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ABSTRACT

A series of 2-aryl pyridine C-region derivatives of 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides were investigated as *h*TRPV1 antagonists. Multiple compounds showed highly potent TRPV1 antagonism toward capsaicin comparable to previous lead **7**. Among them, compound **9** demonstrated anti-allodynia in a mouse neuropathic pain model and blocked capsaicin-induced hypothermia in a dose-dependent manner. Docking analysis of **9** with our *h*TRPV1 homology model provided insight into its specific binding mode.

TRPV1 (transient receptor potential vanilloid 1) has emerged as a promising therapeutic target for neuropathic pain as well as a broad range of other indications.[1] Located predominantly in C-fiber sensory afferent neurons, TRPV1 is a nociceptor which integrates stimuli from exogenous compounds such as capsaicin, endogenous endovanilloids, heat and acidity.[2-7] TRPV1 is further co-regulated by the signaling milieu of the cell, as reflected in the activity of kinases such as protein kinase C, protein kinase A, or the level of phosphatidylinositol-4,5-bisphosphate. Development of antagonists represents the leading therapeutic strategy, while defunctionalization/desensitization subsequent to agonist stimulation also holds promise.[8] Starting with capsaicin as the lead structure, intense research efforts have generated substantial insights into vanilloid structure activity relations and are yielding potent, orally active antagonists.[9-15]

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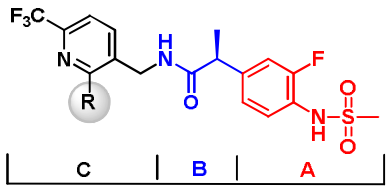

Figure 1. Lead TRPV1 antagonist template

We previously reported a series of 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides as potent *h*TRPV1 antagonists in which the three pharmacophores were designated as A-region (3-fluoro-4-methylsulfonylaminophenyl), B-region (propanamide) and C-region ((6-trifluoromethyl-pyridin-3-yl)methyl), respectively (**Figure 1**).[16] The structure activity relationships of the 2-substituent in the pyridine C-region have been investigated extensively by introducing various groups, including amino,[16] oxy,[17] thio[18] and alkyl[19] groups. In the series, a number of compounds showed highly potent and stereospecific antagonism to multiple TRPV1 activators including capsaicin, pH, heat (45 °C) and *N*-arachidonoyl dopamine (NADA). In