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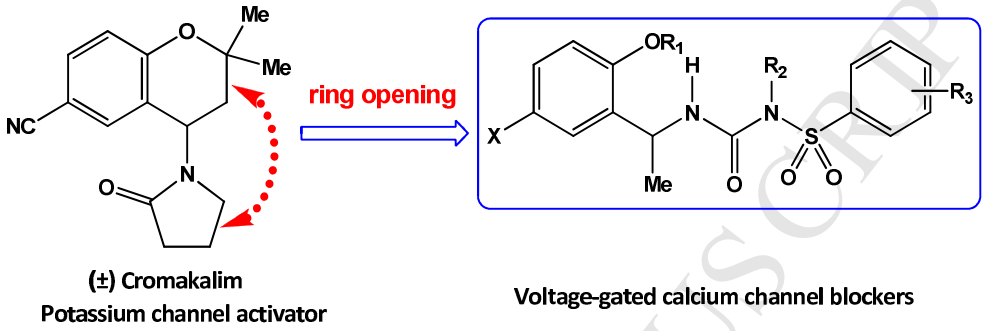

Design, Synthesis and Biological Evaluation of Novel Ring-Opened Cromakalim Analogues with Relaxant Effects on Vascular and Respiratory Smooth Muscles and as Stimulators of Elastin Synthesis

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Abstract

Two new series of ring-opened analogues of cromakalim bearing sulfonylurea moieties (series **A**: with N-unmethylated sulfonylureas, series **B**: with *N*-methylated sulfonylureas) were synthesized and tested as relaxants of vascular and respiratory smooth muscles (rat aorta and trachea, respectively). *Ex vivo* biological evaluations indicated that the most active compounds, belonging to series **B**, displayed a marked vasorelaxant activity on endothelium-intact aortic rings and the trachea. A majority of series **B** compounds exhibited a higher vasorelaxant activity (EC_{50} < 22 µM) than that of the reference compound diazoxide (EC_{50} = 24 µM). Interestingly, several tested compounds of series **B** also presented stronger relaxant effects on the trachea than the reference compound cromakalim (EC_{50} = 124 µM), in particular compounds **B4**, **B7** and **B16** (EC_{50} < 10 µM). By contrast, series **A** derivatives were poorly active on aortic rings (EC_{50} > 57 µM for all, and EC_{50} > 200 µM for a majority of them), but some of them showed an interesting relaxing effect on trachea (i.e. **A15** and **A33**, EC_{50} = 30 µM). The most potent compounds of both series, i.e. **A15**, **A33** and **B16**, tested on aortic rings in the presence of glibenclamide or 80 mM KCl, suggested that they acted as voltage-gated Ca^{2+} channel blockers, like verapamil, instead of being ATP-potassium channel activators, as is cromakalim, the parent molecule. Further investigations on cultured vascular smooth muscle cells showed a strong stimulating effect on elastin synthesis, especially compound **B16**, which was more active at 20 µM than diazoxide, a reference ATP-

sensitive potassium channel activator. Taken together, our results show that the N-methylation of the sulfonylurea moieties of ring-opened cromakalim analogues led to new compounds blocking calcium-gated channels, which had a major impact on the arterial and tracheal activities as well as selectivity.

Keywords: ring-opened cromakalim analogues, Ca^{2+}-gated channels, Ritter reaction, relaxant activity, aortic rings, trachea, elastin synthesis.

1. Introduction

Hypertension is one of most common cardiovascular diseases, which represents the major risk factor for endothelial dysfunction, metabolic syndrome, renal dysfunction, congestive heart failure, coronary artery disease, stroke and sudden death [1-3]. Several antihypertensive drugs used in the treatment of this disease are available, including diuretics, sympatholytics, vasodilators, and calcium channel and angiotensin inhibitors, which control arterial blood pressure at four effector sites: resistance and capacitance vessels, heart, and kidney [4].

The use of drugs relaxing vascular smooth muscle cells (VSMCs) has been one of the major choices in the treatment of hypertension but, unfortunately, they are all associated with undesirable side effects: fatigue, mood change, and sleep disturbances [5]. Therefore, there is an insistent need for developing new vasorelaxant agents with minimal side effects [6]. ATP-sensitive potassium channel (K_{ATP} channel) openers constitute an important class of compounds relaxing VSMCs, including different types of chemical structures such as racemic cromakalim (**1**), diazoxide (**2**), pinacidil (**3**), nicorandil (**4**), and minoxidil (**5**) (Figure 1) [7-10]. Cromakalim (**1**), the first benzopyran-type potassium channel activator, is known to be a potent antihypertensive agent [11-22]. The cromakalim skeleton has been used as a model in a new pharmacological investigation, which led to some potassium channel openers (PCOs) having potential interesting therapeutic applications in various diseases, especially in hypertension, asthma, and urinary incontinence [23]. In our efforts to develop new derivatives of the cromakalim-related PCO family, we previously developed a large number of compounds, with some of which having shown very interesting pharmacological profiles as activators of K_{ATP} channels (compounds **6-13**, Figure 2) [11,14,16]. Indeed, we were the first to report the development of simplified analogues of cromakalim by opening its heterocyclic side (giving more flexible molecules) and introducing amide, urea and sulfonylurea moieties (compounds **10-13**, Figure 2) [16]. More recently, other derivatives of cromakalim showed

interesting antitumor activity, especially an inhibitory activity of the growth of human glioma cell lines [19].

Further derivatives of compounds **10** and **11** (Figure 2) were also prepared. Those bearing urea moieties (compound **12**, Figure 2), whose development is underway, were more active than those with sulfonylurea and amide ones (compound **13**, Figure 2) as vasodilators or inhibitors of insulin secretion by pancreatic β-cells [16]. The urea derivatives were less acidic than sulfonylureas due to the presence, in the latter, of a NH group linked to both a CO and a SO_2 group, which suggests the existence of both neutral and negative ionic forms at physiological pH.

Based on these previous data, we proposed in the present work the synthesis of new sulfonylurea derivatives by alkylation of the NH group, as cited above, in order to reduce the acidity and permit the existence of a neutral form only. Furthermore, we created a chiral center on the benzylic atom, located in the ortho position to the alkoxy groups, similar to the situation in cromakalim itself. The activity and potential tissue-selectivity of these new derivatives (Figure 3) were pharmacologically evaluated in vascular (aortic rings) and respiratory (trachea) smooth muscles of rat precontracted by 30 mM KCl. The most active compounds were tested again in the aortic ring model, in the presence of glibenclamide, a K_{ATP} channel blocker, or 80 mM KCl, in order to determine the mechanism(s) of action of these compounds.

Also, it has already been demonstrated that minoxidil and diazoxide, two K_{ATP} channel openers and vasodilators, increased the expression of the elastin gene, *in vitro*, in skin fibroblasts and vascular smooth muscle cells [24,25] and *in vivo* in young or adult rats, as well as in old mice [26-29]. This led to an increase in the arterial content in elastin, the extracellular matrix protein which mainly provides the extensible tissues (including skin, lungs and arteries) with elasticity [26-29]. This is of particular importance since the elastin gene expression is interrupted after childhood and therefore not replaced when degraded during adulthood and ageing, leading to arteries that are more rigid and provoking several cardiovascular dysfunctions [30-32]. New compounds capable of re-inducing elastin synthesis by VSMCs would be highly useful for the treatment of the pathological stiffening of arteries related to ageing. We therefore also evaluated the efficiency of our target compounds for stimulating elastin synthesis by VSMCs.

2. Results and discussion

2.1. Synthesis

The synthetic routes of simplified cromakalim derivatives bearing sulfonylurea moieties, series **A** and series **B**, are summarized in Scheme 1.

N-(2,5-dimethoxybenzyl)sulfonylureas **A1-3** were prepared by condensation of 2,5-dimethoxbenzylamine **1a** with an appropriate sulfonyl isocyanate. The *N*-methylated sulfonylureas **B1-3** were obtained by methylation of **A1-3** using methyl iodide, in the presence of sodium carbonate, by refluxing in acetonitrile.

The two series of compounds **A4-33** and **B4-33** were obtained from ortho-hydroxyacetophenones according to five or six steps (Scheme 1).

The access to the target compounds required the synthesis of key intermediates, the primary amines *R/S*-1-(2-alkoxy-5-halogenophenyl)ethanamine **6a-j**.

Firstly, hydroxyacetophenones **2a-e** were alkylated using halogenoalkanes under alkaline conditions. The expected compound was easily separated from the starting material using the extraction of their ethyl acetate solution by a saturated solution of sodium hydrogen carbonate.

The resulting *ortho*-alkoxyketones **3a-j** were reduced to secondary alcohols **4a-j** with sodium borohydride in methanol. The acetylamino derivatives **5a-j** were prepared by the Ritter reaction from alcohols **4a-j**. This reaction occurred in acetonitrile supplemented with concentrated sulfuric acid. Access to the corresponding benzylamine derivatives **6a-j** was achieved, in excellent yields, by the hydrolysis of **5** with hydro-methanolic solution of sodium hydroxide. Amines **6a-j** were converted into the desired compounds **A4-33** by condensation with an appropriate sulfonyl isocyanate (series **A**) in methylene chloride at room temperature.

Finally, the *N*-(1-(2-alkoxy-5-halophenyl)ethyl)-*N*'-methyl-*N*'-arylsulfonylureas **B4-33** were obtained by *N*-alkylation of the corresponding sulfonylureas **A4-33,** with methyl iodide in acetonitrile, in the presence of sodium carbonate under reflux (series **B**, Scheme 1).

All these derivatives were crystallized in appropriate solvents and characterized by MS, ^{1}H NMR and ^{13}C NMR. The purity of final compounds was assessed by elemental analysis prior to pharmacological evaluations.

2.2. Biological activity

2.2.1. Myorelaxant effect on rat aortic rings

The vasorelaxant activities of compounds (series **A** and **B**) were evaluated *ex vivo* on endothelium-intact rat aortic rings pre-contracted with a hyperpotassic 30 mM KCl solution. The results obtained from compounds of the series **A** and **B** –in the concentration range of 1-300 µM, reference drugs (diazoxide, pinacidil, cromakalim), and previously described

molecules (**6-11**), were expressed as EC_{50} and E_{max} values and summarized in Tables 1 and 2, respectively. In vascular smooth muscles, (±)-cromakalim displayed a marked myorelaxant activity. As reported, the previously synthesized ring-closed benzopyran-type arylsulfonylureas (**8-9**) also produced a marked vasorelaxant effect but such compounds were less potent than (±)-cromakalim [14].

The biological data reported in Tables 1 and 2 indicate that most of the *un*methalyted sulfonylurea derivatives (series **A**) were poorly active on rat aortic rings, except for the *o*-isopropoxy or *o*-benzyloxy compounds **A11**, **A15** and **A33,** which were the most potent in this series [EC_{50} = 61.8 ± 9.9 (E_{max} = 93.2 ± 3.1), EC_{50} = 57.5 ± 11.7 (E_{max} = 95.1 ± 4.1) and 65.3 ± 5.4 (E_{max} = 125.5 ± 17.8), respectively], although they were much less active than the reference compounds. It can be observed that the preferred R group for the myorelaxant activity was a benzyl or an iPr, while Z should be a methyl or an electron-withdrawing group such as Cl. In most cases, compounds of series **B** (*N*-methalyted sulfonylureas) exerted a more pronounced myorelaxant activity than their analogues in series **A** ($p < 0.05$), except when R corresponded to the benzyl group (compare **A15**, **A32** and **A33** with **B15**, **B32** and **B33**, Table 1). Indeed, the preferred R groups for series **B** were ethyl and methyl. The creation of chiral centers (R' = CH_3) was very favorable for the relaxant activity, which led to the most potent vasorelaxant compounds, **B16** and **B26** [EC_{50} = 7.2 ± 0.8 (E_{max} = 102.7 ± 1.8) and EC_{50} = 7.8 ± 1.1 (E_{max} = 104.4 ± 1.3)], respectively. These compounds have chlorine and fluorine atoms as the X-substituent and a hydrogen atom or methyl group as the Z-substituent, respectively.

Taken as a whole, in series **B**, the rank order of preference for the X-substituent was found to be Cl~F > Br > OCH_3 > H > CH_3, while that of the Z-substituent was H > CH_3 > Cl.

The introduction of a methyl group on the nitrogen atom located between the two withdrawing groups (a sulfonyl and a carbonyl group) of series **A**, leading to series **B**, dramatically increased their biological effects on rat aortic smooth muscles. It could be due to the weak acidity of compound **A15** (pK_a = 5.31). Thus, the non-*N*-methylated compounds of series **A** are able to be deprotonated at physiological pH 7.40 and present in solution as a mixture of ionic and neutral forms. By contrast, the *N*-methylated analogues of series **B** are not ionized and present in solution as neutral species. This feature indicates that the presence of a neutral nitrogen atom linked to the sulfonyl function in the **B** series is good for the biological activity, allowing for a favorable interaction with the receptor protein site. This confirms the results obtained with opened analogues of cromakalim bearing urea moieties, which exist in physiological media only under neutral form [16]. Such a phenomenon has also

been observed in a recent work describing the development of new sulfonylureas and carbonylureas as ATP-dependent potassium openers with vasodilatory activity [33]. The latter are weakly acidic (exist uniquely under neutral form at physiological pH) and have a very powerful vasorelaxant effect, whereas sulfonylureas have a weak acid character (exist in two forms, neutral and ionized negatively charged, at physiological pH) and are poor vasodilators [33]. It could be very interesting to develop other analogues of series **B**, by methylating the other nitrogen atom of the sulfonylurea group or both of its nitrogen atoms. This hypothetic structural modulation could have an interesting impact on the biological activity.

2.2.2. Myorelaxant mechanisms of action on rat aorta rings

Three of the most active products in each series were selected (**A15**, **A33** and **B16**) for further pharmacological investigations in order to identify their mechanisms of action.

First, the compounds were tested in 30 mM K^+-depolarized rat aortic rings incubated in the continuous presence of 1 or 10 µM glibenclamide, a specific blocker of K_{ATP} channels [34,35]. If the drugs acted as a potassium channel opener, then a drastic reduction in myorelaxant activity should be observed in the presence of glibenclamide [12]. As shown in Table 3 and Figure 4 left panel, no dose-dependent decrease in the vasorelaxant effect of drugs was observed when increasing the glibenclamide concentration in the bathing medium ($p > 0.05$). By contrast, under the same experimental conditions, the EC_{50} values of the reference compound cromakalim were markedly increased by 33- and 671-fold in the presence of 1 µM and 10 µM glibenclamide, respectively ($p < 0.05$, Table 3).

Furthermore, the myorelaxant activities of the tested drugs, cromakalim and verapamil were examined in rat aortic rings precontracted by 80 mM KC1, which strongly inhibits or blocks K_{ATP} channels (Table 3 and Figure 4 right panel). In this condition, the vasodilatory potency of K^+ channel openers should be reduced compared to their activity on 30 mM KCl induced contractions [12,35,36], while drugs directly interfering with Ca^{2+} channels, such as Ca^{2+} entry blockers (e.g. verapamil), are expected to express the same myorelaxant efficacy on 30 and 80 mM KCl precontracted aortic rings [37]. Indeed, pure potassium channel openers are able to suppress smooth muscle contractions induced by low K^+ concentrations (30 mM or less), but not high depolarizing K^+ concentrations (80 mM). At high depolarizing K^+ concentrations (80 mM), potassium equilibrium potential and cell membrane potential are so close that the hyperpolarization induced by K^+ channel opening is too weak to close voltage-operated Ca^{2+} channels [8,38,39]. As indicated in Table 3 and Figure 4 (right panel), the vasorelaxant properties of the selected compounds remained unchanged under 80 mM

KCl-induced precontraction ($p > 0.05$), whereas the myorelaxant effect of (±)-cromakalim was extremely reduced ($p < 0.05$). The myorelaxant effects of verapamil were also unaltered by the presence of 1 µM or 10 µM glibenclamide in the bathing medium and persisted in the 80 mM KCl media [36].

Altogether, in vascular smooth muscle cells, the pharmacological profiles of the selected compounds **A15**, **A33** and **B16** are different from those of K_{ATP} channel openers and similar to that of the Ca^{2+} entry blocker verapamil. Interestingly, a certain structural similarity exists between verapamil and series **B** compounds (Figure 5), which could explain the similarity of their pharmacological profile. Indeed, both molecules have two substituted aromatic rings spaced by a chiral benzylic carbon and an *N*-methyl group.

2.2.3. Myorelaxant effect on rat trachea rings

Potassium channel openers, such as cromakalim, are also known to be active as bronchorelaxants [40,41]. This effect is partially antagonized by glibenclamide, suggesting that the bronchodilator activity of the drugs reflects, at least in part, their K_{ATP} channel opening properties [42]. In previous reports, Ca^{2+} entry blockers such as verapamil and nifedipine have also been described as active relaxants on KCl-contracted guinea pig trachea [43,44].

To evaluate the tracheorelaxant activity of the newly synthesized compounds, eight derivatives, **A15**, **A33**, **B1**, **B4**, **B5**, **B6**, **B7** and **B16** were selected and their relaxant activities were measured in rat trachea contracted by 30 mM KCl. (±)-Cromakalim and verapamil were used as reference compounds. The drug concentration that caused a 50% relaxation (EC_{50}) was calculated from concentration-response curves (Table 4). The results clearly showed that the reference compound (±)-cromakalim (EC_{50} = 124.4 µM) was weakly active, whereas all selected products induced marked tracheorelaxant effects ($1.7 < EC_{50} < 39.3$ µM, $4.7 < E_{max} < 65.4$, $p < 0.05$). The *N*-methylated compound **B16** (X = Cl, Z = H) was the most potent (EC_{50} = 1.7 µM) in this series and had an activity similar to that of verapamil. Moreover, the aorta selectivity ratio (tracheal vs vascular tissue) was also calculated using the formula [EC_{50} trachea (µM)/EC_{50} aorta (µM)]. Regarding the selectivity profile, and compared to the parent compound (±)-cromakalim, these new drugs, in particular **B16**, exhibited a relative preference for the tracheal tissue with the exception of **B1**, which showed almost the same potency on the two tissues ($p > 0.05$), and **B6**, which displayed a relative preference ($p < 0.05$) for the vascular smooth muscle (Table 4).

2.2.4. Stimulation of elastin synthesis in cultured vascular smooth muscle cells

Four of the most efficient tested vasodilators, **A15**, **A33**, **B16**, and **B19,** were evaluated for their abilities to enhance elastin synthesis in cultured vascular smooth muscle cells (VSMCs).

In this test, cultured VSMCs from the rat aorta were incubated with selected compounds dissolved in DMSO at different concentrations: 0 (DMSO alone added to cells), 20 and 50 µM (Figure 6). After 48 hours, the extracellular elastin quantities were determined spectrophotometrically at 450 nm by ELISA technique (Figure 6). Diazoxide was used as a positive reference regarding elastin production by vascular smooth muscle cells [26]. Compared to control conditions (DMSO alone), diazoxide induced a significant activation of elastin production at 50 µM (+92%, 1-way ANOVA, $p < 0.05$), but not at 20 µM.

As shown in Figure 6, at 20 µM, compound **B16**, the most active relaxant compound of both vascular and tracheal smooth muscles, stimulated elastin production compared to the effect of vehicle alone (DMSO) and was therefore more active than diazoxide at this concentration. The other analogues (**A15**, **A33** and **B19**), as well as diazoxide, tested at the same concentration, failed to stimulate elastin synthesis.

At 50 µM, compounds **A15** and **B19** were as potent as or slightly less potent than diazoxide, respectively ($p > 0.05$). At 50 µM, compound **B16** expressed the same potency as at 20 µM, reflecting a "ceiling effect", while compound **A33** was completely unable to enhance elastin production ($p > 0.05$).

Keeping in mind that diazoxide is a potassium channel opener, while **A15**, **B16** and **B19** have been shown to be calcium channel blockers, it is legitimate to question the mechanism(s) allowing all of these compounds to stimulate elastin synthesis. We can consider that the activation of potassium channels should not be considered as the sole mechanism for stimulating the synthesis of elastin, but it is is possibly the relaxation of the smooth muscle, which happens by different mechanisms (blocking of Ca^{2+} gated channels in the case of our molecules) that is the triggering event. This hypothesis is strongly supported by a recent study showing that Ca^{2+} influx inhibits elastin synthesis by rat aortic smooth muscle cells [45]. The results of our study confirm this mechanism, since we obtained vasodilatory molecules blocking calcium gated channels and stimulating the synthesis of elastin.

3. Conclusion

Starting from the K_{ATP} channel opener cromakalim, structural modulations by ring opening led to two series of compounds (series **A** and **B**) bearing sulfonylurea moieties. Series **A** molecules (*N*-unmethylated sulfonylureas) were found to have poor relaxant activity on

vascular smooth muscles in contrast to series **B** compounds (*N*-methylated sulfonylureas), with some of the latter drugs being even more active than the reference compound diazoxide, but less active than cromakalim. These results strongly suggest that the lack of activity of series **A** molecules was dependent on their ionization at physiological pH, because of the acidic character linked to their unmethylated sulfonylurea function. In aortic rings precontracted with 80 mM KCl or 30 mM KCl in the presence of glibenclamide, the vasodilatory activities of compounds A**15**, **A33**, **B16** and verapamil (a voltage-gated Ca^{2+} channel blocker) were preserved, while that of cromakalim (a K_{ATP} channel activator) was lost. Such data suggested the involvement of voltage-gated calcium channels, instead of K_{ATP} channels, in the vasorelaxant activity of our new compounds, which would mean that these compounds are verapamil-like.

Interestingly, in the trachea, some selected compounds (A**15**, **A33**, **B1**, **B4**-**B7** and **B16**) showed a potent relaxant activity, stronger than on aortic rings (exept **B6**), in particular compounds **B16**, which was the most active and the most tissue-selective compound, while cromakalim had little activity in this organ.

In addition, compounds **A15**, **B16** and **B19** exhibited a marked stimulating effect on elastin synthesis by cultured vascular smooth muscle cells, close to that of diazoxide regarding **A15** and **B19** (50 µM). Interestingly, 20 µM **B16** markedly stimulated elastin expression while the reference compound diazoxide was inactive at this low dose.

Molecules of series **B** such as **B16** could represent a class of vasorelaxant drugs, relatively selective of tracheal tissue and endowed with interesting stimulating activity of elastin production by vascular smooth muscle cells, which, in a long term, could improve arterial elasticity and hemodynamics. Further *in vivo* tests need to be performed to ascertain such a hypothesis. Additional perspectives are needed to clarify the mechanism(s) involved in the stimulation of elastin production.

4. Experimental section

4.1. Chemistry

Reagents and solvents were purchased from usual commercial suppliers and were used without further purification. Yields reported refer to purified products. All reactions were routinely checked by thin-layer chromatography (TLC) on Merck Silica Gel 60 F_{254} (0.25mmthick) and visualization was performed with UV light (254 nm, 360 nm). Melting points were obtained on a Büchi melting point B540 capillary apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker Advance-400 instrument (400 MHz for ^{1}H and 100 MHz

for ^{13}C) in DMSO-d_6 (except compound **B14** which was recorded in $CDCl_3$), while ^{13}C NMR spectra of compounds **A28-A32** were recorded on a Brüker Avance DPX 250 spectrometer (62.9 MHz) in in DMSO-d_6. Chemical shifts (δ) are reported in ppm relative to TMS as an internal standard, or to the solvent in which the spectrum was recorded. The abbreviations s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, q = quartet, sept = septuplet, br s = broad singlet, CHar = aromatic CH are used throughout. Coupling constants *J* are given in Hertz. Electrospray ionization ESI mass spectra were acquired by the Institut de Chimie Moléculaire de Grenoble (ICMG), on an Esquire 300 plus Brüker Daltonis instrument with a nanospray inlet. Elemental analyses (C, H, N) were performed at the Institut de Chimie Moléculaire de Grenoble (ICMG).

4.1.1. General procedure for the synthesis of *o*-alkoxyacetophenones (3a-j)

4.1.1.1. 5-Bromo-2-methoxyacetophenone (3a) [46,47]

A mixture of 5-Bromo-2-hydroxyacetophenone **2a** (10 g, 46.5 mmol, 1 eq), potassium carbonate (9.62 g, 69.75 mmol, 1.5 eq) and iodomethane (5.8 mL, 93 mmol, 2 eq) in DMF (120 mL) were stirred overnight in a sealed round bottom flask at room temperature. DMF was removed under reduced pression and the residue was partitioned between water and EtOAc. The combined EtOAc extracts were washed with brine, 0.5 M NaOH and then three times with water. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The product was obtained as an off-white solid (9.5 g, 89%). **m.p.** 31-32°C. **SM (ESI):** *m/z* 251-253 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 2.54 (s, **3H**, $COCH_3$), 3.90 (s, **3H**, OCH_3), 7.18 (d, J_{ortho} = 8.9 Hz, **1H**, CHar), 7.66 (d, J_{meta} = 2.6 Hz, **1H**, CHar), 7.72 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.6 Hz, **1H**, CHar).

4.1.1.2. 5-Bromo-2-ethoxyacetophenone (3b)

The title compound was obtained as described for **3a**, starting from **2a** (10 g, 46.5 mmol) and bromoethane (7 mL, 93 mmol). White powder (10 g, 88%). **m.p.** 69-70°C. **SM (ESI):** *m/z* 265-267 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.40 (t, *J* = 6.9 Hz, **3H**, OCH_2CH_3), 2.56 (s, **3H**, $COCH_3$), 4.17 (q, *J* = 6.9 Hz, **2H**, OCH_2CH_3), 7.16 (d, J_{ortho} = 8.9 Hz, **1H**, CHar), 7.66 (d, J_{meta} = 2.6 Hz, **1H**, CHar), 7.69 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.6 Hz, **1H**, CHar).

4.1.1.3. 5-Bromo-2-isopropoxyacetophenone (3c)

The title compound was obtained as described for **3a**, starting from **2a** (10 g, 46.5 mmol) and 2-bromopropane (8.7 mL, 93 mmol). White powder (10.25 g, 85%). **m.p.** 40-41°C. **SM**

(ESI): *m/z* 279-281 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.34 (d, J = 6.0 Hz, **6H**, OCH($C\underline{H}_3$)$_2$), 2.54 (s, **3H**, COC$\underline{H}_3$), 4.79 (sept, J = 6.0 Hz, **1H**, OC$\underline{H}$(CH_3)$_2$), 7.18 (d, **1H**, J_{ortho} = 8.9 Hz, C$\underline{H}$ar), 7.63 (d, **1H**, J_{meta} = 2.6 Hz, C$\underline{H}$ar), 7.67 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.6 Hz, **1H**, C$\underline{H}$ar).

4.1.1.4. 2-Benzyloxy-5-bromoacetophenone (3d)

The title compound was obtained as described for **3a**, starting from **2a** (10 g, 46.5 mmol) and benzylbromide (11 mL, 93 mmol). The crude product was washed with petroleum ether 40/60 to eliminate excess of benzylbromide and recrystallized from cyclohexane to afford **3d** as pure white crystals (9.42 g, 63%). **m.p.** 77-78°C. **SM (ESI):** *m/z* 327-329 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 2.52 (s, **3H**, COC$\underline{H}_3$), 5.26 (s, **2H**, OC$\underline{H}_2$), 7.27 (d, J_{ortho} = 8.7 Hz, **1H**, C$\underline{H}$ar), 7.37 (m, **1H**, C$\underline{H}$ar), 7.43 (m, **2H**, C$\underline{H}$ar), 7.51 (m, **2H**, C$\underline{H}$ar), 7.70 (m, **2H**, C$\underline{H}$ar).

4.1.1.5. 5-Chloro-2-methoxyacetophenone (3e)

The title compound was obtained as described for **3a**, starting from 5-chloro-2-hydroxyacetophenone **2b** (10 g, 58.62 mmol) and iodomethane (7.24 mL, 117.24 mmol). White powder (9.38 g, 86%). **m.p.** 34-35°C. **SM (ESI):** *m/z* 185-187 $[M+H]^+$. **^{1}H NMR (δ ppm):** 2.54 (s, **3H**, COC$\underline{H}_3$), 3.90 (s, **3H**, OC$\underline{H}_3$), 7.23 (d, J_{ortho} = 8.9 Hz, **1H**, C$\underline{H}$ar), 7.54 (d, J_{meta} = 2.7 Hz, **1H**, C$\underline{H}$ar), 7.60 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.7 Hz, **1H**, C$\underline{H}$ar).

4.1.1.6. 5-Chloro-2-ethoxyacetophenone (3f)

The title compound was obtained as described for **3a**, starting from 5-chloro-2-hydroxyacetophenone **2b** (10 g, 58.62 mmol) and bromoethane (8.75 mL, 117.24 mmol). White powder (10.6 g, 91%). **m.p.** 80-81°C. **SM (ESI):** *m/z* 199-201 $[M+H]^+$. **^{1}H NMR (δ ppm):** 1.40 (t, J = 6.9 Hz, **3H**, OCH_2C$\underline{H}_3$), 2.56 (s, **3H**, COC$\underline{H}_3$), 4.17 (q, J = 6.9 Hz, **2H**, OC$\underline{H}_2$CH_3), 7.20 (d, J_{ortho} = 8.9 Hz, **1H**, C$\underline{H}$ar), 7.54 (d, J_{meta} = 2.7 Hz, **1H**, C$\underline{H}$ar), 7.57 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.7 Hz, **1H**, C$\underline{H}$ar).

4.1.1.7. 5-Fluoro-2-methoxyacetophenone (3g)

The title compound was obtained as described for **3a**, starting from 5-fluoro-2-hydroxyacetophenone **2c** (10 g, 64.88 mmol) and iodomethane (8 mL, 129.76 mmol). Yellowish oil (10.18 g, 93%). **SM (ESI):** *m/z* 169 $[M+H]^+$. **^{1}H NMR (δ ppm):** 2.54 (s, **3H**, COC$\underline{H}_3$), 3.89 (s, **3H**, OC$\underline{H}_3$), 7.20 (m, **1H**, C$\underline{H}$ar), 7.34 (m, **1H**, C$\underline{H}$ar), 7.39 (m, **1H**, C$\underline{H}$ar).

4.1.1.8. 5-Fluoro-2-ethoxyacetophenone (3h)

The title compound was obtained as described for **3a**, starting from 5-fluoro-2-hydroxyacetophenone **2c** (10 g, 64.88 mmol) and bromoethane (9.7 mL, 129.76 mmol). White powder (11.11 g, 94%). **m.p.** 78-79°C. **SM (ESI):** *m/z* 183 $[M+H]^+$. **^{1}H NMR (δ ppm):** 1.40 (t, *J* = 6.9 Hz, **3H**, $OCH_2C\underline{H}_3$), 2.57 (s, **3H**, $COC\underline{H}_3$), 4.15 (q, *J* = 6.9 Hz, **2H**, $OC\underline{H}_2CH_3$), 7.19 (m, **1H**, C<u>H</u>ar), 7.34 (m, **1H**, C<u>H</u>ar), 7.39 (m, **1H**, C<u>H</u>ar).

4.1.1.9. 2-Benzyloxyacetophenone (3i)

The title compound was obtained as described for **3a**, starting from 2-hydroxyacetophenone **2d** (10 g, 73.45 mmol) and benzylbromide (17.45 mL, 146.9 mmol). The crude product was washed with petroleum ether 40/60 to eliminate excess of benzylbromide and afforded **3i** as white powder (14.17 g, 85%). **m.p.** 40-41°C. **SM (ESI):** *m/z* 249 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 2.53 (s, **3H**, $COC\underline{H}_3$), 5.26 (s, **2H**, $OC\underline{H}_2$), 7.05 (m, **1H**, C<u>H</u>ar), 7.27 (m, **1H**, C<u>H</u>ar), 7.36 (m, **1H**, C<u>H</u>ar), 7.43 (m, **2H**, C<u>H</u>ar), 7.54 (m, **3H**, C<u>H</u>ar), 7.61 (dd, J_{ortho} = 7.7 Hz, J_{meta} = 1.7 Hz, **1H**, C<u>H</u>ar).

4.1.1.10. 2-Benzyloxy-5-methylacetophenone (3j)

The title compound was obtained as described for **3a**, starting from 2-hydroxy-5-methylacetophenone **2e** (10 g, 66.6 mmol) and benzylbromide (15.82 mL, 133.2 mmol). The crude product was purified by chromatography (petroleum ether) to eliminate excess of benzylbromide and afforded **3j** as yellowish oil (12.5 g, 78%). **SM (ESI):** m/z 263 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 2.27 (s, **3H**, $PhC\underline{H}_3$), 2.51 (s, **3H**, $COC\underline{H}_3$), 5.21 (s, **2H**, $OC\underline{H}_2$), 7.16 (d, J_{ortho} = 8.4 Hz, **1H**, C<u>H</u>ar), 7.35 (m, **2H**, C<u>H</u>ar), 7.42 (m, **3H**, C<u>H</u>ar), 7.51 (m, **2H**, C<u>H</u>ar).

4.1.2. General procedure for the synthesis of *o*-alkoxyalcools (4a-j)

4.1.2.1. R/S-1-(5-bromo-2-methoxyphenyl)-1-ethanol (4a)

Sodium borohydride (2.35 g, 62.21 mmol, 1.5 eq) was added portionvise to a stirred suspension of **3a** (9.5 g, 41.47 mmol, 1 eq) in methanol (140 mL) at 0 °C, and the mixture was kept at this temperature for a further 30 min. The mixture was stirred for an additional 30 min at ambient temperature, and the solvent was evaporated under vacuum. After addition of water the suspension was acidified with 6N hydrochloric acid (80 ml) and the product was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting yellowish oil was dried under vacuum to afford **4a** (9 g, 93%). **SM (ESI):** *m/z* 253-255 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.26 (d, *J* = 6.4 Hz, **3H**, $CHC\underline{H}_3$), 3.79 (s, **3H**, $OC\underline{H}_3$), 4.95 (m, **1H**, $OHC\underline{H}CH_3$), 5.19

(d, *J* = 4.5 Hz, **1H**, OHCH), 6.92 (d, J_{ortho} = 8.8 Hz, **1H**, CHar), 7.37 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.6 Hz, **1H**, CHar), 7.54 (dd, J_{meta} = 2.6 Hz, J_{para} = 0.6 Hz, **1H**, CHar).

4.1.2.2. R/S-1-(5-bromo-2-ethoxyphenyl)-1-ethanol (4b)

The title compound was obtained as described for **4a**, starting from 5-bromo-2-ethoxyacetophenone **3b** (10 g, 41.13 mmol) and sodium borohydride (2.33 g, 61.7 mmol). Yellowish oil (9.35 g, 92%). **SM (ESI):** *m/z* 267-269 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.3 Hz, **3H**, $CHCH_3$), 1.33 (m, **3H**, OCH_2CH_3), 4.02 (m, **2H**, OCH_2CH_3), 4.96 (m, **1H**, $OHCHCH_3$), 5.18 (d, **1H**, *J* = 4.5 Hz, OHCH), 6.89 (d, J_{ortho} = 8.6 Hz, **1H**, CHar), 7.33 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.6 Hz, **1H**, CHar), 7.54 (d, J_{meta} = 2.6 Hz, **1H**, CHar).

4.1.2.3. R/S-1-(5-bromo-2-isopropoxyphenyl)-1-ethanol (4c)

The title compound was obtained as described for **4a**, starting from 5-bromo-2-isopropoxyacetophenone **3c** (10 g, 38.9 mmol) and sodium borohydride (2.21 g, 58.35 mmol). Yellowish oil (9.76 g, 96%). **SM (ESI):** *m/z* 281-283 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 6.0 Hz, **6H**, $OCH(CH_3)_2$), 1.26 (d, *J* = 7.2 Hz, **3H**, $CHCH_3$), 4.60 (sept, *J* = 6.0 Hz, **1H**, $OCH(CH_3)_2$), 4.93 (m, **1H**, $OHCHCH_3$), 5.13 (d, *J* = 4.7 Hz, **1H**, OHCH), 6.91 (d, J_{ortho} = 8.7 Hz, **1H**, CHar), 7.31 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.7 Hz, **1H**, CHar), 7.52 (d, J_{meta} = 2.7 Hz, **1H**, CHar).

4.1.2.4. R/S-1-(2-(benzyloxy)-5-bromophenyl)-1-ethanol (4d)

The title compound was obtained as described for **4a**, starting from 2-benzyloxy-5-bromoacetophenone **3d** (9.4 g, 30.8 mmol) and sodium borohydride (1.75 g, 46.2 mmol). Yellowish oil (8.52 g, 90%). **SM (ESI):** *m/z* 289-291 $[M+H-H_2O]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* = 6.1 Hz, **3H**, $CHCH_3$), 5.00 (m, **1H**, $OHCHCH_3$), 5.13 (m, **2H**, OCH_2), 5.18 (d, *J* = 4.1 Hz, **1H**, OHCH), 6.99 (d, J_{ortho} = 8.7 Hz, **1H**, CHar), 7.34 (m, **2H**, CHar), 7.40 (m, **4H**, CHar), 7.55 (d, J_{meta} = 2.7 Hz, **1H**, CHar).

4.1.2.5. R/S-1-(5-chloro-2-methoxyphenyl)-1-ethanol (4e)

The title compound was obtained as described for **4a**, starting from 5-chloro-2-methoxyacetophenone **3e** (9.3 g, 50.37 mmol) and sodium borohydride (2.86 g, 75.55 mmol). Yellowish oil (7.71 g, 82%). **SM (ESI):** *m/z* 169-171 $[M+H-H_2O]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.5 Hz, **3H**, $CHCH_3$), 3.79 (s, **3H**, OCH_3), 4.96 (m, **1H**, $OHCHCH_3$), 5.19

(d, J = 4.4 Hz, **1H**, OHCH), 6.96 (d, J_{ortho} = 8.7 Hz, **1H**, CHar), 7.24 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.7 Hz, **1H**, CHar), 7.42 (d, J_{meta} = 2.7 Hz, **1H**, CHar).

4.1.2.6. R/S-1-(5-chloro-2-ethoxyphenyl)-1-ethanol (4f)

The title compound was obtained as described for **4a**, starting from 5-chloro-2-ethoxyacetophenone **3f** (10 g, 50.34 mmol) and sodium borohydride (2.86 g, 75.51 mmol). Yellowish oil (9.7 g, 96%). **SM (ESI):** *m/z* 183-185 $[M+H-H_2O]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, J = 6.3 Hz, **3H**, $CHCH_3$), 1.33 (m, **3H**, OCH_2CH_3), 4.02 (m, **2H**, OCH_2CH_3), 4.98 (m, **1H**, $OHCHCH_3$), 5.17 (d, J = 4.4 Hz, **1H**, OHCH), 6.93 (d, J_{ortho} = 8.7 Hz, **1H**, CHar), 7.20 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.7 Hz, **1H**, CHar), 7.43 (d, J_{meta} = 2.7 Hz, **1H**, CHar).

4.1.2.7. R/S-1-(5-fluoro-2-methoxyphenyl)-1-ethanol (4g)

The title compound was obtained as described for **4a**, starting from 5-fluoro-2-methoxyacetophenone **3g** (10 g, 59.47 mmol) and sodium borohydride (3.37 g, 89.2 mmol). Yellowish oil (9.9 g, 97%). **SM (ESI):** *m/z* 153 $[M+H-H_2O]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, J = 6.3 Hz, **3H**, $CHCH_3$), 3.78 (s, **3H**, OCH_3), 4.97 (m, **1H**, $OHCHCH_3$), 5.14 (d, J = 4.4 Hz, **1H**, OHCH), 6.94 (m, **1H**, CHar), 7.00 (m, **1H**, CHar), 7.20 (m, **1H**, CHar).

4.1.2.8. R/S-1-(2-ethoxy-5-fluorophenyl)-1-ethanol (4h)

The title compound was obtained as described for **4a**, starting from 2-ethoxy-5-fluoroacetophenone **3h** (11 g, 60.38 mmol) and sodium borohydride (3.43 g, 90.57 mmol). Yellowish oil (10.75 g, 96%). **SM (ESI):** 167 $[M+H-H_2O]^+$,184 $[M]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, J = 6.3 Hz, **3H**, $CHCH_3$), 1.33 (m, **3H**, OCH_2CH_3), 4.02 (m, **2H**, OCH_2CH_3), 4.97 (m, **1H**, $OHCHCH_3$), 5.12 (d, J = 4.4 Hz, **1H**, OHCH), 6.92 (m, **1H**, CHar), 6.97 (m, **1H**, CHar), 7.19 (m, **1H**, CHar).

4.1.2.9. R/S-1-(2-benzyloxyphenyl)-1-ethanol (4i)

The title compound was obtained as described for **4a**, starting from 2-benzyloxyacetophenone **3i** (14 g, 61.87 mmol) and sodium borohydride (3.51 g, 92.8 mmol). Yellowish oil (13 g, 92%). **SM (ESI):** m/z 211 $[M+H-H_2O]^+$, 251 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.31 (d, J = 6.3 Hz, **3H**, $CHCH_3$), 5.00 (d, J = 4.4 Hz, **1H**, OHCH), 5.10 (m, **1H**, $OHCHCH_3$), 5.14 (m, **2H**, OCH_2), 6.96 (m, **1H**, CHar), 7.02 (m, **1H**, CHar), 7.19 (m, **1H**, CHar), 7.35 (m, **1H**, CHar), 7.42 (m, **2H**, CHar), 7.49 (m, **3H**, CHar).

4.1.2.10. R/S-1-(2-(benzyloxy)-5-methylphenyl)-1-ethanol (4j)

The title compound was obtained as described for **4a**, starting from 2-benzyloxy-5-methylacetophenone **3j** (12 g, 49.94 mmol) and sodium borohydride (2.83 g, 74.91 mmol). Yellowish oil (11.61 g, 96%). **SM (ESI):** *m/z* 255 $[M+H-H_2O]^+$, 265 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.29 (d, *J* = 6.3 Hz, **3H**, CHC<u>H</u>$_3$), 2.25 (s, **3H**, PhC<u>H</u>$_3$), 4.95 (d, *J* = 4.4 Hz, **1H**, O<u>H</u>CH), 5.05 (m, **1H**, OHC<u>H</u>CH$_3$), 5.09 (m, **2H**, OC<u>H</u>$_2$), 6.90 (d, J_{ortho} = 8.2 Hz, **1H**, C<u>H</u>ar), 6.97 (dd, J_{ortho} = 8.2 Hz, J_{meta} = 2.2 Hz, **1H**, C<u>H</u>ar), 7.28 (d, J_{meta} = 2.2 Hz, **1H**, C<u>H</u>ar), 7.33 (m, **1H**, C<u>H</u>ar), 7.41 (m, **2H**, C<u>H</u>ar), 7.46 (m, **2H**, C<u>H</u>ar).

4.1.3. General procedure for the synthesis of acetamides (5a-j) by Ritter reaction

4.1.3.1. R/S-N-(1-(5-bromo-2-methoxyphenyl)ethyl)acetamide (5a)

A suspension of **4a** (9 g, 38.95 mmol) in acetonitrile (112.5 mL) was added dropwise to a stirred solution of acetonitrile (22 mL) in 98% sulfuric acid (5.63 mL) kept between10°C and 0°C. Stirring was pursued for 1 h at room temperature. The solution was poured into cold water, and the precipitate was collected by filtration, washed with water, and purified by recrystallization from ethyl acetate to afford compound **5a** as a white solid (9.5 g, 89%). **m.p.** 165-166°C. **SM (ESI):** *m/z* 270-272 $[M-H]^-$. **^{1}H NMR (δ ppm):** 1.23 (d, *J* = 6.9 Hz, **3H**, CHC<u>H</u>$_3$), 1.87 (s, **3H**, COC<u>H</u>$_3$), 3.81 (s, **3H**, OC<u>H</u>$_3$), 5.18 (m, **1H**, NHC<u>H</u>CH$_3$), 6.95 (d, J_{ortho} = 8.9 Hz, **1H**, C<u>H</u>ar), 7.39 (m, **2H**, C<u>H</u>ar), 8.30 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH).

4.1.3.2. R/S-N-(1-(5-bromo-2-ethoxyphenyl)ethyl)acetamide (5b)

The title compound was obtained as described for **5a**, starting from R/S-1-(5-bromo-2-ethoxyphenyl)-1-ethanol **4b** (9 g, 36.72 mmol). White solid (8.77 g, 83%). **m.p.** 113-114°C. **SM (ESI):** *m/z* 284-286 $[M-H]^-$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 1.35 (t, *J* = 6.9 Hz, **3H**, OCH$_2$C<u>H</u>$_3$), 1.87 (s, **3H**, COC<u>H</u>$_3$), 4.06 (q, *J* = 6.9 Hz, **2H**, OC<u>H</u>$_2$CH$_3$), 5.16 (m, **1H**, NHC<u>H</u>CH$_3$), 6.93 (m, **1H**, C<u>H</u>ar), 7.35 (m, **2H**, C<u>H</u>ar), 8.28 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH).

4.1.3.3. R/S-N-(1-(5-bromo-2-isopropoxyphenyl)ethyl)acetamide (5c)

The title compound was obtained as described for **5a**, starting from R/S-1-(5-bromo-2-isopropoxyphenyl)-1-ethanol **4c** (9 g, 34.73 mmol). White solid (9.36 g, 89%). **m.p.** 138 °C. **SM (ESI):** *m/z* 298-300 $[M-H]^-$. **^{1}H NMR (δ ppm):** 1.23 (d, *J* = 6.9 Hz, **3H**, CHC<u>H</u>$_3$), 1.27 (d, *J* = 6.0 Hz, **3H**, OCH(C<u>H</u>$_3$)$_2$), 1.28 (d, *J* = 6.0 Hz, **3H**, OCH(C<u>H</u>$_3$)$_2$), 1.85 (s, **3H**, COC<u>H</u>$_3$),

4.62 (sept, *J* = 6.0 Hz, **1H**, OC<u>H</u>$(CH_3)_2$), 5.13 (m, **1H**, NHC<u>H</u>CH_3), 6.95 (d, J_{ortho} = 8.7 Hz, **1H**, C<u>H</u>ar), 7.32 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.6 Hz, **1H**, C<u>H</u>ar), 7.35 (d, J_{meta} = 2.6 Hz, **1H**, C<u>H</u>ar), 8.23 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH).

4.1.3.4. R/S-N-(1-(2-(benzyloxy)-5-bromophenyl)ethyl)acetamide (5d)

The title compound was obtained as described for **5a**, starting from R/S-1-(2-(benzyloxy)-5-bromophenyl)-1-ethanol **4d** (8 g, 26.04 mmol). White solid (7.53 g, 83%). **m.p.** 176-177 °C. **SM (ESI):** *m/z* 346-348 $[M-H]^-$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 1.85 (s, **3H**, COC<u>H</u>$_3$), 5.17 (m, **2H**, OC<u>H</u>$_2$), 5.26 (m, **1H**, NHC<u>H</u>CH_3), 7.03 (d, J_{ortho} = 8.7 Hz, **1H**, C<u>H</u>ar), 7.36 (m, **2H**, C<u>H</u>ar), 7.42 (m, **3H**, C<u>H</u>ar), 7.49 (m, **2H**, C<u>H</u>ar), 8.33 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH).

4.1.3.5. R/S-N-(1-(5-chloro-2-methoxyphenyl)ethyl)acetamide (5e)

The title compound was obtained as described for **5a**, starting from R/S-1-(5-chloro-2-methoxyphenyl)-1-ethanol **4e** (7 g, 37.5 mmol). White solid (7.32 g, 85%). **m.p.** 151-152°C. **SM (ESI):** 228-230 $[M+H]^+$, 250-252 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.23 (d, *J* = 6.9 Hz, **3H**, CHC<u>H</u>$_3$), 1.87 (s, **3H**, COC<u>H</u>$_3$), 3.82 (s, **3H**, OC<u>H</u>$_3$), 5.15 (m, **1H**, NHC<u>H</u>CH_3), 7.00 (m, **1H**, C<u>H</u>ar), 7.26 (m, **2H**, C<u>H</u>ar), 8.30 (d, *J* = 8.0 Hz, **1H**, N<u>H</u>CH).

4.1.3.6. R/S-N-(1-(5-chloro-2-ethoxyphenyl)ethyl)acetamide (5f)

The title compound was obtained as described for **5a**, starting from R/S-1-(5-fluoro-2-methoxyphenyl)-1-ethanol **4f** (9 g, 44.85 mmol). White solid (9.45 g, 87%). **m.p.** 129-130°C. **SM (ESI):** *m/z* 242-244 $[M+H]^+$, 264-266 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 1.35 (t, *J* = 7.0 Hz, **3H**, OCH_2C<u>H</u>$_3$), 1.87 (s, **3H**, COC<u>H</u>$_3$), 4.05 (q, *J* = 7.0 Hz, **2H**, OC<u>H</u>$_2CH_3$), 5.17 (m, **1H**, NHC<u>H</u>CH_3), 6.97 (d, J_{ortho} = 8.7 Hz, **1H**, C<u>H</u>ar), 7.23 (m, **2H**, C<u>H</u>ar), 8.28 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH).

4.1.3.7. R/S-N-(1-(5-fluoro-2-methoxyphenyl)ethyl)acetamide (5g)

The title compound was obtained as described for **5a**, starting from R/S-1-(5-fluoro-2-ethoxyphenyl)-1-ethanol **4g** (9 g, 52.88 mmol). White solid (10.1 g, 90%). **m.p.** 147-148°C. **SM (ESI):** *m/z* 212 $[M+H]^+$, 234 $[M+Na]^+$, 445 $[2M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 1.87 (s, **3H**, COC<u>H</u>$_3$), 3.81 (s, **3H**, OC<u>H</u>$_3$), 5.17 (m, **1H**, NHC<u>H</u>CH_3), 6.97 (m, **1H**, C<u>H</u>ar), 7.02 (m, **1H**, C<u>H</u>ar), 7.07 (m, **1H**, C<u>H</u>ar), 8.22 (d, *J* = 8.0 Hz, **1H**, N<u>H</u>CH).

4.1.3.8. R/S-N-[1-(2-ethoxy-5-fluorophenyl)ethyl]acetamide (5h)

The title compound was obtained as described for **5a**, starting from R/S-1-(2-ethoxy-5-fluorophenyl)-1-ethanol **4h** (10 g, 54.28 mmol). White solid (11.19 g, 91%). **m.p.** 140-141°C. **SM (ESI):** *m/z* 226 $[M+H]^+$, 248 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.26 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 1.35 (t, *J* = 7.0 Hz, **3H**, OCH$_2$C$\underline{H}_3$), 1.87 (s, **3H**, COC$\underline{H}_3$), 4.04 (q, *J* = 7.0 Hz, **2H**, OC$\underline{H}_2$CH$_3$), 5.19 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.95 (m, **1H**, C$\underline{H}$ar), 7.00 (m, **1H**, C$\underline{H}$ar), 7.06 (m, **1H**, C$\underline{H}$ar), 8.20 (d, *J* = 8.0 Hz, **1H**, N$\underline{H}$CH).

4.1.3.9. R/S-N-(1-(2-(benzyloxy)phenyl)ethyl)acetamide (5i)

The title compound was obtained as described for **5a**, starting from *R/S*-1-(2-benzyloxyphenyl)-1-ethanol **4i** (12 g, 52.56 mmol). White solid (12.88 g, 91%). **m.p.** 148-149°C. **SM (ESI):** *m/z* 270 $[M+H]^+$, 292 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.29 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 1.86 (s, **3H**, COC$\underline{H}_3$), 5.17 (m, **2H**, OC$\underline{H}_2$), 5.30 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.94 (m, **1H**, C$\underline{H}$ar), 7.04 (dd, J_{ortho} = 8.2 Hz, J_{para} = 0.7 Hz, **1H**, C$\underline{H}$ar), 7.19 (dd, J_{ortho} = 8.2 Hz, J_{meta} = 1.7 Hz, **1H**, C$\underline{H}$ar), 7.29 (m, **1H**, C$\underline{H}$ar), 7.34 (m, **1H**, C$\underline{H}$ar), 7.42 (m, **2H**, C$\underline{H}$ar), 7.51 (m, **2H**, C$\underline{H}$ar), 8.24 (d, *J* = 8.0 Hz, **1H**, N$\underline{H}$CH).

4.1.3.10. R/S-N-(1-(2-(benzyloxy)-5-methylphenyl)ethyl)acetamide (5j)

The title compound was obtained as described for **5a**, starting from *R/S*-1-(2-(benzyloxy)-5-methylphenyl)-1-ethanol **4j** (11 g, 45.4 mmol). White solid (11.5 g, 89%). **m.p.** 131-132°C. **SM (ESI):** *m/z* 284 $[M+H]^+$, 306 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 1.86 (s, **3H**, COC$\underline{H}_3$), 2.24 (s, **3H**, PhC$\underline{H}_3$), 5.12 (m, **2H**, OC$\underline{H}_2$), 5.28 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.92 (d, J_{ortho} = 8.4 Hz, **1H**, C$\underline{H}$ar), 6.98 (dd, J_{ortho} = 8.4 Hz, J_{meta} = 1.9 Hz, **1H**, C$\underline{H}$ar), 7.10 (d, J_{meta} = 1.9 Hz, **1H**, C$\underline{H}$ar), 7.34 (m, **1H**, C$\underline{H}$ar), 7.41 (m, **2H**, C$\underline{H}$ar), 7.49 (m, **2H**, C$\underline{H}$ar), 8.20 (d, *J* = 8.2 Hz, **1H**, N$\underline{H}$CH).

4.1.4. General procedure for the synthesis of amines (6a-j)

4.1.4.1. R/S-1-(5-bromo-2-methoxyphenyl)ethanamine hydrochloride (6a)

R/S-(1-(5-bromo-2-methoxyphenyl)ethyl)acetamide **5a** (9.5 g, 34.91 mmol, 1 eq) was dissolved in methanol (300 mL). A solution of sodium hydroxide (140 g, 3500 mmol, 100 eq) in water (100 mL) was added carefully. The mixture was heated under Argon, for 60 h at 250°C, and then methanol was removed under vacuum. The mixture was poured into ice and extracted with diethyl ether (3×150 mL). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and the filtrate was

decolorized with charcoal. After concentration under reduced pressure to half of the volume and treatment with ether saturated with gaseous hydrochloric acid, the solvent was evaporated. The oily residue was precipitated from diethyl ether after stirring overnight, and the precipitate formed was collected by filtration, washed with diethyl ether and then recrystallized in methanol/acetonitrile (1:9). The amine hydrochloride was obtained as a white crystals (7.83 g, 84%). **m.p.** 176-177°C. **SM (ESI):** *m/z* 213-215 [M+H-$NH_4Cl]^+$, 230-232 [M+H-HCl]$^+$, 252-254 [M+Na-HCl]$^+$. **^{1}H NMR (δ ppm):** 1.47 (d, *J* = 6.7 Hz, **3H**, CHC$\underline{H}_3$), 3.85 (s, **3H**, OC$\underline{H}_3$), 4.56 (m, **1H**, C$\underline{H}$CH$_3$), 7.07 (d, J_{ortho} = 8.9 Hz, **1H**, C$\underline{H}$ar), 7.55 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.4 Hz, **1H**, C$\underline{H}$ar), 7.69 (d, J_{meta} = 2.4 Hz, **1H**, C$\underline{H}$ar), 8.53 (br s, **3H**, N$\underline{H}_3^+$).

4.1.4.2. R/S-1-(5-bromo-2-ethoxyphenyl)ethanamine hydrochloride (6b)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(5-bromo-2-ethoxyphenyl)ethyl)acetamide **5b** (8.5 g, 29.7 mmol) and sodium hydroxide (119 g, 2.97 mol). White crystals (6.67 g, 80%). **m.p.** 237-238°C. **SM (ESI):** *m/z* 227-229 [M+H-$NH_4Cl]^+$, 244-246 [M+H-HCl]$^+$, 266-268 [M+Na-HCl]$^+$. **^{1}H NMR (δ ppm):** 1.37 (m, **3H**, OCH$_2$C$\underline{H}_3$), 1.47 (d, *J* = 6.7 Hz, **3H**, CHC$\underline{H}_3$), 4.11 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.58 (m, **1H**, C$\underline{H}$CH$_3$), 7.06 (d, J_{ortho} = 8.9 Hz, **1H**, C$\underline{H}$ar), 7.52 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.68 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 8.50 (br s, **3H**, N$\underline{H}_3^+$).

4.1.4.3. R/S-1-(5-bromo-2-isopropoxyphenyl)ethanamine hydrochloride (6c)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(5-bromo-2-isopropoxyphenyl)ethyl)acetamide **5c** (9 g, 29.98 mmol) and sodium hydroxide (120 g, 3 mol). White crystals (6.22 g, 70%). **m.p.** 214-215°C. **SM (ESI):** *m/z* 241-243 [M+H-$NH_4Cl]^+$, 258-260 [M+H-HCl]$^+$, 280-282 [M+Na-HCl]$^+$. **^{1}H NMR (δ ppm):** 1.29 (d, *J* = 6.0 Hz, **3H**, OCH(C$\underline{H}_3$)$_2$), 1.32 (d, *J* = 6.0 Hz, **3H**, OCH(C$\underline{H}_3$)$_2$), 1.46 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 4.54 (m, **1H**, C$\underline{H}$CH$_3$), 4.69 (sept, *J* = 6,0 Hz, **1H**, OC$\underline{H}$(CH$_3$)$_2$), 7.08 (d, J_{ortho} = 8.9 Hz, **1H**, C$\underline{H}$ar), 7.49 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.73 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 8.65 (br s, **3H**, N$\underline{H}_3^+$).

4.1.4.4. R/S-1-(2-(benzyloxy)-5-bromophenyl)ethanamine hydrochloride (6d)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(2-(benzyloxy)-5-bromophenyl)ethyl)acetamide **5d** (7.5 g, 21.54 mmol) and sodium hydroxide (86 g, 2.154 mol). White crystals (5.51 g, 74%). **m.p.** 159-160°C. **SM (ESI):** *m/z* 289-291 [M+H-

$NH_4Cl]^+$, 306-308 $[M+H\text{-}HCl]^+$, 328-330 $[M+Na\text{-}HCl]^+$. **^{1}H NMR (δ ppm):** 1.48 (d, J = 6.7 Hz, **3H**, $CHC\underline{H}_3$), 4.64 (m, **1H**, $C\underline{H}CH_3$), 5.21 (m, **2H**, $OC\underline{H}_2$), 7.14 (d, J_{ortho} = 8.9 Hz, **1H**, C<u>H</u>ar), 7.36 (m, **1H**, C<u>H</u>ar), 7.43 (m, **2H**, C<u>H</u>ar), 7.50 (m, **2H**, C<u>H</u>ar), 7.53 (dd, J_{ortho}= 8.9 Hz, J_{meta} = 2.5 Hz, **1H**, C<u>H</u>ar), 7.74 (d, J_{meta} = 2.5 Hz, **1H**, C<u>H</u>ar), 8.58 (br s, **3H**, $N\underline{H}_3^+$).

4.1.4.5. R/S-1-(5-chloro-2-methoxyphenyl)ethanamine hydrochloride (6e)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(5-chloro-2-methoxyphenyl)ethyl)acetamide **5e** (7 g, 30.74 mmol) and sodium hydroxide (123 g, 3.074 mol). White crystals (5.33 g, 78%). **m.p.** 190-191°C. **SM (ESI):** *m/z* 169-171 $[M+H\text{-}NH_4Cl]^+$, 186-188 $[M+H\text{-}HCl]^+$, 208-210 $[M+Na\text{-}HCl]^+$. **^{1}H NMR (δ ppm):** 1.48 (d, J = 6.8 Hz, **3H**, $CHC\underline{H}_3$), 3.85 (s, **3H**, $OC\underline{H}_3$), 4.56 (m, **1H**, $C\underline{H}CH_3$), 7.12 (d, J_{ortho} = 8.9 Hz, **1H**, C<u>H</u>ar), 7.42 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.6 Hz, **1H**, C<u>H</u>ar), 7.59 (d, J_{meta} = 2.6 Hz, **1H**, C<u>H</u>ar), 8.56 (br s, **3H**, $N\underline{H}_3^+$).

4.1.4.6. R/S-1-(5-chloro-2-ethoxyphenyl)ethanamine hydrochloride (6f)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(5-chloro-2-ethoxyphenyl)ethyl)acetamide **5f** (9 g, 37.23 mmol) and sodium hydroxide (149 g, 3.723 mol). White crystals (7.3 g, 83%). **m.p.** 226-227°C. **SM (ESI):** *m/z* 183-185 $[M+H\text{-}NH_4Cl]^+$, 200-202 $[M+H\text{-}HCl]^+$, 222-224 $[M+Na\text{-}HCl]^+$. **^{1}H NMR (δ ppm):** 1.37 (m, **3H**, $OCH_2C\underline{H}_3$), 1.48 (d, J = 6.7 Hz, **3H**, $CHC\underline{H}_3$), 4.10 (m, **2H**, $OC\underline{H}_2CH_3$), 4.57 (m, **1H**, $C\underline{H}CH_3$), 7.10 (d, J_{ortho} = 8.9 Hz, **1H**, C<u>H</u>ar), 7.39 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.3 Hz, **1H**, C<u>H</u>ar), 7.60 (d, J_{meta} = 2.3 Hz, **1H**, C<u>H</u>ar), 8.61 (br s, **3H**, $N\underline{H}_3^+$).

4.1.4.7. R/S-1-(5-fluoro-2-methoxyphenyl)ethanamine hydrochloride (6g)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(5-fluoro-2-methoxyphenyl)ethyl)acetamide **5g** (10 g, 47.34 mmol) and sodium hydroxide (189 g, 4.734 mol). white crystals (6.7 g, 68%). **m.p.** 201-202°C. **SM (ESI):** *m/z* 153 $[M+H\text{-}NH_4Cl]^+$, 170 $[M+H\text{-}HCl]^+$, 192 $[M+Na\text{-}HCl]^+$. **^{1}H NMR (δ ppm):** 1.48 (d, J = 6.8 Hz, **3H**, $CHC\underline{H}_3$), 3.83 (s, **3H**, $OC\underline{H}_3$), 4.57 (m, **1H**, $C\underline{H}CH_3$), 7.09 (m, **1H**, C<u>H</u>ar), 7.20 (m, **1H**, C<u>H</u>ar), 7.47 (m, **1H**, C<u>H</u>ar), 8.66 (br s, **3H**, $N\underline{H}_3^+$).

4.1.4.8. R/S-1-(2-ethoxy-5-fluorophenyl)ethanamine hydrochloride (6h)

The title compound was obtained as described for **6a**, starting from *R/S-N*-[1-(2-ethoxy-5-fluorophenyl)ethyl]acetamide **5h** (11 g, 48.83 mmol) and sodium hydroxide (195 g, 4.883

mol). White crystals (7.6 g, 70%). **m.p.** 184-185°C. **SM (ESI):** *m/z* 167 $[M+H-NH_4Cl]^+$, 184 $[M+H-HCl]^+$, 206 $[M+Na-HCl]^+$. **^{1}H NMR (δ ppm):** 1.36 (m, **3H**, $OCH_2C\underline{H}_3$), 1.49 (d, *J* = 6.8 Hz, **3H**, $CHC\underline{H}_3$), 4.08 (m, **2H**, $OC\underline{H}_2CH_3$), 4.59 (m, **1H**, $C\underline{H}CH_3$), 7.08 (m, **1H**, C<u>H</u>ar), 7.17 (m, **1H**, C<u>H</u>ar), 7.47 (m, **1H**, C<u>H</u>ar), 8.66 (br s, **3H**, $N\underline{H}_3^+$).

4.1.4.9. R/S-1-(2-benzyloxyphenyl)ethanamine hydrochloride (6i)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(2-(benzyloxy)phenyl)ethyl)acetamide **5i** (12 g, 44.55 mmol) and sodium hydroxide (178 g, 4.455 mol). White crystals (10.42 g, 88%). **m.p.** 138-139°C. **SM (ESI):** *m/z* 211 $[M+H-NH_4Cl]^+$, 228 $[M+H-HCl]^+$. **^{1}H NMR (δ ppm):** 1.50 (d, *J* = 6.8 Hz, **3H**, $CHC\underline{H}_3$), 4.67 (m, **1H**, $C\underline{H}CH_3$), 5.21 (m, **2H**, $OC\underline{H}_2$), 7.05 (d, J_{ortho} = 7.5 Hz, **1H**, C<u>H</u>ar), 7.16 (d, J_{ortho} = 8.2 Hz, **1H**, C<u>H</u>ar), 7.36 (m, **2H**, C<u>H</u>ar), 7.43 (m, **2H**, C<u>H</u>ar), 7.51 (m, **2H**, C<u>H</u>ar), 7.56 (d, J_{ortho} = 7.5 Hz, **1H**, C<u>H</u>ar), 8.56 (br s, **3H**, $N\underline{H}_3^+$).

4.1.4.10. R/S-1-(2-(benzyloxy)-5-methylphenyl)ethanamine hydrochloride (6j)

The title compound was obtained as described for **6a**, starting from *R/S-N*-(1-(2-(benzyloxy)-5-methylphenyl)ethyl)acetamide **5j** (11 g, 38.82 mmol) and sodium hydroxide (155 g, 3.882 mol). White crystals (9.74 g, 90%). **m.p.** 156-157°C. **SM (ESI):** *m/z* 225 $[M+H-NH_4Cl]^+$, 242 $[M+H-HCl]^+$. **^{1}H NMR (δ ppm):** 1.49 (d, *J* = 6.7 Hz, **3H**, $CHC\underline{H}_3$), 2.27 (s, **3H**, $PhC\underline{H}_3$), 4.63 (m, **1H**, $C\underline{H}CH_3$), 5.16 (m, **2H**, $OC\underline{H}_2$), 7.03 (d, J_{ortho} = 8.4 Hz, **1H**, C<u>H</u>ar), 7.14 (dd, J_{ortho} = 8.4 Hz, J_{meta} = 1.5 Hz, **1H**, C<u>H</u>ar), 7.35 (m, **1H**, C<u>H</u>ar), 7.42 (m, **3H**, C<u>H</u>ar), 7.49 (m, **2H**, C<u>H</u>ar), 8.59 (br s, **3H**, $N\underline{H}_3^+$).

4.1.5. General procedure for the synthesis of sulfonylureas (A1-33)

4.1.5.1. 1-(2,5-dimethoxybenzyl)-3-phenylsulfonylurea (A1)

Benzenesulfonyl isocyanate (0.96 mL, 7.18 mmol, 1.2 eq) was added to a solution of amine **1a** (1 g, 5.98 mmol, 1 eq) in anhydrous methylene chloride (10 mL). After 30 min, the resulting white precipitate was collected by filtration, washed with diethyl ether, and dried. The product was recrystallized in ethyl acetate. White solid (1.5 g, 71%). **m.p.** 144-145°C. **SM (ESI):** *m/z* 351 $[M+H]^+$, 373 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 3.64 (s, **3H**, $OC\underline{H}_3$), 3.73 (s, **3H**, $OC\underline{H}_3$), 4.11 (d, *J* = 5.8 Hz, **2H**, $C\underline{H}_2NH$), 6.64 (d, J_{meta} = 3.0 Hz, **1H**, C<u>H</u>ar), 6.79 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 3.0 Hz, **1H**, C<u>H</u>ar), 6.87 (t, *J* = 5.8 Hz, **1H**, $CH_2N\underline{H}$), 6.89 (d, J_{ortho} = 8.8 Hz, **1H**, C<u>H</u>ar), 7.61 (m, **2H**, C<u>H</u>ar), 7.70 (m, **1H**, C<u>H</u>ar), 7.91 (m, **2H**, C<u>H</u>ar), 10.77 (s, **1H**, $SO_2N\underline{H}$). **^{13}C NMR (δ ppm):** 38.4, 55.3, 55.7, 111.4, 112.1, 114.2, 127.1, 127.4, 129.0,

133.2, 140.1, 150.7, 151.2, 152.9. Anal. Calcd for $C_{16}H_{18}N_2O_5S$: C, 54.85, H, 5.18, N, 7.99, found: C, 55.18, H, 5.26, N, 8.11.

4.1.5.2. 1-(2,5-dimethoxybenzyl)-3-(4-methylphenyl)sulfonylurea (A2)

The title compound was obtained as described for **A1**, starting from **1a** (1 g, 5.98 mmol) and 4-methylbenzenesulfonyl isocyanate (1.1 mL, 7.18 mmol). White solid (1.5 g, 68%). **m.p.** 147-148°C. **SM (ESI):** *m/z* 365 $[M+H]^+$, 387 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 2.40 (s, **3H**, PhC$\underline{H}_3$), 3.64 (s, **3H**, OC$\underline{H}_3$), 3.73 (s, **3H**, OC$\underline{H}_3$), 4.10 (d, J = 6.1 Hz, **2H**, C$\underline{H}_2$NH), 6.62 (d, J_{meta} = 3.0 Hz, **1H**, C$\underline{H}$ar), 6.78 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 3.0 Hz, **1H**, C$\underline{H}$ar), 6.83 (t, J = 6.1 Hz, **1H**, $CH_2N\underline{H}$), 6.89 (d, J_{ortho} = 8.8 Hz, **1H**, C$\underline{H}$ar), 7.40 (d, J_{ortho} = 8.1 Hz, **2H**, C$\underline{H}$ar), 7.79 (d, J_{ortho} = 8.1 Hz, **2H**, C$\underline{H}$ar), 10.68 (s, **1H**, $SO_2N\underline{H}$). **^{13}C NMR (δ ppm):** 21.0, 38.3, 55.2, 55.7, 111.4, 112.0, 114.2, 127.2, 127.5, 129.4, 137.3, 143.6, 150.7, 151.3, 152.9. Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03, H, 5.53, N, 7.69, found: C, 56.40, H, 5.52, N, 7.68.

4.1.5.3. 1-(2,5-dimethoxybenzyl)-3-(4-chlorophenyl)sulfonylurea (A3)

The title compound was obtained as described for **A1**, starting from **1a** (1 g, 5.98 mmol) and 4-chlorobenzenesulfonyl isocyanate (1.07 mL, 7.18 mmol). White solid (1.95 g, 85%). **m.p.** 186-187°C. **SM (ESI):** *m/z* 385-387 $[M+H]^+$, 407-409 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 3.65 (s, **3H**, OC$\underline{H}_3$), 3.73 (s, **3H**, OC$\underline{H}_3$), 4.11 (d, J = 6.0 Hz, **2H**, C$\underline{H}_2$NH), 6.61 (d, J_{meta} = 3.1 Hz, **1H**, C$\underline{H}$ar), 6.78 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 3.1 Hz, **1H**, C$\underline{H}$ar), 6.89 (m, **2H**, $CH_2N\underline{H}$ + C$\underline{H}$ar), 7.69 (m, **2H**, C$\underline{H}$ar), 7.92 (m, **2H**, C$\underline{H}$ar), 10.84 (s, **1H**, $SO_2N\underline{H}$). **^{13}C NMR (δ ppm):** 38.3, 55.3, 55.7, 111.4, 112.0, 114.2, 127.4, 129.1, 129.2, 138.1, 139.0, 150.7, 151.3, 152.9. Anal. Calcd for $C_{16}H_{17}ClN_2O_5S$: C, 49.94, H, 4.45, N, 7.28, found: C, 50.08, H, 4.32, N, 7.50.

4.1.5.4. R/S-1-[1-(5-bromo-2-methoxyphenyl)ethyl]-3-phenylsulfonylurea (A4)

The title compound was obtained as described for **A1**, starting from amine **6a** (1 g, 4.35 mmol) and benzenesulfonyl isocyanate (0.7 mL, 5.22 mmol). White solid (1.4 g, 77%). **m.p.** 171-172°C. **SM (ESI):** *m/z* 413-415 $[M+H]^+$, 435-437 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.24 (d, J = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 3.79 (s, **3H**, OC$\underline{H}_3$), 4.86 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.95 (d, J_{ortho} = 8.7 Hz, **1H**, C$\underline{H}$ar), 7.10 (d, J = 8.4 Hz, **1H**, CHN$\underline{H}$), 7.33 (d, J_{meta} = 2.6 Hz, **1H**, C$\underline{H}$ar), 7.39 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.6 Hz, **1H**, C$\underline{H}$ar), 7.60 (m, **2H**, C$\underline{H}$ar), 7.68 (m, **1H**, C$\underline{H}$ar), 7.89 (m, **2H**, C$\underline{H}$ar), 10.68 (s, **1H**, $SO_2N\underline{H}$). **^{13}C NMR (δ ppm):** 21.2, 44.6, 55.7, 112.0, 113.3, 127.1, 128.7, 129.0, 130.5, 133.2, 134.2, 140.1, 150.4, 155.2. Anal. Calcd for $C_{16}H_{17}BrN_2O_4S$: C, 46.50, H, 4.15, N, 6.78, found: C, 46.82, H, 4.34, N, 6.63.

4.1.5.5. R/S-1-[1-(5-bromo-2-methoxyphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A5)

The title compound was obtained as described for **A1**, starting from amine **6a** (1 g, 4.35 mmol) and 4-methylbenzenesulfonyl isocyanate (0.8 mL, 5.22 mmol). White solid (1.43 g, 77%). **m.p.** 165-166°C. **SM (ESI):** *m/z* 427-429 $[M+H]^+$, 449-451 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.24 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 2.39 (s, **3H**, PhC$\underline{H}_3$), 3.79 (s, **3H**, OC$\underline{H}_3$), 4.85 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.95 (d, J_{ortho} = 8.7 Hz, **1H**, C$\underline{H}$ar), 7.05 (d, *J* = 8.4 Hz, **1H**, N$\underline{H}$CH), 7.31 (d, J_{meta} = 2.4 Hz, **1H**, C$\underline{H}$ar), 7.39 (m, **3H**, C$\underline{H}$ar), 7.77 (m, **2H**, C$\underline{H}$ar), 10.59 (s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 21.0, 21.2, 44.6, 55.7, 111.9, 113.3, 127.1, 128.7, 129.4, 130.5, 134.3, 137.3, 143.6, 150.4, 155.2. Anal. Calcd for $C_{17}H_{19}BrN_2O_4S$: C, 47.78, H, 4.48, N, 6.56, found: C, 48.01, H, 4.54, N, 6.67.

4.1.5.6. R/S-1-[1-(5-bromo-2-methoxyphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A6)

The title compound was obtained as described for **A1**, starting from amine **6a** (1 g, 4.35 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.78 mL, 5.22 mmol). White solid (1.5 g, 77%). **m.p.** 173-174°C. **SM (ESI):** *m/z* 445-447-449 $[M-H]^-$. **^{1}H NMR (δ ppm):** 1.24 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 3.79 (s, **3H**, OC$\underline{H}_3$), 4.86 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.95 (d, J_{ortho} = 8.6 Hz, **1H**, C$\underline{H}$ar), 7.14 (d, *J* = 8.3 Hz, **1H**, N$\underline{H}$CH), 7.31 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.38 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.68 (d, J_{ortho} = 8.8 Hz, **2H**, C$\underline{H}$ar), 7.90 (d, J_{ortho} = 8.8 Hz, **2H**, C$\underline{H}$ar), 10.77 (s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 21.1, 44.5, 55.7, 111.9, 113.3, 128.6, 129.2, 130.5, 134.2, 138.1, 138.9, 150.4, 155.2. Anal. Calcd for $C_{16}H_{16}BrClN_2O_4S$: C, 42.92, H, 3.60, N, 6.26, found: C, 43.13, H, 3.66, N, 6.34.

4.1.5.7. R/S-1-[1-(5-bromo-2-ethoxyphenyl)ethyl]-3-phenylsulfonylurea (A7)

The title compound was obtained as described for **A1**, starting from amine **6b** (1 g, 4.1 mmol) and benzenesulfonyl isocyanate (0.66 mL, 4.92 mmol). White solid (1.38 g, 78%). **m.p.** 179-180°C. **SM (ESI):** *m/z* 427-429 $[M+H]^+$, 449-451 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 1.32 (m, **3H**, OCH$_2$C$\underline{H}_3$), 4.03 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.86 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.93 (d, J_{ortho} = 8.6 Hz, **1H**, C$\underline{H}$ar), 7.04 (d, *J* = 8.3 Hz, **1H**, N$\underline{H}$CH), 7.31 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.36 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.60 (m, **2H**, C$\underline{H}$ar), 7.68 (m, **1H**, C$\underline{H}$ar), 7.89 (m, **2H**, C$\underline{H}$ar), 10.77 (s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 14.4, 21.0, 44.8, 63.8, 111.8, 114.1, 127.0, 128.8, 129.0, 130.5, 133.2, 134.2, 140.1, 150.4, 154.6. Anal. Calcd for $C_{17}H_{19}BrN_2O_4S$: C, 47.78, H, 4.48, N, 6.56, found: C, 47.57, H, 4.45, N, 6.49.

4.1.5.8. R/S-1-[1-(5-bromo-2-ethoxyphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A8)

The title compound was obtained as described for **A1**, starting from amine **6b** (1 g, 4.1 mmol) and 4-methylbenzenesulfonyl isocyanate (0.75 mL, 4.92 mmol). White solid (1.41 g, 78%). **m.p.** 184-185°C. **SM (ESI):** *m/z* 441-443 $[M+H]^+$, 463-465 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.24 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 1.32 (m, **3H**, OCH$_2$C$\underline{H}_3$), 2.38 (s, **3H**, PhC$\underline{H}_3$), 4.03 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.86 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.93 (d, J_{ortho} = 8.6 Hz, **1H**, C$\underline{H}$ar), 6.99 (d, *J* = 8.3 Hz, **1H**, N$\underline{H}$CH), 7.29 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.36 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.39 (d, J_{ortho} = 8.3 Hz, **2H**, C$\underline{H}$ar), 7.77 (d, J_{ortho} = 8.3 Hz, **2H**, C$\underline{H}$ar), 10.61 (br s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 14.4, 21.0, 44.8, 63.7, 111.8, 114.1, 127.1, 128.8, 129.4, 130.5, 134.3, 137.3, 143.6, 150.4, 154.6. Anal. Calcd for $C_{18}H_{21}BrN_2O_4S$: C, 48.99, H, 4.80, N, 6.35, found: C, 49.08, H, 4.85, N, 6.50.

4.1.5.9. R/S-1-[1-(5-bromo-2-ethoxyphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A9)

The title compound was obtained as described for **A1**, starting from amine **6b** (1 g, 4.1 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.73 mL, 4.92 mmol). White solid (1.33 g, 70%). **m.p.** 190-191°C. **SM (ESI):** m/z 461-463-465 $[M+H]^+$, 483-485-487 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 1.32 (m, **3H**, OCH$_2$C$\underline{H}_3$), 4.03 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.86 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.92 (d, J_{ortho} = 8.6 Hz, **1H**, C$\underline{H}$ar), 7.07 (d, *J* = 8.1 Hz, **1H**, N$\underline{H}$CH), 7.29 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.36 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.68 (m, **2H**, C$\underline{H}$ar), 7.90 (m, **2H**, C$\underline{H}$ar), 10.79 (s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 14.4, 20.9, 44.7, 63.8, 111.8, 114.1, 128.7, 129.1, 129.2, 130.5, 134.2, 138.1, 138.9, 150.3, 154.5. Anal. Calcd for $C_{17}H_{18}BrClN_2O_4S$: C, 44.22, H, 3.93, N, 6.07, found: C, 44.18, H, 3.88, N, 6.12.

4.1.5.10. R/S-1-[1-(5-bromo-2-isopropoxyphenyl)ethyl]-3-phenylsulfonylurea (A10)

The title compound was obtained as described for **A1**, starting from amine **6c** (1 g, 3.87 mmol) and benzenesulfonyl isocyanate (0.62 mL, 4.64 mmol). White solid (1.13 g, 66%). **m.p**. 180-181°C. **SM (ESI):** *m/z* 441-443 $[M+H]^+$, 463-465 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.23 (d, *J* = 6.0 Hz, **3H**, CHC$\underline{H}_3$), 1.26 (d, *J* = 6.3 Hz, **6H**, OCH(C$\underline{H}_3$)$_2$), 4.63 (sept, *J* = 6.3 Hz, **1H**, OC$\underline{H}$(CH$_3$)$_2$), 4.86 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.96 (d, J_{ortho} = 8.9 Hz, **1H**, C$\underline{H}$ar), 6.98 (d, *J* = 8.2 Hz, **1H**, N$\underline{H}$CH), 7.30 (d, J_{meta} = 2.6 Hz, **1H**, C$\underline{H}$ar), 7.35 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.6 Hz, **1H**, C$\underline{H}$ar), 7.60 (m, **2H**, C$\underline{H}$ar), 7.69 (m, **1H**, C$\underline{H}$ar), 7.89 (m, **2H**, C$\underline{H}$ar), 10.70 (br s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 20.9, 21.5, 21.6, 44.8, 69.8, 111.5, 115.2, 127.0, 127.3, 129.0, 130.5, 133.2, 134.9, 140.1, 150.3, 153.5. Anal. Calcd for $C_{18}H_{21}BrN_2O_4S$: C, 48.99, H, 4.80, N, 6.35, found: C, 48.73, H, 4.76, N, 6.75.

4.1.5.11. R/S-1-[1-(5-bromo-2-isopropoxyphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A11)

The title compound was obtained as described for **A1**, starting from amine **6c** (1 g, 3.87 mmol) and 4-methylbenzenesulfonyl isocyanate (0.71 mL, 4.64 mmol). White solid (1.34 g, 76%). **m.p.** 152-153°C. **SM (ESI):** *m/z* 455-457 $[M+H]^+$, 477-479 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.24 (d, *J* = 6.0 Hz, **3H**, CHC$\underline{H}_3$), 1.26 (d, *J* = 6.0 Hz, **3H**, OCH(C$\underline{H}_3$)$_2$), 1.27 (d, *J* = 6.0 Hz, **3H**, OCH(C$\underline{H}_3$)$_2$), 2.39 (s, **3H**, PhC$\underline{H}_3$), 4.63 (sept, *J* = 6.0 Hz, **1H**, OC$\underline{H}$(CH$_3$)$_2$), 4.84 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.91 (d, *J* = 8.3 Hz, **1H**, N$\underline{H}$CH), 6.96 (d, J_{ortho} = 8.8 Hz, **1H**, C$\underline{H}$ar), 7.28 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.34 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.39 (d, J_{ortho} = 8.3 Hz, **2H**, C$\underline{H}$ar), 7.77 (d, J_{ortho} = 8.3 Hz, **2H**, C$\underline{H}$ar), 10.58 (br s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (ppm):** 20.9, 21.0, 21.5, 21.6, 44.8, 69.8, 111.5, 115.2, 127.1, 129.0, 129.4, 130.4, 135.0, 137.4, 143.6, 150.4, 153.5. Anal. Calcd for $C_{19}H_{23}BrN_2O_4S$: C, 50.11, H, 5.09, N, 6.15, found: C, 50.14, H, 5.10, N, 6.11.

4.1.5.12. R/S-1-[1-(5-bromo-2-isopropoxyphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A12)

The title compound was obtained as described for **A1**, starting from amine **6c** (1 g, 3.87 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.7 mL, 4.64 mmol). White solid (1.38 g, 75%). **m.p.** 152-153°C. **SM (ESI):** *m/z* 475-477-479 $[M+H]^+$, 497-499-501 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.22 (d, *J* = 6.1 Hz, **3H**, CHC$\underline{H}_3$), 1.26 (d, *J* = 6.3 Hz, **3H**, OCH(C$\underline{H}_3$)$_2$), 1.27 (d, *J* = 6.3 Hz, **3H**, OCH(C$\underline{H}_3$)$_2$), 4.62 (sept, *J* = 6.3 Hz, **1H**, OC$\underline{H}$(CH$_3$)$_2$), 4.85 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.95 (d, J_{ortho} = 8.8 Hz, **1H**, C$\underline{H}$ar), 6.98 (d, *J* = 8.3 Hz, **1H**, N$\underline{H}$CH), 7.29 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.34 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.68 (m, **2H**, C$\underline{H}$ar), 7.90 (m, **2H**, C$\underline{H}$ar), 10.75 (br s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 20.8, 21.5, 21.6, 44.7, 69.8, 111.5, 115.2, 128.9, 129.1, 129.3, 130.4, 134.9, 138.1, 139.0, 150.3, 153.4. Anal. Calcd for $C_{18}H_{20}BrClN_2O_4S$: C, 45.44, H, 4.24, N, 5.89, found: C, 45.57, H, 4.48, N, 6.08.

4.1.5.13. R/S-1-[1-(2-(benzyloxy)-5-bromophenyl)ethyl]-3-phenylsulfonylurea (A13)

The title compound was obtained as described for **A1**, starting from amine **6d** (1 g, 3.26 mmol) and benzenesulfonyl isocyanate (0.52 mL, 3.91 mmol). White solid (1.04 g, 65%). **m.p.** 167-169°C. **SM (ESI):** *m/z* 489-491 $[M+H]^+$, 511-513 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 4.96 (m, **1H**, NHC$\underline{H}$CH$_3$), 5.15 (m, **2H**, OC$\underline{H}_2$), 7.01 (d, J_{ortho} = 9.1 Hz, **1H**, C$\underline{H}$ar), 7.10 (d, *J* = 8.1 Hz, **1H**, N$\underline{H}$CH), 7.38 (m, **7H**, C$\underline{H}$ar), 7.59 (m, **2H**,

CHar), 7.67 (m, **1H**, CHar), 7.88 (m, **2H**, CHar), 10.66 (br s, **1H**, SO_2NH). **^{13}C NMR (δ ppm):** 21.1, 44.3, 69.5, 112.3, 114.5, 127.0, 127.2, 127.8, 128.5, 128.6, 128.9, 130.4, 133.1, 134.9, 136.7, 140.3, 150.6, 154.0. Anal. Calcd for $C_{22}H_{21}BrN_2O_4S$: C, 53.99, H, 4.33, N, 5.72, found: C, 54.00, H, 4.72, N, 5.64.

4.1.5.14. R/S-1-[1-(2-(benzyloxy)-5-bromophenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A14)

The title compound was obtained as described for **A1**, starting from amine **6d** (1 g, 3.26 mmol) and 4-methylbenzenesulfonyl isocyanate (0.6 mL, 3.91 mmol). White solid (1.2 g, 73%). **m.p.** 181-183°C. **SM (ESI):** *m/z* 503-505 $[M+H]^+$, 525-527 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* = 6.8 Hz, **3H**, $CHCH_3$), 2.38 (s, **3H**, $PhCH_3$), 4.95 (m, **1H**, $NHCHCH_3$), 5.15 (m, **2H**, OCH_2), 7.01 (d, J_{ortho} = 8.8 Hz, **1H**, CHar), 7.06 (d, *J* = 8.1 Hz, **1H**, NHCH), 7.39 (m, **9H**, CHar), 7.77 (m, **2H**, CHar), 10.59 (br s, **1H**, SO_2NH). **^{13}C NMR (δ ppm):** 21.0, 21.1, 44.3, 69.5, 112.3, 114.5, 127.1, 127.2, 127.8, 128.5, 128.6, 129.4, 130.4, 134.8, 136.7, 137.3, 143.6, 150.5, 154.1. Anal. Calcd for $C_{23}H_{23}BrN_2O_4S$: C, 54.88, H, 4.61, N, 5.56, found: C, 54.64, H, 4.58, N, 5.53.

4.1.5.15. R/S-1-[1-(2-(benzyloxy)-5-bromophenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A15)

The title compound was obtained as described for **A1**, starting from amine **6d** (1 g, 3.26 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.58 mL, 3.91 mmol). White solid (1.31 g, 76%). **m.p.** 161-162°C. **SM (ESI):** *m/z* 523-525-527 $[M+H]^+$, 545-547-549 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* = 6.8 Hz, **3H**, $CHCH_3$), 4.96 (m, **1H**, $NHCHCH_3$), 5.15 (m, **2H**, OCH_2), 7.01 (d, J_{ortho} = 8.6 Hz, **1H**, CHar), 7.15 (d, *J* = 8.1 Hz, **1H**, NHCH), 7.39 (m, **7H**, CHar), 7.66 (d, J_{ortho} = 8.4 Hz, **2H**, CHar), 7.89 (d, J_{ortho} = 8.4 Hz, **2H**, CHar), 10.77 (br s, **1H**, SO_2NH). **^{13}C NMR (δ ppm):** 21.1, 44.2, 69.5, 112.3, 114.5, 127.2, 127.8, 128.4, 128.5, 129.1, 130.4, 134.8, 136.7, 138.0, 139.0, 150.5, 154.0. Anal. Calcd for $C_{22}H_{20}BrClN_2O_4S$: C, 50.44, H, 3.85, N, 5.35, found: C, 50.83, H, 3.86, N, 5.28.

4.1.5.16. R/S-1-[1-(5-chloro-2-methoxyphenyl)ethyl]-3-phenylsulfonylurea (A16)

The title compound was obtained as described for **A1**, starting from amine **6e** (1 g, 5.39 mmol) and benzenesulfonyl isocyanate (0.87 mL, 6.47 mmol). White solid (1.6 g, 80%). **m.p.** 167-168°C. **SM (ESI):** *m/z* 369-371 $[M+H]^+$, 391-393 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 6.8 Hz, **3H**, $CHCH_3$), 3.79 (s, **3H**, OCH_3), 4.87 (m, **1H**, $CHCH_3$), 7.00 (d, J_{ortho} =

8.6 Hz, **1H**, CHar), 7.07 (d, *J* = 8.1 Hz, **1H**, NHCH), 7.21 (s, **1H**, CHar), 7.26 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.3 Hz, **1H**, CHar), 7.60 (m, **2H**, CHar), 7.68 (m, **1H**, CHar), 7.90 (m, **2H**, CHar), 10.66 (br s, **1H**, SO_2NH). **^{13}C NMR (δ ppm):** 21.2, 44.7, 55.8, 112.8, 124.2, 125.9, 127.0, 127.6, 129.0, 133.1, 133.8, 140.2, 150.5, 154.8. Anal. Calcd for $C_{16}H_{17}ClN_2O_4S$: C, 52.10, H, 4.65, N, 7.60, found: C, 52.12, H, 4.70, N, 7.58.

4.1.5.17. R/S-1-[1-(5-chloro-2-methoxyphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A17)

The title compound was obtained as described for **A1**, starting from amine **6e** (1 g, 5.39 mmol) and 4-methylbenzenesulfonyl isocyanate (0.99 mL, 6.47 mmol). White solid (1.8 g, 87%). **m.p.** 194-195°C. **SM (ESI):** *m/z* 383-385 $[M+H]^+$, 405-407 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 6.6 Hz, **3H**, $CHCH_3$), 2.38 (s, **3H**, $PhCH_3$), 3.79 (s, **3H**, OCH_3), 4.87 (m, **1H**, $NHCHCH_3$), 6.99 (d, J_{ortho} = 8.8 Hz, **1H**, CHar), 7.04 (d, *J* = 8.1 Hz, **1H**, NHCH), 7.19 (s, **1H**, CHar), 7.26 (m, **1H**, CHar), 7.39 (d, J_{ortho} = 7.7 Hz, **2H**, CHar), 7.78 (d, J_{ortho} = 7.7 Hz, **2H**, CHar), 10.57 (br s, **1H**, SO_2NH). **^{13}C NMR (δ ppm):** 21.0, 21.2, 44.7, 55.8, 112.8, 124.2, 125.9, 127.1, 127.6, 129.4, 133.8, 137.3, 143.6, 150.4, 154.8. Anal. Calcd for $C_{17}H_{19}ClN_2O_4S$: C, 53.33, H, 5.00, N, 7.32, found: C, 53.47, H, 5.25, N, 7.28.

4.1.5.18. R/S-1-[1-(5-chloro-2-methoxyphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A18)

The title compound was obtained as described for **A1**, starting from amine **6e** (1 g, 5.39 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.97 mL, 6.47 mmol). White solid (1.6 g, 73%). **m.p.** 195-196°C. **SM (ESI):** *m/z* 403-405-407 $[M+H]^+$, 425-427-429 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 6.8 Hz, **3H**, $CHCH_3$), 3.79 (s, **3H**, OCH_3), 4.87 (m, **1H**, $NHCHCH_3$), 6.99 (d, J_{ortho} = 8.8 Hz, **1H**, CHar), 7.11 (d, *J* = 8.3 Hz, **1H**, NHCH), 7.18 (d, J_{meta} = 2.8 Hz, **1H**, CHar), 7.26 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.8 Hz, **1H**, CHar), 7.68 (d, J_{ortho} = 8.6 Hz, **2H**, CHar), 7.90 (d, J_{ortho} = 8.6 Hz, **2H**, CHar), 10.74 (br s, **1H**, SO_2NH). **^{13}C NMR (δ ppm):** 21.1, 44.6, 55.8, 112.8, 124.2, 125.8, 127.6, 129.1, 133.8, 138.1, 138.9, 150.4, 154.8. Anal. Calcd for $C_{16}H_{16}Cl_2N_2O_4S$: C, 47.65, H, 4.00, N, 6.95, found: C, 47.67, H, 4.06, N, 7.03.

4.1.5.19. R/S-1-[1-(5-chloro-2-ethoxyphenyl)ethyl]-3-phenylsulfonylurea (A19)

The title compound was obtained as described for **A1**, starting from amine **6f** (1 g, 5 mmol) and benzenesulfonyl isocyanate (0.8 mL, 6 mmol). White solid (1.68 g, 87%). **m.p.** 177-178°C. **SM (ESI):** *m/z* 383-385 $[M+H]^+$, 405-407 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 7.1 Hz, **3H**, $CHCH_3$), 1.32 (m, **3H**, OCH_2CH_3), 4.03 (m, **2H**, OCH_2CH_3), 4.87 (m, **1H**,

NHC<u>H</u>CH$_3$), 6.97 (d, J_{ortho} = 8.6 Hz, **1H**, C<u>H</u>ar), 7.02 (d, J = 8.3 Hz, **1H**, N<u>H</u>CH), 7.19 (d, J_{meta} = 2.5 Hz, **1H**, C<u>H</u>ar), 7.23 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.5 Hz, **1H**, C<u>H</u>ar), 7.60 (m, **2H**, C<u>H</u>ar), 7.68 (m, **1H**, C<u>H</u>ar), 7.89 (m, **2H**, C<u>H</u>ar), 10.67 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 14.4, 20.9, 44.9, 63.7, 113.6, 124.0, 126.0, 127.0, 127.7, 129.0, 133.2, 133.8, 140.1, 150.4, 154.1. Anal. Calcd for $C_{17}H_{19}ClN_2O_4S$: C, 53.33, H, 5.00, N, 7.32, found: C, 53.21, H, 4.97, N, 7.23.

4.1.5.20. R/S-1-[1-(5-chloro-2-ethoxyphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A20)

The title compound was obtained as described for **A1**, starting from amine **6f** (1 g, 5 mmol) and 4-methylbenzenesulfonyl isocyanate (0.92 mL, 6 mmol). White solid (1.82 g, 91%). **m.p.** 187-188°C. **SM (ESI):** *m/z* 397-399 $[M+H]^+$, 419-421 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, J = 7.1 Hz, **3H**, CHC<u>H</u>$_3$), 1.33 (m, **3H**, OCH$_2$C<u>H</u>$_3$), 2.38 (s, **3H**, PhC<u>H</u>$_3$), 4.04 (m, **2H**, OC<u>H</u>$_2$CH$_3$), 4.86 (m, **1H**, NHC<u>H</u>CH$_3$), 6.98 (m, **2H**, C<u>H</u>ar + N<u>H</u>CH), 7.16 (d, J_{meta} = 2.3 Hz, **1H**, C<u>H</u>ar), 7.23 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.3 Hz, **1H**, C<u>H</u>ar), 7.39 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.77 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 10.58 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 14.4, 21.0, 21.1, 44.9, 63.7, 113.6, 124.0, 126.0, 127.1, 127.5, 129.4, 133.8, 137.3, 143.6, 150.4, 154.1. Anal. Calcd for $C_{18}H_{21}ClN_2O_4S$: C, 54.47, H, 5.33, N, 7.06, found: C, 54.21, H, 5.42, N, 7.07.

4.1.5.21. R/S-1-[1-(5-chloro-2-ethoxyphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A21)

The title compound was obtained as described for **A1**, starting from amine **6f** (1 g, 5 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.9 mL, 6 mmol). White solid (1.87 g, 89%). **m.p.** 184-185°C. **SM (ESI):** *m/z* 417-419-421 $[M+H]^+$, 439-441-443 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, J = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 1.32 (m, **3H**, OCH$_2$C<u>H</u>$_3$), 4.03 (m, **2H**, OC<u>H</u>$_2$CH$_3$), 4.87 (m, **1H**, NHC<u>H</u>CH$_3$), 6.97 (d, J_{ortho} = 8.6 Hz, **1H**, C<u>H</u>ar), 7.05 (d, J = 8.3 Hz, **1H**, N<u>H</u>CH), 7.17 (d, J_{meta} = 2.5 Hz, **1H**, C<u>H</u>ar), 7.23 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.5 Hz, **1H**, C<u>H</u>ar), 7.67 (d, J_{ortho} = 8.6 Hz, **2H**, C<u>H</u>ar), 7.90 (d, J_{ortho} = 8.6 Hz, **2H**, C<u>H</u>ar), 10.76 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 14.4, 20.9, 44.8, 63.3, 113.5, 124.0, 125.9, 127.5, 129.1, 133.8, 138.1, 138.9, 150.3, 154.1. Anal. Calcd for $C_{17}H_{18}Cl_2N_2O_4S$: C, 48.93, H, 4.35, N, 6.71, found: C, 48.64, H, 4.44, N, 6.36.

4.1.5.22. R/S-1-[1-(5-fluoro-2-methoxyphenyl)ethyl]-3-phenylsulfonylurea (A22)

The title compound was obtained as described for **A1**, starting from amine **6g** (1 g, 5.91 mmol) and benzenesulfonyl isocyanate (0.95 mL, 7.09 mmol). White solid (1.4 g, 67%).

m.p. 139-140°C. **SM (ESI):** *m/z* 353 $[M+H]^+$, 375 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 7.1 Hz, **3H**, CHC<u>H</u>$_3$), 3.78 (s, **3H**, OC<u>H</u>$_3$), 4.87 (m, **1H**, NHC<u>H</u>CH$_3$), 7.01 (m, **4H**, 3C<u>H</u>ar + N<u>H</u>CH), 7.59 (m, **2H**, C<u>H</u>ar), 7.68 (m, **1H**, C<u>H</u>ar), 7.90 (m, **2H**, C<u>H</u>ar), 10.64 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 21.2, 44.8, 55.9, 112.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.0 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 113.7 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 127.1, 129.0, 133.1, 133.5 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 140.1, 150.4, 152.2 (d, $^4J_{C\text{-}F}$ = 1.3 Hz), 156.3 (d, $^1J_{C\text{-}F}$ = 236.5 Hz). Anal. Calcd for $C_{16}H_{17}FN_2O_4S$: C, 54.54, H, 4.86, N, 7.95, found: C, 54.50, H, 4.88, N, 8.01.

4.1.5.23. R/S-1-[1-(5-fluoro-2-methoxyphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A23)

The title compound was obtained as described for **A1**, starting from amine **6g** (1 g, 5.91 mmol) and 4-methylbenzenesulfonyl isocyanate (1.08 mL, 7.09 mmol). White solid (1.1 g, 51%). **m.p.** 159-160°C. **SM (ESI):** *m/z* 367 $[M+H]^+$, 389 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 2.38 (s, **3H**, PhC<u>H</u>$_3$), 3.78 (s, **3H**, OC<u>H</u>$_3$), 4.87 (m, **1H**, NHC<u>H</u>CH$_3$), 7.01 (m, **4H**, 3C<u>H</u>ar + N<u>H</u>CH), 7.39 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.77 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 10.64 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 21.0, 21.2, 44.8, 55.9, 112.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.0 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 113.7 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 127.1, 129.4, 133.6 (d, $^3J_{C\text{-}F}$ = 6.1 Hz), 137.3, 143.6, 150.4, 152.2 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 156.2 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{17}H_{19}FN_2O_4S$: C, 55.73, H, 5.23, N, 7.65, found: C, 55.82, H, 5.32, N, 7.72.

4.1.5.24. R/S-1-[1-(5-fluoro-2-methoxyphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A24)

The title compound was obtained as described for **A1**, starting from amine **6g** (1 g, 5.91 mmol) and 4-chlorobenzenesulfonyl isocyanate (1.06 mL, 7.09 mmol). White solid (1 g, 43%). **m.p.** 161-162°C. **SM (ESI):** *m/z* 387-389 $[M+H]^+$, 409-411 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.25 (d, *J* = 7.1 Hz, **3H**, CHC<u>H</u>$_3$), 3.78 (s, **3H**, OC<u>H</u>$_3$), 4.87 (m, **1H**, NHC<u>H</u>CH$_3$), 7.01 (m, **3H**, C<u>H</u>ar), 7.09 (d, *J* = 8.1 Hz, **1H**, N<u>H</u>CH), 7.67 (m, **2H**, C<u>H</u>ar), 7.90 (m, **2H**, C<u>H</u>ar), 10.72 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 21.1, 44.7, 55.9, 112.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.0 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 113.7 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 129.1, 129.2, 133.5 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 138.1, 138.9, 150.4, 152.2 (d, $^4J_{C\text{-}F}$ = 1.3 Hz), 156.3 (d, $^1J_{C\text{-}F}$ = 236.5 Hz). Anal. Calcd for $C_{16}H_{16}ClFN_2O_4S$: C, 49.68, H, 4.17, N, 7.24, found: C, 49.51, H, 4.13, N, 7.29.

4.1.5.25. R/S-1-[1-(2-ethoxy-5-fluorophenyl)ethyl]-3-phenylsulfonylurea (A25)

The title compound was obtained as described for **A1**, starting from amine **6h** (1 g, 5.46 mmol) and benzenesulfonyl isocyanate (0.88 mL, 6.55 mmol). White solid (1.68 g, 84%). **m.p.** 139-140°C. **SM (ESI):** *m/z* 367 $[M+H]^+$, 389 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* =

7.1 Hz, **3H**, CHC<u>H</u>$_3$), 1.32 (m, **3H**, OCH$_2$C<u>H</u>$_3$), 4.01 (m, **2H**, OC<u>H</u>$_2$CH$_3$), 4.88 (m, **1H**, NHC<u>H</u>CH$_3$), 6.99 (m, **4H**, 3C<u>H</u>ar + N<u>H</u>CH), 7.59 (m, **2H**, C<u>H</u>ar), 7.68 (m, **1H**, C<u>H</u>ar), 7.89 (m, **2H**, C<u>H</u>ar), 10.68 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 14.5, 21.0, 44.9, 63.9, 113.1 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 113.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.7 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 127.1, 129.0, 133.2, 133.6 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 140.1, 150.4, 151.6 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 156.1 (d, $^1J_{C\text{-}F}$ = 236.5 Hz). Anal. Calcd for $C_{17}H_{19}FN_2O_4S$: C, 55.73, H, 5.23, N, 7.65, found: C, 55.67, H, 5.24, N, 7.67.

4.1.5.26. R/S-1-[1-(2-ethoxy-5-fluorophenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A26)

The title compound was obtained as described for **A1**, starting from amine **6h** (1 g, 5.46 mmol) and 4-methylbenzenesulfonyl isocyanate (1 mL, 6.55 mmol). White solid (1.79 g, 86%). **m.p.** 166-167°C. **SM (ESI):** *m/z* 381 $[M+H]^+$, 403 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 1.32 (m, **3H**, OCH$_2$C<u>H</u>$_3$), 2.38 (s, **3H**, PhC<u>H</u>$_3$), 4.01 (m, **2H**, OC<u>H</u>$_2$CH$_3$), 4.88 (m, **1H**, NHC<u>H</u>CH$_3$), 6.99 (m, **4H**, 3C<u>H</u>ar + N<u>H</u>CH), 7.38 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.78 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 10.59 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 14.5, 21.0, 21.1, 45.0, 63.9, 113.1 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 113.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.7 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 127.1, 129.4, 133.6 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 137.3, 143.6, 150.4, 151.6 (d, $^4J_{C\text{-}F}$ = 1.3 Hz), 156.1 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{18}H_{21}FN_2O_4S$: C, 56.83, H, 5.56, N, 7.36, found: C, 57.17, H, 5.61, N, 7.46.

4.1.5.27. R/S-1-[1-(2-ethoxy-5-fluorophenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A27)

The title compound was obtained as described for **A1**, starting from amine **6h** (1 g, 5.46 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.98 mL, 6.55 mmol). White solid (1.96 g, 89%). **m.p.** 176-177°C. **SM (ESI):** *m/z* 401-403 $[M+H]^+$, 423-425 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 1.31 (m, **3H**, OCH$_2$C<u>H</u>$_3$), 4.01 (m, **2H**, OC<u>H</u>$_2$CH$_3$), 4.88 (m, **1H**, NHC<u>H</u>CH$_3$), 6.99 (m, **4H**, 3C<u>H</u>ar + N<u>H</u>CH), 7.68 (m, **2H**, C<u>H</u>ar), 7.90 (m, **2H**, C<u>H</u>ar), 10.76 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (δ ppm):** 14.5, 20.9, 44.8, 63.9, 113.0 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 113.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.7 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 129.1, 129.2, 133.6 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 138.1, 138.9, 150.3, 151.5 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 156.1 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{17}H_{18}ClFN_2O_4S$: C, 50.94, H, 4.53, N, 6.99, found: C, 50.87, H, 4.46, N, 6.96.

4.1.5.28. R/S-1-[1-(2-benzyloxyphenyl)ethyl]-3-phenylsulfonylurea (A28)

The title compound was obtained as described for **A1**, starting from amine **6i** (1 g, 4.4 mmol) and benzenesulfonyl isocyanate (0.71 mL, 5.28 mmol). White solid (1.3 g, 72%). **m.p.** 135-136°C. **SM (ESI):** *m/z* 411 $[M+H]^+$, 433 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.30 (d, *J* = 7.0 Hz,

3H, CHC<u>H</u>$_3$), 5.00 (m, **1H**, NHC<u>H</u>CH$_3$), 5.16 (m, **2H**, OC<u>H</u>$_2$), 6.91 (m, **1H**, C<u>H</u>ar), 6.98 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH), 7.05 (d, J_{ortho} = 8.0 Hz, **1H**, C<u>H</u>ar), 7.20 (m, **2H**, C<u>H</u>ar), 7.33 (m, **1H**, C<u>H</u>ar), 7.40 (m, **2H**, C<u>H</u>ar), 7.47 (m, **2H**, C<u>H</u>ar), 7.59 (m, **2H**, C<u>H</u>ar), 7.68 (m, **1H**, C<u>H</u>ar), 7.89 (m, **2H**, C<u>H</u>ar), 10.61 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (*δ* ppm):** 21.6, 44.9, 69.2, 112.3, 120.7, 126.2, 127.2, 127.3, 127.8, 128.2, 128.5, 129.1, 131.8, 133.3, 137.2, 140.2, 150.5, 155.0. Anal. Calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37, H, 5.40, N, 6.82, found: C, 64.37, H, 5.52, N, 6.85.

4.1.5.29. R/S-1-[1-(2-benzyloxyphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A29)

The title compound was obtained as described for **A1**, starting from amine **6i** (1 g, 4.4 mmol) and 4-methylbenzenesulfonyl isocyanate (0.81 mL, 5.28 mmol). White solid (1.44 g, 77%). **m.p.** 164-165°C. SM (ESI): *m/z* 425 $[M+H]^+$, 447 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.30 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 2.38 (s, **3H**, PhC<u>H</u>$_3$), 4.99 (m, **1H**, NHC<u>H</u>CH$_3$), 5.16 (m, **2H**, OC<u>H</u>$_2$), 6.91 (m, **1H**, C<u>H</u>ar), 6.93 (d, *J* = 8.9 Hz, **1H**, N<u>H</u>CH), 7.05 (d, J_{ortho} = 7.6 Hz, **1H**, C<u>H</u>ar), 7.16 (dd, J_{ortho} = 7.6 Hz, J_{meta} = 1.5 Hz, **1H**, C<u>H</u>ar), 7.21 (m, **1H**, C<u>H</u>ar), 7.34 (m, **1H**, C<u>H</u>ar), 7.39 (m, **4H**, C<u>H</u>ar), 7.47 (m, **2H**, C<u>H</u>ar), 7.76 (m, **2H**, C<u>H</u>ar), 10.51 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (*δ* ppm):** 21.1, 21.6, 44.8, 69.2, 112.3, 119.5, 120.7, 126.2, 127.3, 127.8, 128.1, 128.5, 129.5, 131.8, 137.2, 137.3, 143.7, 150.5, 155.0. Anal. Calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07, H, 5.70, N, 6.60, found: C, 65.37, H, 5.88, N, 6.79.

4.1.5.30. R/S-1-[1-(2-benzyloxyphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A30)

The title compound was obtained as described for **A1**, starting from amine **6i** (1 g, 4.4 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.79 mL, 5.28 mmol). White solid (1.44 g, 57%). **m.p.** 127-128°C. **SM (ESI):** *m/z* 445-447 $[M+H]^+$, 467-469 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.30 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 5.00 (m, **1H**, NHC<u>H</u>CH$_3$), 5.15 (m, **2H**, OC<u>H</u>$_2$), 6.91 (m, **1H**, C<u>H</u>ar), 7.01 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH), 7.05 (d, J_{ortho} = 8.0 Hz, **1H**, C<u>H</u>ar), 7.20 (m, **2H**, C<u>H</u>ar), 7.33 (m, **1H**, C<u>H</u>ar), 7.39 (m, **2H**, C<u>H</u>ar), 7.46 (m, **2H**, C<u>H</u>ar), 7.67 (m, **2H**, C<u>H</u>ar), 7.89 (m, **2H**, C<u>H</u>ar), 10.68 (s, **1H**, SO$_2$N<u>H</u>). **^{13}C NMR (*δ* ppm):** 21.5, 44.8, 69.2, 112.3, 119.9, 120.8, 126.2, 127.2, 127.8, 128.1, 128.5, 129.2, 129.3, 131.8, 137.2, 138.1, 150.4, 154.9. Anal. Calcd for $C_{22}H_{21}ClN_2O_4S$: C, 59.39, H, 4.76, N, 6.30, found: C, 59.50, H, 4.99, N, 6.01.

4.1.5.31. R/S-1-[1-(2-(benzyloxy)-5-methylphenyl)ethyl]-3-phenylsulfonylurea (A31)

The title compound was obtained as described for **A1**, starting from amine **6j** (1 g, 4.14 mmol) and benzenesulfonyl isocyanate (0.79 mL, 4.97 mmol). White solid (1.38 g, 78%). **m.p.** 163-164°C. **SM (ESI):** *m/z* 425 $[M+H]^+$, 447 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.28 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 2.20 (s, **3H**, PhC$\underline{H}_3$), 4.95 (m, **1H**, NHC$\underline{H}$CH$_3$), 5.12 (m, **2H**, OC$\underline{H}_2$), 6.97 (m, **4H**, 3C$\underline{H}$ar + N$\underline{H}$CH), 7.33 (m, **1H**, C$\underline{H}$ar), 7.39 (m, **2H**, C$\underline{H}$ar), 7.45 (m, **2H**, C$\underline{H}$ar), 7.59 (m, **2H**, C$\underline{H}$ar), 7.68 (m, **1H**, C$\underline{H}$ar), 7.89 (m, **2H**, C$\underline{H}$ar), 10.59 (s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 20.3, 21.6, 44.9, 69.3, 112.3, 126.9, 127.1, 127.2, 127.7, 128.2, 128.5, 129.1, 129.3, 131.5, 133.2, 137.3, 140.2, 150.4, 152.8. Anal. Calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07, H, 5.70, N, 6.60, found: C, 65.52, H, 5.80, N, 6.90.

4.1.5.32. R/S-1-[1-(2-(benzyloxy)-5-methylphenyl)ethyl]-3-(4-methylphenyl)sulfonylurea (A32)

The title compound was obtained as described for **A1**, starting from amine **6j** (1 g, 4.14 mmol) and 4-methylbenzenesulfonyl isocyanate (0.76 mL, 4.97 mmol). White solid (1.67 g, 92%). **m.p.** 181-183°C. **SM (ESI):** *m/z* 439 $[M+H]^+$, 461 $[M+Na]^+$. **1H NMR (δ ppm):** 1.29 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 2.20 (s, **3H**, PhC$\underline{H}_3$), 2.38 (s, **3H**, PhC$\underline{H}_3$), 4.95 (m, **1H**, NHC$\underline{H}$CH$_3$), 5.12 (m, **2H**, OC$\underline{H}_2$), 6.92 (m, **2H**, C$\underline{H}$ar + N$\underline{H}$CH), 6.96 (m, **1H**, C$\underline{H}$ar), 6.99 (m, **1H**, C$\underline{H}$ar), 7.33 (m, **1H**, C$\underline{H}$ar), 7.39 (m, **4H**, C$\underline{H}$ar), 7.45 (m, **2H**, C$\underline{H}$ar), 7.77 (d, *J* = 8.2 Hz, **2H**, C$\underline{H}$ar), 10.51 (s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 20.3, 21.0, 21.6, 44.9, 69.3, 112.3, 126.9, 127.2, 127.7, 128.2, 128.5, 129.3, 129.5, 131.5, 137.2, 137.3, 143.7, 150.4, 152.8. Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73, H, 5.98, N, 6.39, found: C, 65.79, H, 6.22, N, 6.49.

4.1.5.33. R/S-1-[1-(2-(benzyloxy)-5-methylphenyl)ethyl]-3-(4-chlorophenyl)sulfonylurea (A33)

The title compound was obtained as described for **A1**, starting from amine **6j** (1 g, 4.14 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.74 mL, 4.97 mmol). white solid (1.23 g, 64%). **m.p.** 156-158°C. **SM (ESI):** *m/z* 459-461 $[M+H]^+$, 481-483 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.29 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 2.21 (s, **3H**, PhC$\underline{H}_3$), 4.96 (m, **1H**, NHC$\underline{H}$CH$_3$), 5.11 (m, **2H**, OC$\underline{H}_2$), 6.97 (m, **4H**, 3C$\underline{H}$ar + N$\underline{H}$CH), 7.32 (m, **1H**, C$\underline{H}$ar), 7.38 (m, **2H**, C$\underline{H}$ar), 7.44 (m, **2H**, C$\underline{H}$ar), 7.67 (d, J_{ortho} = 8.7 Hz, **2H**, C$\underline{H}$ar), 7.9 (d, J_{ortho} = 8.7 Hz, **2H**, C$\underline{H}$ar), 10.68 (s, **1H**, SO$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 20.3, 21.6, 44.5, 69.2, 112.3, 126.9, 127.2, 127.6, 128.2, 128.3, 129.2, 129.3, 129.5, 131.6, 136.4, 137.3, 139.3, 150.5, 152.7. Anal. Calcd for $C_{23}H_{23}ClN_2O_4S$: C, 60.19, H, 5.05, N, 6.10, found: C, 60.57, H, 5.31, N, 6.20.

4.1.6. General procedure for the synthesis of *N*-methylated sulfonylurea (B1-33).

4.1.6.1. R/S-1-[1-(5-bromo-2-methoxyphenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B4)

Methyl iodide (0.15 mL, 2.42 mmol, 2 eq) was added to a suspension of **A4** (0.5 g, 1.21 mmol, 1 eq) and sodium carbonate (0.19 g, 1.81 mmol, 1.5 eq) in acetonitrile (15 mL). The mixture was refluxed during 3h. Remaining iodomethane and acetonitrile were removed under vacuum. After cooling, distilled water was added to the residue (20 mL) and the product was extracted twice with ethyl acetate. The organic layers were washed with brine, a saturated aqueous solution of sodium bicarbonate and then with water. The final organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The oily residue was precipitated from petroleum ether 40/60 after stirring overnight. The obtained white precipitate was collected by filtration, and dried under vacuum (0.29 g, 56%). **m.p.** 95-96°C. **SM (ESI):** *m/z* 427-429 $[M+H]^+$, 449-451 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.34 (d, J = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 3.11 (s, **3H**, NC$\underline{H}_3$), 3.82 (s, **3H**, OC$\underline{H}_3$), 4.98 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.99 (d, J_{ortho} = 8.5 Hz, **1H**, C$\underline{H}$ar), 7.42 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.45 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.62 (m, **2H**, C$\underline{H}$ar), 7.74 (m, **1H**, C$\underline{H}$ar), 7.83 (m, **2H**, C$\underline{H}$ar), 8.01 (d, J = 8.0 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 20.9, 33.2, 45.9, 55.8, 112.0, 113.4, 127.0, 129.0, 129.4, 130.6, 133.8, 134.1, 137.9, 151.8, 155.3. Anal. Calcd for $C_{17}H_{19}BrN_2O_4S$: C, 47.78, H, 4.48, N, 6.56, found: C, 47.38, H, 4.59, N, 6.65.

4.1.6.2. 1-(2,5-dimethoxbenzyl)-3-methyl-3-phenylsulfonylurea (B1)

The title compound was obtained as described for **B4**, starting from **A1** (0.5 g, 1.43 mmol), Na_2CO_3 (0.23 g, 2.14 mmol) and methyl iodide (0.18 mL, 2.86 mmol). Yellowish oil (0.46 g, 88%). **SM (ESI):** *m/z* 365 $[M+H]^+$, 387 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 3.12 (s, **3H**, NC$\underline{H}_3$), 3.67 (s, **3H**, OC$\underline{H}_3$), 3.77 (s, **3H**, OC$\underline{H}_3$), 4.24 (d, J = 5.8 Hz, **2H**, C$\underline{H}_2$NH), 6.73 (d, J_{meta} = 3.0 Hz, **1H**, C$\underline{H}$ar), 6.82 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 3.0 Hz, **1H**, C$\underline{H}$ar), 6.94 (d, J_{ortho} = 8.9 Hz, **1H**, C$\underline{H}$ar), 7.61 (m, **2H**, C$\underline{H}$ar), 7.74 (m, **1H**, C$\underline{H}$ar), 7.84 (m, **2H**, C$\underline{H}$ar), 7.96 (t, J = 5.7 Hz, **1H**, CH$_2$N$\underline{H}$). **^{13}C NMR (δ ppm):** 33.1, 39.5, 55.3, 55.8, 111.5, 112.1, 114.5, 127.0, 127.3, 129.4, 133.8, 138.0, 150.7, 152.7, 153.0. Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03, H, 5.53, N, 7.69, found: C, 56.31, H, 5.87, N, 7.35.

4.1.6.3. 1-(2,5-dimethoxbenzyl)-3-methyl-3-(4-methylphenyl)sulfonylurea (B2)

The title compound was obtained as described for **B4**, starting from **A2** (0.5 g, 1.37 mmol), Na_2CO_3 (0.22 g, 2.05 mmol) and methyl iodide (0.17 mL, 2.74 mmol). Yellowish oil (0.22

g, 43%). **SM (ESI):** *m/z* 379 $[M+H]^+$, 401 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 2.41 (s, **3H**, PhC<u>H</u>$_3$), 3.09 (s, **3H**, NC<u>H</u>$_3$), 3.68 (s, **3H**, OC<u>H</u>$_3$), 3.77 (s, **3H**, OC<u>H</u>$_3$), 4.24 (d, *J* = 5.8 Hz, **2H**, C<u>H</u>$_2$NH), 6.70 (d, J_{meta} = 3.0 Hz, **1H**, C<u>H</u>ar), 6.82 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 3.0 Hz, **1H**, C<u>H</u>ar), 6.94 (d, J_{ortho} = 8.8 Hz, **1H**, C<u>H</u>ar), 7.40 (m, **2H**, C<u>H</u>ar), 7.72 (m, **2H**, C<u>H</u>ar), 7.92 (t, *J* = 5.8 Hz, **1H**, CH_2N<u>H</u>). **^{13}C NMR (δ ppm):** 21.0, 32.9, 39.5, 55.3, 55.8, 111.4, 112.1, 114.5, 127.0, 127.4, 129.8, 135.0, 144.5, 150.7, 152.7, 153.0. Anal. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13, H, 5.86, N, 7.40, found: C, 56.84, H, 5.94, N, 7.13.

4.1.6.4. 1-(2,5-dimethoxbenzyl)-3-methyl-3-(4-chlorophenyl)sulfonylurea (B3)

The title compound was obtained as described for **B4**, starting from **A3** (0.5 g, 1.3 mmol), Na_2CO_3 (0.21 g, 1.95 mmol) and methyl iodide (0.16 mL, 2.6 mmol). Yellowish powder (0.35 g, 67%). **m.p.** 68-69°C. **SM (ESI):** *m/z* 399-401 $[M+H]^+$, 421-423 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 3.17 (s, **3H**, NC<u>H</u>$_3$), 3.68 (s, **3H**, OC<u>H</u>$_3$), 3.76 (s, **3H**, OC<u>H</u>$_3$), 4.22 (d, *J* = 5.8 Hz, **2H**, C<u>H</u>$_2$NH), 6.66 (d, J_{meta} = 3.0 Hz, **1H**, C<u>H</u>ar), 6.81 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 3.0 Hz, **1H**, C<u>H</u>ar), 6.92 (d, J_{ortho} = 8.8 Hz, **1H**, C<u>H</u>ar), 7.68 (m, **2H**, C<u>H</u>ar), 7.87 (m, **2H**, C<u>H</u>ar), 7.94 (t, *J* = 5.8 Hz, **1H**, CH_2N<u>H</u>). **^{13}C NMR (δ ppm):** 33.3, 39.2, 55.3, 55.8, 111.5, 111.9, 114.3, 127.3, 129.1, 129.4, 137.1, 138.7, 150.7, 152.7, 153.0. Anal. Calcd for $C_{17}H_{19}ClN_2O_5S$: C, 51.19, H, 4.80, N, 7.02, found: C, 51.49, H, 5.14, N, 6.72.

4.1.6.5. R/S-1-[1-(5-bromo-2-methoxyphenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B5)

The title compound was obtained as described for **B4**, starting from **A5** (0.5 g, 1.17 mmol), Na_2CO_3 (0.19 g, 1.75 mmol) and methyl iodide (0.14 mL, 2.34 mmol). White powder (0.43 g, 83%). **m.p.** 126-127°C. **SM (ESI):** *m/z* 441-443 $[M+H]^+$, 463-465 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.34 (d, *J* = 7.1 Hz, **3H**, CHC<u>H</u>$_3$), 2.40 (s, **3H**, PhC<u>H</u>$_3$), 3.07 (s, **3H**, NC<u>H</u>$_3$), 3.82 (s, **3H**, OC<u>H</u>$_3$), 4.98 (m, **1H**, NHC<u>H</u>CH$_3$), 6.99 (d, J_{ortho} = 8.8 Hz, **1H**, C<u>H</u>ar), 7.42 (m, **4H**, C<u>H</u>ar), 7.71 (m, **2H**, C<u>H</u>ar), 8.00 (d, *J* = 8.1 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 20.9, 21.0, 33.0, 46.0, 55.8, 112.0, 113.4, 127.0, 129.1, 129.9, 130.6, 134.0, 134.9, 144.5, 151.8, 155.4. Anal. Calcd for $C_{18}H_{21}BrN_2O_4S$: C, 48.99, H, 4.80, N, 6.35, found: C, 48.76, H, 4.85, N, 6.03.

4.1.6.6. R/S-1-[1-(5-bromo-2-methoxyphenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B6)

The title compound was obtained as described for **B4**, starting from **A6** (0.5 g, 1.12 mmol), Na_2CO_3 (0.18 g, 1.68 mmol) and methyl iodide (0.14 mL, 2.24 mmol). White powder (0.22

g, 42%). **m.p.** 105-106°C. **SM (ESI):** *m/z* 461-463-465 $[M+H]^+$, 483-485-487 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.33 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 3.15 (s, **3H**, NC$\underline{H}_3$), 3.82 (s, **3H**, OC$\underline{H}_3$), 4.98 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.98 (m, **1H**, C$\underline{H}$ar), 7.41 (m, **2H**, C$\underline{H}$ar), 7.69 (m, **2H**, C$\underline{H}$ar), 7.86 (m, **2H**, C$\underline{H}$ar), 7.98 (d, *J* = 8.1 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 20.9, 33.4, 45.6, 55.8, 112.0, 113.4, 128.8, 129.1, 129.5, 130.6, 134.2, 137.0, 138.7, 151.9, 155.3. Anal. Calcd for $C_{17}H_{18}BrClN_2O_4S$: C, 44.22, H, 3.93, N, 6.07, found: C, 44.58, H, 3.85, N, 6.25.

4.1.6.7. R/S-1-[1-(5-bromo-2-ethoxyphenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B7)

The title compound was obtained as described for **B4**, starting from **A7** (0.5 g, 1.17 mmol), Na_2CO_3 (0.19 g, 1.75 mmol) and methyl iodide (0.14 mL, 2.34 mmol). White powder (0.40 g, 77%). **m.p.** 98-99°C. **SM (ESI):** *m/z* 441-443 $[M+H]^+$, 463-465 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.35 (m, **3H**, OCH$_2$C$\underline{H}_3$), 1.38 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 3.10 (s, **3H**, NC$\underline{H}_3$), 4.07 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.98 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.98 (d, J_{ortho} = 8.5 Hz, **1H**, C$\underline{H}$ar), 7.40 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.43 (d, J_{meta} = 2.5 Hz, **1H**, C$\underline{H}$ar), 7.61 (m, **2H**, C$\underline{H}$ar), 7.74 (m, **1H**, C$\underline{H}$ar), 7.82 (m, **2H**, C$\underline{H}$ar), 8.00 (d, *J* = 8.2 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 14.4, 20.7, 33.1, 46.4, 63.8, 111.8, 114.1, 126.9, 129.3, 129.4, 130.7, 133.8, 133.9, 137.8, 151.7, 154.7. Anal. Calcd for $C_{18}H_{21}BrN_2O_4S$: C, 48.99, H, 4.80, N, 6.35, found: C, 49.01, H, 5.02, N, 6.58.

4.1.6.8. R/S-1-[1-(5-bromo-2-ethoxyphenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B8)

The title compound was obtained as described for **B4**, starting from **A8** (0.5 g, 1.13 mmol), Na_2CO_3 (0.18 g, 1.69 mmol) and methyl iodide (0.14 mL, 2.26 mmol). White powder (0.30 g, 58%). **m.p.** 102-103°C. **SM (ESI):** *m/z* 455-457 $[M+H]^+$, 477-479 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.35 (m, **3H**, OCH$_2$C$\underline{H}_3$), 1.38 (d, *J* = 7.1 Hz, **3H**, CHC$\underline{H}_3$), 2.40 (s, **3H**, PhC$\underline{H}_3$), 3.07 (s, **3H**, NC$\underline{H}_3$), 4.08 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.98 (m, **1H**, NHC$\underline{H}$CH$_3$), 6.98 (m, **1H**, C$\underline{H}$ar), 7.40 (m, **4H**, C$\underline{H}$ar), 7.70 (d, J_{ortho} = 8.3 Hz, **2H**, C$\underline{H}$ar), 7.97 (d, *J* = 8.1 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 14.4, 20.7, 21.0, 33.0, 46.5, 63.8, 111.8, 114.1, 127.0, 129.3, 129.9, 130.7, 133.9, 134.8, 144.5, 151.7, 154.8. Anal. Calcd for $C_{19}H_{23}BrN_2O_4S$: C, 50.11, H, 5.09, N, 6.15, found: C, 50.16, H, 5.39, N, 5.92.

4.1.6.9. R/S-1-[1-(5-bromo-2-ethoxyphenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B9)

The title compound was obtained as described for **B4**, starting from **A9** (0.5 g, 1.1 mmol), Na_2CO_3 (0.17 g, 1.65 mmol) and methyl iodide (0.14 mL, 2.2 mmol). White powder (0.30 g, 73%). **m.p.** 104-105°C. **SM (ESI):** *m/z* 475-477-479 $[M+H]^+$, 497-499-501 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.34 (m, **3H**, $OCH_2C\underline{H}_3$), 1.36 (d, *J* = 6.6 Hz, **3H**, $CHC\underline{H}_3$), 3.15 (s, **3H**, $NC\underline{H}_3$), 4.06 (m, **2H**, $OC\underline{H}_2CH_3$), 4.98 (m, **1H**, $NHC\underline{H}CH_3$), 6.96 (m, **1H**, C<u>H</u>ar), 7.39 (m, **2H**, C<u>H</u>ar), 7.68 (m, **2H**, C<u>H</u>ar), 7.85 (m, **2H**, C<u>H</u>ar), 7.95 (d, *J* = 8.1 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 14.4, 20.7, 33.4, 46.0, 63.7, 111.8, 114.1, 129.0, 129.1, 129.5, 130.6, 134.1, 136.9, 138.7, 151.8, 154.6. Anal. Calcd for $C_{18}H_{20}BrClN_2O_4S$: C, 45.44, H, 4.24, N, 5.89, found: C, 45.32, H, 4.48, N, 6.02.

4.1.6.10. R/S-1-[1-(5-bromo-2-isopropoxyphenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B10)

The title compound was obtained as described for **B4**, starting from **A10** (0.5 g, 1.13 mmol), Na_2CO_3 (0.18 g, 1.69 mmol) and methyl iodide (0.14 mL, 2.26 mmol). White powder (0.25 g, 48%). **m.p.** 79-80°C. **SM (ESI):** *m/z* 455-457 $[M+H]^+$, 477-479 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.0 Hz, **3H**, $OCH(C\underline{H}_3)_2$), 1.30 (d, *J* = 6.0 Hz, **3H**, $OCH(C\underline{H}_3)_2$), 1.37 (d, *J* = 7.0 Hz, **3H**, $CHC\underline{H}_3$), 3.10 (s, **3H**, $NC\underline{H}_3$), 4.68 (sept, *J* = 6.0 Hz, **1H**, $OC\underline{H}(CH_3)_2$), 4.96 (m, **1H**, $NHC\underline{H}CH_3$), 7.01 (d, J_{ortho} = 8.8 Hz, **1H**, C<u>H</u>ar), 7.38 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.6 Hz, **1H**, C<u>H</u>ar), 7.48 (d, J_{meta} = 2.6 Hz, **1H**, C<u>H</u>ar), 7.62 (m, **2H**, C<u>H</u>ar), 7.75 (m, **1H**, C<u>H</u>ar), 7.84 (m, **2H**, C<u>H</u>ar), 7.97 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 20.7, 21.5, 21.6, 33.1, 46.4, 69.9, 111.5, 115.3, 127.0, 129.4, 129.5, 130.6, 133.9, 134.6, 137.8, 151.7, 153.6. Anal. Calcd for $C_{19}H_{23}BrN_2O_4S$: C, 50.11, H, 5.09, N, 6.15, found: C, 50.20, H, 5.08, N, 6.20.

4.1.6.11. R/S-1-[1-(5-bromo-2-isopropoxyphenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B11)

The title compound was obtained as described for **B4**, starting from **A11** (0.5 g, 1.1 mmol), Na_2CO_3 (0.17 g, 1.65 mmol) and methyl iodide (0.14 mL, 2.2 mmol). White powder (0.32 g, 62%). **m.p.** 69-71°C. **SM (ESI):** *m/z* 469-471 $[M+H]^+$, 491-493 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.27 (d, *J* = 6.0 Hz, **3H**, $OCH(C\underline{H}_3)_2$), 1.31 (d, *J* = 6.0 Hz, **3H**, $OCH(C\underline{H}_3)_2$), 1.37 (d, *J* = 7.0 Hz, **3H**, $CHC\underline{H}_3$), 2.40 (s, **3H**, $PhC\underline{H}_3$), 3.06 (s, **3H**, $NC\underline{H}_3$), 4.68 (sept, *J* = 6.0 Hz, **1H**, $OC\underline{H}(CH_3)_2$), 4.95 (m, **1H**, $NHC\underline{H}CH_3$), 7.01 (d, J_{ortho} = 8.2 Hz, **1H**, C<u>H</u>ar), 7.39 (m, **4H**, C<u>H</u>ar), 7.72 (d, J_{ortho} = 8.4 Hz, **2H**, C<u>H</u>ar), 7.94 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 20.7, 21.0, 21.5, 21.6, 33.0, 46.6, 69.9, 111.5, 115.3, 127.0, 129.6, 129.9, 130.6, 134.5, 134.8, 144.5, 151.7, 153.6. Anal. Calcd for $C_{20}H_{25}BrN_2O_4S$: C, 51.18, H, 5.37, N, 5.97, found: C, 51.22, H, 5.80, N, 5.94.

4.1.6.12. R/S-1-[1-(5-bromo-2-isopropoxyphenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B12)

The title compound was obtained as described for **B4**, starting from **A12** (0.5 g, 1.05 mmol), Na_2CO_3 (0.17 g, 1.57 mmol) and methyl iodide (0.13 mL, 2.1 mmol). White powder (0.27 g, 52%). **m.p.** 81-82°C. **SM (ESI):** *m/z* 489-491-493 $[M+H]^+$, 511-513-515 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.25 (d, *J* = 6.0 Hz, **3H**, OCH(C<u>H</u>$_3$)$_2$), 1.28 (d, *J* = 6.0 Hz, **3H**, OCH(C<u>H</u>$_3$)$_2$), 1.36 (d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 3.14 (s, **3H**, NC<u>H</u>$_3$), 4.68 (sept, *J* = 6.1 Hz, **1H**, OC<u>H</u>(CH$_3$)$_2$), 4.96 (m, **1H**, NHC<u>H</u>CH$_3$), 6.99 (d, J_{ortho} = 8.5 Hz, **1H**, C<u>H</u>ar), 7.38 (m, **2H**, C<u>H</u>ar), 7.69 (d, J_{ortho} = 8.7 Hz, **2H**, C<u>H</u>ar), 7.86 (d, J_{ortho} = 8.7 Hz, **2H**, C<u>H</u>ar), 7.92 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (*δ* ppm):** 20.7, 21.5, 21.6, 33.4, 46.0, 69.9, 111.5, 115.3, 129.1, 129.3, 129.5, 130.5, 134.7, 136.9, 138.7, 151.7, 153.5. Anal. Calcd for $C_{19}H_{22}BrClN_2O_4S$: C, 46.59, H, 4.53, N, 5.72, found: C, 46.37, H, 4.85, N, 5.65.

4.1.6.13. R/S-1-[1-(2-benzyloxy-5-bromophenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B13)

The title compound was obtained as described for **B4**, starting from **A13** (0.5 g, 1.02 mmol), Na_2CO_3 (0.16 g, 1.53 mmol) and methyl iodide (0.13 mL, 2.04 mmol). white powder (0.27 g, 53%). **m.p.** 92-93°C. **SM (ESI):** *m/z* 503-505 $[M+H]^+$, 525-527 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.37 (d, *J* = 7.1 Hz, **3H**, CHC<u>H</u>$_3$), 3.10 (s, **3H**, NC<u>H</u>$_3$), 5.08 (m, **1H**, C<u>H</u>CH$_3$), 5.17 (m, **2H**, OC<u>H</u>$_2$), 7.06 (d, J_{ortho} = 8.8 Hz, **1H**, C<u>H</u>ar), 7.34 (m, **1H**, C<u>H</u>ar), 7.40 (m, **3H**, C<u>H</u>ar), 7.47 (m, **3H**, C<u>H</u>ar), 7.60 (m, **2H**, C<u>H</u>ar), 7.73 (m, **1H**, C<u>H</u>ar), 7.82 (d, J_{ortho} = 7.6 Hz, **2H**, C<u>H</u>ar), 7.96 (d, *J* = 7.8 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (*δ* ppm):** 20.8, 33.3, 45.6, 69.7, 112.3, 114.6, 127.1, 127.4, 127.8, 128.5, 129.0, 129.4, 130.5, 133.8, 134.6, 136.6, 137.9, 151.9, 154.2. Anal. Calcd for $C_{23}H_{23}BrN_2O_4S$: C, 54.88, H, 4.61, N, 5.56, found: C, 54.59, H, 4.69, N, 5.46.

4.1.6.14. R/S-1-[1-(2-benzyloxy-5-bromophenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B14)

The title compound was obtained as described for **B4**, starting from **A14** (0.5 g, 1.0 mmol), Na_2CO_3 (0.16 g, 1.5 mmol) and methyl iodide (0.12 mL, 2.0 mmol). White powder (0.33 g, 63%). **m.p.** 132-133°C. **SM (ESI):** *m/z* 517-519 $[M+H]^+$, 539-541 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.48 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 2.41 (s, **3H**, PhC<u>H</u>$_3$), 3.10 (s, **3H**, NC<u>H</u>$_3$), 5.08 (m, **1H**, NHC<u>H</u>CH$_3$), 5.14 (m, **2H**, OC<u>H</u>$_2$), 6.82 (m, **1H**, C<u>H</u>ar), 7.25 (m, **2H**, C<u>H</u>ar), 7.32 (m, **3H**, C<u>H</u>ar), 7.38 (m, **2H**, C<u>H</u>ar), 7.44 (m, **2H**, C<u>H</u>ar), 7.58 (m, **2H**, C<u>H</u>ar), 7.98 (d, *J* = 7.9 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (*δ* ppm):** 20.8, 21.1, 33.1, 45.6, 69.7, 112.3, 114.6, 127.1, 127.3, 127.8,

128.4, 129.0, 129.8, 130.5, 134.6, 134.9, 136.6, 144.4, 151.9, 154.2. Anal. Calcd for $C_{24}H_{25}BrN_2O_4S$: C, 55.71, H, 4.87, N, 5.41, found: C, 55.57, H, 4.95, N, 5.19.

4.1.6.15. R/S-1-[1-(2-benzyloxy-5-bromophenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B15)

The title compound was obtained as described for **B4**, starting from **A15** (0.5 g, 0.95 mmol), Na_2CO_3 (0.15 g, 1.4 mmol) and methyl iodide (0.12 mL, 1.9 mmol). White powder (0.25 g, 48%). **m.p.** 126-128°C. **SM (ESI):** *m/z* 537-539-541 $[M+H]^+$, 559-561-563 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.37 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 3.15 (s, **3H**, NC$\underline{H}_3$), 5.08 (m, **1H**, NHC$\underline{H}$CH$_3$), 5.17 (m, **2H**, OC$\underline{H}_2$), 7.05 (d, J_{ortho} = 8.6 Hz, **1H**, C$\underline{H}$ar), 7.34 (m, **1H**, C$\underline{H}$ar), 7.39 (m, **3H**, C$\underline{H}$ar), 7.45 (m, **3H**, C$\underline{H}$ar), 7.67 (d, J_{ortho} = 8.6 Hz, **2H**, C$\underline{H}$ar), 7.85 (d, J_{ortho} = 8.6 Hz, **2H**, C$\underline{H}$ar), 7.95 (d, *J* = 8.1 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 20.8, 33.5, 45.3, 69.6, 112.3, 114.6, 127.3, 127.8, 128.4, 128.8, 129.2, 129.4, 130.5, 134.7, 136.6, 137.0, 138.6, 152.0, 154.1. Anal. Calcd for $C_{23}H_{22}BrClN_2O_4S$: C, 51.36, H, 4.12, N, 5.35, found: C, 51.15, H, 4.13, N, 5.24.

4.1.6.16. R/S-1-[1-(5-chloro-2-methoxyphenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B16)

The title compound was obtained as described for **B4**, starting from **A16** (0.5 g, 1.35 mmol), Na_2CO_3 (0.21 g, 2.02 mmol) and methyl iodide (0.17 mL, 2.7 mmol). White powder (0.3 g, 57%). **m.p.** 76-77°C. **SM (ESI):** *m/z* 383-385 $[M+H]^+$, 405-407 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.35 (d, *J* = 7.1 Hz, **3H**, CHC$\underline{H}_3$), 3.11 (s, **3H**, NC$\underline{H}_3$), 3.83 (s, **3H**, OC$\underline{H}_3$), 4.99 (m, **1H**, NHC$\underline{H}$CH$_3$), 7.04 (d, J_{ortho} = 8.7 Hz, **1H**, C$\underline{H}$ar), 7.29 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.8 Hz, **1H**, C$\underline{H}$ar), 7.32 (d, J_{meta} = 2.8 Hz, **1H**, C$\underline{H}$ar), 7.61 (m, **2H**, C$\underline{H}$ar), 7.74 (m, **1H**, C$\underline{H}$ar), 7.83 (m, **2H**, C$\underline{H}$ar), 8.01 (d, *J* = 7.8 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 20.9, 33.2, 45.9, 55.8, 112.8, 124.2, 126.2, 127.0, 127.7, 129.4, 133.6, 133.8, 137.9, 151.8, 154.9. Anal. Calcd for $C_{17}H_{19}ClN_2O_4S$: C, 53.33, H, 5.00, N, 7.32, found: C, 53.19, H, 5.20, N, 7.37.

4.1.6.17. R/S-1-[1-(5-chloro-2-methoxyphenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B17)

The title compound was obtained as described for **B4**, starting from **A17** (0.5 g, 1.31 mmol), Na_2CO_3 (0.21 g, 1.96 mmol) and methyl iodide (0.16 mL, 2.62 mmol). White powder (0.39 g, 75%). **m.p.** 123-124°C. **SM (ESI):** *m/z* 397-399 $[M+H]^+$, 419-421$[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.35 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 2.40 (s, **3H**, PhC$\underline{H}_3$), 3.08 (s, **3H**, NC$\underline{H}_3$), 3.83 (s, **3H**, OC$\underline{H}_3$), 4.98 (m, **1H**, NHC$\underline{H}$CH$_3$), 7.04 (m, **1H**, C$\underline{H}$ar), 7.29 (m, **2H**, C$\underline{H}$ar), 7.42 (d,

J_{ortho} = 8.1 Hz, **2H**, CHar), 7.71 (d, J_{ortho} = 8.1 Hz, **2H**, CHar), 7.98 (d, *J* = 7.9 Hz, **1H**, NHCH). **^{13}C NMR (*δ* ppm):** 20.9, 21.0, 33.0, 46.0, 55.8, 112.9, 124.2, 126.2, 127.0, 127.7, 129.8, 133.6, 134.9, 144.5, 151.8, 154.9. Anal. Calcd for $C_{18}H_{21}ClN_2O_4S$: C, 54.47, H, 5.33, N, 7.06, found: C, 54.72, H, 5.28, N, 6.95.

4.1.6.18. R/S-1-[1-(5-chloro-2-methoxyphenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B18)

The title compound was obtained as described for **B4**, starting from **A18** (0.5 g, 1.24 mmol), Na_2CO_3 (0.20 g, 1.86 mmol) and methyl iodide (0.15 mL, 2.48 mmol). White powder (0.3 g, 60%). **m.p.** 112-113°C. **SM (ESI):** *m/z* 417-419-421 $[M+H]^+$, 439-441-443 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.33 (d, *J* = 6.8 Hz, **3H**, CHCH_3), 3.16 (s, **3H**, NCH_3), 3.82 (s, **3H**, OCH_3), 4.98 (m, **1H**, NHCHCH_3), 7.02 (m, **1H**, CHar), 7.28 (m, **2H**, CHar), 7.69 (m, **2H**, CHar), 7.86 (m, **2H**, CHar), 7.98 (d, *J* = 8.1 Hz, **1H**, NHCH). **^{13}C NMR (*δ* ppm):** 20.9, 33.4, 45.6, 55.8, 112.8, 124.2, 126.0, 127.6, 129.1, 129.4, 133.8, 137.0, 138.7, 151.9, 154.7. Anal. Calcd for $C_{17}H_{18}Cl_2N_2O_4S$: C, 48.93, H, 4.35, N, 6.71, found: C, 49.03, H, 4.25, N, 6.67.

4.1.6.19. R/S-1-[1-(5-chloro-2-ethoxyphenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B19)

The title compound was obtained as described for **B4**, starting from **A19** (0.5 g, 1.31 mmol), Na_2CO_3 (0.21 g, 1.96 mmol) and methyl iodide (0.16 mL, 2.62 mmol). White powder (0.47 g, 90%). **m.p.** 82-83°C. **SM (ESI):** *m/z* 397-399 $[M+H]^+$, 419-421 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.36 (m, **3H**, OCH$_2$CH_3), 1.38 (d, *J* = 6.8 Hz, **3H**, CHCH_3), 3.11 (s, **3**H, NCH_3), 4.08 (m, **2H**, OCH_2CH$_3$), 4.99 (m, **1H**, NHCHCH$_3$), 7.03 (d, J_{ortho} = 8.5 Hz, **1H**, CHar), 7.28 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.7 Hz, **1H**, CHar), 7.30 (d, J_{meta} = 2.7 Hz, **1H**, CHar), 7.61 (m, **2H**, CHar), 7.74 (m, **1H**, CHar), 7.83 (m, **2H**, CHar), 7.99 (d, *J* = 8.0 Hz, **1H**, NHCH). **^{13}C NMR (*δ* ppm):** 14.4, 20.7, 33.1, 46.4, 63.8, 113.6, 124.0, 126.5, 127.0, 127.7, 129.4, 133.5, 133.9, 137.8, 151.7, 154.3. Anal. Calcd for $C_{18}H_{21}ClN_2O_4S$: C, 54.47, H, 5.33, N, 7.06, found: C, 54.66, H, 5.51, N, 7.16.

4.1.6.20. R/S-1-[1-(5-chloro-2-ethoxyphenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B20)

The title compound was obtained as described for **B4**, starting from **A20** (0.5 g, 1.26 mmol), Na_2CO_3 (0.20 g, 1.89 mmol) and methyl iodide (0.15 mL, 2.52 mmol). White powder (0.37 g, 70%). **m.p.** 94-95°C. **SM (ESI):** *m/z* 411-413 $[M+H]^+$, 433-435 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.36 (m, **3H**, OCH$_2$CH_3), 1.38 (d, *J* = 7.0 Hz, **3H**, CHCH_3), 2.40 (s, **3H**, PhCH_3), 3.08

(s, **3H**, NC$\underline{H}_3$), 4.08 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.98 (m, **1H**, NHC$\underline{H}$CH$_3$), 7.03 (m, **1H**, C$\underline{H}$ar), 7.28 (m, **2H**, C$\underline{H}$ar), 7.41 (d, J_{ortho} = 8.2 Hz, **2H**, C$\underline{H}$ar), 7.70 (d, J_{ortho} = 8.2 Hz, **2H**, C$\underline{H}$ar), 7.96 (d, *J* = 8.2 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (*δ* ppm):** 14.4, 20.7, 21.0, 33.0, 46.5, 63.8, 113.6, 124.0, 126.5, 127.0, 127.7, 129.9, 133.5, 134.8, 144.5, 151.7, 154.3. Anal. Calcd for $C_{19}H_{23}ClN_2O_4S$: C, 55.54, H, 5.64, N, 6.82, found: C, 55.22, H, 5.77, N, 6.73.

4.1.6.21. R/S-1-[1-(5-chloro-2-ethoxyphenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B21)

The title compound was obtained as described for **B4**, starting from **A21** (0.5 g, 1.2 mmol), Na_2CO_3 (0.19 g, 1.8 mmol) and methyl iodide (0.15 mL, 2.4 mmol). White powder (0.38 g, 73%). **m.p.** 99-100°C. **SM (ESI):** *m/z* 431-433-435 $[M+H]^+$, 453-455-457 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.34 (m, **3H**, OCH$_2$C$\underline{H}_3$), 1.36 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 3.15 (s, **3H**, NC$\underline{H}_3$), 4.07 (m, **2H**, OC$\underline{H}_2$CH$_3$), 4.98 (m, **1H**, NHC$\underline{H}$CH$_3$), 7.01 (m, **1H**, C$\underline{H}$ar), 7.26 (m, **2H**, C$\underline{H}$ar), 7.68 (m, **2H**, C$\underline{H}$ar), 7.85 (m, **2H**, C$\underline{H}$ar), 7.95 (d, *J* = 8.0 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (*δ* ppm):** 14.4, 20.7, 33.4, 46.0, 63.8, 113.6, 124.0, 126.2, 127.6, 129.1, 129.8, 133.7, 137.0, 138.7, 151.8, 154.2. Anal. Calcd for $C_{18}H_{20}Cl_2N_2O_4S$: C, 50.12, H, 4.67, N, 6.49, found: C, 50.46, H, 4.95, N, 6.60.

4.1.6.22. R/S-1-[1-(5-fluoro-2-methoxyphenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B22)

The title compound was obtained as described for **B4**, starting from **A22** (0.5 g, 1.42 mmol), Na_2CO_3 (0.23 g, 2.13 mmol) and methyl iodide (0.17 mL, 2.84 mmol). White powder (0.33 g, 63%). **m.p.** 96-97°C. **SM (ESI):** *m/z* 367 $[M+H]^+$, 389 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.35 (d, *J* = 7.0 Hz, **3H**, CHC$\underline{H}_3$), 3.12 (s, **3H**, NC$\underline{H}_3$), 3.82 (s, **3H**, OC$\underline{H}_3$), 4.99 (m, **1H**, NHC$\underline{H}$CH$_3$), 7.02 (m, **1H**, C$\underline{H}$ar), 7.07 (m, **1H**, C$\underline{H}$ar), 7.12 (m, **1H**, C$\underline{H}$ar), 7.61 (m, **2H**, C$\underline{H}$ar), 7.74 (m, **2H**, C$\underline{H}$ar), 7.83 (m, **2H**, C$\underline{H}$ar), 8.00 (d, *J* = 8.0 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (*δ* ppm):** 20.9, 33.2, 46.1, 56.0, 112.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.4 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 113.8 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 127.0, 129.4, 133.4 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 133.8, 137.9, 151.8, 152.3 (d, $^4J_{C\text{-}F}$ = 1.3 Hz), 156.3 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{17}H_{19}FN_2O_4S$: C, 55.73, H, 5.23, N, 7.65, found: C, 55.82, H, 5.52, N, 7.71.

4.1.6.23. R/S-1-[1-(5-fluoro-2-methoxyphenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B23)

The title compound was obtained as described for **B4**, starting from **A23** (0.5 g, 1.36 mmol), Na_2CO_3 (0.22 g, 2.04 mmol) and methyl iodide (0.17 mL, 2.72 mmol). White powder (0.32

g, 61%). **m.p.** 94-95°C. **SM (ESI):** *m/z* 381 $[M+H]^+$, 403 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.35 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 2.40 (s, **3H**, PhC<u>H</u>$_3$), 3.09 (s, **3H**, NC<u>H</u>$_3$), 3.82 (s, **3H**, OC<u>H</u>$_3$), 4.99 (m, **1H**, NHC<u>H</u>CH$_3$), 7.02 (m, **1H**, C<u>H</u>ar), 7.08 (m, **2H**, C<u>H</u>ar), 7.41 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.71 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.98 (d, *J* = 8.0 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 21.0, 21.1, 33.0, 46.1, 56.0, 112.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.4 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 113.8 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 127.0, 129.8, 133.3 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 134.9, 144.51, 151.83, 152.3 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 156.3 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{18}H_{21}FN_2O_4S$: C, 56.83, H, 5.56, N, 7.36, found: C, 57.21, H, 5.97, N, 7.48.

4.1.6.24. R/S-1-[1-(5-fluoro-2-methoxyphenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B24)

The title compound was obtained as described for **B4**, starting from **A24** (0.5 g, 1.29 mmol), Na_2CO_3 (0.20 g, 1.93 mmol) and methyl iodide (0.16 mL, 2.58 mmol). White powder (0.31 g, 60%). **m.p.** 82-83°C. **SM (ESI):** *m/z* 401-403 $[M+H]^+$, 423-425 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.33 (d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 3.16 (s, **3H**, NC<u>H</u>$_3$), 3.81 (s, **3H**, OC<u>H</u>$_3$), 4.99 (m, **1H**, NHC<u>H</u>CH$_3$), 7.00 (m, **1H**, C<u>H</u>ar), 7.06 (m, **1H**, C<u>H</u>ar), 7.10 (m, **1H**, C<u>H</u>ar), 7.69 (d, J_{ortho} = 8.6 Hz, **2H**, C<u>H</u>ar), 7.86 (d, J_{ortho} = 8.6 Hz, **2H**, C<u>H</u>ar), 7.98 (d, *J* = 7.9 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 20.9, 33.4, 45.7, 56.0, 112.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.1 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 113.8 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 129.2, 129.4, 133.5 (d, $^3J_{C\text{-}F}$ = 6.1 Hz), 137.1, 138.7, 151.9, 152.2 (d, $^4J_{C\text{-}F}$ = 1.3 Hz), 156.3 (d, $^1J_{C\text{-}F}$ = 235.1 Hz). Anal. Calcd for $C_{17}H_{18}ClFN_2O_4S$: C, 50.94, H, 4.53, N, 6.99, found: C, 51.17, H, 4.63, N, 7.16.

4.1.6.25. R/S-1-[1-(2-ethoxy-5-fluorophenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B25)

The title compound was obtained as described for **B4**, starting from **A25** (0.5 g, 1.36 mmol), Na_2CO_3 (0.22 g, 2.04 mmol) and methyl iodide (0.17 mL, 2.72 mmol). Yellowish oil (0.35 g, 67%). **SM (ESI):** *m/z* 381 $[M+H]^+$, 403 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.35 (m, **3H**, OCH$_2$C<u>H</u>$_3$), 1.37 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 3.11 (s, **3H**, NC<u>H</u>$_3$), 4.06 (m, **2H**, OC<u>H</u>$_2$CH$_3$), 4.99 (m, **1H**, NHC<u>H</u>CH$_3$), 7.01 (m, **1H**, C<u>H</u>ar), 7.05 (m, **1H**, C<u>H</u>ar), 7.10 (m, **1H**, C<u>H</u>ar), 7.60 (m, **2H**, C<u>H</u>ar), 7.74 (m, **1H**, C<u>H</u>ar), 7.83 (m, **2H**, C<u>H</u>ar), 7.99 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 14.5, 20.8, 33.1, 46.5, 64.0, 113.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.6 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 113.8 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 127.0, 129.4, 133.3 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 133.8, 137.8, 151.7 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 151.8, 156.1 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{18}H_{21}FN_2O_4S$: C, 56.83, H, 5.56, N, 7.36, found: C, 57.23, H, 5.89, N, 7.20.

4.1.6.26. R/S-1-[1-(2-ethoxy-5-fluorophenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B26)

The title compound was obtained as described for **B4**, starting from **A26** (0.5 g, 1.31 mmol), Na_2CO_3 (0.21 g, 1.96 mmol) and methyl iodide (0.16 mL, 2.62 mmol). White powder (0.25 g, 48%). **m.p.** 75-76°C. **SM (ESI):** *m/z* 395 $[M+H]^+$, 417 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.36 (m, **3H**, $OCH_2C\underline{H}_3$), 1.38 (d, *J* = 6.8 Hz, **3H**, $CHC\underline{H}_3$), 2.40 (s, **3H**, $PhC\underline{H}_3$), 3.08 (s, **3H**, $NC\underline{H}_3$), 4.06 (m, **2H**, $OC\underline{H}_2CH_3$), 4.98 (m, **1H**, $NHC\underline{H}CH_3$), 7.04 (m, **3H**, C<u>H</u>ar), 7.40 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.70 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.96 (d, *J* = 8.2 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 14.5, 20.8, 21.0, 33.0, 46.5, 64.0, 113.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.6 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 113.8 (d, $^2J_{C\text{-}F}$ = 22.91 Hz), 127.0, 129.8, 133.2 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 134.9, 144.5, 151.7, 151.8, 156.2 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{19}H_{23}FN_2O_4S$: C, 57.85, H, 5.88, N, 7.10, found: C, 58.18, H, 6.13, N, 7.14.

4.1.6.27. R/S-1-[1-(2-ethoxy-5-fluorophenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B27)

The title compound was obtained as described for **B4**, starting from **A27** (0.5 g, 1.25 mmol), Na_2CO_3 (0.20 g, 1.87 mmol) and methyl iodide (0.15 mL, 2.5 mmol). White powder (0.20 g, 38%). **m.p.** 80-81°C. **SM (ESI):** *m/z* 415-417 $[M+H]^+$, 437-439 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.33 (m, **3H**, $OCH_2C\underline{H}_3$), 1.36 (d, *J* = 7.2 Hz, **3H**, $CHC\underline{H}_3$), 3.16 (s, **3H**, $NC\underline{H}_3$), 4.05 (m, **2H**, $OC\underline{H}_2CH_3$), 4.99 (m, **1H**, $NHC\underline{H}CH_3$), 6.99 (m, **1H**, C<u>H</u>ar), 7.03 (m, **1H**, C<u>H</u>ar), 7.08 (m, **1H**, C<u>H</u>ar), 7.68 (m, **2H**, C<u>H</u>ar), 7.85 (m, **2H**, C<u>H</u>ar), 7.95 (d, *J* = 8,2 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 14.5, 20.8, 33.4, 46.1, 63.9, 113.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 113.3 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 113.8 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 129.1, 129.4, 133.5 (d, $^3J_{C\text{-}F}$ = 6.1 Hz), 137.0, 138.7, 151.6 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 151.8, 156.2 (d, $^1J_{C\text{-}F}$ = 235.8 Hz). Anal. Calcd for $C_{18}H_{20}ClFN_2O_4S$: C, 52.11, H, 4.86, N, 6.75, found: C, 52.48, H, 5.03, N, 6.95.

4.1.6.28. R/S-1-[1-(2-benzyloxy-phenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B28)

The title compound was obtained as described for **B4**, starting from **A28** (0.5 g, 1.22 mmol), Na_2CO_3 (0.19 g, 1.83 mmol) and methyl iodide (0.15 mL, 2.44 mmol). White powder (0.34 g, 66%). **m.p.** 118-119°C. **SM (ESI):** *m/z* 425 $[M+H]^+$, 447 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.38 (d, *J* = 6.8 Hz, **3H**, $CHC\underline{H}_3$), 3.10 (s, **3H**, $NC\underline{H}_3$), 5.09 (m, **1H**, $NHC\underline{H}CH_3$), 5.18 (m, **2H**, $OC\underline{H}_2$), 6.94 (m, **1H**, C<u>H</u>ar), 7.10 (d, J_{ortho} = 7.5 Hz, **1H**, C<u>H</u>ar), 7.25 (m, **2H**, C<u>H</u>ar), 7.34 (m, **1H**, C<u>H</u>ar), 7.40 (m, **2H**, C<u>H</u>ar), 7.49 (m, **2H**, C<u>H</u>ar), 7.58 (m, **2H**, C<u>H</u>ar), 7.72 (m, **1H**, C<u>H</u>ar), 7.78 (m, **2H**, C<u>H</u>ar), 7.93 (d, *J* = 8.0 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (δ ppm):** 21.1,

33.1, 46.3, 69.3, 112.3, 120.7, 126.6, 127.0, 127.4, 127.7, 128.2, 128.4, 129.4, 131.5, 133.8, 137.0, 137. 9, 151.7, 155.1. Anal. Calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07, H, 5.70, N, 6.60, found: C, 64.89, H, 6.03, N, 6.89.

4.1.6.29. R/S-1-[1-(2-benzyloxy-phenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B29)

The title compound was obtained as described for **B4**, starting from **A29** (0.5 g, 1.18 mmol), Na_2CO_3 (0.19 g, 1.77 mmol) and methyl iodide (0.15 mL, 2.36 mmol). White powder (0.16 g, 31%). **m.p.** 71-72°C. **SM (ESI):** *m/z* 439 $[M+H]^+$, 461 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.38 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 2.38 (s, **3H**, PhC$\underline{H}_3$), 3.07 (s, **3H**, NC$\underline{H}_3$), 5.09 (m, **1H**, NHC$\underline{H}$CH$_3$), 5.18 (m, **2H**, OC$\underline{H}_2$), 6.94 (m, **1H**, C$\underline{H}$ar), 7.10 (d, J_{ortho} = 8.1 Hz, **1H**, C$\underline{H}$ar), 7.25 (m, **2H**, C$\underline{H}$ar), 7.38 (m, **5H**, C$\underline{H}$ar), 7.48 (d, J_{ortho} = 7.5 Hz, **2H**, C$\underline{H}$ar), 7.65 (d, J_{ortho} = 7.5 Hz, **2H**, C$\underline{H}$ar), 7.91 (d, *J* = 8.0 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 21.0, 21.1, 33.0, 46.3, 69.3, 112.3, 120.6, 126.6, 127.0, 127.3, 127.7, 128.2, 128.4, 129.8, 131.5, 134.9, 137.0, 144.4, 151.7, 155.1. Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73, H, 5.98, N, 6.39, found: C, 65.57, H, 6.25, N, 6.46.

4.1.6.30. R/S-1-[1-(2-benzyloxy-phenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B30)

The title compound was obtained as described for **B4**, starting from **A30** (0.5 g, 1.12 mmol), Na_2CO_3 (0.18 g, 1.68 mmol) and methyl iodide (0.14 mL, 2.24 mmol). White powder (0.21 g, 41%). **m.p.** 71-72°C. **SM (ESI):** *m/z* 459-461 $[M+H]^+$, 481-483 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.38 (d, *J* = 6.8 Hz, **3H**, CHC$\underline{H}_3$), 3.14 (s, **3H**, NC$\underline{H}_3$), 5.10 (m, **1H**, NHC$\underline{H}$CH$_3$), 5.17 (m, **2H**, OC$\underline{H}_2$), 6.94 (m, **1H**, C$\underline{H}$ar), 7.09 (d, J_{ortho} = 8.0 Hz, **1H**, C$\underline{H}$ar), 7.25 (m, **2H**, C$\underline{H}$ar), 7.34 (d, J_{ortho} = 7.2 Hz, **1H**, C$\underline{H}$ar), 7.40 (m, **2H**, C$\underline{H}$ar), 7.48 (d, J_{ortho} = 7.2 Hz, **2H**, C$\underline{H}$ar), 7.65 (d, J_{ortho} = 8.4 Hz, **2H**, C$\underline{H}$ar), 7.81 (d, J_{ortho} = 8.4 Hz, **2H**, C$\underline{H}$ar), 7.93 (d, *J* = 7.9 Hz, **1H**, N$\underline{H}$CH). **^{13}C NMR (δ ppm):** 21.1, 33.4, 46.0, 69.3, 112.2, 120.6, 126.4, 127.3, 127.7, 128.1, 128.4, 129.1, 129.4, 131.6, 136.9, 137.0, 138.6, 151.8, 155.0. Anal. Calcd for $C_{23}H_{23}ClN_2O_4S$: C, 60.19, H, 5.05, N, 6.10, found: C, 60.03, H, 5.27, N, 6.17.

4.1.6.31. R/S-1-[1-(2-benzyloxy-5-methylphenyl)ethyl]-3-methyl-3-phenylsulfonylurea (B31)

The title compound was obtained as described for **B4**, starting from **A31** (0.5 g, 1.18 mmol), Na_2CO_3 (0.19 g, 1.77 mmol) and methyl iodide (0.15 mL, 2.36 mmol). White powder (0.28 g, 54%). **m.p.** 80-81°C. **SM (ESI):** *m/z* 439 $[M+H]^+$, 461 $[M+Na]^+$. **^{1}H NMR (δ ppm):** 1.37

(d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 2.23 (s, **3H**, PhC<u>H</u>$_3$), 3.10 (s, **3H**, NC<u>H</u>$_3$), 5.06 (m, **1H**, NHC<u>H</u>CH$_3$), 5.14 (m, **2H**, OC<u>H</u>$_2$), 6.98 (d, J_{ortho} = 8.2 Hz, **1H**, C<u>H</u>ar), 7.04 (dd, J_{ortho} = 8.2 Hz, J_{meta} = 1.5 Hz, **1H**, C<u>H</u>ar), 7.08 (d, J_{meta} = 1.5 Hz, **1H**, C<u>H</u>ar), 7.32 (m, **1H**, C<u>H</u>ar), 7.39 (m, **2H**, C<u>H</u>ar), 7.47 (m, **2H**, C<u>H</u>ar), 7.58 (m, **2H**, C<u>H</u>ar), 7.72 (m, **1H**, C<u>H</u>ar), 7.78 (m, **2H**, C<u>H</u>ar), 7.91 (d, *J* = 8.0 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (*δ* ppm):** 20.2, 21.2, 33.1, 46.4, 69.4, 112.3, 127.0, 127.2, 127.3, 127.7, 128.3, 128.4, 129.3, 129.4, 131.2, 133.8, 137.1, 137.8, 151.6, 153.0. Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73, H, 5.98, N, 6.39, found: C, 66.07, H, 6.32, N, 6.14.

4.1.6.32. R/S-1-[1-(2-benzyloxy-5-methylphenyl)ethyl]-3-methyl-3-(4-methylphenyl)sulfonylurea (B32)

The title compound was obtained as described for **B4**, starting from **A32** (0.5 g, 1.14 mmol), Na_2CO_3 (0.18 g, 1.71 mmol) and methyl iodide (0.14 mL, 2.28 mmol). White powder (0.44 g, 86%). **m.p.** 112-113°C. **SM (ESI):** *m/z* 453 $[M+H]^+$, 475 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.38 (d, *J* = 6.8 Hz, **3H**, CHC<u>H</u>$_3$), 2.23 (s, **3H**, PhC<u>H</u>$_3$), 2.38 (s, **3H**, PhC<u>H</u>$_3$), 3.07 (s, **3H**, NC<u>H</u>$_3$), 5.05 (m, **1H**, NHC<u>H</u>CH$_3$), 5.14 (m, **2H**, OC<u>H</u>$_2$), 6.98 (d, J_{ortho} = 8.2 Hz, **1H**, C<u>H</u>ar), 7.04 (m, **1H**, C<u>H</u>ar), 7.06 (m, **1H**, C<u>H</u>ar), 7.33 (m, **1H**, C<u>H</u>ar), 7.38 (m, **4H**, C<u>H</u>ar), 7.47 (m, **2H**, C<u>H</u>ar), 7.66 (d, J_{ortho} = 8.2 Hz, **2H**, C<u>H</u>ar), 7.89 (d, *J* = 8.0 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (*δ* ppm):** 20.2, 21.0, 21.2, 32.9, 46.4, 69.4, 112.3, 127.0, 127.2, 127.3, 127.7, 128.3, 128.4, 129.3, 129.8, 131.2, 134.9, 137.1, 144.5, 151.6, 153.0. Anal. Calcd for $C_{25}H_{28}N_2O_4S$: C, 66.35, H, 6.24, N, 6.19, found: C, 66.23, H, 6.44, N, 6.18.

4.1.6.33. R/S-1-[1-(2-benzyloxy-5-methylphenyl)ethyl]-3-methyl-3-(4-chlorophenyl)sulfonylurea (B33)

The title compound was obtained as described for **B4**, starting from **A33** (0.5 g, 1.06 mmol), Na_2CO_3 (0.17 g, 1.59 mmol) and methyl iodide (0.13 mL, 2.12 mmol). White powder (0.22 g, 43%). **m.p.** 99-100°C. **SM (ESI):** *m/z* 473-475 $[M+H]^+$, 495-497 $[M+Na]^+$. **^{1}H NMR (*δ* ppm):** 1.37 (d, *J* = 7.0 Hz, **3H**, CHC<u>H</u>$_3$), 2.23 (s, **3H**, PhC<u>H</u>$_3$), 3.13 (s, **3H**, NC<u>H</u>$_3$), 5.06 (m, **1H**, NHC<u>H</u>CH$_3$), 5.13 (m, **2H**, OC<u>H</u>$_2$), 6.97 (d, J_{ortho} = 8.4 Hz, **1H**, C<u>H</u>ar), 7.03 (dd, J_{ortho}= 8.4 Hz, J_{meta} = 1.7 Hz, **1H**, C<u>H</u>ar), 7.07 (d, J_{meta} = 1.7 Hz, **1H**, C<u>H</u>ar), 7.32 (m, **1H**, C<u>H</u>ar), 7.39 (m, **2H**, C<u>H</u>ar), 7.46 (m, **2H**, C<u>H</u>ar), 7.64 (m, **2H**, C<u>H</u>ar), 7.81 (m, **2H**, C<u>H</u>ar), 7.89 (d, *J* = 8.0 Hz, **1H**, N<u>H</u>CH). **^{13}C NMR (*δ* ppm):** 20.2, 21.2, 33.4, 46.1, 69.4, 112.3, 127.0, 127.3, 127.7, 128.3, 128.4, 129.1, 129.3, 129.4, 131.3, 136.9, 137.2, 138.6, 151.7, 152.9. Anal. Calcd for $C_{24}H_{25}ClN_2O_4S$: C, 60.94, H, 5.33, N, 5.92, found: C, 61.01, H, 5.37, N, 6.04.

4.2. Pharmacology

(±) Cromakalim and diazoxide (Sigma Aldrich, St. Louis, MO, USA) were tested as reference compounds. The EC_{50} values (concentration provoking 50% inhibition of the plateau phase induced by KCl) were calculated from concentration-response curves by non-linear regression analysis. E_{max} corresponds to the percentage (%) of relaxation observed at 300 µM for rat aorta rings and 100 µM for trachea. The results are expressed as mean ± SEM.

4.2.1. Measurement of the contraction of rat aorta rings

Experiments were performed in the aorta, harvested from adult female Wistar rats (243-382 g) purchased from Janvier Labs (Le Genest-Saint-Isle, France). After anesthesia by intraperitoneal injection of pentobarbital (60 $mg.kg^{-1}$, i.p.), a section of the thoracic aorta was cleared of adhering fat and connective tissue, without removing the endothelium, and cut into transverse rings (2-3 mm long). The segments were suspended under 1.5 g tension by means of two steel hooks -one being connected to a tension transducer- in an organ bath containing 10 mL of a Krebs physiological solution of the following composition (in mM): NaCl 118, KCl 5.6, $CaCl_2$ 2.4, $NaHCO_3$ 25, KH_2PO_4 1.2, $MgCl_2$ 1.2, D-glucose 11, pH 7.4. The physiological solution was maintained at 37 °C and continuously bubbled with a mixture of O_2-CO_2 (95-5%). Isometric contractions of aortic rings were measured with a force-displacement transducer connected to a PowerLab/8S with Chart software (AD instruments, Paris, France) for recording and analysis. Rings initially stretched at 1.5g were allowed to equilibrate for 60 min and the Krebs solution was replaced each 15 min. After this period, a final mechanical stretch of 1.5 g was applied to the rings for 15 min before starting the experiment. Aorta ring contraction was induced by replacing the bathing Krebs solution by a hyperpotassic physiological solution (30 or 80 mM KCl), which depolarizes VSMC membranes and leads to L-type Ca^{2+} channel opening and extracellular calcium influx, therefore increasing cytosolic free calcium level and triggering constriction of these cells. It has to be noted that the 80mM KCl solution, in addition to inducing aortic constriction, also strongly inhibits or blocks potassium fluxes through K^+ channels (38,39). This is not the case of the 30 mM KCl solution, which only induces an increase in the vessel contraction without affecting K_{ATP} channels (38,39). The composition of the hyperpotassic solutions was similar to that of the Krebs solution, with the exception that the increase in KCl was compensated by a decrease in the NaCl concentration in order to preserve osmolarity. The respective concentrations of KCl and NaCl were (in mM): NaCl 118, KCl 5.6 in the normal Krebs

solution; NaCl 93.6, KCl 30 in the 30mM KCl hyperosmotic solution; NaCl 43.6, KCl 80 in the 80 mM KCl hyperosmotic solution. After KCl-induced elevation, the ring tension stabilized and reached a plateau after 15 min, and the tested drugs diluted in dimethylsulfoxide (DMSO) were added to the organ bath in a cumulative manner until maximal relaxation or up to 300 µM, in a 10-90 µL volume range (maximum final concentration of DMSO <1% v/v). Analogous experiment was performed in the presence of vehicle (same DMSO volume), as control. Some experiments were repeated in the continuous presence of 1 or 10 µM glibenclamide (a K_{ATP} channel blocker) in the bathing medium. The stabilization of the organ response towards KCl, tested drugs and reference compounds, was obtained at least after 15 minutes, the time needed to obtain steady-state contraction or relaxation (plateau). The relaxation response was expressed as the percentage of decrease in the contractile response to KCl.

4.2.2. Measurement of contractile activity of rat trachea rings

Trachea was removed from the same female rats anaesthetized with sodium pentobarbital (60 mg/kg, i.p.), and carefully cleaned of adhering adipose and connective tissue. Trachea rings (3-4 mm long) were suspended in the organ bath (10 ml) and the experiment progressed in the same conditions as those described above for the rat aorta except for the concentration of the contraction inducer KCl (30 mM only) [48,49].

4.2.3. In vitro stimulation of elastin synthesis

4.2.3.1. Vascular smooth muscle cell (VSMC) culture preparation

The thoracic aorta was removed, cleaned of fat and connective tissue and placed in a washing solution (2.5µg.mL^{-1} fungizone; antimycotic, invitrogen, Saint Aubin, France) diluted in Hank's Balanced Salt Solution (HBSS, invitrogen; Saint Aubin, France). The aorta was pre-digested for 30 min at 37°C in Dulbecco's modified Eagle's medium (DMEM; invitrogen, Saint Aubin, France) containing 1 mg.ml^{-1} collagenase type 2 (Worthington Biochemical Corporation, New Jersey, USA). After this step, the external envelope of the extracted aorta, i.e. the adventitia, becomes visibly altered and easily separable. After removing the adventitia with tweezers, the remaining intima-media was cut into small pieces of approximately 1-2 mm length. Then, aorta pieces were digested for 40 min at 37°C in DMEM solution containing 1 mg.ml^{-1} collagenase type 2 and 0.5 mg.ml^{-1} elastase (Worthington Biochemical Corporation, New Jersey, USA). After the digestion step, the rest of tissues were mechanically dissociated by gently flushing the solution for 10 min with a pipeter (P1000).

Culture medium was then added to stop the enzymatic digestion, and the cell suspension was centrifugated at 600xg for 10 minutes. The supernatant was discarded and the cell pellet was then resuspended in washing solution, before second centrifugation at 600xg for 10 minutes. The supernatant was discarded, the cells were resuspended in culture medium and seeded in a gelatin (0.1% in water, MERCK; Darmstadt, Allemagne) precoated well of a 24-well cell culture plate at 37°C, 5% CO_2.

Cell culture medium ingredients: DMEM + 20% (v/v) fetal bovine serum (FBS; invitrogen; Saint Aubin, France) + 1% (v/v) penicillin/streptomycin solution (invitrogen; Saint Aubin, France) + 1% Non-Essential Amino Acids Solution (NEAA, Invitrogen; Saint Aubin, France). The culture medium was replaced every two days, until cell confluence was reached, which was about 6-7 days after the cells were seeded. Amplification of the cell culture was then performed by cell trypsinization and seeding in several 0.1% gelatin-coated wells.

4.2.3.2. Measurement of the extracellular elastin content by ELISA

The method described by Vallet and Wiel (2001) was used in our experiments [50]. VSMC were deprived of serum overnight in DMEM containing only 1% FBS, to limit cell proliferation, before trypsinization and seeding at 25000 cells/well in a P96 plate, where the cells were left for another night for cell adhesion. The culture medium was then removed and replaced by fresh 1% FBS-DMEM in which the molecules to be tested in solution in DMSO were added (<1% DMSO in the final culture medium). For each concentration, 5-7 wells were used. In addition, the cells of 8 wells were bathed in 1% FCS-DMEM containing DMSO only, as the negative control. After 48 hours, i.e. the time to allow for elastin synthesis and excretion, the cells were washed 3 times with PBS (Invitrogen, Life Technologies Ltd., reference #14040174), then fixed for 10 min in 4% paraformaldehyde at room temperature. The wells were washed again 3 times with PBS, before blockade of the non-specific binding sites with 2% BSA containing-PBS for 30 min at 37°C, then washed 3 times with 0.1% Tween-containing PBS. After this step, the cells were incubated in 2% BSA containing-PBS for 1 hour at 37°C with the primary antibody (Elastin Products Company, Inc. Missouri, USA, TP592) at the concentration of 1/1000. The cells were then washed 3 times with 0.1% Tween-containing PBS before incubation for 1hour at 37°C in the dark with the horseradish peroxidase (HRP)-coupled secondary antibodies. The secondary anti-mouse antibody (A4416, Sigma, St Quentin-Fallavier, France) was used at 1/10000. The cells were then washed 3 times with 0.1% Tween-containing PBS, before 100 µl TMB (3,3',5,5'-tetramethybenzidine, Millipore ES022), the substrate of HRP (horseradish peroxidase), was added to each well for

30 min in the dark at room temperature. The reaction was then stopped by the addition of 100 µl 0.3 M-sulfuric acid to each well. After 10 min, the absorbance of each well -a function of extracellular elastin quantities- was measured at 450 nm.

4.2.4. Ionization Constants

The pKa values of the compound **A15** were determined by means of U.V. spectrophotometry using a SHIMADZU UV/VIS 1800 spectrophotometer at 25 °C. UV spectra of compound were taken in different aqueous buffers of pH ranking from 3 to 12. The pKa values were calculated by the Albert and Serjeant equation at the wavelength giving the maximum absorbance difference between the ionized and the neutral forms [33,51].

4.2.5. Statistical evaluation

The statistical significance of the differences between groups was assessed by using 1-way ANOVA for analysis of the effects of the molecules on elastin production. The statistical significance of differences between mean data was assessed by using the Student's *t*-test. The biological results were considered statistically different when $p < 0.05$.

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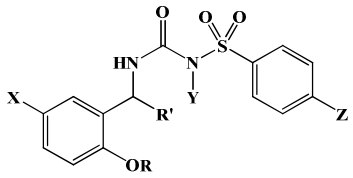
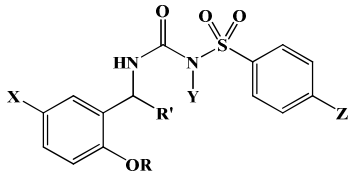
Table 1. Effects of compounds **A1-33** and **B1-33** (EC_{50}) on the contractile activity of rat aorta rings.



				Series A : Y = H		Series B : Y = CH_3	
X	**R**	**R'**	**Z**	**Compd.**	**EC_{50} (µM)[a] aortic rings**	**Compd.**	**EC_{50} (µM)[a] aortic rings**
OMe	Me	H	H	**A1**	>300 (5)	**B1**	21.3 ± 1.7 (6)
OMe	Me	H	Me	**A2**	>300 (6)	**B2**	20.9 ± 2.7 (6)
OMe	Me	H	Cl	**A3**	>300 (5)	**B3**	18.2 ± 3.1 (6)
Br	Me	Me	H	**A4**	>300 (5)	**B4**	16.8 ± 2.3 (6)
Br	Me	Me	Me	**A5**	>300 (5)	**B5**	19.1 ± 1.9 (5)
Br	Me	Me	Cl	**A6**	80.9 ± 42.0 (5)	**B6**	19.1 ± 1.4 (5)
Br	Et	Me	H	**A7**	>300 (5)	**B7**	19.8 ± 2.0 (5)
Br	Et	Me	Me	**A8**	>300 (5)	**B8**	28.6 ± 1.4 (5)
Br	Et	Me	Cl	**A9**	171.0 ± 31.0 (5)	**B9**	55.7 ± 4.0 (5)
Br	iPr	Me	H	**A10**	143.4 ± 36.0 (5)	**B10**	32.1 ± 1.8 (5)
Br	iPr	Me	Me	**A11**	**61.8 ± 9.9 (3)**	**B11**	34.7 ± 2.2 (4)
Br	iPr	Me	Cl	**A12**	122.2 ± 31.1 (3)	**B12**	43.2 ± 4.5 (3)
Br	Bn	Me	H	**A13**	130.0 ± 10.0 (5)	**B13**	60.3 ± 3.1 (4)
Br	Bn	Me	Me	**A14**	138.0 ± 6.0 (5)	**B14**	67.1 ± 11.5 (7)
Br	Bn	Me	Cl	**A15**	**57.5 ± 11.7 (5)**	**B15**	145.8 ± 38.3 (4)
Cl	Me	Me	H	**A16**	>300 (4)	**B16**	**7.2 ± 0.8 (4)**
Cl	Me	Me	Me	**A17**	>300 (4)	**B17**	**13.8 ± 1.7 (6)**
Cl	Me	Me	Cl	**A18**	>300 (9)	**B18**	20.0 ± 1.7 (4)
Cl	Et	Me	H	**A19**	>300 (4)	**B19**	**10.5 ± 0.8 (4)**
Cl	Et	Me	Me	**A20**	>300 (4)	**B20**	**12.2 ± 1.4 (4)**
Cl	Et	Me	Cl	**A21**	281.2 ± 32.7 (3)	**B21**	**14.6 ± 1.2 (3)**
F	Me	Me	H	**A22**	>300 (4)	**B22**	**10.0 ± 3.3 (4)**
F	Me	Me	Me	**A23**	>300 (4)	**B23**	**11.7 ± 2.5 (4)**
F	Me	Me	Cl	**A24**	>300 (4)	**B24**	**12.6 ± 1.2 (5)**
F	Et	Me	H	**A25**	>300 (4)	**B25**	**11.5 ± 1.7 (5)**
F	Et	Me	Me	**A26**	>300 (4)	**B26**	**7.8 ± 1.1 (5)**
F	Et	Me	Cl	**A27**	>300 (4)	**B27**	24.5 ± 3.4 (5)
H	Bn	Me	H	**A28**	>200 (5)	**B28**	21.7 ± 1.6 (3)
H	Bn	Me	Me	**A29**	>200 (5)	**B29**	31.0 ± 5.0 (4)
H	Bn	Me	Cl	**A30**	156.8 ± 16.3 (5)	**B30**	38.4 ± 5.0 (4)
CH_3	Bn	Me	H	**A31**	>200 (5)	**B31**	68.2 ± 1.6 (3)
CH_3	Bn	Me	Me	**A32**	91.9 ± 6.7 (4)	**B32**	180.6 ± 29.5 (4)
CH_3	Bn	Me	Cl	**A33**	**65.3 ± 5.4 (4)**	**B33**	141.6 ± 11.7 (4)
Br	$C(Me)_2$-	CH_2-	Cl	**6**[b]	34.8 ± 3.7 (5)	**8**[b]	**5.4 ± 1.0 (4)**
Cl	$C(Me)_2$-	CH_2-	Cl	**7**[c]	51.0 ± 4.3 (4)	-	-
F	$C(Me)_2$-	CH_2-	Me	-	-	**9**[b]	**1.9 ± 0.1 (4)**
H	Me	H	Cl	**10**[b]	>30 (4)	-	-
H	Et	H	Cl	**11**[b]	>30 (4)	-	-
-	-	-	-	**DZD**[d]	-	-	23.68 ± 3.31 (6)
-	-	-	-	**±PND**[d]	-	-	0.39 ± 0.07 (4)
-	-	-	-	**±CRK**	-	-	0.13 ± 0.05 (4)

Bold represents the most active compounds. [a] EC_{50}: drug concentration giving 50% relaxation of the 30 mM KCl-induced contraction of rat aorta rings (mean ± sem). (n): number in brackets refers to the number of samples.[b] Refs. [11, 14, 16] ; [c] Ref. [12] ; [d] Ref. [52]. DZD: diazoxide, PND: pinacidil, CRK: cromakalim.

Table 2. Effects of compounds **A1-33** and **B1-33** (E_{max}) on the contractile activity of rat aorta rings.



X	R	R'	Z	Series A : Y = H		Series B : Y = CH_3	
				Compd.	E_{max} (%)[a] aortic rings	Compd.	E_{max} (%)[a] aortic rings
OMe	Me	H	H	**A1**	-20.3 ± 9.7 (5)	**B1**	100.0 ± 1.6 (6)
OMe	Me	H	Me	**A2**	-14.5 ± 8.9 (6)	**B2**	92.7 ± 2.1 (6)
OMe	Me	H	Cl	**A3**	-28.0 ± 9.1 (5)	**B3**	93.6 ± 1.1 (6)
Br	Me	Me	H	**A4**	45.5 ± 11.5 (5)	**B4**	98.0 ± 3.5 (6)
Br	Me	Me	Me	**A5**	67.6± 7.0 (5)	**B5**	97.7 ± 2.3 (5)
Br	Me	Me	Cl	**A6**	82.6± 7.4 (5)	**B6**	93.6 ± 2.2 (5)
Br	Et	Me	H	**A7**	35.9±5.8 (5)	**B7**	103.6 ± 8.5 (5)
Br	Et	Me	Me	**A8**	62.2±5.7 (5)	**B8**	90.8 ± 5.1 (5)
Br	Et	Me	Cl	**A9**	77.6 ± 6.6 (5)	**B9**	71.0 ± 4.1 (5)
Br	iPr	Me	H	**A10**	73.2 ± 6.0 (5)	**B10**	81.5 ± 2.2 (5)
Br	iPr	Me	Me	**A11**	93.2± 3.1 (3)	**B11**	102.5 ± 2.9 (4)
Br	iPr	Me	Cl	**A12**	100.1 ± 1.5 (3)	**B12**	93.7 ± 2.6 (3)
Br	Bn	Me	H	**A13**	92.3 ± 1.8 (5)	**B13**	56.8 ± 3.7 (4)
Br	Bn	Me	Me	**A14**	92.5 ± 2.3 (5)	**B14**	47.9 ± 10.2 (7)
Br	Bn	Me	Cl	**A15**	95.1 ± 4.1 (5)	**B15**	97.3 ± 22.1 (4)
Cl	Me	Me	H	**A16**	16.4.1 ± 11.8 (4)	**B16**	102.7 ± 1.8 (4)
Cl	Me	Me	Me	**A17**	36.6 ± 5.0 (4)	**B17**	106.7 ± 1.5 (6)
Cl	Me	Me	Cl	**A18**	40.9 ± 2.8 (9)	**B18**	103.1 ± 4.8 (4)
Cl	Et	Me	H	**A19**	15.8 ± 2.6 (4)	**B19**	104.0 ± 1.2 (4)
Cl	Et	Me	Me	**A20**	45.5 ± 4.8 (4)	**B20**	106.1 ± 1.6 (4)
Cl	Et	Me	Cl	**A21**	69.7 ± 4.8 (3)	**B21**	105.0 ± 3.4 (3)
F	Me	Me	H	**A22**	1.2 ± 2.7 (4)	**B22**	108.9 ± 4.5 (4)
F	Me	Me	Me	**A23**	-4.5 ± 4.7 (4)	**B23**	105.9 ± 2.9 (4)
F	Me	Me	Cl	**A24**	54.7 ± 17.4 (4)	**B24**	100.9 ± 1.3 (5)
F	Et	Me	H	**A25**	46.4 ± 7.9 (4)	**B25**	106.5 ± 2.1 (5)
F	Et	Me	Me	**A26**	26.2 ± 7.7 (4)	**B26**	104.4 ± 1.3 (5)
F	Et	Me	Cl	**A27**	52.7 ± 2.5 (4)	**B27**	101.2 ± 1.2 (5)
H	Bn	Me	H	**A28**	59.0 ± 6.9 (5)	**B28**	92.3 ± 6.6 (3)
H	Bn	Me	Me	**A29**	84.7 ± 3.9 (5)	**B29**	93.2 ± 1.9 (4)
H	Bn	Me	Cl	**A30**	103.0 ± 6.9 (5)	**B30**	91.1 ± 2.8 (4)
CH_3	Bn	Me	H	**A31**	90.7 ± 3.3 (5)	**B31**	86.1 ± 5.6 (3)
CH_3	Bn	Me	Me	**A32**	105.9 ± 5.6 (4)	**B32**	82.9 ± 0.8 (4)
CH_3	Bn	Me	Cl	**A33**	125.5 ± 17.8 (4)	**B33**	76.9 ± 4.3 (4)
Br	$C(Me)_2$-	CH_2-	Cl	**6**[b]	nd	**8**[b]	nd
Cl	$C(Me)_2$-	CH_2-	Cl	**7**[c]	nd	-	-
F	$C(Me)_2$-	CH_2-	Me	-	-	**9**[b]	nd
H	Me	H	Cl	**10**[b]	nd	-	-
H	Et	H	Cl	**11**[b]	nd	-	-
-	-	-	-	**DZD**[d]	-	-	nd
-	-	-	-	**±PND**[d]	-	-	nd
-	-	-	-	**±CRK**	-	-	69.8 ± 9.8 (4)

[b] E_{max} corresponds to the percentage (%) of relaxation observed at 300 µM for rat aorta rings (mean± sem). Bold represents the most active compounds. [a] EC_{50}: drug concentration giving 50% relaxation of the 30 mM KCl-induced contraction of rat aorta rings (mean± sem). (n): number in brackets refers to the number of samples. [b] Refs. [11, 14, 16] ; [c] Ref. [12] ; [d] Ref. [52]. DZD: diazoxide, PND: pinacidil, CRK: cromakalim.

Table 3. Myorelaxant effects of active compounds **A15**, **A33**, **B16**, cromakalim and verapamil on 30 and 80 mM induced contraction of rat aorta rings incubated in the absence or the presence of 1 and 10 µM glibenclamide.

Compound	Myorelaxant activity 30 mM KCl EC_{50} (µM)[a]			Myorelaxant activity 80 mM KCl EC_{50} (µM)[a]
	0 µM Glib	1 µM Glib	10 µM Glib	
A15	57.5 ± 11.7 (5)	78.4 ± 16.0 (3)	54.6 ± 3.4 (3)	61.6 ± 6.2 (4)
A33	65.3 ± 5.4 (4)	90.5 ± 9.9 (4)	69.3 ± 7.2 (3)	60.9 ± 2.3 (3)
B16	7.2 ± 0.8 (4)	6.7 ± 1.0 (5)	8.6 ± 1.2 (4)	5.3 ± 1.3 (4)
±CRK	0.13 ± 0.05 (4)	3.4 ± 0.8 (5)	87.2 ± 10.5 (4)	190.8 ± 39.3 (7)
±Verapamil [b]	0.06 ± 0.02 (4)	0.07 ± 0.02 (4)	0.07 ± 0.02 (4)	0.05 ± 0.02 (4)

[a] Results are expressed as (mean ± SEM); (n): number in brackets refers to the number of samples.
[b] Ref. [36]. CRK: cromakalim, Glib: glibenclamide.

Table 4. Effects of active compounds on the contractile activity of 30 mM K^+ depolarized rat aorta and rat trachea rings.

Compound	Relaxation of precontracted				Selectivity [c]
	rat aorta EC_{50} (µM)[a]	E_{max} (%)[b]	rat trachea EC_{50} (µM)[a]	E_{max} (%)[b]	trachea/aorta
A15	57.5 ± 11.7 (5)	95.1 ± 4.1 (5)	30.8 ± 3.4 (3)	160.7 ± 16.4 (3)	0.5
A33	65.3 ± 5.4 (4)	125.5 ± 17.8 (4)	30.4 ± 5.9 (4)	171.7 ± 8.4 (4)	0.5
B1	21.3 ± 1.7 (6)	100.0 ± 1.6 (6)	18.5 ± 1.7 (4)	150.1 ± 2.4 (4)	0.9
B4	16.8 ± 2.3 (6)	98.0 ± 3.5 (6)	**8.4 ± 0.3 (4)**	124.6 ± 2.5 (4)	0.5
B5	19.1 ± 1.9 (5)	97.7 ± 2.3 (5)	12.8 ± 0.3 (3)	143.3 ± 6.8 (3)	0.7
B6	19.1 ± 1.4 (5)	93.6 ± 2.2 (5)	39.3 ± 10.5 (3)	124.8 ± 21.2 (3)	2.0
B7	19.8 ± 2.0 (5)	103.6 ± 8.5 (5)	**8.4 ± 0.5 (4)**	137.0 ± 3.7 (4)	0.4
B16	7.2 ± 0.8 (4)	102.7 ± 1.8 (4)	**1.7 ± 0.6 (3)**	153.6 ± 16.4 (3)	0.2
±CRK	0.13 ± 0.05 (4)	69.8 ± 9.8 (4)	124.4 ± 28.7 (3)	70.1 ± 21.3 (3)	956.9
±Verapamil	0.06 ± 0.02 (4)[d]	nd	0.89 (5) [e]	nd	28.7

Bold represents the most active compounds. [a] EC_{50} is the drug concentration reducing by 50% the rat aorta and the rat trachea tonus induced by 30 mM KCl. [b] E_{max} corresponds to the percentage (%) of relaxation observed at 300 µM for rat aorta and 100 µM for rat trachea rings (mean ± sem). [c] Selectivity is the tracheal EC_{50} / aortic EC_{50} ratio for a given compound. [d] Ref. [36] ; [e] Refs. [43,44]; CRK: cromakalim.

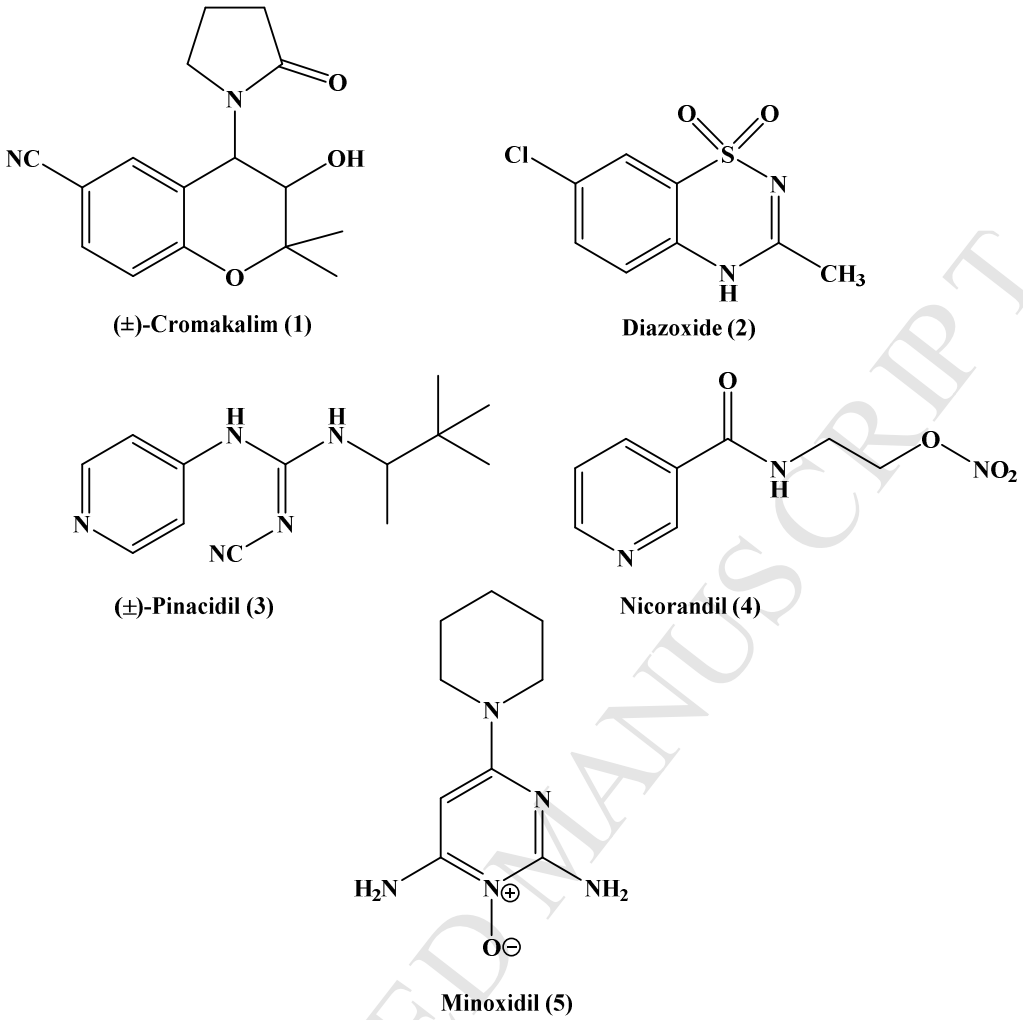


Figure 1. Chemical structures of the first generation potassium channel openers (PCOs), known as antihypertensive agents.

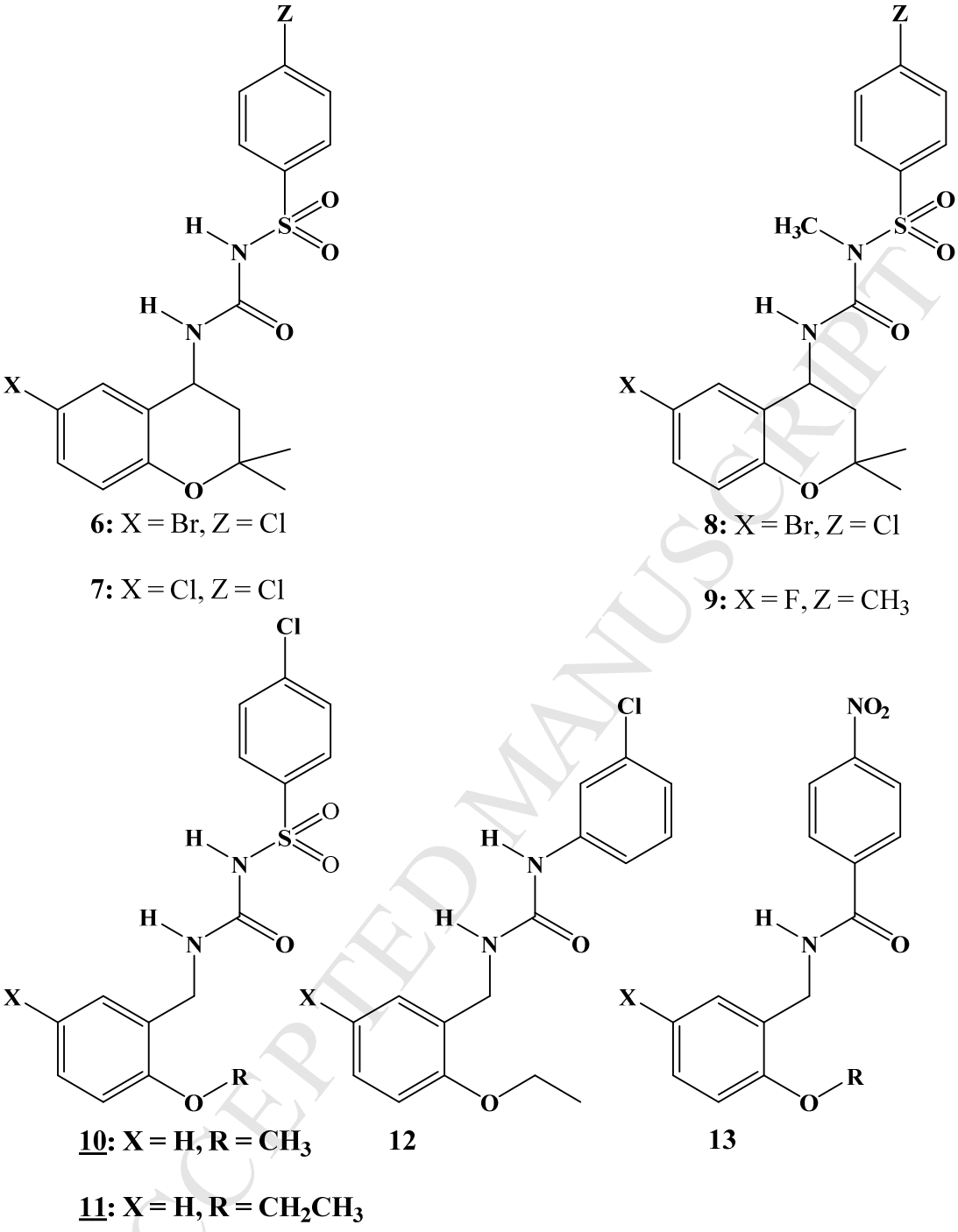


Figure 2: Chemical structures of previously described ring-closed (**6-9**) and ring-opened (**10-13**) analogues of cromakalim.

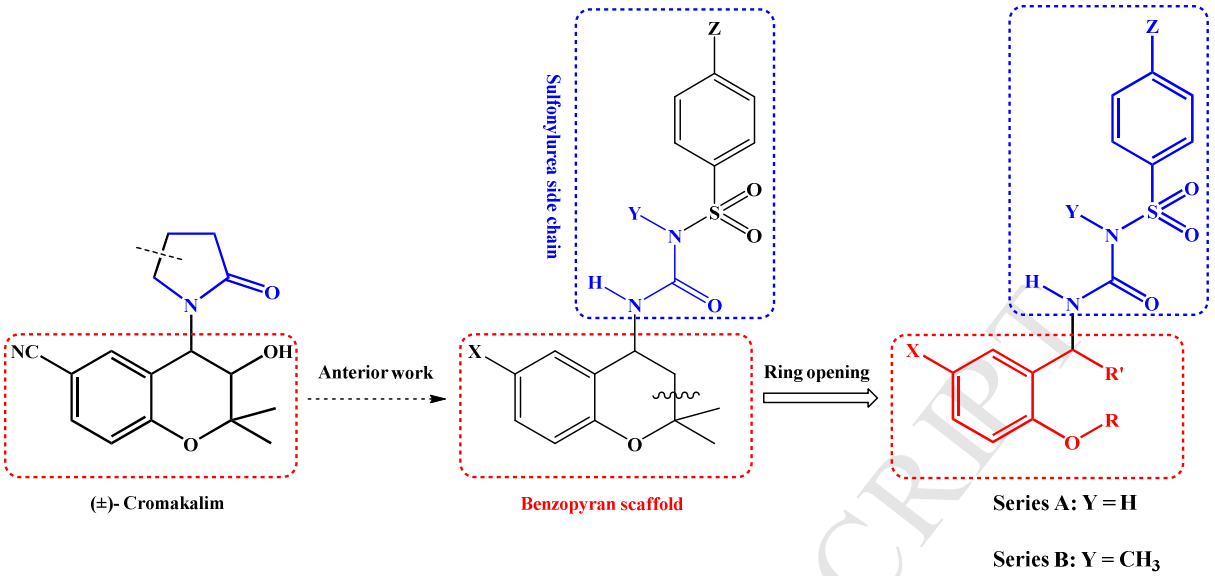


Figure 3: Design of ring-opened cromakalim analogues (series **A** et **B**).

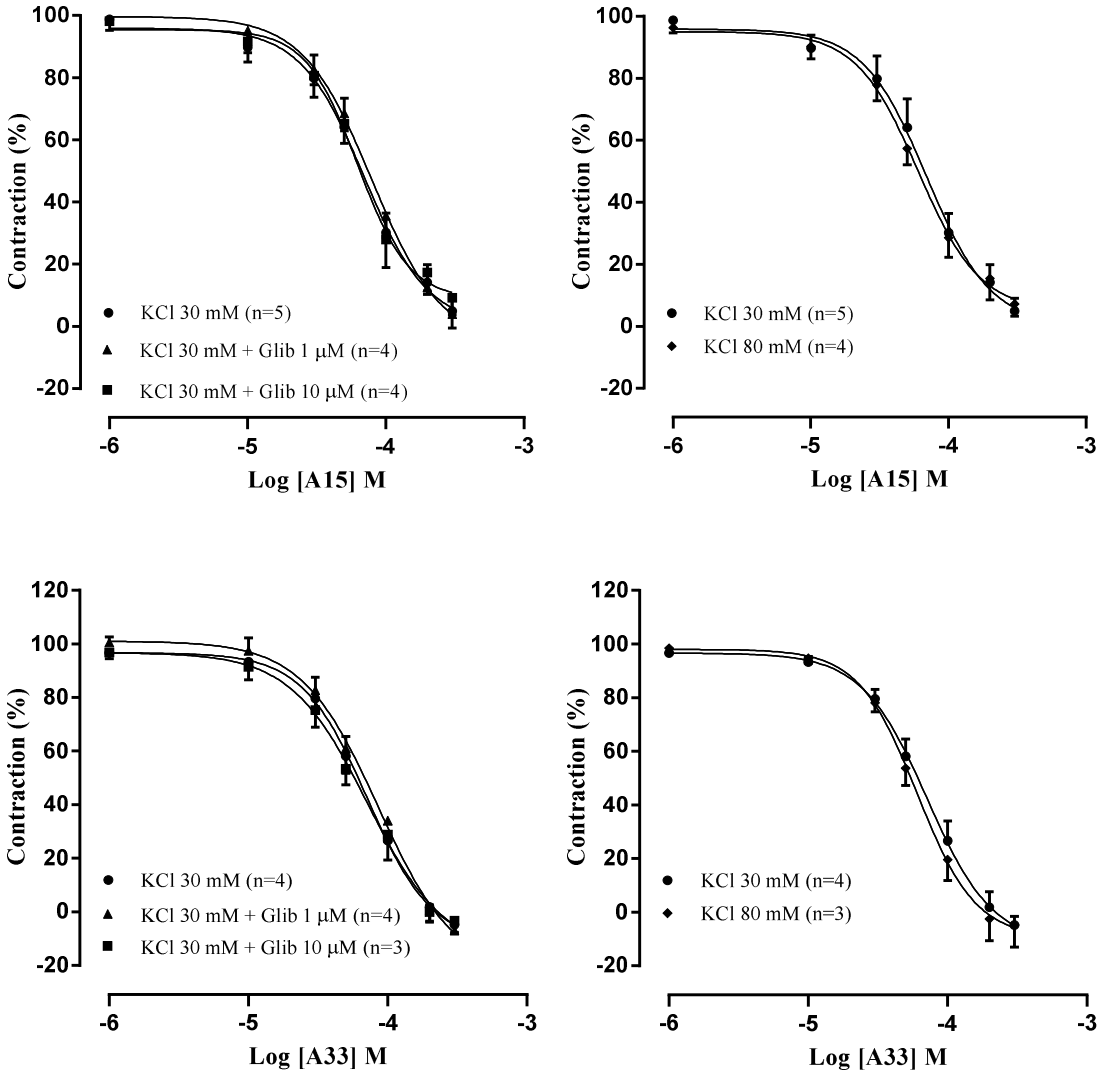


Figure 4: Left panel: concentration-response curves for the myorelaxant effect of compounds **A15**, **A33** and **B16** on 30 mM KCl-induced contraction of rat aorta rings incubated in the absence or presence of different glibenclamide (glib) concentrations. **Right panel**: concentration-response curves for the myorelaxant effect of the most vasoactive compounds **A15**, **A33** and **B16** on KCl (30 mM or 80 mM)-induced contraction of rat aorta rings. Data are expressed as the percentage decrease in the contraction level induced by 30 mM or 80 mM KCl of (n) individual experiments.

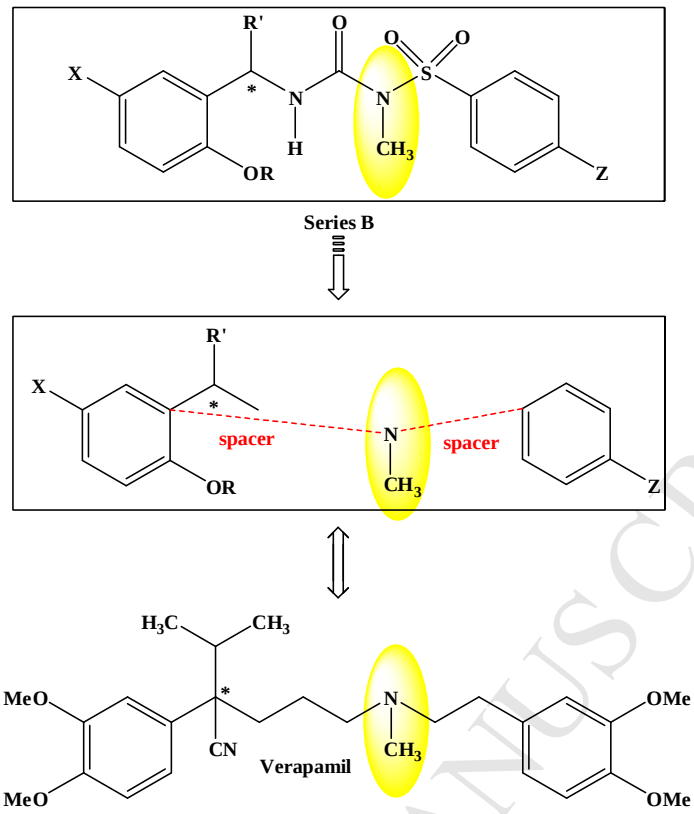


Figure 5: Structural analogies between the *N*-methylated compounds of series **B** and verapamil, a Ca^{2+}-gated channels blocker: both molecules have two substituted aromatic rings spaced by a chiral benzylic carbon and an *N*-methyl group.

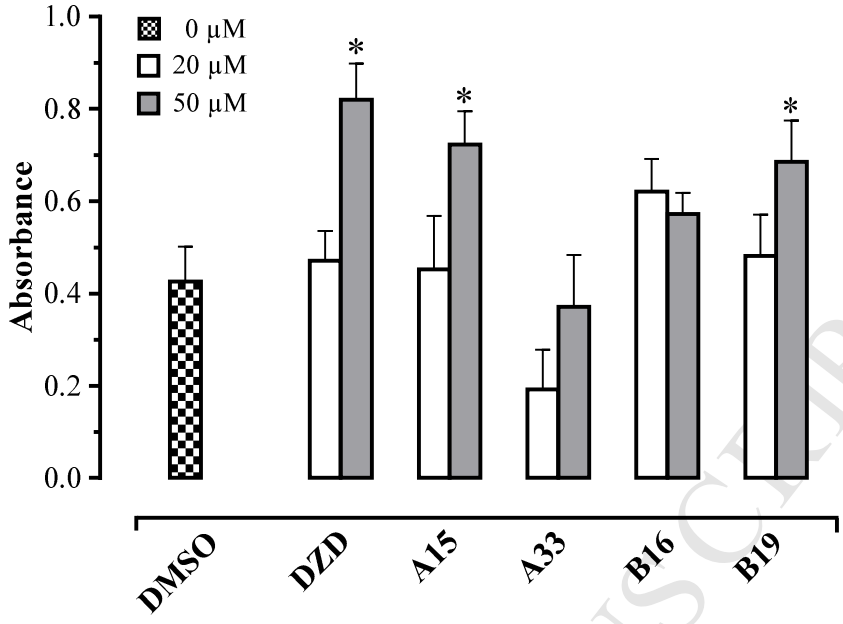
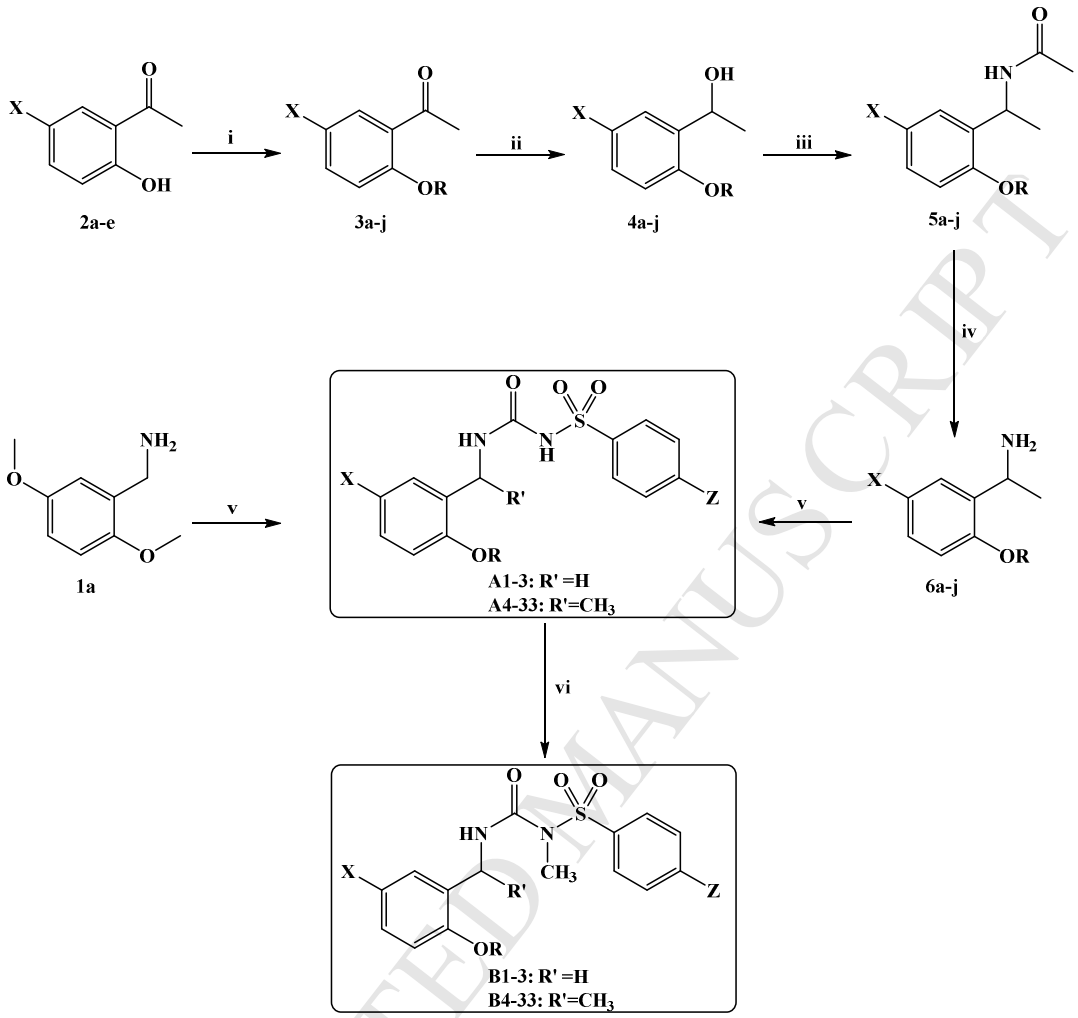


Figure 6: Effect of active compounds on elastin production by cultured vascular smooth muscle cells. Elevation of absorbance as a function of two different concentrations of molecules **A15**, **A33**, **B16** and **B19** was compared to the effects of the carrier alone (DMSO) and diazoxide. The absorbance is representative of extracellular elastin quantity (n = 4-6 in each group of test synthesized molecules, n = 5-6 in each positive or negative control group). *Significant difference with the control (DMSO alone): $P \leq 0.05$.

Schemes



Scheme 1. Synthetic route to the target compounds **A1-33** and **B1-33** Reagents : (i) K_2CO_3, RX, DMF ; (ii) $NaBH_4$, MeOH ; (iii) CH_3CN, H_2SO_4 ; (iv) NaOH in MeOH-H_2O 250 °C ; (v) 4-$ZC_6H_4SO_2NCO$, CH_2Cl_2 ; (vi) Na_2CO_3, CH_3I, CH_3CN, reflux.

Design, Synthesis and Biological Evaluation of Novel Ring-Opened Cromakalim Analogues with Relaxant Effects on Vascular and Respiratory Smooth Muscles and as Stimulators of Elastin Synthesis

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Highlights

- Ring-opened analogues of cromakalim bearing sulfonylurea moieties were synthesized.
- A majority of series B compounds were more active than diazoxide on aorta.
- Some of series B compounds were more active than cromakalim on trachea.
- Selected compounds of series A and B were blockers of voltage-gated Ca^{2+} channels.
- Selected compounds of series B showed a stimulating effect on elastin synthesis.