Synthesis of 1,2,3-Triazole Substituted Isoxazoles *via* Copper (I) Catalyzed Cycloaddition

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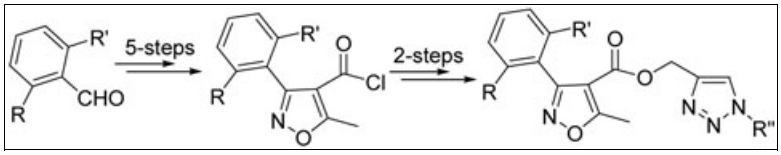
Received September 27, 2010
DOI 10.1002/jhet.837
View this article online at wileyonlinelibrary.com.



The synthesis of a series of 3,5-disubstituted isoxazole-4-carboxylic esters containing *N*-substituted 1,2,3-triazoles (**V**) starting from various benzaldehydes (**I**) is reported. Benzaldehydes undergo oximation with hydroxylamine hydrosulfate. Later, chlorination followed by condensation with methylacetoacetate and the hydrolysis of the resulting ester afforded respective carboxylic acid (**II**), which on chlorination with PCl_5 gave the corresponding acid chlorides (**III**). The coraboxylic acid chlorides (**III**) on propargylation gave propargylic esters (**IV**) and these on click reaction gave the title compounds (**V**).

J. Heterocyclic Chem., **49**, 621 (2012).

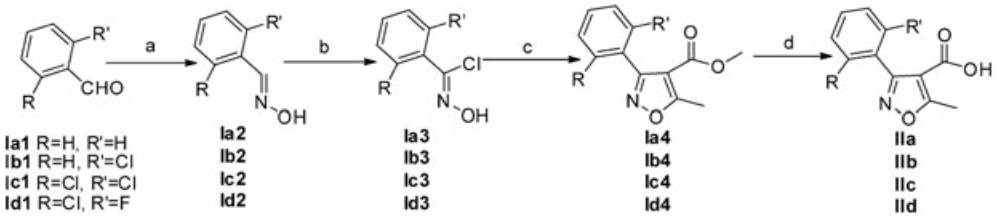
INTRODUCTION

Several compounds of natural and non-natural isoxazole origin possess a broad spectrum of biological properties like fungicidal [1], antibacterial [2], anti-inflammatory [3], antitubercular [4], antitumor [5], herbicidal [6], antifeedent [7], and antiviral [8] activities. Ureido derivatives of 5-amino-3-methylisoxazole-4-carboxylic acid were found to have a significant antileukemic activity [9]. Structure-activity relationship studies of 5-methyl-3-substituted phenylisoxazole-4-carboxamides revealed that they are potent antagonists for secretagogue receptors [10]. 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. Triazole heterocycles are found to be potent antimicrobial [11], antiviral [12], and antiproliferative [13] agents. Isoxazole coupled triazoles were reported as antimicrobial, antifungal [14], and NK-1 antagonists [15]. The pharmaceutical importance of triazoles and isoxazoles has prompted the design and synthesis of various triazole substituted isoxazoles. In an attempt to find new and potent antimicrobials, we report the synthesis of a few (1-(substituted alkyl)-1*H*-1,2,3-triazol-4-yl)methyl 5-methyl-3-(substituted phenyl)-isoxazole-4-caroboxylate. We have focused on introduction of new 1,2,3-triazole ring on C-4 of carboxylic acid group of isoxazole by click reaction.

RESULT AND DISCUSSION

The focus of this investigation is on the development of a few *N*-substituted (1*H*-1,2,3-triazole-4-yl)methyl 5-methyl-3-phenylisoxazole-4-carboxylates (**Va–d**) starting from benzaldehydes. Zhi-Wei et al. [16] reported the synthesis of 3-(2-chloro-6-flourophenyl)-5-methylisoxazole-4-carboxylic acid (**IId**) from 2-chloro-6-fluoro-benzaldehyde (**Id**) in four steps by isolating three respective intermediates. We have developed a one-pot synthesis of 3-aryl-5-methylisoxazole-4-carboxylic acid starting from the respective benzaldehydes with high yield. Benzaldehyde oxime (**Ia2**) or substituted benzaldehyde oxime (**Ib2–d2**) were prepared by oximation of benzaldehyde (**Ia1**) or substituted benzaldehyde (**Ib1–d1**) (1 equiv) with hydroxylamine hydrosulfate (1.7 equiv) in methanol. The resulting oxime solution (**Ia2–d2**) in methanol was treated with Cl_2 gas at 0°C to form chloro compound (**1a3–d3**). Later, to this mixture was added a methanolic solution of the sodium salt of methylacetoacetate at 0–5°C to form methyl 5-methyl-3-phenylisoxazole-4-carboxylates (**Ia4–d4**). Saponification of methyl esters (**Ia4–d4**) by aqueous 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 a one-pot experiment without isolating the intermediate molecules by following TLC as depicted in Scheme 1. The formation of **IIa–d** was confirmed by a broad singlet for a carboxylic acid proton in the ^{1}H-NMR spectrum at δ 12.52–13.12 (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 C-atom gave a peak at around 175 ppm. In compound **IId**, the fluorine containing ipso-C signal appeared at δ 162.1. The Me group at C-(5) of isoxozole resonated around 13 ppm in the ^{13}C-NMR spectrum of **IIa–d**. Mass

Scheme 1. One pot synthesis of 5-methyl-3-substituted phenyl isoxazole-4-carboxylic acids from benzaldehyde/substituted benzaldehydes. Reagents and conditions: a = hydroxylamine hydrosulfate, MeOH, Na_2CO_3, reflux; b = Cl_2 gas, 0–5°C; c = methylacetoacetate, MeOH, NaOH, reflux; d = aqueous NaOH (25%), reflux.



spectrum of **IIb** and **IId** exhibited molecular ion peaks at $[M + 2]^+$ (30%) 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 ^{1}H-NMR of **IIIa–d**.

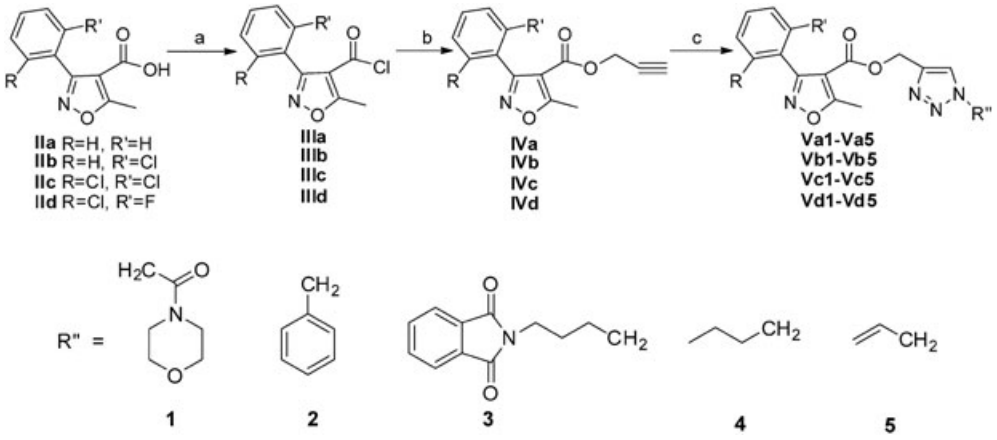
Compounds (**IIIa–IIId**) on reaction with propargylic alcohol in presence of Et_3N yielded propargylic esters (**IVa–IVd**). The ^{1}H-NMR spectrum of compound **IVa** showed signals at δ 2.48 and 4.79 due to propargylic and terminal alkyne protons. These two protons underwent propargylic ^4J coupling and was split into doublet and triplet. Although separated by four bond lengths, these two types of protons behaved as a spin system with a ^4J value of 2.4 Hz. Similar signals also appeared in the ^{1}H-NMR spectra of **IVb–IVd**. The IR spectra of these compounds exhibited a new weak absorption maximum at around 2100 cm^{-1} characteristic of $\upsilon_{c\equiv c}$, indicating the formation of propargylic ester. In the ^{13}C-NMR spectra of **IVa–IVd**, the propargylic CH_2 resonated around 52 ppm and the two triple bonded carbons resonated around 75 ppm.

These propargylic esters (**IVa–IVd**) on reaction with different azides (**1–5**, **1**, 2-azido-1-morpholineethanone; **2**, benzylazide; **3**, 2-(4-azidobutyl)isoindole-1,3-dione; **4**, *n*-butyl azide; **5**, allyl azide) in the presence of Cu(I) generated by sodium ascorbate (click condition), undergo [2 + 3] dipolar cycloaddition reactions and form **Va–d** (Scheme 2). The formation of triazoles is proved by spectroscopic analysis. The IR spectrum of **V** reveals the disappearance of C≡C stretching frequency. In the ^{1}H-NMR spectrum, H-C-(5) of the newly formed triazole ring resonated around δ 7.50, whereas it was at δ 2.77 acetylenic in its precursor **IV** in $CDCl_3$. However, this proton shifted down field in a more polar aprotic solvent like DMSO-(D_6). For example, the **C-**5 proton of **Vb1** resonated at 7.59 ppm in $CDCl_3$ and at 7.90 ppm in DMSO-(D_6).

The proton NMR of **Va1** contains seven aliphatic signals at 2.69, 3.42, 3.53, 3.59, 3.63, 5.30, and 5.48 ppm. The singlet signal at 2.69 ppm is due to the protons of methyl group on the isoxazole, whereas two other singlets at 5.30 and 5.48 ppm are due to methylene protons attached to the triazole ring at N-1 and C-4. The remaining four triplet signals at 3.47, 3.53, 3.59, and 3.63 ppm are assigned to morpholine ring H-atoms. Instead of two triplet signals expected for morpholine protons, four triplet signals were observed. Probably this may be due to a stable chair conformation in which the bulky triazole ring is locked in the equatorial position there by differentiating the equatorial and axial on each methylene carbon in the morpholine ring. The bulkier triazole ring prevents the ring flipping and restricting the interconversion of axial-equatorial protons resulting in four triplet signals. The two equatorial protons of the methylene adjacent to oxygen of morpholine resonating at 5.48 ppm, whereas the two axial protons adjacent oxygen resonated at 5.3 ppm. Similarly, the two equatorial protons of the methylene adjacent to nitrogen in morpholine have resonated at 3.59 ppm, whereas those of axial protons resonated at 3.53 ppm. ^{13}C-NMR data is also in agreement with the proton NMR data. The ^{13}C-NMR spectra show four different chemical shifts for the four —CH_2— groups in the morpholine ring. Two C-atoms adjacent to the N-atom are placed one above the plane and other one below the plane. These two carbons are resonated around 42.5–45.8. Similarly, the two carbons, which are adjacent to oxygen, gave two peaks around 66 ppm. Similar results were obtained in **Vb1**, **Vc1**, and **Vd1**.

IVa–IVd reacts with azidomethylbenzene (**2**) under click reaction condition to form triazolo isoxazoles (**Va2–Vd2**). The benzylic protons in **Va2–Vd2** resonated at 5.60, 5.59, 5.60, and 5.59 ppm, respectively, in ^{1}H-NMR. This indicates the formation of triazole ring. Similarly, these benzylic carbons exhibited signals at 57.9, 58.0, 57.9, and 57.8 ppm for **Va2**, **Vb2**, **Vc2**, and **Vd2**, respectively, in ^{13}C-NMR. Triazoles (**Va3–Vd3**) were obtained from **IVa** to **IVd** on reacting with 2-(4-azidobutyl)isoindoline-1,3-dione. It has been found that the pseudo molecular ions of **Va3–Vd3** $[M + H]^+$ and $[M + Na]^+$ were matched with their respective molecular weights. The four aromatic protons in indoline ring have shown a multiplet signal at 7.82–7.84 ppm, whereas the isoxazole attached

Scheme 2. Synthesis of isoxazole coupled triazoles. Reagents and conditions: a = PCl_5, rt; b = Propargylic alcohol, TEA, DCM, 0°C—r.t.; c = $R''N_3$, *t*-BuOH-H_2O (7:3), Cu_2SO_4, sodium ascorbate, r.t.



phenyl protons gave a signal at slightly up field less than 7.53 ppm. A new peak at δ 168 in these compounds in ^{13}C-NMR reveals the presence of imide carbon of phthalimide and formation of triazolo isoxazoles. 1-Azidobutane is a common precursor for the preparation of **Va4–Vd4**. In these butyl substituted triazole derivatives, the methyl protons have shown a triplet signal at 1.00 ppm. Methylenic protons attached to nitrogen gave triplet signal at around 4.28 ppm and middle four methylenic protons resonated at around δ 1.31 and 1.83 as multiplet in ^{1}H-NMR of **Va4–d4**. The ^{13}C-NMR of **Va4–d4** represents the presence of alkyl side chain to triazole. The carbon attached to nitrogen resonated at around 50 ppm, the terminal carbon at around 13 ppm, and middle two carbons at around 19 and 32 ppm, respectively. Compounds **IVa–IVd** on reaction with 3-azidoprop-1-ene yielded triazoles, **Va5–Vd5** under click condition. The ^{1}H-NMR of **Va5–Vd5** clearly confirms the formation of triazoles. The N-1 attached methylene protons appeared as a doublet signal around 6.0 ppm. The vinyl cis protons have always resonated at up field than the trans protons.

Morpholine substituted triazoles (**Va1–Vd1**) melted at higher temperature than the benzylazido (**Va2**–**Vd2**) and phthalyl-butylazido triazoles (**Va3**–**Vd3**). However, the butylazido (**Va4**–**Vd4**) and allylazido (**Va5**–**Vd5**) substituted triazoles are liquids.

CONCLUSIONS

In summary, we have successfully demonstrated a simple and convenient route for the synthesis of 1,2,3-triazole substituted isoxazoles by using the Cu(I) catalyzed [2 + 3] dipolar cycloaddition reaction. In addition to its simplicity and mild reaction conditions, this method provides a wide range of triazoles in good yields in a single step operation.

EXPERIMENTAL

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 F254 (Merck). TLC plates were inspected under UV light. Micro-analytical data were obtained by using a Perkin-Elmer 240c analyzer. IR spectra were recorded with a Perkin-Elmer-1700 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Bruker Avance 400 MHz spectrometer. Coupling constants have been assigned and listed without duplication in the ^{1}H-NMR description of the synthesized compounds. ESI-MS were recorded on an LCQ system (Finngan MAT, USA) using MeOH as the mobile phase. M. P. were recorded on a Polmon MP 96.

General experimental procedure for the preparation of 5-methyl-3-(phenyl/substituted phenyl)-isoxazole-4-carboxylic acid (IIa–IId). To a solution of benzaldehyde (**Ia**) or substituted benzaldehyde (**Ib–Id**) (1 equiv), four times of methanol hydroxylamine hydrosulfate (1.4 equiv) was added and stirred for 30 min. The reaction mixture was slowly converted to a clear solution. Later, the pH was adjusted to 8–9 with Na_2CO_3 and refluxed for 0.5 h. 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 solution pH was adjusted to 1–2 by using Na_2CO_3 at 0°C. In another flask, sodium salt of methylacetoacetate was prepared by addition of 1.4 equiv of NaOH to a solution of methyl acetoacetate (1.4 equiv) in four times volume 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 chloro compound during a period 1 h at 0–5°C, and stirred for 1 h at r.t. by maintaining the pH 9. Subsequently, the pH was adjusted to 11–13 with aqueous 25% NaOH solution at r.t. and refluxed the reaction mixture for 1 h. The methanol was distilled then added 5 times of water and adjusted the pH to 2–2.5 with 20% H_2SO_4. The compound was filtered, washed with hot water, and recrystallized in methanol to afford pure product.

5-Methyl-3-phenyl-isoxazole-4-corboxylic acid (IIa). Yield: 82%; M.p.: 189–190°C; IR (KBr): υ 3075, 3020, 2878, 2689, 2613, 1689, 1598, 1471, 1424, 1338, 1162, 1122 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.72 (s, 3H), 7.41–7.47 (m, 3H), 7.63 (d, 2H, *J* = 6.8 Hz) 13.12 (br. S, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.5, 107.5, 127.8, 128.1, 129.4, 129.8, 163.2, 167.1, 175.2; Mass (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-corboxylic acid (IIb). Yield: 85%; M.p.: 193–196°C; IR (KBr): υ 3017, 2881, 2686, 2607, 1690, 1603, 1574, 1456, 1405, 1317, 1250, 1162, 1104 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.75 (s, 3H), 7.38–7.46 (m, 4H), 12.52 (br. s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.0, 110.2, 126.3, 128.8, 129.2, 130.4, 130.9, 133.9, 160.9, 162.9, 174.9; Mass (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-corboxylic acid (IIc). Yield: 79%; M.p.: 225–226°C; IR (KBr): υ 3060, 2927, 2675, 2606, 1695, 1601, 1560, 1514, 1463, 1383, 1320, 1262, 1194 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.79 (s, 3H), 7.29–7.41 (m, 3H), 12.86 (br. S, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.0, 110.0, 127.6, 128.4, 130.7, 135.2, 158.7, 162.4, 175.3; Mass (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-corboxylic acid (IId). Yield: 76%; M.p.: 206–208°C; IR (KBr): υ 3072, 2895, 2686, 2607, 1689, 1605, 1517, 1454, 1379, 1316, 1250, 1188, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.75 (s, 3H), 7.12 (t, 1H, *J* = 8.1 Hz), 7.31 (d, 1H, *J* = 7.6 Hz), 7.40–7.46 (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; Mass (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%.

General experimental procedure for the preparation of 5-methyl-3-substituted phenyl-isoxazole-4-carbonyl chloride (IIIa–IIId). To the compound **IIa–IId** (25 g), PCl_5 (25 g) at r.t. was added and heated to 45°C to become clear solution. It was stirred for 1 h and the byproduct $POCl_3$ distilled out at reduced pressure. To the residue 75 mL of hexane was added for crystallization and filtered.

5-Methyl-3-phenyl-isoxazole-4-corbonyl chloride (IIIa). Yield: 90%; B.p.: 115–117°C (3 Torr); IR (neat): υ 3065, 3010, 1741, 1689, 1605, 1462, 1316, 1250, 1157, 1116 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.79 (s, 3H), 7.42–7.46 (m, 3H), 7.62 (d, 2H, *J* = 7.6 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.6, 107.5, 128.0, 128.1, 129.3, 129.8, 162.6, 166.3, 177.4; Mass (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). Yield: 93%; M.p.: 45–48°C; IR (KBr): υ 3061, 3005, 1732, 1685, 1604, 1458, 1309, 1258, 1141, 1117 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.79 (s, 3H), 7.33–7.40 (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; Mass (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). Yield: 84%; M.p.: 88–89°C; IR (KBr): υ 3089, 3002, 1757, 1689, 1562, 1498, 1432, 1390, 1290, 1249, 1195, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.85 (s, 3H), 7.35–7.41 (m, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 14.2, 114.0, 127.0, 128.0, 131.7, 135.6, 158.1, 158.6, 177.7; Mass (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). Yield: 88%; M.p.: 181–184°C; IR (KBr): υ 3054, 3010, 1757, 1693, 1576, 1514, 1449, 1393, 1290, 1250, 1185, 1162 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.86 (s, 3H), 7.14 (t, 1H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.40–7.46 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 14.2, 109.0, 113.9, 116.5, 125.4, 132.2, 135.2, 155.0, 158.6, 162.1, 177.6; Mass (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%.

General procedure for the preparation of 5-methyl-3-substituted phenyl-isoxazole-4-carboxyl propargyl esters (IVa–IVd). To a cold solution (0°C) of substituted isoxazole carboxyl chloride (**IIIa–IIId**) (2.0 mmol) in DCM (20 mL), triethylamine (2.3 mmol) and propargylic alcohol (2.8 mmol) were added. The resulting solution was stirred at r.t. for 2 h. The reaction mixture was diluted with water and extracted with DCM (3× 20 mL). The organic layers were combined, and the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate 8:2) to afforded pure product.

Prop-2-ynyl 5-methyl-3-phenylisoxazole-4-carboxylate (IVa). Yield: 84%; M.p.: 55–58°C; IR (KBr): υ 3290, 3063, 2949, 2129, 1730, 1599, 1448,1425, 1369, 1304, 1249, 1151, 1132, 1095 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.48 (t, 1H, *J* = 2.4 Hz), 2.77 (s, 3H), 4.79 (d, 2H, *J* = 2.4 Hz), 7.38–7.44 (m, 3H), 7.64 (d, 2H, *J* = 6.9 Hz). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 13.4, 51.9, 75.1, 107.8, 128.0, 128.2, 129.3, 129.7, 160.9, 162.4, 176.2; Mass (ES): *m/z* 242 $[M + H]^+$, 264 $[M + Na]^+$. Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81%. Found: C, 69.57; H, 4.41; N, 5.79%.

Prop-2-ynyl 3-(2-chlorophenyl)-5-methylisoxazole-4-carboxylate (IVb). Yield: 72%; M.p.: 65–67°C; IR (KBr): υ 3292, 3063, 2949, 2131, 1720, 1604, 1575, 1510, 1440, 1309, 1099 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (t, 1H, *J* = 2.4 Hz), 2.79 (s, 3H), 4.71 (d, 2H, *J* = 2.4 Hz), 7.28–7.48 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.0, 51.9, 74.8, 74.9, 109.2, 126.4, 128.5, 129.4, 130.6, 130.9, 134.0, 160.5, 160.6, 175.4; Mass (ES): *m/z* 276 $[M + H]^+$, 297 $[M + Na]^+$. Anal. Calcd. for $C_{14}H_{10}ClNO_3$: C, 69.99; H, 3.66; N, 5.08%. Found: C, 69.99; H, 3.51; N, 5.21%.

Prop-2-ynyl 3-(2,6-chlorophenyl)-5-methylisoxazole-4-carboxylate (IVc). Yield: 79%; M.p.: 62–65°C; IR (KBr): υ 3294, 3076, 2937, 2130, 1729, 1592, 1561, 1455, 1424, 1363, 1303, 1248, 1194, 1154, 1115, 1091 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.43 (t, 1H, *J* = 2.4 Hz), 2.85 (s, 3H), 4.72 (d, 2H, *J* = 2.4 Hz), 7.35–7.43 (m, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.2, 52.0, 74.9, 75.0, 108.9, 127.7, 128.0, 130.9, 135.4, 158.5, 160.1, 176.0; Mass (ES): *m/z* 310 $[M + H]^+$, 311 $[M + 2]^+$, 313 $[M + 4]^+$. Anal. Calcd. for $C_{14}H_9ClNO_3$: C, 57.26; H, 3.09; N, 4.52%. Found: C, 57.27; H, 3.09; N, 4.68%.

Prop-2-ynyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylate (IVd). Yield: 68%; M.p.: 73–75°C; IR (KBr): υ 3300, 3086, 2951, 2131, 1732, 1612, 1574, 1514, 1454, 1369, 1304, 1249, 1186, 1099 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (t, 1H, *J* = 2.4Hz), 2.81 (s, 3H), 4.71 (d, 2H, *J* = 2.7 Hz), 7.11 (t, 1H, *J* = 8.2 Hz), 7.29 (d, 1H, *J* = 7.6 Hz), 7.37–7.45 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.2, 52.0, 75.0, 109.2, 113.9, 117.2, 125.1, 131.5, 135.1, 154.4, 160.1, 162.0, 176.0; Mass

(ES): *m/z* 294 $[M + H]^+$, 295 $[M + 2]^+$. Anal. Calcd. for $C_{14}H_9ClFNO_3$: C, 57.26; H, 3.09; N, 4.77%. Found: C, 57.32; H, 2.91; N, 4.91%.

General experimental procedure for the synthesis of (Va–Vd). Compound (**IVa–IVd**) (2 mmol) and azides (**1–5**) (2.2 mmol) were dissolved in10 mL of *tert*-butanol-H_2O (7:3 V/V). To this mixture, $CuSO_4{\cdot}5H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (39 mg, 0.2 mmol) aqueous solutions were added and stirred for overnight at rt. The reaction mixture was poured into 25 mL of water and was extracted with ethyl acetate (3× 20 mL). The organic layers were combined and washed with water (20 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to give the pure product.

Spectral data of Va–Vd. *(1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 5-methyl-3-phenylisoxazole-4-caroboxylate (Va1).* Yield: 86%; M.p.: 128–130°C; IR (KBr): υ 3142, 2931, 1720, 1667, 1649, 1600, 1439, 1314, 1242, 1198, 1106, 1056 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.69 (s, 3H), 3.42 (t, 2H, *J* = 4.2 Hz), 3.53 (t, 2H, *J* = 4.2 Hz), 3.59 (t, 2H, *J* = 4.2 Hz), 3.63 (t, 2H, *J* = 4.2 Hz), 5.30 (s, 2H), 5.48 (s, 2H), 7.40–7.51 (m, 3H), 7.57 (d, 2H, *J* = 7.2 Hz), 7.98 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.7, 42.5, 45.6, 50.6, 57.8, 66.2, 66.5, 107.9, 125.6, 128.0, 128.3, 129.4, 129.7, 142.3, 161.5, 162.6, 163.3, 176.4; Mass (ES): *m/z* 412 $[M + H]^+$, 434 $[M + Na]^+$. Anal. Calcd. for $C_{20}H_{21}N_5O_5$: C, 58.39; H, 5.14; N, 17.02%. Found: C, 58.02; H, 5.06; N, 17.35%.

(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 5-methyl-3-phenylisoxazole-4-carboxylate (Va2). Yield: 92%; M.p.: 105–107°C; IR (KBr): υ 3130, 3087, 2952, 1762, 1710, 1600, 1579, 1459, 1441, 1391, 1363, 1305, 1260, 1228, 1165, 1092, 1040 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.68 (s, 3H), 5.29 (s, 2H), 5.60 (s, 2H), 7.28–7.41 (m, 8H), 7.58 (d, 2H, *J* = 6.8 Hz), 8.12 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.6, 54.2, 57.9, 108.2, 123.1, 127.9, 128.1, 128.4, 128.8, 129.1, 129.3, 129.7, 134.4, 161.6, 162.4, 176.4; Mass (ES): *m/z* 375 $[M + H]^+$, 397 $[M + Na]^+$. Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96%. Found: C, 67.03; H, 4.51; N, 14.85%.

(1-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-1H-1,2,3-triazol-4-yl) methyl 5-methyl-3-phenylisoxazole-4-3-carboxylate (Va3). Yield: 96%; M.p.: 118–120°C; IR (KBr): υ 3132, 3095, 2961, 1764, 1730, 1712, 1612, 1552, 1423, 1391, 1358, 1296, 1154, 1116, 1047 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.52–1.61 (m, 2H), 1.78–1.85 (m, 2H), 2.63 (s, 3H), 3.60 (t, 2H, *J* = 5.8 Hz), 4.40 (t, 2H, *J* = 6.0 Hz), 5.28 (s, 2H), 7.38–7.46 (m, 3H), 7.55 (d, 2H, *J* = 7.1 Hz), 7.80–7.86 (m, 4H), 8.02 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.5, 25.3, 27.6, 37.1, 49.4, 58.1, 108.7, 123.3, 123.8, 127.9, 128.1, 129.7, 130.0, 131.9, 134.3, 161.9, 162.7, 168.2, 177.0; Mass (ES): *m/z* 486 $[M + H]^+$, 508 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{23}N_5O_5$: C, 64.32; H, 4.78; N, 14.42%. Found: C, 64.03; H, 4.50; N, 14.41%.

(1-Butyl-1H-1,2,3-triazol-4yl)methyl 5-methyl-3-phenylisoxazole-4-carboxylate (Va4). Yield: 76%; IR (neat): υ 3142, 3053, 2961, 1724, 1601, 1574, 1448, 1421, 1304, 1249, 1151, 1099, 1049 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, 3H, *J* = 5.2 Hz), 1.20–1.27 (m, 2H), 1.74–1.82 (m, 2H), 2.70 (s, 3H), 4.36 (t, 2H, *J* = 5.2 Hz), 5.28 (s, 2H), 7.39–7.51 (m, 3H), 7.59 (d, 2H, *J* = 6.8 Hz) 8.03 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.2, 13.4, 19.6, 32.0, 50.1, 57.9, 108.0, 127.9, 128.5, 129.3, 129.5, 161.6, 162.4, 176.2; Mass (ES): *m/z* 341 $[M + H]^+$, 363 $[M + Na]^+$. Anal. Calcd. for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46%. Found: C, 63.12; H, 6.08; N, 16.81%.

(1-Allyl-1H-1,2,3-triazol-4-yl)methyl 5-methyl-3-phenylisoxazole-4-carboxylate (Va5). Yield: 78%; IR (neat): υ 3144, 3072, 2930, 1722, 1601, 1577, 1448, 1423, 1304, 1251, 1226, 1151, 1099, 1049 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.70 (s, 3H), 5.02 (d, 2H, *J* = 6.0 Hz), 5.20 (d, 1H, *J* = 15.6 Hz), 5.31 (d, 1H, *J* = 8.7 Hz), 5.33 (s, 2H), 5.98–6.08 (m, 1H), 7.38–7.52 (m, 3H), 7.58 (d, 2H, *J* = 7.6 Hz), 8.00 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.4, 52.5, 57.9, 108.0, 120.0, 123.1, 127.9, 128.5, 129.3, 129.5, 131.0, 142.6, 161.6, 162.3, 176.1; Mass (ES): *m/z* 325 $[M + H]^+$, 347 $[M + Na]^+$. Anal. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27%. Found: C, 63.18; H, 4.92, N, 17.27%.

(1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 3-(2-chlorophenyl)-5-methylisoxazole-4-caroboxylate (Vb1). Yield: 89%; M.p.: 136–138°C; IR (KBr): υ 3131, 2923, 2855, 1720, 1667, 1649, 1600, 1439, 1314, 1242, 1198, 1106, 1056 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.73 (s, 3H), 3.44 (t, 2H, *J* = 4.6 Hz), 3.52 (t, 2H, *J* = 4.6 Hz), 3.60 (t, 2H, *J* = 4.6 Hz), 3.64 (t, 2H, *J* = 4.6 Hz), 5.21 (s, 2H), 5.43 (s, 2H), 7.39–7.52 (m, 4H), 7.90 (s,1H). ^{13}C-NMR (DMSO, 100 MHz): δ 13.1, 42.6, 45.7, 50.6, 57.8, 66.3, 109.3, 124.9, 126.5, 128.5, 129.4, 130.6, 130.9, 133.9, 142.8, 160.6, 161.1, 163.3, 175.5; Mass (ES): *m/z* 446 $[M + H]^+$, 468 $[M + Na]^+$. Anal. Calcd. for $C_{20}H_{20}ClN_5O_5$: C, 53.88; H, 4.52; N, 15.71%. Found: C, 53.61; H, 4.23; N, 16.00%.

(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 3-(2-chlorophenyl)-5-methylisoxazole-4-carboxylate (Vb2). Yield: 82%; M.p.: 100–102°C; IR (KBr): υ 3145, 2965, 1721, 1603, 1497, 1439, 1415, 1343, 1305, 1253, 1155, 1089 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.72 (s, 3H), 5.18 (s, 2H), 5.59 (s, 2H), 7.27–7.61 (m, 9H), 7.92 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 12.9, 54.0, 58.0, 109.4, 123.0, 126.3, 127.9, 128.6, 128.7, 129.0, 129.2, 130.5, 130.9, 133.8, 134.6, 142.5, 160.5, 161.0, 175.5; Mass (ES): *m/z* 408 $[M + H]^+$, 431 $[M + Na]^+$. Anal. Calcd. for $C_{21}H_{17}ClN_4O_3$: C, 61.69; H, 4.19; N, 13.70%. Found: C, 61.32; H, 3.99, N, 13.70%.

(1-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-1H-1,2,3-triazol-4-yl) methyl 3-(2-chlorophenyl)-5-methylisoxazole-4-carboxylate (Vb3). Yield: 91%; M.p.: 132–135°C; IR (KBr): υ 3131, 3093, 2952, 1769, 1710, 1606, 1466, 1439, 1398, 1305, 1265, 1158, 1097 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.51–1.58 (m, 2H), 1.78–1.83 (m, 2H), 2.73 (s, 3H), 3.64 (t, 2H, *J* = 6.2 Hz), 4.38 (t, 2H, *J* = 6.0 Hz), 5.15 (s, 2H), 7.39–7.47 (m, 4H), 7.80–7.88 (m, 4H), 7.91 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 12.9, 25.5, 27.3, 36.8, 49.5, 58.0, 109.4, 123.1, 126.3, 128.7, 129.3, 130.5, 131.0, 132.1, 133.8, 160.5, 161.1, 168.0, 175.4; Mass (ES): *m/z* 520 $[M + H]^+$, 542 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{22}ClN_5O_5$: C, 60.06; H, 4.26; N, 13.47%. Found: C, 59.82; H, 3.99, N, 13.39%.

(1-Butyl-1H-1,2,3-triazol-4yl)methyl 3-(2-chlorophenyl)-5-methylisoxazole-4-carboxylate (Vb4). Yield: 90%; IR (neat): υ 2964, 2935, 1728, 1702, 1608, 1454, 1311, 1151, 1103, 985 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.93 (t, 2H, *J* = 5.4 Hz), 1.28–1.34 (m, 2H) 1.79–1.86 (m, 2H), 2.73 (s, 3H), 4.28 (t, 2H, *J* = 5.4 Hz), 5.24 (s, 2H), 7.32 (d, 2H, *J* = 7.2 Hz), 7.37 (s, 2H), 7.38 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.3, 13.4, 19.6, 32.1, 50.1, 58.0, 109.3, 126.6, 128.4, 129.3,130.7, 131.0, 133.9, 160.6, 161.3, 175.6; Mass (ES): *m/z* 375 $[M + H]^+$, 398 $[M + Na]^+$. Anal. Calcd. for $C_{18}H_{19}ClN_4O_3$: C, 57.68; H, 5.11; N, 14.95%. Found: C, 57.32; H, 4.97; N, 14.69%.

(1-Allyl-1H-1,2,3-triazol-4-yl)methyl 3-(2-chlorophenyl)-5-methylisoxazole-4 carboxylate (Vb5). Yield: 79%; IR (neat): υ 3148, 3082, 2962, 1728, 1676, 1608, 1508, 1444, 1309, 1267, 1151, 1105, 1051 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.73 (s, 3H), 5.02 (d, 2H, *J* = 5.8 Hz), 5.15 (d, 1H, *J* = 15.9 Hz), 5.20 (s, 2H), 5.28 (d, 1H, *J* = 8.2 Hz), 5.98–6.08 (m, 1H), 7.38–7.44 (m, 2H), 7.47 (d, 2H, *J* = 7.8 Hz), 7.83 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.0, 52.4, 58.0, 109.3, 119.9, 122.9, 126.4, 128.6, 129.2, 130.6, 130.9, 131.1, 133.9, 142.4, 160.5, 161.0, 175.4; Mass (ES): *m/z* 358 $[M + H]^+$, 382 $[M + Na]^+$. Anal. Calcd. for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; N, 15.62%. Found: C, 56.69; H, 4.01; N, 15.79%.

(1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-caroboxylate (Vc1). Yield: 92%; M.p.: 149–152°C; IR (KBr): υ 3118, 3078, 2987, 1719, 1666, 1647, 1595, 1561, 1453, 1419, 1303, 1274, 1239, 1156, 1109, 1052 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.75 (s, 3H), 3.45 (t, 2H, *J* = 4.6 Hz), 3.54 (t, 2H, *J* = 4.6 Hz), 3.59 (t, 2H, *J* = 4.6 Hz), 3.63 (t, 2H, *J* = 4.6 Hz), 5.20 (s, 2H), 5.45 (s, 2H), 7.51–7.58 (m, 3H), 7.88 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.5, 42.5, 45.8, 50.8, 57.8, 66.6, 66.8, 109.2, 125.3, 127.8, 131.1, 135.2, 158.8, 160.7, 163.3, 176.2; Mass (ES): *m/z* 480 $[M + H]^+$, 502 $[M + Na]^+$. Anal. Calcd. for $C_{20}H_{19}Cl_2N_5O_5$: C, 50.01; H, 3.99; N, 14.58%. Found: C, 50.32; H, 4.09; N, 14.31%.

(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxylate (Vc2). Yield: 76%; M.p.: 102–104°C; IR (KBr): υ 3131, 3093, 2952, 1769, 1710, 1606, 1570, 1462, 1439, 1398, 1363, 1305, 1265, 1230, 1158, 1097, 1038 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.73 (s, 3H), 5.17 (s, 2H), 5.60 (s, 2H), 7.25–7.49 (m, 8H), 7.95 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.1, 54.1, 57.9, 109.0, 122.9, 127.6, 128.0, 128.8, 129.1, 130.8, 134.5, 135.3, 142.6, 158.3, 160.7, 176.0; Mass (ES): *m/z* 443 $[M + H]^+$, 465 $[M + Na]^+$. Anal. Calcd. for $C_{21}H_{16}Cl_2N_4O_3$: C, 56.90; H, 3.64; N, 12.64%. Found: C, 56.88; H, 3.81; N, 12.75%.

(1-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-1H-1,2,3-triazol-4-yl)methyl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxylate (Vc3). Yield: 81%; M.p.: 98–100°C; IR (KBr): υ 3126, 3084, 2954, 1770, 1731, 1709, 1612, 1560, 1430, 1399, 1365, 1296, 1165, 1108, 1040 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.52–1.60 (m, 2H), 1.78–1.83 (m, 2H), 2.74 (s, 3H), 3.61 (t, 2H, *J* = 6.0 Hz), 4.37 (t, 2H, *J* = 6.0 Hz), 5.14 (s, 2H), 7.47–7.52 (m, 3H), 7.80–7.86 (m, 4H), 7.92 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 12.7, 25.2, 27.6, 36.7, 49.3, 57.9, 108.3, 122.8, 125.2, 125.6, 130.4, 131.4, 133.7, 134.9, 158.3, 160.1, 167.0, 175.3; Mass (ES): *m/z* 554 $[M + H]^+$, 576 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{21}Cl_2N_5O_5$: C, 56.33; H, 3.82; N, 12.63%. Found: C, 56.58; H, 4.05; N, 12.63%.

(1-Butyl-1H-1,2,3-triazol-4yl)methyl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxylate (Vc4). Yield: 92%; IR (neat): υ 3142, 3084, 2962, 1726, 1608, 1562, 1433, 1302, 1248, 1195, 1195, 1111, 1049, 985 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.87 (t, 3H, *J* = 5.6 Hz), 1.19–1.24 (m, 2H), 1.76–1.81 (m, 2H), 2.79 (s, 3H), 4.33 (t, 2H, *J* = 5.6 Hz), 5.21 (s, 2H), 7.49–7.54 (m, 3H), 7.82 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.4, 19.6, 32.1, 49.9, 57.9, 109.1, 122.9, 127.6, 128.2, 130.8, 135.4, 142.1, 158.4, 160.8, 175.9; Mass (ES): *m/z* 409 $[M + H]^+$, 432 $[M + Na]^+$. Anal. Calcd. for $C_{18}H_{18}Cl_2N_4O_3$: C, 52.83; H, 4.43; N, 13.69%. Found: C, 52.83; H, 4.09; N, 13.86%.

(1-Allyl-1H-1,2,3-triazol-4-yl)methyl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4 carboxylate (Vc5). Yield: 90%; IR (neat): υ 3146, 3086, 2932, 1726, 1676, 1608, 1562, 1433, 1302, 1246, 1195, 1165, 1051 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.78 (s, 3H), 4.94 (d, 2H, *J* = 6.0 Hz), 5.25 (s, 2H), 5.30 (d, 1H, *J* = 15.0 Hz), 5.37 (d, 1H, *J* = 9.0 Hz), 5.80–6.01 (m, 1H), 7.27–7.38 (m, 3H), 8.00 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.4, 52.7, 57.9, 109.0, 120.4, 123.2, 127.7, 128.0, 131.0, 135.3, 142.4, 158.4, 160.8, 176.1; Mass (ES): *m/z* 393 $[M + H]^+$, 415 $[M + Na]^+$. Anal. Calcd. for $C_{17}H_{14}Cl_2N_4O_3$: C, 51.93; H, 3.59; N, 14.25%. Found: C, 51.74; H, 4.12; N, 14.10%.

(1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-caroboxylate (Vd1). Yield: 98%; M.p.: 141–143°C; IR (KBr): υ 3132, 3076, 2992, 1721, 1667, 1646, 1573, 1460, 1425, 1305, 1274, 1240, 1140, 1104, 1054 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.76 (s, 3H), 3.45 (t, 2H, *J* = 5.0 Hz), 3.55 (t, 2H, *J* = 5.0 Hz), 3.59 (t, 2H, *J* = 5.0 Hz), 3.64 (t, 2H, *J* = 5.0 Hz), 5.22 (s, 2H), 5.48 (s, 2H), 7.32 (t, 1H, *J* = 8.1 Hz), 7.42 (d, 1H, J =7.9 Hz), 7.52–7.60 (m, 1H), 7.90 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.1, 42.6, 45.8, 50.6, 57.8, 66.3, 109.4, 113.9, 117.6, 124.9, 125.1, 131.4, 135.1, 143.2, 155.3, 160.7, 162.0, 163.3, 175.9; Mass (ES): *m/z* 465 $[M + H]^+$, 487 $[M + Na]^+$. Anal. Calcd. for $C_{20}H_{20}ClFN_5O_5$: C, 51.79; H, 4.13; N, 15.10%. Found: C, 51.74; H, 4.13; N, 15.00%.

(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylate (Vd2). Yield: 84%; M. p.: 94–96°C; IR (KBr): υ 3141, 3088, 2983, 1717, 1613, 1598, 1571, 1461, 1427, 1310, 1250, 1225, 1140, 1105, 1053 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.74 (s, 3H), 5.17 (s, 2H), 5.59 (s, 2H), 7.18–7.44 (m, 8H), 8.01 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.2. 54.1, 57.8, 109.2, 113.7, 114.0, 123.1, 124.9, 128.0, 129.0, 131.2, 131.3, 134.3, 134.8, 142.4, 158.8, 160.7, 162.1, 176.1; Mass (ES): *m/z* 427 $[M + H]^+$, 449 $[M + Na]^+$. Anal. Calcd. for $C_{21}H_{17}ClFN_4O_3$: C, 59.09; H, 3.78; N, 13.13%. Found: C, 58.97; H, 3.67; N, 13.47%.

(1-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-1H-1,2,3-triazol-4-yl) methyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylate (Vd3). Yield: 87%; M.p.: 90–92°C; IR (KBr): υ 3133, 3094, 2955, 1770, 1732, 1613, 1573, 1457, 1440, 1399, 1365, 1297, 1249, 1149, 1093, 1040 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.55–1.60 (m, 2H), 1.78–1.83 (m, 2H), 2.74 (s, 3H), 3.61 (t, 2H, *J* = 6.2 Hz), 4.38 (t, 2H, *J* = 6.0 Hz), 5.17 (s, 2H), 7.27 (t, 1H, *J* = 7.9 Hz), 7.36 (d, 1H, *J* = 7.6 Hz), 7.53–7.58 (m, 1H), 7.79–7.84 (m, 4H), 7.96 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.1, 25.5, 27.4, 36.8, 49.5, 57.8, 109.4, 114.1, 117.4, 123.2, 125.0, 131.3, 132.0, 133.9, 135.1, 155.3, 160.8, 162.0, 168.1, 175.9; Mass (ES): *m/z* 538 $[M + H]^+$, 560 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{21}ClFN_5O_5$: C, 58.05; H, 3.93; N, 13.02%. Found: C, 58.45; H, 3.71, N, 13.02%.

(1-Butyl-1H-1,2,3-triazol-4yl)methyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylate (Vd4). Yield: 91%; IR (neat): υ 3144, 3084, 2961, 1728, 1680, 1614, 1577, 1454, 1304, 1251, 1186, 1101, 1049, 987 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.87 (t, 3H, *J* = 6.1 Hz), 1.19–1.23 (m, 2H), 1.75–1.80 (m, 2H), 2.76 (s, 3H), 4.34 (t, 2H, *J* = 6.1 Hz), 5.20 (s, 2H), 7.31 (t, 1H, *J* = 8.2 Hz), 7.41 (d, 1H, *J* = 7.2 Hz), 7.56–7.60 (m, 1H), 7.98 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.2, 19.4, 32.0, 49.8, 57.6, 109.2, 114.0, 117.0, 123.4, 124.8, 131.2, 134.8, 143.4, 155.7, 160.6, 162.3, 175.8; Mass (ES): *m/z* 393 $[M + H]^+$, 415 $[M + Na]^+$. Anal. Calcd. for $C_{18}H_{18}ClFN_4O_3$: C, 55.04; H, 4.62; N, 14.26%. Found: C, 54.86; H, 4.39, N, 14.29%.

(1-Allyl-1H-1,2,3-triazol-4-yl)methyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4 carboxylate (Vd5). Yield: 91%; IR (neat): υ 3142, 3084, 2932, 1726, 1674, 1612, 1574, 1498, 1456, 1388, 1304, 1251, 1143, 1099, 1051 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.74 (s, 3H), 5.03 (d, 2H, *J* = 6.4 Hz), 5.18 (d, 1H, *J* = 15.6 Hz), 5.20 (s, 2H), 5.29 (d, 1H, *J* = 9.1 Hz), 6.00–6.07 (m, 1H), 7.32 (t, 1H, *J* = 7.6 Hz), 7.40 (d, 1H, *J* = 7.8 Hz), 7.53–7.61 (m, 1H), 7.93 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 13.1, 52.4, 57.8, 109.3, 113.8, 117.5, 119.9, 123.1, 125.0, 131.2, 131.3, 135.0, 142.3, 155.2, 160.7, 162.4, 175.9; Mass (ES): *m/z* 377 $[M + H]^+$, 399 $[M + Na]^+$. Anal. Calcd. for $C_{17}H_{14}ClFN_4O_3$: C, 54.19; H, 3.75; N, 14.87%. Found: C, 53.90; H, 3.75; N, 14.40%.

Acknowledgment. The author (P.V.R.) is thankful to the Head, Department of Chemistry, and Director, Central Facility Building, Osmania University, Hyderabad, for providing the spectral facility.

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