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Cannabichromene

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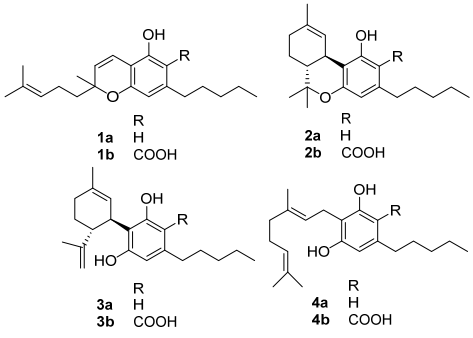
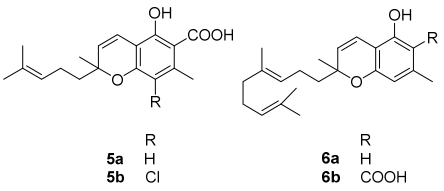
Cannabinochromene (CBC, **1a**) is the archetypal member of a class of more than twenty isoprenylated 5-hydroxy-7-alkyl(aralky)benzo[2*H*]pyranes first reported from *Cannabis sativa* L. but also occurring in unrelated plants (*Rhododendron* species) as well as liverworts and fungi. The chemistry, synthesis, and bioactivity of CBC (**1a**) is reviewed, highlighting its underexploited pharmacological potential and rich chemistry.

Keywords: Cannabichromene, CBC, *Cannabis sativa*, Enantiomeric purity, TRPA1.

Cannabichromene (CBC, **1a**) was first isolated from *Cannabis sativa* L. in 1966, only two years after the isolation of Δ^9-tetrahydrocannabinol (Δ^9-THC, **2a**) [1,2], while its corresponding acid (cannabichromenoic acid, CBCA, **1b**) was isolated two years later from the same plant source [3]. These compounds are the archetypal members of a group of over twenty 5-hydroxy-7-alkyl(aralkyl)benzo[2*H*]pyranes characterized by a limited distribution in Nature, that encompasses, however, not only plants but also fungi. Cannabichromene (**1a**) was isolated at the outset of modern studies on the chemistry of Cannabis, but it has been less investigated compared to other phytocannabinoids in terms of biological profiling and chemical reactivity. It is traditionally considered, along with Δ^9-THC (**2a**), cannabidiol (CBD, **3a**) and cannabigerol (CBG, **4a**), a major phytocannabinoid, and a member of the so-called *big four* of Cannabis constituents. It was even believed to be the second most abundant cannabinoid in recreational marijuana [1,2], but its concentration in Cannabis seems to have been substantially overestimated because of the difficulty to separate CBC (**1a**) and CBD (**3a**) on the gas chromatography conditions of those years [4], with the ensuing attribution of the peak area exclusively to CBC (**1a**). The concentration of CBC (**1a**) in Cannabis is actually much lower than the other "major" phytocannabinoids. It rarely exceeds 0.2-0.3% on dry weight basis, and CBC (**1a**) has never been found to accumulate in modern medicinal and recreational strains of Cannabis at the one- or two-digit percentage concentrations typical of the other major phytocannabinoids [5].



There is considerable confusion in the literature on the physical properties of natural CBC, that was originally reported as an optically active [1,2] crystalline compound [2]. CBC is actually an oil or a gum, and, unlike the other major phytocannabinoids, is scalemic, as shown by chromatography on chiral stationary phases [6]. After the isolation of CBC, various analogues and derivatives (cannabichromenoids) were discovered not only from Cannabis but also from unrelated plants as well as from liverworts and even from fungi [5]. The orcinoids cannabiorcichromenic acid (**5a**), chlororcichromenic acid (**5b**) [7], and confluentin (**6**) [8] are the only phytocannabinoids of non-plant origin, and were isolated from *Cylindrocarpon olidum* Wollenw. a fungal parasite of a nematode (**5a** and **5b**) [7], and from a mushroom (**6**) [8]. Interestingly, confluentin (**6**) is also a constituent of *Rhododendron dauricum* L., a popular ornamental plant but a protected species in its natural environment [9].



The cannabichromenoid chemical space: Diversity of natural cannabichromenoids is mostly associated to the modular scheme of their biosynthesis, as expressed by prenylation or deprenylation of the isoprenyl residue, and/or shortening of the pentyl residue (Figure 1) [5]. Replacement by a phenethyl-type group as well as isomerization to the abnormal series (*ortho*-relationship between the resorcinyl substituents) have also been observed outside Cannabis [5]. As with all other classes of phytocannabinoids, *n*-alkyl residues (methyl-, propyl-, pentyl-) are typical of Cannabis and higher plants (Figure 1, type A cannabichromenoids), while the phenethyl type substituents are mostly, but not exclusively, found in liverworts (type B cannabichromenoids) [5]. Diversity in the natural cannabichromenoids is the result of the combination of a diverse iteration of the elongation step of the isoprenoid pathway that generates the electrophilic isoprenylating agent, and of the nature of the polyketide starter that eventually generates the alkyl-substituent

of the resorcinyl core. Thus, the isoprenylating agent can be prenyl-, geranyl-, or farnesyl pyrophosphate [10], while the polyketide starter can be hexanoic acid [cannabichromene (CBC)-type compounds], propanoic acid [cannabivarichromene (CBCV)-type compounds], acetic acid [cannabiorcichromene (CBOC)-type compounds], or cinnamic acid (phenethyl and stiryl-type compounds). All these phytocannabinoids are assumed to be generated in carboxylated form, and to be next decarboxylated enzymatically or, most probably, during storage of the plant material. Modifications of the benzochromene moiety are rare, and involve hydratation of the pyrane double bond as well as functionalization of the "*peri*-position" of the chromene core by chlorination or acetoxylation [5]. Also rare is the oxidative modification of the isoprenoid group at the terminal and electron-rich double bond.

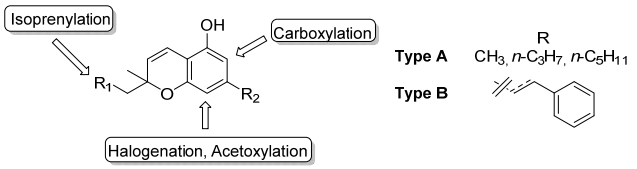


Figure 1: Diversity of naturally occurring cannabichromenoids.

The original biogenetic numbering of phytocannabinoids was based on their meroterpenoid structure, and used two distinct systems for the resorcinyl and the isoprenyl moieties. The numbering of Δ^9-THC was later changed to a systematic one, based on the polycyclic heterocyclic core [5]. Two systems are therefore possible for CBC (Figure 2), but the systematic one (A) is more popular, and will be use throughout.

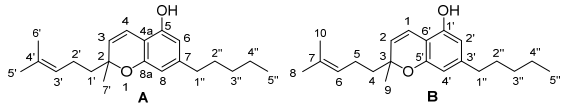


Figure 2: The systematic (A) and the biogenetic (B) numbering system of cannabichromene (CBC, **1a**).

Biosynthesis and enzymology: The skeletal diversity of phytocannabinois is generated by the oxidative cyclization of linear isoprenyl precursors (cannabigerolic acid, CBGA, **4b**) for the terpenyl (C10)-derivatives), with a convergence of the cyclase and the oxidase phases, as observed also in other classes of meroterpenoids (Figure 3). Thus, the enzyme cannabichromenic acid (CBCA, **1b**) synthase is a FAD-oxido-cyclase with little specificity for the length of the alkyl chain of the resorcinyl core, accepting both olivetolic acid and its lower homologue divarinic acid as substrate. Compared to the tetrahydrocannabinolic acid (THCA, **2b**)- and the cannabidiolic acid (CBDA, **3b**) synthases, CBCA synthase has a higher substrate affinity (Km = 23 μM *vs* 134 μM and 137 μM for, respectively, CBDA- and THCA synthases) but a lower catalytic capacity (k_{cat} = 0.04 s^{-1} *vs* 0.19 s^{-1} and 0.20 s^{-1} for CBDA- and THCA-synthases) [11]. CBCA synthase is encoded at a fixed locus (*C*) distinct from the allelic loci of CBDA- and THCA-synthases (B_D and B_T, respectively, with B_0 corresponding to poor functioning synthases and the accumulation of CBG). *C* is expressed mostly in juvenile tissues of Cannabis, declining with maturation. As a result, the concentration of CBC in the flower heads is generally much lower than the one of CBD and THC, and plants whose cannabinoid profile is dominated by CBC are very rare. Overall, the genetic control of CBC synthesis is poorly understood. A substantial accumulation could be related to the persistence of a juvenile gene expression profile related to a not yet characterized inheritable factor [12].

It has also been observed that CBC is accumulated differently compared to and Δ^9-THC (**2**) and CBD (**3**). In general, cannabinoids have a single site for synthesis and accumulation, being produced and stored in the secretory cavity of specialized glandular trichomes, three types of which are, however, present in Cannabis. The large capitate-stalked trichomes only develop on the bracts that surround the flowers and in the bracteols that enclose the ovary, and can accumulate large amounts of phytocannabinoids. Conversely, the small bulbous- and the large capitate-sessile trichomes, that develop all over the leaves , have a 20-fold minor capacity to produce and accumulate phytocannabinoids [12]. CBCA synthase is apparently little, if any, expressed in the cannabinoid-rich capitate-stalked trichomes, and this explain why CBC does not benefit from the cannabinoid biosynthetic bonanza associated to flowering, rather peaking soon after seedling formation, declining during development, and eventually stabilizing at a low level in mature plants. As a result, although pure CBC Cannabis breeds have been produced, the isolation yield remains much lower compared to the other three major phytocannabinoids [12]. Traces (ppm) of cannabinoids were recently detected in the roots of various strains of Cannabis. The highest concentrations of CBC were associated to narcotic high-THC plants, as often observed also in the aerial parts [13].

CBCA synthase performs a chemistry basically distinct from the one leading to CBDA (**3b**) and THCA (**2a**). After initial FAD-mediated hydride removal from the benzallyl carbon, a process common to all three cannabinoid synthases [11,12] (Figure 3), electrocyclization of the resulting quinonmethide (**8**) to a chromene takes place, in line with the classic Ollis-Sutherland proposal for the biosynthesis of chromenes from *ortho*-isoprenylated phenolics [14]. This reaction is, formally, a *6-endo-trig* process, sometimes referred to in the literature as a Wacker cyclization. Alternatively, oxidative removal of the benzallylic hydrogen is associated to removal of the configurational barrier to intramolecular cyclization represented by the proximal *E*-double, as expressed by the resonance formulas **9a-d**. This makes it possible, depending on the folding of the terpenyl residue, intramolecular cyclization by electrophilic addition to the electron-rich terminal double bond, leading to either to CBDA (**3b**) or to THCA (**2b**) according to the nature of the termination step (proton loss or oxygen trapping of the cationic intermediate, Figure 3, a and b, respectively).

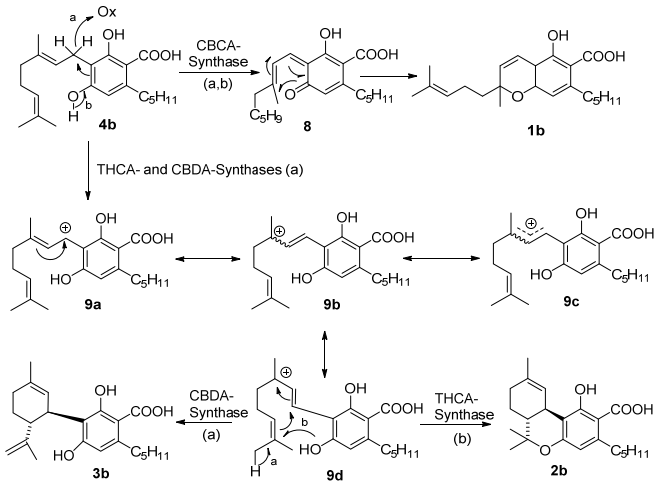


Figure 3: Mechanism of formation of the three main phytocannabinoid chemotypes from cannabigerolic acid (**4b**).

The quinonmethide substrate for the electrocyclization is achiral, and chirality in the final product derives solely from enzymatic

inprinting. Natural CBC (**1a**) is scalemic [6], but analogues from *Rhododendron* species like daurichromenic acid (**6b**) have been isolated in high optical purity [15]. The daurichromenic acid (DCRA) synthase from *R. dauricum* has been cloned and shows high similarity to CBCA synthase from *Cannabis sativa* [16]. An enantioselective transgenic production of (+)-daurichromenic has been developed in *Aspergillus oryzae* by heterologous expression of this synthase coupled to the one of its precursor (grifolic acid, **11**) from the fungus *Stachybotrys bisbyi* (Figure 4) [17].

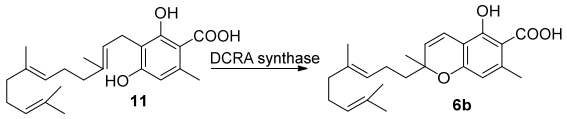


Figure 4: Enzymatic synthesis of daurichromenic acid (**6b**) from grifolic acid (**11**).

Synthesis: CBC (**1a**) is the only phytocannabinoids from Cannabis that can be obtained relatively easily by synthesis. The classic preparation is based on a tandem Knoevenagel-electrocyclic reaction between citral (**12**) and olivetol (5-*n*-pentylresorcinol, **13**). The course of the reaction is different in basic and acidic conditions. CBC could be obtained, via the quinonmethide **14**, only under basic conditions (Figure 5), and the yield was strongly dependent on the base used. With pyridine (Crombie-Razdan conditions [18,19]), the yield was poor (*ca* 10-15%), due to the formation of a complex reaction mixture that included also cannabicyclol (**15**), the product of formal [2+2] intramolecular cycloaddition of CBC, as well as cannabicitran (**17**), resulting from the intramolecular [4+2] cycloaddition of the heterodiene **16** [18, 19]. The formation of the post-condensation products **15** and **17** is surprising, since acid or light promotion would be necessary for the [2+2] cycloaddition that generates cannabicyclol (**15**), and acid conditions for the generation of the heterodiene **16** for the [4+2] cycloaddition to cannabicitran (**17**).

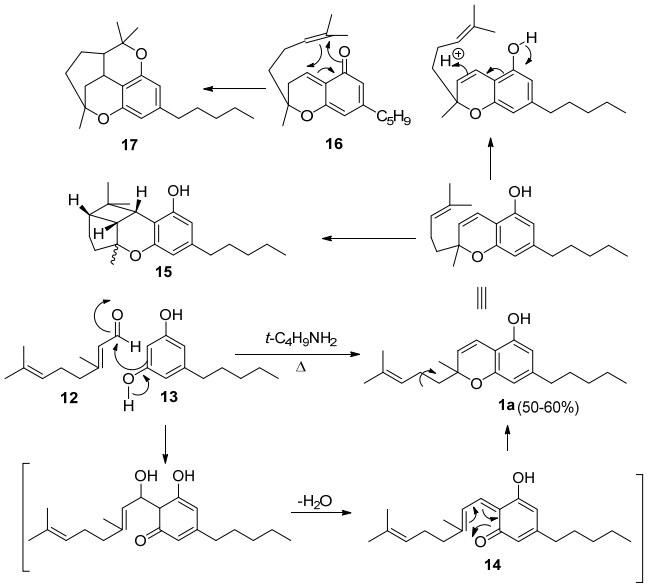
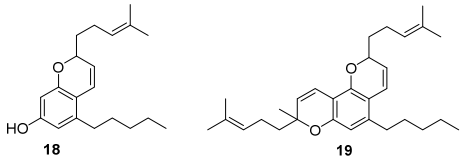


Figure 5: Reaction of citral (**12**) and olivetol (**13**) under basic conditions. Cannabicyclol (**15**) and cannabicitran (**17**) are formed only with pyridine as the base.

The formation of the post-condensation products could be prevented when the reaction of citral and olivetol was carried out in refluxing toluene in the presence of *tert*-butylamine (ElSohly conditions). CBC is obtained in 50-60% yield [20], with abnormal-CBC (**18**) and the product of bis-chromenylation (**19**) as major by-product [20].



Under acidic conditions, the reaction of citral and olivetol afforded instead *cis*-Δ^9-THC as the major reaction product (**20**), the result of a terpenic-type intramolecular cationic cyclization (Figure 6) [18,19].

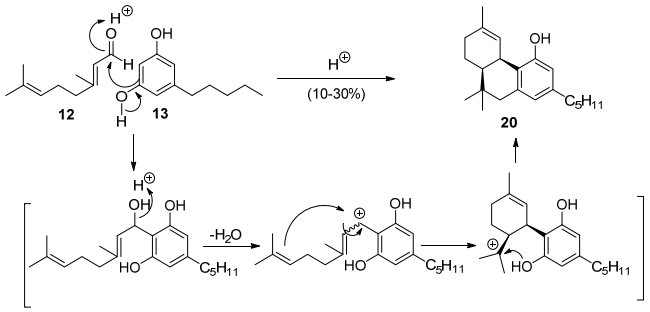


Figure 6: Reaction of citral (**12**) and olivetol (**13**) under acidic conditions

The reaction of citral and olivetol is interesting, and well worth re-investigation to clarify its mechanistic ambiguities and subtleties. An organo-catalytic version was developed based on a pre-formed iminium salt of piperidine and citral, complicating, however, the reaction protocol and without improving the yield [21]. Also the use of the classic Tietze conditions for the reaction (ethanediammonium diacetate, methanol, RT) did not substantially improve the yield [22], even when dihydro-olivetol (5-*n*-pentyl-1,3-cyclohexanedione) was used for the tandem reaction and the resulting adduct was then aromatized by selenylation-oxadeselenylation [23]. Taken together, these observations show that CBC can be obtained from citral (**12**) and olivetol (**13**) under basic conditions, even though yield are only in the range of 50% and chromatography is necessary to purify the product, an oil, from the reaction mixture.

Analogs of CBC could be synthesized in the same way, using prenylogous isoprenic aldehydes or analogues of olivetol where the *n*-pentyl is replace by a *n*-propyl- (viridinol) or a methyl- (orcinol) group [20]. On the other hand, the synthesis of enantiopure analogues requires a different strategy, since the configuration at C-2 cannot be controlled during the electrocyclic step. Of relevance is an organocatalytic strategy based on a formal [4+3]cycloaddition (actually a domino aldol-oxa-Michael reaction) that was developed by Woggon for the enantioselective synthesis of *S*-daurichromenic acid (*S*-**6b**)[24]. Chirality was introduced by reacting 2-hydroxy-4-methyl-6-methoxybenzaldehyde (**23**) with the chiral dienamine **22**. The resulting and optically active semiacetal **24** was next oxidized to a lactone, and the extra carbon removed in a 6-step sequence that eventually afforded the natural *S*-enantiomer of daurichromenic acid (**6b**) (Figure 7)[24].

CBC (**1a**) could also be obtained by the biogenetic oxidation of cannabigerol (CBG) (Figure 3) with dichlorodicyanobenzoquinone (DDQ), a biogenetic reaction typical of *ortho*-isoprenylated phenols first reported by Campbell and extensively investigated by Merlini in the late Sixties [25]. Reaction with chloranil (tetrachlorobenzoquinone) gave a more complicated reaction mixture, containing also cannabicyclol and cannabicitran-type compounds [26].

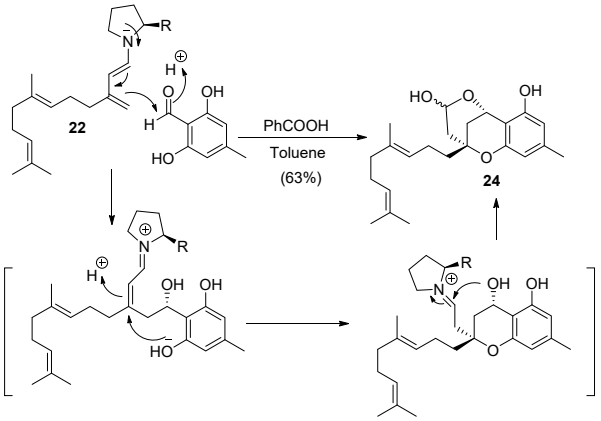


Figure 7: Enantioselective step of the asymmetric synthesis of *S*-daurichromenic acid (**6b**). R = trimethylsilyloxy(bis)(3,5-trifluoromethylphenyl)methyl.

Reactivity: The scalemic nature of natural CBC could be due to racemization via the same electrocyclic mechanism underlying its formation. In this context, it is remarkable that daurichromenic acid (**6b**) and its derivatives were isolated in high optical purity [9], suggesting that the presence of a carboxylic function *para*-to the chromene oxygen could slow down or even prevent racemization, possibly by an increased resonance stabilization of the chromene benzenoid moiety that imposes a higher activation energy for the dearomative electrocyclic opening. If so, decarboxylation of CBCA could be the trigger for the poor optical purity of CBC.

CBC is photochemically unstable, easily undergoing [2+2] photocycloaddition to cannabicyclol (**15**) [27]. The structure originally proposed for this compound [2] involved photocycloaddition from a chair-like transition with bonding of C-2 of the chromene to the gem-dimethyl substituted isoprenyl carbon, opposite to the one actually observed that involves a more compact transition state and bonding of C-3 to the terminal olefinic carbon [27]. The same reaction can occur under acidic conditions, representing a remarkable example of the Gassman [2+2]cationic cycloaddition [22, 28]. The presence of acids also promotes a different reaction course, leading to cannabicitran (**17**) via a [4+2] cycloaddition [22] (Figure 5). On the other hand, treatment of CBC with $BF_3.Et_2O$ or *p*-toluenesulfonic acid afforded a complex reaction mixture, dominated by compounds originating from formation of a benzyl cation and its trapping from the distal olefin double bond, with formation of compounds from the *iso*-THC (**25**) series (Figure 8, path a) [29]. The formation of these compounds is mechanistically related to the one of cannabicitran (**17**), being triggered by formation of a benzylic cation by electrophilic or protic attack to the chromene double bond (cf. Figure 5 and Figure 8). Compounds originating from the heterolytic cleavage of the bond between the chromene oxygen and C-2 and ultimately generating compounds of the THC-series (**26**) via trapping of the resulting benzallyl cation by the terminal olefin bond were not observed (Figure 8, path b) [29].

Of great interest is the observation that, under thermal conditions, CBC (**1a**) could isomerize to tetrahydrocannabinol derivatives like **26** via a cycloreversion-cycloaddition reaction involving in the electrocyclization the terminal olefin bond and not the terminal bond of the quinonmethide intermediate (Figure 9) [30]. Support for this chromene metatesis was observed in a model compound (Figure 9), but no data are available for cannabichromene (**1a**) itself, a surprising observation because of the reaction could occur during vaporization of Cannabis products, and could be therefore of biomedical relevance.

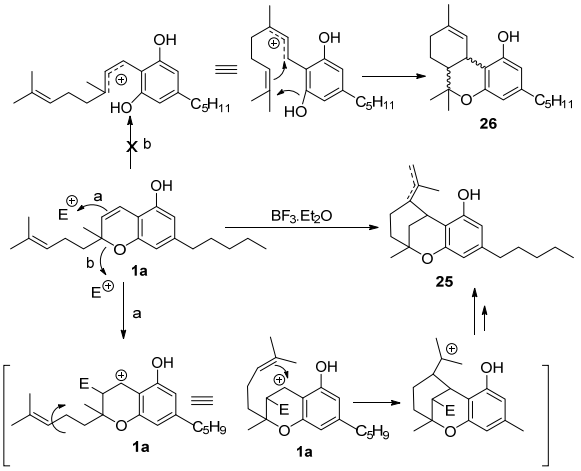


Figure 8: Formation of *iso*-THC derivatives from the acidic treatment of cannabichromene (**1a**)

Overall, many aspects of the chemistry of cannabichromene are unclear and need further investigation. Given the thermal and photochemical instability of cannabichromene, it is surprising that this compound could be detected in historical samples of Cannabis [31].

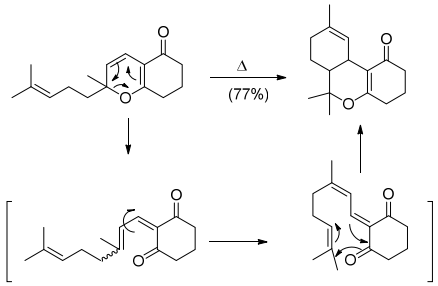


Figure 9: Thermal isomerization of a simplified analogue of canabichromene.

Bioactivity: Most studies on cannabichromenoids were done on CBC (**1a**), and limited information exists on the biological profile of its naturally occurring analogs. The first studies on the pharmacology of CBC were spurred by the wrong assumption that it was the second most abundant cannabinoid in recreational marijuana, an observation due to the poor resolution capacity of the GC columns of the Sixties and Seventies [4]. In in vivo experiments, CBC was not narcotic, but at high dosages, it could, nevertheless, induce the tetrad response typical of Δ^9-THC (hypomotility, catalepsy, hypothermia, analgesia) [32,33]. Since CBC has only marginal affinity for CB1 and CB2, and the tetrad response was not blocked by the CB1 reverse agonist rimonabant, other mechanisms could operate [34,35].

CBC was reported to outperform the other major cannabinoids in terms of anti-bacterial and anti-fungal activity [20], but no significant difference with THC, CBD and CBG was observed on various drug-resistant strains of *Staphylococcus aureus* (MTRSA) [36]. The most important target of CBC is the ion channel TRPA1, that is activated at two-digit nanomolar concentrations (IC_{50} = 90 nM), and desensitized to allylisothiocyanate activation at higher concentration (IC_{50} = 370 nm) [35]. Most potent ligands of TRPA1 are covalent ligands [37], while CBC is devoid of the electrophilic sites necessary to trap reactive cysteine residues, and behaves therefore as a non-covalent modulator. At micromolar concentration, CBC increases the endocannabinoid tone by inhibiting the cellular uptake of anandamide and the enzymatic

degradation of 2-arachidonoyl glycerol [35], an activity in principle potentially involved in the potentiation in vivo of the antinociceptive effects of Δ^9-THC in the mouse-tail flick assay [32,33]. Thus, intratecal administration of CBC reduced tail-flick nociception in a way that was blocked by AM251, a CB1 antagonist [33]. The same effect was, however, blocked by DPCPX, an Adenosine A1-selective antagonist, as well as by the TRPA1 antagonist AP18 [33]. The antinoniceptive effects of CBC might therefore be mediated not only by modulation of the endocannabinoid system, but also by interaction with adenosine and TRPA1 receptors, a well as with other yet-to-be discovered end-points.

The desensitization of TRPA1 and the inhibition of endocannabinoid degradation seemingly also underlie the activity of CBC to ameliorate murine colitis induced by dinitrobenzensulfonic acid (DNBS) [38]. CBC could also selectively reduce inflammation-induced intestinal hypermotility, but neither cannabinoid receptors nor TRPA1 were involved in this activity [39]. CBC showed potent anti-inflammatory activity in the carrageenan-induced rat paw edema assay, outperforming oral phenylbutazone upon peritoneal administration, and being equipotent upon oral administration [40].

In a systematic screening of the potential of non-narcotic phytocannabinoids for the treatment of acne, CBC, along with CBDV and THCV, emerged as the best candidate due its capacity to normalize excessive sebaceous lipid production induced by pro-acne agents, reduce proliferation and alleviating inflammation [41].

Limited information is available on the pharmacokinetics and metabolism of CBC. Allylic hydroxylation of the isoprenyl residue and hydroxylation of the *n*-pentyl substituents were the major metabolic pathways in various rodents and not rodent species [42,43,44,45], but many metabolites could not be identify, and some appear to be artefact from the spontaneous degradation of CBC. The brain penetration from smoke is inferior to the one of THC and CBD, possibly because of the higher reactivity and thermal instability of CBC compared to these two other cannabinoids. CBC has also been reported to increase the brain concentrations of THC after iv co-administration of these compounds [33]. Unlike CBD, CBC is not endowed by significant cytotoxicity against cancer or non-mutated cells [46].

CBC aside, only daurichromenic acid (**6b**) and some of its analogues have received attention because of their bioactivity. These compounds are potent HIV1 inhibitors [16], and are toxic to the producing cells, being only accumulated extracellularly in the apoplasts of glandular scales attached on the surface of young leaves [46]. The molecular mechanisms underlying the antiviral and the phytotoxic activities of daurichromenic acids have not been elucidated.

Taken together, the studies we have summarized show that CBC (**1a**) is endowed with interesting bioactivity, not completely rationalizable on the basis of its agonistic activity on TRPA1, the only high-affinity target identified so far. Equally interesting is its chemistry, since the chromene system can isomerize to other structural types of phytocannabinoids. In the light of the straightforward availability by synthesis, CBC (**1a**) represents therefore an interesting tool to explore the biological space associated to the cannabinoid chemotype.

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