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Full Papers

Synthesis and Biological Evaluation of Hyperforin Analogues. Part I. Modification of the Enolized Cyclohexanedione Moiety

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Modification of the St. John's wort acylphloroglucinol constituent, hyperforin (**1**), by acylation, alkylation, and oxidation resulted in detrimental effects on the inhibition of the synaptosomal accumulation of serotonin, showing the existence of definite structure−activity relationships in this in vitro test system and highlighting the role of the enolized cyclohexanedione moiety for activity on neurotransmitter reuptake.

Over the past few years, clinical evidence[1] for the antidepressant activity of St. John's wort (*Hypericum perforatum* L., Hypericaceae) extracts has sparked great interest in the chemistry and biochemistry of this plant, generating also coverage in the mainstream press.[2] Despite the lack of a clear correlation between the chemical composition of St. John's wort extracts and in vivo activity which would explain the clinical benefits of the plant, *Hypericum* preparations are licensed in Continental Europe for the treatment of depression and anxiety. They have been suggested for the first-line treatment of mild to severe depression, especially in the primary care setting,[3] and are also available over-the-counter or as food supplements in Great Britain and the United States.[4] St. John's wort extracts have per se an excellent record of safety and side effects, but induction of a broad range of drug-metabolizing enzymes and the transport protein P-glycoprotein has been reported, with severe interactions with many important drugs.[5]

Hypericum produces various types of previously characterized secondary metabolites, including flavonoids, xanthones, naphthodianthrones, and prenylated phloroglucinols.[6] In vitro assays with synaptosomal preparations identified the phloroglucinol hyperforin (**1**) as an active constituent, a view also supported by behavioral investigations in animal models of depression[7] as well as by clinical studies.[8] Hyperforin (**1**) is a nonselective and powerful inhibitor of amine reuptake with IC_{50} values in the lower micromolar range,[9] but the mechanism of its inhibition is different from that of conventional antidepressants. Thus, hyperforin (**1**) does not interact directly with transport proteins, but rather decreases gradient-driven neurotransmitter transport by elevating intracellular sodium.[10] On a less positive note, hyperforin was also identified as a most powerful ligand (K_i = 27 nM) for the pregnane X receptor (PXR), an orphan nuclear receptor that regulates the expression of cytochrome P 450 (CYP) 3A4 monooxygenase.[11] This enzyme is involved in the oxidative metabolism of over half of all drugs, and its induction translates into a wide range of pharmacological interactions. There

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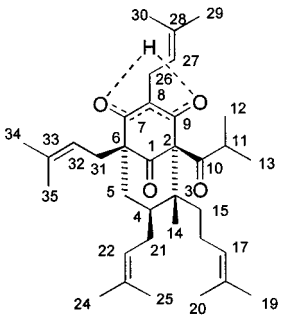
is, therefore, substantial evidence that hyperforin (**1**) plays an important role in both the therapeutic and the side effects of St. John's wort.

The mechanistic details of the neurochemical activity of hyperforin (**1**) are unclear, but this compound might have clinical potential also in other realms of therapy, since binding to PKC-γ,[12] an important end-point for anti-Alzheimer drugs, as well as powerful antibiotic activity against multidrug-resistant bacteria have been reported.[13] The structure of hyperforin (**1**) is unlike that of all known antidepressants, antibiotics, and PKC activators, and this phloroglucinol is therefore an interesting lead for the discovery of new drugs aimed at treating important psychiatric and infective conditions. Hyperforin (**1**) was first isolated in the mid 1970s,[14] but its chemical modification has so far received little attention, while St. John's wort has yielded, at low abundances, only a limited number of analogues.[15] This shortage of natural and semisynthetic derivatives means that structure−activity relationships are virtually unknown for all of the end-points of hyperforin (**1**). On the other hand, the instability of the natural product[16] and its potential for pharmacological interactions provide a rationale for the synthesis of stable analogues of **1** that do not promote drug metabolism. The enolized β-dicarbonyl system is responsible for the instability of hyperforin, since natural analogues lacking this moiety are stable,[15d,e] and its modification is perceived as pivotal to afford derivatives amenable to pharmaceutical development. The present investigation was undertaken to address this issue, focusing on the acylation, alkylation, and oxidation of **1**.



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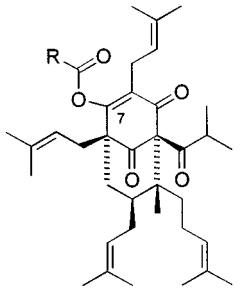
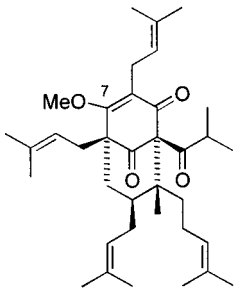


2a R = Me
2b R = 2,4-$(NO_2)_2$Ph
2c R = (2,4,6)-$(OMe)_3$Ph



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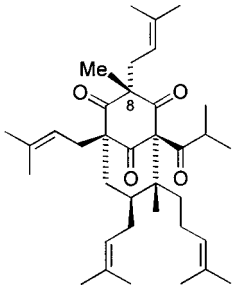

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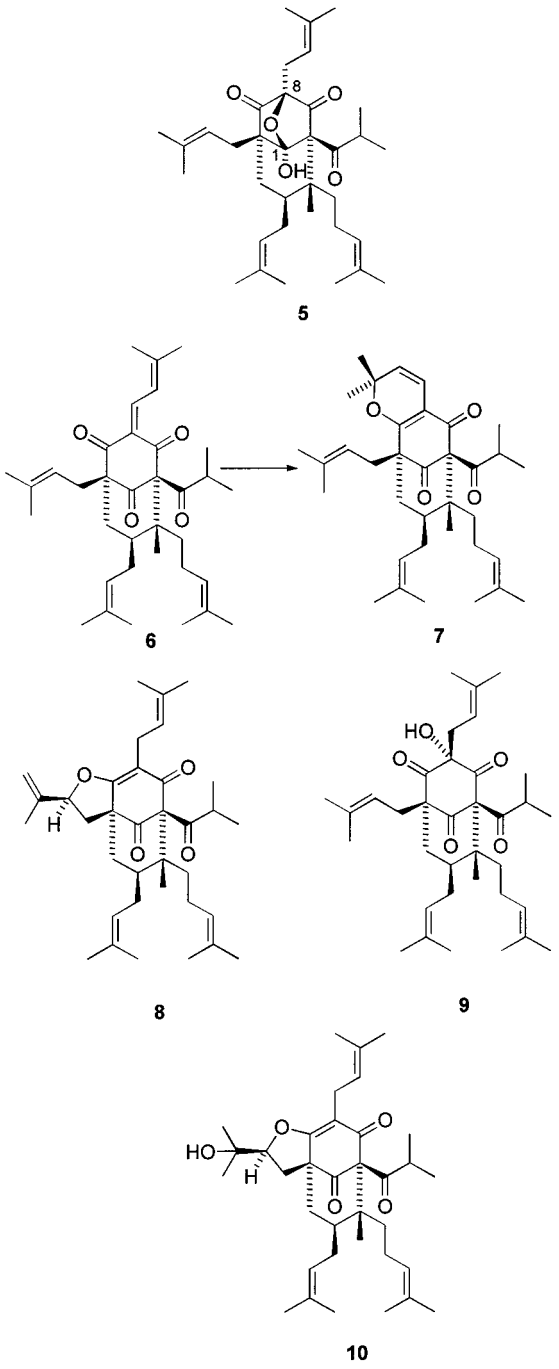
Results and Discussion

Hyperforin (**1**) is a mixture of interconverting tautomers,[15d,e] unstable in most organic solvents[16] but storable as a stable dicyclohexylammonium salt.[12] Certain acylphloroglucinols have been reported to be refractory to chemical modification,[17] but hyperforin (**1**) turned out to be an excellent substrate for acylative, alkylative, and oxidative changes, affording a series of analogues which were investigated in synaptosomal preparations for the inhibition of serotonin- (5-HT) reuptake.

The acylative and alkylative reactions were carried out on the free acid[17] obtained from the salt by acidification and filtration over an ionic exchanger, while the salt could be employed directly for the oxidative reactions. Hyperforin (**1**) could not be acylated under DCC (EDC) coupling conditions, but both trimethoxybenzoyl and dinitrobenzoyl chlorides as well as acetic anhydride gave in good yield the corresponding *O*-acyl derivatives (**2a**−**c**). Hyperforin is a mixture of two tautomers (**1a** and **1b**), and the possibility of reaction at both the C-9 and C-7 oxygen atoms exists. Nevertheless, 7-acyl derivatives were obtained as the exclusive reaction products, possibly because acylation of the other tautomer (7-oxo-Δ^8 form) requires cleavage of an intramolecular hydrogen bonding between the enolic hydroxyl and the carbonyl of the C-2 side chain (C-10) and is therefore kinetically disfavored. The site of esterification could be deduced by HMBC measurements, which resulted in a ^3J correlation between the diastereotopic H-31a,b and H-5a,b protons and the enolic carbon resonance of C-7 at ca. δ 160.

The enol system of hyperforin (**1**) could be easily alkylated, with the regiochemistry of the reaction being governed by the choice of the conditions. *O*-Alkylation could be affected with diazomethane or with methanol under Mitsunobu conditions, affording **3** as the only reaction product. Also in this case, inspection of HMBC correlations showed exclusive formation of the 7-enol tautomer. *C*-Alkylation was instead observed when the anion of hyperforin (generated in DMSO with sodium hydride as a base) was treated with methyl iodide, affording **4**. The formation of *O*- or *C*-alkylated products apparently depends on the hard/soft properties of the alkylating reagent and its steric demand. Thus, the hard electrophile diazomethane reacts at the oxygen terminus of the enolate, while methyl iodide prefers the softer carbon center. The *O*-alkylation observed with Mitsunobu adducts is presumably of steric origin, due to the congestion of the intermediate oxyphosphonium salt, which undergoes nucleophilic attack from the hyperforin enolate.

Hyperforin (**1**) was easily attacked by various oxidants, giving different products according to the reactant and the conditions employed. The oxidation reactions could be generally carried out with the salt of the free acid, but the use of the dicyclohexylammonium salt was mandatory with *m*-CPBA, since the free acid gave a complex mixture, presumably because of the concomitant epoxidation of the double bonds.[15d] Thus, treatment with *m*-CPBA of the dicyclohexylammonium salt of hyperforin afforded in a clean manner the hemiacetal **5**, showing that ionization of the β-dicarbonyl system funnels the reaction toward attack to the enolate double bond. The hemiacetal **5** was also obtained as major product from the reaction of the dicyclohexylammonium salt of hyperforin with TBHP, oxone, and H_2O_2. With nonperoxidic oxidants, both hyperforin and its salt could be used for the reaction, obtaining similar results in terms of yield and products. The hemiacetal **5** was also the major compound formed in the oxidation with HIO_4 (24% yield), accompanied by the pyran **7** (6%), the result of the electrocyclic closure of a fledging 8,26-dehydro derivative (**6**). Both **5** and **7** have been reported as trace components of *H. perforatum*,[15e,f] and the oxidation of hyperforin represents a straightforward way to obtain sizable amounts of these compounds.[18] Also treatment with DDQ or activated MnO_2 provided the pyran **7** as the major



reaction product (23% and 22%, respectively), accompanied by minor amounts of the furan **8** (6% and 9%, respectively). The latter was the major reaction product with the monoelectronic oxidants CAN and MAH, while LTA afforded a rewarding 70% yield of the pyran **7** as the only reaction product. With many of the metal oxidizers, the total material balance was low, probably because of the instability of hyperforin under the reaction conditions. Striking exceptions were with pyridium dichromate and $PdCl_2$. The former afforded in high overall conversion a mixture of four products, encompassing, besides the hemiacetal **5** (26%) and the pyran **7** (11%), also the 8-α-hydroxy derivative, **9** (10%), and the hydroxyfuran, **10** (28%), a known constituent of St. John's wort,[15c] while the latter yielded the pyran **7** as the only reaction product in almost quantitative yield.

The structure elucidation of the new compounds obtained from the oxidizing reactions was essentially based on the analysis of their 1D and 2D NMR spectra and HRMS data. The ^1H NMR spectra showed sharp signals, indicative of a covalent block of the tautomeric equilibrium, and suggested a common structural motif, with modifications limited to one of the prenyls (**7**, **8**, **10**) or to the cyclohexatrienone core (**5**, **9**). Compounds **5** and **9**, both resulting from the hydroxylation of C-8, had the same molecular weight and the same pattern of HMBC correlations, but could be clearly distinguished because in one case (**5**) the newly introduced hydroxyl was engaged in a transannular hemiacetal bridge with the carbonyl at C-1 (δ 108.8), while in its isomer **9** C-1 retained the ketone status (δ 206.6). The cage structure of hyperforin (**1**) requires a β-configuration for the transannular bridge,[15e] settling the configurational argument for these epimeric compounds.

Taken together, these data show that the major or exclusive reaction product with peroxidic oxidants (*m*-CPBA, oxone, TBHP, H_2O_2) is the hemiacetal **5**, presumably formed by attack of the electrophilic oxygen to C-8, while various metallic oxidants (MnO_2, CAN, MAH, LTA, Pd^{2+}) afforded mixtures of the furan **8** and the pyran **7**, all resulting from oxidation at one of the prenyl groups. Remarkably, HIO_4 and PCC gave instead products of both nuclear and side chain oxidation. It is difficult to advance a compelling argument to rationalize in mechanistic terms the results of the various oxidation reactions. An intriguing observation is that, while the oxidation of the prenyl on the central atoms of the β-dicarbonyl system affords a pyran derivative (**7**) via a dehydrogenation pathway, oxidation of the C-6 prenyl proceeds instead via a hydroxylative pathway, affording the furan derivatives **8** and **10**.

Compounds **2**−**10** were assayed for the inhibition of synaptosomal accumulation of tritiated serotonin ([^{3}H]5-HT). Hyperforin (**1**) inhibited the accumulation of [^{3}H]5-HT in rat brain synaptosomes with an IC_{50} value of 1.1 μg/mL, whereas all the other compounds were less potent, with IC_{50} values higher than 10 μg/mL.[19]

In conclusion, we have shown that hyperforin (**1**) is readily amenable to chemical modification and that its acylation, alkylation, and oxidation are detrimental for the inhibition of neurotransmitter reuptake. This clearly indicates that significant structure−activity relationships can be developed and suggests a specific role for the enolized β-diketone moiety, perhaps expressed in the β-carbonyl-α-prenyl enol function.

Experimental Section

Melting points were recorded employing a Buchi SMP-20 apparatus and are uncorrected. Optical rotation values were recorded on a Perkin-Elmer 241 polarimeter. The IR spectra were obtained with a Perkin-Elmer 681 spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were determined by means of a Bruker DRX-500 spectrometer (500 and 125 MHz, respectively) or, alternatively, on a Varian Inova 300 (300 and 75 MHz, respectively). The chemical shifts for ^1H NMR and ^{13}C NMR are referenced to $CHCl_3$ at 7.26 ppm and $CDCl_3$ at 77.0 ppm, respectively. EIMS (EI, 70 eV) were taken on a VG 7070 EQ spectrometer. Column chromatography was performed using silica gel 60 (70−230 mesh, Merck). The reactions were monitored by TLC on Merck 60 F_{254} (0.25 mm) plates, visualizing the spots with fluorescent short-wave light (254 nm) and by spraying with $(NH_4)_2MoO_4$ and heating. Commercially available reagents were used without prior purification. CH_2Cl_2 and DMSO were dried by distillation over CaH_2, and THF by distillation over Na-benzophenone. Solvent extracts of aqueous solutions were dried over anhydrous Na_2SO_4.

Acylation of Hyperforin (1). Reaction with 3,5-dinitrobenzoyl chloride is described as an example. To a solution of hyperforin (**1**) (600 mg, 1.12 mmol) in pyridine (10 mL) was

added an excess of 3,5-dinitrobenzoyl chloride (3.87 g, 16.8 mmol, 15 molar equiv). After stirring 30 min at room temperature, the reaction was worked up by dilution with water and extraction with EtOAc (3 × 10 mL), and the organic phase was washed sequentially with 2 N HCl, saturated $NaHCO_3$, and brine. After drying and removal of the solvent, the residue was purified by column chromatography (petrol/EtOAc, 9:1) and then by recrystallization from hexane, affording 365 mg of **2b** (45%). The mother liquors were further purified by column chromatography (hexane/ether, 9:1) to afford an additional 102 mg of **2b** (overall yield 58%). The acetyl- and trimethoxycinnamoyl derivatives (**2a**, **2c**) were prepared in a similar way, in overall yields of 65% and 81%, respectively.

Hyperforin acetate (2a): colorless oil; $[\alpha]^{25}_D$ +54° (*c* 0.9, CH_2Cl_2); IR (KBr) ν_{max} 1741, 1640, 1597, 1430, 1381, 1246, 1081, 844 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.78 (1H, m, H-4), 1.97 (1H, brdd, J = 13, 4 Hz, H-5), 1.36 (1H, dd, J = 13, 13 Hz, H-5′), 1.94 (1H, qq, J = 6.5, 6.5 Hz, H-11), 1.08 (3H, d, J = 6.5 Hz, H-12), 0.97 (3H, d, J = 6.5 Hz, H-13), 0.98 (3H, s, H-14), 1.86 (1H, m, H-15), 1.39 (1H, m, H-15′), 2.07 (1H, m, H-16), 1.86 (1H, m, H-16′), 5.02 (1H, m, H-17), 1.63 (3H, brs, H-19), 1.57 (3H, brs, H-20), 2.09 (1H, brd, J = 15 Hz, H-21), 1.75 (1H, m, H-21′), 4.98 (1H, m, H-22), 1.67 (3H, brs, H-24), 1.52 (3H, s, H-25), 3.02 (1H, brdd, J = 15, 6.5 Hz, H-26), 2.83 (1H, dd, J = 15, 6.5 Hz, H-26′), 4.98 (1H, brdd, J = 6.5, 6.5 Hz, H-27), 1.63 (3H, brs, H-29), 1.63 (3H, brs, H-30), 2.47 (1H, brdd, J = 15.5, 5 Hz, H-31), 2.31 (1H, brdd, J = 15.5, 6.0 Hz, H-31′), 5.02 (1H, m, H-32), 1.67 (3H, s, H-34), 1.65 (3H, brs, H-35), 2.21 (3H, s, *CH*$_3$CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2 (s, C-1), 84.3 (s, C-2), 49.8 (s, C-3), 42.2 (d, C-4), 38.0 (t, C-5), 57.0 (s, C-6), 162.7 (s, C-7), 133.7 (s, C-8), 193.4 (s, C-9), 208.4 (s, C-10), 42.8 (d, C-11), 20.3 (q, C-12), 21.1 (q, C-13), 13.8 (q, C-14), 36.4 (t, C-15), 24.9 (t, C-16), 124.7 (d, C-17), 131.0 (s, C-18), 25.7 (q, C-19), 17.6 (q, C-20), 27.0 (t, C-21), 122.4 (d, C-22), 133.8 (s, C-23), 25.8 (q, C-24), 17.9 (q, C-25), 23.9 (t, C-26), 119.8 (d, C-27), 134.0 (s, C-28), 25.6 (q, C-29), 17.7 (q, C-30), 30.0 (t, C-31), 119.1 (d, C-32), 133.9 (s, C-33), 25.6 (q, C-34), 18.1 (q, C-35); HREIMS *m/z* 578.8211 $[M]^+$ (8) (calcd for $C_{37}H_{54}O_5$, 578.8217).

Hyperforin 3,5-dinitrobenzoate (2b): colorless leaflets; mp 108−110 °C; $[\alpha]^{25}_D$ +59° (*c* 0.3, CH_2Cl_2); IR (KBr) ν_{max} 1751, 1736, 1721, 1661, 1551, 1461, 1341, 1250, 1136, 1076 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.96 (1H, m, H-4), 2.17 (1H, brdd, J = 13, 4 Hz, H-5), 1.49 (1H, dd, J = 13, 13 Hz, H-5′), 2.05 (1H, qq, J = 6.5, 6.5 Hz, H-11), 1.14 (3H, d, J = 6.5, Hz H-12), 1.04 (3H, d, J = 6.5 Hz, H-13), 1.08 (3H, s, H-14), 1.93 (1H, m, H-15), 1.55 (1H, m, H-15′), 2.16 (1H, m, H-16), 1.63 (1H, m, H-16′), 5.08 (1H, m, H-17), 1.68 (3H, brs, H-19), 1.63 (3H, brs, H-20), 2.22 (1H, brd, J = 15 Hz, H-21), 1.81 (1H, m, H-21′), 5.13 (1H, m, H-22), 1.77 (3H, brs, H-24), 1.60 (3H, s, H-25), 3.17 (1H, brdd, J = 15, 6.5 Hz, H-26), 2.95 (1H, dd, J = 15, 6.5 Hz, H-26′), 5.01 (1H, brdd, J = 6.5, 6.5 Hz H-27), 1.54 (3H, brs, H-29), 1.51 (3H, brs, H-30), 2.65 (1H, brdd, J = 15.5, 5 Hz, H-31), 2.30 (1H, brdd, J = 15.5, 6.0 Hz, H-31′), 5.08 (1H, m, H-32), 1.67 (3H, s, H-34), 1.52 (3H, brs, H-35), 9.28 (1H, t, J = 2 Hz, OR), 9.11 (2H, d, J = 2 Hz, OR); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1 (s, C-1), 80.6 (s, C-2), 50.8 (s, C-3), 42.6 (d, C-4), 38.8 (t, C-5), 57.4 (s, C-6), 162.3 (s, C-7), 134.3 (s, C-8), 193.1 (s, C-9), 207.4 (s, C-10), 43.1 (d, C-11), 20.3 (q, C-12), 21.0 (q, C-13), 13.8 (q, C-14), 36.8 (t, C-15), 25.0 (t, C-16), 124.8 (d, C-17), 131.2 (s, C-18), 25.6 (q, C-19), 17.6 (q, C-20), 27.3 (t, C-21), 122.5 (d, C-22), 133.2 (s, C-23), 25.7 (q, C-24), 17.9 (q, C-25), 24.1 (t, C-26), 119.7 (d, C-27), 134.8 (s, C-28), 25.4 (q, C-29), 17.7 (q, C-30), 30.5 (t, C-31), 119.2 (d, C-32), 134.4 (s, C-33), 25.5 (q, C-34), 18.0 (q, C-35), 159.1 (s, OR), 132.3 (s, OR), 129.6 (d, OR), 149.3 (s, OR), 123.2 (d, OR); HREIMS *m/z* 730.8872 $[M]^+$ (2) (calcd for $C_{42}H_{54}N_2O_9$, 730.8862).

Hyperforin trimethoxybenzoate (2c): white powder; mp 82 °C; $[\alpha]^{20}_D$ +36° (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 3424, 1736, 1721, 1655, 1636, 1595, 1505, 1464, 1418, 1331, 1233, 1132 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.95 (1H, m, H-4), 2.12 (1H, dd, J = 13.5, 3.7 Hz, H-5), 1.43 (1H, m, H-5′), 2.02 (1H, m, H-11), 1.15 (3H, d, J = 6.6 Hz, H-12), 1.04 (3H, d, J = 6.6 Hz, H-13), 1.06 (3H, s, H-14), 1.93 (1H, m, H-15), 1.49 (1H, m, H-15′), 2.15 (1H, m, H-16), 1.93 (1H, m, H-16′), 5.09 (1H, m, H-17), 1.68 (3H, s, H-19), 1.63 (3H, s, H-20), 2.19 (1H, m, H-21), 1.82 (1H, m, H-21′), 5.11 (1H, m, H-22), 1.75 (3H, s, H-24), 1.63 (3H, s, H-25), 3.14 (1H, dd, J = 14.9, 7.1 Hz, H-26), 2.92 (1H, dd, J = 14.1, 7.0 Hz, H-26′), 5.09 (1H, m, H-27), 1.59 (3H, s, H-29), 1.57 (3H, s, H-30), 2.61 (1H, dd, J = 15.3, 6.5 Hz, H-31), 2.34 (1H, dd, J = 15.3, 6.0 Hz, H-31′), 5.09 (1H, m, H-32), 1.57 (3H, s, H-34), 1.59 (3H, s, H-35), 7.36 (2H, s, Ar), 3.95 (6H, s, OCH_3), 3.98 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5 (s, C-1), 84.7 (s, C-2), 50.2 (s, C-3), 42.2 (d, C-4), 38.5 (t, C-5), 57.7 (s, C-6), 162.3 (s, C-7), 134.7 (s, C-8), 193.7 (s, C-9), 208.6 (s, C-10), 43.2 (d, C-11), 20.6 (q, C-12), 21.4 (q, C-13), 13.9 (q, C-14), 36.7 (t, C-15), 25.2 (t, C-16), 125.0 (d, C-17), 131.6 (s, C-18), 25.9 (q, C-19), 17.9 (q, C-20), 27.3 (t, C-21), 123.1 (d, C-22), 133.0 (s, C-23), 26.0 (q, C-24), 17.9 (q, C-25), 24.2 (t, C-26), 120.2 (d, C-27), 133.9 (s, C-28), 25.8 (q, C-29), 18.2 (q, C-30), 30.5 (t, C-31), 119.7 (d, C-32), 134.1 (s, C-33), 25.8 (q, C-34), 18.4 (q, C-35); CIMS, *m/z* 731 $[M]^+ + 1$.

Methylation of Hyperforin (1) with Diazomethane. To a solution of hyperforin (**1**) (300 mg; 0.560 mmol) in ether (2 mL) was added dropwise ethereal CH_2N_2, until evolution of nitrogen ceased. Silica gel was then added to quench the excess diazomethane, and the solution was filtered and evaporated to give 291 mg of **3** (94%) as a colorless gum.

***O*-Methylhyperforin (3):** ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (3H, d, J = 6.5 Hz H-12), 1.01 (3H, d, J = 6.5 Hz, H-13), 0.98 (3H, s, H-14), 1.85 (1H, m, H-15), 1.39 (1H, m, H-15′), 2.07 (1H, m, H-16), 1.87 (1H, m, H-16′), 5.03 (1H, t, J = 7.0 H-17), 1.67 (3H, s, H-19), 1.63 (3H, s, H-20), 2.10 (1H, m, H-21), 1.73 (1H, m, H-21′), 4.94 (1H, t, J = 7.1 Hz, H-22), 1.67 (3H, s, H-24), 1.63 (3H, s, H-25), 3.17 (1H, d, J = 6.5 Hz, H-26), 5.05 (1H, t, J = 7.0, Hz H-27), 1.58 (3H, s, H-29), 1.67 (3H, s, H-30), 2.49 (1H, dd, J = 15.0, 6.0 Hz, H-31), 2.40 (1H, dd, J = 15.0, 7.5 Hz, H-31′), 4.99 (1H, t, J = 7.0 Hz, 32), 1.67 (3H, s, H-34), 1.55 (3H, s, H-35), 3.91 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1 (s, C-1), 84.1 (s, C-2), 49.2 (s, C-3), 43.2 (d, C-4), 38.8 (t, C-5), 58.6 (s, C-6), 173.9 (s, C-7), 133.3 (s, C-8), 193.9 (s, C-9), 209.1 (s, C-10), 42.6 (d, C-11), 20.4 (q, C-12), 21.3 (q, C-13), 13.6 (q, C-14), 36.5 (t, C-15), 24.9 (t, C-16), 124.7 (d, C-17), 131.0 (s, C-18), 25.9 (q, C-19), 17.9 (q, C-20), 27.1 (t, C-21), 122.5 (d, C-22), 132.9 (s, C-23), 25.8 (q, C-24), 17.6 (q, C-25), 23.4 (t, C-26), 121.7 (d, C-27), 127.4 (s, C-28), 25.7 (q, C-29), 18.0 (q, C-30), 30.1 (t, C-31), 119.7 (d, C-32), 133.8 (s, C-33), 25.6 (q, C-34), 17.9 (q, C-35); HREIMS *m/z* 550.8119 $[M]^+$ (6) (calcd for $C_{36}H_{54}O_4$, 550.8116).

Mitsunobu Etherification of Hyperforin (1). To a cooled (0 °C) solution of methanol (80 mg, 2.5 mmol, 2.5 molar equiv) and hyperforin (**1**) (551 mg, 1 mmol) in THF (8 mL) were added triphenylphosphine (655 mg, 2.5 mmol, 2.5 molar equiv) and DEAD (393 μL, 435 mg, 2.5 equiv, 2.5 molar equiv). The reaction was stirred for 2 h, then left to warm to room temperature over 5 h, and eventually worked up by evaporation. The residue was purified by column chromatography (petrol; petrol/diethyl ether, 99:1; and petrol/EtOAc, 95:5) to afford **3** (97 mg, 18%) as a colorless oil.

Methylation of Hyperforin (1) with NaH-DMSO/MeI. To a solution of hyperforin (**1**) (1.2 g, 2.2 mmol) in dry DMSO (12 mL) were added NaH (352 mg of a 60% dispersion in mineral oil, 8.8 mmol, 4 molar equiv) and MeI (0.55 mL, 1.25 g, 8.8 mmol; 4 molar equiv). After stirring 4 h at room temperature, the reaction was worked up by removal under vacuum of the excess MeI, dilution with aqueous NH_4Cl, and extraction with petroleum ether/ether, 3:1 (3 × 30 mL). The organic phase was washed with brine, dried, and evaporated. A yellowish residue was obtained, then purified by column chromatography (petrol/EtOAc, 99:1, and next petrol/EtOAc, 95:5, as eluant) to give 892 mg of **4** (72%).

***C*-Methylhyperforin (4):** colorless oil, $[\alpha]^{25}_D$ +21° (*c* 0,64, CH_2Cl_2); IR (KBr) ν_{max} 2972, 2876, 1728, 1705, 1449, 1377, 1246, 1086, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (1H, m, H-4), 2.19 (1H, m, H-5), 1.62 (1H, m, H-5′), 2.21 (1H, qq, J = 6.5 Hz, H-11), 1.17 (3H, d, J = 6.5 Hz, H-12), 1.00 (3H, d, J = 6.5 Hz, H-13), 1.00 (3H, s, H-14), 1.98 (1H, m, H-15), 2.14 (1H, m, H-16), 1.87 (1H, m, H-16′), 5.01 (1H, t, J = 7 Hz, H-17), 1.69 (3H, s, H-19), 1.62 (3H, s, H-20), 2.02 (1H, m, H-21), 1.65 (1H, m, H-21′), 4.79 (1H, brt, J = 7 Hz, H-22), 1.65 (3H, s,

H-24), 1.59 (3H, s, H-25), 2.76 (1H, dd, J = 14.0, 9.0 Hz, H-26), 2.60 (1H, dd, J = 14.0, 7.0 Hz, H-26′), 5.06 (1H, m, H-27), 1.65 (3H, s, H-29), 1.51 (3H, s, H-30), 2.54 (1H, dd, J = 14.0, 9.0 Hz, H-31), 2.46 (1H, dd, J = 14.0, 6.5 Hz, H-31′), 5.02 (1H, m, H-32), 1.66 (3H, s, H-34), 1.65 (3H, s, H-35), 1.13 (3H, s, CH_3 on C-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1 (s, C-1), 86.4 (s, C-2), 55.7 (s, C-3), 42.2 (d, C-4), 45.4 (t, C-5), 65.8 (s, C-6 or C-8), 208.4 (s, C-7), 65.7 (s, C-8 or C-6), 205.4 (s, C-9), 207.8 (s, C-10), 41.7 (d, C-11), 20.4 (q, C-12), 21.7 (q, C-13), 13.5 (q, C-14), 37.0 (t, C-15), 25.2 (t, C-16), 124.4 (d, C-17), 131.3 (s, C-18), 25.9 (q, C-19), 17.7 (q, C-20), 27.9 (t, C-21), 121.9 (d, C-22), 133.4 (s, C-23), 26.0 (q, C-24), 18 (q, C-25), 31.9(t, C-26), 119.3 (d, C-27), 135.7 (s, C-28), 25.8 (q, C-29), 18.1 (q, C-30), 31.1 (t, C-31), 118.9 (d, C-32), 135.2 (s, C-33), 25.7 (q, C-34), 18.1 (q, C-35); 25.5 (q, CH_3 on C-8); HREIMS m/z 550.8123 $[M]^+$ (5) (calcd for $C_{36}H_{54}O_4$, 550.8116).

Oxidation of Dicyclohexylammonium Hyperforinate with *m*-CPBA. Dicyclohexylammonium hyperforinate (200 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (2 mL), and *m*-CPBA was then added (48 mg, 0.28 mmol; 1 molar equiv). The reaction was stirred at room temperature for 30 min and then brought to completion by the addition of a further 24 mg of *m*-CPBA (0.14 mmol; 0.5 molar equiv). After 30 min, the mixture was diluted with CH_2Cl_2 (50 mL) and sequentially washed with saturated $Na_2S_2O_8$ and saturated Na_2CO_3. The organic phase was dried and evaporated to give 156 mg of **5** (quantitative) as a colorless oil. For the spectroscopic data on **5**, see ref 15e.

Oxidation of Dicyclohexylammonium Hyperforinate with Oxone. To a solution of dicyclohexylammonium hyperforinate (500 mg, 0.70 mmol) in acetone (5 mL) was added oxone (430 mg, 0.70 mmol; 2 molar equiv) at room temperature. After 2 h, the reaction was worked up by washing with water and extraction with petrol/diethyl ether (3:1, 15 mL). The organic phase was dried and evaporated to give a gum, which was purified by column chromatography (petrol/EtOAc gradient, from pure petroleum ether to 9:1), to give **5** (180 mg; 47%).

Oxidation of Dicyclohexylammonium Hyperforinate with DDQ. To a solution of dicyclohexylammonium hyperforinate (5 g, 7.0 mmol) in MeOH (55 mL) was added DDQ (6.34 g, 2.8 mmol, 4 molar equiv). After 2 h, the mixture was worked up by dilution with water (140 mL) and extraction with CH_2Cl_2 (100 mL). The organic phase was dried and evaporated, and the residue purified by column chromatography (petrol/diethyl ether gradient) to afford 80 mg of **5** (2%), 258 mg of **7** (23%), and 207 mg of **8** (6%).

Oxidation of Dicyclohexylammonium Hyperforinate with Activated MnO_2. Activated MnO_2 (30 g, Merck) was added to a stirred solution of dicyclohexylammonium hyperforinate (3 g, 4.18 mmol) in toluene (75 mL) and CH_2Cl_2 (1 mL). After 15 min the reaction was worked up by filtration over Celite and evaporation. The crude residue was purified by column chromatography (petrol/diethyl ether gradient) to give 497 mg of **5** (22%) and 204 mg of **8** (9%).

Oxidation of Dicyclohexylammonium Hyperforinate with Cerium Ammonium Nitrate (CAN). To a solution of dicyclohexylammonium hyperforinate (1 g, 1.39 mmol) in acetonitrile (25 mL) was added dropwise a solution of CAN (1.53 g, 2.80 mmol, 2 molar equiv) in acetonitrile (15 mL). Decoloration of the oxidant solution was instantaneous, and the reaction was then worked up by concentration, dilution with water, and extraction with EtOAc. The organic phase was washed with saturated Na_2CO_3 and evaporated. The residue was purified by column chromatography (petrol/diethyl ether gradient) to afford 51 mg of **5** (7%) and 196 mg of **8** (26%).

Oxidation of Dicyclohexylammonium Hyperforinate with Manganese(III) Acetate Hydrate (MAH). To a solution of dicyclohexylammonium hyperforinate (500 mg, 0.69 mmol) in HOAc (10 mL) was added MAH (924 mg, 3.45 mmol, 5 molar equiv), and the mixture was heated at 90 °C for 30 min. The reaction was worked up by dilution with water and extraction with hexane/EtOAc (1:1), and the organic phase was washed with saturated $NaHCO_3$ and brine and evaporated. The residue was purified by column chromatography (petrol/diethyl ether gradient) to afford 57 mg of **5** (15%) and 103 mg of **8** (25%).

Oxidation of Dicyclohexylammonium Hyperforinate with Lead Tetraacetate. To a stirred solution of dicyclohexylammonium hyperforinate (1 g, 1.4 mmol) in toluene (35 mL) and CH_2Cl_2 (1 mL) was added $Pb(OAc)_4$ (0.74 g, 1.67 mmol; 1.2 molar equiv). After 15 min the reaction was worked up by filtration over Celite and washing with water. After drying, the organic phase was evaporated, and the residue purified by column chromatography (petrol/EtOAc, 95:5), with 499 mg of **8** (67%) being obtained.

Oxidation of Dicyclohexylammonium Hyperforinate with PDC. To a stirred solution of dicyclohexylammonium hyperforinate (2 g, 2.8 mmol) in CH_2Cl_2 (20 mL) was added pyridinium dichromate (2.114 g, 5.6 mmol; 2 molar equiv). After stirring 2 h at room temperature, the reaction was worked up by filtration over Celite and evaporation. The crude product was purified by column chromatography (petrol/EtOAc gradient) to give, in order of elution, **5** (404 mg, 26%), dehydrohyperforin (**7**, 172 mg, 11%), **9** (138 mg, 9%), and **10** (432 mg, 28%).

Oxidation of Dicyclohexylammonium Hyperforinate with $PdCl_2$. To a stirred solution of dicyclohexylammonium hyperforinate (128 mg, 0.167 mmol) in DMSO/H_2O (9:1, 7 mL) was added $PdCl_2$ (40 mg, 0.225 mmol), and a constant stream of oxygen was bubbled through the solution until TLC showed the complete disappearance of hyperforin (**1**). The mixture was worked up by dilution with water and extraction with CH_2Cl_2. The crude product was purified by column chromatography (petrol/Bu*t*OMe, 10:1) to obtain dehydrohyperforin (**7**, 88 mg, 98%).

Dehydrohyperforin (7): colorless viscous oil; $[\alpha]^{25}_D$ +33° (*c* 1.2, $CHCl_3$); IR (KBr) ν_{max} 3453, 1728, 1640, 1586, 1449, 1414, 1377, 1337, 1304 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (1H, m, H-4), 1.89 (1H, m, H-5), 1.42 (1H, m, H-5′), 2.10 (1H, m, H-11), 1.12 (3H, d, J = 6.3 Hz, H-12), 1.04 (3H, d, J = 6.3 Hz, H-13), 1.01 (3H, s, H-14), 1.88 (1H, dd, J = 14.0, 8.0 Hz, H-15), 1.43 (1H, t, J = 13, H-15′), 2.11 (1H, m, H-16), 1.89 (1H, m, H-16′), 5.04 (1H, m, H-17), 1.65 (3H, s, H-19), 1.58 (3H, s, H-20), 2.10 (1H, m, H-21), 1.72 (1H, m, H-21′), 4.98 (1H, m, H-22), 1.65 (3H, s, H-24), 1.57 (3H, s, H-25), 6.48 (1H, d, J = 10.2 Hz, H-26), 5.35 (1H, d, J = 10 Hz, H-27), 1.39 (3H, s, H-29), 1.44 (3H, s, H-30), 2.46 (1H, m, H-31), 1.45 (1H, m, H-31′), 5.00 (1H, m, H-32), 1.66 (3H, s, H-34), 1.68 (3H, s, H-35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4 (s, C-1), 84.6 (s, C-2), 49.2 (s, C-3), 43.7 (d, C-4), 39.1 (t, C-5), 56.8 (s, C-6), 171.1 (s, C-7), 114.8 (s, C-8), 188.7 (s, C-9), 209.6 (s, C-10), 42.7 (d, C-11), 20.7 (q, C-12), 21.6 (q, C-13), 13.8 (q, C-14), 36.7 (t, C-15), 25.1 (t, C-16), 124.9 (d, C-17), 131.3 (s, C-18), 25.9 (q, C-19), 17.9 (q, C-20), 27.4 (t, C-21), 122.9 (d, C-22), 133.5 (s, C-23), 26.1 (q, C-24), 18.1 (q, C-25), 115.6 (t, C-26), 123.9 (d, C-27), 82.1 (s, C-28), 28.8 (q, C-29), 28.6 (q, C-30), 29.2 (t, C-31), 119.6 (d, C-32), 133.9 (s, C-33), 26.0 (q, C-34), 18.4 (q, C-35); HREIMS m/z 534.7680 $[M]^+$ (5) (calcd for $C_{35}H_{50}O_4$, 534.7691).

Dehydrofurohyperforin (8): colorless viscous oil; $[\alpha]^{25}_D$ +76° (*c* 2.25, $CHCl_3$); IR (KBr) ν_{max} 3432, 1732, 1628, 1516, 1447, 1377, 1358, 1233, 1206 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (1H, dd, J = 8.9,3.6 Hz, H-4), 2.08 (1H, m, H-5), 1.56 (1H, m, H-5′), 2.02 (1H, m, H-11), 1.12 (3H, s, H-12), 1.03 (3H, d, J = 6.6 Hz, H-13/H-14), 1.09 (3H, d, J = 6.9 Hz, H-14/H-13), 2.10 (1H, s, H-15), 1.31 (1H, m, H-15′), 2.20 (1H, m, H-16), 5.09 (1H, m, H-17), 1.66 (3H, s, H-19), 1.61 (3H, s, H-20), 2.20 (1H, m, H-21), 1.74 (1H, m, H-21′), 4.98 (1H, m, H-22), 1.66 (3H, s, H-24), 1.59 (3H, s, H-25), 3.15 (1H, dd, J = 14.6, 7.2 Hz, H-26), 3.04 (1H, dd, J = 14.1, 7.1 Hz, H-26′), 5.12 (1H, m, H-27), 1.72 (3H, s, H-29), 1.71 (3H, s, H-30), 2.55 (1H, dd, J = 13.2, 11.1 Hz, H-31), 1.97 (1H, dd, J = 5.6, 13.1 Hz, H-31′), 5.11 (1H, m, H-32), 5.16 (2H, s, H-34), 1.79 (3H, s, H-35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6 (s, C-1), 83.1 (s, C-2), 48.1 (s, C-3), 43.1 (d, C-4), 37.5 (t, C-5), 59.2 (s, C-6), 172.7 (s, C-7), 116.6 (s, C-8), 192.6 (s, C-9), 209.5 (s, C-10), 41.8 (d, C-11), 20.2 (q, C-12), 21.2 (q, C-13), 13.3 (q, C-14), 36.2 (t, C-15), 25.1 (t, C-16), 124.7 (d, C-17), 130.9 (s, C-18), 25.6 (q, C-19), 17.5 (q, C-20), 27.0 (t, C-21), 122.2 (d, C-22), 133.4 (s, C-23), 25.6

(q, C-24), 18.0 (q, C-25), 22.1 (t, C-26), 120.9 (d, C-27), 132.4 (s, C-28), 25.8 (q, C-29), 17.7 (q, C-30), 34.4 (t, C-31), 86.4 (d, C-32), 141.2 (s, C-33), 113.5 (t, C-34), 17.2 (q, C-35); HREIMS *m*/*z* 534.7679 $[M]^+$ (3) (calcd for $C_{35}H_{50}O_4$, 534.7691).

8α-Hydroxyhyperforin (9): colorless viscous oil; $[\alpha]^{25}_D$ +29° (*c* 0.5, CH_2Cl_2); IR (KBr) ν_{max} 3496, 1814, 1728, 1705, 1645, 1447, 1379, 1221, 1177, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.20 (1H, t, J = 8 Hz, H-32), 5.04 (1H, t, J = 7 Hz, H-17), 4.86 (1H, m, H-27), 4.85 (1H, m, H-22), 3.56 (1H, s, OH-8), 2.60 (1H, dd, J = 9.3 and 13.9 Hz, H-31a), 2.51 (1H, dd, J = 6.3 and 13.9 Hz, H-31b), 2.44 (1H, dd, J = 7.9 and 15.4 Hz, H-26a), 2.26 (1H, dd, J = 3.6 and 13.3 Hz, H-5a), 2.20 (1H, dd, J = 5.6 and 15.4 Hz, H-26b), 2.16 (1H, m, H-11), 2.15 (1H, m, H-16a), 2.11 (1H, m, H-21a), 1.99 (1H, ddd, J = 5.3, 13.0 and 14.9 Hz, H-15a), 1.88 (1H, m, H-16b), 1.74 (1H, dd, J = 13 and 13 Hz, H-5b), 1.72 (3H, s, H-29), 1.68 (1H, m, H-21b), 1.68 (6H, s, H-24 and H-34), 1.65 (6H, s, H-20 and H-35), 1.60 (3H, s, H-19), 1.57 (3H, s, H-30), 1.53 (3H, s, H-25), 1.32 (1H, m, H-15b), 1.31 (1H, m, H-4), 1.20 (3H, d, J = 6.4 Hz, H-12), 1.10 (3H, s, H-14), 1.01 (3H, d, J = 6.6 Hz, H-13); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9 (s, C-7), 206.7 (s, C-10), 206.6 (s, C-1), 201.6 (s, C-9), 139.2 (s, C-28), 136.0 (s, C-33), 134.0 (s, C-23), 131.5 (s, C-18), 124.2 (d, C-17), 121.4 (d, C-22), 118.4 (d, C-32), 113.2 (d, C-27), 86.6 (s, C-8), 85.8 (s, C-2), 66.1 (s, C-6), 56.6 (s, C-3), 45.4 (t, C-5), 45.2 (d, C-4), 42.4 (d, C-11), 37.2 (t, C-15), 35.4 (t, C-26), 31.1 (t, C-31), 27.6 (t, C-21), 26.0 (q, C-24), 26.0 (q, C-29), 26.0 (q, C-34), 25.7 (q, C-20), 25.6 (q, C-35), 25.1 (t, C-16), 21.5 (q, C-13), 20.1 (q, C-12), 18.2 (q, C-30), 17.9 (q, C-25), 17.7 (q, C-19), 14.1 (q, C-14); HREIMS *m*/*z* 552.7851 $[M]^+$ (2) (calcd for $C_{35}H_{52}O_5$, 552.7844).

Biological Evaluation. The inhibition of synaptosomal accumulation of tritiated serotonin ($[^3H]$5-HT) and dopamine ($[^3H]$DA) was measured as previously described.[10b]

References and Notes

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