Invited Reviews

Natural Products as Tools for Neuroscience: Discovery and Development of Novel Agents to Treat Drug Abuse[⊥]

Thomas E. Prisinzano*

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

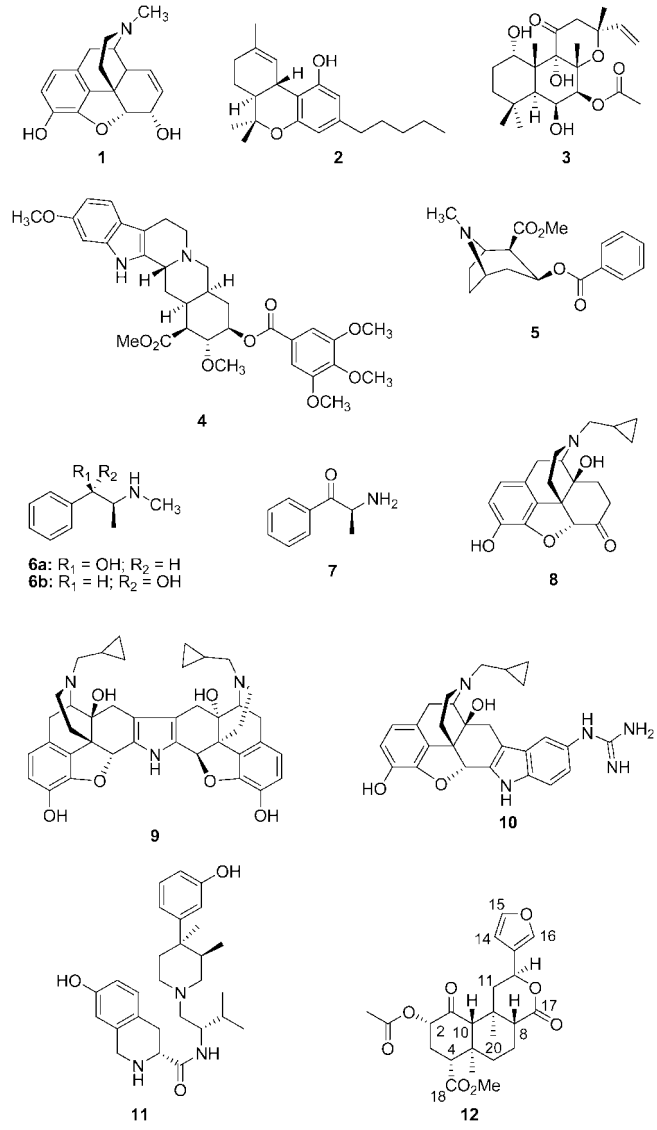
Received September 11, 2008

Much of what we know about the neurosciences is the direct result of studying psychoactive natural products. Unfortunately, there are many gaps in our understanding of the basic biological processes that contribute to the etiology of many CNS disorders. The investigation of psychoactive natural products offers an excellent approach to identify novel agents to treat CNS disorders and to find new chemical tools to better elucidate their biological mechanisms. This review will detail recent progress in a program directed toward investigating psychoactive natural products with the goal of treating drug abuse by targeting κ opioid receptors.

Introduction

The use of psychoactive substances has a long and rich tradition and, except for a few cultures, is almost universal.[1] Historically, psychoactive natural products have been used for their medicinal value and/or their ability to produce altered consciousness. Much of what modern science knows about the neurochemistry of the brain and the functions of the central nervous system can be traced directly to the study of psychoactive natural products.[2] For example, intensive study of the chemistry and pharmacology of the alkaloid morphine (**1**) from *Papaver somniferum* L. (Papaveraceae) led to the identification of opioid receptors and the endogenous opioid system and has given much insight into the mechanisms of nociception.[3−5] Similarly, studies focused on better understanding the effects of Δ^9-tetrahydrocannabinol (**2**) and other cannabinoids, the active principles of marijuana (*Cannabis sativa* L. Cannabaceae), led to the identification of cannabinoid receptors and the endocannabinoid system.[6] Forskolin (**3**), a diterpene isolated from *Coleus forskohlii* Briq. (Lamiaceae), is a potent and specific activator of adenylate cyclase and has been used extensively to investigate the function of CNS receptors.[7,8] Furthermore, the study of alkaloids from *Rauvolfia serpentina* Benth. (Apocynaceae), such as reserpine (**4**), greatly expanded our understanding of the neurotransmitters serotonin, norepinephrine, and dopamine, as well as the etiology of depression.[9]

Unfortunately, the abuse of psychoactive natural products leading to addiction has also had a negative effect on public health, by behavioral and neuropsychiatric morbidity, as well as by facilitating the spread of HIV-1, hepatitis B and C, and drug-resistant tuberculosis.[10,11] Government estimates put the annual demand for the alkaloid cocaine (**5**) from *Erythroxylum coca* Lamarck (Erythroxylaceae) in the United States as being approximately 300 t or about 50% of the world illict production.[12] Further estimates put the number of hard-core cocaine users each year between 3.3 million and 3.6 million.[12] In addition to the problems associated with



[⊥] Dedicated to Dr. David G. I. Kingston of Virginia Polytechnic Institute and State University for his pioneering work on bioactive natural products. Adapted from a Matt Suffness (Young Investigator) Award address, seventh Joint Meeting of AFERP, ASP, GA, PSE, & SIF and 49th Annual Meeting of the American Society for Pharmacognosy, Athens, Greece, August 3−8, 2008.

* Corresponding author. Tel: (785) 864-3267. Fax: (785) 864-5326. E-mail: prisinza@ku.edu.

10.1021/np8005748 CCC: $40.75
Published on Web 12/19/2008

cocaine abuse, a rise in the abuse of methamphetamine has been noted in West Coast cities of the United States, in particular.[13] Methamphetamine may be derived from the alkaloids ephedrine (**6a**) and pseudoephedrine (**6b**), constituents specific of the genus *Ephedra* of the family Ephedraceae. In less than 10 years, methamphetamine has grown from a problem limited to the southwestern and midwestern United States to one of nationwide concern.[13,14] Furthermore, the World Health Organization estimated that 10 million people worldwide chew khat, *Catha edulis* Forsk. (Celastraceae). This use is commonly found in the southwestern part of the Arabian Peninsula and in East Africa, where it has been used for centuries as part of an established cultural tradition. The major pharmacologically active constituent in khat is cathinone (**7**), an amphetamine-like alkaloid.[15] Its current use among particular migrant communities in the United States has raised concern, but there are no reliable estimates of its prevalence.

Stimulant dependence is a chronic relapsing disease that results from the prolonged effects of drugs on the brain.[16] At present, there are no FDA-approved therapeutic agents available for the treatment of stimulant abuse or for the prevention of its relapse. However, various types of medications are currently being pursued based on the dopamine hypothesis.[17−21] This hypothesis speculates that chronic exposure to stimulants causes excessive stimulation of dopamine neurons that, over time, produces dopamine depletion in critical reward circuits in the brain.[22] The drug-induced depletion is then responsible for anhedonia, withdrawal, and relapse.[22,23] To date, some promising clinical results for the dopamine hypothesis have been achieved with dextroamphetamine[24] and modafinil.[25] However, other neurochemical mechanisms appear to be involved and additional therapeutic approaches need to be explored.[26,27] One approach to developing novel medications is to target κ opioid (KOP) receptors.[28]

κ Opioid Receptors and Drug Abuse

Opioid receptors are members of the superfamily of seven transmembrane-spanning (7TM) G-protein coupled receptors (GPCRs) and are divided into three types: μ (MOP), δ (DOP), and κ (KOP).[5,29] The existence of additional opioid receptor subtypes has been suggested through multiple pharmacological studies.[30−32] Each opioid receptor type plays a role in antinociception, as well as other biological responses.[33] Interestingly, a growing body of evidence suggests that KOP receptors modulate the effects of psychostimulants.[34−36] The KOP receptor system has been found to be critical for the development and relapse to drug seeking[36] and have a role in the modulation of dopamine levels.[37−44] More importantly, administration of KOP agonists (1) decreases self-administration of cocaine; (2) inhibits cocaine place preference and locomotor sensitization; and (3) decreases cocaine-induced reinstatement.[45−50] Collectively, these findings suggest that KOP receptor agonists could potentially treat cocaine abuse.[28,51]

Disruption of the KOP receptor also has potential utility in treating drug abuse. A central problem in treating drug addiction is the vulnerability to relapse during abstinence.[52] Behavioral studies have shown that presentation of drug-associated cues, drug priming, and acute foot-shock stress each increased drug self-adminstration.[53−55] It is believed that release of dynorphins, the endogenous agonists for KOP receptors, may mediate a component of stress-induced drug craving in reinstatement models (models of drug relapse).[52] Studies have shown that interference of the KOP system by pretreatment with antagonists or gene disruption of KOP receptor attenuates the reinstatement of extinguished drug-taking behavior.[52,56,57] Interference of the KOP system has also been shown to produce effects in animal models often used to study psychiatric illness. KOP receptor antagonists significantly decrease immobility and increase swimming time in the forced swim stress test similar to the antidepressant desipramine in rats.[56] Furthermore, KOP antagonists have anxiolytic-like effects in models of unlearned and learned fear in rats.[58] This suggests that KOP antagonists may have utility in treating depression and anxiety, as well as drug relapse.

Development of KOP Antagonists

Among the first nonpeptide KOP antagonists identified were those derived from the morphine derivative naltrexone (**8**) such as nor-BNI (**9**) and GNTI (**10**).[59,60] While **9** has been extensively used to study KOP receptors, its pharmacological properties are not optimal. It exhibits a much longer than expected half-life in vivo.[61] Further study of its structure−activity relationships identified **10** as having increased potency in vivo as a KOP antagonist but also had an extended duration of action.[62−68]

More recently, several novel classes of KOP antagonists have been discovered.[69−73] In particular, JDTic (**11**) was identified as a KOP antagonist more potent than **9**.[70] Additional pharmacological studies have shown that **11** blocks KOP agonist induced antinociception in mice and squirrel monkey, antagonizes KOP agonist induced diuresis in rats,[74] decreases withdrawal signs in rodents,[75] significantly reduces foot-shock-induced reinstatement of cocaine responding in rats,[56] and has anxiolytic-like effects in rats.[58]

For the reasons stated above, targeting KOP receptors is an excellent pharmacological approach to treating stimulant abuse and its pendent pathology. However, currently available KOP receptor ligands suffer from several therapeutic limitations. First, KOP agonists have been shown to potentiate cocaine reward and produce psychotomimesis, sedation, and nausea.[34,76−78] Second, almost all currently available KOP antagonists have a slow onset of action and are extremely long in duration of action and disrupt KOP signaling by activating c-Jun N-terminal kinase (JNK).[79,80] Thus, there is a pressing need to identify new molecules that modulate KOP receptors devoid of these limitations.

Most KOP receptor ligands are derivatives of morphine and are likely to suffer from the same therapeutic limitations. One approach to circumvent the problems of therapeutic limitations seen with traditional KOP ligands is to identify novel structural scaffolds for chemical development through investigation of psychoactive natural products, such as *Salvia divinorum* Epling & Játiva (Lamiaceae).[2]

Salvia divinorum

Salvia divinorum is a sage native to the southern Mexican state of Oaxaca, Mexico. The genus *Salvia* is one of the most widespread taxa of the Lamiaceae family and is featured prominently in the pharmacopeias of many countries throughout the world.[81] Mazatec Indians living in Oaxaca utilize the leaves of *S. divinorum* as a divinatory or pyschotomimetic agent.[82,83] An infusion prepared from four or five pairs of fresh or dried leaves is also used by the Mazatecs to stop diarrhea and to relieve headache and rheumatism.[84] The active ingredient in *S. divinorum* is the neoclerodane diterpene salvinorin A (**12**), which was identified nearly simultaneously by two groups.[85−88] A smoked dose of approximately 200 to 500 μg produces profound hallucinations lasting up to one hour.[87,89] The molecular target for the hallucinatory actions of **12** was not clear given its lack of activity at the targets of other known hallucinogens, namely, the serotonin 5-HT_{2A} and NMDA receptors.[87] Remarkably, **12** was identified as a potent and selective KOP agonist in vitro.[90]

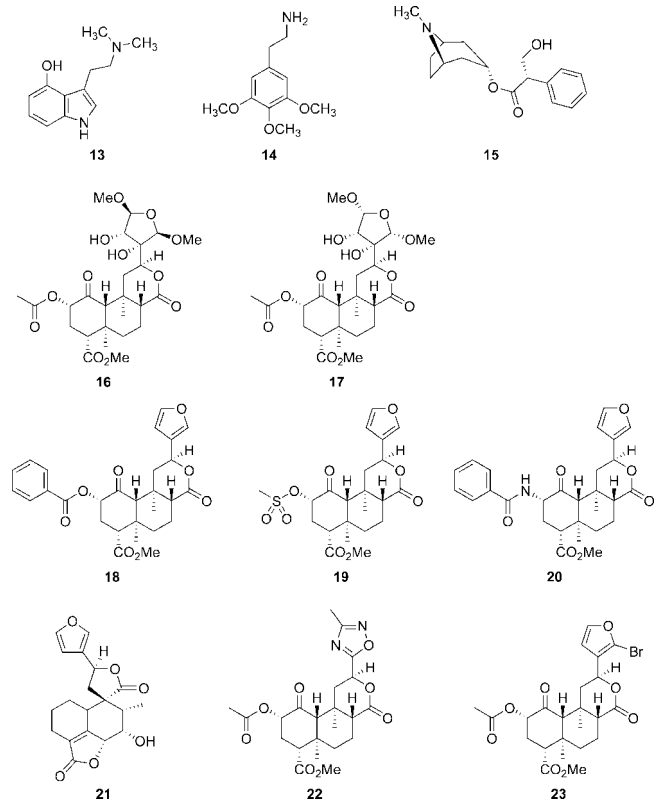
Chemical studies of *S. divinorum* have yielded the structurally related neoclerodanes salvinorins B−I,[89,91−94] divinatorins A−F,[92,93,95] and salvidivins A−D.[93] An extract of *S. divinorum* was found to have no effect on intestinal motility under physiological conditions but did inhibit motility in mice with inflammation.[96,97] However, an extract of *S. divinorum* was shown to inhibit enteric cholinergic transmission in guinea pig ileum.[98] Recently, the biosynthetic route of **12** was found to be consistent with the deoxyxylulose phosphate pathway using several different labeling experiments.[99] Furthermore, the total synthesis of **12** by two different synthetic routes has been described.[100,101]

Additional pharmacological studies have provided further evidence that **12** acts as a KOP agonist. Diterpene **12** produces a discriminative effect similar to other KOP agonists in both nonhuman primates[102] and rats[103] and has been shown to produce antinociception in mice that is blocked by a KOP antagonist.[104,105] It also produces an aversive response in the conditioned place preference assay,[106] decreases dopamine levels in the caudate putamen of mice,[106] dose dependently increases immobility in the forced swim test,[107] disrupts climbing behavior on an inverted screen task,[108] blocks the locomotor-stimulant effects of cocaine,[109] and does not exert DOM-like effects in nonhuman primates.[110] Furthermore, **12** decreases mesostriatal neurotransmission by affecting DA release and not DA uptake.[111] In contrast to other KOP agonists, **12** does not cause diuresis in rats, likely due to its short duration of action.[112] However, differences were seen in the interaction of **12** and other KOP agonists with respect to the behavioral responses to cocaine.[111]

Additional work in nonhuman primates found that **12** acts as a high-efficacy KOP agonist in a translationally viable neuroendocrine biomarker assay and produces facial relaxation and ptosis that can be detected within 1−2 min of injection.[113,114] Previous studies indicated that the half-life of **12** in nonhuman primates was found to be approximately 30 min.[115,116] Recent pharmacokinetic studies in baboons using carbon-11-labeled **12** were highly consistent with this observation and suggest that less than 10 μg in the human brain accounts for the psychoactive effects of **12**.[117]

As a neoclerodane diterpenoid, **12** is a very interesting psychoactive natural product. First, it is structurally unique as an opiomimetic. Until the discovery of **12**, it had been assumed that an alkaloid or a compound bearing a basic nitrogen was required in order to interact with opioid receptors.[118] Given the lack of basic nitrogen in **12**, it would appear this interaction is not an absolute requirement. Second, it is structurally unique among known hallucinogens. Diterpene **12** bears little resemblance to other hallucinogenic natural products such as Δ^9-THC (**2**), psilocin (**13**), mescaline (**14**), and L-hyoscyamine (**15**), the presumed active component responsible for the hallucinogenic effects of jimson weed (*Datura stramonium* L.; Solanaceae). Moreover, **12** is the first report of an exogenous natural product interacting with KOP receptors to produce hallucinations. Given its unique structure and interesting pharmacological properties, we initiated a program to develop **12** as a potential stimulant abuse medication.

As a first step in this program, we sought to better understand the chemistry and pharmacology associated with *S. divinorum*. One early investigation was to isolate and identify other psychoactive compounds that might be present in the same species. This work led to the isolation of two new neoclerodane diterpenes, salvinicins A (**16**) and B (**17**), from the dried leaves of *S. divinorum*.[119] The structures of **16** and **17** were elucidated by spectroscopic techniques, including ^{1}H and ^{13}C, NOESY, HMQC, and HMBC NMR. The absolute stereochemistry of these compounds was assigned on the basis of single-crystal X-ray crystallographic analysis of **16** and a 3,4-dichlorobenzoate derivative of salvinorin B, the desacetyl derivative of **12**. Neoclerodanes **16** and **17** possess a rare 3,4-dihydroxy-2,5-dimethoxytetrahydrofuran ring. Pharmacological evaluation of these compounds at opioid receptors was then conducted and indicated that **16** and **17** showed activity at κ and μ opioid receptors, respectively. Further work indicated that **16** exhibited partial KOP agonist activity with an EC_{50} value of 4.1 ± 0.6 κM [E_{max} = 80% relative to (−)-U50,488H, a standard KOP agonist]. Interestingly, **17** exhibited antagonist activity at κ receptors with a K_i of >1.9 κM. This was the first report of a neoclerodane with opioid antagonist activity. Given the unique pharmacological properties of **16** and **17** and the small amounts isolated, our laboratory developed a practical method for the synthesis of **16** and **17** from **12** isolated from *S. divinorum*.[120] This methodology



proved useful in the further elucidation of the structure−activity relationships of **16** and **17** at opioid receptors.[121,122]

In addition to our isolation efforts, we and others initiated studies to better understand the high affinity and activity of **12** as an opioid receptor ligand.[29] Our initial structural modification transformations of **12** resulted in the synthesis of several neoclerodane diterpenes with opioid receptor affinity and activity.[123] In our structure−activity relationship studies, we identified herkinorin (**18**) as a MOP agonist and mesylate **19** as a likely more metabolically stable KOP agonist roughly equipotent to **12**. The discovery of **18** represented the first report of a non-nitrogenous MOP agonist and identified neoclerodanes as a novel structural class of MOP receptor ligands. To further explore the structure−affinity relationships of this interesting class of compounds, we synthesized additional neoclerodanes from **12**.[124,125] Our efforts showed that chain lengthening in the C-2 position generally decreases affinity for KOPs and increases affinity to MOPs and C-2 esters appear to bind in a different manner than do C-2 sulfonates at both KOPs and MOPs. Furthermore, we found benzamide **20** to be the most potent neoclerodane MOP agonist described to date.[125]

GPCR desensitization and trafficking are important regulators of opioid receptor signaling that can modulate drug responsiveness in vivo. For example, morphine binding produces a MOP receptor with low affinity for β-arrestin proteins and limited receptor internalization, whereas DAMGO, a peptide selective for MOP receptors, promotes robust trafficking of β-arrestins and receptor internalization. Given its unique structure relative to other MOP agonists, we evaluated the effects of **18** on MOP receptor trafficking and internalization.[126] We found that **18**, unlike other MOP receptor ligands, does not promote the recruitment of β-arrestin-2 to MOP receptors and does not lead to receptor internalization under any of the conditions tested. Studies in mice have shown that β-arrestin-2 plays an important role in the development of morphine-induced tolerance, constipation, and respiratory depression.[127−130] Considering the important role MOP receptor regulation plays in determining physiological responsiveness to opioid narcotics, other MOP preferring natural products may offer a unique template for

the development of functionally selective MOP receptor ligands with the ability to produce analgesia while limiting adverse side effects.[125]

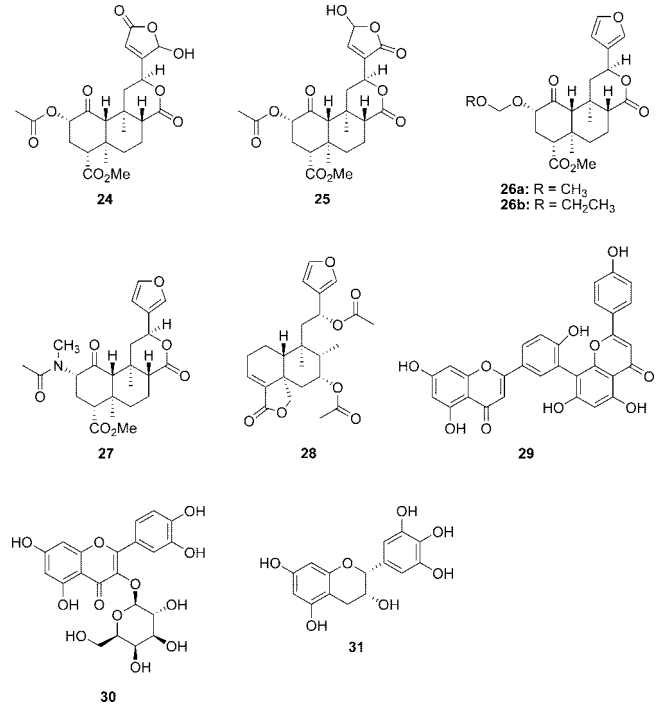
Other studies in our laboratory have focused on gaining a better understanding of the role of the furan ring present in **12**. These studies were initiated based on our discovery of **16** and **17**, as well as the desirability of reducing the potential for hepatotoxicity by **12**. Previous studies have shown that teucrin A (**21**), a neoclerodane present in germander (*Teucrium chamaedrys* L.; Lamiaceae), has the ability to form a reactive metabolite resulting from bioactivation of the furan ring by cytochrome P450 enzymes (CYP450s).[131−134] By analogy, as a furan-containing neoclerodane, **12** has the potential to also form reactive metabolites resulting from bioactivation by CYP450s. Our approach to overcoming this pitfall was to explore structural modifications of the furan ring. Generally, we found that modification of the furan ring of **12** resulted in neoclerodanes with reduced efficacy at opioid receptors.[121,122] Interestingly, we identified oxadiazole **22** as the first neoclerodane with KOP-antagonist activity, and bromo analogue **23** was identified as a potent KOP agonist. In addition, we reported the synthesis of salvidivins A (**24**) and B (**25**), two natural products formed in commercially available *S. divinorum* leaves from **12**.[93] Collectively, these results indicate that additional structural modifications of **12** may lead to analogues with higher potency and utility as drug abuse medications.

Recently, the methoxymethyl ether of salvinorin B (**26a**) was identified as a more potent and longer lasting in vivo analogue of **12**.[135,136] Similarly, the *N*-methylacetamide analogue of **12** (**27**) was found to have similar in vitro potency and selectivity compared to **12** but also has improved stability and longer lasting actions in vivo.[137] Additional structure−activity relationship studies have identified the ethoxymethyl ether of salvinorin B (**26b**) as the most potent neoclerodane KOP agonist described to date.[138]

Other Natural Products Leads

As an opiomimetic, **12** has a unique molecular scaffold for development and opens many interesting questions regarding molecular recognition. However, the neoclerodane nucleus of **12** is readily found in nature, and many similar compounds have been identified.[139,140] Recently, we have begun to explore other naturally occurring and semisynthetic neoclerodanes for their ability to interact with opioid receptors. Several structural congeners of **12** isolated from *Salvia splendens* Ker Gawl. (Lamiaceae), together with a series of semisynthetic derivatives, were tested for affinity at human opioid receptors.[141] None of these compounds showed high affinity binding to these receptors, but **28** showed modest affinity for KOP receptors. However, this indicates that other naturally occurring neoclerodanes may indeed possess opioid affinity and activity. Furthermore, this suggests the likelihood of identifying other non-nitrogenous opioids from natural sources. To further explore this possibility, we have begun to study additional psychoactive plants in search of structurally unique opioids.

Extracts of St. John's Wort (*Hypericum perforatum* L.; Clusiaceae) have been shown to attenuate alcohol self-administration in different strains of alcohol-preferring rats.[142,143] The endogenous opioid system plays a key role in the rewarding properties of alcohol, and opioid receptor antagonists are used clinically to treat alcohol abuse.[144,145] Interestingly, *H. perforatum* extracts have also been shown to act synergistically with opioid receptor antagonists to attenuate ethanol intake in rats and inhibit the binding of [^{3}H]naloxone and [^{3}H]deltorphin to opioid receptors.[146−148] Furthermore, amentoflavone (**29**), a biflavone present in extracts of *H. perforatum*, was found to bind to opioid receptors.[149] Efforts in our laboratory found that **29** is a KOP receptor antagonist more than 10-fold selective over the DOP receptor.[150] This was the first report of a flavonoid with antagonist activity and opens a new structural scaffold for the development of opioid antagonists. Additional structure−activity relationship studies found that hyperoside (**30**), another flavonoid present in extracts of *H. perforatum*, and (−)-epigallocatechin (**31**), a catechin found in green tea, also have KOP antagonist activity in vitro.[150] Collectively, these findings provide evidence that additional investigation of natural sources will identify new leads for opioid receptors and potentially other CNS targets.



Summary and Perspective

As well described elsewhere, natural products have played an important role in the development of medications for a number of diseases.[151−153] However, the search for natural products with utility in the neurosciences is an area much less developed than the search for anticancer agents.[154] Investigation of psychoactive natural products, such as **12**, provides an opportunity to identify novel scaffolds and selective agents to better characterize known receptor types and study their role in various disorders. As highlighted above, these investigations have identified novel agents to potentially treat drug abuse. However, they also have the potential to identify novel agents to other complex CNS disorders such as anxiety, chronic pain, depression, and schizophrenia.

The application of natural products chemistry to neuroscience drug discovery is not without problems or limitations. In contrast to the search for anticancer drugs, there are few, if any, simple, relevant prescreen assays such as the brine shrimp test.[155] Historically, radioligand binding assays have been used to drive bioguided fractionation, but this method is not optimal, as it generates large amounts of radioactive waste. Recent developments in cell-based assays may provide more user-friendly approaches.

Many of the most interesting targets in the neurosciences, such as GPCRs, ion channels, and transporters, trigger Ca^{2+} mobilization upon activation.[156] Currently used cell-based assays are focused on the detection of intracellular Ca^{2+} and use various fluorescence probes to measure levels of increased concentrations of calcium called FLIPR.[157,158] Another available method uses aequorin-derived luminescence to monitor intracellular Ca^{2+} levels.[159] Aequorin is a photoprotein isolated from the jelly fish *Aequorea victoria* that has been used as a calcium indicator for more than three decades.[160,161] The active protein is formed in the presence of molecular oxygen from apoaequorin and its cofactor, coelenterazine.[162] Upon calcium binding, aequorin oxidizes coelenterazine into coelenteramide with production of CO_2 and emission of light, which is a reliable tool for measurement of intracellular Ca^{2+}

flux.[163] This method is amendable for HTS assays where many samples can be tested. Furthermore, a Tango assay to monitor protein interactions in a cell with a high degree of selectivity and sensitivity has been recently developed.[164] In this assay, a transcription factor is tethered to a membrane-bound receptor with a linker that contains a cleavage site for a specific protease. Activation of the receptor of interest recruits a signaling protein fused to the protease that then cleaves and releases the transcription factor to activate reporter genes in the nucleus, which can then be observed. Unfortunately, few reports have used these cell-based assays to identify novel CNS-active natural products. This is likely due to their expense and the fact that these approaches are not widely employed.

Over the past decade, we have witnessed unparalleled advances in our understanding of the basic biological processes that contribute to many human disorders, although a detailed understanding of the etiology of complex CNS disorders remains elusive.[165] However, this lack of detailed understanding offers a unique opportunity for natural products chemists working in collaboration with pharmacologists. Expanding the exploration of natural sources with a focus on the neurosciences is likely to identify novel active agents that may serve as drug leads and new chemical tools to better understand the etiology of complex CNS disorders.

Acknowledgment. The author thanks all former and current group members who have contributed to this research program and Drs. R. B. Rothman, E. R. Butelman, L. M. Bohn, H. A. Navarro, and K. G. Holden for fruitful collaborations. Financial support from the National Institute on Drug Abuse (R01 DA18151) and the Universities of Iowa and Kansas is gratefully acknowledged. The author also thanks Dr. Christopher McCurdy for providing images of *S. divinorum*.

References and Notes

(1) Spinella, M. *The Psychopharmacology of Herbal Medicine: Plant Drugs that Alter Mind, Brain, and Behavior*; MIT Press: Cambridge, MA, 2001.
(2) McKenna, D. J. *Behav. Brain Res.* **1996**, *73*, 109–116.
(3) Calixto, J. B.; Scheidt, C.; Otuki, M.; Santos, A. R. *Expert Opin. Emerging Drugs* **2001**, *6*, 261–279.
(4) Aldrich, J. V.; Vigil-Cruz, S. C. In *Burger's Medicinal Chemistry and Drug Discovery*, 6th ed.; Abraham, D. A., Ed.; John Wiley: New York, 2003; Vol. 6, pp 329−441.
(5) Waldhoer, M.; Bartlett, S. E.; Whistler, J. L. *Annu. Rev. Biochem.* **2004**, *73*, 953–990.
(6) Di Marzo, V. *Rev. Physiol. Biochem. Pharmacol.* **2008**, *160*, 1–24.
(7) Seamon, K. B.; Padgett, W.; Daly, J. W. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 3363–3367.
(8) Insel, P. A.; Ostrom, R. S. *Cell Mol. Neurobiol.* **2003**, *23*, 305–314.
(9) Slattery, D. A.; Hudson, A. L.; Nutt, D. J. *Fundam. Clin. Pharmacol.* **2004**, *18*, 1–21.
(10) McCoy, C. B.; Inciardi, J. A. *Sex, Drugs, and the Continuing Spread of AIDS*; Roxbury: Los Angeles, 1995.
(11) Mitscher, L. A.; Baker, W. *Med. Res. Rev.* **1998**, *18*, 363–374.
(12) National Drug Intelligence Center. *National Drug Threat Assessment 2004*; U.S. Department of Justice: Johnstown, PA; Report 2004-Q0317-002, 2004.
(13) Rawson, R. A.; Anglin, M. D.; Ling, W. *J. Addict. Dis.* **2002**, *21*, 5–19.
(14) Anglin, M. D.; Burke, C.; Perrochet, B.; Stamper, E.; Dawud-Noursi, S. *J. Psychoact. Drugs* **2000**, *32*, 137–141.
(15) Al-Motarreb, A.; Baker, K.; Broadley, K. J. *Phytother. Res.* **2002**, *16*, 403–413.
(16) Leshner, A. I. *Science* **1997**, *278*, 45–47.
(17) Carroll, F. I.; Howell, L. L.; Kuhar, M. J. *J. Med. Chem.* **1999**, *42*, 2721–2736.
(18) Kulkarni, S. S.; Newman, A. H.; Houlihan, W. J. *J. Med. Chem.* **2002**, *45*, 4119–4127.
(19) Kreek, M. J.; LaForge, K. S.; Butelman, E. *Nat. Rev. Drug Discovery* **2002**, *1*, 710–726.
(20) Prisinzano, T.; Rice, K. C.; Baumann, M. H.; Rothman, R. B. *Curr. Med. Chem. CNS Agents* **2004**, *4*, 47–59.
(21) Rothman, R. B.; Baumann, M. H.; Prisinzano, T. E.; Newman, A. H. *Biochem. Pharmacol.* **2008**, *75*, 2–16.
(22) Dackis, C. A.; Gold, M. S. *Neurosci. Biobehav. Rev.* **1985**, *9*, 469–477.
(23) Gawin, F. H. *Science* **1991**, *251*, 1580–1586.
(24) Grabowski, J.; Rhoades, H.; Schmitz, J.; Stotts, A.; Daruzska, L. A.; Creson, D.; Moeller, F. G. *J. Clin. Psychopharmacol.* **2001**, *21*, 522–526.
(25) Hart, C. L.; Haney, M.; Vosburg, S. K.; Rubin, E.; Foltin, R. W. *Neuropsychopharmacology* **2007**, *33*, 761–768.
(26) Vocci, F. J.; Acri, J.; Elkashef, A. *Am. J. Psychiatry* **2005**, *162*, 1432–1440.
(27) Preti, A. *Addict. Biol.* **2007**, *12*, 133–151.
(28) Prisinzano, T. E.; Tidgewell, K.; Harding, W. W *AAPS J.* **2005**, *7*, E592–E599.
(29) Prisinzano, T. E.; Rothman, R. B. *Chem. Rev.* **2008**, *108*, 1732–1743.
(30) Rothman, R. B. *Analgesia* **1994**, *1*, 27–49.
(31) Zaki, P. A.; Bilsky, E. J.; Vanderah, T. W.; Lai, J.; Evans, C. J.; Porreca, F. *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 379–401.
(32) Pasternak, G. W. *Neuropharmacology* **2004**, *47 Suppl 1*, 312–323.
(33) Kieffer, B. L.; Gaveriaux-Ruff, C. *Prog. Neurobiol.* **2002**, *66*, 285–306.
(34) Mello, N. K.; Negus, S. S. *Ann. N.Y. Acad. Sci.* **2000**, *909*, 104–132.
(35) Shippenberg, T. S.; Chefer, V. I.; Zapata, A.; Heidbreder, C. A. *Ann. N.Y. Acad. Sci.* **2001**, *937*, 50–73.
(36) Shippenberg, T. S.; Zapata, A.; Chefer, V. I. *Pharmacol. Ther.* **2007**, *116*, 306–321.
(37) Werling, L.; Frattali, A.; Portoghese, P.; Takemori, A.; Cox, B. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 282–286.
(38) Di Chiara, G.; Imperato, A. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 1067–1080.
(39) Di Chiara, G.; Imperato, A. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 5274–5278.
(40) Spanagel, R.; Herz, A.; Shippenberg, T. S. *J. Neurochem.* **1990**, *55*, 1734–1740.
(41) Spanagel, R.; Herz, A.; Shippenberg, T. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 2046–2050.
(42) Jackisch, R.; Hotz, H.; Hertting, G. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1993**, *348*, 234–241.
(43) Suzuki, T.; Kishimoto, Y.; Ozaki, S.; Narita, M. *Eur. J. Pain* **2001**, *5*, 63–65.
(44) Margolis, E. B.; Hjelmstad, G. O.; Bonci, A.; Fields, H. L. *J. Neurosci.* **2003**, *23*, 9981–9986.
(45) Glick, S. D.; Maisonneuve, I. M.; Raucci, J.; Archer, S. *Brain Res.* **1995**, *681*, 147–152.
(46) Crawford, C. A.; McDougall, S. A.; Bolanos, C. A.; Hall, S.; Berger, S. P. *Psychopharmacology (Berlin, Ger.)* **1995**, *120*, 392–399.
(47) Mello, N. K.; Negus, S. S. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 812–824.
(48) Negus, S. S.; Mello, N. K.; Portoghese, P. S.; Lin, C.-E. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 44–55.
(49) Schenk, S.; Partridge, B.; Shippenberg, T. S. *Psychopharmacology (Berlin, Ger.)* **1999**, *144*, 339–346.
(50) Schenk, S.; Partridge, B.; Shippenberg, T. S. *Psychopharmacology (Berlin, Ger.)* **2000**, *151*, 85–90.
(51) Hasebe, K.; Kawai, K.; Suzuki, T.; Kawamura, K.; Tanaka, T.; Narita, M.; Nagase, H.; Suzuki, T. *Ann. N.Y. Acad. Sci.* **2004**, *1025*, 404–413.
(52) Redila, V.; Chavkin, C. *Psychopharmacology (Berlin, Ger.)* **2008**, *200*, 59–70.
(53) Shaham, Y.; Shalev, U.; Lu, L.; de Wit, H.; Stewart, J. *Psychopharmacology (Berlin, Ger.)* **2003**, *168*, 3–20.
(54) Bossert, J. M.; Ghitza, U. E.; Lu, L.; Epstein, D. H.; Shaham, Y. *Eur. J. Pharmacol.* **2005**, *526*, 36–50.
(55) Epstein, D.; Preston, K.; Stewart, J.; Shaham, Y. *Psychopharmacology (Berlin, Ger.)* **2006**, *189*, 1–16.
(56) Beardsley, P., M.; Howard, J. L.; Shelton, K. L.; Carroll, F. I. *Psychopharmacology* **2005**, *183*, 118–126.
(57) Carey, A. N.; Borozny, K.; Aldrich, J. V.; McLaughlin, J. P. *Eur. J. Pharmacol.* **2007**, *569*, 84–89.
(58) Knoll, A. T.; Meloni, E. G.; Thomas, J. B.; Carroll, F. I.; Carlezon, W. A., Jr. *J. Pharmacol. Exp. Ther.* **2007**, *323*, 838–845.
(59) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. *Life Sci.* **1987**, *40*, 1287–1292.
(60) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. *J. Med. Chem.* **1987**, *30*, 238–239.
(61) Ko, M. C. H.; Johnson, M. D.; Butelman, E. R.; Willmont, K. J.; Mosberg, H. I.; Woods, J. H. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 1113–1120.
(62) Portoghese, P. S.; Nagase, H.; Lipkowski, A. W.; Larson, D. L.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 836–841.
(63) Portoghese, P. S.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 1344–1347.
(64) Portoghese, P. S.; Garzon-Aburbeh, A.; Nagase, H.; Lin, C. E.; Takemori, A. E. *J. Med. Chem.* **1991**, *34*, 1292–1296.

(65) Olmsted, S. L.; Takemori, A. E.; Portoghese, P. S. *J. Med. Chem.* **1993**, *36*, 179–180.
(66) Portoghese, P. S.; Lin, C. E.; Farouz-Grant, F.; Takemori, A. E. *J. Med. Chem.* **1994**, *37*, 1495–500.
(67) Jones, R. M.; Portoghese, P. S. *Eur. J. Pharmacol.* **2000**, *396*, 49–52.
(68) Stevens, W. C., Jr.; Jones, R. M.; Subramanian, G.; Metzger, T. G.; Ferguson, D. M.; Portoghese, P. S. *J. Med. Chem.* **2000**, *43*, 2759–2769.
(69) Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Rothman, R. B.; Mascarella, S. W.; Xu, H.; Partilla, J. S.; Dersch, C. M.; McCullough, K. B.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *J. Med. Chem.* **1998**, *41*, 5188–5197.
(70) Thomas, J. B.; Atkinson, R. N.; Rothman, R. B.; Fix, S. E.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *J. Med. Chem.* **2001**, *44*, 2687–2690.
(71) Thomas, J. B.; Atkinson, R. N.; Namdev, N.; Rothman, R. B.; Gigstad, K. M.; Fix, S. E.; Mascarella, S. W.; Burgess, J. P.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *J. Med. Chem.* **2002**, *45*, 3524–3530.
(72) Thomas, J. B.; Atkinson, R. N.; Vinson, N. A.; Catanzaro, J. L.; Perretta, C. L.; Fix, S. E.; Mascarella, S. W.; Rothman, R. B.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *J. Med. Chem.* **2003**, *46*, 3127–3137.
(73) Cai, T. B.; Zou, Z.; Thomas, J. B.; Brieaddy, L.; Navarro, H. A.; Carroll, F. I. *J. Med. Chem.* **2008**, *51*, 1849–1860.
(74) Carroll, I.; Thomas, J. B.; Dykstra, L. A.; Granger, A. L.; Allen, R. M.; Howard, J. L.; Pollard, G. T.; Aceto, M. D.; Harris, L. S. *Eur. J. Pharmacol.* **2004**, *501*, 111–119.
(75) Carroll, F. I.; Harris, L. S.; Aceto, M. D. *Eur. J. Pharmacol.* **2005**, *524*, 89–94.
(76) Pfeiffer, A.; Brantl, V.; Herz, A.; Emrich, H. M. *Science* **1986**, *233*, 774–776.
(77) Negus, S. S. *Psychopharmacology (Berlin, Ger.)* **2004**, *176*, 204–213.
(78) McLaughlin, J. P.; Land, B. B.; Li, S.; Pintar, J. E.; Chavkin, C. *Neuropsychopharmacology (Berlin, Ger.)* **2005**, *31*, 787–794.
(79) Metcalf, M. D.; Coop, A. *AAPS J.* **2005**, *7*, E704–E722.
(80) Bruchas, M. R.; Yang, T.; Schreiber, S.; Defino, M.; Kwan, S. C.; Li, S.; Chavkin, C. *J. Biol. Chem.* **2007**, *282*, 29803–29811.
(81) Kintzios, S. E., Ed. *Sage: The Genus Salvia*; Harwood Academic Publishers; Amsterdam, 2000.
(82) Epling, C.; Jativa-M, C. D. *Bot. Mus. Leaflets, Harvard Univ.* **1962**, *20*, 75–76.
(83) Tyler, V. E. *Lloydia* **1966**, *29*, 275–292.
(84) Valdes, L. J., III. The Pharmacognosy of *Salvia divinorum* (Epling and Jativa-M): An Investigation of Ska Maria Pastora. Ph.D. Thesis, University of Michigan, Ann Arbor, MI, 1983.
(85) Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2505–2508.
(86) Valdes, L. J., III; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716–4720.
(87) Siebert, D. J. *J. Ethnopharmacol.* **1994**, *43*, 53–56.
(88) Valdes, L. J., III. *J. Psychoact. Drugs* **1994**, *26*, 277–283.
(89) Valdes, L. J., III; Chang, H. M.; Visger, D. C.; Koreeda, M. *Org. Lett.* **2001**, *3*, 3935–3937.
(90) Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11934–11939.
(91) Munro, T. A.; Rizzacasa, M. A. *J. Nat. Prod.* **2003**, *66*, 703–705.
(92) Lee, D. Y.; Ma, Z.; Liu-Chen, L. Y.; Wang, Y.; Chen, Y.; Carlezon, W. A., Jr.; Cohen, B. *Bioorg. Med. Chem.* **2005**, *13*, 5635–5639.
(93) Shirota, O.; Nagamatsu, K.; Sekita, S. *J. Nat. Prod.* **2006**, *69*, 1782–1786.
(94) Ma, Z.; Lee, D. Y. W. *Tetrahedron Lett.* **2007**, *48*, 5461–5464.
(95) Bigham, A. K.; Munro, T. A.; Rizzacasa, M. A.; Robins-Browne, R. M. *J. Nat. Prod.* **2003**, *66*, 1242–1244.
(96) Capasso, R.; Borrelli, F.; Zjawiony, J.; Kutrzeba, L.; Aviello, G.; Sarnelli, G.; Capasso, F.; Izzo, A. A. *Neurogastroenterol. Motil.* **2008**, *20*, 142–148.
(97) Capasso, R.; Borrelli, F.; Cascio, M. G.; Aviello, G.; Huben, K.; Zjawiony, J. K.; Marini, P.; Romano, B.; Di Marzo, V.; Capasso, F.; Izzo, A. A *Br. J. Pharmacol.* **2008**, *155*, 681–689.
(98) Capasso, R.; Borrelli, F.; Capasso, F.; Siebert, D. J.; Stewart, D. J.; Zjawiony, J. K.; Izzo, A. A. *Neurogastroenterol. Motil.* **2006**, *18*, 69–75.
(99) Kutrzeba, L.; Dayan, F. E.; Howell, J. L.; Feng, J.; Giner, J.-L.; Zjawiony, J. K. *Phytochemistry* **2007**, *68*, 1872–1881.
(100) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968–8969.
(101) Nozawa, M.; Suka, Y.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2008**, *10*, 1365–1368.
(102) Butelman, E. R.; Harris, T. J.; Kreek, M. J. *Psychopharmacology (Berlin, Ger.)* **2004**, *172*, 220–224.
(103) Willmore-Fordham, C. B.; Krall, D. M.; McCurdy, C. R.; Kinder, D. H. *Neuropharmacology* **2007**, *53*, 481–486.
(104) John, T. F.; French, L. G.; Erlichman, J. S. *Eur. J. Pharmacol.* **2006**, *545*, 129–133.
(105) McCurdy, C. R.; Sufka, K. J.; Smith, G. H.; Warnick, J. E.; Nieto, M. J. *Pharmacol., Biochem. Behav.* **2006**, *83*, 109–113.
(106) Zhang, Y.; Butelman, E. R.; Schlussman, S. D.; Ho, A.; Kreek, M. J. *Psychopharmacology (Berlin, Ger.)* **2005**, *179*, 551–558.
(107) Carlezon, W. A., Jr.; Beguin, C.; Dinieri, J. A.; Baumann, M. H.; Richards, M. R.; Todtenkopf, M. S.; Rothman, R. B.; Ma, Z.; Lee, D. Y.; Cohen, B. M. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 440–447.
(108) Fantegrossi, W. E.; Kugle, K. M.; Valdes, L. J., 3rd; Koreeda, M.; Woods, J. H. *Behav. Pharmacol.* **2005**, *16*, 627–633.
(109) Chartoff, E. H.; Potter, D.; Damez-Werno, D.; Cohen, B. M.; Carlezon, W. A., Jr. *Neuropsychopharmacology* **2008**, *33*, 2676–2687.
(110) Li, J.-X.; Rice, K. C.; France, C. P. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 827–833.
(111) Gehrke, B.; Chefer, V.; Shippenberg, T. *Psychopharmacology* **2008**, *197*, 509–517.
(112) Inan, S.; Lee, D. Y.; Liu-Chen, L. Y.; Cowan, A. *Naunyn-Schmiedebergs Arch. Pharmacol.* **2008**, doi.10.1007/s00210-008-0358-8.
(113) Butelman, E. R.; Mandau, M.; Tidgewell, K.; Prisinzano, T. E.; Yuferov, V.; Kreek, M. J. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 300–306.
(114) Butelman, E. R.; Prisinzano, T. E.; Deng, H.; Rus, S.; Kreek, M. J. *J. Pharmacol. Exp. Ther.* **2008**, jpet.108.145342.
(115) Schmidt, M. D.; Schmidt, M. S.; Butelman, E. R.; Harding, W. W.; Tidgewell, K.; Murry, D. J.; Kreek, M. J.; Prisinzano, T. E. *Synapse* **2005**, *58*, 208–210.
(116) Schmidt, M. S.; Prisinzano, T. E.; Tidgewell, K.; Harding, W. W.; Butelman, E. R.; Kreek, M. J.; Murry, D. J. *J. Chromatogr. B* **2005**, *818*, 221–225.
(117) Hooker, J. M.; Xu, Y.; Schiffer, W.; Shea, C.; Carter, P.; Fowler, J. S. *NeuroImage* **2008**, *41*, 1044–1050.
(118) Rees, D. C.; Hunter, J. C. In *Comprehensive Medicinal Chemistry*; Emmet, J. C., Ed.; Pergamon: New York, 1990; pp 805−846.
(119) Harding, W. W.; Tidgewell, K.; Schmidt, M.; Shah, K.; Dersch, C. M.; Snyder, J.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. *Org. Lett.* **2005**, *7*, 3017–3020.
(120) Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Gilmour, B.; Navarro, H.; Rothman, R. B.; Prisinzano, T. E. *J. Nat. Prod.* **2006**, *69*, 107–112.
(121) Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Dersch, C. M.; Rothman, R. B.; Prisinzano, T. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3170–3174.
(122) Simpson, D. S.; Katavic, P. L.; Lozama, A.; Harding, W. W.; Parrish, D.; Deschamps, J. R.; Dersch, C. M.; Partilla, J. S.; Rothman, R. B.; Navarro, H.; Prisinzano, T. E. *J. Med. Chem.* **2007**, *50*, 3596–3603.
(123) Harding, W. W.; Tidgewell, K.; Byrd, N.; Cobb, H.; Dersch, C. M.; Butelman, E. R.; Rothman, R. B.; Prisinzano, T. E. *J. Med. Chem.* **2005**, *48*, 4765–4771.
(124) Tidgewell, K.; Harding, W. W.; Lozama, A.; Cobb, H.; Shah, K.; Kannan, P.; Dersch, C. M.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. *J. Nat. Prod.* **2006**, *69*, 914–918.
(125) Tidgewell, K.; Groer, C. E.; Harding, W. W.; Lozama, A.; Schmidt, M.; Marquam, A.; Hiemstra, J.; Partilla, J. S.; Dersch, C. M.; Rothman, R. B.; Bohn, L. M.; Prisinzano, T. E. *J. Med. Chem.* **2008**, *51*, 2421–2431.
(126) Groer, C. E.; Tidgewell, K.; Moyer, R. A.; Harding, W. W.; Rothman, R. B.; Prisinzano, T. E.; Bohn, L. M. *Mol. Pharmacol.* **2007**, *71*, 549–557.
(127) Bohn, L. M.; Lefkowitz, R. J.; Gainetdinov, R. R.; Peppel, K.; Caron, M. G.; Lin, F. T. *Science* **1999**, *286*, 2495–2498.
(128) Bohn, L. M.; Gainetdinov, R. R.; Lin, F. T.; Lefkowitz, R. J.; Caron, M. G. *Nature* **2000**, *408*, 720–723.
(129) Bohn, L. M.; Lefkowitz, R. J.; Caron, M. G. *J. Neurosci.* **2002**, *22*, 10494–10500.
(130) Raehal, K. M.; Walker, J. K. L.; Bohn, L. M. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1195–1201.
(131) Kouzi, S. A.; McMurtry, R. J.; Nelson, S. D. *Chem. Res. Toxicol.* **1994**, *7*, 850–856.
(132) Dalvie, D. K.; Kalgutkar, A. S.; Khojasteh-Bakht, S. C.; Obach, R. S.; O'Donnell, J. P. *Chem. Res. Toxicol.* **2002**, *15*, 269–299.
(133) Druckova, A.; Marnett, L. J. *Chem. Res. Toxicol.* **2006**, *19*, 1330–1340.
(134) Druckova, A.; Mernaugh, R. L.; Ham, A. J.; Marnett, L. J. *Chem. Res. Toxicol.* **2007**, *20*, 1393–1408.

(135) Lee, D. Y. W.; Karnati, V. V. R.; He, M.; Liu-Chen, L.-Y.; Kondaveti, L.; Ma, Z.; Wang, Y.; Chen, Y.; Beguin, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3744–3747.
(136) Wang, Y.; Chen, Y.; Xu, W.; Lee, D. Y. W.; Ma, Z.; Rawls, S. M.; Cowan, A.; Liu-Chen, L.-Y. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 1073–1083.
(137) Beguin, C.; Potter, D. N.; DiNieri, J. A.; Munro, T. A.; Richards, M. R.; Paine, T. A.; Berry, L.; Zhao, Z.; Roth, B. L.; Xu, W.; Liu-Chen, L.-Y.; Carlezon, W. A., Jr.; Cohen, B. M. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 188–195.
(138) Munro, T. A.; Duncan, K. K.; Xu, W.; Wang, Y.; Liu-Chen, L.-Y.; Carlezon, W. A., Jr.; Cohen, B. M.; Beguin, C. *Bioorg. Med. Chem.* **2008**, *16*, 1279–1286.
(139) Hanson, J. R. *Nat. Prod. Rep.* **2006**, *23*, 875–885.
(140) Hanson, J. R. *Nat. Prod. Rep.* **2007**, *24*, 1332–1341.
(141) Fontana, G.; Savona, G.; Rodríguez, B.; Dersch, C. M.; Rothman, R. B.; Prisinzano, T. E. *Tetrahedron* **2008**, *64*, 10041–10048.
(142) Rezvani, A. H.; Overstreet, D. H.; Perfumi, M.; Massi, M. *Pharmacol., Biochem. Behav.* **2003**, *75*, 593–606.
(143) Overstreet, D. H.; Keung, W. M.; Rezvani, A. H.; Massi, M.; Lee, D. Y. *Alcohol.: Clin. Exp. Res.* **2003**, *27*, 177–185.
(144) Herz, A. *Psychopharmacology (Berlin, Ger.)* **1997**, *129*, 99–111.
(145) Oswald, L. M.; Wand, G. S. *Physiol. Behav.* **2004**, *81*, 339–358.
(146) Simmen, U.; Schweitzer, C.; Burkard, W.; Schaffner, W.; Lundstrom, K. *Pharm. Acta Helv.* **1998**, *73*, 53–56.
(147) Simmen, U.; Burkard, W.; Berger, K.; Schaffner, W.; Lundstrom, K. *J. Recept. Signal Transduct. Res.* **1999**, *19*, 59–74.
(148) Perfumi, M.; Santoni, M.; Cippitelli, A.; Ciccocioppo, R.; Froldi, R.; Massi, M. *Alcohol.: Clin. Exp. Res.* **2003**, *27*, 1554–1562.
(149) Butterweck, V.; Nahrstedt, A.; Evans, J.; Hufeisen, S.; Rauser, L.; Savage, J.; Popadak, B.; Ernsberger, P.; Roth, B. L. *Psychopharmacology (Berlin, Ger.)* **2002**, *162*, 193–202.
(150) Katavic, P. L.; Lamb, K.; Navarro, H.; Prisinzano, T. E. *J. Nat. Prod.* **2007**, *70*, 1278–1282.
(151) Butler, M. S. *Nat. Prod. Rep.* **2005**, *22*, 162–195.
(152) Wilkinson, B.; Micklefield, J. *Nat. Chem. Biol.* **2007**, *3*, 379–386.
(153) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477.
(154) Clement, J. A.; Yoder, B. J.; Kingston, D. G. I. *Mini Rev. Org. Chem.* **2004**, *1*, 183–208.
(155) Meyer, B. N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nichols, D. E.; McLaughlin, J. L. *Planta Med.* **1982**, *45*, 31–34.
(156) Rink, T. J. *FEBS Lett.* **1990**, *268*, 381–385.
(157) Bovolenta, S.; Foti, M.; Lohmer, S.; Corazza, S. *J. Biomol. Screen.* **2007**, *12*, 694–704.
(158) Xin, H.; Wang, Y.; Todd, M. J.; Qi, J.; Minor, L. K. *J. Biomol. Screen.* **2007**, *12*, 705–714.
(159) Fichna, J.; Gach, K.; Piestrzeniewicz, M.; Burgeon, E.; Poels, J.; Broeck, J. V.; Janecka, A. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 1150–1154.
(160) Shimomura, O.; Johnson, F. H.; Saiga, Y. *J. Cell Comp. Physiol.* **1962**, *59*, 223–239.
(161) Poul, E. L.; Hisada, S.; Mizuguchi, Y.; Dupriez, V. J.; Burgeon, E.; Detheux, M. *J. Biomol. Screen.* **2002**, *7*, 57–65.
(162) Shimomura, O.; Johnson, F. H. *Nature* **1975**, *256*, 236–238.
(163) Brini, M.; Marsault, R.; Bastianutto, C.; Alvarez, J.; Pozzan, T.; Rizzuto, R. *J. Biol. Chem.* **1995**, *270*, 9896–9903.
(164) Barnea, G.; Strapps, W.; Herrada, G.; Berman, Y.; Ong, J.; Kloss, B.; Axel, R.; Lee, K. J. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 64–69.
(165) Conn, P. J.; Roth, B. L. *Neuropsychopharmacology* **2008**, *33*, 2048–2060.

NP8005748