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Original article

Novel sulfonylurea derivatives as H_3 receptor antagonists. Preliminary SAR studies

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ABSTRACT

The combination of antagonism at histamine H_3 receptor and the stimulation of insulin secretion have been proposed as an approach to new dual therapeutic agents for the treatment of type 2 diabetes mellitus associated with obesity. We have designed and synthesized a new series of non-imidazole derivatives, based on a basic amine ring connected through an alkyl spacer of variable length to a phenoxysulfonylurea moiety. These compounds were initially evaluated for histamine H_3 receptor binding affinities, suggesting that a propoxy chain linker between the amine and the core ring could be essential for optimal binding affinity. Compound **56**, 1-(naphthalen-1-yl)-3-[(*p*-(3-pyrrolidin-1-ylpropoxy) benzene)]sulfonylurea exhibited the best H_3 antagonism affinity. However, since all these derivatives failed to block K_{ATP} channels, the link of these two related moieties should not be considered a good pharmacophore for obtaining new dual H_3 antagonists with insulinotropic activity, suggesting the necessity to propose a new chemical hybrid prototype.

1. Introduction

Obesity is one of today's major health problems, affecting 400 million people throughout the world. Its alarming rising prevalence and the health risks associated with this disease warrant obesity as one of the most challenging therapeutic areas in the 21st century. Closely linked to obesity is the wide spread increase of type 2 diabetes [1], emerging as a new epidemic: diabesity [2]. The lack of efficacious drugs for this new disease makes this field one of the most attractive targets.

The histamine H_3 receptor has been known to play a critical role in homeostasis regulatory functions, such as control of food intake and maintenance of body weight [3]. The histamine H_3 receptor is an important G protein-coupled receptor, identified in 1983 by Arrang *et. al.* [4] and cloned and characterized in 1999 [5]. The histamine H_3 receptor has been described as a presynaptic autoreceptor [6–8] mainly expressed in the central nervous system (CNS), regulating histamine biosynthesis and release, as well as a heteroreceptor on non-histaminergic neurons, where it is capable of inhibiting the release of other important neurotransmitters, such as acetylcholine, noradrenaline, dopamine and serotonin [6,9–11]. The blockade of this negative feedback mechanism with histamine H_3 receptor antagonists/inverse agonists suggests that they would be useful for the treatment of a variety of CNS disorders affecting cognition, sleep and energy homeostasis [12].

Many classes of potent H_3 receptor antagonists have been reported in the reference literature. Imidazole-based compounds such as ciproxifan, clobenpropit, thioperamide and SCH79687 [13–16] were the first published H_3 receptor antagonists/inverse agonists derived from the endogenous neurotransmitter histamine and containing the classical structure in the form of an imidazole ring connected by a spacer to a polar group, which is attached to a lipophilic end group [17]. The potential liability of imidazole-containing compounds with respect to cytochrome P450 inhibition and drug–drug interactions led to the development of potent and selective non-imidazole derivatives, including compounds such ABT-239, UCL 1972, JNJ-5207852, GSK-189254, Novo Nordisk's and Merck's (Fig. 1) [18–22]. These intense efforts made by numerous pharmaceutical companies led to the development of a new refined H_3 antagonist pharmacophore model which contains three parts: a basic amine moiety (western part) able to interact with ASP3.32, an amino acid of the receptor [23], linked via a variable alkyl spacer to a central core, and an additional eastern part displaying a high chemical diversity (Fig. 2) [24]. A chemical template containing these structural features is depicted by the generic structure (Fig. 2), based on a phenoxyalkylamine skeleton, common to the many reported non-imidazole H_3 antagonists shown in Fig. 1.

Stimulation of glucose-mediated insulin secretion has been the first pharmacological approach for the treatment of type 2 diabetes [25], heralded by the introduction of sulfonylureas in the antidiabetic pharmacopoeia more than 50 years ago. The sulfonylurea

Abbreviations: N.T., Not Tested; SEM, standard error of the media.

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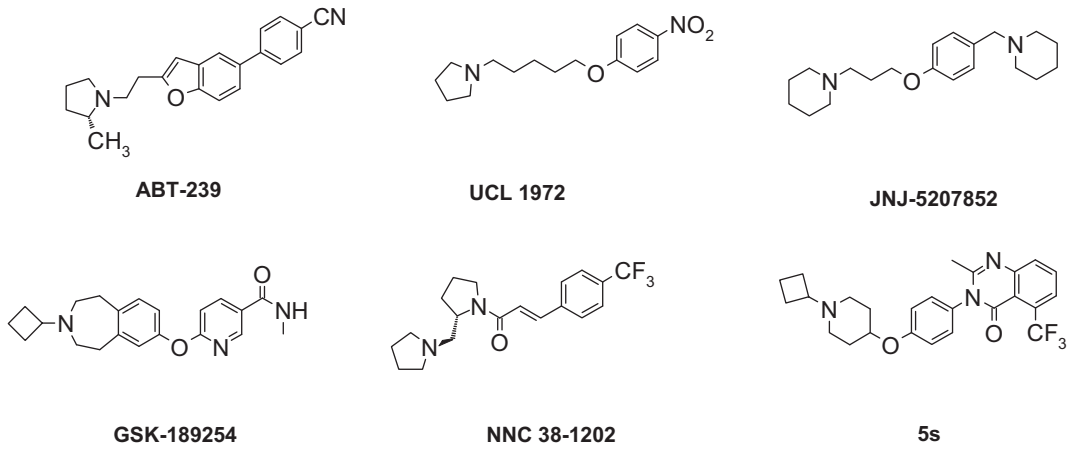


Fig. 1. Non-imidazole histamine H_3 receptor antagonists/inverse agonists.

receptor-1 (SUR1) is the molecular target for the sulfonylurea class of anti-hyperglycemic drugs such as chlorpropamide [26], glipizide [27], glimepiride [28], which have been widely used in the treatment of type 2 diabetes mellitus and are maintained as the front-line therapy in the most recent 2005 IDF Global Guidelines for Type 2 Diabetes [29] (Fig. 3). These compounds are antagonists of the β-cell ATP-dependent K^+ channel (K_{ATP}) and they promote insulin secretion. All of them share a phenylsulfonylurea group with *para*-substitution on the phenyl ring in their structure. Therefore, this sulfonylurea moiety was incorporated into our molecules with the goal of providing antagonism of K_{ATP} channels and anti-diabetic activity.

These observations suggested to us that the combination of H_3 receptor antagonism and the stimulation of insulin secretion might result in synergistic improvements in type 2 diabetes associated with obesity. In this report, we describe our initial hit-finding proposal towards new pharmacodynamic hybrids with dual mechanisms of action. Our strategy towards these dual acting compounds was the multiple target approach designing one new drug by combining two related pharmacophore elements in one structure (Fig. 4). This approach has been carried out by linking the known H_3R antagonist template to a phenylsulfonylurea moiety (sulfonylurea drug structure related to the insulinotropic effect).

Based on this strategy and as part of our ongoing program to develop new anti-obesity drugs, we report the synthesis, human H_3 and K_{ATP} channel binding affinities and preliminary SAR of several members of this novel series of non-imidazole derivatives.

Historically, many of the reported H_3 antagonists have shown substantial hERG channel inhibition which represents a potential safety liability [30,31]. Drugs that block hERG have been associated with QT interval prolongation as well as serious, and sometimes fatal, cardiac arrhythmias (including torsade de pointes) [32]. Blockade of the hERG channel poses a risk of cardiac toxicity and has become a critical issue for regulatory agencies and the pharmaceutical industry [33]. This problem has recently been addressed [34]. In an attempt to overcome hERG channel inhibition related to H_3 antagonists, we decided to evaluate all of the synthesized compounds for the hERG ion channel inhibitory affinity.

2. Chemistry

Forty-four sulfonylurea and ten sulfonamide derivatives were synthesized using the four-step protocol outlined in Scheme 1. Dropwise addition of chlorosulfonic acid to an ice-cooled solution of the corresponding bromoalkoxyphenyl derivatives (**1**–**3**) dissolved in dichloromethane (DCM) gave chlorosulfonyl compounds **4**–**6**, substituted only at the *para* position due to steric impediments *ortho* to the alkoxy group.

Conversion of derivatives **4**–**6** to the corresponding sulfonamides (**7**–**9**) was accomplished via treatment with ammonia in

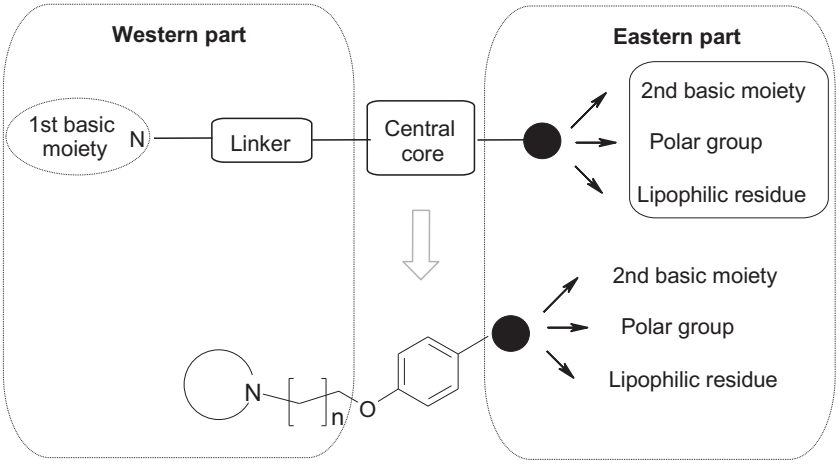


Fig. 2. The H_3 pharmacophore model and the derived chemical H_3 antagonist template based on a phenoxyalkylamine skeleton.

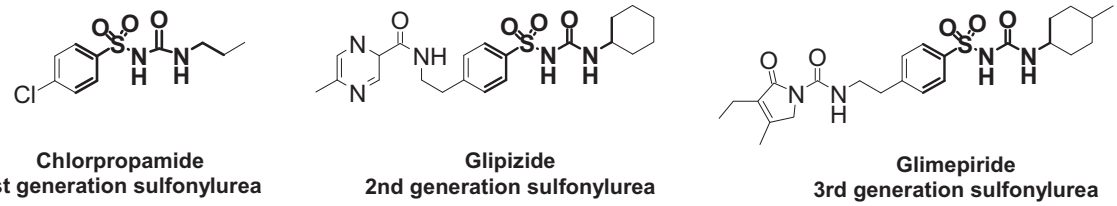


Fig. 3. Some selective sulfonylureas for the treatment of type 2 diabetes.

dichloromethane (DCM) at 0 °C. Condensation of amines with compounds **7**–**9** under reflux in ethanol (EtOH) provided compounds **10**–**19**. Treatment of the resulting sulfonamides with the appropriate isocyanates in acetone yielded the desired sulfonylurea derivatives **20**–**64**.

3. Results and discussion

The first objective of this preliminary study was to evaluate the synthesized compounds as H_3 receptor antagonists. Initially, we synthesized a series of sulfonylurea derivatives with five different substituents in the eastern part of the molecules in order to evaluate the influence of the substituent on the urea rest. The substituents were both aliphatic (isopropyl and cyclohexyl), and aromatic (phenyl, 2,5-dichlorophenyl and 4-trifluoromethylphenyl). At the same time, a series of sulfonamide derivatives was obtained as the precursors of the sulfonylurea compounds. The *in vitro* H_3 receptor binding data for these compounds is summarized in Tables 1 and 2.

In general, compounds with an aromatic moiety for R exhibited lower IC_{50} values than the aliphatic substituents, as exemplified by entries **20** versus **21** and **31** versus **32**. Among all of the aromatic derivatives tested, compounds **32** and **37** were the most potent sulfonylureas, with $IC_{50} = 0.16$ and 0.83 μM, respectively, at H_3R.

Introduction of a propoxy chain linker between the basic amine (pyrrolidine and piperidine) and the core ring led to an increase in the H_3 affinity (compounds **32** and **37**). The shortening or lengthening of the chain linker resulted in a significant loss of affinity (compounds **21** and **43** vs. **32**). Introduction of an ethoxycarbonyl group on the cyclic amine showed a dramatic loss of affinity.

Use of either pyrrolidine or piperidine as the basic amine on the western part of molecule provided similar H_3 affinity, as demonstrated by compounds **32** and **37**.

The sulfonamide intermediates, compounds **10**–**19**, were first screened as an early proof-of-concept. Many of these derivatives, as well as their aromatic sulfonylurea derivatives, displayed good affinity as H_3 receptor antagonists. Although good H_3 receptor affinity was observed with sulfonamides **10**–**19**, we were more interested in compounds containing a sulfonylurea group since these compounds have the potential for anti-diabetic activity.

In an attempt to improve the H_3R *in vitro* affinity, further analogs of the propoxy phenylsulfonylurea **32** and **37** were examined, introducing different aromatic rests as R. The SAR of compounds **53**–**64** is summarized in Table 3.

In general, compounds having a *para*-substituted phenyl group in R showed better affinity to the human histamine H_3 receptor than the corresponding *meta* and *ortho*-substituted phenyl analogs. The 4-trifluoromethylphenyl analog (compound **40**) was significantly more potent than compound **59** (10.40 μM) and **60** (20.90 μM) (6–12-fold improvement in potency).

Comparing the different electronic effects caused by the substituents on the phenyl rest, no substantial differences were observed. Steric effect seems to be more important for these compounds.

Compound **56**, substituted with a 1-naphthyl group, was the most potent sulfonylurea for the H_3 receptor with an $IC_{50} = 0.08$ μM.

In addition, we examined the effects of these synthesized compounds on the ATP-sensitive K^+ channel (K_{ATP}) channel. Unfortunately, no K_{ATP} channel blocker activity was observed. Therefore, these compounds are unlikely to play a role in the stimulation of insulin secretion from pancreatic β-cells and consequently, we are not able to assert that they could exert insulinotropic activity.

Furthermore, in the [^{3}H]dofetilide membrane binding assay, all of the sulfonylureas exhibited low affinity for the hERG channel. In addition, we have observed that the sulfonylureas have less hERG affinity than the corresponding sulfonamides.

In summary, in an approach to finding new dual therapeutic agents for the treatment of type 2 diabetes associated with obesity, we have designed and synthesized a new series of non-imidazole H_3 antagonists, based on a basic amine ring connected through an alkyl spacer of variable length to a phenoxysulfonylurea moiety. SAR was explored, indicating that a propoxy chain linker between the amine and an aromatic ring is optimal in the binding to the H_3 receptor. Compound **56**, 1-(naphthalen-1-yl)-3-(*p*-(3-pyrrolidin-1-ylpropoxy)benzene)sulfonylurea, exhibited the best H_3 antagonism affinity. However, since all these derivatives did not block K_{ATP} channels, the combination of these two related moieties should not be considered a good pharmacophore for obtaining new dual H_3 antagonists with insulinotropic activity, suggesting the necessity to propose a new chemical hybrid prototype.

4. Experimental protocols

4.1. General methods

All reagents and solvents were purchased from commercial sources. E. Merck (Darmstadt, Germany), Scharlau (F E R.O.S.A., Barcelona, Spain), Panreac Química S.A. (Montcada i Reixac,

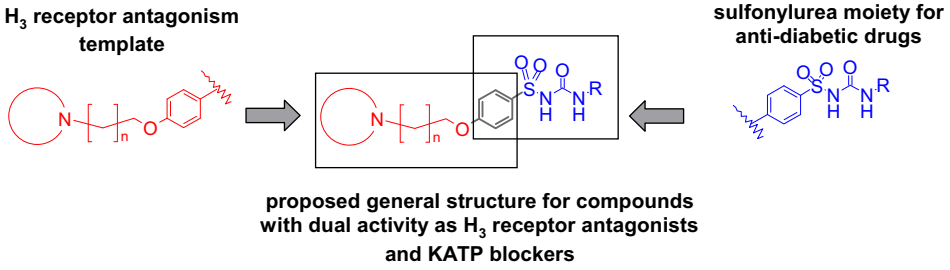
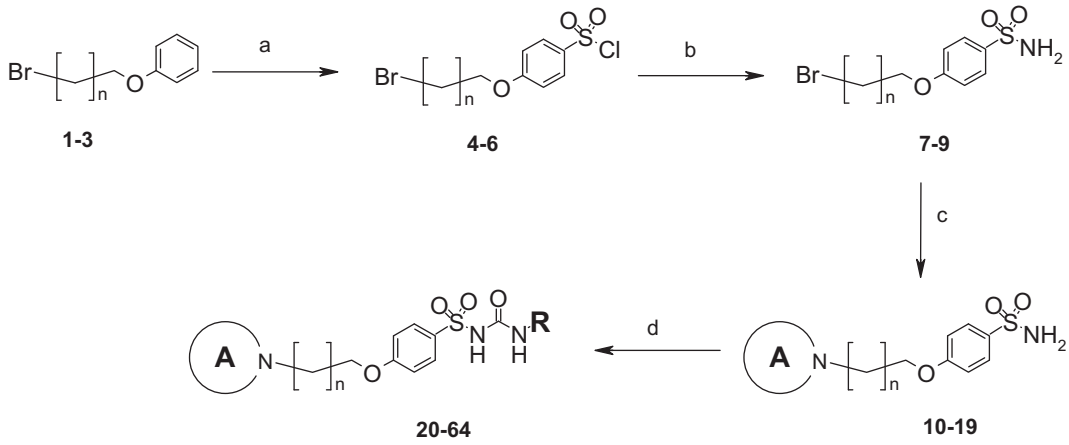


Fig. 4. Drug design of the general structure for a new dual H_3 receptor antagonist and K_{ATP} channel inhibitor.



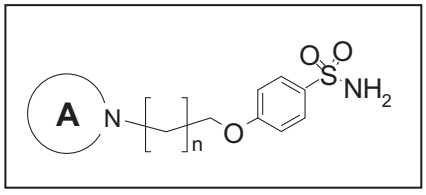
Scheme 1. Reagents and conditions: (a) chlorosulfonic acid, DCM, −10 °C, 2 h, 60%; (b) NH_3, DCM, 0 °C, 1 h, 78%; (c) pyrrolidine, EtOH, reflux, 20 h, 86%; (d) i) acetone, 10% NaOH, 10 min; ii) acetone, phenyl isocyanate, reflux, 4 h, 71% in two steps.

Barcelona, Spain), Sigma–Aldrich Química, S.A., (Alcobendas, Madrid), Acros Organics (Janssen Pharmaceuticalaan 3a, 2440 Geel, België), and Lancaster (Bischheim-Strasbourg, France).

Melting points were determined with a Mettler FP82 + FP80 apparatus (Greifense, Switzerland) and have not been corrected. The ^{1}H NMR spectra were recorded on a Bruker 400 Ultrashield™ (Bruker BioSpin GmbH, Rheinstetten, Germany), using TMS as the internal standard and DMSO-d_6 as the solvent; the chemical shifts (δ) are reported in ppm and the coupling constant (J) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), and m (multiplet). Infrared spectra (IR) were recorded on Thermo Nicolet FT-IR Nexus Euro (Madison, USA) using potassium bromide pellets for solid products and sodium chloride plates for oil products; the frequencies are expressed in cm^{-1}. Signal intensities are expressed by: vs (very strong), s (strong), m (medium), and w (weak). Elemental micro-analyses were obtained on an Elemental Analyzer LECO CHN-900 (Michigan, USA) from vacuum-dried samples. The analytical results for C, H, and N were within ±0.4 of the theoretical values. Mass spectra were measured on an Agilent Technologies Model MSD/DS 5973N (mod. G2577A) mass spectrometer with direct insertion probe (DIP) (Waldbronn, Germany) and the ionization method was electron impact (EI, 70 eV).

The progress of the reactions was followed by thin-layer chromatography and silica gel 60 (0.040–0.063 mm) Alugram® SIL G/UV254 (Layer: 0.2 mm) (Macherey–Nagel GmbH & Co. KG. Postfach 101352. D-52313 Düren, Germany). Flash column chromatography was carried out using flash silica gel (Merck, Germany).

Table 1
Binding affinities of sulfonamide derivatives (**10**–**19**) at histamine H_3 receptor and hERG channel.



Compound	n	A	H_3R IC_{50}[a] (μM) ± SEM	hERG IC_{50}[b] (μM)
10	1	pyrrolidine	7.06 ± 2.42	$>10^2$
11	1	piperidine	10.00 ± 8.96	24.00
12	1	ethyl piperidine-4-carboxylate	$>10^4$	22.90
13	2	pyrrolidine	0.25 ± 0.50	N.T.
14	2	piperidine	0.13 ± 0.33	93.20
15	2	ethyl piperidine-4-carboxylate	$>10^4$	76.50
16	2	morpholine	0.40	N.T.
17	3	pyrrolidine	0.70 ± 0.39	$>10^2$
18	3	piperidine	0.39 ± 0.14	13.60
19	3	ethyl piperidine-4-carboxylate	$>10^4$	18.80

SEM is the standard error of the mean. n is the number of experiments. N.T, not tested.

[a] All experiments were performed in duplicate ($n = 2$).

[b] hERG1(h)/[^{3}H]Dofetilide/HEK293 IC_{50} is the concentration of antagonist that displaces 50% of [^{3}H]Dofetilide in a competitive binding assay. All experiments were performed in duplicate ($n = 2$).

4.2. General procedure for the preparation of 4-(bromoalkoxy) benzenesulfonyl chloride derivatives (**4**–**6**)

Chlorosulfonic acid (20.00 mmol) was added dropwise to an ice-salt bath solution of the appropriate bromoalkoxyphenyl (**1**–**3**) (10.00 mmol) dissolved in dichloromethane (25 ml) at −10 °C. After stirring for 2 h, the reaction mixture was allowed to warm to room temperature, and was stirred for an additional hour. The reaction mixture was then poured into 200 g of cracked ice and extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure to afford the corresponding 4-(bromoalkoxy)benzenesulfonyl chloride derivatives (**4**–**6**).

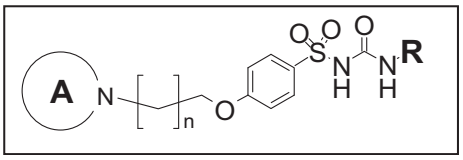
4.2.1. 4-(2-bromoethoxy)benzenesulfonyl chloride (**4**)

White solid. Yield: 60%. M.p.: 51–53 °C. IR (KBr, cm^{-1}): 1374 (s, ν_{SO2N}); 1258 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.70 (t, 2H, Br–**CH$_2$**, $J_{CH2-CH2}$ = 6.1 Hz); 4.42 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.1 Hz); 7.09 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 9.1 Hz); 8.02 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 9.0 Hz). Anal. Calcd for $C_8H_8BrClO_3S$: C, 32.06%; H, 2.67%; N, 0.00%. Found: C, 32.19%; H, 2.60%; N, 0.00%.

4.2.2. 4-(3-bromopropoxy)benzenesulfonyl chloride (**5**)

Rose solid. Yield: 62%. M.p.: 47–50 °C. IR (KBr, cm^{-1}): 1370 (vs, ν_{SO2N}); 1264 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.21–2.25 (m, 2H, Br–CH_2–C**H$_2$**); 3.64 (t, 2H, Br–C**H$_2$**, $J_{CH2-CH2}$ = 6.5 Hz); 4.07 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.0 Hz); 6.90 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.55 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz). Anal. Calcd for $C_9H_{10}BrClO_3S$: C, 34.46%; H, 3.19%; N, 0.00%. Found: C, 34.77%; H, 3.16%; N, 0.00%.

Table 2
Binding affinities of sulfonylurea derivatives (**20**–**52**) at histamine H_3 receptor and hERG channel.



Compound	n	A	R	H_3R IC_{50}[a] (μM) ± SEM	hERG IC_{50}[b] (μM)
20	1	pyrrolidine	isopropyl	$>10^5$	$>10^2$
21	1	pyrrolidine	phenyl	88.60 ± 3.40	$>10^2$
22	1	pyrrolidine	cyclohexyl	$>10^4$	$>10^2$
23	1	pyrrolidine	2,5-dichlorophenyl	$>10^4$	$>10^2$
24	1	pyrrolidine	4-trifluoromethylphenyl	107.00 ± 2.87	$>10^2$
25	1	piperidine	isopropyl	16.60 ± 6.36	26.10
26	1	piperidine	phenyl	10.00 ± 2.75	27.60
27	1	piperidine	cyclohexyl	53.80 ± 15.50	$>10^2$
28	1	piperidine	2,5-dichlorophenyl	93.60	$>10^2$
29	1	piperidine	4-trifluoromethylphenyl	82.00 ± 2.24	$>10^2$
30	1	ethyl piperidine-4-carboxylate	phenyl	77.90 ± 18.00	$>10^2$
31	2	pyrrolidine	isopropyl	13.40 ± 2.63	$>10^2$
32	2	pyrrolidine	phenyl	0.164 ± 0.24	N.T.
33	2	pyrrolidine	cyclohexyl	6.06 ± 0.62	$>10^2$
34	2	pyrrolidine	2,5-dichlorophenyl	8.31 ± 1.45	$>10^2$
35	2	pyrrolidine	4-trifluoromethylphenyl	16.50 ± 2.57	$>10^2$
36	2	piperidine	isopropyl	1.33 ± 0.52	$>10^2$
37	2	piperidine	phenyl	0.83 ± 0.004	$>10^2$
38	2	piperidine	cyclohexyl	N.T.	N.T.
39	2	piperidine	2,5-dichlorophenyl	2.57 ± 0.91	$>10^2$
40	2	piperidine	4-trifluoromethylphenyl	1.74 ± 0.08	$>10^2$
41	2	ethyl piperidine-4-carboxylate	phenyl	91.10 ± 6.53	78.70
42	3	pyrrolidine	isopropyl	19.60 ± 4.26	$>10^2$
43	3	pyrrolidine	phenyl	18.00 ± 5.20	$>10^2$
44	3	pyrrolidine	cyclohexyl	29.90 ± 4.49	$>10^2$
45	3	pyrrolidine	2,5-dichlorophenyl	17.50 ± 3.24	$>10^2$
46	3	pyrrolidine	4-trifluoromethylphenyl	22.60 ± 1.65	49.10
47	3	piperidine	isopropyl	18.50 ± 1.17	$>10^2$
48	3	piperidine	phenyl	4.85 ± 3.50	$>10^2$
49	3	piperidine	cyclohexyl	$>10^4$	$>10^2$
50	3	piperidine	2,5-dichlorophenyl	13.20 ± 5.62	$>10^2$
51	3	piperidine	4-trifluoromethylphenyl	10.00 ± 1.70	$>10^2$
52	3	ethyl piperidine-4-carboxylate	phenyl	$>10^5$	$>10^2$

SEM is the standard error of the mean. *n* is the number of experiments. N.T., not tested.
[a] All experiments were done in duplicate ($n = 2$).
[b] hERG1(h)/[^{3}H]Dofetilide/HEK293 IC_{50} is the concentration of antagonist that displaces 50% of [^{3}H]Dofetilide in a competitive binding assay. All experiments were done in duplicate ($n = 2$).

*4.2.3. 4-(4-bromobutoxy)benzenesulfonyl chloride (**6**)*

Beige oil. Yield: 56%. IR (NaCl, cm^{-1}): 1370 (s, ν_{SO2N}); 1261 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.03–2.10 (m, 4H, Br–CH_2–CH_2–**CH_2**); 3.52 (t, 2H, Br–**CH_2**, $J_{CH2-CH2} = 6.3$ Hz); 4.13 (t, 2H, O–**CH_2**, $J_{CH2-CH2} = 5.8$ Hz); 7.05 (d, 2H, **H_3**+**H_5**, $J_{3,5-2,6} = 9.0$ Hz); 7.99 (d, 2H, **H_2**+**H_6**, $J_{2,6-3,5} = 9.0$ Hz).

*4.3. General procedure for the preparation of 4-(bromoalkoxy) benzenesulfonamide derivatives (**7**–**9**)*

The corresponding 4-(bromoalkoxy)benzenesulfonyl chloride (**4**–**6**) (30.00 mmol) was dissolved in 80 ml of dichloromethane and cooled to 0 °C. Next, the reaction mixture was stirred under ammonia gas atmosphere for 45 min. The obtained precipitate was filtered off and the solvent was removed under vacuum to yield 4-(bromoalkoxy)benzenesulfonamide derivatives (**7**–**9**).

*4.3.1. 4-(2-bromoethoxy)benzenesulfonamide (**7**)*

White solid. Yield: 78%. M.p: 112–114 °C. IR (KBr, cm^{-1}): 3338 (vs, ν_{NH2}); 1388 (vs, ν_{SO2N}); 1296 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.83 (t, 2H, Br–**CH_2**, $J_{CH2-CH2} = 5.4$ Hz); 4.41 (t, 2H, O–**CH_2**, $J_{CH2-CH2} = 5.4$ Hz); 7.12 (d, 2H, **H_3**+**H_5**, $J_{3,5-2,6} = 8.9$ Hz); 7.22 (s, 2H, N**H_2**); 7.76 (d, 2H, **H_2**+**H_6**, $J_{2,6-3,5} = 8.9$ Hz). Anal. Calcd for $C_8H_{10}BrNO_3S$: C, 34.54%; H, 3.60%; N, 5.04%. Found: C, 34.42%; H, 3.36%; N, 4.69%.

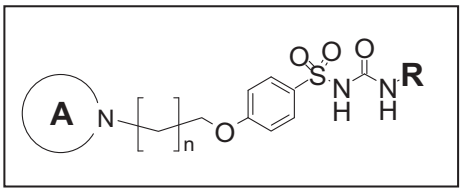
*4.3.2. 4-(3-bromopropoxy)benzenesulfonamide (**8**)*

White solid. Yield: 90%. M.p: 110–112 °C. IR (KBr, cm^{-1}): 3401 (m, ν_{NH2}); 1333 (vs, ν_{SO2N}); 1262 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.27 (q, 2H, Br–CH_2–**CH_2**, $J_{CH2-CH2} = 6.3$ Hz and $J_{CH2-CH2} = 6.2$ Hz); 3.68 (t, 2H, Br–**CH_2**, $J_{CH2-CH2} = 6.5$ Hz); 4.16 (t, 2H, O–**CH_2**, $J_{CH2-CH2} = 6.0$ Hz); 7.11 (d, 2H, **H_3**+**H_5**, $J_{3,5-2,6} = 8.8$ Hz); 7.22 (s, 2H, N**H_2**); 7.75 (d, 2H, **H_2**+**H_6**, $J_{2,6-3,5} = 8.8$ Hz). Anal. Calcd for $C_9H_{12}BrNO_3S$: C, 37.00%; H, 4.11%; N, 4.80%. Found: C, 37.10%; H, 3.98%; N, 4.70%.

*4.3.3. 4-(4-bromobutoxy)benzenesulfonamide (**9**)*

Beige oil. Yield: 66%. IR (NaCl, cm^{-1}): 3354 (vs, ν_{N-H}); 1321 (vs, ν_{SO2N}); 1251 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.97–2.12 (m, 4H, Br–CH_2–CH_2–**CH_2**); 3.61 (t, 2H, Br–**CH_2**, $J_{CH2-CH2} = 6.0$ Hz); 4.09 (t, 2H, O–**CH_2**, $J_{CH2-CH2} = 6.3$ Hz); 4.81 (s, 2H, N**H_2**); 7.08 (d, 2H, **H_3**+**H_5**, $J_{3,5-2,6} = 8.9$ Hz); 7.74 (d, 2H,

Table 3
Binding affinities of sulfonylurea derivatives (**53**–**64**) at histamine H_3 receptor and hERG channel.



Compound	n	A	R	H_3R IC_{50}[a] (μM) ± SEM	hERG IC_{50}[b] (μM)
53	2	pyrrolidine	3-trifluoromethylphenyl	11.80 ± 2.60	$>10^2$
54	2	pyrrolidine	4-acetylphenyl	0.40	$>10^2$
55	2	pyrrolidine	4-methylphenyl	0.32	$>10^2$
56	2	pyrrolidine	1-naphthyl	0.08	$>10^2$
57	2	pyrrolidine	4-(dimethylamino)-phenyl	0.50	$>10^2$
58	2	pyrrolidine	benzhydryl	0.50	N.T.
59	2	piperidine	2-trifluoromethylphenyl	10.40 ± 1.12	$>10^2$
60	2	piperidine	3-trifluoromethylphenyl	20.90 ± 0.97	N.T.
61	2	piperidine	4-methoxyphenyl	29.80 ± 1.19	$>10^2$
62	2	piperidine	4-acetylphenyl	0.32	$>10^2$
63	2	piperidine	4-methylphenyl	0.40	$>10^2$
64	2	piperidine	benzhydryl	0.50	$>10^2$

SEM is the standard error of the mean. *n* is the number of experiments. N.T., no tested.
[a] All experiments were done in duplicate ($n = 2$).
[b] hERG1(h)/[^{3}H]Dofetilide/HEK293 IC_{50} is the concentration of antagonist that displaces 50% of [^{3}H]Dofetilide in a competitive binding assay. All experiments were done in duplicate ($n = 2$).

H_2+**H_6**, $J_{2,6\text{-}3,5} = 8.9$ Hz). Anal. Calcd for $C_{10}H_{14}BrNO_3S$: C, 38.96%; H, 4.54%; N, 4.54%. Found: C, 39.02%; H, 4.41%, N, 4.45%

4.4. General procedure for the preparation of 4-(amine alkoxy) benzenesulfonamide derivatives (**10**–**19**)

The appropriate amine (31.50 mmol) was added to the corresponding 4-(bromoalkoxy)benzenesulfonamide (**7**–**9**) (9.00 mmol) dissolved in 25 ml of ethanol. The mixture reaction was heated under reflux for 20 h. The solvent was removed under reduced pressure and the obtained residue was dissolved in dichloromethane and quenched with water. The organic phase was dried with anhydrous sodium sulfate and filtered. The solvent was removed in vacuo and the resultant solid was precipitated with diethyl ether in order to obtain 4-(amine alkoxy)benzenesulfonamide derivatives (**10**–**19**).

4.4.1. 4-[(2-(pyrrolidin-1-yl)ethoxy)]benzenesulfonamide (**10**)

White solid. Yield: 86%. M.p: 130–135 °C. IR (KBr, cm^{-1}): 3299 (m, ν_{N-H}); 1321 and 1154 (vs, ν_{SO2N}); 1262 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.58–1.69 (m, 4H, **H_3**+**H_4**-pyr); 2.49–2.54 (m, 4H, **H_2**+**H_5**-pyr); 2.80 (t, 2H, N–C**H_2**, $J_{CH2-CH2} = 6.0$ Hz); 4.15 (t, 2H, O–C**H_2**, $J_{CH2-CH2} = 6.0$ Hz); 6.96 (d, 2H, **H_3**+**H_5**, $J_{3,5\text{-}2,6} = 8.9$ Hz); 7.20 (s, 2H, N**H_2**); 7.85 (d, 2H, **H_2**+**H_6**, $J_{2,6\text{-}3,5} = 8.9$ Hz). Anal. Calcd for $C_{12}H_{18}N_2O_3S \cdot \frac{1}{2} H_2O$: C, 51.61%; H, 6.81%; N, 10.03%. Found: C, 52.00%; H, 6.73%; N, 9.79%.

4.4.2. 4-[(2-(piperidin-1-yl)ethoxy)]benzenesulfonamide (**11**)

White solid. Yield: 64%. M.p: 139–141 °C. IR (KBr, cm^{-1}): 3292 (m, ν_{N-H}); 1326 and 1146 (s, ν_{SO2N}); 1257 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.39 (t, 2H, **H_4**-pip); 1.47–1.52 (m, 4H, **H_3**+**H_5**-pip); 2.41–2.45 (m, 4H, **H_2**+**H_6**-pip); 2.67 (t, 2H, N–C**H_2**, $J_{CH2-CH2} = 5.9$ Hz); 4.14 (t, 2H, O–C**H_2**, $J_{CH2-CH2} = 5.9$ Hz); 7.09 (d, 2H, **H_3**+**H_5**, $J_{3,5\text{-}2,6} = 8.9$ Hz); 7.21 (bs, 2H, N**H_2**); 7.73 (d, 2H, **H_2**+**H_6**, $J_{2,6\text{-}3,5} = 8.9$ Hz). Anal. Calcd for $C_{13}H_{20}N_2O_3S \cdot 2/3H_2O$: C, 52.70%; H, 7.09%; N, 9.46%. Found: C, 52.57%; H, 6.64%; N, 9.08%.

4.4.3. 4-{2-[(4-ethoxycarbonyl)piperidin-1-yl]ethoxy} benzenesulfonamide (**12**)

White solid. Yield: 85%. M.p: 129–132 °C. IR (KBr, cm^{-1}): 3296 (s, ν_{N-H}); 1727 (vs, $\nu_{C=O}$); 1327 and 1156 (vs, ν_{SO2N}); 1260 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.17 (t, 3H, C**H_3**, $J_{CH3-CH2} = 7.1$ Hz); 1.51–1.61 (m, 2H, **H_{3eq}**+**H_{5eq}**-pip); 1.79 (d, 2H, **H_{3ax}**+**H_{5ax}**-pip); 2.11 (t, 2H, **H_{2eq}**+**H_{6eq}**-pip); 2.24–2.31 (m, 1H, **H_4**-pip); 2.69 (t, 2H, N–C**H_2**, $J_{CH2-CH2} = 5.8$ Hz); 2.87 (d, 2H, **H_{2ax}**+**H_{6ax}**-pip); 4.06 (q, 2H, CH_3-C**H_2**, $J_{CH2-CH3} = 7.1$ Hz); 4.14 (t, 2H, O–C**H_2**, $J_{CH2-CH2} = 5.8$ Hz); 7.09 (d, 2H, **H_3**+**H_5**, $J_{3,5\text{-}2,6} = 8.8$ Hz); 7.20 (s, 2H, N**H_2**); 7.74 (d, 2H, **H_2**+**H_6**, $J_{2,6\text{-}3,5} = 8.7$ Hz). Anal. Calcd for $C_{16}H_{24}N_2O_5S$: C, 53.93%; H, 6.74%; N, 7.86%. Found: C, 53.90%; H, 6.82%; N, 7.57%.

4.4.4. 4-[(3-(pyrrolidin-1-yl)propoxy)]benzenesulfonamide (**13**)

White solid. Yield: 55%. M.p: 163–165 °C. IR (KBr, cm^{-1}): 3293 (s, ν_{N-H}); 1255 (s, ν_{C-O-C}); 1153 (vs, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.67 (d, 4H, **H_3**+**H_4**-pyr); 1.89 (bs, 2H, N–CH_2–**CH_2**); 2.40–2.45 (m, 4H, **H_2**+**H_5**-pyr); 2.51–2.55 (m, 2H, N–C**H_2**); 4.09 (t, 2H, O–C**H_2**, $J_{CH2-CH2} = 5.9$ Hz); 7.07 (d, 2H, **H_3**+**H_5**, $J_{3,5\text{-}2,6} = 8.9$ Hz); 7.19 (s, 2H, N**H_2**); 7.74 (d, 2H, **H_2**+**H_6**, $J_{2,6\text{-}3,5} = 8.9$ Hz) ppm. Anal. Calcd for $C_{13}H_{20}N_2O_3S \cdot 1/6H_2O$: C, 54.35%; H, 6.97%; N, 9.75%. Found: C, 54.49%; H, 6.93%; N, 9.44%. MS (EI, 70eV): *m*/*z* (%) = 284 ($[M^{\cdot}]^+$, 10); 110 (5); 84 (100).

4.4.5. 4-[(3-(piperidin-1-yl)propoxy)]benzenesulfonamide (**14**)

Beige solid. Yield: 83%. M.p: 160–162 °C. IR (KBr, cm^{-1}): 3288 (m, ν_{N-H}); 1325 and 1158 (vs, ν_{SO2N}); 1255 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.38 (d, 2H, **H_4**-pip); 1.47–1.52 (m, 4H, **H_3**+**H_5**-pip); 1.84–1.90 (m, 2H, N–CH_2–**CH_2**); 2.34–2.40 (m, 6H, **H_2**+**H_6**-pip and N–C**H_2**); 4.07 (t, 2H, O–C**H_2**, $J_{CH2-CH2} = 6.4$ Hz); 7.08 (d, 2H, **H_3**+**H_5**, $J_{3,5\text{-}2,6} = 6.8$ Hz); 7.19 (bs, 2H, N**H_2**); 7.72–7.74 (m, 2H, **H_2**+**H_6**). Anal. Calcd for $C_{14}H_{22}N_2O_3S$: C, 56.38%; H, 7.38%; N, 9.40%. Found: C, 56.61%; H, 7.21%; N, 9.01%. MS (EI, 70eV): *m*/*z* (%) = 298 ($[M^{\cdot}]^+$, 14); 124 (5); 113 (2); 98 (100).

4.4.6. 4-{3-[(4-ethoxycarbonyl)piperidin-1-yl]propoxy} benzenesulfonamide (**15**)

White solid. Yield: 96%. M.p: 153–155 °C. IR (KBr, cm^{-1}): 3326 (m, ν_{N-H}); 1727 (vs, $\nu_{C=O}$); 1327 (vs, ν_{SO2N}); 1260 (s, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.17 (t, 3H, C**H**$_3$, $J_{CH3-CH2} = 7.1$ Hz); 1.55 (t, 2H, N–CH_2–**CH**$_2$); 1.78 (d, 2H, **H**$_{3eq}$+**H**$_{5eq}$-pip); 1.87 (t, 2H, **H**$_{3ax}$+**H**$_{5ax}$-pip); 1.96 (t, 2H, **H**$_{2eq}$+**H**$_{6eq}$-pip); 2.27 (s, 1H, **H**$_4$-pip); 2.40 (t, 2H, N–C**H**$_2$, $J_{CH2-CH2} = 7.0$ Hz); 2.79 (d, 2H, **H**$_{2ax}$+**H**$_{6ax}$-pip); 4.03–4.08 (m, 4H, CH_3–C**H**$_2$ and O–C**H**$_2$); 7.07 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.8$ Hz); 7.20 (s, 2H, N**H**$_2$); 7.73 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.8$ Hz). Anal. Calcd for $C_{17}H_{26}N_2O_5S$: C, 55.14%; H, 7.03%; N, 7.57%. Found: C, 54.76%; H, 7.24%; N, 7.24%.

4.4.7. 4-(3-morpholinopropoxy)benzenesulfonamide (**16**)

White solid. Yield: 37%. M.p: 153–155 °C. IR (KBr, cm^{-1}): 3327 (m, ν_{N-H}); 1304 and 1156 (vs, ν_{SO2N}); 1260 (s, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.86–1.92 (m, 2H, N–CH_2–**CH**$_2$); 2.36–2.43 (m, 6H, **H**$_3$+**H**$_5$-morp and N–C**H**$_2$); 3.56–3.58 (m, 4H, **H**$_2$+**H**$_6$-morp); 4.08 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2} = 8.9$ Hz); 7.12 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.9$ Hz); 7.20 (s, 2H, N**H**$_2$); 7.74 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.9$ Hz). Anal. Calcd for $C_{13}H_{20}N_2O_4S$: C, 52.00%; H, 6.67%; N, 9.33%. Found: C, 52.10%; H, 6.89%; N, 9.32%.

4.4.8. 4-[(4-(pyrrolidin-1-yl)butoxy)]benzenesulfonamide (**17**)

White solid. Yield: 45%. M.p: 142 °C. IR (KBr, cm^{-1}): 3280 (s, ν_{N-H}); 1260 (s, ν_{C-O-C}); 1150 (vs, ν_{SO2N}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.54–1.61 (m, 2H, N–CH_2–**CH**$_2$); 1.67 (d, 4H, **H**$_3$+**H**$_4$-pyr); 1.72–1.76 (m, 2H, O–CH_2–C**H**$_2$); 2.38–2.42 (m, 6H, **H**$_2$+**H**$_5$-pyr and N–C**H**$_2$); 4.05 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2} = 6.3$ Hz); 7.07 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.5$ Hz); 7.20 (s, 2H, N**H**$_2$); 7.74 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.1$ Hz). Anal. Calcd for $C_{14}H_{22}N_2O_3S \cdot \frac{1}{2} H_2O$: C, 54.73%; H, 7.49%; N, 9.10%. Found: C, 55.12%; H, 7.29%; N, 8.84%.

4.4.9. 4-[(4-(piperidin-1-yl)butoxy)]benzenesulfonamide (**18**)

White solid. Yield: 55%. M.p: 147–149 °C. IR (KBr, cm^{-1}): 3290 (vs, ν_{N-H}); 1325 and 1157 (s, ν_{SO2N}); 1259 (s, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.37–1.38 (m, 2H, **H**$_4$-pip); 1.46–1.49 (m, 4H, **H**$_3$+**H**$_5$-pip); 1.54–1.59 (m, 2H, N–CH_2–**CH**$_2$); 1.69–1.76 (m, 2H, O–CH_2–C**H**$_2$); 2.27–2.31 (m, 6H, **H**$_2$+**H**$_6$-pip and N–C**H**$_2$); 4.01–4.05 (m, 2H, O–C**H**$_2$); 7.06 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.8$ Hz); 7.19 (s, 2H, N**H**$_2$); 7.74 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.8$ Hz). Anal. Calcd for $C_{15}H_{24}N_2O_3S$: C, 57.69%; H, 7.69%; N, 8.97%. Found: C, 57.39%; H, 7.49%; N, 8.61%.

4.4.10. 4-{4-[4-(ethoxycarbonyl)piperidin-1-yl]butoxy} benzenesulfonamide (**19**)

White solid. Yield: 71%. M.p: 132–134 °C. IR (KBr, cm^{-1}): 3297 (m, ν_{N-H}); 1733 (vs, $\nu_{C=O}$); 1328 and 1155 (vs, ν_{SO2N}); 1260 (s, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.17 (t, 3H, C**H**$_3$, $J_{CH3-CH2} = 7.1$ Hz); 1.49–1.57 (m, 4H, N–CH_2–CH_2–**CH**$_2$); 1.69–1.78 (m, 4H, **H**$_3$+**H**$_5$-pip); 1.92 (t, 2H, **H**$_{2eq}$+**H**$_{6eq}$-pip); 2.23–2.31 (m, 3H, **H**$_4$-pip and N–C**H**$_2$); 2.78 (d, 1H, **H**$_{2ax}$+**H**$_{6ax}$-pip); 3.99–4.11 (m, 4H, CH_3–C**H**$_2$ and O–C**H**$_2$); 7.07 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 6.9$ Hz); 7.19 (s, 2H, N**H**$_2$); 7.73 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 6.9$ Hz) Anal. Calcd for $C_{18}H_{28}N_2O_5S.1/2H_2O$: C, 54.96%; H, 7.34%; N, 7.12%. Found: C, 54.81%; H, 7.38%; N, 6.91%.

4.5. General procedure for the preparation of 4-(aminealkoxy) benzenesulfonylurea derivatives (**20**–**64**)

A solution of 10% of NaOH (5.00 mmol) was added to a solution of the corresponding 4-(aminealkoxy)benzenesulfonamide **10**–**19** (5.00 mmol) in acetone (25 ml). After 10 min of stirring, the solvent was removed under reduced pressure. The solid was redissolved in acetone (30 ml) and the reaction mixture was stirred under reflux. The appropriate isocyanate derivative (10.00 mmol) was added dropwise and the mixture was stirred at reflux for 4 h. The solvent was concentrated to dryness in vacuo and the obtained residue was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) in order to afford **20**–**64** derivatives.

4.5.1. 1-Isopropyl-3-[4-(2-pyrrolidin-1-ylethoxy)benzene] sulfonylurea (**20**)

White solid. Yield: 53%. M.p: 73–75 °C. IR (KBr, cm^{-1}): 3374 (w, ν_{N-H}); 1704 (s, $\nu_{C=O}$); 1326 and 1119 (s, ν_{SO2N}); 1249 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.00 (d, 6H, (C**H**$_3$)$_2$CH, $J_{CH3-CH} = 6.5$ Hz); 1.72 (bs, 4H, **H**$_3$+**H**$_4$-pyr); 2.66 (bs, 4H, **H**$_2$+**H**$_5$-pyr); 2.94 (t, 2H, N–C**H**$_2$, $J_{CH2-CH2} = 5.6$ Hz); 3.53–3.62 (m, 2H, $(CH_3)_2$C**H** and N**H**–SO_2); 4.19 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2} = 5.6$ Hz); 6.25 (d, 1H, N**H**–CH, $J_{NH-CH} = 7.2$ Hz); 7.10 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.8$ Hz); 7.80 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.8$ Hz). Anal. Calcd for $C_{16}H_{25}N_3O_4S.1/2H_2O$: C, 52.75%; H, 7.14%; N, 11.54%. Found: C, 53.01%; H, 7.30%; N, 11.31%.

4.5.2. 1-Phenyl-3-[4-(2-pyrrolidin-1-ylethoxy)benzene] sulfonylurea (**21**)

White solid. Yield: 71%. M.p: 103–104 °C. IR (KBr, cm^{-1}): 3350 (w, ν_{N-H}); 1717 (s, $\nu_{C=O}$); 1312 and 1131 (s, ν_{SO2N}); 1241 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.87 (t, 4H, **H**$_3$+**H**$_4$-pyr); 3.15 (s, 4H, **H**$_2$+**H**$_5$-pyr); 3.40 (t, 2H, N–C**H**$_2$, $J_{CH2-CH2} = 5.0$ Hz); 3.69 (s, 1H, N**H**–SO_2); 4.28 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2} = 5.6$ Hz); 6.81 (t, 1H, **H**$_4$-ph-$_{NH}$, $J_{4\text{-}3,\ 5} = 7.2$ Hz); 7.01 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.6$ Hz); 7.13 (t, 2H, **H**$_3$+**H**$_5$-ph-$_{NH}$, $J_{3,5\text{-}2,6} = 7.8$ Hz); 7.38 (d, 2H, **H**$_2$ + **H**$_6$-ph-$_{NH}$, $J_{2,6\text{-}3,5} = 8.4$ Hz); 7.79 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.7$ Hz); 9.52 (s, 1H, N**H**-ph). Anal. Calcd for $C_{19}H_{23}N_3O_4S.1/2H_2O$: C, 57.29%; H, 6.03%; N, 10.55%. Found: C, 57.32%; H, 6.05%; N, 10.35%.

4.5.3. 1-Cyclohexyl-3-[4-(2-pyrrolidin-1-ylethoxy)benzene] sulfonylurea (**22**)

White solid. Yield: 10%. M.p: 87–88 °C. IR (KBr, cm^{-1}): 3371 (w, ν_{N-H}); 1595 (s, $\nu_{C=O}$); 1356 and 1123 (s, ν_{SO2N}); 1251 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.07–1.13 (m, 4H, **H**$_3$+**H**$_5$-cyc); 1.21 (d, 1H, **H**$_{4eq}$-cyc); 1.49 (d, 1H, **H**$_{4ax}$-cyc); 1.57–1.63 (m, 4H, **H**$_2$+**H**$_6$-cyc); 1.71–1.75 (m, 4H, **H**$_3$+**H**$_4$-pyr); 2.69 (bs, 4H, **H**$_2$+**H**$_5$-pyr); 2.97 (t, 2H, N–C**H**$_2$, $J_{CH2-CH2} = 5.6$ Hz); 3.54–3.59 (m, 1H, **H**$_1$-cyc); 3.69 (s, 1H, N**H**–SO_2); 4.20 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2} = 5.6$ Hz); 6.32 (d, 1H, N**H**-CHcyc, $J_{NH-CH} = 7.5$ Hz); 7.10 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.9$ Hz); 7.80 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.9$ Hz). Anal. Calcd for $C_{19}H_{29}N_3O_4S$: C, 57.72%; H, 7.34%; N, 10.63%. Found: C, 57.41%; H, 7.45%; N, 10.26%.

4.5.4. 1-(2,5-dichlorophenyl)-3-[4-(2-pyrrolidin-1-ylethoxy) benzene]sulfonylurea (**23**)

White solid. Yield: 54%. M.p: 101–102 °C. IR (KBr, cm^{-1}): 3419 (w, ν_{N-H}); 1593 (s, $\nu_{C=O}$); 1405 and 1134 (s, ν_{SO2N}); 1251 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.91–1.96 (m, 4H, **H**$_3$+**H**$_4$-pyr); 3.26 (bs, 4H, **H**$_2$+**H**$_5$-pyr); 3.51 (bs, 2H, N–C**H**$_2$); 4.30 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2} = 5.5$ Hz); 6.90, 6.92 (dd, 1H, **H**$_4$-2,5-diClph-$_{NH}$, $J_{4-3} = 8.5$ Hz and $J_{4-6} = 2.6$ Hz); 7.00 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6} = 8.9$ Hz); 7.36, 7.38 (dd, 1H, **H**$_3$-2,5-diClph-$_{NH}$, $J_{3-4} = 8.6$ Hz and $J_{3-6} = 0.5$ Hz); 7.68 (d, 1H, N**H**-2,5-diClph, $J_{NH-H6} = 8.9$ Hz); 7.76 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5} = 8.5$ Hz); 8.30 (d, 1H, **H**$_6$-2,5-diClph-$_{NH}$, $J_{4-6} = 2.6$ Hz); 10.05 (bs, 1H, N**H**–SO_2). Anal. Calcd for $C_{19}H_{21}Cl_2N_3O_4S$: C, 49.78%; H, 4.58%; N, 9.17%. Found: C, 49.57%; H, 4.80%; N, 8.93%.

4.5.5. 1-(4-trifluoromethylphenyl)-3-[4-(2-pyrrolidin-1-ylethoxy) benzene]sulfonylurea (**24**)

White solid. Yield: 81%. M.p: 128–130 °C. IR (KBr, cm^{-1}): 3329 (w, ν_{N-H}); 1595 (s, $\nu_{C=O}$); 1324 (vs, ν_{SO2N}); 1241 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.90–1.95 (m, 4H, **H**$_3$+**H**$_4$-pyr); 3.27 (bs, 4H, **H**$_2$+**H**$_5$-pyr); 3.52 (s, 2H, N–C**H**$_2$); 3.71 (bs, 1H,

N**H**–SO_2); 4.29 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2}$ = 4.9 Hz); 6.98 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.43 (d, 2H, **H**$_2$+**H**$_6$-4-CF_3ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 7.60 (d, 2H, **H**$_3$+**H**$_5$-4-CF_3ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.6 Hz); 7.77 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.8 Hz). Anal. Calcd for $C_{20}H_{22}F_3N_3O_4S.1/2H_2O$: C, 51.50%; H, 4.93%; N, 9.01%. Found: C, 51.43%; H, 4.71%; N, 8.89%.

4.5.6. 1-Isopropyl-3-[4-(2-piperidin-1-ylethoxy)benzene] sulfonylurea (**25**)

Beige solid. Yield: 43%. M.p: 80–82 °C. IR (KBr, cm^{-1}): 3375 (w, ν_{N-H}); 1596 (s, $\nu_{C=O}$); 1327 and 1154 (vs, ν_{SO2N}); 1250 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.99 (d, 6H, (C**H**$_3$)$_2$CH, J_{CH3-CH} = 6.6 Hz); 1.39 (d, 2H, **H**$_4$-pip); 1.48–1.54 (m, 4H, **H**$_3$+**H**$_5$-pip); 2.50 (bs, 4H, **H**$_2$+**H**$_6$-pip); 2.74 (t, 2H, N–C**H**$_2$, $J_{CH2-CH2}$ = 5.8 Hz); 3.53–3.62 (m, 1H, $(CH_3)_2$C**H**); 4.17 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2}$ = 5.8 Hz); 6.25 (d, 1H, N**H**–CH, J_{NH-CH} = 6.9 Hz); 7.10 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.80 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.9 Hz). Anal. Calcd for $C_{17}H_{27}N_3O_4S$: C, 55.28%; H, 7.32%; N, 11.38%. Found: C, 54.91%; H, 7.24%; N, 11.30%.

4.5.7. 1-Phenyl-3-[4-(2-piperidin-1-ylethoxy)benzene]sulfonylurea (**26**)

Beige solid. Yield: 50%. M.p: 99–101 °C. IR (KBr, cm^{-1}): 3324 (w, ν_{N-H}); 1593 (s, $\nu_{C=O}$); 1311 and 1127 (vs, ν_{SO2N}); 1229 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.42 (s, 2H, **H**$_4$-pip); 1.54–1.58 (m, 4H, **H**$_3$+**H**$_5$-pip); 2.50 (bs, 4H, **H**$_2$+**H**$_6$-pip); 2.69 (bs, 2H, N–C**H**$_2$); 4.18 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2}$ = 5.3 Hz); 6.77 (t, 1H, **H**$_4$-ph-$_{NH}$, $J_{4\text{-}3,\ 5}$ = 7.3 Hz); 6.85–6.96 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 7.9 Hz); 7.10 (t, 2H, **H**$_3$+**H**$_5$-ph-$_{NH}$, $J_{3,5\text{-}4}$ = 7.4 Hz $J_{3,5\text{-}2,6}$ = 7.1 Hz); 7.39–7.46 (m, 2H, **H**$_2$+**H**$_6$-ph-$_{NH}$); 7.75 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 7.9 Hz); 8.45 (s, 1H, N**H**–SO_2). Anal. Calcd for $C_{20}H_{25}N_3O_4S$: C, 59.55%; H, 6.20%; N, 10.42%. Found: C, 59.89%; H, 6.24%; N, 10.30%. MS (EI, 70eV): *m*/*z* (%) = 401 (0.5); 212 (13); 119 (19); 98 (100).

4.5.8. 1-Cyclohexyl-3-[4-(2-piperidin-1-ylethoxy)benzene] sulfonylurea (**27**)

Beige solid. Yield: 7%. M.p: 67–70 °C. IR (KBr, cm^{-1}): 3376 (w, ν_{N-H}); 1595 (s, $\nu_{C=O}$); 1325 and 1156 (vs, ν_{SO2N}); 1252 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.08–1.26 (m, 6H, **H**$_3$+**H**$_4$+**H**$_5$-cyc); 1.40 (d, 2H, **H**$_4$-pip); 1.50–1.66 (m, 8H, **H**$_3$+**H**$_5$-pip, **H**$_2$+**H**$_6$-cyc); 2.55 (s, 4H, **H**$_2$+**H**$_6$-pip); 2.79 (t, 2H, N–C**H**$_2$, $J_{CH2-CH2}$ = 5.6 Hz); 3.27 (bs, 1H, **H**$_1$-cyc); 4.16–4.21 (m, 2H, O–C**H**$_2$); 6.35 (d, 1H, N**H**-CHcyc, J_{NH-CH} = 7.5 Hz); 7.11 (t, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.80 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.9 Hz). Anal. Calcd for $C_{20}H_{31}N_3O_4S.1/2H_2O$: C, 57.42%; H, 7.66%; N, 10.05%. Found: C, 57.10%; H, 7.39%; N, 9.72%.

4.5.9. 1-(2,5-dichlorophenyl)-3-[4-(2-piperidin-1-ylethoxy) benzene]sulfonylurea (**28**)

White solid. Yield: 53%. M.p: 112–114 °C. IR (KBr, cm^{-1}): 3361 (m, ν_{N-H}); 1629 (vs, $\nu_{C=O}$); 1409 and 1179 (s, ν_{SO2N}); 1253 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.50 (s, 2H, **H**$_4$-pip); 1.69 (bs, 4H, **H**$_3$+**H**$_5$-pip); 2.50–2.52 (m, 4H, **H**$_2$+**H**$_6$-pip); 3.06 (bs, 2H, N–C**H**$_2$); 4.32 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2}$ = 5.3 Hz); 6.91 (dd, 1H, **H**$_4$-2,5-diClph-$_{NH}$, J_{4-3} = 8.6 Hz, J_{4-6} = 2.6 Hz); 7.02 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.6 Hz); 7.38 (d, 1H, **H**$_3$-2,5-diClph-$_{NH}$, J_{3-4} = 8.6 Hz); 7.77 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.18 (s, 1H, **H**$_6$-3,5-diClph-$_{NH}$); 8.27 (d, 1H, N**H**-2,5-diClph). Anal. Calcd for $C_{20}H_{23}Cl_2N_3O_4S$: C, 50.85%; H, 4.87%; N, 8.90%. Found: C, 50.93%; H, 5.08%; N, 8.83%.

4.5.10. 1-(4-trifluoromethylphenyl)-3-[4-(2-piperidin-1-ylethoxy) benzene]sulfonylurea (**29**)

Beige solid. Yield: 22%. M.p: 124–126 °C. IR (KBr, cm^{-1}): 3321 (w, ν_{N-H}); 1595 (s, $\nu_{C=O}$); 1324 and 1107 (vs, ν_{SO2N}); 1242 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.48 (s, 2H, **H**$_4$-pip); 1.68 (s, 4H, **H**$_3$+**H**$_5$-pip); 3.06 (bs, 4H, **H**$_2$+**H**$_6$-pip); 3.31 (bs, 2H, N–C**H**$_2$); 4.31 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2}$ = 4.7 Hz); 6.98 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.43 (d, 2H, **H**$_3$+**H**$_5$-4-CF_3ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.6 Hz); 7.60 (d, 2H, **H**$_2$+**H**$_6$-4-CF_3ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 8.6 Hz); 7.76 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.89 (bs, 1H, N**H**–SO_2). Anal. Calcd for $C_{21}H_{24}F_3N_3O_4S.1/2H_2O$: C, 52.50%; H, 5.00%; N, 8.75%. Found: C, 52.32%; H, 5.09%; N, 8.25%.

4.5.11. 1-Phenyl-3-[4-(2-(4-ethoxycarbonylpiperidin-1-yl)ethoxy) benzene]sulfonylurea (**30**)

White solid. Yield: 61%. M.p: 100–101 °C. IR (KBr, cm^{-1}): 3349 (m, ν_{N-H}); 1727 (vs, $\nu_{C=O\ ester}$); 1597 (m, $\nu_{C=O\ urea}$); 1311 and 1131 (vs, ν_{SO2N}); 1249 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.17 (t, 3H, C**H**$_3$, $J_{CH3-CH2}$ = 7.0 Hz); 1.57 (dq, 2H, **H**$_{3eq}$+**H**$_{5eq}$-pip); 1.79 (d, 2H, **H**$_{3ax}$+**H**$_{5ax}$-pip); 2.10 (dt, 2H, **H**$_{2eq}$+**H**$_{6eq}$-pip); 2.27 (t, 1H, **H**$_4$-pip); 2.67 (t, 2H, N–C**H**$_2$, $J_{CH2-CH2}$ = 5.8 Hz); 2.86 (dt, 2H, **H**$_{2ax}$+**H**$_{6ax}$-pip); 4.02–4.09 (m, 4H, CH_3–C**H**$_2$, O–C**H**$_2$); 6.70 (t, 1H, **H**$_4$-ph-$_{NH}$, $J_{4\text{-}3,\ 5}$ = 7.2 Hz); 6.89 (ddd, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.8 Hz, $J_{3\text{-}5,\ 5\text{-}3}$ = 2.8 Hz, $J_{3\text{-}6,5\text{-}2}$ = 1.8 Hz); 7.06 (d, 2H, **H**$_3$ + **H**$_5$-ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.0 Hz); 7.41 (ddd, 2H, **H**$_2$ + **H**$_6$-ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 7.6 Hz, $J_{2\text{-}6,6\text{-}2}$ = 3.0 Hz, $J_{2\text{-}5,6\text{-}3}$ = 2.0 Hz); 7.69 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.0 Hz). Anal. Calcd for $C_{23}H_{29}N_3O_6S.1/4H_2O$: C, 57.56%; H, 6.15%; N, 8.76%. Found: C, 57.39%; H, 6.26%; N, 7.42%.

4.5.12. 1-Isopropyl-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene] sulfonylurea (**31**)

White solid. Yield: 2%. M.p: 74–78 °C. IR (KBr, cm^{-1}): 3369 (w, ν_{N-H}); 1701 (s, $\nu_{C=O}$); 1254 (vs, ν_{C-O-C}); 1119 (s, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.97 (d, 6H, (C**H**$_3$)$_2$CH, J_{CH3-CH} = 6.6 Hz); 1.72 (bs, 4H, **H**$_3$+**H**$_4$-pyr); 1.93 (q, 2H, N–CH_2–**CH**$_2$, $J_{CH2-CH2}$ = 6.9 Hz); 2.61 (bs, 4H, **H**$_2$+**H**$_5$-pyr); 2.67 (bs, 2H, N–C**H**$_2$); 3.57 (q, 1H, $(CH_3)_2$C**H**, J_{CH-CH3} = 6.5 Hz); 3.90 (s, 1H, N**H**–SO_2); 4.07 (s, 2H, O–C**H**$_2$); 6.16 (s, 1H, N**H**–CH); 7.03 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.74 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.9 Hz). Anal. Calcd for $C_{17}H_{27}N_3O_4S.1/2H_2O$: C, 53.97%; H, 7.41%; N, 11.11%. Found: C, 53.90%; H, 7.32%; N, 10.96%. MS (EI, 70eV): *m*/*z* (%) = 369 (4); 284 (7); 203 (8); 84 (100).

4.5.13. 1-Phenyl-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene] sulfonylurea (**32**)

White solid. Yield: 70%. M.p: 159 °C. IR (KBr, cm^{-1}): 3434 (vs, ν_{N-H}); 1693 (s, $\nu_{C=O}$); 1258 (vs, ν_{C-O-C}); 1148 (vs, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.93 (bs, 4H, **H**$_3$+**H**$_4$-pyr); 2.15 (bs, 2H, N–CH_2–**CH**$_2$); 2.51 (bs, 2H, N–C**H**$_2$); 3.26 (bs, 5H, **H**$_2$+**H**$_5$-pyr, N**H**–SO_2); 4.16 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2}$ = 5.5 Hz); 6.97 (t, 1H, **H**$_4$-ph-$_{NH}$, $J_{4\text{-}3,\ 5}$ = 7.0 Hz); 7.12 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.23 (t, 2H, **H**$_3$+**H**$_5$-ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 7.5 Hz); 7.33 (t, 2H, **H**$_2$+**H**$_6$-ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 7.6 Hz); 7.89 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.9 Hz); 9.26 (s, 1H, N**H**-ph); 10.57 (bs, 1H, NH·**H**Cl). Anal. Calcd for $C_{20}H_{25}N_3O_4S.2HCl$: C, 50.42%; H, 5.68%; N, 8.84%. Found: C, 50.16%; H, 5.86%; N, 8.70%. MS (EI, 70eV): *m*/*z* (%): 476 ($[M^{\cdot}]^+$, 10); 368 (30); 312 (10); 191(45); 57 (100).

4.5.14. 1-Cyclohexyl-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene] sulfonylurea (**33**)

White solid. Yield: 3%. M.p: 89–90 °C. IR (KBr, cm^{-1}): 3379 (s, ν_{N-H}); 1595 (s, $\nu_{C=O}$); 1254 (s, ν_{C-O-C}); 1124 (vs, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.07–1.21 (m, 6H, **H**$_3$+**H**$_4$+**H**$_5$-cyc); 1.58–1.64 (t, 4H, **H**$_2$+**H**$_6$-cyc); 1.91 (bs, 4H, **H**$_3$+**H**$_4$-pyr); 2.15 (bs, 2H, N–CH_2–**CH**$_2$); 3.19–3.26 (m, 8H, **H**$_2$+**H**$_5$-pyr, N–C**H**$_2$, **H**$_1$-cyc, N**H**–SO_2); 4.16 (t, 2H, O–C**H**$_2$, $J_{CH2-CH2}$ = 5.9 Hz); 6.62 (d, 1H, N**H**-CHcyc, J_{NH-CH} = 7.2 Hz); 7.10 (d, 2H, **H**$_3$+**H**$_5$, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.82 (d, 2H, **H**$_2$+**H**$_6$, $J_{2,6\text{-}3,5}$ = 8.8 Hz). Anal. Calcd for $C_{20}H_{31}N_3O_4S$: C, 58.65%; H, 7.63%; N, 10.26%. Found: C, 58.32%; H, 7.45%; N, 9.86%.

*4.5.15. 1-(2,5-dichlorophenyl)-3-[4-(3-pyrrolidin-1-ylpropoxy) benzene]sulfonylurea (**34**)*

White solid. Yield: 2%. M.p: 166–167 °C. IR (KBr, cm^{-1}): 3426 (m, ν_{N-H}); 1626 (s, $\nu_{C=O}$); 1252 (vs, ν_{C-O-C}); 1133 (vs, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.91 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.10 (bs, 2H, N–CH$_2$–**CH$_2$**); 3.20–3.40 (m, 7H, **H$_2$**+**H$_5$**-pyr, N–**CH$_2$**, N**H**–SO$_2$); 4.09 (t, 2H, O–**CH$_2$**, $J_{CH2-CH2}$ = 6.4 Hz); 6.86, 6.89 (dd, 1H, **H$_4$**-2,5-diClph-$_{NH}$, J_{4-3} = 8.6 Hz and J_{4-6} = 2.6 Hz); 6.91 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.36 (d, 1H, **H$_3$**-2,5-diClph-$_{NH}$, J_{3-4} = 8.5 Hz); 7.60 (s, 1H, N**H**-2,5-diClph); 7.74 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.30 (s, 1H, **H$_6$**-2,5-diClph-$_{NH}$). Anal. Calcd for $C_{20}H_{23}Cl_2N_3O_4S.1/2H_2O$: C, 49.89%; H, 4.99%; N, 8.73%. Found: C, 49.51%; H, 4.88%; N, 8.59%. MS (EI, 70eV): *m*/*z* (%) = 481 ([M$^{\cdot}$]$^+$, 10); 310 (7); 284 (14); 187 (100); 161 (81).

*4.5.16. 1-(4-trifluoromethylphenyl)-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene]sulfonylurea (**35**)*

White solid. Yield: 14%. M.p: 89–90 °C. IR (KBr, cm^{-1}): 3322 (vs, ν_{N-H}); 1645 (s, $\nu_{C=O}$); 1229 (s, ν_{C-O-C}); 1133 (s, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.91 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.08 (bs, 2H, N–CH$_2$–**CH$_2$**); 2.50 (bs, 2H, N–C**H$_2$**); 3.23 (bs, 4H, **H$_2$**+**H$_5$**-pyr); 4.08 (t, 2H, O–**CH$_2$**, $J_{CH2-CH2}$ = 6.0 Hz); 6.92 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.41 (d, 2H, **H$_3$**+**H$_5$**-4-CF$_3$ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.60 (t, 2H, **H$_2$**+**H$_6$**-4-CF$_3$ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 8.7 Hz); 7.74 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.84 (s, 1H, N**H**-4-CF$_3$ph-$_{NH}$); 9.70 (bs, 1H, N**H**–SO$_2$). Anal. Calcd for $C_{21}H_{24}F_3N_3O_4S.H_2O$: C, 51.53%; H, 5.31%; N, 8.59%. Found: C, 51.74%; H, 4.97%; N, 8.72%. MS (EI, 70eV): *m*/*z* (%) = 368 (40); 312 (13); 191 (100); 175 (69).

*4.5.17. 1-Isopropyl-3-[4-(3-piperidin-1-ylpropoxy)benzene] sulfonylurea (**36**)*

White solid. Yield: 34%. M.p: 122–124 °C. IR (KBr, cm^{-1}): 3526, 3372 (m, $\nu_{N-HCO-N-H}$); 1592 (vs, $\nu_{C=O}$); 1316, 1151 (vs, ν_{SO2N}); 1261 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.99 (d, 6H, (C**H$_3$**)$_2$CH, J_{CH3-CH} = 6.5 Hz); 1.42 (d, 2H, **H$_4$**-pip); 1.54–1.58 (m, 4H, **H$_3$**+**H$_5$**-pip); 1.92–1.98 (m, 2H, N–CH$_2$–**CH$_2$**); 2.52–2.62 (m, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 3.53–3.62 (m, 1H, (CH$_3$)$_2$C**H**); 4.08 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.3 Hz); 6.33 (bs, 1H, N**H**–CH); 7.07 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.79 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.9 Hz). Anal. Calcd for $C_{18}H_{29}N_3O_4S\cdot H_2O$: C, 53.86%; H, 7.73%; N, 10.47%. Found: C, 53.54%; H, 7.76%; N, 10.13%.

*4.5.18. 1-Phenyl-3-[4-(3-piperidin-1-ylpropoxy)benzene] sulfonylurea (**37**)*

White solid. Yield: 25%. M.p: 106–108 °C. IR (KBr, cm^{-1}): 3336 (w, ν_{N-H}); 1592 (s, $\nu_{C=O}$); 1308, 1129 (vs, ν_{SO2N}); 1228 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.48 (bs, 2H, **H$_4$**-pip); 1.65 (t, 4H, **H$_3$**+**H$_5$**-pip); 2.04 (bs, 2H, N–CH$_2$–**CH$_2$**); 2.81 (bs, 2H, N–C**H$_2$**); 2.93 (bs, 4H, **H$_2$**+**H$_6$**-pip); 4.05–4.12 (m, 2H, O–C**H$_2$**); 6.77 (t, 1H, **H$_4$**-ph-$_{NH}$, $J_{4\text{-}3,\ 5}$ = 7.3 Hz); 6.93 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.6 Hz); 7.07–7.12 (m, 2H, **H$_3$**+**H$_5$**-ph-$_{NH}$); 7.22 (s, 1H, N**H**–SO$_2$); 7.39 (d, 2H, **H$_2$**+**H$_6$**-ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 7.6 Hz); 7.75 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.44 (s, 1H, N**H**-ph-$_{NH}$). Anal. Calcd for $C_{21}H_{27}N_3O_4S\cdot H_2O$: C, 57.93%; H, 6.67%; N, 9.65%. Found: C, 58.19%; H, 7.06%; N, 9.25%. MS (EI, 70eV): *m*/*z* (%) = 435 ([M$^{\cdot}$]$^+$, 5); 324 (1); 298 (25); 119 (19); 98 (100).

*4.5.19. 1-Cyclohexyl-3-[4-(3-piperidin-1-ylpropoxy)benzene] sulfonylurea (**38**)*

White solid. Yield: 13%. M.p: 138 °C. IR (KBr, cm^{-1}): 3378 (w, ν_{N-H}); 1705 (s, $\nu_{C=O}$); 1334, 1124 (vs, ν_{SO2N}); 1255 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.10–1.19 (m, 6H, **H$_3$**+**H$_4$**+**H$_5$**-cyc); 1.46 (bs, 2H, **H$_4$**-pip); 1.64 (bs, 8H, **H$_2$**+**H$_6$**-cyc, **H$_3$**+**H$_5$**-pip); 2.04 (bs, 2H, N–CH$_2$–**CH$_2$**); 2.80 (bs, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 3.28 (m, 2H, **H$_1$**-cyc, N**H**–SO$_2$); 4.11 (bs, 2H, O–C**H$_2$**); 6.57 (d, 1H, N**H**-CHcyc, J_{NH-CH} = 7.6 Hz); 7.10 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.80 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz). Anal. Calcd for $C_{21}H_{33}N_3O_4S\cdot H_2O$: C, 58.33%; H, 7.87%; N, 9.72%. Found: C, 57.90%; H, 8.13%; N, 9.50%.

*4.5.20. 1-(2,5-dichlorophenyl)-3-[4-(3-piperidin-1-ylpropoxy) benzene]sulfonylurea (**39**)*

White solid. Yield: 46%. M.p: 180–182 °C. IR (KBr, cm^{-1}): 3429 (m, ν_{N-H}); 1630 (vs, $\nu_{C=O}$); 1231 (vs, ν_{C-O-C}); 1142 (s, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.51 (bs, 2H, **H$_4$**-pip); 1.68 (bs, 4H, **H$_3$**+**H$_5$**-pip); 2.06–2.10 (m, 2H, N–CH$_2$–**CH$_2$**); 2.50–2.52 (m, 2H, N–C**H$_2$**); 3.07 (bs, 4H, **H$_2$**+**H$_6$**-pip); 4.06–4.13 (m, 2H, O–C**H$_2$**); 6.88–6.96 (m, 3H, **H$_3$**+**H$_5$**, **H$_4$**-2,5-diClph-$_{NH}$); 7.37 (d, 1H, **H$_3$**-2,5-diClph-$_{NH,}$ J_{3-4} = 8.5 Hz); 7.58 (s, 1H, **H$_6$**-2,5-diClph-$_{NH}$); 7.71–7.74 (m, 2H, **H$_2$**+**H$_6$**); 8.32 (s, 1H, N**H**-2,5-diClph). Anal. Calcd for $C_{21}H_{25}Cl_2N_3O_4S$: C, 51.85%; H, 5.14%; N, 8.64%. Found: C, 51.46%; H, 5.16%; N, 8.56%.

*4.5.21. 1-(4-trifluoromethylphenyl)-3-[4-(3-piperidin-1-ylpropoxy) benzene]sulfonylurea (**40**)*

Beige solid. Yield: 40%. M.p: 150–152 °C. IR (KBr, cm^{-1}): 3328 (w, ν_{N-H}); 1594 (m, $\nu_{C=O}$); 1313, 1133 (vs, ν_{SO2N}); 1249 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.51 (bs, 2H, **H$_4$**-pip); 1.68 (bs, 4H, **H$_3$**+**H$_5$**-pip); 2.08 (bs, 2H, N–CH$_2$–**CH$_2$**); 3.06 (bs, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 4.06 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 5.9 Hz); 5.79 (bs, 1H, N**H**–SO$_2$); 6.91 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.7 Hz); 7.41 (d, 2H, **H$_3$**+**H$_5$**-4-CF$_3$ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.7 Hz); 7.60 (d, 2H, **H$_2$**+**H$_6$**-4-CF$_3$ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 8.5 Hz); 7.74 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.83 (s, 1H, N**H**-4-CF$_3$ph-$_{NH}$). Anal. Calcd for $C_{22}H_{26}F_3N_3O_4S$: C, 54.43%; H, 5.36%; N, 8.66%. Found: C, 54.57%; H, 5.21%; N, 8.72%.

*4.5.22. 1-Phenyl-3-[4-(3-(4-ethoxycarbonylpiperidin-1-yl) propoxy)benzene]sulfonylurea (**41**)*

Beige solid. Yield: 25%. M.p: 91–93 °C. IR (KBr, cm^{-1}): 3352 (w, ν_{N-H}); 1727 (vs, $\nu_{C=Oester}$); 1596 (m, $\nu_{C=Ourea}$); 1311, 1131 (vs, ν_{SO2N}); 1244 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.18 (t, 3H, C**H$_3$**, $J_{\ CH3-CH2}$ = 7.1 Hz); 1.69 (d, 2H, N–CH$_2$–**CH$_2$**, $J_{CH2-CH2}$ = 10.0 Hz); 2.01 (d, 4H, **H$_3$**+**H$_5$**-pip); 2.27 (s, 1H, **H$_4$**-pip); 2.56 (bs, 2H, N–C**H$_2$**); 2.83 (s, 2H, **H$_{2eq}$**+**H$_{6eq}$**-pip); 3.17 (bs, 2H, **H$_{2ax}$**+**H$_{6ax}$**-pip); 4.05–4.10 (m, 4H, CH$_3$–C**H$_2$**, O–C**H$_2$**); 6.83 (bs, 1H, **H$_4$**-ph-$_{NH}$); 6.96–7.02 (m, 2H, **H$_3$**+**H$_5$**); 7.16 (d, 2H, **H$_3$**+**H$_5$**-ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 7.5 Hz); 7.37 (d, 2H, **H$_2$**+**H$_6$**-ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 7.8 Hz); 7.70–7.81 (m, 2H, **H$_2$**+**H$_6$**); 8.60 (bs, 1H, N**H**–SO$_2$). Anal. Calcd for $C_{24}H_{31}N_3O_6S\cdot 1/2H_2O$: C, 57.83%; H, 6.42%; N, 8.43%. Found: C, 57.54%; H, 6.17%; N, 8.32%.

*4.5.23. 1-Isopropyl-3-[4-(4-pyrrolidin-1-ylbutoxy)benzene] sulfonylurea (**42**)*

White solid. Yield: 17%. M.p: 135–137 °C. IR (KBr, cm^{-1}): 3369 (w, ν_{N-H}); 1702 (w, $\nu_{C=O}$); 1267 (s, ν_{C-O-C}); 1118 (s, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.98 (d, 6H, (C**H$_3$**)$_2$CH, J_{CH3-CH} = 6.6 Hz); 1.62–1.68 (m, 4H, N–CH$_2$–CH$_2$–**CH$_2$**); 1.76 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.70–2.75 (m, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 3.54–3.57 (m, 1H, (CH$_3$)$_2$C**H**); 3.90 (s, 1H, N**H**–SO$_2$); 4.02 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.2 Hz); 6.20 (s, 1H, N**H**–CH); 7.02 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.74 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.9 Hz). Anal. Calcd for $C_{18}H_{29}N_3O_4S$: C, 56.40%; H, 7.57%; N, 10.97%. Found: C, 56.01%; H, 7.52%; N, 10.59%. MS (EI, 70eV): *m*/*z* (%) = 383 ([M$^{\cdot}$]$^+$, 10); 171 (34); 126 (10); 84 (100).

*4.5.24. 1-Phenyl-3-[4-(4-pyrrolidin-1-ylbutoxy)benzene] sulfonylurea (**43**)*

White solid. Yield: 19%. M.p: 91–92 °C. IR (KBr, cm^{-1}): 3352 (m, ν_{N-H}); 1716 (w, $\nu_{C=O}$); 1249 (s, ν_{C-O-C}); 1176 (s, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.73 (bs, 4H, N–CH$_2$–CH$_2$–**CH$_2$**); 1.89

(bs, 4H, **H$_3$**+**H$_4$**-pyr); 3.11 (s, 2H, N–C**H$_2$**); 3.20 (bs, 4H, **H$_2$**+**H$_5$**-pyr); 3.29 (s, 1H, N**H**–SO_2); 4.01 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.2 Hz); 6.76 (t, 1H, **H$_4$**-ph-$_{NH}$, $J_{4\text{-}3,\ 5}$ = 7.0 Hz); 6.96 (t, 2H, **H$_3$**+**H$_5$**-ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 7.6 Hz); 7.10 (t, 2H, **H$_2$**+**H$_6$**-ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 7.6 Hz); 7.39 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.9 Hz); 7.73 (d, 2H, **H$_2$**+**H$_6$**, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.9 Hz); 8.43 (s, 1H, N**H**-ph). Anal. Calcd for $C_{21}H_{27}N_3O_4S.3/2H_2O$: C, 56.76%; H, 6.76%; N, 9.46%. Found: C, 56.89%; H, 6.69%; N, 9.27%. MS (EI, 70eV): *m*/*z* (%) = 417 (0.5); 298 (1); 119 (45); 84 (100).

4.5.25. 1-Cyclohexyl-3-[4-(4-pyrrolidin-1-ylbutoxy)benzene] sulfonylurea (**44**)

White solid. Yield: 28%. M.p: 96–97 °C. IR (KBr, cm^{-1}): 3275 (m, ν_{N-H}); 1705 (s, $\nu_{C=O}$); 1258 (s, ν_{C-O-C}); 1155 (vs, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.09–1.23 (m, 6H, **H$_3$**+**H$_4$**+**H$_5$**-cyc); 1.48 (t, 4H, **H$_2$**+**H$_6$**-cyc); 1.61 (bs, 4H, N–CH_2–CH_2–**CH_2**); 1.80 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.97 (s, 2H, N–C**H$_2$**); 3.16 (bs, 4H, **H$_2$**+**H$_5$**-pyr); 3.28 (s, 1H, **H$_1$**-cyc); 4.01 (s, 2H, O–C**H$_2$**); 6.86 (d, 1H, N**H**-CHcyc, J_{NH-CH} = 8.8 Hz); 7.10 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.7 Hz); 7.81 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.7 Hz); 10.51 (s, 1H, NH·**H**Cl) ppm. Anal. Calcd for $C_{21}H_{33}N_3O_4S{\cdot}HCl{\cdot}H_2O$: C, 52.77%; H, 7.12%; N, 8.80%. Found: C, 52.40%; H, 6.93%; N, 8.50%. MS (EI, 70eV): *m*/*z* (%) = 423 (10); 368 (48); 191 (90); 84 (100).

4.5.26. 1-(2,5-dichlorophenyl)-3-[4-(4-pyrrolidin-1-ylbutoxy) benzene]sulfonylurea (**45**)

White solid. Yield: 31%. M.p: 162–164 °C. IR (KBr, cm^{-1}): 3322 (w, ν_{N-H}); 1705 (s, $\nu_{C=O}$); 1250 (s, ν_{C-O-C}); 1134 (vs, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.75 (bs, 4H, N–CH_2–CH_2–**CH_2**); 1.90 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 3.00–3.30 (m, 7H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**, N**H**–SO_2); 4.00 (m, 2H, O–C**H$_2$**); 6.90–6.97 (m, 1H, **H$_4$**-2,5-diClph-$_{NH}$); 6.95 (bs, 2H, **H$_3$**+**H$_5$**); 7.40 (bs, 1H, **H$_3$**-2,5-diClph-$_{NH}$); 7.55 (s, 1H, N**H**-2,5-diClph-$_{NH}$); 7.70 (bs, 2H, **H$_2$**+**H$_6$**); 8.30 (s, 1H, **H$_6$**-2,5-diClph-$_{NH}$). Anal. Calcd for $C_{21}H_{25}Cl_2N_3O_4S$: C, 51.85%; H, 5.14%; N, 8.64%. Found: C, 52.12%; H, 5.26%; N, 8.45%.

4.5.27. 1-(4-trifluoromethylphenyl)-3-[4-(4-pyrrolidin-1-ylbutoxy) benzene]sulfonylurea (**46**)

Yellowish solid. Yield: 13%. M.p: 136–138 °C. IR (KBr, cm^{-1}): 3430 (m, ν_{N-H}); 1629 (s, $\nu_{C=O}$); 1242 (vs, ν_{C-O-C}); 1105 (vs, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.77 (bs, 4H, N–CH_2–CH_2–**CH_2**); 1.90 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 3.14–3.60 (m, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 4.02 (s, 2H, O–C**H$_2$**); 6.92 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.6 Hz); 7.42 (d, 2H, **H$_3$**+**H$_5$**-4-CF_3ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.5 Hz); 7.60 (d, 2H, **H$_2$**+**H$_6$**-4-CF_3ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 8.5 Hz); 7.73 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.6 Hz); 8.87 (s, 1H, N**H**-4-CF_3ph-$_{NH}$). Anal. Calcd for $C_{22}H_{26}F_3N_3O_4S$: C, 54.43%; H, 5.36%; N, 8.66%. Found: C, 54.09%; H, 5.11%; N, 8.71%. MS (EI, 70eV): *m*/*z* (%): 429 (3); 187 (57); 161 (85); 84 (100).

4.5.28. 1-Isopropyl-3-[4-(4-piperidin-1-ylbutoxy)benzene] sulfonylurea (**47**)

White solid. Yield: 98%. M.p: 117–119 °C. IR (KBr, cm^{-1}): 3378 (m, ν_{N-H}); 1597 (vs, $\nu_{C=O}$); 1388, 1146 (vs, ν_{SO2N}); 1258 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.98 (d, 6H, (C**H$_3$**)$_2$CH, J_{CH3-CH} = 6.5 Hz); 1.40 (s, 2H, **H$_4$**-pip); 1.54 (t, 4H, **H$_3$**+**H$_5$**-pip); 1.62 (bs, 2H, N–CH_2–**CH_2**); 1.73 (bs, 2H, O–CH_2–C**H$_2$**); 2.46–2.49 (m, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 3.55–3.57 (m, 1H, $(CH_3)_2$C**H**); 4.06 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.3 Hz); 6.20 (s, 1H, N**H**–CH); 7.05 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.8 Hz); 7.77 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz). Anal. Calcd for $C_{19}H_{31}N_3O_4S.1/2H_2O$: C, 56.16%; H, 7.88%; N, 10.34%. Found: C, 56.34%; H, 7.74%; N, 9.98%.

4.5.29. 1-Phenyl-3-[4-(4-piperidin-1-ylbutoxy)benzene] sulfonylurea (**48**)

White solid. Yield: 25%. M.p: 105–107 °C. IR (KBr, cm^{-1}): 1591 (m, $\nu_{C=O}$); 1309, 1127 (s, ν_{SO2N}); 1249 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.49 (s, 2H, **H$_4$**-pip); 1.66–1.73 (m, 8H, **H$_3$**+**H$_5$**-pip, N–C**H$_2$**–C**H$_2$**–CH_2); 2.91–2.95 (m, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 4.02 (s, 2H, O–C**H$_2$**); 6.77 (t, 1H, **H$_4$**-ph-$_{NH}$, $J_{4\text{-}3,\ 5}$ = 7.3 Hz); 6.90–6.94 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.7 Hz); 7.10 (t, 2H, **H$_3$**+**H$_5$**-ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.7 Hz, $J_{3,5\text{-}4}$ = 7.3 Hz); 7.39 (d, 2H, **H$_2$**+**H$_6$**-ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 8.4 Hz); 7.73 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.7 Hz); 8.41 (s, 1H, N**H**-ph). Anal. Calcd for $C_{22}H_{29}N_3O_4S$: C, 61.25%; H, 6.73%; N, 9.74%. Found: C, 61.42%; H, 7.38%; N, 9.99%.

4.5.30. 1-Cyclohexyl-3-[4-(4-piperidin-1-ylbutoxy)benzene] sulfonylurea (**49**)

White solid. Yield: 22%. M.p: 160–162 °C. IR (KBr, cm^{-1}): 1592 (m, $\nu_{C=O}$); 1312, 1117 (m, ν_{SO2N}); 1253 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.07–1.22 (m, 6H, **H$_3$**+**H$_4$**+**H$_5$**-cyc); 1.40 (s, 2H, **H$_4$**-pip); 1.51–1.62 (m, 10H, **H$_3$**+**H$_5$**-pip, N–CH_2–C**H$_2$**, **H$_2$**+**H$_6$**-cyc); 1.69–1.74 (m, 2H, O–CH_2–C**H$_2$**); 2.44–2.51 (m, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 3.26 (s, 1H, **H$_1$**-cyc); 4.05 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.4 Hz); 6.23 (s, 1H, N**H**-cyc); 7.05 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.6 Hz); 7.78 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.7 Hz). Anal. Calcd for $C_{22}H_{35}N_3O_4S{\cdot}½\ H_2O$: C, 59.19%; H, 8.07%; N, 9.41%. Found: C, 59.41%; H, 7.98%; N, 9.30%.

4.5.31. 1-(2,5-dichlorophenyl)-3-[4-(4-piperidin-1-ylbutoxy) benzene]sulfonylurea (**50**)

White solid. Yield: 64%. M.p: 153–155 °C. IR (KBr, cm^{-1}): 3422 (w, ν_{N-H}); 1585 (m, $\nu_{C=O}$); 1351, 1134 (s, ν_{SO2N}); 1253 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.49 (s, 2H, **H$_4$**-pip); 1.66 (bs, 4H, **H$_3$**+**H$_5$**-pip); 1.74 (bs, 4H, N–CH_2–CH_2–**CH_2**); 2.93 (bs, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 4.03–4.09 (m, 2H, O–C**H$_2$**); 6.89–6.93 (dd, 1H, **H$_4$**-2,5-diClph-$_{NH}$, J_{4-3} = 8.5 Hz, J_{4-6} = 2.6 Hz); 7.08 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.5 Hz); 7.36 (d, 1H, **H$_3$**-2,5-diClph-$_{NH}$, J_{3-4} = 8.5 Hz); 7.53 (s, 1H, **H$_6$**-2,5-diClph-$_{NH}$); 7.73 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.6 Hz); 8.28 (d, 1H, N**H**-2,5-diClph-$_{NH}$). Anal. Calcd for $C_{22}H_{27}Cl_2N_3O_4S.1/2H_2O$: C, 51.87%; H, 5.50%; N, 8.25%. Found: C, 51.54%; H, 5.24%; N, 8.11%.

4.5.32. 1-(4-trifluoromethylphenyl)-3-[4-(4-piperidin-1-ylbutoxy) benzene]sulfonylurea (**51**)

White solid. Yield: 9%. M.p: 115–117 °C. IR (KBr, cm^{-1}): 3430 (w, ν_{N-H}); 1622 (s, $\nu_{C=O}$); 1242 (vs, ν_{C-O-C}); 1107 (s, ν_{SO2N}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.23–1.28 (m, 2H, **H$_4$**-pip); 1.72–1.76 (m, 8H, **H$_3$**+**H$_5$**-pip, N–CH_2–CH_2–**CH_2**); 3.02 (bs, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 3.57 (s, 1H, N**H**–SO_2); 4.04 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 5.5 Hz); 6.92 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.7 Hz); 7.42 (d, 2H, **H$_3$**+**H$_5$**-4-CF_3ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 8.6 Hz); 7.60 (d, 2H, **H$_2$**+**H$_6$**-4-CF_3ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 8.7 Hz); 7.73 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.87 (s, 1H, N**H**-4-CF_3ph-$_{NH}$). Anal. Calcd for $C_{23}H_{28}F_3N_3O_4S{\cdot}H_2O$: C, 53.37%; H, 5.61%; N, 8.41%. Found: C, 53.57%; H, 5.70%; N, 8.03%.

4.5.33. 1-Phenyl-3-{4-[4-(4-ethoxycarbonylpiperidin-1-yl)butoxy] benzene}sulfonylurea (**52**)

White solid. Yield: 50%. M.p: 93–94 °C. IR (KBr, cm^{-1}): 3351 (m, ν_{N-H}); 1727 (vs, $\nu_{C=Oester}$); 1596 (m, $\nu_{C=Ourea}$); 1311, 1131 (vs, ν_{SO2N}); 1249 (s, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.17 (t, 3H, C**H$_3$**, $J_{CH3-CH2}$ = 7.0 Hz); 1.49 (bs, 4H, N–CH_2–CH_2–**CH_2**); 1.57 (dq, 2H, **H$_{3eq}$**+**H$_{5eq}$**-pip); 1.79 (dd, 2H, **H$_{3ax}$**+**H$_{5ax}$**-pip); 2.10 (dt, 2H, **H$_{2eq}$**+**H$_{6eq}$**-pip); 2.27 (t, 1H, **H$_4$**-pip); 2.67 (bs, 2H, N–C**H$_2$**); 2.86 (dt, 2H, **H$_{2ax}$**+**H$_{6ax}$**-pip); 4.06 (m, 4H, CH_3–C**H$_2$**, O–C**H$_2$**); 6.70 (t, 1H, **H$_4$**-ph-$_{NH}$, $J_{4\text{-}3,\ 5}$ = 7.2 Hz); 6.87, 6.89, 6.71 (ddd, 2H, **H$_3$**+**H$_5$**, $J_{3,5\text{-}2,6}$ = 8.8 Hz, $J_{3\text{-}5,\ 5\text{-}3}$ = 2.8 Hz, $J_{3\text{-}6,5\text{-}2}$ = 1.8 Hz); 7.06 (t, 2H, **H$_3$**+**H$_5$**-ph-$_{NH}$, $J_{3,5\text{-}2,6}$ = 7.2 Hz); 7.39, 7.41, 7.44 (ddd, 2H, **H$_2$**+**H$_6$**-ph-$_{NH}$, $J_{2,6\text{-}3,5}$ = 7.6 Hz, $J_{2\text{-}6,6,2}$ = 3.0 Hz, $J_{2\text{-}5,6\text{-}3}$ = 2.0 Hz); 7.69 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6\text{-}3,5}$ = 8.8 Hz); 8.26 (s, 1H, N**H**-ph). Anal. Calcd for $C_{25}H_{33}N_3O_6S.H_2O$: C, 57.58%; H, 6.72%; N, 8.06%. Found: C, 57.71%; H, 6.39%; N, 8.10%.

*4.5.34. 1-(3-trifluoromethylphenyl)-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene]sulfonylurea (**53**)*

White solid. Yield: 13%. M.p: 114–116 °C. IR (KBr, cm^{-1}): 3337 (m, ν_{N-H}); 1722 (m, $\nu_{C=O}$); 1254 (s, ν_{C-O-C}); 1125 (vs, ν_{SO2N}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.92 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.12 (bs, 2H, N–CH$_2$–**CH$_2$**); 3.26 (bs, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 4.11 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 5.8 Hz); 6.97 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.7 Hz); 7.10 (d, 1H, **H$_5$**-3-CF$_3$ph-$_{NH}$, J_{5-6} = 7.6 Hz); 7.34 (t, 1H, **H$_4$**-3-CF$_3$ph-$_{NH}$, J_{4-5} = 8.1 Hz); 7.52 (d, 1H, **H$_6$**-3-CF$_3$ph-$_{NH}$, J_{6-5} = 7.8 Hz); 7.76 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.7 Hz); 7.96 (s, 1H, **H$_2$**-3-CF$_3$ph-$_{NH}$); 8.98 (s, 1H, N**H**-3-CF$_3$ph-$_{NH}$); 10.15 (bs, 1H, NH·**H**Cl). Anal. Calcd for $C_{21}H_{24}F_3N_3O_4S$ ·HCl: C, 49.65%; H, 4.93%; N, 8.28%. Found: C, 49.49%; H, 4.71%; N, 7.91%.

*4.5.35. 1-(4-acetylphenyl)-3-[4-(3-pyrrolidin-1-ylpropoxy) benzene]sulfonylurea (**54**)*

White solid. Yield: 23%. M.p: 161–162 °C. IR (KBr, cm^{-1}): 3286 (m, ν_{N-H}); 1695 (s, $\nu_{C=O\ ketone}$); 1664 (s, $\nu_{C=O\ urea}$); 1234 (vs, ν_{C-O-C}); 1135 (s, ν_{SO2N}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.67 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 1.87 (bs, 2H, N–CH$_2$–**CH$_2$**); 2.42 (bs, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 2.51 (s, 3H, C**H$_3$**–CO); 4.03 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.0 Hz); 6.90 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.4 Hz); 7.54 (d, 2H, **H$_3$**+**H$_5$**-COCH$_3$ph-$_{NH}$, $J_{3,5-2,6}$ = 8.5 Hz); 7.71 (bs, 4H, **H$_2$**+**H$_6$**, **H$_2$**+**H$_6$**-COCH$_3$ph-$_{NH}$); 8.85 (s, 1H, N**H**-4-COCH$_3$ph-$_{NH}$). Anal. Calcd for $C_{22}H_{27}N_3O_5S.1/2H_2O$: C, 58.14%; H, 6.17%; N, 9.25%. Found: C, 57.89%; H, 6.19%; N, 8.98%.

*4.5.36. 1-(4-methylphenyl)-3-[4-(3-pyrrolidin-1-ylpropoxy) benzene]sulfonylurea (**55**)*

White solid. Yield: 15%. M.p: 158–159 °C. IR (KBr, cm^{-1}): 3442 (w, ν_{N-H}); 1635 (s, $\nu_{C=O}$); 1227 (vs, ν_{C-O-C}); 1123 (vs, ν_{SO2N}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.87 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.07–2.14 (m, 2H, N–CH$_2$–**CH$_2$**); 2.17 (s, 3H, C**H$_3$**-ph); 3.08 (bs, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 4.09 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.0 Hz); 6.90–6.96 (m, 4H, **H$_3$**+**H$_5$**, **H$_3$**+**H$_5$**-4–CH$_3$–ph); 7.30 (d, 2H, **H$_2$**+**H$_6$**-4–CH$_3$–ph, $J_{2,6-3,5}$ = 8.2 Hz); 7.74 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.7 Hz); 8.52 (s, 1H, N**H**-4-CH$_3$ph-$_{NH}$). Anal. Calcd for $C_{21}H_{27}N_3O_4S.2/3H_2O$: C, 58.74%; H, 6.53%; N, 9.79%. Found: C, 58.54%; H, 6.61%; N, 9.78%.

*4.5.37. 1-(1-naphthyl)-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene] sulfonylurea (**56**)*

White solid. Yield: 15%. M.p: 136–137 °C. IR (KBr, cm^{-1}): 3415 (w, ν_{N-H}); 1599 (s, $\nu_{C=O}$); 1343, 1134 (vs, ν_{SO2N}); 1248 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.83 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 1.97–2.04 (m, 2H, N–CH$_2$–**CH$_2$**); 3.06 (bs, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 4.04 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.1 Hz); 6.96 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.8 Hz); 7.35 (t, 1H, **H$_3$**-naph, $J_{3-4,2}$ = 7.9 Hz); 7.45–7.49 (m, 3H, **H$_2$**+**H$_6$**+**H$_7$**-naph); 7.79 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.7 Hz); 7.83–7.85 (m, 1H, **H$_4$**-naph); 7.90 (d, 1H, **H$_5$**-naph, J_{5-6} = 7.5 Hz); 8.03–8.05 (m, 1H, **H$_8$**-naph); 8.61 (s, 1H, N**H**-naph). Anal. Calcd for $C_{24}H_{27}N_3O_4S.1/2H_2O$: C, 62.34%; H, 6.06%; N, 9.09%. Found: C, 62.32%; H, 6.10%; N, 8.94%. MS (EI, 70eV): *m/z* (%) = 462 ($[M^{\cdot}]^+$, 5); 327 (14); 285 (20); 239 (46); 110 (5); 84 (100).

*4.5.38. 1-[4-(N,N′-dimethylamino)phenyl]-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene]sulfonylurea (**57**)*

Purple solid. Yield: 21%. M.p: 142–143 °C. IR (KBr, cm^{-1}): 3465 (w, ν_{N-H}); 1601 (s, $\nu_{C=O}$); 1312, 1123 (vs, ν_{SO2N}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.84 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.01–2.07 (m, 2H, N–CH$_2$–**CH$_2$**); 2.76 (bs, 6H, N(C**H$_3$**)$_2$); 3.00–3.04 (m, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 4.07 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.4 Hz); 6.56 (d, 2H, **H$_3$**+**H$_5$**-4–N(CH$_3$)$_2$–ph, $J_{3,5-2,6}$ = 8.6 Hz); 6.87 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.9 Hz); 7.24 (d, 2H, **H$_2$**+**H$_6$**-4–N(CH$_3$)$_2$–ph, $J_{2,6-3,5}$ = 8.8 Hz); 7.73 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.8 Hz); 8.27 (s, 1H, N**H**-4–N(CH$_3$)$_2$–ph). Anal. Calcd for $C_{22}H_{30}N_4O_4S.1/2H_2O$: C, 58.02%; H, 6.81%; N, 12.31%. Found: C, 57.91%; H, 6.64%; N, 12.34%. MS (EI, 70eV): *m/z* (%) = 455 ($[M^{\cdot}]^+$, 10); 327 (12); 284 (10); 239 (33); 134 (52); 84 (100).

*4.5.39. 1-Benzhydryl-3-[4-(3-pyrrolidin-1-ylpropoxy)benzene] sulfonylurea (**58**)*

White solid. Yield: 3%. M.p: 104 °C. IR (KBr, cm^{-1}): 3374 (m, ν_{N-H}); 1707 (s, $\nu_{C=O}$); 1251 (s, ν_{C-O-C}); 1155 (s, ν_{SO2N}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.82 (bs, 4H, **H$_3$**+**H$_4$**-pyr); 2.05–2.08 (m, 2H, N–CH$_2$–**CH$_2$**); 2.96 (d, 6H, **H$_2$**+**H$_5$**-pyr, N–C**H$_2$**); 4.07 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 5.0 Hz); 5.79 (d, 1H, C**H**–C$_{12}$H$_{10}$, J_{CH-NH} = 8.0 Hz); 7.04 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.2 Hz); 7.20–7.28 (m, 10H, CH–C$_{12}$**H$_{10}$**); 7.62 (d, 1H, N**H**–CH–C$_{12}$H$_{10}$, J_{CH-NH} = 7.7 Hz); 7.79 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 7.7 Hz). Anal. Calcd for $C_{27}H_{31}N_3O_4S·H_2O$: C, 63.41%; H, 6.46%; N, 8.22%. Found: C, 63.46%; H, 6.31%; N, 8.26%.

*4.5.40. 1-(2-trifluoromethylphenyl)-3-[4-(3-piperidin-1-ylpropoxy) benzene]sulfonylurea (**59**)*

White solid. Yield: 20%. M.p: 159–160 °C. IR (KBr, cm^{-1}): 3477 (w, ν_{N-H}); 1644 (s, $\nu_{C=O}$); 1322, 1138 (vs, ν_{SO2N}); 1257 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.48 (bs, 2H, **H$_4$**-pip); 1.65 (bs, 4H, **H$_3$**+**H$_5$**-pip); 2.04 (bs, 2H, N–CH$_2$–**CH$_2$**); 2.93 (bs, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 4.05–4.12 (m, 2H, O–C**H$_2$**); 6.91–6.95 (m, 1H, **H$_4$**-2-CF$_3$ph-$_{NH}$); 7.00–7.10 (m, 1H, **H$_5$**-2-CF$_3$ph-$_{NH}$); 7.22–7.32 (m, 2H, **H$_3$**+**H$_5$**); 7.45–7.54 (m, 2H, **H$_3$**+**H$_6$**-2-CF$_3$ph-$_{NH}$); 7.71–7.76 (m, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.8 Hz); 8.20 (bs, 1H, N**H**-2-CF$_3$ph-$_{NH}$). Anal. Calcd for $C_{22}H_{26}F_3N_3O_4S·H_2O$: C, 52.48%; H, 5.57%; N, 8.35%. Found: C, 52.75%; H, 5.49%; N, 8.04%.

*4.5.41. 1-(3-trifluoromethylphenyl)-3-[4-(3-piperidin-1-ylpropoxy) benzene]sulfonylurea (**60**)*

White solid. Yield: 34%. M.p: 108–110 °C. IR (KBr, cm^{-1}): 3321 (w, ν_{N-H}); 1596 (s, $\nu_{C=O}$); 1338, 1169 (vs, ν_{SO2N}); 1253 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.52 (bs, 2H, **H$_4$**-pip); 1.70 (bs, 4H, **H$_3$**+**H$_5$**-pip); 2.07–2.11 (m, 2H, N–CH$_2$–**CH$_2$**); 3.10–3.14 (bs, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 4.07 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 5.9 Hz); 6.93 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.9 Hz); 7.05 (d, 1H, **H$_5$**-3-CF$_3$ph-$_{NH}$, $J_{5-4,6}$ = 8.0 Hz); 7.30 (t, 1H, **H$_4$**-3-CF$_3$ph-$_{NH}$, J_{4-5} = 8.0 Hz); 7.51 (d, 1H, **H$_6$**-3-CF$_3$ph-$_{NH}$, J_{6-5} = 8.2 Hz); 7.74 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.8 Hz); 8.00 (s, 1H, **H$_2$**-3-CF$_3$ph-$_{NH}$); 8.79 (bs, 1H, N**H**-3-CF$_3$ph-$_{NH}$) ppm. Anal. Calcd for $C_{22}H_{26}F_3N_3O_4S$: C, 54.43%; H, 5.36%; N, 8.66%. Found: C, 54.57%; H, 5.41%; N, 8.37%.

*4.5.42. 1-(4-methoxyphenyl)-3-[4-(3-piperidin-1-ylpropoxy) benzene]sulfonylurea (**61**)*

Beige solid. Yield: 39%. M.p: 85–87 °C. IR (KBr, cm^{-1}): 3351 (w, ν_{N-H}); 1596 (s, $\nu_{C=O}$); 1338, 1136 (vs, ν_{SO2N}); 1243 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.47 (bs, 2H, **H$_4$**-pip); 1.65 (bs, 4H, **H$_3$**+**H$_5$**-pip); 2.02–2.07 (m, 2H, N–CH$_2$–**CH$_2$**); 2.93 (m, 6H, **H$_2$**+**H$_6$**-pip, N–C**H$_2$**); 3.66 (s, 3H, OC**H$_3$**); 4.06 (t, 2H, O–C**H$_2$**, $J_{CH2-CH2}$ = 6.0 Hz); 6.73 (d, 2H, **H$_2$**+**H$_6$**-4-OCH$_3$ph-$_{NH}$, $J_{2,6-3,5}$ = 8.9 Hz); 6.96 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.5 Hz); 7.29 (d, 2H, **H$_3$**+**H$_5$**-4-OCH$_3$ph-$_{NH}$, $J_{3,5-2,6}$ = 8.9 Hz); 7.77 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.5 Hz); 8.79 (s, 1H, N**H**-4-OCH$_3$ph-$_{NH}$). Anal. Calcd for $C_{22}H_{29}N_3O_5S·1/2H_2O$: C, 57.89%; H, 6.58%; N, 9.21%. Found: C, 57.52%; H, 6.77%; N, 8.86%.

*4.5.43. 1-(4-acetylphenyl)-3-[4-(3-piperidin-1-ylpropoxy)benzene] sulfonylurea (**62**)*

White solid. Yield: 64%. M.p: 146–148 °C. IR (KBr, cm^{-1}): 3420 (w, ν_{N-H}); 1686 (s, $\nu_{C=Oketone}$); 1599 (s, $\nu_{C=Ourea}$); 1359, 1173 (vs, ν_{SO2N}); 1232 (vs, ν_{C-O-C}). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.36 (bs, 2H, **H$_4$**-pip); 1.46–1.51 (m, 4H, **H$_3$**+**H$_5$**-pip); 1.63 (s, 3H,

CO−C**H$_3$**); 1.85 (t, 2H, N−CH$_2$-**CH$_2$**, $J_{CH2-CH2}$ = 6.8 Hz); 2.31−2.37 (m, 4H, **H$_2$**+**H$_6$**-pip); 2.44 (s, 2H, N−C**H$_2$**); 4.01 (t, 2H, O−C**H$_2$**, $J_{CH2-CH2}$ = 6.4 Hz); 6.89 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.9 Hz); 7.54 (d, 2H, **H$_2$**+**H$_6$**-4-COCH$_3$ph-$_{NH}$, $J_{2,6-3,5}$ = 8.8 Hz); 7.69−7.72 (m, 4H, **H$_2$**+**H$_6$**, **H$_3$**+**H$_5$**-4-COCH$_3$ph-$_{NH}$); 8.86 (s, 1H, N**H**-4-COCH$_3$ph-$_{NH}$). Anal. Calcd for $C_{23}H_{29}N_3O_5S\cdot H_2O$: C, 57.86%; H, 6.50%; N, 8.80%. Found: C, 58.25%; H, 6.39%; N, 8.40%.

4.5.44. 1-(4-methylphenyl)-3-[4 -(3-piperidin-1-ylpropoxy) benzene]sulfonylurea (**63**)

Beige solid. Yield: 76%. M.p: 120−122 °C. IR (KBr, cm^{-1}): 3394, 3326 (m, ν_{N-H}); 1594 (s, $\nu_{C=O}$); 1309, 1138 (vs, ν_{SO2N}); 1230 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.37 (d, 2H, **H$_4$**-pip); 1.45−1.50 (m, 4H, **H$_3$**+**H$_5$**-pip); 1.84 (t, 2H, N−CH$_2$-**CH$_2$**, $J_{CH2-CH2}$ = 6.8 Hz); 2.15 (s, 3H, C**H$_3$**-ph-$_{NH}$); 2.22 (bs, 2H, N−C**H$_2$**); 2.31−2.38 (m, 4H, **H$_2$**+**H$_6$**-pip); 4.00 (t, 2H, O−C**H$_2$**, $J_{CH2-CH2}$ = 6.4 Hz); 6.87 (d, 4H, **H$_3$**+**H$_5$**, **H$_3$**+**H$_5$**-4-CH$_3$ph-$_{NH}$); 7.30 (d, 2H, **H$_2$**+**H$_6$**-4-CH$_3$ph-$_{NH}$, $J_{2,6-3,5}$ = 8.4 Hz); 7.68 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.5 Hz); 8.18 (s, 1H, N**H**-4-COCH$_3$ph-$_{NH}$). Anal. Calcd for $C_{22}H_{29}N_3O_4S\cdot 1/2H_2O$: C, 60.00%; H, 6.98%; N, 9.54%. Found: C, 60.14%; H, 6.82%; N, 9.17%.

4.5.45. 1-Benzhydryl-3-[4-(3-piperidin-1-ylpropoxy)benzene] sulfonylurea (**64**)

White solid. Yield: 21%. M.p: 182−184 °C. IR (KBr, cm^{-1}): 3367 (m, ν_{N-H}); 1634 (s, $\nu_{C=O}$); 1306, 1123 (vs, ν_{SO2N}); 1262 (vs, ν_{C-O-C}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.41 (bs, 2H, **H$_4$**-pip); 1.56 (bs, 4H, **H$_3$**+**H$_5$**-pip); 1.94 (t, 2H, N−CH$_2$-**CH$_2$**, $J_{CH2-CH2}$ = 6.3 Hz); 2.67 (bs, 6H, **H$_2$**+**H$_6$**-pip, N−C**H$_2$**); 4.07 (t, 2H, O−C**H$_2$**, $J_{CH2-CH2}$ = 6.4 Hz); 5.81 (d, 1H, C**H**−C$_{12}$**H$_{10}$**, J_{CH-NH} = 7.9 Hz); 7.00 (d, 2H, **H$_3$**+**H$_5$**, $J_{3,5-2,6}$ = 8.9 Hz); 7.20−7.28 (m, 12H, CH−C$_{12}$**H$_{10}$**, N**H**CON**H**); 7.63 (d, 2H, **H$_2$**+**H$_6$**, $J_{2,6-3,5}$ = 8.0 Hz). Anal. Calcd for $C_{28}H_{33}N_3O_4S\cdot 1/2H_2O$: C, 65.12%; H, 6.59%; N, 8.14%. Found: C, 65.35%; H, 6.23%; N, 8.28%.

4.6. Pharmacology

4.6.1. [^{125}I]Iodoproxyfan binding assay

All compounds described in this paper were assayed for their ability to displace radiolabelled [^{125}I]Iodoproxyfan from hH$_3$ receptors in a competitive binding assay [35].

CHO-K1 cells (American type culture collection, CCL61) were maintained in Ham-F12 medium supplemented with 10% (v/v) fetal calf serum, 2 mM glutamine, 500 units/ml penicillin and 500 μg/ml streptomycin. The coding regions of the human H3 receptor were subcloned into the pcDNA-neo expression vector (Invitrogen) and transfected into CHO-K1 cells using lipofectAMINE™, as described by the manufacturer (Life Technologies). Stably transfected cells were selected with neomycin (500 μg/ml) and tested for their ability to bind [^{125}I]Iodoproxyfan.

Cells grown to confluence were harvested in 2 mM EDTA/PBS and centrifuged at 1000 *g* for 5 min (4 °C). The resulting pellet was suspended in 20 mM Tris}HCl (pH 7.7) containing 5 mM EDTA, and was homogenized using a Kinematica polytron (Fisher Bioblock Scientific, Illkirch, France). The homogenate was then centrifuged at 95000 *g* for 30 min (4 °C) and the pellet was suspended in binding buffer [50 mM Na/HPO%/KH/PO$_4$ (pH 7.5)]. Aliquots of membrane preparations were stored at −80 °C and were used for [^{125}I]iodoproxyfan binding experiments.

Membranes (5 μg/ml) obtained from cells stably expressing hH$_3$ receptors were incubated for 1 h at room temperature in binding buffer in a final volume of 250 μl. For competition studies, 25 pM [^{125}I]Iodoproxyfan (2000 Ci/mmol; Amersham Pharmacia Biotech) was used. Nonspecific binding was determined in the presence of 1 μM R(−)-α-methylhistamine. The reaction was stopped by rapid filtration through GF/B unifillters pretreated with 0.1% polyethyleneimine, followed by three ice-cold buffer washes [50 mM Tris}HCl (pH 7.4)]. The binding data were analyzed by a non-linear regression curve-fitting (single site) procedure using the computer program PRISM (Graphpad Software Inc., San Diego, CA, U.S.A.) to yield IC$_{50}$ values.

4.6.2. K_{ATP} channel binding assay

The inhibitory effect on K_{ATP} channels of all sulfonylurea derivatives was studied in rat cerebral cortex membranes as previously described [36].

4.6.3. hERG binding assay

4.6.3.1. Cell culture. HERG-transfected HEK 293 cells were obtained from the University of Wisconsin. These cells have been fully characterized [37] and are widely used in functional isolated whole-cell patch clamp assays for measuring hERG current block. The cells were routinely cultured in T-175 cm^2 flasks in MEM (Gibco/BRL 11095-080) supplemented with 2 mM L-glutamine (Gibco/BRL 25030-081), 10% fetal bovine serum (Gibco/BRL 16000-036), 0.2 mg/ml geneticin (Gibco/BRL 10131-027), 1% penicillin/streptomycin (Gibco/BRL 15140-122), 0.1 mM non-essential amino acids (Gibco/BRL 11140-050), and 1 mM sodium pyruvate (Gibco/BRL 11360-070) in a 37 °C incubator with 5% CO_2.

For membrane preparation, cells from two T-175 flasks were combined, added to 2 l of complete MEM, seeded into a cell factory (10 trays/chamber, 6320 cm^2 culture area, Nunc catalog #170009), and incubated at 37 °C, 5% CO_2 for 5 days with no media changes. Six cell factories were typically seeded at the same time. Several different membrane homogenate preparations and cell passages (ranging from 17 to 66) were used to generate the data.

4.6.3.2. Membrane preparations. When the cells were approximately 80% confluent, the media were aspirated and the cell factory chambers were washed with 1 l D-PBS (Gibco/BRL 14190-136). Cells from each cell factory were harvested with 200 ml PBS-based, enzyme-free cell dissociation buffer and rinsed with 250 ml DPBS. Cells were then centrifuged at 14000x *g* for 15 min at 4 °C, resuspended in cold 0.32 M sucrose (10 ml/g of wet weight), and homogenized using a Tekmar Tissuemizer. The cell homogenate was centrifuged at 1000x *g* at 4 °C for 10 min and the supernatant was centrifuged at 41,000x *g* at 4 °C for 30 min. The resulting membrane pellets were suspended in 6.25 ml of 50 mM Tris (pH 8.5)/5 mM KCl per each gram of wet pellet weight, flash-frozen in liquid nitrogen and stored at −80 °C. Protein content was determined by the Coomasie method using Pierce's Dry Protein Assay Plate (cat. # 1856296).

4.6.3.3. [^{3}H]Dofetilide-isolated membrane binding assay. The assay conditions for [^{3}H]dofetilide binding in membrane homogenates were adapted from previously published methods [38]. The incubation temperature was maintained at 37 °C in order to more accurately correlate our results to those in the reference literature, and the incubation time for competition assays was 45 min. Preliminary studies demonstrated that equilibrium binding was achieved at 15 min and maintained until 90 min. This coincides fairly well with incubation times ranging from 30 to 60 min reported in the literature. Astemizole, a selective H$_1$-receptor antagonist and potent hERG current blocker, was used to determine nonspecific binding.

Stock solutions of drugs were prepared in dimethylsulfoxide (DMSO) at 10- or 30-mM concentrations. Serial drug dilutions were prepared in binding assay buffer containing 1% DMSO for a final DMSO assay concentration of 0.1%. Each concentration point was tested in duplicate in each experiment.

hERG-transfected HEK 293 cells were suspended in binding assay buffer (37 °C) at a concentration of 106 cells/ml. Membrane aliquots were thawed and homogenized again in a glass Dounce homogenizer (approximately 10 passes). The following were added to each 200-μl well of a 96-well polystyrene plate (Packard Optiplate, cat. # 6005290): 20 μl of assay binding buffer (for total bound determination), 1 μM astemizole (for nonspecific binding) or test compound, 50 μl of [^{3}H]dofetilide, and 130 μl of membrane homogenate (final protein concentration = 30 μg/well). The plates were incubated at 37 °C for 45 min, aspirated onto GF/B filter plates, and washed with 2 ml of cold wash buffer. The radioactivity was counted in a Packard Topcount Scintillation Counter after adding 50 μl of scintillant (Packard Microscint-20, cat. # 6013621). Counts per minute data from binding experiments were converted to percent total specific bound (%TSB) using the following formula: % TSB = [(cpm _NSB)/(TB _NSB)]_100. The data was analyzed with a four parameter logistic equation (PRISM, Graphpad) and reported as IC_{50} where IC_{50} was the concentration that gives 50% inhibition of [^{3}H]dofetilide binding. For drugs that failed to displace more than 50% of labeled dofetilide at the highest concentration tested, IC_{50} values were reported as >10 μM. Drugs were typically tested at seven concentrations, at half-log intervals. Each concentration point was tested in duplicate.

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References

[1] R. Sicree, J.E. Shaw, P.Z. Zimmet, The global burden of diabetes, in: D. Gan (Ed.), Diabetes Atlas, second ed. International Diabetes Federation, Brussels, Belgium, 2003, pp. 15–71.
[2] A. Astrup, N. Finer, Obes. Rev. 1 (2) (2000) 57–59.
[3] A.A. Hancock, M.E. Brune, Expert Opin. Investig. Drugs 14 (2005) 223–241.
[4] J.M. Arrang, M. Garbarg, J.C. Schwartz, Nature 302 (1983) 832–837.
[5] T.W. Lovenberg, B.L. Roland, S.J. Wilson, X. Jiang, J. Pyati, A. Huvar, M.R. Jackson, M.G. Erlander, Mol. Pharmacol. 55 (1999) 1101–1107.
[6] S. Threlfell, S.J. Cragg, I. Kalló, G.F. Turi, C.W. Coen, S.A. Greenfield, J. Neurosci. 24 (2004) 8704–8710.
[7] T.A. Esbenshade, G.B. Fox, M.D. Cowart, Mol. Interventions 6 (2) (2006) 77–88.
[8] S. Morisset, A. Rouleau, X. Ligneau, F. Gbahou, J. Tardivel-Lacombe, H. Stark, W. Schunack, C.R. Ganellin, J.C. Schwartz, J.M. Arrang, Nature 408 (2000) 860–864.
[9] J. Clapham, G.J. Kilpatrick, Br. J. Pharmacol. 107 (1992) 919–923.
[10] E. Schlicker, K. Fink, M. Hinterthaner, M. Gothert, Naunyn Schmiedebergs Arch. Pharmacol. 340 (1989) 633–638.
[11] E. Schlicker, K. Fink, M. Detzner, M. Gothert, J. Neural Transm. Gen. Sect. 93 (1993) 1–10.
[12] (a) T.A. Esbenshade, K.E. Browman, R.S. Bitner, M. Strakhova, M.D. Cowart, J.D. Brioni, Br. J. Pharmacol. 154 (2008) 1166–1181;
(b) G.B. Fox, J.B. Pan, R.J. Radek, A.M. Lewis, R.S. Bitner, T.A. Esbenshade, R. Faghih, Y.L. Bennani, M. Williams, B.B. Yao, M.W. Decker, A.A. Hancock, J. Pharmacol. Exp. Ther. 305 (2003) 897–908;
(c) A.A. Hancock, Y.L. Bennani, E.N. Bush, T.A. Esbenshade, R. Faghih, G.B. Fox, P. Jacobson, V. Knourek- Segel, K.M. Krueger, M.E. Nuss, J.B. Pan, R. Shapiro, D.G. Witte, B.B. Yao, Eur. J. Pharmacol. 487 (2004) 183–197;
(d) S. Celanaire, M. Wijtmans, P. Talaga, R. Leurs, I.J.P. de Esch, Drug Discov. Today 10 (2005) 1613.
[13] X. Ligneau, J. Lin, G. Vanni-Mercier, M. Jouvet, J.L. Muir, C.R. Ganellin, H. Stark, S. Elz, W. Schunack, J.J. Schwartz, J. Pharmacol. Exp. Ther. 287 (1998) 658–666.
[14] H. Van der Goot, M.J.P. Schepers, G.J. Sterk, H. Timmerman, Eur. J. Med. Chem. 27 (1992) 511–517.
[15] T.W. Lovenberg, J. Pyati, H. Chang, S.J. Wilson, M.G. Erlander, J. Pharmacol. Exp. Ther. 293 (2000) 771–778.
[16] R. Aslanian, M.W. Mutahi, N. Shih, K.D. McCormick, J.J. Piwinski, P.C. Ting, M.M. Albanese, M.Y. Berlin, X. Zhu, S. Wong, S.B. Rosenblum, Y. Jiang, R. West, S. She, S.M. Williams, M. Bryant, J.A. Hey, Bioorg. Med. Chem. Lett. 12 (2002) 937–941.
[17] M. Mor, F. Bordi, C. Silva, S. Rivara, V. Zuliani, F. Vacondio, M. Rivara, E. Barocelli, S. Bertoni, V. Ballabeni, F. Magnanini, M. Impicciatore, P.V. Plazzi, Bioorg. Med. Chem. 12 (2004) 663–674.
[18] (a) M. Cowart, J.K. Pratt, A.O. Stewart, Y. Bennani, T.A. Esbenshade, A.A. Hancock, Bioorg. Med. Chem. Lett. 14 (2004) 689–693;
(b) G.B. Fox, T.A. Esbenshade, J.B. Pan, R.J. Radek, K.M. Krueger, B.B. Yao, K.E. Browman, M.J. Buckley, M.E. Ballard, V.A. Komater, H. Miner, M. Zhang, R. Faghih, L.E. Rueter, R.S. Bitner, K.U. Drescher, J. Wetter, K. Marsh, M. Lemaire, R.D. Porsolt, Y.L. Bennani, J.P. Sullivan, M.D. Cowart, M.W. Decker, A.A. Hancock, J. Pharmacol. Exp. Ther. 313 (2005) 176–190.
[19] C.R. Ganellin, F. Leurquin, A. Piripitsi, J.M. Arrang, M. Garbang, X. Ligneau, W. Schunack, J.C. Schwartz, Arch. Pharm. Pharm. Med.Chem. 331 (1998) 395–404.
[20] R. Apodaca, C.A. Dvorak, W. Xiao, A.J. Barbier, J.D. Boggs, S.J. Wilson, J. Med. Chem. 46 (2003) 3938–3944.
[21] W.K. Kroeze, S.J. Hufeisen, B.A. Popadak, S.M. Renock, S. Steinberg, P. Ernsberger, K. Jayathilake, H.Y. Meltzer, B.L. Roth, Neuropsychopharmacology 28 (2003) 519–526.
[22] F. Zaragoza, H. Stephensen, S.M. Knudsen, L. Pridal, B.S. Wulff, K. Rimvall, J. Med. Chem. 47 (2004) 2833–2838.
[23] B.B. Yao, C.W. Hutchins, T.L. Carr, S. Cassar, J.N. Masters, Y.L. Bennani, T.A. Esbenshade, A.A. Hancock, Neuropharmacology 44 (2003) 773–786.
[24] (a) S. Celanire, M. Wijtmans, P. Talaga, R. Leurs, J.P. de Esch, Drug Discov. Today 10 (2005) 1613–1627;
(b) F.U. Axe, S.D. Bembenek, S. Szalma, J. Mol. Graph. Model. 24 (2006) 456–464.
[25] M.E. Doyle, J.M. Egan, Pharmacol. Rev. 55 (2003) 105–131.
[26] (a) F. Contreras, B. Romero, N. Suárez, M. González, C. Fouillioux, E. Guevara, M.C. Betancourt, D. Torres, M. Velasco, AVFT 21 (2002) 148–155;
(b) S. Del Patro, C. Bianchi, P. Marchetti, Diabetes Metab. Res. Rev. 23 (2007) 518–527;
(c) P. Serrano, R. Chavez, Ann. N. Y. Acad. Sci. 74 (1959) 931–935.
[27] (a) H.E. Lebovitz, M.N. Feinglos, Am. J. Med. 75 (1983) 46–54;
(b) J. Scheen, P.J. Lefèbvre, Drugs 55 (1998) 225–236.
[28] (a) S.N. Davis, J. Diabetes Complicat. 18 (2004) 367–376;
(b) R. Perfetti, A. Ahmad, Trends Endocrinol. Metab. 11 (2000) 218–223.
[29] International Diabetes Federation, Global Guidelines for Type 2 Diabetes Available at: (2005) http://www.idf.org/home.
[30] A.A. Hancock, Biochem. Pharmacol. 71 (2006) 1103–1113.
[31] M. Wijtmans, R. Leurs, I. de Esch, Expert Opin. Investig. Drugs 16 (2007) 967–985.
[32] N. El-Sherif, G. Turitto, Curr. Opin. Cardiol. 18 (2003) 6–13.
[33] F. De Ponti, E. Poluzzi, N. Montanaro, Eur. J. Clin. Pharmacol. 56 (2000) 1–18.
[34] J.A. Covel, V.J. Santora, J.M. Smith, R. Hayashi, C. Gallardo, M.I. Weinhouse, J.B. Ibarra, J.A. Schultz, D.M. Park, S.A. Estrada, B.J. Hofilena, M.D. Pulley, B.M. Smith, A. Ren, M. Suarez, J. Frazer, J. Edwards, E.K. Hauser, J. Lorea, G. Semple, A.J. Grottick, J. Med. Chem. 52 (2009) 5603–5611.
[35] F. Cogé, S. Guénin, V. Audinot, A. Renouard-Try, P. Beauverger, C. Macia, C. Ouvry, N. Nagel, H. Rique, J. Galizzii, Biochem. J. 355 (2001) 279–288.
[36] I. Angel, S. Bidet, Fundam. Clin. Pharmacol. 5 (1991) 107–115.
[37] Z. Zhou, Q. Gong, B. Ye, Z. Fan, J.C. Makielski, G.A. Robertson, C.T. January, Biophys. J. 74 (1998) 230–241.
[38] K. Finnlayson, L. Turnbull, C.T. January, J. Sharkey, J.S. Kelly, Eur. J. Pharmacol. 430 (2001) 147–148.