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N-Tetrahydroquinolinyl, *N*-quinolinyl and *N*-isoquinolinyl biaryl carboxamides as antagonists of TRPV1

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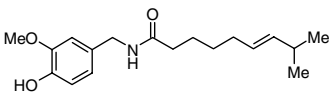
Abstract—Starting from the high throughput screening hit (**3**), novel *N*-tetrahydroquinolinyl, *N*-quinolinyl and *N*-isoquinolinyl carboxamides have been identified as potent antagonists of the ion channel TRPV1. The *N*-quinolinylnicotinamide (**46**) showed excellent potency at human, guinea pig and rat TRPV1, a favourable *in vitro* DMPK profile and activity in an *in vivo* model of inflammatory pain.

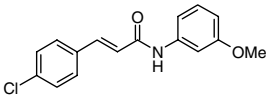
Capsaicin (**1**), the pungent component of hot chilli peppers, has been shown to activate the ligand gated, non-specific cation channel TRPV1 (formerly known as vanilloid receptor-1, VR-1) which is located on the nociceptive primary afferents of the C-fibre pain pathway.[1] The receptor may also be stimulated by low extracellular pH, noxious heat and a variety of other endogenous and exogenous compounds such as the cannabinoid anandamide and the natural diterpene, resiniferatoxin (RTX). Activation of TRPV1 leads to an influx of calcium and sodium ions through the channel, causing depolarisation of the cell and ultimately the sensation of pain. TRPV1 agonists have been shown to be effective for the relief of pain in humans through desensitisation of the receptor.[2] However, disadvantages of this approach include the initial pain and irritation caused on administration and unsuitability for systemic based therapy due to widespread desensitisation. A competitive antagonist of TRPV1 possessing a shorter duration of action could provide an alternative strategy for the treatment of chronic pain,[3] with the possibility that it may also offer an improved safety profile when compared to established analgesics such as NSAIDs and COX-2 inhibitors.

Capsazepine (**2**) was the first competitive antagonist[4] to be developed but has been of limited use due to its low in vivo potency and non-specific effects (blockage of voltage-gated calcium channels and nicotinic acetylcholine receptors). We have previously reported on cinnamide SB-366791[5] and a series of ureas, exemplified by SB-452533,[6] as potent and selective inhibitors of TRPV1. A number of other groups have reported on thioureas,[7] carboxamides,[8] alternative series of cinnamides[9] and ureas.[8b,10]

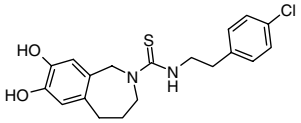
Herein, we report the results of SAR studies on a novel series of carboxamides as TRPV1 antagonists leading to the identification of a compound possessing activity in a pre-clinical model of chronic inflammatory pain.



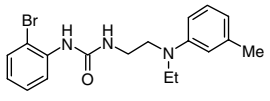
Capsaicin **1**



SB-366791



Capsazepine **2**



SB-452533

Keywords: TRPV1 antagonist; VR1 antagonist; Vanilloid.
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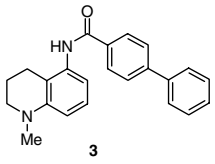
High throughput screening of the GSK collection using a FLIPR (FLuorescence Imaging Plate Reader) based Ca^{2+} antagonist assay with capsaicin as the agonist[11] resulted in the identification of the 1,2,3,4-tetrahydroquinoliny-5-yl (THQ) carboxamide (**3**). This compound possessed moderate antagonist potency at human TRPV1 (pK_b 6.5) and a lead optimisation programme was initiated.



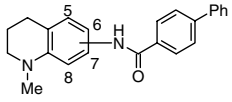
3

First, the effects of changing the position of attachment of the biphenyl amide were investigated through preparation of the analogues of (**3**) as shown in Scheme 1. Testing compounds (**3**–**6**) in the FLIPR assay revealed that substitution at the 7-position of the THQ (**5**) was optimal for antagonist potency at TRPV1 (Table 1).

Second, the requirements for the nature of the substituent at the 1-position of the THQ in (**5**) were examined (Table 2). The unsubstituted THQ (**11**, pK_b 7.7) had similar potency to (**5**). Increasing the chain length and introducing polar groups into the side chain offered the opportunity to modulate the physicochemical properties of the series (**12**–**15**). However, while these substituents were generally well tolerated, potency levels were lower than those for the simple N-Me and N-unsubstituted analogues (**5**) and (**11**). Replacement of the alkyl side chain with acetyl (**16**) or methoxyacetyl (**17**) was also tolerated, indicating that the moderate basicity of the THQ nitrogen is not crucial for activity.

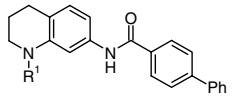
Alternatives to the THQ moiety were investigated next. Thus, the quinolinyl amide isomers (**18**–**21**) were prepared from the appropriate amine via EDCI mediated coupling with the relevant carboxylic acid.[14] The 7-aminoquinoline precursor to amide (**20**) was initially prepared in low yield from 3-nitroaniline via the Skraup quinoline synthesis[15] followed by catalytic hydrogenation of the resultant 7-nitroquinoline. An improved procedure was required for larger-scale synthesis and

Table 1. Antagonist activity (FLIPR) versus capsaicin at human TRPV1 for 1-Me-tetrahydroquinoline derivatives **3**–**6**



Compound[12]	Substitution	hTRPV1 pK_b[13]
3	5-	<6.5
4	6-	7.1
5	7-	7.5
6	8-	<6.3

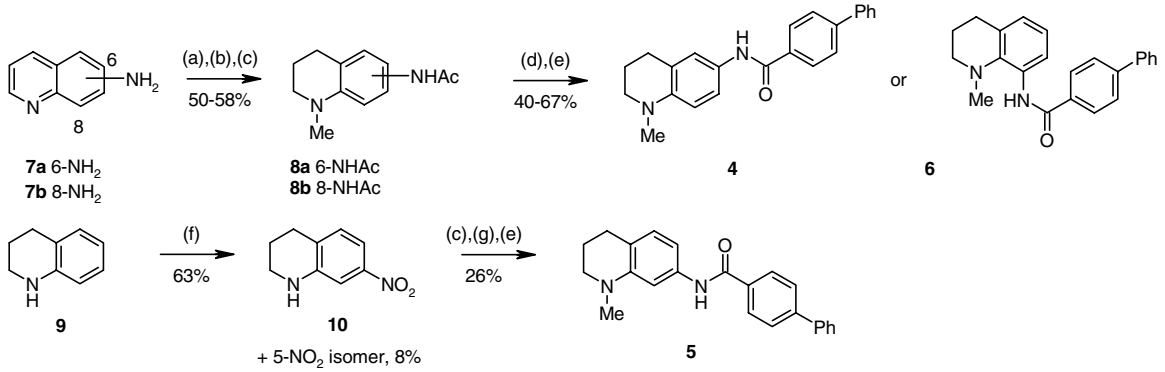
Table 2. Antagonist activity (FLIPR) versus capsaicin at human TRPV1 for 7-tetrahydroquinoline derivatives **11**–**17**



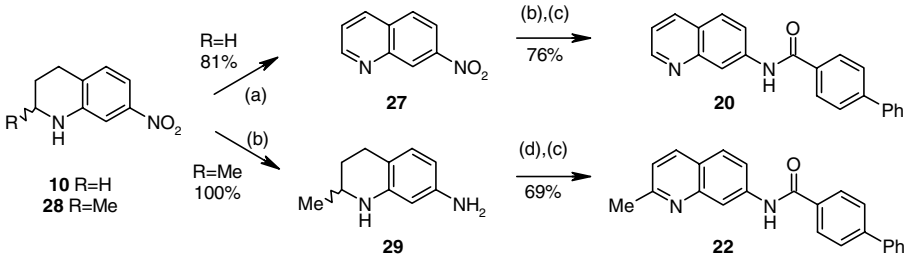
Compound[12]	R^1	hTRPV1 pK_b[13]
11	H	7.7
12	$-(CH_2)_2OMe$	7.3
13	$-(CH_2)_2NMe_2$	7.4
14	$-(CH_2)_2$-(1-morpholinyl)	7.0
15	$-(CH_2)_2NHC(O)Me$	6.9
16	–C(O)Me	7.2
17	$-C(O)CH_2OMe$	7.2

Scheme 2 outlines an effective procedure using as a key step, DDQ oxidation of the 7-nitro-1,2,3,4-THQ intermediate (**10**) used for the synthesis of (**5**).[16] Evaluation of this series (Table 3) indicated that the preference for 7-substitution was even more marked than in the THQ series, with compound (**20**) showing an 80-fold increase in TRPV1 antagonist potency over the 1-Me substituted THQ (**5**).

Modification of the conditions for the oxidation step enabled the efficient preparation of the 2-Me analogue (**22**) as shown in Scheme 2. This analogue was targeted as 2-unsubstituted quinoline templates have previously been shown to be metabolically unstable through the action of aldehyde oxidase.[17] Interestingly, it was found that introduction of the 2-methyl substituent was

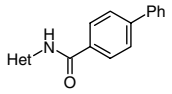


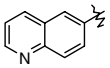
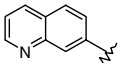
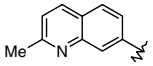
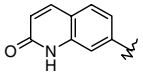
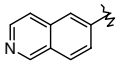
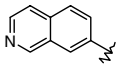
Scheme 1. Reagents and conditions: (a) Ac_2O, DCM, 0 °C, rt; (b) H_2, PtO_2, EtOH, 50 °C, 50 psi; (c) MeI, K_2CO_3, DMF, rt; (d) $3MHCl_{aq}$, 60 °C; (e) $ArCO_2H$, EDCI–HCl, DMAP, DCM, rt; (f) HNO_3, H_2SO_4, 0–5 °C; (g) H_2, 10% Pd/C, MeOH, rt, 1 atm.



Scheme 2. Reagents and conditions: (a) DDQ, PhMe, 100 °C; (b) H_2, 10% Pd/C, EtOH, rt, 1 atm; (c) $ArCO_2H$, EDCI–HCl, DMAP, DCM, rt; (d) 10% Pd/C, xylene, reflux.

Table 3. Antagonist activity (FLIPR) versus capsaicin at human TRPV1 for quinoline and isoquinoline derivatives **18**–**26**

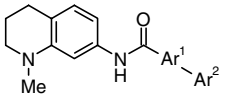


Compound[12]	Het	hTRPV1 pK_b[13]
18		<6.5
19		6.9
20		9.4
21		<6.5
22		8.0
23		8.5
24		7.7
25		7.7
26		7.4

detrimental to potency at TRPV1 when compared to (**20**) (Table 3) and offered no improvement in its *in vitro* DMPK profile. The carbostyril analogue (**23**) showed good potency at TRPV1 with pK_b 8.5 but suffered from poor aqueous solubility compared to (**20**). Replacement of the quinolinyl moiety with isoquinoline also gave compounds with lower but acceptable potency at TRPV1. The 5-, 6- and 7-analogues (**24**–**26**) shown in Table 3 possessed a level of activity similar to that displayed by the 7-THQs (**5**) and (**11**).

Investigation into the SAR of the biaryl portion of the molecule was initially focused on the 1-methyl-7-THQ (**5**). A 76-membered array was prepared around this template, using methods similar to those described in Scheme 1, and results for a selection of examples are shown in Table 4.

Table 4. Antagonist activity (FLIPR) versus capsaicin at human TRPV1 for 1-Me-7-tetrahydroquinoline derivatives **30**–**45**



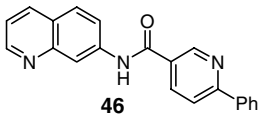
Compound[12]	Ar^1	Ar^2	hTRPV1 pK_b[13]
5	Ph	4-Ph	7.5
30	Ph	3-Ph	<6.8
31	Ph	2-Ph	<6.6
32	2-MeOPh	4-Ph	<6.8
33	2-ClPh	4-Ph	7.1
34	3-MePh	4-Ph	7.4
35	Ph	4-[4-(Me_2NCO)Ph]	7.1
36	Ph	4-[3-(MeCO)Ph]	7.0
37	Ph	4-[3-($MeNHSO_2$)Ph]	7.0
38	Ph	4-(2-Thienyl)	7.6
39	Ph	4-(3-Thienyl)	7.8
40	Ph	4-(5-Pyrimidinyl)	6.9
41	Ph	4-(1-Pyrazolyl)	6.9
42	Ph	4-(2-Pyrazinyl)	7.1
43	2-Thienyl	5-Ph	7.0
44	3-Pyridyl	6-Ph	7.8
45	2-Pyrazinyl	5-Ph	<6.8

These data indicated that the 4-substituted biaryl was optimal for TRPV1 potency, see compounds (**5**), (**30**) and (**31**). In addition, a number of functional groups were tolerated, compounds (**33**–**37**), as well as heteroaromatic replacements for the biphenyl moiety, compounds (**38**–**44**). Of particular interest was the 6-phenylnicotinamide (**44**) which combined a good level of potency at hTRPV1 (pK_b 7.8) with an improved metabolic stability profile (CL_i: 4 (human), 6 (rat) ml/min/g liver) when compared to biphenyl carboxamide (**5**) (CL_i: 7 (human), 12 (rat) ml/min/g liver).

Incorporation of this nicotinamide moiety into the quinoline series, (**46**), again led to increased potency (pK_b 8.7) compared to the THQ (**44**). Further screening against rat and guinea pig TRPV1 receptors showed a good level of antagonist potency against both capsaicin and acid as agonists (Table 5).

In addition, (**46**) exhibited good levels of *in vitro* metabolic stability (CL_i < 5 ml/min/g liver) at human, rat,

Table 5. Antagonist activity (FLIPR) of **46** versus capsaicin and acid at human, rat and guinea pig TRPV1 receptors



46

Agonist	TRPV1 pK_b/pIC_{50}[a]		
	Human	Guinea pig	Rat
Capsaicin	8.7	8.4	8.4
Acid (pH 5.3)	8.1	Not tested	7.6

[a] data given are pK_b with capsaicin and pIC_{50} with acid as agonists, respectively.

guinea pig and dog liver microsomes and a P450 inhibition profile with IC_{50} values > 18 μM at five major human isoforms (1A2, 2C9, 2C19, 2D6 and 3A4).

Compound (**46**) was also evaluated in a model of Freund's Complete Adjuvant (FCA) induced inflammatory hyperalgesia in the guinea pig.[18] One hour after dosing at 30 mg/kg sc, (**46**) gave 32% reversal of mechanical hyperalgesia.[19]

In summary, early lead optimisation chemistry around the HTS lead (**3**) led to the identification of series of *N*-tetrahydroquinolinyl, *N*-quinolinyl and *N*-isoquinolinyl carboxamides which showed excellent antagonist potency versus capsaicin at recombinant human TRPV1. A key exemplar from the *N*-quinolinyl series, (**46**),[20] also showed similar levels of potency at rat and guinea pig receptors. Furthermore, (**46**) possessed excellent potency versus acid at human and rat TRPV1 receptors and has been used as a tool compound to demonstrate activity in a model of inflammatory pain.

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12. All new compounds gave satisfactory ^{1}H NMR and/or mass spectral data.
13. All pK_b values represent means from at least three independent experiments with SD $\leqslant$ 0.3 in all cases.
14. Typical procedure: A mixture of aminoquinoline (0.5 mmol), 4-biphenylcarboxylic acid (0.75 mmol), EDCI–HCl (0.75 mmol) and DMAP (0.075 mmol) in DCM (3 ml) was stirred at room temperature for 24 h. Aqueous work-up followed by column chromatography on silica gave the desired product.
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16. A solution of (**10**) (2.20 g) in toluene (300 ml) was treated with DDQ (5.88 g) and stirred for 1.5 h at 100 °C. The cooled mixture was filtered, concentrated and purification of the residue by column chromatography on silica eluting with an ethyl acetate/petroleum ether gradient gave (**27**) (1.75 g, 81%).
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19. Compound (**46**) significantly reversed FCA-induced hyperalgesia by 32 ± 9% compared to the vehicle reversal of 8 ± 3%. *P < 0.05 ANOVA followed by post hoc LSD test comparing to vehicle response.
20. Characterising data for (**46**): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.23 (1H, d, J 2.2 Hz), 8.92 (1H, dd, J 4.2, 1.6 Hz), 8.33 (1H, dd, J 8.3, 2.3 Hz), 8.23 (1H, s), 8.15, (2H, m), 8.08 (3H, m), 7.90 (1H, d, J 8.3 Hz), 7.87 (1H, d, J 8.9Hz), 7.50 (3H, m), 7.38 (1H, dd, J 8.2, 4.2 Hz).