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Selective angiotensin II AT_2 receptor agonists with reduced CYP 450 inhibition

A. K. Mahalingam [a], Yiqian Wan [a], A. M. S. Murugaiah [a], Charlotta Wallinder [a], Xiongyu Wu [a], Bianca Plouffe [b], Milad Botros [c,d], Fred Nyberg [c,d], Anders Hallberg [a], Nicole Gallo-Payet [b,*], Mathias Alterman [a,*]

[a] Department of Organic Pharmaceutical Chemistry, BMC, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden
[b] Service of Endocrinology, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec, Canada J1H 5N4
[c] Department of Physiology and Biophysics, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec, Canada J1H 5N4
[d] Department of Biological Research on Drug Dependence, BMC, Uppsala University, PO Box 591, SE-751 23 Uppsala, Sweden

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ABSTRACT

Structural alterations to the benzylic position of the first drug-like selective angiotensin II AT_2 receptor agonist (**1**) have been performed, with the emphasis to reduce the CYP 450 inhibitory property of the initial structure. The imidazole moiety, responsible for the CYP 450 inhibitory effect in **1**, was replaced with various heterocycles. In addition, the modes of attachment of the heterocycles, that is, carbon versus nitrogen attachment, and introduction of carbonyl functionalities to the benzylic position have been evaluated. In all the three series, AT_2 receptor ligands with affinity in the lower nanomolar range were identified. None of the analogues, regardless of the substituents, exhibited any affinity for the AT_1 receptor. Compounds with substantially reduced inhibition of the CYP 450 enzymes were obtained. Among them the compound **60** was found to induce neurite elongation in NG 108-15 cells and served as potent AT_2 selective agonist.

1. Introduction

Angiotensin II (Ang II), recognized as the most important bioactive peptide of the renin-angiotensin system, is the endogenous ligand to the AT_1 and the AT_2 receptors where it acts as an agonist. The AT_1 receptor is closely associated with the regulation of blood pressure, fluid and electrolyte balance, while the role of the AT_2 receptor has been less clear due to the low level of AT_2 expression in healthy adults.[1] One interesting feature of the AT_2 receptor is the high level of expression in most fetal tissues, including the brain. Notably, the AT_2/AT_1 receptor ratio decreases dramatically after birth,[2,3] which suggests that the AT_2 receptor may be involved in fetal development. This is further supported by the observed induction of neurite outgrowth, elongation and the modulated neuronal excitability upon AT_2 receptor activation in cells of neuronal origin.[4,5] In adults, activation of the AT_2 receptor exhibits effects that could be considered more 'anti AT_1', for example, activation lowers blood pressure, inhibits cell proliferation, induces programmed cell death and extra cellular matrix remodeling, as well as axonal regeneration.[6–11] Moreover, AT_2 receptor expression is up-regulated in pathological conditions such as heart failure, renal failure, myocardial infarction, brain lesions, vascular injury and wound healing.[9,12–14] In addition, it has been demonstrated that activation of the AT_2 receptor stimulates alkaline secretion by the duodenal mucosa in rats.[15]

The first non-peptidic selective AT_2 receptor agonist M024 (**1**, Fig. 1), that we reported recently,[16] was designed by introducing a small unsubstituted imidazole in the benzylic position of the non-selective AT_1/AT_2 agonist L-162,313 (Fig. 1).[17–19] The unsubstituted imidazole provided a good moiety to obtain high affinity, AT_1/AT_2 selectivity as well as agonism. We have also shown that

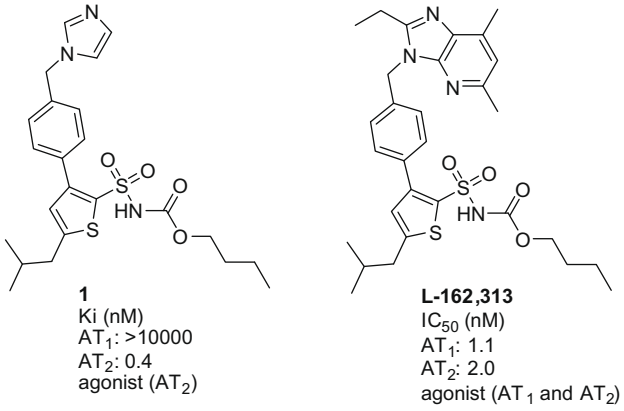

Figure 1.

* Corresponding authors. Tel.: +46 18 4714905; fax: +46 18 4714474 (M.A.); tel.: +1 819 5645243; fax: +1 819 5645292 (N.G.-P.).
E-mail addresses: nicole.gallo-payet@usherbrooke.ca (N. Gallo-Payet), mathias.alterman@orgfarm.uu.se (M. Alterman).

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the unsubstituted imidazole could be combined with substituents other than *iso*-butyl in the 5-postion of the thiophene.[20] Furthermore, we have shown that compounds where the thiophene has been exchanged with a phenyl maintain affinity and selectivity towards the AT_2 receptor.[20] Although the imidazole provided an excellent moiety for high affinity and selectivity towards the AT_2 receptor, it is known from literature that benzylic imidazoles frequently possess CYP 450 inhibition.[21] Expectedly, the selective AT_2 antagonist **1** was also found to be an inhibitor of the CYP 450 metabolic enzyme system (Inhibition an 10 μM: 94% 2C9; 82% 3A4). The CYP 450 metabolic enzymes are an important system for metabolism of drug substances in the body. Inhibition of these enzymes could lead to reduced metabolism of other drugs that might lead to unwanted side effects or toxicity. We therefore sought to modify the imidazole structure and eliminate the unwanted CYP 450 inhibition but with maintained AT_2 selectivity, affinity, and agonistic property. We were also interested in examining the attachment mode of the heterocycles, that is, carbon attachment instead of nitrogen attachment, and additionally to introduce carbonyls to the benzylic position to further explore the structure–activity of this class of compounds.

2. Results

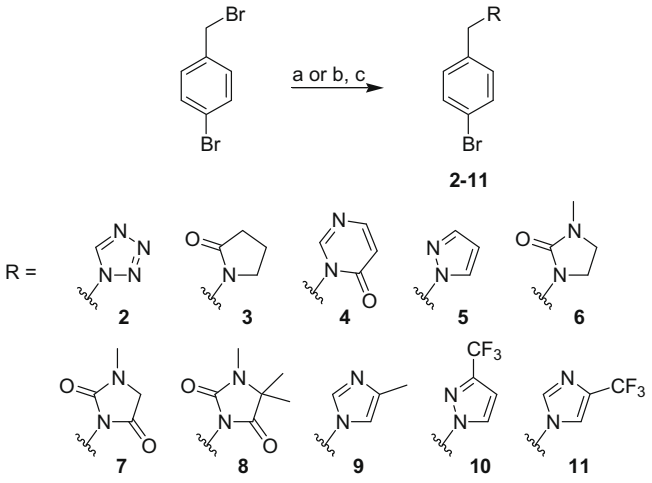
2.1. Chemistry

The 4-bromo-benzyl heterocycles (**2–11**, Scheme 1) were obtained by treating the selected heterocycles with base and subsequently adding 4-bromobenzylbromide to give the desired compounds in moderate to good yields.

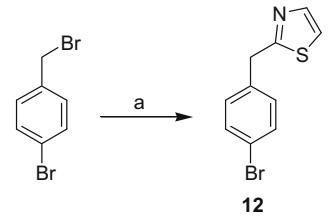
To produce compound **12** (Scheme 2), which contains a carbon attached thiazole, tri-butyl tin thiazole was reacted with 4-bromobenzylbromide under Stille coupling conditions with $Pd(PPh_3)_4$ as catalyst. The reaction was very sluggish and gave only 31% yield.

The carbon attached oxazole compound **13** (Scheme 3), was synthesized by using 4-bromobenzeneacetamide as starting material, since the direct alkylation of oxazole was unsuccessful. 4-Bromobenzeneacetamide was treated with vinylene carbonate in polyphosphoric acid to obtain the 2-(4-bromo-benzyl)-oxazole (**13**) in a modest 30% yield.

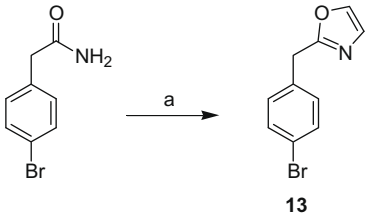
The carbonyl compounds **19–23** (Scheme 4) were obtained by treatment of the heterocycles with *n*-BuLi followed by addition of 4-bromobenzaldehyde. This process gave the corresponding alcohols **14–18** in good yields. The alcohols (**14–18**) were then subsequently oxidized with pyridiniumchlorochromate in dichloromethane to give the (4-bromophenyl)-heterocyclic-methanones (**19–23**) in high yields.



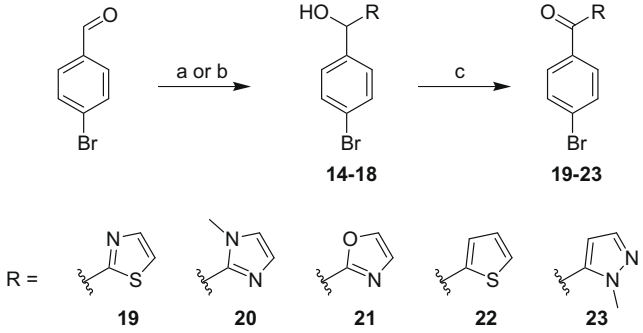
Scheme 1. Reagents: (a) heterocycle, KOH, DMSO (**2**, **3**, **9**); (b) heterocycle, KO-*t*Bu, DMSO (**4**, **6**, **7**, **8**, **10**, **11**); (c) pyrazole KO-*t*Bu, THF (**5**).



Scheme 2. Reagents: (a) 2-tributylstannanyl-thiazole, DIEA, $Pd(PPh_3)_4$, DMF.



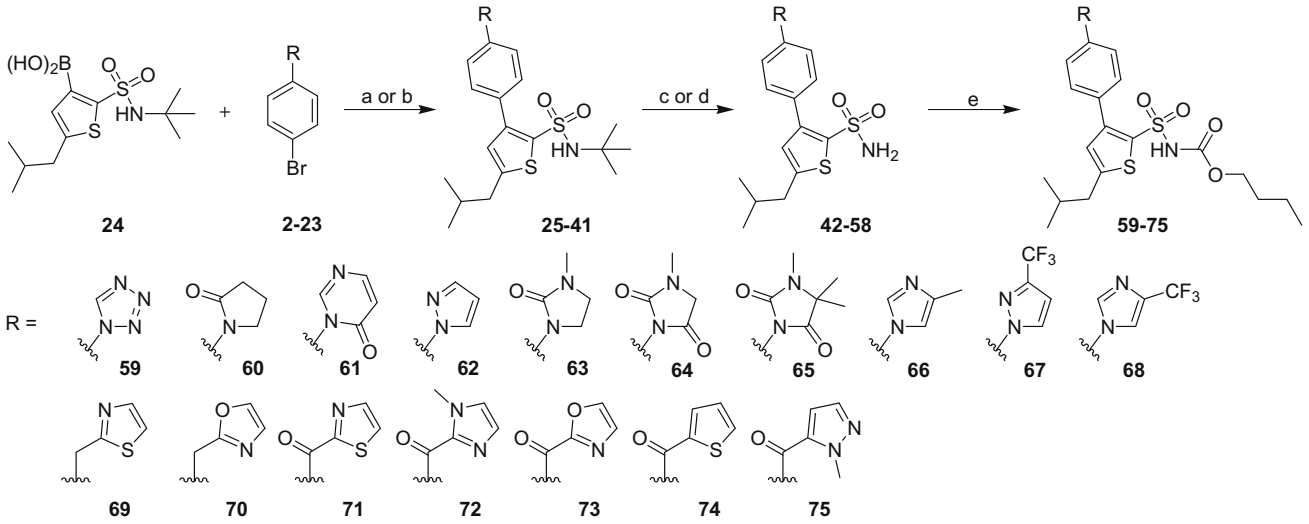
Scheme 3. Reagents: (a) vinylene carbonate, polyphosphoric acid.



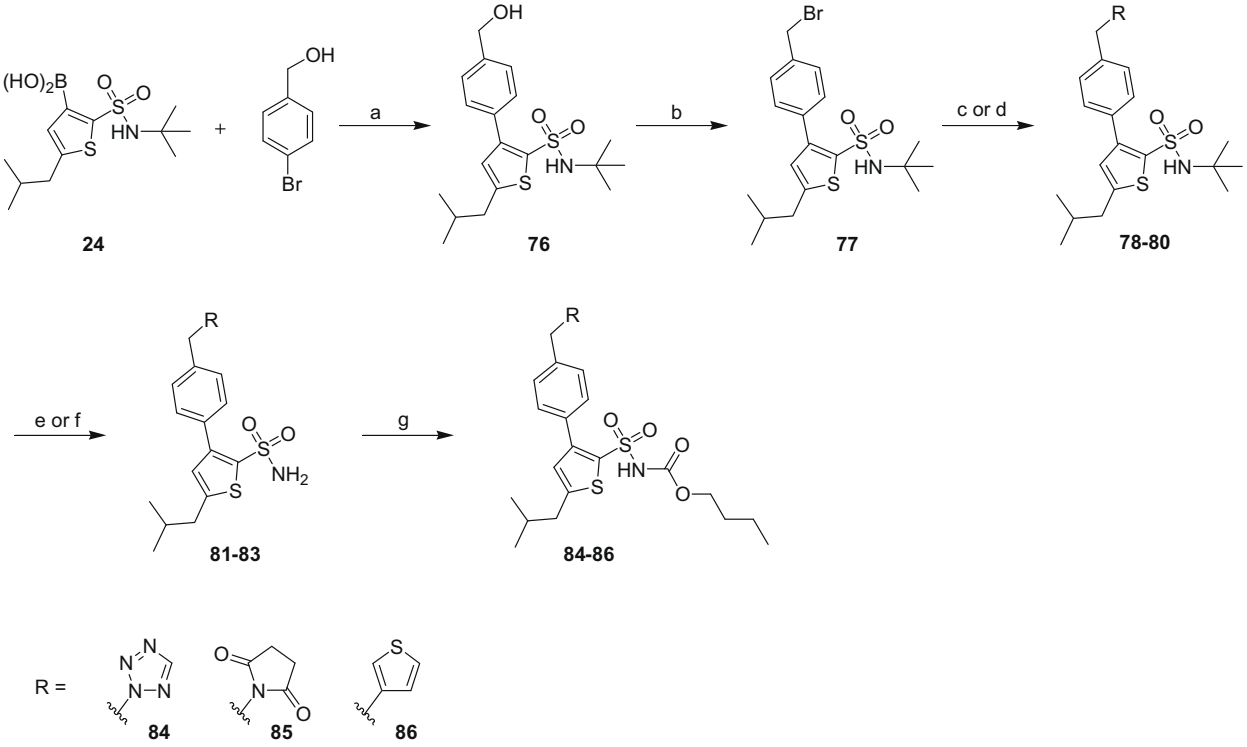
Scheme 4. Reagents: (a) *n*-BuLi, heterocycle, THF (**14**, **15**, **17**, **18**); (b) oxazole, BH_3–THF, *n*-BuLi (**16**); (c) PCC, CH_2Cl_2.

Bromides (**2–23**) were then coupled with the thiopheneboronic acid **24** (Scheme 5), prepared in essence as described by Kevin et al.,[22] under Suzuki conditions with $Pd(PPh_3)_4$ as catalyst and with KOH (or CsF) as base to give the *tert*-butyl protected compounds **25**–**41** in 31–88% yield. Deprotection of compounds **25–41** by TFA or alternatively by BCl_3, a milder deprotecting reagent,[23] delivered the primary sulfonamides (42–58) that were subsequently reacted with *n*-butyl chloroformate, at ambient temperature, in pyridine with 4-pyrrolidin-1-yl-pyridine nucleophilic catalyst, to afford the target compounds **59–75**.

To prepare the compounds **84–86** a different synthetic approach was used (Scheme 6). The reason for this were that the tetrazole alkylation gave a different isomer with this synthetic procedure and that the pyrrolidine-2,5-dione was not stable under the Suzuki reaction conditions. The thiophene was coupled to explore the possibility of using palladium-catalyzed reaction at the benzylic bromide position. The thiopheneboronic acid **24** was coupled under Suzuki conditions with 4-bromobenzylalcohol to give the benzylalcohol **76** in 76% yield. The alcohol was then substituted with a bromide by using CBr_4 and PPh_3 at room temperature to give the benzyl bromide **77** in good yield. Treatment of tetrazole and pyrrolidine-2,5-dione with KOH in DMSO and subsequent addition of benzyl bromide **77** gave compounds **78** and **79** in



Scheme 5. Reagents: (a) $Pd(PPh_3)_4$, NaOH, toluene, EtOH (**25–29**, **32–41**); (b) $Pd(PPh_3)_4$, CsF, DME (**30**, **31**); (c) BCl_3, CH_2Cl_2 (**42–45**, **49–52**); (d) TFA (**46–48**, **53–58**); (e) *n*-butyl chloroformate, pyridine, pyrrolidinopyridine.

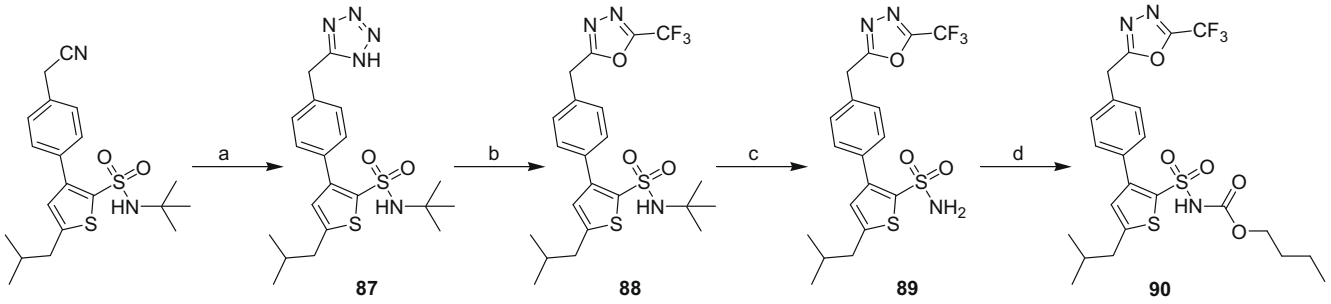


Scheme 6. Reagents: (a) $Pd(PPh_3)_4$, NaOH, toluene, EtOH; (b) CBr_4, PPh_3, DMF; (c) heterocycle, KOH, DMSO (**78**, **79**); (d) 3-thiophene boronic acid, $Pd(PPh_3)_4$, NaOH, toluene, EtOH; (e) BCl_3, CH_2Cl_2 (**81**, **82**); (f) TFA (**83**); (g) *n*-butyl chloroformate, pyridine, pyrrolidinopyridine.

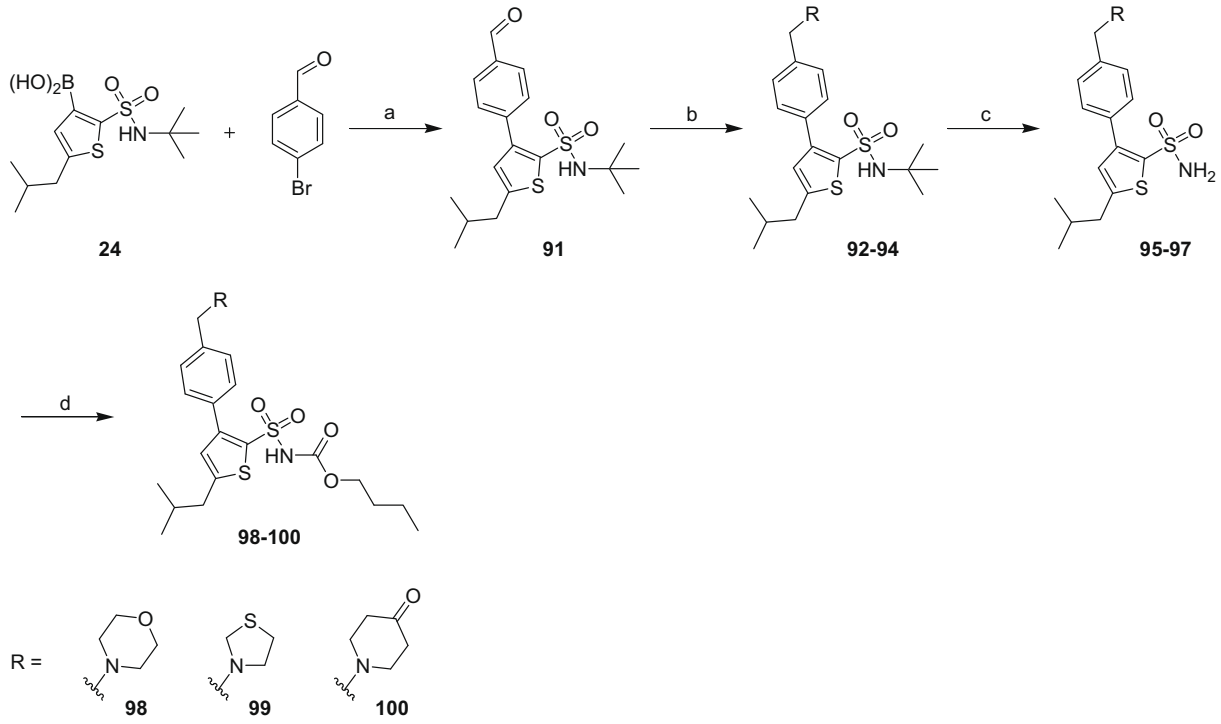
modest yields. Thiophene-2-boronic acid was coupled with 77 via a Suzuki reaction using $Pd(PPh_3)_4$ and NaOH as base. After heating at 80 °C for 3 h, the reaction gave the thiophene compound **80** in high yield. The *tert*-butyl protecting group was then removed and the resulting primary sulfonamides were acylated with *n*-butyl chloroformate, as described above, to deliver the final compounds **84–86**.

For the preparation of trifluoromethyl-[1,3,4]-oxadiazol compound **90**, 3-(4-cyanomethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide[16] was used as starting material (Scheme 7). The nitrile compound was converted to its corresponding tetrazole (**87**) by reacting it with NaN_3 and NH_4Cl under microwave irradiation.[24] After workup the tetrazole compound was then reacted with trifluoroacetic anhydride in excess at 50 °C for 30 min. This gave the trifluoromethyl-[1,3,4]-oxadiazol compound **88** in 30% overall yield. The *tert*-butyl protecting group was then removed and the resulting primary sulfonamide was acylated with *n*-butyl chloroformate, as described above, to deliver the final compound **90**.

In the synthesis of the cyclic amines the aldehyde **91**,[25] synthesized via a Suzuki coupling of the thiopheneboronic acid **24** with 4-bromo-benzaldehyde, was used as common starting material for all the compounds **98–100** (Scheme 8). The cyclic amines were



Scheme 7. Reagents: (a) NaN_3, NH_4Cl, DMF; (b) trifluoroacetic anhydride; (c) TFA; (d) *n*-butyl chloroformate, pyridine, pyrrolidinopyridine.



Scheme 8. Reagents: (a) $(OAc)_2$, $P(Ph)_3$, K_2CO_3, THF/DME/EtOH/H_2O; (b) amine, $NaBH_4$, MeOH; (c) TFA, anisole; (d) *n*-butyl chloroformate, pyrrolidinopyridine, Et_3N, CH_2Cl_2.

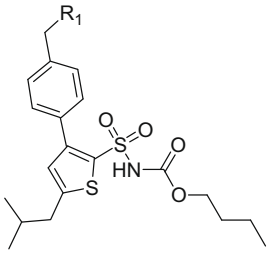
attached via a reductive amination using sodium triacetoxyborohydride as reducing agent, to give the tertiary amines **92–94** in quantitative yields. After a convenient solid/liquid extraction the products were pure enough to use in the next step. The *tert*-butyl protecting group was then removed and the resulting primary sulfonamides were acylated with *n*-butyl chloroformate, as described above, to deliver the final compounds **98–100**.

2.2. Binding assays

Compounds **59–75**, **84–86**, **90**, and **98–100** were evaluated in radioligand-binding assays by displacement of [^{125}I]Ang II from AT_1 receptors in rat liver membranes and from AT_2 receptors in pig uterus membranes as described previously (Tables 1–3).[26,27] The natural substrate Ang II, the selective AT_1 receptor antagonist losartan,[28] and the selective AT_2 receptor antagonist PD 123,319[29] were used as reference substances (Fig. 2).

In the first set of compounds, various nitrogen attached heterocyclic moieties were examined as replacement for the un-substituted imidazole lead structure **1** (K_i AT_2: 0.4 nM, AT_1: >10000 nM). As seen in Table 1, introduction of a methyl group in the 4-position of the imidazole diminish the affinity for the AT_2 receptor 50-fold (**66**). Some activity could be regained by the introduction of a trilfluoromethyl group (**68**). The corresponding pyrazole compound **62** displayed a slight drop in affinity (AT_2: 2.3 nM) but not as pronounced as for the methylation of the imidazole. As was shown with the imidazole, the introduction of a trifluoromethyl substituent decreased the affinity for the pyrazole ring (**67**, AT_2: 9.2 nM). Introduction of more nitrogens to the ring, that is, tetrazole, gave a drop in affinity (**59**, **84**). Interestingly, the affinity for 1*H*-tetrazole was three times higher than the corresponding 2*H*-tetrazole. When the imidazole was replaced with the non-aromatic pyrrolidin-2-one (**60**) the affinity for the AT_2 receptor was decreased slightly, although not as pronounced as for the other modifications. However, the introduction of a second carbonyl to the heterocyclic ring rendered the inactive pyrrolidine-2,5-dione compound (**85**). Modification with a second methylated nitrogen in the ring, that is, 3-methyl-imidazolidin-2-one, lowered the affinity fivefold (**63**). The affinity was even lower when a second carbonyl was incorporated to obtain a methylated hydantoin structure (**64**). Surprisingly, the affinity was improved when two methyl groups were attached to the hydantoin moiety (**65**),

Table 1
AT_1 and AT_2 affinity of compounds with nitrogen attached heterocycles



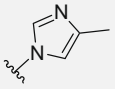
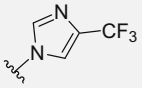
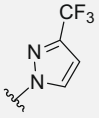
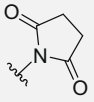
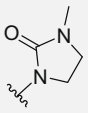
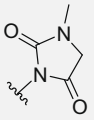
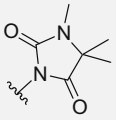
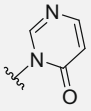
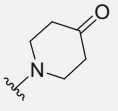
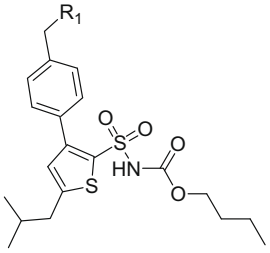
Compound	R_1	K_i[a] (nM)	
		AT_2	AT_1
Losartan		>10000	12.1
PD 123,319		34	>10000
1		0.4	>10000
66		17.6	>10000
68		7.3	>10000
62		2.3	>10000
67		9.5	>10000
59		49	>10000
84		16	>10000
60		3.5	>10000
85		>10000	>10000
63		16.5	>10000
64		68.6	>10000
65		3.6	>10000
61		107.8	>10000
100		16.1	>10000

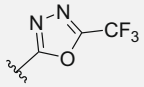
Table 1 (*continued*)

Compound	R_1	K_i[a] (nM)	
		AT_2	AT_1
98		280	>10000
99		280	>10000

[a] K_i values are an average from three determinations. Standard deviations are less than 15% in all cases.

Table 2
AT_1 and AT_2 affinity of compounds with carbon attached heterocycles



Compound	R_1	K_i[a] (nM)	
		AT_2	AT_1
69		3.2	>10000
70		3.9	>10000
86		175	>10000
90		328.3	>10000

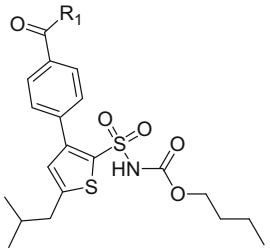
[a] K_i values are an average from three determinations. Standard deviations are less than 15% in all cases.

contrary to the result obtained with the imidazole and pyrazole rings structure. With the 3*H*-pyrimidin-4-one structure (**61**) a significant loss of affinity was observed. This was not the case for the piperidin-4-one compound (**100**), which showed a high affinity for the AT_2 receptor. Exchanging the carbonyl in compound **100** to oxygen led to a drop in affinity (**98**). A similar affinity was also obtained with the thiazolidine moiety (**99**).

In the second set of compounds, the nitrogen attached heterocycles were exchanged with carbon attached heterocycles. As seen in Table 2 both the thiazole and the oxazole showed high affinity (**69**, **70**). When a thiophene was attached the affinity dropt, this was also for the case for the 5-trifluoromethyl-[1,3,4]oxadiazole (**86**, **90**).

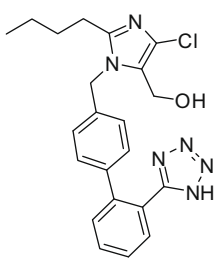
The introduction of a carbonyl group in the benzylic position was surprisingly well accepted by the AT_2 receptor (Table 3). Again the imidazole and the pyrazole compounds were shown to possess the highest affinity. Interestingly, the carbonyl thiophene compound **74** showed a high affinity compared to benzylic attached thiophene (**86**), however the position of the sulfur is not the same for the two compounds.

Table 3
AT_1 and AT_2 affinity of compounds with carbonyl linked heterocycles

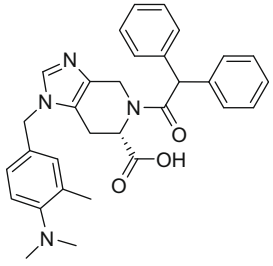


Compound	R_1	K_i[a] (nM)	
		AT_2	AT_1
71		18.6	>10000
72		2.9	>10000
73		13.8	>10000
74		18.8	>10000
75		3.4	>10000

[a] K_i values are an average from three determinations. Standard deviations are less than 15% in all cases.



Losartan
IC_{50} (nM)
AT_1: 12.1
AT_2: >10000
antagonist (AT_1)



PD 123,319
IC_{50} (nM)
AT_1: >10000
AT_2: 34
antagonist (AT_2)

Figure 2. Structure of reference compounds.

2.3. CYP 450 inhibition

CYP450 inhibition assays, the compounds were tested at 10 μM with a spectrofluorometric assay. The fluorescent intensity (*fu*) measured at (t = 0) was subtracted from that measured after the appropriate incubation time (t = final). The percent of control activity was calculated and reported as percent inhibition (Table 4).

The un-substituted imidazole lead structure (**1**) showed a significant inhibition of most of the tested CYP 450, and in the case for the 2C9 and 3A4 the inhibition was very high (Table 4). This strong inhibition could be decreased by introducing substitutes on the imidazole ring (**68**, **62**). By replacing the imidazole with a pyrazole (**62**) almost all of the inhibitory effect was eliminated. In contrast to the imidazole moiety, the inhibitory effect was increased by substituting the pyrazole with a trifluoromethylgroup (**67**). All the non-aromatic moieties (**60**, **63–65**) showed low inhibitory effect with the exception of compound **100** which showed high inhibition of 2C9. The two carbon attached heterocycles (**69**, **70**) were proven to be good inhibitors of 2C9, this was also the case for the carbonyl decorated analogues (**71**, **73**). Surprisingly, the carbonyl methylimidazole compound **72** gave very little inhibition of the CYP 450 enzymes.

2.4. In vitro morphological effects induced by 60 in NG 108-15 cells

To study the effects of compound **60** on AT_2 induced differentiation, NG108-15 cells were used. In their undifferentiated state, neuroblastoma × glioma hybrid NG108-15 cells have a rounded shape and divide actively. We have shown previously that these cells express only the AT_2 receptor[30,31] and that a three-day treatment with Ang II or the selective peptidic AT_2 receptor agonist CGP-42112 induces neurite outgrowth.[31] The mechanisms involve a sustained increase in $p42/p44^{mapk}$ activity[5] and activation of the nitric oxide/guanylyl cyclase/cGMP pathway (for a review see Ref. 11).

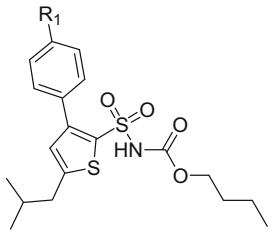
The cells were plated at the same initial density (3.6×10^4 cells /35 mm Petri dish), and were treated in with or without of Ang II, compounds **60**. After three days of culture, cells were examined under a phase contrast microscope and micrographs were taken. The compound **60** were first examined at concentrations ranging from 1 pM to 1 μM. Except for the higher concentration of 1 μM, none of the other doses induced cell death. As shown in Figure 3, treatment for three days with compounds **60** (0.1 nM) induced neurite outgrowth, comparable with Ang II. This effect was mediated through the AT_2 receptor, since co-incubation of **60** with the AT_2 receptor antagonist, PD 123,319,[22] virtually abolished neurite elongation (Fig. 3), while alone, PD 123,319 did not alter the morphology compared to the untreated cells (data not shown).

3. Discussion

Replacement of the imidazole in compound **1** with various substituted and unsubstituted heterocycles rendered analogues with high affinity for the AT_2 receptor. Considering the variety of substituents used in the benzylic position, with a maintained high AT_2 affinity and selectivity, it could be concluded that the AT_2 receptor is very tolerant to modifications in this position. This is in line with our previous results with tertiary amides as replacement for the imidazole.[25] Considering the aromatic substituents, it was interesting to find that the position and number of nitrogens in the heterocycle was shown to have limited effect on the affinity to the AT_2 receptor (Table 1, entries 3, 5, 6). Introduction of substituents on the aromatic rings rendered compounds with decreased affinity compared to the unsubstituted analogs. This trend was also consistent in the non-aromatic heterocycles, with the exception of compound **65** that possessed a higher affinity than its smaller analog **64**. To our surprise, the small unsubstituted compound **99** showed a low affinity for the AT_2 receptor. Regarding the pyrrolidin-2-one compound (**60**), which could be considered as a rigidified version of the previously reported non-cyclic acetylmethylamine analog.[25] As expected, we found that the cyclic version possess a higher affinity to the AT_2 receptor than the non-cyclic analogue.

The mode of attachment to the heterocycles was shown to have limited effect on the affinity for the AT_2 receptor, as seen in carbon attached thiazole and oxazole compounds (**69**, **70**, Table 2), which both showed an affinity in the rage of the initial N-attached imidazole compound (**1**).

Table 4



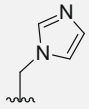
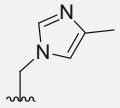
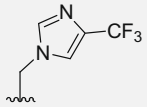
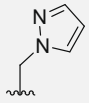
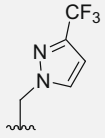
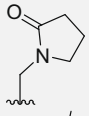
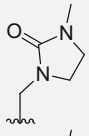
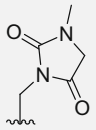
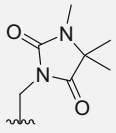
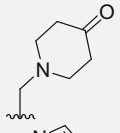
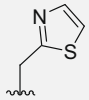
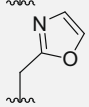
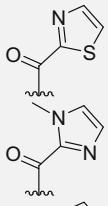
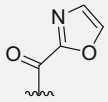
Compound	R_1	CYP 450 Inhibition (% at 10 μM)							
		1A2	2B6	2C9	2C19	2D6	2E1	3A4	3A5
1		63%	40%	94%	67%	41%	–	82%	
66				37%				44%	
68				31%				71%	
62		–	29%	23%	12%	–	–	16%	20%
67				56%				33%	
60		–	33%	24%	25%	–	5%	28%	25%
63				24%				20%	
64				40%				25%	
65				38%				20%	
100				71%				51%	
69				86%				70%	
70				83%				57%	
71				92%				16%	

Table 4 (*continued*)

Compound	R_1	CYP 450 Inhibition (% at 10 μM)							
		1A2	2B6	2C9	2C19	2D6	2E1	3A4	3A5
72		–	31%	38%	6%	–	–	14%	17%
73				75%				36%	

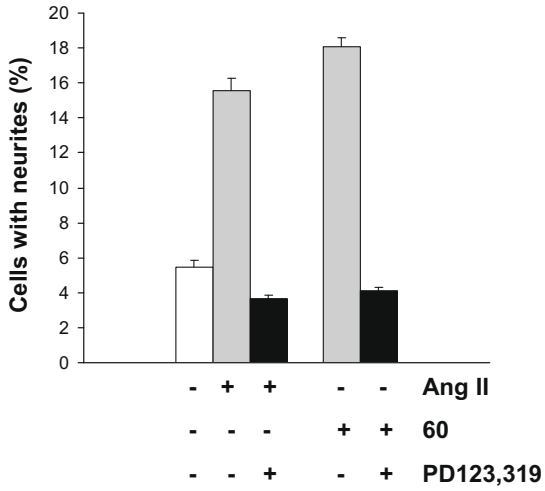


Figure 3. Effect of **60** on neurite outgrowth in NG108-15 cells. NG108-15 cells were plated at a density of 3.6×10^4 cells per dish in 35 mm Petri dishes and were cultured for three days in the absence or in the presence of 100 nM Ang II, compound **60** (0.1 nM), alone or in the presence of 1 μM PD 123,319. Cells with at least one neurite longer than a cell body were counted as positive for neurite outgrowth. The number of cells with neurites represent the percentage of the total number of cells in the micrographs (at least 290 cells according to the experiment).

Introducing a carbonyl to the benzyl carbon lowered the affinity slightly, cf. **69**, **70** versus **71**, **73**, although the carbonyl seems to compensate when only one hetero atom is present in the heterocycle, as seen in the thiophene compound **74** which showed a good affinity for the AT_2 receptor (cf. **86**). Both the N-methylated imidazole (**72**) and the N-methylated pyrrazole (**75**) carbonyl compounds showed higher affinity than its non-carbonyl analogs (**66**, **67**). Whether the positive effect is deduced from the introduction of the carbonyl or the change of methylation position is not fully clear.

The CYP 450 metabolic enzymes are an important system for metabolism of drug substances in the body. Inhibition of these enzymes could lead to reduced metabolism of other drugs that might lead to unwanted side effects or toxicity. Compounds with imidazoles have been shown to inhibit enzymes of the CYP 450 metabolic system.[21] We were therefore interested to determine the inhibitory effect of compound **1** on these enzymes. As we suspected the compound was shown to inhibit the CYP 450 enzymes, especially 2C9 and 3A4 which are the highly important enzymes in drug metabolism. The inhibitory effect was also pronounced in the analogs with unsubstituted aromatic heterocycles. With the exception of the pyrazole compound **62** that showed almost no inhibition. The inhibitory effect of the aromatic heterocycles was reduced by the introduction of methyl substituents (**66–68**), on the other hand the introduction of a carbonyl in the benzylic position seems to have limited effect on the inhibitory effect. For the non-aromatic heterocyclic substituents the inhibitory effect was limited regardless of substituents, with the exception of the piperidin-4-one compound **100** that showed inhibition on both 2C9 and 3A4.

To study the effect of the structural modifications on the agonistic properties, one of the most potent AT_2 ligand with almost no inhibition of the CYP 450 enzymes, compound **60** was selected for further in vitro studies to determine if the compound acted as AT_2 agonist. Our results demonstrate that both compounds induce neurite outgrowth (Fig. 3), one of the first steps of neuronal differentiation, as does Ang II and the AT_2 selective peptide CGP-42112.[31] Hence, structural modifications to overcome the CYP 450 inhibition are possible while maintaining agonistic effect.

4. Conclusion

In summary, we have presented that the imidazole moiety, responsible for the CYP 450 inhibitory effect in initial structure **1**, could be replaced with various heterocycles and thereby minimize the CYP 450 inhibition of this class of compounds. In addition, we demonstrated the mode of attachment can be altered, that is, carbon versus nitrogen attachment, and that carbonyls could be introduced to the benzylic position obtaining compounds with maintained high AT_2 receptor selectivity. In all the three series, AT_2 receptor ligands with affinity in the lower nanomolar range were identified. None of the analogues, regardless of the substituents, exhibited any affinity for the AT_1 receptor. Furthermore, the compound **60** was found to induce neurite elongation in NG 108-15 cells and served as potent AT_2 selective agonist.

5. Experimental section

5.1. Chemistry. General considerations

^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 270.2 and 67.8 MHz, respectively. Chemical shifts are given as δ values (ppm) downfield from tetramethylsilane. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden or Analytische Laboratorien, Lindlar, Germany. Flash column chromatography was performed on Silica Gel 60 (0.04–0.063 mm, E. Merck). Thin-layer chromatography was performed on precoated silica gel F-254 plates (0.25 mm, E. Merck) and was visualized with UV light. Analytical RP-LC/MS was performed on a Gilson HPLC system with a Zorbax SB-C8, 5 μm 4.6×50 mm

(Agilent Technologies) column, with a Finnigan AQA quadrupole mass spectrometer at a flow rate of 1.5 mL/min (H_2O/CH_3CN/0.05% HCOOH). All the organic phases were dried over $MgSO_4$, unless otherwise is stated. All chemicals were purchased from commercial suppliers and used directly without further purification.

5.1.1. 1-(4-Bromo-benzyl)-1*H*-tetrazole (2)

DMSO (10 ml, dried over 4 Å molecular sieve) was added to KOH (1.1 g, 0.020 mol, crushed pellets) and the mixture was stirred for 5 min. 1*H*-tetrazole (0.4 g, 0.005 mol) was then added and the mixture was stirred for 2 h. 4-Bromobenzyl bromide (1.9 g, 0.0075 mol) was added and the mixture was cooled briefly and stirred for a further 1 h before water (50 mL) was added. The mixture was extracted with ether (3 × 80 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified on silica gel with $CHCl_3$/MeOH (40:1) as eluent to get desired product, **2** (0.98 g, 4.1 mmol) in 82% yield. ^{1}H NMR δ ($CDCl_3$): 8.64 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.56 (s, 2H); ^{13}C NMR δ ($CDCl_3$): 142.4, 132.4, 131.8, 129.9, 123.4, 51.3. Anal. Calcd for $C_8H_7BrN_4$: C, 40.2; H, 3.0; N, 23.4. Found: C, 40.3; H, 3.0; N, 23.4.

5.1.2. 1-(4-Bromo-benzyl)-pyrrolidin-2-one (3)

DMSO (20 mL, dried over 4 Å molecular sieve) was added to grinded KOH (2.2 g, 40 mmol) and the mixture was stirred for 5 min. 2-Pyrrolidinone (850 mg, 10.0 mmol) was then added and the mixture was stirred for 2 h. 4-Bromobenzylbromide (5.0 g, 20 mmol) was added and the mixture was cooled briefly and stirred for a further 1 h before water (20 mL) was added. The mixture was extracted with ether (3 × 100 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $CaCl_2$ and the solvent was removed under vacuum. The residue was purified on silica gel with hexane/acetone (2:1) as eluent to obtain the desired product as colorless solids in 64% yield (1.63 g, 6.41 mmol). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.46 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.40 (s, 2H), 3.26 (t, J = 7.1 Hz, 2H), 2.44 (t, J = 7.1 Hz, 2H), 2.00 (qn, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 174, 136.6, 131.7, 129.8, 121.4, 46.5, 45.9, 30.8, 17.7; IR (compression cell): 3405, 3059, 2923, 1678, 1482 cm^{-1}; Anal. Calcd for $C_{11}H_{12}BrNO$: C, 52.0; H, 4.8; N, 5.5. Found: C, 52.0; H, 4.8; N, 5.5.

5.1.3. 3-(4-Bromo-benzyl)-3*H*-pyrimidin-4-one (4)

3*H*-Pyrimidin-4-one (480 mg, 5.00 mmol), 4-bromobenzylbromide (1.29 g, 5.25 mmol) and KO*t*-Bu (617 mg, 5.50 mmol) were mixed in DMSO (20 mL, dried over 4 Å molecular sieve). The reaction mixture was stirred for 1 h at room temperature before water (50 mL) was added. The mixture was extracted with ether (3 × 50 mL) and the combined organic phase was washed with water (3 × 50 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuum. The residue was purified by column chromatography using hexane/acetone (4:1) as eluent to give **4** (976 mg, 3.68 mmol) in 78% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.16 (s, 1H), 7.86 (d, J = 5.9 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.45 (d, J = 6.4 Hz, 1H), 5.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 160.6, 153.1, 150.9, 133.9, 132.1, 129.7, 122.5, 116.1, 49.2; IR (compression cell): 3051, 3001, 2962, 1670, 1587 cm^{-1}; Anal. Calcd for $C_{11}H_9BrN_2O$: C, 49.8; H, 3.4; N, 10.6. Found: C, 49.9; H, 3.4; N, 10.5.

5.1.4. 1-(4-Bromo-benzyl)-1*H*-pyrazole (5)

To a solution of pyrazole (0.50 g, 7.3 mmol) in THF (10 mL) at 10 °C was added KO-*t*Bu (0.99 g, 8.8 mmol) and the solution was stirred for 30 min at room temperature. The solution was cooled to 0 °C and 4-bromo-benzylbromide (2.2 g, 8.8 mmol) dissolved in THF (5 mL) was added slowly to the reaction mixture. The mixture was stirred for 1 h at room temperature before water (50 mL) was added. The mixture was extracted with EtOAc and each extract was washed with water. The combined ether layers were dried over $MgSO_4$ and the solvent was removed in vacuum. The residue was purified on silica gel with pet.ether/acetone (6:1) as eluent to obtain **5** (1.4 g) in 82% yield. ^{1}H NMR δ ($CDCl_3$): 7.52 (d, J = 1.7 Hz, 1H), 7.42 (m, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.05 (m, 2H), 6.26 (t, J = 2.0 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR δ ($CDCl_3$): 139.7, 135.6, 131.8, 129.1, 121.9, 106.1, 55.1. Anal. Calcd for $C_{10}H_9BrN_2$: C, 50.7; H, 3.8; N, 11.8. Found: C, 50.6; H, 3.8; N, 11.9.

5.1.5. 1-(4-Bromo-benzyl)-3-methyl-imidazolidin-2-one (6)

KO-*t*Bu (0.282 g, 2.51 mmol) was added to a stirred solution of 1-methylimidazolidone (0.21 g, 2.1 mmol) in THF (5 mL) at room temperature and after 30 min. 4-bromobenzylbromide (0.63 g, 2.51 mmol) in THF (3 mL) was added slowly and stirred the mixture for 3 h. Reaction mixture was quenched with NH_4Cl (satd aq) and extracted with ethyl acetate (3 × 5 mL). Combined organic phase was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography using acetone/pet.ether (1:4) to afford **6** (0.493 g, 1.83 mmol) in 87% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.43 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.30 (s, 2H), 3.27 (m, 2H), 3.13 (m, 2H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 161.3, 136.3, 131.6, 129.8, 121.2; IR (compression cell): 2981, 2934, 1701, 1450, 1156 cm^{-1}. Anal. Calcd for $C_{11}H_{13}BrN_2O$: C, 49.1; H, 4.9; N, 10.4. Found: C, 49.4; H, 4.8; N, 10.8.

5.1.6. 3-(4-Bromo-benzyl)-1-methyl-imidazolidine-2,4-dione (7)

KO-*t*Bu (0.27 g, 2.4 mmol) was added to a stirred solution of 1-methylhydantoin (0.25 g, 2.2 mmol) in THF (5 mL) at rt and after 30 min. 4-bromobenzylbromide (0.575 g, 2.30 mmol) in THF (3 mL) was added slowly and stirred the mixture at 50 °C for 6 h. Reaction mixture was quenched with NH_4Cl (satd aq) and extracted with ethyl acetate (3 × 5 mL). Combined organic phase was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography using acetone/pet.ether (1:3) to afford **7** (0.354 g, 1.25 mmol) in 57% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.40 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 4.55 (s, 2H), 3.82 (m, 2H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 169.3, 155.7, 134.9, 131.7, 130.5, 122.0, 51.6, 41.9, 29.6; IR (compression cell): 2987, 2956, 1738, 1705, 1450, 1131 cm^{-1}. Anal. Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.7; H, 3.9; N, 9.9. Found: C, 46.6; H, 3.8; N, 9.8.

5.1.7. 1-(4-Bromo-benzyl)-3,4,4-trimethyl-imidazolidine-2,5-dione (8)

KO-*t*Bu (0.237 g, 2.11 mmol) was added to a stirred solution of 1,5,5-trimethylhydantoin (0.25 g, 1.8 mmol) in THF (5 mL) at room temperature and after 30 min. 4-Bromobenzylbromide (0.483 g, 1.93 mmol) in THF (3 mL) was added slowly and stirred the mixture at 50 °C for 6 h. Reaction mixture was quenched with NH_4Cl (satd aq) and extracted with ethyl acetate (3 × 5 mL). Combined organic phase was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography using acetone/pet.ether (1:3) to afford **8** (0.218 g, 0.701 mmol) in 40% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.24 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 4.41 (s, 2H), 2.69 (s, 3H), 1.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 138.7, 131.7, 130.0, 129.0, 128.3, 105.9, 105.6, 54.8, 52.2, 13.5, 11.0; IR (compression cell): 2981, 2934, 1761, 1714, 1450, 1133 cm^{-1}. Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.2; H, 4.9; N, 9.0. Found: C, 50.3; H, 4.7; N, 9.1.

5.1.8. 1-(4-Bromo-benzyl)-4-methyl-1*H*-imidazole (9)

DMSO (20 mL) (dried over 4 Å molecular sieve) was added to KOH (2.24 g, 0.040 mol, crushed to powders) and the mixture was stirred for 5 min. 4-Methylimidazole (0.82 g, 0.010 mol) was then added and the mixture was stirred for 2 h. 4-Bromo benzyl bromide (5 g, 0.02 mol) was added and the mixture was cooled briefly and stirred for a further 1 h before water (20 mL) was added. The mixture was extracted with ether (3 × 100 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $CaCl_2$ and the solvent was removed under vacuum. The crude product was purified by flash chromatography using hexane/acetone (1:1) to afford **9** (1.89 g, 7.53 mmol) in 75% yield. ^{1}H NMR δ ($CDCl_3$): 7.91 (1H, s), 7.51 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.63 (s, 1H), 5.06 (s, 2H), 2.24 (s, 3H); ^{13}C NMR δ ($CDCl_3$): 136.9, 136.3, 134.7, 132.9, 129.9, 123,4, 116.8, 51.4, 12.8. IR (compression cell): 3109.9, 2923, 1711, 1490, 1445, 1407 cm^{-1}. Anal. Calcd for $C_{11}H_{11}BrN_2 \times 1/3HCOOH$: C, 51.1; H, 4.4; N, 10.5. Found: C, 51.0; H, 4.3; N, 10.6.

5.1.9. 1-(4-Bromo-benzyl)-3-trifluoromethyl-1*H*-pyrazole (10)

3-(Trifluoromethyl)pyrazole (567 mg, 4.17 mmol), 4-bromobenzylbromide (1.09 g, 4.38 mmol) and of KO-*t*Bu (515 mg, 4.59 mmol) were mixed in DMSO (20 mL, dried over 4 Å molecular sieve). The mixture was stirred for 1 h at room temperature before water (50 mL) was added. The mixture was extracted with ether (3 × 50 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $MgSO_4$ and the solvent was removed in vacuum. The residue was purified on silica gel with hexane/acetone (10:1) as eluent to obtain **10** (1.17 g, 3.83 mmol) as colorless solids, yield: 91%. ^{1}H NMR δ ($CDCl_3$): 7.42 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 6.53 (s, 1H), 5.26 (s, 2H); ^{13}C NMR δ ($CDCl_3$): 142.8, 142.2, 134.3, 131.9, 130.6, 129.3, 122.4, 104.9, 55.7; IR (compression cell): 3061, 2980, 2946, 1627, 1494 cm^{-1}. Anal. Calcd for $C_{11}H_8BrF_3N_2$: C, 43.3; H, 2.6; N, 9.2. Found: C, 43.6; H, 2.9; N, 9.2.

5.1.10. 1-(4-Bromo-benzyl)-4-trifluoromethyl-1*H*-imidazole (11)

4-(Trifluoromethyl)imidazole (272 mg, 2.01 mmol),[32] 4-bromobenzylbromide (525 mg, 2.12 mmol) and of KO-*t*Bu (247 mg, 2.21 mmol) were mixed in DMSO (20 mL, dried over 4 Å molecular sieve). The mixture was stirred for 2 h at room temperature before water (50 mL) was added. The mixture was extracted with ether (3 × 50 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $MgSO_4$ and the solvent was removed in vacuum. The residue was purified on silica gel with hexane/acetone (5:1) as eluent to obtain **11** (412 mg, 1.35 mmol) as colorless solids, yield: 68%. ^{1}H NMR δ ($CDCl_3$): 7.56 (s, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.20 (s, 1H), 7.07 (d, J = 8.3 Hz, 2H), 5.08 (s, 2H); ^{13}C NMR δ ($CDCl_3$): 138.1, 133.7, 132.6(m), 132.3, 132.2, 129.1, 122.8, 119.0; IR (compression cell): 3110, 2946, 1574, 1489 cm^{-1}. Anal. Calcd for $C_{11}H_8BrF_3N_2$: C, 43.3; H, 2.6; N, 9.2. Found: C, 43.5; H, 2.6; N, 9.0.

5.1.11. 2-(4-Bromo-benzyl)-thiazole (12)

4-Bromobenzylbromide (150 mg, 0.601 mmol), 2-tributylstannanyl-thiazole (337 mg, 0.912 mmol), ethyl-diisopropyl-amine (160 μL), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and DMF (2 mL) were mixed and heated to 80 °C for 6 h. After cooling to room temperature water (50 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with water and brine and dried over $MgSO_4$. After removing the solvents, the residues was purified by column chromatography using hexane/EtOAc (5:1) as eluent to give **12** (46.7 mg, 0.18 mmol) in 31% yield. ^{1}H NMR δ ($CDCl_3$): 7.72 (d, J = 3.3 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 3.3 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 4.30 (s, 2H); ^{13}C NMR δ ($CDCl_3$): 169.5, 143.9, 142.4, 136.7, 131.9, 130.7, 121.1, 120.9, 119.2, 38.7; IR (compression cell): 3115, 3079, 2913, 1487, 1424 cm^{-1}. Anal. Calcd for $C_{10}H_8BrNS$: C, 47.3; H, 3.2; N, 5.5. Found: C, 47.1; H, 3.3; N, 5.5.

5.1.12. 2-(4-Bromobenzyl)-oxazole (13)

A mixture of 4-bromobenzeneacetamide (0.5 g, 2.3 mmol) and vinylene carbonate (241 mg, 2.80 mmol) in polyphosphoric acid (1.5 g) was heated at 170 °C for 3 h. The residue was added into water (25 mL) and extracted with ethyl acetate (3 × 10 mL). Combined organic extracts were washed with water, brine, dried and evaporated. The residue was purified by column chromatography using pet.ether/ethyl acetate (4:1) as eluent to give **13** (165 mg, 0.693 mmol, yield: 30%). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.54 (s, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.01(s, 1H), 4.04 (s, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 162.5, 138.8, 134.2, 131.7, 130.4, 127.1, 121.0, 33.9; IR (compression cell): 2356, 1571, 1489 cm^{-1}. Anal. Calcd for $C_{10}H_8BrNO$: C, 50.5; H, 3.4; N, 5.9. Found: C, 50.7; H, 3.5; N, 5.7.

5.1.13. (4-Bromophenyl)-thiazol-2-yl-methanol (14)

n-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) was slowly added to a cooled (−78 °C) solution of 2-bromothiazole (500 mg, 3.05 mmol) in THF (7 mL) and stirred for 15 min at the same temperature, then slowly warmed to −20 °C and stirred for 1 h. The mixture was cooled back to −78 °C and added 4-bromobenzaldehyde (0.564 g, 3.05 mmol) in THF (3 mL), after addition, temperature of the reaction mixture was slowly raised to room temperature and stirred about 3 h. Reaction was quenched with NH_4Cl (satd aq) and diluted with ether (30 mL), the separated aqueous layer was extracted with ether (10 mL). Combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography using acetone/pet.ether (1:4) to give **14**[33] (220 mg, 0.814 mmol) in 27% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.69 (d, J = 3.3 Hz, 1H), 7.49 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 3.3 Hz, 1H), 6.02 (s, 1H), 3.61 (br s, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 142.2, 140.2, 131.8, 128.2, 122.5, 119.8, 73.1

5.1.14. (4-Bromophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanol (15)

n-BuLi (1.6 M in hexane, 4.77 mL, 6.99 mmol) was slowly added to a cooled (−78 °C) solution of 1-methyl-1-*H*-imidazole (574 mg, 6.99 mmol) in THF (10 mL) and stirred for 15 min at the same temperature, then slowly warmed to −20 °C and stirred for 1 h. Mixture was cooled to −78 °C and added 4-bromobenzaldehyde (1.293 g, 6.99 mmol) in THF (4 mL), after addition, temperature was slowly raised to room temperature and stirred about 3 h. Reaction was quenched with NH_4Cl (satd aq) and diluted with ether (30 mL), the separated aqueous layer was extracted with ether (10 mL). Combined organic layer was washed with brine and dried over $MgSO_4$. When the solvent was slowly evaporated under low temperature, solids separated was filtered while minimum amount of solvent were left and dried under vacuum to give **15**[33] (1.23 g, 4.60 mmol) in 66% yield.^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.36 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.78 (s, 1H), 6.71 (s, 1H), 5.81 (s, 1H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 148.2, 139.5, 131.2, 127.4, 125.9, 122.3, 121.2, 68.1, 33.1; IR (compression cell): 3113, 2839, 1487, 1070, 1010 cm^{-1}.

5.1.15. (4-Bromophenyl)-oxazol-2-yl-methanol (16)

To a solution of oxazole (96 mg, 1.4 mmol) in THF (5 mL) at room temperature under N_2 was added BH_3–THF (1 M in THF, 1.5 mL, 1.50 mmol). After 30 min, the solution was cooled to −78 °C, and *n*-BuLi (1.6 M in hexane, 0.94 mL, 1.5 mmol) was added dropwise. After 30 min, 4-bromobenzaldehyde (265 mg,

1.43 mmol) in THF (3 mL) was added. The mixture was stirred for 1 h and HOAc (5% in ethanol, 3.4 mL) was added, the temperature of the reaction was raised room temperature and stirred for 24 h. The mixture was partitioned between ether (20 mL) and $NaHCO_3$ (5% aq, 20 mL). The organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and purified by flash chromatography using acetone/pet.ether (1:4) as eluent to give **16** (40 mg, 0.16 mmol) in 11% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.62 (s, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.12 (s, 1H), 5.93 (s, 1H), 5.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 139.7, 137.6, 131.8, 128.3, 125.9, 122.6, 69.1. Anal. Calcd for $C_{10}H_8BrNO_2$: C, 47.3; H, 3.2; N, 5.5. Found: C, 47.4; H, 3.3; N, 5.6.

5.1.16. (4-Bromo-phenyl)-thiophen-2-yl-methanol (17)

n-BuLi (1.6 M in hexane, 1.78 mL, 2.85 mmol) was slowly added to a cooled (−78 °C) solution of thiophene (0.2 g, 2.37 mmol) in THF (5 mL) and stirred for 15 min at the same temperature, then slowly warmed to −20 °C and stirred for 1 h. Mixture was cooled to −78 °C and added 4-bromobenzaldehyde (0.439 g, 2.37 mmol) in THF (4 mL), after addition temperature was slowly raised to room temperature and stirred about 2 h. Reaction was quenched with NH_4Cl (satd aq) and diluted with ether (20 mL), the separated aqueous layer was extracted with ether (10 mL). Combined organic layer was washed with brine and dried over $MgSO_4$. Solvents were evaporated under low temperature and the crude product was purified by flash chromatography using acetone/pet.ether as eluent to afford **17**[34] (0.53 g, 1.97 mmol) in 83% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.47 (d, J = 8.3 Hz, 2H), 7.31–7.22 (m, 3H), 6.93 (m, 1H), 6.86 (s, 1H), 5.98 (d, J = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 147.4, 141.9, 131.5, 127.9, 126.7, 125.7, 125.0, 121.8, 71.6; IR (compression cell): 3283, 2889, 2292, 1898, 1591, 1488, 1229 cm^{-1}.

5.1.17. (4-Bromo-phenyl)-(2-methyl-2*H*-pyrazol-3-yl)-methanol (18)

n-BuLi (1.6 M in hexane, 1.83 mL, 2.92 mmol) was slowly added to a cooled (−78 °C) solution of 1-methylpyrazole (0.20 g, 2.4 mmol) in THF (5 mL) and stirred for 15 min. at the same temperature, then slowly warmed to −20 °C and stirred for 1 h. Mixture was cooled to −78 °C and added 4-bromobenzaldehyde (0.45 g, 2.4 mmol) in THF (4 mL), after addition temperature was slowly raised to room temperature and stirred about 2 h. Reaction was quenched with NH_4Cl (satd aq) and diluted with ether (20 mL), the separated aqueous layer was extracted with ether (10 mL). Combined organic layer was washed with brine and dried over $MgSO_4$. Solvents were evaporated under low temperature and the crude product was purified by flash chromatography using acetone/pet.ether as eluent to afford **18**[33] (0.45 g, 1.7 mmol) in 69% yield.^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.50 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.04 (d, J = 2.0 Hz, 1H), 5.88 (s, 1H), 3.79 (s, 3H), 2.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 144.1, 139.3, 131.7, 128.0, 122.2, 106.1, 77.1, 67.6, 37.1; IR (compression cell): 3220, 2943, 2353, 1487, 1396, 1201 cm^{-1}.

5.1.18. (4-Bromophenyl)-thiazol-2-yl-methanone (19)

Pyridiniumchlorochromate (PCC) (180 mg, 0.844 mmol) was added to a stirred solution of **14** (152 mg, 0.563 mmol) in CH_2Cl_2 (5 mL) at ambient temperature and stirred for 30 min. Solvent was evaporated and residue was passed through silica-gel column using dimethylether as eluting solvent to give the **19**[35] (120 mg, 0.448 mmol) in 80% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.38 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 3.0 Hz, 1H), 7.73 (d, J = 3.0 Hz, 1H), 7.65 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 144.8, 133.9, 132.5, 131.6, 129.0, 126.5. Anal. Calcd for $C_{10}H_6BrNOS$: C, 44.8; H, 2.3; N, 5.2. Found: C, 45.1; H, 2.4; N, 4.9.

5.1.19. (4-Bromophenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanone (20)

PCC (242 mg, 1.12 mmol) was added to a stirred solution of **15** (200 mg, 0.748 mmol) in CH_2Cl_2 (5 mL) at ambient temperature and stirred for 30 min. Solvent was evaporated and residue was passed through silica-gel column using ether as eluent to give **20** (174 mg, 0.656 mmol) in 88% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.15 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.20 (s, 1H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 135.9, 132.3, 131.3, 129.2, 127.9, 127.0, 36.5; IR (compression cell): 2345, 1762, 1649, 1404 cm^{-1}. Anal. Calcd for $C_{11}H_9BrN_2O$: C, 49.8; H, 3.4; N, 10.6. Found: C, 49.5; H, 3.6; N, 10.9.

5.1.20. (4-Bromophenyl)-oxazol-2-yl-methanone (21)

PCC (51.0 mg, 0.236 mmol) was added to a stirred solution of **16** (40.0 g, 0.157 mmol) in CH_2Cl_2 (5 mL) at ambient temperature and stirred for 30 min. Solvent was evaporated and residue was passed through silica-gel column using ether as eluent to give **21** (34 mg, 0.13 mmol) in 87% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.39 (d, J = 8.6 Hz, 2H), 7.92 (s, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 157.4, 141.7, 133.5, 132.3, 131.8, 129.6, 129.1; IR (compression cell): 3132, 1661, 1583, 1473 cm^{-1}. Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.7; H, 2.4; N, 5.6. Found: C, 47.8; H, 2.6; N, 5.4.

5.1.21. (4-Bromo-phenyl)-thiophen-2-yl-methanone (22)

PCC (0.3 g, 1.39 mmol) was added to a stirred solution of **17** (0.25 g, 0.93 mmol) in CH_2Cl_2 (10 mL) at ambient temperature and stirred for 30 min. Solvent was evaporated and residue was passed through silica-gel column using ether as eluting solvent to give **22**[36] (0.198 g, 0.741 mmol) in 80% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.70–7.75 (m, 3H), 7.65–7.59 (m, 3H), 7.17–7.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 187.0, 143.1, 136.8, 134.7, 134.5, 131.6, 130.6, 128.0, 127.2; IR (compression cell): 3087, 1634, 1620, 1565, 1393 cm^{-1}.

5.1.22. (4-Bromo-phenyl)-(2-methyl-2*H*-pyrazol-3-yl)-methanone (23)

PCC (0.24 g, 1.12 mmol) was added to a stirred solution of **18** (0.20 g, 0.75 mmol) in CH_2Cl_2 (5 mL) at ambient temperature and stirred for 30 min. Solvent was evaporated and residue was passed through silica-gel column using ether as eluting solvent to give **23** (0.166 g, 0.626 mmol) in 84% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.73 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 4.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 184.6, 137.6, 137.4, 136.7, 130.8, 130.3, 128.0, 113.4, 39.7; IR (compression cell): 3125, 2954, 1644, 1582, 1395 cm^{-1}. Anal. Calcd for $C_{11}H_9BrN_2O$: C, 49.8; H, 3.4; N, 10.6. Found: C, 50.1; H, 3.7; N, 10.9.

5.1.23. 5-*iso*-Butyl-*N*-*tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)-thiophene-2-sulfonamide (25)

Compound **24** (401 mg, 1.26 mmol), **2** (199 mg, 0.834 mmol), toluene (20 mL), ethanol (3.0 mL), NaOH (1.0 M, 5.0 mL, 5.0 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.25 mmol) was mixed under N_2. The mixture was warmed to reflux for 2 h. The mixture was diluted with EtOAc (20 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by column chromatography with $CHCl_3$/MeOH (40:1) as an eluent to give **25** (222 mg, 0.513 mmol) in 62% yield. IR (compression cell): 3284, 3134, 2958, 2870, 1513, 1436 cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 8.71 (s, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 6.74 (s, 1H), 5.65 (s, 2H), 2.67 (d, J = 7.1 Hz, 2H), 1.94 (m, 1H), 0.99 (m,

15H). ^{13}C NMR δ ($CDCl_3$): 148.5, 142.6, 142.2, 136.8, 135.9, 133.1, 129.9, 128.8, 128.3, 54.6, 51.7, 39.2, 30.5, 29.5, 22.1; Anal. Calcd for $C_{20}H_{27}N_5O_2S_2$: C, 55.4; H, 6.3; N, 16.2. Found: C, 55.9; H, 6.4; N, 15.9.

5.1.24. 3-[4-(2-Oxo-pyrrolidin-1-yl-methyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (26)

Compound **24** (200 mg, 0.626 mmol), **3** (106 mg, 0.418 mmol), toluene (20 mL), ethanol (1.5 mL), NaOH (2.5 mL, 1.0 M, 2.5 mmol) and $Pd(PPh_3)_4$ (15 mg, 13 μmol) was mixed under N_2. The mixture was warmed to reflux for 2 h. The mixture was diluted with EtOAc (50 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using hexane/acetone (2:1) as eluent to give **26** (157 mg, 0.350 mmol) in 84% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.60 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.74 (s, 1H), 4.50 (s, 2H), 3.31 (t, J = 7.3 Hz, 2H), 2.69 (d, J = 7.1 Hz, 2H), 2.50 (t, J = 8.4 Hz, 2H), 2.05 (m, 2H), 1.91 (m, 1H), 0.98 (s, 9H), 0.96 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 175.2, 148.4, 142.6, 136.8, 134.3, 132.2, 129.4, 128.9, 128.1, 54.5, 46.8, 46.3, 39.1, 30.8, 30.5, 29.4, 22.1, 17.7; IR (compression cell): 3281, 2955, 1686, 1465 cm^{-1}; Anal. Calcd for $C_{23}H_{32}N_2O_3S_2$: C, 61.6; H, 7.2; N, 6.2. Found: C, 61.7; H, 7.1; N, 6.0.

5.1.25. 3-[4-(6-Oxo-6*H*-pyrimidin-1-ylmethyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (27)

Compound **24** (200 mg, 0.646 mmol), **4** (111 mg, 0.418 mmol), $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), NaOH (2.5 mL, 1 M, 2.5 mmol), toluene (20 mL) and ethanol (1.5 mL) was mixed under N_2. The mixture was warmed to reflux for 2 h. The mixture was diluted with EtOAc (150 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using hexane/EtOAc (5:1) as eluent to give **27** (73.1 mg, 0.159 mmol) in 31% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.55 (s, 1H), 7.90 (m, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.72 (s, 1H), 6.51 (d, J = 6.6 Hz, 1H), 5.19 (s, 2H), 2.67 (d, J = 7.1 Hz, 2H), 1.91 (m, 2H), 0.98 (s, 9H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 160.0, 151.5, 150.8, 148.6, 142.3, 136.7, 135.4, 134.7, 129.8, 129.4, 128.8, 128.4, 116.2, 54.6, 50.0, 39.1, 30.5, 29.5, 22.1; IR (compression cell): 3134, 2959, 2870, 1685 cm^{-1}; Anal. Calcd for $C_{23}H_{29}N_3O_3S_2$: C, 60.1; H, 6.4; N, 9.1. Found: C, 60.0; H, 6.4; N, 8.7.

5.1.26. 3-(4-Pyrazole-1-ylmethyl-phenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (28)

Compound **24** (438 mg, 1.370 mmol), **5** (250 mg, 1.054 mmol), toluene (10 mL), ethanol (3 mL), NaOH (4.2 mL, 1.0 M) and $Pd(PPh_3)_4$ (37 mg, 0.031 mmol) was mixed under N_2. The mixture was warmed to reflux for 2 h at 100 °C. The mixture was diluted with H_2O (50 mL), extracted with EtOAc (3 × 50 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by flash c.c. with petroleum ether/acetone (3:1) as an eluent to give **28** (251 mg, 0.581 mmol) in 55% yield. ^{1}H NMR δ ($CDCl_3$): 7.53 (m, 3H), 7.40 (m, 1H), 7.25 (m, 2H), 6.70 (s, 1H), 6.27 (t, J = 2.3 Hz, 1H), 5.34 (s, 2H), 4.11 (s, 1H), 2.63 (m, 2H), 1.88 (m, 1H), 0.93 (m, 15H); ^{13}C NMR δ ($CDCl_3$): 148.3, 142.5, 139.6, 137.0, 134.6, 129.4, 129.2, 128.7, 127.6, 106.1, 55.4, 54.4, 39.1, 30.4, 29.4, 22.1; IR (compression cell): 3313, 3095, 2957, 2868, 1731, 1613, 1514, 1466 cm^{-1}. Anal. Calcd for $C_{22}H_{29}N_3O_2S_2$: C, 61.2; H, 6.8; N, 9.7. Found: C, 61.1.4; H, 6.8; N, 9.7.

5.1.27. 3-[4-(3-Methyl-2-oxoimidazolidin-1-yl-methyl)-phenyl]-5-*iso*-butyl-N-*tert*-butylthiophene-2-sulfonamide (29)

Compound **24** (0.444 g, 1.39 mmol), **6** (0.25 g, 0.93 mmol), toluene (3.5 mL), ethanol (1 mL) and NaOH (1.0 M, 1.5 mL, 3.70 mmol), $Pd(PPh_3)_4$ (0.032 g, 0.026 mmol) were mixed under N_2. The mixture was heated at 100 °C for 6 h and then diluted with EtOAc (20 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone (2:1) as an eluent to give **29** (255 mg, 0.550 mmol) in 59% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.56 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 6.73 (s, 1H), 4.39 (s, 2H), 4.16 (s, 1H), 3.27 (m, 2H), 3.17 (m, 2H), 2.82 (s, 3H), 2.66 (d, J = 6.9 Hz, 2H), 1.90 (m, 1H), 0.95 (m, 15H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 161.4, 148.2, 142.7, 137.7, 136.2, 133.9, 129.1, 128.8, 128.1, 54.4, 48.1, 44.9, 42.1, 39.1, 31.4, 30.4, 29.3, 22.1; IR (compression cell): 3302, 3049, 2869, 1700, 1512 cm^{-1}, Anal. Calcd for $C_{23}H_{33}N_3O_3S_2$: C, 59.6; H, 7.2; N, 9.1. Found: C, 59.7; H, 7.1; N, 9.0.

5.1.28. 3-[4-(3-Methyl-2,5-dioxo-imidazolidin-1-yl-methyl)-phenyl]-5-*iso*-butyl-N-*tert*-butyl-thiophene-2-sulfonamide (30)

Compound **24** (0.147 g, 0.459 mmol), **7** (0.10 g, 0.35 mmol), CsF (0.139 g, 0.918 mmol) and DME (5 mL), $Pd(PPh_3)_4$ (0.012 g, 0.01 mmol) were mixed under N_2. The mixture was heated at 100 °C for 2 h and then diluted with EtOAc (15 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as an eluent to give **30** (129 mg, 0.270 mmol) in 76% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.54 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 6.71 (s, 1H), 4.68 (s, 2H), 4.08 (s, 1H), 3.88 (s, 2H), 3.00 (s, 3H), 2.66 (d, J = 6.6 Hz, 2H), 1.90 (m, 1H), 0.96 (s, 9H), 0.93 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 169.3, 156.4, 148.3, 142.6, 136.3, 134.5, 129.2, 128.8, 128.5, 54.4, 51.7, 42.1, 39.1, 30.4, 29.6, 29.4, 22.1; IR (compression cell): 3272, 2981, 1756, 1712, 1442, 1142 cm^{-1}; Anal. Calcd for $C_{23}H_{31}N_3O_4S_2$: C, 57.8; H, 6.5; N, 8.8. Found: C, 57.9; H, 6.4; N, 9.0.

5.1.29. 3-[4-(3,4,4-Trimethyl-2,5-dioxo-imidazolidin-1-yl-methyl)-phenyl]-5-*iso*-butyl-*tert*-butyl-thiophene-2-sulfonamide (31)

Compound **24** (0.16 g, 0.50 mmol), **8** (0.12 g, 0.39 mmol), CsF (0.152 g, 1.00 mmol) and DME (5 mL), $Pd(PPh_3)_4$ (0.017 g, 0.015 mmol) were mixed under N_2. The mixture was heated at 100 °C for 3 h and then diluted with EtOAc (15 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as an eluent to give **31** (132 mg, 0.261 mmol) in 68% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.53 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 6.70 (s, 1H), 4.66 (s, 2H), 4.03 (s, 1H), 2.86 (s, 3H), 2.64 (d, J = 6.6 Hz, 2H), 1.88 (m, 1H), 1.34 (s, 6H), 0.94 (d, J = 6.9 Hz, 6H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 176.3, 155.1, 148.3, 142.5, 136.6, 134.4, 129.2, 128.7, 128.2, 61.2, 54.4, 41.8, 39.1, 30.4, 29.4, 24.4, 22.1, 22.0; IR (compression cell): 3317, 2973, 1765, 1708, 1442, 1136 cm^{-1}. Anal. Calcd for $C_{25}H_{35}N_3O_4S_2$: C, 59.4; H, 7.0; N, 8.3. Found: C, 59.6; H, 8.4; N, 8.4.

5.1.30. 3-[4-(4-Methyl-imidazole-1-ylmethyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (32)

Compound **24** (401 mg, 0.628 mmol), **9** (210 mg, 0.836 mmol), toluene (20 mL), ethanol (3 mL), NaOH (5 mL, 1.0 M) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) was mixed under N_2. The mixture was warmed to reflux for 2 h at 100 °C. The reaction mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was purified on LC/MS to give **32** (211 mg, 0.473 mmol) in 57% yield. ^{1}H NMR δ (10%CD_3OD in $CDCl_3$): 7.68 (s, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.76 (s, 1H), 6.70 (s, 1H), 5.14 (s, 2H), 2.70 (d, J = 6.4 Hz, 2H), 2.21 (s, 3H), 1.92 (m, 1H), 1.01 (s, 9H), 0.97 (d, J = 6.7 Hz, 6H); ^{13}C NMR δ ($CDCl_3$): 148.6, 142.8, 137.4, 136.6, 136.0, 135.2, 129.9, 129.2, 127.7, 116.3, 54.3, 50.9, 39.3, 30.7,

29.5, 22.2, 12.8; IR (compression cell): 3060, 2996, 2870, 1512, 1444, 1392 cm^{-1}. Anal. Calcd for $C_{23}H_{31}N_3O_2S_2$: C, 61.99; H, 7.01; N, 9.43. Found: C, 62.0; H, 7.0; N, 9.4.

5.1.31. 3-[4-(3-Trifluoromethyl-1*H*-pyrazole-1-ylmethyl)-phenyl] -5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (33)

Compound **24** (200 mg, 0.314 mmol), **10** (128 mg, 0.418 mmol), toluene (20 mL), ethanol (1.5 mL), NaOH (2.5 mL, 1.0 M) and $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) was mixed under N_2. The mixture was reflux for 2 h at 100 °C. The reaction mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by flash c.c. with hexane/acetone (5:1) as an eluent to give **33** (131 mg, 0.262 mmol) in 63% yield. ^1H NMR δ ($CDCl_3$): 7.60 (d, J = 8.1 Hz, 2H), 7.45 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 6.74 (s, 1H), 6.55 (d, J = 2.3 Hz, 1H), 5.38 (s, 2H), 2.68 (d, J = 7.1 Hz, 2H), 1.95 (m, 1H), 0.98 (s, 9H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR δ ($CDCl_3$): 148.6, 142.3, 136.7, 135.6, 135.2,130.6, 129.7, 128.8, 127.9, 105.0, 56.3, 54.6, 39.2, 30.5, 29.4, 22.1; IR (compression cell): 3289, 3104, 1495, 1431, 1388 cm^{-1}. Anal. Calcd for $C_{23}H_{38}F_3N_3O_2S_2$: C, 55.29; H, 5.65; N, 8.41. Found: C, 55.7; H, 6.1; N, 8.2.

5.1.32. 3-[4-(4-Trifluoromethyl-1*H*-imidazole-1-ylmethyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (34)

Compound **24** (200 mg, 0.314 mmol), **11** (128 mg, 0.418 mmol), toluene (20 mL), ethanol (1.5 mL), NaOH (2.5 mL, 1.0 M) and $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) was mixed under N_2. The mixture was warmed to reflux for 2 h at 100 °C. The reaction mixture was diluted with H_2O (50 mL), extracted with EtOAc (3 × 50 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by flash c.c. with hexane/acetone (2:1) as an eluent to give **34** (140 mg, 0.280 mmol) in 67% yield. ^1H NMR δ ($CDCl_3$): 7.74 (s, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.26 (d, J = 7.7 Hz, 2H), 6.74 (s, 1H), 5.20 (s, 2H), 3.19 (br s, 1H), 2.68 (d, J = 7.1 Hz, 2H), 1.92 (m, 1H), 0.99 (s, 9H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR δ ($CDCl_3$): 148.7, 142.2, 138.2, 136.7, 135.6, 134.8, 132.3(m), 130.2, 129.9, 128.8, 128.4, 123.2, 119.2, 54.6, 51.2, 39.1, 30.5, 29.5, 22.1; IR (compression cell): 3295, 3120, 2962, 1465, 1391 cm^{-1}. Anal. Calcd for $C_{23}H_{38}F_3N_3O_2S_2$: C, 55.3; H, 5.7; N, 8.4. Found: C, 55.4; H, 5.8; N, 8.3.

5.1.33. 3-[4-(Thiazole-2-ylmethyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (35)

Compound **24** (100 mg, 0.313 mmol), **12** (40 mg, 0.157 mmol), $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), NaOH (2.5 mL, 1 M, 2.5 mmol), toluene (20 mL) and ethanol (1.5 mL) was mixed under N_2. The mixture was refluxed for 2 h. The mixture was diluted with EtOAc (150 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using $CHCl_3$/MeOH (40:1) as eluent to give **35** (43 mg, 0.095 mmol) in 60% yield. ^1H NMR δ ($CDCl_3$): 7.72 (d, J = 3.3 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 3.2 Hz, 1H), 6.74 (s, 1H), 4.40 (s, 2H), 2.66 (d, J = 7.1 Hz, 2H), 1.90 (m, 1H), 0.97 (s, 9H), 0.94 (d, J = 6.6 Hz, 6H); ^{13}C NMR δ ($CDCl_3$): 148.3, 142.6, 137.9, 136.3, 133.8, 129.9, 129.5, 129.1, 128.8, 119.2, 54.5, 39.2, 38.9, 30.5, 29.4, 22.1; IR (compression cell): 3289, 3117, 2959, 1433, 1389 cm^{-1}. Anal. Calcd for $C_{23}H_{28}N_2O_2S_3$: C, 58.9; H, 6.3; N, 6.2. Found: C, 59.0; H, 6.6; N, 6.2.

5.1.34. 3-(4-Oxazol-2-yl-methylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (36)

Compound **24** (218 mg, 0.683 mmol), **13** (125 mg, 0.525 mmol), toluene (5 mL), ethanol (1.5 mL) and NaOH (1.0 M, 2.1 mL, 2.1 mmol), $Pd(PPh_3)_4$ (18 mg, 16 μmol) were mixed under N_2. The mixture was heated at 100 °C for 3 h. The mixture was diluted with EtOAc (30 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as eluent to give **36** (89 mg, 0.21 mmol) in 40% yield. ^1H NMR ($CDCl_3$, 270 MHz): δ 7.62 (s, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.14(s, 1H), 6.70 (s, 1H), 4.26 (s, 2H), 4.12 (br s, 1H), 2.65 (d, J = 6.9 Hz, 2H), 1.88 (m, 1H), 0.95 (s, 9H), 0.93 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 163.5, 148.4, 142.5, 139.4, 136.4, 134.5, 134.1, 129.5, 129.0, 128.8, 126.7, 125.4, 54.5, 39.1, 33.9, 30.5, 29.4, 22.1; IR (compression cell): 2958, 2344, 1313, 1146 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_2O_3S_2$: C, 61.1; H, 6.5; N, 6.5. Found: C, 60.9; H, 6.4; N, 6.3.

5.1.35. 3-[4-(Thiazole-2-carbonyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (37)

Compound **24** (170 mg, 0.533 mmol), **19** (110 mg, 0.410 mmol), toluene (4 mL), ethanol (1 mL) and NaOH (1.0 M, 1.65 mL, 1.64 mmol), $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) were mixed under N_2. The mixture was heated at 100 °C for 2 h. The mixture was diluted with EtOAc (20 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as an eluent to give **37** (149 mg, 0.322 mmol) in 79% yield. ^1H NMR ($CDCl_3$, 270 MHz): δ 8.58 (d, J = 8.6 Hz, 2H), 8.11 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.74 (s, 1H), 6.80 (s, 1H), 4.17 (s, 1H), 2.70 (d, J = 7.3 Hz, 2H), 1.93 (m, 1H), 1.01 (s, 9H), 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 148.7, 144.9, 141.9, 140.0, 134.6, 131.1, 129.0, 128.7, 126.4, 54.6, 39.1, 30.5, 29.5, 22.1. Anal. Calcd for $C_{22}H_{26}N_2O_3S_3$: C, 57.1; H, 5.7; N, 6.1. Found: C, 57.4; H, 6.0; N, 6.0.

5.1.36. 3-[4-(1-Methyl-1*H*-imidazole-2-carbonyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (38)

Compound **24** (157 mg, 0.490 mmol), **20** (100 mg, 0.377 mmol), toluene (4 mL), ethanol (1 mL) and NaOH (1.0 M, 1.5 mL, 1.5 mmol), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) were mixed under N_2. The mixture was heated at 100 °C for 3 h. The mixture was diluted with EtOAc (30 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as eluent to give **38** (130 mg, 0.277 mmol) in 75% yield. ^1H NMR ($CDCl_3$, 270 MHz): δ 8.35 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.22 (s, 1H), 7.12 (s, 1H), 6.76 (s, 1H), 4.24 (br s, 1H), 4.08 (s, 3H), 2.67 (d, J = 6.9 Hz, 2H), 1.90 (m, 1H), 0.98 (s, 9H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 148.6, 142.3, 139.1, 136.8, 130.9, 129.2, 128.8, 127.0, 54.5, 39.1, 36.5, 30.5, 29.5, 22.1; IR (compression cell): 3224, 2966, 1732, 1634, 1542, 1142 cm^{-1}. Anal. Calcd for $C_{23}H_{29}N_3O_3S_2$: C, 60.1; H, 6.4; N, 9.1. Found: C, 60.3; H, 6.4; N, 9.0.

5.1.37. 3-[4-(Oxazole-2-carbonyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (39)

Compound **24** (53 mg, 0.17 mmol), **21** (32 mg, 0.13 mmol), toluene (2 mL), ethanol (0.5 mL) and NaOH (1.0 M, 0.5 mL, 0.51 mmol), $Pd(PPh_3)_4$ (5.0 mg, 4.0 μmol) were mixed under N_2. The mixture was heated at 100 °C for 3 h. The mixture was diluted with EtOAc (15 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as eluent to give **39** (50 mg, 0.11 mmol) in 88% yield. ^1H NMR ($CDCl_3$, 270 MHz): δ 8.56 (d, J = 8.6 Hz, 2H), 7.92 (s, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.43 (s, 1H), 6.78 (s, 1H), 4.14 (s, 1H), 2.68 (d, J = 6.9 Hz, 2H), 1.91 (m, 1H), 0.99 (s, 9H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.0, 157.6, 148.8, 141.6, 140.4, 137.5, 134.4, 130.9, 129.2, 128.7, 54.7, 39.1, 30.5, 29.5, 22.1; IR (compression cell): 2960, 1664, 1605, 1145 cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_2O_4S_2$: C, 59.2; H, 5.9; N, 6.3. Found: C, 58.9; H, 5.9; N, 6.0.

5.1.38. 3-[4-(Thiophene-2-carbonyl)-phenyl]-5-isobutyl-*N*-*tert*-butylthiophene-2-sulfonamide (40)

Compound **24** (0.233 g, 0.73 mmol), **22** (0.15 g, 0.56 mmol), toluene (5 mL), ethanol (1.5 mL) and NaOH (1.0 M, 2.2 mL, 2.2 mmol), $Pd(PPh_3)_4$ (0.019 g, 0.016 mmol) were mixed under N_2. The mixture was heated at 80 °C for 3 h and then diluted with EtOAc (25 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as an eluent to give of **40** (123 mg, 0.266) in 48% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.92 (d, J = 8.6 Hz, 2H), 7.76–7.72 (m, 3H), 7.65 (m, 1H), 7.16 (m, 1H), 6.79 (s, 1H), 4.18 (br s, 1H), 2.68 (d, J = 7.3 Hz, 2H), 1.92 (m, 1H), 1.01 (s, 9H), 0.96 (d, J = 6.60 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 187.4, 148.8, 143.3, 141.9, 138.8, 137.7, 137.2, 134.8, 134.4, 129.2, 1.29.1, 128.6, 128.0, 54.7, 39.1, 30.5, 29.5, 22.1; IR (compression cell): 3283, 2958, 2360, 1635, 1414, 1313 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_3S_3$: C, 59.8; H, 5.9; N, 3.0. Found: C, 59.9; H, 6.2; N, 3.1.

5.1.39. 3-[4-(2-Methyl-2*H*-pyrazole-3-carbonyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (41)

Compound **24** (0.24 g, 0.73 mmol), **23** (0.15 g, 0.57 mmol), toluene (5 mL), ethanol (1.5 mL) and NaOH (1.0 M, 2.3 mL, 2.3 mmol), $Pd(PPh_3)_4$ (0.019 g, 0.016 mmol) were mixed under N_2. The mixture was heated at 100 °C for 3 h and then diluted with EtOAc (25 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as an eluent to give of **41** (182 mg, 0.396 mmol) in 69% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.93 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 6.80 (s, 1H), 6.67 (d, J = 2.0 Hz, 1H), 4.47 (br s, 1H), 4.21 (s, 3H) 2.69 (d, J = 6.9 Hz, 2H), 1.92 (m, 1H), 1.02 (s, 9H), 0.97 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 185.1, 144.8, 141.7, 139.4, 137.8, 137.5, 137.4, 137.3, 129.4, 129.1, 128.7, 113.6, 54.6, 39.1, 30.4, 29.5, 22.1; IR (compression cell): 3165, 2967, 1644, 1391, 1137 cm^{-1}. Anal. Calcd for $C_{23}H_{29}N_3O_3S_2$: C, 60.1; H, 6.4; N, 9.1. Found: C, 60.2; H, 6.5; N, 9.1.

5.1.40. *N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)-thiophene-2-sulfonamide (59)

To a solution of **25** (177 mg, 0.408 mmol) in CH_2Cl_2 (10 mL) was BCl_3 (1.0 mL, 1 M, 1.0 mmol) added under N_2 (g) and the reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethylacetate (3 × 50 mL). The combined organic phases was washed with brine and dried over $MgSO_4$ and the solvent was removed under vacuum. The crude product was directly used without any purification. The crude of **42** was dissolved in pyridine (1 mL, dried over 4 Å molecular sieve) then 4-pyrrolidinopyridine (58.8 mg, 0.408 mmol) and butyl chloroformate (504 μL, 4.08) was added. The mixture was stirred under N_2(g) at room temperature for 24 h. The solvent was removed in vacuum and co-evaporated with acetonitrile. The residue was purified on column chromatography with $CHCl_3$/MeOH (10:1) as eluent to give **59** (89.6 mg, 0.188 mmol) in 46% yield. IR (compression cell): 3135, 2959, 2875, 1747, 1464 cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 8.73 (1H, s), 7.43 (d, J = 7.7 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 6.72 (s, 1H), 5.59 (s, 2H), 4.00 (br s, 2H), 2.69 (br s, 2H), 1.91 (m, 1H), 1.46 (m, 2H), 1.19 (m, 2H), 0.95 (d, J = 6.9 Hz, 6H), 0.83 (t, J = 6.8 Hz, 3H). ^{13}C NMR δ ($CDCl_3$): 151.8, 151.4, 145.3, 143.0, 134.8, 133.5, 129.6, 129.1, 127.8, 66.9, 51.4, 39.2, 30.9, 30.4, 22.2, 18.7, 13.6. Anal. Calcd for $C_{21}H_{27}N_5O_4S_2 \times 1/2H_2O$: C, 51.8; H, 5.8; N, 14.4. Found: C, 51.4; H, 5.6; N, 14.1.

5.1.41. *N*-Butyloxycarbonyl-3-[4-(2-oxo-pyrrolidin-1-yl-methyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (60)

BCl_3 (2 mL, 1 M in hexane) was added to a solution of **26** (100 mg, 0.223 mmol) in CH_2Cl_2 and the mixture was stirred under N_2 atmosphere for 40 min at ambient temperature. The reaction mixture was then diluted with EtOAc (50 mL) and washed with water, brine, dried over $MgSO_4$ and concentrated. The crude **43** was dissolved in pyridine (2 mL), pyrrolidinopyridine (64 mg, 0.35 mmol) and followed by *n*-butyl chloroformate (414 μL, 6.41 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. The reaction mixture was evaporated and co-evaporated. The residue was purified by flash chromatography using MeOH/$CHCl_3$ (1:30) as eluent to give **60** (92 mg, 0.19 mmol) in 84% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.98 (br s, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.76 (s, 1H), 4.46 (s, 2H), 4.08 (t, J = 6.6 Hz, 2H), 3.30 (t, J = 6.5 Hz, 2H), 2.72 (d, J = 6.9 Hz, 2H), 2.50 (t, J = 8.2 Hz, 2H), 2.05 (t, J = 7.6 Hz, 2H), 1.94 (m, 1H), 1.51 (m, 2H), 1.27 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 175.4, 151.5, 150.2, 146.0, 137.0, 133.4, 129.4, 129.3, 128.0, 66.8, 46.8, 46.4, 39.3, 30.5, 30.4, 22.2, 18.8, 17.8, 13.6; IR (compression cell): 2959, 2870, 1743, 1656, 1465 cm^{-1}; Anal. Calcd for $C_{24}H_{32}N_2O_5S_2$: C, 58.51; H, 6.55; N, 5.69. Found: C, 58.4; H, 6.5; N, 5.6.

5.1.42. *N*-Butyloxycarbonyl-3-[4-(6-oxo-6*H*-pyrimidin-1-ylmethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (61)

BCl_3 (1 mL, 1 M in hexane) was added to a solution of **27** (65 mg, 0.14 mmol) in CH_2Cl_2 and the mixture was stirred under N_2 atmosphere for 40 min at ambient temperature. The reaction mixture was then diluted with EtOAc (100 mL) and washed with water, brine, dried over $MgSO_4$ and concentrated. The crude **44** was dissolved in pyridine (1 mL), pyrrolidinopyridine (21.8 mg, 0.141 mmol) and followed by *n*-butyl chloroformate (183 μL, 1.44 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. The reaction mixture was evaporated and co-evaporated. The residue was purified by preparative LC/MS chromatography using acetonitrile/water (0.1% formic acid, 20–80%) as eluent to give **61** (12.8 mg, 0.0254 mmol) in 18% yield. ^{1}H NMR (10% $CDCl_3$ in CD_3OD, 270 MHz): δ 8.90 (br s, 1H), 7.85 (br s, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.76 (s, 1H), 6.50 (s, 1H), 5.14 (s, 2H), 3.92 (t, J = 6.6 Hz, 2H), 2.62 (d, J = 6.9 Hz, 2H), 1.84 (m, 1H), 1.41 (m, 1H), 1.18 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (10% $CDCl_3$ in CD_3OD, 67.5 MHz): δ 159.4, 152.3, 151.0, 145.0, 134.7, 133.6, 131.4, 129.6, 129.1, 128.9, 128.1, 126.9, 66.1, 50.7, 39.0, 30.3, 30.2, 21.9, 18.5, 13.3; IR (compression cell): 2959, 2871, 1745, 1686 cm^{-1}; Anal. Calcd for $C_{24}H_{29}N_3O_5S_2 \times$ CHOOH: C, 54.6; H, 5.7; N, 7.6. Found: C, 54.5; H, 5.9; N, 7.3.

5.1.43. *N*-Butyloxycarbonyl-3-(4-pyrazole-1-yl-methylphenyl)-5-*iso*-butylthiophene-2-sulfonamide (62)

Trifluoroacetic acid (5 mL) was added **28** (0.21 g, 0.49 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (5 mL × 3). The crude **45** was dissolved in pyridine (5 mL), pyrrolidinopyridine (0.059 g, 0.40 mmol) and followed by *n*-butyl chloroformate (516 μL, 3.99 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as eluent gave **62** (0.190 g, 0.399 mmol) in 80% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.48 (s, 1H), 7,37 (m, 3H), 7.02 (d, J = 8.3 Hz, 2H), 6.69 (s, 1H), 6.23 (s, 1H), 5.26 (s, 2H), 4,01 (t, J = 6.6 Hz, 2H), 2.66 (d, J = 6.9 Hz, 2H), 1,90 (m, 1H), 1.48 (m, 2H), 1.22 (m, 2H), 0.95 (d, J = 6.6 Hz, 6H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 151.2, 150.6, 145.7, 139.4, 136.9,

133.7, 129.6, 129.3, 127.3, 106.0, 66.5, 55.1, 39.2, 30.4, 22.2, 18.7, 13.6. Anal. Calcd for $C_{23}H_{29}N_3O_4S_2$: C, 58.1; H, 6.2; N, 8.8. Found: C, 57.8; H, 6.2; N, 8.8.

5.1.44. *N*-Butyloxycarbonyl-3-[4-(3-methyl-2-oxoimidazolidin-1-yl-methyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (63)

Trifluoroacetic acid (10 mL) was added **29** (0.235 g, 0.50 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile. The crude **46** was dissolved in pyridine (5 mL), pyrrolidinopyridine (0.075 g, 0.50 mmol) and followed by *n*-butyl chloroformate (0.69 g, 5.06 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (25 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using chloroform/methanol as an eluent gave of **63** (183 mg, 0.360 mmol) in 71% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.70 (br s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 6.71 (s, 1H), 4.26 (s, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.27 (s, 2H), 3.17 (s, 2H), 2.80 (s, 3H), 2.67 (d, J = 6.9 Hz, 2H), 1.94 (m, 1H), 1.49 (m, 2H), 1.25 (m, 2H), 0.96 (d, J = 6.6 Hz, 6H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 161.4, 148.2, 142.7, 137.7, 133.9, 129.1, 128.8, 128.1, 54.4, 48.1, 44.9, 42.1, 39.1, 31.4, 30.4, 29.4, 22.1; IR (compression cell): 2956, 1747, 1696, 1156 cm^{-1}. Anal. Calcd for $C_{24}H_{33}N_3O_5S_2$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.8; H, 6.5; N, 8.4.

5.1.45. *N*-Butyloxycarbonyl-3-[4-(3-methyl-2,5-dioxo-imidazolidin-1-yl-methyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (64)

Trifluoroacetic acid (5 mL) was added **30** (0.1 g, 0.24 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (5 mL × 3). The crude **47** was dissolved in pyridine (3 mL), pyrrolidinopyridine (0.036 g, 0.24 mmol) and followed by *n*-butyl chloroformate (0.328 g, 2.41 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as an eluent gave of **64** (70 mg, 0.13 mmol) in 56% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.40 (s, 4H), 6.71 (s, 1H), 4.64 (s, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.87 (s, 2H), 2.98 (s, 3H), 2.68 (d, J = 7.3 Hz, 2H), 1.92 (m, 1H), 1.50 (m, 2H), 1.23 (m, 2H), 0.96 (d, J = 6.3 Hz, 6H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 169.6, 156.5, 151.3, 150.2, 145.9, 136.3, 133.6, 129.4, 129.1, 128.5, 66.7, 51.6, 42.1, 39.2, 30.4, 29.6, 29.1, 22.1, 18.7, 13.5; IR (compression cell): 2959, 1747, 1715, 1450, 1157 cm^{-1}. Anal. Calcd for $C_{24}H_{31}N_3O_6S_2$: C, 55.3; H, 6.0; N, 8.1. Found: C, 55.6; H, 6.2; N, 8.3.

5.1.46. *N*-Butyloxycarbonyl-3-[4-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl-methyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (65)

Trifluoroacetic acid (5 mL) was added **31** (0.12 g, 0.24 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (3 × 5 mL). The crude **48** was dissolved in pyridine (3 mL), pyrrolidinopyridine (0.035 g, 0.24 mmol) and followed by *n*-butyl chloroformate (0.324 g, 2.37 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using chloroform/methanol (10:1) as an eluent gave of **65** (92 mg, 0.17 mmol) in 71% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.40–7.33 (m, 4H), 6.70 (s, 1H), 4.61 (s, 2H), 3.99 (t, J = 6.6 Hz, 2H), 2.85 (s, 3H), 2.66 (d, J = 6.9 Hz, 2H), 1.89 (m, 1H), 1.46 (m, 2H), 1.35 (s, 6H), 1.21 (m, 2H), 0.94 (d, J = 6.6 Hz, 6H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 176.4, 154.9, 151.2, 145.8, 136.6, 133.5, 129.3, 129.1, 128.0, 66.8, 61.3, 41.8, 39.2, 30.3, 29.1, 24.3, 22.1, 21.9, 18.6, 13.5; IR (compression cell): 2960, 1749, 1708, 1460, 1156 cm^{-1}. Anal. Calcd for $C_{26}H_{35}N_3O_6S_2$: C, 56.8; H, 6.4; N, 7.6. Found: C, 56.9; H, 6.2; N, 7.8.

5.1.47. *N*-Butyloxycarbonyl-3-[4-(4-methyl-imidazole-1-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (66)

BCl_3 (2 mL, 1 M in hexane) was added into the solution of **32** (211 mg, 0.474 mmol) in CH_2Cl_2 under N_2. The stirring continued for 40 min and then ethyl acetate (50 mL) was added. The organic layer was washed with water and brine, dried over $MgSO_4$. Removed the solvents and the crude product can be directly used to do next step reaction without further purification. The crude **49** was dissolved in of pyridine (2 mL), pyrrolidinopyridine (108 mg, 0.698 mmol) was added and then of *n*-butyl chloroformate (828 μL, 6.41 mmol) was added. The mixture was stirred overnight under N_2 atmosphere at room temperature. Evaporated and co-evaporated with acetonitrile to remove the solvents and then purified on LC/MS to give **66** (20 mg, 0.041) in 9% yield. ^{1}H NMR δ ($CDCl_3$): 8.22 (s, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 6.84 (s, 1H), 6.75 (s, 1H), 5.19 (s, 2H), 4.03 (t, J = 6.6 Hz, 2H), 2.71 (d, J = 7.1 Hz, 2H), 2.24 (s, 3H) 1.94 (m, 1H), 1.51 (m, 2H), 1.28 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ ($CDCl_3$): 152.5, 150.7, 144.6, 135.2, 134.4, 132.6 130.0, 129.1, 127.8, 117.2, 116.7, 66.3, 51.7, 39.3, 30.6, 29.8, 22.3, 18.9, 13.6, 11.4; IR (compression cell): 3135, 2958, 1458, 1340 cm^{-1}. Anal. Calcd for $C_{24}H_{31}N_3O_4S_2 \times H_2O$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.8; H, 6.4; N, 7.9.

5.1.48. *N*-Butyloxycarbonyl-3-[4-(3-trifluoromethyl-1*H*-pyrazole-1-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (67)

BCl_3 (2 mL, 1 M in hexane) was added into the solution **33** (110 mg, 0.220 mmol) in CH_2Cl_2 under N_2. The stirring continued for 45 min and then EtOAc (50 mL) was added. The organic layer was washed with water and brine, dried over $MgSO_4$. Removed the solvents and the crude product as white solids can be directly used to do next step reaction without further purification. The crude **50** was dissolved in pyridine (2 mL,), pyrrolidinopyridine (64 mg, 0.35 mmol) was added and then *n*-butyl chloroformate (414 μL, 6.41 mmol) was added. The mixture was stirred for 48 h under N_2 atmosphere at room temperature. Evaporated and co-evaporated with acetonitrile to remove the solvents the product was purified on LC/MS to obtain **67** (82 mg, 0.15 mmol) in 68% yield. ^{1}H NMR δ ($CDCl_3$): 7.68 (s, 1H), 7.50 (s, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 6.74 (s, 1H), 6.55 (d, J = 2.1 Hz, 1H), 5.40 (s, 2H), 4.06 (t, J = 6.6 Hz, 2H), 2.71 (d, J = 6.9 Hz, 2H), 1.94 (m, 1H), 1.50 (m, 2H), 1.27 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ ($CDCl_3$): 151.8, 150.2, 146.0, 136.0, 134.0, 131.1, 130.6, 129.4, 127.4, 104.8, 66.9, 56.1, 39.3, 30.5, 30.4, 21.2, 18.7, 13.5; IR (compression cell): 3229, 3129, 2961, 1490, 1438 cm^{-1}. Anal. Calcd for $C_{24}H_{28}F_3N_3O_4S_2$: C, 53.0; H, 5.2; N, 7.7. Found: C, 53.0; H, 5.3; N, 7.5.

5.1.49. *N*-Butyloxycarbonyl-3-[4-(4-trifluoromethyl-1*H*-imidazole-1-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (68)

BCl_3 (2 mL, 1 M in hexane) was added into the solution **34** (100 mg, 0.200 mmol) in CH_2Cl_2 under N_2. The stirring continued for 45 min and then EtOAc (150 mL) was added. The organic layer was washed with water and brine, dried over $MgSO_4$. Removed the solvents and the crude product as white solids can be directly used to do next step reaction without further purification. The crude **51** was dissolved in of pyridine (2 mL,), pyrrolidinopyridine (64 mg, 0.35 mmol) was added and then *n*-butyl chloroformate (414 μL 3.21 mmol) was added. The mixture was stirred for 48 h under N_2 atmosphere at room temperature. Evaporated and co-evaporated with acetonitrile to remove the solvents and the product was purified on LC/MS to give **68** (72 mg, 0.13 mmol) in 66% yield. ^{1}H NMR δ ($CDCl_3$): 9.20 (br s, 1H), 7.75 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.27 (s, 1H), 7.11 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 5.18 (s, 2H), 4.05 (t, J = 6.6 Hz, 2H), 2.71 (d, J = 6.9 Hz, 2H), 1.95 (m, 1H), 1.50 (m, 2H), 1.26 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ ($CDCl_3$): 151.8, 150.6, 145.5, 138.8, 135.2, 134.4, 131.0(m) 130.9, 129.8, 129.7, 129.3, 127.2, 119.6, 66.8, 51.0, 39.3, 30.5, 30.4, 22.2, 18.7, 13.5; IR (compression cell): 2960, 2930, 2871, 1746, 1577, 1465 cm^{-1}. Anal. Calcd for $C_{24}H_{28}F_3N_3O_4S_2$: C, 53.0; H, 5.2; N, 7.7. Found: C, 52.9 H, 5.3; N, 7.7.

5.1.50. *N*-Butyloxycarbonyl-3-[4-(thiazole-2-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (69)

BCl_3 (1 mL, 1 M in hexane) was added to a solution of **35** (42.5 mg, 0.0947 mmol) in CH_2Cl_2 and the mixture was stirred under N_2 atmosphere for 40 min. at ambient temperature. The reaction mixture was then diluted with EtOAc (50 mL) and washed with water, brine, dried over $MgSO_4$ and concentrated. The crude **52** was dissolved in pyridine (2 mL), pyrrolidinopyridine (32 mg, 0.17 mmol) and followed by *n*-butyl chloroformate (276 μL, 2.17 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. The reaction mixture was evaporated and co-evaporated. The residue was purified by preparative LC/MS chromatography using acetonitrile/water (0.1% formic acid, 20–80%) as eluent gave **69** (8.9 mg, 0.018 mmol) in 19% yield. ^{1}H NMR δ ($CDCl_3$): 7.71 (d, J = 3.3 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 3.3 Hz, 1H), 6.76 (s, 1H), 4.33 (s, 2H), 4.04 (t, J = 6.6 Hz, 2H), 2.71 (d, J = 6.9 Hz, 2H), 1.94 (m, 1H), 1.50 (m, 2H), 1.25 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ ($CDCl_3$): 169.8, 151.3, 150.2, 146.0, 142.5, 138.8, 132.9, 129.4, 129.3, 128.9, 119.0, 66.7, 39.3, 38.9, 30.5, 30.4, 22.2, 18.8, 13.6; IR (compression cell): 2958, 2872, 1647, 1510, 1465 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_2O_4S_3$: C, 56.1; H, 5.7; N, 5.7. Found: C, 55.8; H, 6.0; N, 5.4.

5.1.51. *N*-Butyloxycarbonyl-3-(4-oxazol-2-yl-methylphenyl)-5-*iso*-butylthiophene-2-sulfonamide (70)

Trifluoroacetic acid (4 mL) was added **36** (81 mg, 0.19 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (3 × 5 mL). The crude **53** was dissolved in pyridine (3.0 mL), pyrrolidinopyridine (27 mg, 0.19 mmol) and followed by *n*-butyl chloroformate (237 mg, 1.87 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (30 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as eluent to give **70** (46 mg, 0.097 mmol) in 52% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 10.0 (br s, 1H), 7.51 (s, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 6.95 (s, 1H), 6.69 (s, 1H), 4.04 (s, 1H), 4.00 (t, J = 6.6 Hz, 2H), 2.66 (d, J = 7.3 Hz, 2H), 1.90 (m, 1H), 1.50–1.38 (m, 2H), 1.28–1.15 (m, 2H), 0.95 (d, J = 6.6 Hz, 6H), 0.83 (t, J = 7.3 Hz, 3H), ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 151.0, 150.7, 145.6, 138.8, 135.2, 133.0, 131.1, 129.4, 129.2, 128.6, 126.3, 66.4, 53.6, 39.2, 33.6, 30.4, 29.1, 22.1, 18.7, 13.5; IR (compression cell): 2959, 1747, 1345, 1158 cm^{-1}. Anal. Calcd for $C_{23}H_{28}N_2O_5S_2$: C, 58.0; H, 5.9; N, 5.9. Found: C, 57.8; H, 6.2; N, 6.0.

5.1.52. *N*-Butyloxycarbonyl-3-[4-(thiazole-2-carbonyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (71)

Trifluoroacetic acid (10 mL) was added **37** (142 mg, 0.307 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 14 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (10 mL × 3). The crude **54** was dissolved in pyridine (5 mL), pyrrolidinopyridine (46 mg, 0.31 mmol) and followed by *n*-butyl chloroformate (390 μL, 3.07 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (30 mL), washed with citric acid (10% aq) followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as eluent to give **71** (73 mg, 0.14 mmol) in 47% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.51 (d, J = 8.3 Hz, 2H), 8.08 (d, J = 3.0 Hz, 1H), 7.75 (d, J = 3.3 Hz, 1H), 6.63 (d, J = 8.3 Hz, 2H), 6.18 (s, 1H), 4.04 (t, J = 6.3 Hz, 2H), 2.73 (d, J = 6.9 Hz, 2H), 1.96 (m, 1H), 1.54–1.44 (m, 2H), 1.30–1.17 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 151.9, 150.0, 144.8, 139.2, 135.0, 130.8, 129.1, 126.6, 67.0, 39.3, 30.3, 22.2, 18.7, 13.4; IR (compression cell): 2957, 2356, 2326, 1747, 1711, 1154 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_2O_5S_3$: C, 54.5; H, 5.2; N, 5.5. Found: C, 54.6; H, 5.4; N, 5.5.

5.1.53. *N*-Butyloxycarbonyl-3-[4-(1-methyl-1*H*-imidazole-2-carbonyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (72)

Trifluoroacetic acid (5 mL) was added **38** (125 mg, 0.271 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (3 × 5 mL). The crude **55** was dissolved in pyridine (5 mL), pyrrolidinopyridine (44 mg, 0.30 mmol) and followed by *n*-butyl chloroformate (384 μL, 2.97 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (30 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as eluent to give **72** (104 mg, 0.206 mmol) in 75% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.22 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.15 (s, 1H), 7.10 (s, 1H), 6.76 (s, 1H), 4.06 (s, 3H), 3.99 (t, J = 6.3 Hz, 2H), 2.69 (d, J = 6.9 Hz, 2H), 1.92 (m, 1H), 1.52–1.41 (m, 2H), 1.27–1.14 (m, 2H), 0.97 (d, J = 6.6 Hz, 6H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 142.8, 138.3, 137.1, 130.6, 129.2, 129.1, 128.7, 126.9, 66.7, 39.2, 36.4, 30.5, 30.3, 22.2, 18.7, 13.5; IR (compression cell): 2958, 1747, 1650, 1396, 1157 cm^{-1}. Anal. Calcd for $C_{23}H_{29}N_3O_3S_2$: C, 60.1; H, 6.4; N, 9.1. Found: C, 60.3; H, 6.6; N, 9.0.

5.1.54. *N*-Butyloxycarbonyl-3-[4-(oxazole-2-carbonyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (73)

Trifluoroacetic acid (3 mL) was added **39** (44 mg, 0.098 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (5 mL × 3). The crude **56** was dissolved in pyridine (3 mL),

pyrrolidinopyridine (15 mg, 0.097 mmol) and followed by *n*-butyl chloroformate (123 μL, 0.973 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as eluent to give **73** (36 mg, 0.073 mmol) in 77% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.56 (d, J = 8.6 Hz, 2H), 7.91 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.41 (s, 1H), 6.79 (s, 1H), 4.02 (t, J = 6.6 Hz, 2H), 2.71 (d, J = 6.9 Hz, 2H), 1.93 (m, 1H), 1.52–1.42 (m, 2H), 1.30–1.15 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.1, 157.6, 152.0, 150.0, 144.9, 141.7, 139.6, 134.7, 130.7, 129.1, 66.9, 39.2, 30.5, 30.3, 22.2, 18.7, 13.5; IR (compression cell): 2960, 1751, 1664, 1474, 1159 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_2O_6S_2$: C, 56.3; H, 5.3; N, 5.7. Found: C, 56.5; H, 5.3; N, 5.7.

5.1.55. *N*-Butyloxycarbonyl-3-[4-(thiophene-2-carbonyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (74)

Trifluoroacetic acid (10 mL) was added **40** (0.2 g, 0.4 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile. The crude **57** was dissolved in pyridine (4 mL), pyrrolidinopyridine (0.064 g, 0.43 mmol) and followed by *n*-butyl chloroformate (0.59 g, 4.3 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as an eluent of **74** (175 mg, 0.346 mmol) in 80% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.16 (br s, 1H), 7.84 (d, J = 7.92 Hz, 2H), 7.72 (d, J = 4.62 Hz, 1H), 7.65 (d, J = 2.97 Hz, 1H), 7.60 (d, J = 7.92 Hz, 2H), 7.13 (s, 1H), 6.81 (s, 1H), 4.03 (t, J = 6.60 Hz, 2H), 2.72 (d, J = 6.93 Hz, 2H), 1.95 (m, 1H), 1.49 (m, 2H), 1.25 (m, 2H), 0.99 (d, J = 6.60 Hz, 6H), 0.84 (t, J = 7.26 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 187.6, 151.7, 150.2, 145.1, 143.0, 137.8, 137.7, 135.1, 134.5, 131.3, 129.0, 128.0, 66.8, 39.1, 30.4, 30.2, 22.1, 18.6, 13.4; IR (compression cell): 3208, 2960, 1751, 1630, 1410, 1158 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_5S_3$: C, 57.0; H, 5.4; N, 2.8. Found: C, 56.6; H, 5.4; N, 2.9

5.1.56. *N*-Butyloxycarbonyl-3-[4-(2-methyl-2*H*-pyrazole-3-carbonyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (75)

Trifluoroacetic acid (10 mL) was added **41** (0.15 g, 0.32 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (3 × 5 mL). The crude **58** was dissolved in pyridine (4 mL), pyrrolidinopyridine (0.048 g, 0.32 mmol) and followed by *n*-butyl chloroformate (0.45 g, 3.26 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography using pet.ether/acetone as an eluent gave of **75** (118 mg, 0.234 mmol) in 73% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 10.69 (br s, 1H), 7.57 (m, 5H), 6.79 (s, 1H), 6.59 (s, 1H), 4.07 (t, J = 6.60 Hz, 2H), 3.86 (s, 3H), 2.73 (d, J = 7.26 Hz, 2H), 1.96 (m, 1H), 1.53 (m, 2H), 1.28 (m, 2H), 1.00 (d, J = 6.60 Hz, 6H), 0.89 (t, J = 7.26 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 184.5, 151.4, 150.6, 143.9, 138.7, 137.5, 137.2, 132.4, 129.2, 128.9, 128.8, 113.5, 66.5, 39.2, 30.4, 22.1, 18.7, 13.5; IR (compression cell): 2959, 2871, 1747, 1656, 1346, 1259 cm^{-1}. Anal. Calcd for $C_{24}H_{29}N_3O_5S_3$: C, 57.2; H, 5.8; N, 8.3. Found: C, 56.8; H, 5.9; N, 8.2.

5.1.57. 3-(4-Hydroxymethylphenyl)-5-*iso*-butyl-*N*-*tert*-butyl-thiophene-2-sulfonamide (76)

Compound **24** (319 mg, 1.00 mmol), 4-bromobenzylalchol (374 mg, 2.00 mmol), toluene (20 mL), ethanol (4 mL), NaOH (1.0 M, 4 mL) and $Pd(PPh_3)_4$ (34 mg, 0.030 mmol) was mixed under N_2. The mixture was reflux for 2 h. The mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by column chromatography with $CHCL_3$/MeOH (40:1) as an eluent to give **76** (289 mg, 0.757 mmol) in 76% yield. IR(compression cell): 3465, 3162, 2952, 2867, 1441 cm^{-1}. ^{1}H NMR δ (CD_3OD): 7.59 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 6.75 (s, 1H), 4.75 (s, 2H), 4.11 (br s, 1H), 2.69 (d, J = 7.1 Hz, 2H), 1.92 (m, 1H), 0.99 (d, J = 7.2 Hz, 6H), 0.98 (s, 9H). ^{13}C NMR δ (CD_3OD): 148.3, 142.9, 141.1, 134.2, 130.3, 128.9, 127.6, 126.8, 64.8, 54.5, 39.2, 30.5, 29.5, 22.1. Anal. Calcd for $C_{19}H_{27}NO_3S_2$: C, 59.8; H, 7.3; N, 3.7. Found: C, 59.6; H, 7.0; N, 3.5.

5.1.58. 3-(4-Bromomethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (77)

Compound **76** (280 mg, 0.734 mmol) was dissolved in DMF (10 mL) and to the solution PPh_3 (459 mg, 1.75 mmol) and CBr_4 (580, 1.75 mmol) was added. The mixture was stirred for 24 h at room temperature and then diluted with ethylacetate. The organic phase was washed with water and brine and then dried over $MgSO_4$. After removing the solvents the residue was purified on column chromatography with hexane/acetone (5:1) as an eluent to give **77** (315 mg, 0.709 mmol) in 97% yield. IR(compression cell): 3302, 2952, 2866, 1442 cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 7.62 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 6.75 (s, 1H), 4.56 (s, 2H), 4.11 (br s, 1H), 2.69 (d, J = 7.1 Hz, 2H), 1.92 (m, 1H), 0.99 (d, J = 7.2 Hz, 6H), 0.98 (s, 9H). ^{13}C NMR δ ($CDCl_3$): 148.5, 142.4, 138.2, 136.9, 135.1, 129.5, 129.1, 128.7, 54.6, 39.2, 32.8, 30.5, 29.5, 22.1. Anal. Calcd for $C_{19}H_{26}BrNO_2S_2$: C, 51.3; H, 5.9; N, 3.2. Found: C, 51.4; H, 5.8; N, 2.9.

5.1.59. 5-*iso*-Butyl-*N*-*tert*-butyl-3-(4-tetrazol-2-ylmethyl-phenyl)-thiophene-2-sulfonamide (78)

KOH (112 mg, 2.00 mmol, crushed pellets) was added to DMSO (10 mL, dried over 4 Å molecular sieve) and stirred for 5 min. Tetrazole (28 mg, 0.40 mmol) was then added to the mixture and stirred for 2 h. **77** (130 mg, 0.292 mmol) was added and cooled briefly and stirred for a additional 1 h before water (50 mL) was added. The reaction mixture was extracted whit ethylacetate (250 mL) and the extract was washed with water (2 × 50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuo. The residue was purified on column chromatography with chloroform/methanol (50:1) as eluent to give **78** (28.6 mg, 0.0660 mmol) in 23% yield. IR (compression cell): 3328, 3134, 2980, 1501, 1466 cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 8.52 (s, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 6.73 (s, 1H), 5.85 (s, 2H), 2.69 (d, J = 7.1 Hz, 2H), 1.91 (m, 1H), 1.58 (s, 1H), 0.98 (br s, 15H). ^{13}C NMR δ ($CDCl_3$): 153.2, 148.5, 142.4, 136.8, 135.8, 133.2, 129.7, 128.8, 128.5, 56.3, 54.6, 39.2, 30.5, 29.5, 22.1. Anal. Calcd for $C_{20}H_{27}N_5O_2S_2 \times H_2O$: C, 53.2; H, 6.5; N, 15.5. Found: C, 53.7; H, 6.1; N, 15.2.

5.1.60. 3-[4-(Pyrrolidin-2,5-dione-1-ylmethyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (79)

DMSO (10 mL, dried over 4 Å molecular sieve) was added to KOH (67 mg, 1.2 mmol, crushed pellets) and the mixture was stirred for 5 min. Pyrrolidine-2,5-dione (25 mg, 0.25 mmol) was then added and the mixture was stirred for 2 h. Compound **77** (107 mg, 0.240 mmol) was added and the mixture was cooled

briefly and stirred for a further 30 h before water (50 mL) was added. The mixture was extracted with ethyl acetate (150 mL) and the extract was washed with water (2 × 50 mL) and brine, dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified on silica gel with hexane/acetone (3:1) as eluent to give **79** (48.0 mg, 0.104 mmol) in 43% yield. ^{1}H NMR δ ($CDCl_3$): 7.57 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 6.72 (s, 1H), 4.70 (s, 2H), 2.75 (s, 4H), 2.69 (d, J = 7.1 Hz, 2H), 1.91 (m, 1H), 1.57 (br s, 1H), 0.98 (s, 9H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR δ ($CDCl_3$): 176.8, 148.5, 142.7, 139.6, 136.0, 134.6, 129.3, 128.8, 128.7, 54.4, 42.0, 39.1, 30.5, 29.4, 28.2, 22.1; IR (Compression cell): 3299, 2957, 2869, 1775, 1745, 1515, 1466, 1431 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O_4S_2$: C, 59.7; H, 6.5; N, 6.1. Found: C, 60.0; H, 6.4; N, 5.9.

5.1.61. 3-[4-(Thiophene-3-ylmethyl)-phenyl]-5-*iso*-butyl-N-*tert*-butylthiophene-2-sulfonamide (80)

3-Thiophene boronic acid (0.036 g, 0.33 mmol), **77** (0.1 g, 0.23 mmol), toluene (2.5 mL), ethanol (0.7 mL) and NaOH (1.0 M, 1.0 mL, 1.0 mmol), $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) were mixed under N_2. The mixture was heated at 80 °C for 3 h and then diluted with EtOAc (20 mL), washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography using pet.ether/acetone as an eluent to give **80** (81 mg, 0.18 mmol) in 79% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.54 (d, J = 8.3 Hz, 2H), 7.31–7.24 (m, 3H), 6.96 (m, 1H), 6.89 (m, 1H), 6.75 (s, 1H), 4.05 (s, 1H), 4.01 (s, 2H), 2.67 (d, J = 6.9 Hz, 2H), 1.91 (m, 1H), 1.00–0.93 (m, 15H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 148.2, 142.9, 141.1, 140.9, 132.8, 129.1, 128.9, 128.8, 128.1, 125.8, 121.2, 54.4, 39.1, 36.2, 30.5, 29.4, 22.1; IR (compression cell): 3293, 2960, 1310, 1144 cm^{-1}. Anal. Calcd for $C_{23}H_{29}NO_2S_3$: C, 61.7; H, 6.5; N, 3.1. Found: C, 61.4; H, 6.6; N, 3.0.

5.1.62. *N*-Butyloxycarbonyl-5-*Iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide (84)

To a solution of **78** (42.1 mg, 0.111 mmol) in CH_2Cl_2 (10 mL) was BCl_3 (0.5 mL, 1 M, 0.5 mmol) added under N_2 (g) and the reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethylacetate (3 × 50 mL). The combined organic phases was washed with brine and dried over $MgSO_4$ and the solvent was removed under vacuo. The crude product was directly used without any purification. The crude of **81** was dissolved in pyridine (1 mL, dried over 4 Å molecular sieve) then 4-pyrrolidinopyridine (14 mg, 0.0095 mmol) and *n*-butyl chloroformate (120 μL, 0.97) was added. The mixture was stirred under N_2(g) at room temperature for 30 h. The solvent was removed in vacuo and co-evaporated with acetonitrile. The residue was purified on column chromatography with $CHCl_3$/MeOH (35:1) as eluent to give **84** (24.9 mg, 0.0521 mmol) in 47% yield. ^{1}H NMR δ ($CDCl_3$): 8.49 (s, 1H), 7.68 (s, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.73 (s, 1H), 5.82 (s, 2H), 4.07 (t, J = 6.6 Hz, 2H), 2.70 (d, J = 7.1 Hz, 2H), 1.91 (m, 1H), 1.50 (m, 2H), 1.24 (m, 2H), 0.98 (d, J = 6.9 Hz, 6H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ ($CDCl_3$): 153.2, 151.8, 150.1, 145.6, 134.8, 133.4, 129.6, 129.3, 128.3, 66.9, 56.3, 39.2, 30.5, 30.4, 22.2, 18.7, 13.6; IR (Compression cell): 3330, 2961, 2875, 1743, 1466 cm^{-1}. Anal. Calcd for $C_{21}H_{27}N_5O_4S_2$: C, 52.8; H, 5.7; N, 14.7. Found: C, 53.0; H, 5.8; N, 14.1.

5.1.63. *N*-Butyloxycarbonyl-3-[4-(pyrrolidin-2,5-dione-1-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (85)

BCl_3 (2 mL, 1 M in hexane) was added into the solution of **79** (40 mg, 0.086 mmol) in CH_2Cl_2 under N_2. The stirring continued for 40 min and then ethyl acetate (50 mL) was added. The organic layer was washed with water and brine, dried over $MgSO_4$. Removed the solvents and the crude product can be directly used to do next step reaction without further purification. The crude **82** was dissolved in pyridine (2 mL), pyrrolidinopyridine (32 mg, 0.1744 mmol) was added and then *n*-butyl chloroformate (212 μL, 3.20 mmol) was added. The mixture was stirred overnight under N_2 atmosphere at room temperature. Evaporated and co-evaporated with acetonitrile to remove the solvents and the crude product was purified on column chromatography with MeOH in chloroform (1:40) as eluent to afford **85** (20 mg, 0.039 mmol) in 46% yield. ^{1}H NMR δ ($CDCl_3$): 7.98 (br s, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.76 (s, 1H), 4.46 (s, 2H), 4.08 (t, J = 6.6 Hz, 2H), 3.30 (t, J = 6.5 Hz, 2H), 2.72 (d, J = 6.9 Hz, 2H), 2.50 (t, J = 8.2 Hz, 2H), 2.05 (t, J = 7.6 Hz, 2H), 1.94 (m, 1H), 1.51 (m, 2H), 1.27 (m,. 2H), 1.00 (d, J = 6.6 Hz, 6H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR δ ($CDCl_3$): 175.4, 151.5, 150.2, 146.0, 137.0, 133.4, 129.4, 129.3, 128.0, 66.8, 46.8, 46.4, 39.3, 30.5, 30.4, 22.2, 18.8, 17.8, 13.6; IR (compression cell): 2959, 2870, 1743, 1656, 1509, 1465 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_2O_5S_2$: C, 58.51; H, 6.55; N, 5.69. Found: C, 58.4; H, 6.5; N, 5.6.

5.1.64. *N*-Butyloxycarbonyl-3-[4-(thiophene-3-ylmethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (86)

Trifluoroacetic acid (3 mL) was added **80** (60 mg, 0.13 mmol) and five drops (ca. 0.1 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 12 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (3 × 5 mL). The crude **83** was dissolved in pyridine (3 mL), pyrrolidinopyridine (0.02 g, 0.1 mmol) and followed by *n*-butyl chloroformate (0.18 g, 1.3 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by column chromatography using $CHCl_3$/MeOH (35:1) as eluent to give **86** (43 mg, 0.087 mmol) in 67% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.40 (d, J = 8.3 Hz, 2H), 7.30–7.21 (m, 3H), 7.10 (s, 1H), 6.97–6.91 (m, 2H), 6.76 (s, 1H), 4.05–4.00 (m, 4H), 2.70 (d, J = 7.3 Hz, 2H), 1.94 (m, 1H), 1.47 (m, 2H), 1.23 (m, 2H), 0.99 (d, J = 6.6 Hz, 6H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 151.4, 149.9, 146.4, 141.3, 140.7, 131.8, 130.2, 129.4, 128.9, 128.7, 128.3, 125.7, 121.4, 66.8, 39.2, 36.1, 30.4, 30.3, 22.2, 18.7, 13.5; IR (compression cell): 3233, 2958, 1753, 1346, 1160 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_4S_3$: C, 58.6; H, 5.9; N, 2.9. Found: C, 58.4; H, 6.2; N, 2.9.

5.1.65. 3-[4-(5-Trifluoromethyl-[1,3,4]-oxadiazol-2-ylmethyl)-phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (88)

A dried heavy-walled Pyrex tube was charged with 3-(4-cyanomethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide[16] (0.3 g, 0.8 mmol), NaN_3 (0.06 g, 0.9 mmol) and NH_4Cl (0.05 g, 0.9 mmol) in DMF (1 mL). The reaction mixture was flushed with N_2 and caped tightly before mixing with a Whirlimixer. The reaction mixture was exposed on microwave reactor at 150 °C for 2 h. The mixture was diluted with satd $NaHCO_3$ (aq) (50 mL) and washed with ether (3 × 10 mL, to remove unreacted starting material). The aqueous phase was acidified to pH <1 with concd HCl and extracted with chloroform (3 × 10 mL). Combined organic phase was dried, the solvent was evaporated and residue was taken into Trifluoroacetic anhydride (4 mL, excess) and heated at 50 °C for 30 min. The mixture was evaporated and purified by column chromatography using acetone/pet.ether as eluent to afford **88** (116 mg, 0.231 mmol) in 30% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.65 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 6.77 (s, 1H), 4.37 (s, 2H), 4.13 (br s, 1H), 2.70 (d, J = 7.3 Hz, 2H), 1.94 (m, 1H), 1.00 (s, 9H), 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 167.2, 155.9, 155.2, 154.6, 148.5, 142.2, 136.6, 134.8, 132.4, 129.8, 128.9, 128.7, 127.9, 122.0, 118.1, 114.0, 77.0, 54.5, 39.1, 31.4, 30.5, 29.4, 22.1; IR (Compression cell): 3291, 2962, 1558, 1313, 1210,

1170 cm^{-1}. Anal. Calcd for $C_{22}H_{26}F_3N_3O_3S_2$: C, 52.7; H, 5.2; N, 8.4. Found: C, 52.5; H, 5.4; N, 8.6.

5.1.66. *N*-Butyloxycarbonyl-3-[4-(5-trifluoromethyl-[1,3,4]-oxadiazol-2-ylmethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide (90)

Trifluoroacetic acid (5 mL) was added **88** (0.1 g, 0.19 mmol) and two drops (ca. 0.05 mL) of anisole was also added and stirred the mixture under N_2 atmosphere for 18 h at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile. The crude **89** was dissolved in pyridine (3 mL), pyrrolidinopyridine (0.029 g, 0.19 mmol) and followed by *n*-butyl chloroformate (0.272 g, 1.99 mmol) were added. The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. Evaporation and co-evaporation of the mixture with acetonitrile and the residue taken in chloroform (20 mL), washed with 10% aq citric acid followed by water, brine and dried over $MgSO_4$. The residue was purified by column chromatography using pet.ether/acetone as eluent to give of **90** (76 mg, 0.14 mmol) in 73% yield. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.81 (br s, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 6.75 (s, 1H), 4.33 (s, 2H), 4.05 (t, J = 6.6 Hz, 2H), 2.70 (d, J = 6.9 Hz, 2H), 1.93 (m, 1H), 1.50 (m, 2H), 1.26 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 167.3, 156.5, 155.9, 155.2, 154.5, 151.7, 150.1, 145.7, 133.8, 132.7, 130.7, 129.6, 129.3, 128.8, 128.5, 118.1, 114.1, 66.8, 39.2, 31.3, 30.4, 30.3, 22.1, 18.6, 13.5; IR (Compression cell): 3227, 2961, 1750, 1346, 1212, 1160 cm^{-1}. Anal. Calcd for $C_{23}H_{26}F_3N_3O_5S_2 \times H_2O$: C, 49.0; H, 5.0; N, 7.5. Found: C, 49.2; H, 5.1; N, 7.3.

5.1.67. *N*-Butyloxycarbonyl-3-[4-(morpholine-4-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (98)

To a solution of **91**[25] (50 mg, 0.13 mmol), morpholine (0.057 mL, 0.70 mmol) in CH_2Cl_2 (1 mL) was added sodium triacetoxyborohydride (44 mg, 0.20 mmol) at room temperature. The reaction mixture was stirred overnight (LCMS control). After adding saturated sodium bicarbonate solution (1 mL), the clear solution was partitioned between ethyl acetate (10 mL) and water (5 mL). The organic part was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was taken in trifluoroacetic acid (1 mL) containing anisole (one drop) and the resulting solution stirred at 30 °C. After completion of the reaction LCMS control), aqueous saturated $NaHCO_3$ solution was added dropwise at 0 °C until basic pH. Ethyl acetate (10 mL) was then added. The separated organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The crude product was directly used in the next step. To a solution of sulfonamide (from penultimate step), triethylamine (39.4 mg, 0.39 mmol) and pyrrrolidinopyridine (19.3 mg, 0.130 mmol) in CH_2Cl_2 (2 mL) was added *n*-butyl chloroformate (0.033 mL in 0.50 mL of CH_2Cl_2, 0.26 mmol). After 3 h, the reaction was incomplete. After adding an appropriate proportion of reagents, the resulting mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with water, dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product was purified by circular chromatography (5% methanol in DCM, 230–400 mesh) to afford **98** (40 mg, 0.081 mmol) as colourless solid in 62% overall yield for three steps. ^{1}H NMR (270 MHz, $CDCl_3$ + CD_3OD): δ 0.73 (t, J = 7.3 Hz, 3H), 0.85 (d, J = 6.6 Hz, 6H), 1.04–1.18 (m, 2H), 1.29–1.41 (m, 2H), 1.72–1.88 (m, 1H), 2.48 (t, J = 4.3 Hz, 4H), 2.56 (d, J = 6.6 Hz, 2H), 3.45 (s, 2H), 3.61 (t, J = 4.6 Hz, 4H), 3.84 (s, 2H), 6.60 (s, 1H), 7.21(d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 13.6, 18.5, 22.0, 30.0, 30.5, 52.3, 60.8, 64.3, 65.0, 129.0, 129.2, 129.5, 129. 8, 133.6, 134.2, 134.3, 141.7, 146.1, 146.9, 154.0, 154.3; IR (Compression cell): 3017, 2964, 1657, 1461 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_5S_2 \times H_2O$: C, 56.2; H, 7.1; N, 5.5; Found: C, 56.2; H, 6.8, N, 5.5.

5.1.68. *N*-Butyloxycarbonyl-3-[4-(thiazolidine-3-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (99)

The compound **99** was synthesised with the appropriate amine, thiazolidine, following the procedure for **98**. The crude product in the final step was purified by LCMS (40–85% aqueous acetonitrile, reverse phase) to afford **99** as a colourless solid (51 mg, 0.10 mmol) in 78% overall yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87 (t, J = 7.3 Hz, 3H), 0.99 (d, J = 6.6 Hz, 6H), 1.27–1.31 (m, 2H), 1.4–1.52 (m, 2H), 1.86–2.04 (m, 1H), 2.7 (d, J = 6.9 Hz, 2H), 2.9 (t, J = 5.6 Hz, 2H), 3.08 (t, J = 5.9 Hz, 2H), 3.58 (s, 2H), 3.95–4.07 (m, 4H), 6.76 (s, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 13.6, 18.7, 22.2, 29.4, 30.4, 30.5, 39.2, 56.2, 57.3, 59.6, 66.7, 128.0, 129.0, 129.4, 130.9, 133.3, 138.5, 145.9, 150.4, 151.2; IR (Compression cell): 2958, 1748, 1444, 1345 cm^{-1}. Anal. Calcd for $C_{23}H_{32}N_2O_4S_3$: C, 55.6; H, 6.5; N, 5.6; Found: C, 55.5; H, 6.6; N, 5.5.

5.1.69. *N*-Butyloxycarbonyl-3-[4-(piperidin-4-one-1-ylmethyl)-phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide (100)

The compound **100** was synthesised following the procedure for **98** with the appropriate amine, 1,4-dioxa-8-azaspiro[4.5]decane. The crude product in the final step was purified by preparative LCMS (20–50% aqueous acetonitrile) to afford the pure **100** as the colourless solid (72 mg, 0.14 mmol) in 54% overall yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.84–0.99 (m, 9H), 1.24 (m, 2H), 1.47 (m, 2H), 1.64 (s, 1H), 1.93 (m, 1H), 2.42–2.52 (m, 4H), 2.69 (d, J = 6.9 Hz, 2H), 2.87 (t, J = 5.9 Hz, 3H), 3.60 (s, 2H), 3.76 (t, J = 6.3 Hz, 1H), 4.01& 4.13 (t, J = 6.6 Hz, 2H), 6.73 (s, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 13.6, 18.8, 19.2, 22.2, 30.5, 31.0, 39.3, 40.4, 41.1, 43.0, 52.3, 60.8, 65.8, 66.4, 128.4, 129.3, 132.2, 134.1, 135.9, 145.2, 150.6, 151.7, 207.6; IR (Compression cell): 2959, 1731, 1694, 1456, 1274, 1142, 1091 cm^{-1}; Anal. Calcd for $C_{25}H_{34}N_2O_5S_2$: C, 59.3; H, 6.8; N, 5.5; Found: C, 59.0; H, 7.0; N, 5.4.

5.2. Rat liver membrane AT_1 receptor binding assay

Rat liver membranes were prepared according to the method of Dudley et al.[26] Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris–HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, [^{125}I]Ang II (80000–85000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25 °C for 2 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets, which had been pre-soaked overnight with 0.3% polyethylamine, using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris–HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a γ-counter. The characteristics of the Ang II binding AT1 receptor was determined by using six different concentrations (0.03–5 nmol/L) of the labeled [^{125}I]-AngII. Nonspecific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the nonspecific binding from the total bound [^{125}I]AngII. The apparent dissociation constant K_i values were calculated from IC_{50} values using the Cheng–Prusoff equation (K_d = 1.7 ± 0.1 nM, [L] = 0.057 nM). The binding data were best fitted with a one-site fit. All determinations were performed in triplicate.

5.3. Porcine (pig) myometrial membrane AT_2 receptor binding assay

Myometrial membranes were prepared from porcine uteri according to the method by Nielsen et al.[27] A presumable

interference by binding to AT_1 receptors was blocked by addition of 1 μM losartan.[28] Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris–HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, [^{125}I]Ang II (80000–85000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25 °C for 1.5 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets, which had been pre-soaked overnight with 0.3% polyethylamine, using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris–HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a γ-counter. The characteristics of the Ang II binding AT1 receptor was determined by using six different concentrations (0.03–5 nmol/L) of the labeled [^{125}I]-AngII. Nonspecific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the nonspecific binding from the total bound [^{125}I]AngII. The apparent dissociation constant K_i values were calculated from IC_{50} values using the Cheng–Prusoff equation (K_d = 1.7 ± 0.1 nM, [L] = 0.057 nM). The binding data were best fitted with a one-site fit. All determinations were performed in triplicate.

5.4. In vitro morphological effects. General

The chemicals used in the present study were obtained from the following sources: Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), HAT supplement (Hypoxanthine, Aminopterin, Thymidine), gentamycin from Gibco BRL (Burlington, Ont, Canada); [Val5]-angiotensin II from Bachem (Marina Delphen, CA, USA). PD123,319 was from RBI (Natick, MA, USA). All other chemicals were of grade A purity.

5.5. Cell culture

NG108-15 cells (provided by Drs M. Emerit and M. Hamon; INSERM, U. 238, Paris, France) were cultured (passage 7–30) in DMEM with 10% fetal bovine serum (FBS, Gibco BRL, Burlington, ONT, Canada), HAT supplement and 50 mg/L gentamycin at 37 °C in 75 cm^2 Nunclon Delta flasks in a humidified atmosphere of 93% air and 7% CO_2, as previously described.[30] Subcultures were performed at subconfluency. Under these conditions, cells express only the AT_2 receptor subtype.[30,31] Cells were stimulated once a day for three days (first stimulation 24 h after plating). Cells were cultured for three subsequent days under these conditions. For all experiments, cells were plated at the same initial density of 4×10^4 cells /35 mm Perti dish. Cells were treated without (control cells), with [Val5]Ang II (0.1 μM) or **60** (0.1 nM), in the absence or in the presence of the inhibitor, PD123,319 (1 μM), an AT_2 receptor antagonist (each introduced daily with inhibitors applied 30 min prior to Ang II or **60**).

5.6. Determination of cells with neurites

Cells were examined daily under a phase contrast microscope and micrographs were taken after three days under the various experimental conditions. Cells with at least one neurite longer than a cell body were counted as positive for neurite outgrowth. At least 140 cells were counted in three independent experiments.[37]

5.7. Data analysis

The data were presented as mean ± SEM of the number of experiments indicated in the text, each performed in duplicate or triplicate. Statistical analyses of the data were performed using the one-way analysis of variance (ANOVA) test. Homogeneity of variance was assessed by Bartlett's test and p values were obtained from Dunnett's tables.

5.8. CYP450 inhibition assays[38]

The compounds were tested at 10 μM in duplicate with a 0.25% final concentration of both methanol and acetonitrile. Spectrofluorimetric measurements were performed with a multiplate reader. The fluorescent intensity (fu) measured at (t = 0) was subtracted from that measured after the appropriate incubation time (t = final). The ratio of signal-to-noise was calculated by comparing the fluorescence in incubations containing the test compound to the control samples containing the same solvent vehicle. The percent of control activity was calculated and reported as percent inhibition.

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