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Original article

6-Sulfonylbenzothiazolones as potential scaffolds for the design of 5-HT_6 ligands

Paul-Emmanuel Larchanche [a, b, c], Vincent Ultré [a, d], Delphine Le Broc [a, e], Céline Ballandone [f], Christophe Furman [a, e], Patrick Dallemagne [f], Patricia Melnyk [a, b, c, *], Pascal Carato [a, b, *]

[a] Université de Lille, F-59000 Lille, France
[b] UDSL, EA 4481, UFR Pharmacie, F-59000 Lille, France
[c] Inserm UMR-S1172, Jean-Pierre Aubert Research Center, F-59000 Lille, France
[d] UDSL, Laboratoire de RMN, UFR Pharmacie, F-59000 Lille, France
[e] UDSL, EA 4483, UFR Pharmacie, F-59000 Lille, France
[f] CERMN, EA 4258, UFR des Sciences Pharmaceutiques, UNICAEN, F-14032 Caen, France

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ABSTRACT

5-HT_6 Receptors are relatively recently discovered receptors that interact with cholinergic, glutamatergic, GABAergic and dopaminergic transmission systems. These receptors have been implicated in the CNS system as therapeutic targets in applications such as psychosis, reduction of body weight or Alzheimer's disease. As part of our efforts to develop 5-HT_6 antagonists, we explored the benzothiazolone scaffold substituted in position 3 or 6 respectively with ethylamino chains and an aromatic ring connected through a sulfonyl linker. Final compounds were evaluated in radioligand binding assays for their ability to interact with 5-HT_6 receptors. Their potential cytotoxic effects were determined on the human neuroblastoma cell line SY5Y. They showed very low cytotoxicity, and one of them has submicromolar affinity for 5-HT_6 receptors.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) mediates a wide range of physiological functions. This neurotransmitter interacts with seven serotoninergic receptor families (5-HT_1 to 5-HT_7) subdivided into 14 subpopulations [1–5]. One of them, the 5-HT_6 receptor (5-HT_6R), was most recently identified by molecular biology in the early 1990s [6–8]. The 5-HT_6R belongs to G-protein coupled receptors, and is positively linked to adenylyl cyclase via Gs-protein [9,10]. Extensive investigation has shown that 5-HT_6R is almost exclusively localised in the central nervous system (CNS), and is associated with psychosis [11], convulsive disorders, appetite control [12,13], learning, memory impairment [14], and related CNS diseases such as Alzheimer's disease [15,16]. Numerous studies have shown that 5-HT_6Rs regulate several neurotransmitter pathways including cholinergic, noradrenergic, glutamatergic and dopaminergic systems. Blockade of 5-HT_6R function specifically increases cholinergic and glutamatergic neurotransmission [17,18], and improves cognition in rodent behavioural models [19].

Crystallographic data are presently unavailable, and the structural requirements of 5-HT_6R are unknown, but a three-dimensional pharmacophore model has been reported for 5-HT_6 antagonists [20–22]. The structural features hypothesis, for high potency of 5-HT_6 ligands, entails the following three key elements on an aromatic hydrophobic site (AR): a positive ionisable atom (PI, usually secondary or tertiary amino group), a hydrogen bond acceptor group (HBA, usually a sulfone or sulfonamide group) connected to a hydrophobic site (HYD) (aromatic or heteroaromatic ring). The amino group could interact with the sulfonyl group by an intramolecular hydrogen bond to stabilise and afford an advantageous binding conformation [23]. However, no publications

* Corresponding authors. UFR Pharmacie, 3 rue du Pr Laguesse, BP83, 59006 Lille, France.
E-mail addresses: paul-emmanuel.larchanche@univ-lille2.fr (P.-E. Larchanche), vincent.ultre@univ-lille2.fr (V. Ultré), delphine.lebroc@univ-lille2.fr (D. Le Broc), celine.ballandone@unicaen.fr (C. Ballandone), christophe.furman@univ-lille2.fr (C. Furman), patrick.dallemagne@unicaen.fr (P. Dallemagne), patricia.melnyk@univ-lille2.fr (P. Melnyk), pascal.carato@univ-poitiers.fr (P. Carato).

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convincingly demonstrate the need for a basic side chain for effective interaction with 5-HT_6R. In recent work, the replacement of the N-methylamino group by a methylthio or a methyl group established that the basic side chain is not essential for the high affinity binding of ligands to 5-HT_6Rs [24,25].

In our laboratory, we previously explored imidazopyridine as the aromatic hydrophobic site (AR) of the 5-HT_6R pharmacophore [26], and introduced various ethylamino chains at position 3, and sulfonyl or sulfamide aromatic rings at position 6 of the heterocycle. Given the low affinity of these compounds, we turned our attention to the benzothiazolone heterocycle as a potential scaffold.

In the present study, three series were successively studied with sulfonyl, sulfamide and retrosulfonylamide groups as the linker between the heterocycle core and the aryl ring. A few variations were envisaged with dimethylamino, pyrrolidino and piperidino ethyl chains as the R_1 group. Phenyl and naphthyl were introduced as R_2 groups. These two aryl rings have already been successfully introduced into 5-HT_6R antagonists [20]. In Fig. 1, the key elements (HYD, HBA and PI) and the benzothiazolone as aromatic site (AR) are represented with an example of a synthesised compound. Three different schemes were developed to synthesise these three series of compounds.

2. Chemistry

Sulfone series could be synthesised according to two different synthetic pathways (Scheme 1). In the first method, benzothiazolone **1** was brominated in $CHCl_3$ with Br_2 to afford the corresponding 6-bromobenzothiazolone **2** [27], with good yield (85%), which was allowed to react in DMF with potassium carbonate [28] and the corresponding 2-chloroethylalkylamine derivatives to yield the *N*-substituted compounds **3**–**4**. The Stille reaction [29,30] was then performed in two steps to furnish final compounds. Reaction in dry toluene under inert atmosphere with tetrakis(triphenylphosphine) palladium and hexabutylditin provided the expected tributyltin intermediates. The subsequent coupling reaction with 5-tri-n-butyltin derivatives in dry toluene under inert atmosphere with dichloro(diphenylphosphine) palladium and the desired chlorosulfonyl reagent never afforded the expected compounds, but only the *N*-substituted benzothiazolones corresponding to destannylated compounds. Modification of the experimental conditions never allowed us to obtain sulfonylbenzothiazolones **6** and **7**.

The second pathway was based on Friedel–Crafts reaction followed by alkylation of the thiocarbamate function. Using a mixture of $AlCl_3$-DMF [28], the Friedel–Crafts acid-catalysed acylation of benzothiazol-2-one **1** with the corresponding phenylsulfonyl chloride afforded 6-phenylsulfonylbenzothiazol-2-one **5** in low yield (15%), with a reaction time of 2 h. The conversion was not complete, and continuation of the reaction led to the degradation of the reaction medium. In the presence of Eaton's reagent (P_2O_5/CH_3SO_3H), expected compound **5** was obtained with higher yield (57%), together with minor degradation products. The synthesis of the naphthyl derivative was attempted without success. Friedel–Crafts reaction with a mixture of $AlCl_3$-DMF led to the complete degradation of the reaction medium, whereas no reaction occurred between starting benzothiazolone **1**, naphthylsulfonyl chloride and Eaton's reagent. For the second step, substitution of chloroalkyl- or cycloalkylamine with potassium carbonate in DMF with derivative **5** afforded final products **6**–**7** (Yield: 17–36%).

For the synthesis of retrosulfonylamide derivatives **16**–**21** (Scheme 2), we again took advantage of the reactivity of this heterocycle and the possibility of easily performing a selective electrophilic aromatic substitution in position 6. Benzothiazolone **1** reacted in 70% nitric acid to give 6-nitro benzothiazolone **8** [27,31], which was allowed to react in DMF with potassium carbonate and the corresponding 2-chloroethylalkylamine derivatives to yield compounds **9**–**11** with moderate yields (35–42%). Reduction of the nitro group of derivatives **9**–**11** in methanol with Pd/C under hydrogen atmosphere gave compounds **12**–**14** in good yields (73–82%). A first attempt at nucleophilic reaction of the amino derivatives (1 eq) with phenyl sulfonylchloride (1.5 eq) in ethyl acetate with triethylamine or a solution of potassium carbonate in ethyl acetate/water gave a mixture of mono- and disubstituted sulfonyl compounds **15**, **17**. Indeed, the presence of a base, such as triethylamine or potassium carbonate, generated a second reaction of the *in situ* formed sulfonamide derivatives with phenyl sulfonylchloride to afford disubstituted sulfonyl compound **15**. In a second attempt, the reaction was performed in pyridine with amino derivatives and the desired chlorosulfonyl products, to afford only monosubstituted compounds **16**–**21** with reasonable yields (53–78%).

For the synthesis of sulfonylamide derivatives **28**–**33** (Scheme 3), again an electrophilic substitution of benzothiazolone **1** was used as the first step. Using chlorosulfonic acid, 6-chlorosulfonic benzothiazol-2-one **22** was obtained with 82% yield. Starting from compound **22**, two routes were envisaged. A first route (route A) was attempted by introducing 1-amino naphthalene in pyridine to afford derivative **23** with 59% yield, which was placed in dry THF with methyl iodide to afford only the *N*-methyl benzothiazol-2-one derivative **24**, and not the expected *N*-methylsulfonamide derivative. In the literature, substitution reaction of halogenoalkyl benzothiazolone derivatives with amino reagent was performed in acetone or acetonitrile in the presence of triethylamine [32]. In these conditions no substitution reaction was observed at the free NH benzothiazolone compound. Substitution reaction at this 3 position could be performed in DMF with potassium carbonate [28].

By the second route B, *N*-methylsulfonamide compounds **28**–**33** were prepared in two steps starting from commercially available *N*-methylaniline and synthesised *N*-methyl-1-amino naphthalene. In a first step, N-methyl-1-amino naphthalene was synthesised in two steps [33]. A reaction in absolute ethanol with 1-amino naphthalene and benzotriazole, followed by a reduction in dry THF with sodium borohydride, gave the *N*-methyl-1-amino naphthalene. Reaction of the 6-chlorosulfonic benzothiazol-2-one **22** with *N*-methylaniline or *N*-methyl-1-amino naphthalene in pyridine gave the *N*-methylsulfonamide derivatives **25**–**26** with 65–70% yields. It was observed that compound **22** also reacted with pyridine, used as solvent and base, to give the pyridinium derivative **27**, as a secondary product with a 16% yield. Final compounds **28**–**33** were obtained in DMF with potassium carbonate and the corresponding 2-chloroethylalkylamine reagents with satisfactory yields

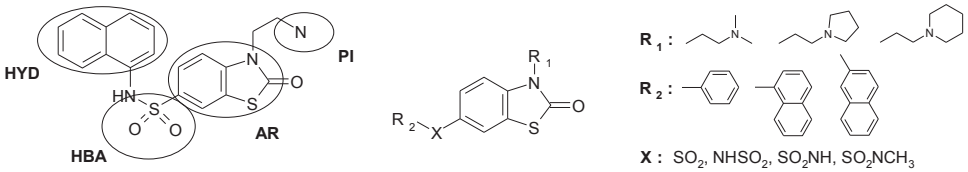
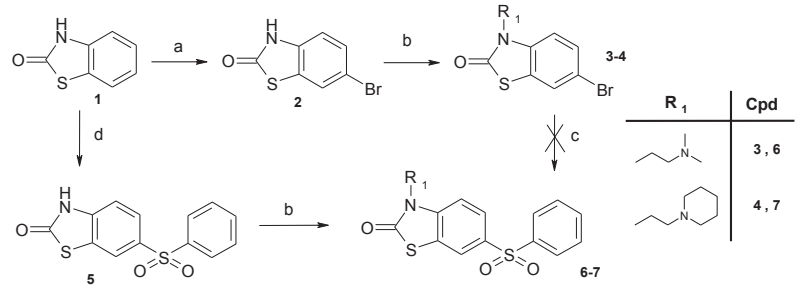
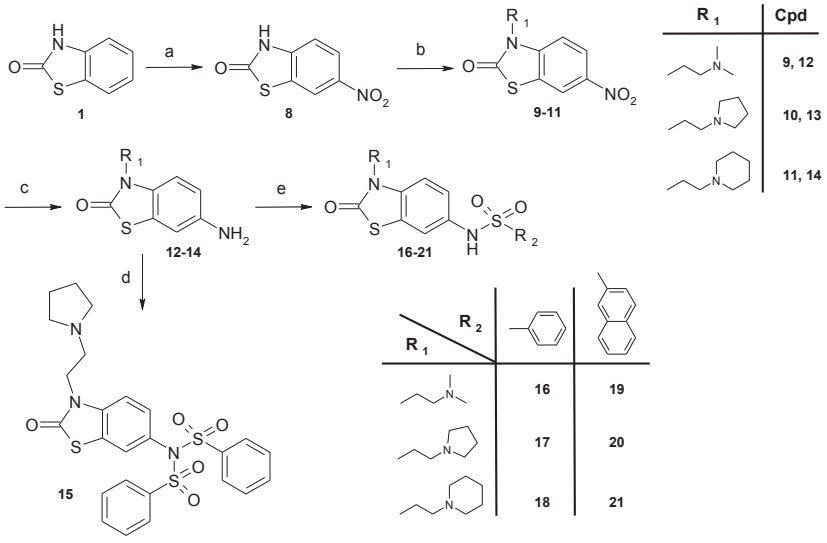


Fig. 1. Design of benzothiazolone derivatives.



Scheme 1. Synthesis of the 6-phenylsulfonyl compounds (**6**–**7**). **Reagents and conditions**: (a) Br_2, $CHCl_3$, rt, 3 h, 85%, (b) 2-chloroethylamine derivatives, K_2CO_3, DMF, 80 °C, 18 h, 17–61%, (c) i: $Sn(Bu_3)_2$, $Pd(PPh_3)_4$, toluene, ii: phenylsulfonyl chloride, $PdCl_2(PPh_3)_2$, toluene, (d) phenylsulfonyl chloride, $AlCl_3$, DMF, 80 °C, 2 h, 15% or P_2O_5/CH_3SO_3H (1/10), 110 °C, 24 h, 57%.



Scheme 2. Synthesis of the 6-retrosulfonylamide compounds (**16**–**21**). **Reagents and conditions**: (a) HNO_3 70%, rt, 3 h, 90%, (b) 2-chloroethylamine derivatives, K_2CO_3, DMF, 80 °C, 18 h, 35–42%, (c) H_2, Pd/C, MeOH, rt, 4 h, 73–82%, (d) arylsulfonyl chloride, Et_3N, AcOEt or arylsulfonyl chloride, K_2CO_3, H_2O, AcOEt, rt, 24 h, 68%, (e) arylsulfonyl chloride, pyridine, rt, 24 h, 53–78%.

(42–63%).

The NH analogue derivatives **37**–**42** (Scheme 3) could not be obtained by route A. Indeed, after chlorosulfonyl reaction to afford compound **23**, reaction in DMF, with chloroethylamine and potassium carbonate, furnished the corresponding *N*,*N*-disubstituted compound at the *N*-3 and *N*-sulfonamide positions. These final compounds **37**–**42** were prepared in two steps. A reaction in DMF with potassium carbonate with benzothiazolone **1** and the desired chloroethylamine reagents furnished the corresponding compounds **34**–**36**. A chlorosulfonyl reaction of compounds **34**–**36** in $CHCl_3$ with chlorosulfonic acid gave chlorosulfonyl intermediates which were reacted *in situ* with triethylamine, and addition of the corresponding arylamine derivatives afforded final compounds **37**–**42**, with low yield for the two steps (6–26%). It could be noticed that attempts were made to isolate the chlorosulfonyl derivatives, but the intermediates could not be extracted or isolated in acid medium, and sulfonyl acid derivatives were obtained in basic medium.

3. Results and discussion

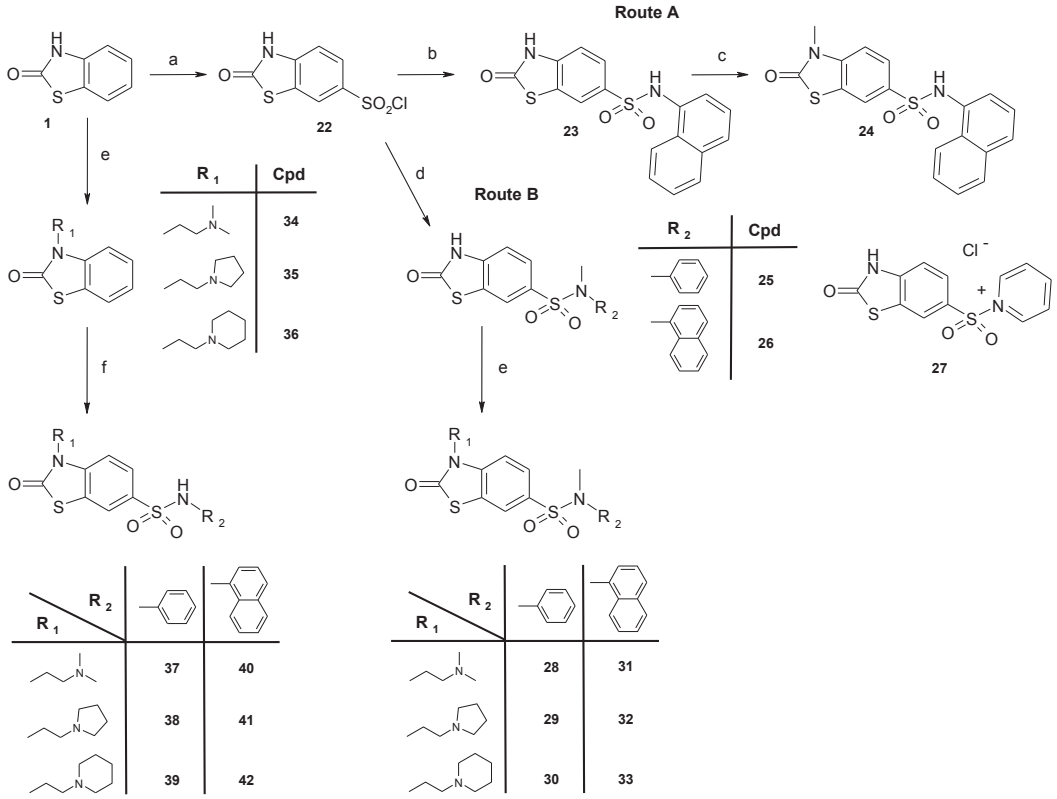
3.1. Biological evaluations and SAR

Receptor affinities were investigated in competition experiments with [^{3}H]-LSD, according to the methods of Monsma et al. [34], on membranes of HEK-293 cells transiently expressing the human 5-HT_6 receptors.

Starting from benzothiazolone as a scaffold for the aromatic hydrophobic site, we introduced into position 3, dimethylamino, pyrrolidino and piperidino ethyl chains (R_1) and into position 6, sulfonyl (**6**–**7**), sulfamide (**28**–**33**, **37**–**42**) and retrosulfonylamide (**16**–**21**) functions substituted by phenyl and naphthyl as the aromatic ring (R_2). Derivative **15**, with an ethylpyrrolidino chain and disubstituted with a phenylsulfonyl group, was also evaluated. The percentage inhibition of specific control binding was determined at a concentration of 100 nM and the inhibition constant Ki was then calculated (Table 1).

The evaluated derivatives showed disappointing results with respect to affinity for 5-HT_6 receptors. Only one derivative (**40**) showed a K_i value of 100 nM. For the other compounds, with inhibition of less than 50% at 100 nM of the evaluated compound, the affinity for 5-HT_6 receptors was not determined.

The disubstituted compound **15** also showed low inhibition (20%) for 5-HT_6 receptors. For the two series of sulfonyl and retrosulfonylamide compounds, respectively **6**–**7** and **16**–**21**, the inhibition was less than 22%. In the sulfonylamide series, derivatives **28**–**31**, **33**, **37**, **39**, **41**–**42** provided low inhibition (0–21%) and moderate inhibition for compounds **32**, **38** (respectively 40 and 37%). The sulfonylamide compound **40**, with dimethylamino chain as R_1 and a naphthyl ring as R_2, showed a moderate K_i of 100 nM.



Scheme 3. Synthesis of the 6-sulfonylamide compounds (**28**–**33**, **37**–**42**). **Reagents and conditions**: (a): chlorosulfonic acid, reflux, 2 h, 82% (b): aniline, pyridine, rt, 24 h, 59% (c): CH_3I, Et_3N, CH_3CN, rt, 30 min, 18% (d): N-methylarylamine derivatives, pyridine, rt, 24 h, 65–70% (e): chloroethylamine derivatives, K_2CO_3, DMF, 80 °C, 18 h, 42–68% (f): i: chlorosulfonic acid, $CHCl_3$, reflux, 1 h ii: arylamine derivatives, Et_3N, rt, 1 h, 6–26%.

3.2. Evaluation of cytotoxic effects

To determine the potential cytotoxic effects of our synthetic derivatives, the human neuroblastoma cell line SY5Y was treated with all the compounds at different concentrations up to 100 μM. Cell viability was calculated using a colorimetric MTT assay.

All compounds exhibited moderate to low cytotoxicity (Table 1). In particular, the retrosulfonylamide series, with derivatives **15**–**21**, showed very low cytotoxicity (6–39% at 100 μM). The sulfonyl and sulfonylamide series, with compounds **6**–**7**, **28**–**33**, **38**–**42**, showed moderate cytotoxicity, with IC_{50} in the 10–102 μM range. In the sulfonylamide series, compound **37** exhibited no cytotoxicity on the human neuroblastoma cell line SY5Y.

4. Conclusion

The 5-HT_6 receptors have been implicated in several therapeutic targets with agonist and antagonist ligands, as potential antidepressant, cognitive effects, decrease of body weight and food intake. We synthesised compounds with a benzothiazolone scaffold, and introduced an alkylamino chain and an aromatic ring respectively at positions 3 and 6 of this heterocycle according to the previously published pharmacophore. These compounds were evaluated for their affinity for 5-HT_6 receptors and their cytotoxic effect on neuronal cells. Unfortunately, most of them showed an inhibition inferior to 50% at 100 nM, compared to derivative SB 271046, which has an excellent K_i of 1.7 nM. Compound **40**, with a dimethylamino chain in position 3 and naphthylsulfonylamide in position 6, exhibited the best affinity of the sulfonylamide series (K_i = 100 nM). The 3D pharmacophore model described in the literature, and molecular modelling techniques will make it possible to understand the relation-structure-affinity for these compounds in the three series. Furthermore, these studies will allow us to optimise and generate new series of 5-HT_6 ligands.

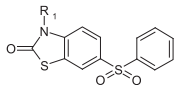
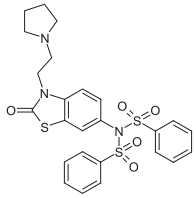
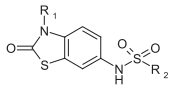
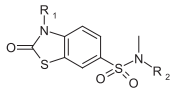
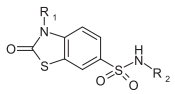
5. Experimental section

5.1. Chemistry

5.1.1. General

Chemicals and solvents were obtained from commercial sources, and used without further purification unless otherwise stated. Reactions were monitored by TLC performed on Macherey–Nagel Alugram® Sil 60/UV_{254} sheets (thickness 0.2 mm). Products were purified using column chromatography. Column chromatography was carried out using Macherey–Nagel silica gel (230–400 mesh). NMR spectra were recorded on a Bruker DRX 300 spectrometer (operating at 300 MHz for ^1H and 75 MHz for ^{13}C). Chemical shifts are expressed in ppm relative to either tetramethylsilane (TMS) or to residual proton signal in deuterated solvents. Chemical shifts are reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = double doublet, br = broad and m = multiplet), coupling constant (*J* in Hz), relative integral and assignment. The attributions of protons and carbons were made by analysis of 2D experiments (COSY, HSQC and HMBC). Mass spectra were recorded on a Varian triple quadrupole 1200W mass spectrometer equipped with a non-polar C18 TSK-gel Super ODS (4.6 × 50 mm) column, using electrospray ionisation and a UV detector (diode array). All compounds were found to be >96% pure by HPLC analysis.

Table 1
Evaluation of 5-HT_6R affinity and cytotoxicity of target compounds.

Compound	Structure	R_1	R_2	5-HT6 affinity		Cytotoxicity (SY5Y)	
				% Inhibition of specific control binding[a]	Ki (nM)	% Inhibition of cell growing[b]	IC_{50} (μM)
SB 271046	–	–	–	–	1.7		–
6			–	16%	–		86.9
7			–	11%	–		44.1
15		–	–	20%	–	19%	
16				5%	–	20%	
17				11%	–	25%	
18				6%	–	39%	
19				22%	–	17%	
20				0%	–	28%	
21				4%	–	5%	
28				5%	–		91.0
29				10%	–		49.5
30				0%	–		50.0
31				0%	–		29.0
32				40%	–		102
33				14%	–		91.9
37				21%	–	0%	
38				37%	–		10.0
39				7%	–		17.4
40				–	100		45.7
41				0%	–		68.6
42				3%	–		25.2

Mean IC_{50} or K_i values for 2-3 independent experiments are shown with less than 10% deviation.
[a] Competition binding assay at 100 nM giving the displacement (%) of compounds (radioligand: [^{3}H]-LSD, n = 3).
[b] Determination of the potential cytotoxic effects at the concentration of 100 μM.

5.1.2. General procedure for the synthesis of N-substituted-3H-benzothiazol-2-one derivatives

To DMF (20 mL) were added potassium carbonate (0.4 g, 3 mmol), *3H*-benzothiazol-2-one derivative (1 mmol) and the corresponding chloroethylamine derivative (1 mmol). The mixture was warmed at 80 °C for 18 h. The mineral was filtered and the solution evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40–63 mesh), eluting with dichloromethane/methanol (95/5, v/v). The hydrochloride product was obtained by solubilising the free base in dry ethyl acetate and treated with gaseous hydrochloric acid in diethyl ether (20 mL). The precipitate obtained was filtered and washed with ethyl acetate (2 × 20 mL) to afford the desired compound. Compounds were described as free base or hydrochloride form.

5.1.2.1. 6-Bromo-3-dimethylaminoethyl-3H-benzothiazol-2-one ***3***. Yield 61%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.20 (s, 6H, $N(CH_3)_2$), 2.58 (t, J = 7.1 Hz, 2H, NCH_2), 4.01 (t, J = 7.2 Hz, 2H, CH_2), 6.95 (d, J = 8.6 Hz, 1H, H_4), 7.41 (dd, J = 8.5 Hz, J = 1.9 Hz, 1H, H_5), 7.53 (d, J = 2.0 Hz, 1H, H_7). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.1 (CH_2), 45.7 (2 CH_3), 56.1 (CH_2), 111.8 (CH), 115.8 (C_{aro}), 124.5 (C_{aro}), 125.2 (CH), 129.4 (CH), 136.1 (C_{aro}), 169.2 (CO). LCMS (ESI^+): calc for [M+H^+]: 301.0–303.0; found: 301.0–302.9.

5.1.2.2. 6-Bromo-3-piperidino ethyl-3H-benzothiazol-2-one ***4***. Yield 58%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (m, 2H, CH_2), 1.60 (m, 4H, CH_2), 2.50 (m, 4H, NCH_2), 2.62 (t, J = 7.3 Hz, 2H, CH_2), 4.05 (t,

J = 7.3 Hz, 2H, CH_2), 7.00 (d, J = 8.5 Hz, 1H, H_4), 7.41 (dd, J = 8.6 Hz, J = 1.9 Hz, 1H, H_5), 7.53 (d, J = 1.9 Hz, 1H, H_7). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.2 (CH_2), 25.9 (2 CH_2), 40.9 (CH_2), 54.9 (2 CH_2), 55.7 (CH_2), 112.0 (CH), 115.3 (C_{aro}), 124.5 (C_{aro}), 125.1 (CH), 129.2 (CH), 136.3 (C_{aro}), 169.1 (CO). LCMS (ESI^+): calc for [M+H^+]: 341.0-343.0; found: 340.9–343.0.

5.1.2.3. 6-Benzenesulfonyl-3-(2-dimethylaminoethyl)-3H-benzothiazol-2-one hydrochloride ***6***. Yield 17%; mp 236–238 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.82 (m, 6H, $N(CH_3)_2$), 3.38 (m, 2H, CH_2), 4.39 (t, J = 6.3 Hz, 2H, CH_2), 7.56 - 7.23 (m, 3H, H_{Ar}), 7.76 (d, J = 8.5 Hz, 1H, H_4), 7.95 (dd, J = 8.5 Hz, J = 1.8 Hz, 1H, H_5), 7.98 (m, 2H, H_{Ar}), 8.46 (d, J = 1.8 Hz, 1H, H_7), 10.75 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 38.1 (CH_2), 42.6 (2 CH_3), 53.2 (CH_2), 112.7 (CH), 123.3 (CH), 123.9 (C_{aro}), 126.6 (CH), 127.7 (2 CH), 130.3 (2 CH), 134.2 (CH), 136.1 (C_{aro}), 140.9 (C_{aro}), 141.9 (C_{aro}), 170.4 (CO). LCMS (ESI^+): calc for [M+H^+]: 363.1; found: 363.0.

5.1.2.4. 6-Benzenesulfonyl-3-(2-piperidin-1-ylethyl)-3H-benzothiazol-2-one hydrochloride ***7***. Yield 36%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.36 (m, 1H, CH_2), 1.62–1.88 (m, 6H, 3 CH_2), 2.93 (m, 2H, 2 NCH_2), 3.30 (m, 2H, NCH_2), 3.53 (m, 2H, 2 NCH_2), 4.43 (t, J = 6.8 Hz, 2H, NCH_2), 7.58–7.73 (m, 3H, H_{Ar}), 7.81 (d, J = 8.9 Hz, 1H, H_4), 7.95 (dd, J = 8.9 Hz, J = 1.8 Hz, 1H, H_5), 7.98 (m, 2H, H_{Ar}), 8.46 (d, J = 1.8 Hz, 1H, H_7), 10.66 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.7 (CH_2), 22.8 (2 CH_2), 37.5 (CH_2), 52.2 (CH_2), 52.5 (2 CH_2), 112.7 (CH), 123.3 (CH), 123.8 (C_{aro}), 126.6 (CH), 127.7 (CH), 130.3 (CH), 134.2 (CH), 136.1 (C_{aro}), 140.8 (C_{aro}), 141.9 (C_{aro}), 170.2 (CO). LCMS (ESI^+): calc for [M+H^+]: 403.1; found: 403.0.

5.1.2.5. 3-(2-Dimethylaminoethyl)-6-nitro-3H-benzothiazol-2-one hydrochloride ***9***. Yield 37%; mp > 240 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.85 (d, J = 4.2 Hz, 6H, $N(CH_3)_2$), 3.42 (m, 2H, CH_2), 4.45 (t, J = 6.7 Hz, 2H, CH_2), 7.79 (d, J = 9.0 Hz, 1H, H_4), 8.29 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H, H_5), 8.78 (d, J = 2.4 Hz, 1H, H_7), 10.78 (m, 1H, NH^+). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.3 (CH_2), 42.7 (2 CH_3), 53.3 (CH_2), 112.2 (CH), 119.8 (CH), 123.1 (CH), 123.6 (C_{aro}), 142.2 (C_{aro}), 143.5 (C_{aro}), 170.7 (CO). LCMS (ESI^+): calc for [M+H^+]: 268.3; found: 268.0.

5.1.2.6. 6-Nitro-3-(2-pyrrolidin-1-ylethyl)-3H-benzothiazol-2-one hydrochloride ***10***. Yield 35%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.87 (m, 2H, 2 CH_2), 2.01 (m, 2H, 2 CH_2), 3.09 (m, 2H, 2 NCH_2), 3.50 (m, 2H, NCH_2), 3.58 (m, 2H, 2 NCH_2), 4.42 (t, J = 6.4 Hz, 2H, NCH_2), 7.74 (d, J = 9.0 Hz, 1H, H_4), 8.29 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H, H_5), 8.78 (d, J = 2.4 Hz, 1H, H_7), 10.67 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.1 (2 CH_2), 39.5 (CH_2), 50.7 (CH_2), 53.7 (2 CH_2), 112.1 (CH), 119.8 (CH), 123.1 (CH), 123.6 (C_{aro}), 142.2 (C_{aro}), 143.5 (C_{aro}), 170.8 (CO). LCMS (ESI^+): calc for [M+H^+]: 294.3; found: 294.0.

5.1.2.7. 6-Nitro-3-(2-piperidin-1-ylethyl)-3H-benzothiazol-2-one hydrochloride ***11***. Yield 42%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.38 (m, 1H, CH_2), 1.65–1.78 (m, 3H, 3 CH_2), 1.84 (m, 2H, 2 CH_2), 2.97 (m, 2H, 2 NCH_2), 3.40 (m, 2H, NCH_2), 3.58 (m, 2H, 2 NCH_2), 4.47 (t, J = 7.0 Hz, 2H, NCH_2), 7.78 (d, J = 9.0 Hz, 1H, H_4), 8.30 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H, H_5), 8.79 (d, J = 2.4 Hz, 1H, H_7), 10.20 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6), δ = 21.7 (CH_2), 22.9 (2 CH_2), 37.8 (CH_2), 52.5 (CH_2), 52.7 (2 CH_2), 112.1 (CH), 119.8 (CH), 123.1 (CH), 123.6 (C_{aro}), 142.1 (C_{aro}), 143.5 (C_{aro}), 170.7 (CO). LCMS (ESI^+): calc for [M+H^+]: 308.1; found: 307.9.

5.1.2.8. 3-(2-Dimethylaminoethyl)-2-oxo-2,3-dihydro-benzothiazole-6-sulfonic acid methylphenylamide hydrochloride ***28***. Yield 68%; mp 203–204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.85 (m, 6H, $N(CH_3)_2$), 3.17 (s, 3H, NCH_3), 3.39 (m, 2H, NCH_2), 4.39 (t, J = 6.8 Hz, 2H, NCH_2), 7.17 (m, 2H, H_{Ar}), 7.26–7.40 (m, 3H, H_{Ar}), 7.44 (dd, J = 8.6 Hz, J = 1.9 Hz, 1H, H_5), 7.68 (d, J = 8.6 Hz, 1H, H_4), 8.08 (d, J = 1.9 Hz, 1H, H_7), 10.46 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 38.1 (CH_2), 38.5 (CH_3), 42.6 (2 CH_3), 53.1 (CH_2), 112.1 (CH), 123.2 (CH), 123.4 (C_{aro}), 126.5 (CH), 126.7 (2 CH), 127.8 (CH), 129.5 (2 CH), 131.4 (C_{aro}), 140.5 (C_{aro}), 141.5 (C_{aro}), 170.4 (CO). LCMS (ESI^+): calc for [M+H^+]: 392.1; found: 392.0.

5.1.2.9. 3-Methyl-2-oxo-3-(2-pyrrolidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid methylphenylamide hydrochloride ***29***. Yield 42%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.86 (m, 2H, 2 CH_2), 2.01 (m, 2H, 2 CH_2), 3.09 (m, 2H, 2 NCH_2), 3.18 (s, 3H, NCH_3), 3.50 (m, 2H, NCH_2), 3.59 (m, 2H, 2 NCH_2), 4.37 (t, J = 6.3 Hz, 2H, NCH_2), 7.14 (m, 2H, H_{Ar}), 7.26–7.40 (m, 3H, H_{Ar}), 7.45 (dd, J = 8.5 Hz, J = 1.8 Hz, 1H, H_5), 7.65 (d, J = 8.5 Hz, 1H, H_4), 8.09 (d, J = 1.8 Hz, 1H, H_7), 10.45 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.2 (2 CH_2), 38.5 (CH_3), 39.1 (CH_2), 50.4 (CH_2), 53.5 (2 CH_2), 112.0 (CH), 123.2 (CH), 123.4 (C_{aro}), 126.5 (CH), 126.7 (2 CH), 127.8 (CH), 129.4 (2CH), 131.3 (C_{aro}), 140.4 (C_{aro}), 141.5 (C_{aro}), 170.3 (CO). LCMS (ESI^+): calc for [M+H^+]: 418.1; found: 418.0.

5.1.2.10. 3-Methyl-2-oxo-3-(2-piperidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid methylphenylamide hydrochloride ***30***. Yield 58%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.37 (m, 1H, CH_2), 1.76–1.88 (m, 5H, 3CH_2), 2.96 (m, 2H, 2 NCH_2), 3.17 (s, 3H, NCH_3), 3.32 (m, 2H, NCH_2), 3.56 (m, 2H, 2 NCH_2), 4.44 (t, J = 7.0 Hz, 2H, NCH_2), 7.14 (m, 2H, H_{Ar}), 7.26–7.40 (m, 3H, H_{Ar}), 7.44 (dd, J = 8.6 Hz, J = 1.9 Hz, 1H, H_5), 7.73 (d, J = 8.6 Hz, 1H, H_4), 8.08 (d, J = 1.9 Hz, 1H, H_7), 10.45 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.7 (CH_2), 22.8 (2 CH_2), 37.6 (CH_2), 38.5 (CH_3), 52.1 (CH_2), 52.4 (2 CH_2), 112.1 (CH), 123.3 (C_{aro}), 123.3 (CH), 126.5 (CH), 126.7 (2 CH), 127.8 (CH), 129.4 (2 CH), 131.4 (C_{aro}), 140.4 (C_{aro}), 141.5 (C_{aro}), 170.1 (CO). LCMS (ESI^+): calc for [M+H^+]: 432.1; found: 432.2.

5.1.2.11. 3-(2-Dimethylaminoethyl)-2-oxo-2,3-dihydro-benzothiazole-6-sulfonic acid methylnaphthalen-1-yl amide hydrochloride ***31***. Yield 63%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.88 (m, 6H, $N(CH_3)_2$), 3.28 (s, 3H, NCH_3), 3.44 (m, 2H, NCH_2), 4.43 (t, J = 6.3 Hz, 2H, NCH_2), 6.95 (dd, J = 7.4 Hz, J = 1.0 Hz, 1H, H_{Ar}), 7.43 (dd, J = 8.3 Hz, J = 7.4 Hz, 1H, H_{Ar}), 7.55–7.68 (m, 2H, H_{Ar}), 7.68 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H, H_5), 7.74 (d, J = 8.4 Hz, 1H, H_4), 7.96 (d, J = 8.4 Hz, 1H, H_{Ar}), 8.00 (m, 1H, H_{Ar}), 8.16 (m, 1H, H_{Ar}), 8.25 (d, J = 1.8 Hz, 1H, H_7), 10.23 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 38.1 (CH_2), 40.2 (CH_3), 42.7 (2 CH_3), 53.2 (CH_2), 112.2 (CH), 123.5 (CH), 123.6 (C_{aro}), 124.0 (CH), 125.3 (CH), 126.0 (CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 128.5 (CH), 129.1 (CH), 132.1 (C_{aro}), 132.2 (C_{aro}), 134.7 (C_{aro}), 138.4 (C_{aro}), 140.5 (C_{aro}), 170.5 (CO). LCMS (ESI^+): calc for [M+H^+]: 442.1; found: 442.0.

5.1.2.12. 3-Methyl-2-oxo-3-(2-pyrrolidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid methylnaphthalen-1-yl amide hydrochloride ***32***. Yield 48%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.88 (m, 2H, 2 CH_2), 2.03 (m, 2H, 2 CH_2), 3.12 (m, 2H, 2 NCH_2), 3.28 (s, 3H, NCH_3), 3.54 (m, 2H, NCH_2), 3.61 (m, 2H, 2 NCH_2), 4.42 (t, J = 6.3 Hz, 2H, NCH_2), 6.95 (dd, J = 7.4 Hz, J = 1.0 Hz, 1H, H_{Ar}), 7.43 (dd, J = 8.2 Hz, J = 7.4 Hz, 1H, H_{Ar}), 7.56–7.67 (m, 2H, H_{Ar}), 7.67 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H, H_5), 7.74 (d, J = 8.4 Hz, 1H, H_4), 7.96 (d, J = 8.4 Hz, 1H, H_{Ar}), 8.00 (m, 1H, H_{Ar}), 8.16 (m, 1H, H_{Ar}), 8.25 (d, J = 1.8 Hz, 1H, H_7), 10.48 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.2 (2 CH_2), 39.2 (CH_2), 40.2 (CH_3), 50.6 (CH_2), 53.6 (2 CH_2), 112.2 (CH), 123.5 (CH), 123.6 (C_{aro}), 124.0 (CH), 125.3 (CH), 126.0 (CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 128.5 (CH), 129.1 (CH), 132.1 (C_{aro}), 132.2 (C_{aro}), 134.7 (C_{aro}), 138.4 (C_{aro}), 140.6 (C_{aro}), 170.5 (CO). LCMS (ESI^+): calc for [M+H^+]: 468.1; found: 468.0.

5.1.2.13. 3-Methyl-2-oxo-3-(2-piperidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid methylnaphthalen-1-yl amide hydrochloride ***33***. Yield 57%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.39 (m, 1H, CH_2), 1.66–1.91 (m, 5H, 3 CH_2), 2.98 (m, 2H, 2 NCH_2), 3.27 (s, 3H, NCH_3), 3.32 (m, 2H, NCH_2), 3.59 (m, 2H, 2 NCH_2), 4.44 (t, J = 6.8 Hz, 2H, NCH_2), 6.95 (dd, J = 7.4 Hz, J = 1.0 Hz, 1H, H_{Ar}), 7.43 (dd, J = 8.2 Hz, J = 7.4 Hz, 1H, H_{Ar}), 7.56–7.68 (m, 2H, H_{Ar}), 7.67 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H, H_5), 7.84 (d, J = 8.4 Hz, 1H, H_4), 7.96 (d, J = 8.4 Hz, 1H, H_{Ar}), 8.00 (m, 1H, H_{Ar}), 8.16 (m, 1H, H_{Ar}), 8.24 (d, J = 1.8 Hz, 1H, H_7), 10.48 (m, 1H, NH^+). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8 (CH_2), 22.8 (2 CH_2), 37.6 (CH_2), 38.5 (CH_3), 52.3 (CH_2), 52.6 (2 CH_2), 112.2 (CH), 123.5 (CH), 123.6 (C_{aro}), 124.0 (CH), 125.3 (CH), 126.0 (CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 128.5 (CH), 129.1 (CH), 132.1 (C_{aro}), 132.2 (C_{aro}), 134.7 (C_{aro}), 138.4 (C_{aro}), 140.5 (C_{aro}), 170.3 (CO). LCMS (ESI^+): calc for $[M+H^+]$: 482.1; found: 482.0.

5.1.2.14. 3-(2-Dimethyaminoethyl)-3H-benzothiazol-2-one hydrochloride ***34***. Yield 45%; mp 218–220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.84 (d, J = 3.8 Hz, 6H, $N(CH_3)_2$), 3.36 (m, 2H, NCH_2), 4.40 (t, J = 7.2 Hz, 2H, NCH_2), 7.24 (ddd, J = 8.1 Hz, J = 7.8 Hz, J = 1.0 Hz, 1H, H_6), 7.41 (ddd, J = 8.1 Hz, J = 7.8 Hz, J = 1.3 Hz, 1H, H_5), 7.60 (dd, J = 8.1 Hz, J = 0.6 Hz, 1H, H_4), 7.70 (dd, J = 7.8 Hz, J = 1.0 Hz, 1H, H_7), 11.26 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 37.7 (CH_2), 42.5 (2 CH_3), 53.0 (CH_2), 112.1 (CH), 122.1 (C_{aro}), 123.5 (CH), 124.0 (CH), 127.2 (CH), 136.7 (C_{aro}), 169.7 (CO). LCMS (ESI^+): calc for $[M+H^+]$: 223.1; found: 222.9.

5.1.2.15. 3-(2-Pyrrolidin-1-ylethyl)-3H-benzothiazol-2-one hydrochloride ***35***. Yield 43%; mp 215–217 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 3.06 (m, 2H, 2 NCH_2), 3.46 (m, 2H, NCH_2), 3.59 (m, 2H, 2 NCH_2), 4.37 (t, J = 7.0 Hz, 2H, NCH_2), 7.25 (td, J = 7.7 Hz, J = 1.1 Hz, 1H, H_6), 7.41 (ddd, J = 8.1 Hz, J = 7.7 Hz, J = 1.3 Hz, 1H, H_5), 7.58 (dd, J = 8.1 Hz, J = 1.1 Hz, 1H, H_4), 7.70 (dd, J = 7.7 Hz, J = 1.3 Hz, 1H, H_7), 11.25 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.1 (2 CH_2), 38.7 (CH_2), 50.4 (CH_2), 53.4 (2 CH_2), 112.0 (CH), 122.1 (C_{aro}), 123.5 (CH), 124.0 (CH), 127.2 (CH), 136.7 (C_{aro}) 169.7 (CO). LCMS (ESI^+): calc for $[M+H^+]$: 249.1; found: 249.0.

5.1.2.16. 3-(2-Piperidin-1-ylethyl)-3H-benzothiazol-2-one hydrochloride ***36***. Yield 51%; mp 226–227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.38 (m, 1H, CH_2), 1.72 (m, 1H, CH_2), 1.77-1.85 (m, 4H, 2 CH_2), 2.97 (m, 2H, 2 NCH_2), 3.30 (m, 2H, NCH_2), 3.55 (m, 2H, 2 NCH_2), 4.45 (t, J = 7.5 Hz, 2H, NCH_2), 7.25 (ddd, J = 7.8 Hz, J = 7.5 Hz, J = 1.0 Hz, 1H, H_6), 7.42 (ddd, J = 8.2 Hz, J = 7.5 Hz, J = 1.3 Hz, 1H, H_5), 7.66 (dd, J = 8.2 Hz, J = 1.0 Hz, 1H, H_4), 7.71 (dd, J = 7.8 Hz, J = 1.3 Hz, 1H, H_7), 11.03 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.8 (CH_2), 22.8 (2 CH_2), 37.2 (CH_2), 52.2 (CH_2), 52.5 (2 CH_2), 112.1 (CH), 122.1 (C_{aro}), 123.6 (CH), 124.0 (CH), 127.2 (CH), 136.7 (C_{aro}), 169.6 (CO). LCMS (ESI^+): calc for $[M+H^+]$: 263.1; found: 263.0.

5.1.3. General procedures for Friedel Crafts reaction for the synthesis of compound ***5***

5.1.3.1. Procedure in the presence of aluminium chloride reagent. To aluminium chloride (36 g, 264 mmol) in DMF (8.5 mL) were added benzothiazol-2-one **1** (5 g, 33 mmol) and phenylsulfonyl chloride (66 mmol). The mixture was warmed at 80 °C for 2 h. The solution was hydrolysed in cooled water (200 mL). The precipitate obtained was filtered and recrystallised in absolute ethanol (yield: 15%).

5.1.3.2. Procedure in the presence of Eaton's reagent. Eaton's reagent was prepared from phosphorus pentoxide (1.0 g, 7.0 mmol) and methanesulfonic acid (11.0 g, 114.6 mmol) (weight ratio P_2O_5/CH_3SO_3H 1:10). The mixture was heated at 60 °C under nitrogen atmosphere until complete homogeneity was obtained. Phenylsulfonyl chloride (3.0 g, 17.0 mmol) and benzothiazol-2-one **1** (3.8 g, 25.5 mmol) were then added to Eaton's reagent. The mixture was heated at 110 °C under inert atmosphere for 24 h. After cooling at 20 °C, the reaction medium was hydrolysed in cooled water (200 mL) and stirred for 1 h. The precipitate obtained was filtered and recrystallised in absolute ethanol (yield: 57%).

5.1.3.3. 6-Benzenesulfonyl-3H-benzothiazol-2-one ***5***. Mp 225–227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.26 (d, J = 8.4 Hz, 1H, H_4), 7.57–7.70 (m, 3H, H_{Ar}), 7.80 (dd, J = 8.4 Hz, J = 1.9 Hz, 1H, H_5), 7.93 (m, 2H, H_{Ar}), 8.30 (d, J = 1.9 Hz, 1H, H_7), 12.40 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 112.4 (CH), 123.3 (CH), 125.3 (C_{aro}), 126.7 (CH), 127.6 (2 CH), 130.2 (2 CH), 134.0 (CH), 135.2 (C_{aro}), 141.1 (C_{aro}), 142.0 (C_{aro}), 170.8 (CO). LCMS (ESI^-): calc for $[M-H^+]$: 290.0; found: 290.0.

5.1.4. 6-Nitro-3H-benzothiazol-2-one ***8*** *[27,31]*

To 70% HNO_3 (20 mL) was added 3H-benzothiazol-2-one (10 g, 66 mmol) and the mixture stirred at 20 °C for 3 h. The precipitate was filtered and washed with water. The product was recrystallised in absolute ethanol. Yield 90%; mp 228–229 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.28 (d, J = 8.9 Hz, 1H, H_4), 8.18 (dd, J = 8.9 Hz, J = 2.4 Hz, 1H, H_5), 8.65 (d, J = 2.5 Hz, 1H, H_7), 12.54 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 111.9 (CH), 119.6 (CH), 123.2 (CH), 125.0 (C_{aro}), 142.5 (C_{aro}), 142.9 (C_{aro}), 171.0 (CO). LCMS (ESI^-): calc for $[M-H^+]$: 195.0; found: 195.0.

5.1.5. General procedure for the synthesis of compounds ***12–14***

To a solution of compounds (10 mmol) in methanol was added 10% Pd/C (100 mg). The resulting solution was stirred at 20 °C under atmospheric pressure of hydrogen for 4 h. The solution was filtered and concentrated to dryness. The residue was purified by column chromatography using dichloromethane/methanol (95/5, v/v) as eluent to afford the corresponding oily compounds.

5.1.5.1. 6-Amino-3-(2-dimethylaminoethyl)-3H-benzothiazol-2-one ***12***. Yield 73%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 6H, NCH_3), 2.60 (t, J = 6.7 Hz, 2H, NCH_2), 3.65 (br s, 2H, NH_2), 4.00 (t, J = 6.7 Hz, 2H, NCH_2), 6.65 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, H_5), 6.78 (d, J = 2.0 Hz, 1H, H_7), 6.86 (d, J = 8.6 Hz, 1H, H_4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.9 (CH_2), 45.7 (2 CH_3), 56.1 (CH_2), 109.1 (CH), 111.2 (CH), 113.8 (CH), 123.9 (C_{aro}), 129.5 (C_{aro}), 142.7 (C_{aro}), 169.4 (CO). LCMS (ESI^+): calc for $[M+H^+]$: 237.1; found: 238.0.

5.1.5.2. 6-Amino-3-(2-pyrrolidin-1-ylethyl)-3H-benzothiazol-2-one ***13***. Yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.83 (m, 4H, 2 CH_2), 2.63 (m, 4H, 2 NCH_2), 2.80 (t, J = 6.6 Hz, 2H, NCH_2), 3.65 (br s, 2H, NH_2), 4.05 (m, J = 6.6 Hz, 2H, NCH_2), 6.65 (dd, J = 8.7 Hz, J = 2.2 Hz, 1H, H_5), 6.78 (d, J = 2.2 Hz, 1H, H_7), 6.93 (d, J = 8.7 Hz, 1H, H_4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6 ($2CH_2$), 41.9 (CH_2), 52.9 (CH_2), 54.4 ($2CH_2$), 109.1 (CH), 111.4 (CH), 113.9 (CH), 123.6 (C_{aro}), 129.2 (C_{aro}), 142.7 (C_{aro}), 169.2 (CO). LCMS (ESI^+): calc for $[M+H^+]$: 264.1; found: 264.0.

5.1.5.3. 6-Amino-3-(2-piperidin-1-ylethyl)-3H-benzothiazol-2-one ***14***. Yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (m, 2H, CH_2), 1.54 (m, 4H, 2 CH_2), 2.40 (m, 4H, 2 NCH_2), 2.55 (t, J = 6.7 Hz, 2H, NCH_2), 3.63 (br s, 2H, NH_2), 3.95 (t, J = 6.8 Hz, 2H, NCH_2), 6.58 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H, H_5), 6.69 (d, J = 2.0 Hz, 1H, H_7), 6.83 (d, J = 8.8 Hz, 1H, H_4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8 (CH_2), 22.8 (2 CH_2), 38.1 (CH_2), 52.2 (CH_2), 52.5 (2 CH_2), 112.7 (CH), 117.1 (CH), 120.9 (CH), 123.4 (C_{aro}), 130.5 (C_{aro}), 135.1 (C_{aro}), 169.6 (CO). LCMS (ESI^+): calc for $[M+H^+]$: 278.1; found: 278.0.

5.1.6. Diphenylsulfonic acid-(3-(2-pyrrolidin-1-ylethyl)-2-oxo-2,3-dihydro-benzothiazol-6-yl)amide hydrochloride ***15***

To AcOEt (20 mL) with triethylamine (0.3 mL, 2.2 mmol) or a solution of AcOEt/H_2O (10/10 v/v) with potassium carbonate (0.3 g, 2.2 mmol) were added 6-amino-3-(2-pyrrolidin-1-ylethyl)-3H-benzothiazol-2-one (**13**) (0.3 g, 1.1 mmol) and chlorosulfonylphenyl (0.3 mL, 1.9 mmol). The reaction mixture was stirred for 24 h. Water (10 mL) was added. The organic layer was evaporated under reduced pressure. The product was purified by chromatography on silica gel using dichloromethane/methanol (95/5, v/v). The product was solubilised in dry ethyl acetate and treated with gaseous hydrochloric acid in diethyl ether (20 mL). The precipitate obtained was filtered and washed with ethyl acetate (2 × 20 mL) to afford the desired compound. Yield 68%; mp 238–239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.87 (m, 2H, 2 CH_2), 2.02 (m, 2H, 2 CH_2), 3.09 (m, 2H, 2 NCH_2), 3.48 (m, 2H, NCH_2), 3.60 (m, 2H, 2 NCH_2), 4.36 (t, J = 6.4 Hz, 2H, CH_2), 6.95 (dd, J = 8.6 Hz, J = 2.2 Hz, 1H, H_5), 7.57 (d, J = 8.6 Hz, 1H, H_4), 7.63 (d, J = 2.2 Hz, 1H, H_7), 7.71 (m, 4H, H_{Ar}), 7.84 (m, 4H, H_{Ar}), 7.85 (m, 2H, H_{Ar}), 10.83 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.2 (2 CH_2), 39.0 (CH_2), 50.4 (CH_2), 53.5 (2 CH_2), 112.3 (CH), 123.2 (C_{aro}), 126.9 (CH), 128.5 (4 CH), 128.7 (C_{aro}), 130.1 (4 CH), 130.3 (CH), 135.3 (2 CH), 138.4 (C_{aro}), 138.8 (C_{aro}), 170.1 (CO). LCMS (ESI^+): calc for [M+H^+]: 544.1; found: 543.8.

5.1.7. General procedure for the synthesis of compounds ***16–21***

To pyridine (20 mL) were added 6-aminobenzothiazol-2-one (1 g, 6 mmol) and the corresponding chlorosulfonylaryl (9 mmol). The reaction mixture was stirred at 20 °C for 24 h. The solution was evaporated under reduced pressure. The product was purified by chromatography on silica gel using dichloromethane/methanol (96/4, v/v). The product was solubilised in dry ethyl acetate and treated with gaseous hydrochloric acid in diethyl ether (20 mL). The precipitate obtained was filtered and washed with ethyl acetate (2 × 20 mL) to afford the desired compound.

5.1.7.1. Phenyl-1-sulfonic acid-(3-(2-dimethylaminoethyl)-2-oxo-2,3-dihydro-benzothiazol-6-yl)amide hydrochloride ***16***. Yield 78%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.86 (d, J = 4.6 Hz, 6H, $N(CH_3)_2$), 3.35 (m, 2H, CH_2), 4.26 (t, J = 6.5 Hz, 2H, CH_2), 7.06 (dd, J = 8.7 Hz, J = 2.2 Hz, 1H, H_5), 7.37 (d, J = 8.7 Hz, 1H, H_4), 7.46 (d, J = 2.2 Hz, 1H, H_7),7.52–7.66 (m, 3H, H_{Ar}), 7.78 (m, 2H, H_{Ar}), 10.13 (m, 1H, NH^+), 10.41 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 37.8 (CH_2), 42.6 (2 CH_3), 53.1 (CH_2), 112.4 (CH), 116.3 (CH), 120.4 (CH), 122.9 (C_{aro}), 127.2 (2 CH), 129.8 (2 CH), 133.4 (CH), 133.6 (C_{aro}), 133.8 (C_{aro}), 139.8 (C_{aro}), 169.5 (CO). LCMS (ESI^+): calc for [M+H^+]: 378.1; found: 378.0.

5.1.7.2. Phenyl-1-sulfonic acid-(3-(2-pyrrolidin-1-ylethyl)-2-oxo-2,3-dihydro-benzothiazol-6-yl)amide hydrochloride ***17***. Yield 65%; mp 164–165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.83 (m, 2H, 2 CH_2), 2.00 (m, 2H, 2 CH_2), 3.06 (m, 2H, 2 NCH_2), 3.43 (m, 2H, NCH_2), 3.57 (m, 2H, 2 NCH_2), 4.24 (t, J = 6.1 Hz, 2H, NCH_2), 7.05 (dd, J = 8.7 Hz, J = 2.2 Hz, 1H, H_5), 7.35 (d, J = 8.7 Hz, 1H, H_4), 7.46 (d, J = 2.2 Hz, 1H, H_7),7.52–7.66 (m, 3H, H_{Ar}), 7.77 (m, 2H, H_{Ar}), 10.12 (m, 1H, NH^+), 10.39 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.1 (2 CH_2), 38.9 (CH_2), 50.4 (CH_2), 53.6 (2 CH_2), 112.4 (CH), 116.3 (CH), 120.4 (CH), 122.9 (C_{aro}), 127.2 (2 CH), 129.8 (2 CH), 133.4 (CH), 133.7 (C_{aro}), 133.8 (C_{aro}), 139.8 (C_{aro}), 169.6 (CO). LCMS (ESI^+): calc for [M+H^+]: 404.1; found: 404.0.

5.1.7.3. Phenyl-1-sulfonic acid-(3-(2-piperidin-1-ylethyl)-2-oxo-2,3-dihydro-benzothiazol-6-yl)amide hydrochloride ***18***. Yield 59%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.36 (m, 1H, CH_2), 1.55–1.90 (m, 5H, 3CH_2), 2.93 (m, 2H, 2 NCH_2), 3.29 (m, 2H, NCH_2), 3.53 (m, 2H, 2 NCH_2), 4.40 (t, J = 7.0 Hz, 2H, CH_2), 7.01 (tt, J = 7.2 Hz, J = 1.2 Hz, 1H, H_{Ar}), 7.14 (m, 2H, H_{Ar}), 7.23 (m, 2H, H_{Ar}), 7.76 (m, 2H, H_4, H_5), 8.22 (m, 1H, H_7), 10.45 (s, 1H, NH), 10.58 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.7 (CH_2), 22.8 (2 CH_2), 37.3 (CH_2), 52.2 (CH_2), 52.5 (2 CH_2), 112.4 (CH), 116.3 (CH), 120.4 (CH), 122.9 (C_{aro}), 127.2 (2 CH), 129.8 (2 CH), 133.4 (CH), 133.6 (C_{aro}), 133.8 (C_{aro}), 139.8 (C_{aro}), 169.4 (CO). LCMS (ESI^+): calc for [M+H^+]: 418.1; found: 418.1.

5.1.7.4. Naphthalen-2-sulfonic acid-(3-(2-dimethylaminoethyl)-2-oxo-2,3-dihydro-benzothiazol-6-yl)amide hydrochloride ***19***. Yield 65%; mp 228–229 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.80 (d, J = 4.3 Hz, 6H, $N(CH_3)_2$), 3.30 (m, 2H, CH_2), 4.22 (t, J = 6.7 Hz, 2H, CH_2), 7.08 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H, H_5), 7.34 (d, J = 8.7 Hz, 1H, H_4), 7.51 (d, J = 2.1 Hz, 1H, H_7), 7.61–7.74 (m, 2H, H_{Ar}), 7.81 (dd, J = 8.7 Hz, J = 1.8 Hz, 1H, H_{Ar}), 8.02 (d, J = 8.1 Hz, 1H, H_{Ar}), 8.11 (d, J = 8.3 Hz, 1H, H_{Ar}), 8.13 (d, J = 8.2 Hz, 1H, H_{Ar}), 8.45 (d, J = 1.8 Hz, 1H, H_{Ar}), 10.15 (m, 1H, NH^+), 10.53 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 37.8 (CH_2), 42.7 (2 CH_3), 53.4 (CH_2), 112.4 (CH), 116.3 (CH), 120.3 (CH), 122.5 (CH), 123.0 (C_{aro}), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.5 (CH), 129.7 (CH), 130.0 (CH), 132.0 (C_{aro}), 133.7 (2 C_{aro}), 134.7 (C_{aro}), 136.8 (C_{aro}), 169.8 (CO). LCMS (ESI^+): calc for [M+H^+]: 428.1; found: 428.0.

5.1.7.5. Naphthalen-2-sulfonic acid-(3-(2-pyrrolidin-1-ylethyl)-2-oxo-2,3-dihydro-benzothiazol-6-yl)amide hydrochloride ***20***. Yield 53%; mp 221–222 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.82 (m, 2H, 2 CH_2), 1.96 (m, 2H, 2 CH_2), 3.00 (m, 2H, 2 NCH_2), 3.36 (m, 2H, NCH_2), 3.60 (m, 2H, 2 NCH_2), 4.23 (t, J = 6.7 Hz, 2H, NCH_2), 7.10 (dd, J = 8.7 Hz, J = 2.2 Hz, 1H, H_5), 7.40 (d, J = 8.7 Hz, 1H, H_4), 7.52 (d, J = 2.2 Hz, 1H, H_7), 7.60–7.72 (m, 2H, H_{Ar}), 7.84 (dd, J = 8.7 Hz, J = 1.9 Hz, 1H, H_{Ar}), 8.00 (dd, J = 7.9 Hz, J = 1.2 Hz, 1H, H_{Ar}), 8.10 (d, J = 8.7 Hz, 1H, H_{Ar}), 8.12 (dd, J = 7.3 Hz, J = 1.2 Hz, 1H, H_{Ar}), 8.45 (d, J = 1.9 Hz, 1H, H_{Ar}), 10.61 (s, 1H, NH), 10.96 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.1 (2 CH_2), 38.8 (CH_2), 50.4 (CH_2), 53.4 (2 CH_2), 112.4 (CH), 116.3 (CH), 120.3 (CH), 122.6 (CH), 122.9 (C_{aro}), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.5 (CH), 129.7 (CH), 130.0 (CH), 132.0 (C_{aro}), 133.6 (C_{aro}), 133.8 (C_{aro}), 134.7 (C_{aro}), 136.8 (C_{aro}), 170.1 (CO). LCMS (ESI^-): calc for [M–H^+]: 452.1; found: 451.9.

5.1.7.6. Naphthalen-2-sulfonic acid-(3-(2-piperidin-1-ylethyl)-2-oxo-2,3-dihydro-benzothiazol-6-yl)amide hydrochloride ***21***. Yield 58%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.20–1.88 (m, 6H, 3 CH_2), 2.90 (m, 2H, 2 NCH_2), 3.26 (m, 2H, NCH_2), 3.52 (m, 2H, 2 NCH_2), 4.25 (t, J = 6.7 Hz, 2H, NCH_2), 7.08 (dd, J = 8.9 Hz, J = 2.1 Hz, 1H, H_5), 7.35 (d, J = 8.9 Hz, 1H, H_4), 7.52 (d, J = 2.1 Hz, 1H, H_7), 7.62–7.74 (m, 2H, H_{Ar}), 7.81 (dd, J = 8.7 Hz, J = 1.8 Hz, 1H, H_{Ar}), 8.02 (d, J = 8.2 Hz, 1H, H_{Ar}), 8.11 (d, J = 8.7 Hz, 1H, H_{Ar}), 8.14 (d, J = 8.2 Hz, 1H, H_{Ar}), 8.45 (d, J = 1.8 Hz, 1H, H_{Ar}), 9.74 (m, 1H, NH^+), 10.51 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.7 (CH_2), 22.8 (2 CH_2), 37.3 (CH_2), 52.2 (CH_2), 52.5 (2 CH_2), 112.4 (CH), 116.3 (CH), 120.3 (CH), 122.5 (CH), 122.9 (C_{aro}), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.5 (CH), 129.7 (CH), 130.0 (CH), 132.0 (C_{aro}), 133.6 (C_{aro}), 133.8 (C_{aro}), 134.7 (C_{aro}), 136.8 (C_{aro}), 169.4 (CO). LCMS (ESI^+): calc for [M+H^+]: 468.1; found: 468.1.

5.1.8. 2-Oxo-2,3-dihydro-benzothiazole-6-sulfonic acid naphthalen-1-ylamide ***23***

To pyridine (20 mL) were added 6-chlorosulfonylbenzothiazol-2-one (4.0 g, 16 mmol) and naphthalen-1-ylamine (3.1 g, 22 mmol). The reaction mixture was stirred at 20 °C for 24 h. The solution was evaporated under reduced pressure. The resulting crude product was washed with diethyl ether, CH_2Cl_2 and water. The solid product was recrystallised in absolute ethanol. Yield 59%; mp 210–211 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.14 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.17 (d, J = 8.4 Hz, 1H, H_4), 7.40 (dd, J = 8.0 Hz, J = 7.7 Hz, 1H, H_{Ar}), 7.41–7.52 (m, 2H, H_{Ar}), 7.58 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H, H_5), 7.78 (d,

J = 8.0 Hz, 1H, H_{Ar}), 7.89 (m, 1H, H_{Ar}), 7.96 (d, J = 1.8 Hz, 1H, H_7), 8.04 (m, 1H, H_{Ar}), 10.19 (br s, 1H, NH), 12.30 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 112.0 (CH), 122.3 (CH), 123.6 (CH), 123.7 (CH), 124.5 (C_{aro}), 126.0 (CH), 126.1 (CH), 126.5 (CH), 126.7 (CH), 127.2 (CH), 128.4 (CH), 129.9 (C_{aro}), 132.8 (C_{aro}), 134.3 (C_{aro}), 134.4 (C_{aro}), 140.2 (C_{aro}), 170.7 (CO). LCMS (ESI^-): calc for [M−H]: 355.0; found: 355.0.

5.1.9. 3-Methyl-2-oxo-2,3-dihydro-benzothiazole-6-sulfonic acid naphthalen-1-ylamide ***24***

To acetonitrile (10 mL) were added 2-oxo-2,3-dihydro-benzothiazole-6-sulfonic acid naphthalen-1-ylamide (0.3 g, 0.9 mmol), triethylamine (0.2 mL, 1.4 mmol) and methyl iodide (0.06 mL, 1.1 mmol). The reaction mixture was stirred at 20 °C for 30 min. The solution was stirred for 24 h and evaporated under reduced pressure. The reaction was quenched with water (50 mL), the product extracted with dichloromethane, and the organic layer evaporated under reduced pressure. The product was purified by chromatography on silica gel using dichloromethane/methanol (95/5, v/v). Yield 18%; mp 227–228 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ: 3.47 (s, 3H, NCH_3), 7.32 (d, J = 8.4 Hz, 1H, H_4), 7.35 (dd, J = 7.4 Hz, J = 1.4 Hz, 1H, H_{Ar}), 7.42 (dd, J = 8.0 Hz, J = 7.4 Hz, 1H, H_{Ar}), 7.42–7.53 (m, 2H, H_{Ar}), 7.74 (dd, J = 8.4 Hz, J = 1.9 Hz, 1H, H_5), 7.81 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.90 (m, 1H, H_{Ar}), 7.99 (d, J = 1.9 Hz, 1H, H_7), 8.18 (m, 1H, H_{Ar}), 9.05 (br s, 1H, NH). ^{13}C NMR (75 MHz, acetone-d_6) δ: 28.7 (CH_3), 110.8 (CH), 121.9 (CH), 122.6 (C_{aro}), 122.9 (CH), 123.3 (CH), 125.4 (CH), 126.0 (CH), 126.1 (CH), 126.2 (CH), 127.0 (CH), 128.1 (CH), 129.7 (C_{aro}), 132.5 (C_{aro}), 134.5 (C_{aro}), 134.8 (C_{aro}), 141.3 (C_{aro}), 168.9 (CO). LCMS (ESI^+): calc for [M−H^+]: 369.0; found: 369.0.

5.1.10. General procedure for the synthesis of compounds ***25–26***

To pyridine (20 mL) were added 6-chlorosulfonylbenzothiazol-2-one (1 g, 4 mmol) and the corresponding arylamine derivative (6 mmol). The reaction mixture was stirred at 20 °C for 24 h. The solution was evaporated under reduced pressure. The resulting crude product was hydrolysed in aqueous HCl 5% (20 mL), extracted with dichloromethane, and the organic layer evaporated under reduced pressure. The precipitate obtained was recrystallised in the appropriate solvent.

5.1.10.1. 2-Oxo-2,3-dihydro-benzothiazole-6-sulfonic acid methyl-phenylamide ***25****.* Yield 70% (absolute ethanol); mp 177–178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.14 (s, 3H, CH_3), 7.12 (m, 2H, H_{Ar}), 7.21 (d, J = 8.4 Hz, 1H, H_4), 7.25–7.38 (m, 4H, H_5, H_{Ar}), 7.90 (d, J = 1.9 Hz, 1H, H_7), 12.37 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 38.4 (CH_3), 111.9 (CH), 123.0 (CH), 124.7 (C_{aro}), 126.7 (CH), 126.8 (2 CH), 127.7 (CH), 129.4 (2 CH), 130.3 (C_{aro}), 140.6 (C_{aro}), 141.6 (C_{aro}), 170.8 (CO). LCMS (ESI^-): calc for [M−H^+]: 319.0; found: 319.0.

5.1.10.2. 2-Oxo-2,3-dihydro-benzothiazole-6-sulfonic acid methyl-naphthalen-1-yl amide ***26****.* Yield 65% (absolute ethanol); mp 219–220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.25 (s, 3H, NCH_3), 6.95 (dd, J = 7.4 Hz, J = 1.0 Hz, 1H, H_{Ar}), 7.30 (d, J = 8.4 Hz, 1H, H_4), 7.43 (dd, J = 8.3 Hz, J = 7.4 Hz, 1H, H_{Ar}), 7.55 (dd, J = 8.4 Hz, J = 1.9 Hz, 1H, H_5), 7.55–7.65 (m, 2H, H_{Ar}), 7.94 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.99 (m, 1H, H_{Ar}), 8.08 (d, J = 1.9 Hz, 1H, H_7), 8.15 (m, 1H, H_{Ar}), 12.41 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 40.1 (CH_3), 112.0 (CH), 123.3 (CH), 124.0 (CH), 124.9 (C_{aro}), 125.3 (CH), 126.0 (CH), 127.0 (2 CH), 127.2 (CH), 128.5 (CH), 129.0 (CH), 131.2 (C_{aro}), 132.1 (C_{aro}), 134.6 (C_{aro}), 138.5 (C_{aro}), 140.8 (C_{aro}), 170.9 (CO). LCMS (ESI^-): calc for [M−H^+]: 369.0; found: 369.0.

5.1.11. 6-(Pyridinium-1-sulfonyl)-3H-benzothiazol-2-one chloride ***27***

To pyridine (20 mL) were added 6-chlorosulfonylbenzothiazol-2-one (1 g, 4 mmol) and naphthalen-1-ylamine (0.8 mL, 6 mmol). The reaction mixture was stirred for 24 h and the solution evaporated under reduced pressure. The resulting crude product was washed with diethyl ether and CH_2Cl_2. Yield 16%; mp 216–217 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.05 (d, J = 8.2 Hz, 1H, H_4), 7.52 (dd, J = 8.2 Hz, J = 1.7 Hz, 1H, H_5), 7.76 (d, J = 1.7 Hz, 1H, H_7), 8.03 (dd, J = 7.8 Hz, J = 6.5 Hz, 2H, H_{Ar}), 8.55 (tt, J = 7.8 Hz, J = 1.5 Hz, 1H, H_{Ar}), 8.91 (dd, J = 6.5 Hz, J = 1.5 Hz, 2H, H_{Ar}), 11.94 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 111.0 (CH), 120.6 (CH), 123.0 (C_{aro}), 124.6 (CH), 127.6 (2CH), 136.8 (C_{aro}), 142.8 (2CH), 143.5 (C_{aro}), 146.6 (CH), 170.8 (CO).

5.1.12. General procedure for the synthesis of compounds ***37–42***

To $CHCl_3$ (15 mL) were added 3-(2-alkyl or cycloalkylaminoethyl)-3H-benzothiazol-2-one (1.1 mmol) and chlorosulfonic acid (0.3 mL, 5.8 mmol). The reaction mixture was refluxed for 1 h. After cooling the mixture, the corresponding arylamine (3.5 mmol) and Et_3N (1.2 mL, 8.1 mmol) were added and the mixture stirred at 20 °C for 1 h. An aqueous solution of 1% sodium hydroxide (100 mL) was added. The solution was extracted with dichloromethane, and the organic layer evaporated under reduced pressure. The product was purified by chromatography on silica gel using dichloromethane/methanol (98/2, v/v). The product was solubilised in dry ethyl acetate and treated with gaseous hydrochloric acid in diethyl ether (20 mL). The precipitate obtained was filtered and washed with ethyl acetate (2 × 20 mL) to afford desired compound.

5.1.12.1. 3-(2-Dimethylaminoethyl)-2-oxo-2,3-dihydro-benzothiazole-6-sulfonic acid phenylamide hydrochloride ***37****.* Yield 26%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.83 (d, J = 2.8 Hz, 6H, $N(CH_3)_2$), 3.37 (m, 2H, NCH_2), 4.37 (t, J = 6.8 Hz, 2H, NCH_2), 7.02 (tt, J = 7.3 Hz, J = 1.1 Hz, 1H, H_{Ar}), 7.15 (dd, J = 8.4 Hz, J = 1.1 Hz, 2H, H_{Ar}), 7.24 (dd, J = 8.4 Hz, J = 7.3 Hz, 2H, H_{Ar}), 7.71 (d, J = 8.7 Hz, 1H, H_4), 7.78 (dd, J = 8.7 Hz, J = 1.9 Hz, 1H, H_5), 8.23 (d, J = 1.9 Hz, 1H, H_7), 10.49 (s, 1H, NH), 10.74 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 38.1 (CH_2), 42.6 (2 CH_3), 53.2 (CH_2), 112.4 (CH), 120.2 (2 CH), 122.6 (CH), 123.1 (C_{aro}), 124.4 (CH), 125.8 (CH), 129.7 (2 CH), 134.9 (C_{aro}), 138.1 (C_{aro}), 140.1 (C_{aro}), 170.3 (CO). LCMS (ESI^+): calc for [M+H^+]: 378.1; found: 377.8.

5.1.12.2. 2-Oxo-3-(2-pyrrolidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid phenylamide hydrochloride ***38****.* Yield 6%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80 (m, 2H, 2 CH_2), 2.00 (m, 2H, 2 CH_2), 3.06 (m, 2H, 2 NCH_2), 3.46 (m, 2H, NCH_2), 3.57 (m, 2H, 2 NCH_2), 4.34 (t, J = 6.5 Hz, 2H, NCH_2), 7.02 (tt, J = 7.2 Hz, J = 1.3 Hz, 1H, H_{Ar}), 7.14 (dd, J = 8.6 Hz, J = 1.3 Hz, 2H, H_{Ar}), 7.24 (dd, J = 8.6 Hz, J = 7.2 Hz, 2H, H_{Ar}), 7.68 (d, J = 8.6 Hz, 1H, H_4), 7.77 (dd, J = 8.6 Hz, J = 1.9 Hz, 1H, H_5), 8.23 (d, J = 1.9 Hz, 1H, H_7), 10.45 (s, 1H, NH), 10.76 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.1 (2 CH_2), 39.2 (CH_2), 50.6 (CH_2), 53.6 (2 CH_2), 112.3 (CH), 120.1 (2 CH), 122.6 (CH), 123.2 (C_{aro}), 124.4 (CH), 125.7 (CH), 129.7 (2 CH), 134.8 (C_{aro}), 138.1 (C_{aro}), 140.2 (C_{aro}), 170.3 (CO). LCMS (ESI^+): calc for [M+H^+]: 404.1; found: 404.0.

5.1.12.3. 2-Oxo-3-(2-piperidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid phenylamide hydrochloride ***39****.* Yield 8%; mp > 240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.36 (m, 1H, CH_2), 1.62–1.86 (m, 5H, 3CH_2), 2.93 (m, 2H, 2 NCH_2), 3.29 (m, 2H, NCH_2), 3.53 (m, 2H, 2 NCH_2), 4.40 (t, J = 7.0 Hz, 2H, NCH_2), 7.01 (tt, J = 7.2 Hz, J = 1.2 Hz, 1H, H_{Ar}), 7.14 (m, 2H, H_{Ar}), 7.23 (m, 2H, H_{Ar}), 7.71–7.80 (m, 2H, H_4, H_5), 8.22 (m, 1H, H_7), 10.45 (s, 1H, NH), 10.58 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.7 (CH_2), 22.8 (2 CH_2), 37.6 (CH_2), 52.2 (CH_2), 52.5 (2 CH_2), 112.3 (CH), 120.1 (2 CH), 122.6 (CH), 123.1 (C_{aro}), 124.4 (CH), 125.8 (CH), 129.7 (2 CH), 134.9

(C_{aro}), 138.1 (C_{aro}), 140.1 (C_{aro}), 170.2 (CO). LCMS (ESI^-): calc for [$M-H^+$]: 416.1; found: 416.1.

5.1.12.4. 3-(2-Dimethylaminoethyl)-2-oxo-2,3-dihydro-benzothiazole-6-sulfonic acid naphthylamide hydrochloride ***40***. Yield 7%; mp > 240 °C; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.62 (m, 6H, $N(CH_3)_2$), 3.10 (m, 2H, NCH_2), 4.25 (t, $J = 5.6$ Hz, 2H, NCH_2), 7.16 (dd, $J = 7.4$ Hz, $J = 1.0$ Hz, 1H, H_{Ar}), 7.39 (dd, $J = 8.2$ Hz, $J = 7.4$ Hz, 1H, H_{Ar}), 7.42 - 7.53 (m, 2H, H_{Ar}), 7.58 (d, $J = 8.5$ Hz, 1H, H_4), 7.71 (dd, $J = 8.5$ Hz, $J = 1.9$ Hz, 1H, H_5), 7.78 (dd, $J = 8.2$ Hz, $J = 1.0$ Hz, 1H, H_{Ar}), 7.89 (m, 1H, H_{Ar}), 8.07 (m, 1H, H_{Ar}), 8.10 (d, $J = 1.9$ Hz, 1H, H_7), 10.35 (m, 2H, NH, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 39.0 (CH_2), 43.7 (2 CH_3), 54.3 (CH_2), 112.1 (CH), 122.5 (CH), 122.9 (C_{aro}), 123.3 (CH), 123.6 (CH), 125.9 (CH), 126.0 (CH), 126.5 (CH), 126.7 (CH), 127.1 (CH), 128.4 (CH), 129.8 (C_{aro}), 132.8 (C_{aro}), 134.4 (C_{aro}), 135.2 (C_{aro}), 140.2 (C_{aro}), 170.2 (CO). LCMS (ESI^+): calc for [$M+H^+$]: 428.1; found: 428.0.

5.1.12.5. 2-Oxo-3-(2-pyrrolidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid naphthylamide hydrochloride ***41***. Yield 7%; mp > 240 °C; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.80 (m, 2H, 2 CH_2), 2.00 (m, 2H, 2 CH_2), 3.06 (m, 2H, 2 NCH_2), 3.46 (m, 2H, NCH_2), 3.57 (m, 2H, 2 NCH_2), 4.35 (t, $J = 6.4$ Hz, 2H, NCH_2), 7.17 (d, $J = 7.4$ Hz, 1H, H_{Ar}), 7.40 (dd, $J = 8.2$ Hz, $J = 7.4$ Hz, 1H, H_{Ar}), 7.46–7.54 (m, 2H, H_{Ar}), 7.65 (d, $J = 8.6$ Hz, 1H, H_4), 7.74 (dd, $J = 8.6$ Hz, $J = 1.8$ Hz, 1H, H_5), 7.79 (d, $J = 8.2$ Hz, 1H, H_{Ar}), 7.90 (m, 1H, H_{Ar}), 8.11 (m, 1H, H_{Ar}), 8.14 (d, $J = 1.8$ Hz, 1H, H_7), 10.35 (s, 1H, NH), 10.72 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.1 (2 CH_2), 39.2 (CH_2), 50.6 (CH_2), 53.7 (2 CH_2), 112.1 (CH), 122.6 (CH), 123.1 (C_{aro}), 123.1 (CH), 123.6 (CH), 125.9 (CH), 126.0 (CH), 126.6 (CH), 126.7 (CH), 127.1 (CH), 128.4 (CH), 129.8 (C_{aro}), 132.8 (C_{aro}), 134.4 (C_{aro}), 135.4 (C_{aro}), 140.0 (C_{aro}), 170.4 (CO). LCMS (ESI^+): calc for [$M+H^+$]: 454.1; found: 454.0.

5.1.12.6. 2-Oxo-3-(2-piperidin-1-ylethyl)-2,3-dihydro-benzothiazole-6-sulfonic acid naphthylamide hydrochloride ***42***. Yield 5%; mp 172–174 °C; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.36 (m, 1H, CH_2), 1.71 (m, 1H, CH_2), 1.74–1.86 (m, 4H, 2 CH_2), 2.95 (m, 2H, 2 NCH_2), 3.30 (m, 2H, NCH_2), 3.53 (m, 2H, 2 NCH_2), 4.43 (t, $J = 7.0$ Hz, 2H, NCH_2), 7.17 (d, $J = 7.3$ Hz, 1H, H_{Ar}), 7.40 (dd, $J = 8.3$ Hz, $J = 7.3$ Hz, 1H, H_{Ar}), 7.46–7.54 (m, 2H, H_{Ar}), 7.75 (dd, $J = 8.6$ Hz, $J = 1.6$ Hz, 1H, H_5), 7.77 (d, $J = 8.6$ Hz, 1H, H_4), 7.79 (d, $J = 8.3$ Hz, 1H, H_{Ar}), 7.90 (m, 1H, H_{Ar}), 8.12 (m, 1H, H_{Ar}), 8.13 (d, $J = 1.6$ Hz, 1H, H_7), 10.38 (br s, 1H, NH), 10.84 (m, 1H, NH^+). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.7 (CH_2), 22.8 (2 CH_2), 37.5 (CH_2), 52.2 (CH_2), 52.5 (2 CH_2), 112.2 (CH), 122.7 (CH), 123.0 (C_{aro}), 123.1 (CH), 123.6 (CH), 126.0 (2 CH), 126.6 (CH), 126.7 (CH), 127.1 (CH), 128.4 (CH), 129.8 (C_{aro}), 132.8 (C_{aro}), 134.4 (C_{aro}), 135.4 (C_{aro}), 140.0 (C_{aro}), 170.2 (CO). LCMS (ESI^+): calc for [$M+H^+$]: 468.1; found: 468.1.

5.2. In vitro testing

5.2.1. Pharmacological characterisation of drugs on 5-HT_6 receptors

Drugs were evaluated on the basis of their possibility to compete for the binding of [^3H]-LSD on membranes of HEK-293 cells transiently expressing the human 5-HT_6 receptors (ref. RBHS6M, Perkin Elmer) according to Monsma et al. [34]. In brief, 4 μg of protein was incubated at 37 °C for 60 min in duplicate in the absence or the presence of 10^{-7} M of each drug and 2.5 nM [^3H]-LSD (ref. NET638250UC, Perkin Elmer), in 50 mM Tris–HCl buffer (pH 7.4) supplemented with 10 mM $MgCl_2$ and 0.5 mM EDTA. At the end of the incubation, the homogenates were then filtered through Whatman GF/C filters and washed five times with ice-cold 50 mM Tris–HCl buffer. Non-specific binding was evaluated in the presence of 100 μM serotonin. Radioactivity associated with proteins was then quantified and expressed as the percentage of inhibition of the drugs under study.

The method was validated from saturation studies: 6 concentrations of [^3H]-LSD were used to give final concentrations of 0.25–8 nM, and non-specific binding of [^3H]-LSD was defined in the presence of 100 μM serotonin to determine the Kd and the Bmax.

5.2.2. Cell culture and cytotoxicity assay

The human neuroblastoma cell line (SY5Y) was cultured in DMEM (Dulbecco's Modified Eagle Medium) (Gibco) supplemented with 2 mM L-glutamine, 172 μM streptomycin, 100 IU/mL penicillin, 1 mM non-essential amino acids and 10% (v/v) heat-inactivated foetal bovine serum (Sigma Aldrich), and grown at 37 °C in a humidified incubator with 5% CO_2.

Cells were seeded at 2000 cells per well onto 96-well plates in DMEM medium. Cells were starved for 24 h to obtain synchronous cultures, and were then incubated in culture medium that contained various concentrations of test compounds, each dissolved in less than 0.1% DMSO. After 72 h of incubation, cell growth was estimated by the colorimetric MTT (thiazolyl blue tetrazolium bromide) assay.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.01.052.

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