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Synthesis of Active Pharmaceutical Ingredient Derivatives And Their Anti-Inflammatory And Analgesic Activity Studies

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ABSTRACT

*Novel series of isoxazoline containing Bis (heterocycle) in combination of imidazole has been synthesized via [3+2] cycloaddition reaction of N- (substituted) methyl-imidazole nitrile oxides with different dipolarophiles. All the newly synthesized compounds were screened for their anti-inflammatory and analgesic activity and were compared with the standard drugs. The compounds exhibited excellent anti-inflammatory and analgesic activity. Out of the compounds studied, compounds**4e** and **4f** showed significant activitycomparable to the standard drugs Ibuprofen and Aspirin at the same dose.*

Keywords: Anti-inflammatory, analgesic *N*-(substituted)imidazolealdehyde, chloramine-T.

INTRODUCTION

Heterocycles have got importance in synthetic organic chemistry due to their wide occurrence in natural bioactive molecule and pharmaceuticals. The[3+2] reaction of olefin and nitrile oxide to give isoxazoline has long been valued as an important transformation for chemical synthesis. These heterocyclic products are not only themselves of interest but are also valuable because they may be readily elaborated to a variety of highly functionalized compounds [1]. For instance, isoxazoline possess broad spectrum of biological activities like [2] anti-tuberculosis, antifungal, anticancer, antiviral, insecticidal, antibiotic activities and precursors for different natural products. Infact, Valdecoxib, an isoxazole derivative is now widely used in the market as anti-inflammatory drug[3].The chemistry of the imidazole ring occupies an extremely important niche possessing diverse pharmacological activity within the family of five-membered ring heterocycles. For instance, imidazole moiety possessesbiological activity like anti- inflame matory [4], analgesic[5], antibacterial [6], antifungal[7], antituberculosis[8], anticonvulsant[9] and potential anti cytokine agents[10].Compounds possessing imidazole moiety acts as new potent and selective 20-HETE syntheses inhibitors[11], 2-n-butyl-4- chloro-5-farmyl-imidazole is a key intermediate for the synthesis of Losartana nonpeptide angiotensin antagonist, which is an orally active anti hypertensive drug[12].

Hetero Deilds-Alder reactions are useful tools for constructing cyclic compounds like isoxazoline [13] and nitrileoxides serves as excellent1,3-dipoles.Cycloaddition of nitrile oxide to olefinic compounds are of synthetic interest, since the product isoxazoline obtained are the versatile intermediates for the synthesis of

bifuctional compounds[14].There are currently two well- established, widely used methods for the *insitu* formation of nitrile oxides. The most common approach, base-induced elimination of HCl from hydroximinoyl chlorides, has seen numerous applications in a vast range of cycloadditions [15]. The requisite ehydroximinoyl chlorides are prepared from the corresponding oxime, derived from an aldehyde, and an electrophilic chlorine source (NCS, NaOCl, Cl_2).This method is not amenable, however, for substrates highly sensitive to oxidation or halogenation, including electron-rich aromatics, olefins, and sulfides[16].The second approach, known as the Mukaiyama method, involves the dehydration of nitroalkanes by the action of phenylisocyanate, DCC, or similar reagents in the presence of base[17].This procedure has been widely utilized.

Recently we extensively used chloramine-T for the generation of nitrileoxide and nitrileimine from aldoxime and aldehyde hydrazone in the syntheses of isoxazoline and pyrazoline respectively [18]. For instance, we have reported the synthesis of ether-linked bis(isoxazoline) via 1,3-dipolar cycloaddition reactions of nitrileoxides with allyl alcohol and allyl ethers[19]. Isoxazoline bearing *bis* (heterocycles) has been synthesized by the reaction of bis chalcones and bis sulfones as dipolarophiles with nitrile oxides, generated using chloramine-T as 1,3-dipole has been reported.[20].

With this background new series of Bis (heterocycle) has been synthesized starting from the N-(substituted-biphenyl) methyl-imidazole aldehyde and evaluate their anti-inflammatory and analgesic activity. Upon biological evaluation combined and enhanced anti-inflammatory and analgesic activity were achieved. Significant activities were observed in the isoxazole derivatives possessing halo and cyano substitution.

MATERIALS AND METHODS

Melting points were determined on Thomas Hoover melting point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AM 300MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C-NMR spectra were measured on Jeol400(100MHz) instrument. The chemical shifts are expressed in and following were used Singlet, doublet, triplet and multiplet. Infrared (IR) spectra were recorded on Shimadzu 8300IR spectrometer. Elemental analyses were obtained on a Vario-EL instrument. Thin layer chromatography was carried out with BDH silica gel G on glass slides.

Pharmacology: Albino rats of either sex(150-180g) and albino mice of either sex(8-25g) were used. The compounds were administered posing a feeding tube as homogenized suspensions in 0.5% sodium carboxy methyl cellulose; 0.5% sodium carboxy methyl cellulose was administered as the vehicle control.

General procedure for the synthesis of Bis(heterocycle):(7a-g)

3-(2-butyl-4-chloro-1-(biphenyl-2-carboxylic acid methyl ester)-1H-imidazol-5-yl)-4,5-dihydro isoxa zole-5-carbonitrile [7a]: A mixture of **6a**(0.50g,1.17mmol) and chloramine-T trihydrate (0.34g, 1.18mmol) in ethanol(15mL) was stirred at room temperature for 5min. To this mixture, **3a** (0.065g, 1.20mmol) in ethanol (5mL) was added and the reaction mixture was heated on a water bath for 3h. After completion of the reaction (monitored by TLC) the reaction mixture was cooled to room temperature. Sodium chloride formed was filtered off and washed with ethanol (15mL). Filtrate and washing were combined and evaporated in vacuum. The residue was extracted with ether (25mL), the ether extract was washed successively with water (2×15mL), 5%NaOH (2×15mL) and saturated brine solution (10mL). The organic layer was dried over anhydrous sodium sulphate. After evaporation of the solvent the product was purified by the column chromatography using the chloroform/acetone (7:3) as eluent, and yellow solid **7a** was obtained (0.33g,59%).m.p152-154°C ^{1}H-NMR (300MHz,$CDCl_3$): δ0.95(t,3H,CH_3), 1.32(m,2H, CH_2), 1.61(m, 2H, CH_2), 2.54(t, 2H, CH_2), 3.26(dd, *J*=6.8, 2.0Hz, 1H, 4-CH_A), 3.58 (dd, *J*=6.8, 2.0Hz,

1H,4-CH_B), 3.85(s, 3H, CH_3), 4.98(s, 2H, CH_2), 5.10(dd, *J*=5.6Hz, 2.0Hz, 1H, 5-CH), 7.13–8.04 (m8H,H_{Ar}).^{13}C-NMR (100MHz, $CDCl_3$): δ14.2(CH_3), 22.2(CH_2), 25.3(CH_2), 33.5(CH_2), 40.7(CH_2), 41.2(CH_2), 51.4(CH_3), 70.1(CH), 118.3 (C), 122.8 (C), 126.1 (C), 127.4 (CH),127.8 (3CH), 128.8 (CH), 129.6 (2CH),130.3 (CH), 133.4 (C),133.7 (CH), 134.7 (C), 135.1 (C), 148.0 (C), 164.5 (C), 166.1(C). IR (KBr pellets cm^{-1})ν 2940, 2336, 1658, 1329, 1114. Anal.Calc.for $C_{26}H_{25}ClN_4O_3$: C, 65.47; H, 5.28; N, 11.75; Found: C,65.42, H,5.32, N,11.79%.

Spectral data of the compounds

2-butyl-4-chloro-5-(4,5-dihydro-5-phenylisoxazol-3-yl)-1-(biphenyl-2-carboxylic acid methyl ester)-1H-imidazole[7b]:^{1}H-NMR(300MHz, $CDCl_3$):δ0.97(t, 3H, CH_3), 1.35(m, 2H, CH_2), 1.64(m, 2H, CH_2), 2.57(t, 2H, CH_2), 3.29(dd, *J*=7.0, 2.2Hz, 1H, 4-CH_A), 3.61(dd, *J*=7.0, 2.2Hz, 1H, 4-CH_B), 3.90(s, 3H, CH_3), 4.99(s, 2H, CH_2), 5.13(dd, *J*=6.2Hz, 2.0Hz, 1H, 5-CH), 7.14-7.21(m, 7H, H_{Ar}), 7.38–8.10 (m6H, H_{Ar}).^{13}C-NMR(100 MHz, $CDCl_3$): δ14.0(CH_3), 22.2(CH_2), 25.4(CH_2), 33.4 (CH_2), 41.0(CH_2), 41.4 (CH_2), 51.4(CH_3), 80.5 (CH), 123.4 (C),127.2 (2CH), 127.6 (2CH), 127.8 (3CH), 128.9(C), 129.1(2CH), 129.8(2CH),130.5(CH), 133.6(2CH), 134.7(C), 135.1(C), 140.8(C), 148.0(C), 164.7(C), 166.2(C). IR(KBr pellets cm^{-1}) ν 2964, 1672, 1660, 1330, 1217. Anal.Calc.for $C_{31}H_{30}ClN_3O_3$: C, 70.51; H,5.73; N, 7.96; Found:C,70.54 H,5.71, N,7.94.Yield 65%. mp145-147°C.

2-butyl-4-chloro-5-(4,5-dihydro-5-methyl-5-phenylisoxazol-3-yl)-1-(biphenyl-2-carboxylic Acid methyl ester) -1H-imidazole[7c]: ^{1}H-NMR (300MHz, $CDCl_3$): δ0.94(t, 3H, CH_3), 1.32(m, 2H, CH_2), 1.57(s, 3H, CH_3), 1.60(m, 2H, CH_2), 2.53(t, 2H, CH_2), 3.22(s, 2H, CH_2), 3.86(s, 3H, CH_3), 4.96(s, 2H, CH_2), 7.10-7.20(m, 7H, H_{Ar}), 7.34–7.97(m6H, H_{Ar}).^{13}C- NMR(100MHz, $CDCl_3$): δ14.3(CH_3), 22.6(CH_2), 25.7(CH_2), 29.8(CH_3), 33.8(CH_2), 37.9(CH_2), 41.4(CH_2), 51.7(CH_3), 87.5(C), 123.3(C), 126.1(CH), 126.4(2CH), 126.7(C), 127.7(CH), 127.9(3CH), 128.7(2CH), 128.9(C), 129.8(2CH), 130.6 (CH), 133.5(C), 133.8(CH), 134.8(C), 135.4(C), 148.3(C), 149.8(C), 164.8(C), 166.2(C). IR (KBr pellets cm^{-1})ν 2938,1680,1662,1390,1120.Anal.Calc.for $C_{32}H_{32}ClN_3O_3$: C,70.90; H,5.95; Cl,6.54; N,7.75; Found: C,70.94, H,5.93, N,7.74. Yield 69%. m.p.161-163°C.

3-(2-butyl-4-chloro-1-(biphenyl-2-carboxylicacid-methylester)-1H-imidazol-5-yl)-4,5-dihydroisoxazol -5-yl acetate[7d]: ^{1}H-NMR(300MHz, $CDCl_3$): δ0.96(t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.62(m, 2H, CH_2), 2.06(s, 3H, CH_3), 2.54(t, 2H, CH_2), 3.36(dd, J=7.4, 2.2Hz, 1H, 4-CH_A), 3.61(dd, J=7.4, 2.2Hz, 1H, 4-CH_B), 3.87(s, 3H, CH_3),4.99(s, 2H, CH_2), 5.72 (dd, J=6.6Hz, 2.6Hz, 1H, 5-CH),7.14–7.99(m8H, H_{Ar}). ^{13}C-NMR (100MHz, $CDCl_3$): δ14.4(CH_3), 22.5(CH_2), 25.7(CH_2), 21.3(CH_3), 33.6(CH_2), 41.2(CH_2), 51.7(CH_3), 69.5 (CH_2), 96.5(C), 123.1(C), 126.2(C), 127.7(CH), 127.9(3CH), 128.9(C), 129.7(2CH), 130.6(CH), 133.6(C), 133.8(CH), 134.8(C), 135.4(C), 148.3(C), 164.7(C), 166.1(C), 170.5(C). IR(KBr pellets cm^{-1})ν 2944, 1756, 1656,1380,1124 Anal.Calc for $C_{27}H_{28}ClN_3O_5$: C,63.59; H,5.53;N, 8.24; Found:C,63.56,H,5.52,N,8.29.Yield 71%.mp170-172°C.

2-butyl-4-chloro-5-(5-(chloromethyl)-4,5-dihydroisoxazol-3-yl)-1-(biphenyl-2-carboxylic acid methyl ester)-1H-imidazole[7e]:^{1}H-NMR(300MHz, $CDCl_3$):δ 0.97(t, 3H, CH_3), 1.35(m, 2H, CH_2), 1.64(m, 2H, CH_2), 2.56(t, 2H ,CH_2), 3.24-3.67(m, 4H, 2CH_2), 3.88(s, 3H, CH_3), 4.63-4.73(m, 1H, 5-CH), 4.98(s, 2H, CH_2), 7.13–7.99(m8H, H_{Ar}). ^{13}C-NMR(100MHz, $CDCl_3$):δ 14.4(CH_3), 22.5(CH_2), 25.7(CH_2), 33.6

(CH_2), 41.2(CH_2), 37.6(CH_2), 51.5(CH_3), 51.8(CH_2), 69.6(CH_2), 123.1(C), 126.2(C), 127.6(CH), 127.8 (3CH), 128.9(C), 129.6(2CH), 130.4(CH), 133.5(C), 133.6(CH), 134.6(C), 135.2(C), 148.1(C), 164.6(C), 166.1(C). IR (KBr pellets cm^{-1})ν 2954, 1670, 1390, 1136, 1108 Anal.Calc.for $C_{26}H_{27}Cl_2N_3O_3$: C,62.40; H,5.44; N,8.40; Found:C,62.44,H,5.43,N,8.38. Yield 48% m.p.137-139°C.

5-(5-(bromomethyl)-4,5-dihydroisoxazol-3-yl)-2-butyl-4-chloro-1-(biphenyl-2-carboxylic acid methyl ester)-1H-imidazole[7f]: ^{1}H-NMR(300MHz, $CDCl_3$):δ 0.94(t, 3H, CH_3), 1.31(m, 2H, CH_2), 1.61(m, 2H, CH_2), 2.53(t, 2H, CH_2), 3.21-3.62(m, 4H, $2CH_2$), 3.87(s, 3H, CH_3), 4.61-4.72(m, 1H, 5-CH), 4.97(s, 2H, CH_2), 7.13–8.08(m8H, H_{Ar}). ^{13}C-NMR(100MHz, $CDCl_3$):δ14.2(CH_3), 22.5(CH_2), 25.6(CH_2), 33.6 (CH_2), 38.6(CH_2), 40.5(CH_2), 41.3 (CH_2), 51.5(CH_3), 70.8(CH_2), 123.2(C), 126.3(C), 127.5(CH), 127.9(3CH), 128.9(C), 129.7(2CH), 130.6(CH), 133.7(C), 133.8(CH), 134.6(C), 135.4(C), 148.3(C), 164.8(C), 166.4(C).IR (KBr pellets cm^{-1})ν 2938, 1654, 1380, 1126, 1078.Anal.Calc.for $C_{26}H_{27}Br$ Cl N_3 O_3 :C,57.31; H,4.99; N,7.71; Found: C,57.33, H,4.97, N,7.75. Yield46% .m.p134-136°C.

Methyl3-(2-butyl-4-chloro-1-(biphenyl-2-carboxylicacidmethylester)-1H-imidazol-5-yl)-4,5-dihydro iso xazole-5-carboxylate[7g]: ^{1}H-NMR(300MHz, $CDCl_3$):δ 0.95(t, 3H, CH_3), 1.34 (m, 2H, CH_2),1.63(m, 2H, CH_2), 2.54(t, 2H, CH_2), 3.27(dd, J=8.0, 2.0Hz, 1H, 4-CH_A), 3.58(dd, J=8.0, 2.0Hz, 1H, 4-CH_B), 3.65 (s,3H, CH_3), 3.89(s, 3H, CH_3), 4.99(s, 2H, CH_2), 5.52(dd, J=6.8Hz, 2.8Hz,1H, 5-CH), 7.14–8.12 (m8H, H_{Ar}). ^{13}C-NMR(100MHz, $CDCl_3$):δ 14.2(CH_3), 22.5(CH_2), 25.4(CH_2), 33.6(CH_2), 38.6(CH_2), 41.2(CH_2), 51.7 (CH_3), 52.3(CH_3), 77.5(CH_2), 123.1(C),126.2(C), 127.8(CH), 128.1(3CH), 128.9(C), 129.7(2CH),130.5(CH), 133.5(C), 133.7(CH), 134.7(C), 135.3(C), 148.2(C), 164.7(C), 166.3(C), 170.5(C). IR(KBr pellets cm^{-1})ν 2944, 1752, 1662, 1388, 1130. Anal.Calc.for $C_{27}H_{28}ClN_3O_5$: C,63.59; H, 5.53; Cl, 6.95; N,8.24; Found:C,63.58,H,5.50,N,8.28. Yield74%, m.p.171-173°C.

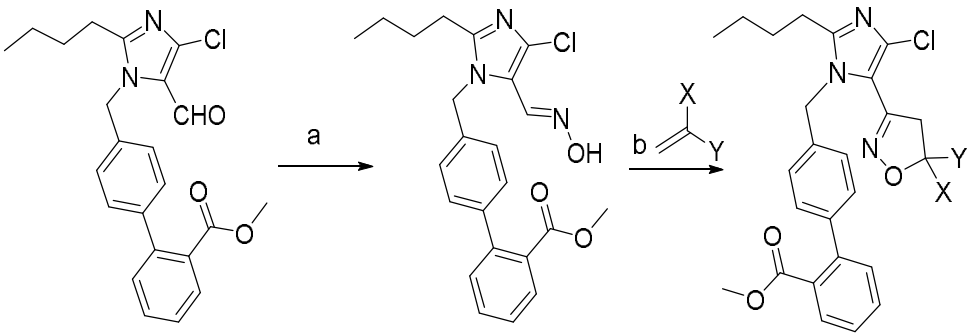
RESULTS AND DISCUSSION

The starting material *N*-(substituted)methyl-imidazole aldehyde**1** and its oxime**2** were prepared according to the literature procedure [21]. Oxidative dehydrogenation of *N*- (substituted)methyl-imidazole aldoxime**2** by chloramine-T trihydrate afforded nitrile oxides, which were intercepted *insitu* by different alkenes **3a-h** in refluxing ethanol. The pale yellow compounds obtained were identified by NMR spectroscopy as3-[2-butyl-4-chloro-1-{(biphenyl-2-carboxylic acid-methyl ester)methyl}-1*H*-imidazol-5-yl]-4,5-dihydro isoxa zoline derivatives (*Bis*-heterocycle) **4(a-g)** (Scheme).Compound **4a**(X=H) exhibits as doublet of doublet in the region δ 5.0-5.80 assigned to 5-H of the isoxazoline ring, while in cycloadducts **4c** (when X=CH_3)there was no signal in this region.4-CH_AH_B protons resonate as doublet of doublet in the region δ3.25-3.57.Remaining protons are resonates at expected region. Thus, the formation of cycloadducts **4(a-g)** indicates a regio selective nature of the reaction.

Pharmacological results: All the compounds were tested for anti-inflammatory activity in carrageen-induced edema assay in rats at a dosage of 100mg kg^{-1} bodyweight (table I). Amongst these compounds, the two halogenated derivatives, **4e** and **4f** have more than 60% activity. At all of the doses they were less active than Ibuprofen. All of these compounds were tested for analgesic activity at 100 mg kg^{-1} in acetic-acid induced assay in mice (Fig 1 and Fig 2). Seven compounds had significant activity and the compound **4e** exhibited the highest activity in the series. The percentage inhibition of carrageenen induced paw edema volume was calculated using the formula

Percentage inhibition = 100 (1-Vt/Vc)

Where, Vt = increase in paw volume in treatment group, Vc = increase in paw volume in the control group



Code	4a	4b	4c	4d	4e	4f	4g
X	CN	Ph	Ph	$OCOCH_3$	CH_2Cl	CH_2Br	$COOCH_3$
Y	H	H	CH_3	H	H	H	H

Scheme 1

Reaction conditions: a)$NH_2OH{\cdot}HCl$, CH_3COONa/EtOH, b) Chloramine-T/EtOH

Table I. Anti-inflammatory activities of **4 a-g**

Compound	Edema volume (mL) ±SD[1]	Edema Inhibition (%)[2]
4a	0.22±0.07[3]	48.8
4b	0.24±0.06[4]	53.8
4c	0.31±0.08[5]	46.5
4d	0.29±0.06[4]	44.2
4e	0.20±0.08[4]	60.2*
4f	0.18±0.04[3]	58.1*
4g	0.32±0.07[4]	44.8
Ibuprofen	0.15±0.07[4]	71.1*

1.At100mg kg^{-1},Body weightedemavolumemeasured3haftercarra-geeneninjection,andexpressedas mean ±standarddeviations(n=4); 2.percentedemainhibitioncalculatedbycomparingwith thevehicle-treatedcontrolanimals; 3.controledemavolume=0.43±0.03;4.controledema volume=0.52±0.03;5.controledemavolume=0.58± 0.04;*statisticallysignificant.

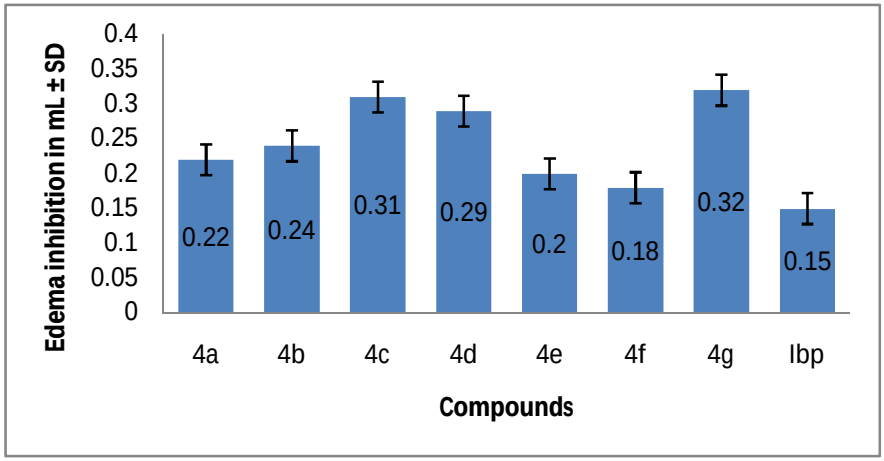


Fig 1: Anti-inflammatoryactivitiesof **4 a-g**

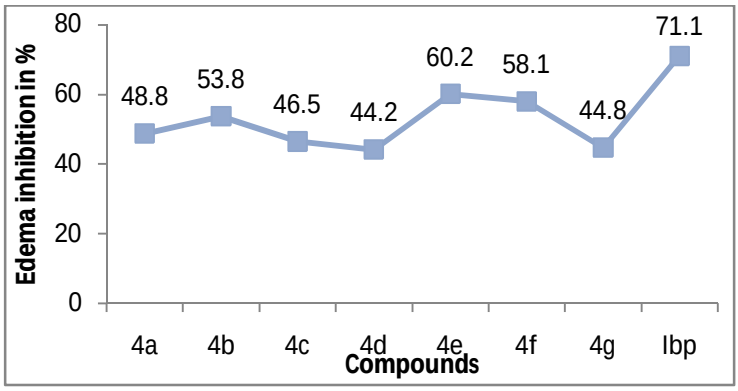


Fig 2: Percentage edema inhibition of Anti-inflammatoryactivitiesof **4 a-g**

APPLICATIONS

Carrageenen-induced edema: Groups of four rats were dosed at 100mg kg^{-1} powith the test compounds,1h before 0.05ml of a 1% suspension of Type IV Lambda(Sigma) carrageenen was injected into the sub plant arraign at the right hind paw; additional groups of four rats were similarly pretreated with100 mg kg^{-1} ibuprofen (positive control) or 10 mL kg^{-1} 0.5% sodium carboxymethyl cellulose (vehicle controls) [22].Paw volumes were measured by water displacement in a plethysmograph immediately after carrageenen injection, and again 3h later. Edema volumes for test-compound-treated and positive-control rats were compared statistically with those for the vehicle-treated control rats; data are reported as percentage edema inhibition.

Analgesic activity: This method is based on acetic-acid-induced writhing in mice [23].Groups of six mice each were doused with the test compounds or with aspirin at a dose of100mg kg^{-1}, 1h before the ipinjection of 0.6%aceticacid (10mL kg^{-1}). Mice were observed for1.5min beginning 5min after the acetic acid injection, and the total number of writhes recorded. The mean value of writhes for each group was calculated and compared statistically with that for the vehicle- treated control group(n=6); data were reported as percent inhibition of the number of writhes. The test was repeated on additional groups of six mice, treated with compounds for which the reduction in writhes had been calculated to be>10%; these results are shown in table 2 and in figs. 3,4.

Table 2. Analgesicactivities of**4 a-h** and **7a-g**

Compound	No. of Writhes in 15 min ±SD[1]	% Reduction from control[2] (%)[2]
4a	30±09[3]	55.2*
4b	33±07[3]	50.7
4c	39±06[5]	49.3
4d	37±14[4]	47.8
4e	28±08[4]	60.6*
4f	28±09[3]	58.2*
4g	46±08[3]	31.3
Aspirin	29±05[5]	59.1*

[1]At100mg/kgpo,numberof writhesin15minbeginning5minafteraceticacidinjection, expressedmean ±standarddeviation(*n*=6); [2]percentagewrithinginhibitioncalculatedby comparing with vehicle-treated controlanimals;[3]controlnumber ofwrithes =67±10; [4]controlnumberofwrithes=71±8; [5]controlnumberofwrithes=77±9;*statisticallysignificant.

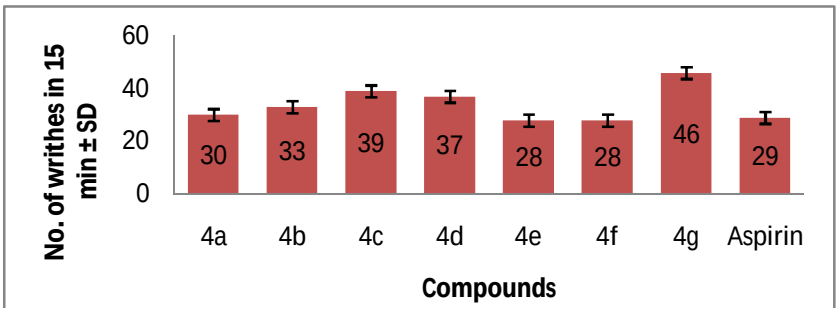


Fig 3: Analgesic activities of**4 a-g**

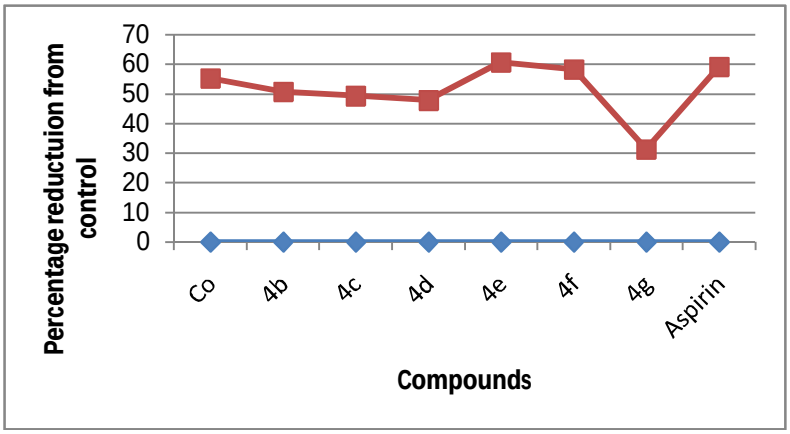


Fig 4: Percentage reduction from control of Analgesic activities of**4 a-h** and **7a-g**

CONCLUSIONS

Isoxazoline and imidazole bearing were obtained in good yield via 1,3-dipolar cycloaddition reaction, and it is found that all the seven new molecules shown significant anti-inflammatory and analgesic activity. Compounds **4e** and **4f** possess chloro and bromo substitutions on one of the isoxazole ring shown good analgesic and anti-inflammatory activity. Further detailed *in situ* and cellular level studies will be taken up for these biologically important molecules.

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