

‘Click Synthesis’ of Some Novel *O*-Substituted Oximes Containing 1,2,3-Triazole-1,4-diyl Residues as New Analogs of β -Adrenoceptor Antagonists

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The ‘click synthesis’ of some novel *O*-substituted oximes, **7a–7t**, which contain 1,2,3-triazole-diyl residues, as new analogs of β -adrenoceptor antagonists is described (*Schemes 1–4*). The synthesis of these compounds was achieved in four to five steps. The formation of oximes of 9*H*-fluoren-9-one and benzophenone, *i.e.*, **9a** and **9b**, respectively, followed by their reaction with propargyl bromide, afforded *O*-propargyl oximes **10a** and **10b**, respectively, which by a subsequent CuI-catalyzed *Huisgen* cycloaddition with prepared β -azido alcohols **11a–11j** (*Schemes 2 and 3*), led to the target compounds **7a–7t** in good yields.

Introduction. – Oximes and *O*-substituted oximes are prominent structural motifs found in several drug scaffolds and biologically active compounds [1–6].

The use of β -adrenoceptor antagonists is well established in the treatment of various cardiovascular disorders [7], and their benefits have been demonstrated in many clinical investigations [8]. It is well-recognized that β -adrenoceptor blockers are homogeneous in their chemical structures. With a few exceptions of ‘arylethanolamines’ (2-amino-1-arylethanol) **1**, virtually all the clinically useful β -adrenoceptor antagonists contain an ‘(aryloxy)propanolamine’ (3-amino-1-(aryloxy)propan-2-ol) moiety **2**, typically with *i*-Pr or *t*-Bu as an *N*-substituent (*Fig. 1*) [9]. Propranolol (**3**), atenolol (**4**), and metipranolol (**5**) are the lead compounds in ‘(aryloxy)propanolamines’ [10] (*Fig. 1*). To attain other new β -adrenoceptor-blocking agents, efforts have focussed in modifying the aryloxy moiety so far that led to the synthesis of the current 35 ‘(aryloxy)propanolamines’ largely used in clinical medicine. The structures of the most frequently used β -adrenoceptor-blocking drugs **3–5** are shown in *Fig. 1* [2]. In addition, a number of *O*-substituted oximes such as IPS-339 (**6**; *Fig. 1*) have shown β_2 -selective adrenergic blocking activity [11].

As a prototype of ‘click chemistry’ [12], the recent advance of Cu^I-catalyzed *Huisgen*’s azide–alkyne cycloaddition (CuAAC), which led to high tolerance of other functionalities and almost quantitative transformation under mild conditions, has emerged the powerful tool for introducing a 1,2,3-triazole-diyl residue into the molecule [13]. The incorporation of 1,2,3-triazole-diyl group is an important strategy, since this group has favorable physiochemical properties, which can be readily associated with biologically relevant targets through H-bonding and dipole interactions [12][14].

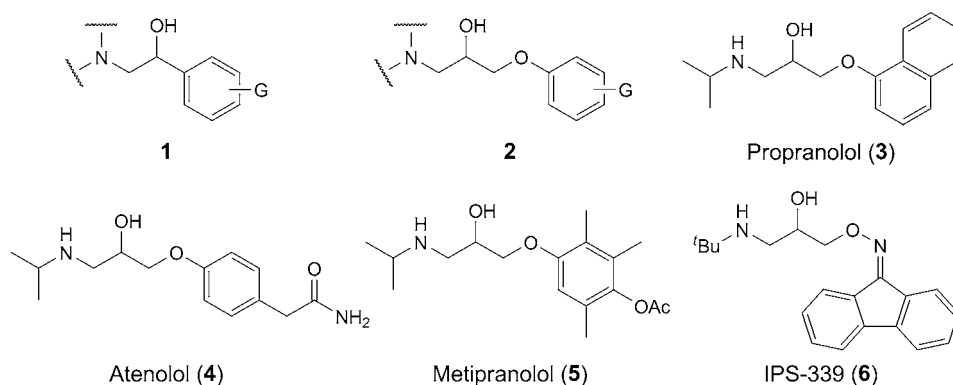


Fig. 1. Structures of well-known β -adrenoceptor-blocking agents

With regard to IPS-339 and in continuation of our research on design and synthesis of new β -adrenoceptor-antagonist analogs [15] as well as oxime chemistry [15][16], we now report the synthesis of some new β -blockers on the basis of '(aryloxy)propanolamine' scaffolds with 1,2,3-triazole diyl and an *O*-substituted oxime residue in their structures. In these compounds, the 1,2,3-triazole derivatives were considered as a substitute for the amine moiety in peculiar fragments of β -blocking agents. The general structures of the title compounds **7a–7j** and **7k–7t** are shown in Fig. 2.

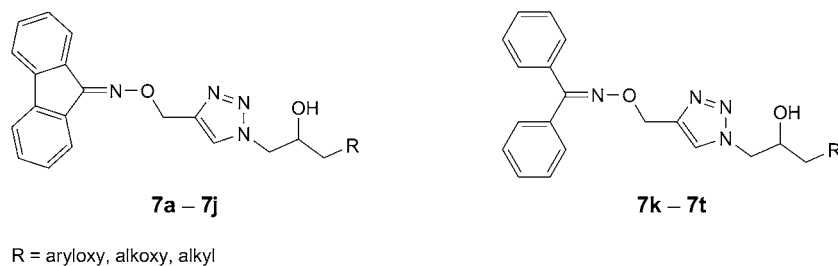
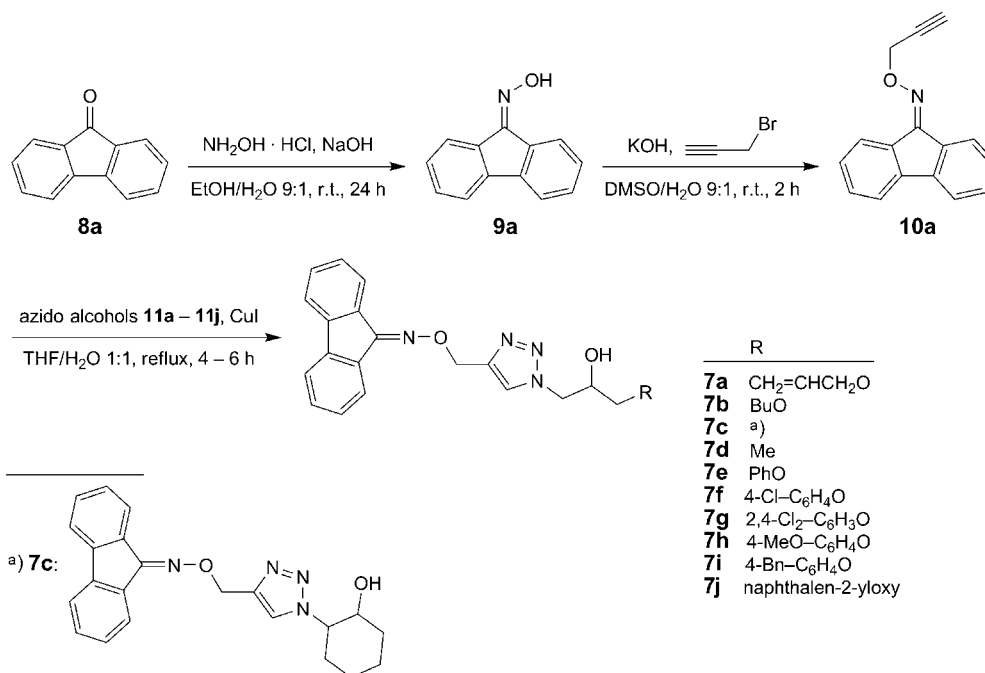


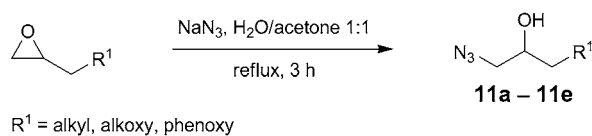
Fig. 2. General structures of potential β -adrenoceptor-blocking agents **7**

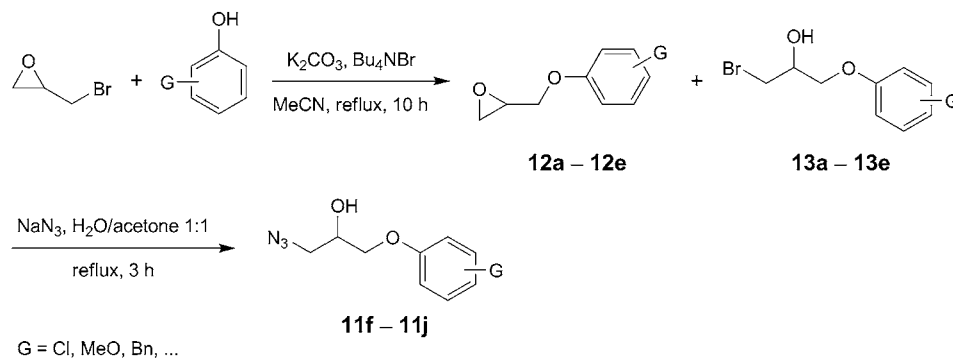
Results and Discussion. – The synthesis of **7a–7j** is outlined in *Scheme 1*. The first step was the preparation of the prerequisite ketoxime **9a** [16b]. The 9*H*-fluoren-9-one *O*-prop-2-ynyl oxime (**10a**) was the next intermediate, as it is a key precursor for the *Huisgen* cycloaddition. Recently, we have reported the *O*-alkylation of oximes with various electrophiles using KOH in DMSO/H₂O at room temperature [15][16a,d]. By this method, the reaction of **9a** with 3-bromoprop-1-yne afforded the corresponding *O*-propargyl oxime **10a** in 89% yield.

The other precursors for the synthesis of the title compounds were β -azido alcohols **11a–11j**. In an effort to consider other groups containing an *O*-atom instead of the aryloxy moiety in '(aryloxy)propanolamines', several structurally diverse β -azido alcohols with an alkoxy and/or alkyl residue were synthesized. Additionally, some β -azido alcohols with various substituents, including Cl, MeO, and Bn, in the aryloxy

Scheme 1. Synthesis of **7a–7j**


residue were prepared. The synthesis of β -azido alcohol derivatives can be achieved *via* regioselective ring opening of corresponding epoxides with NaN₃ [17]. Unfortunately, some epoxides used in the above synthesis are not commercially available; however, they can be easily prepared *via* the reaction of epibromohydrin (=2-(bromomethyl)-oxirane) with appropriate phenols. To this end, two different strategies were applied to prepare β -azido alcohols **11a–11e** and **11f–11j**, respectively (*Schemes 2 and 3*). The β -azido alcohols **11a–11e** were synthesized *via* the reaction of corresponding epoxides with NaN₃ in refluxing acetone/H₂O 1:1. The ring opening of the epoxides was mostly achieved by regioselective attack at the less hindered C-atom of the epoxide. The β -azido alcohols **11f–11j** were prepared in two steps (*Scheme 3*). The first step involved the reaction of various phenols with epibromohydrin using K₂CO₃ in refluxing MeCN. A mixture of **12a–12e** and **13a–13e** was obtained *via* nucleophilic attack of phenols at CH₂-Br and at the less-hindered C-atom of the epoxide, accordingly. The crude mixtures were then treated with NaN₃ in refluxing acetone/H₂O 1:1 to afford the

 Scheme 2. Synthesis of β -Azido Alcohols **11a–11e**


Scheme 3. Synthesis of β -Azido Alcohols **11f–11j**

desired β -azido alcohols **11f–11j**, which were used in the *Huisgen* cycloaddition without further purification.

As expected, the CuI-mediated 1,3-dipolar cycloaddition of *O*-propargyl oxime **10a** with β -azido alcohols **11a–11j** in THF/H₂O 1:1 under reflux condition led regioselectively to 1,2,3-triazole-1,4-diyl containing compounds **7a–7j** in excellent yields (70–88%; *Scheme 1*). By this method, the 1,4-diyl isomers were exclusively attained, and 1,5-diyl isomers were not formed even in trace amounts. The structures and yields of the synthesized compounds are shown in *Schemes 1* and *4*, and in the *Table*, respectively.

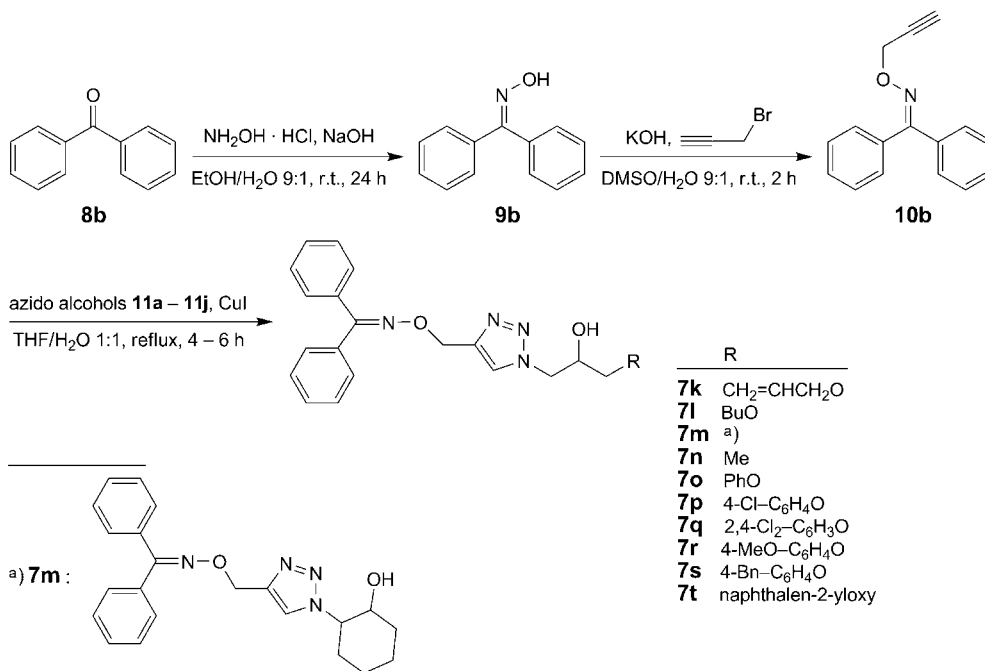
Scheme 4. Synthesis of the New Analogs of β -Adrenoceptor-Blocking Agents **7k–7t**

Table. Synthesized New Analogs of β -Adrenoceptor-Blocking Agents

Compound ^{a)}	M.p. [°]	Yield [%] ^{b)}	Compound ^{a)}	M.p. [°]	Yield [%] ^{b)}
7a	Oil	70	7k	Oil	81
7b	Oil	75	7l	Oil	87
7c	179.0	78	7m	127.0	81
7d	109.4	86	7n	100.0	88
7e	114.0	88	7o	131.0	78
7f	130.0	83	7p	109.0	77
7g	96.0	80	7q	123.0	83
7h	Oil	76	7r	Oil	72
7i	108.0	70	7s	Oil	72
7j	194.4	77	7t	Oil	75

^{a)} All products were characterized by ¹H- and ¹³C-NMR, IR, MS, and elemental analyses. See *Schemes 1* and *4* for the structures of synthesized compounds. ^{b)} Yield of isolated product.

Compounds **7k–7t** were synthesized as outlined in *Scheme 4*. Benzophenone (**8b**) was chosen as the conformationally flexible analog of 9*H*-fluoren-9-one (**8a**). The synthesis of benzophenone oxime (**9b**) [16b] and benzophenone *O*-(prop-2-ynyl)oxime (**10b**) [18] was performed according to the procedures for the preparation of **9a** and **10a**. Consequently, oxime **9b** and *O*-prop-2-ynyl oxime **10b** were obtained in 95 and 86% yields, respectively. The CuI-mediated 1,3-dipolar cycloaddition between **10b** and β -azido alcohols **11a–11j** afforded the corresponding benzophenone *O*-[1-(2-OH-substituted alkyl/aryl)-1*H*-1,2,3-triazol-4-yl]methyl oximes **7k–7t** in 72–88% yields (*Scheme 4*).

All compounds were fully characterized, and their structures were confirmed by IR, and ¹H- and ¹³C-NMR spectroscopy, mass spectrometry, and elemental analysis. Compounds **7a–7t** display close structural similarity with IPS-339 (**6**). Furthermore, compounds **7k–7t** can be considered as conformationally flexible analogs of compounds **7a–7j**. The biological studies of **7a–7t** are currently under investigation and will be reported in due course.

In summary, we have elaborated four to five step syntheses of the new analogs of β -adrenoceptor-blocking agents, *i.e.*, **7a–7t** containing 1,2,3-triazoldiyl and *O*-substituted oxime moieties in their structures. In these syntheses, the formation of the oximes of 9*H*-fluoren-9-one and benzophenone, *i.e.*, **9a** and **9b**, and the subsequent reaction of **9a** and **9b** with 3-bromoprop-1-yne yielded *O*-propargyloximes **10a** and **10b**, respectively. Finally, the CuI-catalyzed *Huisgen* cycloaddition of **10a** and **10b** with pre-synthesized β -azido alcohols **11a–11j** led to the regioselective formation of the target molecules **7a–7t** in good-to-excellent yields.

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Experimental Part

1. *General*. All chemicals were obtained from *Fluka* or *Merck*. Solvents were purified and dried by standard procedures, and stored over 3-Å molecular sieves. TLC: *SILG/UV 254* silica-gel plates. Column chromatography (CC): silica gel *60* (SiO₂; 0.063–0.200 mm, 70–230 mesh; *ASTM*). M.p.: *Büchi-510*

apparatus; in open capillaries; uncorrected. IR Spectra: *Shimadzu-FT-IR-8300* spectrophotometer; $\tilde{\nu}$ in cm^{-1} . ^1H - and ^{13}C -NMR Spectra: *Bruker-Avance-DPX-250* spectrometer; at 250 and 62.5 MHz, resp., δ in ppm, J in Hz. GC/MS: *Shimadzu GC/MS-QP 1000-EX* apparatus; in m/z (rel. %). Elemental analyses (CHNS): *Perkin-Elmer-240-B* microanalyzer.

2. *General Procedure for the Synthesis of Oximes 9a [16b] and 9b [16b]*. In a round-bottomed flask (100 ml), a mixture of the appropriate ketone (0.01 mol), $\text{NH}_2\text{OH} \cdot \text{HCl}$ (1.03 g, 0.015 mol), NaOH (0.6 g, 0.015 mol), and H_2O (2 ml) was dissolved in EtOH (18 ml), and the soln. was stirred for 24 h at r.t. Then, the mixture was poured into 20 g of ice/10 g of H_2O . The oxime precipitated immediately, and it was filtered, washed with cold H_2O , and dried in vacuum oven (60° for 2 h). Recrystallization from hot $\text{MeOH}/\text{H}_2\text{O}$ afforded pure **9a** and **9b**.

3. *General Procedure for the Synthesis of Oxime Ethers 10a and 10b [18]*. In a round-bottomed flask (100 ml), 3-bromoprop-1-yne (1.55 g, 0.013 mol) was added portionwise to a soln. of the appropriate oxime **9** (0.01 mol), KOH (0.56 g, 0.01 mol), and 2 ml of H_2O in DMSO (18 ml). The mixture was stirred for 2 h at r.t. (TLC control). Then, the crude product was dissolved in CHCl_3 (150 ml) and washed with H_2O (3×200 ml). The org. layer was dried (Na_2SO_4 , 10 g) and concentrated to afford the crude product, which was purified by CC (SiO_2 , hexane/ AcOEt 10:1).

9H-Fluoren-9-one O-(Prop-2-yn-1-yl)oxime (**10a**). Yield 2.07 g (89%). Yellow solid. R_f ($\text{AcOEt}/\text{hexane}$ 1:2) 0.70. M.p. $98-100^\circ$. IR (KBr): 3050s, 2975m, 2157s, 1650s, 1473m, 1224s. ^1H -NMR (CDCl_3): 3.09 (s, $\equiv\text{CH}$); 4.26 (s, NOCH_2); 7.28–7.41 (m, 4 arom. H); 7.63–7.69 (m, 2 arom. H); 7.80–7.83 (m, 1 arom. H); 8.39–8.42 (m, 1 arom. H). ^{13}C -NMR (CDCl_3): 59.47; 76.38; 78.90; 119.26; 120.56; 120.93; 121.46; 127.81; 128.37; 129.58; 129.92; 130.46; 130.95; 134.29; 135.84; 154.79. MS: 233.08 (5.8, M^+). Anal. calc. for $\text{C}_{16}\text{H}_{11}\text{NO}$ (233.26): C 82.38, H 4.75, N 6.00; found: C 82.46, H 4.63, N 6.09.

4. *General Procedure for the Synthesis of β -Azido Alcohols 11a–11e [17a–c]*. In a double-necked round-bottomed flask (100 ml), equipped with a condenser, a mixture of the appropriate epoxide (0.03 mol) and NaN_3 (2.60 g, 0.04 mol) was dissolved in acetone/ H_2O 1:1 (40 ml) and heated under reflux for 3 h (TLC control). The solvent was evaporated at reduced pressure, and the residue was dissolved in CHCl_3 (150 ml) and washed with H_2O (2×150 ml). The org. layer was dried (Na_2SO_4 , 10 g) and concentrated to afford the corresponding β -azido alcohols **11a–11e**. These compounds were used in the next step without further purification or characterization.

5. *General Procedure for the Synthesis of β -Azido Alcohols 11f–11j*. In a double-necked round-bottomed flask (100 ml), equipped with a condenser, a mixture of the appropriate phenol (0.03 mol), K_2CO_3 (4.14 g, 0.03 mol), epibromohydrin (=2-(bromomethyl)oxirane; 4.92 g, 0.036 mol), and cat. amounts of Bu_4NBr (0.1 g) were dissolved in MeCN (40 ml). Then, the mixture was heated to reflux for 10 h (TLC control). The solvent was evaporated at reduced pressure, and the residue was dissolved in CHCl_3 (150 ml) and washed with H_2O (2×150 ml). The org. layer was dried (Na_2SO_4 , 10 g) and concentrated to afford the crude product consisting of a mixture of **12a–12e** and **13a–13e**. The crude product was then used without any further purification for the synthesis of **11f–11j** according to the procedure described above. All products have been reported previously [17a,c] except β -azido alcohols **11g** ($G = 2,4\text{-Cl}_2$) and **11i** ($G = 4\text{-Bn}$).

1-Azido-3-(2,4-dichlorophenyl)propan-2-ol (**11g**). Pale-yellow liquid. R_f ($\text{AcOEt}/\text{hexane}$ 1:2) 0.48. IR (film): 3340 (br.), 3050s, 2974m, 2124s, 1457s, 810m.

1-Azido-3-(4-benzylphenyl)propan-2-ol (**11i**). Pale-yellow liquid. R_f ($\text{AcOEt}/\text{hexane}$ 1:2) 0.44. IR (film): 3365 (br.), 3045s, 2982m, 2115s, 1467s, 825m.

6. *General Procedure for the Synthesis of β -Adrenoceptor-Blocking Agents 7a–7t*. In a double-necked round-bottomed flask (100 ml), equipped with a condenser, a mixture of the appropriate alkyne **10** (0.005 mol), appropriate β -azido alcohol **11** (0.007 mol), and cat. amounts of CuI (0.1 g) were dissolved in $\text{THF}/\text{H}_2\text{O}$ 1:1 (20 ml). Then, the mixture was heated to reflux for 4–6 h (TLC control). The solvent was evaporated at reduced pressure, and the residue was dissolved in CHCl_3 (100 ml) and washed with H_2O (2×100 ml). The org. layer was dried (Na_2SO_4 , 10 g) and concentrated to afford the crude product, which was purified by CC (SiO_2) eluting with proper solvents.

9H-Fluoren-9-one O-([1-[2-Hydroxy-3-(prop-2-en-1-yloxy)propyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (**7a**). Purified by CC (SiO_2 ; $\text{AcOEt}/\text{hexane}$ 2:1). Yield 0.54 g (70%). Yellow oil. R_f ($\text{AcOEt}/\text{hexane}$ 8:1) 0.49. IR (film): 3400 (br.), 3025s, 2947m, 1655s, 1520m, 1474s, 1230s. ^1H -NMR (CDCl_3): 3.25–3.41

(complex, CH_2OCH_2); 4.13 (s, OH, exchangeable with D_2O); 4.27–4.51 (m, NCH_2); 4.89–4.91 (m, CHOH); 5.05–5.18 (m, $=\text{CH}_2$); 5.47 (s, NOCH_2); 5.70–5.81 (m, $=\text{CH}$); 7.18–7.32 (m, 6 arom. H); 7.50–7.56 (m, 2 arom. H); 7.73 (s, H–C(5) of triazole). $^{13}\text{C-NMR}$ (CDCl_3): 52.82; 63.09; 69.23; 70.72; 72.37; 117.75; 119.86; 120.29; 121.66; 121.91; 124.31; 124.70; 127.84; 128.23; 129.47; 129.99; 130.11; 131.07; 131.19; 134.68; 145.61; 165.28. MS: 390.17 (2.9, M^+). Anal. calc. for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_3$ (390.44): C 67.68, H 5.68, N 14.35; found: C 67.60, H 5.73, N 14.48.

9H-Fluoren-9-one O-([1-(3-Butoxy-2-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (7b). Purified by CC (SiO_2 ; AcOEt/hexane 2:1). Yield 0.61 g (75%). Brown oil. R_f (AcOEt/hexane 8:1) 0.55. IR (film): 3360 (br.), 3045s, 2968m, 1669s, 1500m, 1448s, 1243s. $^1\text{H-NMR}$ ($(\text{D}_6)\text{DMSO}$): 0.78 (t, $J = 7.3$, Me); 1.24–1.30 (m, CH_2 Me); 1.39–1.45 (m, OCH_2CH_2); 3.26–3.39 (m, CH_2OCH_2); 3.98–4.01 (m, CHOH); 4.33–4.46 (m, NCH_2); 5.28 (s, OH, exchangeable with D_2O); 5.49 (s, NOCH_2); 7.30–7.47 (m, 4 arom. H); 7.68–7.83 (m, 3 arom. H); 7.83–8.16 (m, 1 arom. H); 8.19 (s, H–C(5) of triazole). $^{13}\text{C-NMR}$ ($(\text{D}_6)\text{DMSO}$): 13.64; 18.68; 31.09; 52.82; 68.16; 68.63; 70.28; 71.93; 119.81; 120.49; 121.30; 125.57; 128.17; 128.46; 128.80; 129.36; 130.38; 131.58; 134.30; 139.57; 140.67; 142.45; 151.74. MS: 406.20 (4.5, M^+). Anal. calc. for $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_3$ (406.48): C 67.96, H 6.45, N 13.78; found: C 68.08, H 6.52, N 13.71.

9H-Fluoren-9-one O-([1-(2-Hydroxycyclohexyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (7c). Purified by CC (SiO_2 ; AcOEt/hexane 2:1). Yield 0.58 g (78%). Pale-yellow solid. R_f (AcOEt/hexane 8:1) 0.40. M.p. 178–180°. IR (KBr): 3300 (br.), 3045s, 2984m, 1664s, 1500m, 1462m, 1227s. $^1\text{H-NMR}$ ($(\text{D}_6)\text{DMSO}$): 1.31–1.35 (m, CH_2); 1.68–1.71 (m, CH_2); 1.94–1.96 (m, 2 CH_2); 3.72 (s, OH, exchangeable with D_2O); 4.15–4.21 (m, CHOH); 4.91–4.94 (m, NCH); 7.31–7.48 (m, 4 arom. H); 7.69–7.82 (m, 3 arom. H); 8.11–8.13 (m, 1 arom. H); 8.23 (s, H–C(5) of triazole). $^{13}\text{C-NMR}$ ($(\text{D}_6)\text{DMSO}$): 23.73; 24.38; 31.81; 34.77; 65.80; 68.95; 71.20; 120.52; 121.32; 124.02; 128.17; 128.49; 128.82; 128.91; 129.39; 130.34; 131.55; 134.37; 139.58; 140.67; 141.85; 151.61. MS: 374.17 (2.1, M^+). Anal. calc. for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_2$ (374.44): C 70.57, H 5.92, N 14.96; found: C 70.69, H 5.98, N 14.83.

9H-Fluoren-9-one O-([1-(2-Hydroxybutyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (7d). Purified by CC (SiO_2 ; AcOEt/hexane 2:1). Yield 0.60 g (86%). Yellow solid. R_f (AcOEt/hexane 8:1) 0.50. M.p. 109–111°. IR (KBr): 3345 (br.), 3085m, 2973m, 1670s, 1509m, 1425m, 1245s. $^1\text{H-NMR}$ (CDCl_3): 1.47 (t, $J = 6.8$, Me); 1.99–2.04 (m, MeCH_2); 4.50 (s, OH, exchangeable with D_2O); 4.69–4.78 (m, NCH_2); 4.90–4.96 (m, CHOH); 6.00 (s, NOCH_2); 7.76–8.37 (m, 8 arom. H); 8.73 (s, H–C(5) of triazole). $^{13}\text{C-NMR}$ (CDCl_3): 9.74; 27.42; 55.72; 68.79; 71.41; 119.77; 119.86; 121.65; 124.87; 127.83; 128.19; 129.40; 129.99; 130.30; 131.07; 135.24; 140.20; 141.27; 143.79; 152.75. MS: 348.16 (1.2, M^+). Anal. calc. for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2$ (348.40): C 68.95, H 5.79, N 16.08; found: C 68.83, H 5.74, N 16.19.

9H-Fluoren-9-one O-([1-(2-Hydroxy-3-phenoxypropyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (7e). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.75 g (88%). White solid. R_f (AcOEt/hexane 8:1) 0.57. M.p. 113–115°. IR (KBr): 3400 (br.), 3035s, 2985m, 1665s, 1510m, 1461s, 1254s. $^1\text{H-NMR}$ (CDCl_3): 3.69 (s, OH, exchangeable with D_2O); 3.85–3.86 (m, NCH_2); 4.36–4.42 (m, PhOCH_2); 4.53–4.59 (m, CHOH); 5.40 (s, NOCH_2); 6.74–6.77 (m, 3 arom. H); 7.10–7.28 (m, 7 arom. H); 7.48–7.72 (m, 3 arom. H); 8.11 (s, H–C(5) of triazole). $^{13}\text{C-NMR}$ (CDCl_3): 53.01; 55.03; 68.76; 68.84; 114.46; 119.79; 119.88; 121.47; 121.69; 124.93; 127.87; 128.24; 129.46; 129.57; 130.01; 130.38; 131.10; 135.30; 140.28; 141.35; 144.31; 152.88; 158.02. MS: 426.17 (15.6, M^+). Anal. calc. for $\text{C}_{25}\text{H}_{22}\text{N}_4\text{O}_3$ (426.47): C 70.41, H 5.20, N 13.14; found: C 70.48, H 5.24, N 13.26.

9H-Fluoren-9-one O-([1-[3-(4-Chlorophenoxy)-2-hydroxypropyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (7f). Purified by CC (SiO_2 ; AcOEt/hexane 2:1). Yield 0.76 g (83%). Yellow solid. R_f (AcOEt/hexane 8:1) 0.53. M.p. 129–131°. IR (KBr): 3300 (br.), 3027m, 2970m, 1665s, 1508m, 1469m, 1246s. $^1\text{H-NMR}$ (CDCl_3): 3.72–3.77 (m, NCH_2); 4.26–4.54 (complex m, $\text{ArOCH}_2\text{CHOH}$); 5.32 (s, NOCH_2); 6.55 (d, $J = 8.9$, 2 arom. H); 6.96–7.22 (m, 6 arom. H); 7.39–7.69 (m, 4 arom. H); 8.03 (s, H–C(5) of triazole). $^{13}\text{C-NMR}$ (CDCl_3): 53.07; 68.45; 68.64; 69.04; 115.71; 119.85; 121.66; 125.13; 126.17; 127.51; 127.88; 128.22; 129.34; 129.39; 130.08; 130.28; 131.17; 135.17; 140.24; 141.33; 144.09; 152.90; 156.68. MS: 460.13 (7.1, M^+). Anal. calc. for $\text{C}_{25}\text{H}_{21}\text{ClN}_4\text{O}_3$ (460.91): C 65.15, H 4.59, Cl 7.69, N 12.16; found: C 65.27, H 4.68, Cl 7.72, N 12.01.

9H-Fluoren-9-one O-([1-[3-(2,4-Dichlorophenoxy)-2-hydroxypropyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (7g). Purified by CC (SiO_2 ; AcOEt/hexane 2:1). Yield 0.79 g (80%). Pale-yellow solid. R_f (AcOEt/hexane 8:1) 0.47. M.p. 95–97°. IR (KBr): 3360 (br.), 3050m, 2962m, 1671s, 1504m, 1445s, 1248s.

¹H-NMR (CDCl₃): 3.70 (s, OH, exchangeable with D₂O); 3.91–3.93 (m, NCH₂); 4.44–4.50 (m, CHOH); 4.53 (dd, *J* = 6.3, 13.8, 1 H, ArOCH₂); 4.65 (dd, *J* = 3.6, 13.8, 1 H, ArOCH₂); 5.49 (s, NOCH₂); 6.70 (d, *J* = 8.8, 1 arom. H); 7.03 (d, *J* = 8.8, 1 arom. H); 7.20–7.38 (m, 5 arom. H); 7.55–7.82 (m, 4 arom. H); 8.18 (s, H–C(5) of triazole). ¹³C-NMR (CDCl₃): 52.46; 67.54; 68.68; 70.66; 115.20; 120.55; 121.30; 122.47; 124.68; 125.74; 128.05; 128.18; 128.50; 128.81; 129.23; 129.37; 130.38; 131.59; 134.32; 139.60; 140.69; 142.50; 151.70; 152.79; 164.97. MS: 494.09 (4.6, *M*⁺). Anal. calc. for C₂₅H₂₀Cl₂N₄O₃ (495.36): C 60.62, H 4.07, Cl 14.31, N 11.31; found: C 60.76, H 4.17, Cl 14.20, N 11.23.

9H-Fluoren-9-one O-([1-[2-Hydroxy-3-(4-methoxyphenoxy)propyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (**7h**). Purified by CC (SiO₂; AcOEt/hexane 2:1). Yield 0.69 g (76%). Yellow oil. *R*_f (AcOEt/hexane 8:1) 0.47. IR (film): 3370 (br.), 3045s, 2971m, 1665s, 1502m, 1450s, 1235s. ¹H-NMR (CDCl₃): 3.61 (s, MeO); 3.75–3.79 (complex, NCH₂, OH); 4.32–4.34 (m, CHOH); 4.39 (dd, *J* = 0.9, 7.0, 1 H, ArOH₂); 4.51 (dd, *J* = 1.9, 13.5, 1 H, ArOCH₂); 5.39 (s, NOCH₂); 6.65–6.68 (m, 4 arom. H); 7.11–7.15 (m, 4 arom. H); 7.23–7.27 (m, 2 arom. H); 7.44–7.47 (m, 2 arom. H); 7.72 (s, H–C(5) of triazole). ¹³C-NMR (CDCl₃): 53.02; 55.63; 60.40; 68.78; 69.59; 114.65; 115.49; 119.78; 119.86; 121.68; 124.97; 127.85; 128.23; 129.44; 129.99; 130.35; 131.08; 135.28; 140.26; 141.32; 144.22; 152.20; 152.83; 154.24. MS: 456.18 (0.5, *M*⁺). Anal. calc. for C₂₆H₂₄N₄O₄ (456.49): C 68.41, H 5.30, N 12.27; found: C 68.53, H 5.35, N 12.18.

9H-Fluoren-9-one O-([1-[2-Hydroxy-3-[4-(phenylmethyl)phenoxy]propyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (**7i**). Purified by CC (SiO₂; AcOEt/hexane 2:1). Yield 0.72 g (70%). Pale-yellow solid. *R*_f (AcOEt/hexane 8:1) 0.68. M.p. 107–109°. IR (KBr): 3300 (br.), 3058s, 2945m, 1670s, 1500m, 1452s, 1210s. ¹H-NMR ((D₆)DMSO): 3.81 (s, PhCH₂); 3.85–3.87 (m, NCH₂); 4.23 (s, OH, exchangeable with D₂O); 4.40 (dd, *J* = 7.4, 13.8, 1 H, ArOH₂); 4.55 (dd, *J* = 3.9, 13.8, 1 H, ArOCH₂); 5.47 (s, NOCH₂); 5.53–5.56 (m, CHOH); 6.79–6.82 (m, 2 arom. H); 7.04–7.47 (m, 11 arom. H); 7.80–7.85 (m, 3 arom. H); 8.12–8.14 (m, 1 arom. H); 8.24 (s, H–C(5) of triazole). ¹³C-NMR ((D₆)DMSO): 39.46; 52.63; 67.75; 68.72; 69.51; 114.41; 120.55; 121.32; 125.72; 125.77; 128.17; 128.29; 128.56; 128.49; 128.82; 129.41; 129.60; 130.36; 131.56; 133.49; 134.37; 139.21; 139.62; 140.70; 141.61; 142.45; 151.71; 156.58. MS: 516.22 (6.1, *M*⁺). Anal. calc. for C₃₂H₂₈N₄O₃ (516.59): C 74.40, H 5.46, N 10.85; found: C 74.54, H 5.40, N 10.92.

9H-Fluoren-9-one O-([1-[2-Hydroxy-3-(naphthalen-2-yloxy)propyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (**7j**). Purified by CC (SiO₂; AcOEt/hexane 2:1). Yield 0.73 g (77%). White solid. *R*_f (AcOEt/hexane 8:1) 0.56. M.p. 158–160°. IR (KBr): 3410 (br.), 3050m, 2934m, 1665s, 1507m, 1479m, 1285s. ¹H-NMR ((D₆)DMSO): 4.05–4.07 (m, NCH₂); 4.31 (s, OH, exchangeable with D₂O); 4.48 (dd, *J* = 7.3, 13.6, 1 H, ArOCH₂); 4.63 (dd, *J* = 3.8, 13.8, 1 H, ArOCH₂); 5.49 (s, NOCH₂); 5.62–5.64 (m, CHOH); 7.28–7.45 (m, 8 arom. H); 7.75–7.82 (m, 6 arom. H); 8.12 (s, 1 arom. H); 8.29 (s, H–C(5) of triazole). ¹³C-NMR ((D₆)DMSO): 52.65; 67.74; 68.73; 69.57; 106.75; 118.60; 120.53; 121.32; 123.61; 125.75; 125.83; 126.15; 126.34; 126.64; 127.44; 128.17; 128.50; 128.82; 129.26; 129.39; 130.37; 131.57; 134.14; 134.34; 139.61; 140.69; 142.48; 151.71; 156.18. MS: 476.18 (0.6, *M*⁺). Anal. calc. for C₂₉H₂₄N₄O₃ (476.53): C 73.09, H 5.08, N 11.76; found: C 73.23, H 5.01, N 11.87.

Diphenylmethanone O-([1-[2-Hydroxy-3-(prop-2-en-1-yloxy)propyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (**7k**). Purified by CC (SiO₂; AcOEt/hexane 1:1). Yield 0.63 g (81%). Colorless oil. *R*_f (AcOEt/hexane 8:1) 0.62. IR (film): 3400 (br.), 3080m, 2947m, 1660s, 1500m, 1456m, 1209s. ¹H-NMR (CDCl₃): 3.31–3.33 (m, OCH₂CHOH); 3.85–3.87 (m, CH₂CH=C); 4.13 (s, OH, exchangeable with D₂O); 4.23 (dd, *J* = 6.7, 13.8, 1 H, NCH₂); 4.38 (dd, *J* = 3.6, 13.8, 1 H, NCH₂); 4.75–4.77 (m, CHOH); 5.04–5.11 (m, =CH₂); 5.20 (s, NOCH₂); 5.71–5.82 (m, =CH); 7.20–7.42 (m, 10 arom. H); 7.70 (s, H–C(5) of triazole). ¹³C-NMR (CDCl₃): 53.10; 67.62; 68.81; 71.18; 72.17; 117.24; 125.02; 127.96; 128.06; 128.23; 128.89; 129.24; 129.46; 132.98; 134.35; 136.20; 144.10; 157.45. MS: 392.18 (2.1, *M*⁺). Anal. calc. for C₂₂H₂₄N₄O₃ (392.45): C 67.33, H 6.16, N 14.28; found: C 67.46, H 6.28, N 14.20.

Diphenylmethanone O-([1-(3-Butoxy-2-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (**7l**). Purified by CC (SiO₂; AcOEt/hexane 1:1). Yield 0.71 g (87%). Yellow oil. *R*_f (AcOEt/hexane 8:1) 0.57. IR (film): 3380 (br.), 3040s, 2956m, 1678m, 1505m, 1430m, 1242s. ¹H-NMR (CDCl₃): 0.87 (t, *J* = 7.3, Me); 1.32–1.38 (m, CH₂ Me); 1.50–1.55 (m, OCH₂CH₂); 2.93 (s, OH, exchangeable with D₂O); 3.33–3.46 (m, CH₂OCH₂); 4.14–4.18 (m, CHOH); 4.34 (dd, *J* = 6.7, 14.0, 1 H, NCH₂); 4.48 (dd, *J* = 3.8, 13.9, 1 H, NCH₂); 5.32 (s, NOCH₂); 7.26–7.48 (m, 10 arom. H); 7.67 (s, H–C(5) of triazole). ¹³C-NMR (CDCl₃): 13.70; 18.72; 31.13; 52.84; 68.17; 68.71; 70.27; 72.03; 121.30; 125.60; 128.18; 128.49; 128.80;

129.37; 130.38; 131.58; 134.32; 139.60; 142.37. MS: 408.22 (2.4, M^+). Anal. calc. for $C_{23}H_{28}N_4O_3$ (408.49): C 67.63, H 6.91, N 13.72; found: C 67.78, H 7.02, N 13.65.

Diphenylmethanone O-([1-(2-Hydroxycyclohexyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (7m). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.63 g (81%). White solid. R_f (AcOEt/hexane 8:1) 0.56. M.p. 132–134°. IR (KBr): 3375 (br.), 3045s, 2964m, 1661s, 1503m, 1468m, 1235s. 1H -NMR ($CDCl_3$): 1.40–1.43 (m, 2 CH_2); 1.85–1.86 (m, CH_2); 2.14–2.19 (m, CH_2); 3.20 (s, OH, exchangeable with D_2O); 3.98–4.12 (m, $NCHCHOH$); 5.28 (s, $NOCH_2$); 7.31–7.45 (m, 10 arom. H); 7.56 (s, H–C(5) of triazole). ^{13}C -NMR ($CDCl_3$): 23.97; 24.70; 31.55; 33.66; 66.79; 67.98; 72.45; 122.81; 128.00; 128.04; 128.22; 128.92; 129.33; 129.42; 132.94; 136.29; 144.18; 160.01. MS: 376.19 (1.9, M^+). Anal. calc. for $C_{22}H_{24}N_4O_2$ (376.45): C 70.19, H 6.43, N 14.88; found: C 70.27, H 6.56, N 14.80.

Diphenylmethanone O-([1-(2-Hydroxybutyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (7n). Purified by CC (SiO_2 ; AcOEt/hexane 2:1). Yield 0.62 g (88%). Yellow solid. R_f (AcOEt/hexane 8:1) 0.50. M.p. 109–111°. IR (KBr): 3415 (br.), 3050m, 2975m, 1669s, 1500m, 1449m, 1235s. 1H -NMR ($(D_6)DMSO$): 0.83 (t, $J = 7.4$, Me); 1.23–1.39 (m, CH_2 Me); 3.70 (s, OH, exchangeable with D_2O); 4.17 (dd, $J = 7.3$, 13.8, 1 H, NCH_2); 4.30 (dd, $J = 3.6$, 13.7, 1 H, NCH_2); 4.99–5.02 (m, $CHOH$); 5.19 (s, $NOCH_2$); 7.23–7.43 (m, 10 arom. H); 8.04 (s, H–C(5) of triazole). ^{13}C -NMR ($(D_6)DMSO$): 9.59; 27.10; 54.91; 67.36; 70.27; 125.08; 127.40; 128.17; 128.34; 128.74; 128.81; 129.47; 132.75; 135.72; 142.92; 156.51. MS: 350.17 (1.0, M^+). Anal. calc. for $C_{20}H_{22}N_4O_2$ (350.41): C 68.55, H 6.33, N 15.99; found: C 68.62, H 6.38, N 15.91.

Diphenylmethanone O-([1-(2-Hydroxy-3-phenoxypropyl)-1H-1,2,3-triazol-4-yl]methyl)oxime (7o). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.67 g (78%). White solid. R_f (AcOEt/hexane 8:1) 0.67. M.p. 130–132°. IR (KBr): 3400 (br.), 3065s, 2986m, 1664m, 1503m, 1468s, 1235s. 1H -NMR ($(D_6)DMSO$): 3.89–3.91 (m, NCH_2); 4.21 (s, OH, exchangeable with D_2O); 4.39 (dd, $J = 7.4$, 13.8, 1 H, $PhOCH_2$); 4.54 (dd, $J = 4.0$, 13.8, 1 H, $PhOCH_2$); 5.21 (s, $NOCH_2$); 5.54–5.57 (m, $CHOH$); 6.89–6.92 (m, 3 arom. H); 7.22–7.43 (m, 12 arom. H); 8.10 (s, H–C(5) of triazole). ^{13}C -NMR ($(D_6)DMSO$): 52.50; 67.32; 67.74; 69.35; 114.42; 120.71; 125.33; 127.39; 128.18; 128.36; 128.71; 128.81; 129.43; 129.49; 132.72; 135.68; 143.04; 156.52; 158.25. MS: 428.18 (2.8, M^+). Anal. calc. for $C_{25}H_{24}N_4O_3$ (428.48): C 70.08, H 5.65, N 13.08; found: C 70.17, H 5.69, N 12.98.

Diphenylmethanone O-([1-[3-(4-Chlorophenoxy)-2-hydroxypropyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (7p). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.71 g (77%). Pale-yellow solid. R_f (AcOEt/hexane 8:1) 0.80. M.p. 108–110°. IR (KBr): 3370 (br.), 3057m, 2973m, 1669s, 1500m, 1469m, 1250s. 1H -NMR ($(D_6)DMSO$): 3.90–4.00 (m, NCH_2); 4.21 (s, OH, exchangeable with D_2O); 4.40 (dd, $J = 6.6$, 13.7, 1 H, $ArOCH_2$); 4.54 (dd, $J = 3.2$, 13.7, 1 H, $ArOCH_2$); 5.21 (s, $NOCH_2$); 5.57–5.59 (m, $CHOH$); 6.93–6.96 (m, 2 arom. H); 7.25–7.41 (m, 12 arom. H); 8.10 (s, H–C(5) of triazole). ^{13}C -NMR ($(D_6)DMSO$): 52.43; 67.34; 67.66; 69.83; 116.24; 124.45; 125.33; 127.41; 128.18; 128.35; 128.73; 128.81; 129.17; 129.49; 132.73; 135.70; 143.08; 156.54; 157.16. MS: 462.15 (3.9, M^+). Anal. calc. for $C_{25}H_{23}ClN_4O_3$ (462.93): C 64.86, H 5.01, Cl 7.66, N 12.10; found: C 64.98, H 5.04, Cl 7.57, N 12.02.

Diphenylmethanone O-([1-[3-(2,4-Dichlorophenoxy)-2-hydroxypropyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (7q). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.83 g (83%). Pale-yellow solid. R_f (AcOEt/hexane 8:1) 0.64. M.p. 122–124°. IR (KBr): 3250 (br.), 3100m, 2958m, 1657s, 1506m, 1471s, 1232s. 1H -NMR ($(D_6)DMSO$): 3.98 (dd, $J = 3.1$, 5.2, NCH_2); 4.26 (s, OH, exchangeable with D_2O); 4.42 (dd, $J = 7.4$, 13.8, 1 H, $ArOCH_2$); 4.57 (dd, $J = 3.9$, 13.8, 1 H, $ArOCH_2$); 5.21 (s, $NOCH_2$); 5.61–5.63 (m, $CHOH$); 7.12–7.43 (m, 13 arom. H); 8.10 (s, H–C(5) of triazole). ^{13}C -NMR ($(D_6)DMSO$): 52.37; 67.32; 67.56; 70.66; 115.23; 122.52; 124.71; 125.32; 127.39; 128.04; 128.18; 128.35; 128.72; 128.82; 129.23; 129.49; 132.72; 135.67; 143.12; 152.81; 156.54. MS: 496.11 (0.3, M^+). Anal. calc. for $C_{25}H_{22}Cl_2N_4O_3$ (497.37): C 60.37, H 4.46, Cl 14.26, N 11.26; found: C 60.45, H 4.40, Cl 14.37, N 11.18.

Diphenylmethanone O-([1-[2-Hydroxy-3-(4-methoxyphenoxy)propyl]-1H-1,2,3-triazol-4-yl]methyl)oxime (7r). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.66 g (72%). Pale-yellow oil. R_f (AcOEt/hexane 8:1) 0.55. IR (film): 3400 (br.), 3037s, 2982m, 1673m, 1505m, 1458s, 1232s. 1H -NMR ($CDCl_3$): 3.73 (s, MeO); 3.86–3.90 (m, NCH_2); 3.97 (s, OH, exchangeable with D_2O); 4.37–4.39 (m, $CHOH$); 4.40 (dd, $J = 6.1$, 19.7, 1 H, $ArOCH_2$); 4.59 (dd, $J = 3.3$, 13.6, 1 H, $ArOCH_2$); 5.28 (s, $NOCH_2$); 6.79–6.82 (m, 4 arom. H); 7.25–7.45 (m, 10 arom. H); 7.68 (s, H–C(5) of triazole). ^{13}C -NMR ($CDCl_3$): 52.86; 55.69; 67.78; 68.85; 69.49; 114.72; 115.52; 115.71; 124.70; 127.98; 128.05; 128.93; 129.28; 129.46;

132.92; 136.22; 144.80; 152.18; 154.33; 157.63. MS: 458.20 (10.9, M^+). Anal. calc. for $C_{26}H_{26}N_4O_4$ (458.51): C 68.11, H 5.72, N 12.22; found: C 68.24, H 5.70, N 12.29.

Diphenylmethanone O-[(1-[2-Hydroxy-3-[4-(phenylmethyl)phenoxy]propyl]-1H-1,2,3-triazol-4-yl)-methyl]oxime (7s). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.79 g (76%). Pale-yellow oil. R_f (AcOEt/hexane 8:1) 0.71. IR (film): 3385 (br.), 3073m, 2976m, 1668s, 1500m, 1445m, 1243s. 1H -NMR ($CDCl_3$): 3.72 (s, $PhCH_2$, NCH_2); 4.20–4.41 (complex, $ArOCH_2CHOH$); 5.09 (s, $NOCH_2$); 6.59 (d, $J = 8.6$, 2 arom. H); 6.87–7.28 (m, 17 arom. H); 7.52 (s, H–C(5) of triazole). ^{13}C -NMR ($CDCl_3$): 41.06; 53.09; 67.68; 68.57; 69.02; 114.60; 125.00; 126.09; 128.06; 128.13; 128.52; 128.86; 128.97; 129.33; 129.53; 129.99; 133.03; 134.03; 136.28; 141.47; 144.34; 144.42; 156.69; 157.65. MS: 518.23 (4.8, M^+). Anal. calc. for $C_{32}H_{30}N_4O_3$ (518.61): C 74.11, H 5.83, N 10.80; found: C 74.27, H 5.90, N 10.67.

Diphenylmethanone O-[(1-[2-Hydroxy-3-(naphthalen-2-yloxy)propyl]-1H-1,2,3-triazol-4-yl)methyl]-oxime (7t). Purified by CC (SiO_2 ; AcOEt/hexane 1:1). Yield 0.75 g (75%). Pale-yellow oil. R_f (AcOEt/hexane 8:1) 0.68. IR (film): 3420 (br.), 3056m, 2957m, 1667s, 1508m, 1459s, 1228s. 1H -NMR ($CDCl_3$): 3.82–3.84 (m, NCH_2); 4.25–4.32 (complex, $CHOH$); 4.37–4.44 (m, $ArOCH_2$); 5.11 (s, $NOCH_2$); 6.88–6.91 (m, 2 arom. H); 7.10–7.31 (m, 12 arom. H); 7.48–7.54 (m, 3 arom. H); 7.58 (s, H–C(5) of triazole). ^{13}C -NMR ($CDCl_3$): 53.13; 67.70; 68.51; 68.99; 107.00; 118.62; 123.98; 125.10; 126.57; 126.92; 127.72; 128.09; 128.14; 128.25; 128.32; 128.99; 129.20; 129.34; 129.59; 133.02; 134.45; 136.27; 144.42; 156.21; 157.69. MS: 478.20 (14.6, M^+). Anal. calc. for $C_{29}H_{26}N_4O_3$ (478.54): C 72.79, H 5.48, N 11.71; found: C 72.83, H 5.41, N 11.65.

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