Synthesis of Triazole and Isoxazole Based Novel Unsymmetrical Bis-heterocycles

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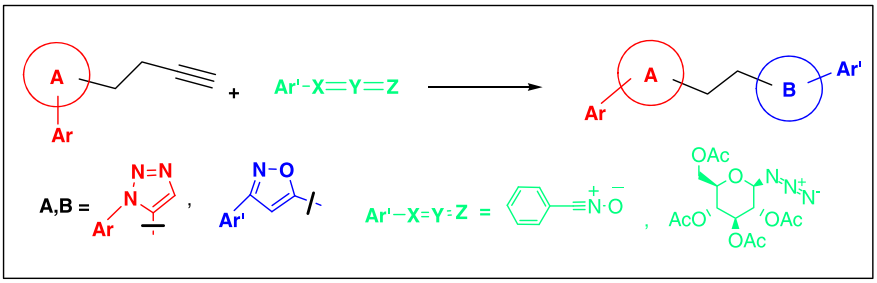

Novel unsymmetrical bis-heterocyclic compounds encompassing triazole and isoxazole moieties were synthesized by employing 1,3-dipolar cycloaddition/click chemistry approach using 5-butynyl-1,2,3-triazoles and 5-butynyl isoxazoles.

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INTRODUCTION

Organic compounds bearing heteroaromatic moieties are valuable synthetic templates for the preparation of new molecules with useful material and pharmacological properties. The synthesis of such constructs is possible either through rapid assembly and variation of multiple pendant substituents on the heteroaromatic core or through the construction of diverse aromatic heterocycles with defined substitution patterns. In recent years, attention has been increasingly paid to the synthesis of aromatic heterocycles and bis-heterocyclic compounds, which exhibit various biological activities [1] including antibacterial, fungicidal, tuberculostatic, and plant growth regulative properties. Bis-heterocyclic compounds have found numerous applications as electrical materials [2], biologically active molecules [3], chelating agents, and metal ligands [4] owing to which have attracted great deal of attention in recent years.

Of particular interest would be the bis-heterocycles that encompass isoxazoles and triazoles as their components, which gained importance because of their diverse applications and pharmacological activities. Bis-triazole-based size-specific mRNA hairpin loop-binding agents have been developed to target mRNAs coding for proteins [5]. Recent studies have disclosed a series of 1,2,3-triazole-based bis-heterocycles as potent HIV-1 protease inhibitors for the inhibition of viral replication [6]. Efforts are being made to combine the variety of multiple heterocyclic cores in a single molecular framework as symmetrical or unsymmetrical bis, tris, or multiple heterocycles to exploit the pharmacological and altered physical properties of the resulting multivalent ligands [7].

RESULTS AND DISCUSSION

With the wide range of pharmacological activities and applications of bis-heterocyclic systems with particular emphasis on their mRNA hairpin loop-binding potential, we envisaged the design and synthesis of a focused library of novel 1,2,3-triazole-isoxazole hybrids. Herein, we report the synthesis of such novel unsymmetrical bis-heterocyles encompassing biologically active isoxazole and triazole moieties separated by two carbon flexible spacers by employing stepwise approach involving combination of domino addition and 1,3-dipolar cycloaddition strategy. One of the most frequently used methods to synthesize isoxazoles is 1,3-dipolar cycloaddition involving a nitrile oxide, and the usual dipolarophile for this process is an alkyne [8]. Further, the bio-orthogonality has allowed the use of the copper-catalyzed azide–alkyne [3 + 2] cycloadditions in various biological applications, which has been termed the "cream of the crop" of click reactions [9] affording 1,2,3-triazoles with high regiospecificity.

The acetylenic dipolarophiles that are used as precursors of bis-heterocycles were prepared through the domino addition of allenylmagnesium bromide to azides/nitrileoxides [10]. Several *in situ* generated nitrile oxides were reacted with

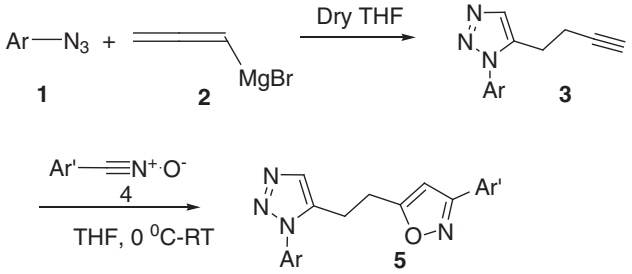
1,5-disubstituted 1,2,3-triazoles at ambient temperature to afford novel bis-heterocyclic compounds that are separated by two carbon spacer (Scheme 1). The reaction was found to be general with regard to various substituted nitrile oxides and butynyltriazoles bearing electron-donating or electron-withdrawing groups on the aromatic ring.

Click chemistry approach was applied for the generation of sugar triazole as one of the heteromer in bis-heterocyclic system.

Sugar azides were reacted with 1,5-disubstituted isoxazoles to form the novel bis-heterocyclic compounds regiospecifically, and two heterocyclic moieties are separated by two methylene flexible spacers to facilitate effective target interaction. In the case of sugar-substituted compounds, deacetylation of the click product affords the final bis-heterocycle in quantitative yields (Scheme 2).

In conclusion, we present in this communication the synthesis of novel bis-heterocycles encompassing triazole and isoxazole moieties designed for effective target binding, which might find application as pharmacologically active ligands for future lead discovery.

Scheme 1



EXPERIMENTAL

All chemicals (reagent grade) used were commercially available. Melting points were measured on a Boetius micro melting point apparatus.

General procedure for the 1,3-polar cycloaddition between alkynyl 1,2,3-triazole and nitrile oxides (synthesis of bis-heterocycles). 5-Butynyl triazole (20 mg, 0.088 mmol) was added to the *in situ* generated *p*-tolylbenzonitrileoxide (using corresponding chlorooxime and triethylamine) (0.88 mmol) in THF (10 ml) at 0°C. After stirring at this temperature for 0.5 h, the reaction mixture was continually stirred for further 22 h at room temperature. Excess of water (100 mL) was charged, and the organic compound was extracted with ethyl acetate (2×20 mL). Combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude product, which was subjected to column chromatography (basic alumina, elution; *n*-hexane : EtOAc gradient) to afford pure bis-heterocycle.

1-(4-Methoxy-phenyl)-5-[2-(3-*p*-tolyl-isoxazol-5-yl)-ethyl]-1*H*-[1,2,3]triazole (Table 1, entry 1). White solid; mp 120–121°C; IR (KBr, cm^{-1}): 3063, 2963, 2920, 2857, 2360, 2119, 1602, 1514, 1438, 1363, 1222, 1105, 1020, 813, 774; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.08 (s, 4H), 3.85 (s, 3H), 6.21 (s, 1H), 7.01–7.06 (m, 2H), 7.21–7.34 (m, 4H), 7.60–7.74 (m, 3H); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 20.43, 21.14, 24.53, 54.49, 98.64, 113.67, 124.56, 125.12, 125.48, 125.58, 127.67, 128.10, 128.46, 130.58, 131.16, 139.07, 155.15, 161.00, 169.50. ESI–MS: 361 $(M+1)^+$, 383 $(M+Na)^+$; *Anal.* Calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.54. Found: C, 69.91; H, 5.64; N, 15.60.

5-(2-(3-(4-Chlorophenyl)isoxazol-5yl)ethyl)-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (Table 1, entry 2). Light yellow solid; mp 188–190°C; IR (KBr, cm^{-1}): 2923, 2853, 2361, 2337, 1598, 1402, 1343, 1258, 1021, 858, 800, 672; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.15 (s, 4H), 6.26 (s, 1H), 7.43 (d, 2H, $J = 8.38$ Hz), 7.65–7.71 (m, 5H), 8.44 (d, 2H, $J = 8.75$); ^{13}C-NMR (50 MHz, CDCl3): δ 22.50, 26.14, 100.47, 125.65, 126.06, 128.38, 129.70, 133.73, 136.61, 136.4, 136.64, 141.02, 148.67, 161.98, 170.81; ESI–MS: $m/z = 396.5$ $(M+1)^+$; *Anal.* Calcd for $C_{19}H_{14}ClN_5O_3$: C,

Scheme 2

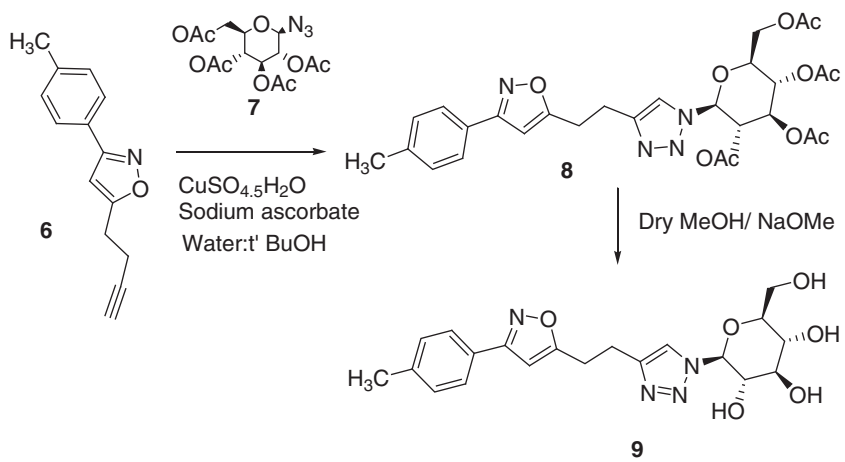
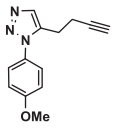
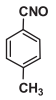
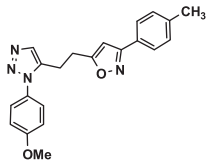
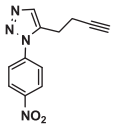
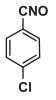
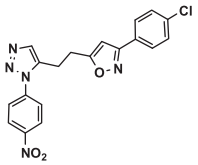
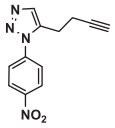
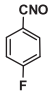
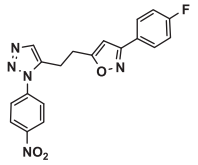
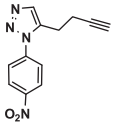
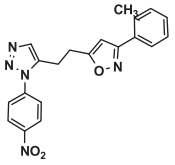
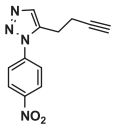
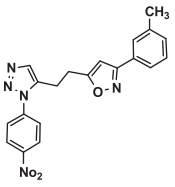
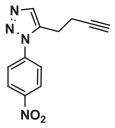
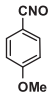
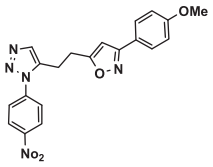
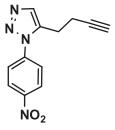
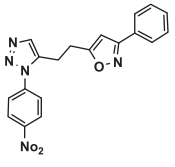
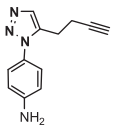
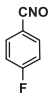
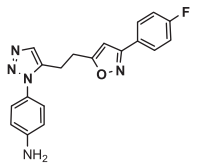


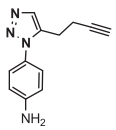
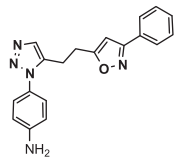
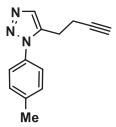
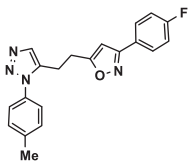
Table 1

Synthesis of novel bis-heterocycles.

Entry	Butynyl triazole	Nitrile oxide	Bis-heterocycle[a]	Reaction time (h)	Yields[b] (%)
1				22	92
2				20	94
3				28	90
4				26	94
5				20	94
6				28	96
7				22	91
8				22	91

(*Continued*)

Table I.
(Continued)

Entry	Butynyl triazole	Nitrile oxide	Bis-heterocycle[a]	Reaction time (h)	Yields[b] (%)
9				22	91
10				22	91

[a]All products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, and mass spectroscopy.
[b]Yields obtained after column chromatography.

57.66; H, 3.57; Cl, 8.96; N, 17.69. Found: C, 57.74; H, 3.48; Cl, 9.06; N, 17.75.

5-(2-(3-(4-Fluorophenyl)isoxazol-5yl)ethyl)-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (Table 1, entry 3). Light yellow solid; mp 173–174°C; IR (KBr, cm^{-1}): 3063, 2963, 2920, 2857, 2360, 1602, 1514, 1438, 1363, 1222, 1105, 1020, 774, 738; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.15–3.28 (m, 4H), 6.24 (s, 1H), 7.15 (t, 2H, J = 8.82 Hz), 7.65–7.76 (m, 5H), 8.42–8.46 (dd, 2H, J = 4.89 and 2.01 Hz); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 20.47, 24.09, 98.46, 114.44, 114.61, 123.18, 123.62, 124.03, 126.98, 127.05, 131.70, 134.48, 139.23, 146.40, 160.03, 161.27, 163.26, 168.63: ESI–MS: 379(M^+); *Anal*. Calcd for $C_{19}H_{14}FN_5O_3$: C, 60.16; H, 3.72; F, 5.01; N, 18.46. Found: C, 60.09; H, 3.77; F, 5.11; N, 18.36.

1-(4-Nitro-phenyl)-5-(2-(3-*o*-tolylisoxazol-5-yl)-ethyl)-1*H*-1,2,3-triazole (Table 1, entry 4). Light brown solid; mp 128–130°C; IR (KBr, cm^{-1}): 2923, 2853, 2361, 2337, 1598, 1524, 1402, 1344, 1256, 1020, 767, 725; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.16–3.29 (s, 4H), 6.16 (s, 1H), 7.25–7.43 (m, 4H), 7.67–7.72 (m, 3H), 8.42–8.47 (dd, 2H, J = 4.99 and 2.03 Hz); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 21.30, 22.34, 25.85, 103.00, 125.47, 125.90, 126.27, 128.55, 129.51, 129.87, 131.38, 133.50, 136.44, 137.01, 141.14, 148.31, 163.46, 169.37; ESI–MS: m/z = 375 (M^+); *Anal*. Calcd for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.66. Found: C, 63.91; H, 4.45; N, 18.75.

1-(4-Nitro-phenyl)-5-(2-(3-*m*-tolyl-isoxazol-5-yl)-ethyl)-1*H*-1,2,3-triazole (Table 1, entry 5). Light yellow solid; mp 101–103°C; IR (KBr, cm^{-1}): 2923, 2853, 2361, 2337, 1598, 1524, 1501, 1456, 1343, 1256, 1020, 856, 767; ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.43 (s, 3H), 3.16–3.29 (m, 4), 6.16 (s, 1H), 7.25–7.43 (m, 4H), 7.67–7.72 (m, 3H), 8.42–8.47 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 20.48, 21.16, 24.85, 98.64, 123.26, 124.15, 125.84, 126.05, 127.16, 128.18, 130.13, 130.75, 131.61, 139.40, 155.01, 162.91, 169.67; ESI–MS: m/z = 398 ($M + Na)^+$; *Anal*. Calcd for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.66. Found: C, 64.06; H, 4.48; N, 18.72.

5-(2-(3-(4-Methoxyphenyl)isoxazol-5yl)ethyl)-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (Table 1, entry 6). Light brown solid; mp 182–184°C; IR (KBr, cm^{-1}): 2924, 2853, 2338, 1651, 1611, 1524, 1456, 1402, 1344, 1255, 1021, 856, 668; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.17-3.27 (s, 4H), 3.95 (s, 3H), 6.21 (s, 1H), 6.94–7.01 (m, 2H), 7.60–7.75 (m, 5H), 8.41–8.46 (dd, 2H, J = 6.98 and 2.90 Hz); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 22.51, 26.15, 56.69, 100.31, 112.61, 123.58, 126.67, 128.51, 129.01, 138.72, 141.30, 146.34, 148.46, 156.88, 161.64, 170.17; ESI–MS: m/z = 391 (M^+); *Anal*. Calcd for $C_{20}H_{17}N_5O_4$: C, 61.38; H, 4.38; N, 17.89. Found: C, 61.48; H, 4.31; N, 17.84.

1-(4-Nitrophenyl)-5-(2-(3-phenylisoxazol-5-yl)ethyl)-1*H*-1,2,3-triazole (Table 1, entry 7). Light brown solid; mp 167–168°C; IR (KBr, cm^{-1}): 2923, 2852, 2360, 2342, 1613, 1597, 1519, 1469, 1406, 1342, 1262, 1094, 1020, 856, 771, 669; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.13–3.31 (s, 4H), 6.28 (s, 1H), 7.45 (m, 3H), 7.65–7.75 (m, 5H), 8.44 (d, 2, J = 8.80); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 22.15, 25.78, 100.20, 125.24, 125.67, 126.70, 128.59, 129.01, 130.25, 132.37, 135.13, 138.97, 146.71, 152.83, 161.33, 170.06: ESI–MS: m/z = 361 (M^+); *Anal*. Calcd for $C_{19}H_{15}N_5O_3$: C, 63.15; H, 4.18; N, 19.38. Found: C, 63.19; H, 4.04; N, 19.47.

4-(5-(2-(3-(4-Fluorophenyl)isoxazol-5-yl)ethyl)-1*H*-1,2,3-triazol-1yl)benzenamine (Table 1, entry 8). Light yellow solid; mp 166–168°C; IR (KBr, cm^{-1}): 3305, 3300, 2923, 2852, 2360, 2342, 1613, 1597, 1519, 1469, 1406, 1342, 1262, 1094, 921, 771; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.29–3.32 (s, 4H), 6.51 (s, 1H), 6.79–6.83 (m, 2H), 7.12–7.24 (m, 4H), 7.68 (s, 1H), 7.77–7.84 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 22. 46, 26.33, 100.91, 115.84, 116.93, 117.17, 126.24, 126.71, 127.74, 129.96, 130.08, 133.01, 138.72, 151.57, 163.06, 166.31, 173.52; ESI–MS: m/z = 372 $(M + Na)^+$; *Anal*. Calcd for $C_{19}H_{16}FN_5O$: C, 65.32; H, 4.62; F, 5.44; N, 20.05. Found: C, 65.39; H, 4.54; F, 5.57; N, 19.93.

4-(5-(2-(3-Phenylisoxazol-5-yl)ethyl)-1*H*-1,2,3-triazol-1yl) benzenamine (Table 1, entry 9). Light yellow solid; mp 146–148°C; IR (KBr, cm^{-1}): 3324, 3322, 2923, 2852, 2360, 2342, 1613, 1597, 1519, 1469, 1406, 1342, 1262, 1094, 824, 771, 669; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.13–3.31 (m, 4H), 6.28 (s, 1H), 7.45 (m, 3H), 7.65–7.75 (m, 5H), 8.44 (d, J = 8.80, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 22.11, 25.73, 100.26, 125.24, 125.63, 126.78, 128.55, 129.01, 130.22, 132.33, 135.09, 138.89, 146.72, 152.86, 161.43,

170.10; ESI–MS: $m/z = 354$ $(M + Na)^+$; *Anal*. Calcd for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.79; H, 5.24; N, 21.18.

5-(2-(3-(4-Fluorophenyl)isoxazol-5yl)ethyl)-1-*p*-tolyl-1*H*-1,2,3-triazole (Table 1, entry 10). Light brown solid; mp 88–90°C; IR (KBr, cm^{-1}): 3074, 2954, 2925, 2855, 1715, 1611, 1519, 1434, 1388, 1230, 1158, 1015, 950, 843,821, 757; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.11 (s, 4H), 6.20 (s, 1H), 7.09–7.17 (m, 2H), 7.27–7.33 (m, 4H), 7.64–7.76 (m, 3H); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 21.04, 21.84, 24.66, 100.86, 113.68, 124.85, 125.62, 126.13, 126.46, 128.76, 132.81, 133.24, 144.02, 154.35, 161.64, 163.89; ESI–MS: 372 $(M + Na)^+$; *Anal*. Calcd for $C_{20}H_{18}FN_4O$: C, 68.75; H, 5.19; F, 5.44; N, 16.04. Found: C, 68.79; H, 5.14; F, 5.40; N, 11.06.

Typical procedure for the synthesis of compound 9 (Scheme 2). In a typical procedure, 0.020-g butynylisoxazole **6** (0.095 mmol) was dissolved in 5 mL of tertiary butanol and water (1:1 mixture). Copper sulfate (0.114 mmol) followed by sodium ascorbate (0.475 mmol) were charged into the reaction mixture. After 15 min, glucose azide **7** (0.0353 g, 0.095 mmol) was added to the aforementioned mixture, and the reaction mixture was stirred for 8 h. The mixture was diluted with water and added with ethyl acetate. Organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude product, which, on re-crystallization with ethyl acetate/hexane, affords pure compound **8** as light yellow solid. Further, it was deprotected with sodium methoxide in dry methanol to afford the titled bis-heterocycle **9** as a light yellow solid.

2-Hydroxymethyl-6-{4-[2-(3-*p*-tolyl-isoxazol-5-yl)-ethyl]-[1,2,3]triazol-1yl-}-tetrahydro-pyran-3,4,5-triol (compound 9, Scheme 2). $[\alpha]_D^{28} - 2.0$ (*c* 0.0025, MeOH): mp 202–204°C; IR (KBr, cm^{-1}): 3384, 3063, 2920, 2846, 2399, 1603, 1508, 1444, 1384, 1363, 1238, 1223, 1143, 951, 914, 818, 775; ^{1}H-NMR (200 MHz, CD_3OD): δ 2.40 (s, 3H), 3.22 (s, 4H), 3.52–3.67 (m, 3H), 3.85–3.91 (t, 3H, $J = 3.91$ Hz), 5.58 (d, 1H, $J = 9.15$ Hz), 6.59 (s, 1H), 7.30 (d, 2H, $J = 7.88$), 7.70 (d, 2H, $J = 8.07$ Hz), 8.03 (s, 1H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 19.7, 21.41, 26.26, 55.35, 61.20, 70.07, 72.59, 77.43, 79.11, 87.88, 99.98, 121.89, 126.89, 130.09, 140.01, 142.89, 159.03, 173.34; ESI–MS: 439 (M + Na)+; *Anal*. Calcd for $C_{20}H_{24}N_4O_6$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.72; H, 5.77; N, 13.51.

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