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Benzothiazoles as probes for the $5HT_{1A}$ receptor and the serotonin transporter (SERT): A search for new dual-acting agents as potential antidepressants

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Abstract

The synthesis and evaluation of several benzothiazole based compounds are described in an attempt to identify novel dual-acting $5HT_{1A}$ receptor and SERT inhibitors as new antidepressants. Binding affinities at the $5HT_{1A}$ receptor and the serotonin transporter do not appear to be congruent and other areas of the binding sites would need to be explored in order to improve binding simultaneously at both sites. Compounds **20** and **23** show moderate binding affinity at the $5HT_{1A}$ receptor and the SERT site and thus, have the potential to be further explored as dual-acting agents. In addition, compound **20** binds with low affinity to the dopamine transporter (DAT), the norepinephrine transporter (NET) and $5HT_{2C}$ receptor, which are desirable properties as selectivity for SERT (and not DAT or NET) is associated with an absence of cardiovascular side-effects.

Keywords

Benzothiazoles; SERT inhibition; $5HT_{1A}$ binding; dual-acting antidepressants; $5HT_{1A}$ agents; potential SERT inhibitors

1. Introduction

According to the National Institute of Mental Health (NIMH), depressive disorders affect approximately 19 million American adults or 9.5% of the U.S. population age 18 and older in a given year. This includes major depressive disorder, dysthymic disorder, and bipolar disorder [1]. The most widespread treatment option for depression is the use of antidepressants. Selective serotonin reuptake inhibitors (SSRIs) such as Prozac (**1**), have changed the landscape of antidepressant therapy for some time now and have several advantages over their predecessors, the tricyclic antidepressants (TCAs). The superior clinical profile of SSRIs is said to be related to their overall selectivity resulting in the absence of cardiovascular disease (<0.0003%) and a high therapeutic index [2]. However,

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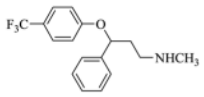
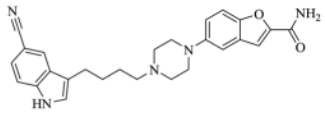
antidepressants in general, including SSRIs suffer from a variety of drawbacks including the fact that up to a third of patients do not respond to treatment. There is also a delay of about 4 – 6 weeks in the onset of action of SSRIs. One hypothesis suggests that the delay in the onset of action is due to a negative feedback control exerted by $5HT_{1A}$ autoreceptors on nerve terminal 5HT release [3]. According to this hypothesis, onset of action is initiated only when this impulse flow is restored following desensitization of $5HT_{1A}$ autoreceptors and coincident increases in postsynaptic 5HT levels are achieved. Clinical proof of this hypothesis has been suggested in studies that found a significant augmentation of the effect of SSRIs when the β-adrenergic/$5HT_{1A}$ receptor antagonist pindolol was co-administered with SSRI treatment [4]. Indeed, the FDA has recently approved the first drug developed on the basis of this hypothesis, vilazodone (Viibryd®), for the treatment of depression [5]. Vilazodone has been demonstrated to act as an inhibitor of SERT and a partial agonist at the $5HT_{1A}$ receptor, binding with very high affinities at these sites [6] (Table 1). Its binding affinities at other receptors such as DAD_2 and $5HT_{2A}$ receptors, DAT and NET are said to be low and this selectivity appears to support the basis for its superior therapeutic profile [7–9].



Prozac, 1



Vilazodone, 2

As part of our on-going drug discovery effort to identify new leads for the treatment of mental illnesses, we evaluated several benzothiazoles at DA and 5HT receptors [10] (Table 1). Further screening at other CNS receptors has led to the identification of compounds **3** and **6** as SERT inhibitors as well as $5HT_{1A}$ receptor ligands (Chart 1). Based on the pharmacological properties of various CNS receptors, we have hypothesized that an agent which antagonizes the $5HT_{1A}$ receptor, inhibits SERT and does not interact avidly with DAT, NET, DA D_2-like subtypes, $5HT_{2C}$ and H_1 receptors will have a potentially superior therapeutic profile as novel antidepressants [11–17]. Thus, the aim of this research was to study the structure-activity relationships of newly designed benzothiazoles in order to understand the contributions of the component parts towards selectivity for the $5HT_{1A}$ receptor and inhibition of SERT.

2. Chemistry

The syntheses of compounds **3 – 6** were previously reported [10]. To obtain key alkylating agents **27, 28, 34** and **35,** the method of Chikashita et al [18] as reported in Peprah, et al [10] was followed, taking advantage of the reactivity of 2-lithiobenzothiazole to various electrophiles. Alkylating agent 2-(3-chloropropyl)benzo[d]thiazole **27** was prepared by reacting 2-aminothiophenol **24** and 4-chlorobutanoyl chloride **25** in toluene, followed by purification on silica gel. Alkylating agent 2-(4-chlorobutyl)benzo[d]thiazole **28** was obtained in a similar manner using 5-chloropentanoyl chloride as described in Scheme 1. Target compounds **7 – 12**, were obtained by coupling each alkylating agent **27** and **28** with different amines in the presence of K_2CO_3 and KI (Scheme 2).

Alkylating agent, 1-(benzo[d]thiazol-2-yl)-4-iodobutan-1-one **34** was prepared by a two-step transformation starting from benzothiazole **29**. Deprotonation of **29** with n-BuLi in THF at −78 °C was followed by treatment with lactone **30** to obtain 1-(benzo[d]thiazol-2-yl)-4-hydroxybutan-1-one **32**. Treatment of alcohol **32** with I_2 in the presence of imidazole and Ph_3P in CH_2Cl_2 afforded 1-(benzo[d]thiazol-2-yl)-4-iodobutan-1-one **34**. Using the same procedure, alkylating agent, 1-(benzo[d]thiazol-2-yl)-5-iodopentan-1-one **35** was synthesized, as described in Scheme 3. Compounds **13–23** were synthesized by reacting

each alkylating agent, **34** and **35** with different amines in the presence of K_2CO_3 and KI in CH_3CN as solvent as shown in Scheme 4.

3. Results and Discussion

During a search for new atypical antipsychotic agents [10], we synthesized and screened several compounds, among which were compounds **3 – 6,** for their binding affinities at dopamine D_2, D_3 and D_4 receptor subtypes as well as serotonin $5HT_{1A}$, $5HT_{2A}$ and $5HT_{2C}$ receptors. Screening of these compounds at additional 5HT receptors and at SERT showed that compounds **3, 4** and **6** have affinity to SERT as well as the $5HT_{1A}$ receptor (Table 1). This observation provided the impetus for the current study to design new agents and conduct a structure-activity relationship study of benzothiazole-based compounds as new potential dual-acting antidepressants.

Compound **3** is a benzothiazole linked by a propyl chain to a 4-chlorophenyl homopiperazine moiety. Compound **4** differs from **3** by a methylene group which extends the propyl to a butyl linkage. This modification has resulted in minimal change in binding at both the $5HT_{1A}$ receptor and SERT. Insertion of a carbonyl group in compound **3** to form **5** or in **4** to form **6**, resulted in loss of binding affinity to the $5HT_{1A}$ receptor. However, at SERT, compound **5** binds with over 6-fold increase compared to **3** and compound **6** binds with the same affinity compared to **4** suggesting that the presence of the carbonyl group has a mixed effect on binding to the $5HT_{1A}$ receptor and the SERT site.

The next design strategy was to replace the 4-chlorophenyl homopiperazine moiety with arylcycloalkyl amine pharmacophores with affinity to CNS receptors including the $5HT_{1A}$ receptor. The results are recorded in Table 2. Compounds **7** and **8** are obtained by replacement of the homopiperazine ring in compounds **3** and **4** respectively with a piperazine ring. Compound **7** binds with less affinity to both the $5HT_{1A}$ receptor and SERT as compared to compound **3**, suggesting that the homopiperazine ring is better tolerated at these receptors when the chain length is three. Compound **8** on the other hand, showed about a 3-fold increase in binding to the $5HT_{1A}$ receptor but a 2.6-fold decrease in binding at the SERT site. Comparing the binding affinities of **7** and **8** suggests that increasing chain length from 3 to 4 with the piperazine ring in place, is better tolerated at both receptors. Interestingly, the carbon chain length in vilazodone is 4 as well. Considering compounds **9 – 11**, the contributions of 4-chlorophenyl piperidinol, 2-(piperazin-1-yl)pyrimidine and tetrahydroisoquinoline moieties respectively, were probed by substituting them in place of the 4-chlorophenyl piperazine moiety in **8**. Evaluation of compound **9**, with the 4-chlorophenyl piperidinol moiety resulted in significant decreases in binding at both the $5HT_{1A}$ receptor and SERT.

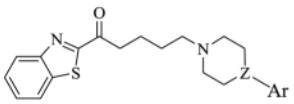
In previous publications, [17, 19] we observed that 2-(piperazin-1-yl)pyrimidine moiety enhanced binding affinity to the $5HT_{1A}$ receptor. Replacing the 4-chlorophenyl moiety in **8** with the pyrimidinyl moiety to form **10** led to an increase of over 13-fold binding affinity over compound **8**. In a similar manner, replacement of the 4-chlorophenyl piperazine with a tetrahydroisoquinoline ring produced compound **11** and about 18-fold increase in the binding affinity to the $5HT_{1A}$ receptor. Unfortunately, both compounds have significantly less binding at the SERT. Compound **12** in which the 4-chlorophenyl moiety is replaced by an isoindole ring, had only moderate binding at both receptors.

Compound **13** was obtained by insertion of a carbonyl group into compound **7** and compound **14** is the unsubstituted analog of **13**. Evaluation of **13** and **14** showed that the presence of the carbonyl group produced a decrease on binding affinity at both the $5HT_{1A}$ receptor and SERT as shown in Table 3. Interestingly, the absence of N-1 from the

piperazine ring in compound **14** to form **15** improved the binding affinity at both $5HT_{1A}$ and SERT. Replacement of the phenyl group in compound **14** with a 2-pyrimidinyl ring to form **16**, also led to an improvement in binding affinity to the $5HT_{1A}$ receptor as expected. However, compound **16** has little or no affinity to SERT.

Replacement of the 2-(piperazin-1-yl)pyrimidine moiety in compound **16** with 5-chloro-1-(piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one to form compound **17** resulted in diminished binding to the $5HT_{1A}$ receptor and only a low binding affinity to SERT. Chain extension by one methylene group and exploration of two arylcycloalkyl amine groups; 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (Compound **18**) and isoindoline (Compound **19**) by replacing the 4-chlorophenyl homopiperazine moiety did not result in significant improvements in binding affinity at $5HT_{1A}$ and SERT.

Compound **20** was obtained by inserting a carbonyl group between the benzothiazole ring and the first methylene group in compound **8.** Evaluation of its binding affinities showed that binding to the $5HT_{1A}$ receptor was enhanced by over 3-fold and to SERT by over 2-fold. In compound **21**, the 4-chlorophenyl ring is replaced by 2,6-pyrimidinyl ring. As expected, the binding to the $5HT_{1A}$ receptor again increased about 8-fold over compound **20** and more than 25-fold over compound **8**. Surprisingly, compound **21** demonstrated little or no binding to SERT. The contribution of the 4-chloro group to binding affinity was investigated by evaluating compound **22**. The presence of the chloro group imparted a 7.9 fold increase in the binding affinity at the $5HT_{1A}$ receptor but binding to the SERT site showed over 3-fold decrease. This observation suggests the possibility that substituents on the phenyl ring may affect binding to these receptors. Finally, when the piperazine ring in compound **22** was replaced by a piperidine ring to form compound **23**, binding affinity decreased by 2-fold at the $5HT_{1A}$ receptor but increased to 64 nM at the SERT site.



20. Z = N; Ar = 4-Chlorophenyl
21. Z = N; Ar = 2,6-Pyrimidinyl
22. Z = N; Ar = Phenyl
23. Z = CH; Ar = Phenyl

In addition to the evaluations at the $5HT_{1A}$ and SERT, it was also of interest to investigate the binding of the compounds at receptors which might influence antipsychotic and antidepressant pharmacology and/or side effects, including $5HT_{2A}$, $5HT_7$, $5HT_{2C}$, D_2 and D_4 receptors, H_1, DAT and NET. Only two compounds, **7** and **23** (*Ki* = 36 and 3.4 nM respectively) bind with moderately high affinity to the $5HT_{2A}$ receptor. Similarly, only compounds **11** and **22** bind with moderately high affinity at the $5HT_7$ receptor (Ki = 35.6 and 62.6 nM respectively). At the $5HT_{2C}$ receptor, none of the compounds has affinity better than 1000 nM which is desirable as high affinity to this receptor may be associated with weight gain [19–21]. We have previously presented a set of criteria for compounds to be considered for further screening as new antipsychotic agents [19]. These include binding to dopamine D_2 receptor within $10 < Ki < 150$ nM range, high affinity for D_4 receptor ($Ki \leq 10$ nM), high affinity for $5HT_{1A}$ and $5HT_{2A}$ receptors and a low affinity for $5HT_{2C}$ and H_1 receptors. Only compounds **10**, **11** and **18** meet the dopamine D_2 binding requirement and will be further screened at relevant receptors. At the D_4 receptor, only compounds **8** and **10 (**Ki = 4.0 and 0.8 nM respectively) have binding affinity better than 10 nM. Interestingly, compound **10** turned out to be the most potent and D_4 selective agent (with selectivity index, $D_2/D_4 = 33.1$) among the compounds evaluated.

4. Conclusion

Overall, the binding affinities at the $5HT_{1A}$ receptor and the SERT site do not appear to be congruent and other areas of the binding sites would need to be explored in order to improve binding simultaneously at both sites. Only compounds **20** and **23** demonstrate simultaneously relatively moderate affinity binding at both $5HT_{1A}$ receptor and the SERT site and thus have the potential to be further explored as dual-acting agents. Compound **20** shows low affinity for DAT, NET and $5HT_{2C}$ receptor, which are desirable properties as selectivity for SERT (and not DAT or NET) is associated with an absence of cardiovascular problems. The low affinity for $5HT_{2C}$ is also desirable because of its association with weight gain and type II diabetes [20]. The moderate affinity for the H_1 receptor is undesirable for the same reasons indicated for the $5HT_{2C}$ receptor [21]. For compound **23**, there is a need to decrease the binding affinity to NET and the H_1 receptor for the same reasons stated. Efforts in this direction are ongoing. Plans are also ongoing to conduct functional assays to determine whether compounds with high affinity to the $5HT_{1A}$ receptor are agonists or antagonists.

5. Experimental

5.1 Reagents and general procedures

Melting points were determined on a Gallenkamp (UK) apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian 300 MHz Mercury Spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, and are within 0.4% of theory unless otherwise noted. Flash chromatography was performed on Combi-Flash (Teledyne Isco) using RediSep columns. N,N Dimethylformamide was distilled from $CaSO_4$ and stored over 4Å molecular sieves. Starting materials were obtained from Sigma-Aldrich and were used without further purification.

5.2. General procedure for synthesis of alkylating agents (27, 28)

To a solution of 2-aminothiophenol (5 g, 39.9 mmol) in toluene (100 mL), 5-chlorobutanoyl chloride (**25**) or 5-chloropentanoyl chloride (**26**) (43.9 mmol) was added drop wise over a 15 min period and during the addition, an off-white precipitate was formed. The reaction mixture was stirred at room temperature (rt) overnight, then water (100 mL) was added, the two layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extract was washed with water (100 mL) and saturated NaCl solution, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified on Combiflash using EtOAc/Hexanes, to afford 2-(3-chloropropyl)benzo-[d]thiazole **27** or 2-(4-chlorobutyl)benzo[d]thiazole **28** as an oily liquid.

5.2.1 2-(3-Chloropropyl)benzo[d]thiazole (27)—Oily liquid (72% yield). ^{1}H NMR (CD_3OD): δ 8.14 (d, 1H, *J* = 4.1 Hz), 8.02 (d, 1H, *J* = 4.1 Hz), 7.72-7.59 (m, 2H), 3.64-3.57 (m, 2H), 3.38-3.28 (m, 2H), 1.95-1.86 (m, 2H).

5.2.2 2-(4-Chlorobutyl)benzo[d]thiazole (28)—Oily liquid (56% yield). ^{1}H NMR ($CDCl_3$) : δ 7.98-7.95 (m, 1H), 7.85-7.82 (m, 1H), 7.48-7.42 (m, 1H), 7.37-7.32 (m, 1H), 3.60 (t, 2H, *J* = 7.5 Hz), 3.15 (t, 2H, *J* = 7.5 Hz), 2.09-1.97 (m, 2H), 1.95-1.90 (m, 2H).

5.3. General procedure for synthesis of alkylating agents (34, 35)

A stirred solution of benzo[d]thiazole **29** (10 g, 74 mmol) in dry THF (37 mL) under N_2 was cooled to −78 °C (dry ice /acetone bath) and 10% excess of *n*-BuLi (37 mL 1M solution in THF) was added in a drop-wise manner. Just before the addition was completed, the solution gave rise to a clear orange colored solution. Thereafter, a solution of lactone, **30** (7.0 g, 81

mmol) or **31** (8.14 g, 81 mmol) in dry THF (37 mL) was added to the reaction mixture at −78 °C, and the mixture was stirred at −78 °C for 1h. After removal of the cold bath, the reaction mixture was continuously stirred for 30 minutes and then quenched with a large excess of 0.1 M HCl (300 mL). The aqueous mixture was extracted with EtOAc (3 × 150 mL) and the combined organic extracts was washed with H_2O (2 × 100 mL) and saturated NaCl (100 mL) and dried over Na_2SO_4. The solution was concentrated *in vacuo,* the crude product was dissolved in EtOAc (50 mL), hexane (200 mL) was added to precipitate an orange solid. The precipitate was filtered, washed with 10% EtOAc/Hexane (200 mL) and dried *in vacuo* to obtain the pure products, 1-(benzo[d]thiazol-2-yl)-4-hydroxybutan-1-one **32** and 1-(benzo[d]thiazol-2-yl)-5-hydroxypentan-1-one **33**, as solids.

5.3.1. 1-(Benzo[d]thiazol-2-yl)-4-hydroxybutan-1-one (32)—Solid (49 % yield), mp: 93–94 °C. ^{1}H NMR ($CDCl_3$) : δ 8.20-8.17 (m, 1H), 8.00-7.97 (m, 1H), 7.61-7.51 (m, 2H), 3.79-3.75 (m, 2H), 3.41 (t, 2H, *J* = 6.9 Hz), 2.14-2.05 (m, 2H).

5.3.2. 1-(Benzo[d]thiazol-2-yl)-5-hydroxypentan-1-one (33)—Solid (37% yield), mp: 81–83 °C; ^{1}H NMR ($CDCl_3$) : δ 8.18 (dd, 1H, *J* = 1.8, 6.9 Hz), 7.97 (dd, 1H, *J* = 1.5, 7.2 Hz), 7.62-7.52 (m, 2H), 3.71 (t, 2H, *J* = 6.3 Hz), 3.40 (t, 2H, *J* = 7.2 Hz), 2.00-1.88 (m, 2H), 1.76-1.67 (m, 2H).

To a solution of TPP (3.12 g, 11.9 mmol), imidazole (810 mg) in CH_2Cl_2 (30 mL) was added iodine (3.02 g, 11.9 mmol) at 0–5 °C. The reaction mixture was stirred at 0–5 °C for 30 minutes and a solution of 1-(benzo[d]thiazol-2-yl)-4-hydroxybutan-1-one (**32**) (1.9 g, 8.6 mmol) or 1-(benzo[d]thiazol-2-yl)-5-hydroxypentan-1-one (**33)** (2.0 g, 8.5 mmol) in CH_2Cl_2 (15 mL) was added drop wise for 5 min. The reaction mixture was stirred at 0–5 °C for another 30 min, and then the ice bath was removed and stirring continued at rt for 12 h. When TLC showed the reaction was complete, the reaction mixture was treated with water (100 mL), the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts was washed with water (2 × 100 mL) and 10% sodium thiosulfate solution (50 mL), water (100 mL) then saturated aqueous NaCl solution (75 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was further purified on Combiflash using EtOAc/Hexane (1 : 9) to obtain the pure product as 1-(benzo[d]thiazol-2-yl)-4-iodobutan-1-one (**34**) or 1-(benzo[d]thiazol-2-yl)-5-iodopentan-1-one (**35**) as a solid.

5.3.3 1-(Benzo[d]thiazol-2-yl)-4-iodobutan-1-one (34)—Solid (43 % yield), mp: 91–92 °C; ^{1}H NMR ($CDCl_3$): δ 8.21-8.18 (m, 1H), 8.00-7.97 (m, 1H), 7.62-7.52 (m, 2H), 3.45 (t, 2H, *J* = 6.9 Hz), 3.34 (t, 2H, *J* = 6.6 Hz), 2.35 (q, 2H, *J* = 6.90 Hz).

5.3.4 1-(Benzo[d]thiazol-2-yl)-5-iodopentan-1-one (35)—Solid (61 % yield), mp: 88–89 °C; ^{1}H NMR ($CDCl_3$) : δ 8.20 (dd, 1H, *J* = 1.5, 7.8 Hz), 8.98 (dd, 1H, *J* = 1.2, 7.8 Hz), 7.61-7.51 (m, 2H), 3.34-3.23 (m, 4H), 2.02-1.90 (m, 4H).

5.4. General alkylation procedure for compounds (7–12)

A mixture of 2-(3-chloropropyl)benzo[d]thiazole (**27**) (1.33 mmol), or 2-(4-chlorobutyl)benzo[d]thiazole **(28)**, the appropriate amine, (1.33 mmol), KI (100 mg), K_2CO_3 (13.3 mmol), and CH_3CN (15 mL) was heated to reflux for 12-24 h. The mixture was cooled to room temperature and then loaded onto a cartridge and purified by flash chromatography using EtOAc and hexane (9:1) to give the desire products.

5.4.1 2-(3-(4-(4-Chlorophenyl)piperazin-1-yl)propyl)benzo[d]thiazole hydrochloride (7)—Yield (32 %), mp: 158–160 °C; ^{1}H NMR (CD_3OD): δ 7.94–8.01 (m,

2H), 7.52–7.57 (m, 1H), 7.43–7.49 (m, 1H), 7.26 (dd, 2H, *J* = 6.6, 2.4 Hz), 7.01 (dd, 2H, *J* = 6.8, 2.4 Hz), 3.62–3.94 (m, 4H), 3.34–3.42 (m, 4H), 3.29–3.32 (m, 4H), 2.39–2.46 (m, 2H). Anal.Calcd for $C_{20}H_{24}Cl_3N_3S.0.6\ H_2O$: C, 52.72; H, 5.31; N, 9.22. Found: C, 52.60; H, 5.57; N, 9.15.

5.4.2. 2-(4-(4-(4-Chlorophenyl)piperazin-1-yl)butyl)benzo[d]thiazole (8)—Yield (20%), mp: 104–106 °C; ^{1}H NMR ($CDCl_3$) : δ 7.98-7.95 (m, 1H), 7.86-7.83 (m, 1H), 7.48-7.43 (m, 1H), 7.38-7.35 (m, 1H), 7.20 (dd, 2H, *J* = 2.4, 9.3 Hz), 6.84 (dd, 2H, *J* = 2.4, 9.0 Hz), 3.19-3.14 (m, 6H), 2.58 (t, 2H, *J* = 5.1 Hz), 2.45 (t, 2H, *J* = 7.5 Hz), 1.97-1.92 (m, 2H), 1.70-1.65 (m, 2H). Anal. Calcd for $C_{21}H_{24}ClN_3S$: C, 65.35; H, 6.27; N, 10.89. Found: C, 65.11; H, 6.05; N, 10.71.

5.4.3. 2-(4-(4-(4-Chlorophenyl)piperazin-1-yl)butyl)benzo[d]thiazole (8)hydrochloride—Yield (48 %), mp: 214–216 °C. ^{1}H NMR (CD_3OD): δ 8.22 (d, 1H, *J* = 8.1 Hz), 8.07 (d, 1H, *J* = 8.1 Hz), 7.79-7.74 (m, 1H), 7.70-7.65 (m, 1H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.02 (d, 2H, *J* = 9 Hz), 3.91-3.63 (m, 4H), 3.52-3.46 (m, 2H), 3.40-3.20 (m, 6H), 2.18-1.98 (m, 4H). Anal. Calcd for $C_{21}H_{26}Cl_3N_3S.H_2O$: C, 51.72; H, 5.37; N, 8.62. Found: C, 51.61; H, 5.68; N, 8.35.

5.4.4. 1-(4-(Benzo[d]thiazol-2-yl)butyl)-4-(4-chlorophenyl)piperidin-4-ol (9)—Yield (18%), mp: 143–145 °C; ^{1}H NMR ($CDCl_3$) : δ 7.97-7.94 (m, 1H), 7.86-7.83 (m, 1H), 7.48-7.42 (m, 3H), 7.37-7.26 (m, 3H), 3.16 (t, 2H, *J* = 7.8 Hz), 2.98-2.88 (m, 2H), 2.60-2.52 (m, 4H), 2.30-2.18 (m, 2H), 1.97-1.90 (m, 2H), 1.80-1.70 (m, 4H). Anal. Calcd for $C_{22}H_{25}ClN_2OS$: C, 65.90; H, 6.28; N, 6.99. Found: C, 65.16; H, 6.17; N, 6.91.

5.4.5 2-[4-(4-Pyrimidin-2-yl-piperazin-1-yl)-butyl]-benzo[d]thiazole hydrochloride (10)—The product was converted into HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (19%), mp: 236–237 °C; ^{1}H NMR (DMSO-*d*6): δ 11.44 (brs, 1H), 8.44 (d, 2H, *J* = 5.1 Hz), 8.04 (d, 1H, *J* = 8.1 Hz), 7.91 (d, 1H, *J* = 8.1 Hz), 7.50-7.44 (m, 1H), 7.41-7.36 (m, 1H), 6.77 (t, 1H, *J* = 5.1 Hz), 4.66 (d, 2H, *J* = 14.4 Hz), 3.53-3.42 (m, 4H), 3.19-3.10 (m, 4H), 3.04-2.97 (2H, m), 1.88-1.82 (m, 4H). Anal. Calcd for $C_{19}H_{24}ClN_5S$: C, 58.52; H, 6.20; N, 17.96. Found: C, 58.40; H, 6.17; N, 17.86.

5.4.6 2-(4-Benzo[d]thiazol-2-yl-butyl)-1,2,3,4-tetrahydro-isoquinoline p-toluenesulfonate (11)—The product was converted into the tosylate salt, followed by crystallization from MeOH-Et_2O to afford the pure compound. Yield (18%), mp: 154–155 °C; ^{1}H NMR (DMSO-*d*6): δ 9.65 (brs, 1H), 8.05 (d, 1H, *J* = 7.8 Hz), 7.92 (d, 1H, *J* = 8.1 Hz), 7.49 (d, 1H, *J* = 7.5 Hz), 7.46-7.42 (m, 4H), 7.38 (d, 1H, *J* = 8.1 Hz), 7.29 - 7.19 (m, 3H), 7.14 (d, 4H, *J* = 7.5 Hz), 7.04-7.01 (m, 1H), 4.54 (d, 2H, *J* = 13.5 Hz), 4.28 (dd, 1H, *J* = 7.8, 15.6 Hz), 3.72-3.69 (m, 1H), 3.34-3.26 (m, 3H), 3.19-3.15 (m, 2H), 3.11-3.03 (m, 2H), 2.26 (s, 3H), 1.89-1.85 (m, 4H). Anal. Calcd for $C_{34}H_{38}N_2O_6S_3$: C,61.24; H, 5.74; N, 4.20. Found: C, 61.23; H, 5.92; N, 4.12.

5.4.7 2-(4-(Isoindolin-2-yl)butyl)benzo[d]thiazole hydrochloride (12)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (7%), mp: 188–190 °C; ^{1}H NMR (DMSO-d_6): δ 11.08 (s, 1H), 8.05 (dd, 1H, *J* = 0.9, 7.2 Hz), 7.91 (dd, 1H, *J* = 0.6, 7.8 Hz), 7.50-7.44 (m, 1H), 7.41-7.32 (m, 4H), 7.22 (s, 1H), 4.75 (dd, 2H, *J* = 5.7, 13.8 Hz), 4.45 (dd, 2H, *J* = 6.9, 13.8 Hz), 3.41 (q, 2H, *J* = 5.7 Hz), 3.17 (t, 2H, *J* = 6.6 Hz), 1.90-1.87 (m, 4H). Anal. Calcd for $C_{21}H_{24}ClN_3S\ 2HCl\ 0.3H_2O$: C, 59.00; H, 5.73; N, 7.24. Found: C, 59.00; H, 5.73; N, 7.24.

5.6 General alkylation procedure for compounds (13–23)

A mixture of 1-(4-chlorophenyl)piperazine (0.65 mmol), 1-(benzo[d]thiazol-2-yl)-5-iodopentan-1-one (**35**) (0.84 mmol), K_2CO_3 (5.18 mmol), and CH_3CN (15 mL) was heated to reflux for 12-24 h. The mixture was cooled to room temperature and then loaded onto a cartridge and purified by flash chromatography using EtOAc and hexane (9.5:0.5) to give the desired products.

5.6.1. 1-(Benzo[d]thiazol-2-yl)-4-(4-(4-chlorophenyl)piperazin-1-yl)butan-1-one hydrochloride (13)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (19%), mp: 251–253 °C; ^{1}H NMR (CD_3OD): δ 8.19-8.16 (m, 1H), 8.13-8.09 (m, 1H), 7.66-7.57 (m, 2H), 7.26 (d, 2H, *J* = 6.6 Hz), 7.03 (d, 2H, *J* = 7.2 Hz), 3.88-3.73 (m, 4H), 3.49 (t, 2H, *J* = 7.2 Hz), 3.39-3.31 (m, 4H), 3.19-3.06 (m, 2H), 2.30-2.25 (m, 2H). Anal. Calcd for $C_{21}H_{23}Cl_2N_3OS$ 0.15MeOH: C, 56.96; H, 5.33; N, 9.42. Found: C, 57.13; H, 5.60; N 9.04.

5.6.2 1-(Benzo[d]thiazol-2-yl)-4-(4-phenyl-piperazin-1-yl)-butan-1-one (14)— Yield (48%), mp: 160–161 °C; ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 1H, *J* = 7.8 Hz), 7.94 (d, 1H, *J* = 8.1 Hz), 7.59-7.54 (m, 1H), 7.53-7.48 (m, 1H), 7.26-7.20 (m, 2H), 6.84 - 6.80 (m, 3H), 3.27 (t, 2H, *J* = 6.6 Hz), 2.97-2.94 (m, 4H), 2.55-2.47 (m, 6H), 2.13-2.08 (m, 2H). Anal.Calcd for $C_{21}H_{23}N_3OS$: C, 69.10; H, 6.34; N, 11.50. Found: C, 68.89; H, 6.31; N, 11.37.

5.6.3. 1-(Benzo[d]thiazol-2-yl)-4-(4-phenyl-piperidin-1-yl)-butan-1-one hydrochloride (15)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to afford the pure compound. Yield (48%), mp: 269–270 °C; ^{1}H NMR (DMSO-d6): δ 10.37 (brs, 1H), 8.27-8.22 (m, 2H), 7.69 -7.67 (m, 2H), 7.34-7.30 (m, 2H), 7.24-7.19 (m, 3H), 3.58 (d, 2H, *J* = 14.7 Hz), 3.44-3.37 (m, 2H), 3.20-3.14 (m, 2H), 3.09-2.99 (m, 2H), 2.86-2.78 (m, 1H), 2.20-2.08 (m, 2H), 2.08-2.04 (m, 2H), 1.98-1.93 (m, 2H). Anal. Calcd for $C_{22}H_{25}ClN_2OS$: C, 65.90; H, 6.28; N, 6.99. Found: C, 65.70; H 6.22; N, 6.86.

5.6.4. 1-(Benzo[d]thiazol-2-yl)-4-(4-pyrimidin-2-yl-piperazin-1-yl)-butan-1-one hydrochloride (16)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to afford the pure HCl salt. Yield (42%), mp: 242–243 °C; ^{1}H NMR (DMSO-*d*6): δ 10.76 (brs, 1H), 8.42 (d, 2H, *J* = 4.8 Hz), 8.26-8.21 (m, 2H), 7.69-7.60 (m, 2H), 6.75 (t, 1H, *J* = 4.8 Hz), 4.68 (d, 2H, *J* = 14.1 Hz), 3.64-3.58 (m, 2H), 3.47-3.34 (m, 4H), 3.24-3.17 (m, 2H), 3.06-3.01 (m, 2H), 2.162.11 (m, 2H). Calcd for $C_{19}H_{23}Cl_2N_5OS$: C 51.82, H 5.26, N 15.90; Found: C 51.86, H 5.35, N 15.77.

5.6.5 1-(1-(5-(Benzo[d]thiazol-2-yl)-5-oxopentyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (17)—Yield (49%), mp: 221–222 °C; ^{1}H NMR (DMSO-*d*6) : δ 10.99 (s, 1H), 8.24-8.21 (m, 2H), 7.64-7.60 (m, 2H), 7.12 (d, 1H, *J* = 8.7 Hz), 6.96-6.90 (m, 2H), 4.04-4.16 (m, 1H), 3.28 (t, 4H, *J* = 8.4 Hz), 3.00-2.97 (m, 2H), 2.44-2.30 (m, 2H), 2.27-2.19 (m, 2H), 2.10-2.00 (m, 2H), 1.76-1.68 (m, 2H), 1.63-1.52 (m, 4H). Anal. Calcd for $C_{24}H_{25}ClN_4O_2S$: C, 61.46; H, 5.37; N, 11.95. Found: C, 61.16; H, 5.45; N, 11.66.

5.6.6. 8-(5-(Benzo[d]thiazol-2-yl)-5-oxopentyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (18)—Yield (60%), mp: 206–207 °C; ^{1}H NMR (DMSO-*d*6) : δ 8.58 (s, 1H), 8.24-8.19 (m, 2H), 7.63-7.60 (m, 2H), 7.17 (t, 2H, *J* = 8.4 Hz), 6.81 (d, 2H, *J* = 7.8 Hz), 6.69 (t, 1H, *J* = 7.2 Hz), 4.54 (s, 2H), 3.29 (t, 4H, *J* = 6.6 Hz), 2.80-2.54 (m, 4H), 2.36 (t, 2H, *J* = 7.2 Hz), 1.80-1.70 (m, 2H), 1.58-1.52 (m, 4H). Anal. Calcd for

$C_{25}H_{28}N_4O_2S$ 0.075 EtOAc: C, 65.97; H, 6.20; N, 12.31. Found: C, 65.99; H, 6.37; N, 12.03

5.6.7. 1-(Benzo[d]thiazol-2-yl)-5-(isoindolin-2-yl)pentan-1-one hydrochloride (19)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (29%), mp: 248–250 °C; ^{1}H NMR (DMSO-*d*6): δ 11.36 (s, 1H), 8.22-8.19 (m, 2H), 7.64-7.60 (m, 2H), 7.32-7.24 (m, 4H), 4.37 (s, 4H), 3.33 (t, 2H, *J* = 6.6 Hz), 3.20 (brs, 2H), 1.75 (t, 4H, *J* = 2.7 Hz). Calculated for $C_{20}H_{21}ClN_2OS$: C, 64.42; H, 5.68; N, 7.51; Found: C, 64.51; H, 5.92; N, 7.31.

5.6.8. 1-(Benzo[d]thiazol-2-yl)-5-(4-(4-chlorophenyl)piperazin-1-yl)pentan-1-one hydrochloride (20)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (58%), mp; 227–229 °C; ^{1}H NMR (CD_3OD) : δ 8.18-8.15 (m, 1H), 8.12-8.09 (m, 1H), 7.65-7.56 (m, 2H), 7.26 (d, 2H, *J* = 6.6 Hz), 7.00 (d, 2H, *J* = 6.6 Hz), 3.85 (d, 2H, *J* = 14.1 Hz), 3.70 (d, 2H, *J* = 12.6 Hz), 3.39 (t, 2H, *J* = 6.9 Hz), 3.32-3.22 (m, 6H), 3.19-3.04 (m, 2H), 1.93-1.90 (m, 4H). Anal. Calcd for $C_{22}H_{26}Cl_3N_3OS$: C, 54.27; H, 5.38; N 8.63. Found: C, 54.35; H, 5.12; N 8.90.

5.6.9 1-(Benzo[d]thiazol-2-yl)-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pentan-1-one hydrochloride (21)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (35%), mp: 202–203 °C; ^{1}H NMR (DMSO-*d*6): δ 11.06 (brs, 1H), 8.41 (d, 2H, *J* = 4.8 Hz), 8.25-8.21 (m, 2H), 7.68-7.61 (m, 2H), 6.74 (t, 1H, *J* = 4.8 Hz), 4.65 (d, 2H, *J* = 7.8 Hz), 3.54-3.50 (m, 2H), 3.47-3.38 (m, 2H), 3.34-3.30 (m, 2H), 3.17-3.11 (m, 2H), 3.05-2.94 (m, 2H), 1.87-1.82 (m, 2H), 1.79-1.71 (m, 2H). Anal. $C_{20}H_{25}Cl_2N_5OS$: C, 52.86; H, 5.55; N, 15.41. Found: C, 52.66; H, 5.66; N, 15.36.

5.6.10. 1-(Benzo[d]thiazol-2-yl)-5-(4-phenyl-piperazin-1-yl)-pentan-1-one hydrochloride (22)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (37%). mp: 216–217 °C; ^{1}H NMR (DMSO-*d*6): δ 10.85 (brs, 1H), 8.26-8.22 (m, 2H), 7.68-7.59 (m, 2H), 7.24 (dd, 2H, *J* = 7.2, 8.7 Hz), 6.97 (d, 2H, *J* = 7.8 Hz), 6.84 (t, 1H, *J* = 7.2 Hz), 3.80-3.77 (m, 2H), 3.55-3.52 (m, 2H), 3.35-3.31 (t, 2H, *J* = 6.6 Hz), 3.17-3.07 (m, 6H), 1.85-1.81 (m, 2H), 1.78-1.71 (m, 2H). Anal. Calcd for $C_{22}H_{26}ClN_3OS$ 0.7H_2O: C, 61.65; H, 6.11; N, 9.80. Found: C, 61.82; H, 6.45; N 9.62.

5.6.11. 1-(Benzo[d]thiazol-2-yl)-5-(4-phenyl-piperidin-1-yl)-pentan-1-one hydrochloride (23)—The product was converted into the HCl salt, followed by crystallization from MeOH-Et_2O to give the pure compound. Yield (39%), mp: 204–205 °C; ^{1}H NMR (DMSO-*d*6): δ 10.71 (brs, 1H), 8.26-8.22 (m, 2H), 7.68-7.59 (m, 2H), 7.34-7.29 (m, 2H), 7.23-7.18 (m, 3H), 3.54-3.51 (m, 2H), 3.30-3.24 (m, 2H), 3.12-3.05 (m, 2H), 2.93-3.01 (m, 2H), 2.83-2.75 (m, 1H), 2.02 – 2.15 (m, 2H), 1.90-1.94 (m, 2H), 1.88-1.82 (m, 2H), 1.77-1.70 (m, 2H). Anal. Calcd for $C_{23}H_{28}Cl_2N_2OS$: C, 66.57; H, 6.56; N, 6.75. Found: C, 66.37; H, 6.56; N, 6.77.

5.7. Receptor binding studies

Binding affinities reported in Tables 1–4 were conducted by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP). Details of the methods and radioligands used for the binding assays were previously reported [22].

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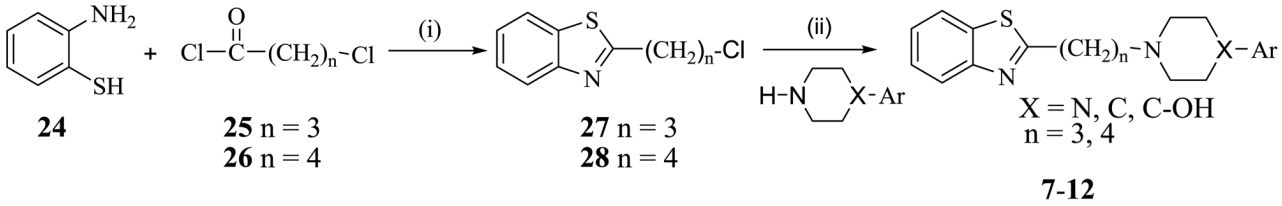
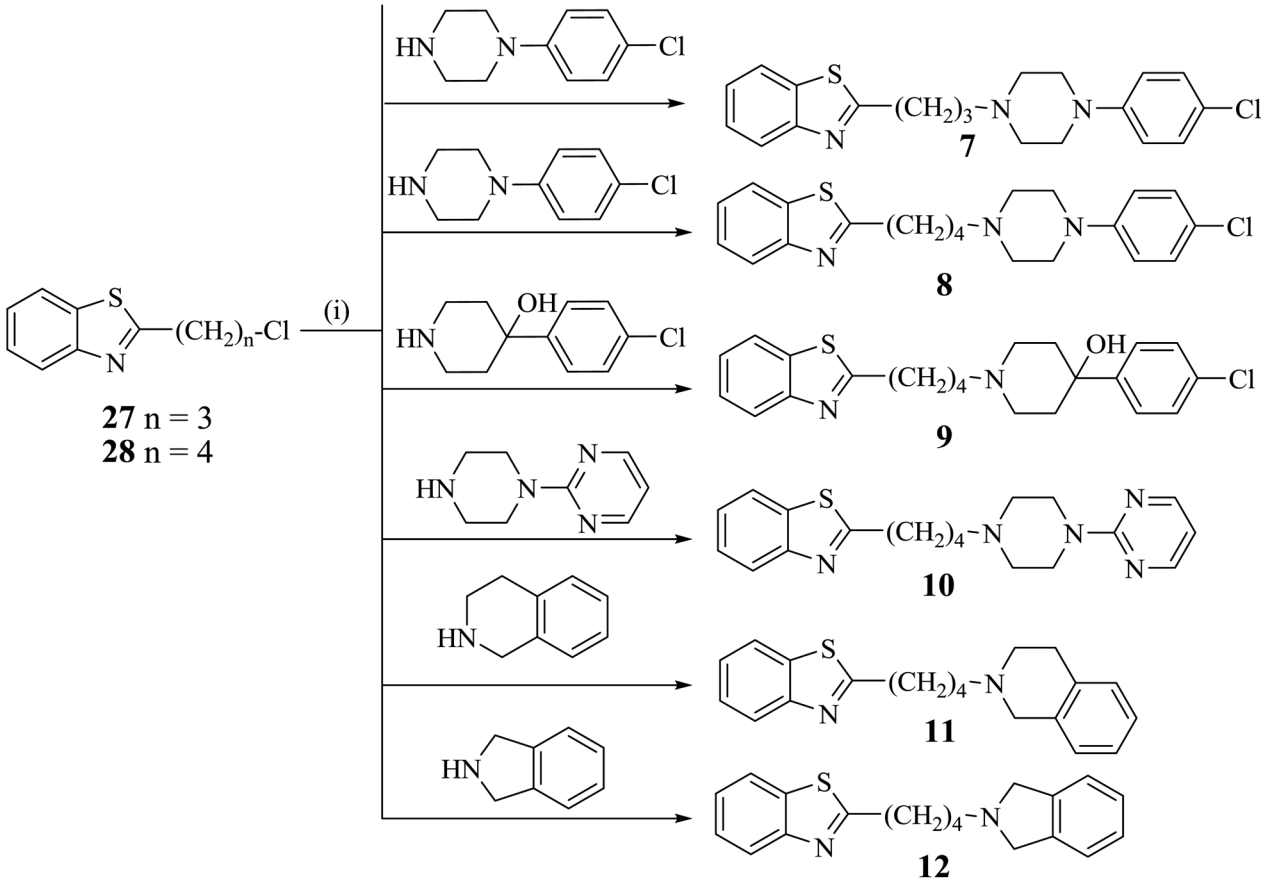
Research Highlights

- Four old and 17 new benzothiazoles have been synthesized and screened for binding to CNS receptors related to neuropsychiatric illnesses.
- Several benzothiazoles have been identified as potential leads in the development of dual-acting agents at $5HT_{1A}$ and SERT sites.
- One of the identified agents has little or no binding to receptors implicated in the off-target pharmacology of known SSRIs and thus will undergo an elaborate SAR studies.

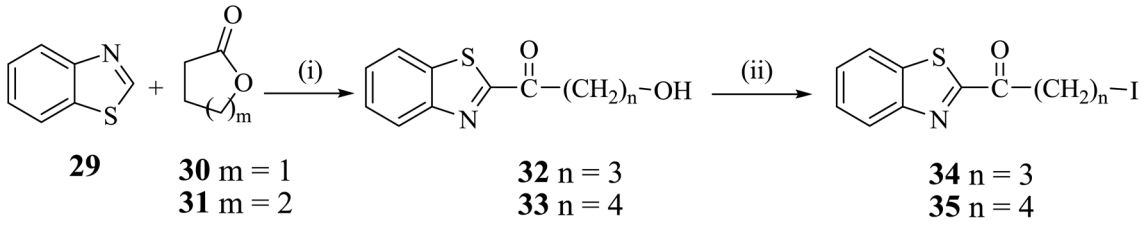


Scheme 1.

Synthesis of Target Compounds **7–12**. Reagents and conditions: (i) Toluene, rt; (ii) KI, K_2CO_3, CH_3CN, reflux.

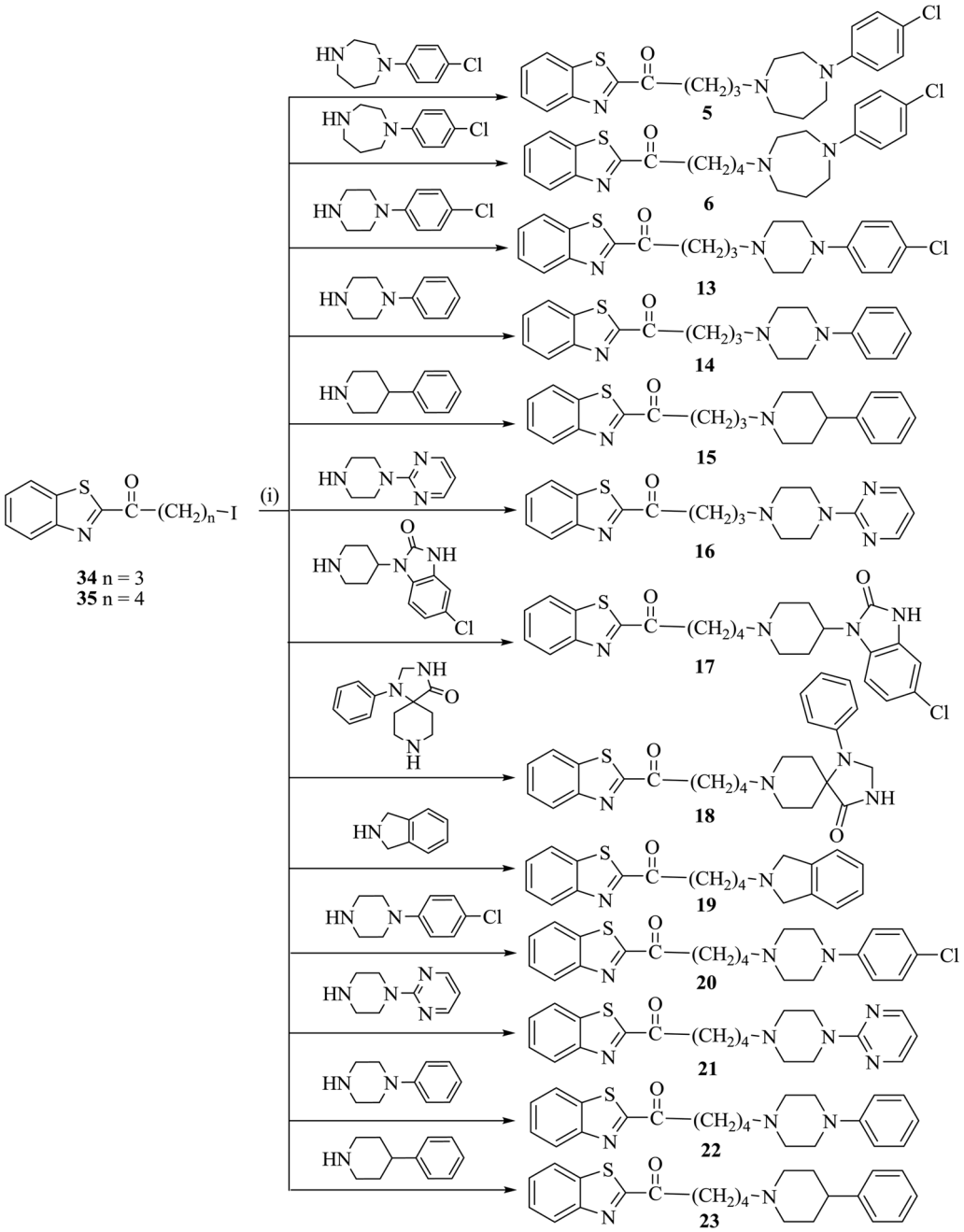


Scheme 2.
Synthesis of Target Compounds. Reagents and conditions: (i) KI, K_2CO_3, CH_3CN, reflux.



Scheme 3.

Synthesis of alkylating agents, **34** and **35**. Reagents and conditions: (i) n-BuLi, −78 °C, THF; (ii) TPP, imidazole, I_2, DCM, 0 °C - rt.



Scheme 4.
Synthesis of Target Compounds. Reagents and conditions: (i) KI, K_2CO_3, CH_3CN, reflux.

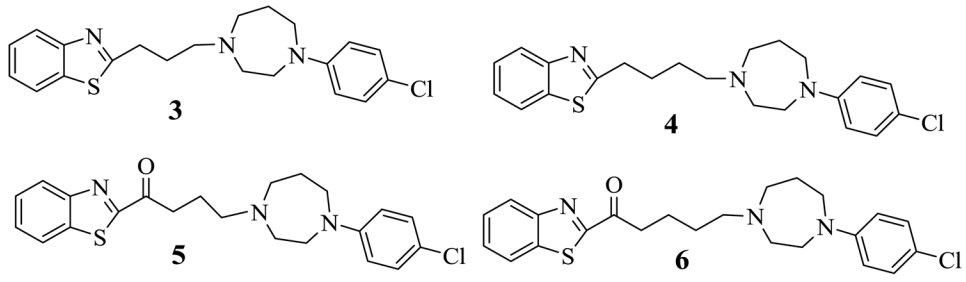


Chart 1.

Table 1

Binding affinity constants of benzothiazoles at selected CNS receptors.

Compd #	Binding data; *Ki* ± SEM (nM)[c]						
	$5HT_{1A}$	**SERT**	**$5HT_{2A}$**	**$5HT_{2C}$**	**$5HT_7$**	**DAD_2**	**DAD_4**
Prozac, 1[a]	ND	1.1 ± 0.01	ND	72 ± 1	ND	ND	ND
Vilazodone, 2[b]	0.3±0.06	0.5±0.4	ND	ND	ND	666±75	ND
3	216±30	34.0±3.9	696±51	MP	2060±353	MP	431±41
4	263	65.0	159	1420	413±61	259±48	28.6±3.4
5	MP	5.3	1038	MP	356	MP	126
6	495±91	65.0±6.0	1003±96	5920±769	2810±658	1983±163	1215±67

[a] Binding data (IC_{50}) from reference 11 :

[b] Binding data (IC_{50}) from reference 12 ;

[c] Where no SEM is given, SEM is within 20% of the mean value.

MP = Missed primary assay threshold of 50% inhibition. ND = Not determined.

Table 2

Binding Affinity constants of benzothiazoles at selected CNS receptors

	Binding data; *Ki* ± SEM (nM)[a]						
Compd #	**$5HT_{1A}$**	**SERT**	**$5HT_{2A}$**	**$5HT_{2C}$**	**$5HT_7$**	**DAD_2**	**DAD_4**
7	312±31	1184±244	36.0±4.0	4647±632	790±120	2321±314	31.0±4.0
8	90.5±31.0	166±16	132±11	6210±1452	329±52	219±12	4.0±0.0
9	771	922	4255	MP	983	201	140
10	6.6	MP	224	>10000	228.9±33.7	26.5±4.5	0.8±0.09
11	5.1	1325	3812	6265±1397	35.6±5.9	30.8±4.2	65.5±9.7
12	111.0	186.0	>10000	MP	211.0	990.0	141.0

[a]Where no SEM is given, SEM is within 20% of the mean value.

MP = Missed primary assay threshold of 50% inhibition.

Table 3

Binding Affinity constants of benzothiazoles at selected CNS receptors

	Binding data; *Ki* ± SEM (nM)[a]						
Compd #	**$5HT_{1A}$**	**SERT**	**$5HT_{2A}$**	**$5HT_{2C}$**	**$5HT_7$**	**DAD_2**	**DAD_4**
13	>10000	491±65	1996±263	MP	MP	8355	342±34
14	350	>10000	>10000	MP	MP	>10000	MP
15	85.0	706	287	MP	425.8±66.8	530±146	44.4±5.0
16	63.0	MP	2206	MP	2467± 400	1522±489	51.5±5.8
17	252	565	1564	MP	127.0	217	1710
18	103	284	3720	MP	518	25.0	162
19	214.0	237	>10000	MP	242	2931	512

[a] Where no SEM is given, SEM is within 20% of the mean value.

MP = Missed primary assay threshold of 50% inhibition.

Table 4

Binding affinity constants of benzothiazoles at selected CNS receptors

Binding data; *Ki* ± SEM (nM)[a]							
Compd #	**$5HT_{1A}$**	**SERT**	**$5HT_{2A}$**	**$5HT_{2C}$**	**$5HT_7$**	**DAD_2**	**DAD_4**
20	28.3±9.2	81.0±7.0	523±68	MP	2917±464	4793±356	100±10
21	3.6	MP	6982	MP	337±35	505±77	346±35
22	3.6	298	204.0	2140±464	62.6±6.8	198±27	105±10
23	7.3	64.0	3.4	3738±807	107±12	642±153	180±17

[a]Where no SEM is given, SEM is within 20% of the mean value.

MP = Missed primary assay threshold of 50% inhibition.

Table 5

Binding affinity constants of compounds **20** and **23** at selected CNS receptors

Compd #	Binding data; Ki ± SEM (nM)[a]					
	$5HT_{1A}$	**SERT**	**DAT**	**NET**	**H_1**	**$5HT_{2C}$**
20	28.3±9.2	81.0±7.0	4742±938.01	>10,000	46.0±5.0	MP
23	7.3	64.0	ND	49.0	52.0	3738±808

[a]Where no SEM is given, SEM is within 20% of the mean value.

MP = Missed primary assay threshold of 50% inhibition. ND = Not determined.