Novel sydnone derivatives carrying azidomethyl-1,2,4-oxadiazole unit and their 1,3-dipolar cycloadditions

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ABSTRACT

A series of 1,2,4-oxadiazolylmethyl sydnones carrying azido group were synthesized and subjected to react with a variety of alkenic and acetylenic dipolarophilic reagents; *N*-phenyl maleimide, phenyl vinyl sulfone, and phenyl propiolic acid. All the new products are identified by spectral/physical data including high-resolution mass measure-ments and X-ray diffraction data.

GRAPHICAL ABSTRACT
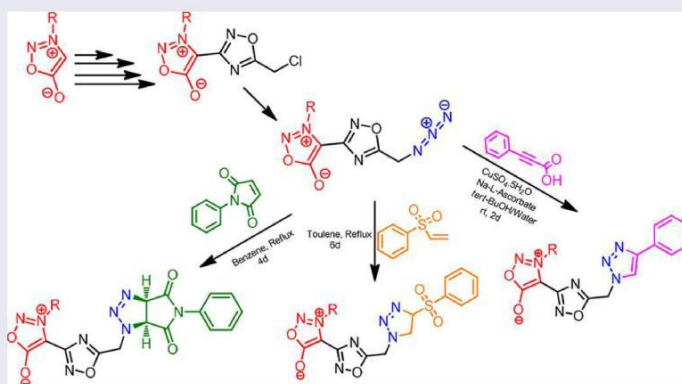
Introduction

Sydnones are among the important classes of mesoionic systems which were discovered by Earl and Mackney[1] and they have been receiving an increasing interest over the decades due to their capability to be converted into heterocycles with potent biological activities.[2–4] The electrophilic substitution of sydnones in C4 position is a well-known method for the preparation of a wide range of 4-heterocycle-substituted sydnones.[5,6]

1,2,4-Oxadiazole derivatives are also important skeletons of biologically or pharmaco-logically important compounds. For example, muscarinic agonists, histamine H3 antagonists, antitumoral, anti-inflammatory, and antimycobacterium tuberculosis agents containing a

1,2,4-oxadiazole ring are among them.[7–12] On the other hand, triazole rings have also attracted remarkable attention due to their biological activities such as antifungal, anti-convulsant agents and especially popular in designing anticancer agents.[13–17]

1,3-Dipolar cycloaddition route is a valuable process to assemble molecules having fragments in biologically active agents of five-membered nitrogen heterocycles. From a synthetic standpoint, it may be considered worthy and in principle, available by a sequence involving sydnone functionalization with azido group followed by cycloaddition.

Taking account of the above considerations together with our continuing interest in the 1,3-dipolar cycloaddition chemistry of various ylides leading to triazoles and spiropyrroles,[18–21] we focus herein on the synthesis of oxadiazolyl-substituted sydnones starting from sydnones and their carboxamidoxime derivatives which were subsequently converted into azidomethyl compounds. The latter were engaged in a series of representative electron-deficient alkenes and alkynes, and their cycloaddition reactions. These series of sydnones were reacted with three representative dipolarophiles: N-phenyl maleimide, phenyl vinyl sulfone, and phenyl propiolic acid.

Results and discussion

N-Aryl sydnones **5a–f** have been synthesized starting from 4-substituted anilines **1** through cyclodehydration of corresponding N-nitroso α-amino carboxylic acids **4** according to the previously reported procedures (Scheme 1).[22,23] In this way, we have prepared 6 sydnone derivatives.

To convert sydnones **5** into 4-carboxamidoxime derivatives **9**, a reaction sequence has been utilized, which, first, transformed starting materials to sydnone aldehydes **6** by Vilsmeer–Haack formylation.[24] Aldehydes **6** were then transformed into aldoximes **7** which were dehydrated to give nitriles **8**.[25] Sydnone nitriles **8** have been reacted with hydroxylamine to yield sydnone amidoximes **9** (Scheme 2). In this way, we have prepared 3 sydnone carboxamide oximes.

Sydnone-4-carboxamidoximes **9** have been converted into 5-chloromethyl-3-substitutedphenyl-1,2,4-oxadiazoles **10a–c**[26] by their reaction with chloroacetyl chloride in benzene under reflux. Sydnone azides **11a–d** were obtained from the reaction of oxadiazoles **10a–d** with NaN3 according to previously reported procedure (Scheme 3).[21]

	R		R
a	CH3	d	F
b	CH3O	e	Cl
c	Br	f	H
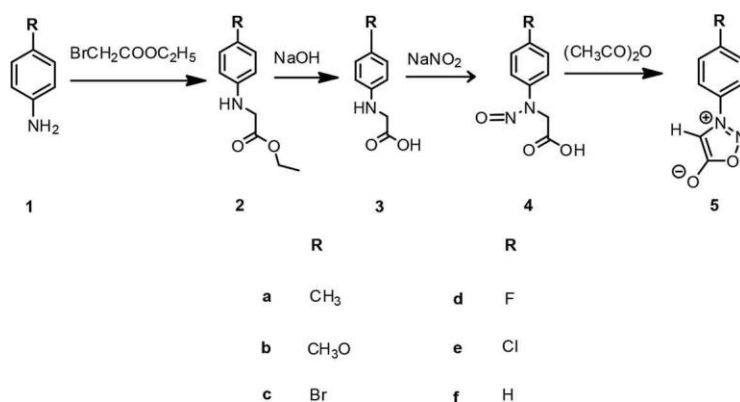
Scheme 1. Synthesis of N-aryl sydnones **5a–f**.
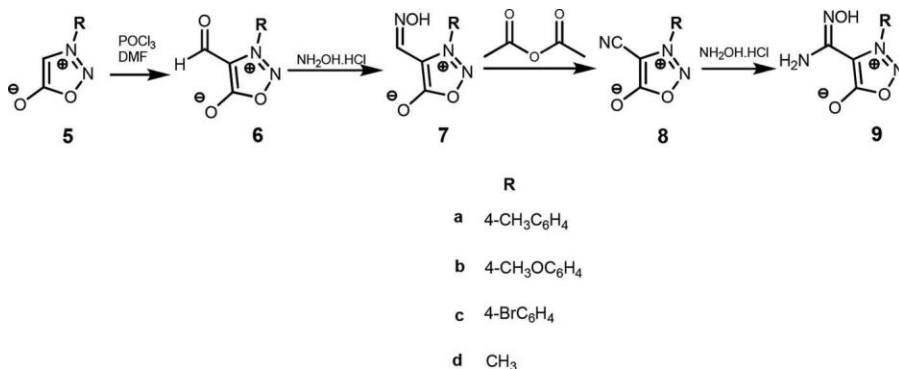
Scheme 2. Synthesis of sydnone-4-carboxamidoximes **9a–d**.
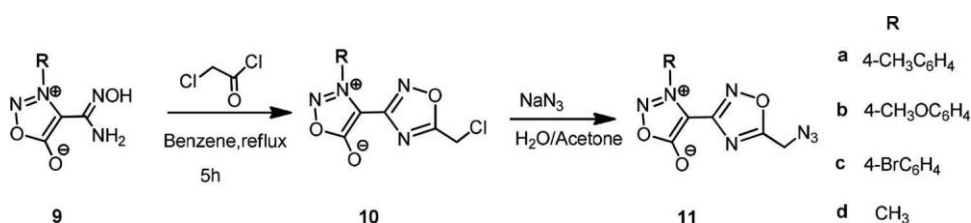
Scheme 3. Synthesis of azido sydnones **11a–d**.

Among the important spectral characteristics of these novel compounds are azide and carbonyl stretching absorptions in the IR spectra at around 2100 and 1750 cm^{-1}; CH$_2$ protons and carbon at around 4.50 and 45 ppm, respectively, in the NMR spectra.

One of the chloromethyl oxadiazolyl sydnones, **10c** has been elucidated by obtaining X-Ray ORTEP view (Fig. 1).

Sydnone azides **11a–c** were then subjected to 1,3-dipolar cycloaddition with *N*-phenyl maleimide **12** to give cycloadducts **13a–c** which were absolutely identified by X-ray diffraction data (Scheme 4, Fig. 2).

Upon examination of the IR data, strong absorptions arising from both sydnone and maleimide portions of the cycloadducts at around 1770–1720 cm^{-1} were observed. ^{1}H NMR spectra also showed the methylene protons as separate doublets at around 5.55 and 5.20 ppm, while the bridge protons resonated as doublets at 5.65 and 4.55 ppm. Carbonyl carbons appeared at 175–165 ppm region, bridge carbons at around 83 and 56 ppm and methylene carbons at 44 ppm, respectively. These results are in accord with the previous findings.[21] We were also able to obtain an X-ray ORTEP diagram of **13b** (Fig. 2).

Azido sydnones **11a** and **11b** were also assayed for 1,3-dipolar cycloaddition with electron-deficient alkene, and phenyl vinyl sulfone **14** and cycloadducts **15a,b** were obtained in lower yields of 13 and 10%, respectively (Scheme 5).

Spectral characteristics of these cycloadducts included a carbonyl absorption in the IR spectrum emerged from the sydnone fragment, symmetric, and asymmetric stretching vibrations of sulfone moiety at 1325–1140 cm^{-1}. The proton NMR signals of the triazoline ring and methylene hydrogens existing in the region of 5.60–3.50 ppm were indicative. All these resonances coincide with the previous reports regarding the associated
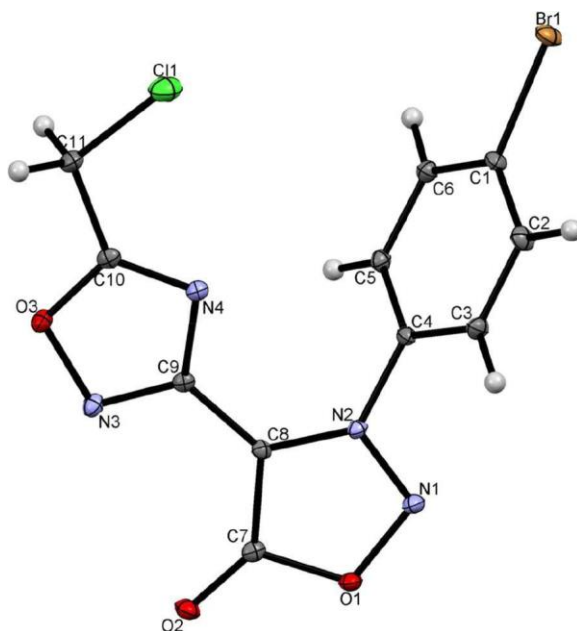
Figure 1. X-ray ORTEP view of **10c**.

compounds.[27,28] We have utilized a number of different reaction conditions for other azido sydnones (**11c,d**) to obtain a variety of cycloadducts carrying phenyl sulfonyl group, but all the attempts failed, that is, no triazole products were formed.

To explore the cycloaddition of novel azides with an alkyne dipolarophile, we used phe-nyl propiolic acid **16** and it smoothly underwent cycloaddition to afford the cycloadducts **17a–d** with the azido sydnones **11a–d** (Scheme 6).

1,3-Dipolar cycloadditon of azido sydnones **11a–d** with phenyl propiolic acid resulted in regioselective formation of 4-phenyl regioisomers (triazoline ring numbering) but not

	R
a	4-CH$_3$C$_6$H$_4$
b	4-CH$_3$OC$_6$H$_4$
c	4-BrC$_6$H$_4$
d	CH$_3$
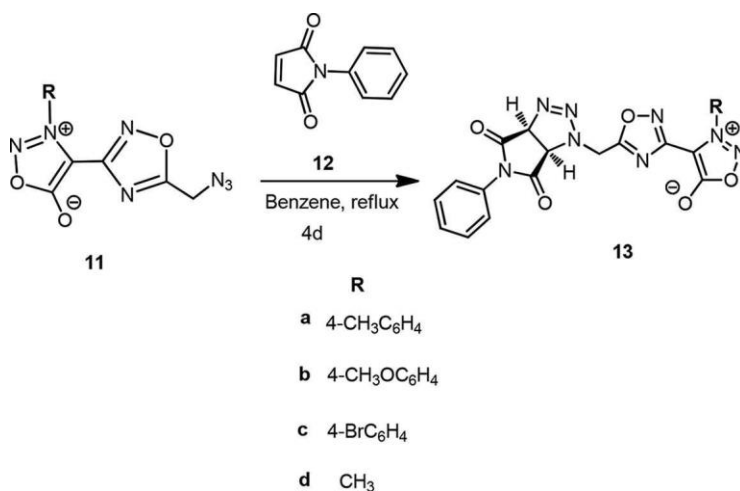
Scheme 4. Cycloaddition of azido sydnones **11a–c** with *N*-phenyl maleimide **12**.
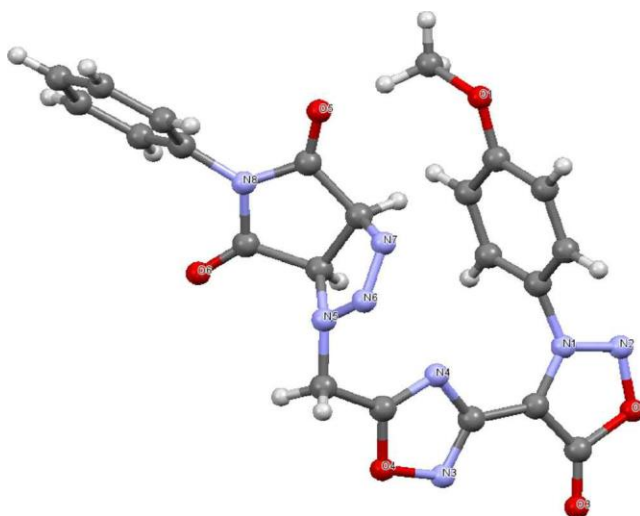
Figure 2. X-ray ORTEP view of **13b**.
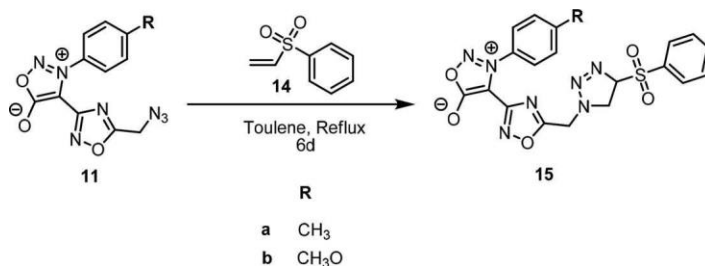
Scheme 5. Cycloaddition of azido sydnones **11a,b** with phenyl vinyl sulfone **14**.

5-phenyl regioisomers which are supported by the X-ray diffraction data of **17b** (Fig. 3) as well as by an earlier report utilizing electron-deficient alkyne esters.[25] Indicative spectral characteristics are the carbonyl absorptions of sydnone part, and C=N absorptions in the IR spectra. ^{1}H NMR spectra of products showed a triazole proton at around 7.90 ppm and metyhylene protons at around 5.90 ppm.
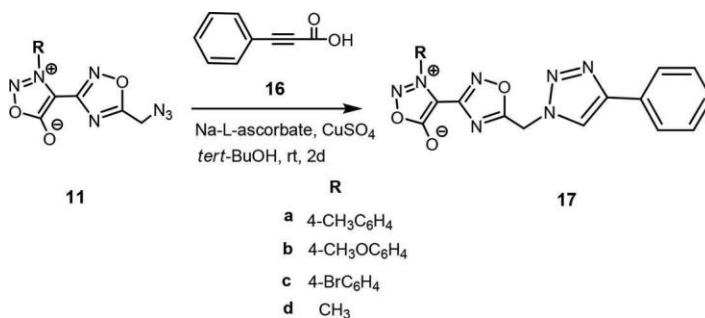
Scheme 6. Cycloaddition of **11a–d** with phenyl propiolic acid **16** affording **17a–d**.
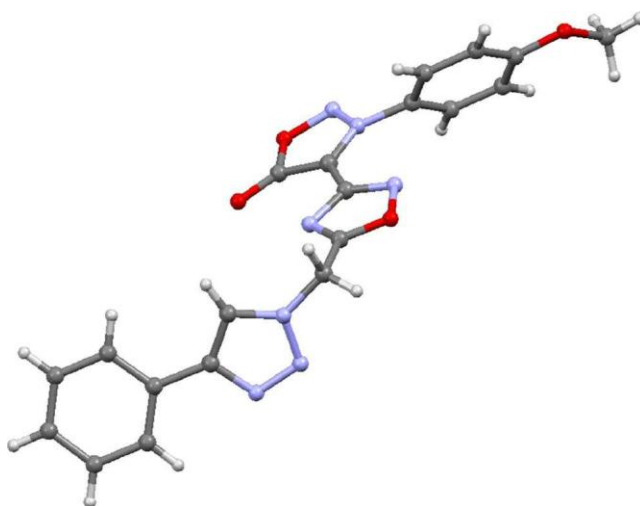
Figure 3. X-ray ORTEP view of **17b**.

Table 1. Estimated Lipinski values for **13, 15, 17**.

Entry	R (sydnone N3-substitution)	cLogP	Solubility	MW	TPSA	Druglikeness	Drug score
13a	C_6H_4-Me	3.13	4.39	472.0	157.2	0.64	0.54
13b	C_6H_4-OMe	3.54	4.06	488.0	166.4	2.1	0.62
13c	C_6H_4-Br	2.75	4.88	536.0	157.2	0.09	0.41
15a	C_6H_4-Me	2.11	4.28	467.0	162.3	10.6	0.33
15b	C_6H_4-OMe	2.52	3.95	483.0	171.6	9.09	0.34
17a	C_6H_4-Me	1.43	4.36	401.0	122.6	2.54	0.39
17b	C_6H_4-OMe	1.84	4.03	417.0	131.8	1.05	0.47
17c	C_6H_4-Br	1.04	4.85	465.0	122.6	3.11	0.32
17d	CH_3	3.16	3.04	325.0	122.6	1.25	0.54

We also attempted to perform a second cycloaddition with the sydnone fragment of the cycloadducts, but despite numerous trials, no reaction occurred; much likely to be attributed to the sterical bulkiness around the ylide that prevents from the approach of dipolarophiles.

One of our goals associated with this work was to screen the novel products for their bioactivities, but, due to low amounts of the end products, it was not possible at this moment. However, we have made some predictions by Lipinski's rule of five (RO5), a rule of thumb to evaluate druglikeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans.[29–31] Below is given a table indicating the estimated Lipinski values (Table 1). In this regard, higher scores are related to the methoxy- and methyl-substituted adducts.

Conclusion

Through this work, we have demonstrated a ten-step reaction sequence leading to the synthesis of the novel sydnones bearing azidomethyl-1,2,4-oxadiazole fragment and their 1,3-dipolar cycloaddition reaction with a series of electron-deficient dipolarophilic reagents; *N*-phenyl maleimide, phenyl vinyl sulfone, and phenyl propiolic acid. The compounds **13, 15**, and **17** resulted from 1,3-dipolar cycloaddition of the sydnone azides

preferrentially by azide-dipolarophile reaction, but no further reactivity has been observed between sydnone azide cycloadducts and dipolarophiles, even if too many reaction conditions were assayed.

Experimental

Melting points were determined on a Meltemp apparatus and are uncorrected. Infrared spectra were obtained from KBr pellets or neat on NaCl plates for liquids and were recorded on a SHIMADZU FTIR-8400S spectrophotometer. NMR spectra were recorded on Jeol and Varian spectrometers operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, all at 25 °C, as specified for each data set. LC–MS spectra were obtained from Waters 2695 Alliance Micromass ZQ instrument. High-resolution mass spectra have been obtained from Waters Lct Premier XE oa-TOF mass spectrometer (Waters Corporation, Milford, MA, USA). Single-crystal X-ray diffraction data were obtained by Bruker Smart Apex II Quazar and Nonius Kappa CCD instruments. All chemical shifts are reported in ppm relative to TMS. Coupling constants (J) are reported in Hz. Routine TLC analyses were performed on pre-oated silica gel plates with fluorescent indicator. Flash column chroma-tography was performed on silica gel (230–400 mesh ASTM). A rotary TLC apparatus (Chromatotron) was utilized for further separation and purifications. Stain solutions of potassium permanganate and iodine were used for visualization of the TLC spots.

Typical reaction procedure for the synthesis of 4-(5-(chloromethyl)-1,2, 4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (10a)[22]

A solution of chloroacetylchloride (0.070 g, 0.62 mmol) in benzene (2 mL) was added dropwise to a solution of 3-(4-methoxyphenyl)sydnone-4-carboxamidoxime **9a** (0.360 g, 1.54 mmol) in benzene (20 mL) and the mixture was heated under reflux for 24 h. The progress of reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane:ethyl acetate; 4:1) to give **10a** as a white solid.

4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (10a)

Yield: 0.400 g, 89%. mp 155–156 °C. R_f: 0.59 (*n*-hexane:ethyl acetate; 1:1). IR (KBr, *v*:cm[-1]): 3014, 2960, 1797, 1778 (sydnone C=O), 1568 (C=N), 1510, 1444, 1282, 1199, 1058, 1010, 954, 891, 779, 750 (C–Cl). ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ ¼ 7.45 (d, J ¼ 8.4 Hz, 2H), 7.41 (d, J ¼ 8.4 Hz, 2H), 4.66 (s, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ ¼ 174.5 (sydnone C=O), 158.5 (C=N), 143.6, 130.3, 124.7, 32.9 (CH$_2$), 21.6 (CH$_3$). LC–MS (80 eV) (*m*/*z*) (%): 356 ([MþCH$_3$CNþNa]þ, 100), 293 ([MþH]þ, 48), 248 (21). HRMS: *m*/*z* (ESI-TOF, [MþH]þ) calcd for C$_{12}$H$_{10}$N$_4$O$_3$Cl: 293.0441; found: 293.0428.

Typical reaction procedure for the synthesis of 4-(5-(azidomethyl)-1,2, 4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (11a)[19,23]

To a stirred solution of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)syd-none, **10a** (0.400 g, 1.37 mmol) in a 10 mL of water/acetone mixture (1:4) was added

sodium azide (0.098 g, 1.51 mmol). The resulting suspension was stirred at room tempera-ture for 24 h. Dichloromethane (DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3 ⊗ 10 mL aliquots of DCM and the combined organic layers were dried over sodium sulfate. Solvent was removed under reduced pressure to give **11a** as a light yellow solid.

4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (11a)

Yield: 0.200 g, 49%. mp 98–101 °C. R_f: 0.58 (*n*-hexane:ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3061, 2991, 2922, 2098 (N=N=N), 1759, 1743 (C=O), 1558 (C=N), 1508, 1435, 1319, 1273, 1197, 1056, 1016, 960, 817, 740. ^{1}H NMR (400 MHz, CDCl$_3$): δ_H ¼ 7.44 (d, *J* ¼ 8.8 Hz, 2H), 7.40 (d, *J* ¼ 8.8 Hz, 2H), 4.51 (s, 2H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ_C ¼ 174.2 (sydnone C=O), 164.8 (C=N), 158.4 (C=N), 143.4, 131.8, 130.3, 124.5, 44.6 (CH$_2$), 21.5 (CH$_3$). LC–MS (80 eV) (*m/z*) (%): 363 ([M⊕CH$_3$CN⊕Na]$^⊕$, 94), 300 ([M⊕H]$^⊕$, 100). HRMS: *m/z* (ESI-TOF, [M⊕H]$^⊕$) calcd for C$_{12}$H$_{10}$N$_7$O$_3$: 300.0845; found: 300.0834.

Typical reaction procedure for the synthesis of 4-(5-(((3aS,6aR)-4,6-dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-d][1,2,3]triazol-1(3aH)-yl)methyl)-1,2, 4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (13a)

A mixture of *N*-phenyl maleimide **12** (0.030 g, 0.175 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **11a** (0.050 g, 0.167 mmol) was stirred in benzene (17 mL) and the mixture was heated under reflux for 2–4 d. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane:ethyl acetate; 1:2) to give **13a** as a light yellow solid.

4-(5-(((3aS,6aR)-4,6-dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-d][1,2,3] triazol-1(3aH)-yl)methyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (13a)

Yield: 0.020 g, 25%. mp 143–144 °C. R_f: 0.19 (*n*-hexane:ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 1766 (sydnone C=O), 1720 (C=O), 1564 (C=N), 1492, 1379, 1195, 1041, 817, 742. ^{1}H NMR (400 MHz, CDCl$_3$): δ_H ¼ 7.48–7.38 (m, 4H), 7.35 (d, *J* ¼ 2.8 Hz, 2H), 7.2 (t, *J* ¼ 2.0 Hz, 1H), 7.19 (t, *J* ¼ 1.6 Hz, 1H), 5.62 (d, *J* ¼ 10.8 Hz, 1H), 5.48 (d, *J* ¼ 18.0 Hz, 1H), 5.22 (d, *J* ¼ 18.0 Hz, 1H), 4.56 (d, *J* ¼ 10.8 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ_C ¼ 174.3 (sydnone C=O), 170.9 (C=O), 168.3 (C=O), 164.8 (C=N), 158.1 (C=N), 143.7 (C–CH$_3$), 131.7, 130.4, 129.5, 129.3, 126.8, 126.3, 126.0, 124.6, 83.2 (CH), 57.0 (CH), 44.3 (CH$_2$), 21.5 (CH$_3$). HRMS: *m/z* (ESI-TOF, [M⊕H]$^⊕$) calcd for C$_{22}$H$_{17}$N$_8$O$_5$: 473.1322; found: 473.1325.

Typical reaction procedure for the synthesis of 3-(4-methylphenyl)-4-(5-((5-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazol-1-yl)methyl)-1,2, 4-oxadiazol-3-yl)sydnone (15a)

A mixture of phenyl vinyl sulfone **14** (0.024 g, 0.135 mmol) and 4-(5-(azidomethyl)-1,2, 4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **11a** (0.040 g, 0.134 mmol) was stirred in

toluene (7 mL) and the mixture was heated under reflux for 6 d. The reaction was moni-tored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane:ethyl acetate; 1:2) to give **15a** as a light yellow solid.

3-(4-methylphenyl)-4-(5-((5-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazol-1-yl) methyl)-1,2,4-oxadiazol-3-yl)sydnone (15a)

Yield: 8 mg, 13%. mp 84–86 °C. R_f : 0.20 (*n*-hexane:ethyl acetate; 1:1). IR (KBr, v:cm ^{1}): 2958, 2927, 2852, 1770 (sydnone C=O), 1564 (C=N), 1446, 1321 (asym SO$_2$), 1240, 1151 (sym SO$_2$), 1082, 1056, 935, 821, 744. ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ ¼ 7.95 (dd, *J* ¼ 8.0, 0.4 Hz, 2H), 7.72 (t, *J* ¼ 7.6 Hz, 1H), 7.60 (t, *J* ¼ 8.0 Hz, 2H), 7.42 (dd, *J* ¼ 11.6, 8.8 Hz, 4H), 5.56 (dd, *J* ¼ 8.4, 7.2 Hz, 1H), 5.19 (d, *J* ¼ 17.6 Hz, 1H), 4.96 (d, *J* ¼ 17.2 Hz, 1H), 3.85 (dd, *J* ¼ 11.6, 7.6 Hz, 1H), 3.52 (t, *J* ¼ 12.0 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ ¼ 173.5 (sydnone C=O), 164.7 (C=N), 158.2 (C=N), 143.6 (C–CH$_3$), 136.0, 134.8, 131.7, 130.3, 129.5, 129.3, 124.7, 95.1 (C–SO$_2$), 44.9 (CH$_2$), 44.2 (CH$_2$), 21.5 (CH$_3$). LC–MS (80 eV) (*m/z*) (%): 490 ([MþNa]^þ, 100), 468 ([MþH]^þ, 19), 459 (60). ESI-MS (80 eV) (*m/z*) (%): 466 ([M H], 100). HRMS: *m/z* (ESI-TOF, [MþH]^þ) calcd for C$_{20}$H$_{18}$N$_7$O$_5$S: 468.1090; found: 468.1081.

Typical reaction procedure for the synthesis of 3-(4-methylphenyl)-4-(5-((5-phenyl-1H-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (17a)

Method A
A mixture of phenylpropiolic acid **16** (0.026 g, 0.175 mmol) and 4-(5-(azidomethyl)-1,2, 4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **11a** (0.050 g, 0.167 mmol) was stirred in benzene (17 mL) and the mixture was heated under reflux for 4 d. The reaction was monitored by TLC. But no reaction was occurred.

Method B
A mixture of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **11a** (0.050 g, 0.167 mmol), catalytic amount of CuSO$_4$·5H$_2$O (0.002 g, 0.008 mmol), Na-L-ascorbate (0.009 g, 0.043 mmol), and phenylpropiolic acid **16** (0.026 g, 0.175 mmol) was stirred in *t*-BuOH/water mixture (1:2) at room temperature for 2 d. Then, the reaction mixture was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate. The solvent was evaporated under reduced pressure to give **17a** as a brown solid.

3-(4-methylphenyl)-4-(5-((5-phenyl-1H-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (17a)

Yield: 0.060 g, 90%. mp 129–131 °C. R_f: 0.21 (*n*-hexane:ethyl acetate; 1:1). IR (KBr, v:cm ^{1}): 3047, 2935, 1780 (sydnone C=O), 1625, 1568 (C=N), 1450, 1338, 1232, 1068, 908, 815, 761. ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ ¼ 7.88 (s, 1H), 7.80 (d, *J* ¼ 7.2 Hz, 2H), 7.44 (t, *J* ¼ 7.2 Hz, 2H), 7.40–7.34 (m, 3H), 7.29 (d, *J* ¼ 8.4 Hz, 2H), 5.85 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ ¼ 167.4 (sydnone C=O), 164.8 (C=N), 143.7, 131.5, 130.2, 129.7, 128.9,

128.6, 125.7, 124.6, 124.1, 120.2, 96.8, 45.0 (CH_2), 21.4 (CH_3). LC–MS (80 eV) (*m/z*) (%): 424 ([M$þ$Na]^þ, 83), 402 ([M$þ$H]^þ, 100), 282 (93). ESI-MS (80 eV) (*m/z*) (%): 400 ([M H] , 100). HRMS: *m/z* (ESI-TOF, [M$þ$H]^þ) calcd for $C_{20}H_{16}N_7O_3$: 402.1315; found: 402.1296.

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