Identification of (*R*)-1-(5-*tert*-Butyl-2,3-dihydro-1*H*-inden-1-yl)-3-(1*H*-indazol-4-yl)urea (ABT-102) as a Potent TRPV1 Antagonist for Pain Management

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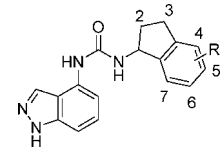
Abstract: Vanilloid receptor TRPV1 is a cation channel that can be activated by a wide range of noxious stimuli, including capsaicin, acid, and heat. Blockade of TRPV1 activation by selective antagonists is under investigation by several pharmaceutical companies in an effort to identify novel agents for pain management. Here we report that replacement of substituted benzyl groups by an indan rigid moiety in a previously described *N*-indazole-*N*′-benzyl urea series led to a number of TRPV1 antagonists with significantly increased in vitro potency and enhanced drug-like properties. Extensive evaluation of pharmacological, pharmacokinetic, and toxicological properties of synthesized analogs resulted in identification of **(*R*)-7** (**ABT-102**). Both the analgesic activity and drug-like properties of **(*R*)-7** support its advancement into clinical pain trials.

The nociceptive role of vanilloid receptor TRPV1, which is a member of the transient receptor potential ion channel family, has been extensively discussed.[1,2] Since its cloning in 1997,[3] TRPV1 has generated significant interest among academic and industrial pain researchers as a result of its unique role in pain pathways. TRPV1 can be activated by a wide range of stimuli, including exogenous capsaicin, endogenous arachidonic acid metabolites, physical stimuli, such as heat, and chemical stimuli, such as acidic media.[4] In addition, activation of TRPV1 can be potentiated by pro-nociceptive mediators such as bradykinin, ATP, NGF, and others.[5] Such promiscuity of TRPV1 regulation makes this receptor a principle integrator of noxious stimuli and, therefore, points to a significant role that TRPV1 may play in pain pathways.

While both TRPV1 agonists[6] and antagonists[7] are being targeted as potential analgesics, the major focus of the drug discovery effort has been on the identification of TRPV1 antagonists. It has been well documented that TRPV1 antagonists can effectively reduce inflammatory hyperalgesia in animal models.[8] More recently, it was demonstrated that the analgesic profile of TRPV1 antagonists can be significantly broaden if the blockade of TRPV1 receptors occur both in the periphery as well as in the central nervous system.[9]

Our early lead compound **1**[10] (Figure 1) possessed good selectivity and in vitro potency[11] in blocking the activation of TRPV1 by several ligands, but in spite of analgesic activity in animal models after intraperitoneal administration,[12] its oral activity was modest. The short half-life and low volume of distribution of **1** likely contributed to weak analgesic potency. Alkylation at the benzylic carbon atom (e.g., compounds **2** and **3**) improved these pharmacokinetic parameters, but their in vitro potencies were 5–10-fold lower than the unsubstituted analogs.[13] Therefore, the goal was to find ways of increasing TRPV1 antagonist potency of α-benzyl-substituted compounds such as **2** and **3**, but at the same time retaining their improved PK profile. Further SAR studies in which substitution at the benzylic carbon atom was extended to form rigid bicyclic fragments accomplished that goal. While there are several different ways of forming such conformationally restricted fragments, for example, indan **4**, chroman **5**, and tetrahydroquinoline **6**, this paper describes SAR studies on the indan chemotype that culminated in the identification of **(*R*)-7** (**ABT-102**), a TRPV1 antagonist possessing activity in a wide range of preclinical pain models.

Table 1. In Vitro Functional Potencies of Selected Indan TRPV1 Antagonists to Block Human TRPV1 Receptor-Mediated Ca^{2+} Influx[a]



cmpd	R	hTRPV1 IC_{50} (nM)[b]
4	5-CF_3	3 ± 1.6
7	5-*tert*-Bu	6 ± 1
8	5-Br	9 ± 4
9	5-Cl	10 ± 6
10	5-F	52 ± 21
11	5-piperidino	14 ± 4
12	4-piperidino	10 ± 2
13	4-(4-CF_3-piperidino)	7 ± 2
14	4-cyclopropyl	5 ± 1
15	5-cyclopropyl	4 ± 1
16	4-CF_3	10 ± 3
17	4-tert-Bu	4 ± 1
18	5-OMe	40 ± 16
19	4-pyrrolidino	21 ± 2
20	4-C(CN)Me_2	19 ± 5
21	4-morpholino	65 ± 14
22	5-F, 4-morpholino	5 ± 2
23	4-Me	46 ± 5
24	5-Me	11 ± 1
25	6-Me	7200 ± 3500
26	7-Me	595 ± 210
27	H	151 ± 76

[a] For the assay details, see ref 11. [b] All values are means ± SEM of at least three separate experiments.

The general synthetic strategy was based on using appropriately substituted indanones that were converted to amines in two steps and then reacted with indazole isocyanate to yield the target molecules after carbamate deprotection (Scheme 1). Utilization of an indan scaffold resulted in two important SAR findings. First, cyclic TRPV1 antagonists were significantly more potent than their acyclic analogs (compare compounds **2** and **3** with **4**, Figure 1). Second, although *para*-substitution was superior to *meta*-substitution in the acyclic series,[10,14] both 5-(*para*-) and neighboring 4-(*meta*-) positions offered equally good opportunities for activity improvements in the indan series. The representative examples include indans with trifluoromethyl (**4** vs **16**), *tert*-butyl (**7** vs **17**), piperidino- (**11** vs **12**), and cyclopropyl (**14** vs **15**) substitutions (Table 1).

The least favorable positions for the phenyl ring substitution were 6 and 7, as evidenced by comparison of regioisomers **23**–**26**. Incorporation of a nitrogen atom into the phenyl ring of

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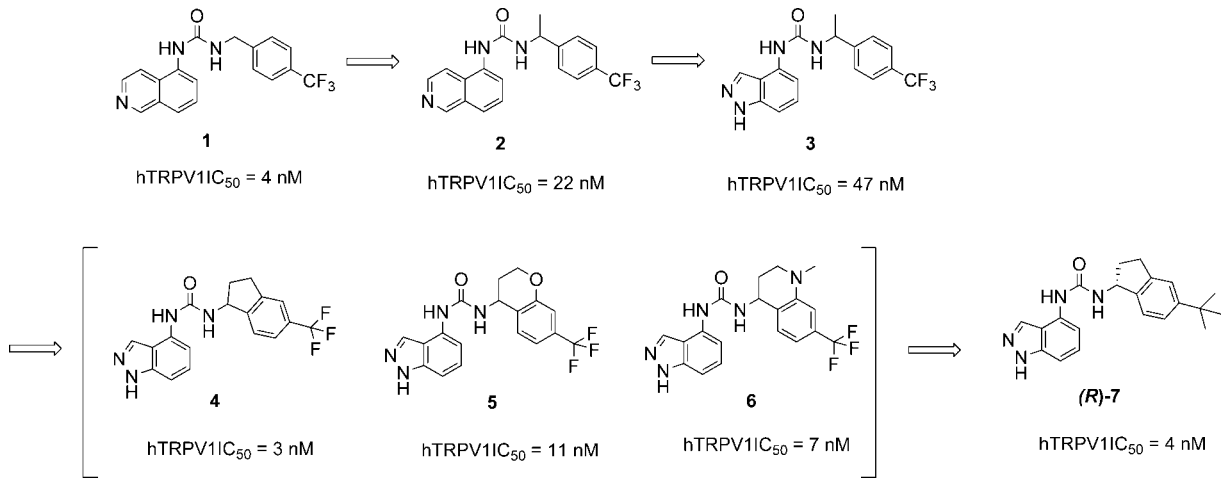
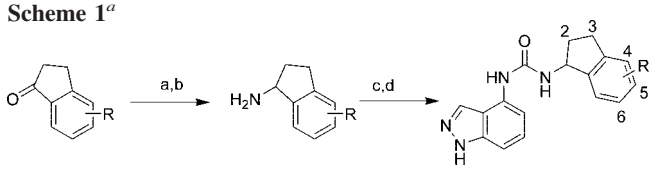


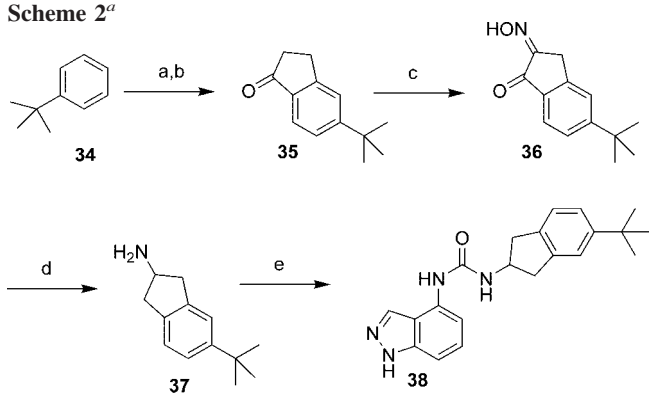
Figure 1

Scheme 1[a]



[a] Reagents and conditions: (a) $H_2NOMe \cdot HCl$, Py, 16 h, rt; (b) H_2, 10% Pd/C, MeOH-NH_3; (c) 4-isocyanato-1-methoxycarbonyl-1*H*-indazole, CH_2Cl_2, rt; (d) 5 M NaOH in MeOH, 30 min, rt.

Scheme 2[a]



[a] Reagents and conditions: (a) 3-chloropropionyl chloride, $AlCl_3$, CH_2Cl_2, 0 °C; (b) concd H_2SO_4, 90 °C, 36% for 2 steps; (c) isoamyl nitrite, concd HCl, MeOH, 44 h, rt, used crude in the next step; (d) H_2, 10% Pd/C, AcOH-concd H_2SO_4, 17 h, 60 psi, rt, 50% for 2 steps; (e) see Scheme 1, steps (c) and (d).

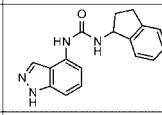
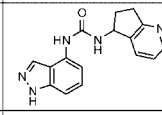
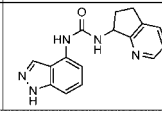
the indan moiety did not prove to be advantageous (Table 2). It was previously reported that in the cinnamide series of TRPV1 antagonists the lipophilic aryl fragment tolerates replacement of the phenyl group with pyridine.[15] However, in our case, two model aza-indan compounds **28** and **29** were much less potent at TRPV1 receptors than the parent indan **27**.

Additional SAR studies that consisted of replacements of the urea fragment with thiourea and cyanoguanidine, as well as attachment of fluorine atoms on the saturated indan ring, did not yield superior compounds in terms of functional antagonist activity at TRPV1 (Table 3).

Moving the site of attachment of urea moiety from position 1 to 2 in the indan fragment resulted in the compound **38** (Scheme 2). Friedel–Crafts acylation of the 4-*tert*-butylbenzene (**34**) by 3-chloropropionyl chloride, followed by cyclization of the resulting chloroketone in the presence of concd H_2SO_4, provided the indanone **35**. The latter was first converted to the keto-oxime **36**, which was then hydrogenated to obtain the amine **37** by using a modified version of a previously reported procedure.[16] Acylation of **37** by indazole isocyanate followed by deprotection gave urea **38** with TRPV1 IC_{50} value of 10 nM, which is comparable to regioisomeric **7**.

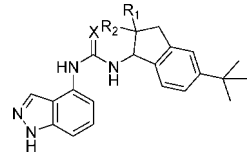
Several potent TRPV1 antagonists shown in Table 1 were evaluated for their pharmacokinetic profile, metabolism, brain penetration, activity in animal pain models, and cardiovascular side effects in anesthetized rats and dogs (data not shown). Based on that evaluation, compound **7** showed the best combination of favorable properties and was chosen for further studies. Due to the presence of stereogenic center in **7**, both enantiomers were synthesized (Scheme 3). The indanone **35** was converted to the amine **39**, which was subjected to chiral resolution by

Table 2. In Vitro Comparison of Indan with aza-Indans to Block Human TRPV1 Receptor-Mediated Ca^{2+} Influx[a]

Compound	Structure	hTRPV1 IC_{50} (nM)
27		151 ± 76
28		5820 ± 120
29		1350 ± 600

[a] All values are means ± SEM of at least three separate experiments.

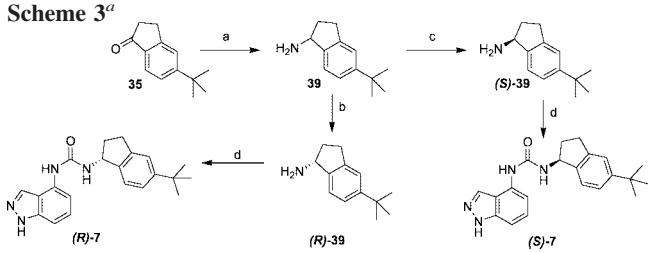
Table 3. SAR variations to the compound 7[a]



cmpd	R_1	R_2	X	hTRPV1 IC_{50} (nM)
7	H	H	O	6 ± 1
30	H	H	S	97 ± 36
31	H	H	N−CN	34 ± 20
32	F	H	O	35 ± 8
33	F	F	O	216 ± 65

[a] All values are means ± SEM of at least three separate experiments.

Scheme 3[a]



[a] Reagents and conditions: (a) see Scheme *1*, (a) and (b); (b) (i) *N*-acetyl-(D)-leucine, MeOH, 65 °C, 1 h, then cool to rt, filter, repeat the process with the solid, (ii)1 N NaOH; (c) (i) *N*-acetyl-(L)-leucine, MeOH, 65 °C, 1 h, then cool to rt, filter, repeat the process with the solid, (ii)1 N NaOH; (d) see Scheme 1, (c) and (d).

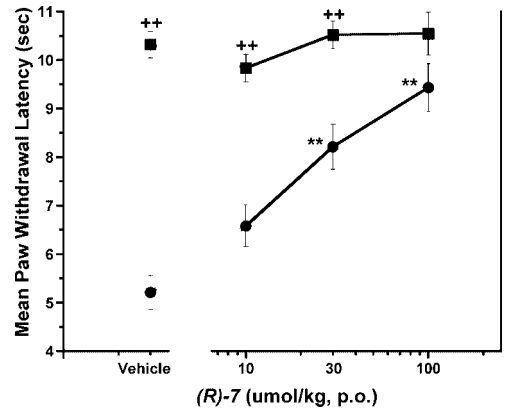


Figure 2. (***R***)**-7** has full efficacy against acute inflammatory thermal hyperalgesia induced by intraplantar carrageenan in the rat. Circles represent paw withdrawal latencies ipsilateral to the injury; squares represent paw withdrawal latencies contralateral to the injury. Data represent mean ± SEM [$F(7,95) = 26.61$, $p < 0.0001$]. $^{**}p < 0.01$, as compared to vehicle-treated animals. $^{++}p < 0.01$, as compared to carrageenan-treated paw ($n = 12$ per group).

Table 4. Selected Pharmacokinetic Properties of (***R***)**-7** (10 μmol/kg) in Rat, Dog, and Monkey, Administered in PEG-400[a]

species	$T_{1/2}$ (h) iv	V_β (L/kg), iv	CLp (L/h·kg), iv	C_{max} (μg/mL) po	*F* (%)
rat	1.7	2.8	1.10	0.25	70
dog	1.8[b]	1.6[b]	0.62[b]	0.39, 0.65[c]	22,60[c]
monkey	1.9[b]	1.7[b]	0.59[b]	0.31	25

[a] Three animals per each group, iv and oral. [b] Administered at 5 μmol/kg. [c] Oleic acid/cremophor/PEG-400 (80:10:10).

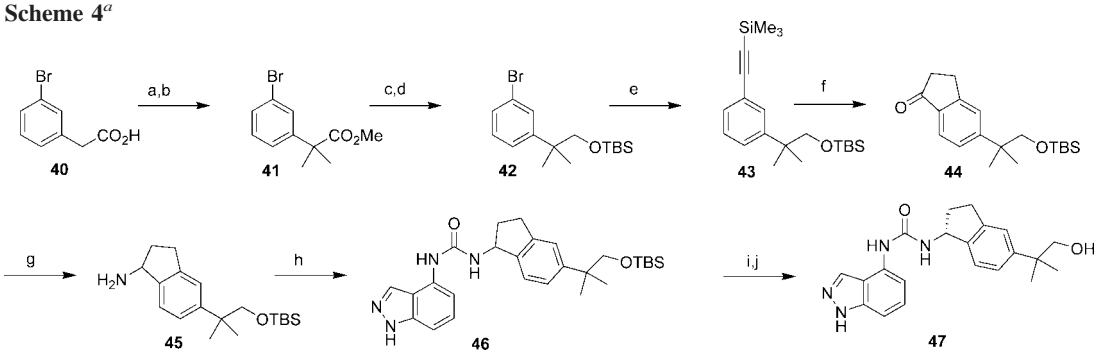
N-acetyl-L- and D-leucine by analogy to a similar reported procedure.[17] The absolute configuration of the enantiomerically pure amine (***S***)**-39** was established by X-ray analysis of its *N*-acetyl-L-leucine salt. Elaboration of the chiral amines to the target compounds (***R***)**-7** and (***S***)**-7** proceeded as shown in Scheme 1.[18] (***R***)**-7** displayed 30-fold higher potency in blocking activation of TRPV1 by capsaicin than its enantiomeric counterpart (***S***)**-7** (IC_{50} 4 nM vs 123 nM). Because of the polymodal nature of the TRPV1 receptor and its ability to integrate numerous signals present during chronic pain, it is likely that an ideal antagonist would also be one that shows good potency across multiple modes of TRPV1 activation.[2] (***R***)**-7** blocked the activation of TRPV1 by other stimuli such as *N*-arachidonoyldopamine (NADA) and pH 5.5, with IC_{50} values of 3 nM and 0.7 nM, respectively. Full blockage of heat activation (50 °C) of the receptor was observed after application of (***R***)**-7** at the concentration of 100 nM.[19] In addition to the in vitro potency difference, chiral discrimination was also observed in PK properties such as half-lives, volumes of distribution, and C_{max} (see Supporting Information). (***R***)**-7** was highly selective and showed little or no effect at 10 μM in a study using a panel of ion channels, other receptors, and transporters (CEREP, Poitiers, France).[19]

Pharmacokinetic evaluation of (***R***)**-7** was performed in rats, dogs, and monkeys (Table 4). Although aqueous solubility of (***R***)**-7** is very low (102 ng/mL at pH 1 and 57.3 ng/mL at pH 6.8), it is predicted to be well absorbed in humans based on the value of $P_{app} > 18 \times 10^{-6}$ cm/s in human Caco-2 permeability studies. Because the oral bioavailability of poorly soluble compounds is highly dependent on formulation, a number of formulations were tested in an effort to improve the oral bioavailability of (***R***)**-7**. For example, oral bioavailability of 5 μmol/kg (***R***)**-7** in dog was increased from 22 to 60% by replacing PEG-400 with a lipid vehicle (Table 4).

(***R***)**-7** exhibited potent analgesic activity in a number of animal pain models after oral administration. For example, in the carrageenan-induced thermal hyperalgesia model, (***R***)**-7** significantly decreased thermal hyperalgesia induced by carrageenan injection, as is evidenced by an increase in paw withdrawal latency to a thermal stimulus. There was a dose-dependent effect of (***R***)**-7** with an ED_{50} of 20 μmol/kg and full efficacy at 100 μmol/kg (Figure 2). (***R***)**-7** was also potent in a number of animal models of chronic pain, including inflammatory, osteoarthritis, bone cancer, and postoperative pain.[20] The ability of (***R***)**-7** to penetrate CNS (brain/plasma ratio 0.32) could be one of the reasons for its broad-spectrum analgesic profile compared to other previously described TRPV1 receptor antagonists.[9]

The in vitro rate of metabolism of (***R***)**-7** in rat, dog, and human liver microsomes was low and similar across species: in vitro intrinsic clearance values Cl_{int} in liver microsomes were 0.34 mL/min/mg (rat), 0.12 mL/min/mg (dog), and 0.10 mL/

Scheme 4[a]



[a] Reagents and conditions: (a) MeOH, AcCl, reflux, 2.5 h, 100%; (b) MeI, NaH, THF, 0 °C−rt, 14 h, 66%; (c) $LiAlH_4$, THF, rt, 2 h, 98%; (d) *t*-$BuMe_2SiCl$, imidazole, DMF, rt, 2 h, 97%; (e) trimethylsilylacetylene, $Pd(PPh_3)_2Cl_2$,CuI, MeCN−Et_3N, reflux, 14 h, 66%; (f) CO, 500 psi, $[Rh(COD)Cl]_2$, Ph_3P,THF−H_2O−Et_3N, 160 °C, 71%; (g) see Scheme *1*, steps a, b; (h) see Scheme *1*, steps c, d; (i) TBAF (1 M in THF), THF, 14 h, rt, 70%; (j) chiral separation with Chiralcel OD-column, hexane−MeOH−EtOH, 75:12.5:12.5.

min/mg (human). The major metabolite was identified as the alcohol **47**. To characterize pharmacological properties of **47** and to assess its possible contribution to in vivo effects of **(*R*)-7**, the synthesis of the metabolite was carried out in 10 steps as shown in Scheme 4. The key step was preparation of the indanone **44** in 71% yield from the alkynyl intermediate **43** by Rh-catalyzed cyclocarbonylation reaction. The alcohol **47** was about 30-fold weaker (IC_{50} 127 nM) than **(*R*)-7** at TRPV1 and was significantly less active in animal pain models as can be illustrated by comparison of its ED_{50} value of >100 μmol/kg versus 20 μmol/kg for **(*R*)-7** in the carrageenan-induced thermal hyperalgesia pain model.

Recent data indicate that TRPV1 antagonists produce about 1 °C increase in core body temperature at analgesic doses.[21,22] Consistent with this data, systemically administered **(*R*)-7** produced a similar increase in core body temperature. However, this hyperthermic effect is transient and ameliorates following repeated dosing.[20]

In summary, replacement of the benzyl lipophilic portion in the urea series of TRPV1 antagonists with an indan moiety led to the identification of **(*R*)-7**. Despite low aqueous solubility, this compound exhibited good oral bioavailability when suitable lipid formulations were employed. Its broad-spectrum analgesic profile across preclinical pain models makes **(*R*)-7** a suitable candidate for clinical studies. Full pharmacological profile of the compound will be described elsewhere.[19,20]

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Supporting Information Available: Complete experimental and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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