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Synthesis and in vitro pharmacological studies of new C(2) modified salvinorin A analogues

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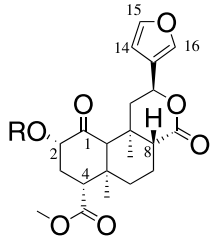
Abstract—Salvinorin A is the most potent naturally occurring opioid agonist yet discovered with high selectivity and affinity for κ-opioid receptor. To explore its structure and activity relationships, a series of salvinorin A derivatives modified at the C(2) position were prepared and studied. These salvinorin A derivatives were screened for binding and functional activities at the human κ-opioid receptor. Compound **4**, containing a methoxymethyl group at the 2-position, was a full κ-agonist with an EC_{50} value at 0.6 nM, which is about 7 times more potent than salvinorin A.

Activation of the κ-opioid receptor triggers many effects, including analgesia, dysphoria, antipruritic effect, corticosteroid elevations, diuresis, immunomodulation, and decreases in pilocarpine-induced seizures and associated mossy fiber sprouting and hilar neuron loss.[1] The κ-opioid receptors also participate in the expression of chronic morphine-induced withdrawal syndromes and mediate the aversive effects of Δ-9-tetrahydrocannabinol.[2,3] Synthetic arylacetamides, including U50488H, U69593, spiradoline, enadoline, ICI-204448, and asimadoline, have been demonstrated to be selective κ-opioid receptor agonists.[4,5] Interestingly, κ-agonist U69593 produces depressive-like effects and κ-antagonists, such as norBNI (nor-binaltorphimine) and ANTI (5′-acetamidinoethylnaltrindole), produce antidepressant-like effects in animal models.[6,7] Furthermore, κ-agonists appear to affect the mood in humans.[8,9] Other κ-active compounds, such as TRK 820 and HZ2, were reported to be useful as analgesics, water diuretics, and antipruritic drugs.[10–13]

Recently, salvinorin A has been identified as a selective κ-agonist.[14–17] Salvinorin A (**1**) was isolated from the dry leaves of *Salvia divinorum*, a 'magic mint' that has been in use for several hundreds of years mainly because of its psychoactive (hallucinogenic) effects during the divination rites of the Mazatec people of Mexico (Fig. 1).[18] Salvinorin A, a non-nitrogenous neoclerodane diterpenoid, was isolated and identified to be the key ingredient producing these psychoactive effects.[19] As part of our ongoing research on the development of κ-active ligands, we initiated the synthesis of C(2) modified salvi-



1: Salvinorin A, R= Ac
3: Salvinorin B, R= H

Figure 1.

Keywords: κ Opioid-receptor; Salvinorin A; Diterpenoid; Agonist; Binding activity.
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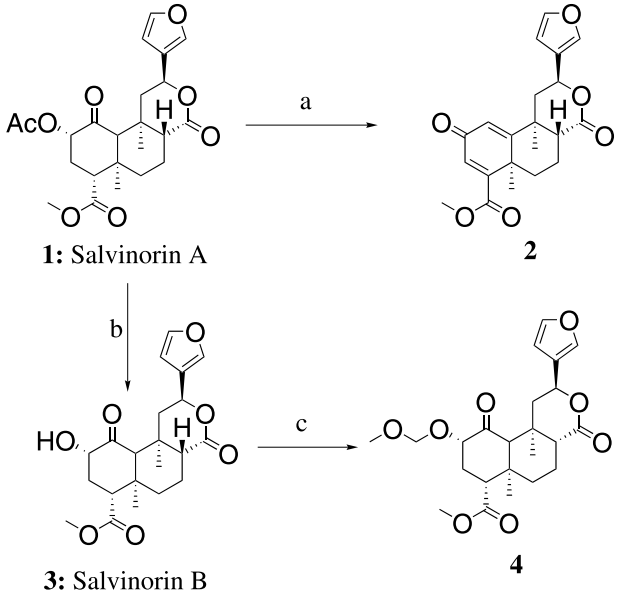
norin A analogues (Fig. 1). Our own findings, as well as those reported by several other laboratories, suggest that C(2) is a sensitive and critical site for binding the κ-receptor, with very limited tolerance in regard to size and electronegativity of the substituent group.[16,20]

Salvinorin A (**1**) was first converted to salvinorin B (**3**) by using potassium carbonate as the base at 0 °C in methanol (Scheme 1).[21] The C(8)-epimer (*epi*-**3**) was also isolated in this process, which has the same R_f value as **1** ($R_f = 0.61$, in 50% EtOAc/hexane). Various inorganic bases and organic bases have been tested and afforded no improvement in the yield of **3**. When $Ba(OH)_2$ was employed as the base in methanol, an unexpected oxidative-eliminated product **2** was isolated and identified. ^{1}H NMR shows two additional peaks at 6.92 and 6.98 ppm, in addition to furan protons at C(14), C(15), and C(16). ^{13}C NMR shows a corresponding peak pattern in which the C(1) signal had disappeared. Structural assignment of **2** was also confirmed by extensive H-H COSY and HMQC studies. Compound **4** was synthesized by reacting **3** with chloromethyl methyl ether in the presence of Hünig's Base and 4-(dimethyl-amino)pyridine (DMAP) (Scheme 1).

Although previous modifications at the C(2) position and corresponding binding studies have generated numerous C(2)-analogues, only the 2-propionate and formate derivatives, however, showed submicromolar affinity,[16,22] equivalent to salvinorin A, for the human κ-opioid receptor (hKOR). Several reports show that salvinorin B (**3**) is inactive.[16,23] A molecular modeling study reveals that residue **Y313** in the 7th transmembrane helix of the hKOR might interact with the carbonyl group at C(2) via H-bonding. To further explore the SAR at the C(2)-position and synthesize potential agonists and antagonists of hKOR, we have synthesized a series of C(2)-esters and carbonates, as shown in Table 1.



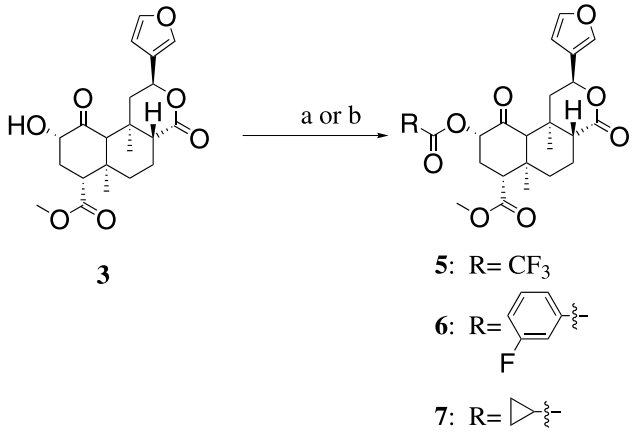
Scheme 1. Reagents and conditions: (a) $Ba(OH)_2$, MeOH, rt (75%); (b) K_2CO_3, MeOH, 0 °C, (70%); (c) MOM-Cl, ^{i}Pr$_2$NEt, DMAP, CH_2Cl_2, rt (72%).

Esters **5**, **6**, and **7** were prepared according to standard acylation procedures (Scheme 2). By reacting salvinorin B (**3**) with trifluoroacetic anhydride in the presence of pyridine at room temperature, **5** was obtained in good yield. Fluoride atoms have been used extensively in drug discovery on account of their unique electronic proper-

Table 1. Affinities (K_i), potencies (EC_{50}), and efficacies of C(2)-substituted salvinorins **1–9** at the κ-opioid receptor

Compound	K_i[a,b] (nM)	EC_{50}[b,c] (nM)	Efficacy[d]
2	>1000	—[e]	—
3	111 ± 12	492 ± 75	97
epi-**3**	43 ± 5	193 ± 4	102
Esters			
1	1.3 ± 0.5	4.5 ± 1.2	106
epi-**1**	77 ± 4	307 ± 92	94
5	>1000	—[e]	—
epi-**5**	>1000	—[e]	—
6	>1000	—[e]	—
7	>1000	—[e]	—
Carbonates			
8	>1000	—[e]	—
9	>1000	—[e]	—
Ethers			
4	0.4 ± 0.02	0.6 ± 0.2	98
epi-**4**	30 ± 3	92 ± 31	100
U50,488H	1.4 ± 0.3	4.5 ± 1.2	100

[a] K_i values of salvinorin A (**1**) and its analogues in inhibiting [^{3}H]diprenorphine binding to the human κ-receptor.
[b] Each value represents the mean of at least three independent experiments performed in duplicate.
[c] EC_{50} values in activating the human κ-receptor to enhance [^{35}S]GTPγS binding.
[d] Efficacy determined as the percentage of maximal response produced by U50,488H.
[e] Not determined.



Scheme 2. Reagents and conditions: (a) Compound **5**—$(CF_3CO)_2O$, Pyr., DMAP, CH_2Cl_2, rt (62%); (b) RCOCl, DMAP, CH_2Cl_2, rt.