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Synthesis of dihydrooxazoylarylisoxazoles by conventional and under microwave conditions

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ABSTRACT

The synthesis of series of 3-aryl-4-dihydrooxazolyl-5-methyl trisubstituted isoxazoles (**VI**) is reported, both under thermal and microwave conditions starting from various benzaldehydes (**I**). Benzaldehydes undergo oximation with hydroxylamine hydrosulphate to provide oximes that upon chlorination, followed by condensation with methylacetoacetate, resulted in the formation of esters. Hydrolysis of the esters to acids followed by treatment with PCl_5, resulted in the formation of acid chlorides (**III**) that upon reaction with hydroxyamines, gave *N*-*β*-hydoxyalkyl amides (**IV**). These on further reaction with $SOCl_2$, followed by cyclization with 2 N NaOH provided oxazoline substituted isoxazoles (**VI**) in good yields. The conversion acid chlorides (**III**) to isoxazoles (**VI**) was also achieved by microwave irradiation in moderate to excellent yields, with shorter reaction times compared to the conventional thermal method.

1. Introduction

Several compounds of natural and synthetic isoxazole scaffold posses a broad spectrum of biological properties like fungicidal [1-3], antibacterial [4,5], anti-inflammatory [6,7], antitubercular [8], antitumor [9,10], herbicidal [11-13], antifeedent [14] and antiviral [15-17] activities. Ureido derivatives of 5-amino-3-methylisoxazole-4-carboxylic acid were found to have a significant antileukemic activity [18]. Structure-activity relationship (SAR) studies of 5-methyl-3-substituted phenylisoxazole-4-carboxamides revealed that they are potent antagonists for secretagogue receptors [19]. It was also demonstrated that the C=O group at the C-(4) is the most adaptable site for chemical change and is an area that greatly influences potency spectrum and safety. On the other hand oxzoline heterocycles are found to be potential anticancer [20,21], antidepressant [22], anti-inflammatory [23], antioxidant [24], LpxC [25] and FAAH inhibitors [26]. Some of the oxazoline compounds show ovicidal activity [27]. Oxazoline complexes are useful as catalysts for the enantioselective C-C bond formation [28,29] and enantioselective terminal alkene hydrogenation [30]. Isoxazole coupled oxazolines were reported as Ca-activated K channel openers [31] and also reported as catalysts for regioselective ring opening of propylene_oxides [32]. The importance of oxazolines and isoxazoles has prompted the design and synthesis of various oxazoline substituted isoxazoles and herein, we report the synthesis of a few 4-(4,5-dihydrooxazol-2-yl)-5-methyl-3-aryl isoxazole under thermal and microwave irradiation.

2. Experimental

2.1. Instrumentation

The reagents and solvents were of analytical grade and were used without further purification unless otherwise mentioned. Thin layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 F_{254} (Merck). TLC plates were inspected under UV light. Micro-analytical data were obtained by employing a Perkin-Elmer 240c analyzer. IR spectra were recorded with a Perkin-Elmer-1700 spectro-photometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance 400 MHz spectrometer. The following abbreviations have been used to explain the observed multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; br s, broad singlet. Coupling constants in Hz have been assigned and listed without duplication in the ^{1}H NMR description of the synthesized compounds. Electron spray-mass spectra were recorded on an LCQ system (Finnigan MAT, USA) using methanol as the mobile phase. Melting points were recorded on a Polmon MP 96. Microwave reactions performed in MARS 240/50, model No. 907510.

2.2. General procedure for the preparation of 5-methyl-3-phenyl/substituted phenyl- isoxazole-4-carboxylic acid (IIa-IId)

To a solution of aldehyde (**Ia-Id**) (1 mol) in 400 mL of methanol, hydroxylamine hydrosulphate (1.4 mol) was added and stirred for 30 min (Scheme 1). The turbid reaction mixture was slowly converted to a clear solution. Later the pH was adjusted to 8-9 with Na_2CO_3 and refluxed for 30 min. Subsequently, it was cooled to 0-5 °C and was chlorinated by passing Cl_2 gas over a period of 1-2 h. The excess Cl_2 gas was removed by passing the nitrogen and the highly acidic pH was adjusted to 1-2 by using Na_2CO_3 at 0 °C (**Ia3** to **Id3**) (mild effervescence of CO_2 observed in the beginning).

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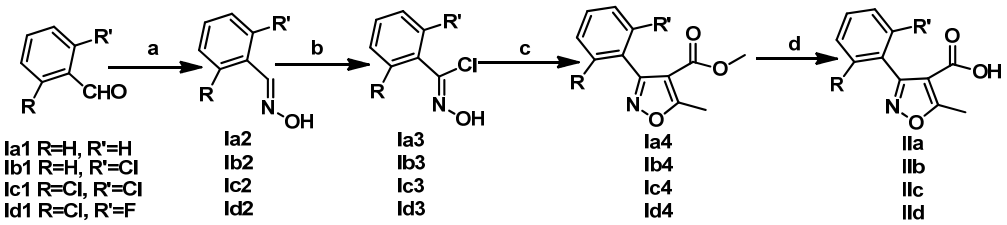


Reagents and conditions: a = hydroxylamine hydrosulfate, MeOH, Na_2CO_3, reflux, 30 min; b = Cl_2 gas, 0-5 °C, 1-2 h; c = methylacetoacetate, MeOH, NaOH, rt, 1 h; d = aq. NaOH (25%), reflux, 1 h.

Scheme 1

In another flask sodium salt of methylaceto acetate was prepared by the addition of 1.4 mol of NaOH to a solution of methyl acetoacetate (1.4 mol) in 400 mL of methanol at 0-5 °C and stirred for 30 min by maintaining the pH at 10. The precipitate, sodium salt of methylaceto acetate formed during the course of reaction in methanol was added to the chloro compound (**Ia3** to **Id3**) during a period of 1 h at 0-5 °C and subsequently stirred for 1 h at room temperature by maintaining the pH = 9 with NaOH. Later the pH was adjusted to 11-13 with aq. 25% NaOH and the reaction mixture was refluxed for 1 h. The methanol was distilled, suspended the residue in 5 times of water and adjusted the pH to 2.0-2.5 with 20% H_2SO_4. The compound was filtered, washed with hot water and recrystallized in methanol to afford a pure product (Scheme 1).

5-Methyl-3-phenyl-isoxazole-4-carboxylic acid (**IIa**): Color: white. Yield: 82%. M.p.: 189-190 °C. IR (KBr, ν): 3075, 3020, 2878, 2689, 2613, 1689, 1598, 1471, 1424, 1338, 1162, 1122 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.72 (s, 3H), 7.45 (m, 3H), 7.63 (d, *J* = 6.8 Hz, 2H) 13.12 (br S, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 13.5, 107.5, 127.8, 128.1, 129.4, 129.8, 163.2, 167.1, 175.2. MS (ES, m/z): 204 $[M+H]^+$. Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.88; H, 4.32; N, 6.95%.

3-(2-Chlorophenyl)-5-methyl-isoxazole-4-carboxylic acid (**IIb**): Color: white. Yield: 85%. M.p.: 193-196 °C. IR (KBr, ν): 3017, 2881, 2686, 2607, 1690, 1603, 1574, 1456, 1405, 1317, 1250, 1162, 1104 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.75 (s, 3H), 7.42 (m, 4H), 12.52 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 13.0, 110.2, 126.3, 128.8, 129.2, 130.4, 130.9, 133.9, 160.9, 162.9, 174.9. MS (ES, m/z): 238 $[M+H]^+$. Anal. Calcd. for $C_{11}H_8ClNO_3$: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.48; H, 3.32; N, 5.99%.

3-(2,6-Dichlorophenyl)-5-methyl-isoxazole-4-carboxylic acid (**IIc**): Color: white. Yield: 79%. M.p.: 225-226 °C. IR (KBr, ν): 3060, 2927, 2675, 2606, 1695, 1601, 1560, 1514, 1463, 1383, 1320, 1262, 1194 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.79 (s, 3H), 7.38 (m, 3H), 12.86 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 13.0, 110.0, 127.6, 128.4, 130.7, 135.2, 158.7, 162.4, 175.3 MS (ES, m/z): 272 $[M+H]^+$. Anal. Calcd. for $C_{11}H_7Cl_2NO_3$: C, 48.56; H, 2.59; N, 5.15. Found: C, 48.41; H, 2.45; N, 5.15%.

3-(2-Chloro-6-flourophenyl)-5-methyl-isoxazole-4-carboxylic acid (**IId**): Color: white. Yield: 76%. M.p.: 206-208 °C. IR (KBr, ν): 3072, 2895, 2686, 2607, 1689, 1605, 1517, 1454, 1379, 1316, 1250, 1188 1161 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.75 (s, 3H), 7.12 (t, 1H, *J* = 8.1 Hz), 7.31(d, 1H, *J* = 7.6 Hz), 7.43 (m, 1H), 12.91 (br s, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz, *δ*): 13.2, 110.3, 114.0, 117.8, 125.0, 131.2, 135.0, 155.6, 159.5, 162.6, 175.4. MS (ES, m/z): 256 $[M+H]^+$. Anal. Calcd. for $C_{11}H_7ClFNO_3$: C, 51.68; H, 2.76; N, 5.48. Found: C, 51.41; H, 2.73; N, 5.61%.

2.3. General procedure for the preparation of 5-methyl-3-aryl-isoxazole-4-carboxyl chloride (IIIa-IIId)

To the compound **IIa**-**IId** (1 mol) in neat condition (with out any solvent) was added PCl_5 (1 mol) at room temperature and heated to 45 °C to become clear solution. It was stirred for 1h and the by product $POCl_3$ was distilled under reduced pressure. To the residue 75 mL of hexane was added and set for crystallization. The crystallized acid chloride was filtered (Scheme 2).

5-Methyl-3-phenyl-isoxazole-4-corbonyl chloride (**IIIa**): Color: Color less liquid. Yield: 90%. B.p.: 115-117°C (3 Torr). IR (neat, ν): 3065, 3010, 1741, 1689, 1605, 1462, 1316, 1250, 1157, 1116 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.79 (s, 3H), 7.45 (m, 3H), 7.62 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 13.6, 107.5, 128.0, 128.1, 129.3, 129.8, 162.6, 166.3, 177.4. MS (ES, m/z): 222 $[M+H]^+$. Anal. Calcd. for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32%. Found: C, 59.58; H, 3.73; N, 6.31%.

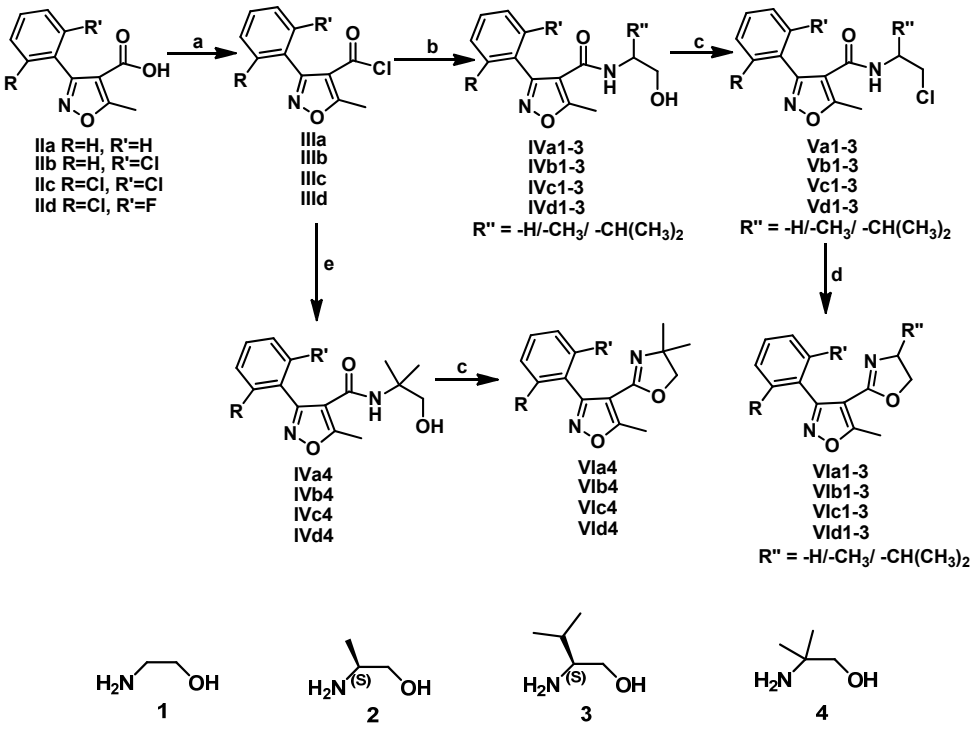
3-(2-Chlorophenyl)-5-methyl-isoxazole-4-corbonyl chloride (**IIIb**): Color: white. Yield: 93%. M.p.: 45-48 °C. IR (KBr, ν): 3061, 3005, 1732, 1685, 1604, 1458, 1309, 1258, 1141, 1117 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.79 (s, 3H), 7.39 (m, 4H).^{13}C NMR ($CDCl_3$, 300 MHz, *δ*): 13.9, 114.8, 126.7, 127.4, 129.6, 131.0, 131.3, 134.2, 158.9, 160.2, 176.7. MS (ES, m/z): 256 $[M+H]^+$. Anal. Calcd. for $C_{11}H_7Cl_2NO_2$: C, 51.59; H, 2.76; N, 5.47%. Found: C, 51.42; H, 2.83; N, 5.47%.

3-(2,6-Dichlorophenyl)-5-methyl-isoxazole-4-corbonyl chloride (**IIIc**): Color: white. Yield: 84%. M.p.: 88-89 °C. IR (KBr, ν): 3089, 3002, 1757, 1689, 1562, 1498, 1432, 1390, 1290, 1249, 1195, 1145 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.85 (s, 3H), 7.38 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 14.2, 114.0, 127.0, 128.0, 131.7, 135.6, 158.1, 158.6, 177.7. MS (ES, m/z): 290 $[M+H]^+$. Anal. Calcd. for $C_{11}H_6Cl_3NO_2$: C, 45.47; H, 2.08; N, 4.82%. Found: C, 45.61; H, 2.03; N, 4.90%.

3-(2-Chloro-6-flourophenyl)-5-methyl-isoxazole-4-corbonyl chloride (**IIId**): Color: white. Yield: 88%. M.p.: 181-184 °C. IR (KBr, ν): 3054, 3010, 1757, 1693, 1576 1514, 1449, 1393, 1290, 1250, 1185, 1162 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.86 (s, 3H), 7.14 (t, 1H, *J* = 8.0 Hz), 7.31(d, 1H, *J* = 8.0 Hz), 7.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 14.2, 109.0, 113.9, 116.5, 125.4, 132.2, 135.2, 155.0, 158.6, 162.1, 177.6. MS (ES, m/z): 274 $[M+H]^+$. Anal. Calcd. for $C_{11}H_6Cl_2FNO_3$: C, 48.21; H, 2.21; N, 5.11%. Found: C, 48.10; H, 2.08; N, 5.11%.

2.4. General procedure for the synthesis of N-(2-hydroxy-ethyl/substituted ethyl)-5-methyl-3-arylisoxazole-4-carboxamide (IVa-IVd)

To a turbid solution of 12 mmol of compound **IIIa**-**IIId** in 20 mL of $CHCl_3$ was added triethylamine (20 mmol) at 10 °C and obtined a clear solution.



Reagents and conditions: a = PCl_5, rt, 1 h; b = **1/2/3**, TEA, $CHCl_3$, 10 °C, rt, 3 h; c = $CHCl_3$, $SOCl_2$, 0-5 °C, rt, overnight; d = MeCN, 2N NaOH, rt, overnight; e = **4**, TEA, $CHCl_3$, 10 °C, rt, 3 h;

Scheme 2

To the resulting mixture ethanolamine/substituted ethanolamine (16 mmol) was added drop wise while maintaining the temperature at 10 °C. The reaction was fast and exothermic. The resulting solution was stirred for 3 h at room temperature, monitored by TLC. The reaction mixture was extracted with $CHCl_3$ (2 x 30 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane: EtOAc (90:10%) to afford **IVa-IVd**.

2.5. General procedure for the synthesis of N-(2-hydroxyethyl/substituted ethyl)-5-methyl-3-aryl-isoxazole-4-carboxamide (IVa-IVd) in microwave

Compound **IIIa-IIId** (5 mmol) was adsorbed on silicagel (200-400 mesh) and added ethanolamine/substituted ethanolamine (8 mmol) followed by triethyl amine (10 mmol) in to a microwave vial. The vial was sealed and placed in microwave. The reaction was run at 50 °C for 3 min. For the entire experiment, the power setting was held at 100 W. The reaction mixture was then cooled to room temperature and purified by SiO_2 gel column chromatography with hexane: EtOAc (90:10%) to afford **IVa-IVd** (^{c} = yield of conventional method; ^{m} = yield of microwave method) (Scheme 2).

N-(2-Hydroxyethyl)-5-methyl-3-phenylisoxazole-4-carboxamide (**IVa1**): Color: white. Yield: 88%^{m} (73%)^c. M.p.: 121-123 °C. IR (KBr, ν): 3411, 3228, 3068, 2912, 1689, 1609, 1564, 1462, 1402, 1368, 1260, 1174, 1124, 1071, 1040 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.69 (s, 3H), 3.38 (q, *J* = 5.6 Hz, 2H), 3.60 (t, *J* = 5.6 Hz, 2H) 5.89 (br s, 1H), 7.49 (m, 3H), 7.59 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.5, 42.1, 61.7, 111.2, 128.5, 128.9, 130.2, 160.1, 162.3, 173.5. MS (ES, m/z): 247 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38%. Found: C, 63.73; H, 6.01; N, 11.03%.

N-((*S*)-1-Hydroxypropan-2-yl))-5-methyl-3-phenylisoxazole-4-carboxamide (**IVa2**): Color: white. Yield: 97%^{m} (82%)^c. M.p.: 130-132 °C. IR (KBr, ν): 3379, 3234, 3076, 2972, 1626, 1562, 1467, 1419, 1338, 1263, 1180, 1143, 1099, 1055 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.97 (d, *J* = 6.8 Hz, 3H), 2.69 (s, 3H), 3.38 (dd, *J* = 11.2 Hz, *J'* = 3.6 Hz, 1H), 3.54 (dd, *J* = 11.2 Hz, *J'* = 3.6 Hz, 1H), 4.09 (m, 1H), 5.60 (br d, *J* = 6.0 Hz, 1H), 7.50 (m, 3H), 7.61 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.6, 16.5, 47.7, 66.5, 111.1, 128.3, 128.9, 129.0, 130.3, 160.1, 161.8, 173.7. MS (ES, m/z): 261 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%. Found: C, 64.46; H, 6.18; N, 11.12%.

N-((*S*)-1-Hydroxy-3-methylbutan-2-yl)-5-methyl-3-phenyl isoxazole-4-carboxamide (**IVa3**): Color: white. Yield: 92%^{m} (88%)^c. M.p.: 118-120 °C. IR (KBr, ν): 3464, 3270, 3088, 2967, 1669, 1616, 1567, 1488, 1435, 1378, 1287, 1165, 1017 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.71 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), 1.37 (m, 1H), 2.75 (s, 3H), 3.07 (m, 2H). 3.55 (m, 1H), 6.05 (br d, *J* = 6.4 Hz, 1H), 7.44 (m, 3H), 7.68 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 17.2, 18.3, 29.0, 56.5, 62.8, 108.3, 127.3, 128.4, 128.8, 162.1, 162.9, 175.0. MS (ES, m/z): 289 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72%. Found: C, 66.78; H, 7.16; N, 9.86%.

N-(1-Hydroxy-2-methylpropan-2-yl)-5-methyl-3-phenylisoxazole-4-carboxamide (**IVa4**): Color: white. Yield: 96%^{m} (71%)^c. M.p.: 110-112 °C. IR (KBr, ν): 3459, 3259, 2982, 1651, 1621, 1557, 1469, 1418, 1363, 1338, 1280, 1235, 1185, 1062 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.08 (s, 6H), 2.69 (s, 3H), 3.49 (s, 2H), 4.63 (br s), 5.51 (br s, 1H), 7.54 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.5, 24.1, 56.2, 70.0, 111.6, 128.5, 128.9, 129.1, 129.3, 130.2, 160.0, 161.9, 173.6. MS (ES, m/z):

275 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21%. Found: C, 65.51; H, 6.58; N, 10.21%.

3-(2-Chlorophenyl)-N-(2-hydroxyethyl)-5-methylisoxazole-4-carboxamide (**IVb1**): Color: white. Yield: 80%[m] (64%)[c]. M.p.: 91-93 °C. IR (KBr, ν): 3342, 3273, 2937, 1643, 1597, 1529, 1437, 1375, 1265, 1180, 1043 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.72 (s, 3H), 3.31 (q, *J* = 5.6 Hz, 2H), 3.51 (t, *J* = 5.6 Hz, 2H), 5.79 (br s, 1H), 7.46 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 41.9, 61.4, 112.0, 127.3, 127.8, 130.2, 131.5, 131.6, 134.0, 158.3, 161.8, 173.7. MS (ES, m/z): 281 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98%. Found: C, 55.62; H, 4.42; N, 10.12%.

3-(2-Chloropheyl)-N-((S)-1-hydroxypropan-2-yl)-5-methyl isoxazole-4-carboxamide (**IVb2**): Color: white. Yield: 96%[m] (87%)[c]. M.p.: 117-119 °C. IR (KBr, ν): 3485, 3427, 3249, 3094, 2979, 2928, 1633, 1607, 1575, 1450, 1422, 1361, 1269, 1169, 1057 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.96 (d, *J* = 6.8 Hz, 3H), 2.72 (s, 3H), 3.34 (dd, *J* = 11.0 Hz, *J'* = 4.8 Hz, 1H) 3.42 (dd, *J* = 11.0 Hz, *J'* = 4.8 Hz, 1H), 4.02 (m, 1H), 5.71 (br s, 1H), 7.46 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.5, 16.5, 47.2, 65.6, 112.4, 127.1, 127.9, 129.2, 130.0, 131.4, 133.9, 158.4, 160.9, 172.9. MS (ES, m/z): 295 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.50%. Found: C, 57.05; H, 5.34; N, 9.81%.

3-(2-Chlorophenyl)-N-((S)-1-hydroxy-3-methylbutan-2yl)-5-methylisoxazole-carboxamide (**IVb3**): Color: white. Yield: 97%[m] (68%)[c]. M.p.: 117-120 °C. IR (KBr, ν): 3381, 3252, 3079, 2962, 1638, 1608, 1557, 1437, 1369, 1328, 1258, 1140, 1088, 1029 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.54 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H), 1.64 (m, 1H), 2.76 (s, 3H), 3.47 (dd, *J* = 11.5 Hz, *J'* = 4.8 Hz, 1H). 3.52 (dd, *J* = 11.5 Hz, *J'* = 4.8 Hz, 1H), 3.78 (m, 1H), 5.46 (br d, *J* = 8.0 Hz, 1H), 7.49(m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 17.6, 19.0, 28.8, 56.8, 63.8, 112.1, 127.5, 129.4, 130.3, 131.5, 131.7, 134.5, 158.1, 161.9, 174.4. MS (ES, m/z): 323 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{19}ClN_2O_3$: C, 59.54; H, 5.93; N, 8.68%. Found: C, 59.21; H, 5.71; N, 8.76%.

3-(2-Chlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-5-methyl isoxazole-4-carboxamide (**IVb4**): Color: white. Yield: 87%[m] (79%)[c]. M.p.: 126-130 °C. IR (KBr, ν): 3422, 3290, 2962, 1642, 1606, 1551, 1430, 1407, 1370, 1320, 1254, 1194, 1172, 1088 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.10 (s, 6H), 2.78 (s, 3H), 3.48 (s, 2H), 5.22 (br s, 1H), 7.51 (m, 4H).^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.5, 23.8, 56.4, 70.0,107.2, 126.5, 128.6, 130.3, 130.9, 131.5, 134.3, 156.0, 161.4, 172.3. MS (ES, m/z): 309 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; N, 9.07%. Found: C, 58.31; H, 5.69; N, 9.00%.

3-(2,6-Dichlorophenyl)-N-(2-hydroxyethyl)-5-methylisoxazole-4-carboxamide (**IVc1**): Color: white. Yield: 73%[m] (78%)[c]. M.p.: 160-164 °C. IR (KBr, ν): 3327, 3284, 3042, 2918, 1691, 1626, 1581, 1448, 1417, 1370, 1347, 1234, 1174, 1149, 1059 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.82 (s, 3H), 3.38 (t, *J* = 5.1 Hz, 2H), 3.58 (t, *J* = 5.1 Hz, 2H), 5.68 (br s, 1H), 7.45 (m, 1H), 7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.9, 41.9, 61.7, 111.9, 127.7, 128.6, 131.9, 136.1, 156.1, 161.4, 174.3. MS (ES, m/z): 315 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O_3$: C, 49.54; H, 3.84; N, 8.89%. Found: C, 49.32; H, 3.62; N, 8.56%.

3-(2,6-dichlorophenyl)-N-((S)-1-hydroxypropan-2-yl)-5-methylisoxazol-4-carboxamide (**IVc2**): Color: white. Yield: 91%[m] (80%)[c]. M.p.: 171-174 °C. IR (KBr, ν): 3434, 3273, 2990, 1679, 1621, 1568, 1461, 1411, 1384, 1319, 1264, 1184, 1130, 1081 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.95 (d, *J* = 4.9 Hz, 3H), 2.82 (s, 3H), 3.39 (dd, *J* = 11.0 Hz, *J'* = 4.9 Hz, 1H) 3.53 (dd, *J* = 11.0 Hz, *J'* = 4.9 Hz, 1H), 4.05 (m, 1H), 5.36 (br s, 1H), 7.47 (m, 1H), 7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 16.5, 47.2, 66.3, 111.7, 127.6, 128.4, 131.8, 136.1, 155.9, 160.8, 174.3. MS (ES, m/z): 329 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{14}Cl_2N_2O_3$: C, 51.08; H, 4.29; N, 8.51%. Found: C, 50.72; H, 4.03; N, 8.69%.

3-(2,6-dichlorophenyl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-5-methylisoxazole-4-carboxamide (**IVc3**): Color: white. Yield: 88%[m] (75%)[c]. M.p.: 124-127 °C. IR (KBr, ν): 3422, 3290, 2962, 1642, 1606, 1551, 1430, 1407, 1370, 1320, 1254, 1194, 1172, 1088 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.55 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H), 1.65 (m, 1H), 2.79 (s, 3H), 3.45 (d, *J* = 4.8 Hz, 2H), 3.76 (m, 1H), 5.43 (br d, *J* = 8.1 Hz, 1H), 7.39 (m, 1H), 7.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.9, 17.5, 19.1, 28.8, 56.4, 63.4, 111.6, 127.3, 128.5, 132.1, 136.1, 155.8, 161.2, 174.5. MS (ES, m/z): 357 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_3$: C, 53.79; H, 5.08; N, 7.84%. Found: C, 53.63; H, 4.79; N, 7.89%.

3-(2,6-Dichlorophenyl)-N-(1-hydroy-2-methylpropan-2-yl)-5-methylisoxazole-4-carboxamide (**IVc4**): Color: white. Yield: 80%[m] (80%)[c]. M.p.: 120-124 °C. IR (KBr, ν): 3391, 3308, 3074, 2978, 2934, 1651, 1614, 1560, 1520, 1429, 1377, 1315, 1255, 1195 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.04 (s, 6H), 2.79 (s, 3H), 3.44 (s, 2H), 5.26 (br s, 1H), 7.46 (m, 1H), 7.52 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 24.0, 55.9, 69.8, 112.0, 127.6, 128.4, 131.9, 136.2, 155.9, 161.0, 174.4. MS (ES, m/z): 343 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O_3$: C, 54.49; H, 4.70; N, 8.16%. Found: C, 54.64; H, 4.52; N, 8.14%.

3-(2-Chloro-6-fluorophenyl)-N-(2-hydroxyethyl)-5-methyl isoxazole-4-carboxamide (**IVd1**): Color: white. Yield: 86%[m] (78%)[c]. M.p.: 126-128 °C. IR (KBr, ν): 3385, 3267, 3094, 2945, 1648, 1599, 1567, 1454, 1417, 1319, 1253, 1189, 1098 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.76 (s, 3H), 3.35 (q, *J* = 5.2 Hz, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 5.86 (br s, 1H), 7.17 (t, *J* = 8.1 Hz, 1H) 7.35 (d, *J* = 7.6 Hz, 1H), 7.40 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 41.8, 61.4, 112.3, 114.6, 117.0, 125.8, 132.4, 135.5, 153.0, 161.3, 162.1, 173.7. MS (ES, m/z): 299 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{12}ClFN_2O_3$: C, 52.27; H, 4.05; N, 9.38%. Found: C, 52.00; H, 3.89; N, 9.09%.

3-(2-Chloro-6-fluorophenyl)-N-((S)-1-hydroxypropan-2-yl)-5-methylisoxazol-4-carboxamide (**IVd2**): Color: white. Yield: 88%[m] (70%)[c]. M.p.: 136-139 °C. IR (KBr, ν): 3458, 3301, 2997, 1684, 1629, 1584, 1479, 1403, 1369, 1321, 1262, 1174, 1112, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.97 (d, *J* = 6.8 Hz, 3H), 2.76 (s, 3H), 3.37 (dd, *J* = 11.2 Hz, *J'* = 3.2 Hz, 1H), 3.51 (dd, *J* = 11.2 Hz, *J'* = 3.2 Hz, 1H), 4.03 (m, 1H), 5.53 (br d, *J* = 6.4 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H) 7.18 (d, *J* = 8.6 Hz, 1H), 7.47 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 16.6, 47.3, 66.1, 112.3, 114.8, 116.8, 125.8, 132.4, 135.5, 152.9, 160.8, 162.1, 173.9. MS (ES, m/z): 313 $[M+H]^+$; Anal. Calcd. for $C_{14}H_{14}ClFN_2O_3$: C, 53.77; H, 4.51; N, 8.96%. Found: C, 53.40; H, 4.50; N, 9.11%.

3-(2-Chloro-6-fluorophenyl)-N-((S)-1-hydroxy-3-methyl butan-2-yl)-5-methylisoxazole-4-carboxamide (**IVd3**): Color: white. Yield: 89%[m] (64%)[c]. M.p.: 147-149 °C. IR (KBr, ν): 3401, 3269, 2966, 2931, 1639, 1608, 1557, 1455, 1417, 1324, 1251, 1167, 1030, 983 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.61 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H), 1.67 (m, 1H), 2.79 (s, 3H), 3.54 (m, 2H), 3.79 (m, 1H), 5.53 (br d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H) 7.40 (d, *J* = 7.2 Hz, 1H), 7.49 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 17.7, 19.0, 28.9, 56.6, 63.6, 112.2, 114.8, 117.2, 125.8, 132.4, 135.7, 152.6, 161.3, 162.3, 174.4. MS (ES, m/z): 341 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{18}ClFN_2O_3$: C, 56.39; H, 5.32; N, 8.22%. Found: C, 56.10; H, 5.32; N, 8.54%.

3-(2-Chloro-6-fluorophenyl)-N-(1-hydroy-2-methylpropan-2-yl)-5-methylisoxazole-4-carboxamide (**IVd4**): Color: white. Yield: 80%[m] (83%)[c]. M.p.: 146-149 °C. IR (KBr, ν): 3452, 3274, 3051, 1684, 1664, 1568, 1458, 1427, 1368, 1309, 1280, 1124, 1182, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.08 (s, 6H), 2.76 (s, 3H), 3.46 (s, 2H), 5.35 (br s, 1H), 7.21 (t, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.6, 24.0, 55.9, 69.8, 112.6, 114.8, 117.2, 125.8, 132.4, 135.7, 152.7, 161.0, 162.2, 174.0. MS (ES, m/z): 327 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{16}ClFN_2O_3$: C, 55.14; H, 4.94; N, 8.57%. Found: C, 55.39; H, 4.70; N, 8.39%.

2.6. General procedure for the synthesis of N-(2-chloroethyl/substituted ethyl)-5-methyl-3-aryl-isoxazole-4-carboxamide (Va-Vd)

To the solution of 10 mmol of compound **IVa-IVd** in 20 mL of $CHCl_3$ was added 20 mmol of $SOCl_2$ drop wise while maintaining the temperature at 0-5 °C. After the addition, the reaction mixture was stirred over night at room temperature. The reaction mixture was extracted with $CHCl_3$ (2 x 30 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified on a silica gel column with hexane: EtOAc (95:5%) (Scheme 2).

2.7. General procedure for the synthesis of N-(2-chloroethyl/substituted ethyl)-5-methyl-3-aryl-isoxazole-4-carboxamide (Va-Vd) in microwave

Compound **IVa-IVd** (5 mmol) was dissolved in 25 mL of dichloroethane in a microwave vial to which $SOCl_2$ (16 mmol) was added. The vial was sealed and placed in microwave. The reaction was run at 60 °C for 3 min. The entire experiment power setting was held at 100 W. The reaction mixture was then cooled to room temperature and purified by column chromatography with hexane: EtOAc (95:5%) to afford **Va-Vd** (Scheme 2).

N-(2-Chloroethyl)-5-methyl-3-phenylisoxazole-4-carboxamide (**Va1**): Color: white. Yield: 91% [m] (72%)[c]. M.p.: 158-161 °C. IR (KBr, ν): 3212, 3062, 2964, 2924, 1687, 1624, 1584, 1471, 1361, 1262, 1174, 1091, 983 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.72 (s, 3H), 3.55 (m, 4H), 5.84 (br s, 1H), 7.52 (m, 3H), 7.58 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.6, 41.2, 43.1, 110.8, 128.4, 128.9, 129.0, 130.2, 160.0, 161.5, 174.0. MS (ES, m/z): 265 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58%. Found: C, 58.64; H, 5.10; N, 10.54%.

N-((S)-1-Chloropropan-2-yl)-5-methyl-3-phenylisoxazole-4-carboxamide (**Va2**): Color: white. Yield: 74%[m] (76%)[c]. M.p.: 141-143 °C. IR (KBr, ν): 3194, 3075, 2980, 2934, 2882, 1675, 1611, 1571, 1448, 1350, 1234, 1128, 1086, 993 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.05 (d, *J* = 6.4 Hz, 3H), 2.71 (s, 3H), 3.44 (dd, *J* = 11.2 Hz, *J'* = 3.6 Hz, 1H), 3.60 (dd, *J* = 11.2 Hz, *J'* = 3.6 Hz, 1H), 4.37 (m, 1H), 5.57 (br d, *J* = 5.2 Hz, 1H), 7.50 (m, 3H), 7.59 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 17.4, 45.5, 48.7, 110.9, 128.3, 129.0, 129.1, 130.3, 160.1, 160.8, 174.0. MS (ES, m/z): 279 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05%. Found: C, 60.41; H, 5.42; N, 9.88%.

N-((S)-1-Chloro-3-methylbutan-2-yl)-5-methyl-3-phenyl isoxazole-4-carboxamide (**Va3**): Color: white. Yield: 91%[m] (89%)[c]. M.p.: 170-172 °C. IR (KBr, ν): 3202, 3045, 2968, 1666, 1581, 1521, 1402, 1369, 1317, 1277, 1218, 1178, 1125, 1070, 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.66 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 1.63 (m, 1H), 2.66 (s, 3H), 3.50 (m, 2H), 3.94 (m, 1H), 5.89 (br s, 1H), 7.35 (m, 3H), 7.59 (d, *J* = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.6, 17.5, 18.4, 28.1, 45.1, 54.6, 108.1, 127.1, 128.1, 128.4, 128.7, 161.9, 162.8, 174.9. MS (ES, m/z): 307 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13%. Found: C, 62.65; H, 6.11; N, 9.46%.

N-(2-Chloroethyl)-3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamide (**Vb1**): Color: white. Yield: 73%[m] (85%)[c]. M.p.: 125-127 °C. IR (KBr, ν): 3283, 3091, 2970, 1644, 1596, 1557, 1417, 1321, 1300, 1260, 1201, 1181, 1122, 1054, 1035 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.77 (s, 3H), 3.49 (t, *J* = 5.2 Hz, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 5.72 (br s, 1H), 7.49 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 41.0, 43.5, 111.6, 127.4, 127.7, 130.4, 131.5, 134.1, 158.1, 161.1, 174.2. MS (ES, m/z): 299 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.19; H, 4.04; N, 9.36%. Found: C, 52.08; H, 4.15; N, 9.69%.

3-(2-Chlorophenyl)-N-((S)-1-chloropropan-2-yl)-5-methyl isoxazole-4-carboxamide (**Vb2**): Color: white. Yield: 79%[m] (78%)[c]. M.p.: 119-121 °C. IR (KBr, ν): 3262, 3009, 2968, 1671, 1618, 1562, 1474, 1420, 1330, 1305, 1249, 1177, 1128, 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.24 (d, *J* = 7.2 Hz, 3H), 2.80 (s, 3H), 3.42 (dd, *J* = 11.0 Hz, *J'* = 4.8 Hz, 1H) 3.89 (dd, *J* = 11.0 Hz, *J'* = 4.8 Hz, 1H), 4.41 (m, 1H), 5.41 (br s, 1H), 7.53 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 16.1, 47.5, 66.0, 111.1, 127.0, 127.5, 129.1, 129.7, 131.5, 134.2, 158.9, 161.4, 173.0. MS (ES, m/z): 313 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{14}Cl_2N_2O_2$: C, 53.69; H, 4.51; N, 8.94%. Found: C, 53.39; H, 4.63; N, 9.12%.

N-((S)-1-Chloro-3-methylbutan-2yl)-3-(2-chlorophenyl)-5-methylisoxazole-4-N-((S)-1-Chloro-3-methylbutan-2yl)-3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamide (**Vb3**): Color: white. Yield: 74%[m] (61%)[c]. M.p.: 127-131 °C. IR (KBr, ν): 3212, 3038, 2951, 1668, 1601, 1574, 1465, 1424, 1359, 1334, 1287, 1156, 1130, 1041 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.68 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 1.64 (m, 1H), 2.78 (s, 3H), 3.49 (dd, *J* = 11.6 Hz, *J'* = 4.0 Hz, 1H). 3.56 (dd, *J* = 11.6 Hz, *J'* = 4.0 Hz, 1H), 3.98 (m, 1H), 5.42 (br d, *J* = 8.0 Hz, 1H), 7.49(m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 17.9, 19.0, 45.8, 49.1, 54.6, 111.6, 127.4, 129.3, 130.4, 130.6, 130.9, 134.2, 158.0, 160.7, 174.4. MS (ES, m/z): 341 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_2$: C, 56.32; H, 5.32; N, 8.21%. Found: C, 56.09; H, 5.67; N, 8.21%.

N-(2-Chloroethyl)-3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamide (**Vc1**): Color: white. Yield: 78%[m] (73%)[c]. M.p.: 120-122 °C. IR (KBr): ν 3262, 3009, 2968, 1671, 1618, 1562, 1474, 1420, 1330, 1305, 1249, 1177, 1128, 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.82 (s, 3H), 3.50 (t, *J* = 4.4 Hz, 2H), 3.59 (t, *J* = 4.4 Hz, 2H), 5.69 (br s, 1H), 7.45 (m, 1H), 7.52 (m, 2H). ^{13}C NMR (CDCl3, 100 MHz, δ, ppm): 12.9, 40.9, 43.6, 111.4, 127.4, 128.6, 131.9, 136.1, 155.9, 160.6, 174.5. MS (ES, m/z): 333 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{11}Cl_3N_2O_2$: C, 46.80; H, 3.32; N, 8.40%. Found: C, 46.44; H, 3.14; N, 8.12%.

3-(2,6-dichlorophenyl)-N-((S)-1-chloropropan-2-yl)-5-methyl isoxazole-4-carboxamide (**Vc2**): Color: white. Yield: 88%[m] (75%)[c]. M.p.: 119-121 °C. IR (KBr, ν): 3223, 3074, 2941, 1663, 1623, 1565, 1479, 1410, 1335, 1306, 1237, 1170, 1124, 1084 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.05 (d, *J* = 6.8 Hz, 3H), 2.80 (s, 3H), 3.42 (dd, *J* = 11.2 Hz, *J'* = 3.2 Hz, 1H), 3.55 (dd, *J* = 11.2 Hz, *J'* = 3.2 Hz, 1H), 4.38 (m, 1H), 5.43 (br d, *J* = 7.2 Hz, 1H), 7.45 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 13.0, 17.6, 44.9, 49.4, 111.5, 127.4, 128.8, 132.2, 136.0, 156.0, 160.0, 174.8. MS (ES, m/z): 347 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{13}Cl_3N_2O_2$: C, 48.37; H, 3.77; N, 8.06%. Found: C, 48.35; H, 3.53; N, 8.25%.

N-((S)-1-Chloro-3-methylbutan-2-yl)-3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamide (**Vc3**): Color: white. Yield: 79%[m] (70%)[c]. M.p.: 96-99 °C. IR (KBr, ν): 3287, 3065, 2972, 1645, 1604, 1545, 1444, 1307, 1178, 1130, 1089 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.70 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 1.59 (m, 1H), 2.81 (s, 3H), 3.49 (dd, *J* = 11.6 Hz, *J'* = 4.3 Hz, 1H), 3.57 (dd, *J* = 11.6 Hz, *J'* = 4.3 Hz, 1H), 3.97 (m, 1H), 5.38 (br d, *J* = 8.0 Hz, 1H), 7.44 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 17.8, 18.9, 29.1, 45.9, 54.4, 111.4, 127.7, 128.4, 131.9, 136.3, 155.8, 160.3, 174.8. MS (ES, m/z): 375 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{17}Cl_3N_2O_2$: C, 51.15; H, 4.56; N, 7.46%. Found: C, 50.84; H, 4.50; N, 7.11%.

3-(2-Chloro-6-fluorophenyl)-N-(2-Chloroethyl)-5-methyl isoxazole-4-carboxamide (**Vd1**): Color: white. Yield: 73%[m] (59%)[c]. M.p.: 108-111 °C. IR (KBr, ν): 3297, 3070, 2924, 1646, 1606, 1540, 1470, 1420, 1353, 1306, 1204, 1175, 1114, 1094 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.79 (s, 3H), 3.51 (q, *J* = 4.8 Hz, 2H), 3.60 (t, *J* = 4.8 Hz, 2H), 5.81 (br s, 1H), 7.20 (t, *J* = 6.8 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.48 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 54.6, 66.8, 106.9, 113.9, 118.2, 124.9, 131.0, 135.4, 154.9, 157.3, 162.3, 172.4. MS (ES, m/z): 317 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{11}Cl_2FN_2O_2$: C, 49.23; H, 3.50; N, 8.83%. Found: C, 49.48; H, 3.19; N, 8.96%.

3-(2-Chloro-6-fluorophenyl)-N-((S)-1-chloropropan-2-yl)-5-methylisoxazol-4-carboxamide (**Vd2**): Color: white. Yield: 68%[m] (71%)[c]. M.p.: 125-128 °C. IR (KBr, ν): 3256, 3067, 2942, 1676,

1622, 1551, 1461, 1413, 1341, 1300, 1222, 1167, 1111, 1094 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.07 (d, *J* = 6.8 Hz, 3H), 2.78 (s, 3H), 3.44 (dd, *J* = 11.2 Hz, *J'* = 3.2 Hz, 1H), 3.56 (dd, *J* = 11.2 Hz, *J'* = 3.2 Hz, 1H), 4.39 (m, 1H), 5.49 (br d, *J* = 6.4 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 6.5 Hz, 1H), 7.49 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 17.5, 45.0, 49.1, 112.0, 114.9, 116.9, 125.9, 132.5, 135.6, 152.8, 159.9, 162.1, 174.3. MS (ES, m/z): 331 $[M+H]^+$; Anal. Calcd. for $C_{14}H_{13}Cl_2FN_2O_2$: C, 50.77; H, 3.96; N, 8.46%. Found: C, 51.06; H, 3.96; N, 8.51%.

N-((S)-1-Chloro-3-methylbutan-2-yl)-3-(2-chloro-6-fluoro phenyl)-5-methylisoxazole-4-carboxamide (**Vd3**): Color: white. Yield: 88%[m] (72%)[c]. M.p.: 116-119 °C. IR (KBr, ν): 3192, 3071, 2954, 1668, 1616, 1549, 1443, 1317, 1162, 1128, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.74 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H), 1.65 (m, 1H), 2.81 (s, 3H), 3.53 (dd, *J* = 11.6 Hz, *J'* = 4.3 Hz, 1H), 3.61 (dd, *J* = 11.6 Hz, *J'* = 4.3 Hz, 1H), 4.00 (m, 1H), 5.46 (br d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 17.9, 18.9, 29.2, 45.9, 54.5, 112.0, 114.9, 117.3, 125.9, 132.4, 135.7, 152.6, 160.3, 162.3, 174.5. MS (ES, m/z): 360 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{17}Cl_2FN_2O_2$: C, 53.50; H, 4.77; N, 7.80%. Found: C, 53.41; H, 4.89; N, 7.39%.

2.8. General procedure for the synthesis of 4-(4,5-dihydrooxazol-2-yl)-5-methyl-3-aryl-isoxazole (VIa-VId)

To a solution of 10 mmol of compound **Va-Vd** in 10 mL of MeCN was added dropwise 5 mL of 2 N NaOH at rt. The resulting solution was stirred over night at rt. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with EtOAc (2 x 20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product was subjected to column chromatography with hexane: EtOAc (95:5%) to yield pure compound (Scheme 2).

2.9. General procedure for the synthesis of 4-(4,5-dihydro oxazol-2-yl)-5-methyl-3-aryl-isoxazole (VIa-VId) in microwave

Compounds **Va-Vd** (5 mmol) were adsorbed on silicagel (200-400 mesh) and were suspended in MeCN and 2N NaOH (3 mL) and transfered in to a microwave vial. The vial was sealed and placed in microwave. The reaction was run at 85 °C for 2 min. For the entire experiment, the power setting was held at 180 W. The reaction was then cooled to room temperature and purified by SiO_2 gel column chromatography with hexane: EtOAc (95:5%) to afford **VIa-Vid** (Scheme 2).

4-(4,5-Dihydrooxazol-2-yl)-5-methyl-3-phenylisoxazole (**VIa1**): Color: white. Yield: 85%[m] (77%)[c]. M.p.: 81-84 °C. IR (KBr, ν): 3036, 2974, 2810, 1694, 1623, 1484, 1345, 1221, 1065, 1011 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.68 (s, 3H), 3.97 (t, *J* = 9.2 Hz, 2H), 4.26 (t, *J* = 9.2 Hz, 2H), 7.43 (m, 3H), 7.65 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 54.7, 66.8, 105.2, 127.8, 129.0, 129.1, 129.4, 158.2, 161.7, 172.6. MS (ES, m/z): 229 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%. Found: C, 68.12; H, 5.16; N, 12.27%.

4-((S)-4,5-Dihydro-4-methyloxazol-2-yl)-5-methyl-3-phenyl isoxazole (**VIa2**): Color: white. Yield: 88%[m] (70%)[c]. M.p.: 114-117 °C. IR (KBr, ν): 3065, 2966, 2930, 1672, 1612, 1452, 1342, 1244, 1147, 1109, 1053 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.32 (d, *J* = 6 Hz, 3H), 2.69 (s, 3H), 3.83 (t, *J* = 6.8 Hz, 1H), 4.31 (m, 2H), 7.46 (m, 3H), 7.69 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 21.2, 61.8, 73.4, 105.2, 127.9, 128.8, 129.0, 129.5, 157.1, 161.6, 172.6. MS (ES, m/z): 243 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56%. Found: C, 69.32; H, 5.85; N, 11.69%.

4-((S)-4,5-Dihydro-4-isopropyloxazol-2-yl)-5-methyl-3-phenylisoxazole (**VIa3**): Color: white. Yield: 84%[m] (81%)[c]. M.p.: 128-131 °C. IR (KBr, ν): 3039, 2995, 2876, 1659, 1620, 1568, 1458, 1376, 1221, 1069, 1028 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.90 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.74 (m, 1H), 2.65 (s, 3H), 3.97 (m, 2H), 4.22 (m, 1H), 7.39 (m, 3H), 7.71 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.6, 18.3, 18.4, 32.8, 69.7, 72.7, 105.4, 127.7, 129.0, 129.1, 129.3, 156.9, 161.7, 172.4. MS (ES, m/z): 271 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36%. Found: C, 69.98; H, 6.67; N, 10.32%.

4-(4,5-Dihydro-4,4-dimethyloxazol-2-yl)-5-methyl-3-phenyl isoxazole (**VIa4**): Color: white. Yield: 89%[m] (85%)[c]. M.p.: 102-105 °C. IR (KBr, ν): 3063, 2970, 2930, 1728, 1668, 1614, 1454, 1321, 1257, 1190, 1059 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.26 (s, 6H), 2.56 (s, 3H), 3.87 (s, 2H), 7.34 (m, 3H), 7.59 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.4, 28.0, 67.6, 78.6, 105.4, 127.9, 128.8, 129.0, 129.4, 155.8, 161.5, 172.3. MS (ES, m/z): 257 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93%. Found: C, 70.13; H, 6.29; N, 11.06%.

3-(2-Chlorophenyl)-4-(4,5-dihydrooxazol-2-yl)-5-methyl isoxazole (**VIb1**): Color: white. Yield: 88%[m] (71%)[c]. M.p.: 113-115 °C. IR (KBr, ν): 2984, 2935, 2885, 1726, 1672, 1610, 1508, 1454, 1356, 1278, 1232, 1149, 1082 cm^{-1}. ^1H NMR (CDCl3, 400 MHz, δ, ppm): 2.73 (s, 3H), 3.82 (t, *J* = 6.9 Hz, 2H), 4.17 (t, *J* = 6.9 Hz, 2H), 7.38 (m, 4H). ^{13}C NMR (CDCl3, 100 MHz, δ, ppm): 12.8, 54.7, 66.9, 106.7, 126.3, 128.9, 129.3, 130.5, 131.1, 134.2, 157.9, 160.3, 172.1. MS (ES, m/z): 263 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66%. Found: C, 59.70; H, 4.14; N, 10.79%.

3-(2-Chlorophenyl)-4-((S)-4,5-dihydro-4-methyloxazol-2yl)-5-methylisoxazole (**VIb2**): Color: white. Yield: 90%[m] (79%)[c]. M.p.: 147-150 °C. IR (KBr, ν): 3012, 2974, 2896, 1726, 1658, 1621, 1432, 1368, 1249, 1112, 1059 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.23 (d, *J* = 3.2 Hz, 3H), 2.73 (s, 3H), 3.71 (m, 1H), 4.22 (m, 2H), 7.38 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 21.1, 61.7, 73.4, 106.8, 126.3, 128.9, 129.3, 130.5, 131.1, 134.2, 156.8, 160.3, 172.0. MS (ES, m/z): 277 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.12%. Found: C, 60.36; H, 4.82; N, 10.36%.

3-(2-Chlorophenyl)-4-((S)-4,5-dihydro-4-isopropyloxazol-2-yl)-5-methylisoxazole (**VIb3**): Color: white. Yield: 95%[m] (85%)[c]. M.p.: 94-97 °C. IR (KBr, ν): 3064, 2954, 2867, 1680, 1601, 1456, 1384, 1239, 1084, 1061 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.70 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 1.67 (m, 1H), 2.72 (s, 3H), 3.88 (m, 2H), 4.15 (m, 1H), 7.38(m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.6, 18.3, 18.4, 32.8, 69.8, 72.6, 106.8, 126.1, 129.2, 130.3, 131.2, 131.5, 134.3, 156.5, 160.4, 171.8. MS (ES, m/z): 305 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19%. Found: C, 62.85; H, 5.42; N, 9.42%.

3-(2-Chlorophenyl)-4-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-5-methylisoxazole (**VIb4**): Color: white. Yield: 79%[m] (73%)[c]. M.p.: 135-138 °C. IR (KBr, ν): 3011, 2973, 2923, 1730, 1632, 1602, 1579, 1463, 1321, 1287, 1161, 1012 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.29 (s, 6H), 2.74 (s, 3H), 3.86 (s, 2H), 7.42 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.5, 28.0, 67.4, 78.6, 107.0, 126.2, 129.0, 129.2, 130.3, 131.2, 134.2, 155.4, 160.3, 171.8. IR (KBr): υ 2991, 2942, 28874, 1732, 1652, 1610, 1501, 1464, 1354, 1271, 1228, 1168, 1087 cm^{-1}. MS (ES, m/z): 291 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; N, 9.64%. Found: C, 61.76; H, 5.29; N, 9.72%.

3-(2,6-Dichlorophenyl)-4-(4,5-dihydrooxazol-2-yl)-5-methyl isoxazole (**VIc1**): Color: white. Yield: 86%[m] (81%)[c]. M.p.: 141-144 °C. IR (KBr, ν): 3054, 2989, 2926, 1742, 1675, 1609, 1584, 1460, 1297,1156, 1045 cm^{-1}. ^1H NMR (CDCl3, 400 MHz, δ, ppm): 2.80 (s, 3H), 3.89 (t, *J* = 10.8 Hz, 2H), 4.18 (t, *J* = 10.8 Hz, 2H), 7.34 (m, 1H), 7.40 (m, 2H). ^{13}C NMR (CDCl3, 100 MHz, δ, ppm): 12.8, 54.7, 66.8, 106.6, 127.5, 128.7, 130.5, 135.7, 157.3, 158.0, 172.3. IR (KBr): υ cm^{-1}; MS (ES, m/z): 297 $[M+H]^+$. Anal.

Calcd. for $C_{13}H_{10}Cl_2N_2O_2$: C, 52.55; H, 3.39; N, 9.43%. Found: C, 52.36; H, 3.01; N, 9.65%.

3-(2,6-Dichlorophenyl)-4-((S)-4,5-dihydro-4-methyloxazol-2-yl)-5-methylisoxazole (**VIc2**): Color: white. Yield: 94%[m] (92%)[c]. M.p.: 106-108 °C. IR (KBr, ν): 3029, 2971, 2901, 1732, 1656, 1611, 1578, 1463, 1284,1172, 1050 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.12 (d, *J* = 6.8 Hz, 3H), 2.79 (s, 3H), 3.71 (m, 1H), 4.18 (m, 2H), 7.33 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 13.1, 21.3, 61.6, 73.4, 106.6, 127.6, 128.3, 130.8, 135.5, 156.2, 158.1, 172.6. MS (ES, m/z): 311 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_2$: C, 54.04; H, 3.89; N, 9.00%. Found: C, 53.79; H, 3.62; N, 9.00%.

3-(2,6-Dichlorophenyl)-4-((S)-4,5-dihydro-4-isopropyloxazol-2-yl)-5-methylisoxazole (**VIc3**): Color: white. Yield: 83%[m] (83%)[c]. M.p.: 152-154 °C. IR (KBr, ν): 3067, 2959, 2914, 1728, 1680, 1614, 1556, 1431, 1226,1195, 1084 cm^{-1}. ^1H NMR (CDCl3, 400 MHz, δ, ppm): 0.81 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 1.63 (m, 1H), 2.77 (s, 3H), 3.89 (m, 2H), 4.15 (m, 1H), 7.36 (m, 3H). ^{13}C NMR (CDCl3, 100 MHz, δ, ppm): 12.7, 18.2, 32.8, 69.8, 72.3, 106.7, 127.4, 128.8, 130.4, 135.7, 155.8, 158.2, 171.9. MS (ES, m/z): 339 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O_2$: C, 56.65; H, 4.75; N, 8.26%. Found: C, 56.91; H, 4.34; N, 8.05%.

3-(2,6-Dichlorophenyl)-4-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-5-methylisoxazole (**VIc4**): Color: white. Yield: 81%[m] (78%)[c]. M.p.: 104-106 °C. IR (KBr, ν): 2976, 2876, 1724, 1676, 1606, 1562, 1450, 1313, 1249, 1194, 1078 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.24 (s, 6H), 2.78 (s, 3H), 3.81 (s, 2H), 7.37 (m, 1H), 7.41 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.7, 28.0, 67.3, 78.5, 106.9, 127.5, 128.4, 130.4, 135.5, 154.7, 158.0, 172.0. MS (ES, m/z): 325 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_2$: C, 55.40; H, 4.34; N, 8.61%. Found: C, 55.24; H, 4.34; N, 8.88%.

3-(2-Chloro-6-fluorophenyl)-4-(4,5-dihydrooxazol-2-yl)-5-methylisoxazole (**VId1**): Color: white. Yield: 95%[m] (88%)[c]. M.p.: 109-111 °C. IR (KBr, ν): 3055, 2945, 2939, 1728, 1635, 1614, 1525, 1460, 1323, 1251, 1192, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.76 (s, 3H), 3.88 (t, *J* = 9.2 Hz, 2H), 4.17 (t, *J* = 9.2 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 1H) 7.26 (d, *J* = 7.6 Hz, 1H), 7.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 40.9, 43.6, 112.0, 114.7, 116.7, 126.0, 132.4, 135.5, 152.9, 160.7, 162.1, 174.2. MS (ES, m/z): 281 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{10}ClFN_2O_2$: C, 55.63; H, 3.59; N, 9.98%. Found: C, 55.45; H, 3.57; N, 10.16%.

3-(2-Chloro-6-fluorophenyl)-4-((S)-4,5-dihydro-4-methyl oxazol-2-yl)-5-methylisoxazole (**VId2**): Color: white. Yield: 79%[m] (75%)[c]. M.p.: 60-62 °C. IR (KBr, ν): 2974, 2908, 1726, 1668, 1614, 1570, 1514, 1454, 1342, 1307, 1251, 1182, 1143, 1107, 1053 cm^{-1}. ^1H NMR (CDCl3, 400 MHz, δ, ppm): 1.20 (d, *J* = 4.8 Hz, 3H), 2.76 (s, 3H), 3.72 (m, 1H), 4.21 (m, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.38 (m, 1H). ^{13}C NMR (CDCl3, 100 MHz, δ, ppm): 12.6, 21.0, 61.7, 73.4, 107.0, 113.8, 118.0, 124.9, 130.9, 135.4, 154.9, 156.1, 162.2, 172..2. MS (ES, m/z): 295 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{12}ClFN_2O_2$: C, 57.06; H, 4.10; N, 9.51%. Found: C, 56.82; H, 3.85; N, 9.83%.

3-(2-Chloro-6-fluorophenyl)-4-((S)-4,5-dihydro-4-isopropyl oxazol-2-yl)-5-methylisoxazole (**VId3**): Color: white. Yield: 96%[m] (87%)[c]. M.p.: 76-79 °C. IR (KBr, ν): 3086, 2958, 2892, 1681, 1612, 1573, 1462, 1444, 1250, 1237, 1088, 982 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.80 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 1.63 (m, 1H), 2.74 (s, 3H), 3.87 (m, 2H), 4.14 (m, 1H), 7.05 (t, *J* = 8.8 Hz, 1H) 7.25 (d, *J* = 6.8 Hz, 1H), 7.33 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.8, 18.2, 32.8, 69.8, 72.4, 107.0, 113.8, 118.0, 124.9, 131.0, 135.4, 155.1, 155.9, 162.3, 172.1. MS (ES, m/z): 323 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{16}ClFN_2O_2$: C, 59.54; H, 5.00; N, 8.68%. Found: C, 59.11; H, 4.78; N, 8.74%.

3-(2-Chloro-6-fluorophenyl)-4-(4,5-dihydro-4,4-dimethyl oxazol-2-yl)-5-methylisoxazole (**VId4**): Color: white. Yield: 91%[m] (84%)[c]. M.p.: 114-118 °C. IR (KBr, ν): 2971, 2919, 1717, 1656, 1606, 1592, 1524, 1446, 1374, 1316, 1261, 1174, 1134, 1100, 1084 cm^{-1}. ^1H NMR (CDCl3, 400 MHz, δ, ppm): 1.25 (s, 6H), 2.76 (s, 3H), 3.83 (s, 2H), 7.08 (t, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.36 (m, 1H). ^{13}C NMR (CDCl3, 100 MHz, δ, ppm): 12.7, 27.9, 67.3, 78.5, 107.1, 113.8, 118.0, 124.9, 130.9, 135.4, 154.9, 155.4, 162.3, 172.1. MS (ES, m/z): 309 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{14}ClFN_2O_2$: C, 58.35; H, 4.57; N, 9.07%. Found: C, 58.01; H, 4.25; N, 9.08%.

3. Results and discussion

The focus of the present investigation is on the synthesis of a few 4-(4,5-dihydrooxazol-2-yl)-5-methyl-3-phenyl/ substituted phenyl-isoxazole (**VIa-d**) from substituted benzaldelhydes. We have simplified the procedure of *Zhi-Wei et al.* for the preparation of **IIa-d** from benzaldehyde or substituted benzaldehydes [33]. Oximes of aromatic aldehydes (**Ia2-d2**) were prepared by oximation (1 eq) with hydroxylamine hydrosulfate (1.7 eq) in methanol. The resulting oxime solution (**Ia2-d2**) was treated with Cl_2 gas at 0 °C to form chloro compound (**Ia3-d3**). Later, the resulting mixture was added a methanolic solution of the sodium salt of methylaceto acetate at 0-5 °C to form methyl 5-methyl-3-phenylisoxazole-4-carboxylates (**Ia4-d4**). Saponification of methyl esters (**Ia4-d4**) by aq. NaOH (25%) under reflux condition yielded the key intermediates **IIa-d**. All these reactions, *i.e.*, **Ia1-d1** to **IIa-d** were carried out in one pot experiment without isolating the intermediate molecules, as depicted in Scheme 1. The formation of **IIa-d** was confirmed by a broad singlet signal at *δ* 12.52-13.12 for the carboxylic acid proton in the ^1H NMR spectrum and also was confirmed by exchanging with D_2O. In the ^{13}C NMR spectrum of **IIa-d**, C-(4) of the isoxazole ring resonated at up field, between 107.5 and 114.0 ppm and the carboxyl carbon gave a peak at around 175 ppm. In compound **IId**, the fluorine containing aromatic ipso carbon gave a signal at *δ* 162.1. The methyl group at C-(5) of isoxozole resonated around 13 ppm in the ^{13}C NMR spectrum of **IIa-d**. Mass spectrum of **IIb** and **IId** exhibited molecular ion peaks at $[M+2]^+$ (30%) in addition to the molecular ion peak due to the presence of one Cl atom. Similarly, compound **IIc** has given molecular ion peaks at $[M]^+$ (38%), $[M+2]^+$ (56%) and $[M+4]^+$ (6%) due to the presence of two chlorine atoms. Compounds **IIa-IId** on reaction with PCl_5 produced the corresponding acid chlorides (**IIIa-d**), The formation of the respective acid chlorides was confirmed by the disappearance of carboxylic acidic proton signal in ^1H NMR of **IIIa-d**.

Compounds (**IIIa-IIId)** upon reaction with ethanolamine (**1**) or (*S*)-2-methyl ethanolamine (**2**) or 2,2-dimethyl ethanolamine (**3**) or (*S*)-2-isopropyl ethanolamine (**4**) in presence of Et_3N yielded the respective β-hydroxyalkyl amides (**IVa-IVd**). The ^1H NMR and ^{13}C NMR spectra of **IVa2** experienced a different electro negativity effect. In ^1H NMR spectrum, the proton attached to C-(2) of *N*-alkyl gave a multiplet signal at 4.09 *δ*, while the diastereotopic protons at C-(1) gave doublet of a doublet peaks at *δ* 3.38 and 3.54 (*J* = 11.2 Hz, *J'* = 3.6 Hz). However, in ^{13}C NMR reversal in the chemical shifts was observed, i.e., C-(2) carbon gave a signal at up field (*δ* 47.7) compared to C-(1) (*δ* 66.5). The IR spectra of this compound exhibited a new absorption maximum at around 3485 cm^{-1} characteristic of ν_{O-H} and 3249 cm^{-1} characteristic of ν_{N-H} indicating the formation of β-hydroxyalkylamide. The signal corresponding to hydroxy proton was not appeared in all the compounds of **IV** except in **IVa4**. The amide proton in **IV** appeared as broad signal around *δ* 5.22-6.05. The two methyl groups in **IV3** are expected to be chemically equivalent, however, gave two signals between *δ* 0.50 and 0.80. Similarly the non equivalent nature of the these two methyl carbons of the isopropyl group was also observed in ^{13}C NMR spectra and gave two signals between *δ* 17 and 19.

These *β*-hydroxyalkylamides (**IVa, IVb** and **IVc**) upon reaction with thionyl chloride gave *β*-chloroalkylamides (**Va-c**). The formation of *β*-chloroalkylamides was confirmed by spectroscopic analysis. The IR spectrum of **V** reveals the disappearance of O-H stretching frequency at 3400 cm^{-1}. In the

^{13}C NMR spectrum of **Va2** halo group attached carbon shifted to upfield and resonated at δ 48.7.

Compound **IVd** resulted in formation of the corresponding oxazoline (**VId**) in the thionyl chloride reaction, without forming β-chloro amide intermediate. β-Chloroalkylamides (**Va, Vb and Vc**) when stirred in the basic medium, 2 N NaOH in MeCN, provided oxazolines (**VIa, VIb and VIc**) as presented in Scheme 2. It has been found that the pseudo molecular ions of oxazline substituted isoxazoles $[M+H]^+$ and $[M+Na]^+$ have matched with their respective molecular weights. Diastereotopic protons of C-(2) in **VI2** and **VI3** are showing a multiplet signal instead of two double doublet signals in ^{1}H NMR. The imine carbon, C=N, in the newly formed oxazoline ring resonated around 170 ppm in ^{13}C NMR. The IR spectra confirmed the formation of **VI** by showing the disappearance of N-H stretching frequency at 3200 cm^{-1}. The conversion of compounds **III** to **VI** *via* **IV** and **V** under microwave irradiation is more efficient and gave better yields with shorter reaction times compared to conventional heating conditions. Most of the newly synthesized compounds, **IV**, **V and VI** melted between 90 and 120 °C.

4. Conclusion

In summary, we have successfully demonstrated a simple and convenient route for the synthesis of oxazoline substituted isoxazoles by employing conventional as well as microwave irradiation methods. In addition to its simplicity and milder reaction conditions, this method provides a wide range of oxazoline-isoxazoles in moderate to excellent yields. Microwave heating proved be quite effective in improving the yields and decreasing the reaction time.

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