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Synthesis and evaluation of opioid receptor-binding affinity of elaeocarpenine and its analogs

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ABSTRACT

Both enantiomers of elaeocarpenine (**1**) and its analogs, **21**, **22**, **25**, and **27**, were synthesized from bicyclic aldehydes **8**–**10** via a flexible route previously established for total synthesis of grandisines, and their binding affinities for μ-, κ- and δ-opioid receptor subtypes were evaluated. We found that (9*R*)-**1** exhibited higher affinity than (9*S*)-**1** for all the subtypes, but the enantiomers showed little subtype selectivity. Analogs **21** having a pyrrolizidine skeleton and **27** having a stemona-type skeleton in place of the indolizidine unit of (9*S*)-**1** showed μ-selective and μ-, κ-selective binding, respectively.

Agonists of all three opioid receptor subtypes have antinociceptive activity together with unwanted side effects, including respiratory depression, modulation of gastrointestinal motility, and physical dependence.[1] Because endogenous opioid peptides are neither stable nor selective for specific opioid receptor subtypes, highly selective nonpeptide opioid ligands have been developed as research tools and candidate therapeutic agents.[2] Extensive studies over the past decade have shown that δ-opioid receptor agonists produce antinociception in animal models of pain without adverse effects.[3] Therefore, δ-opioid receptor is an attractive target for development of new analgesics.[4]

Elaeocarpenine (**1**), possessing an indolizidine skeleton linked to a methyl phenol unit, was isolated as a racemate from the Papua New Guinean plant, *Elaeocarpus fuscoides*, by Carroll and co-workers, and displays affinity for δ-opioid receptor (Fig. 1).[5,6] Other structurally and pharmacologically related natural products include the indolizidine alkaloids isoelaeocarpicine (**2**), isoelaeocarpine (**3**), elaeocarpine (**4**),[7] and grandisines **5**–**7**.[8] Because of the structural diversity and pharmacological activity, these compounds may become attractive as lead compounds for the development of new analgesics.

Although elaeocarpenine (**1**) has a simple structure and potent δ-opioid receptor affinity among these indolizidine alkaloids, no total synthesis has been reported, and its affinity for other opioid receptor subtypes (μ and κ) has not been evaluated. Hence, we were interested in synthesizing elaeocarpenine (**1**) via a flexible route that would also be applicable to various elaeocarpenine analogs as candidates for selective δ-opioid receptor agonists.

We recently reported the total synthesis of grandisines B (**6**), D (**5**), and F (**7**) from the common key intermediate **9**.[9] Now, we describe the first enantioselective total synthesis of elaeocarpenine (**1**) and its analogs from **8**–**10** via concise and flexible routes similar to those used for the synthesis of grandisines. The affinities of these compounds for the three opioid receptor subtypes were evaluated.

Compounds (9*S*)-**1**, (9*R*)-**1**, **21**, **22**, **25**, and **27** were prepared from aldehydes **8**–**10** and *ent*-**9**, which were synthesized from L- or D-malic acid using a previously reported method (Scheme 1).[9a] Hydroxyacetals **11**–**13** were obtained by reaction of **8**-**10**[10] with ethane-1,2-diol with azeotropic removal of water, followed by deacetylation in the presence of a catalytic amount of NaOEt in EtOH or

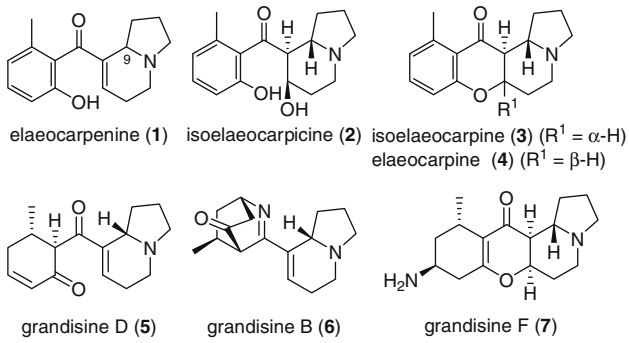

Figure 1. Structures of elaeocarpus alkaloids.

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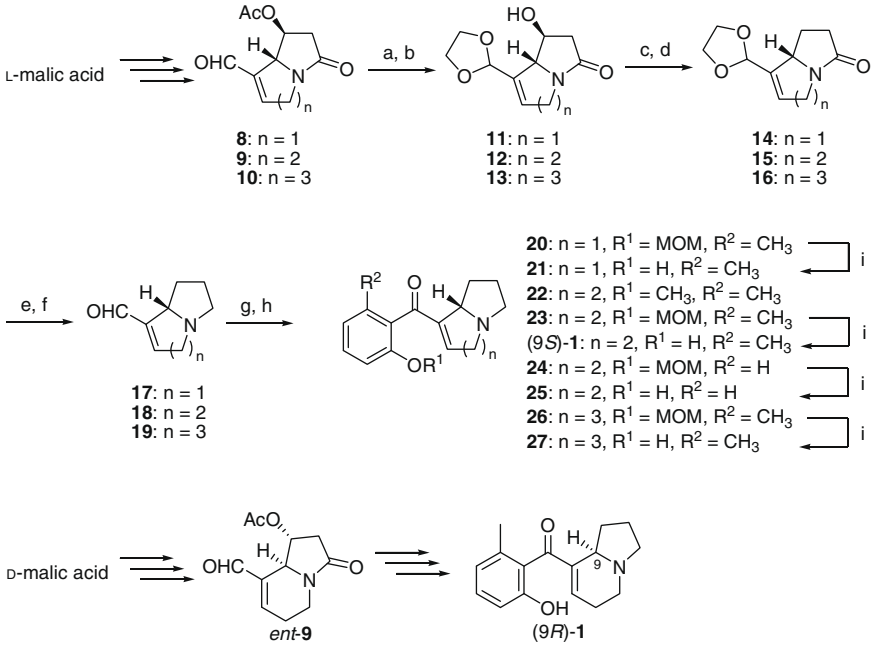


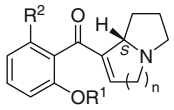
Scheme 1. Reagents and conditions: (a) $HOCH_2CH_2OH$, TsOH (cat), C_6H_6, reflux, 2–13 h, 75–79%; (b) NaOEt, EtOH, rt, 2 h or K_2CO_3 aq, MeOH, rt, 1 h, 70–93%; (c) ClCSOPh, DMAP, $ClCH_2CH_2Cl$, 60 °C, 3–24 h; (d) $n$$Bu_3SnH$, AIBN (cat), C_6H_6, reflux, 30 min, 67–94% (two steps); (e) $LiAlH_4$, THF, reflux, 1 h, 80–93%; (f) TsOH, acetone–H_2O, reflux, 30 min or $HClO_4$ aq, acetone–CH_2Cl_2, rt, 3 h; (g) Ar-I[12,13], nBuLi, THF, −78 °C to rt, 1 h; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h, 15–52% (two steps); (i) TFA, CH_2Cl_2, rt, 1 h, 49–77%.

excess K_2CO_3 in H_2O–MeOH. Removal of the hydroxyl group of **11**–**13** was conducted by using the Barton–McCombie deoxygenation protocol.[11] Thus, alcohols **11**–**13** were converted to the corresponding thionocarbonated, which were treated with $n$$Bu_3SnH$ and AIBN, leading to acetals **14**–**16** in 67–94% overall yields. The amides **14**–**16** were reduced with $LiAlH_4$ to give the amines, in which the acetals were deprotected by acid hydrolysis using TsOH, affording aldehydes **18** and **19**. However, in the case of **17**, the yield of deacetalization under similar conditions was low due to the instability of **17**. Thus, **17** was obtained by treatment with $HClO_4$ at room temperature and was used immediately for the next step without chromatographic purification. Aldehydes **17**–**19** were exposed to lithium reagents generated from aryl iodides[12,13] by lithium–halogen exchange followed by treatment with Dess–Martin periodinane to give ketones **20**, **22**, **23**, **24**, and **26**. Finally, syntheses of **1**, **21**, **25**, and **27** were accomplished by removal of the MOM group with TFA. The ^1H and ^{13}C NMR data of our synthetic (9*S*)-**1** and (9*R*)-**1**[14] were in complete agreement with those previously reported.[5]

Opioid receptor-binding affinities of the new compounds for the human μ- and δ-opioid receptors and the rat κ- opioid receptor were determined by radioligand competition analysis using [^{3}H]DAMGO (μ), [^{3}H]DADLE (δ), and [^{3}H]U69593 (κ).[15] The results are shown in Table 1. In general, the new compounds had weak binding affinities in the micromolar range and showed weaker affinity for δ-opioid receptor than for μ- and κ- receptors. Masking of the phenolic-OH group and removal of the methyl group of (9*S*)-**1** (**22** and **25**) led to unchanged or decreased affinity for all three opioid receptors compared with (9*S*)-**1**. Our data suggest that the absence of a hydrogen-bond donor group on the aromatic group (**22**) increases κ-selectivity by decreasing in vitro μ- and δ-receptor affinity. Interestingly, (9*R*)-**1** is about 2–7-fold more active than (9*S*)-**1**, but shows essentially no opioid receptor subtype selectivity. This result suggested that the absolute configuration of C-9 in **1** is important for activity. Replacement of the indolizidine skeleton of **1** with a pyrrolizidine skeleton (**21**) resulted in a 14-fold increase in μ-affinity with reduced δ- and κ-affinity, resulting in substantial μ-selectivity, whereas **27**, possessing a stemona alkaloid skeleton, showed selectivity for both μ- and κ-receptors.

In summary, we have completed the first enantioselective total synthesis of elaeocarpenine (**1**) and several analogs in a concise and flexible manner and evaluated their binding affinities for opioid receptor subtypes. Our findings demonstrate that the absolute configuration at C-9 in **1** is important for binding to μ-, δ- and κ-opioid receptors; (9*R*)-**1** has markedly higher affinity than (9*S*)-**1**. Moreover, changes in the size of the piperidine ring of **1** may provide a means to modulate the binding affinity and selectivity for receptor subtypes. Our synthetic approach should also provide access to other related analogs to broaden the SAR. Studies are ongoing in our laboratories.

Table 1
Binding affinity of (9*S*)-**1**, **22**, **25**, (9*R*)-**1**, **21**, and **27** for opioid receptor subtypes[a]



Compd	*n*	R^1	R^2	Affinity (K_i, μM)		
				μ^b	δ^c	κ^d
(9*S*)-**1**	2	H	Me	45	94	24
22	2	Me	Me	>200	>200	20
25	2	H	H	49	>200	83
(9*R*)-**1**	2	H	Me	18	14	12
21	1	H	Me	3.2	>200	35
27	3	H	Me	13	>200	4.0

[a] Radioligand-based binding assays were performed with human μ-, δ- and rat κ-opioid receptor in transfected HEK-293 cells (μ) or CHO cells (δ, κ).
[b] [^{3}H]DAMGO was used.
[c] [^{3}H]DADLE was used.
[d] [^{3}H]U69593 was used.

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14. *(9S)*-**1** *trifluoroacetic acid salt:* colorless oil; $[\alpha]_D^{26}$ +7.3 (*c* 0.18, MeOH); IR (ATR) 3030, 1663, 1464, 1177, 1131 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.35 (br s, 1H), 9.73 (br s, 1H), 7.13 (dd, *J* = 8.4, 7.8 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.60 (t, *J* = 3.6 Hz, 1H), 4.55–4.49 (m, 1H), 3.61–3.54 (m, 1H), 3.37–3.31 (m, 2H), 3.18–3.11 (m, 1H), 2.57–2.48 (m, 3H), 2.11–2.04 (m, 2H), 2.02 (s, 3H), 1.86–1.78 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.7, 154.1, 140.5, 136.4, 135.5, 129.9, 125.9, 120.6, 113.0, 58.2, 52.8, 43.3, 28.1, 22.6, 20.5, 18.4; MS (ESI+): *m*/*z*: 258 $[M+H]^+$; HRMS (ESI+): *m*/*z*: calcd for $C_{16}H_{20}NO_2$: 258.1494, found 258.1494 $[M+H]^+$.
(9R)-**1** *trifluoroacetic acid salt:* colorless oil; $[\alpha]_D^{26}$ −7.5 (*c* 0.22, MeOH); The spectral data were identical with those of (9*S*)-**1**.
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