First Reported Nonpeptide AT_1 Receptor Agonist (L-162,313) Acts as an AT_2 Receptor Agonist in Vivo

Yiqian Wan,[†] Charlotta Wallinder,[†] Berndt Johansson,[‡] Mathias Holm,[‡] Mahalingam A. K.,[†] Xiongyu Wu,[†] Milad Botros,[‡] Anders Karlén,[†] Anders Pettersson,[‡] Fred Nyberg,[§] Lars Fändriks,[‡] Anders Hallberg,[†] and Mathias Alterman*[,†]

Department of Medicinal Chemistry, BMC, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden, Department of Gastrosurgical Research, Sahlgrenska Academy at Gothenburg University, SE-413 45 Gothenburg, Sweden, and Department of Biological Research on Drug Dependence, BMC, Uppsala University, P.O. Box 591, SE-751 23 Uppsala, Sweden

Received September 12, 2003

In this investigation, it is demonstrated that the first nonpeptide AT_1 receptor agonist L-162,313 (**1**), disclosed in 1994, also acts as an agonist at the AT_2 receptor. In anesthetized rats, administration of compound **1** intravenously or locally in the duodenum increased duodenal mucosal alkaline secretion, effects that were sensitive to the selective AT_2 receptor antagonist PD-123,319. The data strongly suggest that **1** is an AT_2 receptor agonist in vivo. To the best of our knowledge, this substance is the first nonpeptidic low-molecular weight compound with an agonistic effect mediated through the AT_2 receptor.

Introduction

Selective AT_1 receptor antagonists block well-known functional effects of the octapeptide angiotensin II (Ang II), such as vasoconstriction, aldosterone release, and cardiovascular growth.[1] In 1994, the first nonpeptide Ang II agonist, L-162,313 (**1**) was disclosed (Figure 1).[2] At that time, nonpeptide agonists of peptide receptors were rare, being confined largely to agonists of opioid receptors. Notably, removal of a methyl group from L-162,782, an agonist closely structurally related to the thiophene derivative **1**, provided L-162,389 which was found to act as an antagonist in vivo.[3] Thus, a subtle molecular alteration was shown to determine the agonist/ antagonist properties of these ligands. The three compounds described above were all essentially equipotent as AT_1/AT_2 receptor binding ligands, but by replacing the alkyl group with a *m*-methoxybenzyl group, an agonist, L-163,491, with an approximately 70-fold selectivity for the AT_1 receptor subtype, was obtained.[4]

Ang II exhibits a similar binding affinity to the AT_1 and AT_2 receptors, sharing a sequence homology of only 32−34% at the amino acid level in rat.[5] We felt encouraged to answer the question of whether **1** also would exert agonistic properties toward the AT_2 receptor.[5,6]

Recently, we reported an AT_2 receptor-mediated Ang II stimulation of duodenal mucosal alkaline secretion in the rat,[7] an effect that could be blocked by the AT_2 selective antagonist PD-123,319[8] (**35**) but not by the AT_1 receptor antagonist losartan.[9] Prior to selecting the compounds for studies in this animal model, we decided to (a) assess the impact on AT_1/AT_2 receptor affinity caused by minor alterations of the sulfonylcarbamate part of **1** (Series A, Figure 2) and (b) to determine the receptor selectivities after retaining the lower part of **1** but replacing the bicyclic imidazopyridine ring system with substituted quinazolinones, as the latter structure is found in a large number of selective AT_2 receptor antagonists (Series B, Figure 2).[10]

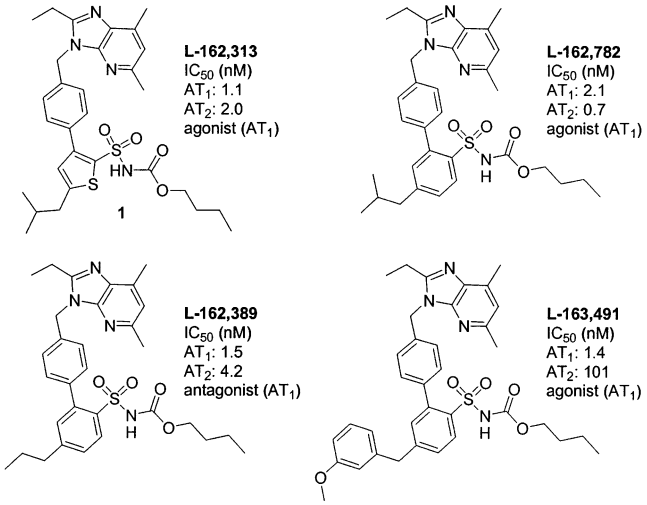


Figure 1.

We herein report that the AT_1 receptor agonist **1**, the compound with the most favorable AT_2/AT_1 affinity ratio in the A series acts as an AT_2 receptor agonist in the animal model. In contrast, compound **12** in series B, with a 40-fold greater affinity for the AT_2 receptor versus the AT_1 receptor, exerts no agonistic effects in this in vivo model.

Chemistry

The thiopheneboronic acid **2**, a key intermediate for the synthesis of the compounds in both series, was prepared essentially as described by Kevin et al.[11] Thus, thiophene-2-sulfonyl chloride was first converted to the *N-tert*-butylsulfonamide. Subsequent alkylation followed

* Corresponding author. Tel: +46−18−4714905. Fax: +46-18-4714474. E-mail: mathias.alterman@orgfarm.uu.se.
[†] Department of Medicinal Chemistry, Uppsala University.
[‡] Sahlgrenska Academy at Gothenburg University.
[§] Department of Biological Research on Drug Dependence, Uppsala University.

10.1021/jm031031i CCC: $27.50
Published on Web 02/14/2004

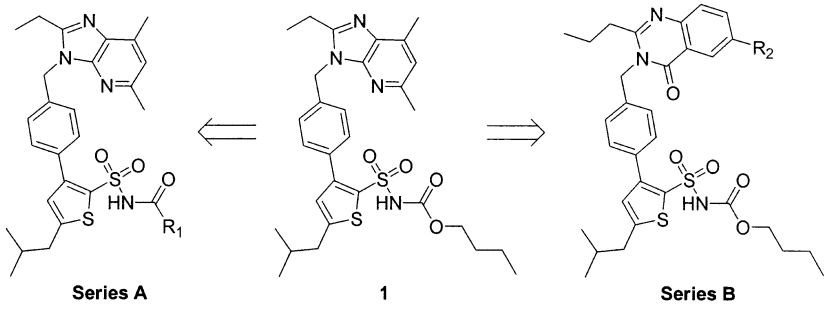
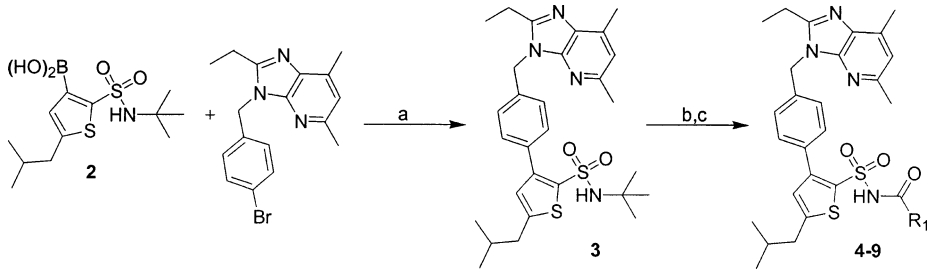


Figure 2.

Scheme 1[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, NaOH (aq), ethanol/toluene; (b) TFA; (c) alkyl chloroformate or acyl chloride, pyrrolidinopyridine, pyridine.

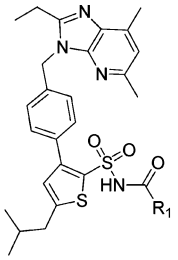
by selective 3-lithiation/boration delivered **2**. A Suzuki coupling of 3-(4-bromobenzyl)-2-ethyl-5,7-dimethyl-3*H*-imidazol[4,5-*b*]pyridine[12] with the boronic acid **2**[11] provided **3** in good yield. Deprotection by TFA, to give the primary sulfonamide followed by reactions with alkyl chloroformates and acyl chlorides, afforded **1**[2], **4**−**6**, and **7**−**9**, respectively (Scheme 1).

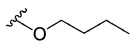
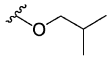
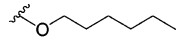
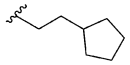
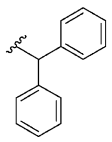
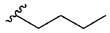
A Suzuki coupling of **2** with 3-(4-bromobenzyl)-6-nitro-2-propyl-3*H*-quinazolin-4-one yielded **10** in high yield. The ethyl group most often found in the 2-position of the quinazolin-4-one scaffold of AT_2 receptor antagonists was replaced with propyl since Glinka et al. had observed that the propyl group in a related series of compounds gave higher AT_2 receptor affinities when combined with the sulfonamide based carboxylic acid bioisostere.[10c]

The compounds in series B were prepared as outlined in Scheme 2. Deprotection of **10** and reaction with butyl chloroformate gave **11** in a good yield. To obtain the derivatives **12**−**21**, the nitro group of **10** was first reduced using ammonium formate and palladium on charcoal to provide **22**. Acylation of the amine function of **22** with acetyl chloride, benzoyl chloride, and thienoyl chloride respectively afforded compounds **23**−**25** which were debutylated and then reacted with butyl chloroformate to yield the secondary amides **12**−**14**. The tertiary amides **15**−**21** were prepared by reductive alkylation using acetaldehyde or benzaldehyde with triacetoxyborohydride as reducing agent to give **26** and **27**, respectively. These secondary amines were thereafter acylated to afford **28**−**34** and subsequently deprotected and treated with butyl chloroformate to deliver the desired tertiary amides.

Binding Assays. Compounds **1**, **4**−**9**, **11**−**21** 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 in essence as described previously (Table 1).[13] The natural substrate Ang II, the selective AT_1 receptor antagonist losartan,[9] and the selective AT_2 receptor antagonist **35**[8] were used as reference substances.

Table 1. Series A

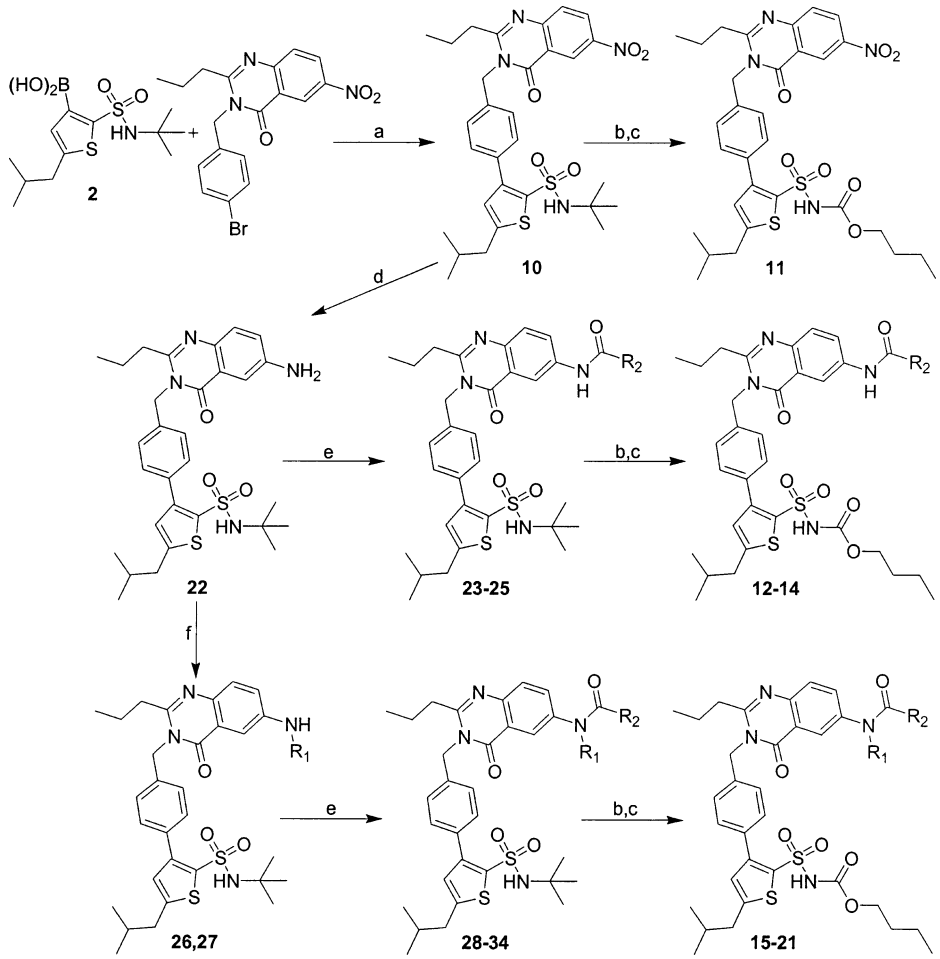


Compound	R_1	K_i[a] (nM)		AT_1/AT_2
		AT_1	AT_2	
1		3.9	2.8	1.3
4		34.9	>10000	>0.0035
5		55.2	>10000	>0.0055
6		121	>10000	>0.012
7		62	>10000	>0.0062
8		109	>10000	>0.011
9		34	400	0.85

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

In Vivo Assays. The in vivo experiments were performed on anaesthetized nonfasted male Sprague−Dawley rats. A femoral artery and one or two veins were catheterized for subsequent blood pressure measurements and drug infusions, respectively. Duodenal mu-

Scheme 2[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, NaOH (aq), ethanol/toluene; (b) TFA; (c) butyl chloroformate, pyrrolidinopyridine, pyridine; (d) Pd/C, HCO_2NH_4, MeOH; (e) acyl chloride, DIEA, CH_2Cl_2; (f) acetaldehyde or benzaldehyde, $NaB(OAc)_3H$, AcOH, CH_2ClCH_2Cl.

cosal alkaline secretion (HCO_3^- secretion) was measured by a pH-stat titration technique.[14] Alkaline secretion to the perfusate was continuously titrated to pH 7.4 with 0.02 M HCl controlled by a pH-stat device.

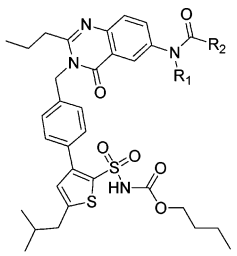
Results and Discussion

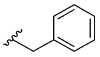
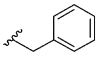
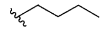
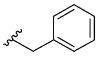
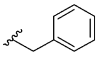
The results obtained in the AT_1 and AT_2 receptor binding assays are presented in Tables 1 and 2. The K_i values for compound **1** were determined as 3.9 nM for the AT_1 and 2.8 nM for the AT_2 receptors (lit. data IC_{50}: 1.1 nM and 2.0 nM, respectively[2b]). As apparent from Table 1 all variations of the butyloxy group investigated were deleterious with respect to AT_2 receptor affinity, although low affinity was encountered by shortening of the side-chain by removal of the oxygen atom (compound **9**). Notably, the ethyloxy derivative **4** exhibited no detectable AT_2 receptor affinity. The lack of AT_2 receptor affinity exhibited by **7** is also somewhat remarkable considering the previous results by Mantlo et al.,[15] who in their series of compounds observed a higher selectivity for the AT_2 receptor with compounds bearing the cyclopentyl side-chain. With regard to AT_1 receptor affinity, the impact of alterations to the butyloxy side-chain was considerably less pronounced. All compounds bound in varying degree to the AT_1 receptor. Thus, the effect caused by alterations of the butyloxycarbonylsulfonamide portion of **1** seemed to resemble the outcome of variations of the isobutyl group in the 5-position, as reported by Kevin et al.,[11a] in that even the small structural modifications performed tended to reduce AT_2 receptor affinity while retaining AT_1 receptor affinity.

The most potent AT_2 receptor ligand in series A, i.e. **1** (not receptor subtype selective but a proven partial AT_1 receptor agonist) was investigated in the rat in vivo. Duodenal mucosal alkaline secretion in rats has been shown previously to be inhibited by AT_1 receptor activation and increased after AT_2 receptor stimulation.[7,16]

As shown in Figure 3, intravenous administration of **1** (bolus 0.3 mg/kg plus 30 μg/kg×h) increases mean arterial pressure by approximately 10 mmHg. This pressor effect was reversed, with a markedly lowered arterial pressure by addition of the AT_1-receptor antagonist losartan (10 mg kg^{-1} iv bolus) indicating that **1** activates AT_1 receptor-mediated vasoconstriction. Interestingly, the compound alone also increased the duodenal mucosal alkaline secretion moderately. The addition of losartan markedly increased this secretory stimulation (Figure 3). When losartan was combined with the AT_2 receptor antagonist **35** this effect was absent (data not shown, $n = 3$). Although a proper dose−response-curve was not performed with regard to intravenous administration, the effect on mucosal alkaline secretion by compound **1** at the presently used infusion rate can be considered of the same order of magnitude as previously reported for the peptide compounds Ang

Table 2. Series B



Compound	R_1	R_2	K_i[a] (nM) AT_1	K_i[a] (nM) AT_2	AT_1/AT_2
11	Nitro		>10000	133	>75
12	H		728	17	43
13	H		343	85	4.2
14	H		455	>10000	<0.046
15			231	4.6	50
16			410	33	12
17			693	8.0	86
18			339	48	7.1
19			185	46	4.0
20			248	32	7.8
21			1038	>10000	>0.10

II and CGP112A.[7] The results support the view that compound **1** is an unselective agonist at both the AT_1 and AT_2 receptors.

However, to investigate the AT_2 agonistic properties of **1** in greater depth, topical administration was employed by administering the compound in the duodenal intraluminal perfusate. The rationale behind this mode of administration was that AT_2 receptors, but not AT_1 receptors, are localized to the secreting epithelium[7] making simultaneous administration of an AT_1 receptor antagonist unnecessary. It was observed that **1** given in the perfusate raised the alkaline secretion in a concentration dependent manner (Figure 4). Simultaneous presence of **35** (0.1 mM) significantly inhibited this effect indicating that an AT_2 receptor-mediated effect was occurring. Such local intraluminal administration of drugs did not influence arterial pressure (data not shown). Taken together these in vivo tests strongly suggest that **1** is a dual AT_1/AT_2 receptor agonist.

Since the data in series A and previous findings[3] suggested that the 2-(*N*-butyloxycarbonyl)sulfonamide and 5-isobutyl were compulsory for fair AT_2 receptor affinity to be achieved, we turned our attention to modifications of the bicyclic upper part of the molecule in the hope of improving the AT_2/AT_1 ratio. We hypothesized that the lower part of **1** might be pivotal for agonism while a proper upper heterocyclic moiety could

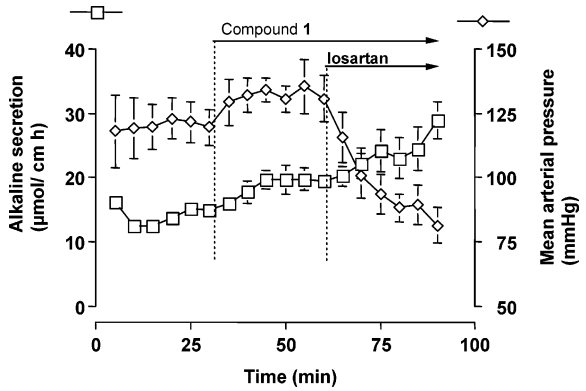


Figure 3. Anesthetized Sprague−Dawley rats ($n = 5$). Effects of intravenous administration of **1** (bolus 0.3 mg/kg plus 30 μg/kg × h) and later addition of the AT_1 receptor antagonist losartan (10 mg/kg bolus iv) on duodenal mucosal alkaline secretion and mean arterial pressure.

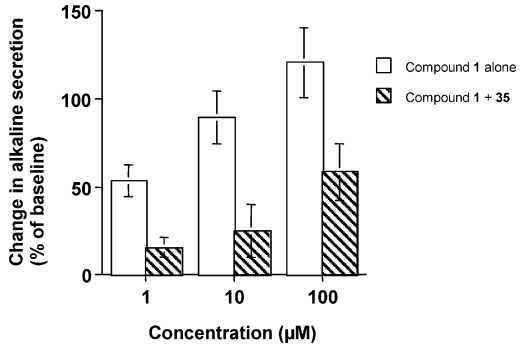


Figure 4. Anesthetized Sprague−Dawley rats. Effects of local (intra duodenal) administration of **1** at consecutively increased concentrations in 30 min periods in absence ($n = 5$) and in the presence ($n = 5$) of **35** (0,1 mM). Values represent means of the last 15 periods of each concentration.

conceivably provide high AT_2 receptor selectivity. We were particularly attracted by a series of AT_2 receptor ligands of the biaryl type reported by Glinka et al.[10] Some of these compounds exhibited an impressive AT_2/AT_1 selectivity (e.g. for one of the derivatives, AT_1: K_i >3000 nM and AT_2: $K_i = 0.06$ nM). The compounds were comprised of a quinazolin-4-one scaffold substituted in the 6-position with, for example, a variety of acylamido groups. Partly guided by the results of Glinka et al., the compounds in Table 2 were designed and synthesized.

From Table 2 it is apparent that the substituent in the 6-position of the quinazolinones can significantly affect the biological activity. While all amides (**12**−**21**) bind to the AT_1 receptor, albeit weakly, minor structural variations could have a dramatic influence on the affinity to the AT_2 receptor. The thiophene and the corresponding benzene rings in **1** and L-162,782, respectively, act as true bioisosteres, but these aromatic nuclei are not necessarily interchangeable when constituting a part of the 6-substituent of the quinazolinone moiety. A comparison of the tertiary ethyl amides **16** and **17** suggests that interchanging the two aromatic systems has no large impact on the binding affinity to the AT_2 receptor. However, substitutions of the ethyl group of the thiophene derivative **17** with either hydrogen (cf. **17** and **14**) or a benzyl group (cf. **17** and **21**) are deleterious for AT_2 receptor affinity. However, when the benzene analogue **16** was subjected to the same modi-

fications, surprisingly, the affinity was largely retained (cf. **16**, **13**, and **20**). These results are difficult to rationalize but demonstrate a complex structure−activity relationship of the compounds in series B. Thus, as in series A where the AT_2 affinity drops significantly after minor structural changes to the oxybutyl chain of the prototype compound **1** or of the isobutyl group, as previously shown,[11a] a similar response is encountered after the "bioisosteric" phenyl to thienyl exchange, conducted in the series B.

One of the most potent and AT_2 receptor selective ligands in series B, the secondary amide **12** (the ligand with the most favorable solubility properties in the series), was selected for in vivo studies in rat. Compound **12** was not soluble in ethanol unlike **1**. Ethanol exerts only marginal effects on the studied secretory variable at the used concentration (<4%). DMSO was the only solvent that could dissolve compound **12** in sufficient concentration for evaluation. Unfortunately, DMSO was found to exert stimulatory effects on mucosal alkaline secretion in concentrations below 5%. However, no additional stimulatory effect of the 40-fold AT_2 receptor selective quinazolinone compound **12** at concentrations 1−100 μM was observed in the rat duodenum, suggesting that **12**, contrary to **1**, does not act as an AT_2 receptor agonist under these test conditions. Although, we cannot rule out that the lack of agonistic effect of compound **12** in the rat is attributed to the fact that affinity to AT_2 receptor in porcine membrane may not be translated to the rat AT_2 receptor.

Conclusion

In summary, the data presented demonstrate that the first nonpeptide AT_1 receptor agonist disclosed, the thiophene derivative **1**, also acts as an agonist at the AT_2 receptor type. Furthermore the finding that **12**, in contrast to **1**, does not promote an effect in the secretor model in vivo may suggest that the agonistic effects are not likely to be retained if the imidazopyridine in the upper part of **1** is replaced with a quinazolinone system, a modification which was made in an attempt to improve the AT_2/AT_1 ratio with respect to binding affinities. Small structural modifications within the two series examined had, in general, a considerably larger impact on the binding affinity to the AT_2 receptor than to the AT_1 receptor subtype. It is our belief that the prototype compound **1** (possibly in combination with a properly selected AT_1 receptor antagonist) may provide a useful research tool for studies of the role of the AT_2 receptor in vivo. This substance is, to the best of our knowledge, the first nonpeptidic low-molecular weight compound demonstrated to exert an agonistic effect mediated through the AT_2 receptor.

Experimental Section

Chemistry. General Considerations. ^{1}H 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. Infrared spectra were recorded on a Perkin-Elmer Model 1605 FT-IR and are reported as λ_{max} (cm^{-1}). For neat solids the instrument was equipped with a Microfocus Beam Condenser with ZnSe lenses in a Diasqueeze Pulse Diamond Compressor Cell (Graseby Specac Inc., Woodstock, GA). 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 quadropole 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 $MgSO_4$. All chemicals were purchased from commercial suppliers and used directly without further purification.

General Procedure for the Preparation of the Compounds 4−9. Compound **3** (50 mg, 0.10 mmol) and anisole (150 μL) were dissolved in TFA (5 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in pyridine (1 mL), and pyrrolidinopyridine (15 mg, 0.10 mmol) was added. The solution was cooled on an ice bath, and the acyl chloride (20 equiv) was added under a N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated, and purified by column chromatography to give the pure compounds **4**−**9**.

***N*-Ethyloxycarbonyl-3-[4-(2-ethyl-5,7-dimethylimidazo-[4,5-*b*]pyridin-3-ylmethyl)phenyl]-5-isobutylthiophene-2-sulfonamide (4).** Compound **3** was used according to the general procedure and reacted with ethyl chloroformate (198 μL, 2.10 mmol), which after purification ($CHCl_3$: MeOH 40:1) gave compound **4** in 85% yield (48 mg, 0.087 mmol). ^{1}H NMR (CD_3OD), δ: 7.52 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 6.99 (s, 1H), 6.78 (s, 1H), 5.55 (s, 2H), 3.92 (q, J = 7.1 Hz, 2H), 2.87 (q, J = 7.6 Hz, 2H), 2.65 (d, J = 7.1 Hz, 2H), 2.60 (s, 3H), 2.56 (s, 3H), 1.86 (m, 1H), 1.29 (t, J = 7.6 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (CD_3-OD), δ: 158.2, 156.0, 154.2, 150.5, 148.4, 145.5, 139.7, 138.2, 135.6, 135.1, 133.0, 130.9, 127.7, 120.8, 63.1, 46.0, 40.0, 31.9, 24.1, 22.6, 22.2, 16.5, 14.8, 12.3; Anal. ($C_{28}H_{34}N_4O_4S_2$) C, H, N.

***N*-Isobutyloxycarbonyl-3-[4-(2-ethyl-5,7-dimethylimidazo[4,5-*b*]pyridin-3-ylmethyl)phenyl]-5-isobutylthiophene-2-sulfonamide (5).** Compound **3** was used according to the general procedure and reacted with *iso*-butyl chloroformate (269 μL, 2.10 mmol), which after purification ($CHCl_3$: MeOH 40:1) gave compound **5** in 85% yield (46 mg, 0.079 mmol). ^{1}H NMR (CD_3OD), δ: 7.50 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.00 (s, 1H), 6.81 (s, 1H), 5.56 (s, 2H), 3.69 (d, J = 6.5 Hz, 2H), 2.87 (q, J = 7.6 Hz, 2H), 2.68 (d, J = 7.1 Hz, 2H), 2.60 (s, 3H), 2.57 (s, 3H), 1.90 (m, 1H), 1.73 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H), 0.96 (d, J = 6.6 Hz, 6H), 0.78 (d, J = 6.7 Hz, 6H); ^{13}C NMR (CD_3OD), δ: 158.2, 154.9, 154.2, 151.1, 148.5, 145.9, 139.7, 138.3, 135.5, 134.6, 133.1, 130.9, 127.8, 120.9, 73.3, 46.0, 40.1, 31.9, 29.1, 24.1, 22.7, 22.3, 19.4, 16.5, 12.3; Anal. ($C_{30}H_{38}N_4O_4S_2$) C, H, N.

***N*-Hexyloxycarbonyl-3-[4-(2-ethyl-5,7-dimethylimidazo-[4,5-*b*]pyridin-3-ylmethyl)phenyl]-5-isobutylthiophene-2-sulfonamide (6).** Compound **3** was used according to the general procedure and reacted with hexyl chloroformate (339 μL, 2.10 mmol), which after purification ($CHCl_3$: MeOH 40:1) gave compound **6** in 74% yield (47 mg, 0.077 mmol). ^{1}H NMR (CD_3OD), δ: 7.45 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 7.00 (s, 1H), 6.81 (s, 1H), 5.57 (s, 2H), 3.91 (t, J = 6.4 Hz, 2H), 2.87 (q, J = 7.6 Hz, 2H), 2.67 (d, J = 7.1 Hz, 2H), 2.60 (s, 3H), 2.56 (s, 3H), 1.88 (m, 1H), 1.45−1.02 (m, 11H), 0.95 (d, J = 6.6 Hz, 6H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (CD_3OD), δ: 158.2, 154.2, 153.3, 151.8, 148.4, 146.5, 139.7, 138.4, 135.2, 133.6, 133.0, 130.8, 127.8, 120.9, 67.4, 46.0, 40.1, 32.6, 31.9, 29.8, 26.5, 23.7, 22.7, 22.3, 16.5, 14.5, 12.3; Anal. ($C_{32}H_{42}N_4O_4S_2$) C, H, N.

***N*-(3-Cyclopentanylpropionyl)-3-[4-(2-ethyl-5,7-dimethylimidazo[4,5-*b*]pyridin-3-ylmethyl)phenyl]-5-isobutylthiophene-2-sulfonamide (7).** Compound **3** was used according to the general procedure and reacted with 3-cyclopentanylpropionyl chloride (317 μL, 2.10 mmol), which after

purification ($CHCl_3$: MeOH 40:1) gave compound **7** in 76% yield (48 mg, 0.079 mmol). ^{1}H NMR (CD_3OD), δ: 7.48 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.00 (s, 1H), 6.82 (s, 1H), 5.58 (s, 2H), 2.89 (q, J = 7.5 Hz, 2H), 2.69 (d, J = 7.0 Hz, 2H), 2.60 (s, 3H), 2.57 (s, 3H), 1.92 (m, 1H), 1.89 (t, J = 7.5 Hz, 3H), 1.66−1.35 (m, 8H), 1.35−1.22 (m, 4H), 0.95 (d, J = 6.6 Hz, 6H), 0.87 (m, 1H); ^{13}C NMR (CD_3OD), δ: 174.2, 158.1, 154.2, 152.0, 148.5, 146.3, 139.8, 138.6, 135.3, 133.6, 133.2, 130.9, 130.8, 127.9, 120.9, 46.0, 40.8, 40.1, 36.3, 33.5, 31.9, 31.8, 26.1, 24.1, 22.6, 22.3, 16.5, 12.3; Anal. ($C_{33}H_{42}N_4O_3S_2$) C, H, N.

***N*-(Diphenylacetyl)-3-[4-(2-ethyl-5,7-dimethylimidazo-[4,5-*b*]pyridin-3-ylmethyl)phenyl]-5-isobutylthiophene-2-sulfonamide (8).** Compound **3** was used according to the general procedure and reacted with diphenylacetyl chloride (485 mg, 2.10 mmol), which after purification ($CHCl_3$: MeOH 40:1) gave compound **8** in 74% yield (50 mg, 0.074 mmol). ^{1}H NMR ($CDCl_3$), δ: 7.8−7.2 (m, 15H), 6.96 (s, 1H), 5.77 (s, 2H), 3.18 (q, J = 7.5 Hz, 2H), 3.05−2.95 (m, 5H), 2.92 (s, 3H), 2.25 (m, 1H), 1.66 (t, J = 7.5 Hz, 3H), 1.30 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$), δ: 155.9, 152.2, 151.6, 147.2, 145.9, 139.4, 138.4, 137.4, 136.8, 133.2, 132.3, 129.3, 128.9, 128.6, 128.5, 128.4, 127.5, 126.2, 119.5, 58.2, 44.9, 39.3, 30.4, 23.9, 22.2, 21.4, 18.2, 16.3, 12.0; Anal. ($C_{39}H_{40}N_4O_3S_2$) C, H, N.

***N*-Pentanoyl-3-[4-(2-ethyl-5,7-dimethylimidazo[4,5-*b*]-pyridin-3-ylmethyl)phenyl]-5-isobutylthiophene-2-sulfonamide (9).** Compound **3** was used according to the general procedure and reacted with valeryl chloride (249 μL, 2.10 mmol), which after purification ($CHCl_3$: MeOH 40:1) gave compound **9** in 79% yield (45 mg, 0.079 mmol). ^{1}H NMR (CD_3-OD), δ: 7.46 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 7.02 (s, 1H), 6.82 (s, 1H), 5.58 (s, 2H), 2.91 (q, J = 7.6 Hz, 2H), 2.70 (d, J = 7.1 Hz, 2H), 2.60 (s, 3H), 2.57 (s, 3H), 1.90 (m, 1H), 1.83 (t, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H), 1.27 (m, 2H), 1.08 (m, 2H), 0.96 (d, J = 6.6 Hz, 6H), 0.75 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD), δ: 173.4, 158.1, 154.3, 152.2, 148.4, 146.5, 139.8, 138.6, 135.3, 133.2, 133.1, 130.9, 130.8, 127.9, 120.9, 46.0, 40.1, 36.4, 31.9, 27.6, 24.1, 23.2, 22.6, 22.3, 16.5, 14.2, 12.3. Anal. ($C_{30}H_{38}N_4O_3S_2\times0.5H_2O$) C, H, N.

5-Isobutyl-3-[4-(6-nitro-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl)phenyl]-*N*-*tert*-butylthiophene-2-sulfonamide (10). 3-(4-Bromo-benzyl)-6-nitro-2-propyl-3*H*-quinazolin-4-one (672 mg, 1.67 mmol), **2** (789 mg, 2.50 mmol), $Pd(PPh_3)_4$ (60 mg, 0.052 mmol), and NaOH (10 mL, 1M) were dissolved in toluene (40 mL) and ethanol (6 mL) under N_2 (g) atmosphere. The reaction mixture was heated to 100 °C and stirred for 2 h. After dilution with water (50 mL), the reaction mixture was extracted with EtOAc and washed with brine and water. The organic phase was dried and concentrated under vacuum. The crude product was purified by column chromatography (hexane:acetone 5:1) to give the entitled product in 82% yield (814 mg, 1.36 mmol). ^{1}H NMR ($CDCl_3$), δ: 9.15 (d, J = 2.6 Hz, 1H), 8.54 (dd, J = 8.9, 2.6 Hz, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.72 (s, 1H), 5.45 (s, 2H), 4.23 (s, 1H), 2.78 (t, J = 7.4 Hz, 2H), 2.66 (d, J = 7.1 Hz, 2H), 1.95−1.79 (m, 3H), 1.05−0.90 (m, 18H); ^{13}C NMR ($CDCl_3$), δ: 161.4, 160.7, 151.1, 148.6, 145.4, 142.3, 136.7, 135.5, 134.6, 129.7, 128.8, 128.6, 128.4, 126.5, 123.8, 120.3, 54.5, 46.5, 39.1, 37.1, 30.5, 29.4, 22.1, 20.2, 13.8; IR (compression cell), cm^{-1}: 3293, 3079, 2964, 2869, 1685, 1573; Anal. ($C_{30}H_{36}N_4O_5S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl3-[4-(6-nitro-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl)phenyl]thiophene-2-sulfonamide (11).** Compound **10** (25 mg, 0.042 mmol) and anisole (50 μL) were dissolved in TFA (1 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in pyridine (1 mL), and pyrrolidinopyridine (6 mg, 0.04 mmol) was added. The solution was cooled on an ice bath, and butyl chloroformate (107 μL, 0.84 mmol) was added under a N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (hexane:acetone 3:1) to give the pure compound **11** in 79% yield (21.3 mg, 0.033 mmol). ^{1}H NMR ($CDCl_3$), δ: 9.13 (d, J = 2.6 Hz, 1H), 8.51 (dd, J = 3.0, 2.6 Hz, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 6.73 (s, 1H), 5.43 (s, 2H), 4.04 (t, J = 6.6 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H), 2.69 (d, J = 7.1 Hz, 2H), 2.00−1.90 (m, 3H), 1.54−1.43 (m, 2H), 1.30−1.19 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H), 0.98 (d, J = 6.6 Hz, 6H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 161.5, 160.7, 151.8, 151.3, 150.0, 145.8, 145.4, 135.9, 133.8, 129.6, 129.4, 128.7, 128.4, 126.5, 123.8, 120.3, 66.9, 46.6, 39.3, 37.2, 30.5, 30.4, 22.2, 20.3, 18.7, 13.8, 13.5; IR (compression cell), cm^{-1}: 3522, 3098, 2963, 2871, 1745, 1679, 1617, 1567, 1524; Anal. ($C_{31}H_{36}N_4O_7S_2$) C, H, N.

5-Isobutyl-3-[4-(6-amino-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl)phenyl]-*N*-*tert*-butylthiophene-2-sulfonamide (22). Compound **10** (428 mg, 0.717 mmol) and Pd/C (10%, 43.2 mg) were dissolved in MeOH (10 mL), and HCO_2-NH_4 (230 mg, 2.98 mmol) was added under N_2 (g) atmosphere. After an additional 30 min, HCO_2NH_4 (55.3 mg) was added, and after 1 h a third portion of HCO_2NH_4 (55.3 mg) was added. The solution was stirred for 1 h and thereafter diluted with EtOAc (150 mL). The organic phase was washed with water and brine, dried, and concentrated under vacuum. The crude product was purified by column chromatography (hexane: acetone 2:1) to afford the entitled product in 92% yield (375 mg, 0.659 mmol). ^{1}H NMR (10%DMSO-d_6 in $CDCl_3$), δ: 7.47−7.39 (m, 4H), 7.12−7.00 (m, 3H), 6.62 (s, 1H), 5.31 (s, 2H), 4.77 (brs, 2H), 2.64−2.55 (m, 4H), 2.06 (s, 1H), 1.77−1.67 (m, 3H), 0.91−0.84 (m, 18H); ^{13}C NMR (10%DMSO-d_6 in $CDCl_3$), δ: 161.6, 153.6, 153.3, 147.9, 145.3, 142.2, 136.2, 136.0, 133.9, 129.3, 128.7, 127.0, 126.0, 123.4, 120.6, 109.0, 54.1, 46.0, 36.0, 30.6, 30.1, 29.2, 21.8, 20.6, 13.6; IR (compression cell), cm^{-1}: 3315, 2961, 2859, 1657, 1591; Anal. ($C_{30}H_{38}N_4O_3S_2$) C, H, N.

5-Isobutyl-3-{4-[6-(acetylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (23). Compound **22** (30 mg, 0.053 mmol) and DIEA (27 mL, 0.16 mmol) were dissolved in CH_2Cl_2 (5 mL) under N_2 (g) atmosphere and cooled on an ice bath. Acetyl chloride (7.5 μL, 0.11 mmol) was added to the stirred solution. The reaction mixture was stirred overnight at ambient temperature. $CHCl_3$ (50 mL) was added, and the organic phase was washed with $NaHCO_3$ (sat.), dried, and evaporated under vacuum. The crude product was purified by column chromatography (isohexane: EtOAc 10:1) to obtain the entitled compound in 93% yield (30 mg, 0.049 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.54 (s, 1H), 8.29 (dd, J = 8.9, 2.3 Hz, 1H), 8.15 (d, J = 2.3 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 2.2 Hz, 2H), 6.70 (s, 1H), 5.40 (s, 2H), 4.46 (s, 1H), 2.80−2.63 (m, 4H), 2.12 (s, 3H), 1.90−1.76 (m, 3H), 1.24 (s, 1H), 0.98−0.85 (m, 18H); ^{13}C NMR ($CDCl_3$), δ: 168.9, 162.3, 155.6, 148.5, 143.5, 142.5, 137.1, 136.3, 136.2, 134.3, 129.6, 128.9, 127.7, 127.3, 126.3, 120.2, 115.9, 54.5, 46.2, 39.1, 36.8, 30.4, 29.4, 24.4, 22.1, 20.5, 13.8; IR (compression cell), cm^{-1}: 3301, 2965, 2870, 1658, 1593, 1537; Anal. ($C_{32}H_{40}N_4O_4S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl3-{4-[6-(acetylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-thiophene-2-sulfonamide (12).** Compound **23** (30 mg, 0.049 mmol) and anisole (50 μL) were dissolved in TFA (1 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in pyridine (1 mL), and pyrrolidinopyridine (7 mg, 0.05 mmol) was added. The solution was cooled on an ice bath, and butyl chloroformate (60 μL, 0.47 mmol) was added under a N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated, and purified by column chromatography (isohexane:EtOAc 9:1) to give the pure compound **12** in 71% yield (22.7 mg, 0.034 mmol). ^{1}H NMR ($CDCl_3$), δ: 9.11 (s, 1H),

8.47 (brs, 1H), 8.17 (s, 1H), 7.61 (d, $J = 8.9$ Hz, 1H), 7.48 (d, $J = 8.3$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 6.72 (s, 1H), 5.45 (s, 2H), 4.04 (t, $J = 6.6$ Hz, 2H), 2.70−2.63 (m, 4H), 1.91 (s, 3H), 1.88−1.70 (m, 2H), 1.53−1.40 (m, 2H), 1.30−1.15 (m, 2H), 0.99−0.80 (m, 12H); ^{13}C NMR ($CDCl_3$), δ: 170.3, 162.6, 162.5, 156.2, 151.1, 151.0, 144.8, 137.3, 135.7, 134.2, 131.8, 129.9, 129.6, 128.2, 127.4, 125.7, 119.5, 116.1, 66.4, 46.5, 39.3, 36.2, 30.5, 23.8, 22.3, 20.7, 18.8, 13.8, 13.6; IR (compression cell), cm^{-1}: 3304, 2960, 2931, 2871, 1749, 1671, 1593; Anal. ($C_{33}H_{40}N_4O_6S_2$) C, H, N.

5-Isobutyl-3-{4-[6-(benzoylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (24). Compound **22** (30 mg, 0.053 mmol) and DIEA (27 mL, 0.16 mmol) were dissolved in CH_2Cl_2 (5 mL) under N_2 (g) atmosphere and cooled on an ice bath. Benzoyl chloride (12 μL, 0.11 mmol) was added to the stirred solution. The reaction mixture was stirred overnight at ambient temperature. $CHCl_3$ (50 mL) was added, and the organic phase was washed with $NaHCO_3$ (sat.), dried, and evaporated under vacuum. The crude product was purified by column chromatography (isohexane:EtOAc 10:1) to obtain the entitled compound in 92% yield (33 mg, 0.049 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.83 (brs, 1H), 8.50 (d, $J = 8.7$ Hz, 1H), 8.34 (s, 1H), 7.91 (d, $J = 7.2$ Hz, 2H), 7.68 (d, $J = 8.8$ Hz, 1H), 7.54−7.41 (m, 5H), 7.07 (m, 2H), 6.71 (s, 1H), 5.30 (brs, 2H), 4.33 (s, 1H), 2.68−2.63 (m, 4H), 1.95−1.76 (m, 3H), 1.24 (s, 1H), 1.01−0.90 (m, 18H); ^{13}C NMR ($CDCl_3$), δ: 166.0, 162.2, 155.9, 148.4, 142.4, 137.4, 136.3, 136.0, 134.4, 134.2, 131.9, 129.5, 128.9, 128.6, 127.5, 127.4, 126.2, 120.0, 116.7, 54.5, 46.1, 39.1, 36.5, 30.4, 29.4, 22.1, 20.5, 13.8; Anal. ($C_{37}H_{44}N_4O_3S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-{4-[6-(benzoylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-thiophene-2-sulfonamide (13).** Compound **24** (33 mg, 0.049 mmol) and anisole (50 μL) were dissolved in TFA (1 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in pyridine (1 mL), and pyrolidinopyridine (7 mg, 0.05 mmol) was added. The solution was cooled on an ice bath, and butyl chloroformate (60 μL, 0.47 mmol) was added under a N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (isohexane:EtOAc 9:1) to give the pure compound **13** in 70% yield (25 mg, 0.034 mmol). ^{1}H NMR ($CDCl_3$), δ: 9.87 (brs, 1H), 9.76 (s, 1H), 8.90 (d, $J = 8.3$ Hz, 1H), 8.47 (d, $J = 2.2$ Hz, 1H), 7.91 (d, $J = 7.3$ Hz, 2H), 7.68 (d, $J = 9.0$ Hz, 1H), 7.56 (m, 1H), 7.47−7.41 (m, 2H), 7.35 (d, $J = 8.2$ Hz, 2H), 6.73−6.69 (m, 3H), 4.91 (brs, 2H), 4.10 (t, $J = 6.7$ Hz, 2H) 2.68 (d, $J = 7.0$ Hz, 2H), 2.51 (m, 2H), 1.93 (sep, $J = 6.7$ Hz, 1H), 1.69 (sxt, $J = 7.4$ Hz, 2H), 1.52 (m, 2H), 1.23 (m, 2H), 0.97 (d, $J = 6.6$ Hz, 6H), 0.90−0.79 (m, 6H); ^{13}C NMR ($CDCl_3$), δ: 165.9, 162.6, 155.5, 151.0, 150.9, 145.1, 137.5, 135.8, 133.9, 133.6, 132.1, 131.6, 129.9, 129.7, 128.3, 128.1, 128.0, 125.7, 119.6, 116.8, 66.5, 45.8, 39.2, 36.3, 30.5, 30.5, 22.2, 20.4, 18.7, 13.7, 13.6; Anal. ($C_{38}H_{42}N_4O_6S_2$) C, H, N.

5-Isobutyl-3-(4-{6-[(thiophene-2-carbonyl)-amino]-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl}phenyl)-*N*-*tert*-butylthiophene-2-sulfonamide (25). Compound **22** (30 mg, 0.053 mmol) and DIEA (27 mL, 0.16 mmol) were dissolved in CH_2Cl_2 (5 mL) under N_2 (g) atmosphere and cooled on an ice bath. Thiophene-2-carbonyl chloride (12 μL, 0.11 mmol) was added to the stirred solution. The reaction mixture was stirred overnight at ambient temperature. $CHCl_3$ (50 mL) was added, and the organic phase was washed with $NaHCO_3$ (sat.), dried, and evaporated under vacuum. The crude product was purified by column chromatography (isohexane:EtOAc 10:1) to obtain the entitled compound in 65% yield (23 mg, 0.034 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.56 (brs, 1H), 8.44 (dd, $J = 8.9$, 2.5 Hz, 1H), 8.26 (d, $J = 2.3$ Hz, 1H), 7.75 (d, $J = 3.6$ Hz, 1H), 7.69 (d, $J = 8.7$ Hz, 1H), 7.55−7.52 (m, 3H), 7.14−7.06 (m, 3H), 6.72 (s, 1H), 5.37 (brs, 2H), 4.32 (s, 1H), 2.68−2.63 (m, 4H), 1.96−1.77 (m, 3H), 1.01−0.95 (m, 18H); ^{13}C NMR ($CDCl_3$), δ: 162.3, 160.2, 155.6, 148.4, 143.6, 142.5, 139.3, 136.9, 136.3, 136.1, 134.2, 131.2, 129.5, 129.0, 128.7, 127.8, 127.6, 126.1, 120.1, 116.6, 54.4, 46.1, 39.1, 36.6, 30.4, 29.4, 22.1, 20.4, 13.8; Anal. ($C_{35}H_{40}N_4O_4S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-(4-{6-[(thiophene-2-carbonyl)-amino]-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl}phenyl)-thiophene-2-sulfonamide (14).** Compound **25** (23 mg, 0.034 mmol) and anisole (50 μL) were dissolved in TFA (1 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in pyridine (1 mL), and pyrrolidinopyridine (7 mg, 0.05 mmol) was added. The solution was cooled on an ice bath, and butyl chloroformate (60 μL, 0.47 mmol) was added under a N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated, and purified by column chromatography (isohexane:EtOAc 9:1) to give the pure compound **14** in 89% yield (22 mg, 0.030 mmol). ^{1}H NMR ($CDCl_3$), δ: 9.70 (brs, 1H), 9.54 (s, 1H), 8.75 (m, 1H), 8.41 (m, 1H), 7.86 (m, 1H), 7.64 (d, $J = 8.9$ Hz, 1H), 7.51 (d, $J = 4.8$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.04 (brs, 1H), 6.76−6.70 (m, 3H), 5.15 (brs, 2H), 4.10 (t, $J = 6.7$ Hz, 2H), 2.68 (d, $J = 7.0$ Hz, 2H), 2.53 (m, 2H), 1.93 (sep, $J = 6.7$ Hz, 1H), 1.69 (sxt, $J = 7.4$ Hz, 2H), 1.53 (m, 2H), 1.25 (m, 2H), 0.97 (d, $J = 6.6$ Hz, 6H), 0.91−0.96 (m, 6H); ^{13}C NMR ($CDCl_3$), δ: 162.7, 160.2, 155.6, 151.0, 150.9, 145.2, 138.8, 137.0, 135.7, 133.4, 131.3, 129.9, 129.7, 129.6, 128.3, 127.7, 125.3, 119.6, 116.9, 66.5, 46.1, 39.2, 36.3, 30.5, 30.5, 22.2, 20.4, 18.8, 13.7, 13.6; Anal. ($C_{36}H_{40}N_4O_6S_3$) C, H, N.

5-Isobutyl-3-{4-[6-(ethylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (26). Compound **22** (200 mg, 0.353 mmol), acetaldehyde (24 μL, 0.42 mmol), and acetic acid (101 μL, 1.76 mmol) were dissolved in CH_2ClCH_2Cl (20 mL) and stirred for 30 min. $NaB(OAc)_3H$ (172 mg, 0.811 mmol) was added, and the reaction mixture was stirred overnight. $CHCl_3$ (50 mL) was added, and the organic phase was washed with $NaHCO_3$ and dried. The solvent was removed under vacuum, and the crude product was purified by column chromatography (isohexane: EtOAc 10:1) to give the entitled product in 95% yield (200 mg, 0.336 mmol). ^{1}H NMR ($CDCl_3$), δ: 7.60−7.53 (m, 3H), 7.29 (d, $J = 2.8$ Hz, 1H), 7.24 (d, $J = 9.6$ Hz, 2H), 7.05 (dd, $J = 2.8$, 8.8 Hz, 1H), 6.71 (s, 1H), 5.43 (s, 2H), 4.14 (s, 1H), 3.23 (q, $J = 7.3$ Hz, 2H), 2.73−2.64 (m, 4H), 1.31−1.77 (m, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.00 (t, $J = 7.3$ Hz, 3H), 0.95−0.93 (m, 15H); ^{13}C NMR ($CDCl_3$), δ: 162.3, 152.9, 148.4, 147.2, 142.5, 137.5, 136.8, 136.4, 134.2, 129.5, 128.8, 127.5, 126.5, 122.5, 121.2, 104.9, 54.5, 46.2, 39.1, 38.5, 36.6, 30.5, 29.5, 22.1, 21.0, 14.6, 13.9; IR (compression cell), cm^{-1}: 3380, 3292, 2965, 2930, 2871, 1657, 1648, 1591, 1512; Anal. ($C_{32}H_{42}N_4O_3S_2$) C, H, N.

5-Isobutyl-3-{4-[6-(benzylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (27). Compound **22** (200 mg, 0.353 mmol), benzaldehyde (39 μL, 0.39 mmol), and acetic acid (101 μL, 1.76 mmol) were dissolved in CH_2ClCH_2Cl (20 mL) and stirred for 30 min. $NaB(OAc)_3H$ (172 mg, 0.811 mmol) was added, and the reaction mixture was stirred overnight. $CHCl_3$ (50 mL) was added, and the organic phase was washed with $NaHCO_3$ and dried. The solvent was removed under vacuum, and the crude product was purified by column chromatography (isohexane: EtOAc 10:1) to give the entitled product in 95% yield (220 mg, 0.335 mmol). ^{1}H NMR ($CDCl_3$), δ: 7.62−7.55 (m, 3H), 7.41−7.28 (m, 6H), 7.26−7.21 (m, 2H), 7.09 (dd, $J = 8.9$, 2.9 Hz, 1H), 6.71 (s, 1H), 5.41 (s, 2H), 4.42 (s, 2H), 4.10 (s, 1H), 2.75−2.62 (m, 4H), 1.95−1.74 (m 3H), 1.03−0.94 (m, 18H); ^{13}C NMR ($CDCl_3$), δ: 148.4, 146.9, 142.4, 136.6, 136.4, 134.2, 129.5, 128.7, 127.5, 126.4, 122.3, 121.1, 105.3, 54.4, 48.1, 46.2, 39.1, 36.5, 30.4, 29.6, 29.4, 22.1, 20.9, 13.8; IR (compression cell), cm^{-1}: 3294, 2960, 1655, 1619, 1509; Anal. ($C_{37}H_{44}N_4O_3S_2$) C, H, N.

General Procedure for the Preparation of Compounds 28−30. Compound **26** (67 mg, 0.11 mmol) and DIEA (97 μL, 0.56 mmol) were dissolved in CH_2Cl_2 (5 mL) and cooled on an ice bath. The acid chloride (5 equiv) was added to the solution, and the reaction mixture was stirred overnight at ambient temperature. $CHCl_3$ (50 mL) was added, and the organic phase was washed with $NaHCO_3$ (sat.), dried, and concentrated under vacuum. The crude products were purified by column chromatography to give the pure products **28**−**30**.

5-Isobutyl-3-{4-[6-(*N*-acetylethylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (28). Compound **26** was used according to the general procedure and reacted with acetyl chloride (40 μL, 0.56 mmol) which gave after purification (isohexane:EtOAc 10:1) compound **28** in 92% yield (66 mg, 0.10 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.10 (d, J = 2.3 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.55 (m, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 6.73 (s, 1H), 5.45 (s, 2H), 4.05 (t, J = 6.6 Hz, 2H), 3.81 (q, J = 7.1 Hz, 2H), 2.83 (t, J = 7.4 Hz, 2H), 2.70 (d, J = 7.1 Hz, 2H), 1.94−1.85(m, 6H), 1.56−1.44 (m, 1H), 1.28−1.19 (m, 2H), 1.16−1.06 (m, 6H), 0.98 (d, J = 6.6 Hz, 6H), 0.85 (t, J = 7.42 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 169.8, 161.1, 159.5, 151.7, 150.2, 145.8, 144.0, 141.7, 135.6, 135.2, 133.9, 130.8, 129.7, 129.3, 127.5, 126.4, 126.2, 120.5, 66.9, 46.8, 44.1, 39.3, 36.2, 30.5, 30.4, 22.9, 22.2, 21.1, 18.7, 13.8, 13.6, 13.1; IR (compression cell), cm^{-1}: 2960, 2871, 1746, 1671, 1591; Anal. ($C_{34}H_{44}N_4O_4S_2$) C, H, N.

5-Isobutyl-3-{4-[6-(*N*-benzoyl-ethylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (29). Compound **26** was used according to the general procedure and reacted with benzoyl chloride (66 μL, 0.56 mmol), which after purification (isohexane:EtOAc 10:1) gave compound **29** in 93% yield (73 mg, 0.10 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.04 (d, J = 2.5 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.34−7.13 (m, 8H), 6.72 (s, 1H), 5.39 (s, 2H), 4.08−4.01 (m, 4H), 2.80−2.68 (m, 4H), 1.99−1.77 (m, 3H), 1.53−1.49 (m, 2H), 1.27−11.20 (m, 5H), 1.03−0.97 (m, 9H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 170.3, 161.6, 158.5, 151.8, 150.0, 145.9, 142.1, 136.0, 135.7, 135.3, 135.1, 133.8, 130.7, 129.9, 129.6, 129.4, 128.7, 128.1, 127.0, 126.4, 124.5, 120.4, 66.9, 46.6, 45.7, 39.3, 36.5, 30.5, 30.4, 22.2, 20.9, 18.7, 13.9, 13.6, 13.1; IR (compression cell), cm^{-1}: 3058, 2961, 2932, 2872, 1745, 1644; Anal. ($C_{39}H_{46}N_4O_4S_2$) C, H, N.

5-Isobutyl-3-(4-{6-[*N*-(thiophene-2-carbonyl)-ethylamino]-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl}phenyl)-*N*-*tert*-butylthiophene-2-sulfonamide (30). Compound **26** was used according to the general procedure and reacted with thiophene-2-carbonyl chloride (60 μL, 0.56 mmol) gave after purification (isohexane:EtOAc 10:1) compound **30** in 92% yield (73 mg, 0.10 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.18 (d, J = 2.3 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.52 (dd, J = 6.1, 2.5 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.30−7.21 (m, 3H), 6.85 (d, J = 2.6 Hz, 1H), 6.77 (m, 1H), 6.73 (s, 1H), 5.41 (s, 2H), 4.10−3.90 (m, 4H), 2.78−2.66 (m, 4H), 1.89−1.83 (m, 3H), 1.54−1.42 (m, 2H), 1.30−1.17 (m, 5H), 1.05−0.94 (m, 9H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 162.2, 162.0, 157.9, 151.6, 150.2, 146.7, 145.8, 140.8, 137.9, 136.4, 135.5, 133.6, 132.5, 130.8, 130.6, 129.5, 129.4, 128.7, 126.7, 126.4, 126.3, 121.0, 66.8, 46.5, 46.2, 39.3, 37.1, 30.5, 30.4, 22.2, 20.5, 18.7, 13.9, 13.6, 12.8; IR (compression cell), cm^{-1}:3074, 2961, 2872, 1747, 1672, 1591; Anal. ($C_{37}H_{44}N_4O_4S_3 \times H_2O$) C, H, N.

General Procedure for the Preparation of the Compounds 31−34. Compound **27** (73 mg, 0.11 mmol) and DIEA (97 μL, 0.56 mmol) were dissolved in CH_2Cl_2 (5 mL) and cooled on an ice bath. The acid chloride (5 equiv) was added to the solution, and the reaction mixture was stirred overnight at ambient temperature. $CHCl_3$ (50 mL) was added, and the organic phase was washed with $NaHCO_3$ (sat.), dried, and concentrated under vacuum. The crude products were purified by column chromatography to give the pure products **31**−**34**.

5-Isobutyl-3-{4-[6-(*N*-acetyl-benzylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (31). Compound **27** was used according to the general procedure and reacted with acetyl chloride (40 μL, 0.56 mmol), which after purification (isohexane:EtOAc 10:1) gave compound **31** in 96% yield (75 mg, 0.11 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.00 (s, 1H), 7.70−7.57 (m, 2H), 7.30−7.18 (m, 9H), 6.71 (s, 1H), 5.41 (brs, 2H), 4.96 (s, 2H), 4.06 (s, 1H), 2.75 (m, 2H), 2.66 (d, J = 7.3 Hz, 2H), 1.95−1.76 (m, 6H), 1.05−0.94 (m, 18H); ^{13}C NMR ($CDCl_3$), δ: 148.5, 142.3, 141.2, 136.8, 136.5, 135.8, 134.8, 134.6, 129.6, 128.8, 128.5, 128.4, 128.2, 127.5, 126.4, 126.1, 120.8, 54.5, 52.8, 46.4, 39.1, 36.6, 30.5, 29.5, 22.9, 22.1, 20.6, 13.8; IR (compression cell), cm^{-1}: 2959, 1672, 1653, 1592; Anal. ($C_{39}H_{46}N_4O_4S_2$) C, H, N.

5-Isobutyl-3-{4-[6-(*N*-pentanoylbenzylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (32). Compound **27** was used according to the general procedure and reacted with pentanoyl chloride (66 μL, 0.56 mmol), which after purification (isohexane:EtOAc 10:1) gave compound **32** in 94% yield (78 mg, 0.11 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.00 (d, J = 2.2 Hz, 1H), 7.67−7.54 (m, 3H), 7.33−7.15 (m, 8H), 6.72 (s, 1H), 5.42 (s, 2H), 4.96 (s, 2H), 4.10 (s, 1H), 2.73 (t, 2H, 7.5 Hz), 2.67 (d, J = 7.1 Hz, 2H), 2.10 (br t, J = 6.9 Hz, 2H), 1.90 (m, 1H), 1.82 (m, 2H), 1.60 (m, 2H), 1.22 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H), 0.98 (s, 9H), 0.96 (d, J = 6.8 Hz, 6H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 172.9, 161.8, 157.7, 148.6, 146.4, 142.4, 141.0, 140.8, 137.1, 136.4, 136.1, 135.0, 134.5, 129.7, 128.8, 128.7, 128.5, 127.5, 126.5, 121.0, 54.5, 53.1, 46.3, 39.1, 36.9, 34.3, 30.5, 29.5, 27.5, 22.3, 22.1, 20.5, 13.9; IR (compression cell), cm^{-1}: 3293, 3063, 2959, 1671, 1593; Anal. ($C_{42}H_{52}N_4O_4S_2$) C, H, N.

5-Isobutyl-3-{4-[6-(*N*-benzoylbenzylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-*N*-*tert*-butylthiophene-2-sulfonamide (33). Compound **27** was used according to the general procedure and reacted with benzoyl chloride (65 μL, 0.56 mmol), which after purification (isohexane:EtOAc 10:1) gave compound **33** in 93% yield (79 mg, 0.10 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.04 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.49−7.35 (m, 3H), 7.34−7.11 (m, 11H), 6.71 (s, 1H), 5.37 (s, 2H), 5.21 (s, 2H), 4.19 (s, 1H), 2.72−2.64 (m, 4H), 1.94 (m, 1H), 1.77 (m, 2H), 1.00−0.94 (m, 18H); ^{13}C NMR ($CDCl_3$), δ: 170.6, 161.5, 157.5, 148.5, 142.3, 141.8, 136.8, 136.5, 135.9, 135.3,134.6, 134.4, 129.9, 129.5, 128.7, 128.5, 128.2, 127.9, 127.4, 126.4, 124.3, 120.4, 54.4, 53.9, 46.3, 39.1, 36.6, 30.4, 29.4, 22.0, 20.5, 13.8; IR (compression cell), cm^{-1}: 3292, 2961, 1672, 1647; Anal. ($C_{44}H_{48}N_4O_4S_2$) C, H, N.

5-Isobutyl-3-(4-{6-[*N*-(thiophene-2-carbonyl)-benzylamino]-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl}phenyl)-*N*-*tert*-butylthiophene-2-sulfonamide (34). Compound **27** was used according to the general procedure and reacted with thiophene-2-carbonyl chloride (60 μL, 0.56 mmol), which after purification (isohexane:EtOAc 10:1) gave compound **34** in 86% yield (73 mg, 0.095 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.13 (d, J = 2.5 Hz, 1H), 7.64−7.50 (m, 3H), 7.36−7.18 (m, 9H), 6.89 (dd, J = 3.8, 1.1 Hz, 1H), 6.79 (dd, J = 4.9, 3.8 Hz, 1H), 6.72 (s, 1H), 5.41 (s, 2H), 5.14 (s, 2H), 4.18 (s, 1H), 2.73 (t, J = 7.6 Hz, 2H), 2.67 (d, J = 6.9 Hz, 2H), 1.98−1.76 (m, 3H), 0.89−1.09 (m, 18H). ^{13}C NMR ($CDCl_3$), δ: 162.5, 161.7, 157.9, 148.5, 146.4, 142.4, 140.8, 137.5, 136.6, 136.4, 136.0, 135.6, 134.4, 132.8, 131.0, 129.6, 128.8, 128.7, 128.5, 128.3, 127.6, 126.7, 126.5, 126.3, 120.9, 54.7, 54.5, 46.4, 39.1, 36.9, 30.5, 29.4, 22.1, 20.4, 13.9; IR (compression cell), cm^{-1}: 3289, 3081, 2963, 1672, 1624, 1609, 1589; Anal. ($C_{42}H_{46}N_4O_4S_3$) C, H, N.

General Procedure for the Preparation of Compounds 15−21. Compounds **28**−**34** and anisole (150 μL) was dissolved in TFA (5 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in pyridine (3 mL), and pyrrolidinopyridine (1 equiv) was added. The solution was cooled on an ice bath and the butyl chloroformate (20 equiv) was added under a N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and coevaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was

dried, evaporated and purified by column chromatography to give the pure compounds **15**−**21**.

***N*-Butyloxycarbonyl-5-isobutyl-3-{4-[6-(*N*-acetyl-ethylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-thiophene-2-sulfonamide (15).** Compound **28** (66 mg, 0.10 mmol) was used according to the general procedure and gave after purification (isohexane:EtOAc 5:1) compound **15** in 40% yield (27 mg, 0.040 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.10 (d, J = 2.3 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.55 (m, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 10.0 Hz, 2H), 6.73 (s, 1H), 5.45 (s, 2H), 4.05 (t, J = 6.6 Hz, 2H), 3.81 (q, J = 7.1 Hz, 2H), 2.83 (t, J = 7.4 Hz, 2H), 2.70 (d, J = 7.1 Hz, 2H), 1.94−1.85 (m, 6H), 1.50 (m, 1H), 1.28−1.19 (m, 2H), 1.16−1.06 (m, 6H), 0.98 (d, J = 6.6 Hz, 6H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 169.8, 161.1, 159.5, 151.7, 150.2, 145.8, 144.0, 141.7, 135.6, 135.2, 133.9, 130.8, 129.7, 129.3, 127.5, 126.4, 126.2, 120.5, 66.9, 46.8, 44.1, 39.3, 36.2, 30.5, 30.4, 22.9, 22.2, 21.1, 18.7, 13.8, 13.6, 13.1; IR (compression cell), cm^{-1}:2960, 2871, 1746, 1671, 1591; Anal. ($C_{35}H_{44}N_4O_6S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-{4-[6-(*N*-benzoylethylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-thiophene-2-sulfonamide (16).** Compound **29** (73 mg, 0.10 mmol) was used according to the general procedure and gave after purification (isohexane:EtOAc 5:1) compound **16** in 44% yield (33 mg, 0.044 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.04 (d, J = 2.5 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.34−7.13 (m, 8H), 6.72 (s, 1H), 5.39 (s, 2H), 4.08−4.01 (m, 4H), 2.80−2.68 (m, 4H), 1.99−1.77 (m, 3H), 1.53−1.49 (m, 2H), 1.27−11.20 (m, 5H), 1.03−0.97 (m, 9H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 170.3, 161.6, 158.5, 151.8, 150.0, 145.9, 142.1, 136.0, 135.7, 135.3, 135.1, 133.8, 130.7, 129.9, 129.6, 129.4, 128.7, 128.1, 127.0, 126.4, 124.5, 120.4, 66.9, 46.6, 45.7, 39.3, 36.5, 30.5, 30.4, 22.2, 20.9, 18.7, 13.9, 13.6, 13.1; IR (compression cell), cm^{-1}: 3058, 2961, 2932, 2872, 1745, 1644; Anal. ($C_{40}H_{46}N_4O_6S_2\times\cdot H_2O$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-(4-{6-[*N*-(thiophene-2-carbonyl)ethylamino]-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl}phenyl)-thiophene-2-sulfonamide (17).** Compound **30** (73 mg, 0.10 mmol) was used according to the general procedure and gave after purification (isohexane:EtOAc 5:1) compound **17** in 93% yield (70 mg, 0.093 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.18 (d, J = 2.3 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.52 (dd, J = 6.1, 2.5 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.30−7.21 (m, 3H), 6.85 (d, J = 2.6 Hz, 1H), 6.77 (m, 1H), 6.73 (s, 1H), 5.41 (s, 2H), 4.10−3.90 (m, 4H), 2.78−2.66 (m, 4H), 1.89−1.83 (m, 3H), 1.54−1.42 (m, 2H), 1.30−1.17 (m, 5H), 1.05−0.94 (m, 9H), 0.85 (t, J = 7.26 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 162.2, 162.0, 157.9, 151.6, 150.2, 146.7, 145.8, 140.8, 137.9, 136.4, 135.5, 133.6, 132.5, 130.8, 130.6, 129.5, 129.4, 128.7, 126.7, 126.4, 126.3, 121.0, 66.8, 46.5, 46.2, 39.3, 37.1, 30.5, 30.4, 22.2, 20.5, 18.7, 13.9, 13.6, 12.8; IR (compression cell), cm^{-1}: 3074, 2961, 2872, 1747, 1672, 1591; Anal. ($C_{38}H_{44}N_4O_6S_3\times\cdot H_2O$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-{4-[6-(*N*-acetyl-benzylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-thiophene-2-sulfonamide (18).** Compound **31** (75 mg, 0.11 mmol) was used according to the general procedure and gave after purification (isohexane:EtOAc 5:1) compound **18** in 77% yield (63 mg, 0.085 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.03 (s, 1H), 7.68−7.62 (m, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.32−7.14 (m, 8H), 6.72 (s, 1H), 5.40 (s, 2H), 4.95 (s, 2H), 4.03 (t, J = 6.6 Hz, 2H), 2.76 (m, 2H), 2.69 (d, J = 7.3 Hz, 2H), 2.01−1.74 (m, 6H), 1.49 (m, 2H), 1.23 (m, 2H), 1.05−0.94 (m, 9H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 170.2, 161.6, 151.6, 150.0, 145.8, 141.0, 136.8, 136.1, 134.8, 133.6, 130.7, 129.5, 128.5, 128.1, 127.5, 126.3, 126.1, 120.8, 66.8, 52.8, 46.5, 39.2, 36.7, 30.4, 30.3, 29.6, 22.8, 22.1, 20.7, 18.7, 13.8, 13.5; IR (compression cell), cm^{-1}: 2959, 1746, 1670, 1591; Anal. ($C_{40}H_{46}N_4O_6S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-{4-[6-(*N*-pentanoyl-benzylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]-phenyl}-thiophene-2-sulfonamide (19).** Compound **32** (78 mg, 0.11 mmol) was used according to the general procedure and gave after purification (isohexane:EtOAc 5:1) compound **19** in 68% yield (59 mg, 0.075 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.01 (d, J = 2.3 Hz, 1H), 7.65 (brs, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.30−7.10 (m, 8H), 6.72 (brs, 1H), 5.40 (s, 2H), 4.95 (s, 2H), 4.04 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 7.7 Hz, 2H), 2.69 (d, J = 7.1 Hz, 2H), 2.09 (br t, J = 7.0 Hz, 2H), 1.92 (m, 1H), 1.82 (m, 2H), 1.59 (m, 2H), 1.49 (m, 2H), 1.32−1.12 (m, 4H), 1.02 (t, J = 7.2 Hz, 3H), 0.98 (d, J = 6.6 Hz, 6H), 0.85 (t, J = 7.2 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 172.9, 161.8, 158.0, 151.6, 150.1, 146.2, 145.9, 140.7, 137.1, 136.3, 135.0, 133.5, 130.7, 129.5, 129.4, 128.6, 128.5, 128.3, 127.4, 126.4, 126.2, 120.9, 66.8, 53.0, 46.5, 39.3, 36.9, 34.2, 30.5, 30.4, 27.5, 22.3, 22.2, 20.6, 18.7, 13.8, 13.5; IR (compression cell), cm^{-1}: 3500−2700(br), 3059, 2959, 1749, 1671, 1592; Anal. ($C_{43}H_{52}N_4O_6S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-{4-[6-(*N*-benzoyl-benzylamino)-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl]phenyl}-thiophene-2-sulfonamide (20).** Compound **33** (79 mg, 0.10 mmol) was used according to the general procedure and gave after purification (isohexane:EtOAc 5:1) compound **20** in 76% yield (61 mg, 0.076 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.02 (d, J = 2.6 Hz, 1H), 7.62 (brs, 1H), 7.45−7.08 (m, 16H), 6.72 (s, 1H), 5.35 (s, 2H), 5.21 (s, 2H), 4.03 (t, J = 6.6 Hz, 2H), 2.77−2.65 (m, 4H), 2.01−1.67 (m, 3H), 1.47 (m, 2H), 1.22 (m, 2H), 1.02−0.94 (m, 9H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 170.6, 161.7, 157.7, 151.6, 150.0, 145.8, 141.8, 136.8, 136.1, 135.3, 134.7, 133.5, 130.8, 129.9, 129.4, 129.3, 128.8, 128.5, 128.2, 128.0, 127.5, 126.4, 124.2, 120.4, 66.8, 53.9, 46.4, 39.2, 36.6, 30.4, 30.3, 22.1, 20.5, 18.6, 13.8, 13.5; IR (compression cell), cm^{-1}: 2960, 2872, 1746, 1649; Anal. ($C_{45}H_{48}N_4O_6S_2$) C, H, N.

***N*-Butyloxycarbonyl-5-isobutyl-3-(4-{6-[*N*-(thiophene-2-carbonyl)benzylamino]-4-oxo-2-propyl-4*H*-quinazolin-3-ylmethyl}phenyl)thiophene-2-sulfonamide (21).** Compound **34** (73 mg, 0.095 mmol) was used according to the general procedure and gave after purification (isohexane:EtOAc 5:1) compound **21** in 63% yield (49 mg, 0.060 mmol). ^{1}H NMR ($CDCl_3$), δ: 8.14 (d, J = 2.3 Hz, 1H), 7.66 (brs, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.36−7.16 (m, 9H), 6.90 (dd, J = 3.8, 1.1 Hz, 1H), 6.78 (dd, J = 5.0, 3.8 Hz, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 5.13 (s, 2H), 4.04 (t, J = 6.5 Hz, 2H), 2.79 (br t, J = 7.4 Hz, 2H), 2.69 (d, J = 6.9 Hz, 2H), 1.93 (m, 1H), 1.85 (m, 2H), 1.49 (m, 2H), 1.24 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H), 0.98 (d, J = 6.6 Hz, 6H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$), δ: 162.6, 161.7, 158.4, 151.7, 150.1, 145.9, 140.9, 137.4, 136.6, 136.2, 135.8, 133.6, 132.9, 131.1, 130.7, 129.5, 129.4, 128.7, 128.5, 128.0, 127.6, 126.8, 126.5, 126.4, 120.8, 66.9, 54.7, 46.5, 39.3, 36.8, 30.5, 30.4, 22.2, 20.6, 18.7, 13.8, 13.6; IR (compression cell), cm^{-1}: 3219, 3062, 2961, 1750, 1673, 1627, 1587; Anal. ($C_{43}H_{46}N_4O_6S_3$) C, H, N.

Rat Liver Membrane AT_1 Receptor Binding Assay. Rat liver membranes were prepared according to the method of Dudley et al.[17] 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 presoaked 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 gamma counter. The characteristics of the Ang II binding AT_1 receptor was determinated 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 mM Ang II. The specific binding was determined by subtracting the nonspecific binding from the total bound [^{125}I]-AngII. The apparent dissociation constant (K_d = 1.7 ± 0.1 nM, [L] = 0.057 nM) were determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software,-UK). The binding data best fitted with a one-site fit. All determinations were performed in triplicate.

Porcine (pig) Myometrial Membrane AT_2 Receptor Binding Assay. Myometrial membranes were prepared from porcine uteri according to the method by Nielsen et al.[18] A presumable interference by binding to AT_1 receptors was blocked by addition of 1 μM losartan. 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 presoaked 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 gamma counter. The characteristics of the Ang II binding AT2 receptor were determined by using six different concentrations (0.03−5 nmol/L) of the labeled [^{125}I]-Ang II. Nonspecific binding was determined in the presence of 1 mM Ang II. The specific binding was determined by subtracting the nonspecific binding from the total bound [^{125}I]-Ang II. The apparent dissociation constant (K_d = 0.7 ± 0.1 nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data best fitted with a one-site fit. All determinations were performed in triplicate.

In Vivo Setting. General. The in vivo experiments were approved by the Animal Ethics Committee of Gothenburg University and performed on nonfasted Male Sprague−Dawley rats (Möllegård Breeding Center Ltd., Ejby, Denmark). For induction of anesthesia, pentobarbital, was injected intraperitoneally (60 mg kg^{-1} bw). General anesthesia was maintained with α-chloralose administered intravenously as a bolus (50 mg kg^{-1} bw) followed by continuous infusion (25 mg kg^{-1} h^{-1}). A catheter was inserted into the trachea to ensure free airways. A femoral artery and one or two veins were catheterized for subsequent blood pressure measurements and drug infusions, respectively. The body temperature was maintained at 38 °C with a heating pad and lamp, both controlled thermostatically. Blood pressure was measured by a Statham P23Dc transducer (Statham, Hato Rey, Puerto Rico) connected to a PE−50 catheter in the right femoral artery. Pressure data were integrated by a microcomputer to mean arterial pressure (MAP) over 5 min. To avoid acidosis and dehydration due to the surgical trauma and the long period of general anesthesia, an 1.7% glucose solution containing 0.03 M $NaHCO_3$, made isotonic with saline, was given intravenously throughout the experiments (1 mL h^{-1}). Vehicle used for losartan: 150 mM $NaCl_{(aq)}$, compound **1**: 1% EtOH in 150 mM $NaCl_{(aq)}$ and compound **11**: 1% DMSO in 150 mM $NaCl_{(aq)}$.

Secretion. Duodenal mucosal alkaline (HCO_3^-) secretion was measured by a pH-stat titration technique. This technique has been described previously,[14] but a brief summary will be given here. After midline laparotomy, a segment of the duodenum, with its proximal end approximately 1 cm distal to the pylorus, with intact vascular supply was isolated between two glass tubes connected to a reservoir containing isotonic saline maintained at 38 °C by a water-jacket. Saline was recirculated through the segment by means of a gas-lift (pure air). The common bile duct was catheterized approximately 5 mm proximal to the papilla of water, to avoid contamination of the segment by bile and pancreatic juice. Alkaline secretion to the perfusate was continuously titrated to pH 7.4 with 0.02 M HCl controlled by a pH-stat device.

Statistics. Changes in alkaline secretion and mean arterial pressure were analyzed by ANOVA (Bonferroni post hoc). Data obtained during the last 15 min before administration of drug were regarded as basal conditions. Net change was defined as the difference between basal conditions and data obtained between 15 min to 30 min following onset of each drug administration. Comparisons between groups were made by one-way ANOVA and a *t*-test. Values given in the figures are means ± SEM. A *p*-value ≤ 0.05 was considered significant.

Acknowledgment. We gratefully acknowledge support from the Swedish Research Council (VR), the Swedish Foundation for Strategic Research (SSF), and Knut and Alice Wallenberg Foundation (VRmedicine 8663).

References

(1) (a) De Gasparo, M.; Catt, K. J.; Inagami, T.; Wright, J. W.; Unger, T. International union of pharmacology. XXIII. The angiotensin II receptors. *Pharmacol. Rev.* **2000**, *52*, 415−472. (b) Birkenhager, W. H.; de Leeuw, P. W. Non-peptide angiotensin type 1 receptor antagonists in the treatment of hypertension. *J. Hypertens.* **1999**, *17*, 873−881. (c) Greenlee, W. J. Hypertension − Treatment by blockade of the renin-angiotensin system. *Pharmacochem. Lib.* **1997**, *28*, 97−107. (d) Timmermans, P. B. M. W. M.; Smith, R. D. Antihypertensive Agents. *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; John Wiley & Sons: New York, 1996. (e) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. Nonpeptide angiotensin II receptor antagonists: The next generation in antihypertensive therapy. *J. Med. Chem.* **1996**, *39*, 625−656. (f) Ashton, W. T.; Chang, L. L.; Flanagan, K. L.; Mantlo, N. B.; Ondeyka, D. L.; Kim, D.; de Laszlo, S. E.; Glinka, T. W.; Rivero, R. A.; Kevin, N. J.; Chang, R. S. L.; Siegl, P. K. S.; Kivlighn, S. D.; Greenlee, W. J. AT1/AT2-balanced angiotensin II antagonists. *Euro. J. Med. Chem.* **1995**, *30*, 255−266. (g) Ashton, W. T. Nonpeptide angiotensin II receptor antagonists. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1105−1142. (h) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. The discovery of DuP 753, a potent, orally active nonpeptide angiotensin II receptor antagonist. *Med. Res. Rev.* **1992**, *12*, 149−191.

(2) (a) Perlman, S.; Schambye, H. T.; Rivero, R. A.; Greenlee, W. J.; Hjorth, S. A.; Schwartz, T. W. Non-peptide angiotensin agonist. Functional and molecular interaction with the AT1 receptor. *J. Biol. Chem.* **1995**, *270*, 1493−1496. (b) Kivlighn, S. D.; Huckle, W. R.; Zingaro, G. J.; Rivero, R. A.; Lotti, V. J.; Chang, R. S. L.; Schorn, T. W.; Kevin, N.; Johnson, R. G., Jr.; Greenlee, W. J.; Siegl, P. K. S. Discovery of L-162,313: a nonpeptide that mimics the biological actions of angiotensin II. *Am. J. Physiol.* **1995**, *268*, R820−R823.

(3) Perlman, S.; Costa-Neto, C. M.; Miyakawa, A. A.; Schambye, H. T.; Hjorth, S. A.; Paiva, A. C. M.; Rivero, R. A.; Greenlee, W. J.; Schwartz, T. W. Dual agonistic and antagonistic property of nonpeptide angiotensin AT1 ligands: susceptibility to receptor mutations. *Mol. Pharmacol.* **1997**, *51*, 301−311.

(4) Huckle, W. R.; Kivlighn, S. D.; Zingaro, G. J.; Kevin, N. J.; Rivero, R. A.; Chang, R. S. L.; Greenlee, W. J.; Siegl, P. K. S.; Johnson, R. G. Angiotensin II receptor-mediated activation of phosphoinositide hydrolysis and elevation of mean arterial pressure by a nonpeptide, L-163, 491. *Can. J. Physiol. Pharmacol.* **1994**, *72*, 543.

(5) Gallinat, S.; Busche, S.; Raizada, M. K.; Sumners, C. The angiotensin II type 2 receptor: an enigma with multiple variations. *Am. J. Physiol.* **2000**, *278*, E357-E374.

(6) de Gasparo, M.; Siragy, H. M. The AT2 receptor: fact, fancy and fantasy. *Regul. Peptides* **1999**, *81*, 11−24.

(7) Johansson, B.; Holm, M.; Ewert, S.; Casselbrant, A.; Pettersson, A.; Fandriks, L. Angiotensin II type 2 receptor-mediated duodenal mucosal alkaline secretion in the rat. *Am. J. Physiol.* **2001**, *280*, G1254-G1260.

(8) Blankley, C. J.; Hodges, J. C.; Klutchko, S. R.; Himmelsbach, R. J.; Chucholowski, A.; Connolly, C. J.; Neergaard, S. J.; Van Nieuwenhze, M. S.; Sebastian, A.; Quin, J., III. Synthesis and structure−activity relationships of a novel series of nonpeptide angiotensin II receptor binding inhibitors specific for the AT2 subtype. *J. Med. Chem.* **1991**, *34*, 3248−3260.

(9) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., 3rd; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, W.-E.; Timmermans, P. B. M. W. M. Nonpeptide angiotensin II receptor antagonists: the discovery of a series of *N*-(biphenylylmethyl)imidazoles as potent, orally active antihypertensives. *J. Med. Chem.* **1991**, *34*, 2525−2547.

(10) (a) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. D.; Schorn, T. S.; Zingaro, G. J.; Siegl, P. K. S. A potent, orally active, balanced affinity angiotensin II AT1 antagonist and AT2 binding inhibitor. *J. Med. Chem.* **1993**, *36*, 3207−3210. (b) Glinka, T. W.; de Laszlo, S. E.; Tran, J.; Chang, R. S.; Chen, T. B.; Lotti, V. J.; Greenlee, W. J. L-161,-638: a potent AT2 selective quinazolinone angiotensin II binding inhibitor. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1479−1484. (c) Glinka, T. W.; de Laszlo, S. E.; Siegl, P. K. S.; Chang, R. S.; Kivlighn, S. D.; Schorn, T. S.; Faust, K. A.; Chen, T. B.; Zingaro,

G. J.; et al. A new class of balanced AT1/AT2 angiotensin II antagonists: quinazolinone AII antagonists with acylsulfonamide and sulfonylcarbamate acidic functionalities. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 81−86. (d) Chakravarty, P. K.; Strelitz, R. A.; Chen, T. B.; Chang, R. S. L.; Lotti, V. J.; Zingaro, G. J.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. Quinazolinone biphenyl acylsulfonamides: a potent new class of angiotensin-II receptor antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 75−80. (e) de Laszlo, S. E.; Chang, R. S.; Chen, T.-B.; Faust, K. A.; Greenlee, W. J.; Kivlighn, S. D.; Lotti, V. J.; O'Malley, S. S.; Schorn, T. W.; et al. The SAR of 6-(N-alkyl-N-acyl)-2-propyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolinones as balanced affinity antagonists of the human AT1 and AT2 receptors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1359−1364. (f) de Laszlo, S. E.; Glinka, T. W.; Greenlee, W. J.; Ball, R.; Nachbar, R. B.; Prendergast, K. The design, binding affinity prediction and synthesis of macrocyclic angiotensin II AT1 and AT2 receptor antagonists. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 923−928. (g) Levin, J. I.; Chan, P. S.; Porter, R. S. 2,3,6-Substituted quinazolinones as angiotensin II receptor antagonists. *Drugs Future* **1995**, *20*, 55−65.

(11) (a) Kevin, N. J.; Rivero, R. A.; Greenlee, W. J.; Chang, R. S. L.; Chen, T. B. Substituted phenylthiophene benzoylsulfonamides with potent binding affinity to angiotensin II AT1 and AT2 receptors. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 189−194. (b) Kivlighn, S.; Lotti, V. J.; Rivero, R. A.; Siegl, P. K. S.; Zingaro, G. J. Preparation of thiophene-substituted imidazo[4,5-b]pyridine angiotensin II receptor agonists. British UK Pat. Appl. GB 2281298 (Merck and Co., Inc., Rahway, NJ) 1995.

(12) Senanayake, C. H.; Fredenburgh, L. E.; Reamer, R. A.; Liu, J.; Roberts, F. E.; Humphrey, G.; Thompson, A. A.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Sinkai, I. New approach to the imidazolutidine moiety of MK-996. *Heterocycles* **1996**, *42*, 821−830.

(13) (a) Dudley, D. T.; Panek, R. L.; Major, T. C.; Lu, G. H.; Bruns, R. F.; Klinkefus, B. A.; Hodges, J. C.; Weishaar, R. E. Subclasses of angiotensin II binding sites and their functional significance. *Mol. Pharmacol.* **1990**, *38*, 370−377. (b) Nielsen, A. H.; Schauser, K.; Winther, H.; Dantzer, V.; Poulsen, K. Angiotensin II receptors and renin in the porcine uterus: myometrial AT2 and endometrial AT1 receptors are down-regulated during gestation. *Clin. Exp. Pharmacol. Physiol.* **1997**, *24*, 309−314.

(14) Flemström, G.; Garner, A.; Nylander, O.; Hurst, B. C.; Heylings, J. R. Surface epithelial $HCO_3(-)$ transport by mammalian duodenum in vivo. *Am. J. Physiol. Gastrointest. Liver Physiol.* **1982**, *243*, G348−358.

(15) Mantlo, N. B.; Kim, D.; Ondeyka, D. L.; Chang, R. S. L.; Kivlighn, S. D.; Sieg, P. K. S.; Greenlee, W. J. Imidazo[4,5-b]pyridine-based AT1/AT2 angiotensin II receptor antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 17−22.

(16) Johansson, B.; Holm, M.; Chen, L. H.; Pettersson, A.; Jonson, C.; Fandriks, L. ANG II prolongs splanchnic nerve-mediated inhibition of duodenal mucosal alkaline secretion in the rat. *Am. J. Physiol.-Regul. Integr. Comput. Physiol.* **1997**, *273*, R942−R946.

(17) Dudley, D. T.; Panek, R. L.; Major, T. C.; Lu, G. H.; Bruns, R. F.; Klinkefus, B. A.; Hodges, J. C.; Weishaar, R. E. Subclasses of angiotensin-II binding-sites and their functional-significance. *Mol. Pharmacol.* **1990**, *38*, 370−377.

(18) Nielsen, A. H.; Schauser, K.; Winther, H.; Dantzer, V.; Poulsen, K. Angiotensin II receptors and renin in the porcine uterus: Myometrial AT(2) and endometrial AT(1) receptors are down-regulated during gestation. *Clin. Exp. Pharmacol. Physiol.* **1997**, *24*, 309−314.

JM031031I