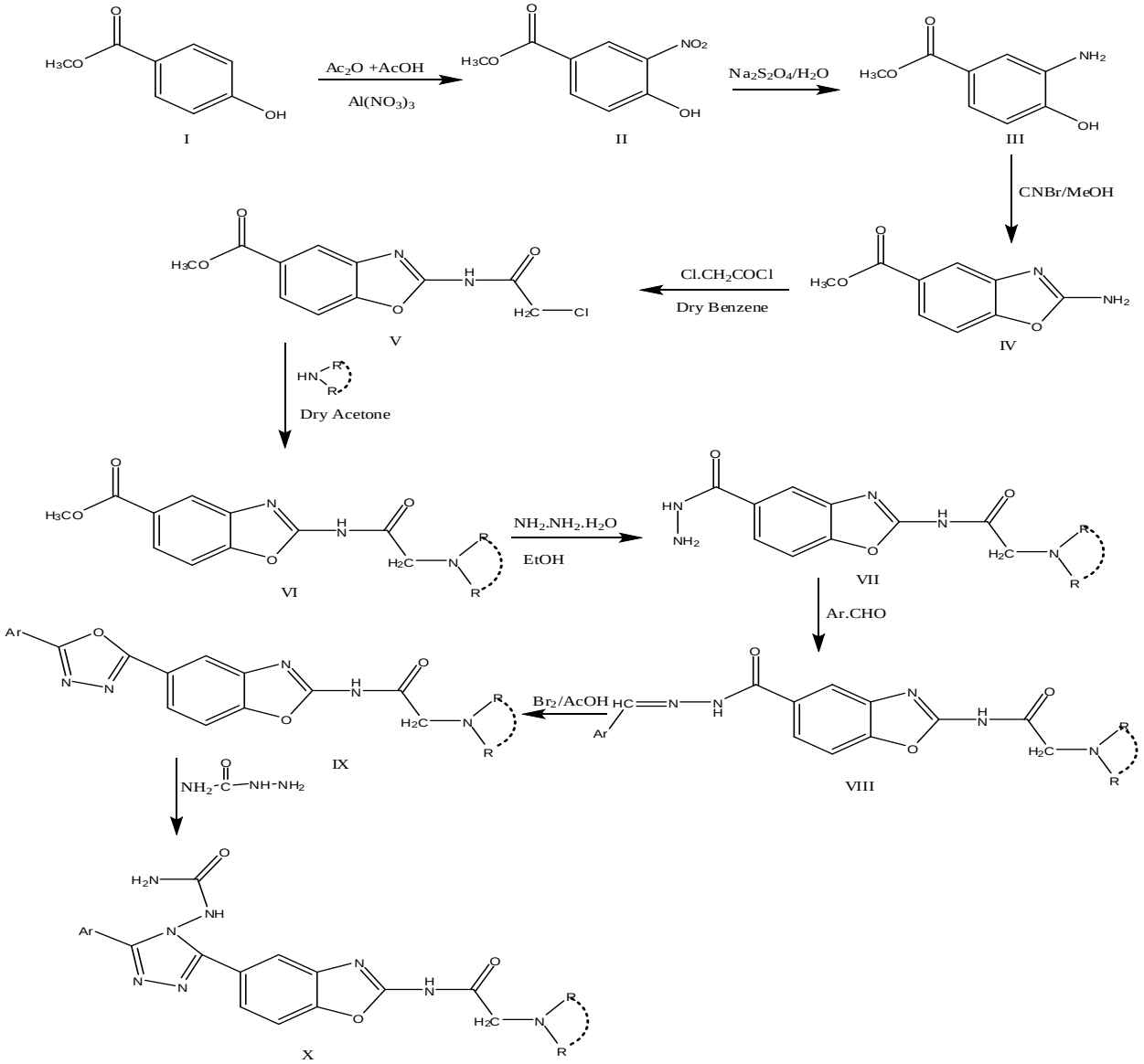
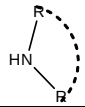


Table 1: Physical Data of 2-(dialkylamino)-N-(5-(5-aryl-4-ureido-4H-1,2,4-triazol-3-yl)benzoxazol-2-yl)acetamides (Xa)

S.No	Compd	X		Ar	Molecular Formula	MP (^{O}C)	% of yield
1	Xa1	O	-N(CH_3)$_2$	Phenyl	$C_{20}H_{20}N_8O_3$	207	60
2	Xa2	O	-N(CH_3)$_2$	4-dimethylaminophenyl	$C_{22}H_{25}N_9O_3$	228	65
3	Xa3	O	-N(CH_3)$_2$	2-hydroxyphenyl	$C_{20}H_{20}N_8O_4$	189	71
4	Xa4	O	-N(CH_3)$_2$	Anisyl	$C_{21}H_{22}N_8O_4$	140	70
5	Xa5	O	-N(CH_2CH_3)$_2$	Phenyl	$C_{22}H_{24}N_8O_3$	210	65
6	Xa6	O	-N(CH_2CH_3)$_2$	4-dimethylaminophenyl	$C_{24}H_{29}N_9O_3$	202	65
7	Xa7	O	-N(CH_2CH_3)$_2$	2-hydroxyphenyl	$C_{22}H_{24}N_8O_4$	180	70
8	Xa8	O	-N(CH_2CH_3)$_2$	Anisyl	$C_{23}H_{26}N_8O_4$	186	64
9	Xa9	O		Phenyl	$C_{23}H_{24}N_8O_3$	210	75
10	Xa10	O		4-dimethylaminophenyl	$C_{25}H_{29}N_9O_3$	214	78
11	Xa11	O		2-hydroxyphenyl	$C_{23}H_{24}N_8O_4$	190	78

12	Xa12	O		Anisyl	$C_{24}H_{26}N_8O_4$	230	65
13	Xa13	O		Phenyl	$C_{22}H_{22}N_8O_4$	221	71
14	Xa14	O		4-dimethylaminophenyl	$C_{24}H_{27}N_9O_4$	180	70
15	Xa15	O		2-hydroxyphenyl	$C_{22}H_{22}N_8O_5$	186	64
16	Xa16	O		Anisyl	$C_{23}H_{24}N_8O_5$	210	75

Table2: COX-2 inhbition activity of 2-(dialkylamino)-N-(5-(5-aryl-4-ureido-4H-1,2,4-triazol-3-yl)benzoxazol-2-yl)acetamides (Xa)

S.No	Compound	IC_{50} Value
1	**Xa1**	**15.245**
2	**Xa2**	**14.154**
3	**Xa3**	**16.021**
4	**Xa4**	**17.012**
5	**Xa5**	**15.462**
6	**Xa6**	**15.381**
7	**Xa7**	**16.461**
8	**Xa8**	**18.201**
9	**Xa9**	**10.210**
10	**Xa10**	**10.387**
11	**Xa11**	**11.031**
12	**Xa12**	**10.210**
13	**Xa13**	**08.241**
14	**Xa14**	**08.210**
15	**Xa15**	**07.101**
16	**Xa16**	**09.198**
Std	**Refecoxib**	**12.790**

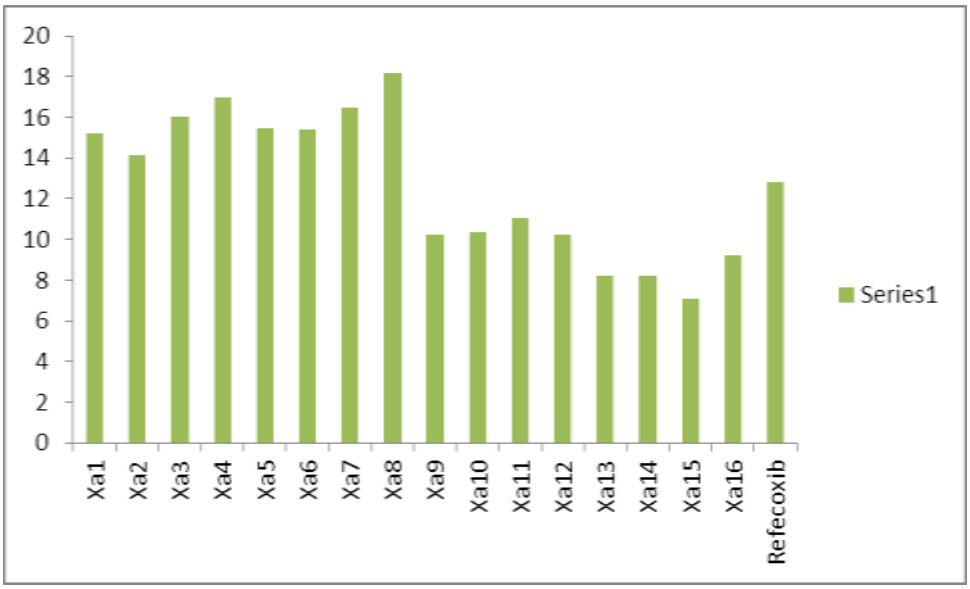


Fig 1: COX-2 inhibitory activity of COX-2 inhbition activity of 2-(dialkylamino)-N-(5-(5-aryl-4-ureido-4H-1,2,4-triazol-3-yl)benzoxazol-2-yl)acetamides (Xa)

CONCLUSION

The study reports a simple approach for the synthesis **1,2,4**-triazolyl-benzoxazole derivatives. The cyclo oxygenase -2 inhibitory activity of synthesized compounds showed moderate to good activity *in vitro*. The overall activity of compounds motivates for the future study.

REFERENCES

1. Hisano. T, Ichikawa. M, Tsumoto. K and Tasaki, M, Synthesis of benzoxazoles, benzothiazoles and benzimidazoles and evaluation of their antifungal,insecticidal and herbici-dal activities. Chem. Pharm. Bull., 1982; 30: 2996-3004.

2. Suresh.K, Tipparaju, Sipak Joyasawal, Marco Pieroni, Marcel Kaiser, Reto Brun, Alan P, Kozikowski, In Pursuit of Natural Product Leads: Synthesis and Biological Evaluation of 2-[3-hydroxy-2-[(3-hydroxypyridine-2carbonyl)amino]phenyl]benzoxazole-4-carboxylic acid (A-33853) and Its Analogues: Discovery of N-(2-Benzoxazol-2-ylphenyl)benzamides as Novel Antileishmanial Chemotypes J. Med. Chem., 2008; 51(23): 7344–7347.
3. Ilkay O rena, Ozlem Temiza, Ismail Yalcına, Esin Senera, Nurten Altanlarb, Synthesis and antimicrobial activity of some novel 2,5- and/or 6-substituted benzoxazole and benzimidazole derivatives European Journal of PharmaceuticalSciences, 1998; 7; 153–160.
4. Esin Akıener, Kamuran K, Bingol, lkay Oren, Ozlem Temiz Arpaci, Smail Yalcın, Nurten Altanlar Synthesis and microbiological activity of some N-(hydroxyphenyl)benzamides and phenylacetamides as the possible metabolites of antimicrobial active benzoxazoles: part II Il Farmaco, 2000; 55(6-7): 469-476.
5. Albert Darque, Aurelien Dumetre, Sebastien Hutter, Gilles Casano, Maxime Robin, Christophe Pannecouque, Nadine Azas, Synthesis and biological evaluation of new heterocyclic quinolinones as anti-parasite and anti-HIV drug candidates Bioorganic & Medicinal Chemistry Letters, 2009; 19(20): 5962-5964.
6. Masahiko Ikeguchi, Masahiko Sawaki, Hitoshi Nakayama, Hiroshi Kikugawa, Hiroshi Yoshii, Synthesis and herbicidal activity of new oxazinone herbicides with a long-lasting herbicidal activity against Echinochloa oryzicola - Pest Management Science 2004; 60(10): 945–1049.
7. Maurice Medebielle, Samia Ait-Mohand, Conrad Burkhloder, William R. Dolbier Jr, Geraldine Laumond, Anne-Marie Aubertin, Syntheses of new difluoromethylene benzoxazole and 1,2,4-oxadiazole derivatives, as potent nonnucleoside HIV-1 reverse transcriptase inhibitors Journal of Fluorine Chemistry, 2005; 126(4): 533-540.
8. Stephen M.Coutts, Atul Khandwala, Ira Weinryb, REV 2871 (CHBZ): A potent antiallergic agent with a novel mechanism of action: II. Studies on the mechanism of action Biochemical Pharmacology, 1987; 36(5): 673-682.
9. Haugwitz R, Angel.D, R.G.Jacobs, G.A. Maurer, B.V. Narayanan,V.L. Cruthers, L.R. Szanto, Antiparasitic agents. - Synthesis and anthelmintic activities of novel heteroaromatic substituted isothiocyanatobenzoxazoles and –benzothiazoles, J.Med. Chem.1982; 21(2): 969-974.
10. A.Srinivas, J.Vidya Sagar, M.Sarangapani, Design, Synthesis and Biological Evaluation of Benzoxazole Derivatives as Cyclooxygensase-2 Inhibitors, International Journal of Pharmaceutical Sciences, 2010; 2(10): 7-12.
11. Vane J R. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol. 1971; 231: 232-5.
12. Xie WL, Chipman JG, Robertson DL, Erikson RL, Simmons DL, Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl Acad Sci USA , 1991; 88(7): 2692-6.
13. Kubuju D.A, Fletcher. B. S, Varnum. B.C, Lim. R. A, Herschman, H. R. J. Biol. Chem. 1991; 266: 12866.
14. Hla. T, Neilson. K, Human cyclooxygenase-2 cDNA, Proc Natl Acad Sci USA, 1992; 89(16):7384-8
15. Parfitt K, Martindale- The Complete Drug Reference, Pharmaceutical Press, 1999; 32: 1010.
16. K. Rajmohan and N.V. Subba Rao, *Indian J. Chem.*, 1973; 11: 1076.
17. A. Finhorn and B.Ptyl, *Ann. Chem.*, 1900; 311: 46.
18. Mohamed Al-Omar A, Ebthehal Al-Abdullah S, Ihsan Shehata A, Elsayed Habib E, Tarek Ibrahim M, Ali El-Emam A, Molecules, 2010; 15: 2526.
19. Harish R, Ravichandran V, Arun Kumar G, Murlidhar K, Pradeep M, Int. Jr of Pharma.Sci. & Nano Tech, 2009; 2(3): 661.
20. Ranatunge RR, Augustyniak M, Bandarage UK, Earl RA, Ellis JL, Garvey DS, Janero DR, Letts LG, Martino AM, Murty MG, Richardson SK, Schroeder JD,Shumway MJ, Tam SW, Trocha AM, Young DV. Synthesis and selective cyclooxygenase-2 inhibitory activity of a series of novel, nitric oxide donor-containing pyrazoles, 2004; J Med Chem. 22; 47(9): 2180-93.