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Discovery of novel pyrrolopyridazine scaffolds as transient receptor potential vanilloid (TRPV1) antagonists

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ABSTRACT

A novel indolizine class of compounds was identified as TRPV1 antagonist from an HTS campaign. However, this indolizine class proved to be unstable and reacted readily with glutathione when exposed to light and oxygen. Reactivity was reduced by the introduction of a nitrogen atom alpha to the indolizine nitrogen. The pyrrolopyridazine core obtained proved to be inert to the action of light and oxygen. The synthesis route followed the one used for the indolizine compounds, and the potency and ADMET profile proved to be similar.

Transient receptor potential vanilloid 1 (TRPV1)[1] is a non-selective ligand-gated cation channel which upon activation by a range of stimuli such as heat,[2] acid,[3] voltage,[4] exogenous capsaicin[5] and inflammatory mediators such as anandamine[6] and lipoxygenase products[7] allows the flow of sodium and calcium ions through the nerve cell. The increased intracellular Ca^{2+} level causes an excitation of the primary sensory neurons and ultimately leads to the central perception of pain. A TRPV1 knockout mice model provided evidence that thermal hyperalgesia depends on TRPV1 activation and sensitization, making this receptor a very attractive target for the treatment of chronic and neuropathic pain.[8–11]

The pharmaceutical industry responded by undertaking significant efforts in finding small molecule TRPV1 antagonist acting as analgesics and several compounds entered clinical trials.[12–15] Further successful development of these compounds was unfortunately hindered by diverse adverse effects.[12–19] Perhaps the most troublesome is the indication that the TRPV1 channel blockade can lead to hyperthermia as well as an impaired noxious heat perception; in other words that this ion channel plays a role in the body temperature regulation and in setting the heat pain threshold.[20,21] It is however important to put these findings into perspective and to realize that the data available as of today is still limited. Meanwhile, the search for a potent small molecule TRPV1 antagonist with the adequate ADMET (absorption, distribution, metabolism, excretion and toxicity) profile continues.[22]

Previous effort in identifying TRPV1 antagonists relied on the traditional Ca^{2+} influx induced by capsaicin assay and led to the identification of several small molecule TRPV1 antagonists with the progression of few of them to clinical trial. Unfortunately, as aforementioned the presence of side effects put a stop to the further development of many of these compounds.

We hypothesized that these adverse effects could be caused by the inherent properties of the molecule and/or by the TRPV1 activation mode profile. In order to identify new hit compounds having a different phenotypic profile we proceeded with a new HTS campaign wherein the Ca^{2+} influx assay was replaced by a Rb^{+} atomic absorption spectroscopy assay.[23] Because one of the aims was to reduce the lipophilicity of the new hit relative to the clinical

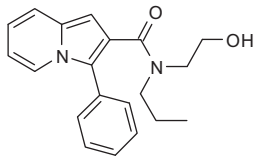

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Figure 1. Novel indolizine TRPV1 antagonist.

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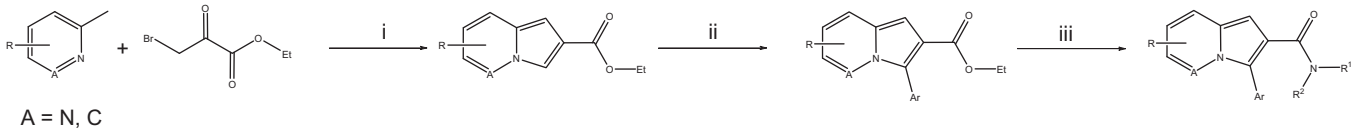
candidates, we placed a special emphasis on the ligand lipophilic efficiency (LLE) parameter with the expectation to obtain a better promiscuity profile.

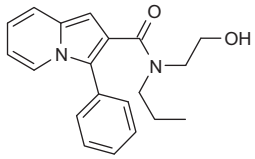
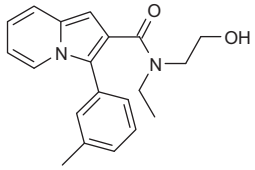
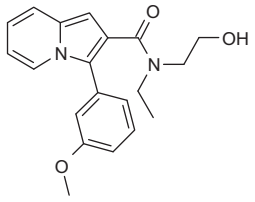
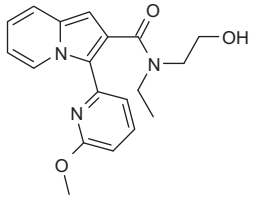
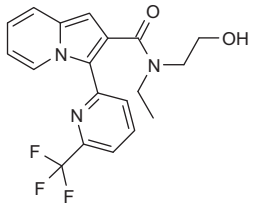
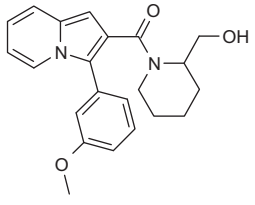
Screening our corporate library led to the identification of indolizine **1** (Fig. 1). This starting point was viewed as attractive because the structure of compound **1** shared few common features with the reported TRPV1 antagonists and has relatively good physical properties (molecular weight 322, *e*Log*D* 3.3). The activity of the hit was subsequently confirmed in a more physiologically relevant assay where an IonWorks™ Quattro (QT) apparatus was used to determine the inhibitory effects of the compound in a human-TRPV1 cell assay as an 8-points concentration–response-curve.[24]

The structure of **1**, an indolizine flanked with a carboxamide and an aryl moiety respectively at the C-6 and C-7 position, provided an opportunity for efficient synthesis of analogues. We have



Scheme 1. Reagents and conditions: (i) $NaHCO_3$, ethanol, 120 °C; (ii) ArX, bis(triphenylphosphine)palladium(II)chloride, KOAc, dioxane, 90–110 °C; (iii) aminoalcohol, bis(trimethylaluminum)-1,4diazabicyclo[2.2.2]octane adduct, THF, 40 °C.

Table 1
Early SAR of the indolizine series

Compound	Structure	MW	*e*Log*D* [a]	TRPV1 [b] pIC_{50}	LLE [c]	Solubility [d] (μM)	hERG [e] pIC_{50}	Caco-2 [f] Papp (10^{-6} cm/s)	RLM/HLM [g] Clint (μL/min/mg)	Rat/human GSH trapping [h] (%)
1		322.4	3.3	5.7	2.4	280	ND	60	>500/220	30/NV
2		322.4	3.2	6.8	3.6	260	ND	ND	170/89	ND/ND
3		338.4	2.8	6.0	3.2	150	<4.48	54	65/54	15/31
4		375.4	2.5	5.9	3.4	190	<4.48	56	31/31	25/22
5		377.3	3.6	6.3	2.7	360	ND	ND	48/62	ND/ND
6		364.4	3.3	6.3	3.0	260	<4.48	58	93/160	9/15

(*continued on next page*)