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Synthesis and Evaluation of Anti-inflammatory and Analgesic activity of Isoxazoline Bearing Bis(heterocycle)

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Abstract : Series of *Bis*(heterocycle) bearing isoxazoline in combination of imidazole and isoxazole has been synthesized via 1,3-dipolar cycloaddition reactions 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 7e and 7f showed significant activity comparable to the standard drugs Ibuprofen and Aspirin at the same dose.

Keywords: Anti-inflammatory, analgesic, N-(substituted) imidazole aldehyde, chloramine-T.

I. INTRODUCTION

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. In fact, 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 possesses biological activity like anti- inflammatory [4], analgesic [5], antibacterial [6], antifungal [7], antituberculosis [8], anticonvolusant [9] and potential anticytokine agents [10]. Compounds possessing imidazole moiety acts as new potent and selective 20-HETE synthase inhibitors [11], 2-n-butyl-4- chloro-5- farmyl-imidazole is a key intermediate for the synthesis of Losartan a nonpeptide angiotensin antagonist, which is an orally active antihypertensive drug [12].

1,3-dipolar cycloaddition reactions are useful tools for constructing isoxazoline [13] and nitrile oxides serves as excellent 1,3-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 *in situ* 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 hydroximinoyl 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 phenyl isocyanate, DCC, or similar reagents in the presence of base [17]. This procedure has been widely utilized.

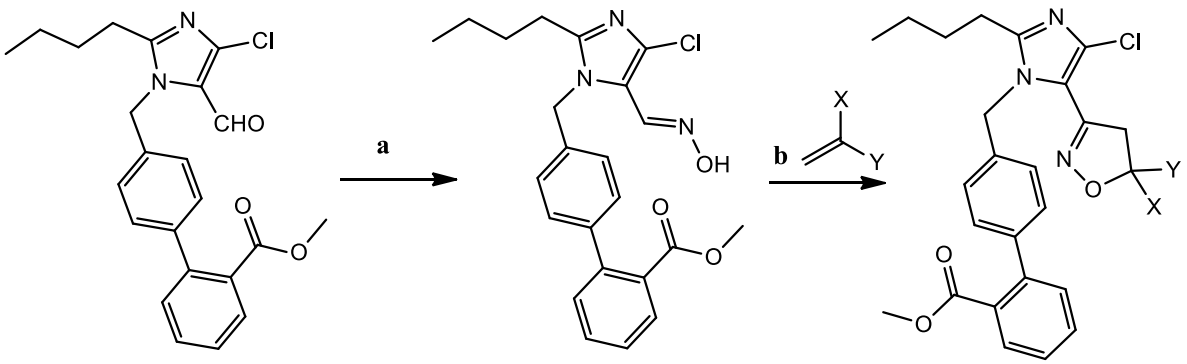
In our laboratory we extensively used chloramine-T for the generation of nitrile oxide and nitrile imine from aldoxime and aldehyde hydrazone in the syntheses of isoxazoline and pyrazoline respectively [18]. For instance, we have reported the synthesis of ether-linked bis(isoxazoline) via 1,3-dipolar cycloaddition reactions of nitrile oxides with allyl alcohol and allyl ethers [19]. Reecently, isoxazoline bearing bis(heterocycles) has been synthesized by the reaction of bischalcones and bis sulfones as dipolarophiles with nitrile oxides, generated using chloramine-T, as 1,3-dipole [20]. With this background, it is considered worthwhile to synthesize hitherto unknown *Tris*(heterocylce) bearing isoxazoline in combination with isoxazole, imidazole and *Bis*(heterocycle) in combination of imidaloe and isoxazoline has been synthesized starting from the *N*-(isoxazolyl)methyl-imidazole aldehyde and *N*- (substituted-biphenyl)methyl-imidazole aldehyde and evaluate their anti-inflammatory and analgesic activity.

Chemistry results and discussion

The starting material *N*-(substituted)methyl-imidazole aldehyde **5** and its oxime **6** were prepared according to the literature procedure [21]. Oxidative dehydrogenation of *N*-(substituted)methyl-imidazole aldoxime **6** by chloramine-T trihydrate afforded nitrile oxides, which were intercepted *in situ* by different alkenes **3a-h** in refluxing ethanol. The pale yellow compounds obtained were identified by NMR spectroscopy as 3-[2-butyl-4-chloro-1-{(biphenyl-2-carboxylicacid-methylester)methyl}-1*H*-imidazol-5-yl]-4,5-dihydro isoxazoline derivatives (*Bis*-heterocycle) **7(a-g)** (Scheme). Compound **7a** (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 **7c** (when X=CH3) there was no signal in this region. 4-CHAHB protons resonate as doublet of doublet in the region δ 3.25-3.57. Remaining protons are resonates at expected region. Thus, the formation of cycloadducts **7(a-g)** indicates a regioselective nature of the reaction.

Pharmacological results and discussion

All the compounds were tested for anti-inflammatory activity in carrageenen-induced edema assay in rats at a dosage of 100 mg/kg Body weight (table I). Five compounds (**7e** and **7f**) have significant 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 in acetic-acid induced assay in mice (table II).



Scheme 1

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

Experimental section:

Melting points were determined on Thomas Hoover melting point apparatus and were uncorrected. ^1H NMR spectra were recorded on a Bruker AM 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were measured on Jeol 400 (100 MHz) instrument. The chemical shifts are expressed in d and following were used Singlet, doublet, triplet and multiplet. Infrared (IR) spectra were recorded on Shimadzu 8300 IR 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 (150-180 g) and albino mice of either sex (8-25 g) were used. The compounds were administered po using a feeding tube as homogenized suspensions in 0.5% sodium carboxymethyl cellulose; 0.5% sodium carboxymethyl cellulose was administered as the vehicle control.

Carrageenen-induced edema

Groups of four rats were dosed at 100 mg/kg po with the test compounds, 1 h before 0.05 ml of a 1% suspension of Type IV Lambda (Sigma) carrageenen was injected into the subplantar region at the right hind paw; additional groups of four rats were similarly pretreated with 100 mg/kg ibuprofen (positive control) or 10 ml/kg 0.5% sodium carboxymethyl cellulose (vehicle controls) [22]. Paw volumes were measured by water displacement in a plethysmograph immediately after carrageenen injection, and again 3 h 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.

Table I. Anti-inflammatory activities of **4 a-h** and **7a-g**

Compound	Edema volume (mL) ±SD[1]	Edema Inhibition (%)[2]
4a	0.18±0.04[3]	58.1*
4b	0.23±0.08[4]	55.7
4c	0.31±0.06[5]	46.5
4d	0.32±0.04[5]	44.8
4e	0.16±0.03[3]	62.8*
4f	0.20±0.07[4]	60.2*
4g	0.32±0.04[5]	46.5
4h	0.23±0.03[3]	46.8
7a	0.22±0.07[3]	48.8
7b	0.24±0.06[4]	53.8
7c	0.31±0.08[5]	46.5
7d	0.29±0.06[4]	44.2
7e	0.20±0.08[4]	60.2*
7f	0.18±0.04[3]	58.1*
7g	0.32±0.07[4]	44.8
Ibuprofen	0.15±0.07[4]	71.1*

[1]At 100 mg/kg, Body weight edema volume measured 3 h after carra-geenen injection, and expressed as mean ± standard deviations (n = 4); [2]percent edema inhibition calculated by comparing with the vehicle-treated control animals; [3]control edema volume = 0.43 ± 0.03;

[4]control edema volume = 0.52 ± 0.03; [5]control edema volume = 0.58 ± 0.04; *statistically significant.

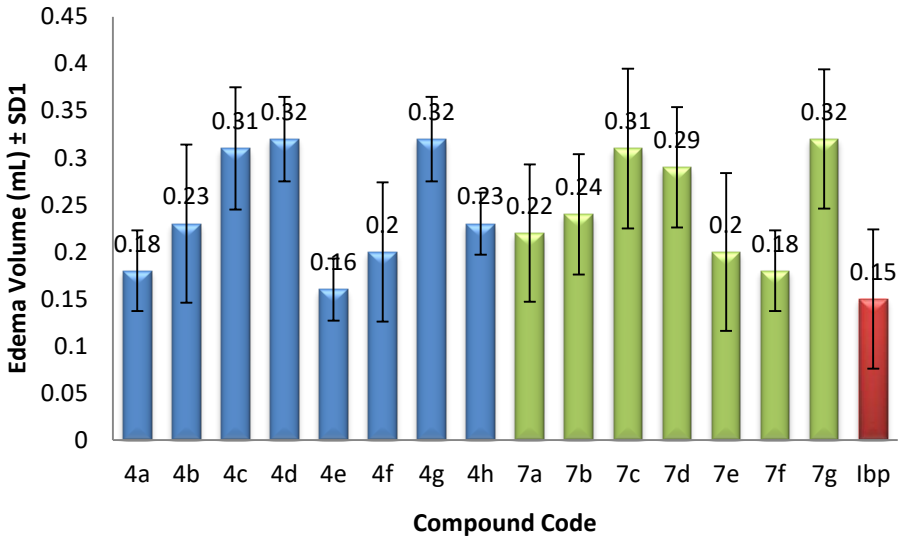


Fig 1: Anti-inflammatory activities of **4 a-h** and **7a-g**

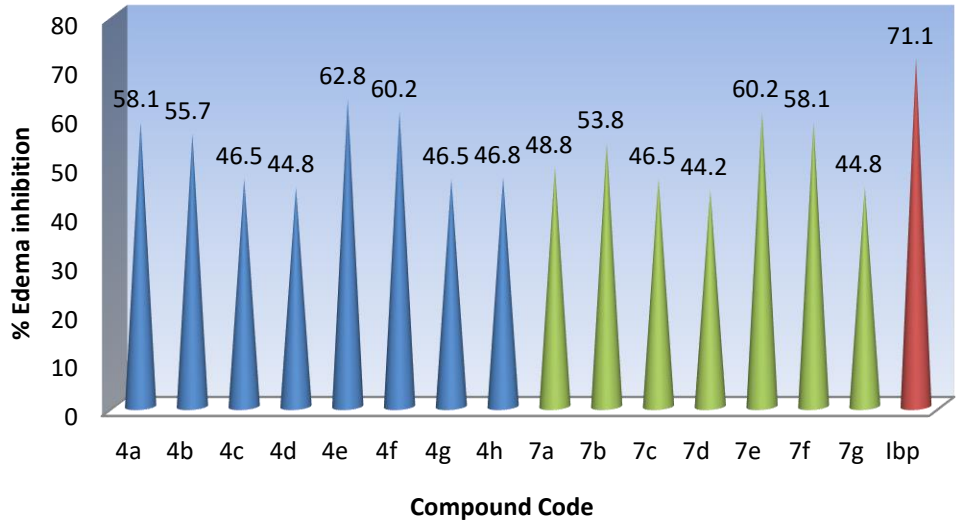


Fig 2: Percentage edema inhibition of Anti-inflammatory activities of **4 a-h** and **7a-g**

Analgesic activity

This method is based on acetic-acid-induced writhings in mice [23]. Groups of six mice each were dosed with the test compounds or with aspirin at a dose of 100 mg/kg po, 1 h before the ip injection of 0.6% acetic acid (10 ml/kg). Mice were observed for 1.5 min beginning 5 min 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 II.

Table II. Analgesic activities of **4 a-h** and **7a-g**

Compound	No. of Writhes in 15 min ±SD[1]	% Reduction from control[2] (%)[2]
4a	31±13[5]	59.7*
4b	31±07[3]	53.7
4c	34±09[4]	52.1
4d	37±10[4]	47.8
4e	25±08[3]	62.7*
4f	30±06[5]	61.0*
4g	43±12[5]	44.1
4h	42±13[4]	40.8
7a	30±09[3]	55.2*
7b	33±07[3]	50.7
7c	39±06[5]	49.3
7d	37±14[4]	47.8
7e	28±08[4]	60.6*
7f	28±09[3]	58.2*
7g	46±08[3]	31.3
Aspirin	29±05[5]	59.1*

[1]At 100 mg/kg po, number of writhes in 15 min beginning 5 min after acetic acid injection, expressed mean ± standard deviation (*n*=6); [2]percentage writhing inhibition calculated by comparing with vehicle-treated control animals; [3]control number of writhes = 67±10; [4]control number of writhes = 71±8; [5]control number of writhes = 77±9; *statistically significant.

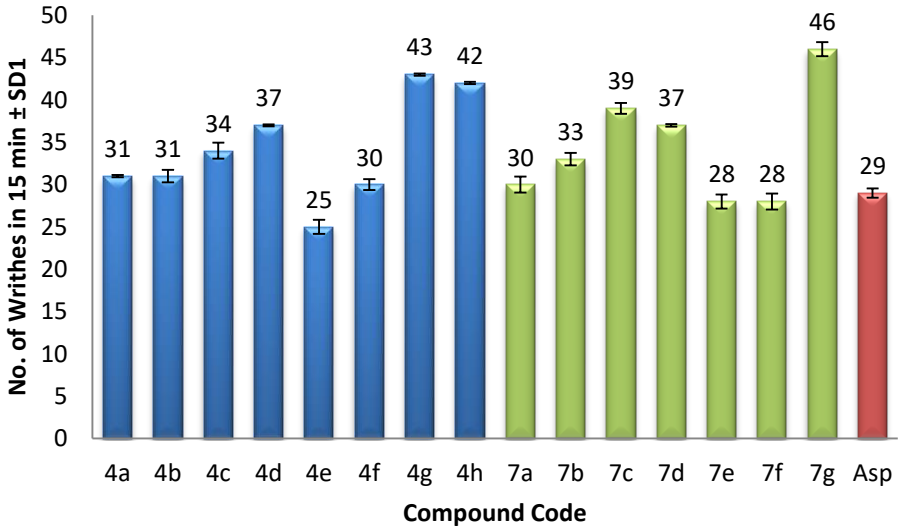


Fig 3: Analgesic activities of **4 a-h** and **7a-g**

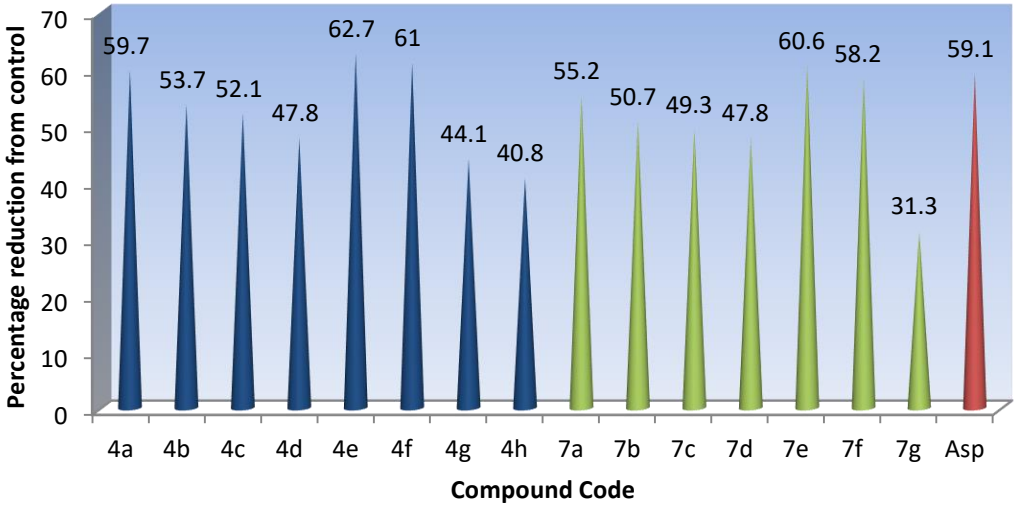


Fig 4: Percentage reduction from control of Analgesic activities of **4 a-h** and **7a-g**

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-dihydroisoxazole-5-carbonitrile [7a]*: Typical procedure:** A mixture of **6a** (0.50 g, 1.17 mmol) and chloramine-T trihydrate (0.34 g, 1.18 mmol) in ethanol (15 mL) was stirred at room temperature for 5 min. To this mixture, **3a** (0.065 g, 1.20 mmol) in ethanol (5 mL) was added and the reaction mixture was heated on a water bath for 3 h. 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 (15 mL). Filtrate and washing were combined and evaporated in vacuum. The residue was extracted with ether (25 mL), the ether extract was washed successively with water (2 × 15 mL), 5% NaOH (2 × 15 mL) and saturated brine solution (10 mL). 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 (0.33 g, 59 %). mp 152-154 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (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, 2.0 Hz, 1H, 4- CH_A), 3.58 (dd, *J* = 6.8, 2.0 Hz, 1H, 4-CH_B), 3.85 (s, 3H, CH_3), 4.98 (s, 2H, CH_2), 5.10 (dd, *J* = 5.6 Hz, 2.0 Hz, 1H, 5-CH), 7.13–8.04 (m 8H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (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. Calcd.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 (300 MHz, $CDCl_3$): δ 0.97 (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, 2.2 Hz, 1H, 4-CH_A), 3.61 (dd, *J* = 7.0, 2.2 Hz, 1H, 4-CH_B), 3.90 (s, 3H, CH_3), 4.99 (s, 2H, CH_2), 5.13 (dd, *J* = 6.2 Hz, 2.0 Hz, 1H, 5-CH), 7.14-7.21 (m, 7H, H_{Ar}) 7.38–8.10 (m 6H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (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. Calcd.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 %. mp 145-147 °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 (300 MHz, $CDCl_3$): δ 0.94 (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 (m 6H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (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. Calcd.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 %. mp 161-163 ℃.

***3-(2-butyl-4-chloro-1-(biphenyl-2-carboxylicacid-methylester)-1H-imidazol-5-yl)-4,5-dihydroisoxazol-5-yl acetate [7d]*:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (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, 2.2 Hz, 1H, 4-CH_A), 3.61 (dd, *J* = 7.4, 2.2 Hz, 1H, 4-CH_B), 3.87 (s, 3H, CH_3), 4.99 (s, 2H, CH_2), 5.72 (dd, *J* = 6.6 Hz, 2.6 Hz, 1H, 5-CH), 7.14–7.99 (m 8H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (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. Calcd.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 %. mp 170-172 °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 (300 MHz, $CDCl_3$): 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 (m 8H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): 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. Calcd.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 % mp 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 (300 MHz, $CDCl_3$): 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 (m 8H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (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. Calcd.for $C_{26}H_{27}BrClN_3O_3$: C, 57.31; H, 4.99; N, 7.71; Found: C, 57.33, H, 4.97, N, 7.75. Yield 46 %. mp 134-136 °C.

***Methyl 3-(2-butyl-4-chloro-1-(biphenyl-2-carboxylic acid methyl ester)-1H-imidazol-5-yl)-4,5-dihydroisoxazole-5-carboxylate [7g]*:** ^{1}H NMR (300 MHz, $CDCl_3$): 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, 2.0 Hz, 1H, 4-CH_A), 3.58 (dd, *J* = 8.0, 2.0 Hz, 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* = 6.8 Hz, 2.8 Hz, 1H, 5-CH), 7.14–8.12 (m 8H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): 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. Calcd.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. Yield 74 %. mp 171-173 °C.

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