

## Synthesis of novel 1,2,3-triazole-based hybrids *via* click reactions

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Dedicated to Professor Girolamo Cirrincione

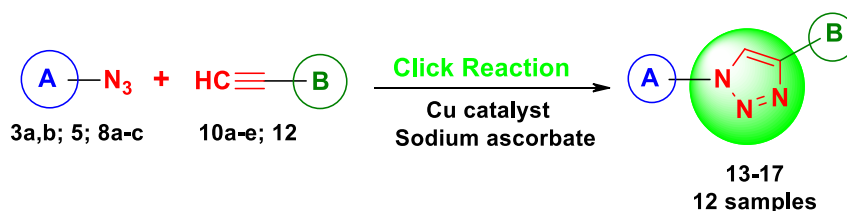
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### Abstract

1,2,3-Triazoles have attracted the interest of researchers due to their wide range of biological activities which include antitumor, anti-leishmanial, bioluminescent and fungicidal activities. This paper describes the synthesis of novel triazole hybrids containing biologically active fragments through cycloaddition (click) reactions, with the aim of increasing the diversity of known and active 1,2,3-triazole derivatives. All new compounds have been characterized by physicochemical methods.



**Keywords:** Condensed pyridines, spirodibutanolides, thiopropargyl-1,2,4-triazoles, 1,2,3-triazoles, click reaction

## Introduction

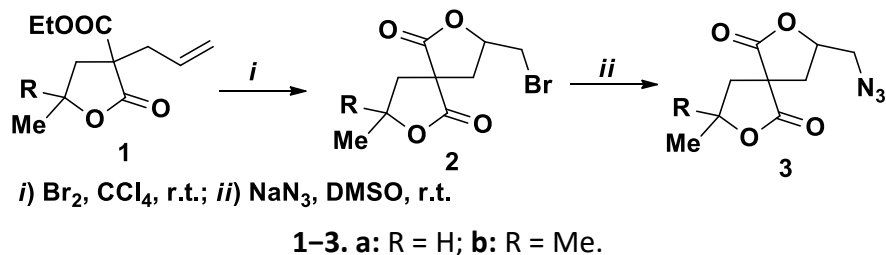
Since many drugs used in medical therapy contain heterocycles in their structure, the introduction in their structure of triazole rings, especially 1,2,3-triazoles, has attracted special attention. The syntheses and the behavior of these heterocyclic compounds have been intensely investigated in the last decades - research into the development of new methods for the synthesis of substituted triazoles and identification of their possible biological/pharmacological properties thus proceed with great interest. In fact, several new methods for producing various 1,2,3-triazole derivatives<sup>1,2</sup> have been recently proposed, and it has been shown that the novel compounds derived through this approach have a wide spectrum of biological properties/activities. Among these bioactivities, cytotoxic,<sup>3</sup> antitumor,<sup>4</sup> leishmanicidal,<sup>5</sup> bioluminescent<sup>6</sup> and fungicidal<sup>7</sup> activities should be noted, all which have been shown to be characteristic of certain 1,2,3-triazoles. The analysis of literature data shows that the nature of substituents on the triazole cycle is very important. Thus, modification of these substituents is expected to result in significant changes in the biological properties of 1,2,3-triazole derivatives thus formed. For this reason, research into the development of methods for the synthesis of novel substituted triazoles is constantly increasing.<sup>8,9</sup> Of particular value are studies on the isolation and investigation of substances from natural raw materials that possess cytotoxic,<sup>10</sup> antitumor<sup>11</sup> activities, or being inhibitors of topoisomerase,<sup>12</sup> DPP-4 and cancer cell growth.<sup>13</sup>

The main method to prepare 1,2,3-triazoles involves the 1,3-cycloaddition of organic azides with a terminal triple bond, *via* a click reaction.<sup>14-16</sup> In this paper we propose the synthesis of novel triazole-linked hybrids containing biologically active fragments, with the aim to increase the structural range of known and active 1,2,3-triazole derivatives.

It is known that disubstituted piperazines can exhibit a wide range of pharmacological activity; they can act as anticonvulsant,<sup>17</sup> antifungal,<sup>18</sup> antiviral,<sup>19</sup> radioprotective,<sup>20</sup> antibacterial and antimalarial<sup>21,22</sup> agents. Accordingly, our studies in this field have shown that piperazine derivatives of pyrano[3,4-*c*]pyridines display high antibacterial<sup>23</sup> and neurotropic activity.<sup>24,25</sup> In addition, bicyclic pyrano[3,4-*c*]pyridines synthesized by us were characterized by eliciting pronounced cardiotoxic activities.<sup>26</sup> Thus, it was our intent to incorporate these moieties (types of structures) into the click-derived compounds, which also included examples containing dioxaspiro[4.4]nonane-1,6-diones and carvone-derived terpenes.

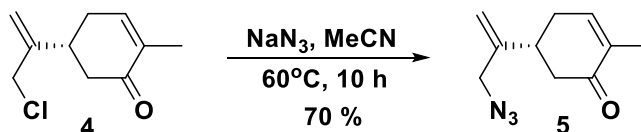
## Results and Discussion

As starting compounds for the synthesis of the first set of required azides, two ethyl 3-allyl-5-methyl-2-oxotetrahydrofuran-3-carboxylates **1**<sup>27</sup> were used. The reaction of compounds **1** with bromine led to the cyclization of the second tetrahydrofuran ring resulting in the formation of 3-(bromomethyl)-8-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **2a,b** as we have previously reported.<sup>27</sup> These results are in good agreement with the Baldwin rules for ring formation. In the case of nucleophilic cyclizations, both 5-*exo-tet* and 6-*exo-tet* cyclizations are favourable.<sup>28,29</sup> However, it was shown by Houk that  $\gamma$ -butyrolactone is less strained than  $\delta$ -valerolactone; therefore, this cyclization is proposed to be a thermodynamically controlled process.<sup>30,31</sup> Finally, the compounds **2** were converted into the desired 3-(azidomethyl)-3,8,8-trisubstituted-2,7-dioxaspiro[4.4]nonane-1,6-diones **3a,b** (Scheme 1) by treatment with sodium azide in DMSO at room temperature. Compounds **2** and **3** were found to be inseparable mixtures of diastereomers in 1:1–1.7:1 ratio, as shown by their NMR spectra.



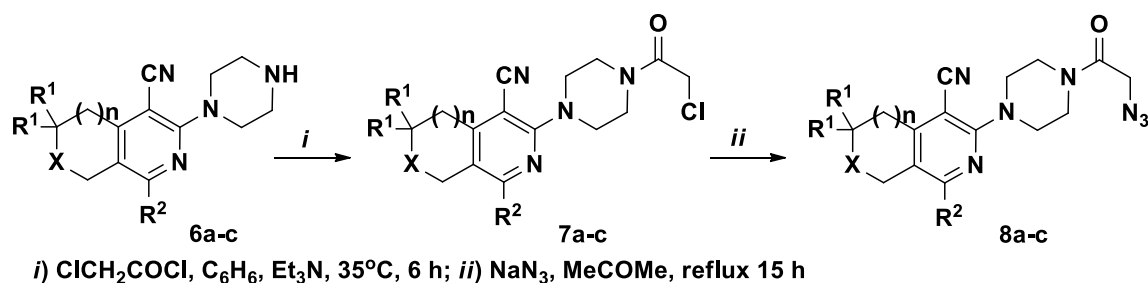
**Scheme 1.** Synthesis of 3-(azidomethyl)-3,8,8-trisubstituted-2,7-dioxaspiro[4.4]nonane-1,6-diones **3**. Yields, %: 83 (**2a**); 86 (**2b**); 80 (**3a**); 83 (**3b**).

Next, the synthesis of the azide **5** derived from the L-carvone, (*R*)-5-(3-azidochloroprop-1-en-2-yl)-2-methylcyclohex-2-enone (**4**) was performed as described in Scheme 2. According to our previous work in collaboration, 1,2,3-triazoles obtained using triazole **5** displayed pronounced antioxidant and fluorescent properties.<sup>32</sup>



**Scheme 2.** Synthesis of (*R*)-5-(3-azido-prop-1-en-2-yl)-2-methylcyclohex-2-enone **5**.

Finally, to add a piperazine group to the structure of the envisaged 1,2,3-triazoles we also synthesized some azide derivatives **8** according to Scheme 3. Thus, by the acylation of 3(6)-piperazine derivatives of fused pyridines **6**<sup>23,24</sup> with chloroacetyl chloride, the relevant 1(8)-alkyl-3(6)-[4-(chloroacetyl)piperazin-1-yl]pyridine-4(5)-carbonitriles **7** were obtained. Reaction of these compounds with sodium azide led to the formation of 1(8)-alkyl-3(6)-[4-(azidoacetyl)piperazin-1-yl][c]pyridine-4(5)-carbonitriles **8** in high yields (Table 1).

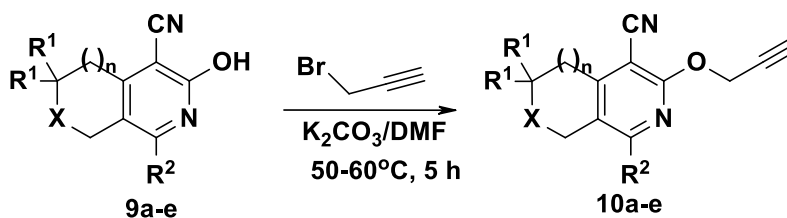


**Scheme 3.** Synthesis of 3(6)-[4-(azidoacetyl)piperazin-1-yl][c]pyridine-4(5)-carbonitriles **8**.

**Table 1.** 3(6)-[4-(Azidoacetyl)piperazin-1-yl]pyridines **8**

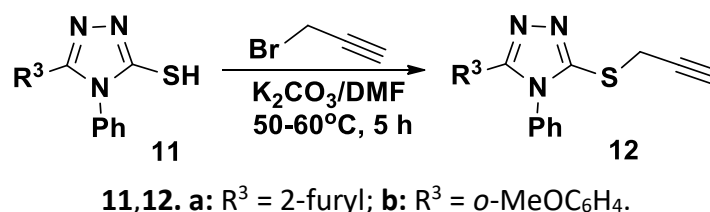
Compound	X	R <sup>1</sup>	n	R <sup>2</sup>	Yield (%)
<b>8a</b>	CH <sub>2</sub>	H	0	<i>i</i> -Bu	74
<b>8b</b>	O	Me	1	Et	81
<b>8c</b>	O	Me	1	Pr	83

The next step for the preparation of the title hybrids required the introduction of terminal alkynes to suitable scaffolds. Thus, by reaction of the 3(6)-hydroxy derivatives of cyclopenta[*c*]pyridine **9a**, 5,6,7,8-tetrahydroisoquinolines **9b,c**<sup>33</sup> and of pyrano[3,4-*c*]pyridines **9d,e**<sup>34</sup> with propargyl bromide, the relevant *O*-alkylated derivatives **10a–e** were synthesized in reasonable yields (Scheme 4, Table 2).

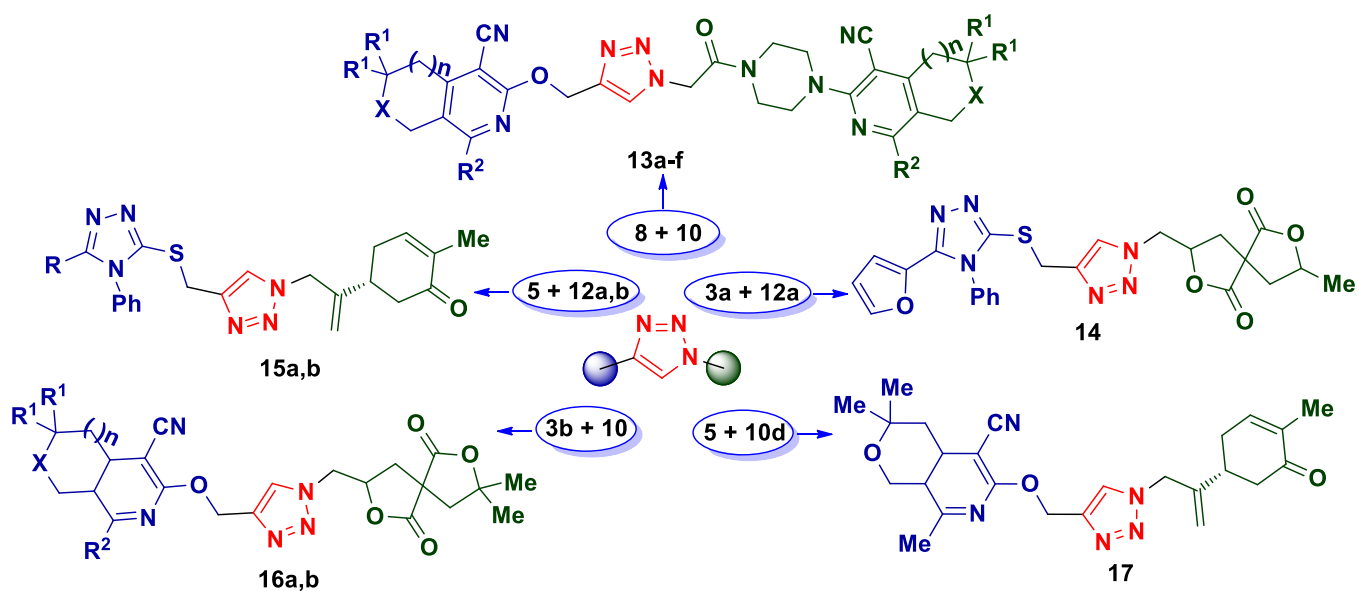
**Scheme 4.** Synthesis of 1(8)-alkyl-3(6)-(prop-2-yn-1-yloxy)pyridine-4(5)-carbonitriles **10**.**Table 2.** 1(8)-Alkyl-3(6)-(prop-2-yn-1-yloxy)pyridines **10**

Compound	X	n	R <sup>1</sup>	R <sup>2</sup>	Yield (%)
<b>10a</b>	CH <sub>2</sub>	0	H	<i>i</i> -Pr	76
<b>10b</b>	CH <sub>2</sub>	1	H	<i>i</i> -Pr	84
<b>10c</b>	CH <sub>2</sub>	1	H	Ph	62
<b>10d</b>	O	1	Me	Me	65
<b>10e</b>	O	1	Me	<i>i</i> -Pr	87

To increase the structural range of the obtained compounds containing a triple bond, we also synthesized thiopropargyl-1,2,4-triazoles **12** from the corresponding 5-aryl-4-phenyl-4*H*-1,2,4-triazole-3-thiols **11**<sup>35</sup> (Scheme 5), which, as mentioned above, have been shown to be physiologically active substances.

**Scheme 5.** Synthesis of 4-phenyl-5-(prop-2-yn-1-ylthio)-4*H*-1,2,4-triazoles **12**. Yields, %: 75 (**12a**); 80 (**12b**).

Finally, the desired hybrid compounds were prepared by a Cu-catalyzed azide-alkyne click reaction<sup>14–16</sup> between the propargylated compounds **10/12** and azido derivatives **3**, **5** and **8** (Scheme 6). As reductant, ascorbic acid was used in most of the syntheses of the triazole derivatives **13–17**, which were obtained in moderate/high yields (Yields = 55–76%; Table 3).

Scheme 6. Synthesis of target hybrids **13–17** via click reaction.Table 3. Synthesis of aimed hybrids **13–17**

Compound	organic azides	propargyl-derivatives	disubstituted 1,2,3-triazoles	Yield (%)
<b>13a</b>	<b>8a</b>	<b>10a</b>		72
<b>13b</b>	<b>8b</b>	<b>10a</b>		75
<b>13c</b>	<b>8b</b>	<b>10b</b>		70
<b>13d</b>	<b>8a</b>	<b>10c</b>		74

Table 3. Continued

13e				71
13f				76
14				68
15a				65
15b				64
16a				73
16b				70
17				55

The structure of the obtained hybrids **13–17** was confirmed by IR and NMR spectroscopy and by elemental analysis. In the IR spectra of these compounds the absorption bands of the azido group and of triple bond at 2095–2107  $\text{cm}^{-1}$  (typical for the starting **3**, **5**, **8**) and at 2115–2133; 3249–3283  $\text{cm}^{-1}$  (typical for the starting **10** and **12**), respectively, were absent. In addition, the  $^1\text{H}$  NMR spectra of compounds **13–17** did not show the triplet signal of the CH group at 2.72–2.97 ppm, characteristic for the initial compounds **10** and **12**, while the singlet attributed to CH group of the triazole ring was observed at 7.93–7.98 ppm, thus supporting the cyclized structures. As far as starting compounds **3** are concerned it should be mentioned that since they are complex structures, containing 2-3 chiral centers, instead of pure products, mixtures of inseparable diastereoisomers were obtained.

## Conclusions

In summary, we synthesized new 1,2,3-triazole based hybrids with possible interesting biological/pharmacological activities by the Cu-catalyzed click reaction between synthesized alkynes and azides, containing novel chemical frameworks potentially responsible for interesting biological activities. These bioactivities will be ascertained in ongoing studies and will be reported in due course.

## Experimental Section

**General.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in DMSO/ $\text{CCl}_4$  (1/3) solution (300 MHz for  $^1\text{H}$  and 75 MHz for  $^{13}\text{C}$ , respectively) on a Varian Mercury 300VX spectrometer. Chemical shifts were reported as  $\delta$  (parts per million) relative to TMS as internal standard. IR spectra were recorded on Nicolet Avatar 330-FT-IR spectrophotometer and the reported wave numbers were given in  $\text{cm}^{-1}$ . All melting points were determined in an open capillary and were uncorrected. Elemental analyses were performed on a Elemental Analyzer Euro EA 3000. Compounds **2**,<sup>27</sup> **5**,<sup>32</sup> **6**,<sup>23,24</sup> **9**,<sup>33,34</sup> **11**<sup>35</sup> were already described.

**General procedure for the synthesis of azido-lactones (3a,b).** To the corresponding bromomethyl-lactone **2** (1 mmol) in DMSO (5 mL)  $\text{NaN}_3$  (1.35 mmol, 0.088 g) was added and the mixture was stirred for 12 h at room temperature. After the reaction mixture was poured in water (60 mL) and extracted with DCM (3×15 mL). Combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , volatiles were evaporated and the residue was passed through a short silica gel pad in hexane-DCM 1:1 to obtain pure product.

**3-(Azidomethyl)-8-methyl-2,7-dioxaspiro[4.4]nonane-1,6-dione (3a).** Yield 80%, viscous oil,  $n_D^{20}$  1.4978. IR  $\nu/\text{cm}^{-1}$ : 1775, 1790 (C=O), 2100 ( $\text{N}_3$ ).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.41 (d,  $J = 6.2$  Hz, 3H,  $\text{CH}_3$ ), 2.06–1.93 (m, 1H,  $\text{CH}_2\text{CH}$ ), 2.20–2.06 (m, 0.5H,  $\text{CH}_2\text{CH}$ ), 2.63–2.31 (m, 0.5H,  $\text{CH}_2\text{CH}$ ), 2.94–2.66 (m, 2H,  $\text{CH}_2\text{CH}$ ), 3.76–3.48 (m, 2H,  $\text{CH}_2\text{N}$ ), 4.96–4.65 (m, 2H, CHO).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.3, 20.0, 32.9, 34.1, 34.2, 35.7, 39.3, 40.1, 40.4, 52.2, 52.6, 52.9, 53.0, 74.6, 74.7, 75.1, 76.6, 76.9, 172.6, 172.5, 172.8, 172.8. Anal. calcd. for  $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4$ : C 48.00; H 4.92; N 18.66%. Found: C 47.91; H 4.99; N 18.75 %.

**8-(Azidomethyl)-3,3-dimethyl-2,7-dioxaspiro[4.4]nonane-1,6-dione (3b).** Yield 83%, mp 43–44 °C. IR  $\nu/\text{cm}^{-1}$ : 1773, 1787 (C=O), 2095 ( $\text{N}_3$ ).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$  - 1/3)  $\delta$  1.48 (s, 3H,  $\text{CH}_3$ ), 1.60–1.50 (m, 3H,  $\text{CH}_3$ ), 2.38–2.17 (m, 1.66H,  $\text{CH}_2$  in lactone), 2.72–2.52 (m, 1.68H,  $\text{CH}_2$  in lactone), 2.88–2.76 (m, 0.66H,  $\text{CH}_2$  in lactone), 3.76–3.51 (m, 2H,  $\text{CH}_2\text{N}$ ), 4.95–4.66 (m, 1H, CHO).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  28.0, 28.2, 28.4, 28.6, 32.7, 36.4, 36.6, 38.0, 40.4, 43.9, 44.7, 52.5, 52.8, 53.0, 53.3, 76.2, 76.5, 76.6, 83.2, 82.9, 172.7, 172.5. Anal. calcd. for  $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4$ : C 50.21; H 5.48; N 17.57%. Found: C 50.32; H 5.35; N 17.69%.

**General procedure for the synthesis of 3(6)-(4-chloroacetyl)piperazin-1-yl)pyridines (7).** To a stirred solution of compound **6** (5 mmol) and pyridine (6 mmol) in absolute benzene (75 mL) the chloroacetyl chloride (4.8 mL, 6 mmol) was added dropwise. The reaction mixture was maintained at 35 °C for 6 h. After cooling of the reaction mixture at room temperature, the solvent was removed under vacuum and water (50 mL) was added. The resulting crystals were filtered off, washed with water, dried and recrystallized from ethanol.

**3-[4-(Chloroacetyl)piperazin-1-yl]-1-isobutyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carbonitrile (7a).** Colorless solid; yield 73%; mp 118–120 °C; IR  $\nu/\text{cm}^{-1}$ : 1655 (C=O), 2207 ( $\text{C}\equiv\text{N}$ ).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  0.93 (t,  $J = 6.6$  Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 2.07–2.21 (m, 3H, 6- $\text{CH}_2$ ,  $\text{CH}(\text{CH}_3)_2$ ), 2.48 (d,  $J = 7.0$  Hz, 2H,  $\text{CHCH}_2$ ), 2.84 (t,  $J = 7.4$  Hz, 2H, 7- $\text{CH}_2$ ), 3.02 (t,  $J = 7.6$  Hz, 2H, 5- $\text{CH}_2$ ), 3.53–3.70 (m, 8H,  $\text{C}_4\text{H}_8\text{N}_2$ ), 4.22 (s, 2H,  $\text{CH}_2\text{Cl}$ ).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  22.14, 23.52, 27.23, 29.34, 32.47, 40.76, 41.08, 44.09, 45.07, 47.71, 48.35, 90.38,

115.93, 129.54, 158.03, 158.95, 160.11, 164.16. Anal. calcd. for C<sub>19</sub>H<sub>25</sub>ClN<sub>4</sub>O: C 63.24; H 6.98; N 15.53%. Found: C 63.55; H 7.15; N 15.77%.

**6-[4-(Chloroacetyl)piperazin-1-yl]-8-ethyl-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (7b).** Colorless solid; yield 70%; mp 114–116 °C; IR  $\nu/\text{cm}^{-1}$ : 1659 (C=O), 2208 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  1.24 (t,  $J$  = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.27 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 2.56 (q,  $J$  = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.71 (s, 2H, CH<sub>2</sub>), 3.57–3.71 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.22 (s, 2H, CH<sub>2</sub>Cl), 4.59 (s, 2H, OCH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  10.86, 25.72, 26.43, 37.84, 45.10, 47.45, 48.09, 58.81, 68.97, 93.21, 115.51, 118.85, 147.85, 159.14, 159.35, 164.20. Anal. calcd. for C<sub>19</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>2</sub>: C 60.55; H 6.69; N 14.87%. Found: C 60.89; H 6.88; N 15.13%.

**6-[4-(Chloroacetyl)piperazin-1-yl]-3,3-dimethyl-8-propyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (7c).** Colorless solid; yield 71%; mp 138–140 °C; IR  $\nu/\text{cm}^{-1}$ : 1639 (C=O), 2209 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  0.99 (t,  $J$  = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.27 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.66–1.79 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.50 (t,  $J$  = 7.4 Hz, 2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.71 (s, 2H, CH<sub>2</sub>), 3.56–3.71 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.22 (s, 2H, CH<sub>2</sub>Cl), 4.59 (s, 2H, OCH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  13.51, 19.99, 25.72, 35.18, 37.87, 40.77, 41.13, 45.11, 47.48, 48.13, 58.93, 68.96, 93.34, 115.49, 119.16, 147.95, 158.52, 159.07, 164.20. Anal. calcd. for C<sub>20</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>2</sub>: C 61.45; H 6.96; N 14.33%. Found: C 61.83; H 7.19; N 14.62%.

**General procedure for the synthesis of 3(6)-(4-azidoacetyl)piperazin-1-ylpyridines (8).** A mixture of compound **7** (5 mmol) and sodium azide (0.36 g, 5.5 mmol) in acetone (30 mL) was refluxed for 15 h. After the filtration the solvent was removed under vacuum and water (50 mL) was added. The resulting crystals were filtered off, washed with water, dried, and recrystallized from ethanol.

**3-[4-(Azidoacetyl)piperazin-1-yl]-1-isobutyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carbonitrile (8a).** Colorless solid; yield 74%; mp 111–113 °C; IR  $\nu/\text{cm}^{-1}$ : 1647 (C=O), 2099 (N<sub>3</sub>), 2212 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  0.93 (t,  $J$  = 6.6 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.06–2.20 (m, 3H, 6-CH<sub>2</sub>, CH(CH<sub>3</sub>)<sub>2</sub>), 2.47 (d,  $J$  = 7.1 Hz, 2H, CHCH<sub>2</sub>), 2.84 (t,  $J$  = 7.4 Hz, 2H, 7-CH<sub>2</sub>), 3.01 (t,  $J$  = 7.6 Hz, 2H, 5-CH<sub>2</sub>), 3.49–3.72 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.04 (s, 2H, CH<sub>2</sub>N<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  22.16, 23.54, 27.25, 29.36, 32.49, 40.96, 43.81, 44.11, 47.75, 48.26, 49.57, 90.33, 115.98, 129.52, 158.06, 158.96, 160.14, 165.26. Anal. calcd. for C<sub>19</sub>H<sub>25</sub>N<sub>7</sub>O: C 62.10; H 6.86; N 26.68%. Found: C 62.42; H 7.03; N 26.93%.

**6-[4-(Azidoacetyl)piperazin-1-yl]-8-ethyl-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (8b).** Colorless solid; yield 81%; mp 102–104 °C; IR  $\nu/\text{cm}^{-1}$ : 1659 (C=O), 2107 (N<sub>3</sub>), 2208 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  1.24 (t,  $J$  = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.27 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 2.56 (q,  $J$  = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.71 (s, 2H, CH<sub>2</sub>), 3.50–3.73 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.05 (s, 2H, CH<sub>2</sub>N<sub>3</sub>), 4.59 (s, 2H, OCH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  10.86, 25.72, 26.43, 37.84, 40.99, 43.81, 47.49, 47.93, 49.55, 58.81, 68.97, 93.10, 115.53, 118.80, 147.85, 159.12, 159.35, 165.30. Anal. calcd. for C<sub>19</sub>H<sub>25</sub>N<sub>7</sub>O<sub>2</sub>: C 59.51; H 6.57; N 25.57%. Found: C 59.86; H 6.78; N 25.84%.

**6-[4-(Azidoacetyl)piperazin-1-yl]-3,3-dimethyl-8-propyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (8c).** Colorless solid; yield 83%; mp 95–97 °C; IR  $\nu/\text{cm}^{-1}$ : 1641 (C=O), 2103 (N<sub>3</sub>), 2211 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  0.98 (t,  $J$  = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.27 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.66–1.79 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.47–2.53 (m, 2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.71 (s, 2H, CH<sub>2</sub>), 3.50–3.72 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.05 (s, 2H, CH<sub>2</sub>N<sub>3</sub>), 4.59 (s, 2H, OCH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  13.52, 20.01, 25.73, 35.19, 37.87, 41.01, 43.84, 47.52, 47.98, 49.57, 58.94, 68.97, 93.25, 115.53, 119.13, 147.96, 158.53, 159.06, 165.30. Anal. calcd. for C<sub>20</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub>: C 60.44; H 6.85; N 24.67%. Found: C 60.81; H 7.07; N 24.96%.

**General procedure for the synthesis of propargyl-derivatives (10a–e and 12a,b).** To a stirred suspension of compound **9** (**11**) (5 mmol) and potassium carbonate (0.76 g, 5.5 mmol) in absolute DMF (30 mL) the propargyl bromide (5.5 mmol) was added dropwise. The reaction mixture was maintained at 50–60 °C for 5 h. Then the



reaction mixture was cooled at room temperature, and water was added (50 mL). The resulting crystals were filtered off, washed with water, dried and recrystallized from ethanol.

**1-Isopropyl-3-(prop-2-yn-1-yloxy)-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carbonitrile (10a).** Colorless solid; yield 76%; mp 103–105 °C; IR  $\nu/\text{cm}^{-1}$ : 2129 (C $\equiv$ CH), 2228 (C $\equiv$ N), 3249 ( $\equiv$ CH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.23 (t,  $J$  = 6.8 Hz, 6H, CH(CH $_3$ ) $_2$ ), 2.13–2.24 (m, 2H, 6-CH $_2$ ), 2.89 (t,  $J$  = 2.4 Hz, 1H,  $\equiv$ CH), 2.89 (t,  $J$  = 7.5 Hz, 2H, 7-CH $_2$ ), 2.98–3.07 (m, 3H, CH(CH $_3$ ) $_2$ , 5-CH $_2$ ), 5.03 (d,  $J$  = 2.4 Hz, 2H, OCH $_2$ ).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.48, 23.88, 28.64, 32.01, 32.56, 53.45, 75.45, 78.07, 89.90, 113.39, 129.95, 160.32, 161.07, 162.40. Anal. calcd. for C $_{15}$ H $_{16}$ N $_2$ O: C 74.97; H 6.71; N 11.66%. Found: C 75.31; H 6.90; N 11.92%.

**1-Isopropyl-3-(prop-2-yn-1-yloxy)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (10b).** Colorless solid; yield 84%; mp 102–104 °C; IR  $\nu/\text{cm}^{-1}$ : 2121 (C $\equiv$ CH), 2220 (C $\equiv$ N), 3256 ( $\equiv$ CH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.21 (t,  $J$  = 6.7 Hz, 6H, CH(CH $_3$ ) $_2$ ), 1.76–1.88 (m, 4H, 6,7-CH $_2$ ), 2.65–2.72 (m, 2H, 8-CH $_2$ ), 2.85–2.90 (m, 2H, 5-CH $_2$ ), 2.88 (t,  $J$  = 2.5 Hz, 1H,  $\equiv$ CH), 3.21 (t,  $J$  = 6.7 Hz, 1H, CH(CH $_3$ ) $_2$ ), 5.03 (d,  $J$  = 2.4 Hz, 2H, OCH $_2$ ).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.77, 20.80, 21.93, 23.82, 28.14, 30.26, 53.02, 75.54, 78.16, 92.80, 113.37, 122.64, 152.65, 159.61, 165.91. Anal. calcd. for C $_{16}$ H $_{18}$ N $_2$ O: C 75.56; H 7.13; N 11.01%. Found: C 75.92; H 7.33; N 11.29%.

**1-Phenyl-3-(prop-2-yn-1-yloxy)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (10c).** Colorless solid; yield 62%; mp 121–123 °C; IR  $\nu/\text{cm}^{-1}$ : 2125 (C $\equiv$ CH), 2218 (C $\equiv$ N), 3283 ( $\equiv$ CH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.67–1.76 (m, 2H, 6-CH $_2$ ), 1.84–1.93 (m, 2H, 7-CH $_2$ ), 2.70 (t,  $J$  = 6.2 Hz, 2H, 8-CH $_2$ ), 2.97 (t,  $J$  = 2.5 Hz, 1H,  $\equiv$ CH), 2.98 (t,  $J$  = 6.5 Hz, 2H, 5-CH $_2$ ), 5.06 (d,  $J$  = 2.4 Hz, 2H, OCH $_2$ ), 7.37–7.55 (m, 5H, Ph).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.91, 22.08, 26.63, 28.04, 53.40, 76.06, 78.05, 94.23, 113.21, 124.35, 127.45, 128.17, 128.50, 138.28, 153.75, 158.06, 159.38. Anal. calcd. for C $_{19}$ H $_{16}$ N $_2$ O: C 79.14; H 5.59; N 9.72%. Found: C 79.47; H 5.77; N 9.97%.

**3,3,8-Trimethyl-6-(prop-2-yn-1-yloxy)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (10d).** Colorless solid; yield 65%; mp 128–130 °C; IR  $\nu/\text{cm}^{-1}$ : 2133 (C $\equiv$ CH), 2223 (C $\equiv$ N), 3259 ( $\equiv$ CH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.28 (s, 6H, C(CH $_3$ ) $_2$ ), 2.37 (s, 3H, CH $_3$ ), 2.76 (s, 2H, CH $_2$ ), 2.94 (t,  $J$  = 2.4 Hz, 1H,  $\equiv$ CH), 4.60 (s, 2H, OCH $_2$ ), 5.05 (d,  $J$  = 2.4 Hz, 2H, OCH $_2$ ).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.69, 25.66, 37.58, 53.35, 59.15, 68.99, 76.05, 77.81, 93.19, 112.86, 121.45, 148.83, 155.11, 159.98. Anal. calcd. for C $_{15}$ H $_{16}$ N $_2$ O $_2$ : C 70.29; H 6.29; N 10.93%. Found: C 70.63; H 6.49; N 11.20%.

**8-Isopropyl-3,3-dimethyl-6-(prop-2-yn-1-yloxy)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (10e).** Colorless solid; yield 87%; mp 147–149 °C; IR  $\nu/\text{cm}^{-1}$ : 2133 (C $\equiv$ CH), 2227 (C $\equiv$ N), 3277 ( $\equiv$ CH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.23 (t,  $J$  = 6.6 Hz, 6H, CH(CH $_3$ ) $_2$ ), 1.28 (s, 6H, C(CH $_3$ ) $_2$ ), 2.77 (s, 2H, CH $_2$ ), 2.92–2.97 (m, 2H,  $\equiv$ CH, CH(CH $_3$ ) $_2$ ), 4.69 (s, 2H, OCH $_2$ ), 5.05 (d,  $J$  = 2.4 Hz, 2H, OCH $_2$ ).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.69, 25.68, 30.32, 37.87, 53.31, 58.71, 68.89, 75.87, 77.94, 93.14, 112.95, 119.84, 149.50, 160.31, 163.15. Anal. calcd. for C $_{17}$ H $_{20}$ N $_2$ O $_2$ : C 71.81; H 7.09; N 9.85%. Found: C 72.13; H 7.26; N 10.09%.

**3-(Furan-2-yl)-4-phenyl-5-(prop-2-yn-1-ylthio)-4H-1,2,4-triazole (12a).** Yield 75%, mp 151–152 °C; IR  $\nu/\text{cm}^{-1}$ : 1600, 1613 (C=C), 1635 (C=N), 2115 (C $\equiv$ CH), 3249 ( $\equiv$ CH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  2.73 (t,  $J$  = 2.6 Hz, 1H,  $\equiv$ CH), 3.95 (d,  $J$  = 2.6 Hz, 2H, SCH $_2$ ), 6.22 (d,  $J$  = 3.4 Hz, 1H $_{\text{furyl}}$ ), 6.40 (dd,  $J$  = 3.5, 1.8 Hz, 1H $_{\text{furyl}}$ ), 7.46–7.33 (m, 2H $_{\text{arom}}$ ), 7.69–7.48 (m, 3H $_{\text{arom}}$ , 1H, =CH-O).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.7, 73.5, 78.0, 110.7, 110.8, 127.1, 129.3, 129.7, 133.1, 141.0, 143.6, 147.0, 149.6. Anal. calcd. for C $_{15}$ H $_{11}$ N $_3$ OS: C 64.04; H 3.94; N 14.94%. Found: C 63.91; H 4.011; N 15.13%.

**3-(2-Methoxyphenyl)-4-phenyl-5-(prop-2-yn-1-ylthio)-4H-1,2,4-triazole (12b).** Yield 80%, mp 105–106 °C; IR  $\nu/\text{cm}^{-1}$ : 1604, 1618 (C=C), 1639 (C=N), 2123 (C $\equiv$ CH), 3256 ( $\equiv$ CH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  2.72 (t,  $J$  = 2.6 Hz, 1H,  $\equiv$ CH), 3.36 (s,  $J$  = 2.6 Hz, 3H, OCH $_3$ ), 3.99 (d,  $J$  = 2.6 Hz, 2H, SCH $_2$ ), 6.79 (br.d,  $J$  = 8.2 Hz, 1H $_{\text{arom}}$ ), 7.01 (td,  $J$  = 7.5, 0.9 Hz, 1H $_{\text{arom}}$ ), 7.21–7.10 (m, 2H $_{\text{arom}}$ ), 7.43–7.31 (m, 4H $_{\text{arom}}$ ), 7.49 (dd,  $J$  = 7.5, 1.7 Hz, 1H $_{\text{arom}}$ ).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  20.4, 54.1, 78.1, 73.3, 110.5, 115.8, 120.0, 125.7, 128.4, 128.5, 131.3,

133.8, 148.7, 152.9, 156.0. Anal. calcd. for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>OS: C 67.27; H 4.70; N 13.07%. Found: C 67.39; H 4.56; N 13.26%.

**General procedure for the synthesis of 1,2,3-triazoles (13a–f).** Propargyl derivatives of fused pyridines **10** (5 mmol) and corresponding azides **8** (5.5 mmol) were suspended in a 1:1 mixture of water and *tert*-butyl alcohol (30 mL). Sodium ascorbate (0.3 mmol, of freshly prepared solution in water) was added, followed by copper(II) sulfate pentahydrate (7.5 mg, 0.03 mmol, in of water). The heterogeneous mixture was stirred vigorously for 5 h at room temperature and then 10 h at 60–65 °C. After cooling water was added (50 mL). The precipitate was collected by filtration, washed with water and recrystallized from a mixture of ethanol-chloroforme (1:3).

**3-[(1-{2-[4-(4-Cyano-1-isobutyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)piperazin-1-yl]-2-oxoethyl}-1H-1,2,3-triazol-4-yl)methoxy]-1-isopropyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carbonitrile (13a).** Colorless solid; yield 72%; mp 162–164 °C; IR  $\nu/\text{cm}^{-1}$ : 1662 (C=O), 2211, 2225 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  0.94 (d, *J* = 6.5 Hz, 6H, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.27 (d, *J* = 6.7 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.08–2.24 (m, 5H, 6,6'-CH<sub>2</sub>, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2.49 (d, *J* = 6.5 Hz, 2H, CH<sub>2</sub>CH), 2.81–2.96 (m, 4H, 7,7'-CH<sub>2</sub>), 2.99–3.10 (m, 5H, 5,5'-CH<sub>2</sub>, CH(CH<sub>3</sub>)<sub>2</sub>), 3.56–3.75 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 5.47 (s, 2H, NCH<sub>2</sub>), 5.55 (s, 2H, OCH<sub>2</sub>), 7.93 (s, 1H, CH<sub>triazole</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  20.60, 22.16, 23.53, 23.89, 27.24, 28.68, 29.35, 32.00, 32.49, 32.69, 41.16, 43.94, 44.09, 47.65, 48.22, 50.32, 59.63, 89.75, 90.23, 113.81, 116.01, 125.19, 129.46, 129.58, 141.79, 158.05, 158.93, 160.14, 161.01, 161.22, 162.61, 163.70. Anal. calcd. for C<sub>34</sub>H<sub>41</sub>N<sub>9</sub>O<sub>2</sub>: C 67.19; H 6.80; N 20.74%. Found: C 67.57; H 7.02; N 21.03%.

**6-{4-[(4-[(4-Cyano-1-isopropyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)oxy]methyl}-1H-1,2,3-triazol-1-yl)acetyl]piperazin-1-yl}-8-ethyl-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (13b).** Colorless solid; yield 75%; mp 225–227 °C; IR  $\nu/\text{cm}^{-1}$ : 1655 (C=O), 2216 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  1.25 (t, *J* = 7.5 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.27 (d, *J* = 6.7 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.28 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 2.13–2.24 (m, 2H, 6'-CH<sub>2</sub>), 2.57 (q, *J* = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.72 (s, 2H, 4-CH<sub>2</sub>), 2.90 (t, *J* = 7.4 Hz, 2H, 7'-CH<sub>2</sub>), 3.03 (t, *J* = 7.4 Hz, 2H, 5'-CH<sub>2</sub>), 3.05 (sp, *J* = 6.7 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.61–3.76 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.60 (s, 2H, 1-CH<sub>2</sub>), 5.48 (s, 2H, NCH<sub>2</sub>), 5.55 (s, 2H, OCH<sub>2</sub>), 7.93 (s, 1H, CH<sub>triazole</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  10.88, 20.61, 23.90, 25.75, 26.45, 28.68, 32.01, 32.70, 37.86, 41.19, 43.96, 47.41, 47.93, 50.35, 58.83, 59.66, 68.98, 89.76, 93.05, 113.81, 115.60, 118.77, 125.18, 129.58, 141.80, 147.86, 159.13, 159.39, 161.01, 161.23, 162.61, 163.78. Anal. calcd. for C<sub>34</sub>H<sub>41</sub>N<sub>9</sub>O<sub>3</sub>: C 65.47; H 6.63; N 20.21%. Found: C 65.83; H 6.82; N 20.47%.

**6-{4-[(4-[(4-Cyano-1-isopropyl-5,6,7,8-tetrahydroisoquinolin-3-yl)oxy]methyl}-1H-1,2,3-triazol-1-yl)acetyl]piperazin-1-yl}-8-ethyl-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (13c).** Colorless solid; yield 70%; mp 197–199 °C; IR  $\nu/\text{cm}^{-1}$ : 1678 (C=O), 2220 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  1.25 (t, *J* = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.25 (d, *J* = 6.6 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.28 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.77–1.88 (m, 4H, 6',7'-CH<sub>2</sub>), 2.57 (t, *J* = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.66–2.73 (m, 2H, 8'-CH<sub>2</sub>), 2.72 (s, 2H, 4-CH<sub>2</sub>), 2.84–2.89 (m, 2H, 5'-CH<sub>2</sub>), 3.22 (sp, *J* = 6.6 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.61–3.76 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.60 (s, 2H, 1-CH<sub>2</sub>), 5.48 (s, 2H, NCH<sub>2</sub>), 5.55 (s, 2H, OCH<sub>2</sub>), 7.93 (s, 1H, CH<sub>triazole</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  10.88, 20.84, 20.90, 21.98, 23.82, 25.75, 26.45, 28.12, 30.36, 37.87, 41.20, 43.96, 47.41, 47.91, 50.34, 58.82, 59.19, 68.98, 92.70, 93.04, 113.71, 115.60, 118.77, 122.25, 125.13, 141.85, 147.86, 152.53, 159.13, 159.39, 160.48, 163.78, 166.05. Anal. calcd. for C<sub>35</sub>H<sub>43</sub>N<sub>9</sub>O<sub>3</sub>: C 65.91; H 6.80; N 19.77%. Found: C 66.30; H 7.03; N 20.05%.

**3-[(1-{2-[4-(4-Cyano-1-isobutyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)piperazin-1-yl]-2-oxoethyl}-1H-1,2,3-triazol-4-yl)methoxy]-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (13d).** Colorless solid; yield 74%; mp 166–168 °C; IR  $\nu/\text{cm}^{-1}$ : 1655 (C=O), 2222, 2224 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3)  $\delta$  0.94 (t, *J* = 6.6 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.67–1.76 (m, 2H, 6-CH<sub>2</sub>), 1.83–1.93 (m, 2H, 7-CH<sub>2</sub>), 2.07–2.22 (m, 3H, 6'-CH<sub>2</sub>, CH(CH<sub>3</sub>)<sub>2</sub>), 2.48 (d, *J* = 7.0 Hz, 2H, CHCH<sub>2</sub>), 2.69 (t, *J* = 6.1 Hz, 2H, 8-CH<sub>2</sub>), 2.85 (t, *J* = 7.4 Hz, 2H, 7'-CH<sub>2</sub>), 2.94–3.06 (m, 4H, 5,5'-CH<sub>2</sub>), 3.56–3.76 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 5.48 (s, 2H, NCH<sub>2</sub>), 5.56 (s, 2H, OCH<sub>2</sub>), 7.38–7.57 (m, 5H, Ph),

7.93 (s, 1H, CH<sub>triazole</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 20.94, 22.10, 22.14, 23.52, 26.57, 27.22, 27.99, 29.33, 32.47, 41.14, 43.93, 44.09, 47.62, 47.64, 50.32, 59.46, 90.20, 94.10, 113.54, 116.01, 123.91, 125.50, 127.51, 128.08, 128.49, 129.45, 138.47, 153.61, 158.05, 158.33, 158.91, 160.13, 160.22, 163.72. Anal. calcd. for C<sub>38</sub>H<sub>41</sub>N<sub>9</sub>O<sub>2</sub>: C 69.60; H 6.30; N 19.22%. Found: C 69.91; H 6.48; N 19.47%.

**6-[(1-{2-[4-(5-Cyano-3,3-dimethyl-8-propyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)piperazin-1-yl]-2-oxoethyl}-1H-1,2,3-triazol-4-yl)methoxy]-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (13e)**. Colorless solid; yield 71%; mp 234–236 °C; IR ν/cm<sup>-1</sup>: 1664 (C=O), 2206, 2228 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.00 (t, *J* = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.28 (s, 12H, 2C(CH<sub>3</sub>)<sub>2</sub>), 1.67–1.80 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 2.48–2.54 (m, 2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.72 (s, 2H, 4-CH<sub>2</sub>), 2.75 (s, 2H, 4'-CH<sub>2</sub>), 3.59–3.76 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.60 (s, 2H, 1-CH<sub>2</sub>), 4.61 (s, 2H, 1'-CH<sub>2</sub>), 5.48 (s, 2H, NCH<sub>2</sub>), 5.55 (s, 2H, OCH<sub>2</sub>), 7.97 (s, 1H, CH<sub>triazole</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 13.53, 20.01, 20.80, 25.68, 25.74, 35.20, 37.57, 37.88, 41.20, 41.22, 43.95, 47.40, 47.96, 50.35, 58.95, 59.18, 59.53, 68.97, 69.00, 92.97, 93.16, 113.27, 115.58, 119.08, 121.00, 125.66, 141.53, 147.96, 148.74, 155.30, 158.55, 159.05, 160.84, 163.79. Anal. calcd. for C<sub>35</sub>H<sub>43</sub>N<sub>9</sub>O<sub>4</sub>: C 64.30; H 6.63; N 19.28%. Found: C 64.65; H 6.86; N 19.55%.

**6-[(1-{2-[4-(5-Cyano-8-ethyl-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)piperazin-1-yl]-2-oxoethyl}-1H-1,2,3-triazol-4-yl)methoxy]-8-isopropyl-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (13f)**. Colorless solid; yield 76%; mp 247–249 °C; IR ν/cm<sup>-1</sup>: 1660 (C=O), 2214, 2234 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.25 (t, *J* = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.27 (d, *J* = 6.7 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.28 (s, 12H, 2C(CH<sub>3</sub>)<sub>2</sub>), 2.57 (q, *J* = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.72 (s, 2H, 4-CH<sub>2</sub>), 2.76 (s, 2H, 4'-CH<sub>2</sub>), 2.95 (sp, *J* = 6.7 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.61–3.76 (m, 8H, C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>), 4.60 (s, 2H, 1-CH<sub>2</sub>), 4.69 (s, 2H, 1'-CH<sub>2</sub>), 5.48 (s, 2H, NCH<sub>2</sub>), 5.57 (s, 2H, OCH<sub>2</sub>), 7.95 (s, 1H, CH<sub>triazole</sub>). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 10.87, 20.81, 25.68, 25.74, 26.44, 30.42, 37.86, 41.18, 43.95, 47.40, 47.91, 50.35, 58.74, 58.78, 58.82, 59.42, 68.87, 68.97, 93.04, 93.07, 113.29, 115.59, 118.77, 119.42, 125.26, 141.61, 147.86, 149.37, 159.12, 159.38, 161.18, 163.28, 163.76. Anal. calcd. for C<sub>36</sub>H<sub>45</sub>N<sub>9</sub>O<sub>4</sub>: C 64.75; H 6.79; N 18.88%. Found: C 65.08; H 6.98; N 19.12%.

**General procedure for the synthesis of 1,2,3-triazoles (14–17)**. A 5 mL vial with a screw cup was charged with corresponding azide **3/5** (0.5 mmol), MeCN (4.5 mL), CuI (0.0048 g, 0.025 mmol, 5 mol%), Et<sub>3</sub>N (0.061 g, 0.6 mmol), Na<sub>2</sub>SO<sub>3</sub> (0.0063 g, 0.05 mmol) and propargyl derivative **10/12** (0.55 mmol) and heated for 5 h at 60–65 °C. Reaction mixture was poured into 0.1 M HCl (30 mL) and extracted with DCM (3×10 mL). Combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, volatiles were evaporated and the residue was purified via column chromatography on silica gel mixture of DCM-MeOH (30:1) as an eluent.

**3-[[4-([5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio)methyl]-1H-1,2,3-triazol-1-yl]methyl]-8-methyl-2,7-dioxaspiro[4.4]nonane-1,6-dione (14)**. Yield 68%, mp 180–181 °C. IR ν/cm<sup>-1</sup>: 1601, 1615 (C=C), 1772, 1792 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub> - 1/3) δ 1.36–1.49 (m, 3H, CH<sub>3</sub>), 1.86–2.11 (m, 1H<sup>a</sup>, CH<sub>2</sub> in cycle), 2.12–2.44 (m, 1H<sup>b</sup>, CH<sub>2</sub> in cycle), 2.52–2.70 (m, 1H<sup>a</sup>, CH<sub>2</sub> in cycle), 2.78–2.87 (m, 1H<sup>b</sup>, CH<sub>2</sub> in cycle), 4.46 (s, 2H, SCH<sub>2</sub>), 4.64–4.79 (m, 2H, NCH<sub>2</sub>), 4.79–4.92 (m, 1H, CH<sub>3</sub>CHO), 4.93–5.22 (m, 1H, NCH<sub>2</sub>CHO), 6.18 (dd, *J* = 3.5, 0.6 Hz, 1H<sub>furyl</sub>), 6.39 (dd, *J* = 3.5, 1.8 Hz, 1H<sub>furyl</sub>), 7.33–7.41 (m, 2H<sub>arom</sub>), 7.51–7.59 (m, 3H<sub>arom</sub>, 1H, =CH-O), 7.97–8.06 (m, 1H, =CH-N). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 20.2, 26.5, 34.0, 51.9, 52.5, 75.1, 76.3, 110.6, 110.8, 127.1, 127.7, 129.3, 129.7, 133.2, 143.5, 172.3, 172.7. Anal. calcd. for C<sub>24</sub>H<sub>22</sub>N<sub>6</sub>O<sub>5</sub>S: C 56.91; H 4.38; N 16.59%. Found: C 57.16; H 4.19; N 16.76%.

**(R)-5-{3-[4-([5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio)methyl]-1H-1,2,3-triazol-1-yl]prop-1-en-2-yl}-2-methylcyclohex-2-en-1-one (15a)**. Yield 65%, mp 135–140 °C, [α]<sub>D</sub><sup>20</sup> –25.00 (C 0.84 CH<sub>2</sub>Cl<sub>2</sub>). IR ν/cm<sup>-1</sup>: 1601, 1615, 1635 (C=C), 1645 (C=N), 1705 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.68 (br.s, 3H, CH<sub>3</sub>), 2.52–2.16 (m, 4H, CH<sub>2</sub> in carbocycle), 2.58 (m, 1H, CH in carbocycle), 4.43 (br.s, 2H, CH<sub>2</sub>S), 4.91 (br.s, 1H<sup>b</sup>, CH<sub>2</sub>N),

5.01 (br.s, 1H<sup>b</sup>, =CH<sub>2</sub>, 1H<sup>a</sup>, CH<sub>2</sub>N), 5.05 (br.s, 1H<sup>a</sup>, =CH<sub>2</sub>), 6.18 (br.d, *J* = 3.2 Hz, 1H<sub>furyl</sub>), 6.39 (br.dd, *J* = 2.9, 1.3 Hz, 1H<sub>furyl</sub>), 6.62–6.77 (m, 1H, CH=C-C=O), 7.23–7.40 (m, 2H<sub>arom</sub>), 7.48–7.61 (m, 3H<sub>arom</sub>, 1H =CHO), 7.99 (br.s, *J* = 4.8 Hz, 1H, =CHN). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 14.9, 30.2, 37.7, 41.8, 52.6, 110.3, 110.7, 113.4, 129.1, 129.5, 126.9, 133.2, 134.2, 141.0, 142.9, 143.4, 145.1, 196.4. Anal. calcd. for C<sub>25</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub>S: C 63.54; H 5.12; N 17.78%. Found: C 63.35; H 5.01; N 17.96%.

**(R)-5-{3-[4-({[5-(2-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio)methyl]-1H-1,2,3-triazol-1-yl]prop-1-en-2-yl}-2-methylcyclohex-2-en-1-one (15b)**. Yield 64%, mp 69–72 °C,  $[\alpha]_D^{20}$  -22.00 (C 0.92 CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu$ /cm<sup>-1</sup>: 1600, 1612, 1640 (C=C), 1645 (C=N), 1706 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.70 (br.s, 3H, CH<sub>3</sub>-C=O). 2.14–2.41 (m, 2H, CH<sub>2</sub> in carbocycle), 2.42–2.55 (m, 2H, CH<sub>2</sub> in carbocycle), 2.56–2.77 (m, 1H, CH in carbocycle), 3.34 (s, 3H, OCH<sub>3</sub>), 4.47 (s, 2H, CH<sub>2</sub>S), 4.91 (s, 1H<sup>b</sup>, H<sub>2</sub>C=), 5.02 (s, 2H, CH<sub>2</sub>N), 5.07 (s, 1H<sup>a</sup>, H<sub>2</sub>C=), 6.65–6.74 (m, 1H, HC=C-C=O), 6.78 (br.d, *J* = 8.4 Hz, 1H<sub>arom</sub>), 7.01 (br.t, *J* = 7.1 Hz, 1H<sub>arom</sub>), 7.06–7.21 (m, 2H<sub>arom</sub>), 7.32–7.44 (m, 4H<sub>arom</sub>), 7.49 (br.d, *J* = 7.1 Hz, 1H<sub>arom</sub>), 7.97 (s, 1H=CHN). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 15.1, 26.3, 30.4, 37.9, 42.0, 52.5, 54.1, 110.5, 113.4, 115.9, 120.0, 125.6, 127.6, 128.3, 128.4, 131.2, 131.2, 133.9, 134.3, 143.1, 145.4, 155.9, 196.6. Anal. calcd. for C<sub>28</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub>S: C 65.60; H 5.51; N 16.39%. Found: C 65.76; H 5.33; N 16.57%.

**6-({1-[(8,8-Dimethyl-1,6-dioxo-2,7-dioxaspiro[4.4]nonan-3-yl)methyl]-1H-1,2,3-triazol-4-yl}methoxy)-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (16a)**. Yield 73%, mp 172–175 °C. IR  $\nu$ /cm<sup>-1</sup>: 1772, 1792 (C=O), 2203 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.27 (s, 6H, OC(CH<sub>3</sub>)<sub>2</sub>), 1.50–1.40 (m, 3H, on lactone), 1.60–1.50 (m, 3H, on lactone), 2.38–2.04 (m, 2H, CH<sub>2</sub> in lactone), 2.40 (s, 3H, N=C-CH<sub>3</sub>), 2.70–2.44 (m, 2H, CH<sub>2</sub> in lactone), 2.74 (s, 2H, CH<sub>2</sub> in pyran), 4.61 (s, 2H, CH<sub>2</sub>O in cycle), 4.85–4.67 (m, 2H, CH<sub>2</sub>N), 5.21–4.94 (m, 1H, CHO), 5.60–5.46 (m, 2H, CH<sub>2</sub>O), 8.14–8.09 (m, 1H, =CHN). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 20.8, 25.6, 25.7, 25.7, 25.8, 28.0, 28.2, 28.4, 28.6, 36.4, 36.7, 37.6, 43.6, 44.5, 51.8, 52.9, 53.2, 59.2, 69.0, 75.8, 76.3, 83.1, 83.2, 93.0, 113.2, 121.1, 121.1, 125.1, 125.2, 141.9, 142.2, 148.7, 155.3, 160.7, 172.4, 172.6. Anal. calcd. for C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>6</sub>: C 60.35; H 6.28; N 14.08%. Found: C 60.52; H 6.10; N 14.15%.

**3-({1-[(6,6-Dimethyl-3,8-dioxo-2,7-dioxaspiro[4.4]nonan-1-yl)methyl]-1H-1,2,3-triazol-4-yl}methoxy)-1-isopropyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carbonitrile (16b)**. Yield 76%, mp 64–65 °C. IR  $\nu$ /cm<sup>-1</sup>: 1775, 1794 (C=O), 2210 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.26 (d, *J* = 6.7 Hz, 6H, CH<sub>3</sub>, <sup>i</sup>Pr), 1.43–1.50 (m, 3H, (CH<sub>3</sub>)<sub>2</sub>CO), 1.51–1.59 (m, 3H, (CH<sub>3</sub>)<sub>2</sub>CO), 2.02–2.42 (m, 2H, CH<sub>2</sub> in lactone, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.52–2.72 (m, 2H, CH<sub>2</sub> in lactone), 2.78–2.94 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.94–3.15 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 1H, CH, <sup>i</sup>Pr), 4.64–4.90 (m, 2H, CH<sub>2</sub>N), 4.93–5.21 (m, 1H, HCO), 5.54 (s, 2H, CH<sub>2</sub>O), 8.01–8.13 (m, 1H, =CH-N). Anal. calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>5</sub>O<sub>5</sub>: C 60.54; H 5.08; N 16.05%. Found: C 60.71; H 4.90; N 16.22%.

**(R)-3,3,8-trimethyl-6-({1-[2-(4-methyl-5-oxocyclohex-3-en-1-yl)allyl]-1H-1,2,3-triazol-4-yl}methoxy)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (17)**. Yield 55%, mp 59–60 °C,  $[\alpha]_D^{20}$  -21.44 (C 1.068 CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu$ /cm<sup>-1</sup>: 1706 (C=O), 2203 (C≡N). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.27 (s, 6H, OC(CH<sub>3</sub>)<sub>2</sub>), 1.63–1.78 (m, 3H, CH<sub>3</sub>), 2.15–2.56 (m, 7H, CH<sub>2</sub> in carbocycle, N=C-CH<sub>3</sub>), 2.56–2.71 (m, 1H, CH in carbocycle), 2.74 (s, 2H, CH<sub>2</sub> in pyran), 4.61 (s, 2H, OCH<sub>2</sub> in pyran), 4.94 (s, 1H<sup>b</sup>, =CH<sub>2</sub>), 5.07 (s, 2H, NCH<sub>2</sub>), 5.08 (s, 1H<sup>a</sup>, =CH<sub>2</sub>), 5.51 (s, 2H, OCH<sub>2</sub>), 6.61–6.80 (m, 1H, CH=C-C=O), 7.98 (s, 1H, =N-CH). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 15.1, 20.7, 25.7, 30.4, 37.6, 37.9, 42.0, 52.5, 59.2, 59.4, 69.0, 93.0, 113.2, 113.5, 121.0, 124.2, 134.4, 142.1, 143.0, 145.5, 148.7, 155.2, 160.8, 196.5. Anal. calcd. for C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>3</sub>: C 66.79; H 6.95; N 15.58%. Found: C 66.60; H 6.84; N 15.77%.

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## Supplementary Material

The copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new synthesized compounds have been submitted along with the manuscript.

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