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A convenient transesterification method for synthesis of AT2 receptor ligands with improved stability in human liver microsomes

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ABSTRACT

A series of AT_2R ligands have been synthesized applying a quick, simple, and safe transesterification-type reaction whereby the sulfonyl carbamate alkyl tail of the selective AT_2R antagonist C38 was varied. Furthermore, a limited number of compounds where acyl sulfonamides and sulfonyl ureas served as carboxylic acid bioisosteres were synthesized and evaluated. By reducing the size of the alkyl chain of the sulfonyl carbamates, ligands **7a** and **7b** were identified with significantly improved *in vitro* metabolic stability in both human and mouse liver microsomes as compared to C38 while retaining the AT_2R binding affinity and AT_2R/AT_1R selectivity. Eight of the compounds synthesized exhibit an improved stability in human microsomes as compared to C38.

The octapeptide hormone angiotensin II (Ang II) is the main effector of the Renin-Angiotensin-Aldosterone system (RAAS). Ang II mediates its effects through activation of two G-protein coupled receptors (GPCRs), the angiotensin II type 1 (AT_1R) and the angiotensin II type 2 (AT_2R) receptors. AT_1R is involved in regulation of blood pressure and electrolyte balance and is a well-established drug target for the treatment of hypertension and heart failure (angiotensin receptor blockers, ARBs). The first ARB, losartan, was introduced into the market in 1995.[1] The antihypertensive angiotensin converting enzyme inhibitors (ACE inhibitors, e.g. captopril introduced into the market 1978) act by suppressing the formation of Ang II.[2] In contrast to the well-investigated AT_1R, less is known about the role of the AT_2R. It is abundant during fetal development but only very low levels of AT_2R can be detected in healthy adults. However, in certain pathological conditions e.g. myocardial infarction, heart and renal failure, and some brain injuries, a pronounced upregulation of AT_2R is frequently observed. Thus, the receptor is upregulated in areas of tissue damage and it is postulated that AT_2R is important in tissue repair. The physiological actions mediated by AT_2R have been reviewed.[3–10]

The use of AT_2R as a potential drug target has recently seen two different approaches and produced compounds that have reached clinical trials. The selective AT_2R agonist C21/M024 (Vicore Pharma) discovered by Anders Hallberg's group at our laboratory[11] has entered Phase I clinical trials for the indication idiopathic pulmonary fibrosis. The malonic acid sulfonamide derivative MP-157, a selective AT_2R agonist from Mitsubishi Tanabe Pharma, is also in Phase I clinical trials in Europe and aimed for the cardiovascular system.[12] The AT_2R antagonist EMA401 (Spinifex/Novartis) has completed a phase II clinical trial with positive results in patients with postherpetic neuralgia,[13] a form of chronic neuropathic pain.[14,15] AT_2R antagonists as potential new chemical agents for the treatment of peripheral neuropathic pain is based on the findings that AT_2R exhibits a higher expression in damaged nerve tissue e.g. in the dorsal root ganglia (DRG). Furthermore, activation of these AT_2Rs by the endogenous ligand Ang II potentiates pain signaling by increasing neurite length and density, and by nociceptor sensitization by phosphorylation of nociceptor ion channels on the DRG via AT_2R secondary messenger pathways.[16–20]

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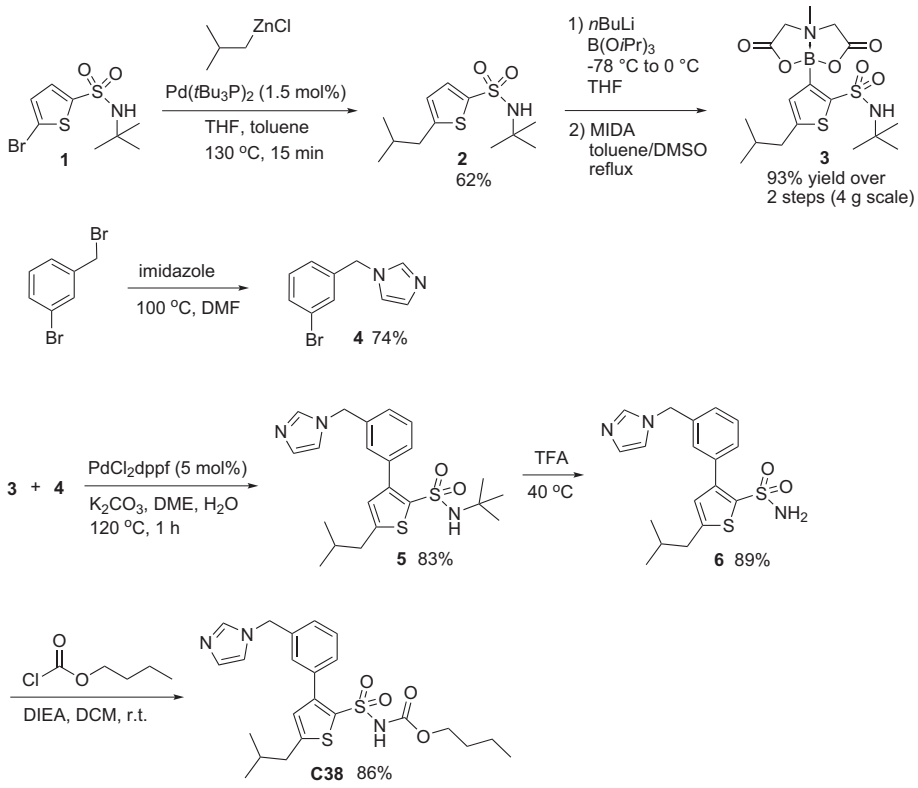


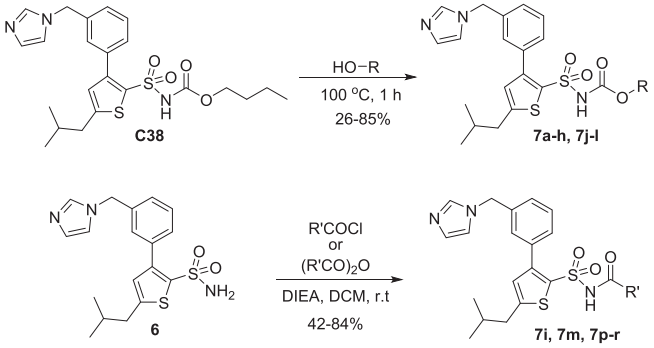
Scheme 1. Improved synthesis of the AT_2R antagonist **C38**.

We published the first selective drug-like AT_2R antagonists in 2012, among them compound **C38** which in structure closely relates to the AT_2R agonist C21.[21–23] Profiling **C38** in various ADME *in vitro* assays revealed a relatively short half-life of **C38** in human liver microsomes indicating poor metabolic stability.

A large number of structural modifications at several different sites of the AT_2R antagonist **C38** were explored but no efforts to alter the butylsulfonyl carbamate moiety were conducted. We had previously in the AT_2R agonist project found the *n*-butyl chain superior in producing potent compounds in all series studied[11,24] and thus the *n*-butyl chain was initially kept intact.[25]

The recent discovery that alkylsulfonyl carbamates can be interconverted to alternative alkylsulfonyl carbamates by a transesterification-type reaction by simply heating in an alkyl alcohol,[26,27] gave us the incentive to explore this part of the **C38** scaffold. In addition, we were encouraged to explore the impact of using acyl sulfonamides and sulfonyl ureas as conceivable replacements for the sulfonyl carbamate group.

During the efforts of profiling the properties of **C38**, a larger batch of the compound was required. This was achieved through a modified version of the previously published procedure (Scheme 1). First, a Negishi coupling of 5-bromo-*N*-(*tert*-butyl) thiophene-2-sulfonamide **1** with isobutylzinc under microwave heating[28] provided *N*-(*tert*-butyl)-5-isobutylthiophene-2-sulfonamide **2** in reasonable yield. This intermediate **2** was then converted to the MIDA boronate **3** in excellent yield. Compared to the corresponding boronic acid (semi-solid, stored in freezer) the MIDA boronate **3** is much easier to handle and store (solid, stable at ambient temperature under air).[29] The MIDA boronate **3** was subjected to a Suzuki coupling with 1-(3-bromobenzyl)-1*H*-imidazole **4** producing **5** in very good yield.[30] Deprotection of the *tert*-butyl sulfonamide **5** was performed in neat TFA to give the primary sulfonamide **6** in quantitative yield and finally the primary sulfonamide was coupled with butyl chloroformate to give the desired



Scheme 2. Synthesis of new AT_2R ligands.

C38 in enough quantity to allow compound profiling as well as use as starting material for variations of the alkylsulfonyl carbamate motif (Scheme 1).

Essentially employing our previously developed transesterification/transcarbamoylation method, **C38** was heated in various alkyl alcohols (straight and branched) of various sizes at 100 °C for 60 min (Scheme 2).[26] The resulting products **7a–l** (Table 1) were successfully isolated in 26–85% yield,[33] except for the reaction with *t*-BuOH where only primary sulfonamide was isolated. The *tert*-butylsulfonyl carbamate **7i** was instead isolated by reacting the primary sulfonamide with Boc anhydride. Also 2-methoxyethanol requires a special permit for use and handling in Sweden and as a consequence 2-methoxyethyl chloroformate was coupled with **6** to give **7m** (Scheme 2, Table 1).

Heating **C38** in primary or secondary alkylamines at 120–150 °C allowed for the formation of sulfonyl ureas **7n** (18%)[33] and **7o** (59%) by aminolysis of the sulfonyl carbamate (Table 1). Acylsulfonamides **7p–7r** were synthesized from primary sulfonamide **6** by