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Synthesis, identification and molecular docking studies of *N*-functionalized piperidine derivatives linked to 1,2,3-triazole ring

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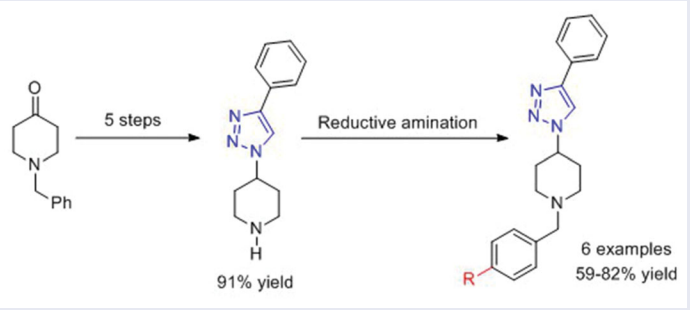
ABSTRACT

New derivatives of piperidine bearing a 1,2,3-triazole ring designed and synthesized smoothly over six steps from *N*-protected piperidone-4-one. These steps included reduction of the carbonyl group/tosylation of the resulting alcohol providing tosyl derivative in a good yield, followed by nucleophilic substitution and Cu-catalysed azide-alkyne cycloaddition. By removing the protecting group and functionalizing amine group *via* reductive amination gave the desired design in moderate to very good yields. Molecular modeling studies of these compounds predicted possible binding modes into the active site of dopamine receptor D2.

GRAPHICAL ABSTRACT



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KEYWORDS
DRD2 binding; ligand docking; piperidine; reductive amination; triazole

Introduction

Piperidine is a saturated six-membered heterocyclic ring bearing one nitrogen atom. It is present in a variety of active synthetic pharmaceutical drugs. For example, paroxetine shows a significant antidepressant activity and serotonin reuptake inhibitor. Clopidogrel is used as a blood-clotting inhibitor, tadalafil as a PDE5 inhibitor and treatment of erectile dysfunction. Methylphenidate shows a remarkable psychostimulant for treating ADHD, and *N*-butyl-deoxyynojirimycin uses as a medication for Gaucher disease. Also, mefloquine is employed as a malarial drug.[1] Piperidine ring is also found in many alkaloid natural products such as (*S*)-coniine, (*S*)-anabasine, (–)-swainsonine and quinine (Figure 1).

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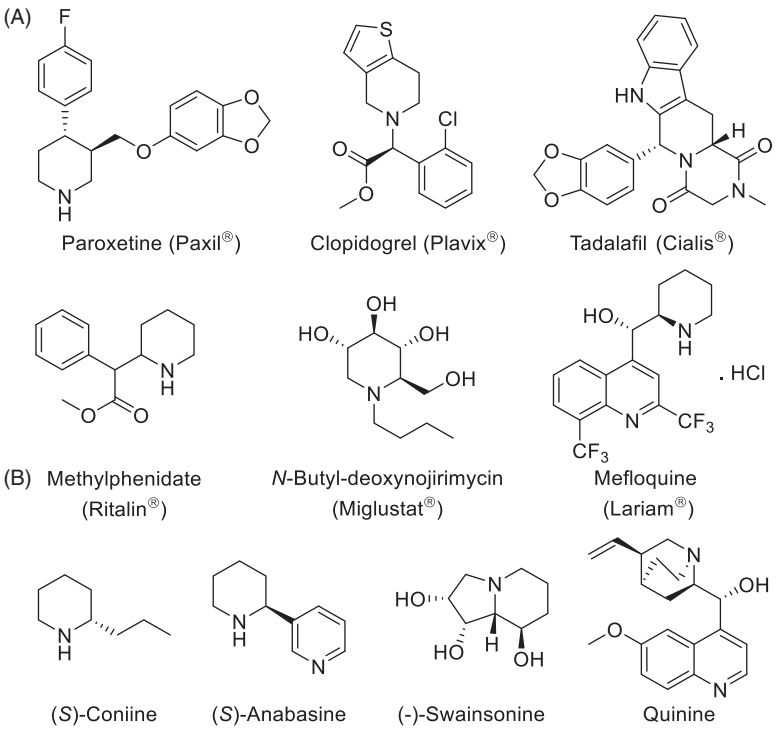


Figure 1. Some compounds containing a piperidine ring in their structures. (A) Synthetic pharmaceutical drugs. (B) Alkaloid natural products.

Also, compounds containing a triazole ring usually possess a wide range of biological activities such as anti-herbicide,[2] anti-fungal,[3] anti-HIV activity,[4] anti-allergic[5] and anti-influenza.[6] The interest in this work is combining two essential rings (the piperidine and 1,2,3-triazole) to afford **6**. Following this, product **6** will be functionalized with substituted aromatic rings using a reductive amination reaction, to furnish a new selection of chemical compounds **8.**

Dopamine receptors play a significant role in life functions including emotions, brain reward system and affect movement. They are expressed in the central and periphery nervous system.[7] Dopamine receptors types are D1, D2, D3, D4, and D5 with a specific function of each kind. Dopamine receptor D2 (DRD2) has a role in attention, memory, sleep, learning and locomotion.[8] The two primary conditions that are targeting dopamine receptors are schizophrenia and Parkinson disease. Most of the antipsychotic's antagonists bind and block DRD2. Piperidine derivatives have been shown as a dopaminergic stabilizer to treat Parkinson disease.[9,10] In this work, a set of piperidine derivatives were synthesized to study their binding modes with DRD2.

Results and discussion

Chemistry

In our work, it was attempted to design and prepare new piperidine-linked triazoles and benzyl derivatives **8a–f** with different R groups that have different chemical

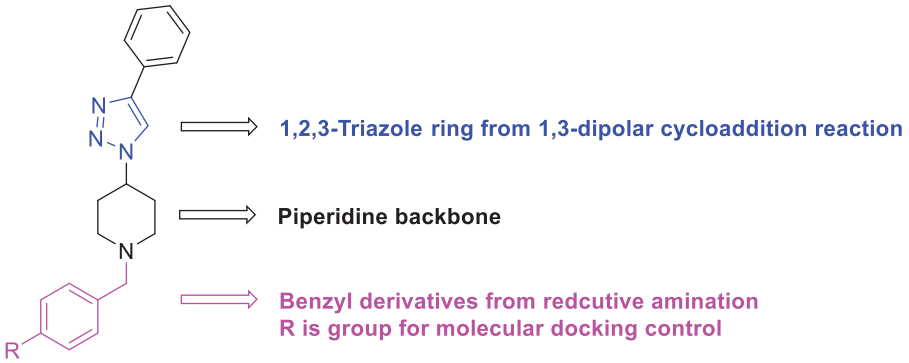
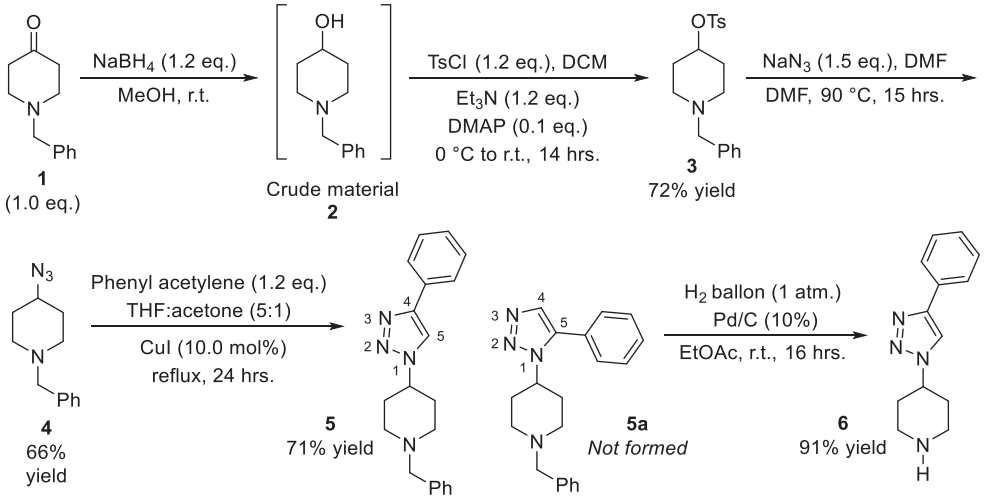


Figure 2. The design strategy for new piperidine-linked triazoles and benzyl derivatives **8a–f**.



Scheme 1. Outline of the synthesis of amine intermediate **6** over five steps from ketone **1**.

properties to study their binding with DRD2 using a molecular docking as described in Figure 2 and Scheme 2.

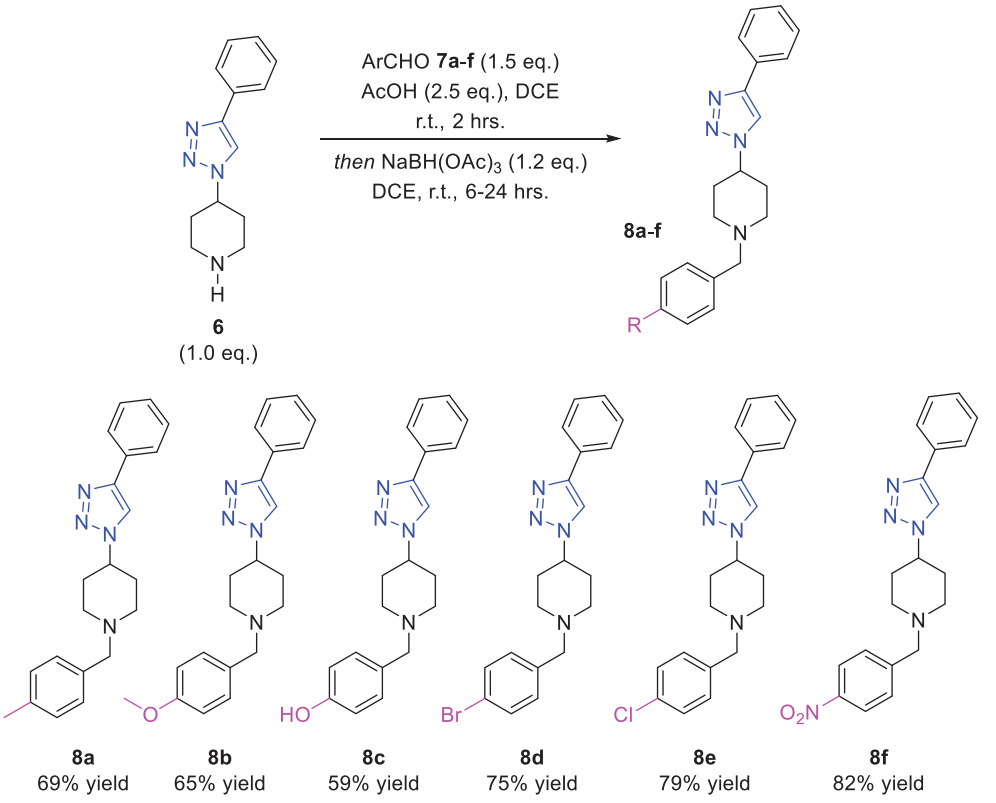
The synthesis of 1-benzyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine derivatives **8a–f** was performed over six sequence steps starting from 1-benzylpiperidin-4-one **1**. From the literature, Denmark and Cresswell have prepared tosyl derivative **3** by nucleophilic substitution of commercially available alcohol **2** with tosyl chloride.[11] While, in our work, ketone **1** was used as a starting material for the preparation of **3** in two steps, which included reduction of **3** with $NaBH_4$ to furnish the corresponding alcohol crude material **2** (Scheme 1). TLC and LCMS showed that there was a full conversion to alcohol **2**. Tosylation of alcohol **2** was then achieved successfully, which gave the tosylate alcohol **3** in good yield (72%). The product **3** can be considered more reactive than **2** toward nucleophilic substitution because of tosyl group is a better leaving group than hydroxyl group. S_N2 displacement of the OTs group at **3** with sodium azide was then performed to provide **4** in 66% yield, which is better than the isolated yield from the literature procedure (48% *vs.* 66%).[12] The starting material **3** was consumed entirely within 15 hours. The azide derivative **4** was confirmed by NMR spectroscopy *via* the

disappearance of the OTs group. FTIR showed an influential absorption band at 2129 cm^{-1}, attributing to the stretch vibrations of the N_3 bond of the azide group at **4**.

The desired product **5** has previously prepared, but it was in a mixture with undesired 1,5-triazole regioisomer **5a** using thermal 1,3-dipolar cycloaddition reaction.[13] In our work, Cu(I)-catalysed 1,3-dipolar cycloaddition reaction was used on **4** with phenylacetylene to afford **5** in good yield (71%). It was noted that there is just one product formed (desired 1,4-regioisomer **5**) in the crude material as judged by ^{1}H NMR spectroscopy. This is due to using CuI as a catalyst, which prevented the formation of the undesired 1,5-triazole regioisomer **5a** as reported in the literature.[14–17]

Furthermore, Funk and coworkers reported that the average chemical shift of C-5 for triazole ring in the 1,4-regioisomers is further upfield ($\delta = 120 \pm 3$ ppm) than C-4 in 1,5-regiosiomers ($\delta = 133 \pm 3$ ppm) due to resonance factor.[18] From this, the structure of the 1,4-regioisomer **5** was further supported by ^{13}C and DEPT NMR experiments (see the Supporting Information), which C-5 signal of the triazole moiety appears at 117.2 ppm (expected range). Following this, deprotection of benzyl group at **5** was accomplished when treated **5** with H_2 over Pd/C, which gave the corresponding amine **6** in excellent yield (91%), and the starting material **5** was consumed within 16 hours.

Reductive amination was then conducted between amine **6** and aldehydes **7a–f** in the presence of $NaBH(OAc)_3$ and AcOH in DCE to provide the desired targets **8a–f** in yields ranging from 59 to 82% (Scheme 2). The ^{1}H NMR spectra of **8a–f** were



Scheme 2. Reductive amination of **6** with aromatic aldehydes **7a–f** to access novel derivatives of piperidine **8a–f**.

characterized by the absence of N–H proton of **6**, and the presence of additional aliphatic, aromatic protons and carbon atoms of substituted benzyl group. It was observed that using aromatic aldehydes bearing electron-withdrawing groups giving the corresponding tertiary amines in better yield than those bearing electron-donating groups in their structures. For example, the aldehyde **6a** affording the desired product **8a** in 69% yield. The decreased yield was obtained when aldehyde **6b** was used, which gave **8b** in 65%. The imine analogues of aldehydes **7a** and **7b** were consumed completely within 5 and 7 hours, respectively (monitored by TLC and HRMS). The use of aldehyde bearing strong donating group (hydroxyl) on the aromatic ring **7c** provided the corresponding tertiary amine **8c** in a lower yield (59%) than aldehydes bearing moderate electron-donating groups (methyl **7a** and methoxy **7b**). The imine analogues of aldehyde **7c** could not be consumed completely within 24 hours. This is explained by the presence of an electron-donating group, which deactivates the carbonyl group of the aldehydes toward the nucleophilic addition by amine **6**.

On the other hand, the reductive amination was tolerant with halogen substituents, such as, chloro and bromo groups on the aromatic ring of aldehydes. This gave the desired tertiary amines in good yields (75% for **8d** and 79% for **8e**). As expected, the use of aromatic aldehydes bearing a strong electron-withdrawing group in their structures will encourage the reductive amination due to increasing the electrophilicity that leading to activate the nucleophilic addition by amine **6**. For example, the use of *p*-nitrobenzaldehyde **7f** afforded the desired product **8f** in very good yield (82%) (Scheme 2).

Molecular docking study

Molecular docking was performed with the crystal structure of D2 dopamine receptor bound to risperidone (6CM4) using AutoDock 4.2.6[19] to predict binding modes, orientation and affinities of the synthesized compounds **8a–f**. Estimated inhibition constant (Ki, nM), docking scores (estimated free energy of binding ΔG°, kcal/mol; binding energy includes hydrogen bonding, π–π interactions, Van der Waals forces, etc.) and possible binding residues of the docking compounds were compared as shown in Table 1. All the docked compounds were occupied the orthosteric site of DRD2 with different orientations. Results from docking scores predicted that compound **8f** has the lowest binding energy in comparison to the other compounds and that is due to the introducing NO_2 group that reduces the final intermolecular energy, vdW, Hbond and dissolve energy comparing to other compounds.

Possible binding residues of the compounds **8a–f** using the lowest energy from the largest cluster were compared. Best solutions of the compounds **8a–f** are predicted to interact with similar binding residues D114, C118, S197, W386, F390 and T412. In comparison to the crystal structure of DRD2 with risperidone bound, the residues D114, C118, S197, W386, F390 and T412 were found to interact with risperidone. Moreover, Wang *et al.* found that D114, W386 and T412 reduced risperidone binding affinity by more than tenfold[20] that suggests these residues are essential in binding DRD2 inhibitors. Furthermore, compound **8f** showed a possible hydrogen bond between one of the nitro group oxygen and sidechain of T412 (distance: 1.9 Å). Compound **8b** predicted to have one hydrogen bond between OCH_3

Table 1. Docking scores (estimated free energy of binding ΔG°, kcal/mol) and the estimated inhibition constant (Ki, nM) of the synthesized compounds **8a–f** with D2 dopamine receptor (6CM4).

Compounds	Interacting residues	Estimated free energy of binding ΔG° (kcal/mol)	Estimated inhibition constant, Ki (nM)
8a	V91, L94, F110, D114, V115, C118, T119, A122, I184, F189, S193, S197, F198, F382, W386, F389, F390, T412, W413, W416	−10.78	12.44
8b	D114, V115, C118, T119, A122, F189, S193, S197, F198, F382, W386, F389, F390, H393, Y408, T412	−10.50	19.98
8c	D114, V115, C118, T119, A122, I184, S193, S197, F198, F382, W386, F389, F390, H393, Y408, T412, Y416	−10.28	29.17
8d	V91, L94, W100, F110, D114, C118, T119, I184, S197, W386, F390, F398, T412, W413, Y416	−11.11	7.17
8e	V91, L94, W100, F110, D114, C118, T119, I184, S197, W386, F390, F398, T412, W413, Y416	−10.89	10.46
8f	D114, V115, C118, A122, F189, S193, S197, F198, F382, W386, F389, F390, H393, Y408, T412	−11.20	6.2
Risperidone	W100, F110, D114, V115, C118, T119, A122, S193, S197, F198, F382, W386, F390, F389, Y408, T412, Y416		

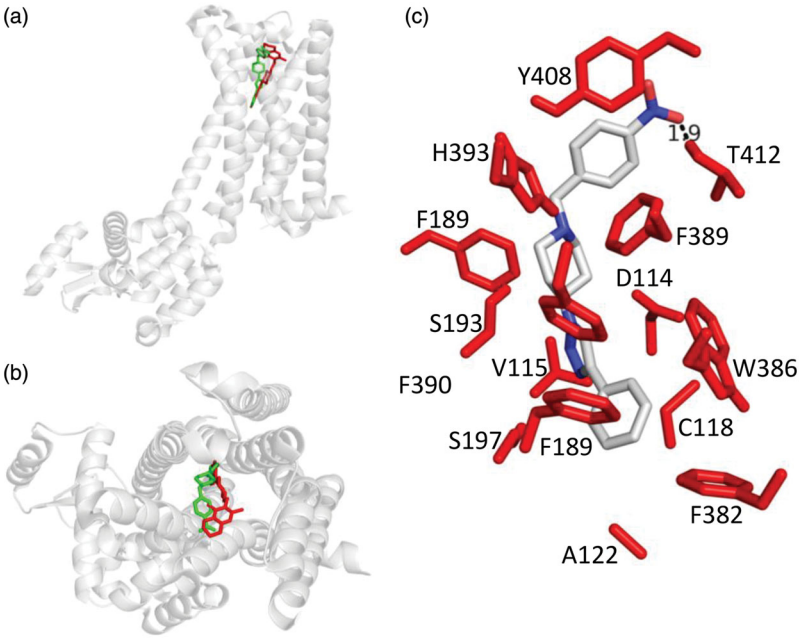


Figure 3. Docking pose of the compound **8f** at the DRD2 crystal structure. (a) and (b) Panels show an extracellular sideview and top of DRD2 crystal structure in gray cartoon representation, respectively. Red and green sticks represent risperidone and compound **8f**, respectively. (c) DRD2 sidechain residues at 4 Å cut-off from compound **8f** are shown as red sticks. Compound **8f** is colored with white, blue and red that represent carbon, nitrogen and oxygen atoms, respectively.

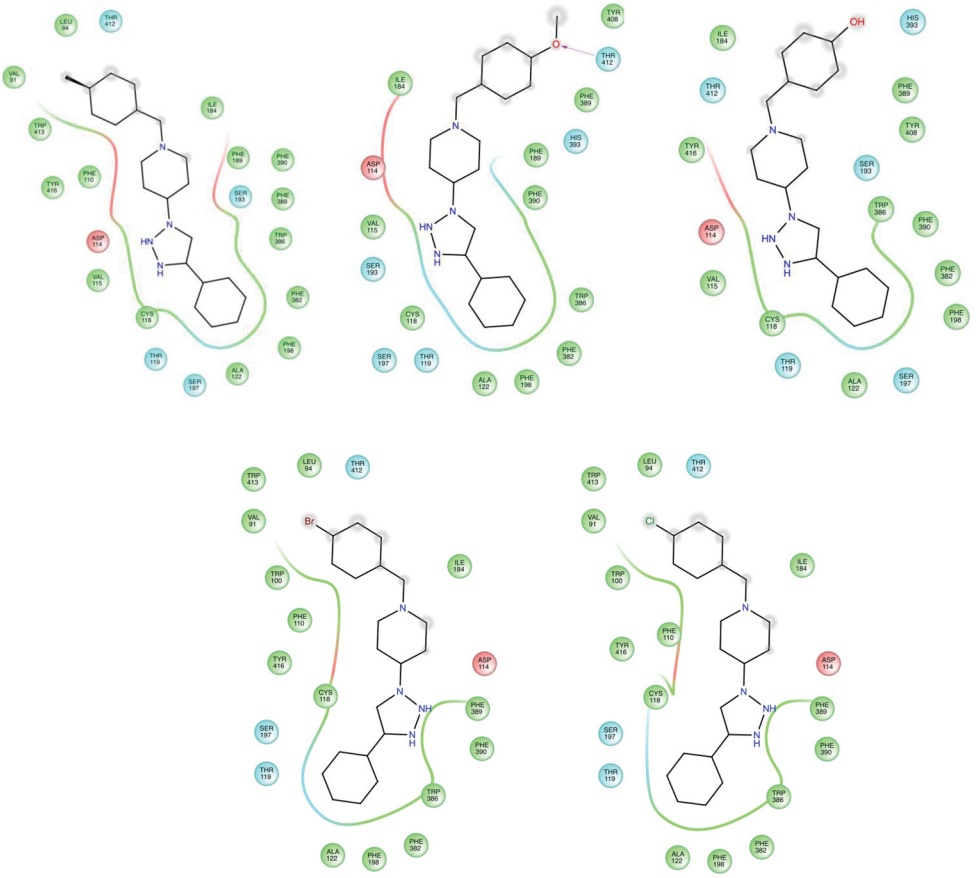


Figure 4. Docking solutions for compounds **8a–e** in the active site of DRD2 showing 2 D ligand-receptor interactions.

group and sidechain of T412 (distance: 1.9 Å). In addition, sidechain of D114 is close to 1,2,3-triazole ring of the docked compounds which rise the possibility of a salt-bridge interaction. It is worth to mention that D114 is part of salt-bridge interaction with the tertiary amine of risperidone,[20] see Figure 3 for docking pose of compound **8f**. Interaction of compounds **8a–e** with the binding site of DRD2 is illustrated in Figure 4.

Conclusion

A series of novel 1-benzyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine derivatives **8a–f** were prepared successfully in yields ranging from 59 to 82%. Molecular docking showed that the prepared compounds could fit in the active site of the DRD2 receptor. Best binding modes of the docked compounds suggested the following binding residues (D114, C118, S197, W386, F390 and T412) that might be important as a useful template for further development of the DRD2 that could be used to improve the efficiency of DRD2 inhibitors

Experimental section

Chemistry

General procedure for reductive amination to synthesize 1-benzyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine derivatives 8a–f

The crude material of amine **6** (350 mg, 1.5 mmol, 1.0 eq.) was dissolved in DCE (20 mL) in a 100 mL round bottom flask. Aromatic aldehydes **7a–f** (2.25 mmol, 1.5 eq.) and acetic acid (215 mL, 3.75 mmol, 2.5 eq.) were then added and the resulting mixture stirred at room temperature for 2 hours. A solution of sodium triacetoxyborohydride (381 mg, 1.8 mmol, 1.2 eq.) in DCE (10 mL) was added dropwise. The reaction mixture was stirred overnight (14 hours) at room temperature then washed with 1.0 M HCl (2×15 mL). The aqueous phase was basified using saturated aqueous $NaHCO_3$ (15 mL) solution then extracted with ethyl acetate (2×15 mL), washed with water (2×15 mL), and the combined extracts, dried over anhydrous $MgSO_4$, filtered and solvent removed *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate) provided the desired products **8a**-**f**.

1-(4-Methylbenzyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine (8a)

General procedure of reductive amination was followed to provide **8a** as a yellow oil (344 mg, 1 mmol, 69%); IR $\nu_{max}(CHCl_3)/cm^{-1}$ = 3115 ($C–H_{alkene}$), 3071, 3056, 3022 ($C–H_{aro}$), 2971, 2952, 2849 ($C–H_{ali}$), 1648 (C = C); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.67–7.61 (2H, m), 7.51–7.44 (2H, m), 7.34–7.27 (5H, m), 6.06 (1H, s), 3.47 (2H, s), 3.41–3.37 (1H, m), 2.69–2.64 (2H, m), 2.39 (3H, s), 2.32–2.27 (2H, m), 1.85–1.75 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.1, 144.6, 138.3, 134.4, 133.0, 129.2, 128.3, 127.2, 126.2, 117.1, 62.4, 57.2, 51.2, 30.2, 21.0; HRMS (ESI) *m/z*, calculated for $[C_{21}H_{25}N_4^+]$ $[M + H]^+$ 333.2074, found 333.2076.

Molecular docking study

ChemDraw was used to draw, set charges and run energy minimization of the compounds **8a–f** and the output files were saved mol2 format. Crystal structure of DRD2 bound to Risperidone (PDB ID: 6CM4; resolution: 2.8 Å) was retrieved from protein data bank.[21] Ligand docking of compounds **8a**-**f** into the crystal structure of DRD2 was carried out using AutoDock 4.2.6.[19] Each of these compounds in the PDBQT format was docked separately into the active site of DRD2. All calculations for protein-ligand docking were carried out using default settings. A grid box with the dimensions of X: −16.098, Y: 9.428 and Z: −15.288 A° with a default grid spacing was used. The best conformation was selected with the lowest docked energy from the largest cluster. The interactions between docked compounds and DRD2 receptor were analyzed.

The entire experimental section can be found in the through the "Supplementary Content" section of this article's webpage, including spectral data and scanned spectra (^1H and ^{13}C NMR) of all compounds.

Disclosure statement

The authors declare no conflict of interest.

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