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ORIGINAL PAPER

Synthesis and crystal structure of isoxazoline derivatives bearing a 1,2,4-triazole moiety

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Abstract Novel isoxazoline derivatives bearing a 1,2,4-triazole moiety have been synthesized starting from 2-bromo-1-phenylethanone. Chalcones were obtained by aldol condensation of 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone and 4-substituted benzaldehydes using piperidine as catalyst. Finally, 1,3-dipolar cycloaddition of the chalcones and a variety of aldoximes in the presence of chloramine-T afforded the title compounds. The structural identities of these compounds were confirmed on the basis of IR, NMR, mass spectral, and elemental analysis data and by X-ray analysis of a typical example of the new class of isoxazoline analogs.

Keywords Isoxazoline · 1,2,4-Triazole · Crystal structure · 1,3-Dipolar cycloaddition

Introduction

The 1,3-dipolar cycloaddition reaction is one of the most important classes of organic reaction and is a versatile preparative method for the synthesis of five-membered heterocycles involving the [3 + 2] principle [1, 2]. Cycloaddition of nitrile oxides to alkenes affords isoxazolines with a variety of biological activity and which have also been used as useful intermediates in organic synthesis [3]. Isoxazoline derivatives have been reported to have a variety of pharmacological activity, for example antimicrobial [4, 5], antidepressant [6], antifungal [7], phosphodiesterase inhibitor [8], and antibacterial [9] activity. Owing to their reputed chemotherapeutic applications, the design and synthesis of new and unique isoxazoline derivatives have enthused many organic chemists [10, 11]. In addition, 1,2,4-triazole is also an important structural motif in the design of new drugs [12]. Use of 1,2,4-triazole derivatives as promising antimicrobial, antibacterial, antihypertensive, and antifungal agents has been described and discussed in several publications [13–16]. Furthermore, some 1,2,4-triazole derivatives, for example fluconazole and itraconazole, are commercially available antifungal agents [17, 18]. Taking into consideration the important biological activity of azole derivatives and the combination principles of drug design, we herein report the synthesis of some new isoxazoline derivatives with a 1,2,4-triazole moiety. The synthetic route is shown in Scheme 1.

Results and discussion

The starting compounds 2-bromo-1-phenylethanone (**1**) and 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (**2**) required for the study were prepared in accordance with reported methods [19, 20]. The intermediate chalcones **3a**–**3d** were synthesized via the Claisen–Schmidt condensation between **2** and substituted benzaldehydes in the presence of piperidine. Finally, compounds **3a**–**3d** underwent 1,3-dipolar cycloaddition with benzaldoximes in the presence of chloramine-T in MeOH under reflux leading to the formation of cycloadducts **4a**–**4l**.

A variety of analytical techniques, including IR, NMR, mass spectrometry, elemental analysis, and X-ray crystallography, were used to confirm the structural identity of the final products. The target compounds were correctly analyzed for their molecular structure. Their infrared spectra

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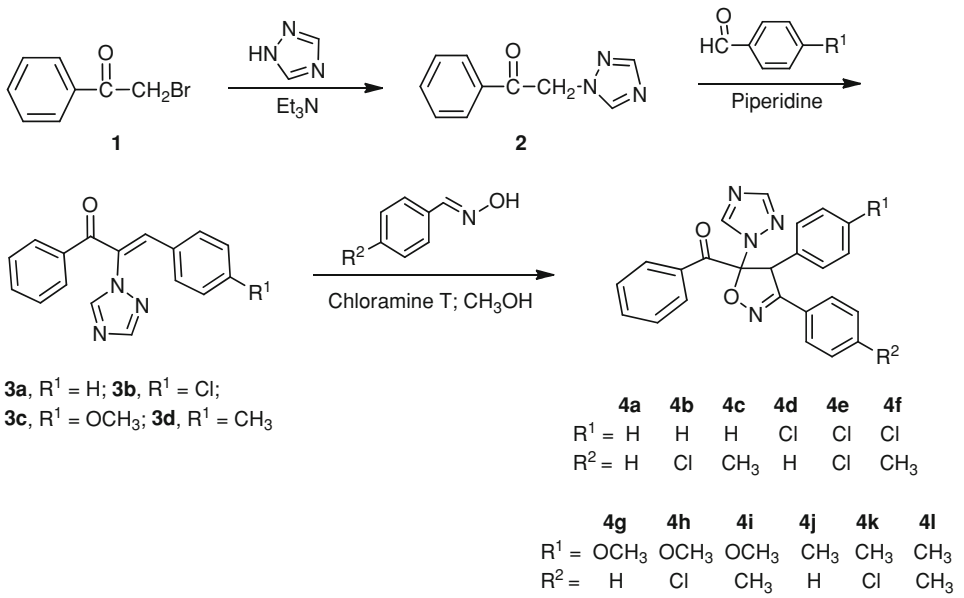
Scheme 1



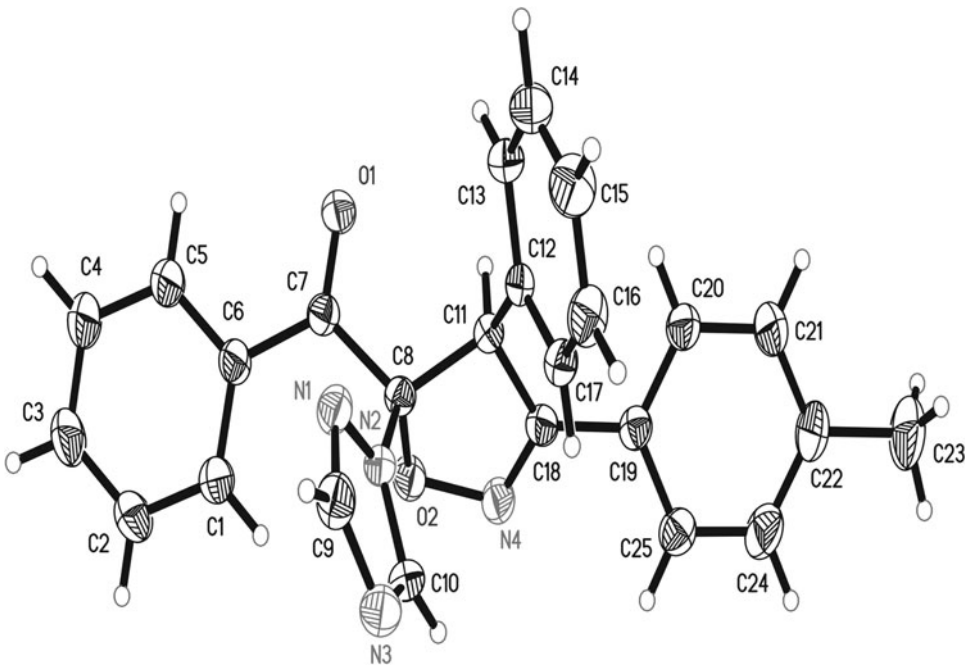


Fig. 1 Molecular structure of **4c**

contained strong bands at 1,693 and 1,632 cm^{-1} because of the presence of C=O and C=N double bonds. Their ^1H NMR spectra contained three singlets at 8.43–8.33, 8.04–7.90, and 6.47–6.32 ppm which could be attributed to the two triazole-H and the isoxazoline-H, respectively. In addition, the presence of a multiplet at 7.94–6.62 ppm was ascribed to the aromatic protons. In the mass spectra, molecular ion peaks of all target compounds were obtained from EI-MS, but the abundance of molecular ion peaks was very weak.

The identities of the title compounds were further confirmed by single-crystal X-ray crystallographic studies. The crystal structure of compound **4c** is shown in Fig. 1. The crystal data and structure refinement are shown in Table 1. Selected bond lengths and angles are listed in Table 2.

There are two five-membered rings, the isoxazoline ring (plane 1) and the 1,2,4-triazole ring (plane 2) in the molecular structure. All atoms are nearly coplanar, with existing mean deviations of 0.0931 Å and 0.0038 Å for plane 1 and plane 2, respectively. The isoxazoline ring is

Table 1 Crystal data and structure refinement for compound **4c**

Empirical formula	$C_{25}H_{20}N_4O_2$
Formula weight	408.45
Temperature/K	293(2)
Wavelength/Å	0.71073
Crystal system	Triclinic
Space group	P-1
a/Å	7.9603(7)
b/Å	11.6857(9)
c/Å	12.1472(9)
α/°	103.256(2)
β/°	100.117(2)
γ/°	99.210(3)
V/Å^3	1,058.82(15)
Z	2
D_{calc}/g cm^{-3}	1.281
Crystal size/mm	0.45 × 0.22 × 0.16
θ range/°	3.34–27.48
μ/mm^{-1}	0.084
Reflections collected	10,514
Data/restraints/parameters	4816/0/281
Final R indices [$I>2\sigma(I)$]	$R_1 = 0.0418$
	$\omega R_2 = 0.1107$
R indices (all data)	$R_1 = 0.0916$
	$\omega R_2 = 0.1598$

Table 2 Selected bond lengths/Å and angles/° of compound **4c**

O(1)-C(7)	1.212(2)	C(8)-O(2)-N(4)	108.38(13)
O(2)-C(8)	1.425(2)	C(9)-N(1)-N(2)	101.69(16)
O(2)-N(4)	1.449(2)	C(10)-N(2)-N(1)	109.69(16)
N(1)-C(9)	1.313(3)	C(10)-N(3)-C(9)	102.43(17)
N(3)-C(10)	1.313(3)	C(18)-N(4)-O(2)	108.12(15)
N(4)-C(18)	1.282(2)	C(6)-C(7)-C(8)	120.80(15)
C(11)-C(18)	1.503(3)	O(2)-C(8)-C(11)	104.53(14)
C(8)-C(11)	1.538(2)	N(4)-C(18)-C(11)	113.98(16)

characterized by the torsion angles (enumerated clockwise and starting with O(2)-N(4)-C(18)-C(11)): −3.4(2)°, 16.4(2)°, −22.37(17)°, −22.41(17)°, −12.68(19)°, and it adopts an envelope conformation with atom C(8) deviating from the plane defined by O(2), N(4), C(18), C(11) of 0.1422 Å. In addition, plane 1 and plane 2 are almost perpendicular to each other with a dihedral angle of 96°. The distances of the plane 1 centroid from plane 2 and the phenyl ring (C(12)-C(17)) are 3.282 Å and 3.986 Å, respectively.

In conclusion, we have obtained a series of 3,4-bis(4-substituted phenyl)-5-(1*H*-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone derivatives **4a**–**4l** by 1,3-dipolar cycloaddition reaction. The molecular conformation of the title compounds was confirmed by X-ray crystallography.

Experimental

Reactions were monitored by TLC. Melting points were determined by use of a Mettler FP-5 melting point apparatus. Elemental analysis was performed with a Perkin–Elmer 2400 elemental analyzer. IR spectra were recorded as KBr pellets on a Bruker Equinox 55 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker 400 MHz spectrometer using TMS as internal reference. Mass spectra were acquired with an Agilent 5975 instrument (EI, 70 eV). X-ray diffraction data were collected on a Hitachi F-4500 R-Axis Spider diffractometer. The benzaldoximes were synthesized according to a reported procedure [21].

General procedure for preparation of 1-phenyl-3-(4-substituted phenyl)-2-(1H-1,2,4-triazol-1-yl)-propen-1-ones ***3a–3d***

The syntheses were carried out according to a known procedure [22]. 1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (**2**, 3.74 g, 0.02 mol) and the appropriate benzaldehyde (0.02 mol) were heated under reflux in the presence of 1 cm^3 piperidine for 7 h under a nitrogen atmosphere with 80 cm^3 toluene in an apparatus equipped with a water separator. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with ethyl acetate–petroleum ether 1:1 as eluent to afford the corresponding chalcones **3a**–**3d**.

1,3-Diphenyl-2-(1H-1,2,4-triazol-1-yl)propen-1-one (**3a**)
Colorless crystals, yield 76%; m.p.: 129.8–130.6 °C (125–127 °C [23]).

3-(4-Chlorophenyl)-1-phenyl-2-(1H-1,2,4-triazol-1-yl)-propen-1-one (**3b**)
Colorless crystals, yield 81%; m.p.: 121.3–122.7 °C (115–116 °C [23]).

3-(4-Methoxyphenyl)-1-phenyl-2-(1H-1,2,4-triazol-1-yl)propen-1-one (**3c**, $C_{18}H_{15}N_3O_2$)
Colorless crystals, yield 75%; m.p.: 80.5–81.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$, 8.15 (2s, 2H, triazole-H), 7.84 (s, 1H, C=CH), 7.81–6.91 (m, 9H, Ar–H), 3.82 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.15$, 152.93, 145.27, 142.79, 142.63, 136.84, 132.68, 131.45, 130.26, 129.86, 129.28, 128.68, 128.07, 55.51 ppm; IR

(KBr): $\bar{\nu}$ = 1,643, 1,492, 1,446, 1,414 cm^{-1}; MS: *m/z* = 305 (M^+).

3-(4-Methylphenyl)-1-phenyl-2-(1H-1,2,4-triazol-1-yl)-propen-1-one (**3d**, $C_{18}H_{15}N_3O$)
Colorless crystals, yield 77%; m.p.: 112.6–114.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21, 8.15 (2s, 2H, triazole-H), 7.84 (s, 1H, C=CH), 7.82–6.91 (m, 9H, Ar–H), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.05, 152.75, 145.16, 142.56, 142.52, 136.59, 132.91, 131.51, 130.39, 129.95, 129.38, 128.72, 128.11, 21.64 ppm; IR (KBr): $\bar{\nu}$ = 1,641, 1,489, 1,442, 1,412 cm^{-1}; MS: *m/z* = 289 (M^+).

*General procedure for preparation of [3,4-bis-(4-substituted phenyl)-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanones **4a–4l***

To a solution of chalcone **3** (1 mmol) in 50 cm^3 methanol the appropriate benzaldoxime (2 mmol) and 0.562 g chloramine-T (2 mmol) were added. The reaction mixture was kept under reflux for 7 h. After the mixture had cooled to room temperature, the separated solid was isolated by filtration and the filter liquor was evaporated under reduced pressure. The resulting crude product was purified by column chromatography with ethyl acetate–petroleum ether 4:1 as eluent and the solid product obtained was recrystallized from petroleum ether–acetone 1:15 to afford the desired products **4a**-**4l**. White single crystals of compound **4c** were obtained from petroleum ether and acetone after slow evaporation at room temperature.

[3,4-Diphenyl-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydro-isoxazol-5-yl]phenylmethanone (**4a**, $C_{24}H_{18}N_4O_2$)
Colorless crystals, yield 38%; m.p.: 171–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41, 7.93 (2s, 2H, triazole-H), 7.11–7.91 (m, 15H, Ar–H), 6.47 (s, 1H, isoxazoline-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.83, 151.56, 143.65, 139.04, 134.16, 132.49, 131.23, 131.09, 130.03, 129.76, 128.88, 128.78, 128.72, 127.96, 126.86, 126.46, 58.81, 21.60 ppm; IR (KBr): $\bar{\nu}$ = 1,690, 1,636 cm^{-1}; MS: *m/z* = 394 (M^+).

[3-(4-Chlorophenyl)-4-phenyl-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone
(**4b**, $C_{24}H_{17}ClN_4O_2$)
Colorless crystals, yield 38%; m.p.: 191–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37, 7.90 (2s, 2H, triazole-H), 6.78–7.59 (m, 14H, Ar–H), 6.46 (s, 1H, isoxazoline-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.76, 151.48, 143.56, 139.10, 134.09, 132.41, 131.16, 131.06, 130.08, 129.66, 128.73, 128.68, 128.59, 127.88, 126.75, 126.39, 58.78, 21.58 ppm; IR (KBr): $\bar{\nu}$ = 1,691, 1,632 cm^{-1}; MS: *m/z* = 428 (M^+).

[3-(4-Methylphenyl)-4-phenyl-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone
(**4c**, $C_{25}H_{20}N_4O_2$)
Colorless crystals, yield 42%; m.p.: 204–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43, 7.93 (2s, 2H, triazole-H), 7.09–7.55 (m, 14H, Ar–H), 6.45 (s, 1H, isoxazoline-H), 2.34 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.81, 151.49, 143.58, 138.98, 134.08, 132.39, 131.16, 131.02, 130.10, 129.68, 128.79, 128.71, 128.68, 127.89, 126.79, 126.38, 58.83, 21.71, 21.64 ppm; IR (KBr): $\bar{\nu}$ = 1,693, 1,632 cm^{-1}; MS: *m/z* = 408 (M^+).

[4-(4-Chlorophenyl)-3-phenyl-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone
(**4d**, $C_{24}H_{17}ClN_4O_2$)
Colorless crystals, yield 45%; m.p.: 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38, 7.96 (2s, 2H, triazole-H), 6.93–7.89 (m, 14H, Ar–H), 6.40 (s, 1H, isoxazoline-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.69, 152.24, 143.51, 141.98, 134.71, 134.24, 132.43, 131.38, 130.35, 130.01, 129.67, 129.00, 128.97, 128.74, 127.92, 126.59, 58.33, 21.47 ppm; IR (KBr): $\bar{\nu}$ = 1,695, 1,630 cm^{-1}; MS: *m/z* = 428 (M^+).

[3,4-Bis(4-chlorophenyl)-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone
(**4e**, $C_{24}H_{16}Cl_2N_4O_2$)
Colorless crystals, yield 42%; m.p.: 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36, 7.94 (2s, 2H, triazole-H), 6.88–7.92 (m, 13H, Ar–H), 6.38 (s, 1H, isoxazoline-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.78, 152.16, 143.23, 139.37, 134.12, 132.18, 131.33, 131.00, 129.51, 129.25, 128.71, 128.65, 128.34, 127.89, 126.26, 124.25, 55.99, 21.62 ppm; IR (KBr): $\bar{\nu}$ = 1,696, 1,629 cm^{-1}; MS: *m/z* = 462 (M^+).

[4-(4-Chlorophenyl)-3-(4-methylphenyl)-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone
(**4f**, $C_{25}H_{19}ClN_4O_2$)
Colorless crystals, yield 48%; m.p.: 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39, 7.91 (2s, 2H, triazole-H), 6.86–7.58 (m, 13H, Ar–H), 6.36 (s, 1H, isoxazoline-H), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.68, 152.19, 143.38, 141.79, 134.16, 132.35, 131.24, 130.21, 130.04, 129.59, 129.08, 128.88, 128.64, 127.77, 126.41, 57.89, 21.64, 21.53 ppm; IR (KBr): $\bar{\nu}$ = 1,698, 1,629 cm^{-1}; MS: *m/z* = 442 (M^+).

[4-(4-Methoxyphenyl)-3-phenyl-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone
(**4g**, $C_{25}H_{20}N_4O_3$)
Colorless crystals, yield 35%; m.p.: 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34, 7.95 (2s, 2H, triazole-H), 6.77–7.94 (m, 14H, Ar–H), 6.35 (s, 1H, isoxazoline-H), 3.78 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 186.79, 151.45, 143.44, 138.97, 133.99, 132.41, 131.15, 131.00, 130.09, 129.58, 128.68, 128.64, 128.59, 127.87, 126.79, 126.31, 57.77, 55.43, 21.39 ppm; IR (KBr): $\bar{\nu}$ = 1,692, 1,633 cm^{-1}; MS: m/z = 424 (M^+).

[3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone (**4h**, $C_{25}H_{19}ClN_4O_3$)
Colorless crystals, yield 37%; m.p.: 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33, 7.92 (2s, 2H, triazole-H), 7.17–7.59 (m, 13H, Ar–H), 6.33 (s, 1H, isoxazoline-H), 3.79 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.71, 151.78, 143.56, 139.01, 133.88, 132.53, 131.26, 131.11, 130.22, 129.49, 128.53, 128.51, 128.44, 127.72, 126.64, 126.18, 57.89, 55.32, 21.45 ppm; IR (KBr): $\bar{\nu}$ = 1,696, 1,632 cm^{-1}; MS: m/z = 458 (M^+).

[4-(4-Methoxyphenyl)-3-(4-methylphenyl)-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone (**4i**, $C_{26}H_{22}N_4O_3$)
Colorless crystals, yield 31%; m.p.: 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36, 7.91 (2s, 2H, triazole-H), 7.10–7.94 (m, 13H, Ar–H), 6.32 (s, 1H, isoxazoline-H), 3.78 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.86, 151.44, 143.69, 139.83, 138.97, 134.11, 132.36, 131.07, 131.00, 130.06, 129.77, 128.76, 128.67, 127.91, 126.78, 126.47, 58.76, 55.47, 21.72, 21.61 ppm; IR (KBr): $\bar{\nu}$ = 1,697, 1,633 cm^{-1}; MS: m/z = 438 (M^+).

[4-(4-Methylphenyl)-3-phenyl-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone (**4j**, $C_{25}H_{20}N_4O_2$)
Colorless crystals, yield 36%; m.p.: 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37, 7.97 (2s, 2H, triazole-H), 7.28–7.93 (m, 14H, Ar–H), 6.39 (s, 1H, isoxazoline-H), 2.19 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.82, 151.46, 143.63, 138.97, 134.01, 132.96, 132.36, 131.08, 129.89, 129.68, 128.78, 128.69, 128.58, 127.87, 126.74, 126.31, 58.74, 21.71, 21.61 ppm; IR (KBr): $\bar{\nu}$ = 1,692, 1,632 cm^{-1}; MS: m/z = 408 (M^+).

[3-(4-Chlorophenyl)-4-(4-methylphenyl)-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone (**4k**, $C_{25}H_{19}ClN_4O_2$)
Colorless crystals, yield 32%; m.p.: 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35, 7.90 (2s, 2H, triazole-H), 7.26–7.56 (m, 13H, Ar–H), 6.36 (s, 1H, isoxazoline-H), 2.20 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.75, 151.39, 143.51, 139.97, 138.88, 132.74, 132.19, 131.02, 129.78, 129.52, 128.63, 128.52, 128.39, 127.68, 126.59, 126.18, 58.66, 21.67, 21.60 ppm; IR (KBr): $\bar{\nu}$ = 1,694, 1,631 cm^{-1}; MS: m/z = 442 (M^+).

[3,4-Bis(4-methylphenyl)-5-(1H-1,2,4-triazol-1-yl)-4,5-dihydroisoxazol-5-yl]phenylmethanone (**4l**, $C_{26}H_{22}N_4O_2$)
Colorless crystals, yield 39%; m.p.: 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38, 8.04 (2s, 2H, triazole-H), 6.62–7.90 (m, 13H, Ar–H), 6.34 (s, 1H, isoxazoline-H), 2.31 (s, 3H, CH_3), 2.18 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.81, 152.18, 143.56, 139.07, 134.16, 132.37, 131.09, 130.11, 129.91, 129.68, 128.74, 128.66, 128.59, 127.74, 126.68, 126.37, 58.79, 21.69, 21.64, 21.58 ppm; IR (KBr): $\bar{\nu}$ = 1,695, 1,630 cm^{-1}; MS: m/z = 422 (M^+).

X-Ray crystallography

CCDC-800915 contains the supplementary crystallographic data for compound **4c**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via e-mail: deposit@ccdc.cam.ac.uk.

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