Total Synthesis of Axially-Chiral Cannabinols: A New Platform for Cannabinoid-Based Drug Discovery

Primali V. Navaratne,[a] Jenny L. Wilkerson,[b] Kavindri D. Ranasinghe,[a] Evgeniya Semenova,[a] Jasmine S. Felix,[b] Lance R. McMahon,[b] Adrian Roitberg,[a] Ion Ghiviriga,[a] and Alexander J. Grenning*[a]

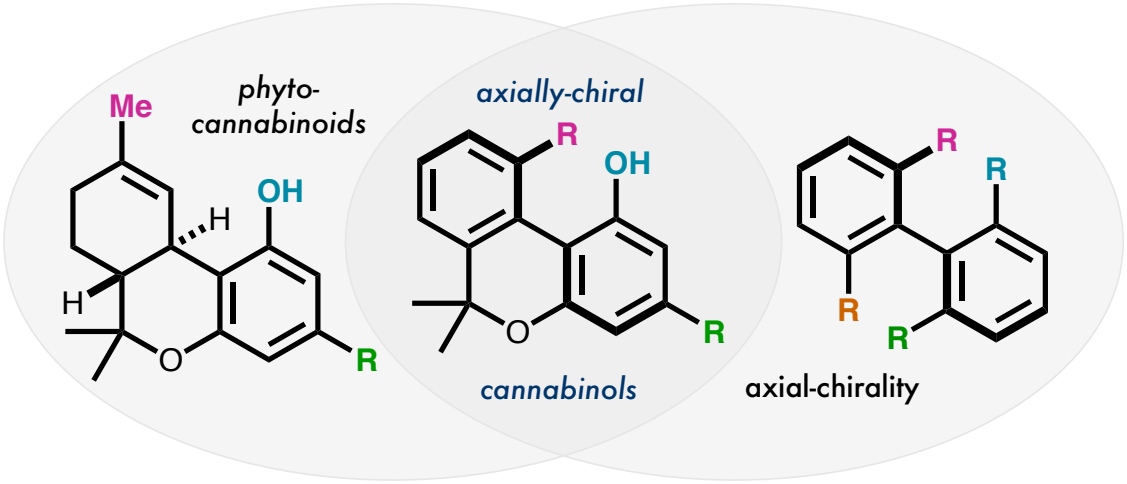
[a]Department of Chemistry, College of Liberal Arts and Sciences, University of Florida, Gainesville, FL 32611
[b]Department of Pharmacodynamics , College of Pharmacy, University of Florida, Gainesville, FL 32611

grenning@ufl.edu

ABSTRACT

Phytocannabinoids, molecules isolated from cannabis, are gaining attention as promising leads in modern medicine, including pain management. Considering the urgent need for combating the opioid crisis, new directions for the design of cannabinoid-inspired analgesics are of immediate interest. In this regard, we have hypothesized that *axially-chiral*-cannabinols (*ax*-CBNs), unnatural (and unknown) isomers of cannabinol (CBN) may be valuable scaffolds for cannabinoid-inspired drug discovery. There are multiple reasons for thinking this: (a) *ax*-CBNs would have ground-state three-dimensionality akin to THC, a key bioactive component of cannabis, (b) *ax*-CBNs at their core structure are biaryl molecules, generally attractive platforms for pharmaceutical development due to their ease of functionalization and stability, and (c) atropisomerism with respect to phytocannabinoids is unexplored "chemical space." Herein we report a scalable total synthesis of *ax*-CBNs, examine physical properties experimentally and computationally, and provide preliminary behavioral and analgesic analysis of the novel scaffolds.

Abstract Figure



concise, scalable, and convergent *de novo* synthesis ● computational ground state and transitionstate analysis ● biological activities validated

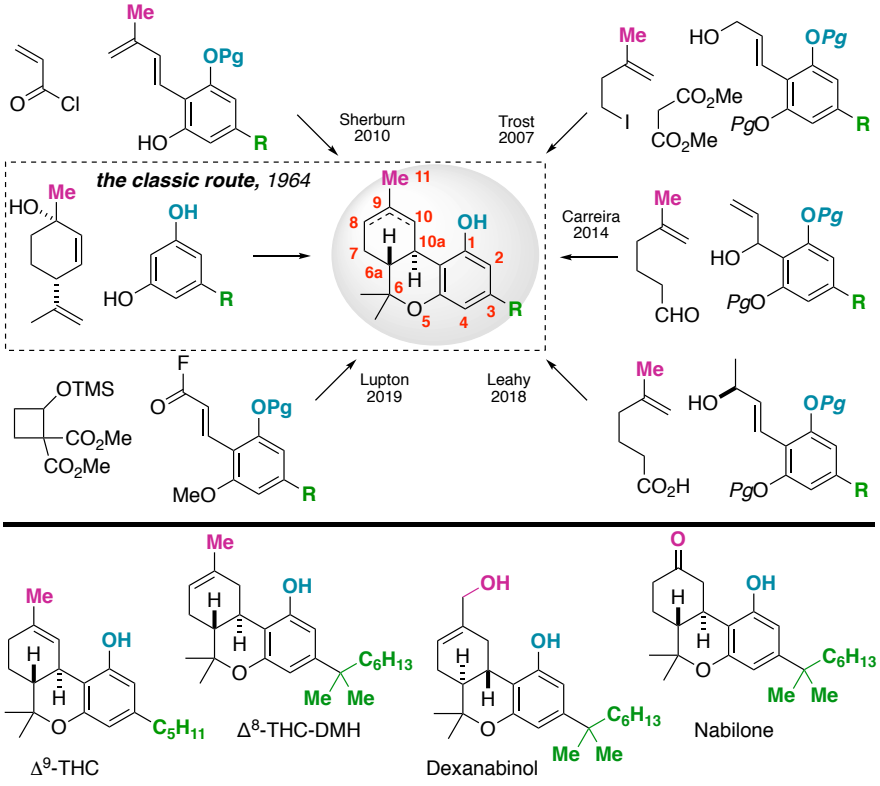
INTRODUCTION

Cannabinoids have captured human interest for millennia. They are most infamously known for their psychoactive properties. Records suggest that humans have known about cannabis intoxication since ~2000 BCE.[1] Medicinal applications have also been known and implemented in both folk and modern medicine, and drugs targeting cannabinoid receptors are promising areas of drug discovery.[2–12] Of particular importance, cannabinoids have been utilized as analgesics with first recorded use in this regard dating back to the Eastern Han Dynasty (25 – 220 CE). Much more recently, cannabinoids have been suggested as *opioid alternatives* for managing pain.[13–16] Identifying non-opioids for pain management is of critical importance considering the opioid epidemic currently crippling the United States and other countries.[17] In addition to their analgesic properties, cannabinoids and analogs are actively being pursued as leads for treating epilepsy,[18] nausea,[19] as well as appetite stimulants and suppressants.[20,21]

Cannabinoids and cannabinoid analogs can be obtained from natural sources, by semisynthesis, and by total synthesis (Figure 1).[22–24] Regarding the latter, the most common route to obtaining cannabinoids for drug discovery is by the *classic route*, reported in 1965 by Mechoulam[25] (inspired by the work of Adams[26,27]), whereby a monoterpene and resorcinol derivative react by a Friedel-Crafts alkylation then etherification pathway. This route has been utilized extensively in modern cannabinoid drug discovery because the chemistry is efficient (few steps) and the resorcinol starting materials are abundant.[28–42] As such, most analogs that have been prepared have had varied arene substitution. For example, structure-activity relationship studies by this route reveal that longer aliphatic chains at C-3 result in more potent cannabinoid receptor ligands.[43] For example, a dimethylheptyl (DMH) chain can be found on the analogs Δ^8-tetrahydrocannabinol-DMH, dexanabinol, and nabilone. Although many other analogs have been synthesized, structure-activity relationship studies at other positions are not nearly as thoroughly analyzed. A few examples of C-9 analogs include dexanabinol and nabilone. The ketone and the C-11 hydroxyl group on nabilone and dexanabinol are accessed from particular monoterpenes; verbenone and myrtenol, respectively.

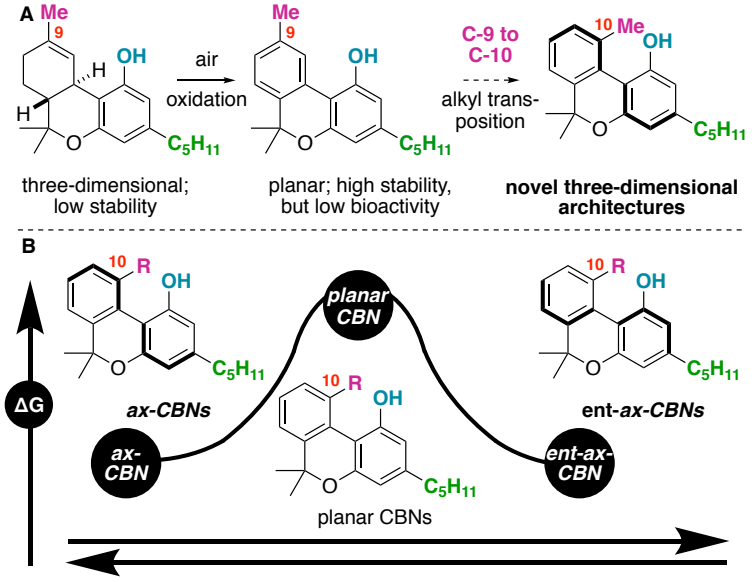
Because of the modern interest in cannabinoid-based drugs, over the past ~10 years new, high efficiency and convergent routes to cannabinoid architectures have been established. Robust total synthesis strategies hold the promise to achieve unprecedented structure-activity relationship understanding about this privileged scaffold, thus yielding new cannabinoid-inspired drug leads. For example, in 2007, Trost reported that an enantioselective allylic alkylation and ring-closing metathesis-based route could rapidly yield (–)-*trans*-Δ^9-THC

Figure 1. A: *Representative synthetic routes for achieving cannabinoid synthesis.* ***B:*** *Representative natural and unnatural cannabinoid analogs.*



from abundant starting materials.[44] Carreira and co-workers demonstrated that any Δ^9-THC enantiomer or diastereomer could be accessed through regioselective allylic alkylation using dual enantioselective catalysis,[45] whereas Leahy described an Ireland-Claisen based approach from easily available enantiopure 2° allyl alcohols.[46] Furthermore, Sherburn *et al*. contributed a Diels-Alder-based approach where a unique Lewis acid catalyst promotes an *exo*-selective [4+2] cycloaddition.[47] Most recently, Lupton disclosed a formal [4+2] cyclization approach to cannabinoids from cyclobutanes and cinnamoyl fluorides *via* the intermediacy of a cyclohexyl-β-lactone.[48]

Figure 2. A: *THC vs CBN vs ax-CBN.* ***B:*** *ax-CBNs are three-dimensional in their ground state and planar in their transition state.*



The aforementioned synthetic achievements will continue to pave way for better understanding of cannabinoid functional activity. However, tetrahydrocannabinols have been the subject of medicinal chemistry campaigns for >50 years. As such, we wished to devise new *THC-inspired* scaffolds that could potentially yield an untapped wealth of research directions for cannabinoid drug discovery. An additional challenge associated with tetrahydrocannabinols is their aerobic oxidation to cannabinols (CBNs); they have a limited shelf life.[22] CBNs, in general, are significantly less studied than THCs both in terms of synthesis and drug discovery.[32,49–53] For these reasons, we believe that *axially*-chiral cannabinols (***ax*-CBNs**); hypothetical, non-natural, hybrid-THCs–CBNs are of potential value to cannabinoid-*inspired* drug discovery. Cannabinol (**CBN**) and *axially-chiral* cannabinol (***ax*-CBN**) are isomers that differ by a C-9 (natural) to C-10 (unnatural) methyl transposition. Such molecules would bear the more stable and pharmaceutically-relevant biaryl carbon framework but would be three-dimensional in their ground state due to steric hinderance.[54,55] Thus, ***ax*-CBNs** would bear a *biaryl* framework akin to CBN, but have ground-state three-dimensionality analogous to THC (hence the term *hybrid* and name *axially-chiral-cannabinol*). As such, they have the potential to have unique physical and biological properties and to be a novel platform for cannabinoid-inspired drug discovery.

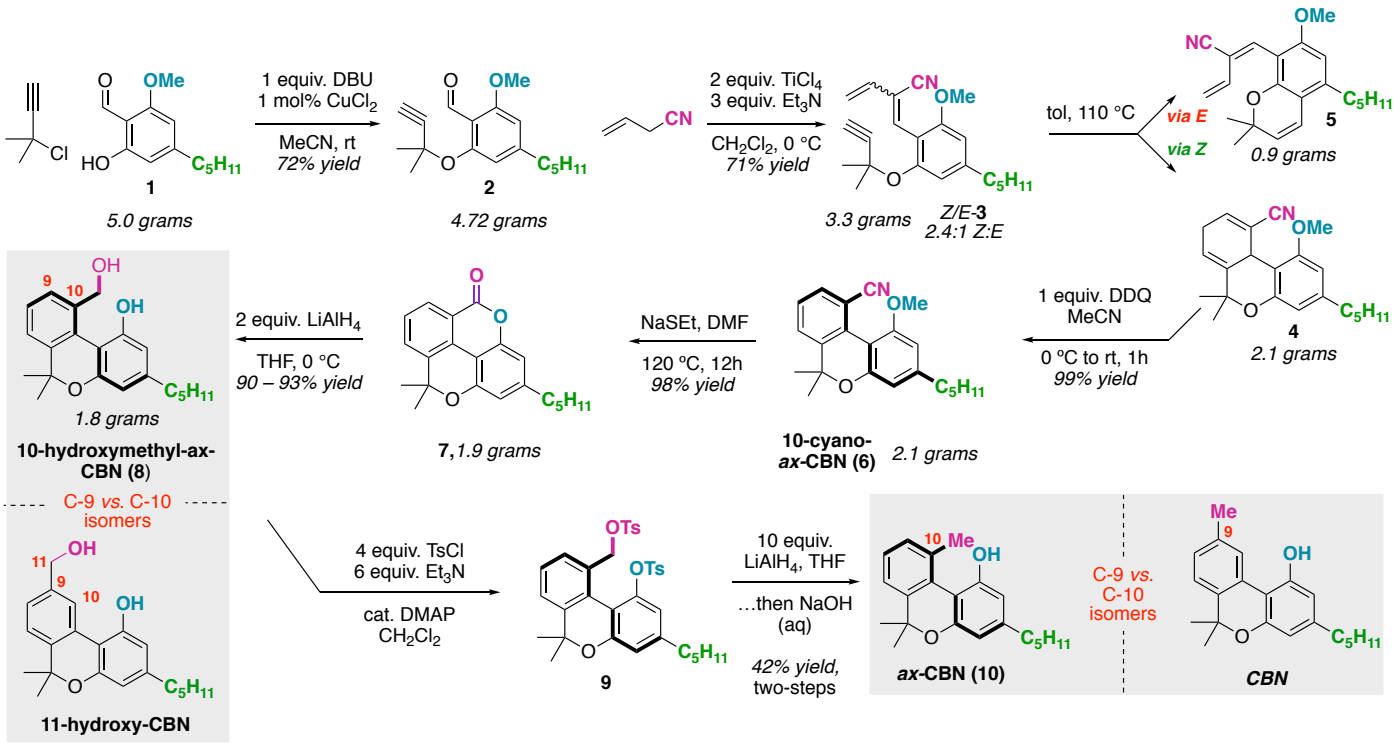
Because of the structural novelty and unknown drug discovery potential of ***ax*-CBNs**, we sought to develop a synthetic protocol to access such scaffolds and examine their bioactivity in standard cannabinoid behavioral paradigms. During the synthetic planning phase, we aimed to develop a route that was concise, operationally simple, and scalable from abundant starting materials, as this would allow ample opportunities for drug discovery (access to material and medicinal chemistry/analog campaigns). Herein, we report a first-generation route to *ax*-CBNs, spectroscopic and computational analysis of *ax*-CBN physical properties, and our initial discoveries related to their biological profiles.

TOTAL SYNTHESIS OF AXIALLY-CHIRAL CANNABINOLS

We have uncovered the following straightforward six- to eight- step route to *axially-chiral* cannabinols (*ax*-CBNs, Figure 3): Salicylaldehyde **1**[56] can react with 1,1-dimethylpropargyl chloride *via* copper-catalysis[57] to yield the phenyl propargyl ether **2**. Condensation of **2** with allyl nitrile yielded an inseparable 2.5:1 *Z:E diene* **3** mixture**.** This Et_3N and $TiCl_4$ mediated condensation is based on a related protocol for the coupling of acrylates

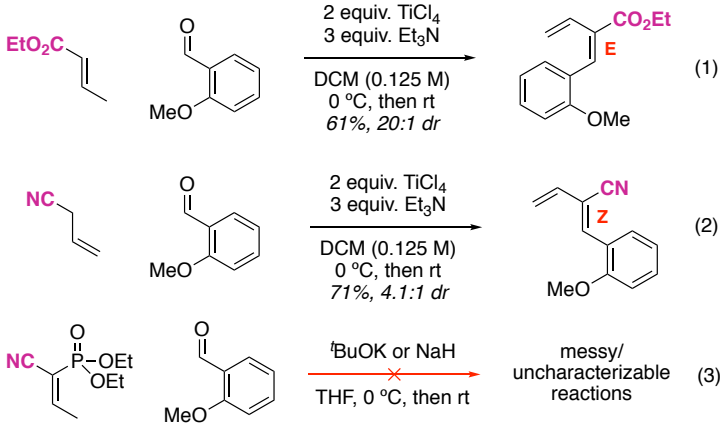
and benzaldehydes.[58] Notably, the conditions and choice of the nitrile functional group were crucial for successful coupling (*vide infra,* Figure 4). Upon heating this mixture of *Z:E* dienes to promote the Diels-Alder reaction, it was found that only the *Z*-diene diastereomer undergoes the desired cycloaddition. The minor *E*-diene isomer converts to a chromene by a propargyl Claisen rearrangement/intramolecular etherification.[59] The two different scaffolds (**4** and **5**) are easily separated by silica gel chromatography. From the Diels-Alder adduct **4**, biaryl scaffold **6** is prepared by DDQ-promoted oxidation.[60] Lactone intermediate **7** is established whereby ethanethiolate promotes a demethylation and intramolecular Pinner sequence. The 10-hydroxymethyl-*ax*-CBN **8** is prepared by $LiAlH_4$ reduction. The overall synthesis of 10-hydroxymethyl-*ax-CBN **8*** is six-steps from salicylaldehyde **1**, dimethyl propargyl chloride, and allyl nitrile and is scalable: From 5 grams of the salicylaldehyde **1**, 1.8 grams of 10-hydroxymethyl-*ax*-CBN (**8**) was prepared in a single pass under the optimized procedure. Additionally, **8** is a C-9 *vs* C-10 isomer of 11-hydroxy-CBN, a natural cannabinoid. From here, the parent *ax*-CBN (**10**) (the C-9 *vs* C-10 isomer of natural CBN) is accessed by benzylic reduction, which is accomplished over a two-step procedure involving *bis*-tosylation (**9**) and $LiAlH_4$ reduction. The phenolic tosylate is partially removed during the reduction and fully removed by a basic work-up.

Figure 3. A: *Six- to eight- step de novo synthesis of* ***ax-CBNs*** *from abundant starting materials:*



The use of allyl nitrile as the carbon source in this synthetic route is notable. Under the *best* conditions we have found to date (reported in Figure 3), allyl nitrile and the aldehyde yield a 2.4:1 mixture of *Z:E* diene isomers and only the major *Z* isomer proceeds to the desired product. In related attempts to optimize this diene synthesis, we explored crotonate-type nucleophiles (Figure 4, equation 1). With a model salicylaldehyde, undesired (for our synthesis) *E-dienes are exclusively prepared.* Thus, the sterically smaller nitrile results in a stereochemical switch to the desired *Z-dienes* (Figure 4, equation 2 and the applied version to *ax*-CBN synthesis in Figure 3). The different stereochemical outcomes for crotonates *vs* allyl nitriles are likely a thermodynamic preference. Finally, in limited attempts, vinylogous Horner-Wadsworth Emmons (HWE) reactions were unsuccessfully explored (Figure 4, equation 3). Furthermore, it is known in the literature that such alkylidene cyanophosphonates react by *vinylogous* HWE reaction, resulting in regioisomeric products.[61] This could be a contributing factor to the messy/uncharacterizable reactions observed.

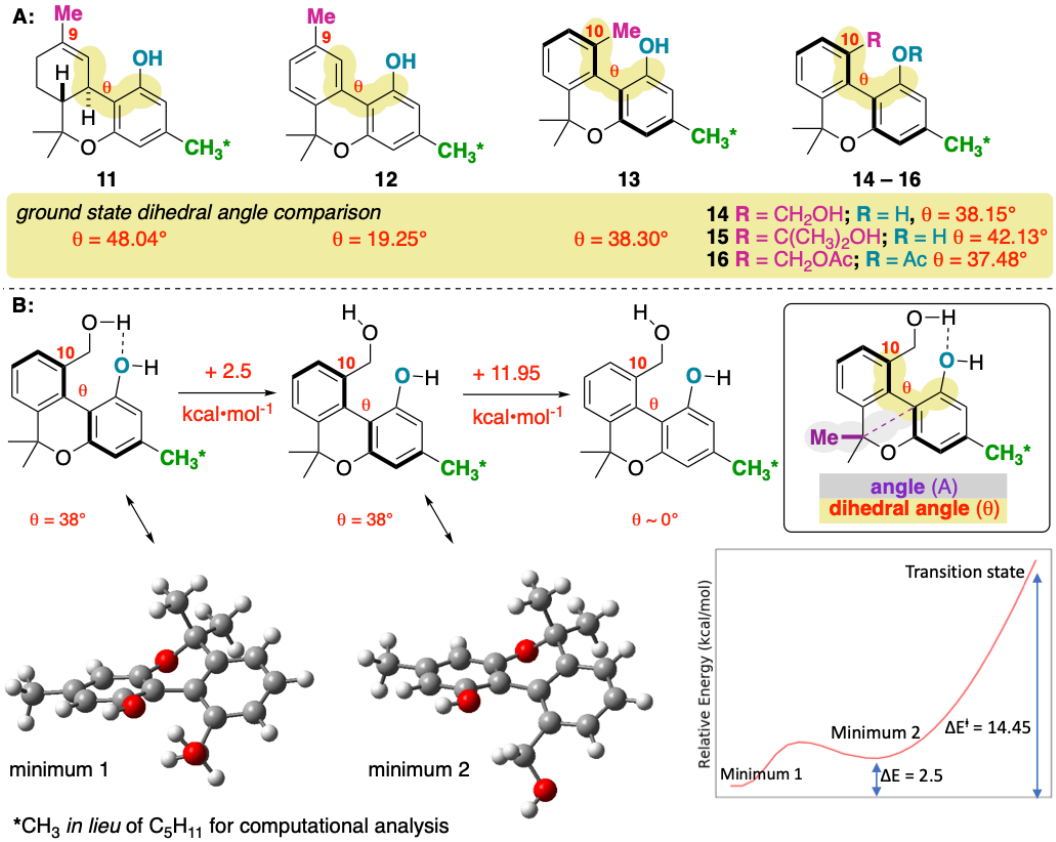
Figure 4. *The nitrile is significant to achieving the necessary Z-diene stereoisomer.*



PHYSICAL PROPERTIES OF AXIALLY-CHIRAL CANNABINOLS

We next sought to understand the physical and structural properties of *ax*-CBN (Figure 5). In particular we were interested in ground state structures of *ax*-CBN, transition-state analysis, and barrier to atropisomerism. Physical and structural property assessment of *ax*-CBN began by comparing its ground state structures to THC, CBN, and a few other *ax*-CBN analogs. To do this, we turned to computational analysis optimized with the ωB97X DFT functional and the 6-31G(d) basis set, using the Gaussian 09 electronic structure package, in the presence of water as the solvent. We also use simplified structures **11 – 16** with a methyl group in place of the pentyl group. It was found that the *ax*-CBN analog (**13**) has three-dimensionality quite similar to the THC analog (**11**). For example, the analogous dihedral angles of THC (**11**), CBN (**12**), and *ax*-CBN (**13**) are 48.04°, 19.25°, 38.30°,

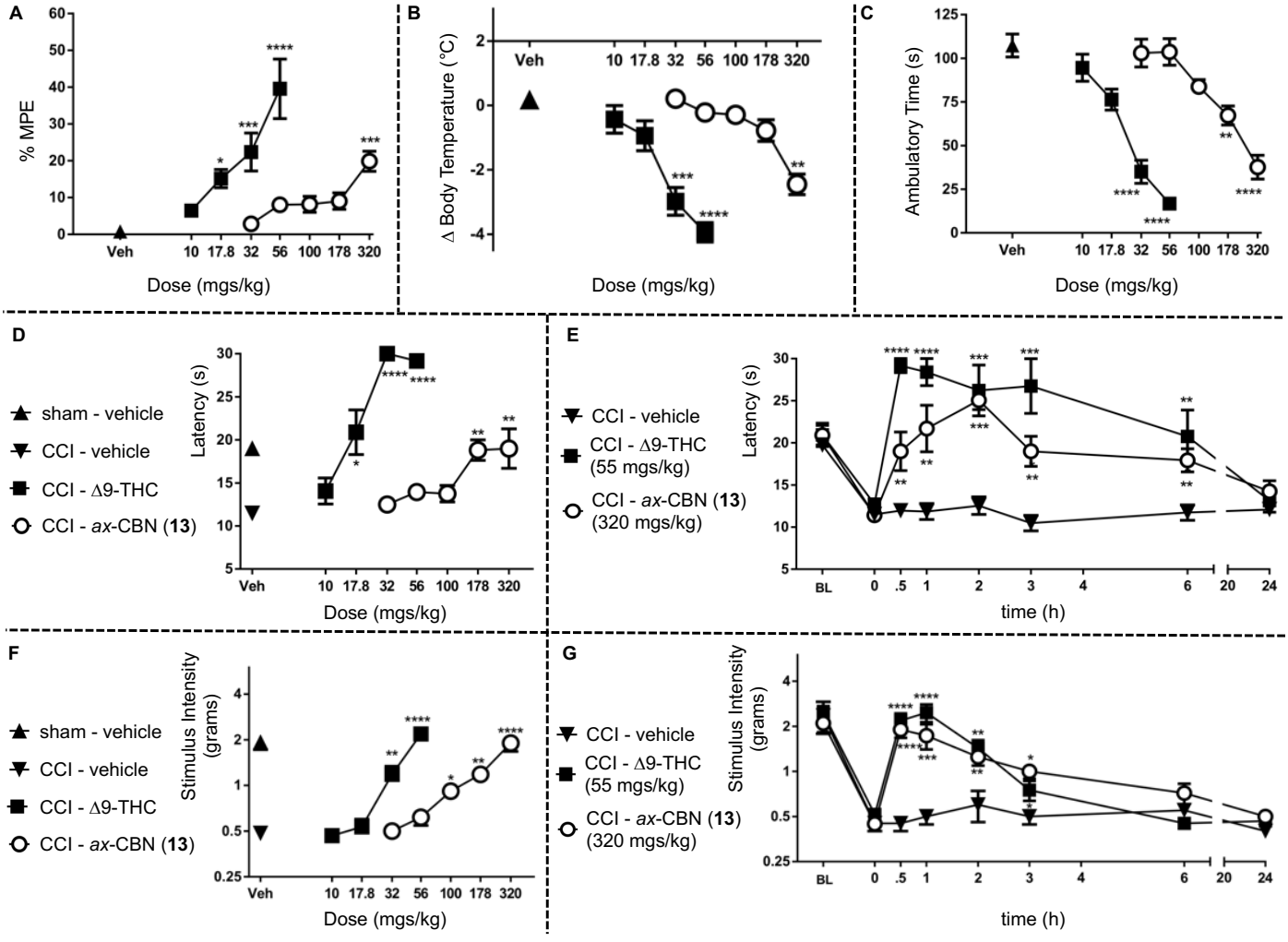
Figure 5. A: *Ground state three-dimensionality of THC vs. CBN vs. ax-CBN vs. ax-CBN analogs.* ***B.*** *Transition state analysis for ax-CBN analog* ***14****.*



respectively. Furthermore, the angle can be further increased by adjusting the steric size of the "R" group (*e.g.* to the 3° alcohol has a dihedral angle of 42°; **14 – 16**; Figure 5A).

Having determined that the structure of *ax*-CBN bears significant three-dimensionality in its ground state, its barrier to atropisomerism was examined next (Figure 5B). A relaxed potential energy surface (PES) scan was carried out to identify the rotational barrier for the conversion from the ground state structure through the transition state, and thus its barrier to undergo *racemization*. A two-dimensional torsional scan was performed on **14** in which the dihedral angle (θ) and the angle (A) corresponding to the inversion in the biaryl carbon framework is fixed to certain values. All other degrees of freedom apart from θ and A were optimized. This analysis revealed that *ax*-CBNs have a barrier to atropisomerism of ~14.5 kcal•mol^{-1}. Notably, **14** had additional ground-state stability *via* H-bonding that must be broken prior to atropisomerism. Nonetheless, the calculated barriers suggest that while three-dimensional in their ground state, *ax*-CBNs of the current design are atropisomerizing at room temperature. Furthermore, this data is supported by variable temperature NMR studies, revealing that **14** has a barrier of 16.3 kcal•mol^{-1} (See the supporting information for details). Thus, at present with the currently synthesized *ax*-CBNs, there is no need to target single enantiomers due to the low barrier to racemization. However, this data supports that *ax-CBN* is conformationally *biased* to have significant three-dimensionality in its ground state akin to THC with the added benefit that we can target an *achiral* cannabinoid (no need for asymmetric synthesis). For these reasons, *ax*-CBNs have high potential to be an attractive, novel platform for cannabinoid-inspired drug discovery.

Figure 6. Behavioral and Biological Studies A: *Tail-Flick Antinociception measured as percent maximum possible effect (% MPE)* ***B:*** *Body Temperature measured as change from baseline* ***C:*** *Locomotion measured as ambulatory time.* ***D,E:*** *Neuropathic Pain-Induced Thermal Hyperalgesia, measured as latency in seconds to respond* ***F,G:*** *Neuropathic Pain-Induced Mechanical Allodynia measured as grams required to produce a stimulus response.*



BIOLOGIAL EVALUATION OF AXIALLY-CHIRAL CANNABINOLS

Having gram-scale access to *ax*-CBNs by the aforementioned synthetic procedure, we next examined the effect of ax-CBNs *vs*. THC in behavioral and analgesic studies. To examine whether *ax*-CBN produces overt physiological effects similar to THC, we assessed *ax*-CBN in a modified version of the tetrad assay, which consists of measuring acute thermal antinociception, body temperature, as well as locomotion and is generally used to screen CB_1 receptor agonists[62,63]. Mice were given vehicle, THC (10 – 56 mg/kg) or *ax*-CBN (56 – 320 mg/kg) and were tested in the three assays (Figure 6). Both THC and *ax*-CBN dose-relatedly produced thermal antinociception, hypothermia and decreased locomotion (see the supporting information for statistical analysis results). Given that THC is well-established to produce anti-pain behavioral effects in numerous animal studies[64,65], we next tested *ax*-CBN in a mouse model of neuropathic pain. Chronic constriction injury (CCI) of the sciatic nerve is widely used as a model of neuropathic pain and produces increased sensitivity to thermal heat, termed thermal hyperalgesia, as well as an increase in light touch sensitivity, termed mechanical allodynia[62,63,65,66]. Both THC and *ax*-CBN dose-relatedly reversed CCI-induced thermal hyperalgesia within 30 min after injection, which persisted for at least 6 h (Figure 6, see the supporting information for statistical analysis results). THC and *ax*-CBN also dose-relatedly reversed CCI-induced mechanical allodynia within 30 min after intraperitoneal administration, which persisted for at least 3 h (Figure 6). Analysis reveals that *ax*-CBN reverses mechanical allodynia and thermal hyperalgesia in an equi-potent manner. THC is less potent in the reversal of mechanical allodynia than in the reversal of thermal hyperalgesia. Further, THC produces cannabimimetic effects at doses required to reverse mechanical allodynia (see the supporting information for potency ratio analysis). Meanwhile, the doses of *ax*-CBN needed to reverse mechanical allodynia are about 2-fold lower than those that produce cannabimimetic effects. Therefore, we conclude that *ax*-CBN has a larger therapeutic dosing window than THC in our mouse model of neuropathic pain. Further, ax-CBN and axially-chiral cannabinols may hold therapeutic promise in the treatment of chronic pain with fewer dose-limiting cannabimimetic effects.

CONCLUSIONS:

We have developed an 8-step synthesis of *axially-chiral* cannabinol (*ax*-CBN), an unnatural isomer of cannabinol (CBN), whereby C9 to C10 methyl transposition results in an isomer with substantially unique *ground-state* three-dimensionality. It was hypothesized that the molecules would *occupy chemical space* more similarly to Δ^9-THC and thus would be attractive scaffolds for cannabinoid-inspired drug discovery. On this line, we validated physical and biological properties, which support our hypothesis. Future studies will take advantage of the concise and convergent strategy for preparing novel analogs for cannabinoid-inspired drug discovery, in particular, we are motivated to discovery better analgesics to combat the opioid crisis.

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