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3-Pyrroline Containing Arylacetamides: A Novel Series of Remarkably Selective κ-Agonists

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Abstract—A series of 2-(substituted phenyl)-*N*-methyl-*N*-[(*1S*)-1-(substituted alkyl)-2-(1-(3-pyrrolinyl))ethyl]acetamides were synthesized and evaluated as highly selective kappa-agonists with K_i values in low nanomolar range. 3-Pyrroline incorporated into the basic amino functionality in combination with 2-(methylthio)ethyl substituent on the carbon adjacent to the amide nitrogen remarkably enhanced the κ-selectivity. 3,4-Dichlorophenyl derivative **1e** was found the most potent and selective analgesic in this series with ED_{50} value of 0.023 mg/kg.

Introduction

It is well established that opioid analgesics mediate their effects through three opioid receptor subtypes, namely, μ, κ and δ.[1] More specifically, highly selective κ-opioid agonists may provide a strong analgesic free from the abuse potential and the adverse side effects of μ-agonists like morphine.[2,3] In addition to their analgesic effects in in vivo models, κ-agonists have been shown to be potent neuroprotective and antihyperalgesic agents.[4] Furthermore, it was reported that κ-agonists can downregulate the expression of the human immunodeficiency virus (HIV-1) in human microglial cells and $CD4^+$lymphocytes.[5,6] However, central-mediated side effects such as sedation, dysphoria, and strong diuresis usually accompany κ-agonist applications.[4]

Peripherally restricted κ-agonists[7–9] were believed to reduce or eliminate the side effects associated with the CNS, yet no selective κ-agonist compound has reached the market. Our strategy is to produce a new class of highly selective κ-agonists, which could be eventually modified to selectively act in the periphery as a potential treatment for visceral pain or HIV-1 infection. To achieve this goal, we chose the most flexible κ-agonist, ICI-199441 as a template and introduced 3-pyrroline instead of conventional pyrrolidine substituent into the κ-pharmacophoric ethylenediamine framework. Amongst the classical κ-agonist series (Chart 1),[10–14] the basic amino functionality incorporated into a pyrrolidine is an important determinant for receptor affinity. But the inclusion of a double bond in the pyrrolidine ring has not been explored well in the context of κ-selectivity, only one case has been reported to display equal potency relative to its pyrrolidinyl counterpart.[12] So we were intrigued to investigate the effect of further variations on the antinociceptive activity and κ-selectivity with respect to the arylacetamide having 3-pyrroline moiety. Our initial effort was focused on modifications of the substituted phenyl acetic acid to give a new series of compounds with general structure **1**.

Chemistry

All compounds were prepared via the route depicted in Scheme 1. Coupling of CBZ-protected (*S*)-(+)-amino acid, that is (*S*)-(+)-valine **2a** or (*S*)-(+)-methionine **2b** with 3-pyrroline gave **3a**–**b**. The product **3a**–**b** was reduced with $LiAlH_4$ to afford the diamine **4a**–**b**. Condensation of the diamine with various arylacetyl chlorides furnished a series of compounds of general structure **1** (see Table 1).[15] 3-Pyrroline was prepared following the literature procedure[16] which always contained a little bit of pyrrolidine.[17] However, by recrystallization we obtained analytically pure products for biological assay.

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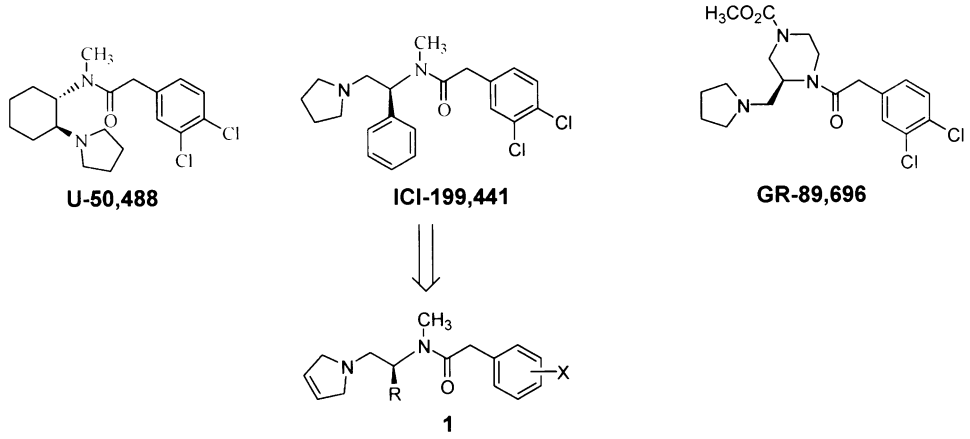
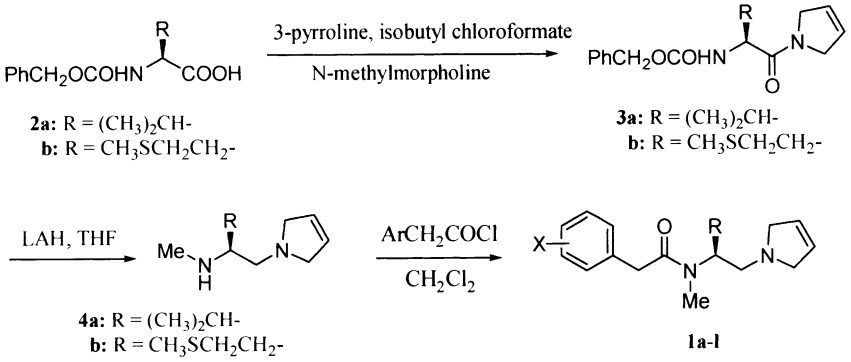
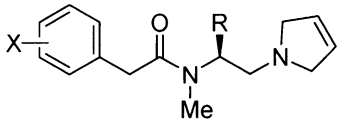


Chart 1. Selected known κ-agonists and designed new series.



Scheme 1.

Table 1. Mouse antinociceptive activity and opioid receptor binding data of 3-pyrroline containing arylacetamides **1a**–**1l**



Compd	R	X	κ-binding affinity[a]	μ-binding affinity[b]	ED_{50} (mg/kg) ip[c]
1a	$(CH_3)_2CH$–	4-F	37.0% (1)[d]	46.5% (10)[d]	1.16
1b	$(CH_3)_2CH$–	4-Cl	60.0% (1)	42.0% (10)	0.25
1c	$(CH_3)_2CH$–	4-Br	90.0% (1)	0 (10)	0.18
1d	$(CH_3)_2CH$–	4-OMe	70.0% (1)	13.5% (10)	2.57
1e	$(CH_3)_2CH$–	3,4-Dichloro	$K_i = 5.72 \pm 1.32$ nM	0 (10)	0.023
1f	$(CH_3)_2CH$–	4-NO_2	80.0% (1)	10.5% (10)	0.17
1g	$CH_3SCH_2CH_2$–	4-F	70.0% (1)	0 (10)	≥ 10
1h	$CH_3SCH_2CH_2$–	4-Cl	64.0% (1)	0 (10)	2.13
1i	$CH_3SCH_2CH_2$–	4-Br	80.0% (1)	0 (10)	2.36
1j	$CH_3SCH_2CH_2$–	4-OMe	80.0% (1)	0 (10)	>10
1k	$CH_3SCH_2CH_2$–	3,4-Dichloro	90.0% (1)	11.5% (10)	0.18
1l	$CH_3SCH_2CH_2$–	4-NO_2	$K_i = 3.06 \pm 1.14$ nM	0 (10)	2.0

[a]Inhibition of [^{3}H]diprenorphine binding in cloned rat κ-opioid receptor expressed in Sf9 insect cells, was presented as inhibition constants K_i or percent inhibition of the radioligand binding.
[b]Inhibition of [^{3}H]diprenorphine binding in cloned human μ-opioid receptor expressed in Sf9 insect cells, was presented as Inhibition Constants K_i or percent inhibition of the radioligand binding.
[c]The compounds were administered intraperitoneally.
[d]The respective test concentration is indicated in parentheses as 10^{-6} M for receptor binding assay.

Biological Results and Discussion

The structure/κ-receptor affinity relationship studies aided with molecular modeling[18] have defined the following pharmacophoric elements: the basic amino functionality, the substituted benzene ring and the amide carbonyl group in the arylacetamides. In the current study with the incorporation of unsaturated pyrroline into the basic amino functionality, the effect of the substituent R at the carbon α to the amide and the substituent X on the phenyl ring was explored to ensure an optimal combination for the most appropriate structural motif.

In vitro.[19a,b] Kappa (κ) opioid receptor affinity was determined by the displacement of bound [^{3}H]diprenorphine in cloned rat κ-opioid receptor expressed in Sf9 insect cells and mu (μ) opioid receptor affinity was obtained by the displacement of bound [^{3}H]diprenorphine using membranes prepared from cells expressing the cloned human μ-opioid receptor (Table 1). The K_i values were calculated by Cheng–Prusoff equation as means ± standard errors from three independent experiments. The affinity for the κ-receptor ranged from nanomolar to micromolar concentrations. However, the affinity of some compounds was found to be too low to perform a full dose–effect curve. In these cases, the percentage of inhibition of the radioligand binding was given. Thus, qualitative SAR will be discussed in the following section.

As shown in Table 1, the 3-pyrroline containing arylacetamides displayed significant κ/μ selectivity. Especially, 2-(methylthio)ethyl substituent at the carbon α to the amide is more favorable than isopropyl for the κ-selectivity. Most of the *N*-{(1S)-1-[2-(methylthio)-ethyl]-2- [1-(3-pyrrolinyl)]ethyl}acetamides (e.g., **1g**, **1h**, **1i**, **1j**, **1l**) showed little binding to the μ-opioid receptor even at the concentration of 1×10^{-5} M while the compound **1l** displayed the highest binding affinity to the κ-receptor with K_i value of 3.06 nM.

Comparing the substituents at the 4-position on the phenyl ring, electron-donating group such as methoxy (**1d** and **1j**) was disadvantageous to the affinity for the κ-receptor, whereas electron-withdrawing group such as nitro (**1f** and **1l**) greatly improved the κ-binding. With respect to the halogenated compounds, the increase in both atom size and lipophilicity may cause parallel increase in the κ binding affinity. The excellent κ-receptor binding was derived from the 4-bromo derivatives (**1c**, **1i**). Furthermore, the 3,4-dichloro substitution (**1e**, **1k**) provided potent affinity to κ-receptor with K_i values in nanomolar range.

In vitro.[20] The analgesic activities were evaluated intraperitoneally using the classical mouse hot plate assay and ED_{50} values were determined in mg/kg with 95% confidence intervals (see Table 1).

This series of 3-pyrroline containing arylacetamides were highly effective in the in vivo analgesic test except for **1g** and **1j** whose substituents on the phenyl ring are less lipophilic or more electron-donating. And both compounds fall in the category of *N*-{(1*S*)-1-[2-(methylthio)ethyl]-2-[1-(3-pyrrolinyl)]ethyl}acetamides. Some structural and metabolite factors might be involved in the in vivo potency. Presumably, the analgesic activity of 2-(methylthio)ethyl derivatives was compromised by their lower lipophilicity or greater liability to oxidation relative to the isopropyl ones. Therefore, the nitro group and the 2-(methylthio)ethyl substitution of **1l** which showed the best κ-activity ($K_i = 3.06$ nM) caused a marked drop in the potency ($ED_{50} = 2.0$ mg/kg); however, the dichloro substitution of the isopropyl derivatives still maintained considerable analgesic activity (**1e**, $ED_{50} = 0.023$ mg/kg; **1k**, $ED_{50} = 0.18$ mg/kg) which produced the best compounds in this series.

Conclusions

The present work demonstrated that the introduction of 3-pyrroline in the basic amino functionality of arylacetamides dramatically improved the κ/μ selectivity, and the 2-(methylthio)ethyl substituent on the carbon adjacent to the amide nitrogen was greatly beneficial for the κ-receptor binding. The SAR study on this new series of 3-pyrroline containing arylacetamides revealed some potent and highly selective κ-agonists, such as **1c**, **1e**, **1k**, **1l**, which could provide promising candidates for the development of the safer analgesics.

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15. The best compound **1e**·HCl salt: yield 65.8%; white plate solid, mp 197–199 °C; $[\alpha]_D^{20} = -26.0°$ (*c* 0.2, CH_3OH); ^1H NMR (DMSO-d_6) δ 0.75 (d, $J = 7$ Hz, 3H), 0.96 (d, $J = 7$ Hz, 3H), 1.64–1.82 (m, 1H), 2.95 (s, 3H, CH_3NCO), 3.40–3.59 (complex, 2H), 3.82 (AB, q, $J = 16.2$ Hz, 2H, CH_2Ar), 3.90–4.38 (complex, 4H), 4.48 (m, 1H, CHN), 5.90 (br, 2H, CH=CH), 7.23–7.58 (m, 3H, ArH), 10.75 (brs, 1H, NH+). MS (EI) *m*/*z*: 356 [(M−HCl)+1]+. Anal. calcd for $C_{18}H_{25}C_{l3}N_2O$: C 55.18%, H 6.43%, N 7.15%. Found: C 55.05%, H 6.42%, N 7.03%.
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