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Heteroaryl β-tetralin ureas as novel antagonists of human TRPV1

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Abstract—We report on a series of α-substituted-β-tetralin-derived and related phenethyl-based isoquinolinyl and hydroxynaphthyl ureas as potent antagonists of the human TRPV1 receptor. The synthesis and Structure–activity relationships (SAR) of the series are described.

TRPV1 receptor, previously known as the capsaicin receptor or VR1, is a non-selective cation channel which is stimulated by a number of endogenous and exogenous activators including capsaicin, the pungent component of chili peppers, as well as acid (low pH) and heat.[1] TRPV1 is a member of the superfamily of transient receptor potential channels or TRP channels and is expressed primarily on small-diameter, nociceptive sensory neurons. In light of its role in the detection of noxious stimuli, human TRPV1 receptor has emerged as a promising target for the development of new agents for the treatment of inflammatory pain and other painful disorders.[2] Our group[3–6] and many others[7] have reported on numerous series of small molecule TRPV1 antagonists. We previously described a series of *N*-isoquinolin-5-yl-*N*′-aralkylureas[6] and 7-hydroxynaphthalen-1-ylureas[4] that were found to be potent functional antagonists of human TRPV1 possessing exquisite binding affinity. We sought to further investigate the requisite pharmacophore elements in order to design improved TRPV1 antagonists. Through detailed SAR studies, we observed that substitution at the α-position of the phenethyl chain produced compounds with enhanced in vitro functional potency. Furthermore, constraint of the open chain analogs within a β-tetralin scaffold resulted in compounds that exhibited outstanding functional antagonist activities and binding affinities.

Keywords: TRPV1; Antagonists; Tetralin ureas.
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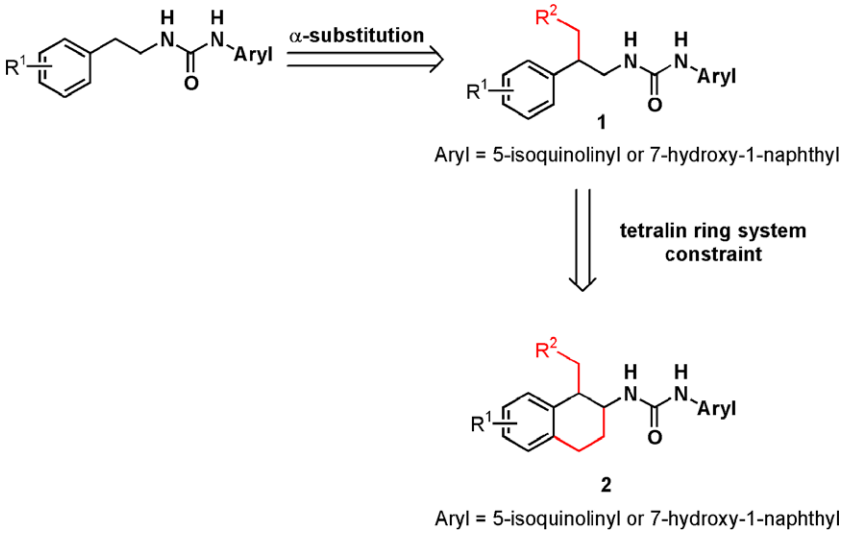
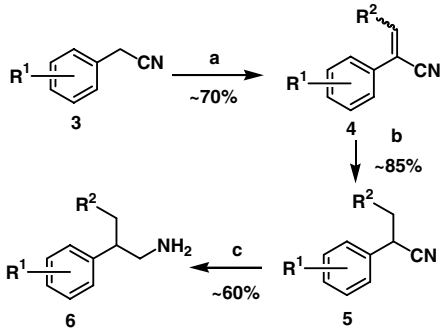
Thus we describe here novel TRPV1 antagonist series that incorporate either a β-phenethylamine or β-aminotetralin scaffold as a key structural element.

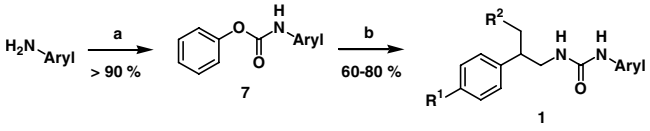
β-Phenethylamino ureas **1** were prepared starting from substituted phenyl acetonitriles **3** (Scheme 1). Condensation with an appropriately substituted aldehyde followed by stepwise reduction of the resulting α-substituted unsaturated nitrile **4** gave the amine intermediate **6**. The β-phenethyl amines **6** were then reacted with the phenyl carbamate **7** derived from either 5-aminoisoquinoline or 2-hydroxy-8-amino naphthalene to give the target ureas as racemic mixtures (Scheme 2).

The aminotetralin scaffolds were synthesized from the corresponding β-tetralones (Scheme 3). The tetralones **10** were obtained by Friedel–Crafts reaction of the appropriate acid chloride **9** with ethylene gas. Condensation of the tetralone **10** with various aldehydes gave the α,β-unsaturated β-tetralone **11**. Alternatively, initial reaction of the β-tetralone **10** with pyrrolidine followed by alkylation of the enamine **12** with the desired bromide and hydrolysis yielded the α-substituted β-tetralone **13**. Reductive amination of either β-tetralone intermediate gave the aminotetralin derivatives **14** in moderate-good yield as a diastereomeric mixture, which was predominantly, composed of the cis isomer.[8] Separation of the diastereomers was achieved by fractional crystallization. The aminotetralins thus obtained were then reacted with the aryl carbamates in a similar man-





Scheme 1. Reagents and condition: (a) R^2CHO, K_2CO_3, MeOH, heat; (b) $NaBH_4$, MeOH; heat (c) BH_3 THF, heat.



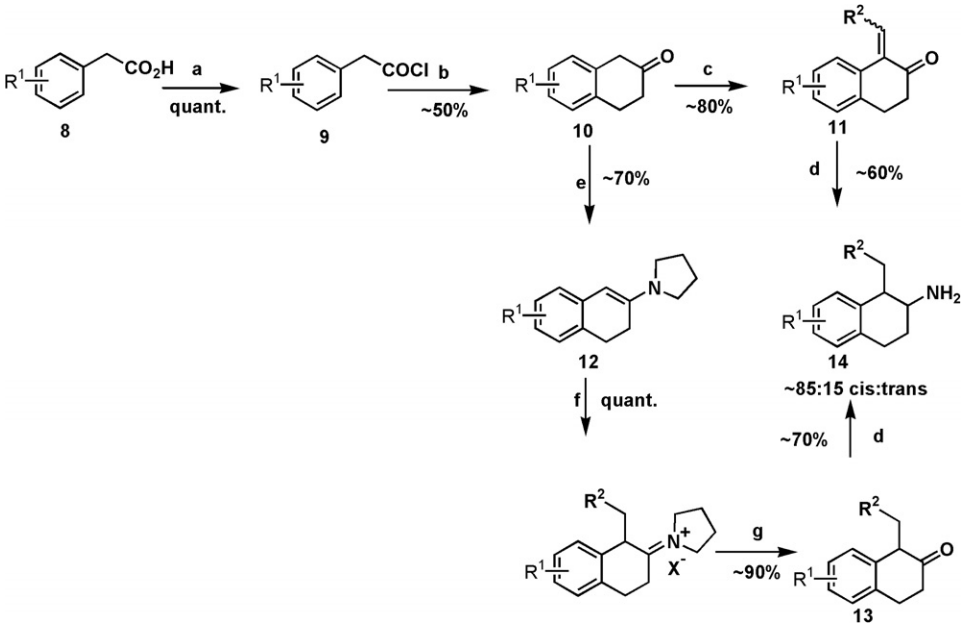
Scheme 2. Reagents: (a) PhOC(O)Cl, aq $NaHCO_3$,CH_2Cl_2 (92%); (b) amine **6**, DMSO (60–80%).

ner as described above to give the requisite racemic ureas **2**. Further biological testing of several of the most potent urea analogs required pure enantiomers. These were obtained by separation of the racemic mixtures of the α-substituted-β-phenethyl amines and the α-substituted-β-aminotetralins either by classical resolution techniques or by chiral chromatography.[9]

The phenethyl and tetralin-derived aryl ureas, **1** and **2**, respectively, were evaluated for their ability to modulate TRPV1 receptor activity in a recombinant HEK293 cell line using a capsaicin-induced calcium flux assay and FLIPR™ technology (Molecular Devices, Inc.) under conditions we have previously reported.[10] In addition, the target compounds were assayed for their binding affinity at human TRPV1, measuring displacement of radiolabeled resiniferatoxin (RTX).[11]

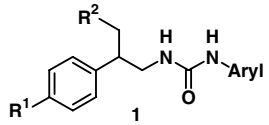
Both the aryl phenethyl and the aryl tetralin ureas **1**–**2** behaved as functional antagonists of the TRPV1 channel and also displayed potent binding affinity (Tables 1 and 2). From previous studies we learned that 5-isoquinolinyl and 7-hydroxy-1-naphthyl groups afforded the most potent analogs. In our work presented herein, substitution at the α-position generally led to an increase in both binding affinity and functional potency relative to these earlier series (Table 1, entry **1a**). The nature of the phenyl substituent, R^1, did not greatly influence the potency as both polar groups such as OCH_3 and lipophilic groups such as F and CF_3 were well tolerated. However, in contrast, substitution at the α-position with a polar substituent such as a 3-pyridylmethyl group yielded compounds with only moderate functional and binding potencies. However, lipophilic substituents gave compounds with excellent functional and binding potencies (Table 1). With few exceptions, the functional and binding activities of the analogs tested were in close agreement (within an order of magnitude).

In the tetralin urea series, heteroaryl substitution was allowed, as evidenced by compounds **2k** and **2l**; however, an α-pyridylmethyl substituent greatly decreased potency (**2m**). This result mirrors what was found in the acyclic series. Indeed, other polar substituents also caused a drop in both antagonist potency and binding affinity (**2q**). Substitution at the α-position appears to require a somewhat lipophilic substituent but not necessarily an aryl group. Both the α-allyl (**2n**) and the α-cyclopropylmethyl analogs (**2o**) exhibited good binding affinity but only moderate functional antagonism as compared with benzyl substituted compounds (**2d**, **2e**). The nature of the R^1 substituent seemed to have little effect on TRPV1 activity except in the case of R^1 = OH (i.e., compound **2p**), wherein both binding affinity and functional antagonism dropped approximately one order of magnitude. Also, the disubstituted phenyl analog



Scheme 3. Reagents and conditions: (a) $SOCl_2$, DCM; (b) $CH_2 = CH_2$, $AlCl_3$, DCE, 0 °C; (c) R^2CHO, cat piperidine, benzene, heat; (d) NH_4OAc, $NaBH_3CN$, MeOH, heat; (e) pyrrolidine, EtOH; (f) R^2CH_2Br, CH_3CN; (g) $HOAc/H_2O/DCM/MeOH$.

Table 1. Human TRPV1 binding affinities of α-substituted-β-phenthylureas[a]



Aryl = 5-isoquinolyl (5-IsoQ)

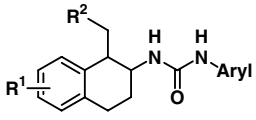
C	Aryl	R^1	R^2	Binding affinity K_i (nM)	Functional activity IC_{50} (nM)
1a	5-IsoQ	OCH_3	—	1290	680
1b	5-IsoQ	OCH_3	3-Pyr	578	184
1c	5-IsoQ	OCH_3	Ph	6	14
1d	5-IsoQ	CF_3	Ph	4	NT
1e	5-IsoQ	F	Ph	8	5
1f	5-IsoQ	F	3-CF_3Ph	20	19

NT, not tested.
[a] Data are reported for racemic compounds.

2j was 2- to 5-fold less potent at binding to TRPV1. While there appears to be a requirement for a lipophilic substituent at R^2, the effect of different aryl substituents on the apparent potency was minimal. In terms of stereochemistry, initial biological results established the cis diastereomer as the more active isomer (data not shown). There was ~5-fold difference in binding potency of the enantiomers but little effect of enantiomers on the functional potency.

In summary, we report on a unique series of α-substituted β-tetralin- and phenethyl-heterocyclic ureas as potent human TRPV1 antagonists[12,13] that possess excellent binding affinity. Due to low aqueous solubility and extensive in vitro metabolism, further optimization is underway to demonstrate the potential of the series of

Table 2. Human TRPV1 binding affinities and functional activity of α-substituted-β-tetralin ureas[a]



Aryl = 5-isoquinolyl (5-IsoQ)
or 7-OH-1-naphthyl (7-OH-1-NAP)

C	Aryl	R^1	R^2	Binding affinity K_i (nM)	Functional activity IC_{50} (nM)
2a	7-OH-1-NAP	6-OCH_3	Ph	10	60
2b	7-OH-1-NAP	6-F	4-CF_3Ph	22	360
2c	5-IsoQ	H	Ph	4	20
2d	5-IsoQ	6-OCH_3	Ph	3	25
2e	5-IsoQ	6-F	Ph	4	12
2f	5-IsoQ	6-Br	Ph	2	17
2g	5-IsoQ	5-Cl	Ph	2	16
2h	5-IsoQ	6-Cl	Ph	11	63
2i	5-IsoQ	7-Cl	Ph	5	86
2j	5-IsoQ	6,7-DiOMe	Ph	20	230
2k	5-IsoQ	6-F	2-Thienyl	4	140
2l	5-IsoQ	6-F	3-Furanyl	16	83
2m	5-IsoQ	6-OCH_3	3-Pyridyl	1540	>1000
2n	5-IsoQ	6-F	Vinyl	2	100
2o	5-IsoQ	6-F	*c*-Propyl	0.8	350
2p	5-IsoQ	6-OH	Ph	280	200
2q	5-IsoQ	6-Cl	CN	NT	>1000
2r	5-IsoQ	6-OCH_3	4-OCH_3 Ph	8	36
2s	5-IsoQ	6-OCH_3	4-CF_3Ph	2	2
2t	5-IsoQ	6-OCH_3	4-CN Ph	17	21
2u	5-IsoQ	6-OCH_3	4-Br Ph	1	22
2v	5-IsoQ	6-F	4-CF_3 Ph	1	10
2w	5-IsoQ	6-OCH_3	3-Cl Ph	2	13

NT, not tested.
[a] Data are reported for racemic compounds.

TRPV1 antagonists as novel agents for the treatment of certain types of pain.

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9. The racemic amines were resolved by chiral salt formation with chiral mandelic or tartaric acid. Diastereomeric salt formation and isolation followed by the efficient determination of %ee by ^{1}H NMR analysis gave >98% pure enantiomeric amines that were then converted into the target ureas. The absolute configuration of the enantiomeric amine was established by X-ray crystallography of the amine co-crystallized with a known chiral acid.
10. hTRPV1/HEK cells[4] were seeded on poly-D-lysine coated 96-well, black-walled plates (BD 354640) and 2 days later loaded with Fluo-3/AM for 1 h and subsequently tested for agonist-induced increases in intracellular Ca^{2+} levels using FLIPR™ technology. Cells were challenged with single concentrations of compound and intracellular Ca^{2+} was measured for 3 min prior to the addition of CAP to all wells to achieve a final CAP concentration of 15 nM to fully activate TRPV1. Antagonist potency was determined using the protocol described by McDonnell et al. *Bioorg. Med. Chem.* **2002**, *12*, 1189). Data were analyzed using Prism software to calculate IC_{50} values.
11. [^{3}H]-RTX binding assay using hVR1/HEK293 cell membranes. Cloning and generation of stable cell lines expressing human TRPV1. Human TRPV1 was cloned and stably expressed in HEK293 cells (hVR1/HEK293) as described by Grant et al. J. Pharm. Exp. Ther. **2002**, *300*, 9. *Preparation of membranes.* Human TRPV1/HEK293 were homogenized with a Polytron twice and centrifuged at 3000 rpm for 10 min in HEPES buffer containing 20 mM HEPES, pH 7.4, NaCl 5.8 mM, sucrose 320 mM, $MgCl_2$ 2 mM, $CaCl_2$ 0.75 mM, and KCl 5 mM. The supernatant was centrifuged at 18,000 rpm for 20 min. The pellet was saved in a tube and 10 mL assay buffer was added into the tube. The pellet and buffer were mixed with a Polytron. *Incubation procedure.* Incubations for 60 min at 37 °C were performed in a total volume of 0.5 mL that contained 120 μg/mL membrane protein and 0.3–0.6 nM [^{3}H]-RTX (NEN, Boston) in the HEPES buffer. After incubation, the samples were cooled on ice and 100 μg of α-acid glycoprotein was added followed by centrifugation at 13,000 rpm for 15 min. The supernatant was aspirated and the tips of tubes were cut off into 6 mL vials. Nonspecific binding was measured in the presence of 200 nM unlabeled RTX in 4 mL scintillation liquid using a Packard scintillation counter. *Data analysis*. Percent (%) inhibition = (total binding − total binding in presence of compound) × 100/(total binding − nonspecific binding). K_i values were obtained from Prism (GraphPad, San Diego, CA) calculated using equation of Cheng–Prusoff ($K_i = IC_{50}/(1 + [Ligand]/K_d)$).
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13. 1-(1-benzyl-6-fluoro-1,2,3,4-tetrahydro-naphthalen-2-yl)-3-isoquinolin-5-yl-urea (**2e**): Isoquinolin-5-yl-carbamic acid phenyl ester (0.005 mol, 1.32 g) was dissolved in 15 mL of DMSO, followed by the addition of 1-benzyl-6-fluoro-1,2,3,4-tetrahydro-naphthalen-2-ylamine (0.0044 mol, 1.12 g). The reaction mixture was stirred at room temperature for 16 h then poured into 50 mL of water containing 10 mL of 1 N NaOH. The precipitated solid was collected by filtration and purified by chromatography on silica gel eluting with methylene chloride/3% methanol (v/v). The obtained product was further purified by recrystallization from ethyl acetate. Thus title compound (1-(1-benzyl-6-fluoro-1,2,3,4-tetrahydro-naphthalen-2-yl)-3-isoquinolin-5-yl-urea) was obtained as an off-white solid (1.25 g, 0.00295 mol). MS (MH^+): 426; ^{1}H NMR (MeOH): δ 1.35 (m, 1H), 1.9 (m, 1H), 2.1–2.2 (m, 1H), 2.9–3.1 (m, 4H) 3.45 (m, 1H), 4.1–4.2 (m, 1H), 6.7 (t, 1H), 6.8–6.9 (m, 2H), 7.1–7.3 (m, 5H), 7.85 (t, 1H), 8.1 (d, 1H), 8.25 (d, 1H), 8.35 (d, 1H), 8.6 (d, 1H).