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# Synthesis and binding affinity of new 1,4-disubstituted triazoles as potential dopamine $D_3$ receptor ligands

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ABSTRACT

A series of new 1,4-disubstituted triazoles was prepared from appropriate arylacetylenes and aminoalkylazides using click chemistry methodology. These compounds were evaluated as potential ligands on several subtypes of dopamine receptors in in vitro competition assays, showing high affinity for dopamine $D_3$ receptors, lower affinity for $D_2$ and $D_4$, and no affinity for the $D_1$ receptors. Compound **18** displayed the highest affinity at the $D_3$ receptor with a $K_i$ value of 2.7 nM, selectivity over $D_2$ (70-fold) and $D_4$ (200-fold), and behaviour as a competitive antagonist in the low nanomolar range.



The neurotransmitter dopamine (DA) plays important roles in behaviour and cognition, ranging from movement to emotion, sensitization to addiction, and development to plasticity. All DA receptors belong to the family of G protein coupled receptors (GPCR), which are characterized by having seven hydrophobic transmembrane-spanning regions, as well as a functionally critical third intracytoplasmic loop that interacts with G-proteins and other effector molecules to mediate the physiological and neurochemical effects of the receptors. Based on their pharmacological profiles, including their effects on different signal transduction cascades, these receptors are currently divided into two protein families: the $D_1$-like ($D_1$ and $D_5$) family or adenylyl-cyclase stimulators, and the $D_2$-like ($D_2$, $D_3$ and $D_4$) family or adenylyl-cyclase inhibitors.[1]

The $D_3$ dopamine receptor was first identified and cloned by Sokoloff et al.[2] in 1990 and has been shown to be an interesting target for different CNS diseases. Although the $D_2$ and $D_3$ receptor subtypes are highly homologous, especially within the transmembrane segments, which serve as the binding site for dopamine, the $D_3$ receptor is generally less abundant than the $D_2$ receptor, and the difference is particularly striking in the caudate putamen, where $D_2$ receptors are displayed at high density, whereas $D_3$ receptors are poorly represented.[3] Moreover, $D_3$-binding sites and mRNA encoding $D_3$ receptors are concentrated in the limbic brain regions known to be associated with cognitive and emotional functions.[4] Due to this observation, the $D_3$ receptor has been suggested to be a potential target in the treatment of neurological disorders[5] such as schizophrenia,[6] Parkinson's disease,[7] drug-induced dyskinesia,[8] and drug abuse.[9] Furthermore, some studies have shown that pro-erectile effects of dopamine $D_2$-like agonists are mediated by the $D_3$ receptor in rats and mice.[10]

An intensive effort has been directed toward the development of selective ligands for dopamine $D_3$ receptors in an attempt to prove these hypotheses.[11] Thus, a number of potent and selective $D_3$ ligands, including antagonists, partial agonists and full agonists have been developed. Some of these well-known $D_3$ ligands include pramipexole and ropinirole (Fig. 1), two highly potent $D_3$ full agonists but with only modest selectivity for the $D_3$ receptor over the $D_2$ receptor.[12] On the other hand, numerous antagonists and partial agonists have been developed so far with a number of lead compounds showing both great potency and selectivity for the $D_3$ receptor (Fig. 1). Most of these compounds contain a piperazine ring connected to a suitable benzamide-type moiety via variable linker size.[11,13] Among the compounds illustrated, it is worth highlighting the values displayed by the piperazines ABT 925 and RGH

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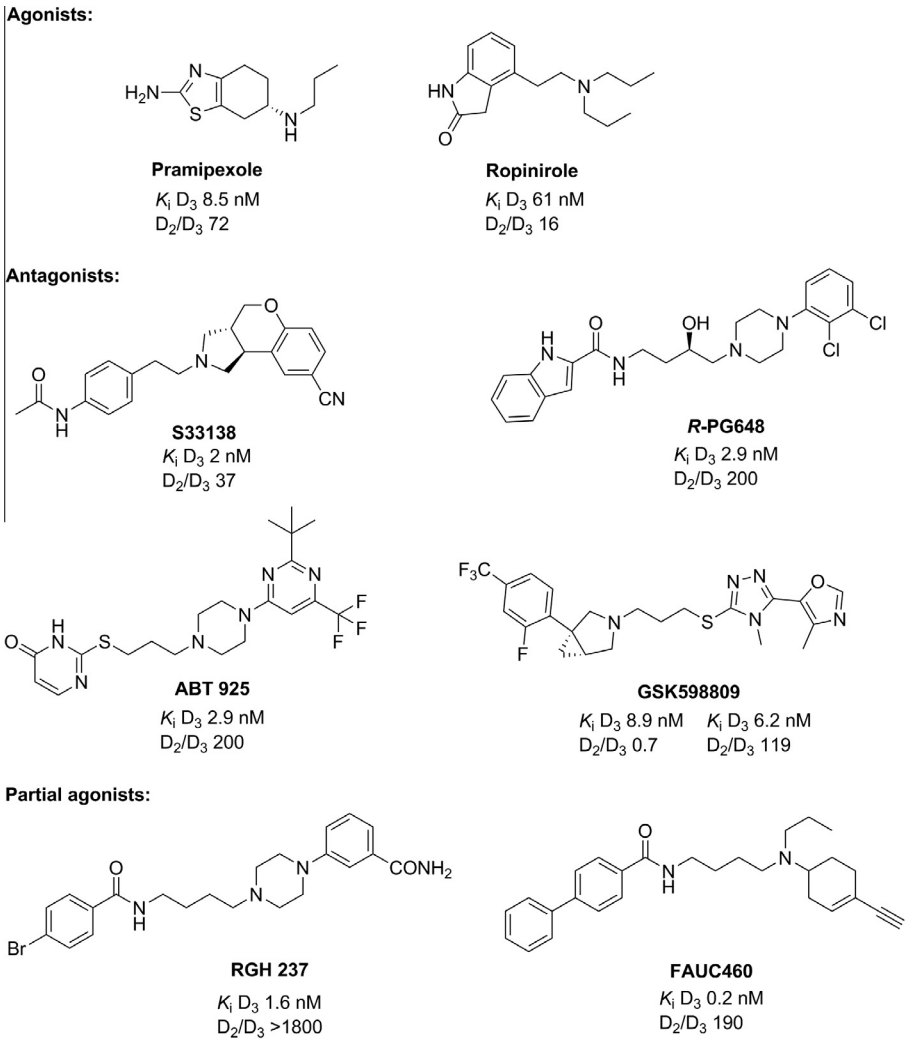



**Figure 1.** Structures of selective $D_3$ receptor ligands.

237 exhibiting a good selectivity pattern of $D_3$ over $D_2$ with a ratio of 200 and 1800, respectively. Nevertheless, despite the significant number of $D_3$ ligands reported, today there is still a need for more selective molecular tools to facilitate a relevant differentiation between $D_3$ actions and those mediated by the $D_2$ receptors, in order to elucidate the function and potential therapeutic advantages of targeting $D_3$ receptors, and for molecules enabling sufficient $D_3$ receptor occupancy to derive conclusions on a $D_3$-mediated therapeutic benefit.

In our laboratories, the synthesis and pharmacological evaluation on $D_1$, $D_2$, $D_3$ and $D_4$ dopamine receptors of a series of cyclic *N*-piperazinilalquil substituted benzolactams (**A**, Fig. 2), have allowed us to determine some of the essential structural requirements for a high-affinity binding on the $D_3$ receptor. The study of the structure–activity relationships (SAR) in this series concluded that both the length of the linker between the lactam and piperazine ring, and the size of the lactam ring influence the affinity for the $D_2$ and $D_3$ receptors.[14] In a continuation of this work, we report in this Letter the replacement of the lactam system for a 1,2,3-triazole ring on the basis of previous studies[15] which report that carboxamide function could be successfully replaced by a five-membered heterocycle in a series of dopamine $D_3$ antagonists. Therefore, new triazole analogues of our benzolactam derivatives were obtained via *click chemistry*, using [3+2] azide–alkyne cycloaddition (Huisgen reaction) promoted by copper(I),[16] and their binding profile on dopamine receptors was determined.

In the search for a general method of synthesis of the new disubtituted triazoles **15**–**20** (Fig. 2), two possible routes (Scheme 1) were investigated starting from 4-clorobutilazide (**1**) which was easily prepared by nucleophilic substitution of the bromine atom in 1-bromo-4-chlorobutane by sodium azide in DMF in 92% yield. The general method was explored using phenylacetylene as alkyne and 1-(2-methoxyphenyl)piperazine as amine. Thus, the reaction of **1** with 1-(2-methoxyphenyl)piperazine (route a) under basic conditions afforded in 65% yield the 1-(4-azidobutyl)-4-(2-methoxyphenyl)piperazine (**2**); subsequent Huisgen 1,3-dipolar cycloaddition[17] with phenylacetylene **3** gave the corresponding triazol **15** (see Scheme 1).

For this *click reaction* several conditions (Table 1) were evaluated. The target compound **15** was obtained in a high yield of 89% (58% two-step yield) (entry 6).

Alternatively (*route b*), cycloaddition reaction of phenylacetylene with the chlorobutylazide **1** afforded 4-phenyl-1-(4-chlorobutyl)-1*H*-1,2,3-triazole (**9**). In this case, the reaction took place in the presence of $Cu_2O$ and benzoic acid in water;[18] after stirring for 30 min at room temperature, triazole **9** was obtained in 96% yield. The chlorine atom in **9** was replaced by 1-(2-methoxyphenyl)piperazine leading to the desired compound **15** in 94% yield. The utilization of microwave irradiation at 130 °C allowed to reduce the reaction time from 16 h (conventional thermal heating conditions) to 30 min. Having successfully established a suitable catalyst and the optimal conditions to synthesize the target compound **15**

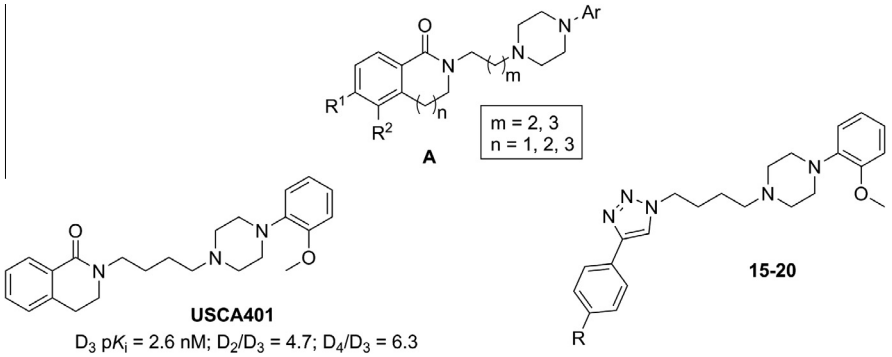
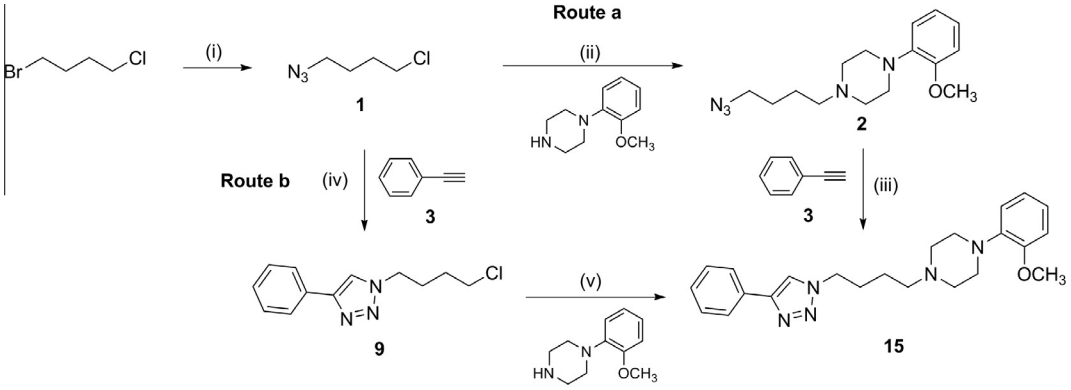
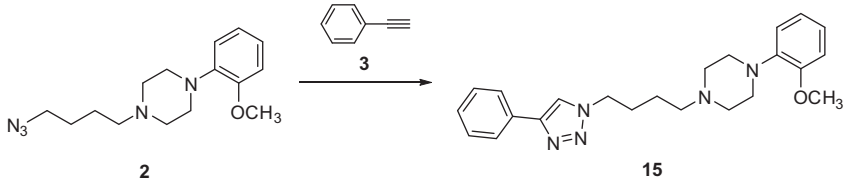



**Figure 2.** Structures of the $D_3$ dopamine benzolactam ligands and proposed 1,2,3-triazole analogues.




**Scheme 1.** Reagents and conditions: (i) $NaN_3$, DMF, rt, 72 h, 92%; (ii) $K_2CO_3$, KI, methylisobutylketone, reflux, 16 h, 65%; (iii) $CuSO_4{\cdot}5H_2O$, Cu(0), *t*-BuOH:$H_2O$ (1:1), microwave, 125 °C, 10 min, 89%; (iv) $Cu_2O$, benzoic acid, $H_2O$, rt, 30 min, 96%; (v) $K_2CO_3$, KI, DMF, microwave (100 W), 130 °C, 30 min, 94%.

**Table 1**
Optimization assays of the click reaction leading to triazole **15**



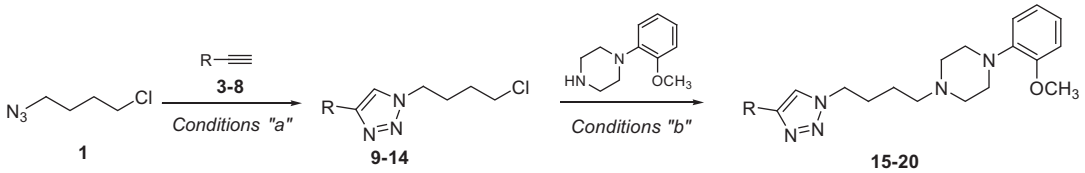

| Entry | Heating conditions | Catalyst | Solvent | Temp (°C) | Time | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Thermal | $CuSO_4{\cdot}5H_2O$, sodium ascorbate | *t*-BuOH/$H_2O$ (1:1) | rt | 15 h | 73 |
| 2 | Thermal | $CuSO_4{\cdot}5H_2O$, sodium ascorbate | *t*-BuOH/$H_2O$ (1:1) | 120 | 2 h | 87 |
| 3 | MW | $CuSO_4{\cdot}5H_2O$, sodium ascorbate | DMF | 110 | 30 min | 58 |
| 4 | MW | $CuSO_4{\cdot}5H_2O$, sodium ascorbate | DMF | 150 | 15 min | 73 |
| 5 | MW | $CuSO_4{\cdot}5H_2O$, sodium ascorbate | *t*-BuOH/$H_2O$ (1:1) | 125 | 10 min | 88 |
| 6 | MW | $CuSO_4{\cdot}5H_2O$, Cu(0) | *t*-BuOH/$H_2O$ (1:1) | 125 | 10 min | 89 |

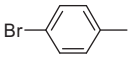
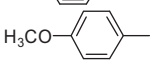
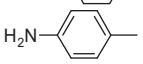
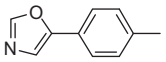
(90% yield in two steps), we tackled the issues of scope and group tolerance, being this second approach the selected procedure for the synthesis of the other 1,4-disubstituted triazoles.[19]

To apply the *route b* to the new series of alkynes (**4**–**8**) the solvent in the click reaction had to be modified: while phenylacetylene is a liquid under normal conditions, which enables the distribution of reagents in the flask, the rest of acetylenes studied are solid and precipitate in water. Changing the media to dichloromethane facilitated the contact between the reagents. Consequently, using the same catalytic system as in the preparation of **9**, triazoles **10** and **11** were obtained in 94% and 53% yield, respectively, (Table 1, entries 2 and 3). However, the reaction of 3-ethynylpyridine (**7**) under these conditions did not allow isolating the expected triazole **13**, so the amount of $Cu_2O$ was increased from 1% to 10%. Under these conditions triazoles **12**–**14** were obtained from alkynes **6**–**8** in yields ranging from 17% to 75%. Finally, subsequent displacement of the chlorine atom by 1-(2-methoxyphenyl)piperazine in basic medium under microwave irradiation furnished the final products **16**–**20** in 42–81% yield (Table 2).[20]

*In vitro dopamine receptor binding studies:* The affinity of the new compounds for cloned human $D_1$, $D_2$ and $D_3$ receptors was evaluated in in vitro binding assays using [$^3$H]SCH23390 for labelling $D_1$ receptors and [$^3$H]spiperone for labelling $D_2$, $D_3$ and $D_4$ recep-

**Table 2**
Reaction conditions for the preparation of 1,2,3-triazoles **9–14** and **15–20**




| Entry | R | Conditions 'a' | Compound (Yield) | Conditions 'b' | Compound (Yield) |
|---|---|---|---|---|---|
| 1 |  | Benzoic acid, 1% $Cu_2O$, $H_2O$, rt, 30 min | **9** (96%) | $K_2CO_3$, KI, DMF, MW (100 W), 130 °C, 30 min | **15** (94%) |
| 2 |  | Benzoic acid, 1% $Cu_2O$, $CH_2Cl_2$, rt, 85 min | **10** (94%) | $K_2CO_3$, KI, DMF, MW (100 W), 130 °C, 30 min | **16** (81%) |
| 3 |  | Benzoic acid, 1% $Cu_2O$, $CH_2Cl_2$, rt, 72 h | **11** (53%) | $K_2CO_3$, KI, DMF, MW (100 W), 130 °C, 30 min | **17** (80%) |
| 4 |  | Benzoic acid, 10% $Cu_2O$, $CH_2Cl_2$, rt, 40 h | **12** (37%) | $K_2CO_3$, KI, DMF, MW (100 W), 130 °C, 45 min | **18** (55%) |
| 5 |  | Benzoic acid, 10% $Cu_2O$, $CH_2Cl_2$, rt, 48 h | **13** (75%) | $K_2CO_3$, KI, DMF, MW (100 W), 130 °C, 55 min | **19** (42%) |
| 6 |  | Benzoic acid, 10% $Cu_2O$, $CH_2Cl_2$, rt, 60 h | **14** (17%) | $K_2CO_3$, KI, DMF, MW (100 W), 130 °C, 60 min | **20** (73%) |

tors, according to our previously described procedures.[21] $K_i$ values were calculated according to the Cheng–Prusoff equation.[22] For the compounds that showed little affinity, a percentage of inhibition at the highest concentration tested (1 μM) is reported. The in vitro receptor binding data are summarized in Table 3.

The new synthesized triazoles showed no significant affinity at the $D_1$ receptor, while on $D_2$–$D_4$ subtypes the affinities were in the sub-micromolar order. In general, the order of affinity for the six new prepared compounds was $D_3 > D_2 > D_4 > D_1$.

The six new compounds showed good affinity and selectivity for the $D_3$ receptor, but it is worth highlighting the profile of compound **18**, with a strong affinity for the $D_3$ receptor ($K_i$ = 2.7 nM) and a selectivity for this receptor subtype of approximately 70-times on the $D_2$, and almost 200-times on the $D_4$ receptors, showing little affinity (>1 μM) for $D_1$ receptors. In this compound, the amine group critically influences the affinity for the $D_3$ dopamine receptors, while it has little influence on the other dopamine receptor subtypes. This behaviour could be attributed to the establishment of an additional H bonding between the $NH_2$ and an acceptor group in the $D_3$ receptor binding site. On the other hand, it seems to be some relationship between the electron density of the aromatic ring attached to the triazole and the $D_3$ receptor affinity such that the higher the electron density (compounds **18** and **17**) the higher the affinity, which could be related to the existence of a pi-stacking interaction with an aromatic residue in the binding site.

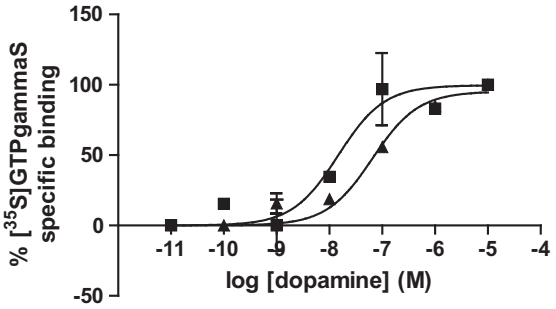



**Figure 3.** Concentration–response curves of dopamine in the absence (■) and in the presence (▲) of 5 nM triazole **18** by measuring $GTP_\gamma S$ specific binding to dopamine $D_3$ receptors. Points represent the mean ± standard deviation (vertical bars) of duplicate measurements of a representative experiment.

Based on the binding results, the next goal of our study was to evaluate the functional activity at the $D_3$ receptor of the most promising compound of the collection. Consequently, triazole **18** was tested in $[^{35}S]GTP_\gamma S$ functional assay to characterize its ability to stimulate $D_3$ receptor in comparison to the endogenous ligand DA according to standard protocols.[23]

As it is illustrated in the Figure 3, compound **18** right-shifted the dopamine concentration–response curve, behaving as an antagonist of dopamine $D_3$ receptors, showing a $K_B$ value of 1.4 ± 0.26

**Table 3**
Human $D_1$–$D_4$ receptor binding affinities of new compounds ($pK_i$ or percent displacement at 1 μM)[a]

| Compound | Affinity | | | | Selectivity | |
|---|---|---|---|---|---|---|
| | $D_1$ (% at 1 μM) | $D_2$ ($K_i$ nM) | $D_3$ ($K_i$ nM) | $D_4$ ($K_i$ nM) | $D_2/D_3$ | $D_4/D_3$ |
| **15** (1T1401) | 39.41 | 228.3 | 81.2 | 639.3 | 2.8 | 7.9 |
| **16** (2T1401) | 44.26 | 226.6 | 110.7 | 386.7 | 2.0 | 3.5 |
| **17** (3T1401) | 44.26 | 211.7 | 40.1 | 394.8 | 5.3 | 9.8 |
| **18** (4T1401) | 38.43 | 198.8 | 2.7 | 532.5 | 73.6 | 197.2 |
| **19** (5T1401) | 40.85 | 181.5 | 132.5 | 1898.2 | 1.4 | 14.3 |
| **20** (6T1401) | 50.01 | 136.6 | 134.6 | 426.4 | 1.0 | 3.2 |

[a] All values are means of two or three separate competition experiments.

nM, this value is in agreement with the affinity of the compound measured in binding experiments.

In conclusion, a new series of 1,4-disubstituted-1,2,3-triazoles was synthesized by a short, efficient, microwave-assisted process, and evaluated as dopamine $D_3$ receptor ligands. The binding affinities of the synthesized compounds on the dopamine receptor subtypes unveiled that triazole **18** (4T1401), bearing a 4-$NH_2$-phenyl group, has a high $D_3$ receptor affinity together with an excellent selectivity on other dopamine receptors. Furthermore, functional assay showed its behaviour as a competitive antagonist at $D_3$ receptor in the nanomolar range.

According to our results, the presence of an electron-rich substituent in the phenyl ring could favor both potency and selectivity on $D_3$ receptor. These data enhance our understanding of the $D_3$ pharmacophore and are expected to lead to novel compounds with higher affinity and selectivity on this receptor taking triazole **18** as a lead molecule. Further optimization of this series is in progress and is directed to the synthesis of new counterparts and will be reported in due course.

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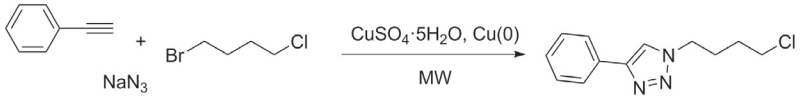
## References and notes

1. Missale, C.; Nash, S. R.; Robinson, S. W.; Jaber, M.; Caron, M. G. *Physiol. Rev.* **1998**, *78*, 189.
2. Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L.; Schwartz, J. C. *Nature* **1990**, *347*, 146.
3. Levant, B. *Pharmacol. Rev.* **1997**, *49*, 231.
4. (a) Joyce, J. N.; Meador-Woodruff, J. H. *Neuropsychopharmacology* **1997**, *16*, 375; (b) Shafer, R. A.; Levant, B. *Psychopharmacology* **1998**, *135*, 1; (c) Joyce, J. N. *Pharmacol. Ther.* **2001**, *90*, 231.
5. Joyce, J. N.; Millan, M. J. *Drug Discovery Today* **2005**, *10*, 917.
6. (a) Gross, G.; Drescher, K. In *Novel Antischizophrenia Treatments*; Geyer, M. A., Gross, G., Eds.; Springer-Verlag: Berlin, 2012; pp 167–210; (b) Gross, G.; Wicke, K.; Drescher, K. U. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2013**, *386*, 155.
7. Joyce, J. N.; Ryoo, H. L.; Beach, T. B.; Caviness, J. N.; Stacy, M.; Gurevich, E. V.; Reiser, M.; Adler, C. H. *Brain Res.* **2002**, *955*, 138.
8. Bezard, E.; Ferry, S.; Mach, U.; Stark, H.; Leriche, L.; Boraud, T.; Gross, C.; Sokoloff, P. *Nat. Med.* **2003**, *9*, 762.
9. (a) Heidbreder, C. A.; Newman, A. H. *Ann. N.Y. Acad. Sci.* **2010**, *1187*, 4; (b) Heidbreder, C. A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2013**, *386*, 167.
10. Collins, G. T.; Truccone, A.; Haji-Abdi, F.; Newman, A. H.; Grundt, P.; Rice, K. C.; Husbands, S. M.; Greedy, B. M.; Enguehard-Gueiffier, C.; Gueiffier, A.; Chen, J.; Wang, S.; Katz, J. L.; Grandy, D. K.; Sunahara, R. K.; Woods, J. H. *J. Pharmacol. Exp. Ther.* **2009**, *329*, 210.
11. (a) Brown, D. A.; Kharkar, P. S.; Parrington, I.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2008**, *51*, 7806; (b) Micheli, F.; Arista, L.; Bonanomi, G.; Blaney, F. E.; Braggio, S.; Capelli, A. M.; Checchia, A.; Damiani, F.; Di-Fabio, R.; Fontana, S.; Gentile, G.; Griffante, C.; Hamprecht, D.; Marchioro, C.; Mugnaini, M.; Piner, J.; Ratti, E.; Tedesco, G.; Tarsi, L.; Terreni, S.; Worby, A.; Ashby, C. R.; Heidbreder, C. *J. Med. Chem.* **2010**, *53*, 374; (c) Newman, A. H.; Grundt, P.; Cyriac, G.; Deschamps, J. R.; Taylor, M.; Kumar, R.; Ho, D.; Luedtk, R. R. *J. Med. Chem.* **2009**, *52*, 2559; (d) Geneste, H.; Backfisch, G.; Braje, W.; Delzer, J.; Haupt, A.; Hutchins, C. W.; King, L. L.; Kling, A.; Teschendorf, H.-J.; Unger, L.; Wernet, W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 490; (e) Zahng, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274; (f) Boeckler, F.; Gmeiner, P. *Pharmacol. Ther.* **2006**, *112*, 281; (g) Gyertyan, I.; Kiss, B.; Gal, K.; Laszlovszky, I.; Horvath, A.; Gemesi, L. I.; Saghy, K.; Pasztor, G.; Zajer, M.; Kapas, M.; Csongor, E. A.; Domany, G.; Tihanyi, K.; Szombathelyi, Z. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 1268; (h) Millan, M. J.; Mannoury la Cour, C.; Novi, F.; Maggio, R.; Audinot, V.; Newman-Tancredi, A.; Cussac, D.; Pasteau, V.; Boutin, J.-A.; Dubuffet, T.; Lavielle, G. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 587.
12. Perachon, S.; Schwartz, J. C.; Sokoloff, P. *Eur. J. Pharmacol.* **1999**, *366*, 293.
13. Elsner, J.; Boeckler, F.; Heinemann, F. W.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2005**, *48*, 5771.
14. (a) Ortega, R.; Raviña, E.; Masaguer, C. F.; Areias, F.; Brea, J.; Loza, M. I.; López, L.; Selent, J.; Pastor, M.; Sanz, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1773; (b) López, L.; Selent, J.; Ortega, R.; Masaguer, C. F.; Domínguez, E.; Aréias, F.; Brea, J.; Loza, M. I.; Sanz, F.; Pastor, M. *ChemMedChem* **2010**, *5*, 1300; (c) Ortega, R.; Hübner, H.; Gmeiner, P.; Masaguer, C. F. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2670.
15. Micheli, F.; Bonanomi, G.; Blaney, F. E.; Braggio, S.; Capelli, A. M.; Checchia, A.; Corcuruto, O.; Damiani, F.; Di Fabio, R.; Donati, D.; Gentile, G.; Gribble, A.; Hamprecht, D.; Tedesco, G.; Terreni, S.; Tarsi, L.; Lightfoot, A.; Stemp, G.; MacDonald, G.; Smith, A.; Pecoraio, M.; Petrone, M.; Perini, O.; Piner, J.; Rossi, T.; Worby, A.; Pilla, M.; Valerio, E.; Griffante, C.; Mugnaini, M.; Wood, M.; Scott, C.; Andreoli, M.; Lacroix, L.; Schwarz, A.; Gozzi, A.; Bifone, A.; Ashby, C. R., Jr.; Hagan, J. J.; Heidbreder, C. *J. Med. Chem.* **2007**, *50*, 5076.
16. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
17. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1–176.
18. Shao, C.; Zhu, R.; Luo, S.; Zhang, Q.; Wang, X.; Hu, Y. *Tetrahedron Lett.* **2011**, *52*, 3782.
19. Additionally, at this point, we explored a one pot, microwave-assisted synthesis of triazole **9** (Scheme 2) by using $CuSO_4{\cdot}5H_2O$/Cu(0) as catalyst system, in *tert*-butanol/water or DMF as solvent, and varying other parameters such as temperature, time and power of irradiation. This method would allow to avoid the purification of the intermediate chlorobutylazide **1**, saving resources and shortening the length of the route. Thus, the best result was obtained at 125 °C (constant power of irradiation of 100 W) in DMF for 15 min, which afforded compound **9** in 46% yield. To our disappointment, the application of this method to other alkynes (4-aminophenylacetylene or pyridin-3-ylacetylene) gave the corresponding triazoles in poor yields, and therefore, this method for the preparation of the target triazoles was discarded.




**9**

**Scheme 2.** One-pot synthesis of triazole **9**. Reagents and conditions: DMF, microwave (100 W), 125 °C, 15 min; 46%.

20. *Spectral data for compound **15**:* mp 89–90 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J$ = 8.1 Hz, 2H); 7.76 (s, 1H); 7.75–7.36 (m, 2H); 7.32–7.26 (m, 1H), 6.99–6.81 (m, 4H); 4.38 (t, $J$ = 7.0 Hz, 2H); 3.81 (s, 3H); 3.06 (br s, 4H); 2.59 (br s, 4H); 2.42 (t, $J$ = 7.0 Hz, 2H); 1.97 (t, $J$ = 7.3 Hz, 2H); 1.56 (t, $J$ = 7.3 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.2, 141.2, 130.6, 128.8, 128.1, 125.7, 122.9, 120.9, 119.5, 118.2, 111.1, 109.9, 55.3, 53.4, 50.6, 50.3, 29.7, 28.3, 23.7. IR: 1499.4, 1448.3, 1238.1, 1153.2, 1025.9, 748.2. MS: 392.2 (M+1), 393.2, 391.2, 247, 204. Anal. ($C_{23}H_{29}N_5O{\cdot}2H_2O$) C, H, N. *Compound **16**:* mp 102–104 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.75 (s, 1H); 7.69 (d, $J$ = 8.7 Hz, 2H); 7.53 (d, $J$ = 8.7 Hz, 2H); 6.95–6.85 (m, 4H); 4.42 (t, $J$ = 7.1 Hz, 2H); 3.84 (s, 3H); 3.06 (br s, 4H); 2.61 (br s, 4H); 2.43 (t, $J$ = 7.2 Hz, 2H); 2.05–1.95 (m, 2H); 1.62–1.55 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.2, 146.7, 141.2, 132.0, 129.7, 127.2, 123.0, 122.0, 121.0, 119.6, 118.2, 111.2, 57.7, 55.3, 53.4, 50.6, 50.3, 28.3, 23.7. IR: 1498.4, 1462.7, 1237.1, 1222.6, 822.5, 745.4. MS: 470.2 (M+1), 472.2, 471.2, 469.2, 247.3, 205.2, 164.1, 150.1. Anal. ($C_{23}H_{28}BrN_5O$) C, H, N. *Compound **17**:* mp 108–110 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 8.9 Hz, 2H); 7.68 (s, 1H); 6.99–6.84 (m, 6H); 4.43 (t, $J$ = 7.1 Hz, 2H); 3.85 (s, 3H, –$OCH_3$); 3.84 (s, 3H, –$OCH_3$); 3.08 (br s, 4H); 2.62 (br s, 4H); 2.45 (t, $J$ = 7.2 Hz, 2H); 2.06–1.96 (m, 2H); 1.62–1.57 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.5, 152.2, 147.6, 141.3, 127.0, 123.4, 122.9, 121.0, 118.7, 118.1, 114.2, 111.2, 57.7, 55.3, 53.4, 50.6, 50.2, 28.3, 23.8 ppm. IR: 1498.4, 1238.1, 1179.3, 1027.9, 830.2, 747.3. MS: 422.1 (M+1), 421.1, 246.9, 204.8, 163.7, 134.7, 83.9 (37). Anal. ($C_{24}H_{31}N_5O_2{\cdot}0.2CH_3OH$) C, H, N. *Compound **18**:* mp 60–61 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.63–7.59 (m, 3H); 7.02–6.84 (m, 4H); 6.74–6.70 (m, 2H); 4.40 (t, $J$ = 7.1 Hz, 2H); 3.85 (s, 3H); 3.70 (br s, 2H, exchange with $D_2O$); 3.07 (br s, 4H); 2.62 (br s, 4H); 2.44 (t, $J$ = 7.4 Hz, 2H); 2.04–1.94 (m, 2H); 1.63–1.53 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.2, 148.1, 146.5, 141.2, 126.9, 122.9, 121.1, 121.0, 118.2, 115.2, 113.7, 111.2, 57.7, 55.3, 53.4, 50.5, 50.1, 28.3, 23.7. IR: 1616.1, 1498.4, 1239.0, 1022.1, 750.2. MS: 407.1 (M+1);

256.9, 246.9, 204.8, 163.7. Anal. ($C_{23}H_{30}N_6O\cdot0.1H_2O$) C, H, N. *Compound* ***19***: mp 90–91 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.01–9.00 (m, 1H); 8.58 (d, $J$ = 4.8 Hz, 2H); 8.24–8.20 (m, 1H), 7.86 (d, $J$ = 1.0 Hz, 1H); 7.40-7.35 (m, 1H); 7.03–6.84 (m, 4H); 4.48 (t, $J$ = 7.1 Hz, 2H); 3.85 (d, 3H, J = 1.0 Hz); 3.09 (br s, 4H); 2.63 (br s, 4H); 2.47 (t, $J$ = 7.4 Hz, 2H); 2.09–2.00 (m, 2H); 1.66–1.56 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.2, 149.2, 147.0, 144.7, 141.2, 133.0, 126.8, 123.8, 122.9, 121.0, 119.8, 118.1, 111.1, 57.7, 55.3, 53.4, 50.6, 50.4, 28.3, 23.8. IR: 1499.4, 1237.1, 1030.8, 808.0, 738.6, 703.9. MS: 393.1 (M+1), 394.1, 392.1, 246.9, 204.8. Anal. ($C_{22}H_{28}N_6O\cdot0.4H_2O$) C, H, N. *Compound* ***20***: mp 157–158 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.93–7.89 (m, 3H); 7.82 (s, 1H); 7.73–7.70 (m, 2H); 7.39 (s, 1H); 7.02–6.84 (m, 4H); 4.46 (t, $J$ = 7.1 Hz, 2H); 3.85 (s, 3H); 3.08 (br s, 4H); 2.63 (br s, 4H); 2.46 (t, $J$ = 7.6 Hz, 2H); 2.06–2.00 (m, 2H); 1.63–1.58 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.2, 151.2, 150.5, 147.0, 141.2, 130.9, 127.3, 126.1, 124.8, 122.9, 121.7, 121.0, 119.7, 118.1, 111.2, 57.7, 55.3, 53.4, 50.6, 50.4, 28.3, 23.8. IR: 1498.4, 1238.1, 1098.3, 1030.8, 940.1, 825.4, 737.6, 726.1. MS: 459.1 (M+1), 460.1, 458.1, 246.9, 204.8, 163.7, 149.7. Anal. ($C_{26}H_{30}N_6O_2\cdot0.85H_2O\cdot0.3CH_3OH$) C, H, N.

21. Brea, J.; Castro, M.; Loza, M. I.; Masaguer, C. F.; Raviña, E.; Dezi, C.; Pastor, M.; Sanz, F.; Cabrero-Castel, A.; Galán-Rodríguez, B.; Fernández-Espejo, E.; Maldonado, R.; Robledo, P. *Neuropharmacology* **2006**, *51*, 251.
22. Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
23. Membranes expressing human $D_3$ receptors (Perkin Elmer) were pre-incubated (10 μg/well) in assay buffer (20 mM HEPES, 3 μM GDP, 3 mM $MgCl_2$, 100 mM NaCl; pH 7.4) with compounds **18** for 15 min at 22 °C in a 96-well polypropilene plate. Then 1 nM [$^{35}$S]$GTP_\gamma S$ (Perkin Elmer) was added to the well and the mixture was incubated for 40 min at 22 °C. The reaction was terminated by filtration on a multiscreen FB 96-well plate.