European Journal of Medicinal Chemistry 86 (2014) 219–234

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and pharmacological investigation of aralkyl diamine derivatives as potential triple reuptake inhibitors

Yong-Yong Zheng [a, 1], Zhi-Jie Weng [a, b, 1], Peng Xie [a], Mei-Yu Zhu [a], Long-Xuan Xing [a], Jian-Qi Li [a, *]

[a] Novel Technology Center of Pharmaceutical Chemistry, Shanghai Institute of Pharmaceutical Industry, 1111 North Zhongshan No. 1 Road, Shanghai 200437, PR China
[b] School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Rd, Shanghai 200240, PR China

ARTICLE INFO

Article history:
Received 25 March 2014
Received in revised form
12 August 2014
Accepted 13 August 2014
Available online 14 August 2014

Keywords:
Aralkyl diamine derivatives
Triple reuptake inhibitory
Monoamine transporters

ABSTRACT

A series of aralkyl diamine derivatives were designed, synthesized, and evaluated for their triple reuptake inhibitory abilities. Compounds **18c** (5-HT, NE, DA, IC_{50} = 389, 69, 238 nM), **36a** (5-HT, NE, DA, IC_{50} = 378, 477, 247 nM), and **36d** (5-HT, NE, DA, IC_{50} = 501, 206, 357 nM) showed *in vivo* activities in the rat forced swim test at 5, 10, and 20 mg/kg PO. **36a** was identified as the most promising candidate in this study. Specifically, **36a** exhibited high selectivity for monoamine transporters over a number of CNS-related targets. Furthermore, **36a** showed a good pharmacokinetic properties and acceptable safety profile in preclinical studies.

1. Introduction

Depression is increasing as a global mental health issue, and this condition can disturb thoughts, feelings, behaviors, and can sometimes lead to suicide [1]. Thus, antidepressants to treat these concerns is of enormous scientific interest [2–5]. Current hypotheses suggest that depression is related to deficiencies of certain neurotransmitters such as serotonin, (5-HT) and norepinephrine (NE) [6].

In particular, onset of action and side effects appear to be a general hurdle, even for the dual reuptake inhibitors. For instance, 5-HT/NE transporters (SNRIs, e.g., venlafaxine, duloxetine and milnacipran, Fig. 1) were reported to exhibit more benign side effect profiles than those of mono-reuptake inhibitors, although they have not been shown to be more efficacious or to have more rapid onset of antidepressant response [7]. Therefore, high efficacy drugs with few side effects should be intensively pursued to identify new therapeutics for treating depression.

To enhance drug efficacy while suppressing unwanted effects, different strategies have been developed, such as the monoamine hypothesis and non-monoamine-based antidepressants [3,8]. Reports suggest that the addition of dopamine (DA) reuptake to 5-HT and NE reuptake may improve efficacy and reduce the time to onset of antidepressant response [9]. In particular, recent experiments suggest that the triple reuptake inhibitors (TRIs), *i.e.* DOV-21947 (EB-1010) [10], PRC200-SS [11], and GSK1360707F [12,13] (Fig. 1), which block the reuptake of 5-HT, NE and DA transporters, offer more rapid onset of action and possess greater efficacy than traditional antidepressants. Therefore, TRIs may be applicable for a broader range of the depressed population [14].

Inspired by these works, reuptake of DA with NE and 5-HT was thought to be a possible solution for producing potent antidepressants. In our previous studies of monoamine transporters, a series of arylalkanol-piperdine derivatives was identified and their triple reuptake inhibition and antidepressant activities were reported [15]. In this study, we designed and synthesized a new series of compounds (Fig. 2) by changing the arylalkanol-piperdine scaffold. We then examined whether monoamine transporter reuptake inhibition was improved by replacing the hydroxyl group at the C1 position in arylalkanol-piperdine derivatives with heterocycles (such as cyclic amines). Subsequently, we replaced the 3-benzo[*b*]thiophene moiety at the C1 position with other aromatic substituents to understand the effect of different aromatic ring substitutions on the affinity and selectivity for different monoamine transporters. Finally, we explored the role of different substituents at the C3 position to produce aralkyl diamine compounds. From

* Corresponding author.
E-mail address: lijianqb@126.com (J.-Q. Li).
[1] Authors Yong-Yong Zheng and Zhi-Jie Weng contributed equally.

http://dx.doi.org/10.1016/j.ejmech.2014.08.045
0223-5234/

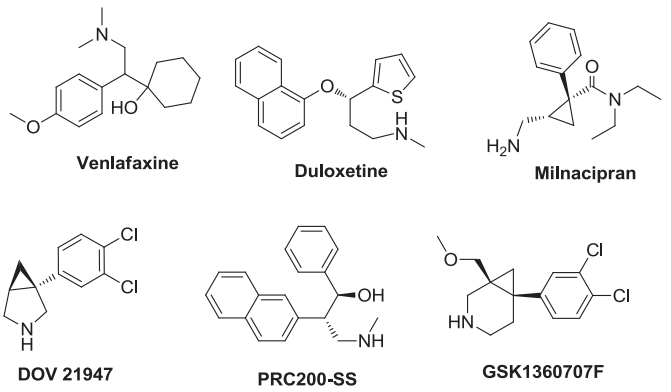


Fig. 1. Molecular structures of selected clinical and preclinical antidepressants.

these studies, we have discovered a series of compounds that potently inhibit the reuptake of 5-HT, NE, and DA transporters.

2. Results and discussion

2.1. Chemistry

Synthetic access to the novel aralkyl diamine derivatives was achieved by seven synthetic routes as illustrated in Schemes 1–7. The synthesis of 4-benzyl-1,2,3,6-tetrahydropyridine derivatives **6** and **12** are depicted in Scheme 1. Briefly, a commercially available 4-benzyl-1,2,3,6-tetrahydropyridine **1** with 3-acetylbenzo[b]thiophene in the presence of paraformaldehyde by the Mannich reaction afforded the intermediate aryl alkaneone amine derivatives **2** (73% yield). Then compound **2** was reduced with sodium borohydride into the corresponding alcohol **3** (89% yield). A strategy to introduce a heterocycle at the C1 position was then applied. Activation of alcohol **3** with 4-toluenesulfonyl chloride in the presence of *N*,*N*-diisopropylethylamine at room temperature provided compound **4**, which was immediately coupled with cyclic amines **5** to yield **6a**–**d** by nucleophilic substitution in moderate yields (47–60% yield). An alternative synthesis was employed for analogs of **12a**–**b**, for which the corresponding aryl ketone was unavailable. In this case, ketone **8** was prepared through Friedel–Crafts acylation reactions. The acylation of the aromatic ring with 3-chloropropanoyl chloride **7** was catalyzed by aluminum chloride. Then **8** was treated with **1** via the SN2 mechanism, yielding **9** (77–82% yield), which were then treated successively with sodium borohydride, 4-toluenesulfonyl chloride and pyrrolidine provided the target compounds **12a**–**b**.

The C3 cyclic amine substituted compounds **18a**–**e** (Scheme 2) were obtained by substitution of aryl ketone **13** with cyclic amines **5** in the C3 position, and subsequent reduction, activation, and substitution with cyclic amines **17**. Synthesis of the corresponding C3 *N*-methyl-1-phenylmethanamine substitution compounds **23a**–**b** and **27a**–**b** is shown in Schemes 3 and 4. Treating aryl ketone **19** or **8** with N-methyl-1-phenylmethanamine resulted in C3 substitution. Furthermore, the target compounds **23a**–**b** and **27a**–**b** were obtained by reduction, activation and substitution. Then the N-methylamine derivative **28** was obtained through *N*-debenzylation of **23b** (81% yield).

Finally, the preparation of the desired *N*,*N*-dimethylamine derivatives **32a**–**m** is outlined in Scheme 5. The key precursors **30** were obtained via a Mannich reaction of aryl ketone **19** with dimethylamine, and then reduction. Then, **30** could be activated with 4-toluenesulfonyl chloride and substituted with cyclic amines **5** to provide target compounds **32a**–**m**. The desired compounds **36a**–**e** and **40** were offered by substitution, reduction, activation, and substitution with cyclic amines (Schemes 6 and 7).

2.2. Biology

All synthesized compounds were tested for their inhibition of 5-HT, NE and DA reuptake. The plasmids were transfected into CHO cells, which encoded the human 5-HT transporter (hSERT), NE transporter (hNET), and DA transporter (hDAT). Then, the stably expressed cell strains were selected and used for the uptake test. ^{3}H-5-HT, ^{3}H-DA, ^{3}H-NE were obtained from PerkinElmer Life Sciences (LesUlis, France). All compounds were initially screened at 10 μM concentration, and selective compounds (inhibition >90%) were then assayed to obtain their IC_{50} values. The triple reuptake inhibitor DOV-21947 was used as a reference. Detailed results are summarized in Table 1.

For the C3 substituent 4-benzyl-1,2,3,6-tetrahydropyridine derivatives, inhibition of 5-HT, NE and DA reuptake were explored (Table 1, **6a**–**d**, **12a**–**b**). Compound **6a** bearing pyrrolidine and 3-benzo[b]thiophene moieties exhibited high potency for all three monoamine transporters, whereas piperidine (**6b**), morpholine (**6c**) and piperazine (**6d**) analogs were moderately inhibitory for 5-HT, DA and NE, respectively. When the pyrrolidine feature remained, the replacement of the 3-benzo[b]thiophene moiety with the 5-chloro-6-methoxynaphthalen moiety (compound **12a**) dramatically decreased inhibition of the three transporters. Data show that the 3,4-dichlorophenyl is a preferred substituent. Thus, **12b** was prepared.

In our next series, we investigated the effects of replacing the C3 substituent 4-benzyl-1,2,3,6-tetrahydropyridine moiety with piperidine and morpholine moieties (Table 1, compounds **18a**–**e**). None of these C3 piperidine or morpholine substituted compounds were potent except the C1 pyrrolidine substituted compound **18c**. Compound **18c** exhibited interesting triple reuptake potency (5-HT, IC_{50} = 389 nM; NE, IC_{50} = 69 nM; DA, IC_{50} = 238 nM), however the C1 substituent with morpholine (**18a** and **18b**), 3-methylpiperidine (**18d**) and ethyl piperidine-3-carboxylate (**18e**) were weak reuptake inhibitors of all three transporters.

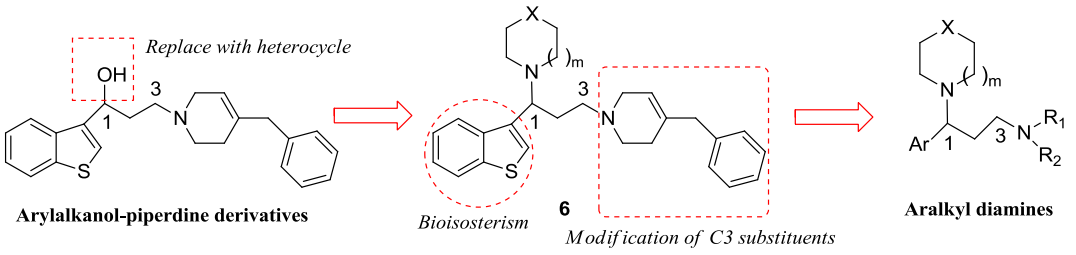
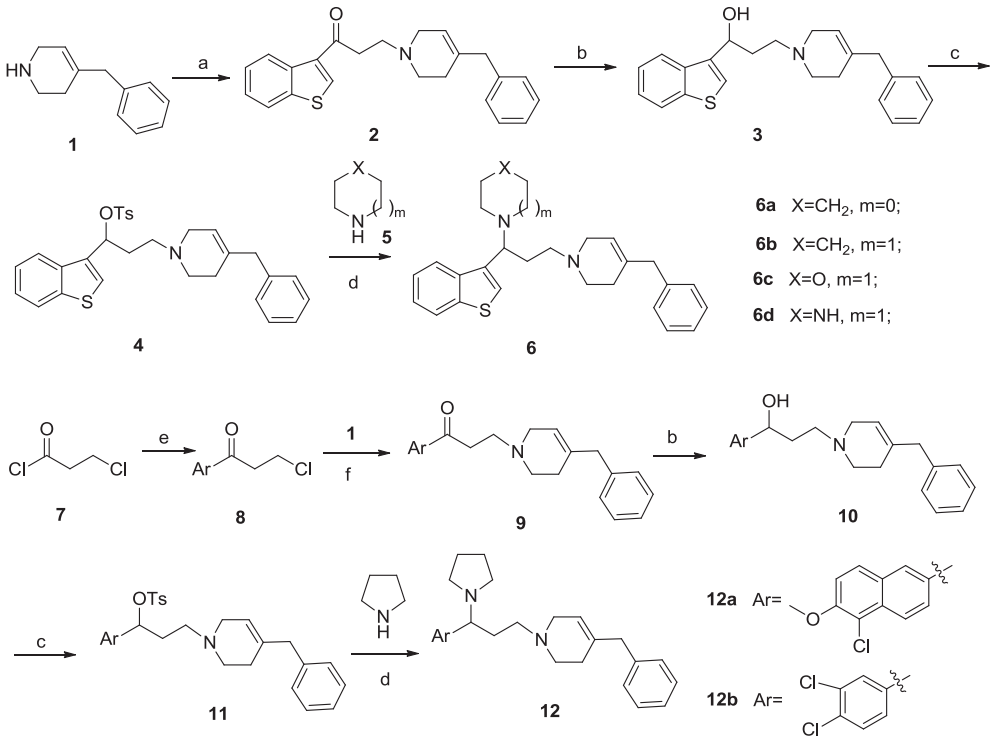


Fig. 2. Rational design of novel triple reuptake inhibitors.

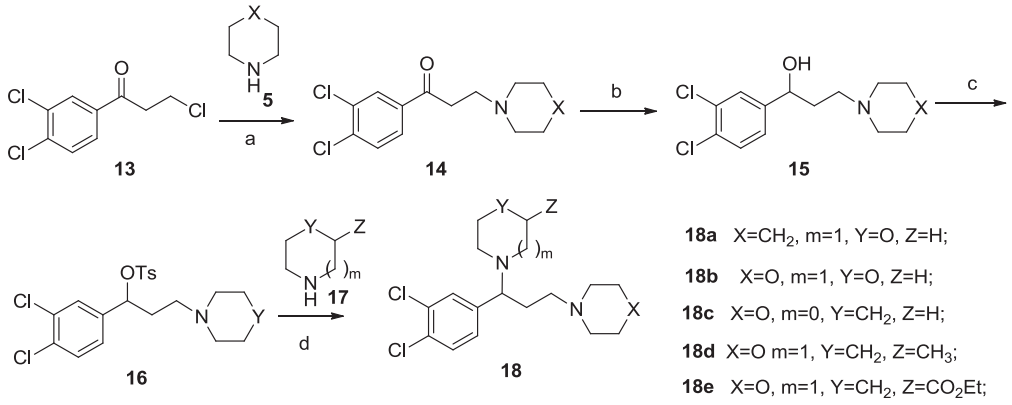


Scheme 1. Reagents and conditions: (a) 3-aetylbenzo[*b*]thiophene, paraformaldehyde, HCl, EtOH, 80 °C; (b) $NaBH_4$, MeOH, rt.; (c) TsCl, CH_3CN, DIPEA, rt.; (d) CH_3CN, K_2CO_3, 70 °C; (e) Ar, $AlCl_3$, CH_2Cl_2; (f) CH_3CN, DIPEA, rt.

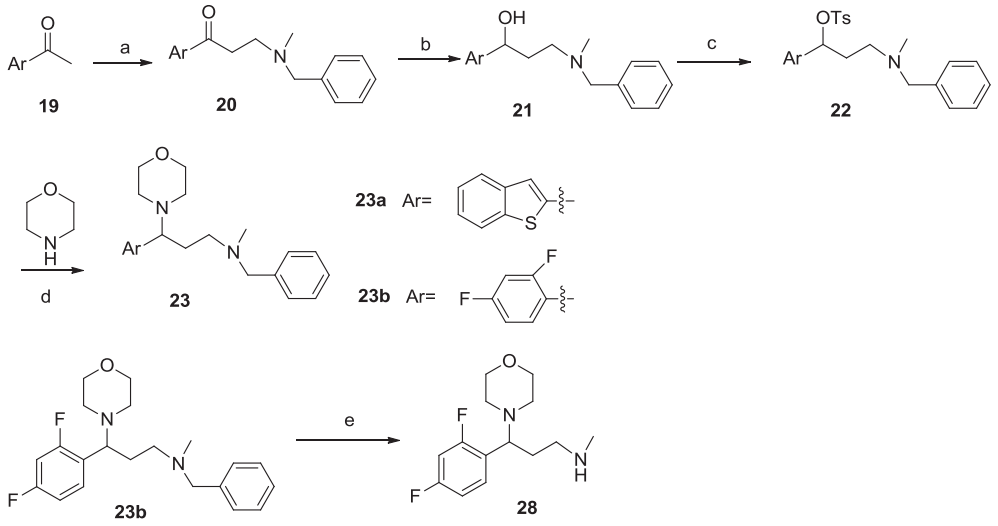
Continuing with evaluation of C3 substituent effect on reuptake inhibition, we introduced an *N*-methylbenzylamine to the C3 position. **23a**, **23b**, **27a**, and **27b** were all weak inhibitors of three monoamine transporters. Interestingly, compared with **23b**, **28** lacked a benzyl group and was selectively potent for reuptake inhibition of the NE transporter. This indicates the importance of C3 substituent interacting with the monoamine transporters.

Based on the above results, dimethylamine substitution was then utilized at the C3 position to explore monoamine reuptake inhibition. In the meantime, the influence of aromatic moieties at the C1 position in this series was systematically studied. For 3,4-dichlorophenyl substituted compounds **36a**–**b**, **36d** exhibited higher potency for all three monoamine transporters than any other substituted phenyl compounds. Compound **36c** showed potent inhibition against 5-HT and NE transporters but had dramatically reduced potency against DA transporter compared to the other 3,4-dichlorophenyl counterparts. Moreover, the 2,4-difluorophenyl analog **32i** and the mono-substituted phenyl compounds **32a**–**h** had no activity, indicating the necessity of a 3,4-dichloro substituent that interacts with monoamine transporters. Compound **40** is structurally identical to **36d** except that the C3–N dimethyl is replaced with diethyl group. This replacement resulted in its preference for the DA and NE transporters over the 5-HT transporter.

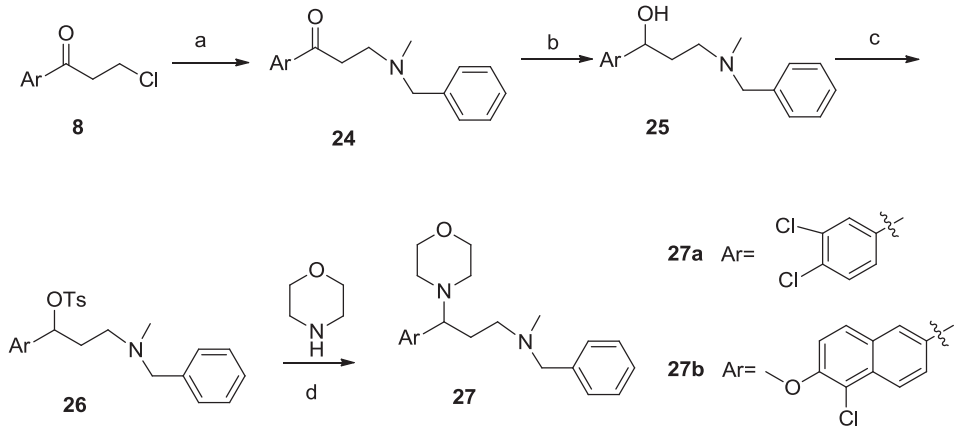
Increased hydrophobicity was the most prominent outcome with aromatic substitutions and these substitutions can change its biological activity. In our exploration to evaluate the effect of enhanced hydrophobicity of phenyl substitution, the phenyl moiety was replaced with 5-chloro-6-methoxymaphthalen and benzo[*b*] thiophen to produce **32j**–**m** and **36e**. Compound **32k** bearing the pyrrolidine and 2-benzo[b]thiophene moieties was potent against all three monoamine transporters (IC_{50} values = 401, 495 and



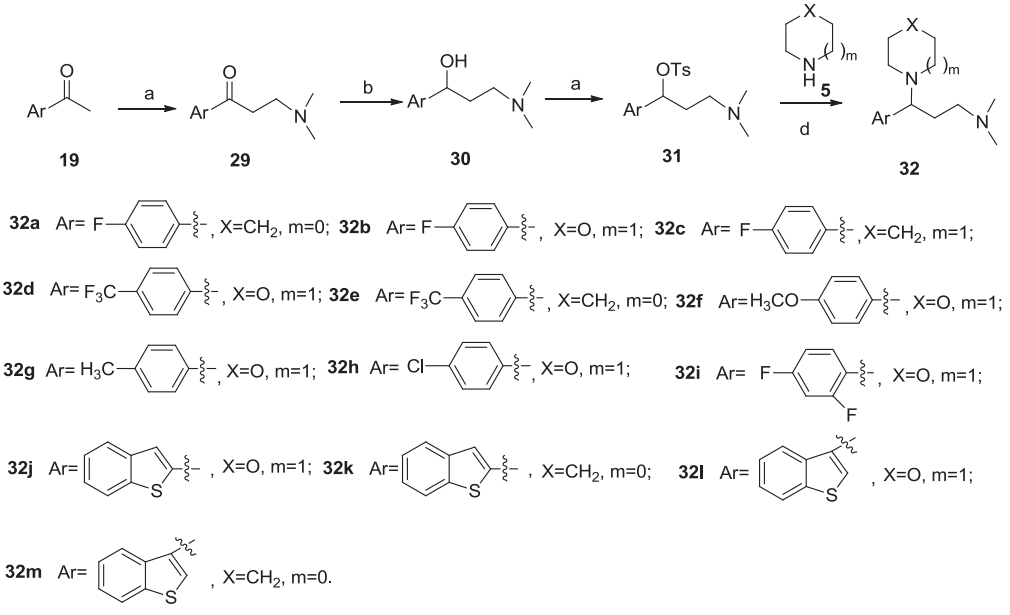
Scheme 2. Reagents and conditions: (a) CH_3CN, DIPEA, rt. (b) $NaBH_4$, MeOH, rt.; (c) TsCl, CH_3CN, DIPEA, rt.; (d) CH_3CN, K_2CO_3, 70 °C.



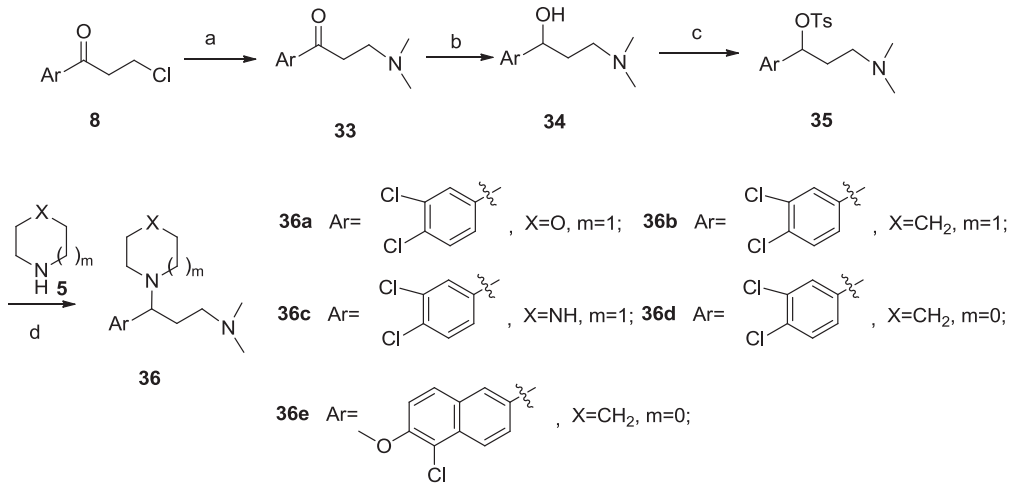
Scheme 3. Reagents and conditions: (a) *N*-methyl-1-phenylmethanamine, paraformaldehyde, HCl, EtOH, 80 °C; (b) $NaBH_4$, MeOH, rt.; (c) TsCl, CH_3CN, DIPEA, rt.; (d) CH_3CN, K_2CO_3, 70 °C; (e) 5%Pd/C, EtOH, rt.



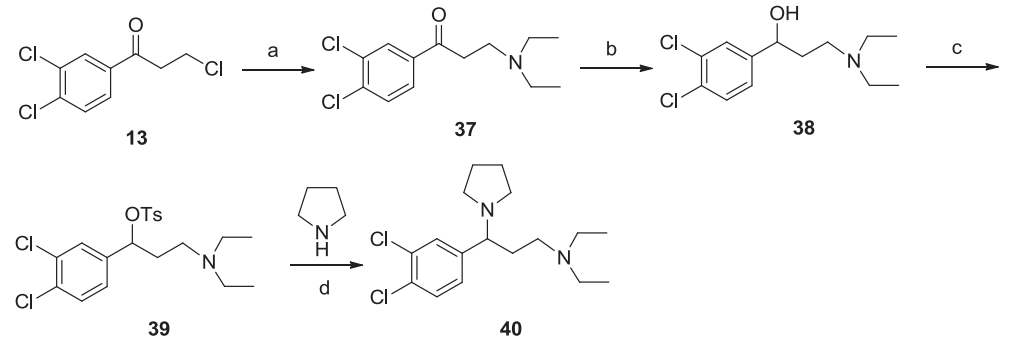
Scheme 4. Reagents and conditions: (a) *N*-methyl-1-phenylmethanamine, CH_3CN, DIPEA, rt; (b) $NaBH_4$, MeOH, rt.; (c) TsCl, CH_3CN, DIPEA, rt.; (d) CH_3CN, K_2CO_3, 70 °C.



Scheme 5. Reagents and conditions: (a) dimethylamine, paraformaldehyde, HCl, EtOH, 80 °C; (b) $NaBH_4$, MeOH, rt.; (c) TsCl, CH_3CN, DIPEA, rt.; (d) CH_3CN, K_2CO_3, 70 °C.



Scheme 6. Reagents and conditions: (a) dimethylamine, CH_3CN, DIPEA, rt. (b) $NaBH_4$, MeOH, rt.; (c) TsCl, CH_3CN, DIPEA, rt.; (d) CH_3CN, K_2CO_3, 70 °C.



Scheme 7. Reagents and conditions: (a) diethylamine, CH_3CN, DIPEA, rt. (b) $NaBH_4$, MeOH, rt.; (c) TsCl, CH_3CN, DIPEA, rt.; (d) CH_3CN, K_2CO_3, 70 °C.

863 nM for 5-HT, NE and DA, respectively). Whereas the corresponding morpholine and 2-benzo[b]thiophene moieties **32j** was observed to be active only for 5-HT and NE (5-HT, IC_{50} = 449 nM; NE, IC_{50} = 1456 nM). When the 2-benzo[b]thiophene aromatic was replaced by 3-benzo[b]thiophene, the pyrrolidine moiety **32m** also had greater potency for all three monoamine transporters than the morpholine moiety **32l**. The 5-chloro-6-methoxynaphthalen and pyrrolidine moieties **36e**, offered potency against the DA transporter that was weaker than the 3,4-dichlorophenyl series **36a** (5-HT, IC_{50} = 378 nM; NE, IC_{50} = 477 nM; DA, IC_{50} = 247 nM) and **36d** (5-HT, IC_{50} = 501 nM; NE, IC_{50} = 206 nM; DA, IC_{50} = 357 nM).

On the basis of *in vitro* studies, 3,4-dichlorophenyl compounds **18c**, **36a** and **36d** were selected for further profiling in the rat forced swim test (FST)[16], an assay in which rats are placed into a beaker of water and the time of animal immobility is recorded. The FST has been used widely as a preclinical model for screening antidepressant activity and is sensitive to known antidepressant drugs. Thus, **18c**, **36a** and **36d** were dosed at 5, 10 and 20 mg/kg (PO) in male rats for the FST, respectively. For comparative purposes, venlafaxine was a positive control (30 mg/kg, PO).

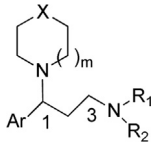
As shown in Fig. 3, the selected compounds **18c**, **36a** and **36d** reduced immobility times in the FST in a dose-dependent manner that was statistically significant compared with vehicle at 5, 10 and 20 mg/kg (PO). The positive control, venlafaxine (30 mg/kg, PO), also produced a similar reduction in immobility with a mid-range dose of **18c** (10 mg/kg, PO; Fig. 3A) and a lower dose of **36d** (5 mg/kg, PO; Fig. 3C). Specifically, the effect of **36a** was statistically significant even at 5 mg/kg. This compound induced a marked antidepressant-like effect and was the most potent in the FST model.

In order to validate the changes in motor activity of rats did not disturb the results obtained in the FST, spontaneous locomotor activity was measured. The test compounds **18c**, **36a** and **36d** were administered at higher dose (20 mg/kg, PO), which was efficacious in the FST. Venlafaxine (30 mg/kg, PO) was selected as a positive control. As shown in Fig. 3D, compounds **18c**, **36a** and **36d** at the effective dose (20 mg/kg, PO) produced no significant changes in locomotor activity compared with the vehicle control and venlafaxine groups.

To conclude that *in vivo* activities in the FST are caused only by triple neurotransmitter reuptake inhibition and not by interaction with other targets, receptor selectivity of these compounds was tested. Compound **36a** was selected for further characterization in several CNS receptor binding assays to assess the selectivity and specific interactions of this series of compounds with the monoamine transporters. Compound **36a** was performed against 55 receptors at Cerep (Celle L'Evescault, France, Cerep study number 100005534) using a test that has been previously described [17].

The description of all receptors targeted and corresponding radioligand used is provided in Supplementary material (SM) Table S1. The default concentration for primary binding experiments was 10 μM. Results indicating inhibition greater than 50% were considered to represent significant effects test compound effects. Thus, compound **36a** does not potently bind to any receptors tested except for 5-HT, NE and DA transporters.

Table 1
Activity at monoamine transporters of target compounds.



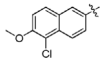
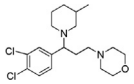
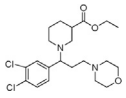
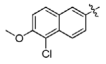
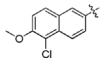
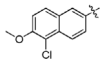
Compd.	Ar	R_1	R_2	X	*m*	[^{3}H]5-HT uptake IC_{50} (nM)	[^{3}H]NE uptake IC_{50} (nM)	[^{3}H]DA uptake IC_{50} (nM)
DOV21947						411.5 ± 34.1	71.4 ± 4.9	159.3 ± 13.2
6a				CH_2	0	621.3 ± 41.5	157.3 ± 6.4	325.4 ± 18.5
6b				CH_2	1	905.3 ± 87.4	52.7%[a]	77.4%[a]
6c				O	1	65.4%[a]	79.1%[a]	852.3 ± 58.4
6d				NH	1	73.9%[a]	635.4 ± 15.2	83.9%[a]
12a				CH_2	0	79.9%[a]	73.5%[a]	79.5%[a]
12b				CH_2	0	79.1%[a]	425.7 ± 46.7	291.4 ± 15.7
18a				O	1	59.9%[a]	74.0%[a]	68.1%[a]
18b				O	1	73.8%[a]	4.9%[a]	54.4%[a]
18c				CH_2	0	389.4 ± 18.8	68.9 ± 5.7	238.1 ± 12.5
18d						30.5%[a]	35.3%[a]	54.3%[a]
18e						34.9%[a]	19.0%[a]	36.6%[a]
23a		Me	Bn	O	1	30.3%[a]	37.8%[a]	41.9%[a]
23b		Me	Bn	O	1	24.1%[a]	5.3%[a]	46.2%[a]
27a		Me	Bn	O	1	35.6%[a]	50.6%[a]	3.4%[a]
27b		Me	Bn	O	1	47.3%[a]	49.5%[a]	2.5%[a]
28		Me	H	O	1	86.1%[a]	327.9 ± 46.8	42.0%[a]
32a		Me	Me	CH_2	0	70.2%[a]	68.9%[a]	46.6%[a]
32b		Me	Me	O	1	50.7%[a]	74.2%[a]	6.4%[a]
32c		Me	Me	CH_2	1	62.7%[a]	87.6%[a]	40.1%[a]
32d		Me	Me	O	1	46.2%[a]	83.2%[a]	8.5%[a]
32e		Me	Me	CH_2	0	57.6%[a]	77.4%[a]	37.1%[a]

Table 1 (*continued*)

Compd.	Ar	R_1	R_2	X	*m*	[^{3}H]5-HT uptake IC_{50} (nM)	[^{3}H]NE uptake IC_{50} (nM)	[^{3}H]DA uptake IC_{50} (nM)
32f		Me	Me	O	1	25.9%[a]	29.3%[a]	22.9%[a]
32g		Me	Me	O	1	39.2%[a]	40.4%[a]	25.8%[a]
32h		Me	Me	O	1	58.5%[a]	52.5%[a]	35.7%[a]
32i		Me	Me	O	1	55.6%[a]	19.4%[a]	50.7%[a]
32j		Me	Me	O	1	449.2 ± 22.9	1456.3 ± 151.7	66.8%[a]
32k		Me	Me	CH_2	0	401.0 ± 16.5	495.0 ± 131.5	863.1 ± 65.2
32l		Me	Me	O	1	1187.8 ± 122.1	2541.5 ± 426.5	56.8%[a]
32m		Me	Me	CH_2	0	425.3 ± 23.2	249.9 ± 12.9	986.1 ± 61.2
36a		Me	Me	O	1	378.5 ± 4.2	477.5 ± 3.5	247.2 ± 24.1
36b		Me	Me	CH_2	1	546.1 ± 41.4	633.5 ± 63.2	602.1 ± 86.0
36c		Me	Me	NH	1	399.3 ± 51.4	427.6 ± 35.9	80.1%[a]
36d		Me	Me	CH_2	0	501.4 ± 25.9	205.7 ± 19.9	356.6 ± 17.6
36e		Me	Me	CH_2	0	337.6 ± 44.3	373.5 ± 112.4	8192.5 ± 482.2
40		Et	Et	CH_2	0	76.5%[a]	136.4 ± 24.5	362.8 ± 15.8

[a] Percent inhibition measured at a concentration of 10 μM.

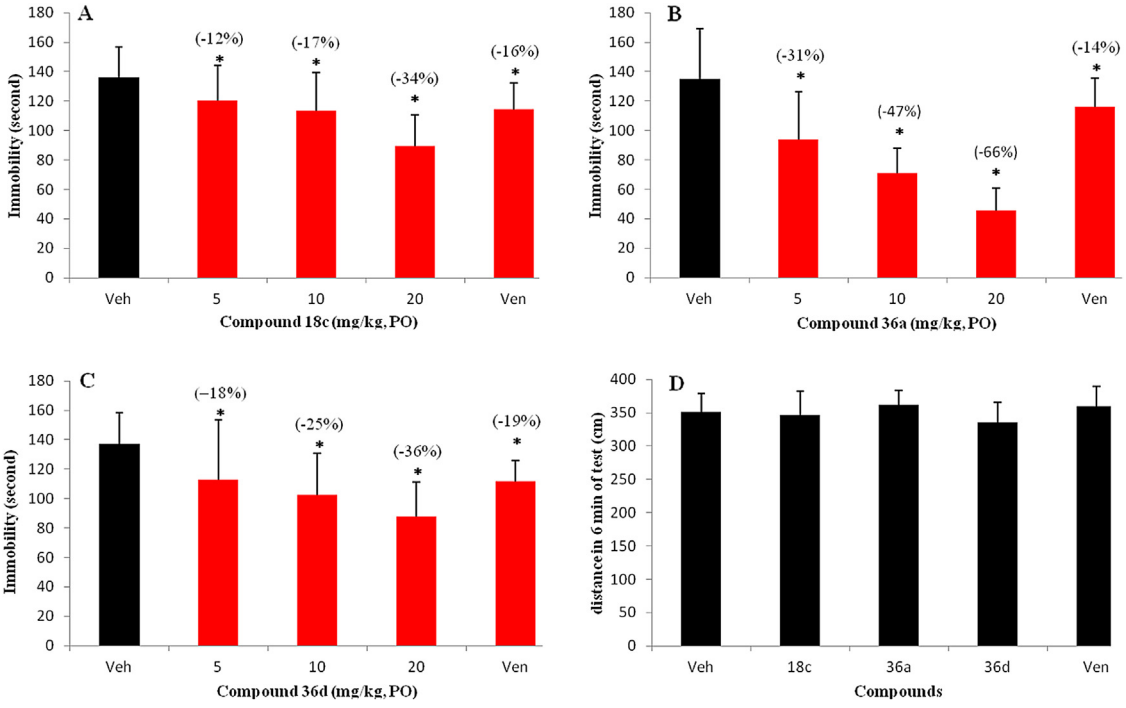


Fig. 3. The effect of compounds **18c**, **36a** and **36d** in the rat test predictive of antidepressant activity.

Table 2
Acute toxicity of **36a** in mice.

Dose (mg/kg)	Mice (N)	Deaths (N)	Survival on day 14 (%)
900	10	6	40%
750	10	4	60%
600	10	2	80%
450	10	0	100%
300	10	0	100%
150	10	0	100%
Vehicle	10	0	100%

To explore the safety profile of these diamine derivatives, the acute toxicity of **36a** was measured in KM mice at a single dose of 150, 300, 450, 600, 750, and 900 mg/kg or vehicle control ($n = 10$) by oral administration. Animal death was closely monitored for 14 days (Table 2). Treatment with **36a** at 900 mg/kg killed 60% of the mice, whereas the lower doses (150, 300, and 450 mg/kg) caused no abnormalities or animal deaths throughout the experiment. These data suggest that administration of **36a** at or below 450 mg/kg (PO) may be safe for mice.

Compound **36a** was also tested in a bacteria reversion mutation assay (Ames test), to ascertain if the compound can cause DNA mutations. Compound **36a** was negative at all dosages tested (3, 10, 30, 100, 300, 1000, and 5000 μg/plate) in two tested strains (TA98 and TA100; SM Table S2).

Next, pharmacokinetics (PK) of **36a** were measured in male SD rats (See Table 3). After administration of 2 mg/kg (PO) **36a** to SD rats, a C_{max} of 26.8 ng/mL was obtained at 30 min. Compound **36a** was cleared well ($CL_{z/F} = 25.0$ L/h/kg) in rats. The elimination half-life of **36a** after oral administration was 4.5 h. Compound **36a** also distributed well ($V_{z/F} = 163.8$ L/kg) and had a moderately orally bioavailable ($F = 19.4\%$) in rats.

Because the brain-blood barrier (BBB) is one of the factors relevant to the success of drugs for CNS disorders [18], compound **36a** was also evaluated for brain penetration. After 0.5 mg/kg (ip) **36a** to SD rats, brain concentrations of **36a** were greater than these in the plasma. The results are shown in Fig. 4. Compound **36a** had a brain to plasma ratio of 23 at 0.08 h (see SM for detailed results).

3. Conclusion

In the present work, we designed and synthesized a series of novel aralkyl diamine derivatives, in our continuous effort to find potent reuptake inhibition of 5-HT, NE, and DA transporters for the treatment of depressive disorders. Our SAR studies revealed that the presence of a 3,4-dichlorophenyl moiety at the C1 position was important for their biological activities. To confirm the potential *in vivo* antidepressant effect of this series of compounds, compounds **18c**, **36a**, and **36d** were selected for FST profiling in rats. These selected compounds showed a dose-dependent reduction of the immobility time in the FST. The most promising compound, **36a**, exhibited high selectivity for monoamine transporters over other CNS receptors. Compound **36a** also had good pharmacokinetic properties in rats, was negative in the Ames test, and had an acceptable safety profile. Our data lay a foundation for successful future development of novel aralkyl diamine derivatives as next generation of antidepressants.

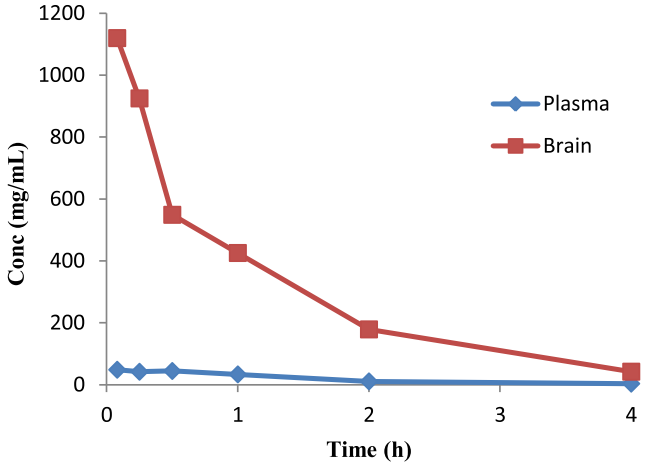


Fig. 4. Brain and plasma concentration–time plots of compound **36a** after IV (0.5 mg/kg) in SD rats.

4. Experimental protocols

4.1. Chemistry

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker NMR AVANCE 600 (600 MHz) or a Varian INOVA-400 (400 MHz) spectrometer with TMS as an internal standard. Chemical shift (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. Signal multiplicities are characterized as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). ESI mass spectra and HRMS were performed on an Agilent 6210 TOF spectrometer. The progress of all reactions was monitored using TLC on precoated silica gel plates GF254 (Qingdao Haiyang Chemical, China). Silica gel column chromatography was performed with Silica gel 60G (Qingdao Haiyang Chemical, China). The chromatograms were viewed under UV light at 254 and/or 265 nm. Uncorrected melting points were determined on an electrothermal melting point apparatus. Solvents and reagents were used without any pretreatment. Compounds purity were evaluated by high performance liquid chromatography (HPLC), and all final test compounds were >98% purity. The HPLC methods were used a Waters XBridge column, C18 (5 μm, 250 mm × 4.6 mm); with a mobile phase A (10 mM NaH_2PO_4 (pH = 7.0)) and B (CH_3CN), 90:10–10:90 v/v; detection at 220 nm; flow: 1.0 mL/min; temp 25 °C.

4.1.1. Procedure A. 1-(Benzo[b]thiophen-3-yl)-3-(4-benzyl-5,6-dihydropyridin-1(2H)-yl)propan-1-one (**2**)hydrochloride [15]

To a stirred mixture of paraformaldehyde (0.74 g, 25.1 mmol), 3-acetylbenzo[*b*]thiophen (3.4 g, 19.3 mmol) and 4-benzyl-1,2,3,6-tetrahydropyridine hydrochloride (4.4 g, 21.2 mmol) in ethanol (95%, 15 mL) was added concentrated hydrochloric acid (0.2 mL). The reaction was slowly heated to reflux, and the refluxing was continued for 5 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude residue was extracted with dichloromethane (50 mL) and water

Table 3
Pharmacokinetic parameters of compound **36a**.

Dose (mg/kg)	$AUC_{(0-t)}$ (ngh/mL)	$AUC_{(0-\infty)}$ (ngh/mL)	$MRT_{(0-t)}$ (h)	$V_{z/F}$ (L/kg)	$CL_{z/F}$ (L/h/kg)	$T_{1/2Z}$ (h)	T_{max} (h)	C_{max} (ng/mL)	F (%)
2 (po)	61.0	80.0	3.05	163.8	25.0	4.5	0.5	26.8	19.4
0.5 (iv)	78.6	83.7	1.06	8.3	6.0	1.0		48.5	

(30 mL). The organic layer was washed with brine (30 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (20 mL) and stirred for 1 h at room temperature to give a hydrochloride product. The white solid was filtered, washed thoroughly with ethyl acetate and ethanol, separately, and to give compound **2** hydrochloride (5.6 g, 73.0%) as a white solid. Mp: 213–215 °C. MS (ESI) *m/z*: 362 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18–2.42 (m, 2H), 3.16–3.51 (m, 2H), 3.38 (s, 2H), 3.47–3.51 (t, J = 7.2 Hz, 2H), 3.68–3.71 (t, J = 7.2 Hz, 2H), 3.74–3.86 (m, 2H), 5.48 (s, 1H), 7.21–7.23 (m, 3H), 7.29–7.33 (t, J = 7.6 Hz, 2H), 7.45–7.55 (m, 2H), 8.08–8.10 (d, J = 8.0 Hz, 1H), 8.58–8.60 (d, J = 8.0 Hz, 1H), 9.04 (s, 1H).

4.1.2. Procedure B. 1-(Benzo[b]thiophen-3-yl)-3-(4-benzyl-5,6-dihydropyridin-1(2H)-yl)propan-1-ol (**3**) hydrochloride [15]

Sodium borohydride (0.18 g, 4.8 mmol) was added dropwise to a stirred solution of 1-(benzo[*b*]thiophen-3-yl)-3-(4-benzyl-5,6-dihydropyridin-1(2*H*)-yl)propan-1-one (**2**) hydrochloride (1.9 g, 4.8 mmol) in methanol (20 mL), and then the mixture was stirred at room temperature for 2 h. Quenched with water (5 mL), and stirred for 10 min, then the solvent was removed under reduced pressure. The crude residue was extracted with dichloromethane (50 mL) and water (30 mL). The organic layer was washed with brine (30 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (20 mL) and added hydrogen chloride ethanol solution (1.25 M, 5 mL) dropwise, and the resulting mixture was stirred for 1 h at room temperature to give a hydrochloride product. The white solid was filtered, washed thoroughly with ethyl acetate and ethanol, separately, and to afford compound **3** hydrochloride (1.7 g, 89.0%) as a white solid. Mp: 170–172 °C. MS (ESI) *m/z*: 364 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.11–2.38 (m, 2H), 2.19–2.27 (m, 2H), 3.09–3.38 (m, 2H), 3.24–3.31 (m, 2H), 3.35 (s, 2H), 3.51–3.78 (m, 2H), 5.04–5.07 (q, J = 4.0 Hz, 1H), 5.43 (s, 1H), 5.72 (br, 1H), 7.19–7.23 (t, J = 8.0 Hz, 3H), 7.28–7.32 (t, J = 7.6 Hz, 2H), 7.35–7.41 (m, 2H), 7.60 (s, 1H), 7.96–7.99 (m, 2H).

4.1.3. Procedure C. General procedure for the preparation of compounds ***6a–d***

To a solution of compound **3** (8 mmol) and *N*,*N*-diisopropylethylamine (9.6 mmol) in acetonitrile (30 mL), *p*-toluenesulfonyl chloride (8.8 mmol) was added, and the resulting mixture was stirred for 12 h. Then cyclic amines **5** (8.8 mmol) and potassium carbonate (8 mmol) were added to the reaction mixture, and stirred at 70 °C for 8 h. After filtering, the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with dichloromethane (60 mL) and water (40 mL), and the organic layer was washed with brine (30 mL) and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was dissolved in ethanol (30 mL) and added hydrogen chloride ethanol solution (1.25 M, 8 mL) dropwise, and the resulting mixture was stirred for 1 h at room temperature to give a hydrochloride product. The crude product was purified by recrystallization from ethanol to yield compounds **6a–d**.

*4.1.3.1. 1-(3-(Benzo[b]thiophen-3-yl)-3-(pyrrolidin-1-yl)propyl)-4-benzyl-1,2,3,6-tetrahydropyridine (**6a**) hydrochloride.* Yield 58.9%, the purity was 98.5% by HPLC analysis. Mp: 168–170 °C. MS (ESI) *m/z*: 417.2 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96–2.22 (m, 4H), 2.49–2.57 (m, 2H), 2.61–2.78 (m, 2H), 2.85–3.06 (m, 4H), 3.29–3.33 (m, 2H), 3.38–3.45 (m, 2H), 3.60–3.80 (m, 2H), 4.01 (s, 2H), 5.28–5.39 (m, 1H), 5.63 (s, 1H), 7.11–7.12 (m, 2H), 7.21–7.30 (m, 3H), 7.43–7.47 (m, 1H), 7.53 (m, 1H), 7.93–7.95 (dd, J = 2.0, 8.0 Hz, 1H), 8.23 (s, 1H), 8.72 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.42, 28.42, 31.45, 32.00, 32.69, 43.29, 44.02, 52.35, 55.33, 58.24, 65.46, 120.31, 121.29, 122.21, 122.34, 124.91, 125.03, 125.14, 126.44, 126.35, 129.36, 130.06, 131.42, 132.87, 136.35. HRMS calcd for $C_{27}H_{33}N_2S$ $(M + H)^+$, 417.2364; found, 417.2365.

*4.1.3.2. 1-(3-(Benzo[b]thiophen-3-yl)-3-(piperidin-1-yl)propyl)-4-benzyl-1,2,3,6-tetrahydropyridine (**6b**) hydrochloride.* Yield 59.7%, the purity was 98.3% by HPLC analysis. Mp: 164–166 °C. MS (ESI) *m/z*: 431.3 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (m, 6H), 2.19–2.26 (m, 2H), 2.58 (m, 2H), 2.63–2.79 (m, 4H), 3.03–3.16 (m, 2H), 3.29 (m, 2H), 3.29 (m, 2H), 3.65 (s, 2H), 4.96–4.99 (t, J = 6.8 Hz, 1H), 5.38 (s, 1H), 7.11–7.26 (m, 5H), 7.44–7.51 (m, 2H), 8.04–8.09 (m, 2H), 8.23 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.26, 25.45, 26.32, 27.83, 30.24, 32.45, 36.37, 44.01, 45.35, 49.29, 56.36, 65.42, 121.25, 121.47, 122.05, 122.44, 123.99, 124.78, 125.51, 126.10, 129.64, 131.22, 131.48, 132.90, 137.24. HRMS calcd for $C_{28}H_{35}N_2S$ $(M + H)^+$, 431.2521; found, 431.2527.

*4.1.3.3. 1-(3-(Benzo[b]thiophen-3-yl)-3-(morpholin-4-yl)propyl)-4-benzyl-1,2,3,6-tetrahydropyridine (**6c**) hydrochloride.* Yield 47.1%, the purity was 98.8% by HPLC analysis. Mp: 152–154 °C. MS (ESI) *m/z*: 433.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (m, 2H), 2.66–2.69 (m, 2H), 2.74 (m, 2H), 3.00–3.10 (m, 4H), 3.13 (m, 2H), 3.29 (m, 4H), 3.64 (m, 2H), 3.83 (s, 2H), 4.98–5.00 (d, J = 9.2 Hz, 1H), 5.38 (s, 1H), 7.11–7.27 (m, 5H), 7.42–7.52 (m, 2H), 8.04–8.09 (m, 2H), 8.21 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.28, 27.45, 32.16, 44.23, 44.57, 49.79, 52.05, 53.41, 61.24, 67.40, 121.43, 121.87, 123.12, 123.45, 124.35, 124.93, 125.43, 126.49, 127.28, 129.48, 131.22, 132.45, 133.11, 137.42. HRMS calcd for $C_{27}H_{33}N_2OS$ $(M + H)^+$, 433.2314; found, 433.2318.

*4.1.3.4. 1-(3-(Benzo[b]thiophen-3-yl)-3-(piperazin-1-yl)propyl)-4-benzyl-1,2,3,6-tetrahydropyridine (**6d**) hydrochloride.* Yield 48.7%, the purity was 99.0% by HPLC analysis. Mp: 171–173 °C. MS (ESI) *m/z*: 432.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (m, 1H), 2.30 (m, 1H), 2.63–2.69 (m, 2H), 2.81–2.86 (m, 2H), 3.03–3.06 (m, 2H), 3.14–3.19 (m, 4H), 3.26–3.36 (m, 4H), 3.55 (m, 1H), 3.76–3.78 (m, 1H), 3.87 (s, 2H), 4.79–4.83 (t, J = 6.0 Hz, 1H), 5.39 (s, 1H), 7.12–7.27 (m, 5H), 7.41–7.48 (m, 2H), 8.00–8.05 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.43, 28.24, 30.45, 45.11, 45.67, 47.29, 48.51, 51.46, 52.89, 59.35, 65.27, 120.27, 121.46, 123.10, 123.67, 124.56, 125.59, 126.37, 128.11, 128.46, 131.72, 132.63, 135.29, 137.81. HRMS calcd for $C_{27}H_{34}N_3S$ $(M + H)^+$, 432.2473; found, 432.2469.

4.1.4. General procedure for the synthesis of 1-aryl-3-chloropropan-1-ones (***8***) [15]

Aluminum chloride (8.4 g, 62.0 mmol) was added dropwise to a solution of 3-chloropropanoyl chloride (7.2 g, 57.0 mmol) in chloroform (70 mL) at room temperature. The reaction mixture was stirred at the same temperature for 1 h. After cooling to 10 °C, a solution of aromatic ring (57.0 mmol) in chloroform (25 mL) was added dropwise, and then the mixture was stirred at room temperature for 2.5 h. The reaction was complete as determined by thin layers chromatography (TLC) with EtOAc/hexane (1/15, v/v). The reaction mixture was poured slowly into ice water, after stirred for 30 min, the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in reduced pressure. The crude product was purified by silica gel column chromatography with EtOAc/hexane (1/20, v/v) as mobile phase to give compound **8**.

4.1.5. Procedure D. General procedure for the synthesis of aryl ketone ***9*** [15]

To a stirred mixture of ketone **8** (7.1 mmol) and 4-benzyl-1,2,3,6-tetrahydropyridine hydrochloride (1.1 g, 6.4 mmol) in acetonitrile

(20 mL) was added diisopropylethylamine (1.7 g, 12.9 mmol). After being stirred overnight at room temperature, the solvent was removed under reduced pressure. The crude residue was extracted with dichloromethane (30 mL) and water (30 mL). The organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and hydrogen chloride ethanol solution (1.25 M, 8 mL) was added dropwise, the resulting mixture was stirred for 1 h at room temperature to give a hydrochloride product. The white solid was filtered, washed thoroughly with ethyl acetate and ethanol, separately, and to give compound **9**.

*4.1.5.1. 3-(4-Benzyl-5,6-dihydropyridin-1(2H)-yl)-1-(5-chloro-6-methoxynaphthalen-2-yl)propan-1-one (**9a**) hydrochloride.* Yield 81.9% as a white solid. Mp: 183–185 °C. MS (ESI) *m*/*z*: 420.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.16–2.43 (m, 2H), 3.18–3.56 (m, 2H), 3.38 (s, 2H), 3.50–3.53 (t, J = 7.2 Hz, 2H), 3.74–3.78 (t, J = 7.2 Hz, 2H), 3.74–3.90 (m, 2H), 4.05 (s, 3H), 5.50 (s, 1H), 7.22–7.24 (m, 3H), 7.30–7.34 (t, J = 7.6 Hz, 2H), 7.69–7.71 (d, J = 9.2 Hz, 1H), 8.10–8.20 (m, 3H), 8.75 (s, 1H).

*4.1.5.2. 3-(4-Benzyl-5,6-dihydropyridin-1(2H)-yl)-1-(3,4-dichlorophenyl)propan-1-one (**9b**) hydrochloride.* Yield 76.9% as a white solid. Mp: 190–193 °C. MS (ESI) *m*/*z*: 374.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15–2.44 (m, 2H), 3.11–3.51 (m, 2H), 3.37 (s, 2H), 3.41–3.45 (t, J = 7.2 Hz, 2H), 3.67–3.71 (t, J = 7.2 Hz, 2H), 3.67–3.84 (m, 2H), 5.47 (s, 1H), 7.20–7.23 (m, 3H), 7.29–7.33 (m, 2H), 7.82–7.84 (d, J = 8.4 Hz, 1H), 7.93–7.96 (m, 1H), 8.20–8.21 (d, J = 2.4 Hz, 1H).

*4.1.6. General procedure for the synthesis of aryl alcohol **10** [15]*

Aryl ketone **9** (4 mmol) was treated with sodium borohydride (4 mmol) in methanol (20 mL) using procedure B. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **10** hydrochloride.

*4.1.6.1. 3-(4-Benzyl-5,6-dihydropyridin-1(2H)-yl)-1-(5-chloro-6-methoxynaphthalen-2-yl)propan-1-ol (**10a**) hydrochloride.* Yield 88.5% as a white solid. Mp: 164–166 °C. MS (ESI) *m*/*z*: 422.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07–2.26 (m, 2H), 2.29–2.32 (m, 2H), 2.67–3.01 (m, 2H), 3.19–3.24 (m, 2H), 3.36 (s, 2H), 3.39–3.55 (m, 2H), 4.00 (s, 3H), 5.15–5.18 (t, J = 5.2 Hz, 1H), 5.33 (s, 1H), 7.10–7.12 (d, J = 6.8 Hz, 2H), 7.19–7.32 (m, 4H), 7.51–7.54 (d, J = 8.8 Hz, 1H), 7.69–7.71 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 8.12–8.15 (d, J = 8.8 Hz, 1H).

*4.1.6.2. 3-(4-Benzyl-5,6-dihydropyridin-1(2H)-yl)-1-(3,4-dichlorophenyl)propan-1-ol (**10b**) hydrochloride.* Yield 82.9% as a white solid. Mp: 160–163 °C. MS (ESI) *m*/*z*: 376.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.01–2.06 (t, J = 8.0 Hz, 2H), 2.10–2.40 (m, 2H), 3.05–3.41 (m, 2H), 3.08–3.15 (t, J = 8.0 Hz, 2H), 3.35 (s, 2H), 3.51–3.76 (m, 2H), 4.69–4.72 (q, J = 4.0 Hz, 1H), 5.42 (s, 1H), 5.80 (br, 1H), 7.19–7.23 (m, 3H), 7.28–7.32 (t, J = 7.6 Hz, 2H), 7.35–7.37 (dd, J = 2.0, 6.0 Hz, 1H), 7.58–7.61 (m, 2H), 10.60 (br, 1H).

*4.1.7. General procedure for the preparation of compounds **12a–b***

Aryl alcohol **10** (8 mmol) was first reacted with *p*-toluenesulfonyl chloride (8.8 mmol) in acetonitrile (30 mL), and then treated with pyrrolidine (8.8 mmol) as procedure C. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **12** hydrochloride.

*4.1.7.1. 4-Benzyl-1-(3-(5-chloro-6-methoxynaphthalen-2-yl)-3-(pyrrolidin-1-yl)propyl)-1,2,3,6-tetrahydropyridine (**12a**) hydrochloride.* Yield 48.0% as a white solid, the purity was 98.9% by HPLC analysis. Mp: 209–211 °C. MS (ESI) *m*/*z*: 475.2 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94–2.20 (m, 4H), 2.59–2.63 (m, 2H), 2.71–2.92 (m, 2H), 2.98–3.16 (m, 4H), 3.23–3.25 (m, 2H), 3.27–3.36 (m, 2H), 3.38–3.39 (m, 2H), 3.49 (s, 2H), 4.02 (s, 3H), 5.08–5.10 (m, 1H), 5.28–5.36 (m, 1H), 7.05–7.07 (m, 2H), 7.12–7.25 (m, 3H), 7.36–7.38 (d, J = 8.8 Hz, 1H), 7.90–7.93 (d, J = 8.8 Hz, 1H), 8.06–8.08 (d, J = 7.2 Hz, 1H), 8.30–8.33 (dd, J = 0.8, 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.18, 28.30, 30.24, 31.45, 32.34, 45.31, 45.69, 54.13, 55.22, 57.15, 66.34, 115.23, 120.24, 121.35, 122.12, 122.47, 124.30, 124.98, 125.62, 126.47, 126.79, 129.21, 130.23, 131.05, 132.44, 147.47. HRMS calcd for $C_{30}H_{36}ClN_2O$ $(M + H)^+$, 475.2516; found, 475.2520.

*4.1.7.2. 4-Benzyl-1-(3-(3,4-dichlorophenyl)-3-(pyrrolidin-1-yl)propyl)-1,2,3,6-tetrahydropyridine (**12b**) hydrochloride.* Yield 50.0% as a white solid, the purity was 98.4% by HPLC analysis. Mp: 230–232 °C. MS (ESI) *m*/*z*: 429.2 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.14 (m, 4H), 2.22–2.26 (m, 2H), 2.71–2.82 (m, 2H), 2.83–2.96 (m, 4H), 3.10–3.20 (m, 2H), 3.27–3.33 (m, 2H), 3.36–3.46 (m, 2H), 4.01 (s, 2H), 5.08 (m, 1H), 5.36–5.42 (m, 1H), 7.13–7.15 (d, J = 7.6 Hz, 2H), 7.23–7.34 (m, 3H), 7.58–7.60 (d, J = 8.4 Hz, 1H), 7.97–8.01 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.22, 28.35, 31.55, 32.34, 44.31, 44.62, 51.48, 53.26, 57.90, 66.37, 122.45, 122.89, 123.26, 124.83, 125.46, 125.67, 126.17, 126.35, 128.87, 130.62, 131.31, 133.46, 135.89. HRMS calcd for $C_{25}H_{31}Cl_2N_2$ $(M + H)^+$, 429.1864; found, 429.1869.

*4.1.8. General procedure for the synthesis of aryl ketone **14***

Ketone **13** (50 mmol) was reacted with cyclic amines **5** (50 mmol) in acetonitrile (100 mL) using procedure D. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **14** hydrochloride.

*4.1.8.1. 1-(3,4-Dichlorophenyl)-3-(piperidin-1-yl)propan-1-one (**14a**) hydrochloride.* Yield 77.7% as a white solid. MS (ESI) *m*/*z*: 286.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92–2.05 (m, 2H), 2.08–2.35 (m, 4H), 3.11–3.15 (m, 2H), 3.37–3.43 (m, 2H), 3.52–3.54 (d, J = 8.0 Hz, 2H), 3.84–3.86 (t, J = 8.0 Hz, 2H), 7.79–7.81 (d, J = 8.0 Hz, 1H), 7.93–7.96 (m, 1H), 8.15–8.16 (d, J = 4.0 Hz, 1H).

*4.1.8.2. 1-(3,4-Dichlorophenyl)-3-morpholinopropan-1-one (**14b**) hydrochloride.* Yield 81.7% as a white solid. MS (ESI) *m*/*z*: 288.1 $(M + H)^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.14–3.16 (m, 2H), 3.45–3.46 (m, 2H), 3.51–3.53 (d, J = 12.0 Hz, 2H), 3.73–3.76 (t, J = 7.8 Hz, 2H), 3.86–3.90 (t, J = 12.0 Hz, 2H), 3.98–3.99 (m, 2H), 7.85–7.86 (d, J = 8.4 Hz, 1H), 7.95–7.97 (dd, J = 1.8, 8.4 Hz, 1H), 8.22–8.23 (d, J = 1.8 Hz, 1H).

*4.1.9. General procedure for the synthesis of aryl alcohol **15***

Aryl ketone **14** (10 mmol) was treated with sodium borohydride (10 mmol) in methanol (50 mL) using procedure B. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **15** hydrochloride.

*4.1.9.1. 1-(3,4-Dichlorophenyl)-3-(piperidin-1-yl)propan-1-ol (**15a**) hydrochloride.* Yield 93.2% as a white solid. MS (ESI) *m*/*z*: 288.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94–2.06 (m, 2H), 2.05–2.33 (m, 4H), 3.13–3.17 (m, 2H), 3.25–3.36 (m, 2H), 3.37–3.51 (m, 2H), 3.54–3.62 (m, 2H), 4.75–4.77 (m, 1H), 5.83 (br, 1H), 7.35–7.37 (d, J = 8.0 Hz, 1H), 7.57–7.61 (m, 2H).

*4.1.9.2. 1-(3,4-Dichlorophenyl)-3-morpholinopropan-1-ol (**15b**) hydrochloride.* Yield 93.5% as a white solid. MS (ESI) *m/z*: 290.2 $(M + H)^+$. ^1H NMR (600 MHz, DMSO-d_6): δ 2.01–2.06 (m, 1H), 2.11–2.16 (m, 1H), 3.04 (m, 2H), 3.14 (m, 2H), 3.40–3.42 (d, J = 12.0 Hz, 1H), 3.83–3.87 (t, J = 12.0 Hz, 2H), 3.91–3.93 (m, 2H), 4.72–4.74 (q, J = 3.6 Hz, 1H), 5.85 (s, 1H), 7.37–7.39 (dd, J = 1.8, 8.4 Hz, 1H), 7.61–7.62 (m, 2H).

*4.1.10. General procedure for the preparation of compounds **18a–e***

Aryl alcohol **15** (8 mmol) was first reacted with *p*-toluenesulfonyl chloride (8.8 mmol) in acetonitrile (30 mL), then treated with cyclic amines **17** (8.8 mmol) as procedure C. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **18** hydrochloride.

*4.1.10.1. 4-(1-(3,4-Dichlorophenyl)-3-(piperidin-1-yl)propyl)morpholine (**18a**) hydrochloride.* Yield 60.3% as a white solid, the purity was 99.0% by HPLC analysis. Mp: 229–231 °C. MS (ESI) *m/z*: 357.2 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.20–1.26 (m, 6H), 2.06–2.11 (m, 2H), 2.28–2.33 (m, 6H), 2.80–3.03 (m, 4H), 3.35–3.56 (m, 4H), 3.61–3.63 (d, J = 8.0 Hz, 1H), 7.26–7.29 (m, 1H), 7.55 (s, 1H), 7.37–7.39 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.45, 22.94, 25.87, 26.17, 50.21, 51.43, 52.37, 52.62, 63.31, 66.79, 127.21, 130.88, 131.21, 132.42, 132.83, 135.45. HRMS calcd for $C_{18}H_{27}Cl_2N_2O$ $(M + H)^+$, 357.1500; found, 357.1508.

*4.1.10.2. 4,4′-(1-(3,4-Dichlorophenyl)propane-1,3-diyl)dimorpholine (**18b**) hydrochloride.* Yield 58.3% as a white solid, the purity was 98.9% by HPLC analysis. Mp: 248–250 °C. MS (ESI) *m/z*: 359.1 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.68–2.71 (m, 2H), 2.92–3.12 (m, 6H), 3.40–3.46 (m, 2H), 3.55–3.61 (m, 2H), 3.77–4.05 (m, 8H), 4.12 (m, 1H), 7.64–7.66 (d, J = 8.0 Hz, 1H), 7.77–7.79 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.18, 25.23, 26.33, 29.52, 51.12, 51.44, 52.39, 53.27, 61.23, 66.37, 127.43, 130.25, 131.78, 131.81, 133.24, 135.16. HRMS calcd for $C_{17}H_{25}Cl_2N_2O_2$ $(M + H)^+$, 359.1293; found, 359.1290.

*4.1.10.3. 4-(3-(3,4-Dichlorophenyl)-3-(pyrrolidin-1-yl)propyl)morpholine (**18c**) hydrochloride.* Yield 48.3% as a white solid, the purity was 99.1% by HPLC analysis. Mp: 206–208 °C. MS (ESI) *m/z*: 343.3 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.99–2.03 (m, 4H), 2.60–2.66 (m, 1H), 2.73–2.80 (m, 2H), 2.80–3.00 (m, 5H), 3.20 (m, 1H), 3.36 (m, 2H), 3.79–3.85 (m, 3H), 3.92–3.94 (m, 2H), 4.67–4.69 (d, J = 7.6 Hz, 1H), 7.77–7.83 (m, 2H), 8.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.90, 26.00, 51.09, 51.32, 52.20, 52.72, 63.38, 64.77, 129.49, 131.35, 131.63, 132.17, 132.86, 135.03. HRMS calcd for $C_{17}H_{25}Cl_2N_2O$ $(M + H)^+$, 343.1338; found, 343.1338.

*4.1.10.4. 4-(3-(3,4-Dichlorophenyl)-3-(3-methylpiperidin-1-yl)propyl)morpholine (**18d**) hydrochloride.* Yield 28.2% as a white solid, the purity was 98.5% by HPLC analysis. Mp: 224–226 °C. MS (ESI) *m/z*: 371.2 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 0.90–0.92 (d, J = 8.0 Hz, 3H), 0.93 (m, 1H), 1.78–1.84 (t, J = 12.0 Hz, 2H), 1.93–2.05 (m, 1H), 2.16–2.21 (m, 2H), 2.27–2.35 (m, 6H), 2.44–2.46 (m, 1H), 2.65 (m, 2H), 2.84 (m, 1H), 3.28–3.34 (t, J = 12.0 Hz, 1H), 3.73–3.75 (t, J = 4.0 Hz, 1H), 4.20 (s, 1H), 7.46–7.48 (d, J = 8.0 Hz, 1H), 7.52–7.56 (t, J = 8.0 Hz, 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.52, 21.46, 22.94, 25.89, 50.17, 51.24, 52.37, 52.82, 55.49, 61.40, 66.79, 129.13, 130.27, 131.35, 132.10, 132.89, 136.17. HRMS calcd for $C_{19}H_{29}Cl_2N_2O$ $(M + H)^+$, 371.1657; found, 371.1662.

*4.1.10.5. Ethyl 1-(1-(3,4-dichlorophenyl)-3-morpholinopropyl)piperidine-3-carboxylate (**18e**) hydrochloride.* Yield 30.2% as a white solid, the purity was 98.0% by HPLC analysis. Mp: 181–183 °C. MS (ESI) *m/z*: 429.2 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.16–1.20 (t, J = 8.0 Hz, 3H), 1.43–1.46 (m, 2H), 1.73–2.11 (m, 4H), 2.51–3.15 (m, 11H), 3.39 (m, 4H), 4.05–4.10 (q, J = 8.0 Hz, 2H), 4.78–4.84 (m, 1H), 7.64–7.71 (m, 2H), 8.03 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.78, 20.25, 21.78, 22.66, 25.57, 49.87, 51.24, 51.95, 52.36, 53.47, 61.25, 66.45, 128.66, 131.47, 131.82, 132.35, 132.37, 137.28, 170.25. HRMS calcd for $C_{21}H_{31}Cl_2N_2O_3$ $(M + H)^+$, 429.1712; found, 429.1719.

*4.1.11. General procedure for the synthesis of aryl ketone **20***

Aryl ketone **19** (20 mmol) was treated with paraformaldehyde (22 mmol) and *N*-methyl-1-phenylmethanamine hydrochloride (22 mmol) in ethanol (15 mL) as procedure A. The crude product was purified by recrystallization from ethanol.

*4.1.12. General procedure for the synthesis of aryl alcohol **21***

Aryl ketone **20** (10 mmol) was treated with sodium borohydride (10 mmol) in methanol (30 mL) using procedure B. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **21** hydrochloride.

*4.1.12.1. 1-(Benzo[b]thiophen-2-yl)-3-(benzyl(methyl)amino)propan-1-ol (**21a**) hydrochloride.* Yield 92.0% as a white solid. MS (ESI) *m/z*: 312.1 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.65 (s, 3H), 2.75–2.91 (m, 2H), 3.75–3.80 (m, 2H), 4.25 (m, 2H), 5.01 (m, 1H), 5.75 (br, 1H), 7.31–7.35 (m, 3H), 7.38–7.43 (m, 2H), 7.56–7.59 (m, 2H), 7.73 (s, 1H), 7.89 (m, 1H), 7.98–8.03 (m, 1H).

*4.1.12.2. 3-(Benzyl(methyl)amino)-1-(2,4-difluorophenyl)propan-1-ol (**21b**) hydrochloride.* Yield 90.2% as a white solid. MS (ESI) *m/z*: 292.1 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.45–2.75 (m, 2H), 2.66 (s, 3H), 2.87–3.03 (m, 2H), 4.25 (s, 2H), 4.57 (m, 1H), 5.73 (br, 1H), 7.11–7.15 (m, 1H), 7.23–7.27 (m, 1H), 7.35–7.39 (m, 2H), 7.41 (m, 1H), 7.43–7.48 (m, 2H), 7.66–7.71 (m, 1H).

*4.1.13. General procedure for the preparation of compounds **23a–b***

Aryl alcohol **21** (8 mmol) was first reacted with *p*-toluenesulfonyl chloride (8.8 mmol) in acetonitrile (30 mL), then treated with morpholine (8.8 mmol) as procedure C. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **23** hydrochloride.

*4.1.13.1. 3-(Benzo[b]thiophen-2-yl)-N-benzyl-N-methyl-3-morpholinopropan-1-amine (**23a**) hydrochloride.* Yield 43.2% as a white solid, the purity was 98.1% by HPLC analysis. Mp: 205–207 °C. MS (ESI) *m/z*: 381.2 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.67 (s, 3H), 2.78–2.93 (m, 2H), 2.98–3.16 (m, 4H), 3.79–3.81 (m, 2H), 3.91–4.02 (m, 4H), 4.23–4.31 (m, 2H), 5.03 (s, 1H), 7.32–7.35 (m, 3H), 7.40–7.46 (m, 2H), 7.56–7.58 (m, 2H), 7.75 (s, 1H), 7.87–7.90 (m, 1H), 7.99–8.02 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.87, 37.82, 42.15, 42.19, 48.23, 50.12, 50.23, 62.45, 65.19, 120.45, 121.58, 123.10, 123.17, 123.82, 124.15, 125.21, 126.24, 128.43, 132.14, 133.79, 135.67, 138.96, 145.10. HRMS calcd for $C_{23}H_{29}N_2OS$ $(M + H)^+$, 381.2001; found, 381.2009.

*4.1.13.2. N-Benzyl-3-(2,4-difluorophenyl)-N-methyl-3-morpholinopropan-1-amine (**23b**) hydrochloride.* Yield 60.0% as a white solid, the purity was 98.4% by HPLC analysis. Mp: 229–231 °C. MS (ESI) *m/z*: 361.2 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.40–2.79 (m, 2H), 2.67 (s, 3H), 2.86–3.05 (m, 2H), 3.47–3.67 (m, 4H), 3.74–3.75 (m, 4H), 4.27 (s, 2H), 4.45 (s, 1H), 7.12–7.17 (m, 1H), 7.23–7.28 (m, 1H), 7.37–7.41 (m, 3H), 7.42–7.50 (m, 2H), 7.65–7.71 (q, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.46, 37.59, 42.13, 42.25, 47.09, 50.24, 51.36, 61.57, 66.26,

116.54, 121.57, 122.35, 124.38, 125.18, 127.90, 129.21, 130.25, 132.36, 134.58, 155.24, 156.35. HRMS calcd for $C_{21}H_{27}F_2N_2O$ $(M + H)^+$, 361.2091; found, 361.2085.

*4.1.14. General procedure for the synthesis of aryl alcohol **25***

Aryl ketone **8** (50 mmol) was treated with *N*-methyl-1-phenylmethanamine hydrochloride (50 mmol) in acetonitrile (100 mL) as procedure D. The crude product was purified by recrystallization from ethanol to give compound **24**.

Aryl ketone **24** (10 mmol) was treated with sodium borohydride (10 mmol) in methanol (30 mL) using procedure B. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **25** hydrochloride.

*4.1.14.1. 3-(Benzyl(methyl)amino)-1-(3,4-dichlorophenyl)propan-1-ol (**25a**) hydrochloride.* Yield 92.2% as a white solid. MS (ESI) *m*/*z*: 324.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.66 (s, 3H), 2.77–2.93 (m, 2H), 3.73–3.81 (m, 2H), 4.27 (s, 2H), 5.08 (m, 1H), 5.79 (br, 1H), 7.32–7.37 (m, 4H), 7.38–7.42 (m, 1H), 7.52–7.54 (m, 1H), 7.64–7.66 (d, J = 8.0 Hz, 1H), 7.79 (m, 1H).

*4.1.14.2. 3-(Benzyl(methyl)amino)-1-(5-chloro-6-methoxynaphthalen-2-yl)propan-1-ol (**25b**) hydrochloride.* Yield 85.4% as a white solid. MS (ESI) *m*/*z*: 370.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.64 (s, 3H), 2.74–2.88 (m, 2H), 3.72–3.79 (m, 2H), 4.03 (s, 3H), 4.23 (m, 2H), 5.04 (m, 1H), 5.73 (br, 1H), 7.27–7.31 (m, 3H), 7.38–7.40 (m, 2H), 7.61–7.63 (d, J = 8.0 Hz, 1H), 7.76–7.78 (m, 1H), 7.94–7.96 (d, J = 8.4 Hz, 1H), 8.07–8.11 (m, 2H).

*4.1.15. General procedure for the preparation of compounds **27a–b***

Aryl alcohol **25** (8 mmol) was first reacted with *p*-toluenesulfonyl chloride (8.8 mmol) in acetonitrile (30 mL), then treated with morpholine (8.8 mmol) as procedure C. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **27** hydrochloride.

*4.1.15.1. N-Benzyl-3-(3,4-dichlorophenyl)-N-methyl-3-morpholinopropan-1-amine (**27a**) hydrochloride.* Yield 48.5% as a white solid, the purity was 98.3% by HPLC analysis. Mp: 257–259 °C. MS (ESI) *m*/*z*: 393.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45–2.58 (m, 2H), 2.49–2.58 (m, 2H), 2.69 (s, 3H), 2.87–2.95 (m, 2H), 3.08–3.15 (m, 2H), 3.73–3.79 (m, 4H), 4.24 (s, 2H), 4.31–4.33 (d, J = 6.4 Hz, 1H), 7.36–7.48 (m, 6H), 7.66–7.68 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.37, 33.42, 43.17, 43.29, 49.13, 51.21, 51.32, 61.33, 66.24, 121.20, 121.69, 122.38, 123.02, 123.54, 123.89, 125.09, 126.15, 127.36, 130.25, 132.82, 135.58. HRMS calcd for $C_{21}H_{27}Cl_2N_2O$ $(M + H)^+$, 393.1500; found, 393.1508.

*4.1.15.2. N-Benzyl-3-(5-chloro-6-methoxynaphthalen-2-yl)-N-methyl-3-morpholinopropan-1-amine (**27b**) hydrochloride.* Yield 44.3% as a white solid, the purity was 98.9% by HPLC analysis. Mp: 248–250 °C. MS (ESI) *m*/*z*: 439.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46–2.74 (m, 2H), 2.68 (s, 3H), 2.84–2.94 (m, 2H), 2.96–3.01 (m, 4H), 3.86 (m, 4H), 4.01 (s, 3H), 4.26 (s, 2H), 4.59–4.61 (d, J = 8.8 Hz, 1H), 7.26–7.29 (t, J = 6.4 Hz, 3H), 7.39–7.40 (d, J = 6.0 Hz, 2H), 7.62–7.64 (d, J = 9.2 Hz, 1H), 7.76–7.79 (dd, J = 0.8, 8.0 Hz, 1H), 7.96–7.99 (d, J = 8.8 Hz, 1H), 8.09–8.13 (t, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.43, 38.29, 42.18, 48.31, 49.67, 50.17, 51.24, 63.35, 67.18, 117.09, 120.18, 121.24, 122.15, 122.36, 124.49, 125.81, 126.57, 126.92, 128.43, 130.16, 131.25, 136.90, 142.13, 156.27. HRMS calcd for $C_{26}H_{32}ClN_2O_2$ $(M + H)^+$, 439.2152; found, 439.2158.

*4.1.16. 3-(2,4-Difluorophenyl)-N-methyl-3-morpholinopropan-1-amine (**28**) hydrochloride*

A 100 mL hydrogenation reactor was charged with Pd/C (5% Pd content, 0.1 g), methanol (20 mL) and **23b** hydrochloride (1.3 g, 3 mmol). The reactor was pressurized with hydrogen (0.1 MPa), and then stirred at room temperature for 6 h. The reaction mixture was filtered to remove catalyst, and the solvent was concentrated under reduced pressure (~30 mmHg) to give a light white solid. The solid was purified by recrystallization from ethanol (10 mL) to yield compound **28** hydrochloride (0.83 g, 80.9% yield) as a white solid. The purity was 99.3% by HPLC analysis. Mp: 202–204 °C. MS (ESI) *m*/*z*: 271.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.52–2.55 (m, 4H), 2.62–2.67 (m, 2H), 2.79–2.82 (m, 2H), 3.03–3.06 (m, 4H), 3.89 (s, 3H), 4.69–4.73 (dd, J = 4.4, 10.8 Hz, 1H), 7.21–7.25 (m, 1H), 7.30–7.35 (m, 1H), 7.82–7.88 (dd, J = 8.4, 14.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.26, 38.43, 42.25, 49.21, 50.38, 52.01, 61.34, 63.18, 115.39, 119.65, 121.34, 132.27, 154.31, 155.29. HRMS calcd for $C_{14}H_{21}F_2N_2O$ $(M + H)^+$, 271.1622; found, 271.1616.

*4.1.17. General procedure for the synthesis of aryl alcohol **30***

Aryl ketone **19** (20 mmol) was treated with paraformaldehyde (22 mmol) and dimethylamine hydrochloride (22 mmol) in ethanol (15 mL) as procedure A. The crude product was purified by recrystallization from ethanol to yield aryl ketone **29**.

Compound **29** (10 mmol) was treated with sodium borohydride (10 mmol) in methanol (30 mL) using procedure B. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **30** hydrochloride.

*4.1.17.1. 3-(Dimethylamino)-1-(4-fluorophenyl)propan-1-ol (**30a**) hydrochloride.* Yield 82.1% as a white solid. MS (ESI) *m*/*z*: 198.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84–1.96 (m, 2H), 2.35 (s, 6H),3.01–3.03 (m, 2H), 4.55 (m, 1H), 5.81 (br, 1H), 7.29–7.31 (d, J = 8.0 Hz, 2H), 7.63–7.65 (d, J = 8.0 Hz, 2H).

*4.1.17.2. 3-(Dimethylamino)-1-(4-(trifluoromethyl)phenyl)propan-1-ol (**30b**) hydrochloride.* Yield 86.5% as a white solid. MS (ESI) *m*/*z*: 248.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81–1.91 (m, 2H), 2.36 (s, 6H),3.00–3.03 (m, 2H), 4.51 (m, 1H), 5.79 (br, 1H), 7.26–7.31 (d, J = 8.0 Hz, 2H), 7.72–7.76 (d, J = 8.0 Hz, 2H).

*4.1.17.3. 3-(Dimethylamino)-1-(4-methoxyphenyl)propan-1-ol (**30c**) hydrochloride.* Yield 92.9% as a white solid. MS (ESI) *m*/*z*: 210.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01–2.12 (m, 2H), 2.43 (s, 6H), 2.87–2.89 (m, 2H), 3.45 (s, 3H), 4.73 (m, 1H), 5.65 (m, 1H), 6.53–6.55 (d, J = 8.4 Hz, 2H), 7.27–7.29 (d, J = 8.0 Hz, 2H).

*4.1.17.4. 3-(Dimethylamino)-1-(p-tolyl)propan-1-ol (**30d**) hydrochloride.* Yield 90.2% as a white solid. MS (ESI) *m*/*z*: 194.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12–2.26 (m, 2H), 2.37 (s, 3H), 2.670 (s, 6H), 2.84–2.89 (m, 2H), 4.57–4.60 (m, 1H), 5.67 (br, 1H), 7.28–7.30 (d, J = 8.0 Hz, 2H), 7.55–7.57 (d, J = 8.0 Hz, 2H).

*4.1.17.5. 1-(4-Chlorophenyl)-3-(dimethylamino)propan-1-ol (**30e**) hydrochloride.* Yield 93.2% as a white solid. MS (ESI) *m*/*z*: 214.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93–2.03 (m, 2H), 2.69 (s, 6H), 2.79–2.84 (m, 2H), 4.51–4.64 (m, 1H), 5.79 (s, 1H), 7.25–7.27 (d, J = 8.0 Hz, 2H), 7.40–7.42 (d, J = 8.0 Hz, 2H).

*4.1.17.6. 1-(2,4-Difluorophenyl)-3-(dimethylamino)propan-1-ol (**30f**) hydrochloride.* Yield 85.2% as a white solid. MS (ESI) *m*/*z*: 216.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24–2.45 (m, 2H), 2.72 (s, 6H), 2.79–2.83 (m, 2H), 4.67–4.69 (m, 1H), 5.73 (br, 1H), 7.23–7.27 (m, 1H), 7.38–7.41 (m, 1H), 8.02–8.03 (m, 1H).

*4.1.17.7. 1-(Benzo[b]thiophen-2-yl)-3-(dimethylamino)propan-1-ol (**30g**) hydrochloride.* Yield 95.0% as a white solid. MS (ESI) *m/z*: 236.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15–2.23 (m, 2H), 2.69 (s, 6H), 2.81–2.85 (m, 2H), 4.83–4.86 (m, 1H), 5.69 (br, 1H), 7.41–7.46 (m, 2H), 7.75 (s, 1H), 7.89–7.93 (m, 1H), 8.00–8.02 (m, 1H).

*4.1.17.8. 1-(Benzo[b]thiophen-3-yl)-3-(dimethylamino)propan-1-ol (**30h**) hydrochloride.* Yield 90.5% as a white solid. MS (ESI) *m/z*: 236.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13–2.24 (m, 2H), 2.67 (s, 6H), 2.83 (m, 2H), 4.87 (m, 1H), 5.72 (br, 1H), 7.45–7.61 (m, 2H), 7.85–7.96 (m, 1H), 8.19 (s, 1H), 8.57 (m, 1H).

*4.1.18. General procedure for the preparation of compounds **32a–m***

Aryl alcohol **30** (8 mmol) was first reacted with *p*-toluenesulfonyl chloride (8.8 mmol) in acetonitrile (30 mL), then treated with cyclic amines **5** (8.8 mmol) as procedure C. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **32** hydrochloride.

*4.1.18.1. 3-(4-Fluorophenyl)-N,N-dimethyl-3-(pyrrolidin-1-yl) propan-1-amine (**32a**) hydrochloride.* Yield 16.7% as a white solid, the purity was 98.0% by HPLC analysis. Mp: 245–247 °C. MS (ESI) *m/z*: 251.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80–1.98 (m, 4H), 2.51–2.53 (m, 2H), 2.67 (s, 6H), 2.80–2.84 (m, 2H), 3.04–3.75 (m, 4H), 4.55–4.57 (m, 1H), 7.26–7.28 (dd, J = 8.0, 12.0 Hz, 2H), 7.74–7.83 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.58, 30.46, 30.52, 32.67, 46.43, 55.57, 57.94, 69.87, 122.34, 122.57, 134.37, 134.69, 142.87, 162.53. HRMS calcd for $C_{15}H_{24}FN_2$ $(M + H)^+$, 251.1924; found, 251.1929.

*4.1.18.2. 3-(4-Fluorophenyl)-N,N-dimethyl-3-morpholinopropan-1-amine (**32b**) hydrochloride.* Yield 39.8% as a white solid, the purity was 99.0% by HPLC analysis. Mp: 251–253 °C. MS (ESI) *m/z*: 267.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51–2.61 (m, 2H), 2.72 (s, 6H), 3.01–3.08 (m, 2H), 3.87 (m, 8H), 4.49 (m, 1H), 7.31–7.35 (t, J = 8.0 Hz, 2H), 7.65–7.69 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.38, 42.23, 42.68, 47.59, 51.24, 52.27, 52.35, 64.37, 67.06, 123.03, 123.18, 134.12, 134.34, 144.93, 165.65. HRMS calcd for $C_{15}H_{24}FN_2$ $(M + H)^+$, 267.1873; found, 267.1865.

*4.1.18.3. 3-(4-Fluorophenyl)-N,N-dimethyl-3-(piperidin-1-yl)propan-1-amine (**32c**) hydrochloride.* Yield 54.2% as a white solid, the purity was 99.3% by HPLC analysis. Mp: 226–228 °C. MS (ESI) *m/z*: 265.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24–2.01 (m, 6H), 2.51–2.53 (m, 2H), 2.67 (s, 6H), 2.80–2.84 (m, 2H), 3.04–3.75 (m, 4H), 4.55–4.57 (m, 1H), 7.26–7.30 (t, J = 8.0 Hz, 2H), 7.74–7.78 (t, J = 8.0, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.56, 25.79, 28.34, 36.23, 43.98, 45.43, 47.69, 55.21, 64.43, 122.77, 122.95, 133.32, 134.45, 145.95, 167.23. HRMS calcd for $C_{16}H_{26}FN_2$ $(M + H)^+$, 265.2080; found, 265.2074.

*4.1.18.4. N,N-Dimethyl-3-morpholino-3-(4-(trifluoromethyl)phenyl) propan-1-amine (**32d**) hydrochloride.* Yield 25.8% as a white solid, the purity was 98.6% by HPLC analysis. Mp: 236–238 °C. MS (ESI) *m/z*: 317.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51–2.62 (m, 2H), 2.64 (s, 6H), 2.86–2.88 (m, 4H), 3.53 (m, 2H), 3.84–4.03 (m, 4H), 4.79 (m, 1H), 7.25–7.27 (d, J = 8.0 Hz, 2H), 7.74–7.76 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.45, 42.23, 42.79, 49.57, 51.44, 52.27, 63.76, 65.16, 128.51, 129.32, 129.41, 131.43, 132.09, 135.11, 138.24. HRMS calcd for $C_{16}H_{24}F_3N_2O$ $(M + H)^+$, 317.1841; found, 317.1833.

*4.1.18.5. N,N-Dimethyl-3-(pyrrolidin-1-yl)-3-(4-(trifluoromethyl) phenyl)propan-1-amine (**32e**) hydrochloride.* Yield 35.6% as a white solid, the purity was 98.1% by HPLC analysis. Mp: 231–233 °C. MS (ESI) *m/z*: 301.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.65–2.01 (m, 4H), 2.55–2.60 (m, 2H), 2.68 (s, 6H), 2.78–2.88 (m, 2H), 3.16–3.80 (m, 4H), 4.78–4.79 (m, 1H), 7.23–7.25 (d, J = 8.0 Hz, 2H), 7.71–7.73 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.41, 30.87, 45.26, 45.79, 57.24, 57.38, 67.41, 125.31, 127.40, 129.00, 131.42, 132.11, 137.44, 137.13. HRMS calcd for $C_{16}H_{24}F_3N_2$ $(M + H)^+$, 301.1892; found, 301.1884.

*4.1.18.6. 3-(4-Methoxyphenyl)-N,N-dimethyl-3-morpholinopropan-1-amine (**32f**) hydrochloride.* Yield 40.0% as a white solid, the purity was 98.2% by HPLC analysis. Mp: 194–196 °C. MS (ESI) *m/z*: 279.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.14–2.36 (m, 2H), 2.41 (s, 6H), 2.47–2.74 (m, 4H), 3.29–3.87 (m, 4H), 3.41 (s, 3H), 3.52–3.54 (m, 2H), 4.29–4.31 (m, 1H), 6.55–6.58 (d, J = 8.4 Hz, 2H), 7.25–7.29 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.01, 42.12, 42.24, 48.36, 51.53, 53.02, 54.90, 61.43, 67.09, 121.45, 122.38, 133.51, 133.62, 145.43, 161.47. HRMS calcd for $C_{16}H_{27}N_2O_2$ $(M + H)^+$, 279.2073; found, 279.2079.

*4.1.18.7. N,N-Dimethyl-3-morpholino-3-(p-tolyl)propan-1-amine (**32g**) hydrochloride.* Yield 50.0% as a white solid, the purity was 98.7% by HPLC analysis. Mp: 234–236 °C. MS (ESI) *m/z*: 263.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H), 2.62–2.65 (t, J = 6.4 Hz, 2H), 2.70 (s, 6H), 2.80–2.84 (t, J = 6.4 Hz, 2H), 2.87–2.94 (m, 4H), 3.66–3.87 (m, 4H), 4.51–4.53 (d, J = 8.0 Hz, 1H), 7.30–7.32 (d, J = 8.0 Hz, 2H), 7.57–7.59 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.42, 26.18, 42.58, 42.73, 47.57, 51.24, 52.59, 54.21, 61.38, 65.10, 122.31, 122.42, 132.35, 132.44, 145.24, 148.37. HRMS calcd for $C_{16}H_{27}N_2O$ $(M + H)^+$, 263.2123; found, 263.2128.

*4.1.18.8. 3-(4-Chlorophenyl)-N,N-dimethyl-3-morpholinopropan-1-amine (**32h**) hydrochloride.* Yield 50.5% as a white solid, the purity was 98.4% by HPLC analysis. Mp: 178–180 °C. MS (ESI) *m/z*: 283.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.01–2.06 (m, 1H), 2.29–2.37 (m, 4H), 2.39–2.42 (m, 1H), 2.69 (s, 6H), 2.79–2.86 (m, 1H), 3.01–3.08 (m, 1H), 3.51–3.55 (m, 4H), 3.57–3.61 (t, J = 7.2 Hz, 1H), 7.28–7.30 (d, J = 8.0 Hz, 2H), 7.41–7.43 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.47, 43.05, 43.15, 46.81, 51.41, 52.09, 52.24, 65.68, 128.41, 128.67, 133.73, 134.25, 138.41, 141.24. HRMS calcd for $C_{15}H_{24}ClN_2O$ $(M + H)^+$, 283.1577; found, 283.1568.

*4.1.18.9. 3-(2,4-Difluorophenyl)-N,N-dimethyl-3-morpholinopropan-1-amine (**32i**) hydrochloride.* Yield 55.0% as a white solid, the purity was 98.1% by HPLC analysis. Mp: 246–248 °C. MS (ESI) *m/z*: 285.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61–2.66 (m, 2H), 2.71 (s, 6H), 2.78–2.84 (m, 2H), 2.93–3.03 (m, 4H), 3.90 (m, 4H), 4.67–4.69 (m, 1H), 7.25–7.30 (m, 1H), 7.37–7.43 (m, 1H), 8.02–8.03 (d, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.15, 42.35, 43.62, 47.33, 50.14, 53.00, 53.14, 57.24, 64.17, 118.19, 121.68, 123.24, 134.58, 154.10, 157.28. HRMS calcd for $C_{15}H_{23}F_2N_2O$ $(M + H)^+$, 285.1778; found, 285.1785.

*4.1.18.10. 3-(Benzo[b]thiophen-2-yl)-N,N-dimethyl-3-morpholinopropan-1-amine (**32j**) hydrochloride.* Yield 45.9% as a white solid, the purity was 98.8% by HPLC analysis. Mp: 221–223 °C. MS (ESI) *m/z*: 305.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.49–2.51 (m, 1H), 2.75 (s, 6H), 2.75–2.83 (m, 2H), 3.07 (m, 1H), 3.07–3.28 (m, 4H), 3.85–3.92 (m, 4H), 4.95–4.98 (m, 1H), 7.43–7.47 (m, 2H), 7.79 (s, 1H), 7.90–7.93 (m, 1H), 8.00–8.03 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.21, 44.07, 44.20, 49.29, 50.13, 52.32, 53.00, 56.81, 61.42, 121.35, 123.62, 124.14, 127.26,

129.30, 133.50, 139.44, 147.27. HRMS calcd for $C_{17}H_{25}N_2OS$ $(M + H)^+$, 305.1688; found, 305.1680.

*4.1.18.11. 3-(Benzo[b]thiophen-2-yl)-N,N-dimethyl-3-(pyrrolidin-1-yl)propan-1-amine (**32k**) hydrochloride.* Yield 45.6% as a white solid, the purity was 98.6% by HPLC analysis. Mp: 205–207 °C. MS (ESI) *m/z*: 289.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93 (m, 4H), 2.52–2.60 (m, 2H), 2.75 (s, 6H), 2.76 (m, 2H), 3.05–3.11 (m, 2H), 3.20 (m, 2H), 4.96–5.00 (m, 1H), 7.41–7.45 (m, 2H), 7.79 (s, 1H), 7.88–7.90 (m, 1H), 7.99–8.02 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.62, 30.45, 32.18, 47.24, 55.34, 55.62, 58.29, 68.38, 120.76, 122.31, 124.22, 126.31, 128.35, 132.41, 139.79, 145.63. HRMS calcd for $C_{17}H_{25}N_2S$ $(M + H)^+$, 289.1738; found, 289.1746.

*4.1.18.12. 3-(Benzo[b]thiophen-3-yl)-N,N-dimethyl-3-morpholinopropan-1-amine (**32l**) hydrochloride.* Yield 46.8% as a white solid, the purity was 99.3% by HPLC analysis. Mp: 229–231 °C. MS (ESI) *m/z*: 305.2 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$-d): δ 2.82–2.85 (m, 2H), 2.87–2.91 (m, 2H), 2.87–3.01 (m, 2H), 3.26–3.30 (s, 6H), 3.86–3.93 (t, J = 4.8 Hz, 2H), 3.99–4.05 (t, J = 4.8 Hz, 2H), 4.11–4.17 (t, J = 11.6 Hz, 1H), 4.28–4.34 (t, J = 12.0 Hz, 1H), 5.48–5.50 (d, J = 6.4 Hz, 1H), 7.44–7.63 (m, 2H), 7.87–7.99 (m, 1H), 8.20 (s, 1H), 8.62 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.17, 42.35, 42.67, 47.24, 50.14, 51.46, 55.45, 56.41, 65.14, 122.21, 123.31, 123.84, 126.32, 126.58, 131.49, 134.27, 139.33. HRMS calcd for $C_{17}H_{25}N_2OS$ $(M + H)^+$, 305.1688; found, 305.1694.

*4.1.18.13. 3-(Benzo[b]thiophen-3-yl)-N,N-dimethyl-3-(pyrrolidin-1-yl)propan-1-amine (**32m**) hydrochloride.* Yield 43.2% as a white solid, the purity was 98.0% by HPLC analysis. Mp: 206–208 °C. MS (ESI) *m/z*: 289.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91 (m, 4H), 2.62–2.70 (m, 2H), 2.73 (s, 6H), 2.97–3.02 (m, 2H), 3.12 (m, 4H), 4.98–5.01 (d, J = 9.6 Hz, 1H), 7.44–7.52 (m, 2H), 8.05–8.09 (t, J = 8.4 Hz, 2H), 8.22 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.32, 30.09, 32.58, 45.21, 54.61, 54.74, 55.28, 57.36, 64.30, 121.90, 122.35, 122.45, 125.58, 126.31, 130.14, 132.47, 137.22. HRMS calcd for $C_{17}H_{25}N_2S$ $(M + H)^+$, 289.1738; found, 289.1747.

*4.1.19. General procedure for the synthesis of aryl alcohol **34***

Aryl ketone **8** (50 mmol) was treated with dimethylamine hydrochloride (50 mmol) in acetonitrile (100 mL) as procedure D. The crude product was purified by recrystallization from ethanol to give compound **33**.

Aryl ketone **33** (10 mmol) was treated with sodium borohydride (10 mmol) in methanol (30 mL) using procedure B. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **34** hydrochloride.

*4.1.19.1. 1-(3,4-Dichlorophenyl)-3-(dimethylamino)propan-1-ol (**34a**) hydrochloride.* Yield 93.6% as a white solid. MS (ESI) *m/z*: 248.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82–1.93 (m, 2H), 2.37 (s, 6H), 3.06 (m, 2H), 4.56 (s, 1H), 5.83 (br, 1H), 7.35–7.37 (d, J = 8.4 Hz, 1H), 7.63–7.65 (m, 2H).

*4.1.19.2. 1-(5-Chloro-6-methoxynaphthalen-2-yl)-3-(dimethylamino)propan-1-ol (**34b**) hydrochloride.* Yield 90.3% as a white solid. MS (ESI) *m/z*: 294.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.85–1.97 (m, 2H), 2.35 (s, 6H), 3.07–3.09 (m, 2H), 3.98 (s, 3H), 4.59 (s, 1H), 5.79 (br, 1H), 7.52–7.54 (d, J = 8.0 Hz, 1H), 7.64–7.66 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H, Ar–H), 7.90–7.92 (d, J = 8.0 Hz, 1H), 8.05–8.07 (d, J = 8.8 Hz, 1H).

*4.1.20. General procedure for the preparation of compounds **36a–e***

Aryl alcohol **34** (8 mmol) was first reacted with *p*-toluenesulfonyl chloride (8.8 mmol) in acetonitrile (30 mL), then treated with cyclic amines **5** (8.8 mmol) as procedure C. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **36** hydrochloride.

*4.1.20.1. 3-(3,4-Dichlorophenyl)-N,N-dimethyl-3-morpholinopropan-1-amine (**36a**) hydrochloride.* Yield 52.2% as a white solid, the purity was 99.7% by HPLC analysis. Mp: 172–174 °C. MS (ESI) *m/z*: 317.1 $(M + H)^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.66–2.69 (m, 2H), 2.11–2.16 (m, 1H), 2.70 (s, 6H), 2.82–2.94 (m, 5H), 3.74–3.85 (m, 1H), 3.85 (m, 2H), 3.99–4.04 (m, 2H), 4.67 (s, 1H), 7.75 (s, 1H), 7.79–7.81 (d, J = 7.8 Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 24.36, 42.05, 42.63, 49.61, 51.01, 53.25, 63.50, 66.11, 130.78, 131.82, 132.42, 132.71, 133.36. HRMS calcd for $C_{15}H_{23}Cl_2N_2O$ $(M + H)^+$, 317.1182; found, 317.1191.

*4.1.20.2. 3-(3,4-Dichlorophenyl)-N,N-dimethyl-3-(piperidin-1-yl)propan-1-amine (**36b**) hydrochloride.* Yield 51.8% as a white solid, the purity was 99.5% by HPLC analysis. Mp: 169–171 °C. MS (ESI) *m/z*: 315.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.46 (m, 2H), 1.76 (m, 4H), 2.54–2.57 (m, 2H), 2.57–2.72 (m, 2H), 2.75 (s, 6H), 2.95–3.06 (m, 4H), 4.42–4.45 (d, J = 10.8 Hz, 1H), 7.53–7.55 (d, J = 8.4 Hz, 1H), 7.71–7.73 (t, J = 4.4 Hz, 1H), 7.83 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.62, 26.58, 27.83, 36.27, 44.36, 45.27, 47.57, 54.28, 62.39, 127.62, 129.32, 132.45, 132.57, 133.61, 134.27. HRMS calcd for $C_{16}H_{25}Cl_2N_2$ $(M + H)^+$, 315.1392; found, 315.1387.

*4.1.20.3. 3-(3,4-Dichlorophenyl)-N,N-dimethyl-3-(piperazin-1-yl)propan-1-amine (**36c**) hydrochloride.* Yield 50.2% as a white solid, the purity was 99.1% by HPLC analysis. Mp: 257–259 °C. MS (ESI) *m/z*: 316.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26–2.50 (m, 1H), 2.26–2.50 (m, 1H), 2.74 (s, 6H), 2.78–2.83 (m, 1H), 2.96–3.06 (m, 4H), 3.08–3.12 (m, 1H), 3.25–3.27 (m, 4H), 4.19–4.23 (t, J = 8.0 Hz, 1H), 7.43–7.46 (dd, J = 2.0, 8.0 Hz, 1H), 7.75–7.77 (t, J = 3.2 Hz, 1H), 7.92 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.44, 37.42, 42.56, 43.69, 49.28, 54.10, 54.35, 64.23, 127.32, 129.00, 131.05, 132.44, 132.87, 135.62. HRMS calcd for $C_{15}H_{24}Cl_2N_3$ $(M + H)^+$, 316.1345; found, 316.1353.

*4.1.20.4. 3-(3,4-Dichlorophenyl)-N,N-dimethyl-3-(pyrrolidin-1-yl)propan-1-amine (**36d**) hydrochloride.* Yield 47.0% as a white solid, the purity was 99.8% by HPLC analysis. Mp: 256–258 °C. MS (ESI) *m/z*: 301.1 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82–1.99 (m, 4H), 2.52–2.57 (m, 3H), 2.70 (s, 6H), 2.89–2.92 (m, 3H), 3.18 (m, 1H), 3.43 (m, 1H), 4.67 (s, 1H), 7.77–7.80 (d, J = 8.4 Hz, 2H), 8.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.79, 31.73, 47.28, 57.75, 57.83, 69.65, 134.34, 136.22, 136.67, 137.21, 137.92, 139.79. HRMS calcd for $C_{15}H_{23}Cl_2N_2$ $(M + H)^+$, 301.1233; found, 301.1237.

*4.1.20.5. 3-(5-Chloro-6-methoxynaphthalen-2-yl)-N,N-dimethyl-3-(pyrrolidin-1-yl)propan-1-amine (**36e**) hydrochloride.* Yield 44.9% as a white solid, the purity was 99.5% by HPLC analysis. Mp: 215–217 °C. MS (ESI) *m/z*: 347.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93 (m, 4H), 2.51–2.62 (m, 2H), 2.63–2.74 (m, 2H), 2.68 (s, 6H), 2.91–2.97 (m, 2H), 3.07 (m, 2H), 4.02 (s, 3H), 4.66–4.70 (dd, J = 4.0, 9.6 Hz, 1H), 7.64–7.66 (d, J = 9.2 Hz, 1H), 7.98–8.00 (d, J = 8.8 Hz, 1H), 8.05–8.07 (d, J = 8.8 Hz, 1H), 8.17–8.19 (d, J = 8.8 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.66, 26.57, 27.68, 43.24, 52.77, 52.98, 57.24, 58.92, 64.98, 117.35, 121.21, 123.35, 125.67, 125.81, 125.92, 126.53, 127.02, 139.26, 158.32. HRMS calcd for $C_{20}H_{28}ClN_2O$ $(M + H)^+$, 347.1885; found, 347.1893.

*4.1.21. 3-(3,4-Dichlorophenyl)-N,N-diethyl-3-(pyrrolidin-1-yl) propan-1-amine (**40**) hydrochloride*

3-Chloro-1-(3,4-dichlorophenyl)propan-1-one **13** (50 mmol) was treated with diethylamine hydrochloride (50 mmol) in acetonitrile (100 mL) as procedure D. The crude product was purified by recrystallization from ethanol to give compound **37**. MS (ESI) *m*/*z*: 274.1 $(M + H)^+$.

Aryl ketone **37** (10 mmol) was treated with sodium borohydride (10 mmol) in methanol (30 mL) using procedure B. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **38** hydrochloride. MS (ESI) *m*/*z*: 276.1 $(M + H)^+$.

Aryl alcohol **38** (8 mmol) was first reacted with *p*-toluenesulfonyl chloride (8.8 mmol) in acetonitrile (30 mL), then treated with pyrrolidine (8.8 mmol) as procedure C. The crude product was converted into the corresponding hydrochloride salt and purified by recrystallization from ethanol to yield compound **40** hydrochloride. Yield 53.1% as a white solid, the purity was 99.3% by HPLC analysis. Mp: 249–251 °C. MS (ESI) *m*/*z*: 329.2 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13–1.16 (t, J = 7.2 Hz, 6H), 1.85–1.98 (m, 4H), 2.58–2.61 (m, 2H), 2.61–2.83 (m, 2H), 2.91–2.96 (m, 2H), 3.06 (m, 4H), 3.19 (m, 1H), 3.74 (m, 1H), 4.63 (m, 1H), 7.75–7.81 (dd, J = 3.2, 8.4 Hz, 2H), 8.10 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.28, 24.45, 35.72, 48.54, 48.92, 49.35, 51.22, 53.15, 62.45, 67.28, 130.65, 132.01, 132.68, 133.45, 133.79, 135.25. HRMS calcd for $C_{17}H_{27}Cl_2N_2$ $(M + H)^+$, 329.1551; found, 329.1557.

4.2. Biology evaluation

4.2.1. Inhibition of [^{3}H] neurotransmitter uptake in HEK293 cells expressing the hSERT, hNET and hDAT

Assays were conducted using procedures identical to those described by Eshleman [19]. The cells were seeded in 24-well cluster plates at a density of 1.5 million cells per well. On the second day, the cells were incubated with HBSS buffer containing the tested compound and ^{3}H-serotonin (3 nM) for ten minutes at 37 °C. Then, serotonin uptake was terminated by rinsing three times with ice-cold PBS buffer and cells were lysed using 0.1 mL of 2 M NaOH. Cell lysate was analyzed for radioactivity using a scintillation counter. Nonspecific uptake was defined with 10 μM DOV 21947. The protocols for dopamine and epinephrine uptake were the same with that for serotonin.

4.2.2. CNS receptor screening

Compound **36a** was characterized in 55 CNS receptor binding assays to assess the selectivity and specific interactions of **36a** with the monoamine transporters. The test was carried by Cerep (Celle L'Evescault, France, Cerep study number 100005534), the test using a similar procedure as described previously [17].

4.2.3. In vivo pharmacology

4.2.3.1. Measurement of antidepressants activity in rat forced swim test (FST). To evaluate the antidepressants activity of the compounds, the inhibitory effects on immobility in forced swim test in rats were measured according to the methods described by Porsolt et al. [16]. Rats were individually placed into clear glass cylinders (40 cm tall × 18 cm in diameter) containing 25 ± 1 °C water 15 cm deep. Rats were administered vehicle, venlafaxine (30 mg/kg) as a positive control, or test compounds **18c**, **36a**, or **36d** (5, 10 and 20 mg/kg). 1 h following PO administration, rats were placed in the water, and the time of the animal spent immobile was recorded over a 6 min trial. Immobility was defined as the postural position of floating in the water. Data were analyzed by one way analysis of variance (ANOVA) with treatment group (vehicle, venlafaxine, or test compounds) as the between group variable and total time immobile (seconds over the 6 min trial) as the dependent variable. Significant main effects were followed up with the post hoc Fisher's test.

4.2.3.2. Measurement of locomotor activity. Locomotor activity was assessed with an animal activity monitoring apparatus (Shanghai Jiliang Software Technology Co. Ltd.). 60 min after administration, rats were placed individually in 40 cm × 40 cm × 50 cm plastic cages, to which they had not been previously exposed, under dim light and sound-attenuated conditions. Locomotor activity was monitored at 5 min intervals for up to 30 min. The results of the locomotor activity tests were expressed as mean ± SEM.

4.2.4. Pharmacokinetic study

Male SD rats (SLRC Laboratory Animal Inc., Shanghai, China) were used. For intravenous administration, prepared dosing solution was injected via the femoral vein. The rats were fasted overnight before drug administration and until 6 h after dosing. For the PO experiment, rats (24 in each group) were given a single dose of 2 mg/kg, and heparinized samples of blood were collected at 5, 15, 30 min, 1, 2, 4, 8, and 24 h postdose. For the iv experiment, rats (24 in each group) were given a single 0.5 mg/kg dose, and blood samples were collected at 5, 15, 30 min, 1, 2, and 4 h postdose. Plasma was harvested after centrifugation and stored frozen at −40 °C until analyzed. The concentrations of compounds in plasma were determined by LC/MS/MS (Shimadzu LC-30AD). The results are shown as the maximum plasma concentration (C_{max}), the time to reach peak plasma concentration (T_{max}), terminal half-life ($T_{1/2}$), and the area under the plasma concentration-time curve from zero to time infinity ($AUC_{0\text{-inf}}$).

4.2.5. Acute toxicity test

Male and female KM mice (18–22 g) were purchased from SLRC Laboratory Animal Inc., Shanghai, China. Mice were randomly divided into seven groups with ten mice each (five males, five females). Mice were orally given **36a** with a single dose 150, 300,450, 600,750, and 900 mg/kg or vehicle control, respectively. The mouse death was monitored daily and recorded up to 14 days after treatment. All animals were euthanized and necropsied for gross lesion examination for possible damage to the heart, liver, and kidneys.

4.2.6. Ames test

The TA98 and TA100 strains of *Salmonella typhimurium* were utilized for mutagenicity assay. Compound 36a was dissolved in DMSO and added to bacterial cultures at concentrations up to 5000 μg/plate in the presence or absence of rat liver S9 metabolic activating system. Each dose level, vehicle, and positive control was plated in triplicate. The test methodology was based on established procedures as reported [20].

Acknowledgments

This work is supported by National Natural Science Foundation of China (Grant No. 81302631), Shanghai Rising-Star Program (Grant No. 13QB1403800), Key Technologies R&D Program of Shanghai Municipal Science and Technology Commission (Grant No. 14431901500), and the National Science and Technology Major Project (Grant No. 2012ZX09103101-038). We thank Professor Lei Fu (Shanghai Jiao Tong University, China) for helpful discussion.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.08.045.

References

[1] S.C. Dilsaver, Y.W. Chen, A.C. Swann, A.M. Shoaib, K.J. Krajewski, Suicidality in patients with pure and depressive mania, Am. J. Psychiatry 151 (1994) 1312–1315.

[2] P. Skolnick, P. Popik, A. Janowsky, B. Beer, A. Lippa, "Broad spectrum" antidepressants: Is more better for the treatment of depression? Life Sci. 73 (2003) 3175–3179.

[3] J. Rakofsky, P. Holtzheimer, C. Nemeroff, Emerging targets for antidepressant therapies, Curr. Opin. Chem. Biol. 13 (2009) 291–302.

[4] M.Z. Wróbel, A. Chodkowski, F. Herold, A. Gomółka, J. Kleps, A.P. Mazurek, F. Pluciński, A. Mazurek, G. Nowak, A. Siwek, K. Stachowicz, A. Sławińska, M. Wolak, B. Szewczyk, G. Satała, A.J. Bojarski, J. Turło, Synthesis and biological evaluation of novel pyrrolidine-2,5-dione derivatives as potential antidepressant agents. Part 1, Eur. J. Med. Chem. 63 (2013) 484–500.

[5] A.M. Helguera, A. Pérez-Garrido, A. Gaspar, J. Reis, F. Cagide, D. Vina, M.N.D.S. Cordeiro, F. Borges, Combining QSAR classification models for predictive modeling of human monoamine oxidase inhibitors, Eur. J. Med. Chem. 59 (2013) 75–90.

[6] J. Prins, B. Olivier, S.M. Korte, Triple reuptake inhibitors for treating subtypes of major depressive disorder: the monoamine hypothesis revisited, Expert Opin. Inv. Drug 20 (2011) 1107–1130.

[7] R.C. Shelton, The dual-action hypothesis: does pharmacology matter? J. Clin. Psychiatry 65 (2004) 5–10.

[8] O. Berton, E. Nestler, New approaches to antidepressant drug discovery: beyond monoamines, Nat. Rev. Neurosci. 7 (2006) 137–151.

[9] Y. Liang, E. Richelson, Triple reuptake inhibitors: next-generation antidepressants, Prim. Psychiatry 15 (2008) 50–56.

[10] P. Skolnick, P. Popik, A. Janowsky, B. Beer, A.S. Lippa, Antidepressant-like actions of DOV 21,947: a "triple" reuptake inhibitor, Eur. J. Pharmacol. 461 (2003) 99–104.

[11] Y. Liang, A.M. Shaw, M. Boules, S. Briody, J. Robinson, A. Oliveros, E. Blazar, K. Williams, Y. Zhang, P.R. Carlier, E. Richelson, Antidepressant-like pharmacological profile of a novel triple reuptake inhibitor, (1S,2S)-3-(methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (PRC200-SS), J. Pharmacol. Exp. Ther. 327 (2008) 573–583.

[12] F. Micheli, P. Cavanni, D. Andreotti, R. Arban, R. Benedetti, B. Bertani, M. Bettati, L. Bettelini, G. Bonanomi, S. Braggio, 6-(3,4-Dichlorophenyl)-1-[(methyloxy) methyl]-3-azabicyclo [4.1.0] heptane: a new potent and selective triple reuptake inhibitor, J. Med. Chem. 53 (2010) 4989–5001.

[13] N.M. Deschamps, V.I. Elitzin, B. Liu, M.B. Mitchell, M.J. Sharp, E.A. Tabet, An enyne cycloisomerization approach to the triple reuptake inhibitor GSK1360707F, J. Org. Chem. 76 (2011) 712–715.

[14] F. Micheli, P. Cavanni, R. Arban, R. Benedetti, B. Bertani, M. Bettati, L. Bettelini, G. Bonanomi, S. Braggio, A. Checchia, 1-(Aryl)-6-[alkoxyalkyl]-3-azabicyclo [3.1.0] hexanes and 6-(aryl)-6-[alkoxyalkyl]-3-azabicyclo [3.1.0] hexanes: a new series of potent and selective triple reuptake inhibitors, J. Med. Chem. 53 (2010) 2534–2551.

[15] Y.Y. Zheng, L. Guo, X.C. Zhen, J.Q. Li, Synthesis and antidepressant activity of arylalkanol-piperidine derivatives as triple reuptake inhibitors, Eur. J. Med. Chem. 54 (2012) 123–136.

[16] R.D. Porsolt, G. Anton, N. Blavet, M. Jalfre, Behavioural despair in rats: a new model sensitive to antidepressant treatments, Eur. J. Pharmacol. 47 (1978) 379–391.

[17] A.C. McCreary, J.C. Glennon, C.R. Ashby, H.Y. Meltzer, Z. Li, J.H. Reinders, M.B. Hesselink, S.K. Long, A.H. Herremans, H. Van Stuivenberg, SLV313 (1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-4-[5-(4-fluoro-phenyl)-pyridin-3-ylmethyl]-piperazine monohydrochloride): a novel dopamine D2 receptor antagonist and 5-HT1A receptor agonist potential antipsychotic drug, Neuropsychopharmacology 32 (2006) 78–94.

[18] A. Reichel, The role of blood-brain barrier studies in the pharmaceutical industry, Curr. Drug Metab. 7 (2006) 183–203.

[19] A. Eshleman, M. Carmolli, M. Cumbay, C. Martens, K. Neve, A. Janowsky, Characteristics of drug interactions with recombinant biogenic amine transporters expressed in the same cell type, J. Pharm. Exp. Ther. 289 (1999) 877–885.

[20] D.M. Maron, B.N. Ames, Revised methods for the Salmonella mutagenicity test, Mutat. Res. 113 (1983) 173–215.