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Discovery of TRPV1 antagonist ABT-116

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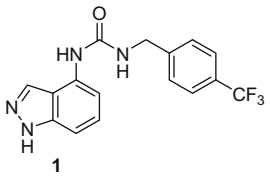
ABSTRACT

The synthesis and SAR of a series of indazole TRPV1 antagonists leading to the discovery of **21** (ABT-116) is described. Biological studies demonstrated potent in vitro and in vivo activity for **21**, as well as suitable physicochemical and pharmacokinetic properties for advancement to clinical development for pain management.

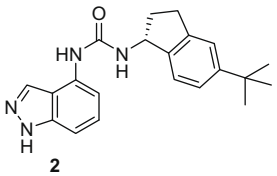
Considerable effort has been recently devoted to the search for antagonists of the vanilloid receptor TRPV1,[1] which is the receptor for capsaicin, the pungent component of chili peppers. This receptor is also activated in response to noxious heat and low pH, defining it as a polymodal receptor of painful stimuli.[2] TRPV1 modulators have therefore been broadly examined as potential therapeutics for pain.

We have previously disclosed our medicinal chemistry studies around the indazolyl urea TRPV1 antagonists typified by **1**, which showed potent blockade of in vitro activation of hTRPV1 in response to capsaicin (Fig. 1).[3] Compound **1** had modest activity in the complete Freund's adjuvant (CFA) model of inflammatory thermal hyperalgesia[4] in rats following intraperitoneal (IP) administration, but failed to show significant effects upon oral dosing due to its poor pharmacokinetic properties. Further exploration of this core structure led to the discovery of indan **2** (ABT-102),[5] a more potent antagonist which demonstrated good oral activity in several pre-clinical in vivo pain models, and was then advanced to human clinical studies as a potential analgesic agent. However, the low aqueous solubility of **2** presented significant challenges in its formulation. Therefore, follow-on efforts were undertaken to find compounds which retained the potent biological activity of **2**, but possessed improved physical properties.

Accordingly, two series of ureas were examined. In the first series, the benzyl group of **1** was replaced by a pyridinylmethyl group, with the goal of improving aqueous solubility with inclusion of additional heteroatoms on this moiety. The synthesis of the required amine fragments was straightforward, employing established displacement[6] or cross-coupling chemistry[7] of nicotinic nitriles, followed by hydrogenation to the corresponding amines, as shown in general fashion in Scheme 1. Urea formation proceeded as previously reported using **3**.[3a] Although the replacement of the phenyl ring of **1** by the 3-pyridinyl ring of **4** led to a 20-fold reduction of in vitro activity (a similar reduction was seen for azaindans related to **2**[5]), the compound was orally active in the rat CFA pain model. For most other examples in Table 1, potent in vitro activity was retained, with the 6-CF_3 group preferred over 6-Me and -Ph substituents to varying degrees depending on the 2-substitution (cf. **5** vs **6** or **7**, and **8** vs **9**). The attempt to further increase



1
hTRPV1 IC_{50}= 9 ± 1 nM
CFA ED_{50} = 60 μmol/kg, ip
(CFA ED_{50} > 300 μmol/kg, po)



2
hTRPV1 IC_{50}= 4 ± 1 nM
CFA ED_{50}= 10 μmol/kg, po
Aq. Sol. = 0.06 μg/mL (pH 7.2)

Figure 1. First generation TRPV1 antagonists.

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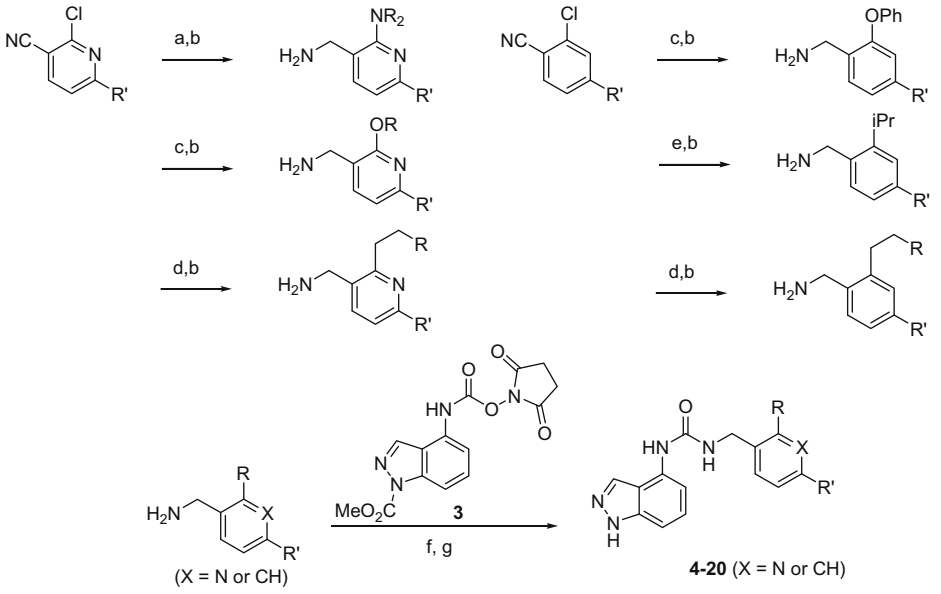
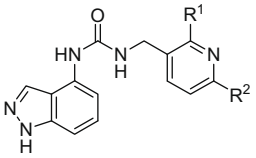
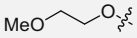
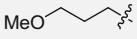
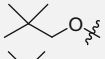


Scheme 1. Preparation of urea antagonists. Reagents and conditions: (a) HNR_2, EtOH, 83–98%; (b) Ra Ni, H_2, NH_3, MeOH, 61–100%; (c) ROH, Na or NaH, 18–86%; (d) HCCR, Pd_2dba_3 $CHCl_3$, CuI, DavePhos, Et_3N, 64–94%; (e) iPr_2Zn, $PdCl_2$(dppf), THF, 62%; (f) iP_2NEt, DMF; (g) NaOH, MeOH, 8–82% for two steps.

Table 1
SAR of pyridinylmethyl urea TRPV1 antagonists



Compd	R^1	R^2	IC_{50}[a] (nM)	CFA ED_{50} (μmol/kg, po)
4	H	CF_3	184 ± 5	81
5		CF_3	3.5 ± 0.4	30
6		Me	16 ± 3	53
7		Ph	14 ± 4	37
8		CF_3	12 ± 1	33
9		Me	125 ± 14	—
10	PhO–	CF_3	9 ± 2	30
11		CF_3	18 ± 1	—
12		CF_3	12 ± 1	>30
13		CF_3	6 ± 1	>100
14		CF_3	5 ± 1	100

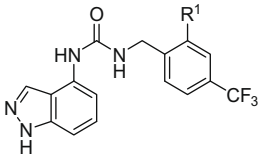
[a] All values are the mean ± SEM of at least two independent experiments run in triplicate.

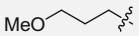
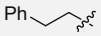
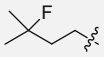
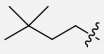
hydrophilicity by replacing the piperidine group with a morpholine led to reduced in vitro antagonist potency (**5** vs **8**, **6** vs **9**). Several 2-alkoxyl groups also offered potent antagonism, and the corresponding 2-alkyl groups showed similar, or marginally better, in vitro activity (e.g., **11** vs **12**, and **13** vs **14**). A further preference for large, lipophilic groups tethered to the 2-position was observed (**12** vs **14**).

Overall, however, the in vivo activities of the pyridinyl series were weaker than the lead compound **2**. This effect is partially attributable to a loss of CNS exposure, related to an increase in the polar surface area of these compounds.[8] For example, **8** and **13** each have [brain]:[plasma] ratios of only 0.02. TRPV1 receptors are found in both the peripheral and central nervous systems, with expression in primary afferents, dorsal root ganglion (DRG) neurons, and various brain regions, and the influence of receptors in different compartments on different modalities of pain has been demonstrated previously.[9a,b] Since CNS exposure is required for broad-spectrum analgesic activity, we changed our strategy to find less polar, more CNS-penetrant compounds which could be formulated using lipid vehicles. We re-examined the benzyl urea series, maintaining the preferred 4-CF_3 substituent from the pyridinylmethyl amines, and varying the lipophilic groups at R^1 (Table 2). The benzyl compounds showed potent in vitro antagonism, with some offering improved in vivo activities relative to the corresponding pyridinyl analogs. The 2-(*tert*-butyl)ethyl substitution imbued **20** with the best in vitro activity of the analogs, as well as potent in vivo activity, with a sevenfold improvement over the pyridinyl **14** in the rat CFA model. Methyl ether **15** was not examined in vivo due to its low CNS penetration, equivalent to that of **8**.

Given these promising initial results, additional characterization of **20** was undertaken. The synthetic route was straightforward and efficient (77% over four steps), providing ready access to material for advanced studies. In further in vivo studies in rats, **20** demonstrated good activity in the carageenan-induced thermal hyperalgesia model and modest potency in an osteoarthritis pain model[4b] (Table 3). Compound **20** also displayed a favorable pharmacokinetic profile, increased CNS exposure relative to **2** ([brain]:[plasma] = 0.45 vs 0.32 for **2**), and a sevenfold increase in aqueous solubility, despite the solubility remaining quite low. Increasing the lipophilicity of the series to improve CNS exposure also led to good solubility in lipid vehicles, as shown below for PEG-400. Generally favorable safety findings were also observed for **20**, which displayed a >80-fold therapeutic index for cardiovascular safety (based on its CFA efficacious plasma level). Also, a binding screen showed little cross-reactivity against a panel of 79 neurotransmitter receptors and ion channels (Cerep, Paris), and no genetic toxicity was observed in the Ames test of mutagenicity or the micronucleus test of clastogenicity. However, **20** was found to be a potent, time-dependent inhibitor of CYP3A4

Table 2
SAR of benzyl urea TRPV1 antagonists



Compd	R^1	IC_{50}[a] (nM)	CFA ED_{50} (μmol/kg, po)
15		8 ± 1	–
16		8 ± 3	30
17	PhO–	9 ± 1	22
18	*i*Pr	9 ± 1	14
19		6 ± 1	58
20		4.3 ± 0.4	15

[a] All values are the mean ± SEM of at least two independent experiments run in triplicate.

Table 3
In vitro and in vivo characterization of **20**

Assay		PK	
Carageenan ED_{50}	7 μmol/kg, po	V_β (iv)	5.4 L/kg
OA ED_{50}	71 μmol/kg, po	CLp (iv)	1.2 L/kg h
Solubility, aq	0.42 μg/mL	$t_{1/2}$ (po)	4.3 h
Solubility, PEG-400	>100 μg/mL	*F* (po)	35%
		[brain]:[plasma]	0.45

metabolism[10] (86% inhibition of midazolam oxidation @ 10 μM), which precluded any further development due to the likelihood of drug–drug interactions.

Previously, interactions of unsubstituted indazoles have been described with CYP enzymes showing binding to N2, and hydrogen bonding to the N1 hydrogen.[11] Since studies of earlier indazole TRPV1 antagonists found that methylation of N1 only slightly reduced antagonist activity,[3b] indazole alkylation was pursued to disrupt this CYP interaction while retaining potency as a TRPV1 antagonist. Alkylation of **20** was accomplished by standard chemistry, providing **21**, **22**, and **23**, as well as varying amounts of the corresponding N2 alkylation products. The SAR of **21–23** showed a correlation of TRPV1 antagonist activity with reduced steric bulk, with the methyl-substituted **21** being 10-fold more potent than the isopropyl analog **23** (Scheme 2). Most importantly, while **21** was nearly as potent a TRPV1 antagonist as **20**, the CYP3A4 inhibition was almost completely abrogated, showing only 10% inhibition of

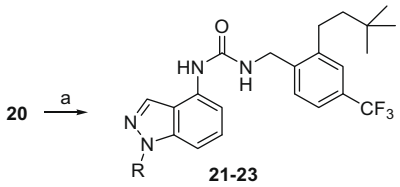
Table 4
In vitro and in vivo characterization of **21**

Assay		PK[c]	
hTRPV1 IC_{50} (3 μM NADA, nM)	15 ± 3[a]	V_{ss}	3.4 L/kg
hTRPV1 IC_{50} (pH 5.5, nM)	7 ± 1[a]	CLp	0.8 L/kg h
rTRPV1 IC_{50} (cap, nM)	277 ± 106	C_{max}	0.14 μg/mL
Carageenan ED_{50}	25 μmol/kg, po	$t_{1/2}$	3.1 h
OA ED_{50}	66 μmol/kg, po	*F*	58%[b]
Solubility, aq	<0.010 μg/mL	[brain]:[plasma]	0.32
Solubility, lipid[b]	>67 μg/mL		

[a] All values are the mean ± SEM of at least two independent experiments run in triplicate in transiently transfected HEK-293 cells.
[b] Caprol MPGO:Capmul MCM:Acconon CC-6 (10:10:80) vehicle.
[c] 10 μmol/kg, po.

midazolam oxidation at 10 μM, which no longer occurred in a time-dependent manner. The metabolism of **21** was examined, since the formation of **20** by in vivo demethylation would restore the potential for drug–drug interactions. In a PK study in rats, the primary site of metabolism was found to be the *tert*-butyl group, predominantly forming the corresponding primary alcohol, as well as the carboxylic acid oxidation products. Based on AUC, the ratio of **20**:**21** was only ~1:8, indicating relatively little metabolism by demethylation. Moreover, the rate of demethylation of **21** by human microsomes was only ~30% that of rat microsomes, which further reduced concerns of drug–drug interactions in humans.

The favorable in vitro activity and CYP inhibition profile of **21** prompted the development of an optimized synthesis[12] to provide material in sufficient quantities for characterization in pre-clinical efficacy and pharmacokinetic studies. Various biological studies in rats showed **21** to possess similar activities in inflammatory and arthritic pain models as **20**, with similar CNS exposures (Table 4). Additionally, **21** showed greater effects following chronic treatment in the OA model relative to a single dose (67% effect after 12 days, 10 μmol/kg, po BID dosing vs 20% acute 10 μmol/kg, po response). The compound also reduced pain after a single dose in a post-operative pain model in rats (45% effect @ 100 μmol/kg, po).[4b] The ~40-fold lower potency of **21** versus capsaicin at rat TRPV1 than at hTRPV1 is similar to shifts observed with other antagonists in our assays, and appears to be an effect of cell line differences. The reversal of antagonism at hTRPV1 to agonism at rTRPV1 has been previously reported for some compounds,[13] and could potentially produce similar in vivo pain reduction via agonist-induced TRPV1 desensitization. However, no agonism was observed for **21** in either species indicating antinociception via TRPV1 antagonism. Furthermore, in rat telemetry studies **21** produced hyperthermia characteristic of TRPV1 antagonists (0.9 °C increase in body temperature 1 h after a 100 μmol/kg oral dose). Compound



R =	Me	Et	iPr
	21	**22**	**23**
hTRPV1 IC_{50} (cap, nM)[a]	7 ± 1	53 ± 17	69 ± 15

[a]All values are the mean ± SEM of at least two independent experiments run in triplicate.

Scheme 2. Synthesis and activities of alkylindazoles. Reagents and conditions: (a) For **21**, NaH, $(MeO)_2SO_2$, DMF, 50%; for **22**, NaH, EtI, DMF, 66%; for **23**, NaH, $(iPrO)_2SO_2$, DMF, 41%.

21 also potently inhibited hTRPV1 versus the putative endogenous activators *N*-arachidonoyldopamine (NADA) and low pH, which may have more relevance to native pain states. While aqueous solubility was greatly reduced relative to **20**, **21** maintained very good solubility in lipid mixtures, affording good oral bioavailability in the vehicle described below.

Although failing to improve upon the aqueous solubility of **2**, **21** did meet the overarching goal of enhanced ease of formulation with the use of lipid-based vehicles. Additionally, **21** provided an improved PK profile relative to **2**, with predictions of reduced human clearance and extended half-life, and was therefore advanced for clinical development as ABT-116.

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