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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 5114–5119

Potent and highly selective kappa opioid receptor agonists incorporating chroman- and 2,3-dihydrobenzofuran-based constraints

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Received 28 July 2005; revised 24 August 2005; accepted 24 August 2005
Available online 3 October 2005

Abstract—Two novel chemical classes of kappa opioid receptor agonists, chroman-2-carboxamide derivatives and 2,3-dihydrobenzofuran-2-carboxamide derivatives, were synthesized. These agents exhibited high and selective affinity for the kappa opioid receptor.

Opioid analgesics mediate their effects through three opioid receptor types, μ, κ, and δ.[1] Most of the opioid analgesics at present, for example, morphine, act by binding to the μ-opioid receptor, and their analgesic potency is associated with a spectrum of undesirable side effects, such as physical dependence, respiratory depression, and constipation. In recent years, considerable attention has been focused on the development of receptor selective κ-agonists as potent and efficacious analgesics devoid of the undesirable side effects of the μ analgesics.[2] The most important selective κ-agonists developed so far are the arylacetamide derivatives. Since the discovery of the one of the first selective arylacetamide κ-agonists, U-50,488 in the early 1970s, which displayed analgesic effects in vivo and did not produce respiratory depression, constipation, or tolerance,[3] a number of related, but chemically diverse, arylacetamide κ-agonists have been reported. Among these is ICI 199441, which is 146-fold more potent than U-50,488 in vitro.[4] However, these centrally acting κ-agonists produced their own set of CNS side effects such as dysphoria and diuresis, which prevented their further development as analgesic therapeutics.[2,5,6] To avoid the side effects associated with the CNS, peripherally acting κ-agonists are at present the focus of interest.[2,5,6]

Previously, we reported the design and synthesis of a novel series of azepinones as constrained analogs of ICI 199441, exemplified by compound **1**, which showed high and selective κ binding affinity.[6] During a screening of a combinatorial library, aryloxyacetamides (e.g., **2** and **3**) were identified as highly potent κ-agonists.[7] Here, we describe the synthesis and biological evaluation of two novel series of constrained aryloxyacetamides with the general structure **I**: chroman-2-carboxamides ($n = 1$) and 2,3-dihydrobenzofuran-2-carboxamides ($n = 0$) with various substitution groups on the phenyl ring, especially polar substituents including acetylamino, sulfonylamino, and carbamoyl groups. The inclusion of such polar substituents was by design to yield compounds, which may limit CNS penetration and display peripheral selectivity in vivo. This is expected to be beneficial to decrease or avoid the CNS side effects of the centrally active kappa opioid receptor ligands while retaining antihyperalgesic activity.[2] The in vitro receptor binding assay showed that many of these new compounds possess high and selective κ binding affinity. Two representative compounds from these two novel series of constrained aryloxyacetamides were evaluated in the in vivo nociceptive assays and demonstrated potent analgesic effects.

Keywords: Kappa opioid receptor agonists; Analgesic.
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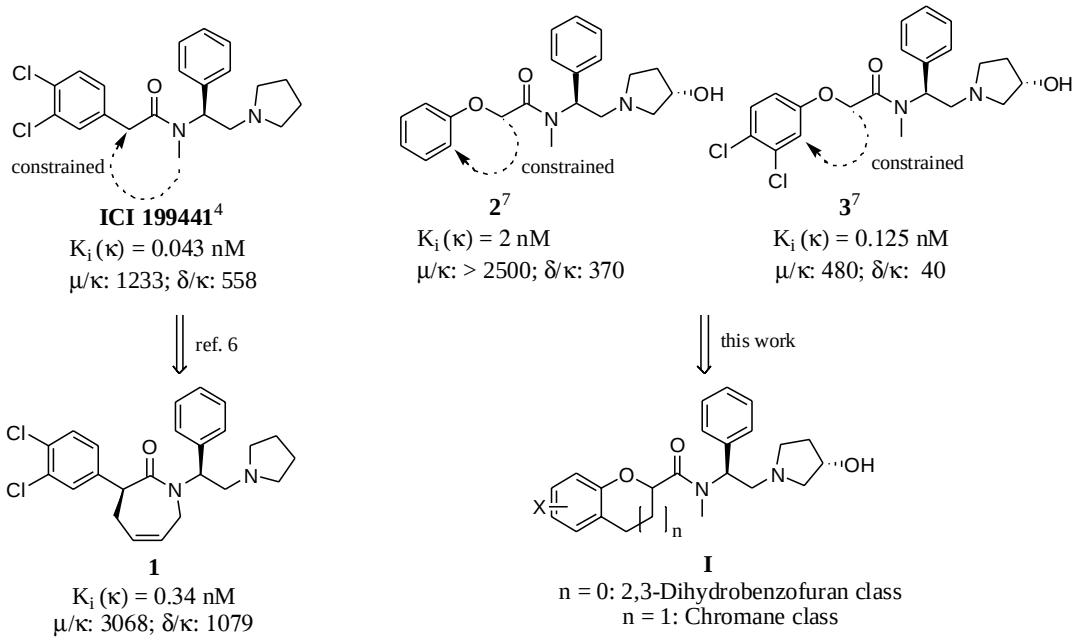
doi:10.1016/j.bmcl.2005.08.094

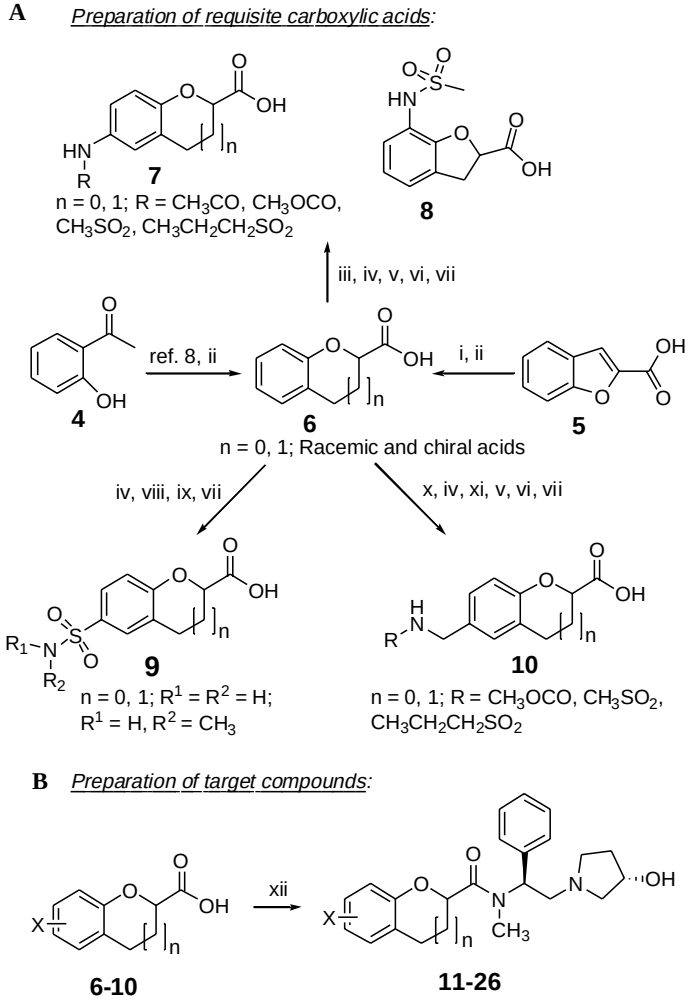


The synthesis of the chroman-2-carboxamide and 2,3-dihydrobenzofuran-2-carboxamide constrained analogs **11**–**26** is summarized in Scheme 1. The synthesis began with the preparation of various substituted racemic and enantiomerically pure (*R*)- and (*S*)-chroman-2-carboxylic acids and 2,3-dihydro-benzofuran-2-carboxylic acids, compounds **6**–**10**. Racemic chroman-2-carboxylic acid (**6**: $n = 0$) was prepared based on a literature procedure using 2′-hydroxyacetophenone (**4**) as starting material.[8] Racemic 2,3-dihydro-benzofuran-2-carboxylic acid (**6**: $n = 1$) was easily prepared by hydrogenation of the commercially available benzofuran-2-carboxylic acid **5** at 60–70 psi. The corresponding enantiomerically pure acids were obtained via chiral separation of the racemic acids.[9] The absolute stereochemistry was assigned based on the comparison of the optical rotation data with those reported in the literature.[10,11]

Derivatization of the chroman-2-carboxylic acid and 2,3-dihydrobenzofuran-2-carboxylic acid was carried out on either racemic or chiral material. Treatment of chroman-2-carboxylic acid with nitric acid gave the 6-nitro-chroman-2-carboxylic acid as a single isomer, which was converted to the ester under standard conditions. Reduction of the nitro group by hydrogenation followed by reaction of the resulting aniline with acetyl chloride, methyl chloroformate, methanesulfonyl chloride, and propanesulfonyl chloride afforded amide, carbamate, and sulfonamides, respectively, which were hydrolyzed with lithium hydroxide to yield the acids **7** ($n = 1$). In contrast to chroman-2-carboxylic acid, nitration of 2,3-dihydro-benzofuran-2-carboxylic acid under the same reaction conditions yielded two regioisomers: 5-nitro-2,3-dihydrobenzofuran-2-carboxylic acid as the major isomer and 7-nitro-2,3-dihydrobenzofuran-2-carboxylic acid as the minor isomer (4:1 ratio). Without further purification, the crude mixture of acids was esterified and the two esters readily separated by silica gel chromatography. The structural assignment of these two isomers was based on the coupling pattern of the aromatic protons in ^{1}H NMR spectra.[12] Both regioisomers were subjected to the same derivatization and hydrolysis sequence as described above for the synthesis of substituted chroman-2-carboxylic acids **7** ($n = 1$), to furnish the corresponding substituted 2,3-dihydrobenzofuran-2-carboxylic acids **7** ($n = 0$) and **8**.

The acids **9** with reversed sulfonylamino substituents at the 6- ($n = 1$) or 5-position ($n = 0$) were synthesized via a four-step reaction sequence from chroman-2-carboxylic acid and 2,3-dihydro-benzofuran-2-carboxylic acid: methyl ester formation, chlorosulfonylation with sulfur trioxide–DMF complex/oxalyl chloride, or chlorosulfonic acid, reaction of the resulting sulfonyl chloride with ammonia or methylamine, and then saponification. The synthesis of the acids **10**, or methylene analogs of the acids **7**, required six reaction steps. Iodination of chroman-2-carboxylic acid and 2,3-dihydro-benzofuran-2-carboxylic acid with benzyltrimethylammonium dichloroiodate gave the iodides in which iodine regiospecifically substituted at the *para* position to the ring oxygen.[8] Esterification of the iodoacids, followed by treatment with copper(I) cyanide, yielded the benzonitrile derivatives. These intermediates were in turn subjected to hydrogenation (nitrile to benzylamine) and capping with methyl chloroformate, methanesulfonyl chloride, and propanesulfonyl chloride to afford carbamates and sulfonamides, respectively, which were hydrolyzed with lithium hydroxide to yield the acids **10**.

With the requisite acid set **6**–**10** on hand, the synthesis of the target compounds **11**–**26** was conducted by coupling the acids with 1-(2-methylamino-(*S*)-2-phenyl-ethyl)-pyrrolidin-(*S*)-3-ol[13] using either Mukaiyama reagent[14] or *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU) as coupling reagent. In both series, the target compounds with the (*R*)-configuration at the 2-position had consistently HPLC retention times shorter than those of the target compounds with the (*S*)-configuration.



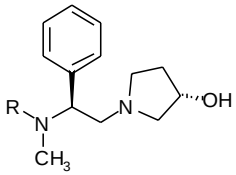
Scheme 1. Synthesis of chroman-2-carboxylic acids and 2,3-dihydrobenzofurn-2-carboxylic acids and coupling to yield κ opioid receptor agonists. Reagents: (i) H_2, 60–70 psi, 10% Pd/C, EtOAc; (ii) chiral separation; (iii) HNO_3; (iv) MeOH, HCl; (v) H_2, 10% Pd/C; (vi) CH_3COCl or EtOCOCl or RSO_2Cl, Et_3N; (vii) LiOH, MeOH-THF-H_2O; (viii) $HCON(CH_3)_2$ SO_3, $(COCl)_2$ or $ClSO_3H$; (ix) R_1R_2NH; (x) $ZnCl_2$, $PhCH_2N(CH_3)_3ICl_2$, HOAc; (xi) CuCN; (xii) (*S*)-1-((*S*)-2-(methylamino)-2-phenylethyl)pyrrolidin-3-ol, TBTU or Mukaiyama reagent, DCM.

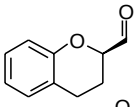
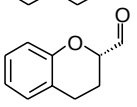
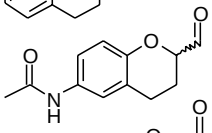
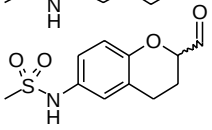
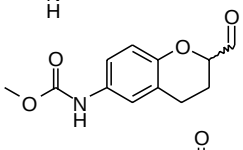
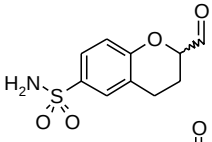
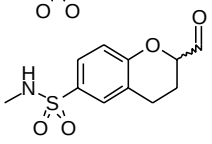
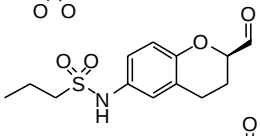
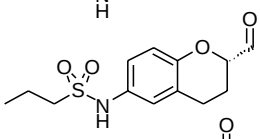
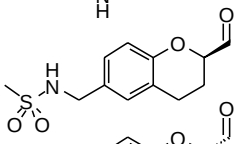
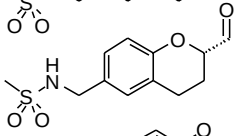
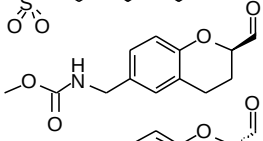
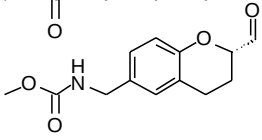
The in vitro opioid receptor binding results of chromanes **11**–**19** and 2,3-dihydrobenzofurans **20**–**26** are summarized in Tables 1 and 2.[15] In the chromane series (Table 1), compound **11-R**, the unsubstituted constrained analog of phenoxyacetamide **2**, exhibited comparable high κ binding affinity (K_i = 1.6 nM) but with much greater overall selectivity versus the μ and δ receptors (>3000-fold). In contrast, diastereomer **11-S** was ca. 20-fold less active at κ relative to **11-R**, indicating that the configuration at the 2-position (chromane ring) is important for optimal κ binding. This stereochemical preference held true for all compounds in the series, for example, **17-R** > **17-S**, **18-R** > **18-S**, and **19-R** > **19-S**. The substituents at the 6-position of the phenyl ring affected κ binding. Among the different substitution groups, the sulfonylamino groups (compounds **13**, **17-R**, and **18-R**) are most preferred for κ affinity. Compound **19-R** with a carbamoylmethylene substituent also displayed good κ binding affinity and selectivity. In the case of the reversed sulfonamide analogs, compound **15** displayed comparable affinity to **13**, but increasing the bulk on the sulfonamide nitrogen atom as in **16** led to decreased κ receptor affinity versus **17-R**.

In the 2,3-dihydrobenzofuran series (Table 2), compounds **20-R** and **20-S**, the unsubstituted constrained analogs of phenoxyacetamide **2**, also possessed high and selective κ affinity. This activity is similar to that of compound **11-R** in the chromane series. However, in contrast to the chromane series, the configuration at the 2-position did not significantly influence κ affinity, and in most cases, the κ binding affinity of the two diastereomeric pairs was within a factor of 2.[16] Analogous to the chromane series, sulfonylamino groups are the most preferred substituents for κ affinity, as all the compounds having the sulfonylamino moiety in the molecules including compounds **23-R**, **-S**, **24-R**, **-S**, and **26-R**, **-S** had low nanomolar κ binding affinity. The carbamoyl group (**22-R**, **-S**) was also well tolerated by the κ receptor. The regioisomers with methanesulfonylamino substituent at the 5- and 7-position, **23-R** versus **24-R** and **23-S** versus **24-S**, had comparable κ binding affinity. Similar to that observed in the chromane series, the reversed sulfonamide **25** was 20-fold less potent than sulfonamide **23-S**.

In both the chromane series and 2,3-dihydrobenzofuran series, polar substituents were generally well tolerated by

Table 1. SAR of the chromane series

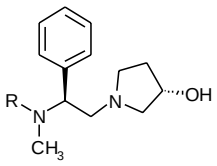


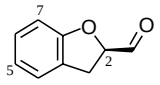
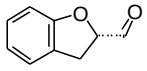
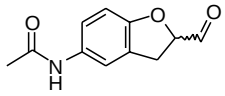
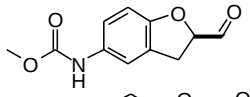
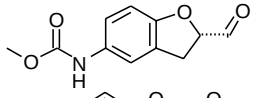
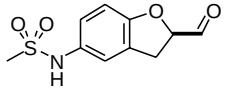
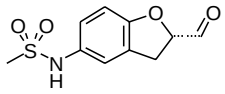
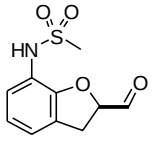
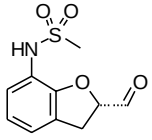
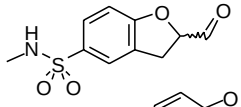
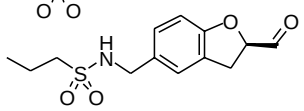
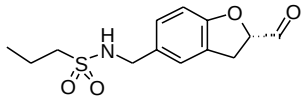
Compounds	R	κ K_i (nM)	μ/κ	δ/κ	CYP2D6 IC_{50} (nM)
11-R		1.6	>3125[a]	>3125[b]	150
11-S		30.5	>164[a]	45	1600
12[c]		17	>294[a]	>294[b]	2900
13[c]		1.7	>2940[a]	224	6200
14[c]		31	>161[a]	>161[b]	7400
15[c]		3.3	364	44	1800
16[c]		18.8	>266[a]	20	320
17-R		1.6	300	75	6700
17-S		14.2	>352[a]	71	9500
18-R		4.5	>1111[a]	132	3900
18-S		99	>51[a]	5	>10 μM
19-R		2.6	>1923[a]	615	4200
19-S		130	>39[a]	9	14,000

[a] μ K_i is estimated to be >5 μM.
[b] δ K_i is estimated to be >5 μM.
[c] Mixture of diastereomers (1:1).

the κ receptor. Such substituents also confer low CYP2D6 inhibitory activity with IC_{50} values in the micromolar range (Tables 1 and 2). In contrast, the kappa agonists of the arylacetamide class have been shown to bind tightly to CYP2D6, for example, ICI 199441 has an IC_{50} = 26 nM against this cytochrome P450 en-

Table 2. SAR of the 2,3-dihydrobenzofuran series



Compounds	R	κ K_i (nM)	μ/κ	δ/κ	CYP2D6 IC_{50} (nM)
20-R		0.8	>6250[a]	861	250
20-S		2.4	>2083[a]	250	760
21[c]		52.4	>95[a]	>95[b]	770
22-R		14.7	238	>340[b]	4200
22-S		5.8	155	145	4800
23-R		1.3	744	25	5400
23-S		1.2	375	525	4500
24-R		3.9	167	14	1100
24-S		1.3	639	26	1200
25[c]		24.5	>204[a]	27	11
26-R		3.6	>1389[a]	93	5700
26-S		3.3	515	29	5000

[a] μ K_i is estimated to be >5 μM.
[b] δ K_i is estimated to be >5 μM.
[c] Mixture of diastereomers (1:1).

zyme.[17] Cytochrome P450 enzymes serve an important detoxification role in the body.[18] Inhibition of the enzymes, in particular CYP2D6, may interfere with the body's ability to metabolize xenobiotics. From a drug development perspective, it is desirable to identify agents that are not potent CYP2D6 inhibitors.

Two representative compounds from these two novel series of constrained aryloxyacetamides, chroman-2-carboxamide **19-R** and 2,3-dihydrobenzofuran-2-carboxamide **23-S**, the two diastereomerically pure compounds both showing high and selective κ binding affinity (K_i = 2.6 and 1.2 nM) and low CYP2D6 inhibitory activity (IC_{50} = 4.2 and 4.5 μM) were evaluated for activity in vivo nociceptive assays. Compounds **19-R** and **23-S** displayed potent analgesic effects, producing 95% and 88% antinociception at 300 μg given intrapaw (sc injection in dorsal surface of paw), respectively, in the late phase formalin-induced flinching assay.[19] Compounds **19-R** and **23-S** also inhibited acetic acid-induced writhing[19] when administered sc and p.o. with sc ED_{50} values of 0.53 and 0.75 mg/kg, respectively, and p.o. ED_{50} values of 1 and 3.9 mg/kg, respectively. The peripheral selectivity of these compounds will be investigated at a latter time.

In summary, two novel chemical classes of kappa opioid receptor agonists, chroman- and 2,3-dihydrobenzofuran-based constrained analogs of the aryloxyacetamides, were synthesized and found to be potent κ receptor ligands. Among these, eight compounds had single digit nanomolar κ binding affinity and >100-fold selectivity over μ and δ. Chroman-2-carboxamide **19-R** and 2,3-dihydrobenzofuran-2-carboxamide **23-S** both demonstrated analgesic effects in the in vivo formalin-induced nociception and acetic acid-induced writhing assays.

References and notes

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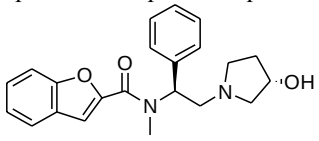
16. Benzofuran-2-carboxamide 27 displays moderate κ binding affinity indicating that saturation at the 2-position in this series is important for opioid receptor binding affinity.



27: K_i (κ) = 490 nM;
K_i (μ) > 5 μM; K_i (δ) > 5 μM

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