

Axially Chiral Cannabinoids: Design, Synthesis, and Cannabinoid Receptor Affinity

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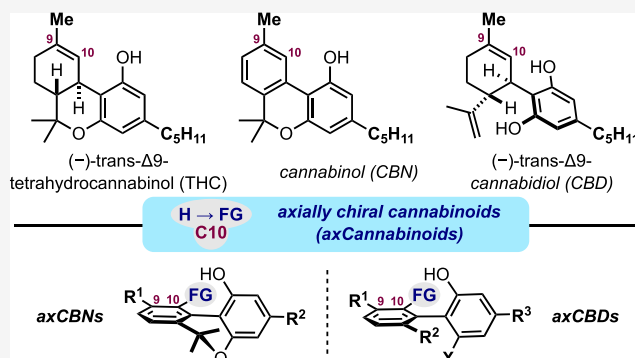


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ABSTRACT: The resorcinol-terpene phytocannabinoid template is a privileged scaffold for the development of diverse therapeutics targeting the endocannabinoid system. Axially chiral cannabinoids (*ax*CBNs) are unnatural cannabinoids (CBNs) that bear an additional C10 substituent, which twists the cannabinol biaryl framework out of planarity creating an axis of chirality. This unique structural modification is hypothesized to enhance both the physical and biological properties of cannabinoid ligands, thus ushering in the next generation of endocannabinoid system chemical probes and cannabinoid-inspired leads for drug development. In this full report, we describe the philosophy guiding the design of *ax*CBNs as well as several synthetic strategies for their construction. We also introduce a second class of axially chiral cannabinoids inspired by cannabidiol (CBD), termed axially chiral cannabidiols (*ax*CBDs). Finally, we provide an analysis of axially chiral cannabinoid (*ax*Cannabinoid) atropisomerism, which spans two classes (class 1 and 3 atropisomers), and provide first evidence that *ax*Cannabinoids retain—and in some cases, strengthen—affinity and functional activity at cannabinoid receptors. Together, these findings present a promising new direction for the design of novel cannabinoid ligands for drug discovery and exploration of the complex endocannabinoid system.



INTRODUCTION

Phytocannabinoids and their synthetic analogues are prime candidates for pharmaceutical innovation in the quest for alternatives to highly addictive opioid analgesics, though they are yet to achieve Food and Drug Administration (FDA) approval for this formidable goal.^{1,2} More generally, cannabinoid-based chemical probes and leads are essential for continued exploration of the endocannabinoid system, a complex neuro- and immunomodulating network implicated in a variety of neurodegenerative diseases as well as inflammation, metabolic disorders, and cancer.^{1,3} Most phytocannabinoid research to date has focused on the natural *trans*-tetrahydrocannabinol (*trans*-THC) and cannabidiol (CBD) frameworks, which have led to several approved medications (Figure 1A).^{4–11} For example, (–)-*trans*-Δ⁹-THC is FDA-approved (Dronabinol) for the treatment of HIV/AIDS-induced anorexia¹² as well as chemotherapy-induced nausea and vomiting.¹³ The approval of CBD (Epidiolex) to treat refractory childhood seizures marked the first time a *cannabis*-derived product was approved by the FDA.¹⁴ Synthetic cannabinoids inspired by THC have emerged due to well-established synthetic protocols dating back to the 1940s¹⁵ via a renaissance of research over the past ~60 years.¹⁶ Additionally,

there are numerous inspiring routes to CBD¹⁷ and minor cannabinoids.¹⁸ In this regard, nabilone is approved to treat chemotherapy-induced nausea and vomiting,¹⁹ and ajulemic acid has reached various clinical trial phases as a treatment for systemic sclerosis, dermatomyositis, cystic fibrosis, and systemic lupus erythematosus (Figure 1B).²⁰ Beyond the THC scaffold, other frameworks for synthetic cannabinoids have appeared, including cyclohexylphenols (e.g., CP55940),²¹ cannabidiol derivatives (e.g., KLS-13019),²² cannabiolactones (e.g., AM1714),²³ and a variety of other heterocyclic scaffolds described elsewhere.²⁴

Recently, we proposed that axially chiral analogues of cannabinoids may serve as valuable tools and leads for cannabinoid-based drug discovery (*ax*Cannabinoids, Figure 1C).²⁵ Scaffolds of this type are attractive for the following reasons: (i) *ax*Cannabinoids are three-dimensional biased

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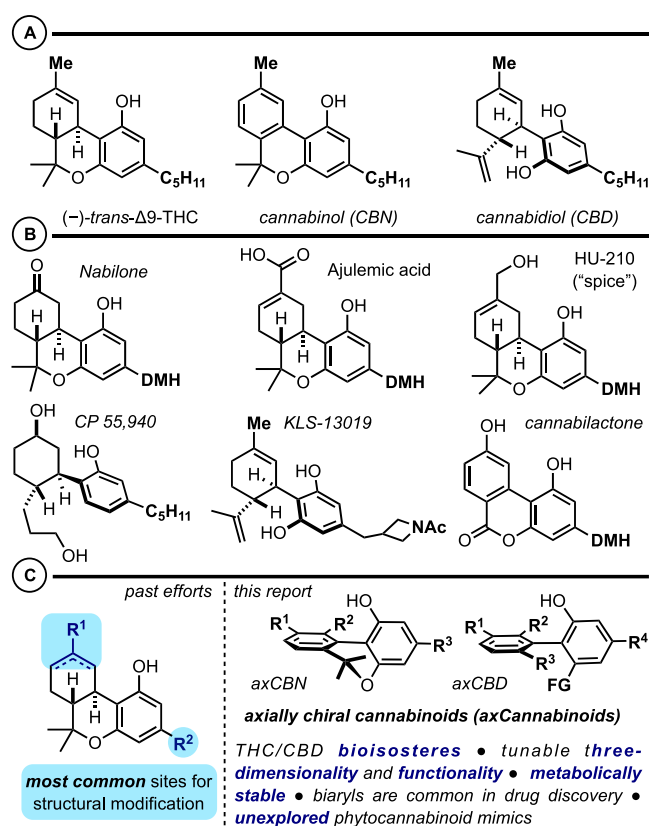


Figure 1. (A) Major phytocannabinoids (THC, CBN, and CBD). (B) Representative synthetic cannabinoids. (C) Past efforts and this work: *axCannabinoids* as bioisosteric variants with improved physical and biological properties.

ligands where additional *ortho*-substitution results in rotational and dihedral angle restrictions about the biaryl linkage. The significance of atropisomerism and the tuning of biaryl dihedral angles is a challenge and opportunity in modern drug design.^{26–30} (ii) *axCannabinoids* are built upon a central

biaryl framework. Biaryls are readily prepared and functionalized by numerous methods and are often metabolically stable. These features have made biaryls a common template in drug discovery campaigns.^{31,32} This quality is particularly relevant to cannabinoid design as many phytocannabinoids and synthetic variants are prone to aerobic and metabolic oxidation.³³ (iii) Atropisomerism is unexplored with respect to cannabinoid ligands, providing potentially rich grounds for discovery and innovation. This hypothesis that structural modification of (synthetic) phytocannabinoids to *axCannabinoids* can impact both physical/biological properties and retrosynthesis/forward synthesis logic is strongly aligned with a recent call from Shenvi et al. for “creative editing of natural products” as an “invitation for [chemical and biological] discovery”.³⁴ In this report, we describe our initial efforts to establish *axCannabinoids* as valuable lead molecules with high affinity for cannabinoid receptors. This includes synthetic strategies for accessing axially chiral cannabinoids (*axCBNs*), introduction to and synthesis of axially chiral cannabidiols (*axCBDs*), and affinity studies for select *axCannabinoids* at the cannabinoid receptors (hCB₁R and hCB₂R).

RESULTS AND DISCUSSION

Synthetic Methods toward Axially Chiral Cannabinols (*axCBNs*). We previously reported a scalable, first-generation synthesis of “parent” axially chiral cannabinol (*axCBN*), the C9-to-C10 methyl-transposed isomer of cannabinol (CBN) (Figure 2A).¹² By design, this transposition results in significant topological changes to the cannabinoid architecture: the ground-state biaryl dihedral angle increases from 19° in CBN to 38° in *axCBN*. CBNs are relatively planar ($\theta = 19^\circ$) with little barrier to inversion, whereas *axCBNs* have increased three dimensionality ($\theta = 38^\circ$) and barriers to atropisomerism ranging from 14 to 17 kcal/mol (class 1 atropisomerism).^{26–30} Retrosynthetically, we envisaged access to *axCBN* via an intramolecular Diels–Alder approach to biaryls (DAB).^{35–37} This revealed dimethylpropargyl chloride 1, allylcyanide 2, and the olivetol derivative 3 as potential

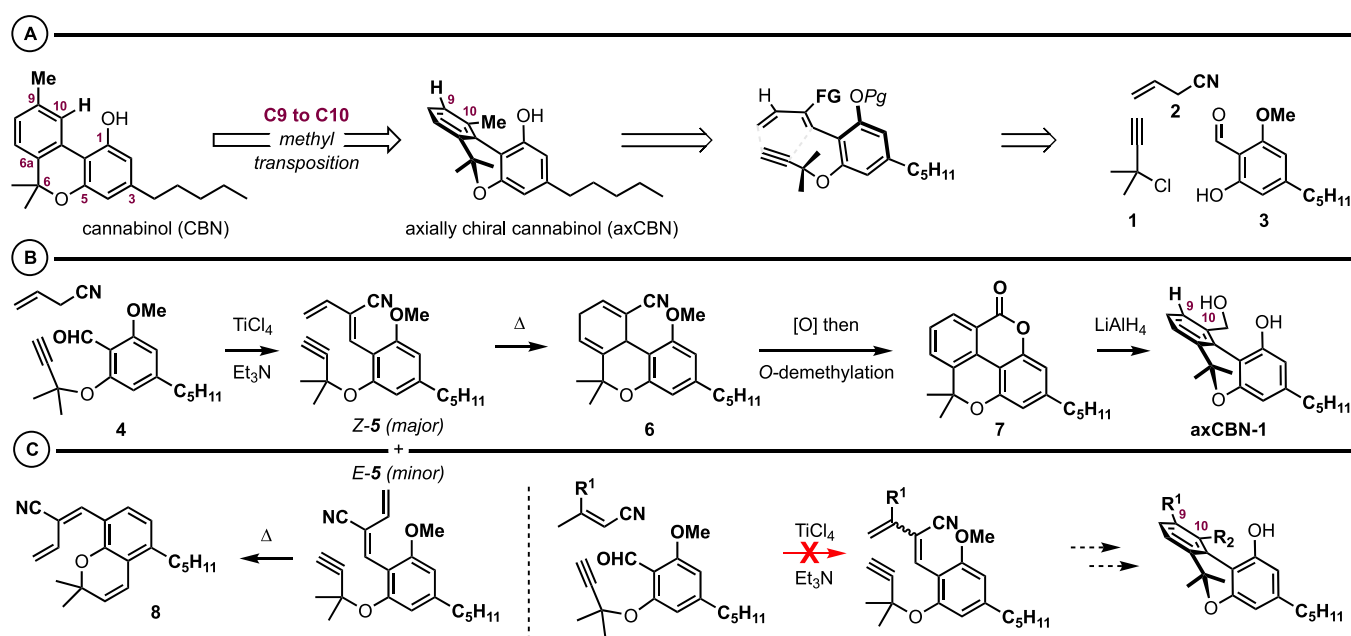
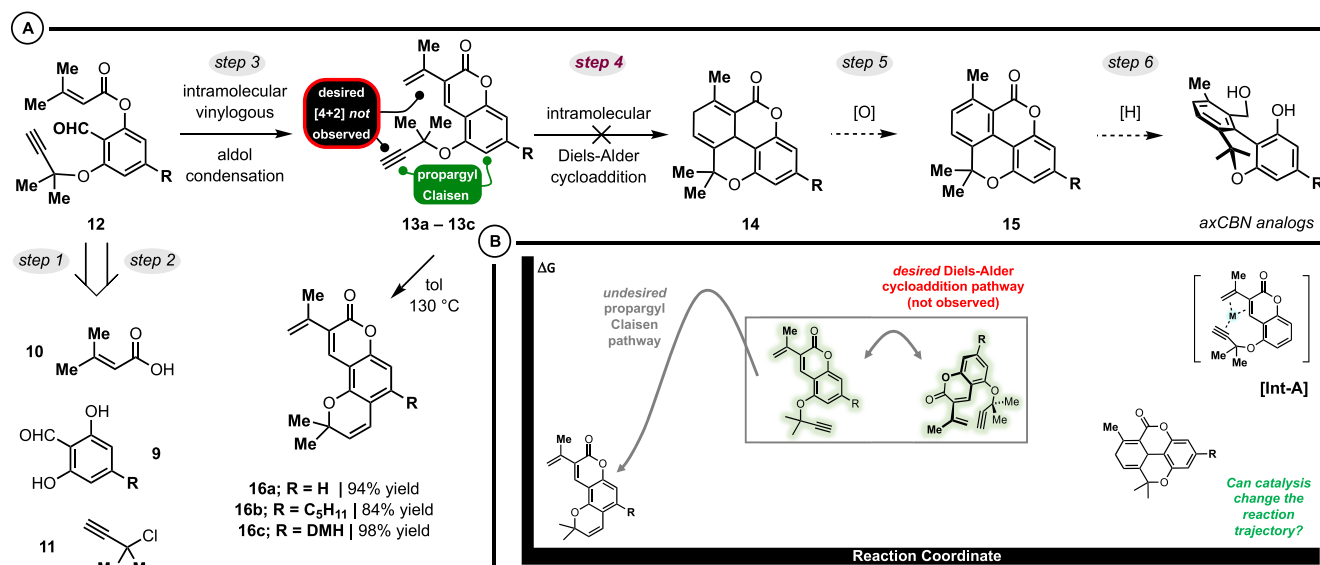
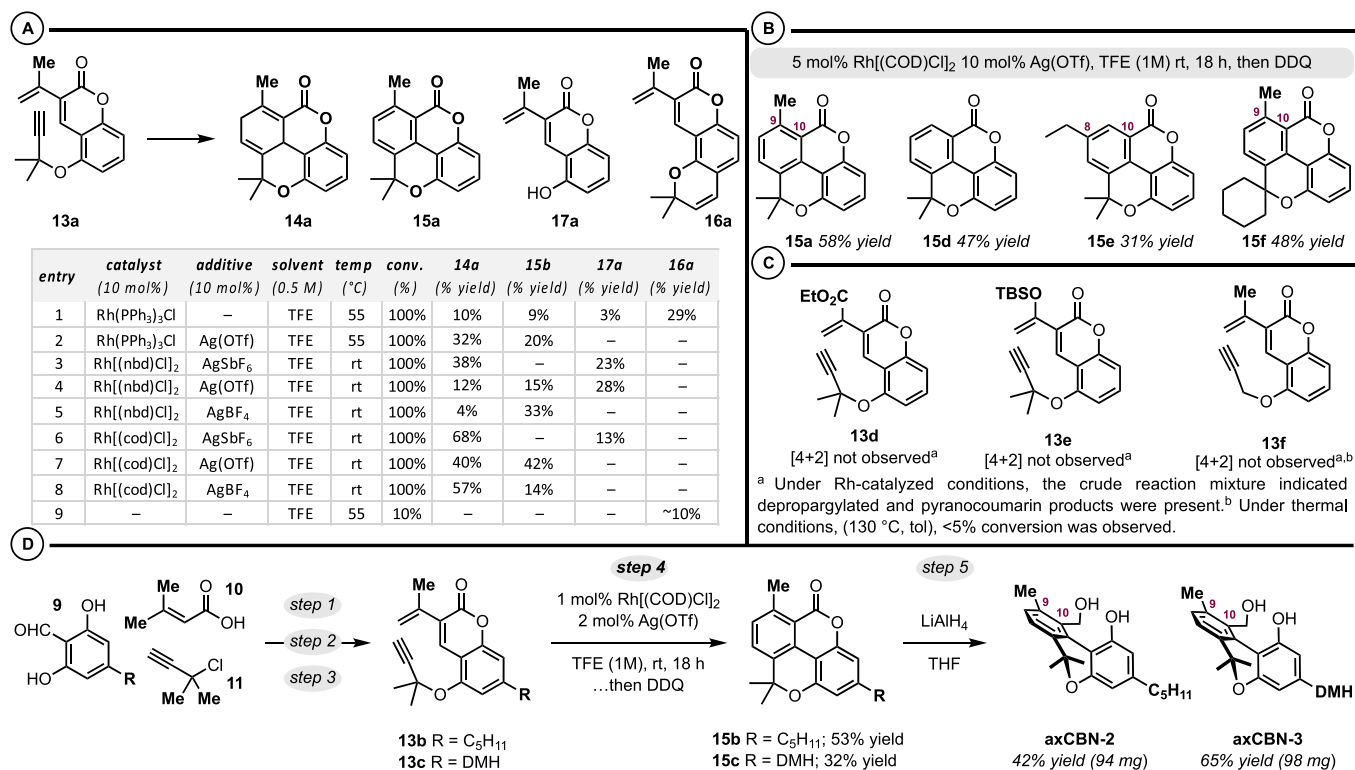


Figure 2. *axCBN* retrosynthesis (A), forward synthesis (B), and representative synthetic shortcomings (C).

Scheme 1. (A): Second-Generation Strategy Capable of Achieving C9 and C10 Disubstitution Is Challenged by a Competitive Propargyl Claisen Rearrangement. (B): Can the Innate [3,3] Reactivity Be Overturned in Favor of Dearomative [4+2] Cycloaddition?



Scheme 2. Optimization (A), Scope (B), and Limitations (C) of Rh-Catalyzed Dearomative [4+2] Cycloaddition. (D) Synthesis of axCBN-2 and axCBN-3



starting materials. A successful route to axCBN and other C10-substituted analogues was achieved through a key biaryllactone intermediate **7** (Figure 2B). This advanced scaffold was prepared via Cu-catalyzed dimethylpropargylation between **1** and **3** (yielding **4**), TiCl₄/Et₃N-promoted condensation between **4** and allylcyanide **2** (yielding an inseparable mixture of *E*-**5** and *Z*-**5**), intramolecular Diels-Alder cycloaddition (yielding **6**), DDQ oxidation, and demethylative Pinner reaction (yielding **7**). axCBN-1 was prepared via LiAlH₄

reduction (Figure 2B) and “parent” axCBN was prepared in two additional steps.

While this initial synthetic strategy provided ample amounts of parent axCBN and axCBN-1 over a reasonably efficient synthetic sequence (6–8 steps from **1**, **2**, and **3**), it is not without shortcomings. Synthetic challenges include a non-selective vinylogous aldol condensation that produces an inseparable mixture of *E*-**5** and *Z*-**5**, and only the *Z* isomer reacts as desired in the subsequent step. As shown in Figure

2C, the *E*-5 isomer undergoes a propargyl Claisen rearrangement to benzochromene 8. More significantly, the key $\text{TiCl}_4/\text{Et}_3\text{N}$ -promoted condensation was unsuccessful with substituted crotonitriles ($\text{R} \neq \text{H}$), limiting the modularity of the synthetic route with respect to C9 substitution (Figure 2C).

The issues we encountered during our initial studies (Figure 2C) prompted us to explore an alternative protocol that would be capable of accessing *ax*CBNs bearing both C9 and C10 substitution, as we hypothesized that the most active *ax*CBN analogues would have substituents at both positions. Simple transposition of the C9 methyl group to the C10 position generates a “methyl void” on the parent scaffold, and methyl groups are known to have significant impact on drug properties (the “magic methyl effect”).^{38,39} Consequently, deletion of the C9 methyl substituent may negatively impact the affinity and efficacy at cannabinoid receptors.³⁸ Thus, we aimed to develop a synthetic route capable of facilitating C9-methylation and C10 functionalization, as well as variation at other positions. In this regard, we envisioned access to *ax*CBN analogues from 12 by a sequential intramolecular aldol condensation/Diels-Alder cycloaddition yielding the advanced tetracyclic intermediate 14 (Scheme 1A). Upon cyclohexadiene oxidation and biaryl lactone ring opening, *ax*CBN analogues would be unveiled. We postulated that the key scaffold 12 could be prepared simply from the requisite olivetol-aldehyde 9, 3,3-dimethylacrylic acid 10, and dimethylpropargyl chloride 1, with known literature procedures for preparing aryl dimethylpropargyl ethers^{40–42} and divinylcoumarins serving as inspiration.^{43,44}

At the outset of our studies, we successfully prepared model Diels-Alder precursors 13a–13c by the proposed Cu-catalyzed dimethylpropargyl ether synthesis, phenol acylation with 3,3-dimethylacrylic acid 10, and intramolecular vinylogous aldol condensation (Scheme 1A). At this point, we realized that the desired thermal [4+2] transformation would be more challenging than we initially anticipated: under thermal conditions, these substrates exclusively react via propargyl Claisen rearrangement to yield pyranocoumarins.^{42,45} It became apparent that a critical Curtin-Hammett kinetics challenge exists in which the desired product 14 is neither thermodynamically nor kinetically favored over the propargyl Claisen rearrangement (Scheme 1B). Recall from Figure 2 that the *Z*-cyano-1,3-diene underwent favorable [4+2] cycloaddition over propargyl Claisen rearrangement. While 13 has the correct 1,3-diene geometry, the kinetics and thermodynamics of the desired [4+2] cycloaddition are less favorable due to the aromaticity of the coumarin (which must be broken during the Diels-Alder reaction).^{43,46,47} Thus, to achieve the desired transformation, reversal of the innate Curtin-Hammett controlled reactivity is necessary. Toward this goal, we envisioned that a transition-metal catalyst could template the diene and dienophile (via intermediate-A (Int-A); Scheme 1B), resulting in an altered kinetic profile and mechanism favoring formation of the coumarin-dearomatized [4+2] product (Figure 2). While there are many examples of metal-catalyzed [4+2] cycloisomerization,^{48–55} vinylcoumarins as dienes, dearomatization, and Curtin-Hammett kinetics challenges are novel to this research area.

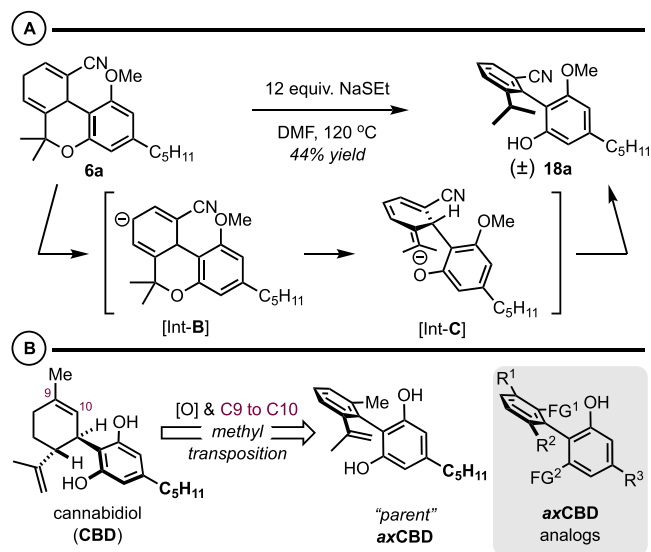
To achieve the desired [4+2] reactivity, rhodium(I) catalysis was examined (Scheme 2A).^{53–55} Using Wilkinson's catalyst ($(\text{PPh}_3)_3\text{RhCl}$) in trifluoroethanol (entry 1), we observed a complex mixture of products that notably contained the desired [4+2] cycloadduct 14a and its oxidation product, biaryl 15a. Also observed were the depropargylated product 17a and

the propargyl Claisen rearrangement product 16a. The addition of catalytic $\text{Ag}(\text{OTf})$ improved the result to 32% yield 14a and 20% yield 15a (entry 2). Catalytic $[\text{Rh}(\text{NBD})\text{Cl}]_2/\text{Ag}(\text{I})$ additives performed comparably to Wilkerson's catalyst/ $\text{Ag}(\text{OTf})$ (entries 3–5 versus entry 2). The best results were achieved with catalytic $[\text{Rh}(\text{COD})\text{Cl}]_2/\text{Ag}(\text{I})$ salts in trifluoroethanol (entries 6–8) where combined 68–82% yields of 14a and 15a were obtained. Notably, the reaction performed similarly well on the 1 mmol scale (see the Supporting Information). As a control, we examined the reaction catalyst-free in trifluoroethanol (entry 9), confirming the essential impact of the catalyst. We briefly examined the scope of the transformation targeting the tetracyclic scaffolds 15a–15f (Scheme 2B,C). Products 15 were directly prepared from 13 via a one-pot, two-step $\text{Rh}(\text{I})$ -catalyzed [4+2] cycloaddition followed by in situ DDQ oxidation of the intermediate 1,4-cyclohexadiene.⁵⁶ Products 15d and 15e represent variations in the diene component. Unsubstituted (15d) and ethyl-substituted (15e) dienes were reasonably tolerated. In contrast, modifications to the diene electronics resulted in little to no sign of the desired products (Scheme 2C). For example, ester substrate 13d and the silyl-enol ether diene 13e were not competent Diels-Alder substrates. With respect to the propargylic substitution on the dienophile, a cyclohexyl group was tolerated yielding 15f. However, in the absence of substitution, the transformation did not occur (Scheme 2C, 13f).

The scope studies related to the $\text{Rh}(\text{I})$ -catalyzed [4+2] cycloaddition suggest that a variety of C8/C10 (15e) and C9/C10 (15a and 15f) disubstituted *ax*CBNs can be accessed. Along these lines, coumarins 13b and 13c bearing the common cannabinoid aliphatic chains (pentyl and dimethylheptyl (DMH), respectively) on the resorcinol-portion of the scaffold were prepared (Scheme 2D). Gratifyingly, the $\text{Rh}(\text{I})$ -catalyzed [4+2] cycloaddition/oxidation sequence yielded the desired pyrano-biaryllactones 15b and 15c. LiAlH_4 reduction furnished the targeted *ax*CBN analogues, *ax*CBN-2 and *ax*CBN-3.

Synthetic Methods toward Axially Chiral Cannabidiols (*ax*CBDs). During our studies related to the first-generation route to *ax*CBNs (Figure 2), specifically, the attempted demethylation to free the phenol on 6, we encountered a transformation that converted the Diels-Alder adduct 6a into the biaryl 18a with concomitant pyran ring cleavage (Scheme 3). We surmised that this transformation occurred by an “ E1_{cb} aromatization.” In this process, the nitrile group directs deprotonation yielding int-B, which is poised for pyran ring-cleavage to phenoxide int-C. In situ or upon acidic work up, int-C undergoes a thermodynamically favorable isomerization from the nonaromatic isotoluene to the biaryl product 18. This was an interesting outcome as it resulted in an axially chiral biaryl by a unique method, and the structure is reminiscent of the theoretical “parent” axially chiral cannabidiol (*ax*CBD). Regarding the method, the Diels-Alder reaction between dienes and alkynes to yield arenes usually relies on oxidation of the intermediate 1,4-cyclohexadiene⁵⁷ or elimination of an endocyclic leaving group.^{58,59} Thus, this represents a unique strategy for targeting substituted and functionalized arenes. With respect to CBD, *ax*CBD is formulated in analogy to the relationship between THC and *ax*CBN: the cyclohexene ring of the parent natural product is formally oxidized to the arene, and the methyl group is transposed from the C9 to the C10 position, thus resulting in axially chiral cannabidiols. This term should be considered

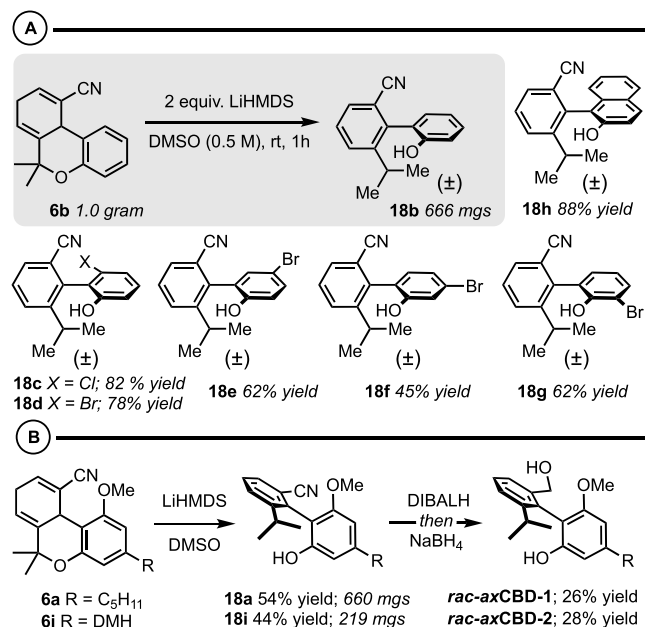
Scheme 3. (A) Observation of an E1_{cb} Elimination Reaction Yielding a Biaryl Reminiscent of Parent *ax*CBD. (B) Cannabidiol (CBD) and Axially Chiral Cannabidiol (*ax*CBD)



loosely as parent *ax*CBD is *prochiral* rather than chiral, but it bears an orthogonal, conformationally restricted biaryl linkage and thus is three-dimensional. That said, many *ax*CBD analogues have the potential to be axially chiral biaryls.

Intrigued by the initial result and the potential to mimic the structure of cannabidiol (CBD) with axially chiral analogues, we designed a model substrate to optimize the E1_{cb} aromatization sequence for targeting *ax*CBDs (Scheme 4). The key substrates (6a–6i) were prepared by the same synthetic sequence outlined in Figure 2: (i) TiCl₄/Et₃N-mediated aldol condensation between allyl cyanide and the requisite O-dimethylpropargylsalicylaldehyde then (ii) intra-

Scheme 4. (A) Biaryl Synthesis via E1_{cb} Aromatization: Scalability and Scope Studies. (B) Synthesis of *ax*CBD-1 and *ax*-CBD-2 Utilizing E1_{cb} Aromatization

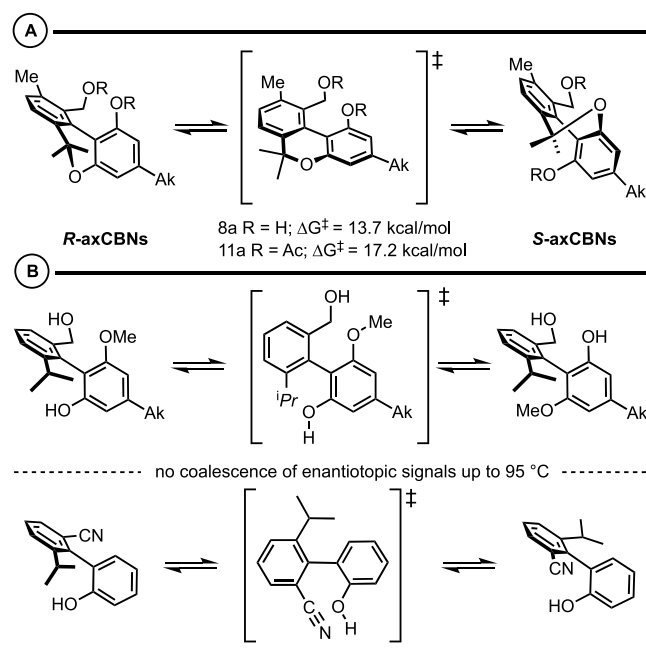


molecular Diels-Alder cycloaddition. It was found that various bases could instigate the E1_{cb} aromatization, but LiHMDS was optimal (see the Supporting Information for select optimization reactions). This reaction can be performed on the gram scale, and a variety of unique *o*-benzonitrile-*o*'-phenol biaryls were prepared in good yields under the optimized protocol. Notably, halogen functional handles are tolerated at every position about the phenol (18c–18g), and an *o*-benzonitrile-*o*'-naphthol biaryl 18h is accessible. With the goal of applying this method to the synthesis of *ax*CBD analogues, Diels-Alder adducts 6a and 6i were accessed on the 0.5–1 g scale. Under the standard E1_{cb} aromatization conditions, we prepared the advanced axially chiral biaryl intermediates 18a and 18i in good yields (54 and 44%, respectively). Nitrile reduction to the alcohol was achieved via sequential addition of DIBALH and NaBH₄ yielding *ax*CBD-1 (R = pentyl) and *ax*CBD-2 (R = dimethylheptyl (DMH)).

Atropisomerism of Axially Chiral Cannabinoids.

Axially chiral cannabinoids (*ax*CBNs) and cannabidiols (*ax*CBDs) differ from their respective natural product counterparts, THC and CBD in two main ways: (1) by oxidation of the natural cyclohexene to a benzene ring and (2) by C9 to C10 methyl transposition. These structural modifications result in nonplanar biaryl scaffolds, rotational restrictions about the biaryl linkage, and tunable three dimensionality: variation of the *ortho*-substituents and ring types directly influences the dihedral angles and barriers to atropisomerism. For example, the barrier to atropisomerism for *ax*CBN-2 and its *bis*-acetate, *ax*CBN-4, was found by VT-NMR to be 14 and 17 kcal/mol, respectively (Scheme 5).

Scheme 5. (A) *ax*CBNs Display “type 1” Atropisomerism. (B) *ax*CBDs Display “type 3” Atropisomerism.



Regarding *ax*CBDs, VT-NMR experiments indicated that the biaryl linkage was conformationally stable: no coalescence of the enantiotopic signals was observed up to 95 °C in toluene-D₈. These studies revealed that we have synthesized two classes of axially chiral cannabinoid thus far: *ax*CBNs are class 1 atropisomers while *ax*CBDs are class 3 atropisomers.^{26–30} As

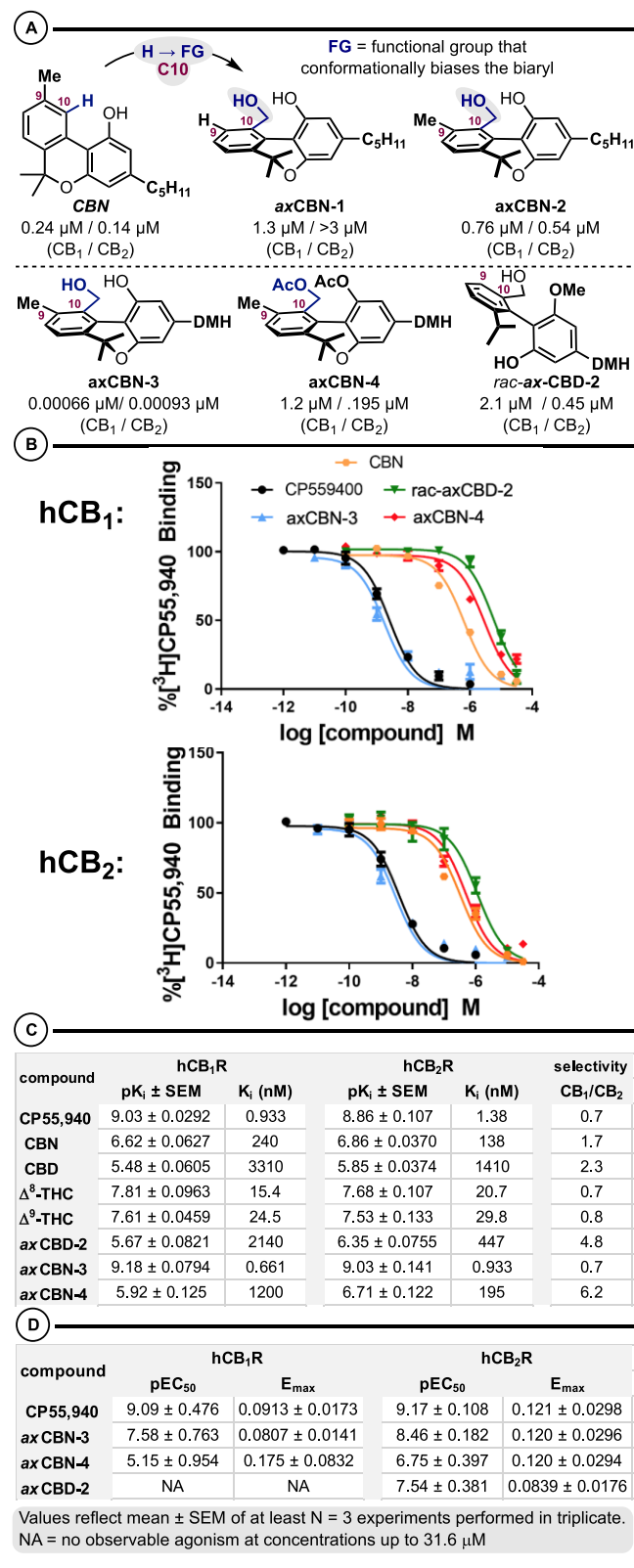
such, *ax*CBNs can be treated as achiral molecules due to the rapid interconversion of the individual atropisomers, though they would presumably bind their targets in *chiral non-racemic configurations* (vide infra). Conversely, *ax*CBDs are *configurationally stable* and the individual atropisomers could have different binding affinities for their targets (vide infra).

Molecular Pharmacology of Axial Chiral Cannabinoids at Cannabinoid Receptors. We have examined a small series of *ax*Cannabinoids for binding affinity and functional activity at human cannabinoid receptors (hCB₁R and hCB₂R) (Schemes 6 and 7). From this initial series, several compounds emerged with desirable pharmacology relative to the relevant parent phytocannabinoid in terms of affinity and selectivity. *ax*CBN-3 exhibited sub-nanomolar affinity for both receptors, approximately 360-fold higher than CBN at hCB₁R and 134-fold higher at hCB₂R.⁶⁰ When compared to the dimethylheptyl derivative of CBN (CBN-DMH) reported by Rhee and co-workers,^{60,61} *ax*CBN-3 has approximately 5–10-fold higher affinity. This suggests that the addition of the C-10 group, which biases the biaryl to a nonplanar configuration, confers additional beneficial interactions with hCB₁R and hCB₂R that result in higher affinity. Notably, *ax*CBN-3 demonstrated affinity similar to that of the positive control, CP55940, at both receptors.⁵⁸ Additionally, *ax*CBD-2 and *ax*CBN-4 exhibited increased selectivity for hCB₂R, 4.8- and 6.2-fold, respectively.

Importantly, these compounds maintained functional activity as determined by stimulation of [³⁵S]GTPγS binding, an assay of native G protein activation (Supplementary Tables 4 and 5). *ax*CBN-3 exhibited an 8-fold greater potency to stimulate [³⁵S]GTPγS binding at hCB₂R than at hCB₁R while exhibiting increased efficacy over CBN. *ax*CBN-4 also maintained agonist activity at hCB₂R. Notably, *ax*CBD-2 exhibited 7.4-fold greater potency in [³⁵S]GTPγS binding. Further, *ax*CBD-2 exhibited agonism at hCB₂R in the TRUPATH assay of Gαi1β3γ9 protein activation (Supplementary Tables 6 and 7), but not at hCB₁R at concentrations up to 31.6 μM (Scheme 6D), suggesting a potential route for development of selective hCB₂R agonists. This functional activity diverges from that of the parent CBD which exhibits no efficacy at either cannabinoid receptor in either of these assays (data not shown). Interestingly, in contrast to CBN [$F(2, 64) = 1.21, p = 0.305$], *ax*CBN-3 [$F(2, 91) = 42.7, p < 0.0001$] exhibited distinct affinities for two binding sites following an extra sum-of-squares F test for one site versus two site binding models (Scheme 7). The higher affinity binding may reflect selection for the active conformation, which is also supported by the higher efficacy of *ax*CBN-3 in [³⁵S]GTPγS binding (Supplementary Tables 4 and 5). Further, because *ax*CBN-3 is a class 1 atropisomer, it exists as two enantiomeric conformers rapidly equilibrating, each of which may have unique affinities for different conformations and give rise to multiphasic binding curves as depicted in Scheme 6. Thus, these compounds may exhibit particularly unique pharmacology in terms of the receptor populations they could stabilize to give rise to unique signaling profiles.

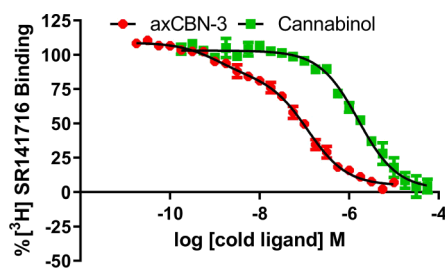
Racemic *ax*CBD-2 is configurationally stable (Scheme 5) and demonstrably active at cannabinoid receptors and selective for hCB₂R (Scheme 6). To understand the impact of *axial chirality* on cannabinoid receptor affinity, the enantiomers were separated and subject to further molecular pharmacology studies (Scheme 8). Regarding the separation, this was achieved using Supercritical Fluid Chromatography (SFC) as

Scheme 6. (A) *ax*Cannabinoid Summary. (B) Displacement of [³H]CP55940 Binding. (C) *ax*Cannabinoid Binding Affinity at Cannabinoid Receptors. (D) TRUPATH Gαi Activation



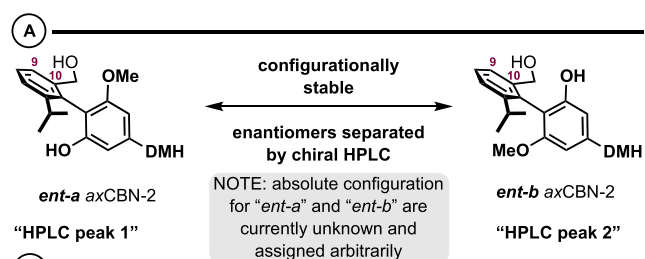
described in the Supporting Information. By this method, we were able to access single enantiomers of *ax*CBD2 (*ent-a* *ax*CBD-2 and *ent-b* *ax*CBD-2), but the absolute stereo-

Scheme 7. *ax*CBN-3 Exhibits Two Distinct Affinities at hCB₁R (pK_i_{Hi} = 9.4, pK_i_{Lo} = 7.3), Unlike CBN (pK_i = 6.2), Suggesting High Affinity Binding to the Active Conformation^a



^aData are mean $\pm$ SEM of $N = 3$ –4 experiments performed in triplicate.

Scheme 8. Effect of Absolute Configuration on Affinity and Activity at Cannabinoid Receptors. (A) Preparation of Single Enantiomers. (B) Affinity Assays. (C) GTP γ S. (D) TRUPATH *Gai*1 Activation



(B)

compound	hCB ₁ R		hCB ₂ R		selectivity CB ₁ /CB ₂
	pK _i $\pm$ SEM	K _i (nM)	pK _i $\pm$ SEM	K _i (nM)	
CP55,940	8.90 $\pm$ 0.0786	1.27	9.07 $\pm$ 0.115	0.85	0.7
<i>rac-ax</i> CBD-2	5.67 $\pm$ 0.0821	2140	6.35 $\pm$ 0.0755	447	4.8
<i>ent-a-ax</i> CBD-2	5.54 $\pm$ 0.0781 ^a	2900	6.19 $\pm$ 0.0437 ^a	642	4.5
<i>ent-b-ax</i> CBD-2	5.31 $\pm$ 0.0561 ^a	4840	6.56 $\pm$ 0.0665 ^{a,b}	278	17.4

^a $p < 0.0001$ vs. CP55,940 ^b $p < 0.01$ vs *ent-a*

(C)

compound	hCB ₁ R			hCB ₂ R		
	pEC ₅₀	EC ₅₀	E _{max}	pEC ₅₀	EC ₅₀	E _{max}
CP55,940	8.37 $\pm$ 0.04	4.27 nM	346 $\pm$ 29.7	9.60 $\pm$ 0.124	0.25 nM	122 $\pm$ 8.94
<i>rac-ax</i> CBD-2	ND	ND	ND	6.72 $\pm$ 0.330 ^b	189 nM	56.3 $\pm$ 8.51 ^b
<i>ent-b-ax</i> CBD-2	ND	ND	ND	6.74 $\pm$ 0.284 ^c	183 nM	87.5 $\pm$ 4.24 ^a

^a $p < 0.05$ vs. CP55,940 ^b $p < 0.001$ vs. CP55,940 ^c $p < 0.0001$ vs. CP55,940

(D)

compound	hCB ₂ R	
	pEC ₅₀	E _{max}
CP55,940	9.25 $\pm$ 0.0989	0.0991 $\pm$ 0.00848
<i>rac-ax</i> CBD-2	6.47 $\pm$ 0.157 ^a	0.0852 $\pm$ 0.0166
<i>ent-a-ax</i> CBD-2	5.96 $\pm$ 0.156 ^a	0.0906 $\pm$ 0.00843
<i>ent-b-ax</i> CBD-2	6.34 $\pm$ 0.155 ^a	0.0996 $\pm$ 0.0100

^a $p < 0.0001$ vs. CP55,940

Values reflect mean $\pm$ SEM of at least $N = 3$ experiments performed in duplicate or triplicate. ND = Not determined.

chemistry of the atropisomers was not determined for this study (Scheme 8A). With respect to pharmacology, *ent-b ax*CBD-2 exhibited 2.3-fold greater affinity at hCB₂R compared to *ent-a ax*CBD-2 in receptor binding, 278 and 642 nM, respectively (Scheme 8B). However, there was no significant difference in affinity at hCB₁R (Scheme 8A, footnote a). In the case of *ent-b ax*CBD-2, this translates to

an up to 17-fold selectivity for hCB₂R, which is directly linked to the axial chirality element of the cannabinoid analogues. Both enantiomers exhibited similar potency at stimulating [³⁵S]GTP γ S binding in hCB₂R expressing HEK293 cell membranes, but there was no detectable stimulation in hCB₁R expressing HEK293 cell membranes (Scheme 8C). *ent-b ax*CBD-2 trended to exhibit higher efficacy at stimulating [³⁵S]GTP γ S binding versus *ent-a ax*CBD-2 ($P = 0.06$) in hCB₁R membranes. In TRUPATH, the enantiomers stimulated activation of *Gai*1 β 3 γ 9 proteins with similar potency and efficacy (Scheme 8D). The enantiomers exhibited apparent inverse agonism with low potency in HEK293 cells expressing hCB₁R (data not shown).

Together, these data showcase that *ax*CBNs and *ax*CBDs can *mimic*—or even *surpass*—the activity of phyto- and synthetic cannabinoids at cannabinoid receptors. These analogues occupy a unique conformational chemical space (ground-state three-dimensional structures), which may impact affinity and selectivity for biological targets (cannabinoid receptors and beyond). Furthermore, the conformational restrictions unique to *ax*Cannabinoids may also provide improved physical, drug-like properties including metabolic and aerobic stability and solubility. Finally, in cases where the *ax*Cannabinoids are configurationally stable (*ax*CBDs, namely), there is a clear indication that the absolute configuration will have significant impact on the overall affinity and activity at cannabinoid receptors. In this regard, we have found an *axial chirality-dependent* activity of *ent-b ax*CBD-2 at hCB₂R.

Molecular Modeling of *ax*Cannabinoids at Cannabinoid Receptors. We used induced-fit docking (Glide-XP, Schrödinger, Inc.) to predict how *ax*Cannabinoids *ax*CBN-3 and *rac-ax*CBD-2 engage hCB₁R and hCB₂R.⁶² The Glide-XP docking scoring function is an approximated binding affinity that is used to rank predicted poses of a ligand as a result of its interaction with a target: *ax*CBN-3 had an appreciable score with hCB₁R (XPgscore −13.285 kcal/mol) and hCB₂R (XPgscore −13.711 kcal/mol), and *rac-ax*CBD-2 had lower predicted affinity in hCB₁R (XPgscore −12.488 kcal/mol) compared to hCB₂R (XPgscore −13.117 kcal/mol). In each case, the dimethylheptyl tails of the *ax*Cannabinoids occupy the same narrow hydrophobic channel between transmembrane helix (TMH) 3, 5, and 6 as the cocrystallized ligand (Figure 3). Hydrophobic aromatic interactions with Phe268 (hCB₁R) and Phe87, Phe94 and Phe183 (hCB₂R) are also observed. Canonical structure–activity relationships of classical cannabinoids indicate that a free phenol at position 1 is generally required for hCB₁R and hCB₂R binding.⁵⁸ For *ax*CBN-3, this group is not predicted to form beneficial interactions with hCB₁R but is predicted to donate a hydrogen bond to Ser285 in hCB₂R; the equivalent Ser383 in hCB₁R does donate a hydrogen bond to the oxygen in the pyran ring. The 10-hydroxymethyl group of *ax*CBN-3 is predicted to form an intramolecular hydrogen bond (IMHB) with the nearby 1-phenol. This may contribute to target binding by overall lowering the hydrophilicity of this region, allowing this group to occupy an otherwise hydrophobic portion of the binding site. The predicted binding pose of *rac-ax*CBD-2 differs from that of *ax*CBN-3 due to the larger dihedral angle connecting the two phenyl rings (ranging from −27.9° to 29.2° for *ax*CBN-3 and −75.1° to −75.3° for *rac-ax*CBD-2 when docked in hCB₁R and hCB₂R, respectively; see Figures S3–S6 in the Supporting Information). Within hCB₁R, the 6-propyl

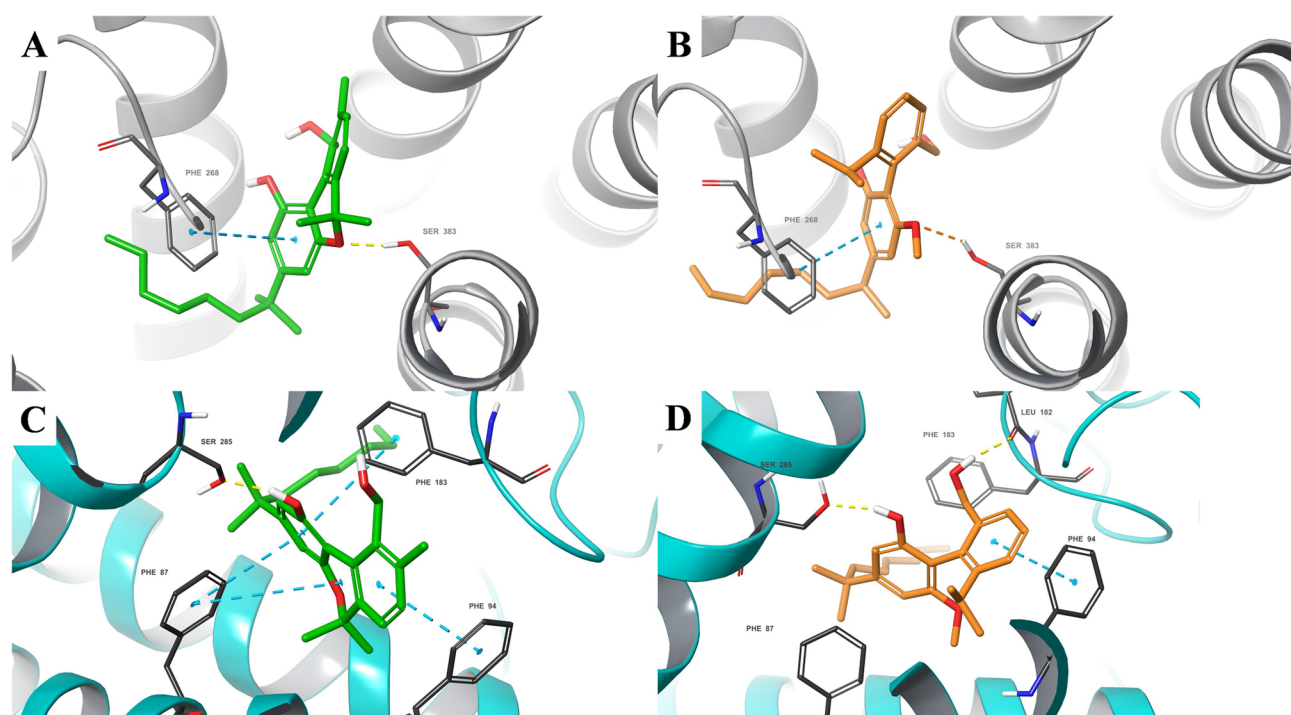


Figure 3. Results from automated docking. *ax*CBN-3 (green) docked within hCB₁R (gray) (A) and hCB₂R (cyan) (C), *rac-ax*CBD-2 (orange) docked within hCB₁R (B) and hCB₂R (D). For docking scores, please see the text.

substituent points toward Phe268, while the 10-hydroxymethyl group occupies a narrow lipophilic region below the plane of aryl ring A. Multiple steric clashes contribute to a lower Glide score, including a clash with Ser383. Within hCB₂R, however, the 10-hydroxymethyl group is able to donate a hydrogen bond to the backbone carbonyl of Leu182, and the phenol forms a beneficial hydrogen bond with Ser285. The presence of these additional beneficial binding interactions may explain the observation that *rac-ax*CBN-2 is a selective hCB₂R agonist. This may also explain the difference in binding affinities between the two resolved atropisomers: the opposite atropisomer would be unable to form a hydrogen bond with Ser285 and would therefore be expected to have lower affinity for hCB₂R than the atropisomer docked in Figure 3. More studies are needed to test this hypothesis and determine how structural modification of this novel hit influences target binding and intrinsic activity.

CONCLUSIONS AND OUTLOOK

We have conceptualized and validated *ax*Cannabinoids as novel leads for cannabinoid-inspired drug discovery. We hypothesize that *ax*Cannabinoids will be uniquely valuable scaffolds due to their three-dimensionality and stability imparted by the central axially chiral biaryl framework. Through the development of various *de novo* synthetic routes and collaborative biological analysis at cannabinoid receptors (hCB₁R/hCB₂R), we have achieved a preliminary understanding of *ax*Cannabinoid structure-activity relationships. With respect to synthesis, disclosed herein are three distinct synthetic strategies capable of producing diverse analogs bearing either a tricyclic cannabinol framework or a bicyclic scaffold inspired by cannabidiol: axially chiral cannabinols (*ax*CBNs) or cannabidiols (*ax*CBDs), respectively. Numerous products were obtained, including eight analogues which were examined for biological activity. The initial structure-activity

relationship study revealed an *ax*Cannabinoid (*ax*CBN-3) with picomolar affinity for the hCB₁R and hCB₂R receptors as well as other promising leads (e.g., *ax*CBN-4 and *rac-ax*CBD-2) that display >5-fold selectivity for the hCB₂R receptor over the hCB₁R receptor. The *ax*Cannabinoids described here offer new opportunities to probe the binding sites of cannabinoid receptors and other protein targets of phytocannabinoids. Based on these findings, we plan to (1) further interrogate the biological activity and therapeutic potential of the initial lead molecules, and (2) utilize these findings to design and synthesize the next generation of *ax*Cannabinoids for drug discovery.

It is also worth noting that this strategy of converting point chirality into axial chirality can be applied *beyond* cannabinoids. Many bioactive natural products contain linked six-membered rings, and we speculate that scaffolds of this type have atropisomeric biaryl bioisosteres that may exhibit improved therapeutic, stability, and other ADMET properties (Figure 4). We propose that this type of structural modification be considered routinely throughout medicinal chemistry campaigns.

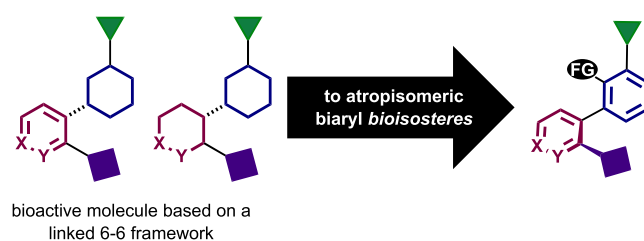


Figure 4. Beyond cannabinoids: other “lead molecules” in principle can have atropisomeric counterparts with potentially improved pharmaceutical/therapeutic properties.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c00129>.

Experimental procedures and characterization data (^1H NMR, ^{13}C NMR, HRMS) (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): AJG and the University of Florida filed a provisional patent on chemical entities described in this manuscript.

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