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Synthesis and in vitro evaluation of salvinorin A analogues: Effect of configuration at C(2) and substitution at C(18)

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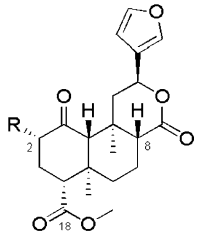
Abstract—κ-opioid receptor ligands have raised interest for their apparent effects on mood. The potent and selective κ-agonist salvinorin A has short-lasting (15 min) depressive-like effects in rats in behavioral models used to study mood disorders. Two series of salvinorin derivatives modified at C(2) and C(18), respectively, were synthesized and their κ-opioid receptor affinities, potencies, and efficacies were evaluated using in vitro receptor binding and biochemical functional assays. Modification at C(2) yielded potent κ-agonists that are predicted to have improved metabolic stability (**14a**, **15a**) or increased water solubility (**10b**). Our preliminary SAR study at C(18) suggested that this part of the molecule interacts with a tight lipophilic pocket of the κ-receptor.

Selective κ-opioid receptor (KOR) ligands have been proposed for the treatment of many disorders including pain, pruritis, obesity, and substance abuse. In addition, these agents may affect mood in humans[1] and our research group and others have shown that they have behavioral effects believed to be related to mood in rodents.[2,3] These observations suggest that κ-ligands could be effective as mood modulators; for example, κ-antagonists might be useful as antidepressants, κ-agonists as antimanic agents, and partial κ-agonists as mood stabilizers for patients with bipolar disorder. Salvinorin A (**1a**), the major psychoactive ingredient of *Salvia divinorum*, is an attractive compound for drug development because it is a selective and potent κ-agonist with unique structural properties.[4] We have reported that **1a** had depressive-like effects (characteristic of κ-agonists) in rat behavioral models used to study mood disorders (the forced swim test and the intracranial self-stimulation assay) and that it displayed its maximum effect within 15 min after intraperitoneal (ip) administration, with effects gone by 30 min.[3] The short duration of action of **1a** may be a limitation in some studies and is believed to be due to its rapid and extensive metabolism into salvinorin B (**2a**),[5,6] a minor component of *S. divinorum* with weak κ-agonist properties.[7] Simultaneously, we have begun to study the Structure–activity relationship (SAR) of **1a**[7] to learn how the following purposes might be achieved: (a) altering its pharmacokinetic properties to increase its in vivo stability; (b) converting **1a** into a selective partial agonist or an antagonist at KOR; and (c) obtaining additional information about the pharmacophore of **1a**. This report describes our progress towards the synthesis and in vitro evaluation of novel salvinorin derivatives.



1a: R = CH_3CO_2
2a: R = OH

Previous SAR studies have shown that the size of the substituent at C(2) is critical for both affinity and selectivity for the KOR. Selectivity for the KOR was observed with 3–4 atom-long substituents.[7–9] Bulkier substituents at C(2) decreased KOR binding activity

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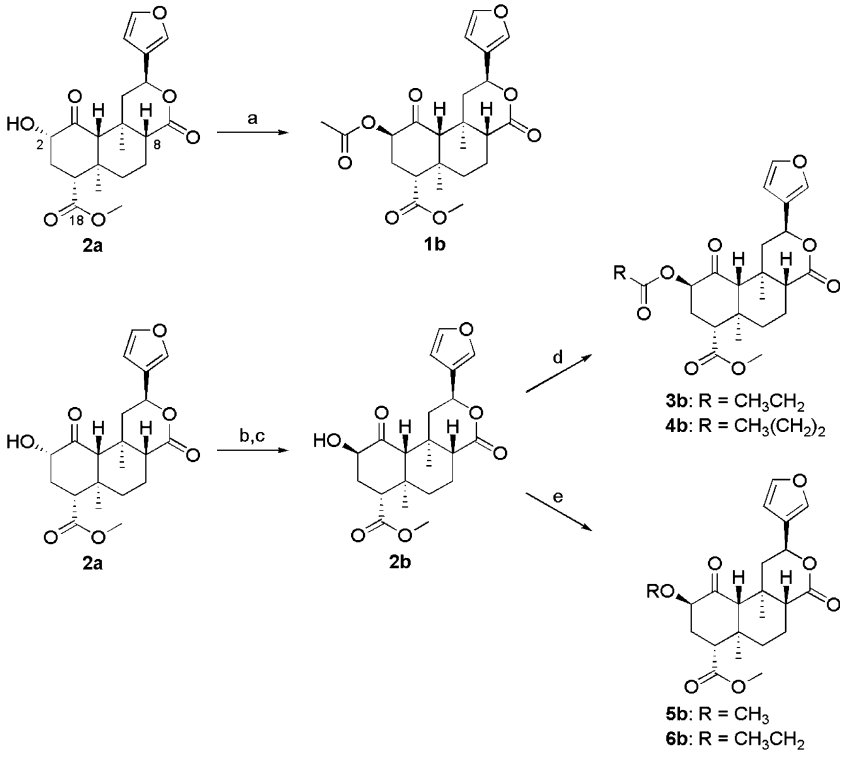
and introduction of a phenyl ring at C(2) led to preferential affinity for the μ-opioid receptor.[10] Functionality at C(2) seems to have a lesser effect in determining binding to the KOR, though the presence of substituents containing hydrogen bond acceptors was preferred.[7] In an elegant study, Munro et al. showed that the lactone and ketone units of **1a** are not necessary for binding, whereas the acetate, methyl ester, and furan moieties are essential for the interaction of **1a** with the KOR.[11] Interestingly, they also reported that introduction of an alcohol at C(18) yields a compound with weak antagonist activity at KOR. This SAR study is supported by a model of the interaction of **1a** with the KOR, developed by Yan et al., which suggests that although **1a** binds in the same pocket as structurally different agonists, it interacts with different residues.[12] In this model, the salvinorin A–KOR complex is stabilized by (a) hydrophobic interactions between the acetate unit and Y313; (b) the methyl ester group and I294 and the side chain of E297; and (c) hydrogen bonding between the furan ring and Y119 and Y320.

Here, we report the synthesis and in vitro evaluation of two subsets of compounds, resulting from modifications at C(2) and C(18), respectively. In a previous study, we varied the functional groups (ester, ether, amine, carbamate) at C(2).[7] As a continuation of these experiments, we now report the effect of C(2) configuration. Introduction of small metabolically stable substituents at the equatorial or axial C(2) positions might produce a compound with pharmacological properties similar to salvinorin A but with a longer duration of action. We have introduced esters (**1**, **3**, **4**), alcohol (**2**), ethers (**5**, **6**), amines (**7**–**11**), and amides (**12**–**17**) at these two positions. For convenience, we will refer to derivatives with the natural configuration at C(2) as **Xa** and to their corresponding analogues with the unnatural configuration at C(2) as **Xb**. In addition, we introduced modifications at C(18). The weak antagonist properties of the C(18) alcohol reported by Munro et al. suggest that small hydrogen bond donating groups at C(18) might convert **1a** into an antagonist. Therefore, we synthesized methyl and ethyl amides **19** and **20**. Fully substituted amide **21**, C(18) alcohol **22**,[11] and methyl ether **23** were prepared to provide comparison data. Additionally, based on the computational model of Yan et al., we hypothesize that introduction of charged substituents at C(18) (e.g., amine, guanidine, amidine) in the appropriate orientation may alter the interaction of the C(18) portion of the molecule with residue E297, possibly forming a stronger ionic interaction and thereby altering the conformation of the KOR. In this preliminary study, we focused on the introduction of small amino units at C(18) and synthesized salvinorin derivatives **24**–**26**. Each C(18)-modified salvinorin was prepared with natural configuration at C(8), and we will refer to them as **Xa**. Their corresponding C(8) epimers were also isolated and will be referred to as **Xc**.

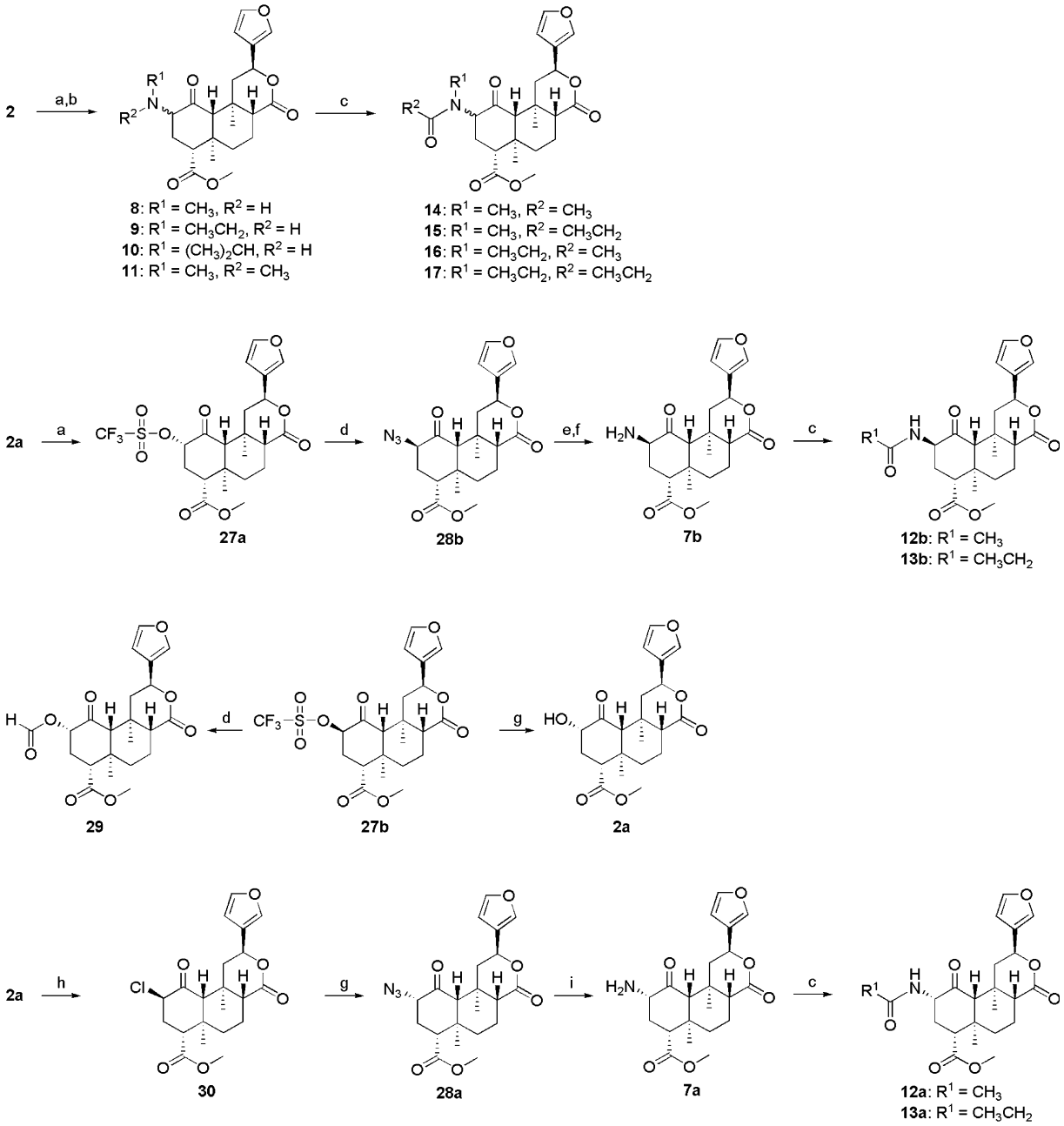
Salvinorin A was isolated from the leaves of *S. divinorum* as previously described.[13] The preparation of C(2) esters, alcohol, and ethers with natural configuration at C(2) (**2a**–**6a**) has been reported in the literature.[7] A Mitsunobu reaction was used to invert the C(2) configuration and prepare esters, alcohol, and ethers **1b**–**6b** (Scheme 1). Treatment of salvinorin B (**2a**) with triphe-



Scheme 1. Synthesis of C(2) esters and ethers. Reagents and conditions: (a) AcOH, PPh_3, DIAD, CH_2Cl_2, 38%; (b) 4-nitrobenzoic acid, PPh_3, DIAD, CH_2Cl_2; (c) K_2CO_3, CH_3OH, 64%, over two steps; (d) appropriate acyl chlorides or acetic anhydride, Et_3N, CH_2Cl_2, 65–73%; (e) appropriate alkyl iodide, Ag_2O, CH_3CN, 52–68%.

nylphosphine, diisopropyl azodicarboxylate, and AcOH provided 2-*epi*-salvinorin A (**1b**).[14] 2-*epi*-Salvinorin B (**2b**)[14] was prepared under Mitsunobu conditions using *p*-nitrobenzoic acid as the nucleophile with subsequent hydrolysis of the *p*-nitrobenzoate intermediate (64% yield, over two steps). Standard acylation conditions (propionyl or butyryl chloride, Et_3N, CH_2Cl_2) were then used to yield esters **3b** and **4b**, respectively. Salvinorin analogues **5b** and **6b** were readily obtained by O-alkylation of **2b** with methyl and ethyl iodide, respectively.

The synthetic routes to C(2) amines and amides **7**–**17** are depicted in Scheme 2. Amines with unnatural configuration at C(2) (**8b**, **9b**, and **11b**) were synthesized as previously described from **2a**.[7] Similar conditions (alcohol activation followed by displacement with isopropylamine) were used for the preparation of the C(2) amine **10b**. Amines with natural configuration at C(2) (**8a**–**11a**) were prepared using the same methodology, starting with 2-*epi*-salvinorin B (**2b**). We employed a three-step synthesis to prepare free amine **7b**. Salvinorin B (**2a**) was first converted to triflate **27a** using trifluoromethanesulfonic anhydride. Displacement of the activated 2-triflate substituent in **27a** with sodium azide gave azide **28b**, which in turn was reduced under Staudinger conditions (PPh_3, H_2O, THF) to obtain **7b** in



Scheme 2. Synthesis of C(2) amines and amides. Reagents and conditions: (a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (b) R^1R^2NH, THF, 24–58%, over two steps; (c) appropriate acyl chlorides or acetic anhydride, Et_3N, CH_2Cl_2, 50–100%; (d) NaN_3, DMF, 53% yield for the preparation of **29**; (e) PPh_3; (f) H_2O, THF, 35%, over three steps; (g) NaN_3, DMSO, 29–48% yield; (h) $SOCl_2$, Et_3N, $ClCH_2CH_2Cl$, 70% yield; (i) TMSCl, NaI, CH_3CN, 16% yield.

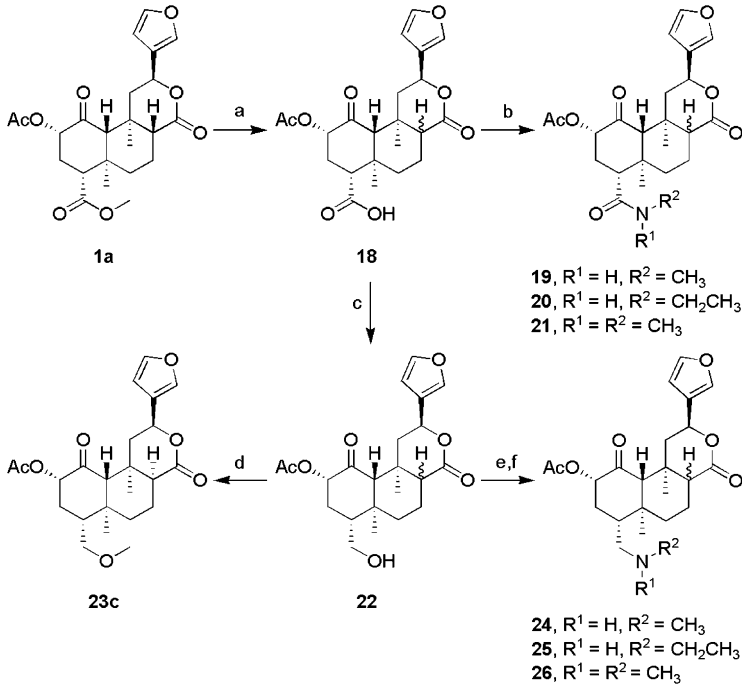
35% yield, over three steps. Interestingly, similar synthetic conditions from epimer **2b** gave unexpected results: treatment of triflate **27b** with sodium azide in DMF gave formate **29**,[11] similar results have been reported previously.[15] When DMSO was used as the solvent the hydrolysis product **2a** was obtained. Creary et al. attributed the formation of such hydrolysis product to the high reactivity of the triflates.[16,17] We, therefore, decided to use the less reactive C(2) chloride **30** as a precursor of free amine **7a**. Accordingly, treatment of **2a** with thionyl chloride afforded the C(2) chloride, which was then converted to azide **28a** by nucleophilic displacement with sodium azide. Surprisingly, the standard Staudinger conditions we used for the reduction of azide **28b** were ineffective for its epimer **28a**. The synthetic approach of Kamal et al.[18] (TMSCl, NaI, CH_3CN) formed primary amine **7a** in 5% yield, over three steps. Acylation of amines **7–9** using Ac_2O or the appropriate acyl chloride in the presence of Et_3N afforded the desired amide products **12–17** with yields ranging from 50–100%.

Scheme 3 describes the modifications at the C(18) position. The methyl ester of **1a** was selectively cleaved according to the method described by Lee et al.[19] to produce carboxylic acid **18**,[11] as a mixture of C(8) epimers, which served as the starting material for the preparation of the C(18)-modified salvinorins **19–26**. Amides **19–21** were prepared from **18** and methylamine, ethylamine, or dimethyl amine, respectively, in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and DMAP. The yields in the amide-forming reactions were low (32–53% yield for both C(8) epimers) due to competitive by-product formation. Presumably, the amine reactants opened the lactone. The natural C(8) epimers were easily separated from the unnatural epimers via SiO_2 chromatography.

Alcohol **22**[11] served as the starting material for methyl ether **23** and amines **24–26**. Using the procedure published by Munro et al.,[11] acid **18** was reduced to alcohol **22** using BH_3·THF, and both C(8) epimers of **22** were isolated in a combined 64% yield. Each C(8) epimer of **22** was treated, separately, with iodomethane in the presence of Ag_2O to create the methyl ether **23**. However, both reactions gave only the unnatural C(8) epimer in fairly low yield. The amines **24–26** were synthesized in two steps. Accordingly, treatment of **18** with trifluoromethanesulfonic anhydride provided an activated triflate intermediate, which was displaced by methylamine, ethylamine, or dimethylamine to form **24**, **25**, and **26**, respectively.

Spectral data (^{1}H NMR, ^{13}C NMR, HRMS) consistent with the proposed structures were obtained for all the compounds prepared in this study.

The affinities of compounds **1–26** for the human KOR were determined by competitive inhibition of [^{3}H]diprenorphine binding to membranes prepared from Chinese hamster ovary cells (CHO-hKOR) stably transfected with the human κ-opioid receptor (hKOR).[20] The potencies and efficacies of compounds **1–26** on hKOR were determined by their abilities to regulate [^{35}S]GTPγS binding to membranes of CHO-hKOR cells.[21] The selective κ-full agonist, U50,488H, was used as a reference compound with its efficacy designated as



Scheme 3. Syntheses of C(18) derivatives. Reagents and conditions: (a) LiI, pyridine, 110 °C, 42 h, 70%; (b) appropriate amine, EDCI, DMAP, CH_2Cl_2, rt, 5–60 min, 32–53 %; (c) BH_3·THF, 55 °C, 2.5 h, 64%; (d) CH_3I, Ag_2O, CH_3CN, rt, 48 h, 29 %; (e) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0 °C, 5 min; (f) appropriate amine, THF, rt, 5–10 min, 22%–quantitative, over two steps.

100%. The in vitro pharmacological data for C(2)-modified salvinorins **1**–**17** and C(18)-modified salvinorins **18**–**26** are listed in Tables 1 and 2, respectively.

We have reported the in vitro pharmacological profile of compounds **1a-6a**, **8b**, **9b**, and **11b** in a previous paper.[7] Our group and others have shown that 3–4 atom-long substituents at C(2) are optimal for binding to the KOR.[7–9] Table 1 shows the in vitro pharmacological data for 1–5 atom-long esters, alcohol, ethers, amines, and amides with natural and unnatural configurations at C(2).

In the ester series, we have shown that a 1–2 carbon increase in chain length was well tolerated: compounds **3a** and **4a** have about the same KOR activity as does **1a**.[7] Inversion of C(2) configuration led to a 89- to 326-fold loss of binding affinity for the KOR and **1b**–**3b** have negligible binding activity (K_i > 400 nM).

A similar trend was observed in the alcohol/ether series: the natural isomers (**2a**, **5a**, **6a**) have >45-fold better affinity for the KOR than the unnatural isomers (**2b**, **5b**, **6b**). In this subset of compounds, only **6a** showed significant affinity for the KOR (K_i = 7.9 ± 0.3 nM).[7]

Our previous pharmacological data for **8b**, **9b**, and **11b** suggested that amines with unnatural configuration at C(2) had moderate or no affinity for the KOR.[7] We have synthesized two additional C(2) unnatural amines: primary amine **7b** also weakly binds to KOR (K_i = 223 nM). Interestingly, isopropylamine **10b** is a potent full agonist at KOR (K_i = 2.3 ± 0.6 nM; EC_{50} = 7.2 ± 0.3 nM, 107% efficacy). We realize that **10b** may be easily metabolized by N-dealkylation and may not be a good candidate for in vivo studies. However, if **10b** is stable and has selectivity for the KOR, it could be used as a salt in studies that require enhanced water solubility, such as administration to animals. In most cases, natural C(2) configuration in the amine series decreased binding affinity: ethylamine **9a**, isopropylamine **10a**, and dimethylamine **11a** exhibited lower affinity for the KOR than their corresponding epimers (1.8- to 7.7-fold). However methylamine **8a**, while showing only modest affinity (K_i = 328 ± 40 nM) was at least 30-fold more active than **8b**. We have not tested free amine **7a**.

Amides containing a hydrogen bond donor (**12**, **13**) are weak agonists of the KOR (K_i = 117–374 nM, EC_{50} = 118–718 nM). The limited number of monosubstituted amides prepared in this study does not allow us to determine if one configuration is preferred. The C(2)

Table 1. Affinities (K_i), potencies (EC_{50}), and efficacies of C(2)-substituted salvinorins at the κ-opioid receptor

Compound	C(2) substituent	**a**, natural configuration at C(2)			**b**, unnatural configuration at C(2)		
		K_i[a,b] (nM)	EC_{50}[b,c] (nM)	Efficacy[d]	K_i[a,b] (nM)	EC_{50}[b,c] (nM)	Efficacy[d]
Esters							
1, Salvinorin A	CH_3CO_2	1.3 ± 0.5	4.5 ± 1.2	99	424 ± 16[e]	306 ± 23	102
3	$CH_3CH_2CO_2$	7.2 ± 0.5	20.4 ± 3.4	94	641 ± 122[f]	—[g]	—[g]
4	$CH_3(CH_2)_2CO_2$	4.9 ± 0.6	9.9 ± 0.6	97	665 ± 100[f]	—[g]	—[g]
Alcohol, ethers							
2, Salvinorin B	HO	155 ± 23	371 ± 49	98	>10,000[e]	—[g]	—[g]
5	CH_3O	220 ± 12	389 ± 76	98	>10,000[e]	—[g]	—[g]
6	CH_3CH_2O	7.9 ± 0.3	18.6 ± 2.6	103	>10,000[e]	—[g]	—[g]
Amines							
7	NH_2	—[g]	—[g]	—[g]	223 ± 123[e]	1373 ± 155	84
8	$CH_3N(H)$	328 ± 40[f]	825 ± 93	82	> 10,000	—[g]	—[g]
9	$CH_3CH_2N(H)$	65.2 ± 24.6[e]	72.8 ± 4.0	104	28.9 ± 1.0	68.9 ± 5.3	111
10	$(CH_3)_2CHN(H)$	17.6 ± 3.1[e]	18.9 ± 0.6	99	2.3 ± 0.6[h]	7.2 ± 0.3	107
11	$(CH_3)_2N$	168 ± 10[i]	240 ± 23	110	90.9 ± 2.5	343 ± 12	105
Amides							
12	$CH_3C(O)N(H)$	149 ± 1[i]	188 ± 2	106	332 ± 41[e]	339 ± 33	103
13	$CH_3CH_2C(O)N(H)$	374 ± 19[i]	444 ± 35	109	117 ± 63[e]	718 ± 31	102
14	$CH_3C(O)N(CH_3)$	3.2 ± 0.1[e]	2.4 ± 0.7	103	16.5 ± 1.1[h]	21.0 ± 0.9	106
15	$CH_3CH_2C(O)N(CH_3)$	1.6 ± 0.1[f]	0.75 ± 0.08	100	6.9 ± 1.1[h]	12.6 ± 0.9	103
16	$CH_3C(O)N(CH_2CH_3)$	27.6 ± 1.8[f]	25.2 ± 0.2	104	240 ± 17[f]	641 ± 92	95
17	$CH_3CH_2C(O)N(CH_2CH_3)$	38.1 ± 1.9[f]	37.2 ± 0.2	100	376 ± 36[f]	857 ± 136	96
U50,488H		1.4 ± 0.3	4.5 ± 1.2	100			

[a] K_i values in inhibiting [^{3}H]diprenorphine binding to hKOR.
[b] Each value represents the mean of at least three independent experiments performed in duplicate.
[c] EC_{50} values in activating the hKOR to enhance [^{35}S]GTPγS binding.
[d] Efficacy determined as the % of maximal response produced by U50,488H run in parallel experiments.
[e] U50,488H values for these assays: K_i = 2.2 ± 0.8 nM; EC_{50} = 3.6 ± 0.3 nM.
[f] U50,488H values for these assays: K_i = 1.6 ± 0.2 nM; EC_{50} = 2.2 ± 0.2 nM.
[g] Not determined.
[h] U50,488H values for these assays: K_i = 0.43 ± 0.16 nM; EC_{50} = 2.0 ± 0.2 nM.
[i] U50,488H values for these assays: K_i = 2.2 ± 0.3 nM; EC_{50} = 2.1 ± 0.9 nM.

Table 2. Affinities (K_i), potencies (EC_{50}), and efficacies of C(18)-modified salvinorins at the κ-opioid receptor

Compound	C(4) substituent	**a**, natural configuration at C(8)			**c**, unnatural configuration at C(8)		
		K_i[a,b] (nM)	EC_{50}[b,c] (nM)	Efficacy[d]	K_i[a,b] (nM)	EC_{50}[b,c] (nM)	Efficacy[d]
Esters							
1, Salvinorin A	CO_2CH_3	2.6 ± 0.2	2.2 ± 0.3	99	140 ± 9	531 ± 145	88
Amides							
19	$C(O)N(H)CH_3$	1392 ± 218	—[e]	71[e]	>1,000	—[f]	—[f]
20	$C(O)N(H)CH_2CH_3$	>10,000	—[f]	—[f]	>10,000	—[f]	—[f]
21	$C(O)N(CH_3)_2$	>10,000[g]	—[f]	—[f]	>10,000[g]	—[f]	—[f]
Alcohol, ethers							
22	CH_2OH	1000 ± 269	—[e]	68[e]	>10,000	—[f]	—[f]
23	CH_2OCH_3	—[f]	—[f]	—[f]	769 ± 180	—[e]	70[e]
Amines							
24	$CH_2N(H)CH_3$	>10,000	—[f]	—[f]	>10,000	—[f]	—[f]
25	$CH_2N(H)CH_2CH_3$	>10,000	—[f]	—[f]	>10,000	—[f]	—[f]
26	$CH_2N(CH_3)_2$	>10,000[g]	—[f]	—[f]	>10,000[g]	—[f]	—[f]
U50,488H		1.6 ± 0.2	2.2 ± 0.2	100			

[a] K_i values in inhibiting [^{3}H]diprenorphine binding to hKOR.
[b] Each value represents the mean of at least three independent experiments performed in duplicate.
[c] EC_{50} values in activating the hKOR to enhance [^{35}S]GTPγS binding.
[d] Efficacy determined as the % of maximal response produced by U50,488H run in parallel experiment.
[e] No plateau was reached; the efficacy numbers represent the response at 10 μM.
[f] Not determined.
[g] U50,488H values for these assays: K_i = 2.2 ± 0.3 nM; EC_{50} = 2.1 ± 0.9 nM.

fully substituted amides follow the trend observed for the C(2) esters and ethers: the natural isomers (**14a**–**17a**) are about 5-10 times more potent than the corresponding unnatural isomers (**14b**–**17b**). The effect of the size of the C(2) amide is independent of the configuration at C(2): the natural and unnatural *N*-methylacetamide (**14**) and *N*-methylpropionamide (**15**) are the most potent compounds in this series. While the metabolism and pharmacokinetics of **1a** have not been studied extensively, there is evidence suggesting that the acetate unit of **1a** is rapidly cleaved in vivo to form salvinorin B (**2a**) as the major metabolite.[5,6] We hypothesized that **14a** and **15a** would be more stable than **1a** and have begun to evaluate **14a** in vivo. Preliminary data (not shown) indicate that the effects of **14a** are longer lasting than those of **1a**.

All molecular changes at C(18) induced a significant loss of activity. Methylamide **19a**, a bioisostere of **1a**, showed negligible affinity for the KOR (K_i = 1392 nM), suggesting that the hydrogen bond donor may prevent the molecule from binding to the receptor. Similar findings were obtained for the C(8) epimer **19c**. Increasing the size of the amide substituent led to a complete loss of binding affinity: ethylamides **20** and dimethylamides **21** at 10 μM caused <50% inhibition of [^{3}H]diprenorphine binding. In our hands, C(18) alcohol **22a**[11] had very little affinity for the KOR. As expected, its C(8) epimer **22c** did not bind to the KOR. We were not able to prepare methyl ether **23a**, but **23c** had only modest affinity for the KOR (K_i = 769 nM). Finally, introduction of secondary (**24** and **25**) or tertiary (**26**) amino units at C(18) led to a complete loss of affinity for the KOR (K_i > 10,000 nM), suggesting that the hydrogen bond acceptors in salvinorin A are crucial for interaction with the receptor. Alternatively, introduction of a charged substituent at C(18) may prevent the molecule from interacting with the hydrophobic binding pocket formed by I294 and the side chain of E297.[12]

In conclusion, natural configuration at C(2) provides better molecular complementarity with the KOR for C(2) esters, ethers, and amides. Preliminary data suggest that the trend is reversed when we introduce charged substituents at C(2). This SAR study generated potent κ-agonists (**14a**, **15a**) that were designed to have longer lasting in vivo effects. Our results also suggest that potent κ-agonists with increased water solubility can be obtained by introduction of charged substituents at the C(2) axial position. None of the changes we made at C(18) were tolerated. That is, introduction of hydrogen bond donors or charged substituents at C(18) prevents the molecule from binding to the KOR. The size of the C(18) substituent also seems to be critical. Our preliminary SAR study suggests that the C(18) methyl ester of salvinorin A interacts with a tight lipophilic pocket of the KOR. Further study is needed to determine if hydrogen bond or charged substituents with other spatial orientations (directly attached to C(4) or further removed) would induce a strong ionic interaction with E297.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2006.05.093.

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