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Further SAR study on 11-O-substituted aporphine analogues: Identification of highly potent dopamine D_3 receptor ligands

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ABSTRACT

A series of new aporphine analogues (aporlogues) were prepared from appropriate aporphine precursors and arylpiperazines using the Click reaction protocol. These compounds displayed good to high affinity at the D_3 receptor, low or no affinity at the D_1 and D_2 receptors. Compounds **7f** and **11c** stood out as the most potent at the D_3 receptor among our newly synthesized aporlogues with K_i values of 2.67 and 1.14 nM, respectively. Further assay at the 5-HT_{1A} receptor revealed that aporlogues **7f** and **11c** also showed high affinity at this receptor with K_i values of 9.68 and 7.59 nM, respectively. They were 3.6- and 6.6-fold more potent at the D_3 over 5-HT_{1A} receptors. Such D_3/5-HT_{1A} dual property of these compounds may be useful in the treatment of several brain disorders.

1. Introduction

Dopamine (DA) D_3 receptor belongs to the D_2-like subfamily of dopamine receptors, including D_2, D_3 and D_4, functionally distinct from the D_1-like subfamily (D_1 and D_5). Compared to the D_2 receptor, D_3 receptor is much less abundant and predominantly distributed in the brain limbic region known to be associated with cognitive and emotional functions.[1] The highest expression of the D_3 receptor in humans is in the ventral striatum and associated striatum.[2,3] Therefore, D_3 receptor is implicated in a variety of brain functions and proposed as a promising therapeutic target for a number of neurological and psychiatric disorders, including schizophrenia, depression, drug abuse, Parkinson's disease and restless leg syndrome.[4–9] Although tremendous D_3 receptor active compounds have been invented and evaluated in vitro and in vivo,[10] truly selective D_3 receptor agonists or antagonists (over the D_2 receptor) with good solubility and bioavailability are rare. For example, the well-known anti-Parkinsonian drug pramipexole (**1**) is a D_3 receptor-preferring agonist but with limited selectivity among the D_2-like receptors.[11,12] The representative D_3 receptor antagonist BP 897 (**2**) is indeed a D_3 receptor partial agonist possessing substantial potency for the D_2 receptor.[5] The major obstacle to achieve highly D_3-selective compounds is attributed to the nearly identity of the amino acid residues in the binding domains of D_2 and D_3 receptors, as well as the high degree (>70%) of sequence identity within their transmembrane helices.[3,8] Fortunately, several differences in the extracellular binding sites of the two DA receptors were identified recently from the crystal structure of the human D_3 receptor in complex with a small D_2/D_3-specific antagonist.[13] Hopefully, this will provide new directions for the development of D_3 receptor selective agents. In addition, accumulating evidences have indicated that alteration of serotonin 1A (5-HT_{1A}) receptor function is also associated with a number of neuropsychological disorders, including anxiety and depression,[14,15] pain,[16] neuroprotection,[17,18] schizophrenia,[19,20] Parkinson's disease,[21–23] and Alzheimer's disease.[24] Therefore, new agents selectively acting at the D_3 or both D_3 and 5-HT_{1A} receptors are highly needed to explore their therapeutic benefits.

During our SAR study on the aporphine analogues (aporlogues),[25] we recently found that replacing the catecholic hydroxyl groups of the D_2 receptor agonist apomorphine (**3**, Fig. 1) with a alkyletheric moiety led to a series of metabolic stable aporlogues. These compounds showed potent affinity at several receptor targets (D_1, D_3, 5-HT_{1A}, 5-HT_{2A}) other than the original D_2 receptors. Among these compounds, 11-prop-2-ynyloxy aporlogue **4**[25b] displayed moderate affinity at the D_3 receptor with K_i value of 2.4 μM, while completely lost activity at both D_1 and D_2 receptors. In view of the readily functional transformation capacity of the

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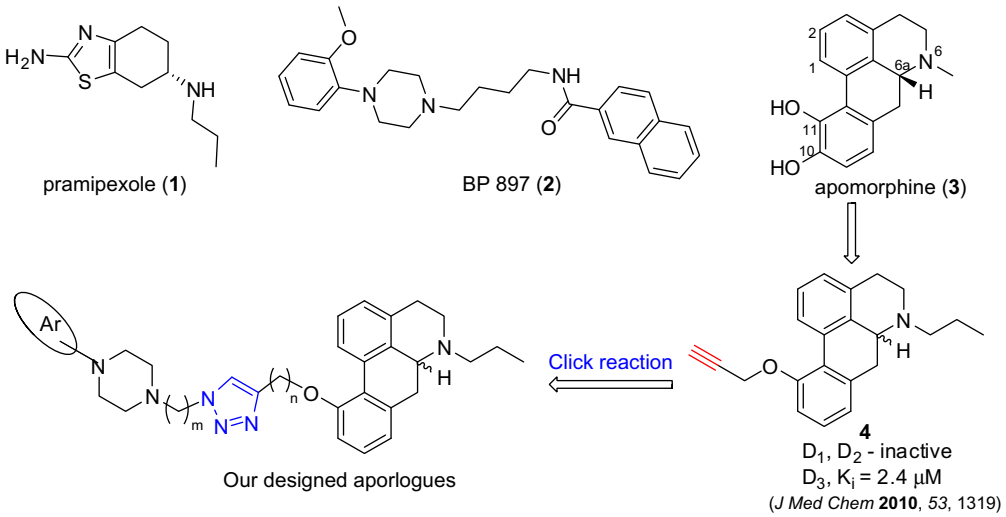


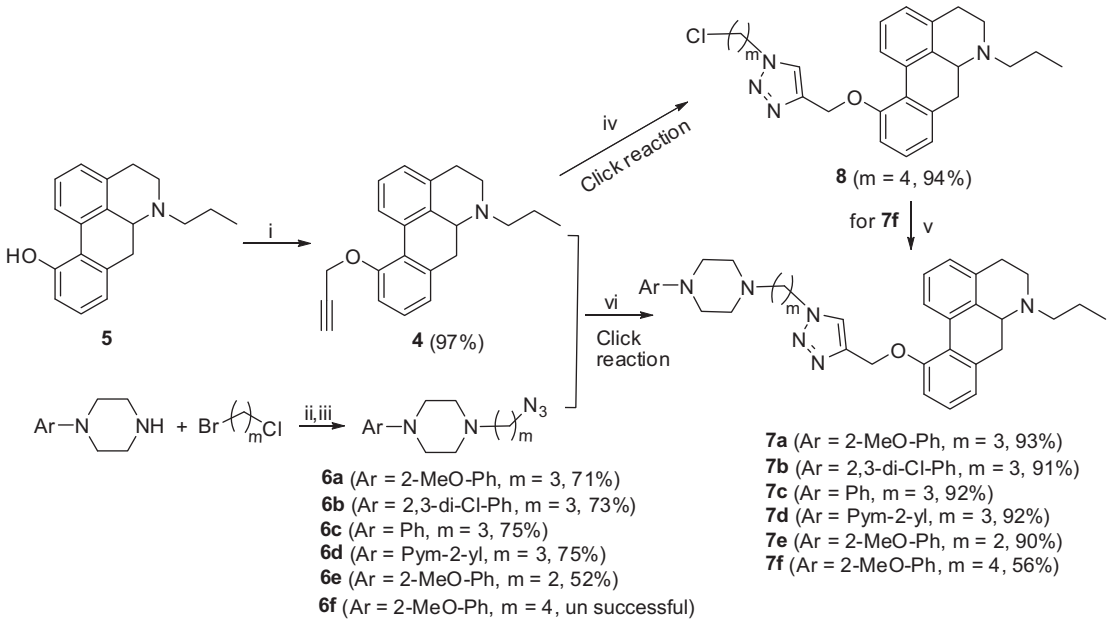
Figure 1. Representative D3 receptor agents and proposed aporphine analogues (aporlogues).

acetylenyl group in compound **4**, we decided to explore the potential of generating more potent D_3 receptor agents. Therefore, a series of novel triazole-containing aporlogues were synthesized based on hit **4** through the widely used click reaction protocol[26] (Fig. 1).

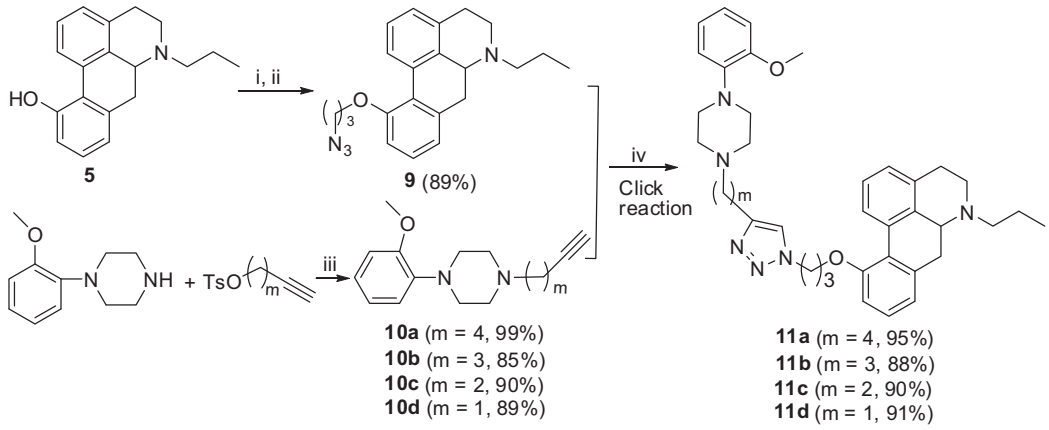
2. Chemistry

The key intermediate, 11-hydroxy-*N*-propylnoraporphine **5**, was prepared by total synthesis in eight steps from Reissert salt and arylmethylbromide according to the reported procedures.[27] Alkylation of phenol **5** with propargyl bromide provided 11-prop-2-ynyloxy *N*-propylnoraporphine **4** in 97% yield (Scheme 1). Alkylation of commercially available arylpiperazines with an appropriate chloroalkyl bromide followed by axidization with NaN_3 gave corresponding azide precursors **6a–e** in 52–75% overall yields. Click reaction[26] of aporphine **4** with azides **6a–e** under CuI/DIPEA yielded the corresponding triazole-derived aporlogues **7a–e** in 90–93% yields (Scheme 1). However, the same procedure was not successful in the preparation of aporlogue **7f** due to the low yield in preparation of precursor **6f**. In the process of preparation of compound **6f**, a β-elimination reaction was generally observed from the substrate 1-(4-chlorobutyl)-4-(2-methoxyphenyl)piperazine. Alternatively, compound **7f** was prepared in 56% yield by alkylation of triazole **8**. The precursor **8** was obtained by Click reaction of aporphine **4** and 1-azido-4-chlorobutane[28] in 94% yield.

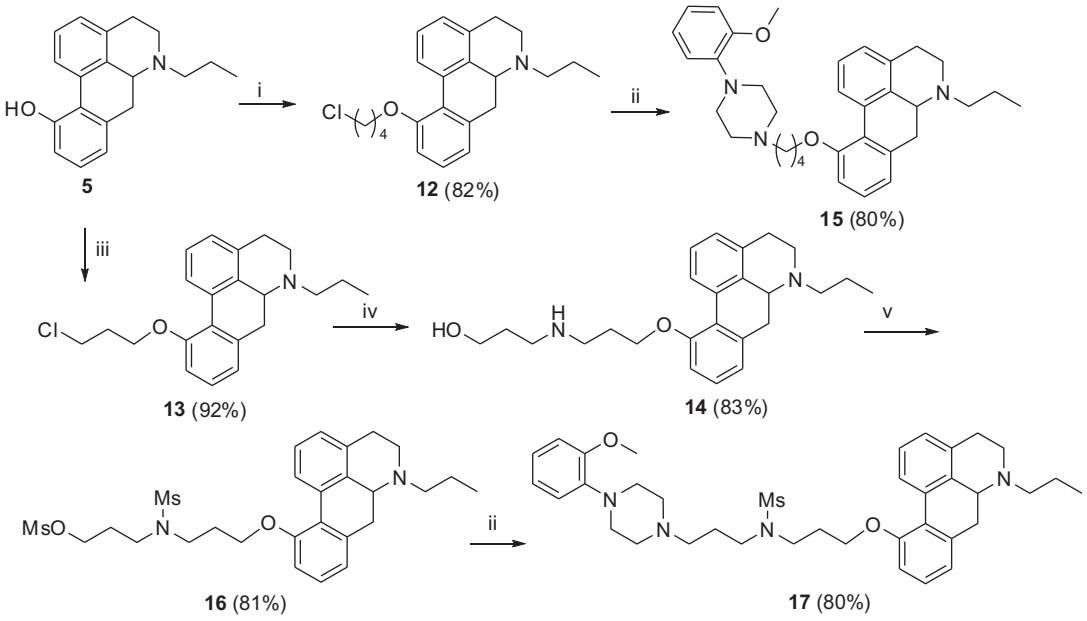
As a comparison, aporlogues **11a–d** were prepared by switching the functional groups (azido and acetylenyl) between the two 'Click' reaction precursors. As described in Scheme 2, azide **9** was prepared by alkylation of phenol **5** followed by azidization in 89% overall yield. Meanwhile, arylpiperazines **10a–d** equipped with the prop-2-ynyl function were obtained in 85–99% yields. Click reaction of azide **9** with arylpiperazines **10a–d** provided the expected aporlogues **11a–d** in 88–95% yields.



Scheme 1. Reagents and conditions: (i) allyl bromide, KOH, KI, acetone, rt; (ii) chloroalkyl bromide, K_2CO_3, MeCN, 50 °C; (iii) DMSO, NaN_3, 100 °C; (iv) 1-azido-4-chlorobutane, CuI, DIPEA, THF, rt; (v) for **7f**: 1-(2-methoxyphenyl)piperazine, NaI, K_2CO_3, MeCN, reflux; (vi) CuI, DIPEA, THF, rt.



Scheme 2. Reagents and conditions: (i) 1-bromo-3-chloropropane, 50% aq NaOH; TBAB, rt; (ii) DMSO, NaN_3, 100 °C; (iii) K_2CO_3, acetone, 50 °C; (iv) CuI, DIPEA, THF, rt.



Scheme 3. Reagents and conditions: (i) 1-bromo-4-chlorobutane, TBAB, 50% aq NaOH, rt; (ii) 1-(2-methoxyphenyl)piperazine, NaI, K_2CO_3, MeCN, reflux; (iii) 1-bromo-3-chloropropane, 50% aq NaOH, TBAB, rt; (iv) 3-aminopropan-1-ol, *n*-BuOH, reflux; (v) MsCl, Et_3N, CH_2Cl_2, rt.

In addition, similar aporlogues without the triazole or arylpiperazine functions were also prepared (Scheme 3). Alkylation of phenol **5** with 1-bromo-4-chlorobutane gave compound **12** in 82% yield. Compound **12** was then treated with an appropriate arylpiperazine leading to aporlogue **15** in 80% yield. Similarly, alkylation of phenol **5** with 1-bromo-3-chloropropane yielded chloride **13** in 92% yield, which was then treated with 3-aminopropanyl alcohol giving aporlogue **14** in 83% yield. Double mesylation of alcohol **14** provided compound **16** in 81% yield. Reaction of mesylate **16** with 1-(2-methoxyphenyl)piperazine yielded aporlogue **17** in 80% yield.

3. Biological activity

3.1. DA D_1, D_2, and D_3 receptor binding assays

All the newly synthetic aporlogues **7a–f**, **11a–d** and **14**, **15**, **17** were subjected to the competitive binding assays for the three DA receptors, respectively, using membrane preparation obtained from stable transfected HEK293 cells. First, the ability at 10 μM concentration to inhibit the binding of a tritiated radioligand to the corresponding receptor was tested. Compounds with inhibited binding by more than 80% were further assayed at six or more concentrations, ranging above and below IC_{50}. The $K_i \pm SE$ was then derived from the equation $K_i = IC_{50}/1+[C/K_d]$. These procedures were similar to those reported previously by us.[25b–d,26] [^{3}H]-SCH23390 (D_1) and [^{3}H]-Spiperone (D_2, D_3) were used as the standard radioligands. The inhibition or K_i values of the newly synthetic aporphines were summarized in Table 1.

Since the phenolic hydroxyl group in apomorphine (**3**) is an essential request[10e,25a] for binding to the D_2 receptor, it is conceivable that the newly synthetic aporlogues, as well as compound **4**, did not show appreciable affinity at this receptor. However, significant potency was observed at the D_3 receptor. First, compounds **7a–d** represented a small series of aporlogues bearing variant arylpiperazine functions. Compared to the initial ether **4**, 4–10-fold higher potency was observed in these compounds at the D_3 receptor. Aporlogues **7a** and **7b** with 2-methoxyphenyl- and 2,3-dichlorophenyl as the *N*-4 aryl substituent in the piperazine component, respectively, showed the highest D_3 receptor affinity among this

Table 1
In vitro binding assays of new aporlogues at D_1, D_2 and D_3 receptors in HEK293 cells[a]

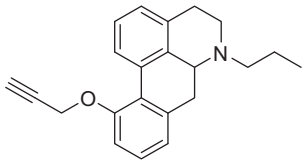
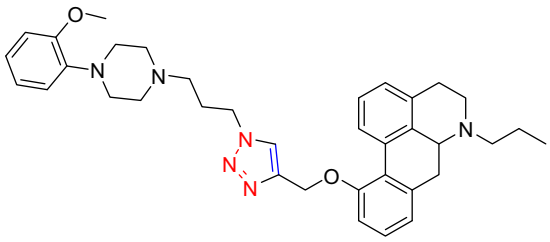
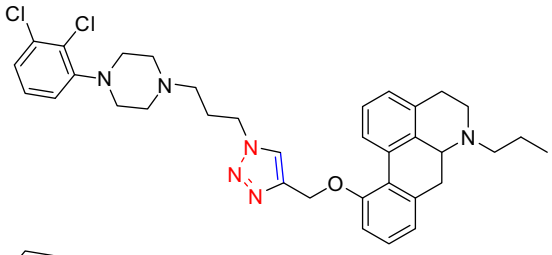
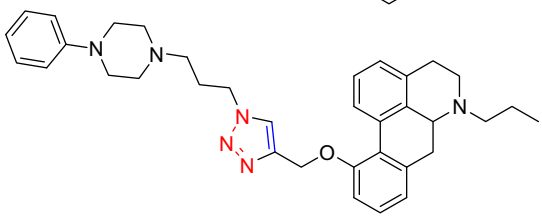
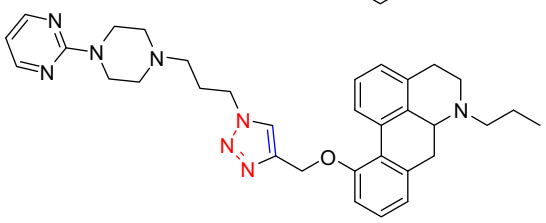
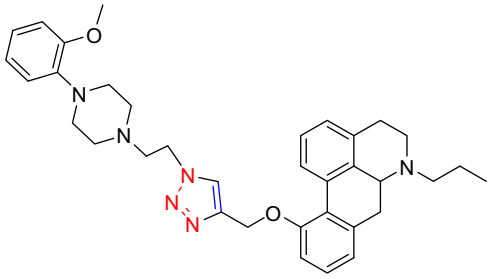
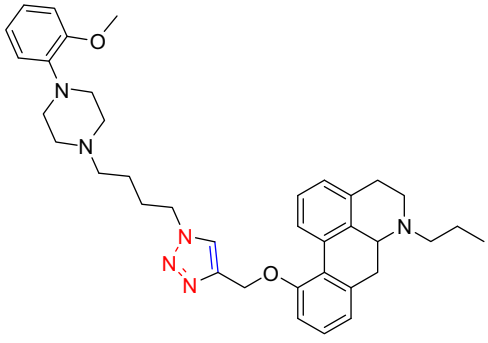
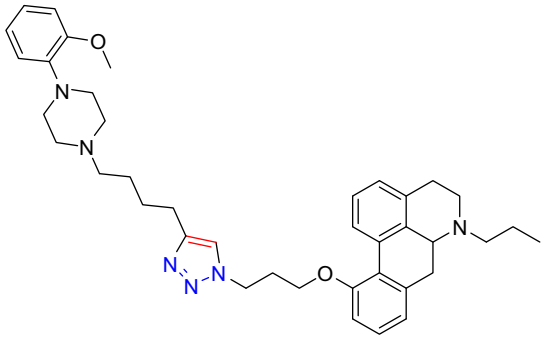
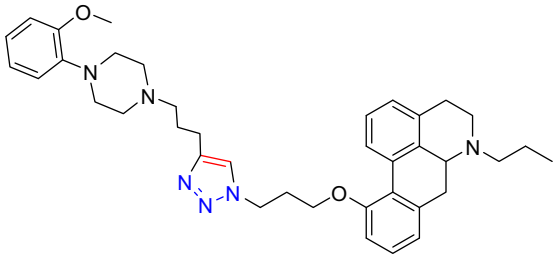
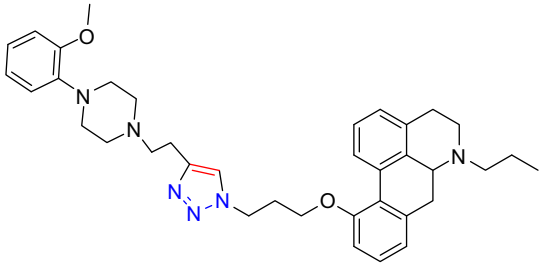
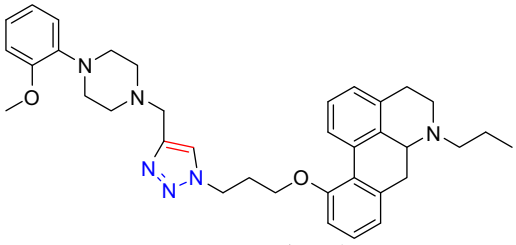
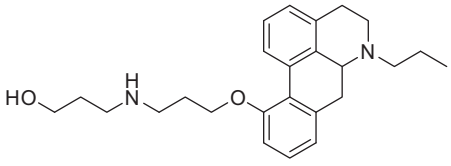
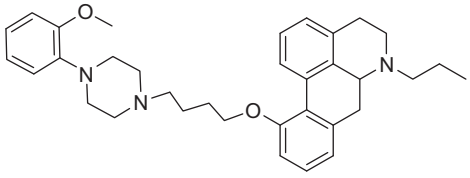
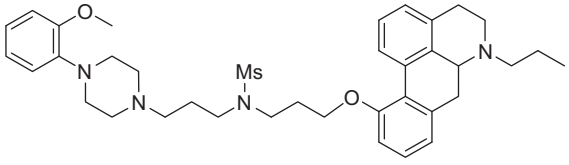
Compound	Structure	Inhibition (%) or K_i[b] (nM)		
		D_1	D_2	D_3
4		–	28%	2400 ± 75
7a		67%	1203 ± 17	21 ± 1.4
7b		2007 ± 206	40.49%	35 ± 4.9
7c		63%	6.0%	191 ± 38
7d		32%	13%	539 ± 71
7e		35%	19%	44 ± 7.7
7f		2700 ± 147	661 ± 1.1	2.67 ± 0.29

Table 1 (*continued*)

Compound	Structure	Inhibition (%) or K_i[b] (nM)		
		D_1	D_2	D_3
11a		1900 ± 53	206 ± 11	8.14 ± 0.79
11b		14%	18%	8.16 ± 0.49
11c		64%	7384 ± 1090	1.14 ± 0.02
11d		42%	51%	281 ± 36
14		44%	9%	4514 ± 406
15		735 ± 40	88 ± 8.0	19.9 ± 1.16
17		910 ± 122	399 ± 12	102 ± 5.7

[a] Values are means of three to five experiments, and all compounds were tested in racemic form.
[b] Only compounds with inhibition of radioligand binding higher than 80% was further tested for K_i values.

small series. They exhibited K_i values of 21 and 35 nM, respectively. Non-substituted phenylpiperazin-4-yl- (**7c**) and 1-heteroaryl (1,3-pyrimid-2-yl) substituted piperazin-4-yl- (**7d**) analogues showed moderate affinity at this receptor. Shortening the alkyl linker between the arylpiperazine and triazole core led to compound **7e** which retained good affinity at the D_3 receptor (44 nM). Elongation of the alkyl linker gave compound **7f** showing a significant enhancement. This compound has a K_i value of 2.7 nM at the D_3 receptor, 100-fold more potent than the initial aporphine **4**. Interestingly, compound **7f** also displayed substantial affinity at the D_2 receptor with a K_i value of 661 nM.

Compounds **11a–d** represented another series of aporlogues with the triazole fragment formed in a different manner. On the basis of the optimizing results in aporlogues **7a–d**, the 2-methoxyphenyl group was directly selected as the terminal N-substituent in piperazine fragment. Compounds **11a** and **11b** contained a four- and three-methylene unit as the linkage between the arylpiperazine and triazole moieties, respectively. They displayed identical K_i values at the D_3 receptor (8.1 nM). It is quite intriguing that the former compound (**11a**) showed moderate affinity at the D_2 receptor as well. Further shortening the linkage to a two-methylene unit led to aporlogue **11c**, exhibiting very potent affinity with a K_i value of 1.14 nM. However, compound **11d** with a one-methylene linkage displayed remarkably reduced potency. It showed a K_i value of 281 nM that is 246-fold less potent than aporlogue **11c**.

To evaluate the contribution of arylpiperazine and triazole functions to the binding affinity at the D_3 receptor, aporlogues **14**, **15** and **17** were investigated as a control. Compound **14** lacking both arylpiperazine and triazole moieties displayed negligible potency at the D_3 receptor. However, compound **15** bearing an arylpiperazine moiety but lacking triazole function retained significant affinity with a K_i value of 20 nM. Interestingly, this compound also showed good affinity at the D_2 and moderate affinity at the D_1 receptors, with K_i values of 88 and 735 nM at the two receptors, respectively. Similar receptor selectivity profile was observed for compound **17**, although it is much less potent at all the three DA receptors. These results indicated that the good potency at the D_3 receptor for these compounds may be irrelevant to the triazole function, whereas the arylpiperazine moiety likely offered significant contribution to the D_3 receptor binding.

3.2. Binding profiles of the (+)- and (−)-enantiomers of compounds 7f, 11c and 15

From the results above, compounds **7f, 11c** and **15** stood out as the most potent D_3 receptor aporlogues synthesized in this report. Since these compounds were recemates, they were resolved to their corresponding (+)- and (−)-enantiomers, respectively by chiral AD column with ethyl alcohol/diethylamine as the mobile phase (Table 2). From the results in Table 2, all the enantiomers of these compounds did not show better affinity at the D_3 receptor than their corresponding racemates. (+)-**7a** and (−)-**7a** exhibited almost identical affinity (8.0 vs 9.18 nM) and were threefold less potent than racemic **7a**. However, in the case of aporlogue **11c**, the (−)-enantiomer (−)-**11c** displayed similar high potency as the racemate with K_i values of 1.8 and 1.1 nM, respectively. While the (+)-enantiomer, (+)-**11c** was fourfold less potent than either the (−)-enantiomer or the racemate. Quite differently, (+)-**15** was equally potent to its racemate **15**, whereas (-)-**15** was 10-fold less potent than the racemate. Although the effect of *C6a*-stereochemistry in aporphine skeleton on the D_3 receptor binding affinity was not universal, significant difference does exist in our study, especially in aporlogues **10c** and **15**. It is of note that such significant difference was not observed at the D_2 receptor.

3.3. 5-HT_{1A} and 5-HT_{2A} receptor binding assays

During our previous report,[25a,b] we found that many aporlogues with lipophilic substituents at either the C10 or C11 or both showed substantial potency at the serotonin (5-HT) receptors, especially 5-HT_{1A} and 5-HT_{2A} subtypes. To confirm if this is also the case for our newly synthetic D_3 receptor ligands, we further evaluated the binding profile of aporlogues **7f**, **11c** and **15** at the 5-HT_{1A} and 5-HT_{2A} receptors. [^{3}H]8-OH-DPAT and [^{3}H]ketanserin were used as the standard radioligands, respectively, by following a procedure we reported before.[25a–d,26] As summarized in Table 3, these compounds generally displayed good affinity at the 5-HT_{1A} receptor, and moderate or no affinity at the 5-HT_{2A} receptor. The triazole-containing aporlogues **7f** and **11c** showed K_i values of 9.68 and 7.59 nM at the 5-HT_{1A} receptor, respectively. There were 18- and 32-fold selective over 5-HT_{2A} receptor. Much lower affinity was observed for compound **15** at the 5-HT_{1A} and 5-HT_{2A} receptors. This result indicated that the H-bonding potential of the triazole moiety may be contributed to the interaction of the new aporlogues with the 5-HT receptors. In spite of the significant potency at the 5-HT_{1A} receptor, compounds **7f** and **11c** were 3.6- and 6.6-fold selective for the D_3 over 5-HT_{1A} receptors, respectively.

4. Conclusion

In summary, a series of new aporlogues were prepared from appropriate aporphine precursors and arylpiperazines using the Click reaction strategy. These compounds generally displayed good to high affinity at the D_3 receptor, whereas low or no affinity at the D_1 and D_2 receptors. Among these new aporlogues, compounds **7f** and **11c** were identified as the most potent at the D_3 receptor. They displayed K_i values of 2.67 and 1.14 nM, respectively, at this receptor. Further assay at the 5-HT_{1A} receptor revealed that aporlogues **7f** and **11c** also showed high affinity at this receptor with K_i values of 9.68 and 7.59 nM, respectively. They were 3.6- and 6.6-fold more potent at the D_3 over 5-HT_{1A} receptors. In view of the promising role of 5-HT_{1A} receptor in a number of neuropsychological disorders, such D_3/5-HT_{1A} dual action compounds may find use in the treatment of these brain disorders. Further efforts will be focused on the functional assay of these compounds at the two receptors.

5. Experimental

^{1}H NMR spectral data were recorded in $CDCl_3$ on Varian Mercury 300 NMR spectrometer and ^{13}C NMR were recorded in $CDCl_3$ on Varian Mercury 400 NMR spectrometer. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at an ionizing voltage of 70 eV on a Finnigan/MAT95 spectrometer. Column chromatography was carried out on silica gel (200–300 mesh). All reactions were monitored using thin-layer chromatography (TLC) on silica gel plates. Yields were of purified compounds and were not optimized. Compounds **4**,[25b] **5**[27] were prepared according to the literature procedures.[27]

5.1. General procedure for preparation of azides 6a–e

An appropriate arylpiperazines (1.0 equiv), chloroalkyl bromide (10.0 equiv) and K_2CO_3 (2.0 equiv) were stirred at 50 °C for 2 h. The reaction suspension was filtered and the filtrate was concentrated. The crude material was chromatographed to give the corresponding chloride derivatives that were used directly for the next step.

The mixture of the chloride obtained above (1.0 equiv) and NaN_3 (2.0 equiv) was dissolved in DMSO (5 mL) and stirred at 100 °C for 2 h. After cooling to rt, the reaction mixture was diluted

Table 2
Binding profiles of (+)- and (−)-enantiomers of the most potent compounds

Compd	ee%	$[\alpha]_D^{20}$	Inhibition (%) or K_i (nM)		
			D_1	D_2	D_3
7f	0	—	2700 ± 147	661 ± 1.1	2.67 ± 0.29
(−)-**7f**	99.8	−32.7 (1.10, MeOH)	66%	293 ± 17	8.0 ± 1.19
(+)-**7f**	100	29.6 (1.25, MeOH)	1600 ± 130	616 ± 38	9.18 ± 1.26
11c	0	—	64%	7384 ± 1090	1.14 ± 0.02
(−)-**11c**	99.7	−63.2 (0.90, MeOH)	68%	600 ± 4.6	1.82 ± 0.09
(+)-**11c**	100	66.2 (0.85, MeOH)	54%	770 ± 156	7.70 ± 1.74
15	0	—	735 ± 40	88 ± 8.0	19.9 ± 1.16
(−)-**15**	99.8	−36.8 (1.30, MeOH)	1174 ± 143	174 ± 4.45	189 ± 13
(+)-**15**	99.0	42.6 (1.25, MeOH)	1307 ± 236	141 ± 0.88	23.4 ± 4.98

Table 3
In vitro binding assays of new aporlogues at 5-HT_{1A} and 5-HT_{2A} receptors in CHO cells

Compound	K_i (nM)		
	5-HT_{1A}	5-HT_{2A}	D_3
7f	9.68 ± 2.11	174 ± 20	2.67 ± 0.29
11c	7.59 ± 0.13	245 ± 41	1.14 ± 0.02
15	58 ± 5.3	100,000	19.9 ± 1.16

with $CHCl_3$, washed with water, brine, and then dried over anhydrous Na_2SO_4. The solvents were removed and the residue was subjected to chromatograph giving the corresponding azides **6a–e**.

5.1.1. 1-(3-Azidopropyl)-4-(2-methoxyphenyl)piperazine (6a)

Yield 71% (for two steps); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (m, 3H), 6.86 (m, 1H), 3.85 (s, 3H), 3.35 (t, 2H, J = 6.9 Hz), 3.09 (br s, 4H), 2.65 (br s, 4H), 2.49 (t, 2H, J = 6.9 Hz), 1.81 (m, 2H).

5.1.2. 1-(3-Azidopropyl)-4-(2,3-dichlorophenyl)piperazine (6b)

Yield 73% (for two steps); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 2H), 6.93 (m, 1H), 3.34 (t, 2H, J = 6.3 Hz, 6.9 Hz), 3.03 (br s, 4H), 2.60 (br s, 4H), 2.47 (dd, 2H, J = 6.3, 7.5 Hz), 1.78 (m, 2H).

5.1.3. 1-(3-Azidopropyl)-4-phenylpiperazine (6c)

Yield 75% (for two steps); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 2H), 6.94 (m, 2H), 6.85 (m, 1H), 3.37 (dd, 2H, J = 6.6, 6.9 Hz), 3.20 (m, 4H), 2.61 (m, 4H), 2.49 (dd, 2H, J = 6.9, 7.5 Hz), 1.81 (m, 2H).

5.1.4. 2-(4-(3-Azidopropyl)piperazin-1-yl)pyrimidine (6d)

Yield 75% (for two steps); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, 2H, J = 4.5 Hz), 6.43 (t, 1H, J = 4.8 Hz), 3.79 (t, 4H, J = 4.8 Hz), 3.33 (t, 2H, J = 6.9 Hz), 2.43 (m, 6H), 1.75 (m, 2H).

5.1.5. 1-(2-azidoethyl)-4-(2-methoxyphenyl)piperazine (6e)

Yield 52% (for two steps); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (m, 4H), 3.85 (s, 3H), 3.39 (dd, 2H, J = 6.0, 6.3 Hz), 3.11 (br s, 4H), 2.69 (m, 6H).

5.2. General procedure for preparation of aporlogues 7a–e by Click reaction

A mixture of alkyne **4** (1.0 equiv), CuI (0.2 equiv), and an appropriate azide **6** (1.1 equiv) in THF (5 mL) was stirred for 5 min. *N*,*N*-Diisopropylethylamine (DIPEA, 5.0 equiv) was added slowly. The mixture was stirred at rt overnight. The solid was filtered off and the filtrate was concentrated. The crude material was subjected to chromatography to afford the desired cyclization products **7a–e**.

5.2.1. 11-((1-(3-(4-(2-Methoxyphenyl)piperazin-1-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-*N*-propylnoraporphine (7a)

Yield 93%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.4 Hz), 7.60 (s, 1H), 7.16 (m, 2H), 6.93 (m, 7H), 5.30 (dd, 2H, J = 12.6, 27.9 Hz), 4.44 (t, 2H, J = 6.9 Hz), 3.85 (s, 3H), 3.36 (d, 1H, J = 12.3 Hz), 3.12 (m, 7H), 3.02 (m, 1H), 2.83 (m, 1H), 2.54 (m, 9H), 2.09 (m, 2H), 1.58 (m, 2H), 0.96 (t, J = 7.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 152.1, 144.3, 141.1, 138.4, 135.2, 132.9, 131.4, 128.0, 127.5, 126.2, 125.6, 123.5, 122.9, 121.4, 120.9, 118.1, 112.1, 111.1, 63.0, 59.5, 56.4, 55.3, 54.4, 53.2, 50.5, 48.8, 48.1, 35.1, 29.1, 27.2, 19.5, 12.0. MS (EI, [M$^+$]) *m/z* 592; HR-MS (EI) calcd for $C_{36}H_{44}N_6O_2$: 592.3544, found: 592.3526.

5.2.2. 11-((1-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-*N*-propylnoraporphine (7b)

Yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, 1H, J = 7.5 Hz), 7.60 (s, 1H), 7.02 (m, 8H), 5.31 (dd, 2H, J = 12.0, 27.0 Hz), 4.44 (t, 2H, J = 6.9 Hz), 3.29 (d, 1H, J = 12.3 Hz), 3.12 (m, 8H), 2.73 (m, 1H), 2.29 (m, 9H), 2.09 (m, 2H), 1.60 (m, 2H), 0.96 (t, 3H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 151.0, 144.3, 138.6, 135.5, 133.9, 133.1, 131.4, 127.9, 127.4, 127.3, 126.1, 125.5, 124.5, 123.6, 122.9, 121.4, 118.5, 112.0, 63.0, 59.5, 56.5, 54.3, 53.0, 51.1, 48.9, 48.0, 35.2, 29.3, 27.1, 19.6, 12.0. MS (EI, [M]$^+$) *m/z* 630; HR-MS (EI) calcd for $C_{35}H_{40}N_6OCl_2$: 630.2483, found: 630.2641.

5.2.3. 11-((1-(3-(4-Phenylpiperazin-1-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-*N*-propylnoraporphine (7c)

Yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.1 Hz), 7.60 (s, 1H), 7.06 (m, 10H), 5.31 (dd, 2H, J = 12.3, 26.7 Hz), 4.44 (t, 2H, J = 6.9 Hz), 3.36 (dd, 1H J = 2.7, 10.8 Hz), 3.14 (m, 7H), 2.90 (m, 1H), 2.73 (m, 1H), 2.50 (m, 7H), 2.32 (t, 2H, J = 3.9 Hz), 2.10 (m, 2H), 1.60 (m, 2H), 0.98 (t, 3H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 151.1, 144.3, 138.6, 135.5, 133.0, 131.4, 129.0, 128.0, 127.5, 126.2, 125.6, 123.6, 122.9, 121.4, 119.7, 116.0, 112.1, 63.0, 59.5, 56.5, 54.3, 53.0, 49.1, 48.9, 48.1, 35.2, 29.3, 27.2, 19.6, 12.0. MS (EI, [M$^+$]) *m/z* 562; HR-MS (EI) calcd for $C_{35}H_{42}N_6O$: 562.3447, found: 562.3420.

5.2.4. 11-((1-(3-(4-Pyrimidinpiperazin-2-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-*N*-propylnoraporphine (7d)

Yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, 2H, J = 5.4 Hz), 8.07 (d, 1H, J = 7.5 Hz), 7.58 (s, 1H), 7.06 (m, 5H), 6.47 (t, 1H, J = 4.5 Hz), 5.29 (dd, 2H. J = 12.6, 27.6 Hz), 4.44 (t, 2H, J = 6.9 Hz), 3.77 (m, 4H), 3.39 (d, 1H, J = 12.3 Hz), 3.14 (m, 3H), 2.90 (m, 1H), 2.73 (m, 1H), 2.35 (m, 9H), 2.09 (m, 2H),1.58 (m, 2H), 0.96 (t, 3H, J = 7.8 Hz). ^{13}C NMR(100 MHz, $CDCl_3$): δ 161.5, 157.6, 155.1, 144.4, 138.5, 135.3, 133.0, 131.4, 128.0, 127.5, 126.2, 125.6, 123.6, 122.8, 121.4, 112.1, 109.8, 63.0, 59.5, 56.4, 54.5, 52.9, 48.9, 48.1, 43.5, 35.1, 29.2, 27.2, 19.6, 12.0. MS (EI, [M$^+$]) *m/z* 564; HR-MS (EI) calcd for $C_{33}H_{40}N_8O$: 564.3325, found: 564.3325.

5.2.5. 11-((1-(3-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl) methoxy)-*N*-propylnoraporphine (7e)

Yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.4 Hz), 7.75 (s, 1H), 7.05 (m, 9H), 5.30 (dd, 2H, J = 12.6,

28.5 Hz), 4.48 (t, 2H, J = 6.9 Hz), 3.85 (s, 3H), 3.18 (d, 1H, J = 7.8 Hz), 2.99 (m, 11H), 2.59 (m, 7H), 1.63 (m, 2H), 0.97 (t, 3H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 152.1, 144.3, 140.9, 138.5, 135.3, 132.9, 131.4, 128.0, 127.5, 126.2, 125.6, 123.6, 123.2, 123.0, 121.4, 120.9, 118.2, 112.2, 111.1, 63.0, 59.5, 57.5, 56.4, 55.3, 53.3, 50.5, 48.9, 47.6, 35.1, 29.2, 19.5, 12.0. MS (EI, [M$^+$]) m/z 578; HR-MS (EI) calcd for $C_{35}H_{42}N_6O_2$: 578.3373, found: 578.3369.

5.3. 11-((1-(3-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-1*H*-1,2,3-triazol-4-yl) methoxy)-*N*-propylnoraporphine (7f)

A mixture of alkyne **4** (32 mg, 0.10 mmol), CuI (4 mg, 0.02 mmol), and 1-azido-4-chlorobutane (16 mg, 0.12 mmol) in THF (5 mL) was stirred for 5 min. *N*,*N*-Diisopropylethylamine (DIPEA, 0.09 mL, 0.5 mmol) was added slowly, and the mixture was stirred at rt overnight. The reaction suspension was filtered and then concentrated. The crude material was chromatographed to afford cyclization product **8** (42 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, 1H, J = 7.5 Hz), 7.56 (s, 1H), 7.17 (m, 2H), 7.03 (dd, 2H, J = 6.9, 8.4 Hz), 6.95 (d, 1H, J = 7.5 Hz), 5.28 (dd, 2H, J = 12.3, 42.6 Hz), 4.38 (t, 2H, J = 6.6, 7.2 Hz), 3.45 (m, 3H), 3.14 (m, 3H), 2.92 (m, 1H), 2.75 (d, 1H, J = 16.2 Hz), 2.50 (m, 3H), 2.07 (m, 2H), 1.78 (m, 2H), 1.61 (m, 2H), 0.97 (dd, 3H, J = 7.2, 7.5 Hz). MS (EI, [M$^+$]) m/z 450.

Compound **8** (27 mg, 0.06 mmol) and NaI (11 mg, 0.07 mmol) were mixed in MeCN (10 mL) and the mixture was refluxed for 1 h. 1-(2-Methoxyphenyl)piperazine (14 mg, 0.07 mmol) and K_2CO_3 (17 mg, 0.12 mmol) were added and the mixture was refluxed overnight. The reaction mixture was concentrated, diluted with CH_2Cl_2 and water. After separation, the organic phase was washed with brine and dried. The solvents were removed and the residue was subjected to chromatography (CH_2Cl_2/MeOH = 25:1, 1% NH_4OH) to give final compound **15** as a colorless oil (20 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, 1H, J = 8.4 Hz), 7.57 (s, 1H), 7.18 (q, 2H, J = 7.6 Hz), 6.94 (m, 7H), 5.29 (dd, 2H, J = 12.0, 29.7 Hz), 4.38 (t, 2H, J = 6.9 Hz), 3.85 (s, 3H), 3.36 (dd, 1H, J = 7.5, 3.0 Hz), 3.14 (m, 7H), 2.90 (m, 1H), 2.74 (m, 1H), 2.53 (m, 4H), 2.43 (m, 4H), 2.02 (m, 3H), 1.63 (m, 4H), 0.97 (t, 3H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 152.2, 144.5, 141.1, 138.6, 135.5, 133.0, 131.4, 128.0, 127.5, 126.2, 125.5, 123.6, 122.9, 122.3, 121.4, 120.9, 118.1, 112.1, 111.0, 63.1, 59.5, 57.6, 56.5, 55.3, 53.4, 50.5, 50.2, 48.9, 35.2, 29.3, 28.2, 23.7, 19.6, 12.0. MS (EI, [M$^+$]) m/z 606; HR-MS (EI) calcd for $C_{37}H_{46}N_6O_2$: 606.3678, found: 606.3682.

5.4. General procedure for preparation of alkynes 10a–d

An appropriate arylpiperazines (1.0 equiv), alkynyl tosylate (1.0 equiv), K_2CO_3 (2.0 equiv) and sodium iodide (cat.) were dissolved in acetone. The resulting mixture was refluxed overnight. The solvent was removed, and the crude material was dissolved in CH_2Cl_2 and water. After filtration, the solvent was removed and the residue was subjected to chromatography to give corresponding alkynes **10a–d**.

5.4.1. 1-(2-Methoxyphenyl)-4-(hex-5-ynyl)piperazine (10a)

Yield 95%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (m, 4H), 3.83 (s, 3H), 3.08 (br s, 4H), 2.63 (br s, 4H), 2.39 (m, 2H), 2.22 (m, 2H), 1.94 (t, 1H, J = 1.2 Hz), 1.60 (m, 4H).

5.4.2. 1-(2-Methoxyphenyl)-4-(pent-4-ynyl)piperazine (10b)

Yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (m, 4H), 3.86 (s, 3H), 3.09 (br s, 4H), 2.66 (br s, 4H), 2.51 (m, 2H), 2.25 (m, 2H), 1.95 (m, 1H), 1.77 (m, 2H).

5.4.3. 1-(2-Methoxyphenyl)-4-(but-3-ynyl)piperazine (10c)

Yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (m, 4H), 3.86 (s, 3H), 3.10 (br s, 4H), 2.68 (m, 6H), 2.42 (m, 2H), 1.99 (m, 1H).

5.4.4. 1-(2-Methoxyphenyl)-4-(prop-2-ynyl)piperazine (10d)

Yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (m, 4H), 3.86 (s, 3H), 3.36 (d, 2H, J = 2.7 Hz), 3.13 (br s, 4H), 2.78 (m, 4H), 2.72 (t, 1H, J = 2.4 Hz).

5.5. General procedure for synthesis of aporlogues 11a–d by Click reaction

The procedure is same as that for preparation of aporlogues **7a–e**.

5.5.1. 11-(3-(4-((4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl) propoxy)-*N*-propylnoraporphine (11a)

Yield 95%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, 1H, J = 7.5 Hz), 7.13 (m, 4H), 6.94 (m, 4H), 6.85 (d, 2H, J = 8.1 Hz), 4.50 (m, 2H), 4.16 (m, 1H), 3.85 (s, 3H), 3.83 (m, 1H), 3.38 (d, 1H, J = 12.9 Hz), 3.15 (m, 7H), 2.93 (m, 2H), 2.74 (m, 7H), 2.43 (m, 6H), 1.65 (br s, 6H), 0.98 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 152.1, 147.6, 140.9, 138.5, 135.4, 133.1, 131.4, 128.0, 127.6, 126.1, 125.7, 123.5, 123.0, 121.4, 121.3, 120.9, 118.2, 112.0, 111.0, 65.1, 59.6, 58.2, 56.4, 55.3, 53.3, 50.1, 48.9, 46.9, 35.1, 30.0, 29.2, 27.2, 25.9, 25.3, 19.5, 12.0. MS (EI, [M$^+$]) m/z 634; HR-MS (EI) calcd for $C_{39}H_{50}N_6O_2$: 634.3995, found: 634.3996.

5.5.2. 11-(3-(4-((4-(2-Methoxyphenyl)piperazin-1-yl)propyl)-1*H*-1,2,3-triazol-1-yl) propoxy)-*N*-propylnoraporphine (11b)

Yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.4 Hz,), 7.04 (m, 10H), 4.53 (m, 2H), 4.16 (m, 1H), 3.85 (s, 3H), 3.84 (m, 1H), 3.35 (m, 1H), 3.15 (m, 7H), 2.91 (m,1H), 2.72 (m, 8H), 2.45 (m, 6H), 1.88 (m, 2H), 1.62 (m, 2H), 0.97 (t, 3H, J = 7.8 Hz). ^{13}C NMR(100 MHz, $CDCl_3$) δ 155.4, 152.2, 147.6, 141.2, 138.6, 135.6, 133.2, 131.4, 128.0, 127.6, 126.0, 125.6, 123.5, 122.9, 121.3, 120.9, 118.1, 111.9, 111.1, 65.0, 59.6, 57.8, 56.5, 55.3, 53.4, 50.5, 48.9, 46.9, 35.2, 30.0, 29.4, 26.6, 23.5, 19.6, 12.1. MS (EI, [M$^+$]) m/z 620; HR-MS (EI) calcd for $C_{38}H_{48}N_6O_2$: 620.3839, found: 620.3813.

5.5.3. 11-(3-(4-((4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)-1*H*-1,2,3-triazol-1-yl) propoxy)-*N*-propylnoraporphine (11c)

Yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.4 Hz), 7.04 (m, 10H), 4.52 (m, 2H), 4.16 (m, 1H), 3.85 (s, 3H), 3.84 (m, 1H), 3.38 (m, 1H), 3.15 (m, 7H), 2.91 (m,3H), 2.76 (m, 6H), 2.45 (m, 6H), 1.62 (m, 2H), 0.97 (t, 3H, J = 7.8 Hz,). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.1, 145.9, 141.1, 138.5, 135.5, 133.2, 131.4, 128.0, 127.6, 126.0, 125.6, 123.4, 122.9, 121.8, 121.3, 120.9, 118.1, 111.8, 111.0, 64.9, 59.5, 57.8, 56.5, 55.3, 53.2, 50.5, 48.9, 46.9, 35.2, 30.0, 29.3, 23.2, 19.6, 12.0. MS (EI, [M$^+$]) m/z 606; HR-MS (EI) calcd for $C_{37}H_{46}N_6O_2$: 606.3682, found: 606.3685.

5.5.4. 11-(3-(4-((4-(2-Methoxyphenyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl) propoxy)-*N*-propylnoraporphine (11d)

Yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.4 Hz), 7.04 (m, 10H), 4.55 (m, 2H), 4.16 (m, 1H), 3.85 (s, 3H), 3.84 (m, 1H), 3.70 (s, 2H), 3.38 (m, 1H), 3.15 (m, 7H), 2.91 (m, 1H), 2.73 (m, 5H), 2.50 (m, 4H), 2.21 (m, 1H), 1.62 (m, 2H), 0.97 (t, 3H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.1, 143.8, 141.1, 138.5, 135.5, 133.2, 131.4, 128.0, 127.6, 126.0, 125.6, 123.5, 123.3, 122.9, 121.9, 121.4, 120.9, 118.1, 111.9, 111.0, 64.9, 59.6, 56.5, 55.3, 53.2, 53.0, 50.4, 48.9, 47.0, 35.2, 29.9, 29.3, 19.6, 12.0. MS (EI, [M$^+$]) m/z 592; HR-MS (EI) calcd for $C_{36}H_{44}N_6O_2$: 592.3526, found: 592.3532.

5.6. Preparation of 11-*O*-(3-azidopropyl)-*N*-propylnoraporphine (13)

To a solution of 50% aq NaOH (4 mL), 11-hydroxyl-*N*-propylnoraporphine **5** (30 mg, 0.10 mmol), and 1-bromo-3-chloropropane (0.03 mL, 0.30 mmol), a catalytic amount of tetrabutylammonium bromide (TBAB) was added. The mixture was stirred at rt for 1 h, and then diluted with EtOAc. The organic phase was washed with brine, and then dried. The solvents were removed and the residue was subjected to chromatography (petroleum ether/EtOAc = 3:1, 1% Et_3N) to give compound **13** as yellow oil (35 mg, 92%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (m, 1H), 7.39 (m, 2H), 7.25 (m, 1H), 7.11 (m, 2H), 4.48 (m, 1H), 4.28 (m, 1H), 3.95 (m, 2H), 3.57 (d, 1H, J = 12.6 Hz), 3.33 (m, 3H), 3.11 (m, 1H), 2.96 (m, 1H), 2.70 (m, 3H), 2.48 (m, 2H), 1.82 (m, 2H), 1.18 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 138.6, 135.5, 133.0, 131.5, 127.8, 127.4, 126.0, 125.6, 123.4, 121.0, 111.5, 65.0, 59.5, 56.6, 48.9, 41.7, 35.3, 32.3, 29.4, 19.6, 12.1. MS (EI, [M^+]) *m/z* 355; HR-MS (EI) calcd for $C_{22}H_{26}NOCl$: 355.1703, found: 355.1700.

5.7. Preparation of 3-(3-(*N*-propylnoraporphin-11-yloxy)propylamino)propan-1-ol (14)

Chloride **13** (43 mg, 0.12 mmol) and 3-aminopropan-1-ol (90 mg, 1.20 mmol) were mixed in *n*-BuOH (8 mL) and the mixture was refluxed for 24 h. The solvent was evaporated and the residue was chromatographed (CH_2Cl_2/MeOH = 20:1, 1% NH_4OH) to give alcohol **14** as brown oil (40 mg, 83%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, 1H, J = 7.8 Hz), 7.18 (m, 2H), 7.04 (d, 1H, J = 7.8 Hz), 6.90 (m, 2H), 4.19 (m, 1H), 3.98 (m, 1H), 3.77 (t, 2H, J = 5.1, 5.4 Hz), 3.36 (d, 1H, J = 11.4 Hz), 3.13 (m, 3H), 2.85 (m, 8H), 2.51 (m, 3H), 2.0 (m, 2H), 1.65 (m, 4H), 0.97 (dd, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 138.5, 135.5, 132.9, 131.5, 127.9, 127.4, 126.1, 125.6, 123.3, 120.9, 111.5, 66.8, 64.2, 59.5, 56.6, 49.9, 48.9, 47.0, 35.3, 30.5, 29.5, 29.4, 19.6, 12.1. MS (EI, [M^+]) *m/z* 394; HR-MS (EI) calcd for $C_{25}H_{34}N_2O_2$: 394.2620, found: 394.2612.

5.8. Preparation of 11-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butoxy)-*N*-propylnoraporphine (15)

To a solution of 50% aq NaOH (4 mL), 11-hydroxy-aporphine **5** (28 mg, 0.10 mmol), and 1-bromo-4-chlorobutane (51 mg, 0.30 mmol), was added a catalytic amount of tetrabutylammonium bromide. The reaction was stirred at rt for 1 h and then diluted with EtOAc. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed (petroleum ether/EtOAc = 3:1, 1% Et_3N) to give chloride **12** as yellow oil (30 mg, 82%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 1H, J = 7.5 Hz), 7.21 (m, 2H), 7.06 (d, 1H, J = 7.2 Hz), 6.91 (m, 2H), 4.16 (m, 1H), 3.97 (m, 1H), 3.69 (m, 2H), 3.35 (m, 1H), 3.14 (m, 3H), 2.93 (m, 1H), 2.77 (d, 1H, J = 16.2 Hz), 2.52 (m, 3H), 2.01 (s, 4H), 1.62 (m, 2H), 0.98 (t, 3H, J = 7.2 Hz).

Chloride **12** (30 mg, 0.08 mmol) and NaI (14 mg, 0.09 mmol) were dissolved in MeCN (8 mL) and the mixture was refluxed for 1 h. 1-(2-Methoxyphenyl)piperazine (18 mg, 0.09 mmol) and K_2CO_3 (22 mg, 0.16 mmol) were added. The mixture was refluxed overnight. After removal of solvents, the mixture was diluted with CH_2Cl_2 and water, and then washed with brine and dried. After evaporation of the solvent, the residue was chromatographed (CH_2Cl_2/MeOH = 40:1, 1% NH_4OH) to give aporlogue **15** as colorless oil (33 mg, 80%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.4 Hz), 7.04 (m, 10H), 4.17 (m, 1H), 4.12 (m, 1H), 3.98 (s, 3H), 3.39 (m, 1H), 3.15 (m, 7H), 2.93 (m,1H), 2.65 (m, 5H), 2.51 (m, 4H), 1.91 (m, 2H), 1.85 (m, 2H), 1.67 (m, 2H), 0.97 (t, 3H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 152.2, 141.2, 138.4, 135.4, 132.8, 131.6, 127.8, 127.3, 126.3, 125.5, 123.2, 122.8, 120.9, 120.6, 120.6, 118.1, 111.4, 111.0, 68.4, 59.5, 58.3, 56.2, 55.3, 53.3, 50.5, 48.9, 35.3, 29.3, 27.4, 23.5, 19.6, 12.1. MS (EI, [M^+]) *m/z* 525; HR-MS (EI) calcd for $C_{34}H_{43}N_3O_2$: 525.3355, found: 525.3333.

5.9. Preparation of *N*-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)-*N*-(3-(*N*-propylnoraporphin-11-yloxy)-propyl)methanesulfonamide (17)

To a solution of alcohol **14** (40 mg, 0.10 mmol) and Et_3N (0.06 mL, 0.41 mmol) in CH_2Cl_2 (10 mL), was added MsCl (0.025 mL, 0.30 mmol) slowly at 0 °C. The reaction was stirred at the same temperature for 15 min and then at rt for 2 h. The reaction mixture was washed with NH_4Cl, $NaHCO_3$ and brine subsequently. After removal of the solvent, the residue was subjected to chromatography (CH_2Cl_2/MeOH = 60:1, 1% NH_4OH) to give mesylate **16** as red oil (45 mg, 82%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, 1H, J = 7.8 Hz), 7.18 (m, 2H), 7.05 (d, 1H, J = 7.8 Hz), 6.90 (dd, 2H, J = 7.8 Hz, 11.7 Hz), 4.19 (m, 3H), 3.94 (m, 1H), 3.06–3.43 (m, 6H), 2.97 (s, 3H), 2.90 (m, 1H), 2.80 (s, 3H), 2.75 (m, 1H), 2.36–2.63 (m, 3H), 2.15 (m, 2H), 1.94 (m, 2H), 1.61 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz).

Mesylate **16** (45 mg, 0.08 mmol) and NaI (18 mg, 0.12 mmol) were mixed in MeCN (8 mL) and the resulting mixture was refluxed for 1 h. 1-(2-Methoxyphenyl)piperazine (18 mg, 0.09 mmol) and K_2CO_3 (22 mg, 0.16 mmol) were added and the mixture continued to reflux overnight. The reaction mixture was diluted with CH_2Cl_2 and water. After separation, the organic phase was washed with brine, and dried. The solvent was evaporated and the residue was chromatographed (CH_2Cl_2/MeOH = 30:1, 1% NH_4OH) to give aporlogue **17** as yellow oil (41 mg, 80%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 8.4 Hz,), 6.83-7.23 (m, 9H), 4.25 (m, 1H), 3.98 (m, 1H), 3.90 (s, 3H), 3.45 (m, 3H), 3.21 (m, 9H), 2.95 (m,1H), 2.90 (s, 3H), 2.85 (m, 1H), 2.60 (m, 5H), 2.40 (m, 4H), 2.15 (m, 2H), 1.75 (m, 2H), 1.67 (m, 2H), 0.97 (t, 3H, J = 7.8 Hz). ^{13}C NMR(100 MHz, $CDCl_3$): δ 156.0, 152.2, 141.2, 138.5, 135.5, 133.0, 131.5, 127.9, 127.4, 126.1, 125.6, 123.3, 122.8, 121.1, 120.9, 118.1, 111.5, 111.2, 65.7, 59.5, 56.5, 55.3, 53.3, 50.5, 48.9, 46.8, 45.7, 37.8, 35.3, 29.3, 26.0, 19.6, 12.0. MS (EI, [M+]) *m/z* 646; HR-MS (EI) calcd for $C_{37}H_{50}N_4O_4S$: 646.3553, found: 646.3640.

5.10. Binding assay of new compounds at the D_1, D_2, D_3 and 5-HT_{1A}, 5-HT_{2A} receptors

The affinity of compounds to the D_1, D_2 and D_3 dopamine receptors, and the 5-HT_{1A} and 5-HT_{2A} receptors were determined by competition binding assay. Membrane homogenates of 5-HT_{1A}, 5-HT_{2A}-CHO cells, D_1-, D_2-, and D_3-HEK293 cells were prepared as described previously. Duplicated tubes were incubated at 30 °C for 50 min with increasing concentrations (1 nM–100 μM) of respective compound and with 0.7 nM [^{3}H]8-OH-DPAT (for 5-HT_{1A}), [^{3}H]Ketanserin (for 5-HT_{2A}), [^{3}H]SCH23390 (for D_1), or [^{3}H]Spiperone (for D_2 and D_3) in a final volume of 200 μL binding buffer containing 50 mM Tris, 4 mM $MgCl_2$, pH 7.4. Nonspecific binding was determined by parallel incubations with either 10 μM WAY100635 for 5-HT_{1A}, Ketanserin for 5-HT_{2A}, SCH23390 for D_1 or Spiperone for D_2, D_3 dopamine receptors, respectively. The reaction was started by addition of membranes (15 μg/tube) and stopped by rapid filtration through Whatman GF/B glass fiber filter and subsequent washing with cold buffer (50 mM Tris, 5 mM ethylenediaminetetraacetic acid (EDTA, pH 7.4) using a Brandel 24-well cell harvester. Scintillation cocktail was added and the radioactivity was determined in a MicroBeta liquid scintillation counter. The IC_{50} and K_i values were calculated by nonlinear regression (PRISM, Graphpad, San Diego, CA) using a sigmoidal function.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.01.053.

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