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Bioorganic & Medicinal Chemistry Letters 16 (2006) 2872–2876
Bioorganic & Medicinal Chemistry Letters

The search for novel TRPV1-antagonists: From carboxamides to benzimidazoles and indazolones

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Received 9 February 2006; revised 28 February 2006; accepted 2 March 2006
Available online 24 March 2006

Abstract—Based on a series of diaryl amides the corresponding inverse amides have been found to be potent TRPV1 receptor antagonists. Benzimidazole and indazolone derivatives prepared retained good potency in vitro and indazolone **4a** was identified as a novel TRPV1 receptor antagonist suitable for evaluating orally in animal models of analgesia.

The search for transient receptor potential vanilloid 1 (TRPV1) antagonists as potential analgesics has attracted much attention of late. This has resulted in the disclosure of several structural classes of compounds.[1,2] We now wish to describe novel, potent benzimidazole and indazolone derivatives.[3]

Discovery of a series of biaryl amides, such as **1**, has recently been described.[2] Upon investigating the SAR within that series and in particular to explore the spatial and orientation requirements of the amide bond, inverse amide **2a** was prepared (Fig. 1). Despite the significant change in orientation of the carbonyl and NH bonds, compounds **1** and **2a** were found to have comparable potency at the TRPV1 receptor in vitro (Table 1). This provided a new avenue for exploration, the results of which are detailed in this letter.

Synthesis of a library of 'inverse' amides **2** was undertaken which rapidly established the in vitro SAR. Selected data are included in Table 1.

This study showed little tolerance for structural variation on the distal aromatic rings. Furthermore, evaluation of pharmacokinetic parameters of **2a** in rat (Table 4) indicated poor oral absorption in the series with low

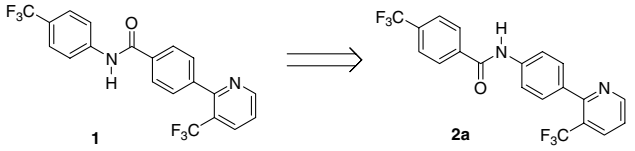

Figure 1.

hepatic portal vein (HPV) and systemic levels detected following oral dosing at 5 mpk.

In an effort to overcome the pharmacokinetic liability of the amides, heterocyclisation was explored. N–H heterocyclic derivatives were considered initially and benzimidazole derivatives **3** and indazolones **4** were targeted (Fig. 2).

A versatile synthesis of benzimidazoles **3** enabling structural variation at both the 2- and 5-positions was employed as shown in Scheme 1. Cross-coupling of 4-bromo-2-nitroaniline (**5**) with a variety of aromatic derivatives afforded the corresponding nitroanilines (**6**). Reduction of the nitro group with iron powder in acetic acid followed by cyclisation of the resulting phenylene diamine with a selection of benzaldehydes by heating at 140 °C in nitrobenzene for 2 h[6] gave the required benzimidazoles **3a**–**d**.

Benzimidazole **3a** showed comparable affinity at the hTRPV1 receptor to the inverse amide **2a** as measured in a FLIPR-based assay (IC_{50}, 22 nM). Whole-cell patch

Keywords: TRPV-1 antagonists; Indazolone; Benzimidazole.
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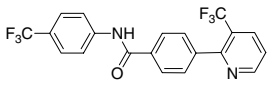
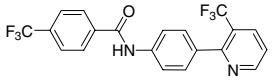
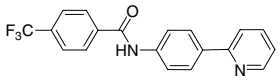
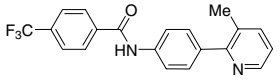
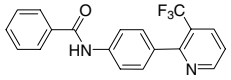
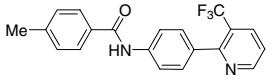
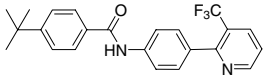
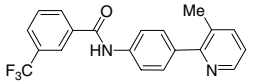
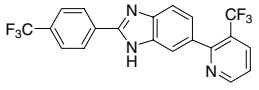
doi:10.1016/j.bmcl.2006.03.004

Table 1. Amides

Compound	Structure	hIC$_{50}$ (nM)	
		FLIPR[4]	Pclamp[5]
1		13	3
2a		24	33
2b		1500	—
2c		160	—
2d		2400	—
2e		1100	—
2f		470	—
2g		640	—
2h		11	5

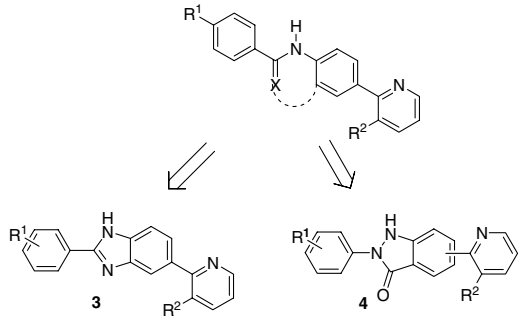


Figure 2.

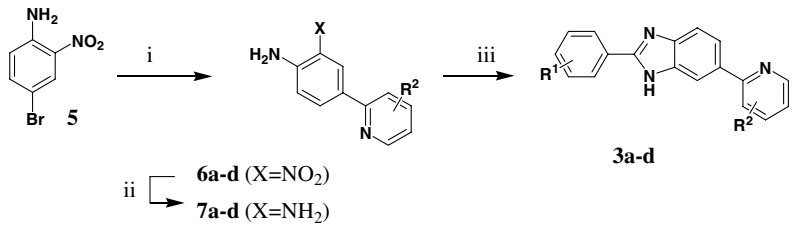
clamp experiments were again used to confirm activity against pH 5.5-dependent activation of the human receptor (Table 2). As was found with the amides, minor modifications to the substituents, such as replacement of the 4-CF_3 group with Me, ^{t}Bu or F, led to loss in potency. Consequently the pharmacokinetics of **3a** was evaluated prior to further SAR studies to assess whether the benzimidazole core would offer any advantage in vivo. The data obtained (Table 4) showed that whilst the benzimidazole led to a modest improvement in absorption ($AUC_{hpv\ (0–7\ h)}$, 1.48 μM h), circulating levels were still low (AUCsys, 1.25 μM h) following oral dosing at 5 mpk. As a consequence of this finding, attention was directed towards preparation of the indazolone derivatives **4**.

The approach taken towards a versatile synthesis of the desired indazolone derivatives was based on the work of Smalley and co-workers[7] who reported that treatment of o-azidobenzanilides with thionyl chloride leads to the formation of 2-aryl-3-chloro-2*H*-indazoles. Consequently, 2-azido-4-bromobenzoic acid was coupled with 4-aminobenzotrifluoride and the resulting anilide treated under the conditions of Smalley et al. with thionyl chloride at reflux. This led to the smooth formation of the 6-bromo-3-chloro-2*H*-indazole **11** as a key intermediate. Selective cross-coupling at the 6-position with 4-methoxyphenyl boronic acid proved possible and hydrolysis of the resulting product gave rise to indazolone **4e** (Scheme 2).

In an alternative use of intermediate **11**, hydrolysis of the 3-chloro substituent was initially carried out using KOH/MeOH to give bromide **13**. Direct cross-coupling with this derivative proved unsuccessful but the SEM-protected bromide **14** could be converted to the pinacolato borane derivative for cross-coupling purposes. In this way, **4a**[8] and **4c** were prepared (Scheme 3).

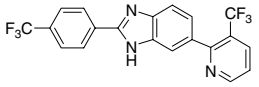
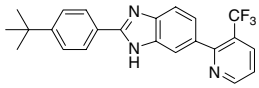
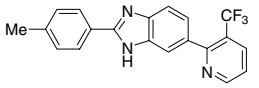
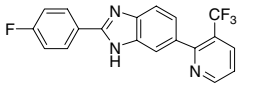
Azaindalone derivatives **4f** and **4g** were synthesised via standard condensation reactions as shown in Schemes 4 and 5. [3]

Since the indazolone lacks the inherent symmetry of the benzimidazole core, two isomeric derivatives **4a** and **4b** were prepared and evaluated. Of the two compounds, **4a** proved to be more active showing comparable affinity at the hTRPV1 receptor to the inverse amide **2a** and benzimidazole **3a** in the FLIPR-based assay (IC_{50}, 35 nM). This was confirmed by whole-cell patch clamp technique following stimulation by H^+ (Table 3). Somewhat disappointingly a similar SAR was observed with small functional group changes again leading to significant loss in potency. In a final effort to enhance affinity in vitro, azaindazole **4f** was prepared since this change had proved successful in the amide series, and tetrahydr-



Scheme 1. Reagents and conditions: (i) bis(pinacolato)diboron, $Pd(dppf)Cl_2$, KOAc, dioxane, reflux, then Na_2CO_3(aq), 2-chloro-3-(trifluromethyl)pyridine, reflux; (ii) Fe, AcOH, THF–water, (iii) ArCHO, nitrobenzene, 140°, 2 h.

Table 2. Benzimidazoles

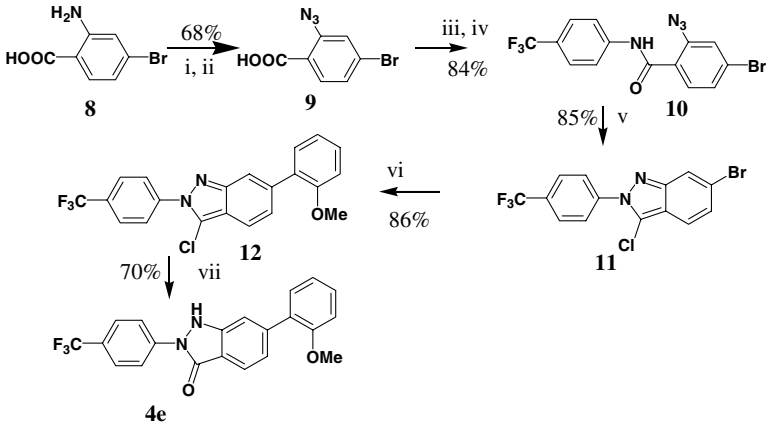
Compound	Structure	hIC$_{50}$ (nM)	% inh at 100 nM
		FLIPR	Pclamp
3a		22	95%
3b		224	—
3c		170	—
3d		320	—

oindazole **4g** was evaluated. Both strategies, however, proved unsuccessful with indazolone **4a** remaining the most active compound in vitro.

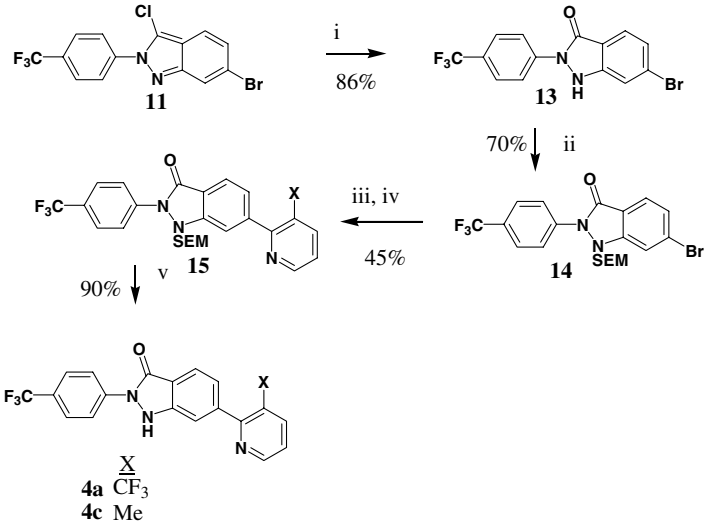
When indazolone **4a** was evaluated in vivo,[9] compared with the amide **2a** and benzimidazole **3a**, a significantly enhanced pharmacokinetic profile was observed (Table 4). Following oral dosing of **4a** at 5 mpk, significant systemic levels were obtained (AUC_{sys}, 3 μM h). The compound was evaluated further and found to have low plasma clearance of 8 mL/min/kg and a half-life of 3.6 h. Thus, indazolone **4a** represents a structurally novel TRPV1 receptor antagonist which is suitable for evaluating orally in animal models of analgesia.

Indazolone **4a** was evaluated in the carrageenan induced thermal hyperalgesia Hargreaves model in rat.[10] Following dosing at 30 mpk (po) a 50% reduction in hyperalgesia was obtained. To rationalize the modest activity, **4a** was evaluated at the rat TRPV1 receptor.[11]

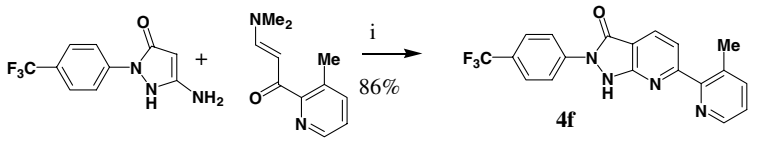
The IC$_{50}$ measured using whole-cell patch clamp studies[5] was 220 nM when stimulated with 500 nM capsaicin and 65 nM at pH 5.5 showing a significant drop in potency compared to the human receptor.



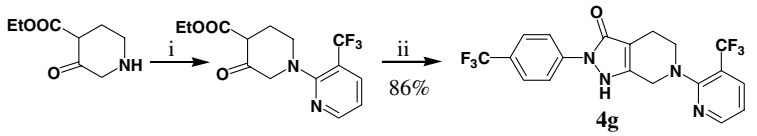
Scheme 2. Reagents and conditions: (i) $NaNO_2$, 2 N HCl, 5 °C; (ii) NaN_3, NaOAc, H_2O; (iii) $SOCl_2$, reflux; (iv) 4-aminobenzotrifluoride, DMAP, CH_2Cl_2; (v) $SOCl_2$, reflux, 96 h; (vi) 2-methoxyphenylboronic acid, Pddppf, Na_2CO_3, 160 °C, 900 s; (vii) KOH, MeOH, 150 °C, 10 min.



Scheme 3. Reagents and conditions: (i) KOH, MeOH, 160 °C, 15 min μwave; (ii) SECML, NaH, THF; (iii) bispinacolatodiborane, KOAc, Pddppf, dioxane, reflux, 18 h; (iv) chloropyridine, K_2CO_3, Pddppf, dioxane, reflux, 18 h; (v) 5 N HCl, EtOH, reflux, 1 h.



Scheme 4. Reagent and condition: (i) pyridine, reflux.



Scheme 5. Reagents and conditions: (i) NaH, 2-chloro-3-(trifluoromethyl)pyridine, DMA, 140 °C, 12 h; (ii) CF_3-phenylhydrazine, TsOH, xylene, reflux, 2 h.

Table 3. Indazolones

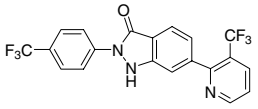
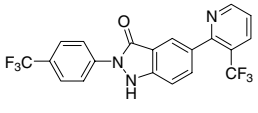
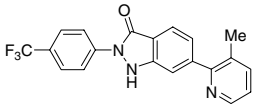
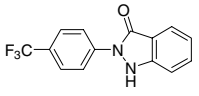
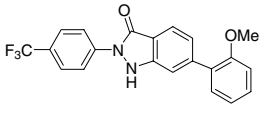
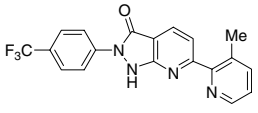
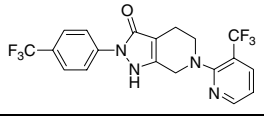
Compound	Structure	hIC_{50} (nM)	
		FLIPR	Pclamp
4a		35	4
4b		370	—
4c		180	—
4d		340	—
4e		170	—
4f		270	—
4g		290	—

Table 4. Pharmacokinetic parameters[8]

	2a	**3a**	**4a**
po_{dose} (mpk)	5	5	5
AUC_{hpv} (μM h)	0.08	1.48	6.2
AUC_{sys} (μM h)	0.04	1.25	3.0
iv_{dose} (mpk)			1
Cl (mL/min/kg)			8
$T_{1/2}$ (h)			3.6
V_d (L/kg)			2.0

In conclusion, we have developed a novel series of potent TRPV1 receptor antagonists. Compound **4a** shows activity in the carrageenan-induced thermal hyperalgesia model following oral dosing.

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4. Inhibition of capsaicin evoked increases in intracellular $[Ca^{2+}]$ was measured in CHO cells, stably expressing recombinant human VR1 receptors using 1uM Fluo-3-AM dye in a Molecular Devices FLIPR. Increases in intracellular $[Ca^{2+}]$ after addition of test compound, prior to addition of capsaicin, allowed determination of intrinsic agonist or partial agonist activity, if present. All compounds tested behaved as antagonists. For further details, see Ref. 3.
5. Whole-cell patch clamp electrophysiology was used to measure the block of currents stimulated by acidic pH (5.5) at human TRPV1 stably expressed in CHO cells. For experimental protocol, see: Sutton, K. G.; Garrett, E. M.; Rutter, A. R.; Bonnert, T. P.; Jarolimek, W.; Seabrook, G. R. *Br. J. Pharmacol.* **2005**, *146*, 702.
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8. Preparation of **4a**: 2-Azido-4-bromo-*N*-(4-(trifluoro methyl)phenyl)benzamide **10** (3 g, 0.0078 mol) in thionyl chloride (15 mL) was heated at reflux for 24 h. The mixture was concentrated and the residue partitioned between ether (3× 20 mL) and aq Na_2CO_3 (10 mL). The organic phase was separated, dried ($MgSO_4$) and concentrated to give 2.5 g (85% yield) of **11** as a tan powder. ^{1}H NMR (360 MHz, $CDCl_3$): 7.25 (1H, d, J = 8.9 Hz), 7.37 (1H, d, J 8.9 Hz), 7.80–7.95 (5H, m). A solution of **11** (2.4 g, 0.0064 mol) in 1 M KOH/MeOH (16 mL) was heated at 150 °C in a sealed tube via microwave irradiation for 15 min. The mixture was acidified with 1 N HCl and the precipitate collected by filtration to give 1.0 g (44% yield) of **13**. ^{1}H NMR (360 MHz, $CDCl_3$): 7.37 (1H, dd, J = 1.4 and 8.5 Hz), 7.66 (1H, d, J = 1.4 Hz), 7.73 (1H, d, J = 8.5 Hz), 7.89 (2H, d, J = 8.5 Hz), 8.13 (2H, d, J = 8.5 Hz), 11.0 (1H, s). A suspension of NaH in mineral oil (60%, 0.17 g, 0.0041 mol) was added to a solution of **13** (1.3 g, 0.0035 mol) in dry THF (50 mL) at room temperature under nitrogen. After 20 min, SEM chloride (0.68 g, 0.0041 mol) in THF (15 mL) was added and the resulting slurry stirred overnight. The mixture was quenched with brine (10 mL) and extracted into ether (3× 20 mL). The organic phase was washed with 1 N HCl (10 mL), 2 N NaOH (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated to give crude **14** as an oil. **14** (1.3 g, 2.6 mmol) was dissolved in dioxane (10 mL) under N_2 and bis(pinacolato) diboron (680 mg, 2.6 mmol), bis(diphenylphosphino)ferrocenyl palladium(II) dichloride (60 mg) and KOAc (380 mg, 3.9 mmol) were added and the mixture stirred at 100 °C overnight. 2-Chloro-3-(trifluoromethyl)pyridine (470 mg, 2.6 mmol), bis(diphenylphosphino)ferrocenyl palladium(II) dichloride (20 mg) and saturated Na_2CO_3 solution (1 mL) were added, and the mixture heated at reflux for a further 18 h. Purification by column chromatography gave 0.2 g of product as an oil, MS: (ES (M+1)) 554. This material was dissolved in concd HCl (2 mL) and EtOH (3 mL) and heated at reflux for 1 h. The mixture was concentrated and the residue crystallized from EtOH/water to give 70 mg of **4a** as a colourless solid. ^{1}H NMR (360 MHz, $CDCl_3$): 7.33 (1H, s), 7.39 (1H, d, J = 8.0 Hz), 7.43 (1H, s), 7.5–7.55 (1H, m), 7.73 (2H, d, J = 8.0 Hz), 7.99 (1H, d, J = 8.0 Hz), 8.09 (2H, d, J = 8.0 Hz), 8.14 (1H, d, J = 8.0 Hz), 8.9 (1H, d, J = 8.0 Hz).
9. For experimental protocol, see: Scott-Stevens, P.; Atack, J. R.; Sohal, B.; Worboys, P. *Biopharm. Drug Dispos.* **2005**, *26*, 13.
10. A beam of light is focussed on the underside of the foot until the animal responds by removing the foot from the light source; three recordings are made on each hind limb with stimulation separated by at least 5 min. Animals were injected intra-plantar with either carrageenan (positive control and drug tested animals) or saline (0.1 mL in the right hind limb). Two hours later, animals were dosed (po) with the **4a** at 30 mpk. After 1 h, animals were retested three times on each hind limb. The change in response following a saline injection is assumed to be an uninflamed state with 0% hyperalgesia, while carrageenan injection is assumed to produce a hyperalgesic response of 100%.
11. Grant, S. K.; Bansal, A.; Mitra, A. W.; Dai, G.; Kaczorowski, G. J.; Middleton, R. E. *Anal. Biochem.* **2001**, *294*, 27.