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C-Ring Cannabinoid Lactones: A Novel Cannabinergic Chemotype

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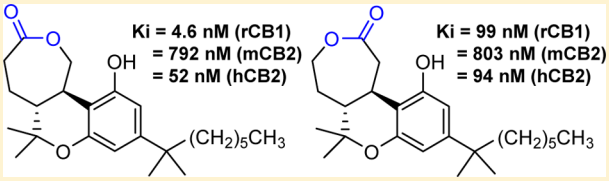
Supporting Information

ABSTRACT: As a part of our controlled-deactivation ligand development project, we recently disclosed a series of (−)-Δ^8-tetrahydrocannabinols (THCs) with a metabolically labile ester group at the 2′-position of the side chain. Now, we have replaced the C-ring in the classical THC structure with a hydrolyzable seven-membered lactone. One of the synthesized analogues binds with high affinity to the CB1 receptor (K_i = 4.6 nM) and exhibits much lower affinities for the mCB2 and the hCB2. Also, in vitro functional characterization found the compound to be an agonist at rCB1. Consistent with our rational design, the lead cannabinergic lactone identified here is susceptible to metabolic inactivation by plasma esterases, while the respective acid metabolite is inactive at CB receptors. These results are highlighted with molecular modeling of the two regiosomeric lactones.



KEYWORDS: *Cannabinoids, lactones, Baeyer−Villiger rearrangement*

Classical cannabinoids including the phytocannabinoid (−)-Δ^9-tetrahydrocannabinol[1] [(−)-Δ^9-THC, **1**, Figure 1] and its congeners produce most of their biological effects by modulating the cannabinoid receptors CB1 and CB2.[2−5] These two GPCRs are currently being targeted for an array of conditions including neurodegeneration, inflammation, pain, glaucoma, and eating disorders.[6−12] Only a limited number of cannabinergic drugs have been approved to date. However, the widespread use of cannabinoid agonists in therapy has been hindered due to the undesirable side effects associated with CB1 receptor activation/deactivation as well as poor pharmacokinetic/pharmacodynamic (PK/PD) properties.[13] Thus, the development of safer THC-based medications with good oral bioavailability, consistent efficacy, and predictable duration of action and detoxification remains to be addressed.

Incorporation of a metabolically labile group into the structure of a lead/drug molecule has been used successfully to improve PK/PD profiles as well as target specificity for a variety of drugs such as anticholinergics, β-blockers, corticosteroids, and opioids.[14−16] A representative example is the drug remifentanyl (Ultiva), a potent and ultra short-acting opioid agonist that is used in surgical anesthesia. These, so-called, "soft" analogues/drugs are designed to undergo a predictable and controllable deactivation to inactive metabolites after the desired biological role has been achieved. Earlier efforts to develop soft-cannabinoids by incorporating an enzymatically labile ester group into a biphenyl template resulted in compounds with very low binding affinities for the CB receptors.[17] In addition, some "Nabitan" inspired *N*-benzylbenzopyrone esters were reported to possess moderate intraocular pressure lowering activity.[6,18] However, there are no reports linking these in vivo effects with cannabinergic activity.

While pursuing the development of novel cannabinoids with controllable deactivation and improved druggability, we reported recently a series of (−)-Δ^8-THCs where a metabolically labile ester group was placed at the 2′-position of the side chain pharmacophore.[19] The synthesized analogues exhibited potent in vitro and in vivo cannabinergic effects, while their metabolic half-lives were calibrated by incorporating suitable stereochemical features in the vicinity of the hydrolyzable group. In this communication, our design replaces the C-ring in the THC structure with a hydrolyzable seven-membered lactone, while the side chain pharmacophore was optimized[20,21] to a dimethylheptyl group (DMH, Figure 1). One of the synthesized regioisomeric lactones (AM4809) exhibited very high binding affinity and 170-fold selectivity for CB1 when compared to mCB2, while the other isomer exhibited much weaker affinities. This selectivity was reduced to 11-fold when the analogue was tested in hCB2 preparations. AM4809 was further evaluated for its functional potency and metabolic stability, while its respective acid metabolite was tested for its affinities for CB receptors. Our studies suggest that the lead cannabinergic lactone identified here has a soft analogue profile and is an agonist at rCB1. These results are highlighted by comparing the stereoelectronic properties of the two isomers using molecular modeling.

Synthesis of lactones **10** and **11** as well as their hydrolytic metabolites **8** and **9** involves a Baeyer−Villiger rearrangement as the key step (Scheme 1). Thus, coupling of commercially available dimethylheptyl resorcinol **2** with diacetates **3**[22] in the

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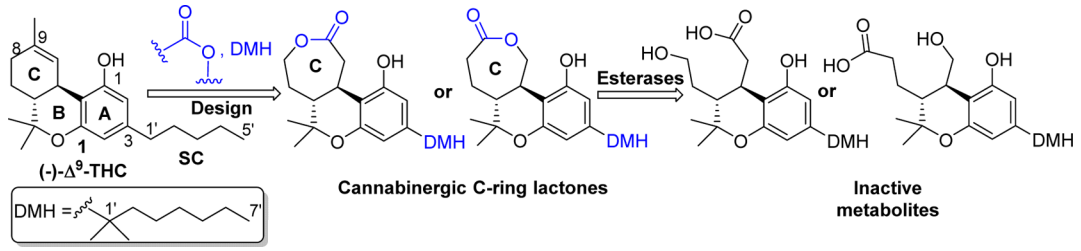
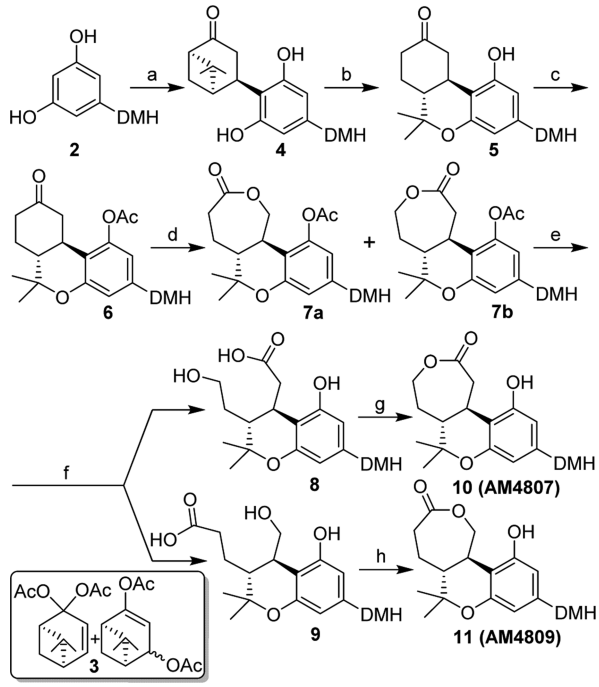


Figure 1. Design and enzymatic inactivation of cannabinergic C-ring lactones.

Scheme 1. Synthesis of Cannabinergic C-Ring Lactones[a]



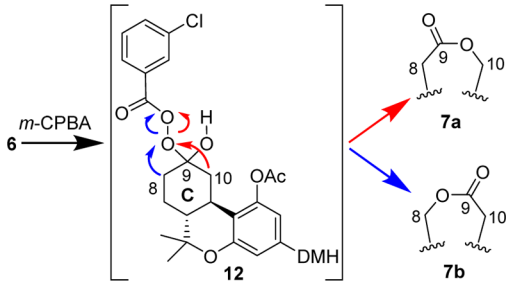
[a]Reagents and conditions: (a) **3**, *p*-TSA, $CHCl_3$, 0 °C to rt, 72%; (b) TMSOTf, CH_2Cl_2/$MeNO_2$, 0 °C to rt, 73%; (c) Ac_2O, pyridine, CH_2Cl_2, rt, 90%; (d) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 97%; (e) LiOH, THF/H_2O, 0 °C, 32−53%; (f) chromatographic separation; (g) CH_3SO_3H, DMAP, toluene, rt, 44%; (h) CH_3SO_3H, DMAP, toluene, rt, 79%.

presence of *p*-toluenesulfonic acid, under our optimized conditions,[23] led to norpinanone **4**.[24]

Dibenzo[*b*,*d*]pyran ring closure proceeded smoothly with catalytic trimethylsilyl triflate to give ketone **5** in 73% yield.[23] Protection of the phenolic hydroxyl group in **5** afforded the acetate ester **6**[24] (90% yield), which was subsequently treated with *m*-chloroperbenzoic acid at 0 °C to give a mixture of inseparable regioisomers **7a** and **7b** in 97% yield.[25] On the basis of ^{1}H NMR (500 MHz) data, the ratio **7a**/**7b** was found to be 1:2.7. Exposure of the **7a**/**7b** mixture to lithium hydroxide in THF/H_2O hydrolyzed all ester groups and produced the required carboxylic acid metabolites **8** and **9** that were separated by flash column chromatography on silica gel.[26] Intramolecular cyclization of the individual carboxylic acid intermediates **8** and **9** using methanesulfonic acid in the presence of 4-dimethylaminopyridine afforded the regioisomeric lactones **10** and **11**, respectively (44−79% unoptimized yield).[27]

It is widely accepted that the Baeyer−Villiger rearrangement/oxidation involves the formation of a tetrahedral (Criegee) intermediate (e.g., **12**, Chart 1), which immediately undergoes an alkyl migration to give the product(s), ester(s), or lactone(s). Also, studies on this reaction have shown that electron density and steric bulk strongly influence the migration ability.[28]

Chart 1. Structure of the Probable Criegee Intermediate 12 and Rearrangement Pathways Leading to Regioisomeric Lactones 7a and 7b



To gain insights regarding the stereochemical outcome of the Baeyer−Villiger rearrangement in our tricyclic system, we have examined the correlation between the conformational properties of the C-ring in **12** and the migratory aptitude of C8 and C10 using molecular modeling. Thus, the Criegee intermediate **12** with the peroxide substituent in either the equatorial or the axial position underwent torsional sampling using Monte Carlo multiple minimum (MCMM) protocol in MacroModel, and the lowest energy conformers were determined (Figure 2, details are given in the experimental section). Our modeling reveals that the cyclohexyl C-ring assumes a chair conformation in which the peroxide substituent exists in two almost equienergetic conformations with the equatorial conformer A being more stable than the respective axial conformer B with a calculated energy difference of approximately 1 kcal/mol. The dihedral angle O−O−C9−C8 is approximately −178 degrees for conformer A and +174 degrees for conformer B, both of which place the C8 carbon in an antiperiplanar orientation with respect to the oxygen−oxygen peroxide bond. As observed in earlier studies on the Baeyer−Villiger rearrangement,[28,29] the group antiperiplanar to the dissociating peroxide bond is expected to have higher migratory aptitude, and thus, the formation of the lactone **7b** is favored over the regioisomer **7a**. It should be noted that in our molecular modeling exercise the conformers with the C10 carbon antiperiplanar to the oxygen−oxygen bond of the peroxide have significantly higher energy (4.6 and 10.2 kcal/mol) than that of A and B (see Supporting Information).

The abilities of compounds **8**−**11** to displace radiolabeled CP-55,940 from membranes prepared from rat brain (source of CB1) and HEK293 cells expressing either mouse CB2 or

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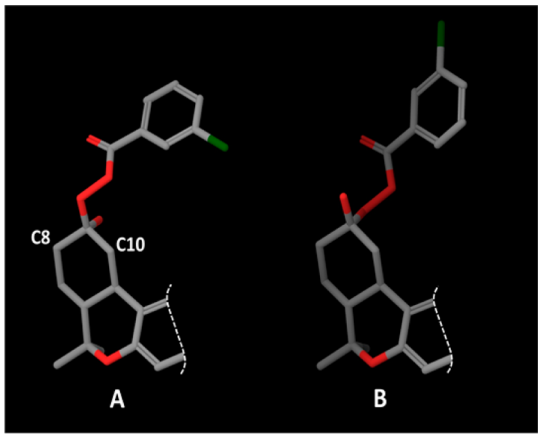

Figure 2. Lowest energy conformers of the Criegee intermediate **12** in which the peroxide group occupies the equatorial (A, calculated energy: −66.069 kcal/mol) or the axial (B, calculated energy: −67.074 kcal/mol) position of the cyclohexane C-ring. Oxygen atoms are presented in red. Aromatic rings are partially displayed, while hydrogen atoms are not shown. In these almost equienergetic conformers, the C8 carbon is in a position antiperiplanar to the oxygen−oxygen bond of the peroxide (dihedral angle O−O−C9−C8: −177.9° for A and +173.7° for B) and is expected to have a higher migratory aptitude when compared to C10.

human CB2 were determined as described in the literature,[23,30] and inhibition constant values (K_i) from the respective competition binding curves are listed in Table 1 in which our prototype (−)-Δ^9-THC is included for comparison. The rat, mouse, and human CB1 receptors have 97−99% sequence identity across species and are not expected to exhibit variations in their K_i values.[19] However, mouse CB2[31] (mCB2) exhibits only 82% sequence identity with the human clone[3] (hCB2). This divergent nature of mCB2 and hCB2 receptors could possibly result in species-based differences in affinity.[32,33] For this reason, the analogues were also tested on hCB2.

Table 1. Affinities (K_i) of Cannabinergic Lactones and Their Hydrolytic Metabolites for CB1 and CB2 Cannabinoid Receptors (95% Confidence Limits)

	K_i (nM)[a]		
compd	rCB1	mCB2	hCB2
1	39.5[b]	40[b]	36.4[c]
8	>1000	>1000	>1000
9	>1000	>1000	>1000
10	99 ± 11	803 ± 87	94 ± 13
11	4.6 ± 2.8	792 ± 76	52 ± 7

[a]Affinities for CB1 and CB2 were determined using rat brain (CB1) or membranes from HEK293 cells expressing mouse or human CB2 and [^{3}H]CP-55,940 as the radioligand following previously described procedures.[19,23,30] Data were analyzed using nonlinear regression analysis. K_i values were obtained from three independent experiments run in duplicate and are expressed as the mean of the three values. [b]Reported previously.[20] [c]Reported previously.[34]

As can be seen from the data in Table 1, the topology of the seven-membered lactone ring plays a major role in determining the ligand's ability to bind to cannabinoid receptors. Thus, for CB1, lactone **11** exhibits the highest binding affinity when compared to its regioisomer **10** as well as to the cannabinoid prototype (−)-Δ^9-THC. The situation is different with the CB2 receptor. Our data show that while both regioisomeric lactones **10** and **11** exhibit moderate binding affinities for the human CB2 (K_i = 94 and 52 nM, respectively), they have no significant affinity for the mouse CB2 receptor. These species-based differences in CB2 affinity data have also been observed in our earlier work on cannabinergic ligands.[32]

In agreement with our rational design, the hydrolytic metabolites **8** and **9** are inactive at both CB1 and CB2 receptors and thus eliminate the possibility of undesirable cannabinoid receptor related side effects. Of the two lactone analogues reported here, the most interesting is compound **11**, which shows very high binding affinity for CB1 (K_i = 4.6 nM) as well as 170-fold and 11-fold selectivity for CB1 over mCB2 and hCB2, respectively. These features place compound **11** among the tricyclic cannabinoid analogues with the highest CB1 versus CB2 selectivity known to date.

Next, the lead analogue **11** was assessed for its in vitro plasma stability toward mouse plasma esterases as described in the literature.[19] Our study showed that the test compound is hydrolyzed by esterases to form the metabolite **9** with a half-life of 15.1 min and thus validated the soft analogue profile of our cannabinergic lactone. In addition, functional characterization of **11** was carried out by measuring the decrease in forskolin-stimulated cAMP, as detailed in the literature,[23] and shown to be an agonist at rCB1 with EC_{50} = 184 nM and 41% maximum inhibition of forskolin stimulated cAMP levels.

The structural features of the lactone moiety in the tricyclic ring system appear to be responsible for the different binding affinity profiles of the two regioisomers. To better understand the stereoelectronic requirements for ligand−receptor interaction within this novel scaffold, we have compared the lowest energy conformers of **10** and **11**. A conformational search of the two compounds in implicit water was carried out as described in the experimental section and the global energy

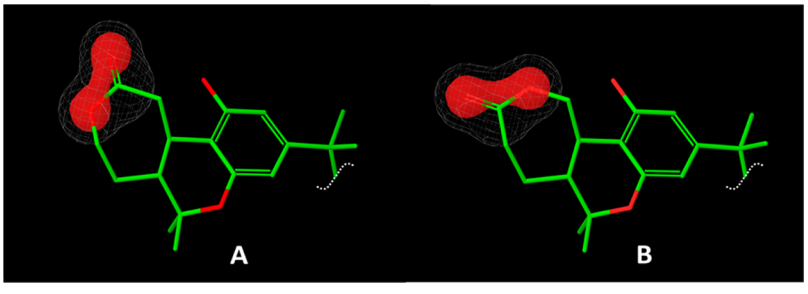

Figure 3. Lowest energy conformers for compounds **10** (A) and **11** (B). The C3 dimethylheptyl side chains are partially displayed, while the 1-hydroxyl group is tilted furthest from the viewer. The white grid shows the van der Waals surface for the ester group. The red contours represent the electron density surfaces of the oxygen atoms.

minimum conformer for each compound was identified. The van der Waals surface for the ester group is represented by the white grid, while the electron density surfaces of the oxygen atoms is highlighted in red (Figure 3). Our modeling shows that the ester groups in the seven-membered lactone rings occupy distinct stereochemical spaces and also that their electron density distribution around the lactone pharmacophore is substantially different. We postulate that the lactone ring in both **10** and **11** encounters some negative pharmacophoric space within the CB2 binding site that should account for the lower binding affinities of the analogues. The observed differences in the binding affinities of the two ligands for CB1 can be explained by invoking that (a) unlike compound **10**, the lactone ring in **11** can be accommodated well within the CB1 binding domain and that (b) the different orientation of the ester group in **10** may engage in unfavorable electrostatic interactions with hydrophobic residues of the CB1 binding site.

In summary, as a part of our controlled-deactivation/detoxification ligand development project, we report a novel tricyclic cannabinergic scaffold. The synthetic approach involves a Baeyer–Villiger rearrangement as the key step. Our data show that one of the regioisomeric lactones binds with high affinity to the CB1 receptor (K_i = 4.6 nM) and exhibits significantly lower affinities for mCB2 (K_i = 792 nM) and hCB2 (K_i = 52 nM). As expected, the lead cannabinergic lactone is susceptible to metabolic inactivation by plasma esterases, while the respective hydrolytic metabolite has no CB1 or CB2 activity. Further biochemical characterization found that AM4809 behaves as an agonist at CB1. In addition, molecular modeling work has helped to define the pharmacophoric elements of the C-ring lactone moiety. It also provides information needed for designing later generation soft analogues possessing higher potencies and selectivities for the CB1 cannabinoid receptor.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, methods, characterization data for compounds, and molecular modeling work. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; (−)-Δ^9-THC, (−)-Δ^9-tetrahydrocannabinol; GPCR, G-protein coupled receptors; CNS, central nervous system; PK/PD, pharmacokinetic/pharmacodynamic; HEK293, human embryonic kidney cell line; DMH, dimethylheptyl

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