Chemistry & Biology Interface, 2017, 7, 2, 154-165

RESEARCH PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Imidazole[1,2-a]pyridine derivatives as selective COX-2 inhibitors

Sunil B. Jadhav[a,b], Samreen Fatema[a,b], Mazahar Farooqui[a,b]*

[a]*Post Graduate and Research Centre, Maulana Azad College, Aurangabad 431001. India.*
[b]*Dr Rafiq Zakaria College for Womens, Navkhanda, Aurangabad. 431001. India*
Email – mazahar_64@rediffmail.com; Mobile: +919422214785
Received 22 December 2016; Accepted 18 March 2017

Abstract: A series of new eighteen compounds were designed and synthesized using hybrid combination approach, wherein imidazo[1,2-a]pyridine, *trans-stilbene* and substituted pyrazole pharmacophores were combined within single frame to look in the better selective COX-2 inhibition. In the preliminary screening, these novel compounds were tested for their COX-2 inhibition ability where COX-2 inhibitor celecoxib was used as standard reference. As a result, the investigative hybrid structural analogy exhibited moderate to good COX-2 inhibitory activities. Within series, compounds **17** and **18** showed good COX-2 inhibition and compound **18** displayed maximum selectivity (COX-1/COX-2).

Keywords: Pyrazole aldehyde, celecoxib, COX-1/COX-2 activity, selectivity.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a useful family of therapeutics, accounting about 5% of entire prescribed medications [1]. Their inhibitory effect on cyclooxygenase (COX) activity and resulting decrease in prostaglandins (PGs) such as PGE2 has been shown to be responsible for their anti-inflammatory actions [2,3]. Cyclooxygenase (COX) is the key enzyme in the arachidonic acid cascade. At 1990s, two isoforms of COX (COX-1 and COX-2) were discovered [4-6], COX-1 is present in several tissues such as stomach, kidney and platelets, other isoform (COX-2) cytokine inducible and is expressed in many inflammatory cells [7] and takes part in inflammation. Hence the molecules or drugs that inhibit the enzymatic activity of COX-2 have been recognized as great therapeutic value. [8]. Marketed coxibs like celecoxib [9], rofecoxib [10], and valdecoxib [11] are the selective COX-2 inhibitors. However, issues of an increased cardiovascular morbidity and mortality followed, and the manufacturer Merck was forced to withdraw rofecoxib (Vivox) from market. Likewise, other coxibs have also either decomposed or had placed limits on their clinical

use [12, 13]. This scenario led to the need of novel selective COX-2 inhibitors, devoid of the undesirable effects associated with classical and nonselective NSAIDs [14].

In persistence with our research activities [15-18] and with an innovative platform to investigate COX-2 selective inhibitor, we focused to the biological importance of imidazo[1,2-a]pyridine and naturally occurring *trans-stilbenes*. Given this ground, we boarded on the structure which is combination of imidazo[1,2-a]pyridine and *trans-stilanoids* along with one additional pharmacophoric unit (**Fig 1**). Imidazo[1,2-a]pyridine is well known moiety in drug discovery research as it is a attractive heterocycle with various biological activities like anti-viral, anti-ulcer, anti-cancer, anti-tuberculosis and anti-inflammatory [19]. Resveratrol, a naturally occurring *trans-stilbenes* and its derivatives are documented for selective COX-2 inhibition [20,21].

To carry structural similarities with COX-2 inhibitor celecoxib, pyrazole (with multi-substituted phenyl and N-substituted phenyl) was employed as third pharmacophoric unit (**Fig 1**). Hence, our targeted hybrid molecules (**1-18**) were combination of three different precursors' viz., imidazo[1,2-a]pyridines, *trans-stilbene* and pyrazole with multi-substituted phenyl ring and *N*-phenyl ring.

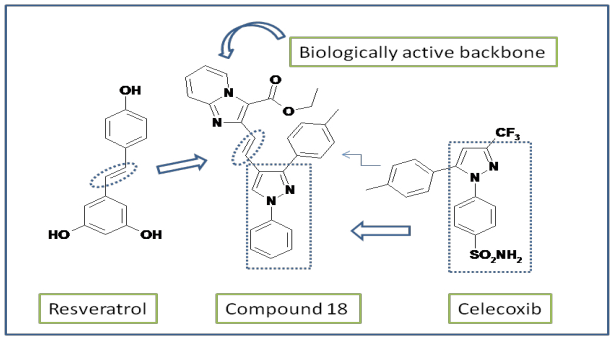


Fig 1: Pharmacophoric model.

2. Materials and methods

2.1 Chemistry

All the reagents and solvents were purchased from commercial sources and were dried and purified when necessary by standard methods. The melting points of the synthesized compound were determined in open capillary tubes using VMP-D melting point apparatus (Veego Instrument Corporation, Mumbai, India) and are uncorrected. The ^{1}H NMR for the compound synthesized were recorded on Varian Mercury plus 400 using TMS as an internal standard and DMSO-d_6 solvent and chemical values are given δ scales. The splitting patterns were assigned as follow: s: singlet, d: doublet, dd: doublet of doublet, t: triplet, m: multiplet. ^{13}C NMR spectra were recorded on Varian Mercury plus 100 spectrometer in DMSO-d_6 and were measured in δ scales. The spectra of mass were recorded on Waters mass spectrometer (Acquity, Waters Corporation). Microanalyses were carried out on elementar (Vario Micro Cube, Germany). The follow up of reactions was monitored by thin layer chromatography (TLC) on silica gel-precoated aluminum sheets (Type 60, F254, Merck, Germany) and the spots were detected by exposer to UV lamp at λ 254 nm for 20-30 seconds.

2.1.1 General Procedure for synthesis of pyrazole aldehyde (D)

A mixture of different acetophenone (1.0 mole) and phenyl hydrazine (1.0 mole) were heated in ethanol (10 volumes) in presence of (1 ml) acetic acid at reflux temperature for 30 minutes. Resulting yellow solid product was separated by the filtration. This solid was washed by cold ethanol (minimum) and was suck dried under vacuum.

A mixture of N,N-dimethylformamide (2.5 mole) and $POCl_3$ (2.5 mole) was stirred together at 0 ^{0}C for 30 minutes. To this reaction mixture the above solid was added at 0 ^{0}C with constant

stirring. The reaction mixture was then allowed to warm up to room temperature and stirred for 12-14 hrs. After completion of reaction, reaction mixture was poured on crushed ice where upon the solid was separated. It was filtered and washed by saturated aq. $NaHCO_3$ solution followed by water. Solid was crystallized from ethanol to get white crystalline product in an average 70% yield.

2.1.2 Synthesis of 2-Methyl-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester (G)

2-chloro ethylacetoacetate **F** (65 g, 0.40 mole) was added to a stirred mixture of 2-aminopyridine **E** (25 g, 0.265mole) and $NaHCO_3$ (27 g, 0.318) in ethanol (250 ml). The mixture was then refluxed for 12 hrs. The reaction mixture was cooled to room temperature and the solvent was concentrated under reduced pressure. Water (150 ml) was added to residue. Reaction mixture was stirred and extracted with ethyl acetate (2 X 150 ml) Total organic layer was washed with brine (100 ml). Organic layer was dried on Na_2SO_4. The solvent was concentrated and crude was purified by silica (60-120) column chromatography to afford 24 g (44%) white solid of product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, 1H), 7.62 (d, 1H), 7.45 (t, 1H), 6.93 (t, 1H), 4.48 (q, 2H), 2.78 (s, 3H), 1.44 (t, 3H). Mass (m/z) 205.2 (M^+1).

2.1.3 Synthesis of 2-Bromomethyl-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester H.

To a solution of **G** (20 g, 0.098 mole) and catalytic amount of AIBN (200 mg) in CCl_4 (400 ml) was added N-bromosuccinamide (21 g, 0.117 mole) at reflux temperature, Reflux was continued for 12 hrs. and then it was cooled to room temperature. Ethyl acetate (1000 ml) was added and stirred, washed the organic layer by water (500 ml). Solvent was dried on anhydrous Na_2SO_4 and then concentrated under reduced pressure. Crude was purified by silica (60-120) column chromatography to yield 17 g (63%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, 1H), 7.70 (d, 1H), 7.44 (t, 1H), 7.09 (t, 1H), 4.98 (d, 2H), 4.54 (q, 2H), 1.49 (t, 3H). Mass (m/z) 285 (M+2).

2.1.4 Synthesis of 3-Ethyloxycarbonylimidazo[1,2-a]pyridine-2-yl-ethyl (triphenyl)phosponium bromide (I)

Triphenylphospine (10 g, 0.0388 mole) was added to a stirred solution of **H** (10 g, 0.0353 mole) in acetonitrile (200 ml), it was reflux for overnight. Reaction mixture was cooled and solvent was concentrated under reduced pressure. Crude was stirred in diethyl ether (2X 200 ml) and filtered. Suck dried the product as solid as in 20 g (99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, 1H), 7.78-7.83 (m, 9H), 7.69-7.71 (m, 6H), 7.44-7.48 (m, 2H), 7.29-7.31 (m, 1H), 5.62 (s, 1H), 5.59 (s, 1H), 4.38 (q, 2H), 1.39 (t, 3H). Mass (m/z) 285 (M^{+2}).

2.1.5 General method for preparation of 1-18.

Sodium hydride (1.2 mole) was added to a stirred solution of 3-ethyloxycarbonylimidazo [1,2-a]pyridine-2-yl-ethyl (triphenyl)phosponium bromide **I** (1.00 mole) in DMSO (5 volume) at 0 ^{0}C. Reaction mixture was stirred for 30 minutes. Then a solution of pyrazole aldehyde **D** (1.1 mole) in minimum quantity of DMSO was added slowly under constant stirring within 10 minute. After addition cooling was removed. Reaction was continued for 5 hrs. at room temperature. Ethyl acetate (10 times of DMSO) was added. After stirring reaction mixture was washed by water and brine. Solvent was removed under reduced pressure. Solid product **1-18** was obtained in an average range of 55-70% after stirring the crude in diethyl ether.

2.1.5.1 2-{2-[1-(4-Methoxy-phenyl)-3-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 1. Yield 35%, M.p. 248-250 ^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.36 (t, 3H, C<u>H</u>$_3$, ethyl ester), 3.81 (s,

3H, ArOC$\underline{H}_3$), 4.38 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.09-7.15 (m, 2H, Ar$\underline{H}$ and olefinic $\underline{H}$ near to pyrazole ring), 7.32-7.36 (m, 4H, Ar$\underline{H}$), 7.51-7.56 (m, 4H, Ar$\underline{H}$), 7.59 (d, 2H, J=16 Hz, olefinic $\underline{H}$ near to imidazole ring), 7.93-7.95 (m, 2H, Ar$\underline{H}$), 8.96 (pyrazole ring $\underline{H}$), 9.19-9.21 (m, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6):14.9 (ethyl ester $\underline{C}H_3$), 59.0 (Ar-O$\underline{C}H_3$), 62.3 (ethyl ester $\underline{C}H_2$), 105.9 (pyrazole $\underline{C}$ attached to olefine), 117, 119.2, 120.4, 120.6, 121.5, 123.3, 124.1, 126.1, 128.6, 129.2, 130.3, 131.4, 133.4, 136.3, 142.5, 151.3 (pyrazole $\underline{C}$ attached to phenyl), 161.9 (Aromatic $\underline{C}$ attached to methoxy), 169 (ethyl ester $\underline{C}$=O); ES-MS, (m/z) 465.3 (M+1). Anal.Calcd.for $C_{28}H_{24}N_4O_3$ (464.3): C, 72.40; H, 5.21; N, 12.06. Found C, 72.90; H, 4.99; N, 11.95.

2.1.5.1 2-{2-[1-(4-Methoxy-phenyl)-3-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 1. Yield 35%, M.p. 248-250 ^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.36 (t, 3H, C$\underline{H}_3$, ethyl ester), 3.81 (s, 3H, ArOC$\underline{H}_3$), 4.38 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.09-7.15 (m, 2H, Ar$\underline{H}$ and olefinic $\underline{H}$ near to pyrazole ring), 7.32-7.36 (m, 4H, Ar$\underline{H}$), 7.51-7.56 (m, 4H, Ar$\underline{H}$), 7.59 (d, 2H, J=16 Hz, olefinic $\underline{H}$ near to imidazole ring), 7.93-7.95 (m, 2H, Ar$\underline{H}$), 8.96 (pyrazole ring $\underline{H}$), 9.19-9.21 (m, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6):14.9 (ethyl ester $\underline{C}H_3$), 59.0 (Ar-O$\underline{C}H_3$), 62.3 (ethyl ester $\underline{C}H_2$), 105.9 (pyrazole $\underline{C}$ attached to olefine), 117, 119.2, 120.4, 120.6, 121.5, 123.3, 124.1, 126.1, 128.6, 129.2, 130.3, 131.4, 133.4, 136.3, 142.5, 151.3 (pyrazole $\underline{C}$ attached to phenyl), 161.9 (Aromatic $\underline{C}$ attached to methoxy), 169 (ethyl ester $\underline{C}$=O); ES-MS, (m/z) 465.3 (M+1). Anal.Calcd.for $C_{28}H_{24}N_4O_3$ (464.3): C, 72.40; H, 5.21; N, 12.06. Found C, 72.90; H, 4.99; N, 11.95.

2.1.5.2 2-{2-[1-(4-methyl-phenyl)-3-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 2. Yield 68%, M.p. 238-240 ^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.39 (q, 3H, C$\underline{H}_3$, ethyl ester), 2.31 (s, 3H, ArC$\underline{H}_3$), 4.41 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.01 (d, 2H, J=15.7Hz, olefinic $\underline{H}$ near to pyrazole ring), 7.15 (t, 2H, Ar$\underline{H}$), 7.37-7.41 (m, 3H, Ar$\underline{H}$ and olefinic $\underline{H}$ near to imidazole ring), 7.54-7.57 (m, 5H, Ar$\underline{H}$), 7.97-7.99 (m, 2H, Ar$\underline{H}$), 9.02 (s, 1H, pyrazole ring $\underline{H}$), 9.22 (d, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6):14.1 (ethyl ester $\underline{C}H_3$), 23.9 (Ar-$\underline{C}H_3$), 62.4 (ethyl ester $\underline{C}H_2$), 106.9 (pyrazole $\underline{C}$ attached to olefine), 117.9, 119.3, 120.1, 120.9, 121.5, 122.0, 122.9, 124.2, 126.1, 127.3, 128.1, 129.4, 129.9, 131.1, 132.1, 135.5, 153.1 (pyrazole $\underline{C}$ attached to phenyl), 168.1(ethyl ester $\underline{C}$=O); ES-MS, (m/z) 449.3 (M+1). Anal. Calcd.for $C_{28}H_{24}N_4O_2$ (448.5): C, 74.98; H, 5.39; N, 12.49. Found C, 74.90; H, 5.49; N, 12.11.

2.1.5.4 2-{2-[3-(2-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 4. Yield 59%, M.p. 229-231^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.39 (t, 3H, C$\underline{H}_3$, ethyl ester), 4.42 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.10 (d, 1H, J=16.1Hz, olefinic $\underline{H}$ near to pyrazole ring), 7.17-7.22 (m, 4H, Ar$\underline{H}$), 7.32-7.35 (m, 2H, Ar$\underline{H}$), 7.38 (d, 1H, J=16.1Hz, olefinic $\underline{H}$ near to imidazole ring), 7.51-7.56 (m, 5H, Ar$\underline{H}$), 8.02-8.09 (m, 2H, Ar$\underline{H}$), 9.01 (s, 1H, pyrazole ring $\underline{H}$), 9.20 (d, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 15.2 (ethyl ester $\underline{C}H_3$), 63.2 (ethyl ester $\underline{C}H_2$), 106.1 (pyrazole $\underline{C}$ attached to olefine), 117.4, 119.2, 120.2 (Olefinic $\underline{C}$), 120.8, 123.1, 124.4, 125.5, 127.5, 128.4, 129.2, 131.9, 132.6, 135.4 (olefinic $\underline{C}$ near to imidazole ring), 141.9 (Aromatic $\underline{C}$ attached to Chloro), 152.9 (pyrazole $\underline{C}$ attached to phenyl), 168.2 (ethyl ester $\underline{C}$=O); ES-MS, (m/z) 470.3 (M+2); Anal. Calcd.for $C_{27}H_{21}ClN_4O_2$ (468.4): C, 69.16; H, 4.51; N, 11.95. Found C, 69.61; H, 4.30; N, 11.20.

2.1.5.5 2-{2-[3-(3-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 5. ***Y***ield

55%, M.p. 219-221^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.37 (t, 3H, C$\underline{H}_3$, ethyl ester), 4.48 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.03 (d, 1H, J=15.8Hz, olefinic $\underline{H}$ near to pyrazole ring), 7.19-7.21 (m, 3H, Ar$\underline{H}$), 7.32-7.35 (m, 3H, Ar$\underline{H}$), 7.36 (d, 1H, J=16Hz, olefinic $\underline{H}$ near to imidazole ring), 7.50-7.53 (m, 2H, Ar$\underline{H}$), 7.55-7.57 (m, 3H, Ar$\underline{H}$), 8.05-8.07 (m, 2H, Ar$\underline{H}$), 9.10 (s, 1H, pyrazole ring $\underline{H}$), 9.21 (d, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 13.7 (ethyl ester $\underline{C}H_3$), 63.1 (ethyl ester $\underline{C}H_2$), 105.9 (pyrazole $\underline{C}$ attached to olefine), 120.6, 121.1 (olefinic $\underline{C}$ near to pyrazole ring), 123.3, 125.1, 127.9, 128.5, 128.9, 131.5, 132.2, 133.6, 135.1 (olefinic $\underline{C}$ near to imidazole ring), 136.1, 142.7 (Aromatic $\underline{C}$ attached to Chloro), 154.3 (pyrazole $\underline{C}$ attached to phenyl), 168.2 (ester $\underline{C}$=O); ES-MS, (m/z) 470.3 (M+2); Anal.Calcd. for $C_{27}H_{21}ClN_4O_2$ (468.4): C, 69.16; H, 4.51; N, 11.95. Found C, 69.78; H, 4.19; N, 11.12.

2.1.5.6 2-{2-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 6. Yield 61%, M.p. 218-220^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.32 (t, 3H, C$\underline{H}_3$, ethyl ester), 4.42 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.07 (d, 1H, J=15.9Hz, olefinic $\underline{H}$ near to pyrazole ring), 7.19-7.21 (m, 3H, Ar$\underline{H}$), 7.39-7.42 (m, 4H, Ar$\underline{H}$ and olefinic $\underline{H}$ near to imidazole ring), 7.50-7.57 (m, 5H, Ar$\underline{H}$), 8.05-8.07 (m, 2H, Ar$\underline{H}$), 9.11 (s, 1H, pyrazole ring $\underline{H}$), 9.19 (d, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ES-MS, (m/z) 470.3 (M+2); Anal. Calcd.for $C_{27}H_{21}ClN_4O_2$ (468.4): C, 69.16; H, 4.51; N, 11.95. Found C, 69.00; H, 4.59; N, 11.43.

2.1.5.7 2-{2-[3-(2-fluoro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 7. Yield 59%, M.p. 211-213^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.32 (t, 3H, C$\underline{H}_3$, ethyl ester), 4.45 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.05 (d, 1H, J=15.8Hz, olefinic $\underline{H}$ near to pyrazole ring), 7.10-7.13 (m, 3H, Ar$\underline{H}$), 7.29-7.31 (m, 3H, Ar$\underline{H}$), 7.40 (d, 1H, J=15.8Hz, olefinic $\underline{H}$ near to imidazole ring), 7.51-7.56 (m, 5H, Ar$\underline{H}$), 8.10-8.12 (m, 2H, Ar$\underline{H}$), 9.01 (s, 1H, pyrazole ring $\underline{H}$), 9.12(d, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6) 14.2 (ethyl ester $\underline{C}H_3$), 63.1 (ethyl ester $\underline{C}H_2$), 107.0 (pyrazole $\underline{C}$ attached to olefine), 117.3, 120.3 (olefinic $\underline{C}$ attached to pyrazole), 121.2, 121.9, 124.9, 127.9, 128.4, 129.3, 130.4, 131.7, 136.5, 139.1, 141.4 (Aromatic $\underline{C}$ attached to Chloro), 142.1 (imidazole $\underline{C}$ attached to ethyl ester), 155.4 (pyrazole $\underline{C}$ attached to phenyl), 167.4 (ethyl ester $\underline{C}$=O); ES-MS, (m/z) 453.4 (M+1); Anal.Calcd.for $C_{27}H_{21}FN_4O_2$ (452.4): C, 71.67; H, 4.68; N, 12.38. Found C, 72.01; H, 4.63; N, 11.99.

2.1.5.8 2-{2-[3-(3-fluoro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 8. Yield 67%, M.p. 214-216^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.38 (t, 3H, C$\underline{H}_3$, ethyl ester), 4.48 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.09 (d, 1H, J=15.2Hz, olefinic $\underline{H}$ near to pyrazole ring), 7.10-7.37 (m, 7H, Ar$\underline{H}$ and olefinic $\underline{H}$ near imidazole ring), 7.51-7.56 (m, 5H, Ar$\underline{H}$), 8.10-8.13 (m, 2H, Ar$\underline{H}$), 9.08 (s, 1H, pyrazole ring $\underline{H}$), 9.18 (d, 1H, Ar$\underline{H}$ near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 16.3 (ethyl ester $\underline{C}H_3$), 65.2 (ethyl ester $\underline{C}H_2$), 106.8 (pyrazole $\underline{C}$ attached to olefine), 117.9, 119.4, 121.4 (olefinic $\underline{C}$ attached to pyrazole), 121.7, 124, 126.3, 127.2, 128.2, 129, 130.2, 143.8 (imidazole $\underline{C}$ attached to ethyl ester), 146.2 (Aromatic $\underline{C}$ attached to fluoro), 152 (pyrazole $\underline{C}$ attached to phenyl), 168.3 (ethyl ester $\underline{C}$=O); ES-MS, (m/z) 453.4 (M+1); Anal.Calcd.for $C_{27}H_{21}FN_4O_2$ (452.4): C, 71.67; H, 4.68; N, 12.38. Found C, 72.09; H, 4.69; N, 12.17.

2.1.5.9 2-{2-[3-(4-fluoro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 9. Yield 69%, M.p. 214-216^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.38 (t, 3H, C$\underline{H}_3$, ethyl ester), 4.42 (t, 2H, C$\underline{H}_2$, ethyl ester), 7.01 (d, 1H, J=15.3Hz,

olefinic H near to pyrazole ring), 7.10-7.13 (m, 2H, ArH), 7.29-7.38 (m, 5H, ArH and olefinic H near imidazole ring), 7.51-7.57 (m, 5H, ArH), 8.12-8.15 (m, 2H, ArH), 9.12 (s, 1H, pyrazole ring H), 9.18 (d, 1H, ArH near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 15.4 (ethyl ester CH_3), 65.7 (ethyl ester CH_2), 106 (pyrazole C attached to olefine), 117.8, 119.1, 121.9, 124.5 (olefinic C near to pyrazole ring), 125.5, 126.3, 127.9, 128.3, 129.6, 130.4, 135.8, 146.9 (Aromatic C attached to fluoro), 143.6 (imidazole C attached to ethyl ester), 151.2 (pyrazole C attached to phenyl), 168.1 (ethyl ester C=O); ES-MS, (m/z) 453.4 (M+1); Anal.Calcd.for $C_{27}H_{21}FN_4O_2$ (452.4): C, 71.67; H, 4.68; N, 12.38. Found C, 72.00; H, 4.71; N, 12.19.

2.1.5.10 2-{2-[3-(2-methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester 10. Yield 57%, M.p. 219-221^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.40 (t, 3H, CH_3, ethyl ester), 3.98 (s, 3H, $ArOCH_3$), 4.47 (t, 2H, CH_2, ethyl ester), 7.10 (d, 1H, J=15.7Hz, olefinic H near to pyrazole ring), 7.10-7.12 (m, 2H, ArH), 7.32-7.36 (m, 4H, ArH and olefinic H near imidazole ring), 7.48-7.50 (m, 2H, ArH), 7.53-7.55 (m, 3H, ArH), 8.12-8.15 (m, 2H, ArH), 9.08 (s, 1H, pyrazole ring H), 9.15 (d, 1H, ArH near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 15.3 (ethyl ester CH_3), 52.3 (Ar-OCH_3), 65.5 (ethyl ester CH_2), 105.8 (pyrazole C attached to olefine), 119.2, 121.5, 124.6, 125.3, 126.5 (olefinic C near to pyrazole ring), 127.9, 128, 129.3, 135.5 (olefinic C near to imidazole ring), 143.7 (imidazole C attached to ethyl ester), 151.9 (pyrazole C attached to phenyl), 157.4 (Aromatic C attached to OCH_3), 168.3 (ethyl ester C=O); ES-MS, (m/z) 465.4 (M+1); Anal.Calcd.for $C_{28}H_{24}N_4O_3$ (464.3): C, 72.41; H, 5.21; N, 12.06. Found C, 72.40; H, 5.59; N, 12.00.

2.1.5.11 2-{2-[3-(3-methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester 11. Yield 58%, M.p. 233-235^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.32 (t, 3H, CH_3, ethyl ester), 4.01 (s, 3H, $ArOCH_3$), 4.42 (t, 2H, CH_2, ethyl ester), 7.01 (d, 1H, J=16Hz, olefinic H near to pyrazole ring), 7.12-7.14 (m, 2H, ArH), 7.32-7.40 (m, 5H, ArH and olefinic H near imidazole ring), 7.48 (t, 1H, ArH), 7.53-7.55 (m, 3H, ArH), 8.09-8.12 (m, 2H, ArH), 9.10 (s, 1H, pyrazole ring H), 9.17 (d, 1H, ArH near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6) 14.9 (ethyl ester CH_3), 54.0 (Ar-OCH_3), 65.8 (ethyl ester CH_2), 104.9 (pyrazole C attached to olefine), 117.9, 119.3, 124.6, 125.2, 126.8 (olefinic C near to pyrazole ring), 127.2, 129.7, 132, 135.9 (olefinic C near to imidazole ring), 144 (imidazole C attached to ethyl ester), 150.9 (pyrazole C attached to phenyl), 157 (Aromatic C attached to OCH_3), 168.1 (ethyl ester C=O); ES-MS, (m/z) 465.4 (M+1); Anal.Calcd.for $C_{28}H_{24}N_4O_3$ (464.3): C, 72.41; H, 5.21; N, 12.06. Found C, 72.47; H, 5.64; N, 12.18.

2.1.5.12 2-{2-[3-(4-methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester 12. Yield 54%, M.p. 238-240^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.35 (t, 3H, CH_3, ethyl ester), 3.89 (s, 3H, $ArOCH_3$), 4.41 (t, 2H, CH_2, ethyl ester), 7.10 (d, 1H, J=16.1Hz, olefinic H near to pyrazole ring), 7.17 (t, 1H, ArH), 7.35-7.42 (m, 6H, ArH and olefinic H near imidazole ring), 7.48-7.54 (m, 4H, ArH), 8.12 (t, 2H, ArH), 9.10 (s, 1H, pyrazole ring H), 9.19 (d, 1H, ArH near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 15.4 (ethyl ester CH_3), 54.5 (Ar-OCH_3), 64.0 (ethyl ester CH_2), 104.7 (pyrazole C attached to olefine), 117.9, 119.2, 121.0, 124.0, 125.3, 126.0 (olefinic C near to pyrazole ring), 127.9, 129.1, 130.6, 135.7 (olefinic C near to imidazole ring), 145 (imidazole C attached to ethyl ester), 150.7 (pyrazole C attached to phenyl), 158.4 (Aromatic C attached to OCH_3), 168.3 (ethyl ester C=O); ES-MS, (m/z) 465.4

(M+1); Anal.Calcd.for $C_{28}H_{24}N_4O_3$ (464.3): C, 72.41; H, 5.21; N, 12.06. Found C, 72.09; H, 5.33; N, 12.45.

2.1.5.13 2-{2-[3-(2-trifluoromethyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester 13. Yield 65%, M.p. 215-217^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.35 (t, 3H, C<u>H</u>$_3$, ethyl ester), 4.40 (t, 2H, C<u>H</u>$_2$, ethyl ester), 7.09 (d, 1H, J=15.7Hz, olefinic <u>H</u> near to pyrazole ring), 7.19-7.34 (m, 6H, ArH), 7.38 (d, 1H, J=15.8Hz, olefinic <u>H</u> near imidazole ring), 7.51-7.59 (m, 5H, Ar<u>H</u>), 8.00 (t, 2H, Ar<u>H</u>), 9.12 (s, 1H, pyrazole ring <u>H</u>), 9.13 (d, 1H, Ar<u>H</u> near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 15.9 (ethyl ester <u>C</u>H$_3$), 64.3 (ethyl ester <u>C</u>H$_2$), 104.9 (pyrazole <u>C</u> attached to olefine), 110.0 (<u>C</u>F$_3$), 119.1, 121.1, 124.3, 125.6, 126.6 (olefinic <u>C</u> near to pyrazole ring), 127.1, 128.3, 129.6, 130.2, 135.2 (olefinic <u>C</u> near to imidazole ring), 144.2 (imidazole <u>C</u> attached to ethyl ester), 152.2 (pyrazole <u>C</u> attached to phenyl), 156.1 (Aromatic <u>C</u> attached to CF$_3$), 168.2 (ethyl ester <u>C</u>=O); ES-MS, (m/z) 503.4 (M+1); Anal.Calcd. for $C_{27}H_{21}F_3N_4O_2$ (502.3): C, 66.93; H, 4.21; N, 11.15. Found C, 67.09; H, 4.41; N, 11.19.

2.1.5.14 2-{2-[3-(3-trifluoromethyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester 14. Yield 67%, M.p. 225-227^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.31 (t, 3H, C<u>H</u>$_3$, ethyl ester), 4.42 (t, 2H, C<u>H</u>$_2$, ethyl ester), 7.12 (d, 1H, J=15.8Hz, olefinic <u>H</u> near to pyrazole ring), 7.20-7.34 (m, 6H, ArH), 7.41 (d, 1H, J=15.6Hz, olefinic <u>H</u> near imidazole ring), 7.55-7.59 (m, 5H, Ar<u>H</u>), 8.04 (t, 2H, Ar<u>H</u>), 9.09 (s, 1H, pyrazole ring <u>H</u>), 9.16 (d, 1H, Ar<u>H</u> near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 15.7 (ethyl ester <u>C</u>H$_3$), 64.4 (ethyl ester <u>C</u>H$_2$), 108 (pyrazole <u>C</u> attached to olefine), 109.9 (<u>C</u>F$_3$), 117.8, 119.7, 121.2, 124.8, 125.4, 126.5 (olefinic <u>C</u> near to pyrazole ring), 127.5, 129.1, 137.1 (olefinic <u>C</u> near to imidazole ring), 145.1 (imidazole <u>C</u> attached to ethyl ester), 152.9 (pyrazole <u>C</u> attached to phenyl), 156.9 (Aromatic <u>C</u> attached to CF$_3$), 167.9 (ethyl ester <u>C</u>=O); ES-MS, (m/z) 503.4 (M+1); Anal.Calcd. for $C_{27}H_{21}F_3N_4O_2$ (502.3): C, 66.93; H, 4.21; N, 11.15. Found C, 67.10; H, 4.34; N, 11.09.

2.1.5.15 2-{2-[3-(4-trifluoromethyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester 15. Yield 69%, M.p. 219-221^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.32 (t, 3H, C<u>H</u>$_3$, ethyl ester), 4.41 (t, 2H, C<u>H</u>$_2$, ethyl ester), 7.02 (d, 1H, J=16.5Hz, olefinic <u>H</u> near to pyrazole ring), 7.19-7.22 (T, 2H, Ar<u>H</u>), 7.25-7.31 (m, 4H, Ar<u>H</u>), 7.42 (d, 1H, J=16.1Hz, olefinic <u>H</u> near imidazole ring), 7.51-7.55 (m, 5H, Ar<u>H</u>), 8.07 (t, 2H, Ar<u>H</u>), 9.08 (s, 1H, pyrazole ring <u>H</u>), 9.16 (d, 1H, Ar<u>H</u> near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 16.2 (ethyl ester <u>C</u>H$_3$), 64.3 (ethyl ester <u>C</u>H$_2$), 106.1 (pyrazole <u>C</u> attached to olefine), 109.2 (<u>C</u>F$_3$), 117.8, 119.1, 121.2, 124.3, 125.2, 126.4 (olefinic <u>C</u> near to pyrazole ring), 127.5, 128.3, 129.1, 130.1, 136.9 (olefinic <u>C</u> near to imidazole ring), 145.9 (imidazole <u>C</u> attached to ethyl ester), 152.8 (pyrazole <u>C</u> attached to phenyl), 156.9 (Aromatic <u>C</u> attached to CF$_3$), 169.7 (ethyl ester <u>C</u>=O); ES-MS, (m/z) 503.4 (M+1); Anal.Calcd.for $C_{27}H_{21}F_3N_4O_2$ (502.3): C, 66.93; H, 4.21; N, 11.15. Found C, 67.02; H, 4.47; N, 11.41.

2.1.5.16 2-{2-[3-(2-methyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester 16. Yield 62%, M.p. 229-231^{0}C, ^{1}H NMR (DMSO-d_6), δ ppm: 1.34 (t, 3H, C<u>H</u>$_3$, ethyl ester), 2.29 (s, 3H, ArC<u>H</u>$_3$), 4.43 (t, 2H, C<u>H</u>$_2$, ethyl ester), 7.01 (d, 1H, J=15.5Hz, olefinic <u>H</u> near to pyrazole ring), 7.20-7.31 (m, 4H, Ar<u>H</u>), 7.35-7.39 (m, 3H, Ar<u>H</u> and olefinic <u>H</u> near imidazole ring), 7.52-7.55 (m, 5H, Ar<u>H</u>), 8.09 (t, 2H, Ar<u>H</u>), 9.11 (s, 1H, pyrazole ring <u>H</u>), 9.17 (d, 1H, Ar<u>H</u> near to bridge head nitrogen); ^{13}C NMR (DMSO-d_6): 16 (ethyl ester <u>C</u>H$_3$),

29.2 (Ar-CH$_3$), 64.6 (ethyl ester CH$_2$), 106.4 (pyrazole C attached to olefine), 119.2, 120.3, 121.9, 124.0, 125.3, 126.7 (olefinic C near to pyrazole ring), 127.5, 128.4, 129.5, 130.3, 139 (olefinic C near to imidazole ring), 139.1, 145.3 (imidazole C attached to ethyl ester), 152.7 (pyrazole C attached to phenyl), 167.7 (ethyl ester C=O); ES-MS, (m/z) 449.3 (M+1); Anal. Calcd.for $C_{27}H_{24}N_4O_2$ (448.5): C, 74.98; H, 5.39; N, 12.49. Found C, 75.09; H, 5,09; N, 12.32.

2.1.5.17 2-{2-[3-(3-methyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 17. Yield 69%, M.p. 229-231^{0}C, ^{1}H NMR (DMSO-d$_6$), δ ppm: 1.38 (t, 3H, CH$_3$, ethyl ester), 2.32 (s, 3H, ArCH$_3$), 4.39 (t, 2H, CH$_2$, ethyl ester), 7.08 (d, 1H, J=15.7Hz, olefinic H near to pyrazole ring), 7.20-7.31 (m, 3H, ArH), 7.33-7.39 (m, 3H, ArH and olefinic H near imidazole ring), 7.49-7.55 (m, 5H, ArH), 8.04 (t, 2H, ArH), 9.09 (s, 1H, pyrazole ring H), 9.11 (d, 1H, ArH near to bridge head nitrogen); ^{13}C NMR (DMSO-d$_6$): 15.1 (ethyl ester CH$_3$), 29.4 (Ar-CH$_3$), 66.0 (ethyl ester CH$_2$), 106.2 (pyrazole C attached to olefine), 119.2, 121.1, 122.3, 125.5, 126.8 (olefinic C near to pyrazole ring), 127.7, 128.5, 129.3, 130.1, 134.3 (olefinic C near to imidazole ring), 145.9 (imidazole C attached to ethyl ester), 152.6 (pyrazole C attached to phenyl), 169.0 (ethyl ester C=O); ES-MS, (m/z) 449.3 (M+1); Anal.Calcd.for $C_{27}H_{24}N_4O_2$ (448.5): C, 74.98; H, 5.39; N, 12.49. Found C, 75.03; H, 5.14; N, 12.39.

2.1.5.18 2-{2-[3-(4-methyl-phenyl)-1-phenyl-1H-pyrazol-4-yl]-vinyl}-imidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester 18. Yield 58%, M.p. 224-226^{0}C, ^{1}H NMR (DMSO-d$_6$), δ ppm: 1.34 (t, 3H, CH$_3$, ethyl ester), 2.37 (s, 3H, ArCH$_3$), 4.37 (t, 2H, CH$_2$, ethyl ester), 7.02 (d, 1H, J=15.9Hz, olefinic H near to pyrazole ring), 7.20-7.34 (m, 3H, ArH), 7.36-7.39 (m, 2H, ArH) 7.43 (d, 1H, J=16Hz olefinic H near imidazole ring), 7.42-7.47 (m, 3H, ArH), 7.53 (t, 2H, ArH), 8.09 (t, 2H, ArH), 9.12 (s, 1H, pyrazole ring H), 9.19 (d, 1H, ArH near to bridge head nitrogen); ^{13}C NMR (DMSO-d$_6$): 15.9 (ethyl ester CH$_3$), 29.7 (Ar-CH$_3$), 64.0 (ethyl ester CH$_2$), 106.4 (pyrazole C attached to olefine), 117.9, 119.6, 121.8, 124.3, 125.6, 126.2 (olefinic C near to pyrazole ring), 127.1, 128.5, 129.5, 130.6, 136.2 (olefinic C near to imidazole ring), 145.0 (imidazole C attached to ethyl ester), 152.9 (pyrazole C attached to phenyl), 168.5 (ethyl ester C=O); ES-MS, (m/z) 449.3 (M+1); Anal.Calcd.for $C_{27}H_{24}N_4O_2$ (448.5): C, 74.98; H, 5.39; N, 12.49. Found C, 74.89; H, 5.34; N, 12.37.

2.2 COX-1/COX-2 inhibitory screening assay

The "COX inhibitor screening assay"" kits with 96-well plates were used to carry in vitro COX-1/2 inhibitory performance of synthesized analogues. Ovine COX-1 and human recombinant COX-2 were used in this experiment. Each activity tube of the experiment kit was initially filled with 10 µL of heme, 10 µL of COX-1 and COX-2 and 950 µL of reaction buffer (0.1M Tris-HCl, pH 8.0, comprising 5 mM EDTA and 2 mM phenol). Similarly, the inhibitory tubes were prepared by addition of all these material along with addition of inhibitory compound with final concertation of 100, 10, 0.1, 0.01 and 0.001 µM, so that the final volume of the tube was adjusted to 1 ml. The COX-1 and COX-2 inactivated enzyme tube were obtained after keeping these tubes in boiling water for a few minutes. Once the tube incubated for 20 minutes at 37^{0}C, the arachidonic acid was added in each tube and initiated the reaction, hence incubated the tubes for 2-3 minutes at 37^{0}C. Afterward the reaction was quenched by adding 1M HCl (50µL). The $SnCl_2$(100 µL) was added to obtain PGF2a by the reduction of PGH2 thus formed. PG antiserum was added to quantify the prostaglandin (PG) generation in each tubes. As there is competition between PG and PGA conjugates (PG tracers) for the limited amount

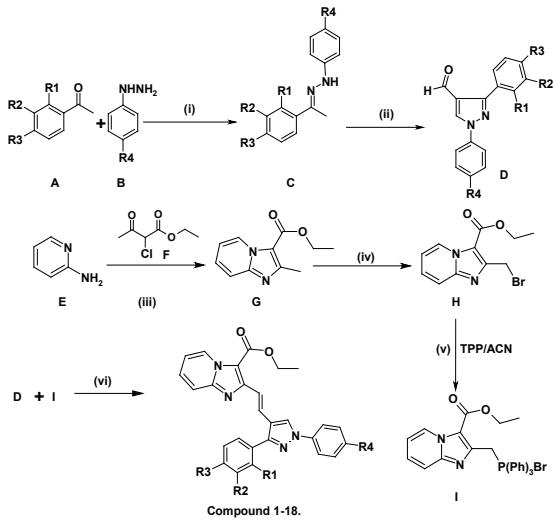
PG antiserum as the concertation of PG varies while the concentration of PG tracers held constant, the concertation of PG tracers binds to PG antiserum is inversely proportional to the concentration of PG in the tube.This rabbit antiserum-P (either free or tracer) complex binds to a mouse monoclonal antirabbit antibody that has been previously attached to the tube. The plate is washed to remove any unbound reagents, and then Ellman's reagent (which contains the substrate to AChe) is added to the well. Typical yellow color was observed due to this enzymatic which was strongly observed at 420 nm. The intensity of color was determined spectrophotometrically. The intensity of color is proportional to the amount of free PG traces bound to the tube, which is inversely proportional to the amount of free PG present in the tube during incubation process. When there is absorption at 420 nm observed in 96 well plates indicates the presence of higher level of PG in the tubes, which intern shows less inhibition of enzymes. These absorption values of different tubes confirm the COX inhibitory activities of synthesized compounds. With the help of GraphPad PRISM, the IC_{50} value (Concentration of test compound responsible for 50% inhibition) of the test compound was determine by plotting dose-response inhibition curve.

3. **Research and Discussion**

3.1 Chemistry

The synthetic strategies utilized are being mention in the synthetic scheme 1. Commercially available different acetophenones (**A)** when treated with commercially available various phenylhydrazines (**B)** in acidic medium under refluxing in ethanol gave imine as an intermediate (**C**). This intermediate upon reaction with $POCl_3$ in DMF underwent cyclization to give different pyrazole aldehydes (**D)** in good yield as key precursors. Follow up of chemical conversion was monitored by TLC techniques. Another important precursor was prepared outlined with literature support [22]. Commercially available 2-aminopyridine (**E)** was cyclized to 2-Methyl-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (**G)** by reaction with 2-chloroacetoacetate (**F)** under reflux condition. Inspection of ^{1}H NMR spectra of **G** revealed a triplet at 1.44 ppm for CH_3 protons, quartet at 4.48 ppm for CH_2 proton attributed to ethyl ester and a singlet at 2.78 assigned to the =C-CH_3 proton, proved the existence of **G**. Then **G** was allowed to react with N-bromosuccinamide in presence of catalytic amount azobisisobutyronitrile (AIBN) and CCl_4 to give 2-Bromomethyl-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester **(H)**. ^{1}H NMR spectrum for **H** revealed disappearance of singlet peak at 2.78 and displayed doublet signal at 4.98 ppm corresponding to CH_2Br protons. The 3-ethyloxycarbonylimidazo[1,2-a]pyridine-2-yl-ethyl (triphenyl)phosponium bromide (**I)** was obtained from **H** using triphenyl phosphine in acetonitirile solvent under reflux condition. ^{1}H NMR spectrum of (**I)** revealed two multiplet signals at 7.78-7.83 for 9 protons and 7.69-7.71 for 6 protons corresponding to three phenyl rings indicating the existence of **I**.

Finally, the reaction of **D** with **I** yielded the targeted compounds **1-18** using sodium hydride as a base at refluxed temperature in average yields of 55-70% (**Scheme 1, Table 1**). The progresses of all reactions were monitored by TLC.



Synthetic Scheme 1 . Reagents and conditions: (i) AcOH/EtOH, reflux, 30 minutes; (ii) DMF/$POCl_3$, 0 ^{0}C-30 ^{0}C, 12-14 h; (iii) $NaHCO_3$, EtOH, Reflux (iv) NBS/AIBN, CCl_4, reflux, 12 h; (v) TPP, ACN, reflux, 12 h; (vi) NaH/DMSO, 0^0C- 30^0C, 5 h.

3.2 Preliminary in-vitro COX-1 and COX-2 inhibition results

As per our synthetic program, we have synthesized total eighteen novel compounds. The results are summarized in **Table 2**. The structural identifications of synthetic compounds (1-18) were done with the help of analytical data (^{1}H NMR, ^{13}C NMR and mass spectroscopy) and elemental analysis. Smaller modifications were carried out at R_1 to R_4 positions (Synthetic scheme 1). The synthesized compounds were exposed to COX-1/COX-2 inhibitory assay at various concentrations of 10^{-5}, 10^{-6}, 10^{-7}& 10^{-8} M along with concern enzyme to notify the reduction on prostaglandin.

Initially, the methoxy, methyl and bromo groups were introduced at R_4 of *N*-Phenyl ring and R_1-R_3 were kept as H; which resulted in first three compounds (**1-3**). Unfortunately, these three compounds were found poor in *in-vitro* COX-2 inhibitory assay. Taking these results we concluded that the substitution at R_4 doesn't help for COX-2 inhibitory activity. Later, the *N*-phenyl ring (R_4 position) was kept un-substituted and variations were carried out at R_1 to R_3 position of another phenyl ring. With this modification, we moved to another novel six compounds (**4-9**) wherein chloro and fluoro groups were introduced at R_1, R_2 and R_3 position respectively. In the inhibitory assay, compound **4** and compound **6** showed poor results than the first three compounds (**1-3**). Compound **9** was most active compound prepared so far (COX-2 IC_{50}=3.17 μM). Moreover, the selectivity index for the entire synthesized compound (**1-9**) was very poor when compared with standard celecoxib. Further to explore SAR, the methoxy substitution was brought at R_1, R_2 and R_3 and following set of compound was prepared (**10-12**). In this set, although the COX-2 inhibitory activity and selectivity was poor than celecoxib, but for us the result was little surprise because of COX-2 activity enhancement when compared with compounds **1-9**. Compound **10-12** displayed almost equivalent COX-2 activity as well as selectivity with each other.

In the next level, trifluoromethyl group was introduced at R_1, R_2, R_3 and compounds **13-15** were synthesized. In this set, the COX-2 inhibitory profile was found far better than all initial compounds **1-12**. Compound **15** exhibited superior result (COX-2 IC_{50}=1.42 μM) with good COX-2 selectivity (SI=6.12). After getting this encouraging result, we moved further and synthesized compounds **16-18** wherein the trifluoromethyl group at R_1, R_2 and R_3 was replaced by methyl. In COX-2 inhibitory assay, the compounds **16-18** were found best compounds than the compounds prepared so far. The compound **17** and **18** showed COX-2 inhibition (COX-2 IC_{50} 1.13 μM and 1.09 μM respectively) wherein compound **18** displayed maximum selectivity (SI=8.03) within series.

4. **Conclusion**

The present article reports the synthesis

and preliminary COX-1/COX-2 inhibition study of novel hybrid molecules containing imidazo[1,2-a]pyridine, *trans-stilbene* and substituted pyrazole. To summarize, within series compound **17** and **18** exhibited best COX-2 inhibitory (IC_{50} 1.13 µM and 1.09 µM respectively) results. Compound **18** displayed maximum selectivity index (SI=8.03). None of the compound demonstrated superior performance than standard celecoxib, hence, further *in-vivo* anti-inflammatory study and ulcerogenic liability study was not performed.

5. Acknowledgement

We are appreciative to the managements of Maulana Azad College and Dr. Rafiq Zakaria College for women's, Aurangabad for their truthful inspiration.

Table 1. Substitution strategy for compounds **1-18**

ID	R_1	R_2	R_3	R_4
1	H	H	H	OMe
2	H	H	H	Me
3	H	H	H	Br
4	Cl	H	H	H
5	H	Cl	H	H
6	H	H	Cl	H
7	F	H	H	H
8	H	F	H	H
9	H	H	F	H
10	OMe	H	H	H
11	H	OMe	H	H
12	H	H	OMe	H
13	CF_3	H	H	H
14	H	CF_3	H	H
15	H	H	CF_3	H
16	Me	H	H	H
17	H	Me	H	H
18	H	H	Me	H

Table 2.IC_{50} (µM) of compounds 1-23 against COX-1, COX-2 enzymes.
Cel- Celecoxib. Selectivity Index (SI)

ID	IC_{50} (µM)		Selectivity Index
	COX-1	COX-2	
1	12	7.77	1.54
2	9.01	6.68	1.34
3	9.78	5.63	1.73
4	9.23	9.08	1.01
5	10.2	3.80	2.68
6	6.80	9.65	0.70
7	8.85	6.92	1.27
8	5.20	7.09	0.73
9	7.86	3.17	2.47
10	8.25	2.92	2.82
11	8.32	2.89	2.87
12	8.42	2.72	3.10
13	7.23	2.01	3.59
14	8.49	1.91	4.45
15	6.11	1.42	6.12
16	9.11	1.21	7.52
17	8.89	1.13	7.86
18	8.76	1.09	8.03
Cel	5.61	0.59	9.51

References

1. N. Yamakawa, S. Suemasu, M. Matoyama, A. Kimoto, M. Takeda, K. Tanaka, T. Ishihara, T. Katsu, Y. Okamoto, M. Otsuka, T. Mizushima; *J. Med. Chem.* **2010**, 53, 7879-7982.
2. C.J. Hawkey, Gastroenterology **2000**, 119, 521–535.
3. C. Velazquez, P. N. Praveen Rao, E. Knaus; *J. Med. Chem.* **2005**, 48, 4061-4067.
4. W. Xie, J.G. Chipman, D.L. Robertson, R.L. Erikson, D.L. Simmons, Proc. Natl. Acad. Sci. USA, **1991**, 88, 2692-2696.
5. D.A. Jujubu, B.S. Fletcher, B.C. Varnum, R.W. Lim, H.R. Herschman, J. Biol. Chem. **1991**, 266, 12866-12872.
6. A, Viegas, J. Manso, M. C. Corvo, M. Manuel B. Marques, E. J. Cabrita; *J. Med. Chem.* **2011**, 54, 8555−8562.
7. K. Chegaev, L. Lazzarato, P. Tosco, C. Cena, E. Marini, B. Rolando, P. Carrupt, R. Fruttero, A. Gasco; *J. Med.*

Chem., **2007**, *50* (7), pp 1449–1457.

8. S. Khanapure, D. Garvey, D. Young, M. Ezawa, R. Earl, R. Gaston, X. Fang, M. Murty, A. Martino, M. Shumway, M. Trocha, P. Marek, S. Tam, D. Janero, L. Letts; *J. Med. Chem.* **2003**, 46, 5484-5504.
9. L.S. Simon, F.L. Lanza, P.E. Lipsky, R.C. Hubbard, S. Talwalkar, B.D. Schwartz, P.C. Isakson, G.S. Geis, Arthritis Rheum. **1998**, 41, 1591-1602.
10. G. Amgad, P.N. Habbeb, P. Rao, E. Edward, J. Med. Chem. 2001, 44, 3039-3042.
11. Leonardo Di Nunno, Paola Vitale, Antonio Scilimati, Stefania Tacconelli and Paola Patrignani, J. Med, Chem. **2004**, 47, 48881-4890.
12. P Soorikumaran, Postgrad Med. J. **2006**, 82, 242-245.
13. S. Khanapure, D. Garvey, D. Young, M. Ezawa, R. Earl, R. Gaston, X. Fang, M. Murty, A. Martino, M. Shumway, M. Trocha, P. Marek, S. Tam, D. Janero, L. Letts; *J. Med. Chem.* **2003**, 46, 5484-5504.
14. C. Almansa, A. F. de Arriba, F. Cavalcanti, L. Go´mez, A. Miralles, M. Merlos, J. Rafanell, J. Forn; J. Med. Chem. **2001**, 44, 350-361.
15. R.O. Bora, B. Dar, V. Pradhan, M. Farooqui; *Mini Rev. Med. Chem.*2014, **14**, 355-369.
16. N. Ali, S. Zakir, M. Patel, M. Farooqui; *Eur. J. Med. Chem.***2012**, 50, 39-43.
17. N. Ali, B. Dar, V. Pradhan, M. Farooqui; *Mini Rev. Med. Chem.***2013**, 13, 1792-1800.
18. M. Farooqui, R. Bora, C.R. Patil; *Eur. J. Med. Chem.* **2009**, 44**,** 794-799.
19. S. Hemasrilatha, K. Sruthi, A. Manjula, V. H. Babu, B. V. Rao, Indian J. of Chem. **2012**, 51(B), 981-987.
20. L.M. Szewezuk, L. Forti, L.A. Stivala, T.M. Penning; *J. Biol. Chem.* **2004**, 279, 22727-22737.
21. M. Murias, N. Handler, T. Erker, K. Pleban, G. Ecker, P. Saiko, T. Szekeres, W. Jager; *Bioorg. Med. Chem.* **2004**, 12, 5571-5578.
22. S.S. Chaudhari, A. Thomas, A.B. Kadam, S.V. Dhone, S.M. Kadam, N. Khairatkar-Joshi, V.G. Kattige; Fused imidazole carboxamides as TRPV3 modulators; **2010**, US 2010/0152192A_1.