Simple and highly efficient synthesis of 3,5-disubstituted isoxazoles using Cu/graphene/clay nanohybrid as a new heterogeneous nano catalyst

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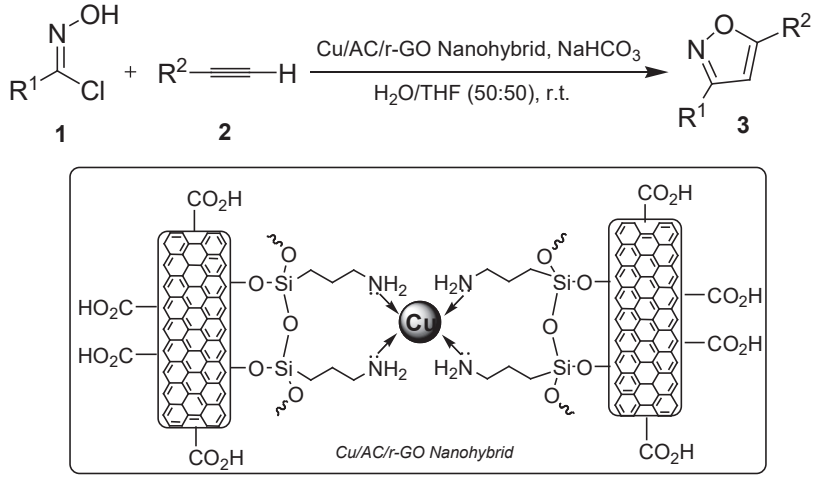
A facile and convenient protocol for 'click' cycloaddition of structurally diverse alkynes with *in situ* generated nitrile oxides catalysed by Cu/aminoclay/reduced graphene oxide nanohybrid (Cu/AC/r-GO nanohybrid) as a highly efficient heterogeneous nano-catalyst is described. In this method, Cu/AC/r-GO nanohybrid catalyses the 1,3-dipolar cycloaddition of alkynes and nitrile oxides in the presence of $NaHCO_3$ in H_2O/THF (50:50, V/V) to afford the corresponding 3,5-disubstituted isoxazoles. The Cu/AC/r-GO nanohybrid is a low cost, non-hygroscopic, chemically and thermally stable catalyst that can be reused for many consecutive reaction runs without significant loss in its reactivity.

Keywords: alkyne, Cu/AC/r-GO nanohybrid, heterogeneous nano-catalyst, isoxazole, nitrile oxide

Isoxazoles are an important class of heterocyclic compounds with a broad range of applications in medicinal and organic chemistry.[1,2] Isoxazole derivatives display a wide spectrum of biological activities.[3] Several isoxazole derivatives such as cloxacillin, isocarboxazid, dicloxacillin, glisoxepide, leflunomide, oxacillin, and valdecoxib are well-known drugs exhibiting different chemotherapeutic activities.[3] As a result of the easy cleavage of the N–O bond in isoxazoles, they play a significant role in organic synthesis as masked 1,3-dicarbonyl equivalents.[4]

There are many synthetic approaches to isoxazoles.[1,4,5] The most common strategies to access 3,5-disubstituted isoxazoles involve oxidation of 2-isoxazolines, cyclisation of alkynyl oxime ethers, condensation of hydroxylamine with α,β-unsaturated carbonyl compounds or 1,3-dicarbonyl compounds, and cyclisation of α,β-unsaturated oximes or β-keto oximes.[1,4,5] The 1,3-dipolar cycloaddition reaction between alkyne and nitrile oxide is a direct and extensively used approach to afford numerous isoxazole derivatives.[1,4-7] In this protocol, the instability of the nitrile oxide leads to dimerisation or the nucleophilic trapping of the nitrile oxide; however, it can be easily minimised by the *in situ* generation of the nitrile oxide. The nitrile oxides can be efficiently prepared *in situ* via the oxidation of aldoximes,[8-12] the dehydrohalogenation of hydroximyl chlorides,[13,14] and the dehydration of nitroalkanes.[15] The non-catalysed thermal cycloaddition reactions between alkynes and nitrile oxides can lead to mixtures of 3,5- and 3,4-regioisomers. Recently, it has become established that the copper and the *N*-heterocyclic carbene-mediated cycloaddition of alkynes with nitrile oxides promotes the formation of 3,5-disubstituted isoxazoles, while ruthenium catalysts afford 3,4-disubstituted isoxazoles.[1,4,5] To prepare 3,5-disubstituted isoxazoles, the presence of active copper(I) as the catalytic species like CuI [16] is essential. Moreover, this active species can be prepared *in situ* by reduction of a copper(II) salt, or a copper(II)/copper(0) combination.[1,4]

It is well established that the application of a heterogeneous catalyst is superior to a homogeneous catalyst from both economic and environmental perspectives. The immobilisation



3a: R^1= 4-Me_2N-C_6H_4; R^2= phenyl
3b: R^1= 4-EtO_2C-C_6H_4; R^2= phenyl
3c: R^1= 3-Br-C_6H_4; R^2= phenyl
3d: R^1= phenyl; R^2= phenyl
3e: R^1= phenyl; R^2= 3-pyridinyl
3f: R^1= 2,6-Cl_2-C_6H_3; R^2= phenyl
3g: R^1= 4-Cl-C_6H_4; R^2= $C(Me)_2OH$
3h: R^1= 4-NO_2-C_6H_4; R^2= 4-MeO-C_6H_4-CH_2O
3i: R^1= 2-furanyl; R^2= 4-MeC(=O)-C_6H_4-CH_2O
3j: R^1= phenyl; R^2= *N*7-theophyllinyl-CH_2
3k: R^1=4-MeO-C_6H_4; R^2= *N*7-theophyllinyl-CH_2
3l: R^1= 4-Cl-C_6H_4; R^2= *N*-saccharinyl-CH_2
3m: R^1= *n*-C_5H_{11}; R^2= *N*-phthalimidyl-CH_2
3n: R^1= *n*-C_4H_9; R^2= *n*-C_5H_{11}
3o: R^1= cyclohexyl; R^2= phenyl

Scheme 1 Cu/AC/r-GO nanohybrid-catalysed synthesis of 3,5-disubstituted isoxazoles.

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of active catalysts on the heterogeneous supports mostly leads to mild reaction conditions, thermal stability of the catalyst, selectivity, the minimisation of undesirable chemical wastes, ease of handling, simple reaction workup, reusability and recyclability of the catalyst by simple flash filtration.[17] The successful application of heterogeneous systems in various organic transformations is well documented. There have also been a few reports on the application of heterogeneous catalysts for 1,3-dipolar cycloadditions of nitrile oxides with alkynes.[18-20] There is a great need for the development of efficient heterogeneous catalytic systems for catalysing 3,5-disubstituted isoxazoles synthesis.

Organic–inorganic hybrid catalysts are well-known heterogeneous catalysts in which an organic spacer is covalently anchored to the surface of inorganic supports.[21] Among solid supports, those which are covalently bonded with amine residues have received particular attention due to their capability to chelate with metals especially copper species. This chelation not only promotes the catalytic activity of copper but also largely prevents desorption of the copper species from the surface of the support and leaching during the course of the reaction. In this context, graphene oxide (GO) has proved to be an ideal candidate due to the presence of different functional groups which allows the possibility of GO grafting with many organic materials. After functionalising or modifying GO with the desired molecules, the modified GO is reduced to graphene (r-GO) to retrieve the exclusive properties characteristic of graphene.[22]

Recently, we have reported the synthesis, characterisation, and application of a Cu/aminoclay/reduced graphene oxide nanohybrid (Cu/AC/r-GO nanohybrid) as a novel and highly efficient heterogeneous nano-catalyst for the synthesis of 1,2,3-triazolyl carboacyclic nucleosides via the Cu(I)-catalysed 'click' cycloaddition of organic azides with terminal alkynes.[23] We now report the application of a Cu/AC/r-GO nanohybrid for synthesis of 3,5-disubstituted isoxazoles through 1,3-dipolar cycloaddition of alkynes with *in situ* generated nitrile oxides from hydroximyl chlorides using $NaHCO_3$ in H_2O/THF (50:50, V/V) at room temperature (Scheme 1).

Results and discussion

After preparing the catalyst,[23] we then evaluated the catalytic potency of the Cu/AC/r-GO nanohybrid in 1,3-dipolar cycloadditions of nitrile oxides from hydroximyl chlorides (**1**) with alkynes (**2**) to afford the corresponding 3,5-disubstituted isoxazoles (**3**). To optimise the reaction conditions, the cycloaddition reaction of *N*-hydroxybenzimidoyl chloride and phenyl acetylene was studied bearing neither electron-donating nor electron-withdrawing functional groups. Thus, the influence of different reaction parameters including solvent type, base and catalyst amount were examined on the model reaction at room temperature to afford 3,5-diphenylisoxazole (**3d**). The results are depicted in Table 1.

The choice of an appropriate solvent is of great importance for the efficient progress of the reaction. There is growing interest in the use of water as the reaction medium in organic transformations since it is cheap, clean, and a universal solvent which has extraordinary physical properties and enviroeconomic benefits. Thus, the cycloaddition reaction of the model substrates was achieved in pure water at room temperature. However, these conditions led to the synthesis of the corresponding 3,5-diphenylisoxazole only in 18% yield

Table 1 Effect of various reaction parameters on the model reaction at room temperature

Entry	Solvent [a]	Base	Catalyst/mol%	Time/h	Yield/%[e]
1	H_2O	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	24	18
2	H_2O [b]	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	12	45
3	H_2O/Dioxane	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	2	88
4	H_2O/Acetone	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	3	85
5	H_2O/MeCN	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	5	76
6	H_2O/DMSO	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	6	68
7	H_2O/DMF	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	6	63
8	H_2O/THF	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	1	94
9	THF	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.008)	8	37
10	H_2O/THF	None	Cu/AC/r-GO nanohybrid (0.008)	48	NR [f]
11	H_2O/THF	Et_3N	Cu/AC/r-GO nanohybrid (0.008)	3	87
12	H_2O/THF	DBU	Cu/AC/r-GO nanohybrid (0.008)	3	85
13	H_2O/THF	NaH	Cu/AC/r-GO nanohybrid (0.008)	6	57
14	H_2O/THF	DMAP	Cu/AC/r-GO nanohybrid (0.008)	5	68
15	H_2O/THF	DABCO	Cu/AC/r-GO nanohybrid (0.008)	6	71
16	H_2O/THF	MgO	Cu/AC/r-GO nanohybrid (0.008)	9	24
17	H_2O/THF	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.002)	7	53
18	H_2O/THF	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.004)	5	67
19	H_2O/THF	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.006)	1	83
20	H_2O/THF	$NaHCO_3$	Cu/AC/r-GO nanohybrid (0.01)	1	96
21	H_2O/THF	$NaHCO_3$	CuI (0.008)	6	81
22	H_2O/THF	$NaHCO_3$	$CuSO_4.5H_2O$ (.008) [c]	7	80
23	H_2O/THF	$NaHCO_3$	$Cu(OAC)_2$ (0.008) [c]	4	87
24	H_2O/THF	$NaHCO_3$	CDSCS (0.008) [d]	3	90

[a] Except for entries 1, 2 and 9 a mixture of 50:50 (v/v) solvents were used.

[b] The reaction was carried out under reflux conditions.

[c] The reaction was carried out in the presence of sodium ascorbate.

[d] Copper-doped silica cuprous sulfate.[19]

[e] Isolated yield.

[f] No reaction.

after 24 h (Table 1, entry 1). To improve the reaction yield, the model reaction was carried out in refluxing pure water which affords the desired isoxazole **3d** in 45% yield after 12 h. This moderate yield can be attributed to the lack solubility of the starting materials in pure water (Table 1, entry 2). Thus, the effects of a water mixture with several organic solvents in 50:50 (V/V) ratios was examined. As the data in Table 1 demonstrate, employing a solution of H_2O/THF (50:50, V/V) afforded the corresponding isoxazole **3d** in high yield and short reaction time in comparison with the other tested solvents (Table 1, entry 8). Consequently, it was selected as the most appropriate solvent for all subsequent reactions. The combination of water with dioxane or acetone led to the corresponding isoxazole **3d** in reasonable yield; however, longer times were needed for completion of the reaction (Table 1, entries 3 and 4). Additionally, the use of water combined with other examined solvents, afforded moderate yields of product (Table 1, entries 5–7). Moreover, only 37% of 3,5-diphenylisoxazole was obtained when pure THF was used as the reaction media (Table 1, entry 9).

To have efficient *in situ* generation of nitrile oxides from hydroximyl chlorides, the choice of an appropriate base is critical. Thus, the effect of various organic and inorganic bases was evaluated on the model reaction. As shown in Table 1, attempts to carry out the model reaction in the absence of base failed even after prolonging the reaction time up to 48 h. (entry 10). As is clear from Table 1, $NaHCO_3$ proved to be the most appropriate base for 1,3-dipolar cycloaddition reactions of the model substrates (entry 8). While Et_3N and DBU provided satisfactory results, they were not as effective as $NaHCO_3$ to achieve the model reaction (Table 1, entries 11 and 12). Other examined bases afforded low to moderate yields of the corresponding isoxazole **3d** (Table 1, entries 13–16).

The results obtained by inductively coupled plasma (ICP) analysis have revealed the presence of 0.013 g of active copper catalyst in each gram of Cu/AC/r-GO nanohybrid (0.02 mol%). In a series of other experiments, different amounts of catalyst were employed for cycloaddition of model substrates. As the data in Table 1 indicate, using 0.008 mol% of catalyst afforded the best results (entry 8). Lower yields of isoxazole were obtained when the amount of the catalyst decreased to less than 0.008 mol % (Table 1, entries 17–19). Using an excess amount of catalyst gave no improvement in the reaction yield (Table 1, entry 20).

Table 2 Cu/AC/r-GO nanohybrid-catalysed synthesis of 3,5-disubstituted isoxazoles

Entry [ref.]	Product [a]	Time/h	Yield/%[b]
1	**3a**	1	84
2	**3b**	1	92
3[18]	**3c**	1.3	90
4[7]	**3d**	1	94
5[24]	**3e**	1.1	92
6[18]	**3f**	1.7	83
7	**3g**	1	91
8[7]	**3h**	1.1	95
9[7]	**3i**	1.4	84
10[19]	**3j**	2	86
11[19]	**3k**	2	81
12	**3l**	2	85
13	**3m**	2	83
14[7]	**3n**	1.5	81
15[7]	**3o**	1.6	87

[a]All products were characterised by ^{1}H- and ^{13}C NMR, IR, CHN, and MS analysis.
[b]Isolated yield.

To evaluate the catalytic potency of Cu/AC/r-GO nanohybrid, the cycloaddition reaction of *N*-hydroxybenzimidoyl chloride and phenyl acetylene was investigated using several reported copper catalysts under the optimised condition. As the results in Table 1 indicate, using Cu/AC/r-GO nanohybrid (entry 8) increased the reaction rate and yield in comparison with other examined catalysts. The use of the other copper catalysts also led to the preparation of 3,5-diphenylisoxazole in satisfactory yields after prolonging the reaction time.

The generality and versatility of this protocol was screened by application to structurally diverse alkynes and hydroximyl chlorides (Table 2). Cu/AC/r-GO nanohybrid proved to be an appropriate nano catalyst that efficiently catalyses the 1,3-dipolar cycloaddition reaction of alkynes-nitrile oxides with excellent regioselectivity. As shown in Table 2, both aromatic and/or aliphatic alkynes and hydroximyl chlorides bearing different electron-rich and/or electron-deficient functional groups underwent the cycloaddition reaction to produce the corresponding 3,5-disubstituted isoxazoles in good to excellent yields. The formation of the Cu(I)-acetylide species is an important step in the Cu(I)-catalysed cycloaddition reaction of alkynes with nitrile oxides; thus, disubstituted alkynes do not participate in this reaction as shown in the attempted cycloaddition reaction of diphenyl acetylene with *N*-hydroxybenzimidoyl chloride. The structure of all synthesised compounds was confirmed by ^{1}H and ^{13}C NMR, elemental analysis, mass and IR spectroscopy methods.

To confirm the recoverability and the heterogeneous nature of the Cu/AC/r-GO nanohybrid, the catalyst was reused for several consecutive runs and through each run, no fresh catalyst was added. In this connection, the model reaction was efficiently performed after 1 h in the presence of 0.008 mol% of Cu/AC/r-GO nanohybrid in the first run. For the reusability study, the catalyst was recycled from the reaction mixture through a sintered glass funnel by vacuum filtration. The catalyst was then washed successively with distilled water (20 mL) and then anhydrous acetone (20 mL) and dried in a vacuum oven at 80 °C for 1 h which was tested for five consecutive runs (Fig. 1). Figure 1 clearly shows that Cu/AC/r-GO nanohybrid is a reusable and recyclable catalyst which undergoes negligible desorption of the copper species from the AC/r-GO matrix. According to the ICP analysis, the amount of leached copper from Cu/AC/r-GO nanohybrid is 0.008% after five consecutive runs and this is rationalised as due to the powerful binding present between the copper species and the aminoclay (AC) group on the surface of the r-GO.

In conclusion, we have described the application of a Cu/AC/r-GO nanohybrid as a highly efficient heterogeneous nano-catalyst for regioselective synthesis of 3,5-disubstituted isoxazoles. The 1,3-dipolar cycloaddition reaction of various structurally diverse alkynes and *in situ* generated nitrile oxides using a Cu/AC/r-GO nanohybrid in the presence of $NaHCO_3$ in

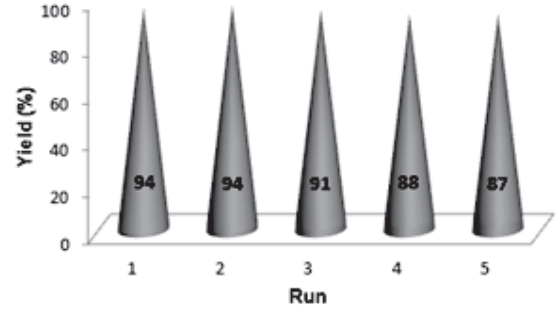

Fig. 1 The reusability of Cu/AC/r-GO nanohybrid.

H_2O/THF (50:50, V/V) at room temperature affords the desired isoxazoles in reasonable yields. The Cu/AC/r-GO nanohybrid proved to be a stable, non-hygroscopic, easy to prepare, inexpensive, and environmentally benign heterogeneous nano-catalyst that can be recycled for several reaction runs without significant loss in its reactivity. The presence of amine groups on the surface of the catalyst provides a ligand-free and leaching-free catalyst which will be highly useful and economical for industrial applications.

Experimental

All chemical reagents were purchased from either Fluka or Merck. Solvents were purified by standard procedures, and stored over 3Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica-gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). Melting points were measured using an Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. ^{1}H and ^{13}C NMR spectrum was recorded on Bruker Avance-DPX-250 spectrometer operating at 250/62.5 MHz, respectively. Chemical shifts are given in δ relative to TMS as an internal standard, coupling constants *J* are given in Hz. Abbreviations used for ^{1}H NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. GC-MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (*m/z*; rel.%). Elemental analyses were performed on a PerkinElmer 240-B micro-analyser. Halogen atoms in compounds were analysed using the oxygen-flask combustion method (Schoniger application) and subsequent potentiometric titration by a 835 Titrando Metrohm Titro processor instrument and ion chromatography analysis using a Dionex IC system.

Synthesis of 3,5-disubstituted isoxazoles using Cu/AC/r-GO nanohybrid; general procedure

In a round-bottom flask (50 mL), a mixture of Cu/AC/r-GO nanohybrid (0.4 g, 0.008 mol %), appropriate hydroximyl chloride (0.01 mol), alkyne (0.012 mol), and $NaHCO_3$ (0.012 mol) were stirred in H_2O/THF (50:50, V/V) for the appropriate times (Table 2). After completion of the reaction, the reaction mixture was vacuum-filtered using a sintered-glass funnel and the residue was washed with acetone (2 × 10 mL). The filtrate was then evaporated under vacuum to remove the solvent. The remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2 × 100 mL). Afterwards, the organic layer was dried over anhydrous sodium sulfate and evaporated. The crude product was purified by short column chromatography on silica gel eluting with *n*-hexane:EtOAc.

Recycling the catalyst

After completion of the reaction, the catalyst was vacuum-filtered from the reaction mixture using a sintered glass funnel followed by successive washing with distilled water (20 mL) and anhydrous acetone (20 mL). The catalyst was then kept in a vacuum oven at 80 °C for 1 h and stored in a sealed vessel in a refrigerator.

N,N-Dimethyl-4-(5-phenylisoxazol-3-yl)benzenamine (**3a**): White solid; yield 84%; m.p. 126–128 °C; IR (ν_{max}): 3105, 2973, 1596, 1483 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.97 (s, 6H, $2CH_3$), 6.02 (s, 1H, C(4)-H of isoxazole), 6.98 (d, *J* = 8.5 Hz, 2H, aryl), 7.39 (d, *J* = 8.5 Hz, 2H, aryl), 7.68–7.73 (m, 2H, aryl), 7.81–7.86 (m, 3H, aryl); ^{13}C NMR ($CDCl_3$) δ 44.6, 99.1, 120.3, 124.5, 125.9, 127.5, 128.1, 129.9, 131.2, 141.5, 169.8, 171.1; MS (EI) *m/z* (%): 264 (10.5) (M^+). Anal. calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; found: C, 77.38; H, 6.17; N, 10.52%.

Ethyl 4-(5-phenylisoxazol-3-yl)benzoate (**3b**): White solid; yield 92%; m.p. 139–141 °C; IR (ν_{max}): 3072, 2973, 1742, 1590, 1483 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.6 Hz, 3H, CH_3), 4.26 (q, *J* = 7.6 Hz, 2H,CH_2), 6.42 (s, 1H, C(4)-H of isoxazole), 7.21–7.26 (m, 3H, aryl), 7.50–7.54 (m, 2H, aryl), 7.69 (d, *J* = 8.1 Hz, 2H, aryl), 7.90 (d, *J* = 8.1 Hz, 2H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.5, 64.2, 97.9, 126.2, 127.0, 127.8, 129.0, 130.4, 131.0, 132.1, 133.7, 163.5, 167.8, 179.9; MS (EI) *m/z* (%): 293 (12.3) (M^+). Anal. calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78; found: C, 73.79; H, 5.04; N, 4.70%.

3-(3-Bromophenyl)-5-phenylisoxazole (**3c**): White solid; yield: 90%; m.p. 30–31 °C (lit.[18] 30–32 °C); IR (ν_{max}): 3100, 1596, 1471 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.72 (s, 1H, C(4)-H of isoxazole), 6.85–6.89 (m, 1H, aryl), 7.41–7.48 (m, 2H, aryl), 7.48–7.53 (m, 4H, aryl), 7.92–7.99 (m, 2H, aryl); ^{13}C NMR ($CDCl_3$) δ 98.5, 123.1, 124.8, 125.1, 126.9, 128.7, 129.2, 130.7, 130.9, 131.5, 133.6, 160.6, 172.0; MS (EI) *m/z* (%): 299 (9.8) (M^+). Anal. calcd for $C_{15}H_{10}BrNO$: 60.02; H, 3.36; Br, 26.62; N, 4.67; found: 60.15; H, 3.47; Br, 26.69; N, 4.73%.

3,5-Diphenylisoxazole (**3d**): White solid; yield: 94%; m.p. 140–141 °C (lit.[7] 139–140 °C).; IR (ν_{max}): 3050, 1594, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.75 (s, 1H, C(4)-H of isoxazole), 7.45–7.52 (m, 6H, aryl), 7.89-7.95 (m, 4H, aryl); ^{13}C NMR ($CDCl_3$) δ 98.1, 120.3, 121.8, 125.9, 127.0, 129.3, 129.8, 130.1, 131.4, 162.8, 170.8; MS (EI) *m/z* (%): 221 (6.9) (M^+). Anal. calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; found: C, 81.56; H, 5.14; N, 6.47%.

3-Phenyl-5-(pyridin-3-yl)isoxazole (**3e**): White solid, yield: 92%; m.p. 143–144 °C (lit.[24] 143–144 °C); IR (ν_{max}): 3112, 1598, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 1H, C(4)-H of isoxazole), 7.34–7.40 (m, 4H, aryl), 7.61–7.69 (m, 2H, aryl), 8.03 (s, 1H, aryl), 8.27 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 97.1, 122.5, 124.7, 127.0, 128.9, 129.4, 131.2, 133.8, 145.9, 152.0, 164.1, 169.3; MS (EI) *m/z* (%): 222 (14.8) (M^+). Anal. calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60; found: C, 75.74; H, 4.62; N, 12.69%.

3-(2,6-Dichlorophenyl)-5-phenyl-isoxazole (**3f**): Colourless liquid; yield: 83%; IR (ν_{max}): 3085, 1563, 1462, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.85 (s, 1H, C(4)-H of isoxazole), 7.38–7.43 (m, 1H, aryl), 7.47–7.52 (m, 5H, aryl), 7.91–7.98 (m, 2H, aryl); ^{13}C NMR ($CDCl_3$) δ 99.8, 126.0, 127.5, 128.9, 129.1, 129.9, 130.8, 132.1, 136.4, 162.7, 171.2; MS (EI) *m/z* (%): 289 (11.9) (M^+). Anal. calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13; Cl, 24.44; N, 4.83; found: C, 62.17; H, 3.21; Cl, 24.49; N, 4.96%.

2-(3-(4-Chlorophenyl)isoxazol-5-yl)propan-2-ol (**3g**): White solid; yield 91%; m.p. 97–98 °C; IR (ν_{max}): 3400, 3048, 2976, 1598, 1461, 784 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 6H, $2CH_3$), 2.81 (s, 1H, OH), 6.68 (s, 1H, C(4)-H of isoxazole),7.25 (d, *J* = 7.9 Hz, 2H, aryl), 7.67 (d, *J* = 7.9 Hz, 2H, aryl); ^{13}C NMR ($CDCl_3$) δ 31.5, 70.4, 98.1, 126.0, 128.4, 130.8, 137.2, 162.7, 175.1; MS (EI) *m/z* (%): 237 (13.7) (M^+). Anal. calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; Cl, 14.92; N, 5.89; found: C, 60.51; H, 5.17; Cl, 15.03; N, 5.96%.

5-((4-Methoxyphenoxy)methyl)-3-(4-nitrophenyl)isoxazole (**3h**): White solid; yield: 95%; m.p. 139–140 °C (lit.[7] 138–140 °C); IR (ν_{max}): 3071, 2943, 1590, 1563, 1480, 1348, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.47 (s, 3H, OCH_3), 5.29 (s, 2H, OCH_2), 6.83 (s, 1H, C(4)-H of isoxazole), 6.75 (d, *J* = 8.0 Hz, 2H, aryl), 6.89 (d, *J* = 8.0 Hz, 2H, aryl), 7.80 (d, *J* = 8.1 Hz, 2H, aryl), 8.01 (d, *J* = 8.1 Hz, 2H, aryl); ^{13}C NMR ($CDCl_3$) δ 53.1, 64.5, 97.6, 117.9, 119.0, 126.2, 129.7, 136.1, 148.5, 152.0, 156.9, 163.4, 171.8; MS (EI) *m/z* (%): 326 (15.6) (M^+). Anal. calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59; found: C, 62.65; H, 4.39; N, 8.72%.

1-(4-((3-(Furan-2-yl)isoxazol-5-yl)methoxy)phenyl)ethanone (**3i**): White solid; yield: 84%; m.p. 136–137 °C (lit.[7] 135–136 °C); IR (ν_{max}): 3100, 2951, 1715, 1561, 1479, 1228 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H, CH_3), 5.29 (s, 2H, OCH_2), 6.58 (s, 1H, C(4)-H of isoxazole), 6.90 (d, *J* = 2.5 Hz, 1H, C(3)-H of furan), 7.15 (d, *J* = 8.3 Hz, 2H, aryl), 7.62 (t, *J* = 2.5 Hz, 1H, C(4)-H of furan), 7.83 (d, *J* = 2.5 Hz, 1H, C(5)-H of furan), 7.98 (d, *J* = 8.3 Hz, 2H, aryl); ^{13}C NMR ($CDCl_3$) δ 23.0, 62.7, 99.2, 108.9, 115.8, 116.3, 131.7, 132.5, 142.9, 143.7, 154.8, 162.5, 168.0, 184.5; MS (EI) *m/z* (%): 283 (12.6) (M^+). Anal. calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94; found: C, 67.92; H, 4.70; N, 5.08 %.

1,3-Dimethyl-7-((3-phenylisoxazol-5-yl)methyl)-1H-purine-2,6(3H,7H)-dione (**3j**): White solid; yield: 86%; m.p. 123–124 °C (lit.[19] 123 °C); IR (ν_{max}): 3075, 2938, 1725, 1708, 1697, 1556, 1462 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (s, 3H, N3-CH_3), 3.59 (s, 3H, N1-CH_3), 5.69 (s, 2H, NCH_2), 6.75 (s, 1H, C(4)-H of isoxazole), 7.44–7.46 (m, 3H, aryl), 7.75–7.79 (m, 3H, aryl, C(8)-H of theophylline); ^{13}C NMR ($CDCl_3$) δ 28.0, 31.2, 41.1, 102.4, 106.2, 126.8, 128.2, 128.9, 130.3, 141.2, 148.8, 151.5, 155.2, 162.8, 165.7; MS (EI) *m/z* (%): 337 (7.4) (M^+). Anal. calcd

for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76; found: C, 60.41; H, 4.45; N, 20.69%.

7-((3-(4-Methoxyphenyl)isoxazol-5-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**3k**): White solid; yield: 81%; m.p. 215–216 °C (lit.[19] 215 °C); IR (ν_{max}): 3100, 2946, 1720, 1706, 1693, 1558, 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (s, 3H, N3-CH_3), 3.50 (s, 3H, N1-CH_3), 3.88 (s, 3H, OCH_3), 5.82 (s, 2H, NCH_2), 6.95 (s, 1H, C(4)-H of isoxazole), 7.08 (d, *J* = 8.5 Hz, 2H, aryl), 7.83 (d, *J* = 8.5 Hz, 2H, aryl), 8.36 (s, 1H, C(8)-H of theophylline); ^{13}C NMR (62.5 MHz): δ 27.9, 29.9, 41.9, 55.7, 101.2, 106.3, 114.8, 120.8, 128.5, 143.3, 148.8, 151.4, 154.7, 161.2, 162.1, 168.2; MS (EI) *m/z* (%): 367 (5.2) (M^+). Anal. calcd for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.66; N, 19.06; found: C, 58.94; H, 4.71; N, 19.02%.

2-{[3-(4-Chlorophenyl)-5-isoxazolyl]methyl}-1,2-benzisothiazol-3-(2H)-one 1,1-dioxide (**3l**): White solid; yield 85%; m.p. 185–186 °C; IR (ν_{max}): 3100, 2983, 1710, 1600, 1481, 1215, 792 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (s, 2H, NCH_2), 6.89 (s, 1H, C(4)-H of isoxazole), 7.26 (d, *J* = 8.2 Hz, 2H, aryl), 7.51 (d, *J* = 8.2 Hz, 2H, aryl), 7.74–7.81 (m, 4H, aryl); ^{13}C NMR ($CDCl_3$) δ 33.6, 100.1, 121.3, 125.6, 127.2, 127.9, 128.1, 129.2, 132.2, 134.7, 136.2, 141.7, 160.6, 162.9, 166.1; MS (EI) *m/z* (%): 374 (15.9) (M^+). Anal. calcd for $C_{17}H_{11}ClN_2O_4S$: C, 54.48; H, 2.96; Cl, 9.46; N, 7.47; S, 8.56; found: C, 54.40; H, 3.07; Cl, 9.51; N, 7.60; S, 8.62%.

2-((3-Pentylisoxazol-5-yl)methyl)isoindoline-1,3-dione (**3m**): White foam; yield 83%; IR (ν_{max}): 3046, 2971, 1720, 1589, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.5 Hz, 3H, CH_3), 1.19–1.23 (m, 2H, CH_3CH_2), 1.50–1.56 (m, 4H, $2CH_2$), 2.62–2.67 (t, *J* = 7.6 Hz, 2H, CH_2C=N), 5.03 (s, 2H, NCH_2), 6.79 (s, 1H, C(4)-H of isoxazole), 7.37–7.46 (m, 4H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.3, 23.0, 29.7, 31.8, 32.9, 45.1, 99.8, 126.8, 133.5, 135.2, 152.9, 159.4, 171.6; MS (EI) *m/z* (%): 298 (8.6) (M^+). Anal. calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39; found: C, 68.53; H, 6.20; N, 9.31%.

3-Butyl-5-pentylisoxazole (**3n**): Pale yellow oil; yield: 81%; IR (ν_{max}): 3079, 2972, 1586, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, *J* = 7.4 Hz, 3H, CH_3), 0.97 (t, *J* = 7.7 Hz, 3H, CH_3), 1.34–1.41 (m, 8H, $4CH_2$), 1.74 (t, *J* = 7.4 Hz, 2H, CH_2), 2.28–2.36 (m, 2H,CH_2), 2.85 (t, *J* = 7.7 Hz, 2H, CH_2), 5.96 (s, 1H, C(4)-H of isoxazole), ^{13}C NMR ($CDCl_3$) δ 10.5, 12.7, 23.0, 26.1, 27.3, 27.9, 28.7, 30.6, 33.5, 97.4, 158.2, 174.0; MS (EI) *m/z* (%): 195 (13.8) (M^+). Anal. calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17; found: C, 73.89; H, 10.94; N, 7.08%.

3-Cyclohexyl-5-phenylisoxazole (**3o**): White solid; yield: 87%; m.p. 33–34 °C (lit.[7] 33–34 °C); IR (ν_{max}): 3049, 2970, 1598, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47–1.95 (m, 10H, $5CH_2$), 2.98 (m, 1H, CHC=N), 6.73 (s, 1H, C(4)-H of isoxazole), 7.12–7.19 (m, 3H, aryl), 7.56–7.62 (m, 2H, aryl); ^{13}C NMR ($CDCl_3$) δ 23.8, 38.0, 31.4, 34.9, 98.3, 126.1, 127.9, 129.2, 131.5, 168.5, 178.2; MS (EI) *m/z* (%): 227 (11.4) (M^+). Anal. calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; found: C, 79.34; H, 7.61; N, 6.08%.

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