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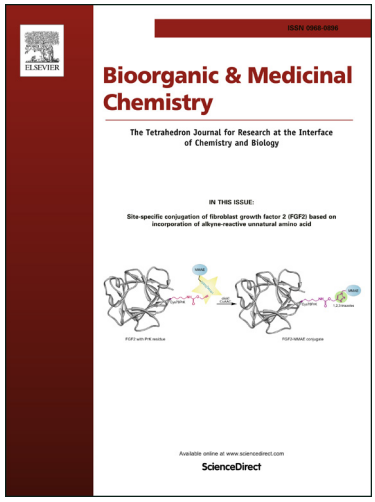

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Triple reuptake inhibitors: Design, synthesis and structure-activity relationship of benzylpiperidine—tetrazoles

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Abstract

Monoamine transporters are important targets in the treatment of various central nervous disorders. Several limitations of traditional reuptake inhibitors, like delayed onset of action, insomnia, and sexual dysfunction, have compelled the search for safer, more effective compounds. In this study, we have sought to identify novel monoamine reuptake inhibitors. Based upon the docking study of compounds that we had reported previously, aromatic rings (A1) were modified to generate a novel series of benzylpiperidine—tetrazoles. Thirty-one compounds were synthesized and evaluated for their triple reuptake inhibition of serotonin, norepinephrine and dopamine. Triple reuptake inhibitor, compound **2q**, in particular, showed potent serotonin reuptake inhibition, validating our design approach.

Keywords: Benzylpiperidine—tetrazoles, Monoamine neurotransmitters, Serotonin, norepinephrine and dopamine reuptake inhibitors, Docking

1. Introduction

Compounds that inhibit both neurotransmitter, serotonin (5-HT) and norepinephrine (NE) reuptake, such as venlafaxine, duloxetine, milnacipran, reboxetine, nisoxetine, and atomoxetine, have been clinically prescribed for the treatment of major depressive disorder, diabetic neuropathy, stress urinary incontinence (SUI), attention deficit hyperactivity disorder (ADHD), fibromyalgia, etc.[1-10] Several limitations of traditional neurotransmitter reuptake inhibitors, like delayed onset of action, insomnia, and sexual dysfunction, have compelled the search for safer, more effective compounds.[11-15]

Recently, more attention has been devoted to the synthesis and evaluation of triple reuptake inhibitors (TRIs) that exhibit promising pharmacological activities.[16-18] Several classes of TRIs, including DOV21,947, SEP-225289, Lu-AA42202, NS-2359, and RG-7166, have been studied extensively and are already in preclinical and early clinical stages of development (Fig. 1). TRIs represent the next generation of antidepressants with desirable therapeutic effects.[19-24]

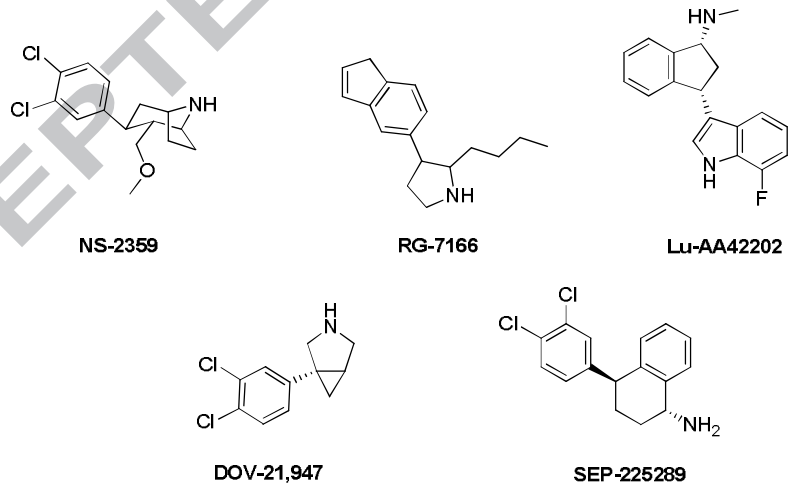


Fig. 1. Several classes of TRIs in preclinical or early clinical stages of development

With an aim to develop safer, more potent and effective neurotransmitter reuptake inhibitors, we have been studying several classes of compounds. These compounds, **I**-**V**, essentially consist of a variable aromatic region (Ar1) linked to a piperazine/piperidine-aromatic region (Ar2) by a linker (aliphatic chain with 2-4 carbons) (**Fig. 2A** and **2B**).[25-28] In addition, they also contain a functional group (FG) such as tetrazole, oxygen, piperazine and amide which acts as a sticky end to connect Ar1 with a linker. In our previous studies, the four fundamental components of the neurotransmitter reuptake inhibitors were modified step-by-step to access their pharmacological effects. This conventional method, however, is a time-consuming process. Thus, rational drug design method for a time-economic and efficient approach has been applied to generate neurotransmitter reuptake inhibitors. The 3-dimensional structure of human SERT and antidepressant agents paroxetine (PDB ID: 5I6X) deposited in Protein Data Bank in 2016 was used for a rational drug design to find potent triple neurotransmitter reuptake inhibitors.[29]

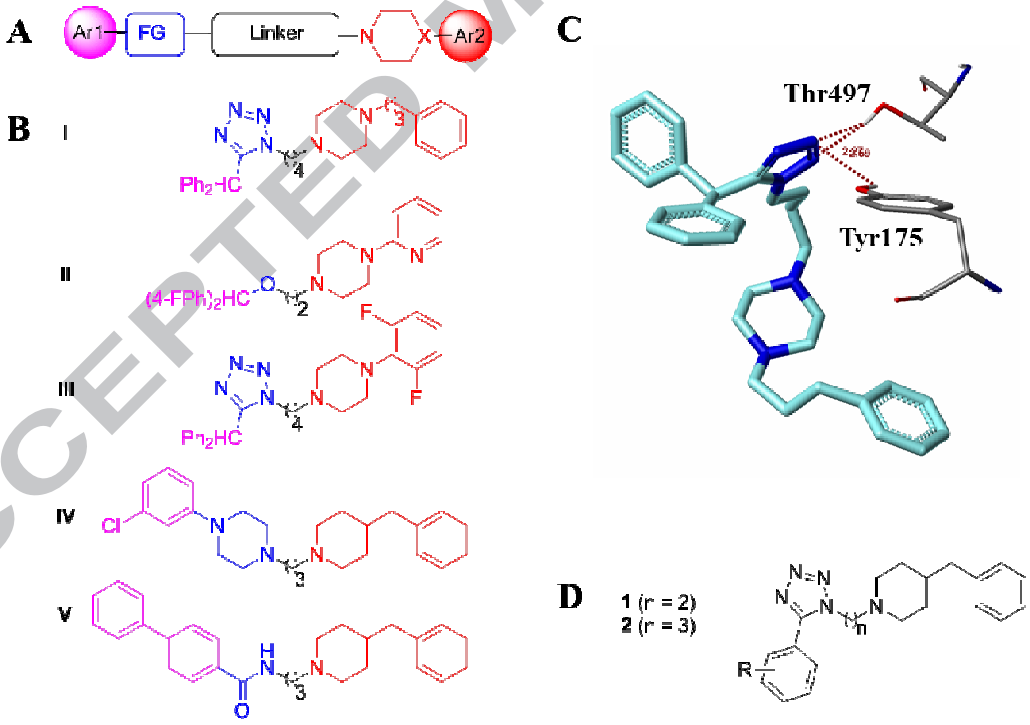


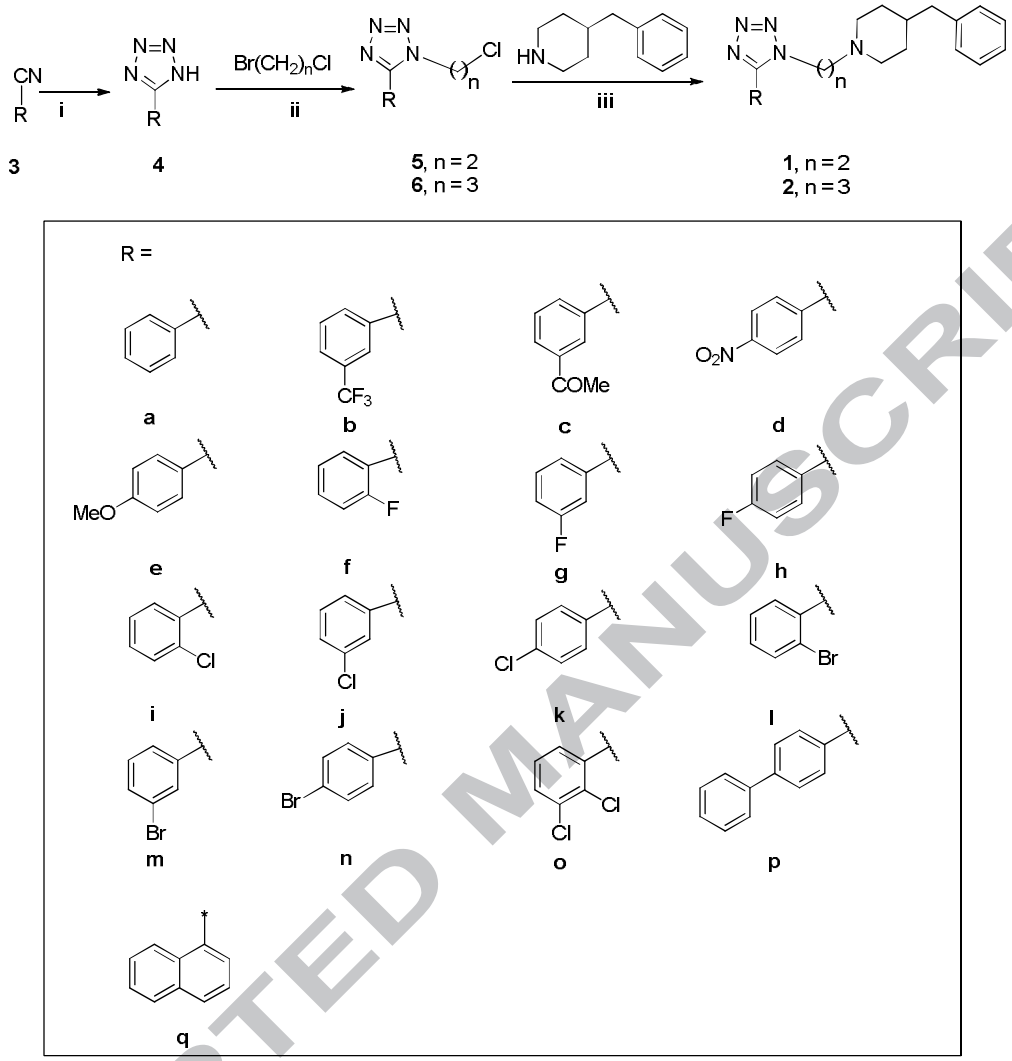
Fig. 2. (A) Structural outline of neurotransmitter reuptake inhibitor. FG: functional group; X: N/C. (B) Known neurotransmitter (5-HT and/or NE and/or DA) reuptake inhibitors. (C) Docking

model of hSERT-**I** showing H-bond interaction between tetrazole and amino acids. (D) Newer benzylpiperidine—tetrazoles **1** (n = 2) and **2** (n = 3).

The tetrazoles (e.g. **I, III**),[25-26] ether (e.g. **II**),[25] piperazine (e.g. **IV**)[27] and amide (e.g. **V**)[28] which were previously examined for inhibition of 5-HT reuptake were subjected to docking study. The Surflex Dock program available in Sybyl-X 2.1.1 (winnt_os5x) was used to dock the compounds into the pocket formed after removal of the ligand from the structure of hSERT-paroxetine. Among the compounds subjected to the docking study, tetrazoles achieved highest docking score and reasonable hypothetical binding mode (**Table S1** and **Fig. 2C**). The tetrazole moiety had H-bond interaction with amino acids Tyr175 and Thr497 surrounding the ligand binding pocket (LBP). Thus, preserving the tetrazole moiety and varying the aromatic rings (Ar1) to investigate their interaction with amino acids in the vicinity and effect on ultimate pharmacological activities, benzylpiperidine-tetrazoles (**1** and **2**) were designed, synthesized and evaluated as triple reuptake inhibitors (TRIs).

2. Chemistry

Scheme 1 represents the detailed procedures for synthesizing benzylpiperidine—tetrazole compounds. Various aromatic nitriles **3a–3q** were refluxed with excess sodium azide and triethylamine hydrochloride to obtain tetrazoles **4a**–**4q**. These tetrazoles were further reacted with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane to yield various chloroalkyl-5-phenyltetrazoles, **5a**–**5q** (n = 2) and **6a**–**6q** (n = 3). The substitution reactions of **5a–5q** and **6a–6q** with 4-benzylpiperidine gave benzylpiperidine—tetrazoles **1a–1q** (n = 2) and **2a–2q** (n = 3). Despite the successful synthesis of many benzylpiperidine—tetrazoles, we failed to synthesize **1f**, **1i**, and **1o** compounds, most likely because of steric hindrance.



Scheme 1. Reagents and conditions: (i) Sodium azide (NaN_3), triethylamine hydrochloride (TEA·HCl), and toluene at 100 °C; (ii) K_2CO_3 and acetone at room temperature (r.t.); (iii) dimethyl sulfoxide (DMSO) and triethylamine (TEA) at 100 °C.

3. Results and discussion

3.1. Monoamine reuptake inhibition

Monoamine reuptake inhibitory activities were assessed by a neurotransmitter uptake assay using human embryonic kidney 293 (HEK-293) cell lines transfected with human serotonin transporter (hSERT), human norepinephrine transporter (hNET), or human dopamine transporter (hDAT). Reuptake inhibitory activities of the synthesized compounds at a single concentration (10 µM) are presented in Figure 3.

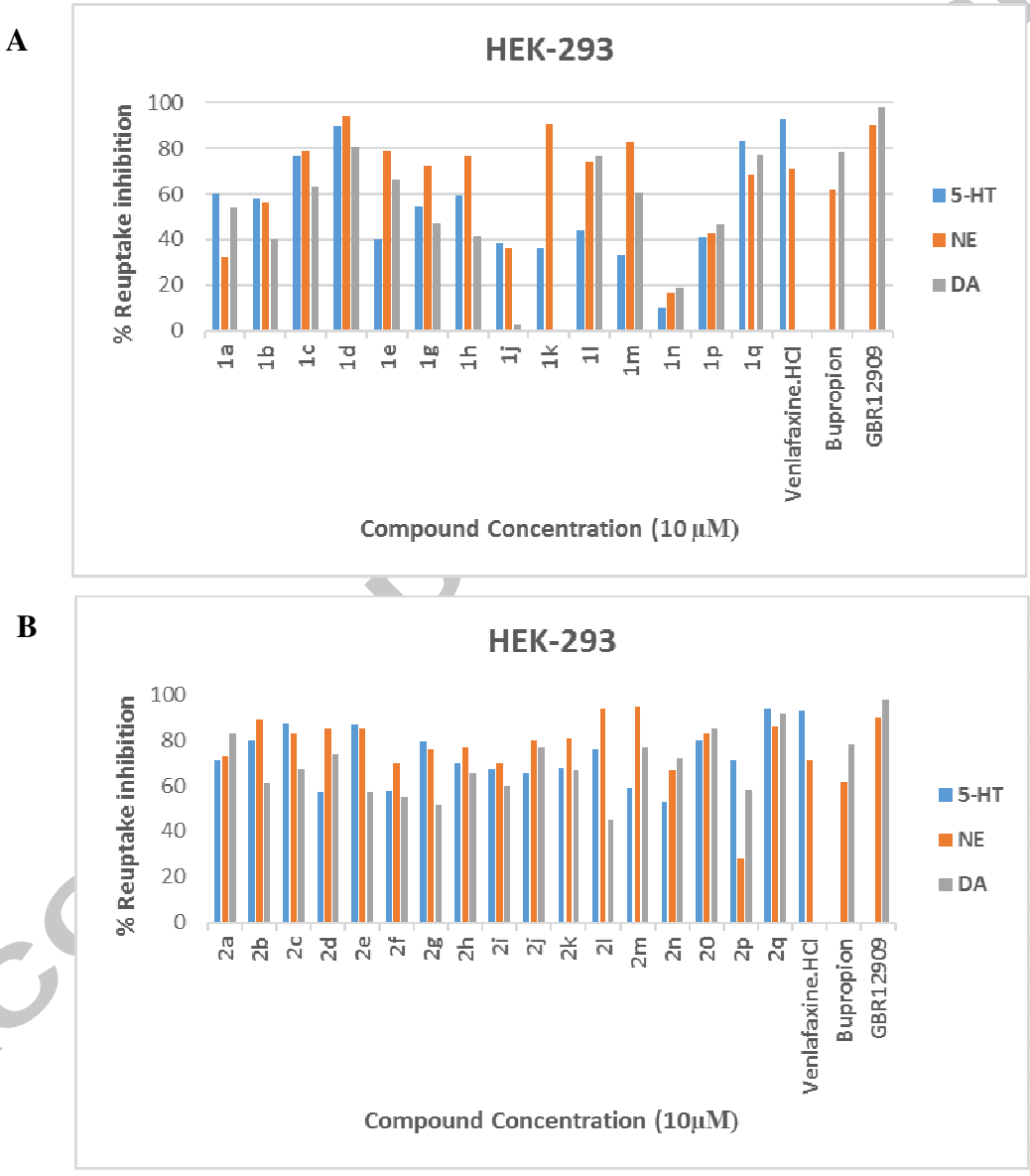


Figure 3: Monoamine reuptake inhibitory activity of benzylpiperidine—tetrazoles, **1** (n = 2) in (A) and **2** (n = 3) in (B) in HEK-293 cells

As expected, the majority of benzylpiperidine—tetrazole compounds with three-carbon units in the linker showed better reuptake inhibitory activties for 5-HT, NE and DA. than did compounds with two-carbon units. The introduction of various substitutions at the *meta*- or *para*-position of the phenyl ring also produced favorable reuptake inhibition. In general, dihalogen substitituted derivatives produced potent neurotransmitter reuptake inhibitory activities than monohalogen substituted compounds. Based upon the primary screening, compounds **1c**, **1d**, **1q**, **2a**-**2e**, **2h**-**2o,** and **2q**, which inhibited reuptake of 5-HT, NE and DA by >55% at 10 μM were selected for the IC_{50} value determination (Table 1).

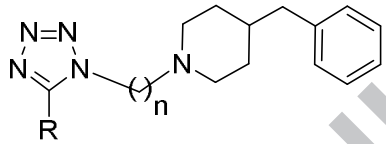


Table 1: IC_{50} (μM) value for monoamine reuptake inhibition of benzylpiperidine—tetrazoles

S.N.	n	R	5-HT	NE	DA
1c	2	Ph-3-COMe	4.05	3.08	14.6
1d	2	Ph-4-NO_2	1.24	1.35	1.98
1q	2	1-Naphthyl	>10	>10	>10
2a	3	Ph	0.88	3.03	4.02
2b	3	Ph-3-CF_3	8.81	5.1	3.74
2c	3	Ph-3-COMe	0.54	3	5.04
2d	3	Ph-4-NO_2	5.25	5.02	>10
2e	3	Ph-4-OMe	4.05	5.52	>10
2h	3	Ph-4-F	2	2.28	3.29
2i	3	Ph-2-Cl	1.32	3.96	6.55
2j	3	Ph-3-Cl	1.35	3.59	5.18
2k	3	Ph-4-Cl	3.13	2.58	8.32

2l	3	Ph-2-Br	5.13	3.46	>10
2m	3	Ph-3-Br	>10	4.34	>10
2o	3	Ph-2,3-Cl_2	3.96	3.45	>10
2q	3	1-Naphthyl	0.31	2.51	6
Venlafaxine HCl	-	-	0.20	2.55	-
Bupropion	-	-	-	3.24	1.20
GBR12909	-	-	-	0.11	0.04

Compound **2q**, with a 1-naphthyl substitution and a longer linker, was the most potent 5-HT reuptake inhibitor among the synthesized compounds (IC_{50} = 0.31 μM). A compound without any substitution in phenyl ring **2a** (IC_{50} = 0.88 μM) had greater 5-HT reuptake inhibitory activity than did substituted compounds, except for 3-acetophenyl derivative, **2c** (IC_{50} = 0.54 μM). The IC_{50} for 5-HT reuptake inhibition of monohalogen-substituted compounds ranged from 1.32 to >10 μM, and they are listed here in increasing order: 2-Cl (**2i**) > 3-Cl (**2j**) > 4-F (**2h**) > 4-Cl (**2k**) > 2-Br (**2l**) > 3-Br (**2m**). Interestingly, the activities of 1-naphthyl compounds (**2q**, IC_{50} = 0.31 μM) increased 30-fold when the length of the linker was extended from two to three carbons (**1q**, IC_{50} > 10 μM). Likewise, the 4-nitro derivative (**1d**) displayed the greatest NE reuptake inhibitory activity among the synthesized compounds (IC_{50} = 1.35 μM). The majority of benzylpiperidine—tetrazoles exhibited equipotent or more potent inhibition of NE reuptake (IC_{50} = 1.35–5.51 μM) than standard drug, bupropion. The compound with a 1-naphthyl substitution (**1q**) showed the lowest (IC_{50} > 10 μM). Furthermore, the compound demonstrating the highest DA reuptake inhibition was the 4-nitro derivative **1d** (IC_{50} = 1.98 μM). A compound with a 4-F substitution **2h** (IC_{50} = 3.29 μM) was superior in DA reuptake activity than those with a Cl substitution **2i**–**2k** (IC_{50} = 5.18–8.31 μM) or a Br substitution **2l** and **2m** (IC_{50} > 10 μM).

3.2. Docking study

A hypothetical binding mode of SERT and compound **2q,** the most potent 5-HT reuptake inhibitor among the compounds synthesized in this study, was generated to identify the interaction responsible for SERT inhibition. 5-HT reuptake inhibitors, like paroxetine, reside at the central binding site and block 5-HT binding (Fig. 4A). The 5-HT reuptake inhibitor locks SERT into an outward-open conformation. In this conformation, the central binding site is situated halfway across the cell membrane-spanning region of SERT. The central binding site connects to the vestibule and opens into the extracellular space. A second molecule of neurotransmitter reuptake inhibitor (maltose in case of PDB ID: 5I6X) also binds to the allosteric site at the extracellular periphery of the vestibule. The additional inhibitor caps the vestibule and prevents dissociation of the inhibitor from the central binding site.

The 5-HT reuptake inhibition potency of a compound is dependent upon the nature and extent of its interaction with SERT. The docking study shows that the compound **2q** interacted with SERT in the same unique manner as paroxetine. The 4-benzylpiperidine moiety of the compound occupied the central binding site, creating a hydrophobic interaction with Ile172, Tyr176, and Phe341 (Fig. 4B). The 3-carbon linker was particularly important as it bent the compound into an optimal placement in the L-shaped pocket. The tetrazole group of the compound, as expected earlier, interacted with Tyr175 and Thr497 through H-bonds. The naphthalene group, that projected the allosteric site, stacked parallel to the ring of Phe335.

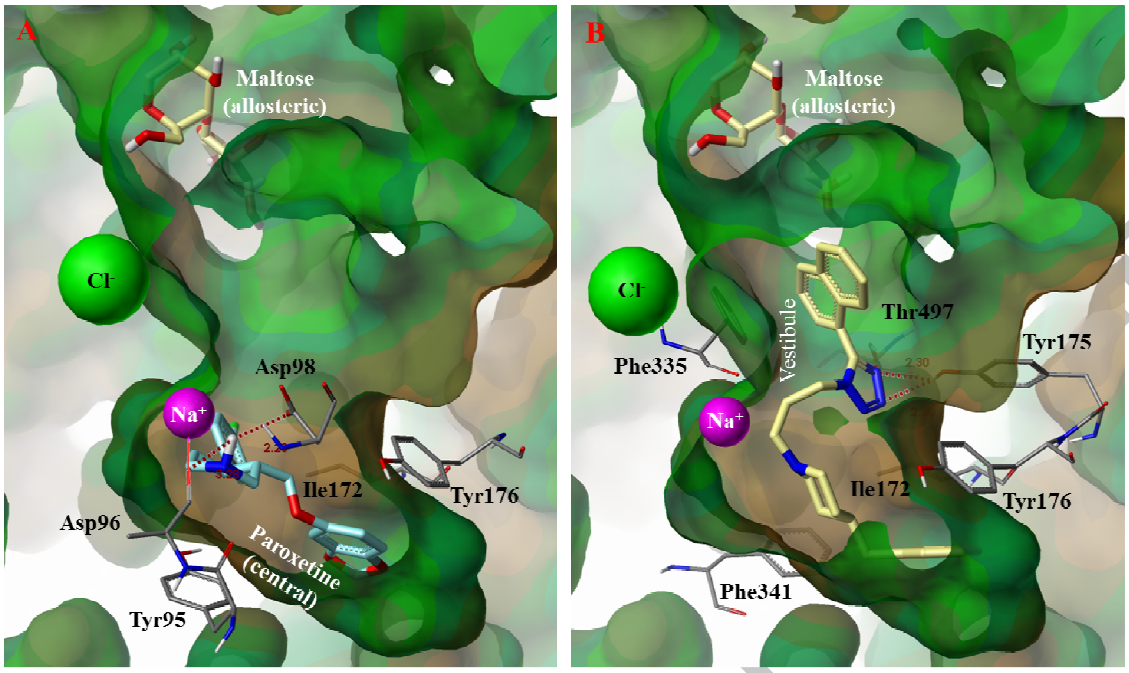


Figure 4. (A) Binding mode of hSERT-paroxetine (PDB ID: 5I6X). (B) Hypothetical binding mode of hSERT-**2q**. H-bonds are displayed as brown discontinuous lines and ionic bond as solid red lines.

4. Conclusion

In conclusion, based upon the docking study we designed and synthesized several benzylpiperidine—tetrazole compounds. As expected, molecules containing three-carbon units in the linker showed potent monoamine reuptake inhibition. For an explanation of the 5-HT reuptake inhibitory activity of **2q**, docking studies were performed using the Surflex-dock program to provide a reasonable binding mode of the compound with the human 5-HT transporter. The SAR data and docking models from this study can help guide the design of safer, more effective therapeutic agents for CNS disorders.

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 300 MHz, Varian Unity Inova 500 MHz and Bruker BioSpin GmbH spectrometers were used to obtain ^{1}H 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, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet, dd: doublet of doublets), coupling constant in Hz and number of protons. Mass spectra were obtained using an Advion Expression CMS, and recorded in a positive ion mode with an electrospray (ESI) source. 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.

*5.1.1. 5-Phenyl-1H-tetrazole (**4a**)*

A mixture of a benzonitrile, **3a** (310 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 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 **4a** as white solid (395 mg, 90%). Mp: 214–216 °C. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 8.04–7.02 (m, 2H), 7.62–7.57 (m, 3H).

*5.1.2. 5-(3-(Trifluromethyl)phenyl)-1H-tetrazole (**4b**)*

The procedure described for the preparation of **3a** was used with compound **3b** (513 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4b** as white solid (514 mg, 80%). Mp: 156–157 °C. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.35–8.33 (m, 2H), 7.97–7.95 (m, 1H), 7.88–7.85 (m, 1H).

*5.1.3. 1-(3-(1H-Tetrazole-5-yl)phenyl)ethanone (**4c**)*

The procedure described for the preparation of **4a** was used with compound **3c** (436 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4c** as white solid (511 mg, 90%). Mp: 189–191 ℃. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.17–8.15 (m, 2H), 8.12–8.12 (m, 2H), 2.61 (s, 3H).

*5.1.4. 5-(4-Nitrophenyl)-1H-tetrazole (**4d**)*

The procedure described for the preparation of **4a** was used with compound **3d** (445 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4d** as yellow solid (459 mg, 80%). Mp: 218–220 ℃. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.47–8.42 (m, 2H), 8.28–8.32 (m, 2H).

*5.1.5. 5-(4-Methoxyphenyl)-1H-tetrazole (**4e**)*

The procedure described for the preparation of **4a** was used with compound **3e** (400 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4e** as white solid (449 mg, 85%). Mp: 229–230 ℃. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.00–7.95 (m, 2H), 7.16–7.11 (m, 2H), 3.82 (s, 3H).

*5.1.6. 5-(2-Flurophenyl)-1H-tetrazole (**4f**)*

The procedure described for the preparation of **4a** was used with compound **3f** (363 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4f** as white solid (295 mg, 60%). Mp: 158–160 ℃. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 16.50 (br, NH), 8.06 (m, 1H), 7.68 (m, 1H), 7.50 (m, 1H), 7.45 (m, 1H).

*5.1.7. 5-(3-Flurophenyl)-1H-tetrazole (**4g**)*

The procedure described for the preparation of **4a** was used with compound **3g** (363 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4g** as white solid (320 mg, 65%) which was used for next reaction

without purification. Mp: 142–144 °C. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 7.78–7.71 (m, 2H), 7.57–7.40 (m, 2H).

*5.1.8. 5-(4-Flurophenyl)-1H-tetrazole (**4h**)*

The procedure described for the preparation of **4a** was used with compound **3h** (363 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4h** as yellow solid (345 mg, 70%). Mp: 112–114 °C. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.11–8.03 (m, 2H), 7.48–7.40 (m, 2H).

*5.1.9. 5-(2-Chlorophenyl)-1H-tetrazole (**4i**)*

The procedure described for the preparation of **4a** was used with compound **3i** (413 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4i** as white solid (325 mg, 60%). Mp: 172–174 °C. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 7.83–7.80 (m, 1H), 7.72–7.69 (m, 1H), 7.65–7.52 (m, 2H).

*5.1.10. 5-(3-Chlorophenyl)-1H-tetrazole (**4j**)*

The procedure described for the preparation of **4a** was used with compound **3j** (413 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4j** as white solid (460 mg, 85%). Mp: 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.90 (br, NH), 7.75 (m, 1H), 7.70 (m, 1H), 7.61 (m, 1H), 7.50 (m, 1H).

*5.1.11. 5-(4-Chlorophenyl)-1H-tetrazole (**4k**)*

The procedure described for the preparation of **4a** was used with compound **3k** (413 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4k** as white solid (514 mg, 95%). Mp: 252–254 °C. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.05 (d, J = 8.4 Hz, 2H), 7.69 (d J = 8.4 Hz, 2H).

*5.1.12. 5-(2-Bromophenyl)-1H-tetrazole (**4l**)*

The procedure described for the preparation of **4a** was used with compound **3l** (546 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4l** as white solid (405 mg, 60%). Mp: 174–176 °C. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 16.70 (br, NH), 7.85 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.68 (dd, *J* = 8.8, 4.0 Hz, 1H), 7.55 (m, 2H).

*5.1.13. 5-(3-Bromophenyl)-1H-tetrazole (**4m**)*

The procedure described for the preparation of **4a** was used with compound **3m** (546 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4m** as white solid (459 mg, 68%). Mp: 155–156 °C. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.22 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H) 7.50 (m, 1H), 7.52 (m, 1H).

*5.1.14. 5-(4-Bromophenyl)-1H-tetrazole (**4n**)*

The procedure described for the preparation of **4a** was used with compound **3n** (546 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4n** as white solid white solid (540 mg, 80%). Mp: 259–261 °C. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.00–7.96 (m, 2H), 7.85–7.81 (m, 2H).

*5.1.15. 5-(2,3-Dichlorophenyl)-1H-tetrazole (**4o**)*

The procedure described for the preparation of **4a** was used with compound **3o** (516 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4o** as white solid (516 mg, 80%). Mp: 180–182 °C. ^{1}H NMR (300

MHz, DMSO-*d6*): δ 7.92 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.7 Hz 1H), 7.59 (t, *J* = 8 Hz, 1H)

*5.1.16. 5-([1,1'-Biphenyl]-4-1yl-1H-tetrazole (**4p**)*

The procedure described for the preparation of **4a** was used with compound **3p** (538 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4p** as white solid as white solid (473 mg, 70%). Mp: 247–249 ℃. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 7.46 (d, *J* = 4 Hz, 2H), 7.44 (d, *J* = 12.4 Hz, 2H), 7.32 (s, 2H), 7.23 (t, *J* = 6.4 Hz, 1H), 6.68 (d, *J* = 8 Hz, 2H).

*5.1.17. 5-(Naphthalen-1yl)-1H-tetrazole (**4q**)*

The procedure described for the preparation of **4a** was used with compound **3q** (460 mg, 3 mmol), sodium azide (586 mg, 9 mmol), and triethylamine hydrochloride (1.24 g, 9 mmol) in toluene (80 mL) to provide **4q** as white solid (477 mg, 81%). Mp: 212–214 ℃. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 8.59–8.56 (m, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.10–8.06 (m, 1H), 7.99 (d, *J* = 7.2, 1.2 Hz, 1H) 7.73–7.62 (m, 3H).

*5.1.18. 1-(2-Chloroethyl)-5-phenyl-1H-tetrazole (**5a**)*

Compound **4a** (200 mg, 1.36 mmol) was dissolved in acetone (10 mL), potassium carbonate (K_2CO_3, 376 mg, 2.72 mmol) was added and followed by dropwise addition of 1-bromo-2-chloroethane (0.17 mL, 2.04 mmol). The reaction mixture was stirred at r.t. The reaction mixture was filtered after the completion of reaction and was concentrated. The obtained product was purified by column chromatography with *n*-hexane: Ethyl acetate (EtOAc) = 5:1 to obtain **5a** (140 mg, 49%) as clear liquid. Retention factor (R_f) = 0.74 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17–8.13 (m, 2H), 7.54–7.44 (m, 3H), 4.96 (t, *J* = 6.3 Hz, 2H), 4.08 (t, *J* = 6.3 Hz, 2H).

*5.1.19. 1-(2-Chloroethyl)-5-(3-(trifluoromethyl)phenyl)-1H-tetrazole (**5b**)*

The procedure described for the preparation of **5a** was used with compound **4b** (500 mg, 2.33 mmol), K_2CO_3 (644 mg, 4.66 mmol) and 1-bromo-2-chloroethane (0.29 mL, 3.5 mmol.) to obtain **5b** (567 mg, 88%) as clear liquid. R_f = 0.57 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40–8.31 (m, 2H), 7.72–7.58 (m, 2H), 4.99 (t, *J* = 6 Hz, 2H), 4.11–4.09 (m, 2H).

*5.1.20. 1-(3-(1-(2-Chloroethyl)-1H-tetrazol-5-yl)phenyl)ethanone (**5c**)*

The procedure described for the preparation of **5a** was used with compound **4b** (400 mg, 2.12 mmol), K_2CO_3 (586 mg, 4.24 mmol) and 1-bromo-2-chloroethane (0.26 mL, 3.18 mmol.) to obtain **5c** (255 mg, 48%) as white solid. R_f = 0.73 (*n*-hexane: EtOAc = 2:1). Mp = 83-85 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73–8.72 (m, 1H), 8.38–8.36 (m, 1H), 8.10–8.08 (m, 1H), 7.64–7.61 (m, 1H), 5.02–5.00 (m, 2H), 4.13–4.11 (m, 2H), 2.71 (s, 3H).

*5.1.21. 1-(2-Chloroethyl)-5-(4-nitrophenyl)-1H-tetrazole (**5d**)*

The procedure described for the preparation of **5a** was used with compound **4d** (200 mg, 1.05 mmol), K_2CO_3 (289 mg, 2.1 mmol) and 1-bromo-2-chloroethane (0.13 mL, 1.56 mmol.) to obtain **5d** (120 mg, 45%) as clear liquid. R_f = 0.77 (*n*-hexane: EtOAc = 1:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 4H), 5.06–5.02 (m, 2H), 4.13 (t, *J* = 6 Hz, 2H)

*5.1.22. 1-(2-Chloroethyl)-5-(4-methoxyphenyl)-1H-tetrazole (**5e**)*

The procedure described for the preparation of **5a** was used with compound **4e** (300 mg, 1.70 mmol), K_2CO_3 (470 mg, 3.40 mmol) and 1-bromo-2-chloroethane (0.17 mL, 2.04 mmol.) to obtain **5e** (263 mg, 65%) as clear liquid. R_f = 0.25 (*n*-hexane: EtOAc = 4:1). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 8.12–8.07 (m, 2H), 7.04–6.99 (m, 2H), 4.96 (t, *J* = 6.3 Hz, 2H), 4.11–4.06 (m, 2H), 3.88 (s, 3H).

*5.1.23. 1-(2-Chloroethyl)-5-(2-flurophenyl)-1H-tetrazole (**5f**)*

The procedure described for the preparation of **5a** was used with compound **4f** (450 mg, 2.12 mmol), K_2CO_3 (757 mg, 5.48 mmol) and 1-bromo-2-chloroethane (0.40 mL, 4.11 mmol.) to obtain **5f** (446 mg, 72%) as clear liquid. R_f = 0.62 (*n*-hexane: EtOAc = 2:1). Mp = 83-85 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18–8.14 (m, 1H), 7.05–7.46 (m, 1H), 7.31–7.23 (m, 2H), 5.04–5.01 (m, 2H), 4.12–4.09 (m, 2H).

*5.1.24. 1-(2-Chloroethyl)-5-(3-flurophenyl)-1H-tetrazole (**5g**)*

The procedure described for the preparation of **5a** was used with compound **4g** (300 mg, 1.82 mmol), K_2CO_3 (503 mg, 3.64 mmol) and 1-bromo-2-chloroethane (0.22 mL, 2.73 mmol.) to obtain **5g** (330 mg, 80%) as clear liquid. R_f = 0.64 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95–7.93 (m, 1H), 7.86–7.83 (m, 1H), 7.48–7.44 (m, 1H), 7.19–7.15 (m, 1H), 4.99–4.97 (m, 2H), 4.09 (t, *J* = 6 Hz, 2H).

*5.1.25. 1-(2-Chloroethyl)-5-(4-flurophenyl)-1H-tetrazole (**5h**)*

The procedure described for the preparation of **5a** was used with compound **4h** (300 mg, 1.82 mmol), K_2CO_3 (503 mg, 3.64 mmol) and 1-bromo-2-chloroethane (0.22 mL, 2.73 mmol.) to obtain **5h** (214 mg, 52%) as white solid. R_f = 0.54 (*n*-hexane: EtOAc = 2:1). Mp = 60-62 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18–8.14 (m, 2H), 7.22–7.17 (m, 2H), 4.99–4.97 (m, 2H), 4.11–4.08 (m, 2H).

*5.1.26. 1-(2-Chloroethyl)-5-(2-chlorophenyl)-1H-tetrazole (**5i**)*

The procedure described for the preparation of **5a** was used with compound **4i** (350 mg, 1.93 mmol), K_2CO_3 (534 mg, 3.86 mmol) and 1-bromo-2-chloroethane (0.24 mL, 2.89 mmol.) to obtain **5i** (328 mg, 70%) as clear liquid. R_f = 0.54 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98–7.94 (m, 1H), 7.55–7.52 (m, 1H), 7.44–7.35 (m, 2H), 5.03–5.01 (m, 2H), 4.11 (t, *J* = 6 Hz, 2H).

*5.1.27. 1-(2-Chloroethyl)-5-(3-chlorophenyl)-1H-tetrazole (**5j**)*

The procedure described for the preparation of **5a** was used with compound **4j** (350 mg, 1.93 mmol), K_2CO_3 (534 mg, 3.86 mmol) and 1-bromo-2-chloroethane (0.19 mL, 2.31 mmol.) to obtain **5j** (352 mg, 75%) as white solid. R_f = 0.60 (*n*-hexane: EtOAc = 2:1). Mp = 72-74 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12–8.09 (m, 2H), 7.50–7.47 (m, 2H), 5.00–4.97 (m, 2H), 4.11–4.08 (m, 2H).

*5.1.28. 1-(2-Chloroethyl)-5-(4-chlorophenyl)-1H-tetrazole (**5k**)*

The procedure described for the preparation of **5a** was used with compound **4k** (200 mg, 1.10 mmol), K_2CO_3 (304 mg, 2.20 mmol) and 1-bromo-2-chloroethane (0.13 mL, 1.65 mmol.) to obtain **5k** (147 mg, 52%) as clear liquid. R_f = 0.40 *n*-hexane: EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_{3)}$: δ 8.11–8.06 (m, 2H), 7.49–7.44 (m, 2H), 4.97 (t, *J* = 6.3 Hz, 2H), 4.09 (t, *J* = 6.3 Hz, 2H).

*5.1.29. 1-(2-Chloroethyl)-5-(2-bromophenyl)-1H-tetrazole (**5l**)*

The procedure described for the preparation of **5a** was used with compound **4l** (400 mg, 1.77 mmol), K_2CO_3 (489 mg, 3.54 mmol) and 1-bromo-2-chloroethane (0.22 mL, 2.65 mmol.) to obtain **5l** (356 mg, 70%) as clear liquid. R_f = 0.61 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85–7.83 (m, 1H), 7.72–7.70 (m, 1H), 7.43–7.39 (m, 1H), 7.33–7.29 (m, 1H), 5.02–4.99 (m, 2H), 4.10–4.07 (m, 2H).

*5.1.30. 1-(2-Chloroethyl)-5-(3-bromophenyl)-1H-tetrazole (**5m**)*

The procedure described for the preparation of **5a** was used with compound **4m** (400 mg, 1.77 mmol), K_2CO_3 (489 mg, 3.54 mmol) and 1-bromo-2-chloroethane (0.22 mL, 2.65 mmol.) to obtain **5m** (356 mg, 70%) as white solid. R_f = 0.64 (*n*-hexane: EtOAc = 2:1). Mp = 63-65 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32–8.31 (m, 1H), 8.10–8.08 (m, 1H), 7.62–7.59 (m, 1H), 7.38–7.35 (m, 1H), 4.98 (t, *J* = 6 Hz, 2H), 4.11–4.08 (m, 2H).

*5.1.31. 1-(2-Chloroethyl)-5-(4-bromophenyl)-1H-tetrazole (**5n**)*

The procedure described for the preparation of **5a** was used with compound **4n** (280 mg, 1.16 mmol), K_2CO_3 (320 mg, 2.32 mmol) and 1-bromo-2-chloroethane (0.14 mL, 1.74 mmol.) to obtain **5n** (185 mg, 52%) as white solid. R_f = 0.70 (*n*-hexane: EtOAc = 2:1). Mp = 348-350 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05–8.01 (m, 2H), 7.66–7.61 (m, 2H), 4.98 (t, *J* = 6.3 Hz, 2H), 4.11–4.07 (m, 2H).

*5.1.32. 1-(2-Chloroethyl)-5-(2,3-dichlorophenyl)-1H-tetrazole (**5o**)*

The procedure described for the preparation of **5a** was used with compound **4o** (430 mg, 1.99 mmol), K_2CO_3 (550 mg, 3.98 mmol) and 1-bromo-2-chloroethane (0.25 mL, 2.99 mmol.) to obtain **5o** (441 mg, 80%) as clear liquid. R_f = 0.77 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.84 (m, 1H), 7.63–7.60 (m, 1H), 7.37–7.32 (m, 1H), 5.06–5.02 (m, 2H), 4.11 (t, *J* = 6.3 Hz, 2H).

*5.1.33. 5-([1,1'-Biphenyl]-4-yl)-1-(2-chloroethyl)-1H-tetrazole (**5p**)*

The procedure described for the preparation of **5a** was used with compound **4p** (400 mg, 1.79 mmol), K_2CO_3 (495 mg, 3.58 mmol) and 1-bromo-2-chloroethane (0.18 mL, 2.15 mmol.) to

obtain **5p** (357 mg, 70%) as white solid. R_f = 0.51 (*n*-hexane: EtOAc = 2:1). Mp = 93-95 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25–8.23 (m, 2H), 7.76–7.73 (m, 2H), 7.67–7.65 (m, 2H), 7.50–7.46 (m, 2H), 7.41–7.38 (m, 1H), 5.02–4.99 (m, 2H), 4.13–4.10 (m, 2H).

*5.1.34. 1-(2-Chloroethyl)-5-(naphthalen-1-yl)-1H-tetrazole (**5q**)*

The procedure described for the preparation of **5a** was used with compound **4p** (261 mg, 1.01 mmol), K_2CO_3 (279 mg, 2.02 mmol) and 1-bromo-2-chloroethane (0.12 mL, 1.51 mmol.) to obtain **5q** (130 mg, 50%) as clear liquid. R_f = 0.90 (n-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90–8.87 (m, 1H), 8.27 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.01–7.09 (m, 2H), 7.65–7.53 (m, 3H), 5.07 (t, *J* = 6.3 Hz, 2H), 4.15 (t, *J* = 6.3 Hz, 2H).

*5.1.35. 1-(3-Chloropropyl)-5-phenyl-1H-tetrazole (**6a**)*

The procedure described for the preparation of **5a** was used with compound **4a** (450 mg, 3.07 mmol), K_2CO_3 (834 mg, 6.04 mmol) and 1-bromo-3-chloropropane (0.38 mL, 4.60 mmol.) to obtain **6a** (481 mg, 81%) as clear liquid. R_f = 0.56 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16–8.11 (m, 2H), 7.52–7.45 (m, 3H), 4.85 (t, *J* = 6.6 Hz, 2H), 3.65–3.61 (m, 2H), 2.57–2.48 (m, 2H).

*5.1.36. 1-(3-Chloropropyl)-5-(3-(trifluoromethyl)phenyl)-1H-tetrazole (**6b**)*

The procedure described for the preparation of **5a** was used with compound **4b** (600 mg, 2.80 mmol), K_2CO_3 (774 mg, 5.60 mmol) and 1-bromo-3-chloropropane (0.41 mL, 4.20 mmol.) to obtain **6b** (757 mg, 93%) as clear liquid. R_f = 0.57 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41–8.31 (m, 2H), 7.74–7.59 (m, 2H), 4.91–4.86 (m, 2H), 3.67–3.63 (m, 2H), 2.60–2.52 (m, 2H).

*5.1.37. 1-(3-(1-(3-Chloropropyl)-1H-tetrazol-5-yl)phenyl)ethanone (**6c**)*

The procedure described for the preparation of **5a** was used with compound **4c** (500 mg, 2.65 mmol), K_2CO_3 (732 mg, 5.30 mmol) and 1-bromo-3-chloropropane (0.39 mL, 3.98 mmol.) to obtain **6c** (547 mg, 78%) as clear liquid. R_f = 0.42 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73–8.72 (m, 1H), 8.37–8.33 (m, 1H), 8.10–8.06 (m, 1H), 7.64–7.59 (m, 1H), 4.89 (t, *J* = 6.6 Hz, 2H), 3.65 (t, *J* = 6 Hz, 2H), 2.69 (s, 3H),.2.60–2.52 (m, 2H).

*5.1.38. 1-(3-Chloropropyl)-5-(4-nitrophenyl)-1H-tetrazole (**6d**)*

The procedure described for the preparation of **5a** was used with compound **4d** (450 mg, 2.35 mmol), K_2CO_3 (652 mg, 4.70 mmol) and 1-bromo-3-chloropropane (0.34 mL, 3.53 mmol.) to obtain **6d** (276 mg, 44%) as white solid. R_f = 0.62 (*n*-hexane: EtOAc = 1:1). Mp = 80-82 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36–8.30 (s, 4H), 4.95–4.91 (m, 2H), 3.70–3.66 (m, 2H), 2.63–2.54 (m, 2H).

*5.1.39. 1-(3-Chloropropyl)-5-(4-methoxyphenyl)-1H-tetrazole (**6e**)*

The procedure described for the preparation of **5a** was used with compound **4e** (594 mg, 3.37 mmol), K_2CO_3 (937 mg, 6.74 mmol) and 1-bromo-3-chloropropane (0.49 mL, 5.0 mmol.) to obtain **6e** (732 mg, 86%) as clear liquid. R_f = 0.36 (*n*-hexane: EtOAc = 4:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08–8.05 (m, 2H), 7.01–6.98 (m, 2H), 4.82 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 3H), 3.64 (t, *J* = 3 Hz, 2H), 2.53–2.49 (s, 2H).

*5.1.40. 1-(3-Chloropropyl)-5-(2-fluorophenyl)-1H-tetrazole (**6f**)*

The procedure described for the preparation of **5a** was used with compound **4f** (450 mg, 2.74 mmol), K_2CO_3 (757 mg, 5.48 mmol) and 1-bromo-3-chloropropane (0.40 mL, 4.11 mmol.) to obtain **6f** (600 mg, 91%) as clear liquid. R_f = 0.29 (*n*-hexane: EtOAc = 4:1). Mp = 83–85 ℃. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 8.16–8.10 (m, 1H), 7.51–7.43 (m, 1H), 7.31–7.20 (m, 2H), 4.92–4.88 (m, 2H), 3.67–3.63 (m, 2H), 2.59–2.51 (m, 2H).

*5.1.41. 1-(3-Chloropropyl)-5-(3-fluorophenyl)-1H-tetrazole (**6g**)*

The procedure described for the preparation of **5a** was used with compound **4g** (480 mg, 2.92 mmol), K_2CO_3 (807 mg, 5.84 mmol) and 1-bromo-3-chloropropane (0.43 mL, 4.38 mmol.) to obtain **6g** (632 mg, 90%) as clear liquid. R_f = 0.64 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95–7.94 (m, 1H), 7.85–7.81 (m, 1H), 7.49–7.42 (m, 1H), 7.20–7.13 (m, 1H), 4.88–4.84 (m, 2H), 3.66–3.62 (m, 2H), 2.58–2.49 (m, 2H).

*5.1.42. 1-(3-Chloropropyl)-5-(4-fluorophenyl)-1H-tetrazole (**6h**)*

The procedure described for the preparation of **5a** was used with compound **4h** (200 mg, 1.21 mmol), K_2CO_3 (334 mg, 2.42 mmol) and 1-bromo-3-chloropropane (0.18 mL, 1.81 mmol.) to obtain **6h** (241 mg, 83%) as clear liquid. R_f = 0.66 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17–8.10 (m, 2H), 7.22–7.14 (m, 2H), 4.85 (t, *J* = 6.6 Hz, 2H) 2H), 3.66–3.62 (m, 2H), 2.57–2.49 (m, 2H).

*5.1.43. 5-(2-Chlorophenyl)-1-(3-chloropropyl)-1H-tetrazole (**6i**)*

The procedure described for the preparation of **5a** was used with compound **4i** (200 mg, 1.10 mmol), K_2CO_3 (304 mg, 2.20 mmol) and 1-bromo-3-chloropropane (0.16 mL, 1.65 mmol.) to obtain **6i** (237 mg, 84%) as clear liquid. R_f = 0.54 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96–7.93 (m, 1H), 7.55–7.52 (m, 1H), 7.44–7.38 (m, 2H), 4.90 (t, *J* = 6.6 Hz, 2H), 3.68–3.64 (m, 2H), 2.59–2.50 (m, 2H).

*5.1.44. 5-(3-Chlorophenyl)-1-(3-chloropropyl)-1H-tetrazole (**6j**)*

The procedure described for the preparation of **5a** was used with compound **4j** (520 mg, 2.87 mmol), K_2CO_3 (793 mg, 5.74 mmol) and 1-bromo-3-chloropropane (0.42 mL, 4.30 mmol) to obtain **6j** (657 mg, 89%) as clear liquid. R_f = 0.50 (*n*-hexane: EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–7.98 (m, 2H), 7.44–7.37 (m, 2H), 4.85 (t, *J* = 6.6 Hz, 2H), 3.66–3.62 (m, 2H), 2.57–2.48 (m, 2H).

*5.1.45. 5-(4-Chlorophenyl)-1-(3-chloropropyl)-1H-tetrazole (**6k**)*

The procedure described for the preparation of **5a** was used with compound **4k** (637 mg, 3.52 mmol), K_2CO_3 (972 mg, 7.04 mmol) and 1-bromo-3-chloropropane (0.52 mL, 5.28 mmol.) to obtain **6k** (497 mg, 55%) as clear liquid. R_f = 0.48 *n*-hexane: EtOAc = 4:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08–8.06 (m, 2H), 7.47–7.44 (m, 2H), 4.86–4.84 (m, 2H), 3.64–3.62 (m, 2H), 2.55–2.51 (m, 2H).

*5.1.46. 5-(2-Bromophenyl)-1-(3-chloropropyl)-1H-tetrazole (**6l**)*

The procedure described for the preparation of **5a** was used with compound **4l** (300 mg, 1.33 mmol), K_2CO_3 (368 mg, 2.66 mmol) and 1-bromo-3-chloropropane (0.19 mL, 1.9 mmol.) to obtain **6l** (300 mg, 75%) as clear liquid. R_f = 0.64 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28–8.21 (m, 1H), 8.01 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.56 –7.52 (m, 1H), 7.34–7.28 (m, 1H), 4.84 (t, *J* = 6.6 Hz, 2H), 3.67–3.62 (m, 2H), 2.56–2.48 (m, 2H).

*5.1.47. 5-(3-Bromophenyl)-1-(3-chloropropyl)-1H-tetrazole (**6m**)*

The procedure described for the preparation of **5a** was used with compound **4m** (250 mg, 1.11 mmol), K_2CO_3 (460 mg, 3.33 mmol) and 1-bromo-3-chloropropane (0.16 mL, 1.66 mmol.) to obtain **6m** (268 mg, 80%) as clear liquid. R_f = 0.61 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (ddd, *J* = 7.5, 1.8, 0.3 Hz, 1H), 7.74–7.71 (m, 1H), 7.45–7.29 (m, 2H), 4.87 (t, *J* = 6.6 Hz, 2H), 3.67–3.63 (m, 2H), 2.57–2.49 (m, 2H).

*5.1.48. 5-(4-Bromophenyl)-1-(3-chloropropyl)-1H-tetrazole (**6n**)*

The procedure described for the preparation of **5a** was used with compound **4n** (1300 mg, 5.77 mmol), K_2CO_3 (2392 mg, 17.31 mmol) and 1-bromo-3-chloropropane (0.5 mL, 8.6 mmol.) to obtain **6n** (1496 mg, 86%) as clear liquid. R_f = 0.51 (*n*-hexane: EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.94 (m, 2H), 7.60–7.56 (m, 2H), 4.86–4.81 (m, 2H), 3.65–3.61 (m, 2H), 2.56–2.47 (m, 2H).

*5.1.49. 1-(3-Chloropropyl)-5-(2,3-dichlorophenyl)-1H-tetrazole (**6o**)*

The procedure described for the preparation of **5a** was used with compound **4o** (215 mg, 1.0 mmol), K_2CO_3 (276 mg, 2 mmol) and 1-bromo-3-chloropropane (0.14 mL, 1.5 mmol.) to obtain **6o** (248 mg, 85%) as clear liquid. R_f = 0.54 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.36–7.31 (m, 1H), 4.94–4.89 (m, 2H), 3.68–3.64 (m, 2H), 2.60–2.51 (m, 2H).

*5.1.50. 5-([1,1'-Biphenyl]-4-yl)-1-(3-chloropropyl)-1H-tetrazole (**6p**)*

The procedure described for the preparation of **5a** was used with compound **4p** (450 mg, 2.02 mmol), K_2CO_3 (558 mg, 4.04 mmol) and 1-bromo-3-chloropropane (0.30 mL, 3.03 mmol.) to obtain **6p** (471 mg, 78%) as clear liquid. R_f = 0.67 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23–8.19 (m, 2H), 7.74–7.62 (m, 4H), 7.49–7.35 (m, 3H), 4.88–4.84 (m, 2H), 3.66–3.62 (m, 2H), 2.58–2.50 (m, 2H).

*5.1.51. 1-(3-Chloropropyl)-5-(naphthalen-1-yl)-1H-tetrazole (**6q**)*

The procedure described for the preparation of **5a** was used with compound **4q** (500 mg, 2.54 mmol), K_2CO_3 (702 mg, 5.08 mmol) and 1-bromo-3-chloropropane (0.37 mL, 3.81 mmol.) to

obtain **6q** (457 mg, 66%) as clear liquid. R_f = 0.42 (*n*-hexane: EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91–8.18 (m, 1H), 8.26 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.00–7.90 (m, 2H), 7.64–7.52 (m, 3H), 4.96–4.91 (m, 2H), 3.69–3.65 (m, 2H), 2.63–2.54 (m, 2H).

*5.1.52. 4-Benzyl-1-(2-(5-phenyl-1H-tetrazol-1-yl)ethyl)piperidine (**1a**)*

The mixture of compound **5a** (140 mg, 0.67 mmol), 4-benzylpiperidine (0.14 mL, 0.80 mmol), TEA (0.28 mL, 2.01 mmol) and DMSO (1 mL) was stirred at 100 ℃. After the reaction was completed, the water was added to the reaction mixture and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, 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 **1a** (81 mg, 35%) as liquid. R_f = 0.66 (*n*-hexane: EtOAc =1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–8.12 (m, 2H), 7.52–7.45 (m, 3H), 7.29–7.16 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.78–4.73 (m, 2H), 3.01 (t, *J* = 6.9 Hz, 2H), 2.91 (d, *J* = 11.4 Hz, 2H), 2.50 (d, *J* = 6.9 Hz, 2H), 2.08–2.01 (m, 2H), 1.63–1.45 (m, 3H), 1.41–1.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 140.7, 130.1, 129.0, 128.9, 128.8, 128.1, 127.4, 126.7, 125.7, 56.9, 53.7, 50.7, 43.0, 37.6, 31.9, 29.6. MS (ESI): *m/z* 348.2 $(M+H)^+$.

*5.1.53. 4-Benzyl-1-(2-(5-(3-(trifluoromethyl)phenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1b**)*

The procedure described for the preparation of **1a** was used with compound **5b** (300 mg, 1.08 mmol), 4-benzylpiperidine (0.22 mL, 1.29 mmol), TEA (0.45 mL, 3.24 mmol) and DMSO (2 mL) to obtain **1b** (197 mg, 44%) as liquid. R_f = 0.56 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.35 (d, *J* = 4.8 Hz, 1H), 7.74–7.61 (m, 2H), 7.29–7.12 (m, 5H), 4.80–4.77 (m, 2H), 3.04–3.01 (m, 2H), 2.91 (d, *J* = 11.5 Hz, 2H), 2.51 (d, *J* = 7 Hz, 2H), 2.08–2.03 (m, 2H), 1.64–1.47 (m, 3H), 1.30–1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 140.5, 131.4 (d, *J* = 32.5 Hz), 129.9, 129.4, 129.1, 128.2, 126.7 (q, *J* = 12.5 Hz), 125.8, 123.6 (q, *J* = 3.7 Hz), 121.6 (d, *J* = 271.2 Hz), 56.9, 53.8, 51.0, 43.1, 37.7, 32.1. MS (ESI): *m/z* 416.1 $(M+H)^+$.

*5.1.54. 1-(3-(1-(2-(4-Benzylpiperidin-1-yl)ethyl)-1H-tetrazol-5-yl)phenyl)ethanone (**1c**)*

The procedure described for the preparation of **1a** was used with compound **5c** (290 mg, 1.15 mmol), 4-benzylpiperidine (0.24 mL, 1.38 mmol), TEA (0.48 mL, 3.45 mmol) and DMSO (2 mL) to obtain **1c** (291 mg, 65%) as liquid. R_f = 0.34 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71–8.70 (m, 1H), 8.36–8.30 (m, 1H), 8.08–8.05 (m, 1H), 7.63–7.58 (m, 1H), 7.25–7.03 (m, 5H), 4.80–4.75 (m, 2H), 3.02 (t, *J* = 6.9 Hz, 2H), 2.91 (d, *J* = 11.4 Hz, 2H), 2.69 (s, 3H), 2.50 (d, *J* = 6.9 Hz, 2H), 2.09–2.02 (m, 2H), 1.61–1.47 (m, 3H), 1.30–1.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 197.5, 164.2, 140.5, 137.7, 133.4, 131.2, 129.8, 129.3, 129.1, 128.2, 128.1, 126.8, 125.8, 56.7, 53.7, 50.9, 43.1, 37.6, 32.0, 26.7. MS (ESI): *m/z* 390.8 $(M+H)^+$.

*5.1.55. 4-Benzyl-1-(2-(5-(4-nitrophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1d**)*

The procedure described for the preparation of **1a** was used with compound **5d** (120 mg, 0.47 mmol), 4-benzylpiperidine (0.1 mL, 0.56 mmol), TEA (0.19 mL, 1.41 mmol) and DMSO (1 mL) to obtain **1d** (59 mg, 32%) as liquid. R_f = 0.73 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 4H), 7.28–7.10 (m, 5H), 4.80–4.76 (m, 2H), 3.03–2.99 (m, 2H), 2.90 (d, *J* = 10.8 Hz, 2H), 2.50 (d, *J* = 6.3 Hz, 2H), 2.08–2.01 (m, 2H), 1.63–1.50 (m, 3H), 1.41–1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 148.8, 140.5, 133.4, 129.1, 128.2, 127.3, 125.8, 124.2, 56.8, 53.8, 51.1, 43.1, 37.7, 32.1. MS (ESI): *m/z* 393.7 $(M+H)^+$.

*5.1.56. 4-Benzyl-1-(2-(5-(4-methoxyphenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1e**)*

The procedure described for the preparation of **1a** was used with compound **5e** (200 mg, 0.83 mmol), 4-benzylpiperidine (0.18 mL, 0.99 mmol), TEA (0.34 mL, 2.49 mmol) and DMSO (2 mL) to obtain **1e** (128 mg, 41%) as solid. R_f = 0.31 (*n*-hexane: EtOAc = 2:1). Mp = 110–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10–8.07 (m, 2H), 7.29–6.99 (m, 7H), 4.74 (t, *J* = 7 Hz, 2H), 3.87 (s, 3H), 3.01 (t, *J* = 7 Hz, 2H), 2.91 (d, *J* = 11.5 Hz, 2H), 2.51 (d, *J* = 7.5 Hz, 2H), 2.08–2.03 (m, 2H), 1.63–1.47 (m, 3H), 1.30–1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 161.2, 140.5,

129.1, 128.3, 128.2, 125.8, 120.1, 114.3, 57.0, 55.4, 53.8, 50.7, 43.1, 37.7, 32.1, 29.7. MS (ESI): *m/z* 378.2 $(M+H)^+$.

*5.1.57. 4-Benzyl-1-(2-(5-(3-fluorophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1g**)*

The procedure described for the preparation of **1a** was used with compound **5g** (230 mg, 1.01mmol), 4-benzylpiperidine (0.21 mL, 1.21 mmol), TEA (0.42 mL, 3.03 mmol) and DMSO (2 mL) to obtain **1g** (153 mg, 42%) as solid. R_f = 0.41 (*n*-hexane: EtOAc = 2:1). Mp = 100–103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96–7.93 (m, 2H), 7.86–7.84 (m, 1H), 7.48–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peak), 4.76 (t, *J* = 7 Hz, 2H), 3.02–3.0 (m, 2H), 2.91 (d, *J* = 11.5 Hz, 2H), 2.51 (d, *J* = 7 Hz, 2H), 2.08–2.03 (m, 2H), 1.63–1.47 (m, 3H), 1.29–1.23 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0 (d, *J* = 12.5 Hz), 163.9, 162.1, 140.5, 130.5 (d, *J* = 12.5 Hz), 129.5 (d, *J* = 12.5 Hz), 129.1, 128.2, 125.8, 122.4 (d, *J* = 12.5 Hz), 117.1 (d, *J* = 12.5 Hz), 113.7 (d, *J* = 25 Hz), 56.9, 53.8, 50.9, 43.1, 37.7, 32.1. MS (ESI): *m/z* 366.3 $(M+H)^+$.

*5.1.58. 4-Benzyl-1-(2-(5-(4-fluorophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1h**)*

The procedure described for the preparation of **1a** was used with compound **5h** (300 mg, 1.32 mmol), 4-benzylpiperidine (0.28 mL, 1.58 mmol), TEA (0.55 mL, 3.96 mmol) and DMSO (2 mL) to obtain **1h** (178 mg, 37%) as liquid. R_f = 0.46 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16–8.12 (m, 2H), 7.29–7.12 (m, 7H), 4.75 (t, *J* = 7 Hz, 2H), 3.01 (t, *J* = 7 Hz, 2H), 2.91 (d, *J* = 11.5 Hz, 2H), 2.52 (d, *J* = 7 Hz, 2H), 2.08–2.03 (m, 2H), 1.63–1.48 (m, 3H), 1.30–1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 164.2, 163.0, 140.5, 129.1, 128.8 (d, *J* = 12.5 Hz), 128.2, 125.8, 123.7 (d, *J* = 12.5 Hz), 116.0 (d, *J* = 25 Hz), 56.9, 53.8, 50.8, 43.1, 37.7, 32.0. MS (ESI): *m/z* 366.0 $(M+H)^+$.

*5.1.59. 4-Benzyl-1-(2-(5-(3-chlorophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1j**)*

The procedure described for the preparation of **1a** was used with compound **5j** (250 mg, 1.02 mmol), 4-benzylpiperidine (0.22 mL, 1.22 mmol), TEA (0.42 mL, 3.06 mmol) and DMSO (2 mL) to obtain **1j** (156 mg, 40%) as solid. R_f = 0.44 (*n*-hexane: EtOAc = 4:1). Mp = 90–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–8.06 (m, 2H), 7.48–7.43 (m, 2H), 7.29–7.10 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.77–4.72 (m, 2H), 2.99 (t, *J* = 6.9 Hz, 2H), 2.90 (d, *J* = 11.4 Hz, 2H), 2.50 (d, *J* = 7 Hz, 2H), 2.08–2.01 (m, 2H), 1.63–1.43 (m, 3H), 1.31–1.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 140.5, 136.2, 129.1, 129.0, 128.2, 128.1, 126.0, 125.8, 56.9, 53.8, 50.9, 43.1, 37.7, 32.1, 29.7. MS (ESI): *m/z* 404.9 $(M+Na)^+$.

*5.1.60. 4-Benzyl-1-(2-(5-(4-chlorophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1k**)*

The procedure described for the preparation of **1a** was used with compound **5k** (250 mg, 1.02 mmol), 4-benzylpiperidine (0.21 mL, 1.22 mmol), TEA (0.42 mL, 3.06 mmol) and DMSO (2 mL) to obtain **1k** (148 mg, 38%) as solid. R_f = 0.39 (*n*-hexane: EtOAc = 1:1). Mp = 92–94 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09–8.07 (m, 2H), 7.47–7.45 (m, 2H), 7.28–7.11 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.76–4.73 (m, 2H), 3.01–2.98 (m, 2H), 2.90 (d, *J* = 11.4 Hz, 2H), 2.50 (d, *J* = 7.2 Hz, 2H), 2.06–2.02 (m, 2H), 1.62–1.47 (m, 3H), 1.28–1.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 140.5, 136.2, 129.1, 129.0, 128.2, 128.1, 126.0, 125.8, 56.9, 53.8, 50.9, 43.1, 37.7, 32.1. MS (ESI): *m/z* 382.0 $(M+H)^+$.

*5.1.61. 4-Benzyl-1-(2-(5-(2-bromophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1l**)*

The procedure described for the preparation of **1a** was used with compound **5l** (300 mg, 1.04 mmol), 4-benzylpiperidine (0.22 mL, 1.24 mmol), TEA (0.43 mL, 3.12 mmol) and DMSO (2 mL) to obtain **1l** (275 mg, 64%) as liquid. R_f = 0.44 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86–7.84 (m, 2H), 7.74–7.73 (m, 1H), 7.44–7.41 (m, 3H) 7.20–7.16 (m, 1H), 7.13–7.12 (m, 2H), 4.81–4.78 (m, 2H), 3.04–3.02 (m, 2H), 2.90 (d, *J* = 11.5 Hz, 2H), 2.51 (d, *J* = 7.5 Hz, 2H), 2.07–2.02 (m, 2H), 1.62–1.46 (m, 3H), 1.29–1.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 140.5, 134.0, 131.7, 131.2, 129.1, 128.7, 128.2, 127.4, 125.8, 122.1, 56.9, 53.7, 51.0, 43.1, 37.7, 32.1. MS (ESI): *m/z* 426.0 $(M+H)^+$.

*5.1.62. 4-Benzyl-1-(2-(5-(3-bromophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1m**)*

The procedure described for the preparation of **1a** was used with compound **5m** (300 mg, 1.04 mmol), 4-benzylpiperidine (0.22 mL, 1.24 mmol), TEA (0.43 mL, 3.12 mmol) and DMSO (2 mL) to obtain **1m** (310 mg, 70%) as liquid. R_f = 0.50 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.08–8.07 (m, 1H), 7.58–7.57 (m, 1H), 7.36–7.10 (m, 6H), 4.75–4.73 (m, 2H), 3.00–2.98 (m, 2H), 2.89 (d, *J* = 11.4 Hz, 2H), 2.49 (d, *J* = 7.2 Hz, 2H), 2.05–2.02 (m, 2H), 1.61–1.46 (m, 3H), 1.27–1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 140.5, 133.2, 130.4, 129.8, 129.4, 129.1, 128.2, 125.8, 125.3, 122.9, 56.9, 53.8, 50.9, 43.1, 37.7, 32.1. MS (ESI): *m/z* 426.5 $(M+H)^+$.

*5.1.63. 4-Benzyl-1-(2-(5-(4-bromophenyl)-1H-tetrazol-1-yl)ethyl)piperidine (**1n**)*

The procedure described for the preparation of **1a** was used with compound **5n** (300 mg, 1.04 mmol), 4-benzylpiperidine (0.22 mL, 1.24 mmol), TEA (0.43 mL, 3.12 mmol) and DMSO (2 mL) to obtain **1n** (168 mg, 38%) as solid. R_f = 0.33 (*n*-hexane: EtOAc = 1:1). Mp = 104–105 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02–8.00 (m, 2H), 7.63–7.61 (m, 2H), 7.27–7.7.25 (m, ≈ 2H, overlapped with $CHCl_3$ peak), 7.19–7.16 (m, 1H), 7.12–7.11 (m, 2H), 4.76–4.74 (m, 2H), 3.01–2.99 (m, 2H), 2.90 (d, *J* = 11.4 Hz, 2H), 2.50 (d, *J* = 7.2 Hz, 2H), 2.06–2.02 (m, 2H), 1.61–1.47 (m, 3H), 1.28–1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 140.5, 132.1, 129.1, 128.3, 128.2, 126.5, 125.8, 124.6, 56.9, 53.8, 50.9, 43.1, 37.7, 32.1. MS (ESI): *m/z* 426.1 $(M+H)^+$.

*5.1.64. 1-(2-(5-([1,1'-Biphenyl]-4-yl)-1H-tetrazol-1-yl)ethyl)-4-benzylpiperidine (**1p**)*

The procedure described for the preparation of **1a** was used with compound **5p** (300 mg, 1.05 mmol), 4-benzylpiperidine (0.22 mL, 1.26 mmol), TEA (0.44 mL, 3.15 mmol) and DMSO (2 mL) to obtain **1p** (173 mg, 39%) as solid. R_f = 0.58 (*n*-hexane: EtOAc = 2:1). Mp = 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26–8.20 (m, 2H), 7.73–7.71 (m, 2H), 7.65–7.71 (m, 3H), 7.48–7.45 (m, 1H), 7.39–7.36 (m, 1H), 7.27–7.25 (m, 2H, overlapped with $CHCl_3$ peak), 7.19–7.16 (m,

1H), 7.13–7.11 (m, 2H), 4.76 (t, *J* = 7.2 Hz, 2H), 3.03–3.01 (m, 2H), 2.91 (d, *J* = 11.4 Hz, 2H), 2.51 (d, *J* = 7.2 Hz, 2H), 2.07–2.03 (m, 2H), 1.69–1.47 (m, 3H), 1.29–1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 143.0, 140.5, 140.3, 129.1, 128.9, 128.2, 127.7, 127.5, 127.2, 127.1, 126.4, 125.8, 56.9, 53.8, 50.9, 37.7, 32.1. MS (ESI): *m/z* 424.9 $(M+H)^+$.

*5.1.65. 4-Benzyl-1-(2-(5-(naphthalen-1-yl)-1H-tetrazol-1-yl)ethyl)piperidine (**1q**)*

The procedure described for the preparation of **1a** was used with compound **5q** (130 mg, 0.50 mmol), 4-benzylpiperidine (0.1 mL, 0.60 mmol), TEA (0.21 mL, 1.56 mmol) and DMSO (1 mL) to obtain **1q** (56 mg, 28%) as liquid. R_f = 0.74 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91–8.87 (m, 1H), 8.24 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.98–7.89 (m, 2H), 7.62–7.52 (m, 3H), 7.29–7.10 (m, 5H), 4.83 (t, *J* = 6.9 Hz, 2H), 3.07–3.02 (m, 2H), 2.92 (d, *J* = 11.4 Hz, 2H), 2.50 (d, *J* = 7.2 Hz, 2H), 2.09–2.01 (m, 2H), 1.64–1.43 (m, 3H), 1.32–1.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 140.5, 133.9, 130.9, 130.6, 129.1, 128.6, 128.3, 128.2, 127.2, , 126.2, 125.8, 125.7, 125.2, 124.4, 110.0, 56.9, 53.8, 50.8, 43.0, 37.7, 32.1. MS (ESI): *m/z* 398.3 $((M+H)^+$.

*5.1.66. 4-Benzyl-1-(3-(5-phenyl-1H-tetrazol-1-yl)propyl)piperidine (**2a**)*

The procedure described for the preparation of **1a** was used with compound **6a** (440 mg, 1.97 mmol), 4-benzylpiperidine (0.42 mL, 2.36 mmol), TEA (1 mL, 7.88 mmol) and DMSO (3 mL) to obtain **2a** (584 mg, 82%) as liquid. R_f = 0.50 (*n*-hexane: EtOA = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16–8.12 (m, 2H), 7.52–7.42 (m, 3H), 7.29–7.10 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.70 (t, *J* = 6.9 Hz, 2H), 2.85 (t, *J* = 11.4 Hz, 2H), 2.50 (d, *J* = 7.2 Hz, 2H), 2.40–2.36 (m, 2H), 2.26–2.16 (m, 2H), 1.90–1.81 (m, 2H), 1.63–1.43 (m, 3H), 1.32–1.19 (m, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 140.6, 130.2, 129.1, 128.9, 128.2, 127.5, 126.8, 125.8, 55.2, 53.8, 51.5, 43.1, 37.8, 32.0, 26.7. MS (ESI): *m/z* 362.0 $(M+H)^+$.

*5.1.67. 4-Benzyl-1-(3-(5-(3-(trifluoromethyl)phenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2b**)*

The procedure described for the preparation of **1a** was used with compound **6b** (500 mg, 1.72 mmol), 4-benzylpiperidine (0.37 mL, 2.06 mmol), TEA (0.72 mL, 5.16 mmol) and DMSO (3 mL) to obtain **2b** (693 mg, 94%) as liquid. R_f = 0.56 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.28–7.09 (m, 5H), 4.72 (*J* = 6.9 Hz, 2H), 2.85 (d, *J* = 11.7 Hz, 2H), 2.49 (d, *J* = 6.9 Hz, 2H), 2.40–2.36 (m, 2H), 2.26–2.17 (m, 2H), 1.90–1.81 (m, 2H), 1.63–1.42 (m, 3H), 1.31–1.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 140.5, 131.4 (d, *J* = 32.5 Hz), 129.9, 129.5, 129.1, 128.2, 126.7 (q, *J* = 12.7 Hz), 125.8, 123.6 (q, *J* = 3.7 Hz), 121.6 (d, *J* = 271.2 Hz), 55.1, 53.8, 51.7, 43.1, 37.8, 31.9, 26.6. MS (ESI): *m/z* 430.3 $(M+H)^+$.

*5.1.68. 1-(3-(1-(3-(4-Benzylpiperidin-1-yl)propyl)-1H-tetrazol-5-yl)phenyl)ethanone (**2c**)*

The procedure described for the preparation of **1a** was used with compound **6c** (500 mg, 1.88 mmol), 4-benzylpiperidine (0.4 mL, 2.25 mmol), TEA (0.78 mL, 5.64 mmol) and DMSO (3 mL) to obtain **2c** (622 mg, 82%) as liquid. R_f = 0.21 (*n*-hexane: EtOAc = 1:1). R_f = 0.21 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71–8.70 (m, 1H), 8.36–8.33 (m, 1H), 8.08–8.05 (m, 1H), 7.63–7.57 (m, 1H), 7.29–7.10 (m, ≈5H, overlapped with $CHCl_3$ peak), 4.76–4.71 (m, 2H), 2.88 (d, *J* = 12 Hz, 2H), 2.68 (s, 3H), 2.51 (d, *J* = 6.9 Hz, 2H), 2.43–2.38 (m, 2H), 2.29–2.22 (m, 2H), 1.93–1.84 (m, 2H), 1.64–1.42 (m, 3H), 1.30–1.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.5, 164.4, 140.1, 137.7, 131.1, 129.8, 129.3, 129.0, 128.3, 127.9, 126.8, 126.0, 55.0, 53.6, 51.5, 42.7, 37.4, 31.1, 26.8, 25.9. MS (ESI): *m/z* 404.8 $(M+H)^+$.

*5.1.69. 4-Benzyl-1-(3-(5-(4-nitrophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2d**)*

The procedure described for the preparation of **1a** was used with compound **6d** (270 mg, 1 mmol), 4-benzylpiperidine (0.21 mL 1.2 mmol), TEA (0.42 mL, 3 mmol) and DMSO (2 mL) to obtain **2d** (170 mg, 42%) as solid. R_f = 0.42 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 91–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34–8.31 (s, 4H), 7.29–7.10 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.75 (t, *J* = 6.9 Hz, 2H), 2.86 (d, *J* = 11.7 Hz, 2H), 2.50 (d, *J* = 6.9 Hz, 2H), 2.43–2.38 (m, 2H), 2.28–2.19 (m, 2H), 1.92–1.83 (m, 2H), 1.64–1.44 (m, 3H), 1.32–1.19 (m, 2H); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 163.1, 148.8, 140.5, 133.4, 129.1, 128.2, 127.6, 125.8, 124.2, 55.1, 53.9, 51.9, 43.1, 37.8, 32.0, 26.7. MS (ESI): *m/z* 407.1 $(M+H)^+$.

*5.1.70. 4-Benzyl-1-(3-(5-(4-methoxyphenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2e**)*

The procedure described for the preparation of **1a** was used with compound **6e** (200 mg, 1.13 mmol), 4-benzylpiperidine (0.24 mL, 1.35 mmol), TEA (0.47 mL, 3.39 mmol) and DMSO (2 mL) to obtain **2e** (289 mg, 74%) as liquid. R_f = 0.20 (*n*-hexane: EtOAc = 2:1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.09–8.05 (m, 2H), 7.27–7.09 (m, ≈ 7H, overlapped with $CHCl_3$ peak), 4.65 (t, *J* = 7 Hz, 2H), 3.82 (s, 3H), 2.83 (d, *J* = 11.4 Hz, 2H), 2.49 (d, *J* = 6.9 Hz, 2H), 2.37–2.33 (m, 2H), 2.22–2.13 (m, 2H), 1.87–1.79 (m, 2H), 1.61–1.40 (m, 3H), 1.31–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ. 164.9, 161.2, 140.5, 129.1, 128.3, 128.2, 125.8, 120.1, 114.3, 55.4, 55.2, 53.8, 51.4, 43.1, 41.0, 37.8, 32.0, 26.7. MS (ESI): *m/z* 414.4 $(M+Na)^+$.

*5.1.71. 4-Benzyl-1-(3-(5-(2-fluorophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2f**)*

The procedure described for the preparation of **1a** was used with compound **6f** (480 mg, 1.99 mmol), 4-benzylpiperidine (0.43 mL, 2.38 mmol), TEA (0.83 mL, 5.97 mmol) and DMSO (3 mL) to obtain **2f** (687 mg, 91%) as liquid. R_f = 0.29 (*n*-hexane: EtOAc = 2:1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.16–8.10 (m, 2H), 7.43–7.38 (m, 1H), 7.27–7.09 (m, ≈ 6H, overlapped with $CHCl_3$ peak), 4.75–4.70 (m, 2H), 2.83 (d, *J* = 11.7 Hz, 2H), 2.49 (d, *J* = 6.9 Hz, 2H), 2.39–2.34 (m, 2H), 2.24–2.15 (m, 2H), 1.88–1.79 (m, 2H), 1.61–1.40 (m, 3H), 1.30–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ. 161.4, 161.2 (d, *J* = 10 Hz), 158.8, 140.6, 131.8 (d, *J* = 10 Hz), 129.9 (d, *J* = 10 Hz), 129.1, 128.2, 125.8, 124.4 (d, *J* = 10 Hz), 116.7 (d, *J* = 20 Hz), 115.6 (d, *J* = 10 Hz), 55.2, 53.9, 51.7, 43.1, 41.0, 37.9, 32.0, 26.7. MS (ESI): *m/z* 379.9 $(M+H)^+$.

*5.1.72. 4-Benzyl-1-(3-(5-(3-fluorophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2g**)*

The procedure described for the preparation of **1a** was used with compound **6g** (520 mg, 2.16 mmol), 4-benzylpiperidine (0.46 mL, 2.59 mmol), TEA (1 mL, 7.8 mmol) and DMSO (3 mL) to obtain **2g** (762 mg, 93%) as liquid. R_f = 0.56 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.84 (m, 1H), 7.78–7.74 (m, 1H), 7.40–7.33 (m, 1H), 7.21–7.02 (m, ≈ 6H, overlapped with $CHCl_3$ peak), 4.65–4.60 (m, 2H), 2.77 (d, *J* = 11.5 Hz, 2H), 2.42 (d, *J* = 7.2 Hz, 2H), 2.32–2.27 (m, 2H), 2.15–2.08 (m, 2H), 1.82–1.73 (m, 2H), 1.55–1.34 (m, 3H), 1.23–1.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ. 164.0 (d, *J* = 10 Hz), 161.8, 140.6, 130.5 (d, *J* = 10 Hz), 129.4 (d, *J* = 10 Hz), 129.1, 128.2, 125.8, 122.4 (d, *J* = 10 Hz), 117.3 (d, *J* = 20 Hz), 113.8 (d, *J* = 20 Hz), 55.2, 53.8, 51.7, 43.2, 40.9, 37.9, 32.0, 26.7. MS (ESI): *m/z* 402.2 $(M+Na)^+$.

*5.1.73. 4-Benzyl-1-(3-(5-(4-fluorophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2h**)*

The procedure described for the preparation of **1a** was used with compound **6h** (250 mg, 1.03 mmol), 4-benzylpiperidine (0.22 mL, 1.23 mmol), TEA (0.43 mL, 3.09 mmol) and DMSO (2 mL) to obtain **2h** (316 mg, 42%) as liquid. R_f = 0.4 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16–8.09 (m, 2H), 7.29–7.10 (m, ≈ 7H, overlapped with $CHCl_3$ peak), 4.70 (t, *J* = 6.9 Hz, 2H), 2.85 (d, *J* = 11.4 Hz, 2H), 2.50 (d, *J* = 6.9 Hz, 2H), 2.40–2.36 (m, 2H), 2.25–2.16 (m, 2H), 1.89–1.81 (m, 2H), 1.63–1.42 (m, 3H), 1.32–1.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 164.2, 162.9, 140.6, 129.1, 128.8 (d, *J* = 12.5 Hz), 128.2, 125.8, 123.8 (d, *J* = 12.5 Hz), 116.1 (d, *J* = 25 Hz), 55.2, 53.9, 51.6, 43.2, 32.9, 32.2, 26.8. MS (ESI): *m/z* 380.3 $(M+H)^+$.

*5.1.74. 4-Benzyl-1-(3-(5-(2-chlorophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2i**)*

The procedure described for the preparation of **1a** was used with compound **6i** (490 mg, 1.9 mmol), 4-benzylpiperidine (0.40 mL, 2.28 mmol), TEA (0.79 mL, 5.7 mmol) and DMSO (3 mL) to obtain **2i** (338 mg, 45%) as liquid. R_f = 0.61 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96–7.93 (m, 1H), 7.55–7.52 (m, 1H), 7.44–7.35 (m, 2H), 7.29–7.10 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.78–4.73 (m, 2H), 2.86 (t, *J* = 11.4 Hz, 2H), 2.51 (d, *J* = 6.9 Hz, 2H), 2.43–2.38 (m, 2H), 2.28–2.19 (m, 2H), 1.91–1.82 (m, 2H), 1.63–1.43 (m, 3H), 1.33–1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 140.2, 133.0, 131.3, 131.1, 130.8,

129.0, 128.2, 126.9, 126.5, 125.9, 55.0, 53.7, 51.4, 42.8, 37.4, 31.1, 25.6. MS (ESI): *m/z* 396.0 $(M+H)^+$.

*5.1.75. 4-Benzyl-1-(3-(5-(3-chlorophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2j**)*

The procedure described for the preparation of **1a** was used with compound **6j** (620 mg, 2.41 mmol), 4-benzylpiperidine (0.51 mL, 2.89 mmol), TEA (1 mL, 7.23 mmol) and DMSO (3 mL) to obtain **2j** (878 mg, 92%) as liquid. R_f = 0.29 (*n*-hexane: EtOAc: MeOH = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–8.13 (m, 2H), 8.04–8.01 (m, 1H), 7.42–7.09 (m, ≈ 6H, overlapped with $CHCl_3$ peak), 4.72–4.67 (m, 2H), 2.84 (d, *J* = 11.7 Hz, 2H), 2.49 (d, *J* = 7.2 Hz, 2H), 2.39–2.35 (m, 2H), 2.22–2.15 (m, 2H), 1.89–1.80 (m, 2H), 1.62–1.43 (m, 3H), 1.31–1.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 140.5, 134.9, 130.23, 129.2, 129.1, 128.2, 126.9, 125.8, 124.9, 55.2, 53.8, 51.7, 43.1, 37.8, 32.0, 26.7. MS (ESI): *m/z* 395.9 $(M+H)^+$.

*5.1.76. 4-Benzyl-1-(3-(5-(4-chlorophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2k**)*

The procedure described for the preparation of **1a** was used with compound **6k** (300 mg, 1.16 mmol), 4-benzylpiperidine (0.25 mL, 1.39 mmol), TEA (0.48 mL, 3.48 mmol) and DMSO (2 mL) to obtain **2k** (330 mg, 72%) as liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–8.03 (m, 2H), 7.41–7.37 (m, 2H), 7.25–7.06 (m, 5H), 4.65–4.61 (m, 2H), 2.79 (d, *J* = 11.4 Hz, 2H), 2.45 (d, *J* = 6.9 Hz, 2H), 2.32–2.29 (m, 2H), 2.18–2.15 (m, 2H), 1.84–1.75 (m, 2H), 1.57–1.38 (m, 3H), 1.27–1.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 140.6, 136.2, 129.2, 129.1, 128.2, 128.1, 126.0, 125.8, 55.2, 53.9, 51.7, 43.2, 41.0, 37.9, 32.1, 26.8. MS (ESI): *m/z* 418.6 $(M+Na)^+$.

*5.1.77. 4-Benzyl-1-(3-(5-(2-bromophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2l**)*

The procedure described for the preparation of **1a** was used with compound **6l** (300 mg, 0.99mmol), 4-benzylpiperidine (0.21 mL, 1.18 mmol), TEA (0.41 mL, 2.97 mmol) and DMSO (2 mL) to obtain **2l** (269 mg, 71%) as liquid. R_f = 0.36 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300

MHz, $CDCl_3$): δ 8.30–8.29 (s, 1H), 8.09–8.05 (m, 1H), 7.58–7.57 (m, 1H), 7.36–7.09 (m, ≈ 6H, overlapped with $CHCl_3$ peak), 4.69 (t, *J* = 6.9 Hz, 2H), 2.83 (d, *J* = 11.4 Hz, 2H), 2.49 (d, *J* = 6.9 Hz, 2H), 2.39–2.14 (m, 2H), 2.23–2.14 (m, 2H), 1.88–1.80 (m, 2H), 1.61–1.41 (m, 3H), 1.30–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ.163.7, 140.6, 133.2, 130.4, 129.7, 129.4, 129.1, 128.2, 125.7, 125.4, 123.0, 55.2, 53.9, 51.7, 43.1, 41.0, 37.8, 32.1, 26.8. MS (ESI): *m/z* 439.0 $(M+H)^+$.

*5.1.78. 4-Benzyl-1-(3-(5-(3-bromophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2m**)*

The procedure described for the preparation of **1a** was used with compound **6m** (300 mg, 0.99 mmol), 4-benzylpiperidine (0.21 mL, 1.18 mmol), TEA (0.41 mL, 2.97 mmol) and DMSO (2 mL) to obtain **2m** (327 mg, 87%) as liquid. R_f = 0.33 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.71 (m, 2H), 7.45–7.11 (m, ≈ 7H, overlapped with $CHCl_3$ peak), 4.75 (t, *J* = 6.9 Hz, 2H), 2.86 (d, *J* = 11.7 Hz, 2H), 2.51 (d, *J* = 6.9 Hz, 2H), 2.43–2.38 (m, 2H), 2.28–2.17 (m, 2H), 1.90–1.82 (m, 2H), 1.64–1.43 (m, 3H), 1.33–1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 140.6, 134.1, 131.7, 131.2, 129.1, 128.7, 128.2, 127.5, 125.8, 122.1, 55.1, 53.8, 51.7, 43.1, 37.8, 32.0, 26.7. MS (ESI): *m/z* 440.3 $(M+H)^+$.

*5.1.79. 4-Benzyl-1-(3-(5-(4-bromophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2n**)*

The procedure described for the preparation of **1a** was used with compound **6n** (300 mg, 0.99 mmol), 4-benzylpiperidine (0.21 mL, 1.18 mmol), TEA (0.41 mL, 2.97 mmol) and DMSO (2 mL) to obtain **2n** (331 mg, 76%) as liquid. R_f = 0.54 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–7.98 (m, 2H), 7.63–7.58 (m, 2H), 7.29–7.09 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.71–4.67 (m, 2H), 2.84 (t, *J* = 11.4 Hz, 2H), 2.49 (d, *J* = 6.9 Hz, 2H), 2.39–3.35 (m, 2H), 2.24–2.15 (m, 2H), 1.89–1.80 (m, 2H), 1.63–1.44 (m, 3H), 1.31–1.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 140.5, 132.1, 129.1, 128.3, 128.2, 126.6, 125.8, 124.5, 55.2, 53.8, 51.6, 43.2, 37.8, 32.2, 26.8. MS (ESI): *m/z* 440.9 $(M+H)^+$.

*5.1.80. 4-Benzyl-1-(3-(5-(2,3-dichlorophenyl)-1H-tetrazol-1-yl)propyl)piperidine (**2o**)*

The procedure described for the preparation of **1a** was used with compound **6o** (400 mg, 1.37 mmol), 4-benzylpiperidine (0.29 mL, 1.64 mmol), TEA (0.57 mL, 4.11 mmol) and DMSO (3 mL) to obtain **2o** (530 mg, 90%) as liquid, R_f = 0.51 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.81 (m, 2H), 7.56–7.51 (m, 1H), 7.26–7.07 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.79–4.75 (m, 2H), 2.73 (d, *J* = 11.4 Hz, 2H), 2.41 (d, *J* = 6.9 Hz, 2H), 2.29–2.25 (m, 2H), 2.13–2.04 (m, 2H), 1.76–1.69 (m, 2H), 1.46–1.34 (m, 3H), 1.18–1.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9, 140.6, 134.5, 131.9, 131.6, 129.6, 129.1, 128.9, 128.2, 127.4, 125.8, 55.2, 53.9, 51.8, 43.1, 37.9, 32.1, 26.8. MS (ESI): *m/z* 430.3 $(M+H)^+$.

*5.1.81. 1-(3-(5-([1,1'-Biphenyl]-4-yl)-1H-tetrazol-1-yl)propyl)-4-benzylpiperidine (**2p**)*

The procedure described for the preparation of **1a** was used with compound **6p** (260 mg, 0.87 mmol), 4-benzylpiperidine (0.18 mL, 1.04 mmol), TEA (0.48 mL, 3.48 mmol) and DMSO (2 mL) to obtain **2p** (319 mg, 84%) as solid. R_f = 0.51 (*n*-hexane: EtOAc = 1:1). Mp = 100–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.74–7.74 (m, 2H), 7.54–7.39 (m, 3H), 7.24–7.07 (m, 5H, overlapped with $CHCl_3$ peak), 4.76–4.73 (m, 2H), 2.75 (d, *J* = 11.1 Hz, 2H), 2.51–2.28 (m, 6H), 1.79–1.71 (m, 2H), 1.47–1.36 (m, 3H), 1.13–1.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 143.0, 140.7, 140.3, 129.1, 128.9, 128.1, 127.8, 127.7, 127.2, 127.1, 126.4, 125.8, 55.3, 53.9, 51.6, 43.2, 40.9, 37.9, 32.2, 26.9. MS (ESI): *m/z* 438.3 $(M+H)^+$.

*5.1.82. 4-Benzyl-1-(3-(5-(naphthalen-1-yl)-1H-tetrazol-1-yl)propyl)piperidine (**2q**)*

The procedure described for the preparation of **1a** was used with compound **6q** (450 mg, 1.64 mmol), 4-benzylpiperidine (0.35 mL, 1.96 mmol), TEA (0.68 mL, 4.92 mmol) and DMSO (3 mL) to obtain **2q** (486 mg, 72%) as liquid. R_f = 0.20 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94–8.90 (m, 1H), 8.27–8.24 (m, 1H), 7.99–7.90 (m, 2H), 7.63–7.52 (m, 3H), 7.29–7.10 (m, ≈ 5H, overlapped with $CHCl_3$ peak), 4.79 (t, *J* = 6.9 Hz, 2H), 2.88 (d, *J* = 11.4 Hz, 2H),

2.51–2.41 (m, 4H), 2.32–2.23 (m, 2H), 1.91–1.83 (m, 2H) 1.63–1.42 (m, 3H), 1.28–1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 140.5, 133.9, 130.9, 130.6, 129.1, 128.6, 128.3, 128.2, 127.2, 126.2, 125.82, 125.77, 125.2, 124.3, 55.23, 53.8, 51.6, 43.0, 37.8, 31.9, 26.7. MS (ESI): *m/z* 412.2 $(M+H)^+$.

5.2. Neurotransmitter uptake assay

The assay was performed following the method described in the literature with slight modification.[28] HEK-293 cells were cultured in a medium supplemented with fetal bovine serum and transfected with hSERT or hNET or hDAT. Radiolabeled [^{3}H]-5-HT (PerkinElmer, Waltham, MA, USA), [^{3}H]-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). Venlafaxine hydrochloride, bupropion, and GBR12909 were used as reference neurotransmitter reuptake inhibitors.

5.3. Docking

The docking study was performed in Sybyl-X 2.1.1 (winnt_os5x) using the Surflex-Dock program. The structure of hSERT-paroxetine was downloaded from Protein Data Bank (PDB ID: 5I6X). Maltose, cholesterol, *N*-acetylglucosamine and chloride ion were deleted. The ligand (paroxetine) was extracted. Hydrogens were added and minimized using the MMFF94s force field with MMFF94 charges, by using a conjugate gradient method, distance-dependent dielectric constant and converging to 0.01 kcal/mol·Å. Protomol, an idealized representation of a ligand that makes every potential interaction with the binding site, was generated on the basis of ligand mode. Compounds intended for docking study including **2q** and paroxetine were constructed in Sybyl; energy was minimized with MMFF94s force field and MMFF94 charged and stored in Sybyl database. The compounds in the Sybyl database were docked into the binding site by Surflex-Dock on the basis of protomol constructed earlier. The extracted paroxetine was considered as a reference molecule. The docking protocol was able to reproduce the position of paroxetine (manually constructed and stored in the Sybyl database) in the binding

site with 0.43 Å root-mean-square deviations (RMSD) of the heavy atoms of the extracted paroxetine.

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Graphical Abstract

Triple reuptake inhibitors: Design, synthesis and structural-activity relationship of benzylpiperidine—tetrazoles

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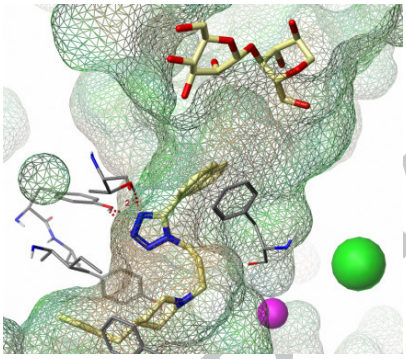

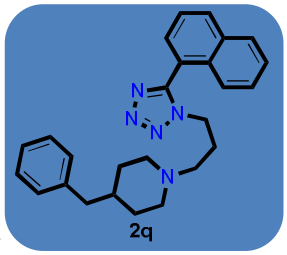

IC_{50} (μM): 0.31 (5-HT)
2.51 (NE)