Using click chemistry toward novel 1,2,3-triazole-linked dopamine D3 receptor ligands

Thomas M. Keck[a,†,‡], **Ashwini K. Banala**[a,§], **Rachel D. Slack**[a], **Caitlin Burzynski**[a], **Alessandro Bonifazi**[a], **Oluyomi M. Okunola-Bakare**[a], **Martin Moore**[b], **Jeffrey R. Deschamps**[b], **Rana Rais**[c], **Barbara S. Slusher**[c,d], and **Amy Hauck Newman**[a,*]

[a] Medicinal Chemistry Section, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse-Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, MD 21224, United States

[b] Naval Research Laboratory, Code 6930, 4555 Overlook Avenue, Washington, DC 20375, United States

[c] Brain Science Institute, Johns Hopkins University, Baltimore, MD 21205 United States

[d] Department of Neurology, Johns Hopkins University, Baltimore, MD 21205, United States

Abstract

The dopamine D3 receptor (D3R) is a target of pharmacotherapeutic interest in a variety of neurological disorders including schizophrenia, Parkinson's disease, restless leg syndrome, and drug addiction. A common molecular template used in the development of D3R-selective antagonists and partial agonists incorporates a butylamide linker between two pharmacophores, a phenylpiperazine moiety and an extended aryl ring system. The series of compounds described herein incorporates a change to that chemical template, replacing the amide functional group in the linker chain with a 1,2,3-triazole group. Although the amide linker in the 4-phenylpiperazine class of D3R ligands has been previously deemed critical for high D3R affinity and selectivity, the 1,2,3-triazole moiety serves as a suitable bioisosteric replacement and maintains desired D3R-binding functionality of the compounds. Additionally, using mouse liver microsomes to evaluate CYP450-mediated phase I metabolism, we determined that novel 1,2,3-triazole-containing compounds modestly improves metabolic stability compared to amide-containing analogues. The 1,2,3-triazole moiety allows for the modular attachment of chemical subunit libraries using copper-catalyzed azide-alkyne cycloaddition click chemistry, increasing the range of chemical entities that can be designed, synthesized, and developed toward D3R-selective therapeutic agents.

*Corresponding author. Tel.: +1 443 740 2887; fax: +1 443 740 2111. anewman@intra.nida.nih.gov (A. Hauck Newman)..
†Present address: Department of Chemistry & Biochemistry, College of Science and Mathematics, Rowan University, 201 Mullica Hill Rd, Glassboro, NJ 08028, United States.
‡Present address: Department of Biomedical & Translational Sciences, School of Biomedical Science & Health Professions, Rowan University, 201 Mullica Hill Rd, Glassboro, NJ 08028, United States.
§Present address: GVK Biosciences, Plot No. 28 A, IDA, Nacharam, Hyderabad 500076, India.

1. Introduction

The neurotransmitter dopamine signals through a family of five (D1–D5) G protein-coupled receptors (GPCRs), subdivided into D1- like (D1R and D5R) and D2-like (D2R, D3R and D4R) sub-families on the basis of pharmacological and sequence similarity.[1] D3R-selective ligands may be used to treat a variety of neuropsychiatric disorders associated with aberrant dopamine signaling, including schizophrenia,[2] Parkinson's disease and associated dyskinesias,[3,4] and drug addiction.[5–7] Since it was cloned and characterized in 1990,[8] the D3R, in particular, has been a target of pharmacotherapeutic interest in the treatment of drug addiction due to its relatively localized expression within mesolimbic neurocircuitry, including the nucleus accumbens, islands of Calleja and ventral striatum.[9–11] Because these regions encode rewarding and motivational aspects of addictive drugs, pharmacological modification of D3R signaling is an appealing treatment option for psychostimulant addiction, for which there is currently no FDA-approved medication.

Many research groups have developed D3R-selective antagonists and partial agonists.[12–14] One common template used to develop D3R-selective ligands incorporates two pharmacophores, a substituted 4-phenylpiperazine and an extended aryl ring system, connected via a butylamide linker chain.[7] Previous structure–activity relationship (SAR) studies have determined that the butyl linker is an optimal length[15,16] and that the amide function is necessary[17] for maximal D3R over D2R selectivity (for review, see references[5,7]). The amide, however, is a potential site for metabolism: amides can be hydrolyzed by systemic esterases and hepatic amidases.[18,19] As such, development of bioisosteric substitutes for the amide bond may be beneficial to the translational potential of substituted 4-phenylpiperazines. 1,2,3-Triazoles have been successfully used as bioisosteres for amides in HIV-1 and mammalian protease inhibitors[20,21] and acetylcholinesterase inhibitors.[22] Indeed, triazole ureas have been designed to inhibit hydrolases.[23] It should be noted that others have recently investigated the 1,2,3-triazole template for novel D3R ligands,[24,25] and the 1,2,4-triazole motif has also provided a rich set of D3R-selective antagonists,[26,27] exemplified by the clinically investigated GSK598,809.[9,28]

In this study, we evaluated the 1,2,3-triazole as a bioisosteric substitute for the amide functional group in a series of substituted 4-phenylpiperazines targeting the D3R, which were synthesized using a copper-catalyzed azide-alkyne cycloaddition (CuAAC).[29–31] Herein, we report the design and synthesis of novel 1,2,3-triazole-containing compounds with high D3R affinity and subtype selectivity. This library was comprised of two series of compounds: those of template A and those of template B (Fig. 1). Analogues designed around template A contained an N1-aryl substituent and a C4-butyl linker. Inversely, those designed around template B possessed an N1-butyl linker and a C4-aryl substituent. Radioligand competition binding assays were performed to evaluate compound affinity for

D2-like receptors. Furthermore, CYP450-mediated phase I metabolic stability in mouse microsomes was evaluated for selected amide and triazole analogues.

2. Chemistry

Triazoles **4–5** (Scheme 1) were prepared starting from tosylate **1**,[32] which was displaced using commercially available 1-(2-methoxyphenyl)piperazine and 1-(2,3-dichlorophenyl)piperazine to give acetylene-containing piperazines **2** and **3**, respectively. Using a CuAAC reaction,[33] these acetylenes **2** and **3** were coupled to azides, formed in situ from the appropriate commercially available amine (or in a preceding step for compound **4d**), which provided the desired template A triazoles **4–5**.

A library of template B triazoles was prepared in a similar manner, as shown in Scheme 2. Tosylate **6**[34] was treated with the appropriate phenylpiperazine to provide the corresponding *N*-alkyl piperazines **7–8**. CuAAC with aryl acetylenes using either a Cu(I)-catalyzed method or a Cu(II) and sodium ascorbate-catalyzed method resulted in triazoles **9–10**.

Racemic 3-OH butyl-linked derivatives **12–13** (Scheme 3) were prepared from a one-pot epoxide-opening click chemistry reaction. 2-(2-Azidoethyl)oxirane (**11**)[35] was treated with the appropriate phenylpiperazine hydrochloride and the prepared aryl acetylene in the presence of $CuSO_4 \cdot 5H_2O$, sodium ascorbate, K_2CO_3, and β-cyclodextrin to facilely provide compounds **12–13**.[36,37]

Racemic indoles **16** and **17a** (Scheme 4), possessing the 3-OH butyl linker, were prepared, starting with the opening of epoxide **11** with the appropriate phenylpiperazine in refluxing acetonitrile to give **14** and **15**. Next, CuAAC with 5-ethynyl-1*H*-indole[38] gave compounds **16** and **17a**. The structure of **17a** was confirmed by X-ray crystallography (Fig. 2).

Lastly, the synthesis of racemic quinoline **17b** (Scheme 4) was accomplished using a tris(benzyltriazolylmethyl)amine (TBTA)-catalyzed CuAAC method.[39,40] The role of the polytriazole, TBTA, is to stabilize the copper intermediates formed throughout the catalytic cycle.[41] Therefore, while the coupling of azide **15** with 3-ethynylquinoline in the absence of TBTA did not provide the triazole **17b**, the addition of the polytriazole to the same reaction conditions cleanly yielded the desired **17b**.[42]

3. Binding results and SAR discussion

To evaluate the D3R binding affinities and receptor subtype selectivity of this series of compounds, we used [^{3}H]*N*-methylspiperone as a competitive radioligand for binding site competition in membranes prepared from HEK293 cells expressing either the human D2R, D3R or D4R. The results of these in vitro tests are listed in Tables 1 and 2 for template A and template B compounds, respectively.

Binding studies showed that several of these butyltriazole-linked analogues had affinities in the low nanomolar range for D3R (Tables 1 and 2). These compare favorably with previous compounds we have synthesized and evaluated from the substituted 4-phenylpiperazine class using the butylamide linker, including **NGB2904**,[15,43] **PG648**,[44] and **OMO5-057**

[Manuscript, in preparation], presented in Table 2 for comparison. These results indicate that the 1,2,3-triazole substitution for the amide group is generally tolerated.

In general, template A triazoles were well-tolerated at D3R, with K_i values in the range of 1–13 nM and D3R over D2R selectivity between 10- and 84-fold; **5b** had the best binding profile in this series, comparable to its amide analogue, **NGB2904** (Table 2). Template B triazoles that were unsubstituted in the butyl linking chain showed a similar range of affinities, with **10c** and **10d** having the highest D3R affinities. However, it must be noted that the analogues with highest D3R selectivity (e.g., **5d**, **10e**, **13a**, and **13b**) were highly lipophilic with cLog$P$ values of 6 or greater. As seen previously with the amide series,[44,45] when a 3-OH group was added, both D3R and D2R affinities tended to decrease compared to the unsubstituted analogues. However, **17a** retained high D3R affinity (K_i = 5.85 nM) and was 165-fold selective for D3R over D2R. Further, its cLog$P$ value of 4.9 was equivalent to its amide analogue, **PG648**. The quinoline homologue (**17b**) of indole **17a**, showed reduced D3R affinity and selectivity. This is consistent with observations we have made in a large series of quinoline amide analogues [Manuscript, in preparation] in which **OMO5-57** had the most promising affinity and subtype selectivity profiles: K_i = 2.91 at D3R and >100-fold D3R versus D2R selectivity (Table 2).

Orientation of the 1,2,3-triazole appeared to have a small impact on the affinity at D2R or D3R. For example, template A compounds **4b** and **5d**, when compared to analogous template B compounds **9b** and **10b**, respectively, had slightly improved D3R affinity and subtype selectivity; the pattern holds for other comparisons as well [e.g., **4a** and **5a** (template A) compared to **9a** and **10a** (template B), respectively]. This suggests that, for the purposes of designing high-affinity D3R ligands with selectivity over D2R, the N1-aryl triazoles may be slightly preferred. We have reported previously that the D3R affinities of the 4-phenylpiperazines appear to be largely dictated by the primary pharmacophore (e.g., 2,3-dichlorophenylpiperazine vs 2-methoxyphenylpiperazine), whereas selectivity over D2R depends on the terminal arylamide.[46] This is due to a larger secondary binding pocket in the D3R that features a critical Gly94 residue.[16] Hence, in the present series of compounds both the nature and orientation of the terminal aryl moiety affect D3R-selectivity by decreasing affinity at D2R; the orientation afforded in template A may be optimal. However, it should be noted that the 3-OH analogues in the template A series could not be prepared, thus direct comparison to highly D3R-selective template B analogues (e.g., **13a**, **13b**, and **17a**) was not possible and may be a limitation of this template. Modification of the butyl linking chain with the 3-OH generally improves D3R selectivity and reduces lipophilicity.

4. Microsomal metabolism results

The triazole moiety has convenient properties for modular synthesis of novel compounds and may offer additional protection against drug metabolism in comparison to the amide bond. Five compounds were tested for phase I metabolism in mouse liver microsomal incubations in the presence of NADPH, two featuring the amide linker (**PG648** and OMO5-57), and three with the 1,2,3-triazole linker (**16**, **17a**, and **17b**). Compound stability over one hour incubation is presented in Figure 3.

The 1,2,3-triazole analogues demonstrated modestly improved microsomal stability over the amide analogues. This is particularly apparent when comparing **OMO5-057** and **17b**, homologous structures that feature a quinoline at the extended aryl position and differ only in the presence of an amide or 1,2,3-triazole linker, respectively: after 60 min incubation in the presence of micro-somes, 26% of **17b** remained, contrasted with only 4% remaining of **OMO5-057**. Similarly, **17a** was more stable than **PG648** (35% vs 11% remaining after 60 min incubation, respectively); however the orientation of the indole differs between **PG648** and **17a**, prohibiting a direct comparison. Finally, there was little stability difference between homologous structures differing only in substitutions at the 4-phenylpiperazine: **17a**, with a 2,3-dichlorophenylpiperazine, and **16**, with 2-methoxyphenylpiperazine, were present at similar amounts after 30 min of incubation (45% vs 44%, respectively) and after 60 min (35% vs 27%, respectively). Liver microsomes measure primarily CYP450-mediated metabolism and thus cannot directly test the hypothesis that our triazole-containing molecules are more resistant to amidase metabolism. The present results, however, demonstrate that the triazole substitution provides some resistance to CYP450-mediated phase I metabolism.

5. Conclusions

In summary, a series of 1,2,3-triazole-containing substituted 4-phenylpiperazines were synthesized to explore the triazole as a bioisosteric substitution for the amide linker commonly found in this chemical class of D3R-selective ligands. Several 1,2,3-triazole-containing compounds had high ($K_i = 1$–10 nM) affinity for D3R and >80-fold selectivity for D3R over D2R; however, several of these are likely too lipophilic to be reasonable drug candidates. An analysis of compound stability in mouse liver microsomes indicates that replacement of the amide linker with a 1,2,3-triazole may provide some protection against hepatic metabolism. In the present series, 2,3-dichlorophenyl-containing indolyltriazole **17a** had the best overall profile in terms of D3R affinity, selectivity, lipophilicity and metabolic stability. Thus, using this molecular template for future D3R drug design is warranted.

6. Experimental methods

6.1. Synthesis

Reaction conditions and yields were not optimized. Anhydrous solvents were purchased from Aldrich and were used without further purification except for tetrahydrofuran, which was freshly distilled from sodium-benzophenone ketyl. All other chemicals and reagents were purchased from Sigma–Aldrich Co. LLC, Combi-Blocks, TCI America, OChem Incorporation, Acros Organics, May-bridge, and Alfa Aesar. Spectroscopic data and yields refer to the free base. Flash column chromatography was performed using silica gel (EMD Chemicals, Inc.; 230–400 mesh, 60 Å) or a Teledyne ISCO CombiFlash® R_f instrument. ^{1}H and ^{13}C NMR spectra were acquired using a Varian Mercury Plus 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in parts-per-million (ppm) and referenced according to a deuterated solvent standard [for ^{1}H spectra (CDCl$_3$, 7.26 or DMSO-d_6, 2.50) and ^{13}C spectra (CDCl$_3$, 77.2 or DMSO-d_6, 39.5)]. Gas chromatography-mass spectrometry (GC/MS) data were acquired (where obtainable) using an Agilent Technologies (Santa Clara, CA) 6890N GC equipped with an HP-5MS column (cross-linked

5% PH ME siloxane, 30 m × 0.25 mm i.d. × 0.25 µm film thickness) and a 5973 mass-selective ion detector in electron-impact mode. Ultra-pure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line temperatures were 250 and 280 °C, respectively, and the oven temperature gradient used was as follows: the initial temperature (100 °C) was held for 3 min and then increased to 295 °C at 15 °C/min over 13 min, and finally maintained at 295 °C for 10 min. Combustion analysis was performed by Atlantic Microlab, Inc. (Norcross, GA) and the results agree within ±0.4% of calculated values. Melting point determination was conducted using a Thomas-Hoover melting point apparatus and are uncorrected. On the basis of NMR and combustion data, all final compounds are   95% pure.

6.1.1. 1-(Hex-5-yn-1-yl)-4-(2-methoxyphenyl)piperazine (2)—A catalytic amount of NaI (5.0 mg) was added to a solution of tosylate **1** (4.2 g, 17 mmol),[32] commercially available 1-(2-methoxyphenyl)piperazine (3.3 g, 17 mmol), and K_2CO_3 (4.7 g, 34 mmol) in acetone (50 mL) at room temperature. This reaction mixture was stirred at reflux for 12 h. The resulting mixture was cooled to room temperature, filtered, and the K_2CO_3 residue was washed with additional acetone. The filtrate was concentrated and the crude product was purified by flash column chromatography (50% EtOAc/Hexanes) to give acetylene 2 in 97% yield (4.5 g, 16.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.88 (m, 3H), 6.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.89 (s, 3H), 3.09 (br s, 4H), 2.65 (br s, 4H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.25–2.21 (m, 2H), 1.95 (t, *J* = 2.8 Hz, 1H), 1.67–1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.43, 141.55, 123.0, 121.13, 118.34, 111.31, 84.52, 58.31, 55.49, 53.63, 50.82, 26.66, 26.13, 18.54; GC–MS (EI) *m/z* 272 (M[+]).

6.1.2. 1-(2,3-Dichlorophenyl)-4-(hex-5-yn-1-yl)piperazine (3)—A catalytic amount of NaI (5.0 mg) was added to a solution of tosylate **1** (3.4 g, 13.5 mmol),[32] commercially available 1-(2,3-dichlorophenyl) piperazine (3.12 g, 13.5 mmol), and K_2CO_3 (3.7 g, 27 mmol) in acetone (50 mL) at room temperature. This reaction mixture was stirred at reflux for 12 h. The resulting mixture was cooled to room temperature, filtered, and the K_2CO_3 residue was washed with additional acetone. The filtrate was concentrated and the crude product was purified by flash column chromatography (50% EtOAc/Hexanes) to give acetylene **3** in 98% yield (4.2 g, 13.2 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.13 (m, 2H), 6.83 (dd, *J* = 6.4, 3.2 Hz, 1H), 3.07 (br s, 4H), 2.64 (br s, 4H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.26–2.22 (m, 2H), 1.95 (t, *J* = 2.8 Hz, 1H), 1.68– 1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.43, 134.08, 127.58, 124.58, 118.67, 84.42, 68.57, 58.10, 53.40, 51.44, 26.54, 26.03, 18.46; GC–MS (EI) *m/z* 310 (M[+]).

6.1.3. General Method A—The appropriate arylamine (1.0 equiv) was dissolved in CH_3CN (0.25 M) and cooled to 0 °C. To the solution was added *t*-BuONO (1.5 equiv) followed by the dropwise addition of azidotrimethylsi-lane (1.2 equiv). The reaction was stirred at room temperature for 2 h before the addition of the appropriate acetylene substrate (0.5 equiv), CuI (0.2 equiv), and DIPEA (5 equiv). The resulting mixture was stirred at room temperature for 12 h before it was concentrated in vacuo. The crude compound was subjected directly to flash column chromatography to provide the desired template A analogues.

6.1.4. 1-(2-Methoxyphenyl)-4-(4-(1-(naphthalen-2-yl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazine (BAK 04-70; 4a)—

Synthesized using General Method A in 80% yield (350 mg, 0.80 mmol) from commercially available naphthalen-1-amine (286 mg, 2 mmol) and acetylene **2** (272 mg, 1 mmol). Mp 167– 168 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16 (d, J = 2.0 Hz, 1H), 8.01–7.98 (m, 1H), 7.93–7.88 (m, 4H), 7.60–7.53 (m, 2H), 7.02–6.89 (m, 3H), 6.86 (dd, J = 7.6, 1.2 Hz, 1H), 3.86 (s, 3H), 3.11 (br s, 4H), 2.89 (t, J = 7.2 Hz, 2H), 2.49 (t, J = 7.6 Hz, 2H), 1.87–1.80 (m, 2H), 1.72–1.65 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.4, 149.0, 141.5, 134.8, 133.4, 132.9, 130.1, 128.3, 128.1, 127.5, 126.9, 123.0, 121.1, 119.2, 119.1, 118.3, 118.3, 111.3, 58.6, 55.5, 53.7, 50.7, 27.5, 26.6, 25.8; Anal. (C$_{27}$H$_{37}$N$_5$O·C$_2$H$_2$O$_4$·1/2H$_2$O) C, H, N.

6.1.5. 1-(4-(1-(9*H*-Fluoren-2-yl)-1*H*-1,2,3-triazol-4-yl)butyl)-4-(2-methoxyphenyl)piperazine (BAK 04-29; 4b)—

Synthesized using General Method A in 86% yield (335 mg, 0.86 mmol) from commercially available 9*H*-fluoren-2-amine (362 mg, 2 mmol) and acetylene **2** (272 mg, 1 mmol). Mp 207–209 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.82–7.80 (m, 2H), 7.70 (dd, J = 8.0, 2.4 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.43–7.33 (m, 2H), 7.01–6.88 (m, 3H), 6.85 (dd, J = 8.0, 1.2 Hz, 1H), 3.98 (s, 2H), 3.86 (s, 3H), 3.13 (br s, 4H), 2.89 (t, J = 7.2 Hz, 2H), 2.69 (br s, 4H), 2.50 (t, J = 7.6 Hz, 2H), 1.87–1.79 (m, 2H), 1.77–1.66 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.4, 148.9, 144.8, 143.6, 142.2, 141.4, 140.5, 135.9, 127.5, 127.2, 125.3, 123.0, 121.1, 120.7, 120.3, 119.4, 119.4, 118.3, 117.6, 111.3, 58.8, 55.5, 53.9, 50.8, 37.2, 27.5, 26.6, 25.75; Anal. (C$_{30}$H$_{33}$N$_5$O·C$_2$H$_2$O$_4$) C, H, N.

6.1.6. 5-(4-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-1*H*-indole (BAK 04-71; 4c)—

Synthesized using General Method A in 68% yield (292 mg, 0.68 mmol) from commercially available 1*H*-indol-5-amine (264 mg, 2 mmol) and acetylene **2** (272 mg, 1 mmol). Mp 195–196 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.48 (br s, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.54 (dd, J = 7.2, 2.0 Hz, 1H), 7.50–7.47 (m, 1H), 7.33 (t, J = 3.2 Hz, 1H), 7.01–6.89 (m, 3H), 6.85 (dd, J = 7.6, 1,2 Hz, 1H), 6.65–6.63 (m, 1H)3.86 (s, 3H), 3.10 (br s, 4H), 2.86 (t, J = 7.6 Hz, 2H), 2.67 (br s, 4H), 2.48 (t, J = 7.6 Hz, 2H), 1.85–1.77 (m, 2H), 1.71–1.63 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.4, 148.5, 141.5, 135.6, 130.8, 128.2, 126.5, 123.0, 121.1, 120.0, 118.3, 115.9, 113.3, 112.0, 111.3, 103.3, 58.6, 55.5, 53.7, 50.8, 27.6, 26.7, 25.8; Anal. (C$_{25}$H$_{30}$N$_6$O·C$_2$H$_2$O$_4$·H$_2$O) C, H, N.

6.1.7. 5-(4-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)quinoline (BAK 04-74; 4d)—

To a solution of 5-azidoquinoline[47] (170 mg, 1.0 mmol) and acetylene **2** (272 mg, 1.0 mmol) in THF (10 mL) were added DIPEA (0.87 mL, 5 mmol), CuI (38 mg, 0.2 mmol). The reaction was heated to 50 °C until TLC analysis indicated the full consumption of starting material. The resulting reaction mixture was concentrated and the crude compound was subjected directly to flash column chromatography (EtOAc followed by 90% CMA) to afford the desired product in 65% yield (287 mg, 0.65 mmol). Mp 150–152 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.01 (dd, J = 4.4, 1.6 Hz, 1H), 8.28 (dt, J = 8.8, 1.2 Hz, 1H), 8.15–8.12 (m, 1H), 7.84–7.80 (m, 1H), 7.69 (s, 1H), 7.64 (dd, J = 8.6, 1.2 Hz, 1H), 7.01–6.84 (m, 4H), 3.86 (s, 3H), 3.11 (br s, 4H), 2.92 (t, J = 7.6 Hz, 2H), 2.67 (br s, 4H), 2.50 (t, J = 7.6 Hz, 2H), 1.90–1.82 (m, 2H),

1.74–1.66 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.4, 151.6, 148.6, 148.5, 141.5, 133.8, 131.7, 131.6, 128.5, 124.1, 123.4, 123.3, 123.0, 122.6, 121.1, 118.3, 111.3, 58.6, 55.5, 53.7, 50.8, 27.5, 26.7, 25.7; Anal. (C$_{26}$H$_{30}$N$_6$O·2C$_2$H$_2$O$_4$·1/2H$_2$O) C, H, N.

6.1.8. 1-(2-Methoxyphenyl)-4-(4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)butyl)piperazine (BAK 04-27; 4e)—Synthesized using General Method A in 87% yield (340 mg, 0.87 mmol) from commercially available aniline (186 mg, 2 mmol) and acetylene **2** (272 mg, 1 mmol). Mp 172–173 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74–7.71 (m, 3H), 7.53–7.49 (m, 2H), 7.44–7.40 (m, 1H), 7.01–6.89 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 3.10 (br s, 4H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 3H), 1.84–1.76 (m, 2H), 1.72–1.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.4, 149.0, 141.5, 137.4, 129.8, 128.6, 123.0, 121.1, 120.6, 119.1, 118.3, 111.3, 58.6, 55.5, 53.7, 50.8, 27.5, 26.7, 25.8; Anal. (C$_{23}$H$_{29}$N$_5$O·C$_2$H$_2$O$_4$) C, H, N.

6.1.9. 1-(2,3-Dichlorophenyl)-4-(4-(1-(naphthalen-2-yl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazine (BAK 04-89; 5a)—Synthesized using General Method A in 72% yield (346 mg, 0.72) from commercially available naphthalen-1-amine (286 mg, 2 mmol) and acetylene **3** (311 mg, 1 mmol). Mp 195–197 °C (oxa-late salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16 (s, 1H), 8.0–7.88 (m, 5H), 7.60–7.53 (m, 2H), 7.15–7.11 (m, 2H), 6.96–6.93 (m, 2H), 3.07 (br s, 4H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.66 (br s, 4H), 2.50 (t, *J* = 6.8 Hz, 2H), 1.87–1.80 (m, 2H), 1.72–1.65 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.39, 134.72, 134.10, 133.35, 132.86, 130.05, 128.32, 128.04, 127.55, 127.50, 126.95, 124,63, 119.19, 119.04, 118.69, 118.22, 58.46, 53.48, 51.41, 27.49, 26.63, 25.7; Anal. (C$_{26}$H$_{27}$Cl$_2$N$_5$·C$_2$H$_2$O$_4$·1/2H$_2$O) C, H, N.

6.1.10. 1-(4-(1-(9*H*-Fluoren-2-yl)-1*H*-1,2,3-triazol-4-yl)butyl)-4-(2,3-dichlorophenyl)piperazine (BAK 04-90; 5b)—Synthesized using General Method A in 82% yield (450 mg, 0.82 mmol) from commercially available 9*H*-fluoren-2-amine (362 mg, 2 mmol) and acetylene **3** (311 mg, 1 mmol). Mp 209– 210 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93(s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.79 (s, 1H), 7.70 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.44–7.34 (m, 2H), 7.16–7.11 (m, 2H), 6.95 (dd, *J* = 6.8, 2.8 Hz, 1H), 3.99 (s, 2H), 3.07 (br s, 4H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.65 (br s, 4H), 2.49 (t, *J* = 7.6 Hz, 2H), 1.86–1.78 (m, 2H), 1.70–1.63 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.41, 148.83, 144.87, 143.56, 142.21, 140.55, 135.97, 134.10, 127.59, 127.56, 127.51, 127.21, 125.30, 124.64, 120.74, 120.34, 119.41, 119.22, 118.70, 117.60, 58.49, 53.51, 51.44, 37.17, 27.53, 26.65, 25.76; Anal. (C$_{29}$H$_{29}$Cl$_2$N$_5$·C$_2$H$_2$O$_4$·1/4H$_2$O) C, H, N.

6.1.11. 5-(4-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-1*H*-indole (BAK 04-92; 5c)—Synthesized using General Method A in 82% yield (450 mg, 0.83 mmol) from commercially available 1*H*-indol-5-amine (264 mg, 2 mmol) and acetylene **3** (311 mg, 1 mmol). Mp 183– 185 °C (oxalate salt); ^{1}H NMR (400 MHz, DMSO) d 11.37 (br s, 1H), 8.46 (s, 1H), 7.96 (s, 1H), 7.53 (s, 2H), 7.47 (t, *J* = 2.8 Hz, 1H), 7.28–7.25 (m, 2H), 7.11 (dd, *J* = 5.6, 4.0 Hz, 1H), 6.53 (t, *J* = 2.4 Hz, 1H), 2.96 (br s, 4H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.51 (br s, 4H), 2.37 (t, *J* = 6.8 Hz, 2H), 1.73–1.66 (m, 2H), 1.57–1.52 (m,

2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.40, 135.59, 134.11, 130.80, 128.15, 127.58, 126.47, 124.65, 119.98, 118.72, 115.89, 113.28, 112.02, 103.42, 58.49, 53.49, 51.41, 27.59, 26.63, 25.78; GC–MS (EI) *m/z* 170 (M$^+$); Anal. (C$_{24}$H$_{26}$Cl$_2$N$_6$·9/8C$_2$H$_2$O$_4$·1/2H$_2$O) C, H, N.

6.1.12. 1-(4-Azidobutyl)-4-(2-methoxyphenyl)piperazine (7)—A catalytic amount of NaI (5.0 mg) was added to a solution of tosylate **6**^{34} (3.23 g, 12 mmol), commercially available 1-(2-methoxyphenyl)piperazine (2.31 g, 12 mmol), and K$_2$CO$_3$ (3.32 g, 24 mmol) in acetone (35 mL) at room temperature. This reaction mixture was stirred at reflux for 12 h. The resulting mixture was cooled to room temperature, filtered, and the K$_2$CO$_3$ residue was washed with additional acetone. The filtrate was concentrated and the crude product was purified by flash column chromatography (50% EtOAc/hexanes) to give the pure product in 98% yield (3.4 g, 11.8 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.02–6.89 (m, 3H), 6.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.86 (s, 3H), 3.31 (t, *J* = 6.8 Hz, 2H), 3.1 (br s, 4H), 2.65 (br s, 4H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.68–1.60 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.31, 141.39, 122.94, 121.02, 128.23, 111.17, 58.09, 55.39, 53.51, 51.45, 50.72, 27.0, 24.14; GC–MS (EI) *m/z* 289 (M$^+$).

6.1.13. 1-(4-Azidobutyl)-4-(2,3-dichlorophenyl)piperazine (8)—A catalytic amount of NaI (5.0 mg) was added to a solution of tosylate **6**^{34} (3.23 g, 12 mmol), commercially available 1-(2,3-dichlorophenyl)piperazine (2.77 g, 12 mmol), and K$_2$CO$_3$ (3.32 g, 24 mmol) in acetone (35 mL) at room temperature. This reaction mixture was stirred at reflux for 12 h. The resulting mixture was cooled to room temperature, filtered, and the K$_2$CO$_3$ residue was washed with additional acetone. The filtrate was concentrated and the crude product was purified by flash column chromatography (50% EtOAc/hexanes) to give the pure product in 97% yield (3.8 g, 11.6 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.16–7.11 (m, 2H), 6.96 (dd, *J* = 6.4, 3.2 Hz, 1H), 3.31 (t, *J* = 6.8 Hz, 2H), 3.06 (br s, 4H), 2.63 (br s, 4H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.66–1.60 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.36, 134.06, 127.54, 127.53, 124.60, 118.66, 57.97, 53.35, 51.45, 51.40, 26.96, 24.13; GC–MS (EI) *m/z* 299 (M$^+$ –N$_2$).

6.1.14. General Method B—To a suspension of CuI (0.2 equiv) in THF (10 mL) was added the appropriate azidobutylphenylpiperazine (1.0 equiv) and ethynylaryl substrate (1.0 equiv). The reaction was stirred at room temperature for 12 h before the resulting mixture was concentrated in vacuo and subjected directly to flash column chromatography to afford the pure product.

6.1.15. 1-(2-Methoxyphenyl)-4-(4-(4-(naphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)butyl)piperazine (BAK 05-21; 9a)—Synthesized using General Method B in 85% yield (338 mg, 0.77 mmol) from azidobutylphenylpiperazine **7** (260 mg, 0.9 mmol) and 2-ethynylnaphthalene (137 mg, 0.9 mmol).^{48} Mp 194–195 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.95–7.83 (m, 5H), 7.52–7.46 (m, 2H), 7.01–6.84 (m, 4H), 4.49 (t, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 3.08 (br s, 4H), 2.63 (br s, 4H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.09–2.01(m, 2H), 1.66–1.59 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.30, 147.86, 141.32, 133.62, 133.19, 128.65, 128.25, 128.10, 127.84, 126.52, 126.19, 124.40, 123.94,

122.99, 121.03, 119.84, 118.23, 111.19, 57.82, 55.40, 53.52, 50.70, 50.42, 28.43, 23.89; Anal. ($C_{27}H_{31}N_5O \cdot C_2H_2O_4 \cdot 1/5H_2O$) C, H, N.

6.1.16. 1-(4-(4-(9H-Fluoren-2-yl)-1H-1,2,3-triazol-1-yl)butyl)-4-(2-methoxyphenyl)piperazine (BAK 05-19; 9b)—

Synthesized using General Method B in 91% yield (393 mg, 0.82 mmol) from azidobutylphenylpiperazine **7** (260 mg, 0.9 mmol) and 2-ethynyl-9H-fluorene (171 mg, 0.9 mmol).[49] Mp 211–212 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (s, 1H), 7.83–7.94 (m, 4H), 7.56 (d, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.32 (dt, J = 7.6, 1.2 Hz, 1H), 7.02–6.84 (m, 2H), 4.47 (t, J = 7.2 Hz, 2H), 3.96 (s, 2H), 3.85 (s, 3H), 3.09 (br s, 4H), 2.63 (br s, 4H), 2.47 (t, J = 7.2 Hz, 2H), 2.08–2.01(m, 2H), 1.66–1.58 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.28, 148.17, 143.95, 143.53, 141.71, 141.37, 141.31, 129.19, 126.91, 126.89, 125.14, 124.53, 122.98, 122.35, 121.01, 120.24, 120.02, 119.42, 118.21, 111.17, 57.80, 55.39, 53.50, 50.68, 50.34, 36.98, 28.40, 23.86; Anal. ($C_{30}H_{33}N_5O \cdot C_2H_2O_4$) C, H, N.

6.1.17. 5-(1-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-1H-1,2,3-triazol-4-yl)-1H-indole (BAK 05-16; 9c)—

Synthesized using General Method B in 72% yield (263 mg, 0.65 mmol) from azidobutylphenylpiperazine **7** (260 mg, 0.9 mmol) and 5-ethynyl-1H-indole (127 mg, 0.9 mmol).[50] Mp 214–215 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (br s, 1H), 8.10 (m, 1H), 7.74 (s, 1H), 7.70 (dd, J = 8.4, 1.6 Hz, 1H), 7.45– 7.42 (m, 1H), 7.23 (t, J = 2.8 Hz, 1H), 7.01–6.84 (m, 4H), 6.60–6.58 (m, 1H), 4.45 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.08 (br s, 4H), 2.63 (br s, 4H), 2.46 (t, J = 8.0 Hz, 2H), 2.06–1.99 (m, 2H), 1.65–1.58 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.35, 149.24, 141.36, 135.90, 128.30, 125.14, 123.04, 122.66, 121.07, 120.43, 118.86, 118.31, 118.12, 111.58, 111.22, 103.0, 57.89, 55.43, 53.54, 50.73, 50.33, 28.48, 23.92; Anal. ($C_{25}H_{30}N_6O \cdot C_2H_2O_4 \cdot 1/2H_2O$) C, H, N.

6.1.18. 5-(4-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-1H-1,2,3-triazol-1-yl)quinoline (BAK 05-27; 9d)—

Sodium ascorbate (27 mg, 15 mol %) and CuSO$_4$·5H$_2$O (11 mg, 5 mol %) were added to a solution of azidobutylphenylpiperazine **7** (260 mg, 0.9 mmol) and 6-ethynylquinoline (138 mg, 0.9 mmol)[51] in THF/H$_2$O (1:1, 6 mL). The reaction was stirred at 50 °C for 12 h. The resulting solution was cooled to room temperature, diluted with H$_2$O (5 mL) and extracted with CHCl3 (3 × 10 mL). The combined organic layer was dried over MgSO$_4$, filtered, and concentrated. The crude compound was purified by flash column chromatography to give the pure compound in 79% yield (314 mg, 0.71 mmol). Mp 186–188 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.91 (dd, J = 4.4, 2.0 Hz, 1H), 8.38 (d, J = 1.2 Hz, 1H), 8.21 (dd, J = 8.0, 1.6 Hz, 1H), 8.17–8.10 (m, 2H), 7.92 (s, 1H), 7.43 (dd, J = 8.4, 4.4 Hz, 1H), 7.02–6.84 (m, 4H), 4.50 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.09 (br s, 4H), 2.64 (br s, 4H), 2.48 (t, J = 7.6 Hz, 2H), 2.10–2.03 (m, 2H), 1.67–1.60 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.30, 150.60, 148.11, 147.15, 141.28, 136.35, 130.16, 128.85, 128.59, 127.54, 124.13, 123.03, 121.75, 121.04, 120.15, 118.23, 111.20, 57.79, 55.41, 53.52, 50.68, 50.50, 28.42, 23.87; Anal. ($C_{26}H_{30}N_6O \cdot 2C_2H_2O_4 \cdot H_2O$) C, H, N.

6.1.19. 1-(4-(4-([1,1′-Biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)butyl)-4-(2-methoxyphenyl)piperazine (BAK 05-18; 9e)—

Synthesized using General Method B

in 82% yield (345 mg, 0.74 mmol) from azidobutylphenylpiperazine **7** (260 mg, 0.9 mmol) and 4-ethynyl-1,1′-biphenyl (160 mg, 0.9 mmol).[52] Mp 181–182 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92–7.90 (m, 2H), 7.80 (s, 1H), 7.68–7.63 (m, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.38–7.34 (m, 1H), 7.01–6.84 (m, 4H), 4.47 (t, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.08 (br s, 4H), 2.63 (br s, 4H), 2.46 (t, J = 7.2 Hz, 2H), 2.07–2.0 (m, 2H), 1.65–1.57 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.22, 147.37, 141.25, 140.72, 140.49, 129.67, 128.83, 127.47, 127.43, 126.93, 126.05, 122.90, 120.95, 119.55, 118.14, 111.12, 57.72, 55.33, 53.43, 50.61, 50.27, 28.32, 23.79; Anal. (C$_{29}$H$_{33}$N$_5$O·C$_2$H$_2$O$_4$·1/2H$_2$O) C, H, N.

6.1.20. 1-(2-Methoxyphenyl)-4-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butyl)piperazine (BAK 04-81; 9f)—

Synthesized using General Method B in 89% yield (209 mg, 0.53 mmol) from azidobutylphenylpiperazine **7** (173 mg, 0.6 mmol) and commercially available ethynylbenzene (61 mg, 0.6 mmol). Mp 176–177 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (dd, J = 8.8, 1.2 Hz, 2H), 7.77 (s, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.34 (tt, J = 7.6, 1.6 Hz, 1H), 7.02–6.97 (m, 1H), 6.94–6.91 (m, 2H), 6.86 (dd, J = 8.0, 1.2 Hz, 1H), 4.45 (t, J = 6.8 Hz, 2H), 3.86 (s, 3H), 3.08 (br s, 4H), 2.63 (br s, 4H), 2.07–1.99 (m, 2H), 1.64–1.57 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.39, 147.93, 141.42, 130.83, 128.96, 128.22, 125.83, 121.11, 119.53, 118.31, 111.30, 57.87, 55.47, 53.59, 50.75, 50.43, 28.48, 23.93; Anal. (C$_{23}$H$_{29}$N$_5$O·C$_2$H$_2$O$_4$) C, H, N.

6.1.21. 1-(2,3-Dichlorophenyl)-4-(4-(4-(naphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)butyl)piperazine (BAK 05-26; 10a)—

Synthesized using General Method B in 88% yield (380 mg, 0.79 mmol) from azidobutylphenylpiperazine **8** (295 mg, 0.9 mmol) and commercially available 2-ethynylnaphthalene (137 mg, 0.9 mmol). Mp 190–192 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.95–7.83 (m, 5H), 7.52–7.48 (m, 2H), 7.16–7.09 (m, 2H), 6.94–6.91 (m, 1H), 4.48 (t, J = 6.8 Hz, 2H), 3.04 (br s, 4H), 2.63 (br s, 4H), 2.47 (t, J = 6.8 Hz, 2H), 2.09–2.01 (m, 2H), 1.66–1.59 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.22, 147.80, 133.98, 133.57, 133.15, 128.63, 128.21, 128.06, 127.82, 127.51, 127.44, 126.52, 126.18, 124.58, 124.35, 123.89, 119.86, 118.63, 57.61, 53.29, 51.28, 50.33, 28.33, 23.79; Anal. (C$_{26}$H$_{27}$Cl$_2$N$_5$·C$_2$H$_2$O$_4$·1/10H$_2$O) C, H, N.

6.1.22. 1-(4-(4-(9*H*-Fluoren-2-yl)-1*H*-1,2,3-triazol-1-yl)butyl)-4-(2,3-dichlorophenyl)piperazine (BAK 05-24; 10b)—

Synthesized using General Method B in 87% yield (406 mg, 0.78 mmol) from azidobutylphenylpiperazine **8** (295 mg, 0.9 mmol) and 2-ethynyl-9*H*-fluorene (171 mg, 0.9 mmol). Mp 228–230 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (s, 1H), 7.83–7.93 (m, 4H), 7.56 (d, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.32 (m, 1H), 7.16–7.10 (m, 2H), 6.93 (dd, J = 7.6, 2.4 Hz, 1H), 4.47 (t, J = 7.2 Hz, 2H), 3.96 (s, 2H), 3.05 (br s, 4H), 2.62 (br s, 4H), 2.48 (t, J = 7.2 Hz, 2H), 2.08–2.01 (m, 2H), 1.65–1.58 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.31, 148.26, 144.01, 143.57, 141.79, 141.40, 134.08, 129.22, 127.55, 126.98, 126.95, 125.19, 124.65, 124.57, 122.41, 120.30, 120.06, 119.43, 118.67, 57.70, 53.37, 51.37, 50.37, 37.03, 28.42, 23.89; Anal. (C$_{29}$H$_{29}$Cl$_2$N$_5$·C$_2$H$_2$O$_4$·1/4H$_2$O) C, H, N.

6.1.23. 5-(1-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)butyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-indole (BAK 05-25; 10c)—

Synthesized using General Method B in 72% yield

(263 mg, 0.65 mmol) from azidobutylphenylpiperazine **8** (295 mg, 0.9 mmol) and 5-ethynyl-1*H*-indole (127 mg, 0.9 mmol). Mp 214– 215 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.32 (br s, 1H), 8.11 (m, 1H), 7.75 (s, 1H), 7.70 (dd, J = 8.4, 1.6 Hz, 1H), 7.46–7.43 (m, 1H), 7.24 (t, J = 2.8 Hz, 1H), 7.16–7.12 (m, 2H), 6.92 (dd, J = 7.6, 2.4 Hz, 1H), 6.60–6.58 (m, 1H), 4.45 (t, J = 7.2 Hz, 2H), 3.04 (br s, 4H), 2.61 (br s, 4H), 2.46 (t, J = 7.6 Hz, 2H), 2.07–1.99 (m, 2H), 1.66–1.57 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.34, 149.26, 135.90, 134.09, 128.31, 127.57, 125.13, 124.66, 122.72, 120.47, 118.84, 118.71, 118.15, 111.58, 103.08, 57.76, 53.39, 51.40, 50.33, 28.46, 23.94; Anal. (C$_{24}$H$_{26}$Cl$_2$N$_6$·3/4C$_2$H$_2$O$_4$) C, H, N.

6.1.24. 6-(1-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)butyl)-1*H*-1,2,3-triazol-4-yl)quinoline (BAK 05-28; 10d)—

Sodium ascorbate (27 mg, 15 mol %) and CuSO$_4$·5H$_2$O (11 mg, 5 mol %) were added to a solution of azidobutylphenylpiperazine **8** (295 mg, 0.9 mmol) and 6-ethynylquinoline (138 mg, 0.9 mmol) in THF/H$_2$O (1:1, 6 mL). The reaction was stirred at 50 °C for 12 h. The resulting solution was cooled to room temperature, diluted with H$_2$O (5 mL) and extracted with CHCl$_3$ (3 × 10 mL). The combined organic layer was dried over MgSO$_4$, filtered, and concentrated. The crude compound was purified by flash column chromatography to give the pure compound in 67% yield (290 mg, 0.60 mmol). Mp 165–167 °C (oxalate salt). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.90 (m, 1H), 8.38 (s, 1H), 8.21–8.10 (m, 3H), 7.91 (s, 1H), 7.42 (dd, J = 8.4, 4.0 Hz, 1H), 7.15–7.10 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 4.50 (t, J = 7.2 Hz, 2H), 3.04 (br s, 4H), 2.61 (br s, 4H), 2.47 (t, J = 7.2 Hz, 2H), 2.10–2.02 (m, 2H), 1.66–1.58 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.24, 150.61, 148.10, 147.14, 136.31, 134.03, 130.15, 128.82, 128.57, 127.53, 127.49, 124.62, 124.11, 121.75, 120.14, 118.63, 57.64, 53.33, 51.33, 50.46, 28.38, 23.86; Anal. (C$_{25}$H$_{26}$Cl$_2$N$_6$·2C$_2$H$_2$O$_4$) C, H, N.

6.1.25. 1-(4-(4-([1,1′-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)-butyl)-4-(2,3-dichlorophenyl)piperazine (BAK 05-23; 10e)—

Synthesized using General Method B in 78% yield (355 mg, 0.70 mmol) from azidobutylphenylpiperazine **8** (295 mg, 0.9 mmol) and 4-ethynyl-1,1′-biphenyl (160 mg, 0.9 mmol). Mp 196–197 °C (oxalate salt). ^{1}H NMR (400 MHz, DMSO) d 8.67 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.78–7.71 (m, 4H), 7.48 (t, J = 8.0 Hz, 2H), 7.40–7.36 (m, 1H), 7.30–7.28 (m, 2H), 7.13–7.11 (m, 1H), 4.45 (t, J = 7.2 Hz, 2H), 2.97 (br s, 4H), 2.51 (br s, 4H), 2.38 (t, J = 6.8 Hz, 2H), 1.95–1.91 (m, 2H), 1.52–1.44 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.27, 147.54, 140.89, 140.60, 134.06, 129.73, 128.92, 127.59, 127.55, 127.04, 126.14, 124.65, 119.58, 118.67, 57.68, 53.35, 51.33, 50.37, 28.39, 23.85; Anal. (C$_{28}$H$_{29}$Cl$_2$N$_5$·C$_2$H$_2$O$_4$) C, H, N.

6.1.26. General Method C—

Sodium ascorbate (15 mol %) and CuSO$_4$·5H$_2$O (5 mol %) were added to a solution of 2-(2-azidoethyl)oxirane (**11**, 1.0 equiv), the appropriate phenylpiperazine hydrochloride (1.0 equiv), the appropriate arylacetylene (1.0 equiv), β-cyclodextrin (3 mol %), and K$_2$CO$_3$ (1.0 equiv) in H$_2$O (0.25 M). The reaction mixture was stirred at room temperature for 30 min and heated to 80 °C for 2 h. The resulting mixture was diluted with water (5 mL), extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layer was dried over MgSO$_4$, filtered, and concentrated under vacuum. The crude solid was purified by flash column chromatography.

6.1.27. 1-(4-(2-Methoxyphenyl)piperazin-1-yl)-4-(4-(naphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-ol (BAK 05-52; 12a)—Synthesized using General Method C in 61% yield (280 mg, 0.61 mmol) from commercially available 1-(2-methoxyphenyl)piperazine hydrochloride (220 mg, 1.0 mmol) and commercially available 2-ethynylnaphthalene (152 mg, 1 mmol). Mp 155–156 °C (free base); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.97–7.83 (m, 5H), 7.52–7.45 (m, 2H), 7.02–6.98 (m, 1H), 6.93–6.86 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 4.68–4.64 (m, 2H), 3.85 (s, 3H), 3.71 (m, 2H), 3.08 (br s, 4H), 2.84 (m, 2H), 2.58 (m, 2H), 2.46–2.36 (m, 2H), 2.22–2.14 (m, 2H), 1.97–1.89 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.21, 147.57, 141.03, 133.55, 133.12, 128.60, 128.19, 128.03, 127.79, 126.48, 126.14, 124.34, 123.89, 123.08, 120.89, 120.70, 118.18, 111.20, 63.82, 63.16, 55.36, 53.42, 50.67, 47.17, 35.23; Anal. (C$_{27}$H$_{31}$N$_5$O$_2$) C, H, N.

6.1.28. 4-(4-([1,1′-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (BAK 05-47; 12b)—Synthesized using General Method C in 65% yield (312 mg, 0.65 mmol) from commercially available 1-(2-methoxyphenyl)piperazine hydrochloride (220 mg, 1.0 mmol) and 4-ethynyl-1,1′-biphenyl (178 mg, 1.0 mmol). Mp 159–160 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94–7.91 (m, 2H), 7.89 (s, 1H), 7.69–7.62 (m, 4H), 7.48–7.44 (m, 2H), 7.38–7.34 (m, 1H), 7.03–6.98 (m, 1H), 6.94–6.91 (m, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.66–4.63 (m, 2H), 3.85 (s, 3H), 3.68 (m, 2H), 3.08 (br s, 4H), 2.83 (m, 2H), 2.58 (m, 2H), 2.46–2.35 (m, 2H), 2.21–2.12 (m, 2H), 1.96–1.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.33, 147.35, 141.16, 140.91, 140.69, 129.79, 128.94, 127.62, 127.54, 127.09, 126.19, 123.18, 121.07, 120.45, 118.27, 111.28, 63.87, 63.12, 55.46, 53.51, 50.82, 47.21, 35.30; Anal. (C$_{29}$H$_{33}$N$_5$O$_2$·C$_2$H$_2$O$_4$·1/4H$_2$O) C, H, N.

6.1.29. 1-(4-(2-Methoxyphenyl)piperazin-1-yl)-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butan-2-ol (BAK 05-51; 12c)—Synthesized using General Method C in 73% yield (300 mg, 0.73 mmol) from commercially available 1-(2-methoxyphenyl)piperazine hydrochloride (220 mg, 1.0 mmol) and commercially available ethynylbenzene (102 mg, 1 mmol). Mp 129–130 °C (free base); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85–7.83 (m, 3H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.35–7.31 (m, 1H), 7.03–6.84 (m, 4H), 4.63 (t, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.68 (m, 2H), 3.07 (br s, 4H), 2.83 (m, 2H), 2.57 (m, 2H), 2.43–2.34 (m, 2H), 2.18–2.11 (m, 2H), 1.95–1.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.24, 147.56, 141.08, 130.74, 128.87, 128.11, 125.72, 123.09, 121.0, 120.37, 118.19, 111.22, 63.83, 63.11, 55.38, 53.43, 50.72, 47.11, 35.23; Anal. (C$_{23}$H$_{29}$N$_5$O$_2$) C, H, N.

6.1.30. 4-(4-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (BAK 05-44; 12d)—Synthesized using General Method C in 65% yield (284 mg, 0.65 mmol) from commercially available 1-(2-methoxyphenyl)piperazine hydrochloride (220 mg, 1.0 mmol) and 1-ethynyl-2-methoxybenzene (132 mg, 1.0 mmol).[53] Mp 158–160 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.10 (s, 1H), 7.33–7.29 (m, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.10–6.84 (m, 6H), 4.62 (m, 2H), 3.94 (s, 3H), 3.85 (s, 3H), 3.71 (m, 2H), 3.07 (br s, 4H), 2.83 (m, 2H), 2.57 (m, 2H), 2.44–2.34 (m, 2H), 2.20–2.11 (m, 2H), 1.98–1.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.68, 152.28, 143.0, 141.14, 128.89, 127.69, 123.73,

123.13, 121.10, 121.02, 119.58, 118.23, 111.25, 110.83, 63.84, 63.26, 55.43, 53.46, 50.78, 46.98, 35.38; Anal. ($C_{24}H_{31}N_5O_3 \cdot C_2H_2O_4 \cdot 1/10H_2O$) C, H, N.

6.1.31. 4-(4-(9*H*-Fluoren-2-yl)-1*H*-1,2,3-triazol-1-yl)-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (BAK 05-43; 12e)—Synthesized using General Method C in 65% yield (321 mg, 0.65 mmol) from commercially available 1-(2-methoxyphenyl)piperazine hydrochloride (220 mg, 1.0 mmol) and 2-ethynyl-9*H*-fluorene (190 mg, 1.0 mmol). Mp 153–155 °C (oxalate salt); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (m, 1H), 7.89 (m, 1H), 7.83 (m, 2H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.34–7.30 (m, 1H), 7.03–6.98 (m, 2H), 6.92 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.64 (t, *J* = 7.2 Hz, 2H), 3.96 (s, 2H), 3.85 (s, 3H), 3.67 (m, 2H), 3.08 (br s, 4H), 2.84 (m, 2H), 2.45–2.35 (m, 2H), 2.21–2.13 (m, 2H), 1.96–1.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.29, 148.01, 143.98, 143.55, 141.74, 141.39, 141.13, 129.23, 126.94, 125.16, 124.57, 123.14, 122.39, 121.04, 120.27, 120.28, 120.04, 118.23, 111.25, 63.85, 63.14, 55.43, 53.51, 50.78, 47.18, 37.01, 35.29; Anal. ($C_{30}H_{33}N_5O_2 \cdot C_2H_2O_4 \cdot 1/2H_2O$) C, H, N.

6.1.32. 1-(4-(2-Methoxyphenyl)piperazin-1-yl)-4-(4-(quinolin-6-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-ol (BAK 05-56; 12f)—Synthesized using General Method C in 87% yield (400 mg, 0.87 mmol) from commercially available 1-(2-methoxyphenyl)piperazine hydrochloride (220 mg, 1.0 mmol) and 6-ethynylquinoline (153 mg, 1.0 mmol). Mp 172–174 °C (free base); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.91 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.37 (d, *J* = 1.2 Hz, 1H), 8.21 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.17–8.12 (m, 2H), 7.43 (dd, *J* = 8.0, 4.0 Hz), 7.02–6.97 (m, 2H), 6.93–6.91 (m, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 4.69–4.66 (m, 2H), 3.86 (s, 3H), 3.71 (m, 2H), 3.08 (br s, 4H), 2.84 (m, 2H), 2.58 (m, 2H), 2.43–2.36 (m, 2H), 2.23–2.15 (m, 2H), 1.98–1.89 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.09, 150.35, 147.82, 146.67, 140.93, 136.17, 129.87, 128.75, 128.39, 127.40, 123.90, 122.94, 121.57, 120.93, 120.86, 118.03, 111.09, 63.81, 63.13, 55.25, 53.36, 50.56, 47.17, 35.13; Anal. ($C_{26}H_{30}N_6O \cdot 1/4H_2O$) C, H, N.

6.1.33. 1-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-4-(4-(naphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-ol (BAK 05-53; 13a)—Synthesized using General Method C in 65% yield (320 mg, 0.65 mmol) from commercially available 1-(2,3-dichlorophenyl)piperazine hydrochloride (268 mg, 1.0 mmol) and commercially available 2-ethynylnaphthalene (152 mg, 1.0 mmol). Mp 165–166 °C (free base); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.97–7.83 (m, 5H), 7.52–7.45 (m, 2H), 7.18–7.11 (m, 2H), 6.93 (dd, *J* = 7.6, 2.4 Hz, 1H), 4.68–4.64 (m, 2H), 3.71 (m, 2H), 3.05 (br s, 4H), 2.83 (m, 2H), 2.58 (m, 2H), 2.48–2.37 (m, 2H), 2.23–2.14 (m, 2H), 1.98–1.89 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.10, 147.80, 134.22, 133.69, 133.26, 128.72, 128.32, 128.16, 127.92, 127.67, 127.59, 126.60, 126.27, 124.89, 124.48, 124.01, 120.72, 118.70, 63.81, 63.18, 53.39, 51.45, 47.25, 35.30; Anal. ($C_{26}H_{27}Cl_2N_5O$) C, H, N.

6.1.34. 4-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)-1-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (BAK 05-55; 13b)—Synthesized using General Method C in 60% yield (314 mg, 0.60 mmol) from commercially available 1-(2,3-dichlorophenyl)piperazine hydrochloride (268 mg, 1.0 mmol) and 4-ethynyl-1,1′-biphenyl

(178 mg, 1.0 mmol). Mp 212–213 °C (free base); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94–7.91 (m, 2H), 7.88 (s, 1H), 7.69–7.62 (m, 4H), 7.48–7.44 (m, 2H), 7.38–7.34 (m, 1H), 7.17–7.12 (m, 2H), 6.94 (dd, J = 7.6, 2.4 Hz, 1H), 4.67–4.63 (m, 2H), 3.68 (m, 2H), 3.05 (br s, 4H), 2.83 (m, 2H), 2.57 (m, 2H), 2.47–2.36 (m, 2H), 2.21–2.12 (m, 2H), 1.97–1.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.12, 147.41, 140.99, 140.71, 134.22, 129.79, 128.96, 127.66, 127.60, 127.11, 126.21, 124.88, 120.88, 120.45, 118.70, 63.81, 63.17, 53.41, 51.49, 47.22, 35.28; Anal. (C$_{28}$H$_{29}$Cl$_2$N$_5$O·1/2H$_2$O) C, H, N.

6.1.35. 4-Azido-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (14)—To a 15 mL round bottom flask was added 1-(2-methoxyphenyl)piperazine (400.0 mg, 2.08 mmol) dissolved in CH$_3$CN (4.4 mL). Sodium iodide (6 mg, 0.042 mmol) and K$_2$CO$_3$ (632.4 mg, 4.58 mmol) were added and allowed to stir for 10 min at room temperature. A solution of azide **11** (470.6 mg, 4.16 mmol) in CH$_3$CN (0.6 mL) was added and the mixture was heated to reflux and stirred for 16 h. The reaction was cooled to room temperature and filtered through a pad of celite, which was washed thoroughly with CH$_3$CN. The filtrate was collected, concentrated in vacuo, redissolved in 9% MeOH/1% NH$_4$OH/90% CH$_2$Cl$_2$ and filtered through a 2^{00} silica plug. The filtrate was collected and concentrated under reduced pressure to yield **14**, which was used directly in the next step.

6.1.36. 4-Azido-1-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (15)—To a 15 mL round bottom flask was added 1-(2,3-dichlorophenyl)piperazine (400.0 mg, 1.74 mmol) dissolved in CH$_3$CN (4.4 mL). Sodium iodide (5 mg, 0.035 mmol) and K$_2$CO$_3$ (529.1 mg, 3.83 mmol) were added and allowed to stir for 10 min at room temperature. A solution of azide **11** (393.2 mg, 3.48 mmol) in CH$_3$CN (0.6 mL) was added and the mixture was heated to reflux and stirred for 16 h. The reaction was cooled to room temperature and filtered through a pad of celite, which was washed thoroughly with CH$_3$CN. The filtrate was collected, concentrated in vacuo, redissolved in 9% MeOH/1% NH$_4$OH/90% CH$_2$Cl$_2$ and filtered through a 2″ silica plug. The filtrate was collected and concentrated under reduced pressure to yield **15**, which was used directly in the next step.

6.1.37. 4-(4-(1*H*-Indol-5-yl)-1*H*-1,2,3-triazol-1-yl)-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (RDS 02-33; 16)—To a 10 mL round bottom flask, charged freshly prepared solutions of 1 M sodium ascorbate (0.26 mL, 0.051 mmol) and CuSO$_4$·5H$_2$O (0.15 mL, 0.031 mmol) in THF/H$_2$O (3:1, 4 mL) was added 5-ethynyl-1*H*-indole (77.7 mg, 0.51 mmol) and azide **14** (155 mg, 0.51 mmol). The reaction mixture was stirred for 16 h at room temperature before it was diluted with H$_2$O (2 mL) and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (9% MeOH/1% NH$_4$OH/90% CH$_2$Cl$_2$) to afford 1,2,3-triazole **16** in 78% yield (177 mg, 0.40 mmol). Mp 82–83 °C (free base) ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.21 (s, 1H), 8.19–8.02 (m, 1H), 7.73 (s, 1H), 7.63 (dd, J = 8.4, 1.7 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 2.8 Hz, 1H), 6.99 (ddd, J = 8.4, 6.2, 2.9 Hz, 1H), 6.95–6.73 (m, 3H), 6.53 (t, J = 2.6 Hz, 1H), 4.67–4.38 (m, 2H), 3.81 (s, 3H), 3.69 (q, J = 6.2 Hz, 1H), 3.04 (s, 4H), 2.77 (dt, J = 10.3, 4.6 Hz, 2H), 2.62–2.46 (m, 2H), 2.35 (d, J = 6.6 Hz, 2H), 2.07 (ddt, J = 16.4, 8.2, 5.2 Hz, 1H), 1.87 (ddt, J = 14.4, 9.2, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$)

δ 152.20, 148.87, 141.05, 135.71, 128.16, 124.90, 123.04, 122.69, 120.94, 120.40, 119.56, 118.16, 118.03, 111.37, 111.14, 103.03, 77.33, 77.21, 77.01, 76.69, 63.75, 63.01, 55.34, 50.71, 46.97, 35.23; Anal. ($C_{25}H_{30}N_6O_2 \cdot 1/2CH_2Cl_2$) C, H, N.

6.1.38. 4-(4-(1*H*-Indol-5-yl)-1*H*-1,2,3-triazol-1-yl)-1-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (RDS 02-28; 17a)—To a 10 mL round bottom flask, charged freshly prepared solutions of 1 M sodium ascorbate (0.26 mL, 0.051 mmol) and CuSO$_4$·5H$_2$O (0.15 mL, 0.031 mmol) in THF/H$_2$O (3:1, 4 mL) was added 5-ethynyl-1*H*-indole (77.7 mg, 0.51 mmol) and azide **15** (175.0 mg, 0.51 mmol). The reaction mixture was stirred for 16 h at room temperature before it was diluted with H$_2$O (2 mL) and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (9% MeOH/1% NH$_4$OH/90% CH$_2$Cl$_2$) to afford 1,2,3-triazole **17a** in 74% yield (185.0 mg, 0.38 mmol). Mp 157–159 °C (free base); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 (s, 1H), 8.12 (dd, J = 1.6, 0.8 Hz, 1H), 7.82 (d, J = 0.7 Hz, 1H), 7.72 (dd, J = 8.5, 1.7 Hz, 1H), 7.52–7.38 (m, 1H), 7.25–7.22 (m, 2H), 7.19–7.05 (m, 2H), 6.93 (dd, J = 7.1, 2.6 Hz, 1H), 6.60 (td, J = 2.2, 1.1 Hz, 1H), 4.63 (t, J = 7.0 Hz, 2H), 3.70 (t, J = 9.7 Hz, 1H), 3.05 (s, 4H), 2.93–2.72 (m, 2H), 2.57 (s, 2H), 2.50–2.28 (m, 2H), 2.25–1.81 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.83, 153.19, 140.08, 137.77, 132.09, 131.42, 129.39, 128.57, 125.16, 123.93, 123.47, 122.51, 121.63, 115.56, 105.76, 68.01, 57.40, 55.01, 51.82, 50.98, 39.36; Anal. ($C_{24}H_{26}Cl_2N_6O \cdot 1/2H_2O$) C, H, N.

6.1.39. 1-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-4-(4-(quinolin-3-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-ol (RDS 02-32; 17b)—To a 10 mL round bottom flask, charged freshly prepared solutions of 1 M sodium ascorbate (0.26 mL, 0.051 mmol) and CuSO$_4$·5H$_2$O (0.15 mL, 0.031 mmol), TBTA (5.41 mg, 0.01 mmol) in THF/H$_2$O (3:1, 4 mL) was added 3-ethynylquinoline (78.1 mg, 0.51 mmol)[42] and azide **15** (175.0 mg, 0.51 mmol). The reaction mixture was stirred for 16 h at room temperature before it was diluted with H$_2$O (2 mL) and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (9% MeOH/1% NH$_4$OH/90% CH$_2$Cl$_2$) to afford 1,2,3-triazole **17b** in 89% yield (226 mg, 0.45 mmol). Mp 147–149 °C (free base); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.28 (d, J = 2.1 Hz, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.05 (d, J = 10.3 Hz, 2H), 7.79 (d, J = 8.1 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.19–6.94 (m, 2H), 6.82 (dd, J = 7.5, 2.1 Hz, 1H), 4.63 (dd, J = 8.0, 5.9 Hz, 2H), 3.84–3.59 (m, 1H), 2.95 (t, J = 4.7 Hz, 4H), 2.74 (dd, J = 10.7, 5.1 Hz, 2H), 2.51 (dd, J = 10.6, 4.8 Hz, 2H), 2.43–2.30 (m, 2H), 2.13 (dtd, J = 11.3, 8.2, 2.6 Hz, 1H), 2.03–1.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.91, 148.39, 147.76, 144.76, 134.07, 131.83, 129.60, 129.33, 128.09, 127.96, 127.50, 127.46, 127.20, 124.76, 123.89, 120.84, 118.55, 100.36, 77.34, 77.22, 77.02, 76.70, 63.68, 63.03, 51.30, 47.29, 35.10.; Anal. ($C_{25}H_{26}Cl_2N_6O \cdot 1/2H_2O$) C, H, N.

6.2. X-ray crystal structure of RDS 02-28 (17a)

Single-crystal X-ray diffraction data on RDS 02-28 (**17a**) was collected at 150 K using MoKα radiation (a = 0.71073 Å) and a Bruker APEX 2 CCD area detector. The sample was

prepared for data collection by coating with high viscosity microscope oil (Par-atone-N, Hampton Research). The oil-coated crystal was mounted on a MicroMesh mount (MiTeGen, Inc.) and transferred immediately to the diffractometer. The $0.301 \times 0.144 \times 0.089$ mm^3 crystal was monoclinic in space group $P2_1/c$ with unit cell dimensions $a = 13.5627(10)$ Å, $b = 12.8948(7)$ Å, $c = 12.9598(9)$ Å, and $b = 93.733(4)°$. Data were 99.8% complete to $26.404°q$. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). The asymmetric unit contains a single molecule. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C–H distance set at 0.96 Å.

Atomic coordinates for this compound have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 1026851). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033 or deposit@ccdc.cam.ac.uk].

6.3. Radioligand competition binding

Binding at dopamine D2-like receptors was determined using previously described methods.[54,55] Membranes were prepared from HEK293 cells expressing human D2R, D3R or D4R, grown in a 50:50 mix of DMEM and Ham's F12 culture media, supplemented with 20 mM HEPES, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 1X antibiotic/antimycotic, 10% heat-inactivated fetal bovine serum, and 200 μg/mL hygromycin (Life Technologies, Grand Island, NY) and kept in an incubator at 37°C and 5% CO_2. Upon reaching 80–90% confluence, cells were harvested using pre-mixed Earle's Balanced Salt Solution (EBSS) with 5 μM EDTA (Life Technologies) and centrifuged at 3000 rpm for 10 min at 21 °C. The supernatant was removed and the pellet was resuspended in 10 mL hypotonic lysis buffer (5 mM $MgCl_2 \cdot 6H_2O$, 5 mM Tris, pH 7.4 at 4 °C) and centrifuged at 20,000 rpm for 30 min at 4 °C. The pellet was then resuspended in fresh EBSS buffer made from 8.7 g/L Earle's Balanced Salts without phenol red (US Biological, Salem, MA), 2.2 g/L sodium bicarbonate, pH to 7.4. A Bradford protein assay (Bio-Rad, Hercules, CA) was used to determine the protein concentration and membranes were diluted to 500 μg/mL and stored in a −80 °C freezer for later use.

Radioligand competition binding experiments were conducted using thawed membranes. Test compounds were freshly dissolved in 30% DMSO and 70% H_2O to a stock concentration of 100 μM. To assist the solubilization of free-base compounds, 10 μl of glacial acetic acid was added along with the DMSO. Each test compound was then diluted into 13 half-log serial dilutions using 30% DMSO vehicle; final test concentrations ranged from 10 μM to 10 pM. Previously-frozen membranes were diluted in fresh EBSS to a 100 μg/ mL (for hD2R or hD3R) or 200 μg/mL (hD4R) stock for binding. Radioligand competition experiments were conducted in glass tubes containing 300 μl fresh EBSS buffer with 0.2 mM sodium metabisulfite, 50 μl of diluted test compound, 100 μl of membranes (10 μg total protein for hD2R or hD3R, 20 μg total protein for hD4R), and 50 μl of [^{3}H]N-

methylspiperone (0.4 nM final concentration; Perkin Elmer). Nonspecific binding was determined using 10 μM butaclamol (Sigma–Aldrich, St. Louis, MO) and total binding was determined with 30% DMSO vehicle. All compound dilutions were tested in triplicate and the reaction incubated for one hour at room temperature. The reaction was terminated by filtration through Whatman GF/B filters, presoaked for one hour in 0.5% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments, Gaithersburg, MD). The filters were washed 3 times with 3 mL of ice cold EBSS buffer and transferred to scintillation vials. 3 mL CytoScint liquid scintillation cocktail (MP Biomedicals, Solon, OH) was added and vials were counted using a Perkin Elmer Tri-Carb 2910 TR liquid scintillation counter (Waltham, MA). IC_{50} values for each compound were determined from dose–response curves and K_i values were calculated using the Cheng–Prusoff equation;[56] these analyses were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA). Reported K_i values were determined from least three independent experiments.

6.4. Mouse microsomal stability assay

Phase I metabolic stability assays were conducted in mouse liver microsomes. The reaction was carried out with 100 mM potassium phosphate buffer, pH 7.4, in the presence of NADPH regenerating system (1.3 mM NADPH, 3.3 mM glucose 6-phosphate, 3.3 mM $MgCl_2$, 0.4 U/mL glucose-6-phosphate dehydrogenase, 50 μM sodium citrate). Reactions in triplicate were initiated by addition of the liver microsomes to the incubation mixture (compound final concentration was 1 μM; 0.2 mg/mL micro-somes). Negative controls in the absence NADPH were carried out to determine the non-CYP mediated metabolism. Positive controls for phase I metabolism (testosterone) were also evaluated. At predetermined times (0, 30 and 60 min), aliquots of the mixture were removed and the reaction quenched by addition of two times the volume of ice cold acetonitrile spiked with the internal standard. Compound disappearance was monitored over time using a liquid chromatography and tandem mass spectrometry (LC/MS/ MS) method. All reactions were performed in triplicate.

Chromatographic analysis was performed using an Accela™ ultra high-performance system consisting of an analytical pump, and an autosampler coupled with TSQ Vantage mass spectrometer (Thermo Fisher Scientific Inc., Waltham, MA). Separation of the analyte from potentially interfering material was achieved at ambient temperature using Agilent Eclipse Plus column (100 × 2.1 mm i.d.) packed with a 1.8 μm C18 stationary phase. The mobile phase used was composed of 0.1% formic acid in acetonitrile and 0.1% formic acid in H_2O with gradient elution, starting with 10% (organic) linearly increasing to 99% up to 2.5 min, maintaining at 99% (2.5–3.5 min) and reequilibrating to 10% by 4.5 min. The total run time for each analyte was 4.5 min. The mass transitions used for each compound are as follows; **PG648** 461.148 > 213.106, 143.989; OMO05-057 473.110 > 155.996; **17a** 485.064 > 301.126, 129.998; **17b** 496.850 > 301.126, 129.998; **16** 447.130 > 263.198, 129.999

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

CuAAC	copper-catalyzed azide-alkyne cycloaddition
DIPEA	diisopropylethylamine
D2R	dopamine D2 receptor
D3R	dopamine D3 receptor
GPCR	G protein-coupled receptors
SAR	structure–activity relationship
TBTA	tris(benzyltriazolylmethyl)amine

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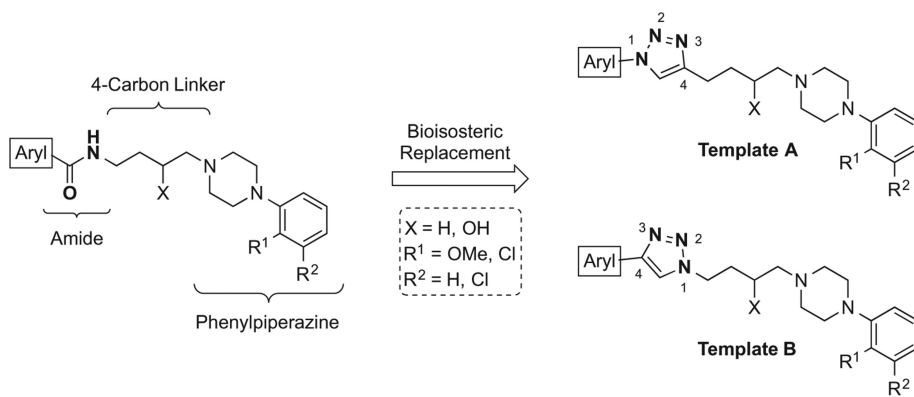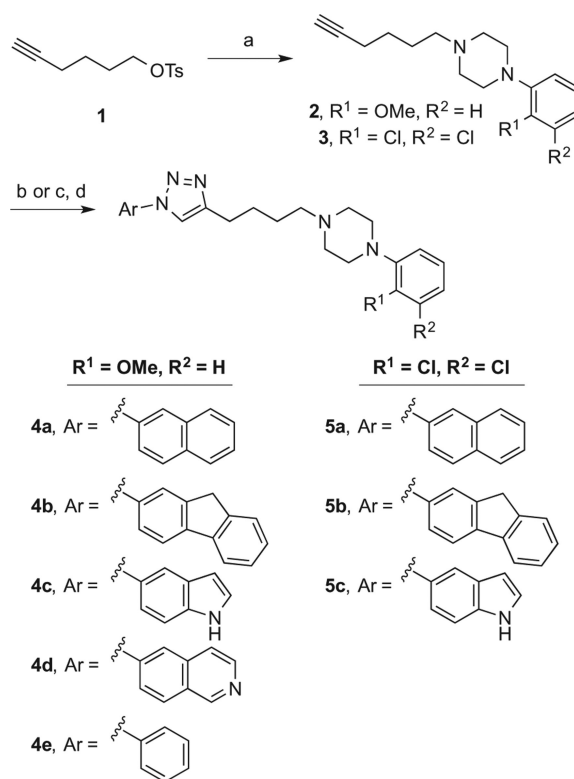56. Cheng Y, Prusoff WH. Biochem. Pharmacol. 1973; 22:3099. [PubMed: 4202581]

Figure 1.
Bioisosteric replacement of the amide with the 1,2,3-triazole in D3R-selective ligands, providing analogues of templates A and B.
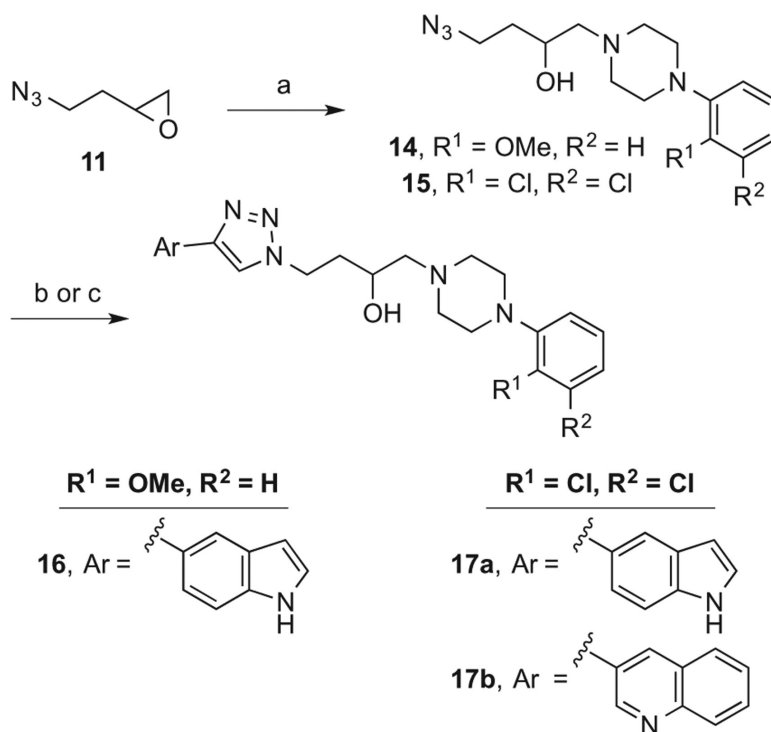
Scheme 1.

Reagents and conditions: (a) K_2CO_3, NaI, appropriate phenylpiperazine, acetone, reflux, 12 h; (b) (i) *t*-BuONO, trimethylsilyl azide, appropriate amine, CH_3CN, rt, 2 h; (ii) CuI, DIPEA, rt, 12 h; (c) appropriate amine, $NaNO_2$, concd H_2SO_4, H_2O, NaN_3, 10 min. rt; (d) 5-azidoquinoline, CuI, DIPEA, appropriate azide, THF, rt, 12 h.
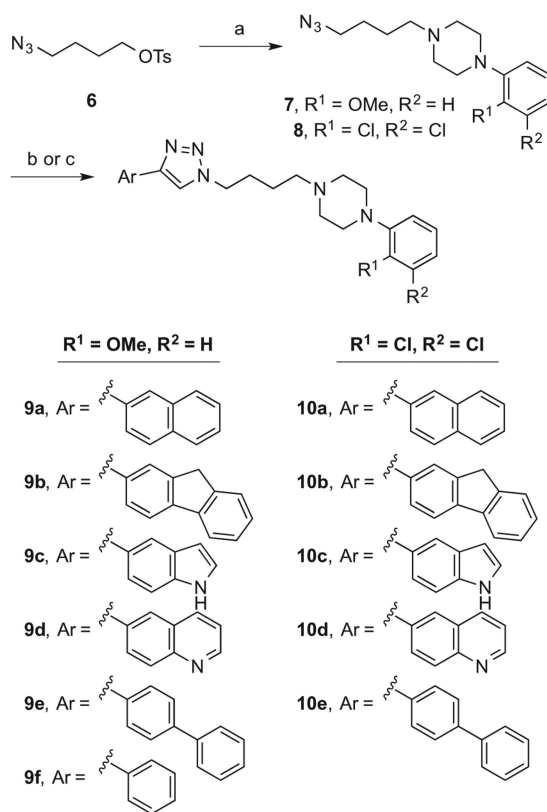
Scheme 2.

Reagents and conditions: (a) K_2CO_3, NaI, appropriate phenylpiperazine, acetone, reflux, 12 h; (b) CuI, DIPEA, appropriate acetylene, THF, rt, 12 h; (c) sodium ascorbate, $CuSO_4 \cdot 5H_2O$, appropriate acetylene, THF:H_2O (1:1), 50 °C, 12 h.
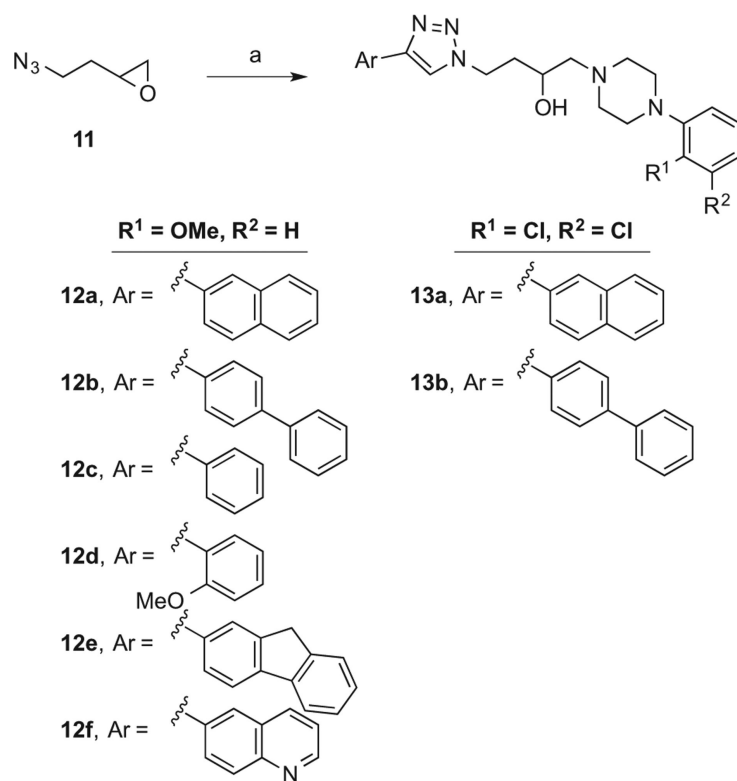
Scheme 3.
Reagents and Conditions: (a) Sodium ascorbate, $CuSO_4 \cdot 5H_2O$, K_2CO_3, β-cyclodextrin, appropriate acetylene, appropriate phenylpiperazine hydrochloride, H_2O, rt for 30 min then 80 °C for 2 h.

Scheme 4.

Reagents and conditions: (a) K_2CO_3, NaI, appropriate phenylpiperazine, acetonitrile, reflux, 16 h; (b) sodium ascorbate, $CuSO_4 \cdot 5H_2O$, ethynyl-1H-indole, THF:H_2O (3:1), rt, 16 h; (c) sodium ascorbate, $CuSO_4 \cdot 5H_2O$, 3-ethynylquinoline, TBTA THF:H_2O (3:1), rt, 16 h.
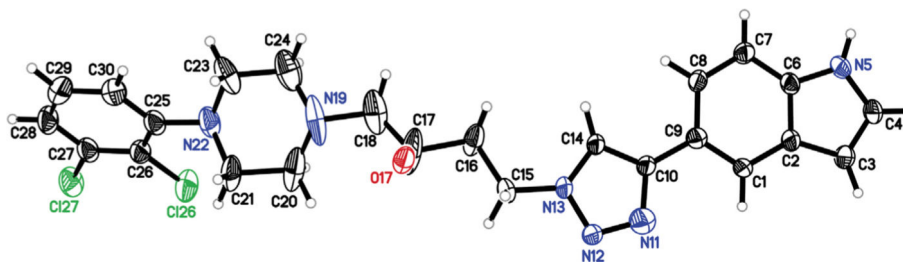
Figure 2.
Structure of 2,3-diClPh-containing indolyltriazole **17a** as determined by X-ray crystallography. Displacement ellipsoids are at the 50% level.
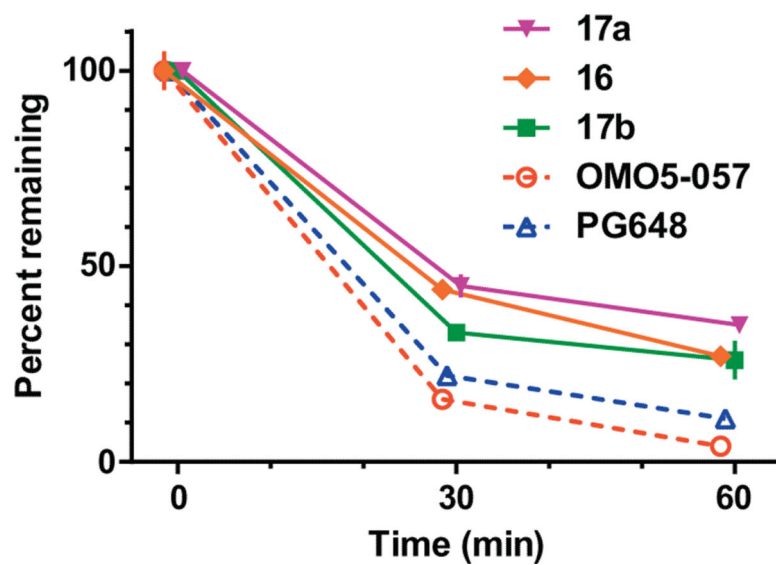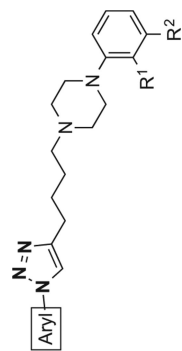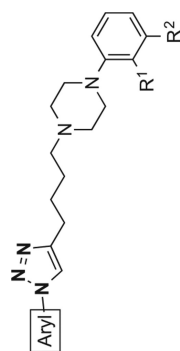
Figure 3.
Phase I metabolic stability. Data is presented as percent original compound remaining (mean ± SEM) at 30 and 60 min. following incubation with mouse liver microsomes in presence of NADPH. Note, the three most stable compounds tested are from the 1,2,3-triazole set.

Table 1

In vitro dopamine receptor binding data for template A 1,2,3-triazoles

Compound	No.	Aryl	R^1	R^2	c Log P	D2R $K_i \pm SEM$[†] (nM)	D3R $K_i \pm SEM$[†] (nM)	D4R $K_i \pm SEM$[†] (nM)	Receptor selectivity D2/D3	D4/D3
BAK 04-70	4a		OMe	H	5.6	31.5 ± 2.06	2.93 ± 0.221	299 ± 28.6	11	102
BAK 04-29	4b		OMe	H	6.3	57.2 ± 7.29	1.59 ± 0.439	329 ± 110	36	207
BAK 04-71	4c		OMe	H	4.6	51.8 ± 7.59	3.10 ± 0.802	353 ± 64.8	17	114
BAK 04-74	4d		OMe	H	4.8	83.4 ± 0.990	13.1 ± 2.72	>1 µM (n = 1)	6.4	–
BAK 04-27	4e		OMe	H	4.4	53.6 ± 3.89	5.42 ± 0.447	486 ± 114	10	90

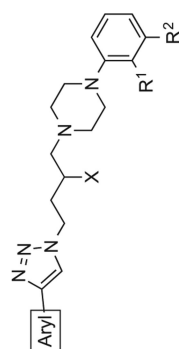| Compound	No.	Aryl	R^1	R^2	c Log P	D2R $K_i \pm$ SEM† (nM)	D3R $K_i \pm$ SEM† (nM)	D4R $K_i \pm$ SEM† (nM)	Receptor selectivity D2/D3	Receptor selectivity D4/D3
BAK 04-89	5a		Cl	Cl	7.1	80.8 ± 15.1	3.80 ± 0.760	>2 µM (n = 1)	21	–
BAK 04-90	5b		Cl	Cl	7.8	424 ± 118	5.05 ± 0.141	4450 ± 1740	84	881
BAK 04-92	5c		Cl	Cl	6.1	46.6 ± 16.1	1.00 ± 0.0960	510 ± 110	47	510

† K_i values were determined via radioligand competition binding experiments using [^{3}H]N-methylspiperone (0.4 nM) and membranes from HEK 293 cells stably expressing human D2R, D3R or D4R. Unless otherwise noted, data are presented as mean ± SEM and derived from 3 or more independent experiments.

Table 2

In vitro dopamine receptor binding data for template B 1,2,3-triazoles
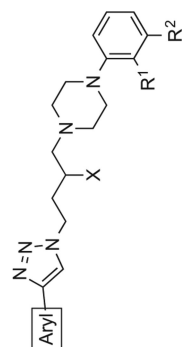
Compound	No.	Ar	R^1	R^2	X	c Log P	D2R $K_i \pm$ SEM[†] (nM)	D3R $K_i \pm$ SEM[†] (nM)	D4R $K_i \pm$ SEM[†] (nM)	Receptor selectivity D2/D3	Receptor selectivity D4/D3
BAK 05-21	9a		OMe	H	H	5.2	23.3 ± 1.38	11.1 ± 3.71	232 ± 92.3	2.1	21
BAK 05-19	9b		OMe	H	H	5.9	50.1 ± 3.82	5.55 ± 1.38	588 ± 147	9.0	106
BAK 05-16	9c		OMe	H	H	4.0	43.7 ± 4.96	5.48 ± 0.430	222 ± 43.4	8.0	41
BAK 05-27	9d		OMe	H	H	3.9	42.5 ± 5.45	6.73 ± 0.445	269 ± 66.6	6.3	40
BAK 05-18	9e		OMe	H	H	5.9	69.0 ± 14.0	5.88 ± 1.02	425 ± 87.8	12	72

Compound	No.	Ar	R^1	R^2	X	c Log P	D2R K_i ± SEM[†] (nM)	D3R K_i ± SEM[†] (nM)	D4R K_i ± SEM[†] (nM)	Receptor selectivity D2/D3	D4/D3
BAK 04-81	9f		OMe	H	H	4.0	137 ± 6.86	22.9 ± 5.38	480 ± 58.8	6.0	21
BAK 05-26	10a		Cl	Cl	H	6.7	103 ± 14.0	7.7 ± 1.87	>1 μM (n = 1)	13	–
BAK 05-24	10b		Cl	Cl	H	7.4	885 ± 298	14.0 ± 4.96	>20 μM (n = 1)	63	–
BAK 05-25	10c		Cl	Cl	H	6.1	56.1 ± 7.20	1.47 ± 0.462	>2 μM (n = 1)	38	–
BAK 05-28	10d		Cl	Cl	H	5.4	53.9 ± 11.8	1.35 ± 0.184	>1 μM (n = 1)	40	–
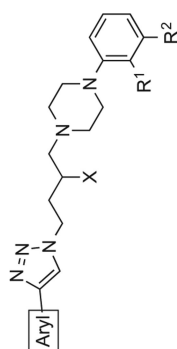
Compound	No.	Ar	R¹	R²	X	$c \log P$	D2R $K_i \pm$ SEM[†] (nM)	D3R $K_i \pm$ SEM[†] (nM)	D4R $K_i \pm$ SEM[†] (nM)	Receptor selectivity	
										D2/D3	D4/D3
BAK 05-23	10e		Cl	Cl	H	7.4	2590 ± 920	8.32 ± 1.20	>10 µM (n = 1)	311	–
BAK 05-52	12a		OMe	H	OH[§]	4.4	189 ± 23.6	40.7 ± 5.34	>2 µM (n = 1)	4.6	–
BAK 05-47	12b		OMe	H	OH[§]	5.2	819 ± 87.1	30.5 ± 6.99	>2 µM (n = 1)	27	–
BAK 05-51	12c		OMe	H	OH[§]	3.3	1210 ± 103	173 ± 9.60	>3 µM (n = 1)	7.0	–
BAK 05-44	12d		OMe	H	OH[§]	2.7	1020 ± 66.9	493 ± 24.1	>3 µM (n = 1)	2.1	–
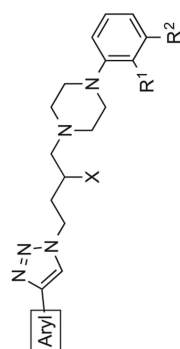
Compound	No.	Ar	R¹	R²	X	$c \log P$	D2R $K_i \pm$ SEM[†] (nM)	D3R $K_i \pm$ SEM[†] (nM)	D4R $K_i \pm$ SEM[†] (nM)	Receptor selectivity	
										D2/D3	D4/D3
BAK 05-43	12e		OMe	H	OH[§]	5.2	607 ± 54.9	18.5 ± 0.248	>1 µM ($n = 1$)	33	–
BAK 05-56	12f		OMe	H	OH[§]	3.2	424 ± 25.9	68.2 ± 6.72	>3 µM ($n = 1$)	6.2	–
BAK 05-53	13a		Cl	Cl	OH[§]	6.0	$18,800 \pm 8960$	25.2 ± 2.17	>20 µM ($n = 1$)	745	–
BAK 05-55	13b		Cl	Cl	OH[§]	6.8	$15,100 \pm 2770$	55.8 ± 12.9	>7 µM ($n = 1$)	270	–
RDS 02-33	16		OMe	H	OH[§]	3.3	789 ± 79.4	33.6 ± 7.27	NT	23	–
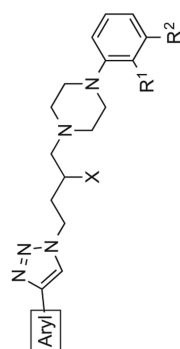
Compound	No.	Ar	R¹	R²	X	c Log P	D2R $K_i \pm$ SEM[†] (nM)	D3R $K_i \pm$ SEM[†] (nM)	D4R $K_i \pm$ SEM[†] (nM)	Receptor selectivity D2/D3	D4/D3
RDS 02-28	17a		Cl	Cl	OH§	4.9	963 ± 168	5.85 ± 0.780	NT	165	–
RDS 02-32	17b		Cl	Cl	OH§	4.9	244 ± 22.8	18.0 ± 5.74	NT	14	–
PG648[44]§						4.9	746 ± 123	1.88 ± 0.112	2600 ± 660	397	1380
OMO5-057§						4.9	321 ± 9.34	2.91 ± 0.499	NT	110	–
NGB2904[15,43]						6.7	54.7 ± 5.20	0.233 ± 0.00893	3670 ± 626	235	15,800

§Compounds are racemic.

[†]K_i values were determined via radioligand competition binding experiments using [³H]N-methylspiperone (0.4 nM) and membranes from HEK 293 cells stably expressing human D2R, D3R or D4R. Unless otherwise noted, data are presented as mean ± SEM and derived from 3 or more independent experiments.