Bioorganic & Medicinal Chemistry xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Exploration of substituted arylpiperazine–tetrazoles as promising dual norepinephrine and dopamine reuptake inhibitors

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ARTICLE INFO

Article history:
Received 8 August 2016
Revised 29 August 2016
Accepted 2 September 2016
Available online xxxx

Keywords:
Arylpiperazine–tetrazoles
Selective norepinephrine and dopamine reuptake inhibitors
Norepinephrine reuptake inhibitors
Dopamine reuptake inhibitors

ABSTRACT

In the search for potent dual norepinephrine and dopamine reuptake inhibitors, several substituted arylpiperazine–tetrazoles were designed, synthesized and evaluated for their neurotransmitter reuptake inhibitory activities. Various derivatives exhibited selective and strong neurotransmitter reuptake inhibitory activity. In particular, compounds with a three-carbon linker displayed selective and stronger potency than those with two-carbon and four-carbon linkers. Interestingly, six compounds, **9b**, **9c**, **9d**, **9o**, **9q** and **9u** displayed more effective activity than the standard drug, bupropion. The provided SAR data and potent biological activity can offer useful guidelines for designing dual norepinephrine and dopamine reuptake inhibitors as effective therapeutic agents for treatment of several central nervous system diseases.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder traditionally expected to affect 3–5% of children and adults. It is characterized by age inappropriate levels of attention, impulsivity, and hyperactivity.[1–3] Pathophysiologically, the cause of ADHD is commonly associated with functional impairments in the neurotransmitter system, mainly dopamine and norepinephrine.[4,5] A number of drugs aimed at improving prefrontal cortex (PFC) cognitive function are being used for the treatment of ADHD. These include dual norepinephrine (NE) and dopamine (DA) reuptake inhibitors (psychostimulants) or selective NE reuptake inhibitors (SNRIs).[6]

The abuse potential of psychostimulants generates significant concerns about their use.[7,8] Similarly, marketed dual NE and DA reuptake inhibitor, nomifensine, was investigated for the treatment of ADHD. However, it was withdrawn from the market due to its association with immune hemolytic anemia.[9–12] Bupropion, a dual NE and DA reuptake inhibitor, has been used for the treatment of ADHD.[13] The limitation of this drug is an increased risk for epileptic seizures, and it was withdrawn from the market for some time.[14] On the other hand, an approved NE inhibitor, atomoxetine, for the treatment of ADHD, was generally considered less efficacious compared to the stimulants.[7,8]

The limitations and side effects of established NE or dual (NE and DA) inhibitors necessitate the development of safer and more effective therapeutic agents for the treatment of ADHD. In addition, there are only few dual NE and DA reuptake inhibitors.[15–17] For treatment of ADHD, it has been hypothesized that a dual NE and DA inhibitor with a potency order of NE > DA would lead to a compound with superior efficacy and safety.[18] Therefore, we undertook to develop a new dual NE and DA inhibitor which, in a single molecule, could improve or balance the activity and might overcome the limitations of existing ADHD therapies.

A common strategy to avoid a drug-related side effect is to design molecules with different chemical scaffolds. Based on this fact, 4-benzylpiperidine carboxamides and arylpiperazine–benzylpiperidines were successfully developed as neurotransmitter reuptake inhibitors.[19,20] These derivatives have three fundamental structures, aromatic region (A), linker (B) and heterocyclic amine (C). Furthermore, GBR-12935 with similar structural moieties possesses dopamine reuptake inhibition.[21] In addition, amine containing compounds are a rich source of reuptake inhibitors with a variety of profiles.[22] Thus, considering the basic structural components (A, B and C), we designed substituted arylpiperazine–tetrazoles as possible dual reuptake inhibitors (Fig. 1). Tetrazole was considered for the design of new dual reuptake inhibitors since it is a bioisosteric form of carboxamide. The details of synthetic pathways employed, the neurotransmitter reuptake inhibitory

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http://dx.doi.org/10.1016/j.bmc.2016.09.005
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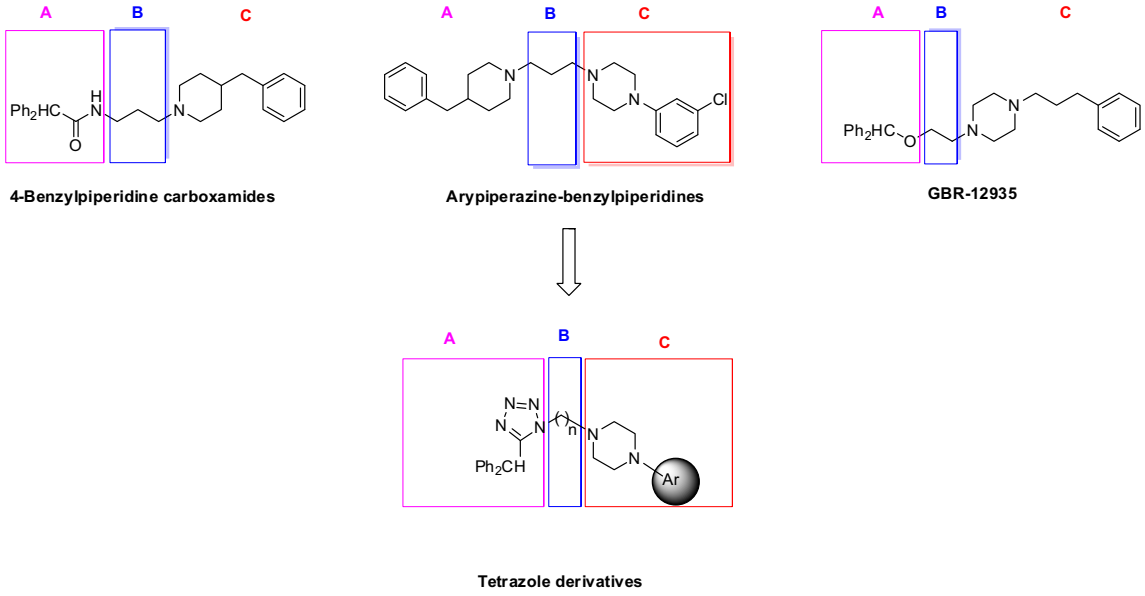


Figure 1. Design of substituted arylpiperazine–tetrazoles.

activities, and the structure–activity relationship (SAR) of these compounds have been discussed in the following sections.

2. Chemistry

The arylpiperazine–tetrazoles were synthesized as illustrated in Scheme 1. The commercially available diphenyl acetonitrile (**1**) was reacted with excess sodium azide in the presence of triethylamine hydrochloride to obtain 5-benzhydryl-1*H*-tetrazole (**2**). Treatment of tetrazole **2** with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane or 1-bromo-4-chlorobutane afforded corresponding haloalkyl-5-benzhydryl-1*H*-tetrazoles, **3** ($n = 2$), **4** ($n = 3$), and **5** ($n = 4$). Furthermore, the reaction of various aromatic amines (**6c**–**6w**), with bis(2-chloroethyl)amine hydrochloride gave *N*-arylpiperazine hydrochloride salts (**7c**–**7w**) (**7a**–**7b** were commercially available). The haloalkyl tetrazoles **3**, **4** and **5** were then reacted with *N*-arylpiperazine hydrochloride salts (**7a**–**7w**) to afford desired substituted arylpiperazine–tetrazoles **8a**–**8e**, **9a**–**9w** and **10a**–**10e**.

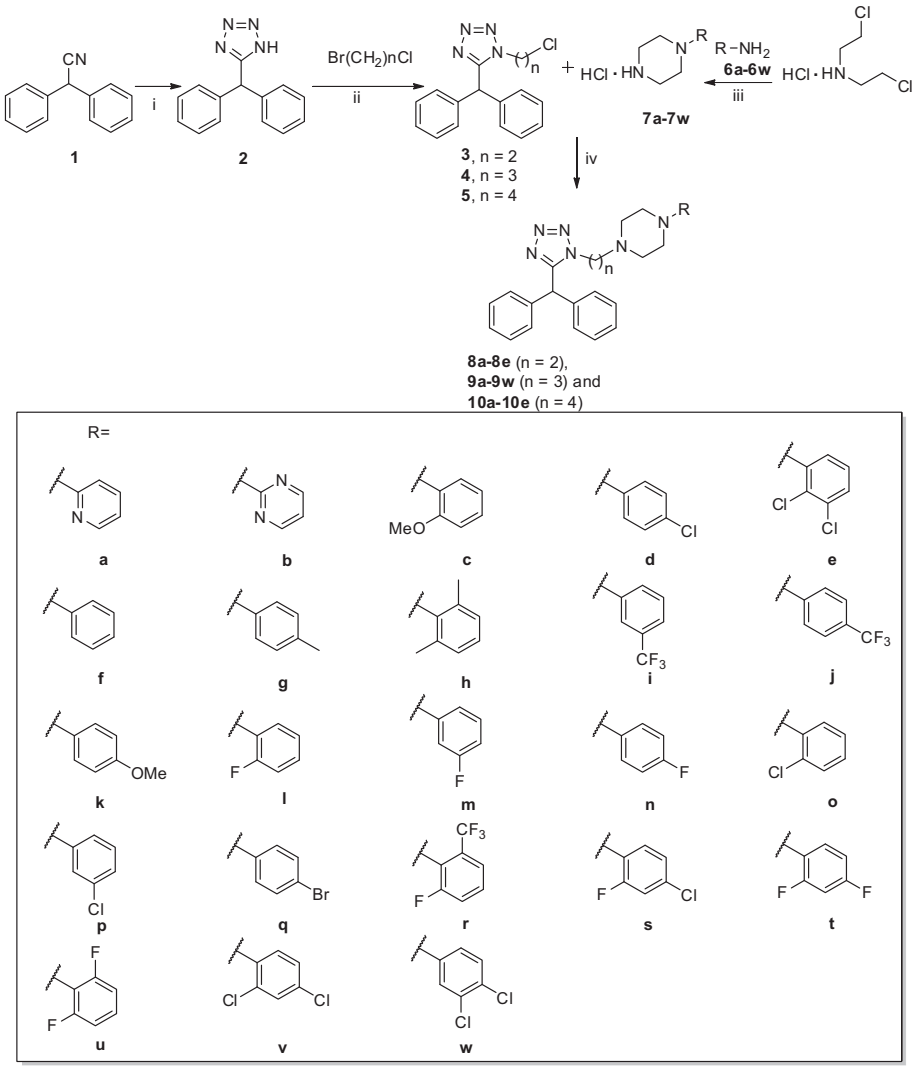
3. Results and discussion

The in vitro neurotransmitter reuptake inhibition experiments of the synthesized compounds were conducted in human embryonic kidney 293 (HEK-293) cells transfected with human norepinephrine transporter (hNET), human dopamine transporter (hDAT) and human serotonin transporter (hSERT) using a neurotransmitter uptake assay. The IC_{50} values for neurotransmitter reuptake inhibitory activity of the compounds are presented in Tables 1 and 2.

Initially, 15 arylpiperazine–tetrazoles (**8a**–**8e**, **9a**–**9e** and **10a**–**10e**) were prepared and examined for their neurotransmitter (norepinephrine, dopamine and serotonin) reuptake inhibitory effects. In contrast to compounds with 2 and 4 carbon linkers, compounds (**9a**–**9e**) having a three carbon linker exhibited selective and potent NE and DA reuptake inhibitory activity ($IC_{50} = 0.46$–1.10 μM for NE and $IC_{50} = 1.04$–3.04 μM for DA). The dopamine reuptake inhibitory activities of derivatives with 2 and 4 carbon linkers at 10 μM were not good. Unfortunately, the serotonin reuptake inhibitory activity of arylpiperazine–tetrazoles was not good at 10 μM. Thus, we further synthesized tetrazole derivatives with a three-carbon linker (**9f**–**9w**).

The structure–activity relationship (SAR) of the synthesized compounds has been summarized in Figure 2. Norepinephrine reuptake inhibition by all derivatives, except **9j** ($IC_{50} > 10$ μM) and **9w** (IC_{50}: 4.00 μM), was greater than that by the standard drug, bupropion. Heterocyclic derivatives (**9a**, **9b**) were stronger inhibitors ($IC_{50} = 0.80$–0.92 μM) than the phenyl derivative (**9f**). Particularly, the introduction of a substituent at position 2 or 4 of the phenyl ring (R) (**9c**, **9d**, **9g**, **9l**, **9m**, **9n**, **9p**, **9q**), lead to improved potency with IC_{50} (0.08–1.20 μM) than substitution at position 3 of the phenyl ring (R) (**9i**, **9m**, **9p**, $IC_{50} = 1.62$–2.48 μM). Interestingly, the activity of tetrazole **9i** with the CF_3 substituent at *m*-position of the phenyl ring was significantly greater than that of its analog **9j** with the CF_3 substituent at *p*-position. Among the arylpiperazine–tetrazoles, **9l** (2-F) and **9n** (4-F) are worth mentioning as **9l** and **9n** had the most potent neurotransmitter reuptake inhibitory activity ($IC_{50} = 0.34$ and 0.08 μM, respectively). The reuptake inhibitory activities of the compounds with mono-halogen substitution were in the following order: 4-F > 2-F > 4-Cl > 2-Cl > 4-Br > 3-Cl > 3-F. Majority of compounds with mono-halogens substitution was more potent than di-halogen substitution derivatives except **9s**–**9u**.

The dopamine reuptake inhibition by heterocyclic derivatives (**9a**, **9b**) was potent. The neurotransmitter reuptake inhibitory activity of **9b** ($IC_{50} = 1.14$ μM) was greater than that of the standard drug, bupropion. The substitution at 2 or 4 position in the phenyl ring produced favorable results (R) (**9c**, **9d**, **9g**, **9l**, **9o**, **9q**) with IC_{50} (0.91–1.42 μM) than the substitution at C_3 in the phenyl ring (**9i**, **9p**, $IC_{50} = 4.74$–5.57 μM). Interestingly, the derivative which contained CF_3 substitution (**9i**, $IC_{50} = 5.57$ μM) at position 3 showed significantly better activity than the derivative which contained CF_3 substitution (**9j**, $IC_{50} > 10$ μM) at position 4. The level of inhibition of dopamine reuptake shown by derivatives, **9d** and **9o**, confirmed that tetrazoles with chlorine substitution were better inhibitors than those with F-substitution. The derivative with 2-Cl substitution (**9o**) was more potent than bupropion. Similarly, compound **9d** with 4-Cl substitution showed potency equal to bupropion. Among the mono-halogen substituted derivatives, the derivative with 4-bromo substitution (**9q**, $IC_{50} = 0.91$ μM)



Scheme 1. Synthesis of substituted arylpiperazine–tetrazoles **8a**–**8e** ($n = 2$), **9a**–**9w** ($n = 3$) and **10a**–**10e** ($n = 4$). Reagents and conditions: (i) NaN_3, triethylamine hydrochloride (NEt_3·HCl), toluene, 100 °C; (ii) K_2CO_3, acetone, room temperature (rt); (iii) diethylene glycol monomethyl ether, 150 °C; (iv) K_2CO_3, NaI, acetonitrile (CH_3CN), reflux.

was the most potent and had greater activity than bupropion. All the mono-halogen substituted derivatives (IC_{50} = 0.91–2.48 μM), except for the derivatives with 4-F and 3-Cl substitution (**9n**, IC_{50} = 2.48 μM and **9p**, IC_{50} = 4.74 μM), were more potent than those with di-halogen substitution (IC_{50} = 2.90–4.20 μM). In contrast to di-halogen substituted compounds, 2,6-$(F)_2$ substituted derivative (**9u**, IC_{50} = 0.82 μM) was the most potent derivative among the synthesized compounds and showed even greater biological activity than bupropion.

4. Conclusion

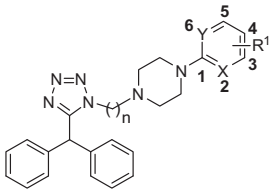
In conclusion, we designed and synthesized various substituted arylpiperazine–tetrazoles based on 4-benzylpiperidine carboxamides, arylpiperazine–benzylpiperidines and GBR12935, and their neurotransmitter reuptake inhibitory activity was examined in the human embryonic kidney cell line (HEK). The arylpiperazine–tetrazoles were obtained mainly through the substitution reaction. The IC_{50} values showed that compounds having a three-carbon linker were selective and more active than those having two-carbon and four-carbon linkers. Among them, six compounds, **9b**, **9c**, **9d**, **9o**, **9q** and **9u**, displayed greater neurotransmitter reuptake inhibitory activity than the standard drug, bupropion. Our results indicate that the newer arylpiperazine–tetrazoles are potent dual norepinephrine and dopamine reuptake inhibitors, and our study provides valuable information for the researchers who are developing therapeutic agents to treat ADHD.

5. Experimental section

5.1. Chemistry

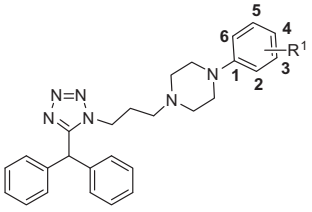
A Thomas Hoover melting point apparatus was used for the determination of the melting point (mp) by the capillary method, and the values were uncorrected. Varian Unity Plus 500, 300 and 125 MHz and Bruker BioSpin GmbH spectrometers were used to obtain ^1H and ^{13}C NMR data, which are reported in ppm downfield from the peak of the internal standard, tetramethylsilane. The data are reported as chemical shift, number of protons, and multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet, dd: doublet of doublets). Merck silica gel 60 (70–230 mesh) was used for column chromatography. Plates coated with silica gel 60 F254 (Merck) were used for thin-layer chromatography. Reagents were purchased from Sigma–Aldrich and Alfa Aesar and used without further purification.

Table 1
Norepinephrine (NE), dopamine (DA) and Serotonin (5-HT) reuptake inhibition (IC_{50}) by substituted arylpiperazine–tetrazoles **8a–8e**, **9a–9e** and **10a–10e**



Compound	R^1	X	Y	*n*	NE (μM)	DA (μM)	5-HT (μM)
8a	H	N	C	2	>10	>10	>10
8b	H	N	N	2	>10	>10	>10
8c	2-OMe	C	C	2	>10	>10	>10
8d	4-Cl	C	C	2	>10	>10	>10
8e	2,3-$(Cl)_2$	C	C	2	>10	>10	>10
9a	H	N	C	3	0.92	1.43	>10
9b	H	N	N	3	0.80	1.14	>10
9c	2-OMe	C	C	3	0.50	1.04	>10
9d	4-Cl	C	C	3	0.46	1.2	>10
9e	2,3-$(Cl)_2$	C	C	3	1.10	3.04	>10
10a	H	N	C	4	4.70	>10	>10
10b	H	N	N	4	8.54	>10	>10
10c	2-OMe	C	C	4	10	>10	>10
10d	4-Cl	C	C	4	>10	>10	>10
10e	2,3-$(Cl)_2$	C	C	4	8.87	>10	>10
Venlafaxine·HCl	—	—	—	—	—	2.55	0.20
Bupropion	—	—	—	—	3.24	1.20	—

Table 2
Norepinephrine (NE) and dopamine (DA) reuptake inhibition (IC_{50}) by substituted arylpiperazine–tetrazoles **9f–9w** (*n* = 3)



Compd	R^1	NE (μM)	DA (μM)	Compd	R^1	NE (μM)	DA (μM)
9f	–H	1.45	1.64	**9o**	2-Cl	0.67	1.01
9g	4-Me	0.87	1.42	**9p**	3-Cl	1.62	4.74
9h	2,6-Me_2	1.72	3.72	**9q**	4-Br	1.20	0.91
9i	3-CF_3	2.48	5.58	**9r**	2-F, 5-CF_3	1.09	2.25
9j	4-CF_3	>10	>10	**9s**	2-F, 4-Cl	1.10	2.25
9k	4-OMe	1.06	3.85	**9t**	2,4-$(F)_2$	2.16	2.90
9l	2-F	0.35	1.33	**9u**	2,6-$(F)_2$	0.51	0.82
9m	3-F	1.89	1.47	**9v**	2,4-$(Cl)_2$	2.05	3.59
9n	4-F	0.08	2.48	**9w**	3,4-$(Cl)_2$	4.00	4.20
				Bupropion	—	3.24	1.20

5.1.1. 5-Benzhydryl-1*H*-tetrazole (2)

A mixture of a diphenylacetonitrile, **1** (1.74 g, 9 mmol), sodium azide (1.75 g, 27 mmol), and triethylamine hydrochloride (3.71 g, 27 mmol) in toluene (80 mL) was heated to 100 °C for 24 h with stirring. After cooling, the reaction mixture was extracted with water. Then, 36% HCl was added dropwise to the aqueous layer. Precipitation occurred, which was filtered off and washed with water to provide **2** (1.53 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.24 (m, 10H), 5.95 (s, 1H).

5.1.2. 5-Benzhydryl-1-(2-chloroethyl)-1*H*-tetrazole (3)

Compound **2** (709 mg, 3 mmol) was dissolved in acetone (80 mL), and potassium carbonate (K_2CO_3, 1.24 g, 9 mmol) was added, followed by dropwise addition of 1-bromo-2-chloroethane (0.37 mL, 4.5 mmol). The reaction mixture was stirred at rt. The reaction mixture was filtered after the completion of reaction and it was concentrated. The obtained product was purified by column chromatography with *n*-hexane/ethyl acetate (EtOAc) = 4:1 to obtain **3** as a clear liquid (429 mg, 48%). Retention factor R_f = 0.62 (*n*-hexane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.20 (m, 11H, overlapped with $CHCl_3$), 5.95 (s, 1H), 4.90–4.85 (m, 2H), 3.99 (t, J = 6.3 Hz, 2H).

5.1.3. 5-Benzhydryl-1-(3-chloropropyl)-1*H*-tetrazole (4)

The procedure described for the preparation of **3** was used with compound **2** (708 mg, 3 mmol), K_2CO_3 (1.24 g, 9 mmol), 1-bromo-3-chloropropane (0.44 mL, 4.5 mmol) and acetone (80 mL) to obtain **4** as a clear liquid (779 mg, 83%). Retention factor R_f = 0.29 (*n*-hexane/EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.16 (m, 10H), 5.80 (s, 1H), 4.70–4.65 (m, 2H), 3.50–3.46 (m, 2H), 2.40–2.31 (m, 2H).

Please cite this article in press as: Paudel, S.; et al. *Bioorg. Med. Chem.* (2016), http://dx.doi.org/10.1016/j.bmc.2016.09.005

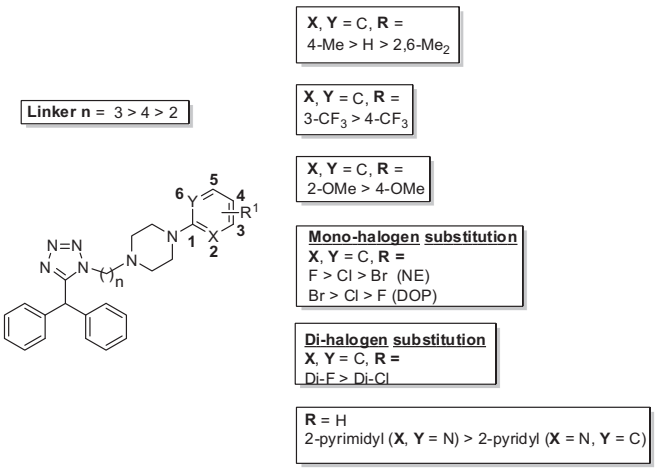


Figure 2. Structure–activity relationship (SAR) of arylpiperazine–tetrazoles.

5.1.4. 5-Benzhydryl-1-(4-chlorobutyl)-1*H*-tetrazole (5)

The procedure described for the preparation of **3** was used with compound **2** (958 mg, 4.05 mmol), K_2CO_3 (1.68 g, 12.15 mmol), 1-bromo-4-chlorobutane (0.69 mL, 6.075 mmol) and acetone (80 mL) to obtain **5** as a clear liquid (1.05 g, 80%). Retention factor R_f = 0.57 (*n*-hexane/EtOAc = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.25 (m, 10H), 5.86 (s, 1H), 4.63 (t, J = 7 Hz, 2H), 3.57–3.54 (m, 2H), 2.21–2.16 (m, 2H), 1.83–1.77 (m, 2H).

5.1.5. 1-(2-Methoxyphenyl)piperazine hydrochloride (7c)

A mixture of 2-methoxyaniline (369.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) was heated at 150 °C for about 12 h. The reaction mixture was cooled to room temperature and dissolved in methanol (4 mL), followed by the addition of diethyl ether (150 mL). The precipitate formed was recovered by filtration and washed with diethyl ether to obtain **7c** as an HCl salt (510 mg, 74%). The HCl salt was used for the next reaction without further purification.

5.1.6. 1-(4-Chlorophenyl)piperazine hydrochloride (7d)

The procedure described for the preparation of **7c** was used with compound **6d** (321.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7d** as an HCl salt (630 mg, 90%). The HCl salt was used for the next reaction without purification.

5.1.7. 1-(2,3-Dichlorophenyl)piperazine hydrochloride (7e)

The procedure described for the preparation of **7c** was used with compound **6e** (486.1 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7e** as an HCl salt (643 mg, 80%). The HCl salt was used for the next reaction without purification.

5.1.8. 1-Phenylpiperazine hydrochloride (7f)

The procedure described for the preparation of **7c** was used with compound **6f** (279.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7f** as an HCl salt (530 mg, 89%). The HCl salt was used for the next reaction without further purification.

5.1.9. 1-(4-Methylphenyl)piperazine hydrochloride (7g)

The procedure described for the preparation of **7c** was used with compound **6g** (321.2 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol), and diethylene glycol monomethyl ether (0.75 mL) to obtain **7g** as an HCl salt (562 mg, 88%). The HCl salt was used for the next reaction without further purification.

5.1.10. 1-(2,6-Dimethylphenyl)piperazine hydrochloride (7h)

The procedure described for the preparation of **7c** was used with compound **6h** (363.5 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol), and diethylene glycol monomethyl ether (0.75 mL) to obtain **7h** as an HCl salt (540 mg, 79%). The HCl salt was used for the next reaction without further purification.

5.1.11. 1-(3-(Trifluoromethyl)phenyl)piperazine hydrochloride (7i)

The procedure described for the preparation of **7c** was used with compound **6i** (483.3 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol), and diethylene glycol monomethyl ether (0.75 mL) to obtain **7i** as an HCl salt (640 mg, 80%). The HCl salt was used for the next reaction without further purification.

5.1.12. 1-(4-(Trifluoromethyl)phenyl)piperazine hydrochloride (7j)

The procedure described for the preparation of **7c** was used with compound **6j** (483.3 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol), and diethylene glycol monomethyl ether (0.75 mL) to obtain **7j** as an HCl salt (520 mg, 65%). The HCl salt was used for the next reaction without further purification.

5.1.13. 1-(4-Methoxyphenyl)piperazine hydrochloride (7k)

The procedure described for the preparation of **7c** was used with compound **6k** (369.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7k** as an HCl salt (549 mg, 80%). The HCl salt was used for the next reaction without further purification.

5.1.14. 1-(2-Fluorophenyl)piperazine hydrochloride (7l)

The procedure described for the preparation of **7c** was used with compound **6l** (333.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7l** as an HCl salt (443 mg, 68%). The HCl salt was used for the next reaction without further purification.

5.1.15. 1-(3-Fluorophenyl)piperazine hydrochloride (7m)

The procedure described for the preparation of **7c** was used with compound **6m** (333.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7m** as an HCl salt (488 mg, 75%). The HCl salt was used for the next reaction without further purification.

5.1.16. 1-(4-Fluorophenyl)piperazine hydrochloride (7n)

The procedure described for the preparation of **7c** was used with compound **6n** (333.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7n** as an HCl salt (550 mg, 85%). The HCl salt was used for the next reaction without further purification.

5.1.17. 1-(2-Chlorophenyl)piperazine hydrochloride (7o)

The procedure described for the preparation of **7c** was used with compound **6o** (321.5 mg, 3 mmol), bis(2-chloroethyl)amine

hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7o** as an HCl salt (595 mg, 85%). The HCl salt was used for the next reaction without further purification.

5.1.18. 1-(2-Chlorophenyl)piperazine hydrochloride (7p)

The procedure described for the preparation of **7c** was used with compound **6p** (321.5 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7p** as an HCl salt (490 mg, 70%). The HCl salt was used for the next reaction without further purification.

5.1.19. 1-(2-Bromophenyl)piperazine hydrochloride (7q)

The procedure described for the preparation of **7c** was used with compound **6q** (537.3 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7q** as an HCl salt (598 mg, 70%). The HCl salt was used for the next reaction without purification.

5.1.20. 1-(2-Fluoro-5-(trifluoromethyl)phenyl)piperazine hydrochloride (7r)

The procedure described for the preparation of **7c** was used with compound **6r** (516.1 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7r** as an HCl salt (540 mg, 65%). The HCl salt was used for the next reaction without purification.

5.1.21. 1-(4-Chloro-2-fluorophenyl)piperazine hydrochloride (7s)

The procedure described for the preparation of **7c** was used with compound **6s** (436.7 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7s** as an HCl salt (362 mg, 48%). The HCl salt was used for the next reaction without purification.

5.1.22. 1-(2,4-Difluorophenyl)piperazine hydrochloride (7t)

The procedure described for the preparation of **7c** was used with compound **6t** (387.3 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7t** as an HCl salt (317 mg, 45%). The HCl salt was used for the next reaction without purification.

5.1.23. 1-(2,6-Difluorophenyl)piperazine hydrochloride (7u)

The procedure described for the preparation of **7c** was used with compound **6u** (387.3 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7u** as an HCl salt (353 mg, 50%). The HCl salt was used for the next reaction without purification.

5.1.24. 1-(2,4-Dichlorophenyl)piperazine hydrochloride (7v)

The procedure described for the preparation of **7c** was used with compound **6v** (486.1 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7v** as an HCl salt (640 mg, 80%). The HCl salt was used for the next reaction without purification.

5.1.25. 1-(3,4-Dichlorophenyl)piperazine hydrochloride (7w)

The procedure described for the preparation of **7c** was used with compound **6w** (486.1 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **7w** as an HCl salt (627 mg, 78%). The HCl salt was used for the next reaction without purification.

5.1.26. 1-(2-(5-Benzhydryl-1*H*-tetrazol-1-yl)ethyl)-4-(pyridin-2-yl)piperazine (8a)

The compound **7a** (0.23 mL, 1.5 mmol), was dissolved in acetonitrile (CH_3CN, 15 mL). K_2CO_3 (276.4 mg, 2 mmol) was added followed by compound **3** (300 mg, 1 mmol) and sodium iodide (NaI, catalyst). The reaction mixture was heated overnight at 100 °C. After completion, the reaction mixture was cooled, filtered and concentrated. The obtained product was purified by column chromatography on silica gel with *n*-hexane/EtOAc/MeOH (10:1.5:0.5) to obtain **8a** (59 mg, 13%) as a white solid. R_f = 0.75 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 166–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20–8.19 (m, 1H), 7.51–7.47 (m, 1H), 7.36–7.22 (m, 11H, overlapped with $CHCl_3$), 6.66–6.62 (m, 2H), 5.83 (s, 1H), 4.30–4.28 (m, 2H), 3.49 (t, J = 3 Hz, 4H), 2.75–2.73 (m, 2H), 2.50 (t, J = 5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 156.6, 147.9, 138.4, 137.6, 129, 128.6, 127.8, 113.6, 107.1, 57.3, 53.1, 46.4, 45.1, 45.

5.1.27. 2-(4-(2-(5-Benzhydryl-1*H*-tetrazol-1-yl)ethyl)piperazin-1-yl)pyrimidine (8b)

The procedure described for the preparation of **8a** was used with compound **3** (300 mg, 1 mmol), **7b** (0.21 mL, 1.5 mmol), K_2CO_3 (276.4 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **8b** (72 mg, 23%) as a white solid. R_f = 0.18 (*n*-hexane/EtOAc = 1:1). Mp = 166–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, J = 4.5 Hz, 2H), 7.37–7.28 (m, 6H), 7.24–7.22 (m, 4H), 6.52–6.50 (m, 1H), 5.83 (s, 1H), 4.30–4.28 (m, 2H), 3.77 (t, J = 5 Hz, 4H) 2.74 (t, J = 6 Hz, 2H), 2.45–2.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 157.7, 156.5, 138.4, 129.1, 128.6, 127.9, 110.1, 57.3, 53.2, 46.4, 45, 43.5.

5.1.28. 1-(2-(5-Benzhydryl-1*H*-tetrazol-1-yl)ethyl)-4-(2-methoxyphenyl)piperazine (8c)

The procedure described for the preparation of **8a** was used with compound **3** (300 mg, 1 mmol), **7c** (288 mg, 1.5 mmol), K_2CO_3 (276.4 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **8c** (59 mg, 13%) as a sticky white solid. R_f = 0.5 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.24 (m, 11H, overlapped with $CHCl_3$), 7.04–6.86 (m, 4H), 5.86 (s, 1H), 4.29 (t, J = 6 Hz, 2H), 3.87 (s, 3H), 3.04 (s, 4H), 2.77 (t, J = 6 Hz, 2H), 2.63–2.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 152.2, 140.9, 138.5, 129, 128.6, 127.8, 123.2, 121, 118.2, 111.15, 57.4, 55.4, 53.9, 50.5, 46.3, 45.0.

5.1.29. 1-(2-(5-Benzhydryl-1*H*-tetrazol-1-yl)ethyl)-4-(4-chlorophenyl)piperazine (8d)

The procedure described for the preparation of **8a** was used with compound **3** (300 mg, 1 mmol), **7d** (349.7 mg, 1.5 mmol), K_2CO_3 (276.4 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **8d** (70 mg, 15%) as a sticky white solid. R_f = 0.75 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.19 (m, 13H, overlapped with $CHCl_3$), 6.82–6.79 (m, 2H), 5.78 (s, 1H), 4.31–4.28 (m, 2H), 3.08–3.06 (m, 4H), 2.76–2.73 (m, 2H), 2.54–2.52 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 149.6, 138.4, 129, 128.99, 128.6, 127.9, 117.4, 57, 53, 49.0, 46.4, 45.

5.1.30. 1-(2-(5-Benzhydryl-1*H*-tetrazol-1-yl)ethyl)-4-(2,3-dichlorophenyl)piperazine (8e)

The procedure described for the preparation of **8a** was used with compound **3** (300 mg, 1 mmol), **7e** (401 mg, 1.5 mmol), K_2CO_3 (276.4 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **8e** (80 mg, 16%) as a sticky white solid. R_f = 0.2 (*n*-hexane/EtOAc = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.24 (m, 11H, overlapped with $CHCl_3$), 7.19–7.13 (m, 2H), 6.88 (dd, J = 7.5 Hz, 2 Hz, 1H), 5.79 (s, 1H), 4.32–4.29 (m, 2H), 2.96 (s, 4H), 2.79–2.77 (m, 2H), 2.58 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ.156.5, 150.8,

138.5, 134.1, 129, 128.6, 127.8, 127.5, 124.8, 118.6, 57, 53.3, 51.1, 46.4, 45.0.

5.1.31. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(pyridin-2-yl)piperazine (9a)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 1 mmol), **7a** (0.22 mL, 1.44 mmol), K_2CO_3 (265 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9a** as a white solid (261 mg, 62%). R_f = 0.44 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 73–76 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20–8.19 (m, 8H), 7.50–7.46 (m, 1H), 7.35–7.29 (m, 8H), 7.25–7.22 (m, 2H), 6.64–6.61 (m, 2H), 5.82 (s, 1H), 4.71 (t, J = 7 Hz, 2H), 3.49 (t, J = 5 Hz, 4H), 2.51 (t, J = 5 Hz, 4H), 2.44–2.42 (m, 2H), 2.24–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 159.5, 147.9, 140.8, 137.4, 128.7, 128.6, 128.4, 127, 113.3, 107, 54.9, 52.9, 51.3, 48.6, 45.2, 26.6.

5.1.32. 2-(4-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)piperazin-1-yl)pyrimidine (9b)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 1 mmol), **7b** (0.20 mL, 1.44 mmol), K_2CO_3 (265 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9b** as a white solid (220 mg, 52%). R_f = 0.6 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 100–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, J = 5 Hz, 2H), 7.36–7.29 (m, 10H), 7.25–7.21 (m, 2H), 5.82 (s, 1H), 6.48–6.46 (m, 2H), 4.10 (t, J = 7 Hz, 2H), 3.78 (t, J = 5 Hz, 4H), 2.46–2.18 (m, 6H), 2.23–2.18 (2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 161.6, 157.7, 140.8, 128.7, 128.6, 127, 109.8, 54.9, 53, 51.3, 48.6, 43.5, 26.5.

5.1.33. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2-methoxyphenyl)piperazine (9c)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 1 mmol), **7c** (276.8 mg, 1.44 mmol), K_2CO_3 (265 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9c** as a light brown liquid (180 mg, 38%). R_f = 0.56 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.21 (m, 11H), 7.02–6.84 (m, 4H), 5.81 (s, 1H), 4.70–4.67 (m, 2H), 3.85 (s, 3H), 3.04 (s, 4H), 2.61 (s, 4H), 2.45 (t, J = 8.5 Hz, 2H), 2.24–2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 152.3, 141.3, 140.8, 128.7, 128.6, 127, 122.9, 121, 118.2, 111.2, 55.4, 55, 53.3, 50.6, 48.6, 26.6.

5.1.34. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(4-chlorophenyl)piperazine (9d)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 1 mmol), **7d** (335.7 mg, 1.44 mmol), K_2CO_3 (265 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9d** as a light brown liquid (230 mg, 51%). R_f = 0.5 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.19 (m, 13H, overlapped with $CHCl_3$), 6.83–6.80 (m, 2H), 5.81 (s, 1H), 4.70 (t, J = 7 Hz, 2H), 3.10 (t, J = 5 Hz, 4H), 2.54 (t, J = 5 Hz, 4H), 2.45–2.43 (m, 2H), 2.24–2.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 149.9, 140.8, 128.9, 128.7, 128.6, 127, 124.5, 117.2, 54.8, 51.1, 49.1, 48.7, 26.5.

5.1.35. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2,3-dichlorophenyl)piperazine (9e)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 1 mmol), **7e** (385 mg, 1.44 mmol), K_2CO_3 (265 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9e** as a light brown liquid (234 mg, 48%). R_f = 0.48 (*n*-hexane/EtOAc = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.13 (m, 12H), 6.93 (dd, J = 7.5, 2.5 Hz, 1H), 5.82 (s, 1H), 4.71 (t, J = 7 Hz, 2H), 3.01 (s, 4H), 2.59 (s, 4H), 2.48–2.45 (m, 2H), 2.25–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ.167.8, 151.2, 140.8, 134.0, 128.7, 128.6, 127.5, 127.4, 127.0, 118.6, 54.8, 53.2, 51.2, 48.6, 26.5.

5.1.36. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-phenylpiperazine (9f)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 1 mmol), **7f** (286 mg, 1.44 mmol), K_2CO_3 (265 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9f** as a light brown liquid (229 mg, 55%). R_f = 0.6 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.23 (m, 13H), 6.94–6.86 (m, 3H), 5.83 (s, 1H), 4.71 (t, J = 7 Hz, 2H), 3.16 (t, J = 5 Hz, 4H), 2.57 (t, J = 5 Hz, 4H), 2.47–2.44 (m, 2H), 2.25–2.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 151.2, 140.8, 129.1, 128.7, 128.6, 128.58, 127.0, 119.7, 116.1, 54.9, 53.1, 51.4, 49.1, 48.7, 26.6.

5.1.37. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(4-methylphenyl)piperazine (9g)

The procedure described for the preparation of **8a** was used with compound **4** (310 mg, 0.99 mmol), **7g** (315.9 mg, 1.48 mmol), K_2CO_3 (273 mg, 1.98 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9g** as a light brown liquid (296 mg, 66%). R_f = 0.58 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 10H), 7.10–7.08 (m, 2H), 6.86–6.83 (m, 2H), 5.83 (s, 1H), 4.70 (t, J = 7 Hz, 2H), 3.13–3.11 (m, 4H), 2.57 (t, J = 5 Hz, 4H), 2.45 (t, J = 5 Hz, 2H), 2.29 (s, 3H), 2.26–2.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 149.2, 140.8, 129.6, 129.2, 128.7, 128.6, 127.0, 116.4, 54.9, 53.2, 51.4, 49.7, 48.6, 26.6, 20.4.

5.1.38. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2,6-dimethylphenyl)piperazine (9h)

The procedure described for the preparation of **8a** was used with compound **4** (313 mg, 1 mmol), **7h** (340.1 mg, 1.5 mmol), K_2CO_3 (276 mg, 2.04 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9h** as a light brown liquid (294 mg, 63%). R_f = 0.64 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.34 (m, 10H), 7.30–7.27 (m, 3H), 5.89 (s, 1H), 4.76–4.73 (m, 2H), 3.13–3.16 (m, 4H), 2.57–2.55 (m, 4H), 2.49 (t, J = 7 Hz, 2H), 2.38 (s, 6H), 2.27 (p, J = 4.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 148.3, 140.9, 137.0, 129.0, 128.8, 128.6, 127.1, 125.1, 55.3, 54.5, 51.4, 49.7, 48.7, 26.7, 19.7.

5.1.39. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(3-(trifluoromethyl)phenyl)piperazine (9i)

The procedure described for the preparation of **8a** was used with compound **4** (315 mg, 1 mmol), **7i** (402.8 mg, 1.5 mmol), K_2CO_3 (278 mg, 2.04 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9i** as a light brown liquid (294 mg, 58%). R_f = 0.67 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.23 (m, 11H), 7.10–7.03 (m, 3H), 5.83 (s, 1H), 4.71 (t, J = 7 Hz, 2H), 3.16 (t, J = 5 Hz, 4H), 2.55 (t, J = 5 Hz, 4H), 2.47–2.44 (m, 2H), 2.25–2.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 151.3, 140.8, 129.5, 128.7, 128.6, 127.0, 118.6, 115.8, 115.78, 115.75, 115.7, 112.1, 112.1, 112.1, 122.0, 54.9, 51.4, 48.7, 48.5.

5.1.40. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(4-(trifluoromethyl)phenyl)piperazine (9j)

The procedure described for the preparation of **8a** was used with compound **4** (315 mg, 1 mmol), **7j** (402.8 mg, 1.5 mmol), K_2CO_3 (278 mg, 2.04 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9j** as a light brown liquid (291 mg, 57%). R_f = 0.67 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 5.1 Hz, 2H), 7.39–7.24 (m, 10H), 6.91 (d, J = 8.5 Hz, 2H), 5.89 (s, 1H), 4.73–4.70 (m, 2H), 3.22 (t, J = 5 Hz, 4H), 2.54 (t, J = 5 Hz, 4H), 2.47–2.44 (m, 2H), 2.25–2.20 (m, 2H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 167.8, 153.2, 140.8, 128.7, 128.6, 127.0, 126.41, 126.4, 126.35, 126.3, 54.9, 51.3, 48.7, 47.9, 26.5.

5.1.41. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(4-methoxyphenyl)piperazine (9k)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 0.96 mmol), **7k** (329 mg, 1.44 mmol), K_2CO_3 (265 mg, 1.92 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9k** as a white solid (184 mg, 41%). R_f = 0.61 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 80–83 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.30 (m, 8H), 7.27–7.23 (m, 2H), 6.91–6.84 (m, 4H), 5.83 (s, 1H), 4.70 (t, *J* = 7 Hz, 2H), 3.78 (s, 3H), 3.07–3.05 (m, 4H), 2.57 (t, *J* = 5 Hz, 4H), 2.46–2.44 (m, 2H), 2.24–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 153.8, 145.7, 140.8, 128.7, 128.6, 127.0, 118.2, 114.4, 55.6, 54.9, 53.2, 50.6, 48.6, 26.6.

5.1.42. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2-flurophenyl)piperazine (9l)

The procedure described for the preparation of **8a** was used with compound **4** (315 mg, 1.01 mmol), **7l** (327.3 mg, 1.57 mmol), K_2CO_3 (278 mg, 2.1 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9l** as a light brown liquid (279 mg, 61%). R_f = 0.67 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.39 (m, 4H), 7.36–7.32 (m, 4H), 7.28–7.25 (m, 2H), 7.10–7.03 (m, 2H), 6.97–6.93 (m, 2H), 5.83 (s, 1H), 4.71 (t, *J* = 7 Hz, 2H), 3.09 (t, *J* = 4.5 Hz, 4H), 2.60 (t, *J* = 4.5 Hz, 4H), 2.46 (t, *J* = 7 Hz, 2H), 2.25–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 156.7, 154.8, 140.9, 140.2, 140.1, 128.8, 128.6, 127.1, 124.5, 124.4, 122.4, 119.0, 118.96, 116.2, 116.0, 54.9, 53.2, 50.5, 48.7, 26.6.

5.1.43. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(3-flurophenyl)piperazine (9m)

The procedure described for the preparation of **8a** was used with compound **4** (320 mg, 1.02 mmol), **7m** (331.5 mg, 1.53 mmol), K_2CO_3 (282 mg, 2.04 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9m** as a white solid (275 mg, 59%). R_f = 0.68 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 90–92 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.44–7.19 (11H), 6.70–6.57 (m, 3H), 5.91 (s, 1H), 4.70 (t, *J* = 7 Hz, 2H), 3.15 (t, *J* = 4.5 Hz, 4H), 2.53 (t, *J* = 5 Hz, 4H), 2.45–2.42 (m, 2H), 2.24–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 164.9, 162.9, 153.0, 152.9, 141.0, 130.2, 130.16, 128.8, 127.1, 111.13, 111.1, 105.8, 105.6, 102.7, 102.5, 54.9, 51.4, 48.8, 48.5, 26.5.

5.1.44. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(4-flurophenyl)piperazine (9n)

The procedure described for the preparation of **8a** was used with compound **4** (330 mg, 1.05 mmol), **7n** (341.2 mg, 1.57 mmol), K_2CO_3 (290 mg, 2.1 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9n** as a white solid (312 mg, 65%). R_f = 0.65 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 93–96 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.23 (m, 10H), 7.09–6.95 (m, 2H), 6.88–6.85 (m, 2H), 5.84 (s, 1H), 4.70 (t, *J* = 7 Hz, 2H), 3.07 (t, *J* = 5 Hz, 4H), 2.56 (t, *J* = 5 Hz, 4H), 2.45 (t, *J* = 7 Hz, 2H), 2.25–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 158.1, 156.2, 147.94, 147.9, 140.8, 128.7, 128.6, 127.0, 117.8, 117.76, 115.6, 115.4, 54.8, 53.1, 51.3, 50.1, 48.7, 26.6.

5.1.45. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2-chlorophenyl)piperazine (9o)

The procedure described for the preparation of **8a** was used with compound **4** (330 mg, 1.05 mmol), **7o** (367.2 mg, 1.57 mmol), K_2CO_3 (290 mg, 2.1 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9o** as a light brown liquid (293 mg, 59%). R_f = 0.64 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.21 (m, 15H), 7.03–6.96 (m, 3H), 5.82 (s, 1H), 4.72–4.69 (m, 2H), 3.04 (s, 4H), 2.61 (s, 4H), 2.49–2.47 (m, 2H), 2.26–2.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 149.2, 140.8, 130.6, 129.1, 128.7, 128.6, 127.6, 127.0, 123.7, 120.4, 54.9, 53.3, 51.3, 51.2, 48.7, 26.6.

5.1.46. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(3-chlorophenyl)piperazine (9p)

The procedure described for the preparation of **8a** was used with compound **4** (310 mg, 0.99 mmol), **7p** (346 mg, 1.48 mmol), K_2CO_3 (273.5 mg, 1.98 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9p** as a white solid (314 mg, 67%). R_f = 0.67 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 100–103 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.22 (m, 12H, overlapped with $CHCl_3$), 7.18–7.15 (m, 3H), 5.82 (s, 1H), 4.70 (t, *J* = 7 Hz, 2H), 3.12 (t, *J* = 5 Hz, 4H), 2.53 (t, *J* = 5 Hz, 4H), 2.46–2.43 (m, 2H), 2.24–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 152.3, 140.9, 134.9, 130.1, 128.7, 128.6, 127.1, 119.2, 115.7, 113.9, 54.9, 52.9, 51.4, 48.7, 48.56, 26.5.

5.1.47. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(4-bromophenyl)piperazine (9q)

The procedure described for the preparation of **8a** was used with compound **4** (312 mg, 1 mmol), **7q** (416.4 mg, 1.5 mmol), K_2CO_3 (276.4 mg, 2 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9q** as a light brown liquid (315 mg, 61%). R_f = 0.61 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.23 (m, 12H), 6.94–6.86 (m, 3H), 5.83 (s, 1H), 4.71 (t, *J* = 7 Hz, 2H), 3.16 (t, *J* = 5 Hz, 4H), 2.57 (t, *J* = 5 Hz, 4H), 2.45 (t, *J* = 7 Hz, 2H), 2.25 (p, *J* = 7 HZ, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 151.2, 140.8, 129.1, 128.7, 128.6, 127.0, 119.7, 116.1, 54.9, 53.1, 51.4, 49.1, 48.7, 26.6.

5.1.48. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2-fluro-5-(trifluromethyl)phenyl)piperazine (9r)

The procedure described for the preparation of **8a** was used with compound **4** (320 mg, 1.02 mmol), **7r** (435.5 mg, 1.53 mmol), K_2CO_3 (276 mg, 2.04 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9r** as a light brown liquid (290 mg, 54.2%). R_f = 0.75 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.38 (m, 4H), 7.34–7.31 (m, 4H), 7.25–7.20 (m, 3H), 7.16–7.08 (m, 2H), 5.85 (s, 1H), 4.72–4.70 (m, 2H), 3.08–3.06 (m, 4H), 2.58–2.56 (m, 4H), 2.47–2.45 (m, 2H), 2.24–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 158.2, 156.2, 140.9, 140.6, 140.5, 128.7, 128.6, 127.0, 125.0, 122.9, 119.33, 119.3, 119.26, 119.2, 116.5, 116.4, 116.1, 116.03, 116.0, 54.8, 52.9, 51.3, 50.14, 50.1, 48.7, 26.5.

5.1.49. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(4-chloro-2-fluorophenyl)piperazine (9s)

The procedure described for the preparation of **8a** was used with compound **4** (310 mg, 0.99 mmol), **7s** (373 mg, 1.48 mmol), K_2CO_3 (274 mg, 1.98 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9s** as a white solid (291 mg, 60%). R_f = 0.65 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 83–85 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.29 (m, 10H), 7.26–7.22 (m, 2H), 7.07–7.03 (m, 1H), 5.83 (s, 1H), 4.70 (t, *J* = 7 Hz, 2H), 3.02–3.00 (m, 4H), 2.57–2.55 (m, 4H), 2.46–2.44 (m, 2H), 2.23–2.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 156.3, 154.3, 140.8, 139.0, 138.9, 128.7, 128.6, 127.0, 126.74, 126.7, 124.5, 124.46, 119.6, 119.5, 116.9, 116.7, 60.39, 54.84, 53.0, 51.3, 50.43, 50.4, 48.7, 26.5.

5.1.50. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2,4-diflurophenyl)piperazine (9t)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 0.96 mmol), **7t** (338 mg, 1.44 mmol),

K_2CO_3 (265 mg, 1.92 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9t** as a white solid (287 mg, 63%). R_f = 0.68 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 75–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.23 (m, 10H), 6.90–6.78 (m, 3H), 5.85 (s, 1H), 4.70 (t, J = 7 Hz, 2H), 3.01–2.99 (m, 4H), 2.58 (s, 4H), 2.47–2.44 (m, 2H), 2.24–2.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 158.9, 158.8, 156.9, 156.8, 156.6, 156.5, 154.6, 140.9, 136.7, 128.7, 128.6, 127.0, 119.5, 119.4, 110.8, 110.7, 110.6, 104.9, 104.7, 104.5, 54.8, 53.1, 51.3, 50.9, 48.7, 26.5.

5.1.51. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2,6-difluorophenyl)piperazine (9u)

The procedure described for the preparation of **8a** was used with compound **4** (300 mg, 0.96 mmol), **7u** (352 mg, 1.44 mmol), K_2CO_3 (265 mg, 1.92 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9u** as a light brown liquid (282 mg, 62%). R_f = 0.75 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.30 (m, 8H), 7.26–7.23 (m, 2H), 6.96–6.90 (m, 1H), 6.87–6.81 (m, 2H), 5.83 (s, 1H), 4.71 (t, J = 7 Hz, 2H), 3.21–3.19 (m, 4H), 2.55–2.53 (m, 4H), 2.46–2.43 (m, 2H), 2.24–2.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 159.6, 159.57, 157.7, 157.6, 140.8, 128.7, 128.6, 127.0, 123.3, 123.2, 123.1, 112.2, 112.1, 112.05, 112.0, 55.0, 53.8, 51.3, 51.1, 51.05, 51.0, 48.7, 26.6.

5.1.52. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(2,4-dichlorophenyl)piperazine (9v)

The procedure described for the preparation of **8a** was used with compound **4** (320 mg, 1.02 mmol), **7v** (409.4 mg, 1.53 mmol), K_2CO_3 (282 mg, 2.04 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9v** as a light brown liquid (321 mg, 61%). R_f = 0.65 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.29 (m, 13H), 6.92 (d, J = 5.1 Hz, 1H), 5.82 (s, 1H), 4.70 (t, J = 4.2 Hz, 2H), 2.98 (s, 4H), 2.58 (s, 4H), 2.48–2.45 (m, 2H), 2.24–2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 148.0, 140.8, 130.3, 129.4.6, 128.7, 128.6, 128.1, 127.6, 127.0, 121.1, 54.8, 53.1, 51.3, 51.1, 48.6, 26.5.

5.1.53. 1-(3-(5-Benzhydryl-1*H*-tetrazol-1-yl)propyl)-4-(3,4-dichlorophenyl)piperazine (9w)

The procedure described for the preparation of **8a** was used with compound **4** (320 mg, 1.02 mmol), **7w** (409.4 mg, 1.53 mmol), K_2CO_3 (282 mg, 2.04 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **9w** as a white solid (290 mg, 56%). R_f = 0.64 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). Mp = 103–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.22 (m, 12H), 6.92 (d, J = 3 Hz, 1H), 6.70 (dd, J = 9, 3, 1H) 5.81 (s, 1H), 4.70 (t, J = 7 Hz, 2H), 3.08–3.06 (m, 4H), 2.51 (t, J = 5 Hz, 4H), 2.45–2.42 (m, 2H), 2.23–2.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 150.6.0, 140.7, 132.7, 130.4, 128.7, 128.6, 127.0, 122.1, 117.2, 115.2, 54.8, 51.3, 48.7, 48.5, 26.5.

5.1.54. 1-(4-(5-Benzhydryl-1*H*-tetrazol-1-yl)butyl)-4-(pyridin-2-yl)piperazine (10a)

The procedure described for the preparation of **8a** was used with compound **5** (300 mg, 0.91 mmol), **7a** (0.20 mL, 1.36 mmol), K_2CO_3 (251.5 mg, 1.82 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **10a** as a light brown liquid (110 mg, 50%). R_f = 0.37 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24–8.19 (m, 1H), 7.49–7.46 (m, 1H), 7.36–7.23 (m, 10H), 6.65–6.62 (m, 2H), 5.83 (s, 1H), 4.64 (t, J = 7 Hz, 2H), 3.52 (t, J = 5 Hz, 4H), 2.50–2.48 (m, 4H), 2.41–2.04 (m, 2H), 2.10–2.04 (m, 2H), 1.58–1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 159.5, 148, 140.8, 137.4, 128.7, 128.6, 127, 113.3, 107, 57.6, 53, 52.9, 48.6, 45.2, 27.3, 23.5.

5.1.55. 2-(4-(4-(5-Benzhydryl-1*H*-tetrazol-1-yl)butyl)piperazin-1-yl)pyrimidine (10b)

The procedure described for the preparation of **8a** was used with compound **5** (300 mg, 0.91 mmol), **7b** (0.19 mL, 1.36 mmol), K_2CO_3 (251.5 mg, 1.82 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **10b** as a light brown liquid (199 mg, 48%). R_f = 0.32 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, J = 4.5 Hz, 2H), 7.34–7.29 (m, 8H), 7.25–7.22 (m, 2H), 6.48–6.46 (m, 1H), 4.63 (t, J = 7 Hz, 2H), 3.81–3.79 (m, 2H), 2.44–2.42 (m, 4H), 2.39–2.37 (m, 2H), 2.09–2.02 (m, 2H), 1.57–1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 161.6, 157.7, 140.8, 128.7, 128.6, 127, 109.8, 57.6, 53, 52.9, 48.6, 43.6, 27.3, 23.5.

5.1.56. 1-(4-(5-Benzhydryl-1*H*-tetrazol-1-yl)butyl)-4-(2-methoxyphenyl)piperazine (10c)

The procedure described for the preparation of **8a** was used with compound **5** (300 mg, 0.91 mmol), **7c** (261.5 mg, 1.36 mmol), K_2CO_3 (251.5 mg, 1.82 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **10c** as a light brown liquid (218 mg, 45%). R_f = 0.58 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.19 (m, 11H), 7.01–6.83 (m, 4H), 5.81 (s, 1H), 4.63–4.60 (m, 2H), 3.84 (s, 3H), 3.06 (s, 4H), 2.58 (s, 4H), 2.43–2.39 (m, 2H), 1.57–1.50 (m, 2H), 1.24 (t, J = 9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 152.3, 141.3, 140.8, 128.7, 128.6, 127, 122.9, 121, 118.2, 111.2, 57.6, 55.4, 53, 50.6, 48.6, 27.4, 23.6.

5.1.57. 1-(4-(5-Benzhydryl-1*H*-tetrazol-1-yl)butyl)-4-(2-chlorophenyl)piperazine (10d)

The procedure described for the preparation of **8a** was used with compound **5** (300 mg, 0.91 mmol), **7d** (318 mg, 1.36 mmol), K_2CO_3 (251.5 mg, 1.82 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **10d** as a light brown liquid (208 mg, 47%). R_f = 0.46 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.13 (m, 13H), 6.96–6.94 (m, 2H), 5.84 (s, 1H), 4.65 (t, J = 7 Hz, 2H), 3.04 (s, 4H), 2.58 (s, 4H), 2.45–2.42 (m, 2H), 2.11–2.06 (m, 2H), 1.58–1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 151.3, 140.8, 134, 128.7, 127.5, 127, 124.5, 118.6, 57.5, 53.2, 53, 51.3, 48.6, 27.2, 23.5.

5.1.58. 1-(4-(5-Benzhydryl-1*H*-tetrazol-1-yl)butyl)-4-(2,3-dichlorophenyl)piperazine (10e)

The procedure described for the preparation of **8a** was used with compound **5** (300 mg, 0.91 mmol), **7e** (363.9 mg, 1.36 mmol), K_2CO_3 (251.5 mg, 1.82 mmol), NaI (catalyst) and CH_3CN (15 mL) to obtain **10e** as a light brown liquid (204 mg, 43%). R_f = 0.46 (*n*-hexane/EtOAc/MeOH = 2.5:1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.19 (m, 12H), 6.84–6.81 (m, 2H), 5.82 (s, 1H), 4.65 (t, J = 7 Hz, 2H), 3.12 (t, J = 5 Hz, 4H), 2.53–2.51 (m, 4H), 2.42–2.39 (m, 2H), 2.10–2.04 (m, 2H), 1.58–1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 149.9, 140.8, 128.9, 128.7, 128.6, 127, 124.5, 117.2, 57.4, 53, 52.9, 49.1, 48.6, 27.2, 23.5.

6. Neurotransmitter uptake assay

The assay was performed following the method described in the literature with slight modification.[19] HEK-293 cells were cultured in a medium supplemented with fetal bovine serum and transfected with hSERT, hNET and hDAT. Radiolabeled [^{3}H]-5-HT (PerkinElmer, Waltham, MA, USA), [^{3}H]-5-NE (PerkinElmer, Waltham, MA, USA) and [^{3}H]-DA (PerkinElmer) were used at a concentration of 20 nM in the assay. Radioactivity was measured using a Wallac 1450 MicroBeta® TriLux liquid scintillation counter (PerkinElmer). Bupropion and venlafaxine hydrochloride were used as standard neurotransmitter reuptake inhibitors.

Acknowledgments

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (grant No. 2012R1A1A2006613) and K.M. Kim was funded by KRF-2014R1A2A2A01002547. The authors would like to thank the Korea Basic Science Institute Gwangju center for performing the ^{1}H NMR and ^{13}C NMR.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2016.09.005.

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