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# From arylureas to biarylamides to aminoquinazolines: Discovery of a novel, potent TRPV1 antagonist

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**Abstract**—Bioisosteric replacement of piperazine with an aryl ring in lead VR1 antagonist **1** led to the biarylamide series. The development of B-ring SAR led to the conformationally constrained analog **70**. The resulting aminoquinazoline **70** represents a novel VR1 antagonist with improved in vitro potency and oral bioavailability vs the analogous compounds from the lead series.


TRPV1 (VR1 receptor) is a member of the transient receptor potential family of ion channels and is localized on primary afferent neurons as well as sensory neurons inervating the bladder and gut. Activation of VR1 on sensory neurons by chemical stimulants including capsaicin and resiniferatoxin, as well as low pH and heat, leads to an influx of calcium and sodium ions through the channel, causing depolarization of the cell and transmission of painful stimuli. It is now generally hypothesized that direct blockade of the channel should provide a clinically effective therapeutic method to treat pain.

Therefore, the identification of selective and potent antagonists of VR1 has become a focus of attention within the pharmaceutical industry.[1]

Among the earliest non-vanilloid VR1 antagonists to appear in the patent literature were the arylureas e.g., **1** (Fig. 1) which we originally discovered several years ago through screening of our compound library.[2] Several other groups have independently reported on the SAR of these and related VR1 antagonists.[3] The arylureas have proven to be valuable tools to explore pre-clinical VR1 pharmacology,[4] although the commercial potential of the best characterized members of the series has generally been limited due to a variety of issues including poor aqueous solubility, poor oral exposure, and metabolic/chemical instability. During our own SAR exploration of the arylurea series it was discovered that bioisosteric replacement of the piperazine B-ring with an aryl-ring was feasible (e.g., **1** and **2**, Fig. 1) with minimal loss of potency at the VR1 receptor.[5] The resulting arylcarboxamides offered several possible advantages, among them: (1) increased metabolic/chemical stability; (2) more direct access to underexplored regions of the arylurea pharmacophore via substitution on the B-ring; (3) a springboard from which to develop novel second generation VR1 antagonists.

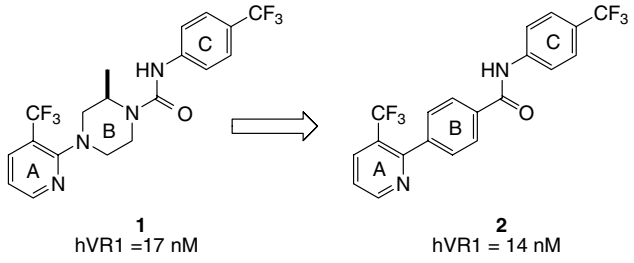


**Figure 1.** Bioisosteric replacement of the piperazine by a phenyl ring.

*Keywords*: VR1; TRPV1; Pain; Bioisostere; Quinazoline; Ureas; Antagonist.
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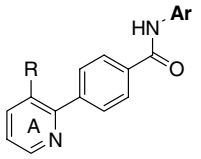
This letter highlights the pertinent SAR of the A-, B-, and C-rings of the biarylamides with emphasis on the B-ring and how this related to the discovery of a series of aminoquinazolines with potent VR1 antagonist activity. The compounds were assayed for their ability to inhibit capsaicin activation of human VR1 receptors using fluorometric imaging plate reader (FLIPR) technology as well as their ability to inhibit the rat VR1 receptor upon activation at low pH (5.0–5.5).[8] The data are presented in Tables 1–3. The compounds in the study were conveniently prepared by the route outlined in Scheme 1.

In general, the SAR with respect to simple substitutions on the A- and C-rings tracked well with the arylurea series. For example, the preferred A-ring was a pyridin-2-yl linkage with a 3-substituent (e.g., 3-$CF_3$, 3-Me or 3-Cl). Substitution at other positions of the A-ring or replacement of the A-ring with a variety of five and six membered heterocycles resulted in a significant loss of potency (data not shown). The optimal substitution on the C-ring incorporated a lipophilic group (e.g., $CF_3$ or $^t$butyl) at the *para*-position of the aniline (**2** and **11**, Table 1). Smaller alkyl groups (**12** or **18**) or more-hydrophilic groups (**9** or **13**) led to a degradation of VR1 antagonist potency. A pyridine C-ring was tolerated as long as the requisite lipophilic group was present in the para-position (see **10** vs **19**). The data illustrate the effectiveness of these compounds in blocking the VR1 receptor irrespective of species (human or rat) or modality of activation (capsaicin or low pH). While the simple biarylamides maintained much of the in vitro potency of the corresponding arylureas (e.g., **2** vs **1**), the compounds also retained the less desirable drug-like properties of the corresponding ureas, most notably poor aqueous solubility. For example, the most potent example, **11** (hVR1 = 6 nM), exhibited a bioavailability in rats of only 2%, as well as poor aqueous solubility (below limit of quantitation, BLQ) in our high throughput solubility (HTSol) assay.[6]

Utilizing our knowledge of arylurea SAR, we focused our efforts to solubilize these compounds on the 3-position of the A-ring, a position more tolerant of substitution (Table 2).

Among the neutral hydrophilic substituents, several sulfonamides (**35**–**37**, and **40**) exhibited a modest improvement in aqueous solubility (HTSol 1–20 μg/mL) versus

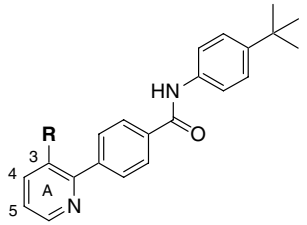
**Table 1.** Biarylamides with A- and C-ring variations[a]




| Compound | R | Ar | hVR1-cap[b] (nM) | rVR1-pH[c] (nM) |
|---|---|---|---|---|
| **1** | Figure 1 | | 17 | 11 |
| **8** | $CF_3$ | Ph | >4000 | nd |
| **2** | $CF_3$ | 4-$CF_3$-Ph | 14 | 26 |
| **9** | $CF_3$ | 4-CN–Ph | 417 | 1299 |
| **10** | $CF_3$ | 5-$CF_3$–pyridin-2-yl | 24 | 65 |
| **11** | $CF_3$ | 4-*tert*-Butyl–Ph | 6 | 4 |
| **12** | Me | 4-$^i$-Propyl–Ph | 73 | 43 |
| **13** | Me | 4-*O*Me–Ph | >4000 | >4000 |
| **14** | Me | 4-F–Ph | >4000 | >4000 |
| **15** | Me | 4-Cl–Ph | 1502 | 2024 |
| **16** | Me | 4-*O*$CF_3$–Ph | 974 | 896 |
| **17** | Me | 4-Br–Ph | 189 | 366 |
| **18** | Me | 4-Me–Ph | 2585 | >4000 |
| **19** | Me | Pyridin-2-yl | >4000 | >4000 |
| **20** | Me | 4-$CF_3$–Ph | 65 | 81 |
| **21** | Me | 4-*tert*-Butyl–Ph | 11 | 9 |
| **22** | Cl | 4-*tert*-Butyl–Ph | 8 | 2 |
| **23** | Cl | 4-$CF_3$–Ph | 58 | nd |

[a] Values are means of 2–4 experiments, (nd = not determined).
[b] Values are $IC_{50}$s at human VR1 receptor activated by capsaicin.
[c] Rat VR1 receptor activated by low pH (5.0–5.5).

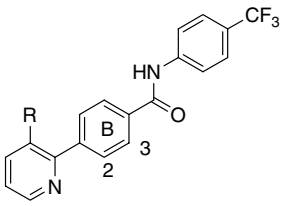
**Table 2.** Biarylamides with A-ring 3-position variations[a]

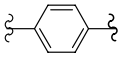
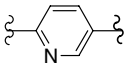
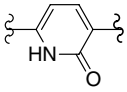
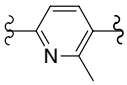
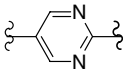
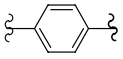
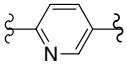
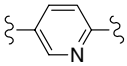



| Compound | R | hVR1-cap[b] (nM) | rVR1-pH[c] (nM) |
|---|---|---|---|
| **24** | H | 11 | 8 |
| **25** | F | 3 | 1 |
| **21** | Me | 13 | 10 |
| **22** | Cl | 8 | 2 |
| **11** | $CF_3$ | 7 | 4 |
| **26** | *O*-propyl | 62 | 20 |
| **27** | CN | 30 | 13 |
| **28** | $NO_2$ | 5 | 5 |
| **29** | $NH_2$ | 123 | 325 |
| **30** | NH–propyl | 158 | 37 |
| **31** | NH–cyclopentyl | 190 | 44 |
| **32** | NH(C=O)Me | 1106 | 290 |
| **33** | NHOH | 49 | 5 |
| **34** | $NHSO_2Me$ | 152 | 35 |
| **35** | $NMeSO_2Me$ | 39 | 9 |
| **36** | $NHSO_2Et$ | 49 | 4 |
| **37** | $N(SO_2Me)_2$ | 0.8 | 0.4 |
| **38** | $NHSO_2$–*n*-butyl | 162 | 141 |
| **39** | $NHSO_2CH_2Ph$ | 377 | 159 |
| **40** | $NHSO_2Ph$ | 91 | 166 |
| **41** | $CH_2OH$ | 168 | 88 |
| **42** | $CO_2H$ | >4000 | 560 |
| **43** | $C(=N)NH_2$ | >4000 | >4000 |
| **44** | $CH_2N(Me)_2$ | 746 | 234 |
| **45** | $CH_2N(Et)_2$ | 1412 | 334 |
| **46** | $CH_2NH$–propyl | 4303 | 639 |
| **47** | $CH_2$–pyrrolidin-1-yl | 1527 | 196 |
| **48** | Imidazol-2-yl | 3669 | 694 |
| **49** | 2-Me–1,3,4-oxadiazol-5-yl | 387 | 34 |
| **50** | 1,3,4-Oxadiazol-2-yl | 91 | 59 |
| **51** | Tetrazol-5-yl | >4000 | >4000 |

[a] Values are means of 2–4 experiments, (nd = not determined).
[b] Values are $IC_{50}$s at human VR1 receptor activated by capsaicin.
[c] Rat VR1 receptor activated by low pH (5.0–5.5).

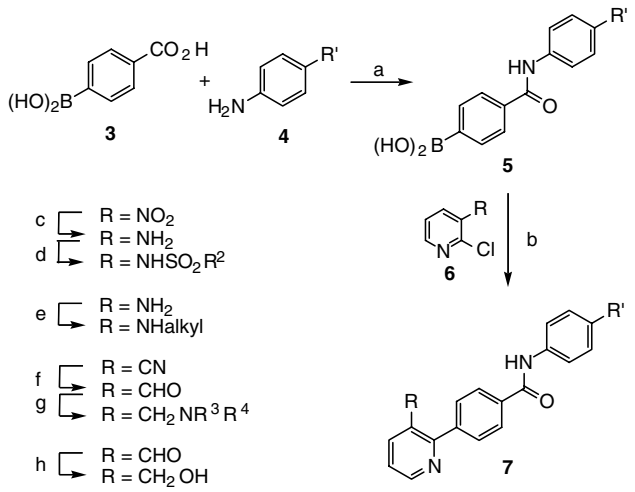
**Table 3.** Biarylamides with B-ring variations[a]



| Compound | R | B-ring (substituents) | hVR1-cap[b] (nM) | rVR1-pH[c] (nM) |
|---|---|---|---|---|
| **1** | Figure 1 | | 17 | 11 |
| **2** | $CF_3$ |  | 14 | 26 |
| **52** | $CF_3$ | 2-Me | 257 | 192 |
| **53** | $CF_3$ | 3-F | 131 | 348 |
| **54** | $CF_3$ | 3-Cl | >4000 | 2403 |
| **55** | $CF_3$ | 3-OH | 43 | 36 |
| **56** | $CF_3$ | 3-$NH_2$ | 93 | 103 |
| **57** | $CF_3$ | 3-$NO_2$ | 392 | 222 |
| **58** | $CF_3$ | 3-OMe | >4000 | 1044 |
| **59** | $CF_3$ | 3-$N(SO_2Me)_2$ | >4000 | >4000 |
| **60** | $CF_3$ | 3-$NHSO_2Me$ | 1015 | 722 |
| **61** | $CF_3$ |  | 60 | 56 |
| **62** | $CF_3$ |  | >4000 | 764 |
| **63** | $CF_3$ |  | 259 | 263 |
| **64** | $CF_3$ |  | 42 | 60 |
| **65** | Me |  | 64 | 79 |
| **66** | Me | 2-Me | 233 | 190 |
| **67** | Me | 3-Me | >4000 | >4000 |
| **68** | Me |  | 624 | 583 |
| **69** | Me |  | 1779 | 1583 |

[a] Values are means of 2–4 experiments, (nd = not determined).
[b] Values are $IC_{50}$s at human VR1 receptor activated by capsaicin.
[c] Rat VR1 receptor activated by low pH (5.0–5.5).

the parent compound **24** (HTSol BLQ) but only double-digit nanomolar potency at VR1 was attainable. The bis-sulfonamide **37** (hVR1 = 0.8 nM) exhibited the highest potency of any of the biarylamides, however, this compound rapidly reverted to the mono-sulfonamide **34** upon treatment with nucleophilic amines, making it unsuitable for further development. Basic amines (e.g., **44**, HTSol 50 μg/mL) or acidic functionalities (e.g., **42**, HTSol 104 μg/mL) offered a much improved solubility profile but were less potent at VR1 (746 to >4000 nM). Similarly, the incorporation of small heterocycles (**48**–**51**) yielded compounds with modest or weak potency.




**Scheme 1.** General synthesis (a) BOP, $CH_2Cl_2$, (b) 2 M $Na_2CO_3$, $Pd(PPh_3)_4$, DME, 80 °C, (c) $SnCl_2 \cdot 2H_2O$, EtOAc, reflux, (d) MsCl, TEA, $CH_2Cl_2$, (e) alkyl-CHO, $NaBH(OAc)_3$, HOAc, DCE, (f) DIBAL, $CH_2Cl_2$, −78 °C, (g) $NHR^3R^4$, $NaBH(OAc)_3$, DCE, HOAc, and (h) $NaBH_4$, EtOH.

Exploration of the central ring (Table 3) was of primary importance since this region was less accessible synthetically in the arylurea series and largely unexplored. The introduction of small lipophilic groups was investigated first. At the 2-position, methyl substitution gave a 4- to 18-fold decrease in potency compared to the parent analogs (**52** vs **2** and **66** vs **65**). At the 3-position, introduction of a chloro- (**54**) or methyl-substituent (**67**) resulted in an even more dramatic loss in potency. A similar trend was observed for the 2-pyridyl analogs **61** and **63** (Table 3). Conformational analysis of **2** using the MMFFs force field[7] suggests that the central phenyl ring is twisted with respect to the amide bond by 35° in the minimized structure, although enforcing planarity of the benzamide requires only 1.2 kcal/mol. By making the planar benzamide unit energetically inaccessible through 3-Cl substitution, a large reduction in VR1 potency was observed. Conversely, introduction of a small hydrogen bond donor at the 3-position gave compounds only slightly less potent at VR1 than the parent **2**. For example, the 3-OH (**55**) and 3-$NH_2$ (**56**) analogs are capable of forming a hydrogen bond with the amide carbonyl thereby enforcing planarity of the benzamide unit. Analogs, such as the 3-OMe (**58**, >4000 nM) or 3-$NO_2$ (**57**, 392 nM) which contain H-bond acceptor groups only and which were capable of forming H-bonding interactions with the aniline NH, were

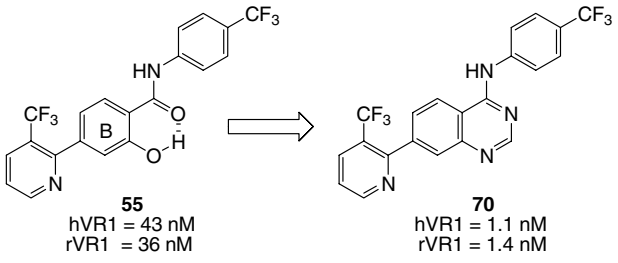
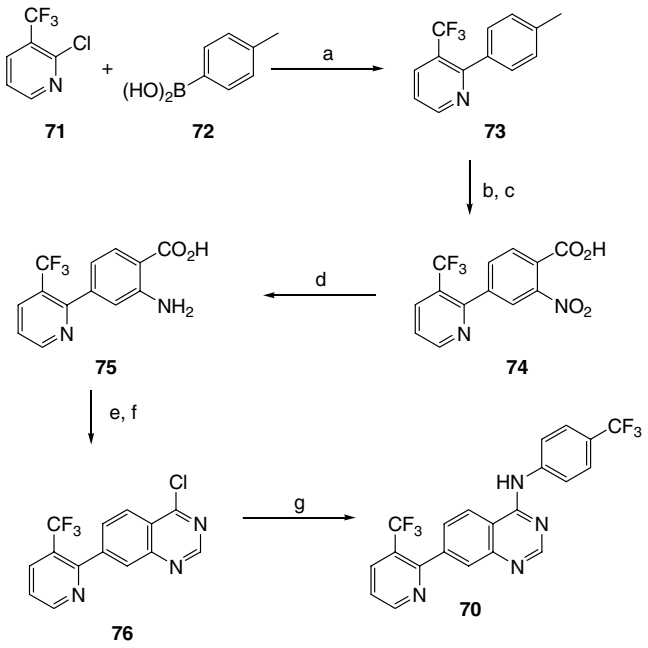



**Figure 2.** Heterocyclization of the biarylamide to the aminoquinazoline.




**Scheme 2.** Reagents and conditions: (a) 2 M $Na_2CO_3$, $Pd(PPh_3)_4$, DME, 80 °C, 83%; (b) $HNO_3$, 0 °C, 100%; (c) $KMnO_4$, pyridine, $H_2O$, 63%; (d) $H_2$, Pd/C, 92%; (e) $HCONH_2$, 63%; (f) $OPCl_3$, 72%; (g) 4-trifluoromethyl aniline, IPA, 94%.

significantly less potent at VR1. Therefore, although it is possible to achieve planarity via intramolecular H-bonding of 3-substituents with either the carboxamide N–H or the carbonyl oxygen, the data in Table 3 suggest that the latter is preferred from a binding energy perspective. The reasons for this are not clear but could be due to severe spatial constraints near the amide N–H.

Incorporation of hetero-atoms into the B-ring was also examined (e.g., **64**, **68**, and **69**) and led to a diminution in VR1 potency.

To investigate the notion that rigidifying the B-ring orientation through hydrogen bonding interaction with the carbonyl group (as in **55**, Fig. 2) is a promising approach to enhance VR1 potency, we synthesized the conformationally constrained biarylamide **70** (Scheme 2, Fig. 2). The resulting quinazoline (**70**, hVR1 = 1.1 nM) was 10-fold more potent in the human VR1 FLIPR assay than either the parent urea **1** (17 nM) or the parent carboxamide **2** (14 nM). As with compounds **1** and **2**, **70** was devoid of agonist activity (HEK 293 cells expressing human VR1) at concentrations up to 4 μM.

The rat pharmacokinetic (PK) profiles of the arylurea **1** and the aminoquinazoline **70** are compared in Table 4. Similar pharmacokinetic profiles were observed for **1** and **70** following intravenous (iv) dosing at 3 mg/kg in 67% PEG/water vehicle. Both compounds exhibited moderately high clearance and relatively long half lives due to a large volume of distribution.

**Table 4.** Pharmacokinetic profiles of **1** and **70**

| Compound | $T_{1/2}$ (h) | CL (mL/min/kg) | $V_d$ (L/kg) | $T_{max}$ (h) | F (%) |
|---|---|---|---|---|---|
| **1** | 7.2 | 39 | 12 | 0.5 | 27 |
| **70** | 8.1 | 23 | 12.5 | 0.7 | 99 |

Although **70** was not demonstrably better in terms of its aqueous solubility (HTSol = BLQ), oral pharmacokinetics experiments revealed that **70** significantly outperformed **1** with respect to oral bioavailability (99 and 27%, respectively). The lower clearance exhibited by **70** is partially responsible for this improvement in oral exposure, however, factors such as increased rigidity and/or fewer rotatable bonds may also contribute.[9]

In conclusion, bioisosteric replacement of the piperazine of the urea lead **1** led to the biarylamide series. The improved VR1 potency of biarylamide analogs with hydrogen bond donors at the 3-position of the B-ring suggested that enforcing planarity of the benzamide unit through interaction with the carbonyl group was a promising approach. To investigate this possibility the conformationally constrained analog (**70**) was prepared. Aminoquinazoline **70** represents a novel VR1 antagonist template with improved in vitro potency and oral bioavailability relative to the corresponding urea or carboxamide series compound. While the aminoquinazoline template retains all the pharmacophore features of the arylureas and biarylamides, the new template also provides additional handles for further optimization. Further exploration of the SAR and biology of the aminoquinazoline series will be reported in due course.

## Acknowledgment

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5. The same bioisosteric replacement was recently disclosed by Park, H.-G. et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 631.
6. High throughput solubility (HTSol) was assessed by diluting DMSO stock solutions of the test article into pH 7.4 buffer and shaking for 4 h at room temperature. Solutions are then filtered and analyzed (HPLC/MS).
7. Energy minimizations were carried out using Maestro 7.0, Schrödinger, <http://www.schrödinger.com>.
8. These assays conveniently provided information regarding species selectivity (rat vs human) as well as the ability of compounds to block different modes of receptor activation (capsaicin or low pH). Data generated in human VR1 low pH or rat VR1 capsaicin assays (data not shown) did not yield an additional understanding of compound pharmacology.
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