Δ^2-ISOXAZOLINE DERIVATIVES AS ANTIMICROBIALS

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Abstract: The inhibitory effect of newly synthesized C- (anthranyl and biphenyl)-5-substituted-δ^2-isoxazolines were characterized by IR, ^{1}H NMR, ^{13}C NMR and CHN analysis and evaluated for their antimicrobial activity against different strains. Such as *Bacillus substilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus, Fusarium oxysporum, Trichoderma* species and *Fusarium monaliforme* . Among the newly synthesized compounds, 6b III, 6b IV and 6b VI showed significant inhibitor activity.

Introduction

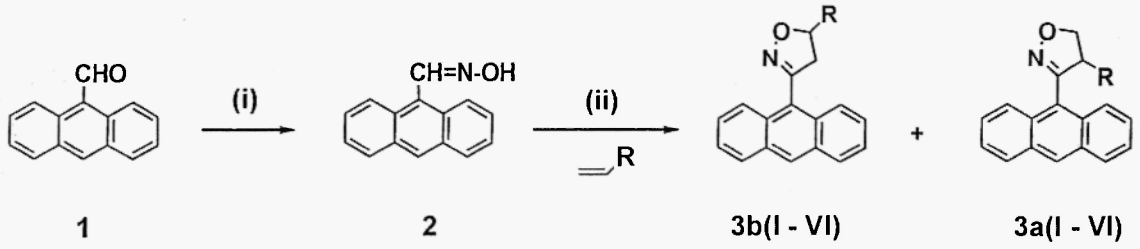
Antimicrobials reduce or completely block the growth and multiplication of bacteria. This has made them unique for the control of deadly infectious diseases caused by a variety of pathogens. They have transformed our ability to treat infectious diseases such as pneumonia, meningitis, tuberculosis, malaria and AIDS. The synthesis of 2-isoxazolines has recently received considerable attention in the search for the compounds with anti-inflammatory (1-2) and antifungal activity (3). Previous reports show that the compounds possessing isoxazole and isoxazoline ring systems show a variety of biological activities like insecticidal, antibacterial, antibiotic, antitumor, antifungal (4-6) and in some pharmaceutical agents such as GPII b/IIIa inhibitors (7) and human leukocyte elastase inhibitors (8). Nitrile oxides undergo (3+2) cycloaddition with olefins and acetylenes to provide isoxazolines and isoxazoles respectively (9). 1, 3 – dipolar cycloaddition of a nitryl oxide to alkenes is a useful procedure for the construction of δ^2-isoxazolines, which are versatile intermediates for the synthesis of a wide variety of natural products and are important pharmacophores in medicinal chemistry. As part of our continuing effort for the discovery of novel synthetic molecules, here in we report the synthesis of some δ^2-isoxazoline derivatives and their antimicrobial activity against *Bacillus substilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus, Fusarium oxysporum, Trichoderma* species and *Fusarium monaliforme* .

Chemistry

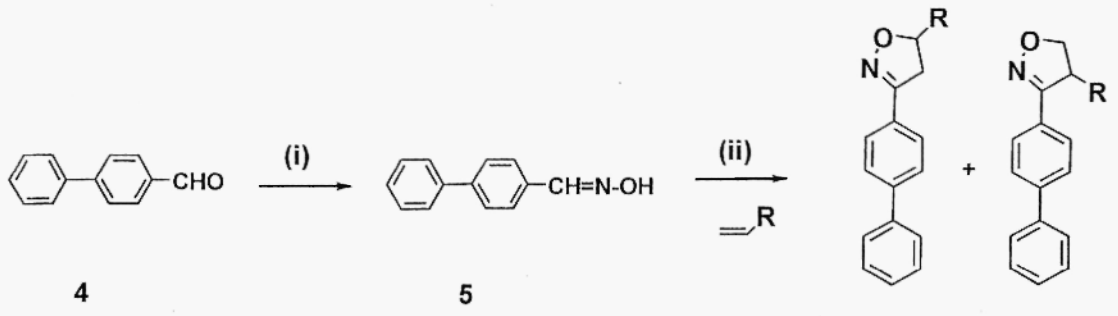
The synthesis of anthranyl and biphenyl substituted δ^2-isoxazolines has been carried out by using their respective aldoximes through 1,3-dipolar cycloaddition with the mono substituted alkenes and Choramine-T as an oxidant (10). The key intermediates anthraldoxime and biphenylaldoxime have been prepared by using hydroxylamine sulphate and sodium acetate from our reported method (3). Since *nitryl oxides* dimerize readily, they are usually generated *in situ* and trapped by dipolarophiles. Even though the chemical diversities on solid phase have attracted tremendous attention because of their potential application in rapid drug discovery (11), but it is very difficult to get pure products in good yields. So we stabilized the solution phase synthesis of isoxazolines via 1,3-dipolar cylcoaddition reactions by using different oxidants.

Results and Discussions
Chemistry

Previous and the present report on several derivatives of bio-applicable isoxazoli (di) nes synthesis involves the trapping or utilization of the *in situ* generated 1,3-dipolar species such as *nitryl oxides* or *nitrones*, which bearing bulky groups generated from aldoximes oxidation by using cheaper reagents. The cycloaddition with the alkenes gave exclusively 5-substituted isoxazolines consisting of high regioselectivity (Scheme-1).



1 2 3b(I - VI) 3a(I - VI)



4 5 6b(I - VI) 6a(I - VI)

Reaction Condition

(i) $(NH_2OH)H_2SO_4$ $NaOCOCH_3$ Methanol (ii) CAT/Ethanol

Where R = I) $-OOCCH_3$ II) $-COOC_6H_5$ III) $-COOC_2H_5$ IV) $-COO(CH_2)_3-CH_3$ V) $-COOCH_3$ VI) $-CH_2OH$

Scheme-1

All the compounds were purified through column chromatography by using n-hexane, ethyl acetate, chloroform and methanol as different solvent systems. The ^1H NMR spectra at 4.6-4.70 (dd) and at 4.9 (t) clearly confirm the formation of the isoxazoline ring moiety as reported earlier (Table-1).

Table 1: Reaction condition and physical data of δ^2- isoxazolines.

δ^2-isoxazolines	Solvent	Reaction time (hrs)	R_f Value	Eluent used in separation	Yield (%)
3b-I	Ethanol	8	0.63	Benzene/Ehtylacetate 9:1	75
3b-II	Ethanol	10	0.50	Benzene/Ehtylacetate 9:1	80
3b-III	Ethanol	10	0.45	n-Hexane/Ehtylacetate 8:2	65
3b-IV	Methanol	12	0.48	n-Hexane/Ehtylacetate 8:2	72
3b-V	Ethanol	12.5	0.62	Benzene/Ehtylacetate 9:1	70
3b-VI	Ethanol	8	0.56	Benzene/Ehtylacetate 9:1	82
6b-I	Methanol	7.5	0.75	n-Hexane/Ehtylacetate 8:2	69
6b-II	Methanol	14	0.50	n-Hexane/Ehtylacetate 8:2	76
6b-III	Ethanol	15	0.49	Benzene/Ehtylacetate 9:1	58
6b-IV	Methanol	9.5	0.56	Benzene/Ehtylacetate 9:1	66
6b-V	Methanol	9.5	0.67	Benzene/Ehtylacetate 9:1	77
6b-VI	Methanol	11	0.44	Benzene/Ehtylacetate 9:1	59

Biology

In view of synthesizing new antimicrobials, we have synthesized Anthranyl **3b(I VI)** and biphenyl substituted **6b(I-VI)** isoxazoline and evaluated for their antimicrobial activity by disk diffusion methods against different strains. Streptomycin, tetracycline and nystatin as positive controls. All tests were performed in duplicate and the results are the means of atleast three determinations. Our results reveals that the biphenyl substituted 2-isoxazolines, **6b III, 6b IV, 6b VI** showed better activity when compared to standard and among anthranyl substituted 2-isoxazolines, **3b III, 3 b IV, 3b VI**exhibited similar potency, comparable to standards against both fungal and bacterial strains tested (Table2 and Table-3).

Table-2 : Inhibitory Zone (diameter) mm of synthesized compounds against tested bacterial strains by disk diffusion method

Compounds	Inhibitory Zone (diameter) mm[a]				
	Bacillus--substilis	*Escherichia--coli*	*Pseudomonas--fluorescens*	*Xanthomonas--campestris pvs.*	*Xanthomonas--oryzae*
3b I	19+0.8	22+0.98	28±1.2	16+0.7	17±0.8
3b II	21+0.9	18±0.8	27±1.3	21±0.98	18±0.72
3b III	10±0.4	11±0.45	18±0.8	13±0.5	12±0.5
3b IV	11+0.42	12+0.5	17±0.7	12+0.42	10±0.42
3b V	20+0.89	21+0.91	29±1.3	23+1.1	20±0.9
3bVI	12±0.52	13±0.56	16±0.7	11±0.45	11±0.42
6b I	17±0.75	16±0.7	21±0.9	14±0.6	15+0.7
6 bII	18±0.76	19+0.9	24±0.95	16±0.7	14±0.52
6 bIII	6±0.21	7+0.31	12±0.5	10±0.4	8±0.32
6 b IV	7±0.3	9±0.4	10±0.4	8±0.32	9±0.41
6b V	19±0.89	18±0.8	23+1.1	19±0.8	18±0.81
6b VI	8+0.32	11±0.41	13±0.6	9±0.4	8±0.3
Streptomycin	12 ±0.5	14± 0.6	18±0.7	-	-
Tetracycline	-	-	-	12±0.5	11+0.5

Streptomycin sulphate (25 µg/disc); Tetracycline (25 µg/disc) were used as positive reference standard antibiotic discs, Synthesized compounds (25 µg/disc).
[a] Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

Table-3 : Inhibitory Zone (diameter) mm of synthesized compounds against tested fungal strains by disk diffusion method.

Compound	Inhibitory Zone (diameter) mm[a]				
	Aspergillus--niger	*Aspergillus--flavus*	*Fusarium--oxysporum*	*Trichoderma--species.*	*Fusarium--monaliforme*
3b I	14±0.6	15+0.65	17±0.8	19±0.81	16±0.71
3b II	15±0.7	14±0.66	19±0.89	22±0.98	18±0.82
3b III	8±0.3	10±0.47	13±0.53	14±0.64	11+0.43
3b IV	10±0.41	9±0.41	13+0.51	15±0.67	10±0.45
3b V	12±0.52	14±0.66	16+0.74	19±0.91	15±0.7
3bVI	9±0.4	11±0.49	14±0.6	16±0.72	12±0.51
6b I	20±0.9	18±0.82	22±0.9	19±0.87	17±0.8
6 bII	18±0.82	17±0.72	19±0.85	17±0.71	18+0.81
6 bIII	5±0.2	5±0.21	9±0.4	8±0.34	7±0.3
6 b IV	6±0.25	7±0.3	11±0.43	10±0.43	9±0.4
6 b V	22+.0.98	17±0.76	19±0.8	18±0.8	16±0.7
6 b VI	7±0.28	6±0.24	10±0.4	9±0.4	8±0.32
Nystatin	8±0.32	10± 0.4	14±0.61	16±0.7	12±0.52

Nystatin (25 µg/disc) was used as positive reference standard antibiotic discs, Synthesized compounds (25 µg/disc)
[a] Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

Conclusions

In conclusion, herein we report the synthesis of anthranyl and biphenyl substituted δ^2-isoxazolines and their efficacy as antimicrobials. Compounds **6b III, 6b IV, 6b VI** showed potent inhibition and also **3b III, 3b IV, 3b VI** showed significant inhibition against standard tested

Experimental

Biology

Bacteria and fungal species used were obtained from microbiology department, University of Mysore, India. Namely, *Bacillus substilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus, Fusarium oxysporum, Trichoderma species and Fusarium monaliforme.* The bacterial strains were maintained on LB agar medium and the filamentous fungi were maintained on Potato dextrose agar (PDA) medium at 28°C. The disk diffusion method (12) was used to determine antimicrobial activity of synthesized compounds. Paper discs with only DMSO were used as negative controls.

The bacteria were grown in LB broth, centrifuged at 10,000 rpm for 5 mins, pellet was dissolved in double distilled and used to inoculate the plates. For the filamentous fungi, the inoculum was prepared with the spores derived from 5 to 15 days culture on PDA medium. The mycelia were covered with 10 mL of distilled water and the conidia were scraped using sterile pipette. The spores were recovered after filtration on sterile absorbent cotton and were resuspended in sterile distilled water. The cell density of each inoculum was adjusted with hemocytometer in order to obtain a final concentration of approximately 10^4 CFU/mL and 10^6 CFU/mL for the bacteria and filamentous fungi respectively.

Nystatin (Himedia) was used as positive control for fungi and streptomycin and tetracycline for bacteria. Each disk contained 25µg of standard drugs and synthesized compounds. Plates were first kept at 4°C for at least 2 hours to allow the diffusion of chemicals, and then incubated at 28°C. Inhibition zones were measured after 24 hours of incubation for bacteria and after 48 hours of incubation for fungi. The Nutrient liquid medium and Potato dextrose liquid medium were used as test media.

Chemistry

The melting points were determined on SELACO-650 hot stage apparatus and are uncorrected. IR (nujol) spectra were measured on Shimadzu 8300 IR spectrophotometer, ^{1}H NMR were recorded on Shimadzu AMX 400-Bruker, 400 MHz spectrometer by using $CDCl_3$ as solvent and TMS as an internal standard (chemical shift in δ ppm). Elemental analyses were obtained on a Vario-EL instrument. TLC was conducted on 0.25 mm silica gel plates ($60F_{254}$, Merck) and Column by silica gel BDH 60-120 meshes. All extracted solvents were dried over Na_2SO_4, followed by evaporation in vacuo.

Synthesis of anthracene-9-carbaldehyde oxime (2)

A solution of 9-anthranyl carbaldehyde (1g, 4.848 mmol) in methanol (15ml) was added to a mixture of hydroxylamine sulfate (1.193g, 7.268 mmol) and sodium acetate (1.193g, 14.54 mmol). The reaction mass was refluxed for 4-5 hrs till the reaction completes. Evaporated the solvent under *vacuo* and added 40ml of demineralised water, cooled to 5-8^0 C and filtered at the same temperature to obtain the crystalline solid (0.987g). m.p = 159-161^{0}C, IR (nujol) cm^{-1} 1675 (CH=N), 3240 (OH).

Synthesis of biphenyl-4-carbaldehyde oxime (5)

The compound **5** was obtained by using 4-biphenyl carbaldehyde (1g, 5.4878 m mol), hydroxylamine sulfate (1.351g, 8.234 mmol) and sodium acetate (1.35g, 16.46 mmol) with the above protocol. m.p = 142-147 ^{0}C, IR (nujol) cm^{-1} 1689 (CH=N), 3235 (OH).

General procedure for the synthesis of novel δ^2-isoxazolines 3b(I - VI) and 6b(I - VI)

A solution of aldoxime **2** (2 equivalent) in ethanol or methanol was added to a solution of alkene (1 equivalent), Chloramine–T (1.5 equivalent) and refluxed for 12–14 hrs to complete the reaction, which was monitored by thin layer chromatography. After completion of the reaction, the solvent was evaporated under *vacuo*. Eight volumes of demineralised water was added to the residue and extracted the crude with 4 volumes of methylendichloride thrice. The organic layer was washed with 5% $NaHCO_3$ solution. Using appropriate mixture solvent systems as eluent in silica gel column separated the pure products.

Synthesis of acetic acid-3-anthracene-9-yl-4, 5-dihydro-isoxazole-5yl-ester 3b-I.

It was obtained from 9-anthralaldoxime **2** (0.25g, 1.1298 mmol) vinyl acetate (0.097g, 1.1298 mmol) and Chloramine-T (0.35 g, 1.242 mmol). IR (nujol) cm^{-1} 1750 (C=O), 1670 (C=N), 840 (N-O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.89 (s, 3H, -$COCH_3$), 5.2-5.28 (dd, 2H, *J*=6.2[Hz] ,C_4H), 6.60 (t, 1H, *J*=8[Hz] ,C_5H), 7.61-7.63 (s, 1H, Ar-H), 7.4 (t, 2H, Ar-H), 7.89-7.94 (s, 2H, Ar-H), 8.29 (s, 2H, Ar-H), 8.05-8.15 (d, 2H, Ar-H); ^{13}C: 125.41 (4C), 126.401 (3C), 128.55 (4C), 128.97 (4C), 130.769, 133.4 (4C), 155.61 (2C), 168.0; Anal. CHN: calcd 74.75, 4.918, 4.590, found 74.15, 4.5321, 4.290

Synthesis of 3-anthracene-9-yl-4, 5-dihydro-isoxazole-5-carboxylic acid phenyl ester 3b-II

It was obtained from 9-anthralaldoxime **2** (0.25g, 1.1298 mmol) vinyl benzoate (0.1674 g, 1.1298 mmol) and Chloramine-T (0.477 g, 1.6947 mmol). IR (nujol) cm^{-1} 1725 (C=O), 1654 (C=N), 845 (N-O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.2-7.4 (m, 3H, Ar-H), 7.0-7.15 (d, 2H, Ar-H), 4.9 (t, 1H, C_5H), 4.3 (dd, 1H, *J*=7[Hz], C_4H); ^{13}C: 125.41 (4C), 128.55 (4C), 120.9 (2C), 133.4 (4C), 126.401 (3C), 152.1, 168.2, 70.5, 25.1, 130.769, 165.2; Anal. CHN: calcd 78.474, 4.632, 3.8147, found 78.17, 4.531, 3.67.

Synthesis of 3-anthracene-9-yl-4, 5-dihydro-isoxazole-5-carboxylic acid ethyl ester 3b-III

It was obtained from 9-anthralaldoxime **2** (0.25g, 1.1298 mmol) ethyl acrylate (0.113 g, 1.1298 mmol) and Chloramine –T (0.477g, 1.6933 mmol). IR (nujol) cm^{-1} 1745 (C=O), 1680 ((C=N), 780 (N-O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (t, 3H, -CH_3), 4.05-4.18 (q, 2H, -OCH_2-), 3.9 (dd, 1H, *J*= 8[Hz], C_5H), 3.25 (d, 2H, C_4H), 7.39 (t, 2H, Ar-H), 7.91 (s, 2H, Ar-H), 8.32 (s, 2H, Ar-H), 8.1-8.18 (d, 2H, Ar-H); ^{13}C: 123.12 (2C), 129.24 (3C), 124.38 (3C), 134.21 (4C), 121.07 (2C), 14.2, 24.4, 58.9, 71.4, 17.3, 165.4; Anal. CHN: calcd 75.235, 5.329, 4.388, found 75.135, 5.410, 4.40.

Synthesis of 3-anthracene-9-yl-4, 5-dihydro-isoxazole-5-carboxylic acid butyl ester 3b-IV

It was obtained from 9-anthralaldoxime **2** (0.25g, 1.1298 mmol) butyl acrylate (0.144 g, 1.1298 mmol) and Chloramine-T (0.477g, 1.6933 mmol). IR (nujol) cm^{-1} 1710 (C=O), 1645 (C=N), 820 (N-O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (t, 3H, -CH_3), 1.25 (m, 2H, -CH_2-CH_3), 1.68 (q, 2H, -CH_2-), 3.95-4.05 (t, 2H, -OCH_2), 3.9-4.12 (t, 1H, *J*=6.4[Hz], C_5H), 3.15 (dd, 1H, *J*=8[Hz], C_4H), 7.75 (t, 2H, Ar-H), 7.94-8.01 (s, 2H, Ar-H), 8.15-8.32 (s, 2H, Ar-H), 8.25 (d, 2H, Ar-H); ^{13}C: 126.4 (2C), 127.9 (3C), 123.65 (3C), 131.5 (4C), 120.54 (2C), 13.5, 20.1, 24.5, 31.8, 65.4, 71.51, 171, 165.4; Anal. CHN: calcd 76.080, 6.05, 4.034, found 75.83, 6.12, 4.1.

Synthesis of 3-anthracene-9-yl-4, 5-dihydro-isoxazole-5-carboxylic acid methyl ester 3b-V

It was obtained from 9-anthralaldoxime **2** (0.25g, 1.1298 mmol) methyl acrylate (0.097 g, 1.1298 mmol) and Chloramine-T (0.35g, 1.242 mmol). IR (nujol) cm^{-1} 1735 (C=O), 1615 (C=N), 805 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.5 (s, 3H, $-OCH_3$), 3.1- 3.22 (dd, 2H, *J*=7.4[Hz], C_4H), 3.8-3.85 (t, 1H, C_5H), 7.3 (t, 2H, Ar-H), 7.7 (s, 2H, Ar-H), 8.34-8.38 (s, 2H, Ar-H), 8.7-7.0 (d, 2H, Ar-H), 7.45 (d, 1H, Ar-H); ^{13}C: 23.2, 51.5, 72.1, 126.2 (3C), 125.9 (3C), 134.51 (4C), 133, 129, 127.4 (2C); Anal. CHN: calcd 74.75, 4.918, 4.290, found 74.35, 4.812, 4.40.

Synthesis of 3-anthracene-9-yl-4, 5-dihydro-isoxazole-5-yl-methanol 3b-VI

It was obtained from 9-anthralaldoxime **2** (0.25g, 1.1298 mmol) allyl alcohol (0.131g, 2.25 mmol) and Chloramine-T (0.477g, 1.6933 mmol). IR (nujol) cm^{-1} 3240 (OH), 1630 (C=N), 835 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.78 (dd, 2H, *J*= 10[Hz], C_4H), 3.2 (m, 1H, C_4H), 3.7 (d, 2H, $-CH_2OH$), 7.42 (t, 2H, Ar-H), 7.65 (s, 2H, Ar-H), 8.28-8.34 (s, 2H, Ar-H), 7.85 (d, 2H, Ar-H), 7.5 (d, 1H, Ar-H); ^{13}C: 25.9, 67.8, 68.4, 123.2 (3C), 125.7 (3C), 127.4 (2C), 131.3 (4C), 133.5, 165.1; Anal. CHN: calcd 77.978, 5415, 5.054, found 78.02, 5215, 5.154.

Synthesis of acetic acid 3-biphenyl-4-yl-4, 5-dihydro-isoxazole-5-yl ester 6b-I

It was obtained from 4-biphenyl aldoxime **5** (0.25g, 1.2676 mmol), vinyl acetate (0.1091 g, 1.2676 mmol) and Chloramine-T (0.535g, 1.9014 mmol). IR (nujol) cm^{-1} 1745 (C=O), 1620 (C=N), 785 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.15 (s, 3H, $COCH_3$), 3.05 - 3.10 (dd, 2H, *J*=8[Hz], C_4H), 5.05 (t, 1H, C_5H), 7.45 - 7.49 (m, 4H, Ar-H), 7.65 (d, 2H, Ar-H), 7.35 (t, 2H, Ar-H), 7.15 (t, 1H, Ar-H); ^{13}C: 16.5, 25.6, 89.1, 128.1 (4C), 126.5 (4C), 125.2 (2C), 126.1, 131.5, 161, 170.4; Anal. CHN: calcd 72.59, 5.338, 4.982, found 71.99, 5.130, 4.673.

Synthesis of 3-biphenyl-4-yl-4, 5-dihydro-isoxazole-5-carboxylic acid phenyl ester 6b-II

It was obtained from 4-biphenyl aldoxime **5** (0.25g, 1.2676 mmol), vinyl benzoate (0.1878 g, 1.2676 mmol) and Chloramine-T (0.535g, 1.9014 mmol). IR (nujol) cm^{-1} 1710 (C=O), 1620 (C=N), 775 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.6-3.8 (dd, 2H, *J*= 4.1[Hz], C_4H), 4.05-4.15 (t, 1H, C_5H), 7.05 (d, 3H, Ar-H), 7.25 (m, 3H, Ar-H), 7.56-7.66 (m, 4H, Ar-H), 7.75-7.81 (d, 2H, Ar-H), 7.15 (t, 1H, Ar-H); ^{13}C: 24.5, 70.4, 167.2, 152.7, 122 (2C), 129.6 (2C), 130.5 (4C), 126.1 (4C), 135, 139, 125.41, 129, 161.3; Anal. CHN: calcd 76.968, 4.956, 4.081, found 76.988, 4.732, 4.180.

Synthesis of 3-biphenyl-4-yl-4, 5-dihydro-isoxazole-5-carboxylic acid ethyl ester 6b-III

It was obtained from 4-biphenyl aldoxime **5** (0.25g, 1.2676 mmol), ethyl acrylate (0.126 g, 1.2676 mmol) and Chloramine-T (0.535g, 1.9014 mmol). IR (nujol) cm^{-1} 1740 (C=O), 1654 (C=N), 785 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.2 (t, 3H, CH_3), 4.05 (q, 2H, OCH_2), 3.1-3.15 (dd, 1H, *J*= 8.4[Hz]) 7.05-7.15 (t, 1H, Ar-H), 7.4-7.65 (m, 4H, Ar-H), 7.85 (d, 2H, Ar-H); ^{13}C: 15, 56.5, 24.1, 70.4, 128.81 (4C), 126.8 (4C), 129, 137, 140.8, 130, 163, 173.1; Anal. CHN: calcd 73.220, 4.956, 4.081, found 73.100, 5.601, 4.652.

Synthesis of 3-biphenyl-4-yl-4, 5-dihydro-isoxazole-5-carboxylic acid butyl ester 6b-IV

It was obtained from 4-biphenyl aldoxime **5** (0.25g, 1.2676 mmol), butyl acrylate (0.162 g, 1.2676 mmol) and Chloramine-T (0.535g, 1.9014 mmol). IR (nujol) cm^{-1} 1745 (C=O), 1620 (C=N), 765 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, 3H, CH_3), 1.14 (m, 2H, CH_2), 1.34 (q, 2H, CH_2), 3.85-3.95 (t, 2H, $-OCH_2$), 3.12-3.2 (dd, 2H, *J*= 6.8[Hz], C_4H), 4.12-4.19 (t, 1H, C_5H), 7.32-7.4 (m, 4H, Ar-H), 7.1 (d, 2H, Ar-H), 7.01-7.05 (t, 1H, Ar-H); ^{13}C: 12.3, 1.5, 25.1, 32.4, 65.9, 70.4, 128.24 (4C), 130.4 (4C), 128.3, 139, 135, 168.1, 173; Anal. CHN: calcd 74.303, 6.5015, 4.334, found 74.102, 6.301, 4.323.

Synthesis of 3-biphenyl-4-yl-4, 5-dihydro-isoxazole-5-carboxylic acid methyl ester 6b-V

It was obtained from 4-biphenyl aldoxime **5** (0.25g, 1.2676 mmol), methyl acrylate (0.1091 g, 1.2676 mmol) and Chloramine-T (0.535g, 1.9014 mmol). IR (nujol) cm^{-1} 1735 (C=O), 1615 (C=N), 815 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.2 (t, 3H, CH_3), 4.05 (q, 2H, OCH_2), 3.1-3.15 (dd, 1H, *J*=8.6[Hz]), 7.05-7.15 (t, 1H, Ar-H), 7.4- 7.65 (m, 4H, Ar-H), 7.85 (d, 2H, Ar-H); ^{13}C: 15, 56.5, 24.1, 70.4, 128.81 (4C), 126.8 (4C), 129, 137, 140.8, 130, 163, 173.1; Anal. CHN: calcd 72.59, 5.338, 4.982, found 72.623, 5.128, 4.763.

Synthesis of 3-biphenyl-4-yl-4, 5-dihydro-isoxazole-5-yl-methanol 6b-VI

It was obtained from 4-biphenyl aldoxime **5** (0.25g, 1.2676 mmol), allyl alcohol (0.073 g, 1.2676 mmol) and Chloramine-T (0.535g, 1.9014 mmol). IR (nujol) cm^{-1} 3100 (OH), 1654 (C=N), 785 (N-O); ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, 3H, CH_3), 1.14 (m, 2H, $-CH_2$), 1.34 (q, 2H, $-CH_2-$), 3.85-3.95 (t, 2H, $-OCH_2$), 3.12-3.2 (dd, 2H, *J*= 6.8[Hz], C_4H), 4.12-4.19 (t, 1H, C_5H), 7.32-7.48 (m, 4H, Ar-H), 7.1 (d, 2H, Ar-H), 7.01-7.05 (t, 1H, Ar-H); ^{13}C: 12.3, 18.5, 25.1, 32.4, 65.9, 70.4, 128.24 (4C), 128, 139, 135, 168.1, 173; Anal. CHN: calcd 75.889, 5.928, 5.533, found 75.752, 5.839, 5.232.

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