



(51) International Patent Classification:

A61K 31/35 (2006.01) C07C 37/68 (2006.01)
B01J 35/02 (2006.01)

(21) International Application Number:

PCT/US2020/013418

(22) International Filing Date:

13 January 2020 (13.01.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/791,122 11 January 2019 (11.01.2019) US

(71) Applicant: ARIELIUM HEALTH, LLC [US/US]; 118
Dent Street, West Roxbury, MA 02132 (US).

(72) Inventor; and

(71) Applicant: NIVOROZHKIN, Alex [US/US]; 118 Dent
Street, West Roxbury, MA 02132 (US).(74) Agent: WEINTRAUB, Jacob, G.; Jwip & Patent Services,
LLC, 670 Depot Street, P.O. Box 1265, Easton, MA 02334
(US).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,
KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

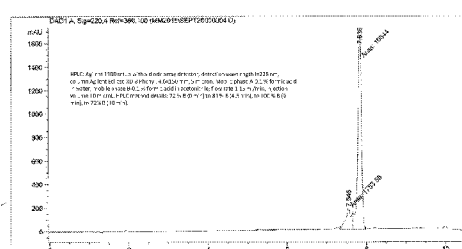
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

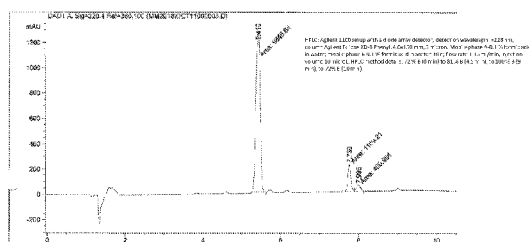
— with international search report (Art. 21(3))

(54) Title: NOVEL METHODS AND RELATED TOOLS FOR CBD CONVERSION TO THC

Fig. 1



Panel A



Panel B

(57) Abstract: The present invention is directed to methods of producing THC from CBD utilizing non-harsh methodology and resulting in substantially increased yields, as well as devices built upon these novel methods. The methods and devices are material efficient, and in certain embodiments, solvent-free. In particular, in certain embodiments, these methods and related devices are suitable for commercial production of THC from CBD. Furthermore, in certain embodiments, the present invention provides methods of producing THC from CBD in manner that affords tunability to select the ratio of THC -8 to THC-9.



NOVEL METHODS AND RELATED TOOLS FOR CBD CONVERSION TO THC

RELATED APPLICATIONS

5 This application claims priority to U.S. Provisional Patent Application No. 62/791,122, filed on January 11, 2019; the entirety of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

10 The predominantly occurring cannabinoids in cannabis plant material, commonly referred to as tetrahydrocannabinol (“THC”) and cannabidiol (“CBD”), are in fact (-)-trans- Δ^9 -THC and (-)-trans- Δ^1 -CBD. In addition, (-)-trans- Δ^8 -THC is also routinely detected in plant isolates, though in small quantities, and is oft subsumed within the category of THC. Such naturally occurring compounds have been suggested for use in treatment of an ever-
15 growing list of medical conditions, including epilepsy, pain, inflammation, anxiety reduction, sleep improvement, multiple sclerosis, neuropathic pain, spasticity, overactive bladder, antiemesis, and appetite stimulation. Others have found these compounds to be indicated for recreational use related to certain of their psychoactive properties. In either case, these compounds have become of major pharmacological interest in the last 20 years.

20 However, despite significant recent advances in synthetic chemistry of cannabinoids and the availability of CBD produced by the plant, *e.g.*, particularly in genetically modified cannabis plant material, very little development has taken place in the advancement in the production of commercially relevant quantities of THC from CBD. In fact, known synthetic processes to produce THC that have been developed have required harsh reagents, including
25 use of Brønsted or Lewis acids and solvation conditions, not suitable for large scale commercial production. Moreover, in many cases the processes for THC synthesis have, at best, resulted in low yields of THC, making use of these synthetic schemes cost prohibitive. Given this lack of success in chemical synthesis of THC, commercial production of THC has been generally relegated to enhancements of isolation techniques and plant based engineering
30 for extraction of the natural product.

As such, there remains a need for methods of producing THC from CBD that utilize non-harsh methodology with increased yields, particularly in a manner suitable for commercial production.

5

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to methods of producing THC from CBD utilizing non-harsh methodology and resulting in substantially increased yields, as well as devices built upon these novel methods. The methods and devices are material efficient, and in certain embodiments, solvent-free. In particular, in certain embodiments, these methods and related devices are suitable for commercial production of THC from CBD. Furthermore, in certain embodiments, the present invention provides methods of producing THC from CBD in manner that affords tunability to select the ratio of THC-8 to THC-9.

As such, one aspect of the present invention provides a material-efficient method for conversion of cannabidiol (CBD) to tetrahydrocannabinol (THC). The method comprises the step of: introducing CBD to acidically enriched solid support particles to create a CBD-activated accelerated conversion environment, such that THC is produced.

Another aspect of the present invention provides a tunable material-efficient method for conversion of cannabidiol (CBD) to tetrahydrocannabinol (THC). The method comprises the step of: introducing CBD to acidically enriched solid support particles to create a CBD-activated accelerated conversion environment, such that THC is selectively produced in the accelerated conversion environment.

Another aspect of the present invention provides a solvent-free method for conversion of cannabidiol (CBD) to tetrahydrocannabinol (THC) comprising the step of: introducing CBD to acidically enriched solid support particles through direct melt of the CBD to create a CBD-activated accelerated conversion environment, such that THC is produced.

Yet another aspect of the present invention provides a tetrahydrocannabinol (THC) production device comprising: a vessel for containing acidically enriched solid support particles; and a plurality of CBD-activated acidically enriched solid support particles positioned inside the vessel, wherein THC is produced from the CBD-activated acidically enriched solid support particles.

Still yet another aspect of the present invention provides a tunable tetrahydrocannabinol (THC) production device comprising: a vessel for containing acidically enriched solid support particles; and a plurality of acidically enriched solid support particles positioned inside the vessel, wherein THC is produced from the CBD-activated acidically enriched solid support particles.

Another aspect of the present invention provides a tetrahydrocannabinol (THC) production personal use device comprising a vessel for containing acidically enriched solid support particles, wherein the vessel is designed for personal use; and a plurality of acidically enriched solid support particles positioned inside the vessel, wherein THC is produced from the CBD-activated acidically enriched solid support particles.

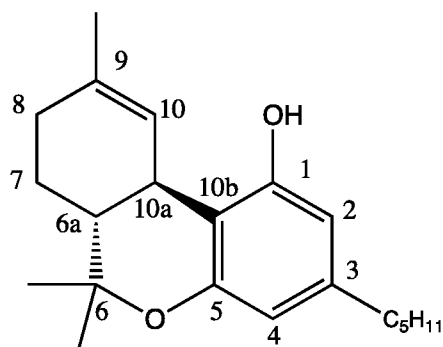
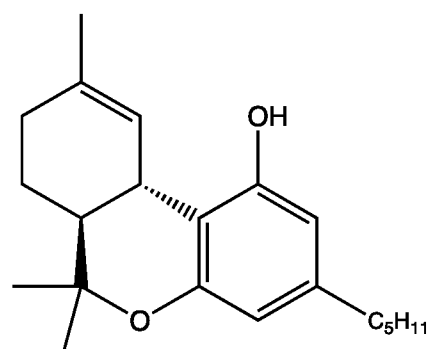
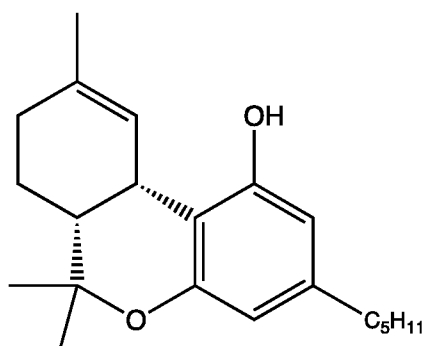
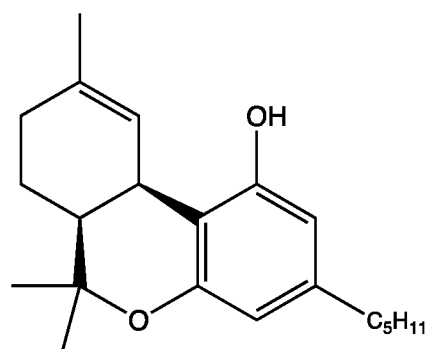
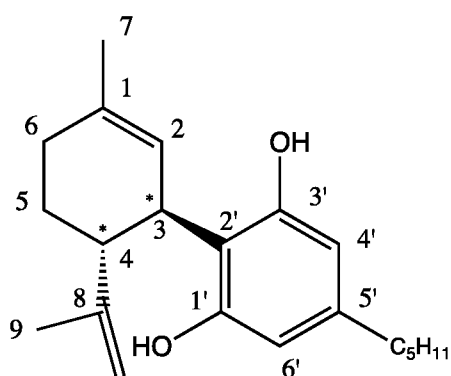
BRIEF DESCRIPTION OF THE FIGURES

Advantages of the present methods and related devices will be apparent from the following detailed description, which description should be considered in combination with the accompanying figures, which are not intended to limit the scope of the invention in any way.

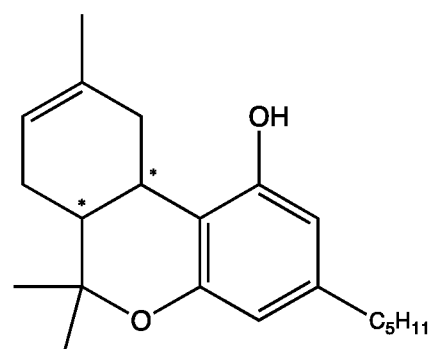
Figure 1 depicts an (A) HPLC trace of the reaction product from the Amberlyst-15-catalyzed CBD to THC transformation (heptane, reflux 45 min); and (B) HPLC trace of the reaction mixture from the Amberlyst-15-catalyzed CBD to THC transformation (heptane, ambient temperature, 2 h). The peak assignment as following: CBD (RT 5.41 min), (-) Δ^9 -THC (RT 7.76 min), (-) Δ^8 -THC (RT 7.99 min).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to methods and related devices for use in conversion of cannabidiol (CBD) (*e.g.*, and simple derivatives thereof) to tetrahydrocannabinol (THC) (*e.g.*, and simple derivatives thereof). Both CBD and THC have two carbon stereo- centers that give rise to four diastereomers, (-)-*cis*-, (+)-*cis*-, (-)-*trans*-, and (+)-*cis*-. The nature-selected ones, and more potent psychoactive compounds, are those with (-)-*trans*- configuration. In this respect, the chemical structures of CBD and THC are as follows:

(-)-trans- Δ^9 -THC(+) -trans- Δ^9 -THC(-)-cis- Δ^9 -THC(+) -cis- Δ^9 -THC

(-)-trans-(3R, 4R)-CBD

 Δ^8 -THC

Positional isomerization of the vinyl group in the CBD carbocycle leads to Δ^9 -, Δ^8 - for
 THC, where the Δ^8 - THC is putatively regarded as thermodynamically more stable than
 5 Δ^9 - THC. Moreover, for convenience, Δ^9 -THC is referred to herein as THC-9, and Δ^8 -
 THC is referred to herein as THC-8.

Cyclization of CBD to THC has previously been reported to be catalyzed by both
 Lewis and Brønsted acids. However, historically such conversion has required harsh solvent
 conditions (such as toluene) and reagents (such as $\text{BF}_3\text{-Et}_2\text{O}$) that entail separation/removal

from the reactions products (*e.g.*, in certain circumstances, difficult separation/removal) after the solution phase conversion. In many cases, beyond the inefficiency with respect to material, the results of this solution phase conversion after standard workups (and further chromatographic separation) were poor yields, at best. The lack of commercial utility may be evidenced by the lack of any known commercial production of THC from CBD.

Accordingly, the present invention utilizes acidically enriched solid support particles with no additional catalytic molecules, *e.g.*, no additional acidic catalytic agents in the methods and devices of the present invention, beyond the acidically enriched solid support particles (no further acid added to reaction other than solid support is required for conversion). The method utilizes the introduction of CBD to the acidically enriched solid support particles to create a CBD-activated accelerated conversion environment in order to convert the CBD to THC in a one-step process.

In certain embodiments, the resulting THC is therefore produced from the one step conversion and the product isolation is achieved simply by a removal of the solid support particles. The process and related devices avoid harsh solvent conditions and are completed within a substantially reduced time frame (*e.g.*, compressed time frame), producing high levels of conversion of CBD (*i.e.*, the conversion reactions go to completion or near completion) with very clean crude reaction product, including low (to no) residual solvent contamination. The processes and devices of the present invention of the invention are therefore material efficient and commercially relevant.

The increased rates of reaction afford the devices of the present invention the ability to take numerous convenient forms, *e.g.*, commercially convenient, including those that afford flow adaptations to CBD isolation systems. Through the selection of the acidically enriched solid support particles, selecting temperature, selecting time of reaction before extraction, and/or selecting a particular solvent, the THC ratio (*i.e.*, between THC-9 and THC-8) may be selectively produced in the final conversion product. In particular, this ratio may be selectively produced as a single product or ratio of multiple products, *e.g.*, including starting material CBD).

As such, the present invention is directed to methods of producing THC from CBD utilizing non-harsh methodology and resulting in substantially increased yields, as well as devices built upon these novel methods. The methods and devices are material efficient, and in certain embodiments, solvent-free. In particular, in certain embodiments, these methods

and related devices are suitable for commercial production of THC from CBD. Furthermore, in certain embodiments, the present invention provides methods of producing THC from CBD in manner that affords tunability to select the ratio of THC-8 to THC-9.

5 The present invention, including devices and methods will be described with reference to the following definitions that, for convenience, are set forth below. Unless otherwise specified, the below terms used herein are defined as follows:

10 ***I. Definitions***

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

15 The language "and/or" is used herein to mean both "and" in the conjunctive form and "or" in the disjunctive form.

 The language "accelerated conversion environment" is used herein to describe the reaction environment that enhances and accelerates conversion of the CBD to THC created by the use of the acidically enriched solid support particles of the present invention. Such
20 enhancement and acceleration is relative to existing solution phase chemistry conversion of CBD to THC, and includes, for example, enhanced conversion efficiency of CBD, increased purity, *e.g.*, of crude reaction, increased rate of production of THC, increased yield of production of THC, any combination thereof.

 The language "acidically enriched" as used in the language "acidically enriched solid
25 support particles" is used herein to describe the functionalization of the solid support particles of the present invention, *i.e.*, the functional groups that are covalently linked to the support particles. Such functional groups must be suitable to achieve residual level acidity (*i.e.*, comprising suitable Lewis or Brønsted acid functional groups) to support the acidic catalysis of a reaction, *i.e.*, the conversion of CBD to THC. This residual level of acidity is a
30 characteristic of the functional groups covalently bound to the solid support particles, and is distinct from the addition of solution phase acid, *e.g.*, in situ or in a pre-conditioning step.

The language “CBD-activated” is used herein to describe the presence of CBD, wherein the CBD has been introduced into or onto a material, *e.g.*, on the acidically enriched solid support particles of the present invention affording a CBD-activated accelerated conversion environment.

5 The term “introduce” or “introducing” is used herein to describe the non-covalent addition of one material, *e.g.*, CBD, to another material, *e.g.*, solid support particles.

 The language “material-efficient” is used herein to describe methods/processes that reduce reaction conditions/reagents to reduce waste (as compared to existing methods/processes or in an absolute fashion when certain conditions/reagents are eliminated
10 entirely), and therefore afford commercially relevant methods/devices such as those provided in the present invention. For example, in the present invention the use of the acidically enriched support particles eliminates the need for harsh solvents and solution based acid catalysts, and are therefore material-efficient.

 The language “reduced time frame” is used herein to describe the reduction in the time
15 window in which a reaction proceeds, *e.g.*, the CBD to THC conversion, as compared to existing/known reactions. In certain embodiments, the reduced time frame is a “compressed time frame” that describes a reaction that is complete within 1 min to 3 hours, *e.g.*, 1 min to 2 hours, *e.g.*, 1 min to 1 hours, *e.g.*, 1 min to 30 min, *e.g.*, 1 min to 20 min, *e.g.*, 1 min to 15 min, *e.g.*, 1 min to 10 min, *e.g.*, 1 min to 5 min, *e.g.*, less than 5 min.

20 The language “solid support particles” is used herein to describe solid particles used for non-covalent reaction support. The present invention utilizes solid support particles that are acidically enriched. In particular embodiments, the acidically enriched support particles are selected from the group consisting of acidically enriched resin beads (*e.g.*, Amberlyst-15 resin beads, Nafion particles), acidically enriched functionalized silica gel (*e.g.*, silica supported
25 sulfonic and phosphoric acids), acidically enriched zirconium oxide, acidically enriched aluminosilicate zeolites, acidically enriched aluminophosphosilicate zeolites, and any combination thereof.

 The term “tetrahydrocannabinol” or “THC” is art-recognized, and comprises all isomers, *e.g.*, double bond isomers, unless otherwise stated.

30 The term “THC-9” is used herein as a representative notation for Δ^9 -THC” or “THC-delta-9.”

 The term “THC-8” is used herein as a representative notation for Δ^8 -THC” or

“THC-delta-8.” This isoform has been found to be close in potency (at the cannabinoid CB1 and CB2 receptors and in human clinical trials) to (-)-*trans*- Δ^9 -THC (Hollister, 1974; Hanus, 2016).

The term “tunable” is used herein to describe the ability to tune to, or select, a given product or product ratio by selecting additional factors for the method used or method-reliant device, such as, for example, selecting the acidically enriched solid support particles, selecting the temperature, selecting the time of reaction before extraction, selecting the particular solvent, or any combination thereof.

The term “zeolite,” as used in the present invention to describe solid support particles of the present invention comprising any member of the family of hydrated aluminosilicate minerals that contain alkali and alkaline-earth metals. In certain embodiments, the zeolites have a well-known three-dimensional tetrahedral framework structure wherein each oxygen atom is shared by two tetrahedral, and which encloses interconnected cavities, *e.g.*, having diameters ranging from about 2 to 8 angstroms, typically occupied by large metal cations (positively charged ions) and water molecules. In fact, in naturally occurring zeolites, these metal ions are typically mono- or di-valent ions such as sodium, potassium, magnesium, calcium, and barium. However, the acidically enriched solid support particles utilized in the methods and devices of the present invention are functionalized with hydrogen in replacement of these metal cations suitably to achieve residual level acidity.

II. Methods of the Invention for Conversion of CBD to THC

In accordance with the methods of the present invention, CBD may be converted into THC by introduction to support particles that are acidically enriched. The introduction of the CBD to the acidically enriched solid support particles creates a CBD-activated accelerated conversion environment. In certain embodiments, the CBD may comprise additional functional groups in accordance with the well-known cannabinoid art, *i.e.*, simple derivatives, which in turn may produce simple derivatives of THC as the final product rather than THC. The methods are material-efficient, tunable, and may be solvent-free in certain embodiments.

As such, one embodiment of the present invention provides a material-efficient method for conversion of cannabidiol (CBD) (*e.g.*, and simple derivatives thereof) to

tetrahydrocannabinol (THC) (*e.g.*, and simple derivatives thereof) comprising the step of:

introducing CBD to acidically enriched solid support particles to create a CBD-activated accelerated conversion environment,

such that THC (*e.g.*, and simple derivatives thereof) is produced.

5 Another embodiment of the present invention provides a tunable material-efficient method for conversion of cannabidiol (CBD) (*e.g.*, and simple derivatives thereof) to tetrahydrocannabinol (THC) (*e.g.*, and simple derivatives thereof) comprising the step of:

introducing CBD to acidically enriched solid support particles to create a CBD-activated accelerated conversion environment,

10 such that THC (*e.g.*, and simple derivatives thereof) is selectively produced in the accelerated conversion environment (*e.g.*, by selecting the acidically enriched solid support particles, selecting temperature, selecting time of reaction before extraction). In certain embodiments, the THC (*e.g.*, and simple derivatives thereof) is selectively produced as a single product or ratio of multiple products, *e.g.*, including starting material CBD.

15 Yet another embodiment of the present invention provides a solvent-free method for conversion of cannabidiol (CBD) (*e.g.*, and simple derivatives thereof) to tetrahydrocannabinol (THC) (*e.g.*, and simple derivatives thereof) comprising the step of:

introducing CBD to acidically enriched solid support particles through direct melt of the CBD to create a CBD-activated accelerated conversion environment,

20 such that THC (*e.g.*, and simple derivatives thereof) is produced.

Another embodiment of the present invention provides a material-efficient method for conversion of THC-9 (*e.g.*, and simple derivatives thereof) to THC-8 (*e.g.*, and simple derivatives thereof) comprising the step of:

25 introducing THC-9 to acidically enriched solid support particles to create a THC-9-activated accelerated conversion environment,
such that THC-8 (*e.g.*, and simple derivatives thereof) is produced.

Certain embodiments of the methods of present invention further comprise the step of heating said CBD-activated accelerated conversion environment.

30 In certain embodiments of the present invention, the accelerated conversion environment is heated to less than or equal to 100 °C.

In certain embodiments of the present invention, the acidically enriched solid support particles are used less than 50%, *e.g.*, less than 40%, *e.g.*, less than 30%, *e.g.*, less than 20%, *e.g.*, less than 10%, by weight ratio with respect to the CBD.

5 In certain embodiments of the present invention, the acidically enriched solid support particles are used in at least 10% by weight ratio with respect to the CBD.

10 In certain embodiments of the methods of present invention, the step of introducing the CBD to the acidically enriched solid support particles is through solvent dissolution (*e.g.*, using a hydrocarbon solvent or an oil, *e.g.*, natural or synthetic) of the CBD to create the CBD-activated accelerated conversion environment. In certain embodiments, the solvent may be recovered following conversion, supporting a more renewable “green” process. In certain embodiments, the isolation/separation of the THC produced may be achieved by separation of the reaction solvent from the acidically enriched solid support particles, *e.g.*, without additional reaction workup. In particular embodiments, this separation may be through additional solvent extraction, *e.g.*, solvent washing of the particles to recover THC produced.

15 In certain embodiments of the methods of present invention, the step of introducing the CBD to the acidically enriched solid support particles is through solvent-free direct melt of the CBD to create the CBD-activated accelerated conversion environment. In certain embodiments, the acidically enriched solid support particles are used at a 50% by weight ratio with respect to the CBD. Such direct melt processing capitalizes on the low melting point of CBD (m.p. 66 °C) and occurrence of THC as oil. In certain embodiments, the acidically enriched solid support particles also serve as a filtration/separation mechanism, *i.e.*, THC impurities/side-products remain behind after solvent washing of the particles to recover the THC produced in the melt on the particles. In particular embodiments, THC produced is greater than 90% pure THC. In specific embodiments, the solvent-free melt method increases the reaction speed as compared with non-melt (solvent based) conditions.

20 Certain embodiments of the methods of present invention further comprise the step of extraction of the solid support particles (*e.g.*, using an appropriate solvent, *e.g.*, a hydrocarbon solvent, an alcohol, or a plant oil).

30 In certain embodiments of the present invention, the THC produced in the accelerated conversion environment is selected from the group consisting of THC-9, THC-8, and any combination or ratio thereof.

In certain embodiments of the present invention, the THC is tunable, or selectively produced in the accelerated conversion environment. In certain embodiments, the selectivity is the result of selecting the acidically enriched solid support particles, selecting temperature, selecting time of reaction before extraction, selecting a particular solvent, or any
5 combination thereof. In particular embodiments, the selectivity is produced as a single product or ratio of multiple products, *e.g.*, including starting material CBD. In specific embodiments, the THC produced in the accelerated conversion environment has a THC-9 bias (*e.g.*, greater than 50%, *e.g.*, greater than 60%, *e.g.*, greater than 70%, *e.g.*, greater than 80%,
10 *e.g.*, greater than 90%). In alternative specific embodiments, the THC produced in the accelerated conversion environment has a THC-8 bias (*e.g.*, greater than 50%, *e.g.*, greater than 60%, *e.g.*, greater than 70%, *e.g.*, greater than 80%, *e.g.*, greater than 90%).

In certain embodiments of the present invention, the THC produced in the accelerated conversion environment is produced with enhanced conversion efficiency of the CBD (*i.e.*, consumption of CBD) with greater than 75% efficiency (*e.g.*, greater than 80% efficiency, *e.g.*,
15 greater than 85% efficiency, *e.g.*, greater than 90% efficiency, *e.g.*, greater than 95% efficiency).

In certain embodiments of the present invention, the THC produced in the accelerated conversion environment (*e.g.*, crude) is greater than 50% pure (*e.g.*, greater than 60% pure,
20 *e.g.*, greater than 70% pure, *e.g.*, greater than 75% pure).

In certain embodiments of the present invention, the THC produced in the accelerated conversion environment (*e.g.*, crude) is greater than 80% pure (*e.g.*, greater than 85% pure,
e.g., greater than 90% pure, *e.g.*, greater than 95% pure).

In certain embodiments of the present invention, the THC produced in the accelerated conversion environment is produced at an enhanced rate (*e.g.*, less than or equal to 3 hours,
25 *e.g.*, less than or equal to 2 hours, less than or equal to 1 hour, *e.g.*, less than or equal to 45 min, *e.g.*, less than or equal to 30 min, *e.g.*, less than or equal to 20 min, *e.g.*, less than or equal to 15 min, *e.g.*, less than or equal to 10 min, *e.g.*, less than or equal to 5 min).

In certain embodiments of the present invention, the THC produced in the accelerated conversion environment is 50 g or greater (*e.g.*, 100 g or greater, *e.g.*, 250 g or greater).

30 In certain embodiments of the present invention, the THC produced in the accelerated conversion environment is 500 g or greater (*e.g.*, 1 kg or greater, *e.g.*, 5 kg or greater, *e.g.*, 10 kg or greater, *e.g.*, 20 kg or greater, *e.g.*, 100 kg or greater, *e.g.*, 500 kg or greater).

i. Solid Support Particles

In certain embodiments of the present invention, the solid support particles are selected from the group consisting of acidically enriched polymer resin beads (*e.g.*, Amberlyst-15 resin beads, Nafion particles), acidically enriched functionalized silica gel (*e.g.*, silica supported sulfonic and phosphoric acids), acidically enriched zirconium oxide, acidically enriched aluminosilicate zeolites, acidically enriched aluminophosphosilicate zeolites, and any combination thereof.

In certain embodiments of the present invention, the solid support particles are selected for additional properties, *e.g.*, related to use of the final THC product, and include, for example, to avoid leaching.

In certain embodiments of the present invention, the solid support particles are selected based on the hydrolytic stability, *e.g.*, related to the linker to the acid functionality.

In particular embodiments, this results in a reduction of sensitivity to moisture.

In certain embodiments, the acidically enriched solid support particles are renewable, *i.e.*, may be used again, supporting a more renewable “green” process.

In certain embodiments of the present invention, the acidically enriched solid support particles are support particles of an ion-exchange type, *e.g.*, such as AMBERLYST-15 or 35 resins that are available in a bead form. These support particles are acidic, *e.g.*, strongly acidic, ion exchange styrene-divinylbenzene polymeric scaffold containing sulfonic acid moieties (5-6 eqv/kg) and developed for binding of cationic impurities in chromatography, purification and other applications. In light of the instant discovery, and without wishing to be bound by theory, it is believed that the pore structure of AMBERLYST 15 and 35 permits ready access of reactants to the hydrogen ion sites located throughout the bead, thus facilitating successful performance even in non-swelling organic media.

In certain embodiments of the present invention, the acidically enriched solid support particles are support particles of an active ion-exchange acidic catalyst, such as Nafion-H[®], a sulfonated polymer prepared by polymerization of perfluorinated vinyls and perfluorinated vinyl esters, tetrafluoro-ethylene-perfluoro-3,6-dioxo-4-methyl-7-octensulfonic acid. Without wishing to be bound by theory, it is believed its superacidity is attributed to the electron-withdrawing effect of the perfluoroalkyl backbone to which the sulfonic acid group is attached.

Mechanistic studies of various transformations show that the acidity of Nafion-H[®] under the reaction conditions is comparable to that of 96-100% H₂SO₄. Nafion-H[®] has relatively high working temperatures as compared to other polymers and is stable up to a temperature of 210 °C. It is an eco-friendly and recyclable catalyst due to the added advantages of its inertness to corrosive environments, ease of recovery and recyclable nature. The catalytic activation of Nafion-H[®] resin utilizes polar solvents due to increased swelling, which leads to better accessibility of the sulfonic acid active sites.

In certain embodiments of the present invention, the acidically enriched solid support particles are support particles of a Lewis acid, *e.g.*, such as silica-bound BF₃ catalyst that is believed to contain as active catalytic centers –OBF₂ and -O-B(F)-O- species (Oshidome, 2001).

In certain embodiments of the present invention, the acidically enriched solid support particles are support particles of an oxide, *e.g.*, such as those with propyl sulfonic and tosyl sulfonic acid incorporated into the amorphous silica network.

In certain embodiments of the present invention, the acidically enriched solid support particles are support particles of aluminosilicates or aluminophosphosilicates.

III. Devices of the Invention

The methods of the present invention may be utilized for the production of THC in certain devices through the conversion from CBD. As such, in certain embodiments, the devices of the present invention will be designed to operate in accordance with the methods of the present invention as described herein. In this way, the devices of the present invention comprise a vessel for containing acidically enriched solid support particles, and a plurality of CBD-activated acidically enriched solid support particles positioned inside the vessel.

The devices of the present invention are well suited for use in commercial THC production or for personal THC production, and for both medical and recreational purposes. In certain embodiments of the present invention, the device is for medical application, *e.g.*, with medical precision.

A. Production Device

One embodiment of the present invention provides a tetrahydrocannabinol (THC) production device comprising:

- 5 a vessel for containing acidically enriched solid support particles; and
 a plurality of CBD-activated acidically enriched solid support particles
positioned inside the vessel, wherein THC is produced from the CBD-activated acidically
enriched solid support particles.

Another embodiment of the present invention provides a tunable tetrahydrocannabinol
10 (THC) production device comprising:

- a vessel for containing acidically enriched solid support particles; and
 a plurality of acidically enriched solid support particles positioned inside the
vessel, wherein THC is produced from the CBD-activated acidically enriched solid support
particles.

15 In certain embodiments of the THC production devices of the present invention are
tunable, where the THC may be selectively produced in the accelerated conversion
environment. In certain embodiments, the selectivity is the result of selecting the acidically
enriched solid support particles, selecting temperature, selecting time of reaction before
extraction, selecting a particular solvent, or any combination thereof. In particular
20 embodiments, the selectivity is produced as a single product or ratio of multiple products, *e.g.*,
including starting material CBD.

 In certain embodiments of the tetrahydrocannabinol (THC) production devices of the
present invention, the vessel is selected from the group consisting of a reaction vessel, a
collection vessel, a column, a vape device, a cartridge for a vape device, a smoking device, a
25 skin applicator, a syringe, an oral delivery device, a sublingual delivery device, and any
combination thereof. In a particular embodiment, the vessel is selected based upon the
desired use, delivery, or application, *e.g.*, commercial production or personal use. In certain
embodiments, the present invention provides methods of producing these device by
introducing the CBD to a precursor device, *i.e.*, a device prior to the introduction of CBD.

30 In certain embodiments of the THC production devices of the present invention, the
vessel is selected for commercial production of THC

In certain embodiments of the THC production devices of the present invention, the vessel is selected for personal use production of THC. In certain embodiments, the personal use production of THC is a medical device, *e.g.*, with medical precision control over the ratio of THC-9 and THC-8.

5 In certain embodiments of the THC production devices of the present invention, the device is programmed with a time controller to select the ratio of THC-9 and THC-8.

i. Commercial Application

10

In certain embodiments of the THC production devices of the present invention, the THC production device further comprises a heating source suitable to control the temperature of vessel.

15 In certain embodiments of the THC production devices of the present invention, the heating source is a heating jacket.

In certain embodiments of the THC production devices of the present invention, the THC production device further comprises a means for extraction of the THC from the acidically enriched solid support particles in the vessel.

20 In certain embodiments of the THC production devices of the present invention, the solid support particles are selected from the group consisting of acidically enriched resin beads (*e.g.*, Amberlyst-15 resin beads, Nafion particles), acidically enriched functionalized silica gel (*e.g.*, silica supported sulfonic and phosphoric acids), acidically enriched zirconium oxide, acidically enriched aluminosilicate zeolites, acidically enriched aluminophosphosilicate zeolites, and any combination thereof.

25 In certain embodiments of the THC production devices of the present invention, the THC produced in the accelerated conversion environment is selected from the group consisting of THC-9, THC-8, and any combination thereof.

30 In certain embodiments of the THC production devices of the present invention, 500 g or greater of THC may be produced in a single use of the device (*e.g.*, 1 kg or greater, *e.g.*, 5 kg or greater, *e.g.*, 10 kg or greater, *e.g.*, 20 kg or greater, *e.g.*, 100 kg or greater, *e.g.*, 500 kg or greater).

In certain embodiments of the THC production devices of the present invention, the THC is produced with enhanced conversion efficiency of the CBD with greater than 75% efficiency (*e.g.*, greater than 80% efficiency, *e.g.*, greater than 85% efficiency, *e.g.*, greater than 90% efficiency, *e.g.*, greater than 95% efficiency).

5 In certain embodiments of the THC production devices of the present invention, the THC produced (*e.g.*, crude) is greater than 80% pure (*e.g.*, greater than 85% pure, *e.g.*, greater than 90% pure, *e.g.*, greater than 95% pure).

10 In certain embodiments of the THC production devices of the present invention, the THC is produced at an enhanced rate (*e.g.*, less than or equal to 3 hours, *e.g.*, less than or equal to 2 hours, *e.g.*, less than or equal to 1 hour, *e.g.*, less than or equal to 45 min, *e.g.*, less than or equal to 30 min, *e.g.*, less than or equal to 20 min, *e.g.*, less than or equal to 15 min, *e.g.*, less than or equal to 10 min, *e.g.*, less than or equal to 5 min).

In certain embodiments of the THC production devices of the present invention, the vessel comprises a first column.

15 In certain embodiments of the THC production devices of the present invention, the device further comprises a second vessel (*e.g.*, for a multi-column device).

In certain embodiments of the THC production devices of the present invention, the THC production device further comprises at least one additional column comprising a second plurality of acidically enriched solid support particles different from the first column.

20

ii. Personal Use

25 Another embodiment of the present invention provides a tetrahydrocannabinol (THC) production personal use device for use in producing amounts of THC that would be for on-demand use, *e.g.*, single administration use. In certain embodiments, the vessel size is selected given the desire to deliver a limited amount of THC doses for personal use.

Another embodiment of the present invention provides a tetrahydrocannabinol (THC) production personal use device comprising

30 a vessel for containing acidically enriched solid support particles, wherein the vessel is designed for personal use; and

a plurality of acidically enriched solid support particles positioned inside the vessel, wherein THC is produced from the CBD-activated acidically enriched solid support particles.

5 In certain embodiments of the THC production personal use devices of the present invention, the vessel is a vaping device.

In certain embodiments of the THC production personal use devices of the present invention, the vessel is an oral delivery device.

In certain embodiments of the THC production personal use devices of the present invention, the vessel is a sublingual delivery device.

10 In certain embodiments of the THC production personal use devices of the present invention, the vessel comprises an extraction means to extract the THC from the acidically enriched solid support particles, *e.g.*, to filter THC from catalyst and/or to stop the conversion reaction.

15 In certain embodiments of the THC production personal use devices of the present invention, the device is tunable to selectively produce THC. In certain embodiments, the device is programmed with a selected reaction time to selectively produce THC. In particular embodiments, the reaction time is between 1 min and 10 min, *e.g.*, 1 min and 5 min.

In certain embodiments of the THC production personal use devices of the present invention, the device is suitable for medical precision dosing of THC.

20

EXEMPLIFICATION

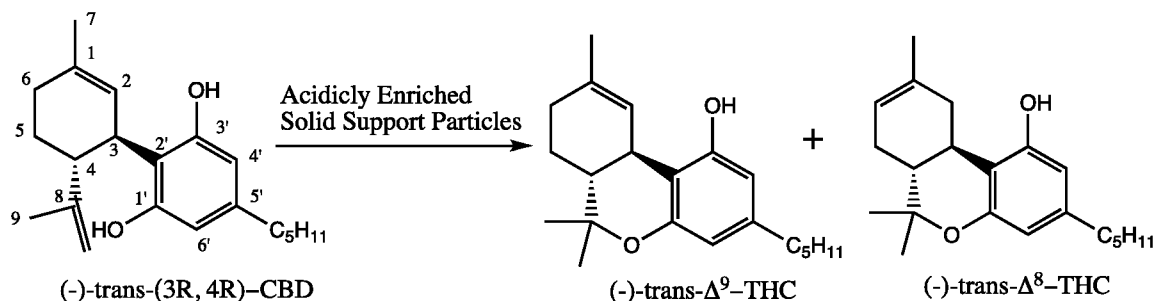
Having thus described the invention in general terms, reference will now be made to exemplary embodiments, and the accompanying drawings of exemplary embodiments, which
25 are not necessarily drawn to scale, and which are not intended to be limiting in any way.

In this respect, it is to be understood that the invention is not limited in its application to the details of construction and to the arrangements of the components set forth in the following description or illustrated in the Figures. The invention is capable of other
30 embodiments and of being practiced and carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein are for the purpose of description and should not be regarded as limiting.

The present invention has identified that the conversion of CBD to THC may be effectively catalyzed by Lewis and Brønsted acidic catalysts on the solid support (*i.e.*, acidically enriched solid support particles) with multiple advantages over the known solution chemistry. The catalytic conversions of CBD and THC may be represented as follows in

5 Scheme 1:

Scheme 1



10

Representative catalysts from certain main groups of acidically enriched solid support particles known in the art, namely, (i) ion-exchange resins, (ii) silica and alumina oxides and (iii) aluminosilicates (zeolites) were tested (Table 1). Moreover, the functionality shown in Table 1 describes the functional groups covalently bound to the solid support particles that result in the acidic enrichment, *i.e.*, creation of acidity, of the acidically enriched solid support particles

20 **Table 1. Representative Brønsted and Lewis acidically enriched solid support particles.**

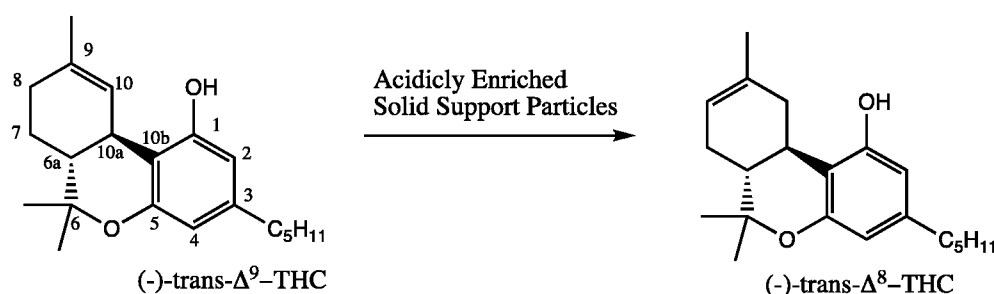
Solid Acid	Type	Core Framework	Acid Type	Functionality
Amberlyst	Ion-exchange resin	Organic-Polystyrene	Brønsted	Toluene Sulfonic
Nafion	Ion-exchange resin	Organic-Tetrafluoroethylene	Brønsted	Fluoroalkyl sulfonic
Al ₂ O ₃ /SO ₃ H	Oxide	Inorganic-Al ₂ O ₃	Brønsted	Sulfonic
SiO ₂ /H ₃ PO ₄	Oxide	Inorganic-SiO ₂	Brønsted	Phosphoric
SiO ₂ /SO ₃ H	Oxide	Inorganic-SiO ₂	Brønsted	Alkyl-, aryl-sulfonic
ZrO ₂ /H ₂ SO ₄	Oxide	Inorganic -ZrO ₂	Lewis/Brønsted	Sulfonic, metal sites
BF ₃ /SiO ₂	Oxide	Inorganic-SiO ₂	Lewis	-OBF ₂
Zeolites	Aluminophospho-	Inorganic-	Lewis/Brønsted	-OH, metal

	silicate	SiO ₂ /Al ₂ O ₃ /PO ₄		sites
Zeolites	Aluminosilicate	Inorganic-SiO ₂ /Al ₂ O ₃	Lewis/Brønsted	-OH, metal sites

The acidically enriched solid support particles described above and in specific examples below were obtained from commercial sources and used in the catalytic conversions described herein. However, the choice of catalyst materials is not limited and may be, in certain embodiments, expanded to other various compositions summarized in Table 1 and based both on organic and inorganic scaffolds. Appropriate selection and design of such catalysts to fine-tune their technical performance (in terms of conversion, selectivity, activity, stability etc.) and overall economics is within the skill of the ordinarily skilled artisan and therefore within the scope of the present invention in light of the disclosure presented herewith.

In certain embodiments, the THC-9 may be converted into THC-9 in accordance with Scheme 2.

Scheme 2



Example 1.

Conversion of CBD to (-)- Δ^8 -THC Using Ambersylt-15 Resin

50 mg of CBD powder (CBDistillery, Denver, CO, >99% purity) was dissolved in 2 ml of heptane to which 10 mg of Amberlyst-15 resin beads (dry, H⁺ form, Dow Chemical

Company; Acros Organics, Cat. No. AC202145000) have been added. The reaction mixture was refluxed in a round-bottom flask equipped with a condenser for 1 h, the catalyst beads were separated by filtration and the solvent removed in the rotovap. The HPLC of the reaction product revealed complete consumption of the starting CBD and formation of (-) Δ^8 -THC in 85 % yield. The identity of the product was confirmed by LC-MS spectroscopy ($M+H^+$, 314.4), HPLC (using a standard sample of (-) Δ^8 -THC from Restek Corporation that displayed an identical to the reaction product retention time of 8.1 min; see HPLC method details below; Figure 1), and by 1H NMR (following the analysis as reported by Choi et al., 2004 and Taylor et al., 1966) –the assignment to Δ^8 - position of the vinyl group (compared to Δ^9 -) was confirmed by the upfield shift from 6.3 to 5.4 ppm and the *trans*- configuration of the H-10/H-6 protons by a related coupling constant of 10.8 Hz (observable for the H-10 proton at 2.7 ppm).

The HPLC Setup: Agilent 1100 setup with a diode array detector, detection wavelength $\lambda=228$ nm, column Agilent Eclipse XD-8 Phenyl, 4.6x150 mm, 5 micron. Mobile phase A-0.1 % formic acid in water; mobile phase B-0.1 % formic acid in acetonitrile; flow rate 1.15 ml/min, injection volume 10 microL. HPLC method details: 72 % B (0 min) to 81 % B (4.5 min), to 100 % B (9 min), to 72% B (10 min). A typical HPLC trace of the reaction mixture is shown in the Figure 1.

1H NMR (400 MHz, $CDCl_3$): 0.88 (3H, t, 7.1 Hz) 5^{''}-Me; 1.10 (3H, s) 9-Me; 1.32 (4H, m) 3^{''}, 4^{''}-CH₂; 1.38 (3H, s) 8-Me; 1.56 (2H, q, 7.6 Hz) 2^{''}-CH₂; 1.70 (3H, s) 3-Me; 1.80 (m) 6-H; 2.13 (1H, m), 1.64 (1H, s) 5-CH₂; 2.13 (1H, m) 5-H; 2.44 (2H, td, 8.3 Hz, 2.1 Hz) 1^{''}-CH₂; 2.70 (1H, td, 10.8 Hz, 4.8 Hz) 1-H; 3.24 (2H, dd, 16.5 Hz, 3.7 Hz) 2-CH₂; 5.43 (1H, brd, 4.8 Hz) 4-CH₂; 6.11 (1H, d, 1.6 Hz) 3[']-H; 6.27 (1H, d, 1.5 Hz) 5[']-H.

The reaction had similar outcomes regarding the product yield and purity when conducted in hexane (at reflux), isopropyl myristate (IMS) at 100°C and medium chain triglycerides (100 °C, 10 h). The higher reaction temperature was not found a prerequisite for completion in hexane or heptane with a full conversion also achieved in 48 h at ambient temperature. The reaction temperatures above 100 °C lead to rapid accumulation of the degradation products.

Reaction proceeded only partially in alcohol – after 2 h at reflux in isopropyl alcohol only ca. 10 % of CBD was consumed and produced a mixture of (-) Δ^8 -THC and (-) Δ^9 -THC.

A full catalytic conversion of CBD to (-)- Δ^8 -THC (78 %) also took place by heating a commercial CBD isolate containing minor quantities of other cannabinoids and terpenes (CBDistillery, Denver, CO, Full Spectrum Isolate, 250 mg CBD in 15 ml MCT coconut oil) for 10 h at 100 °C.

5 In certain embodiments, the optimal amount of catalyst was found to be in the range of 5-25 % w/w to CBD. By running the time course of the Amberlyst-catalyzed reaction at milder conditions (e.g., ambient temperature and refrigerating to 4°C; T=1-336 h), intermittent formation of the (-)-trans- Δ^9 -THC stereoisomer was observed (with shorter retention time, see Figure 1), along with the residual unreacted fractions of the starting CBD.

10 In conclusion, the reaction proceeded in various non-protic solvents and oils and could be completed in light hydrocarbons at ambient temperatures in 2 days or in accelerate mode at higher temperatures in 1-10 h. The use of hydrocarbons makes it possible for direct utilization of the reaction mixture for additional purification using Centrifugal Partitioning
15 Chromatography (CPC) in scale up preparations of THC (Hazecamp, 2004).

Example 2

Conversion of CBD to (-)- Δ^8 -THC Using Nafion

20 50 mg of CBD was dissolved in 2 ml of heptane to which 10 mg of Nafion-SAC-13 (fluorosulfonic acid Nafion[®] polymer on amorphous silica, 10-20% load, 0.6 ml/g pore volume, >10 nm pore diameter, surface area >200 m²/g) was added.

25 The reaction mixture was refluxed in a round-bottom flask equipped with a condenser for 1 h, the catalyst beads were separated by filtration and the solvent removed in the rotovap. The HPLC confirmed the formation of (-)- Δ^8 -THC as a major reaction product in 66 % yield.

Example 3

Conversion of CBD to (-)- Δ^8 -THC Using Silica Supported BF₃

50 mg of CBD was dissolved in 2 ml of heptane to which 10 mg of silica supported BF_3 catalyst (Sigma Aldrich, Cat. No. 718416) was added. The reaction mixture was refluxed in a round-bottom flask equipped with a condenser for 1 h, the catalyst particles were separated by filtration and the solvent removed in the rotovap. The HPLC of the reaction product confirmed the formation of (-)- Δ^8 -THC as a major reaction product in 70 % yield.

Example 4

Conversion of (-)- Δ^9 -THC to (-)- Δ^8 -THC

50 mg of (-)- Δ^9 -THC was dissolved in 2 ml of heptane to which 10 mg of Amberlyst catalyst was added. The reaction mixture was refluxed in a round-bottom flask equipped with a condenser for 2 h, the catalyst beads were separated by filtration and the solvent removed in the rotovap. The HPLC of the reaction product confirmed the formation of (-)- Δ^8 -THC (89 % yield).

Example 5

Conversion of CBD to (-)- Δ^8 -THC and (-)- Δ^9 -THC Using Silica Supported Sulfonic Acids and other Oxides

50 mg of CBD was dissolved in 2 ml of hexane to which 10 mg of SiliaBond Functionalized Silica Gel Propyl Sulfonic acid (SCX-2) or SiliaBond Tosic Acid (SCX) catalyst, both end-capped, particle size 40-60 micron, 0.6-0.8 mmol/g (SiliCycle, Quebec, Canada), were added. The reaction mixture was refluxed in a round-bottom flask equipped with a condenser for 5 min, the catalyst beads separated by filtration and the solvent removed in the rotovap. The HPLC of the reaction product confirmed the formation of (-)- Δ^8 -THC (66 % yield) for both SCX-2 and SCX catalysts.

The CBD conversion was also almost complete in no solvent conditions by heating the melt of CBD with 10% by weight of the catalyst at 100 °C for 5 min and recovering the product by extracting the melt with hexane.

The reaction was also followed by HPLC at ambient temperature for the SCX catalyst. Intermittent formation of both THC-8 and THC-9 was observed. Close to the completion point (6 % residual CBD) at 90 min, there was 31% of THC-9 and 37 % of THC-8 in the mixture (Table 2).

5

Table 2. Reaction Products of CBD-to-THC Conversion Catalyzed by Si-Sulfonic Acids

Composition of reaction products	Reaction Conditions				
	10 min, RT, Hexane	60 min, RT, Hexane	90 min, RT, Hexane	5 min, Reflux Hexane	5 min, 100°C Solid
CBD, %	67	16	6	1	0
THC-9, %	20	35	31	4	3
THC-8, %	5	24	37	66	64

Silicagel catalysts provided a surprising overall acceleration of the CBD conversion (>10x) compared to Amberlyst, Nafion and BF₃/SiO₂. Also silicagels allowed substantial stabilization of the THC-9 isomer in a convenient adaptation of the reaction at room temperature. Three other tested solid catalysts showed intermittent formation THC-9 only at early reaction time points corresponding to very low conversion of CBD and thus bearing little practical utility as an approach to THC-9.

15

Other oxide type catalysts with different core and acid functionality were tested producing results that are summarized in Table 3. Moreover, the functionality shown in Table 3 describes the functional groups covalently bound to the solid support particles that result in the acidic enrichment, *i.e.*, creation of Brønsted acidity, of the acidically enriched solid support particles.

20

Table 3. Oxide Type of Catalysts Tested

Catalyst	Core	Vendor	Functionality	Catalytic Activity
SCX-2	SiO ₂	Silicycle R51230B	Propylsulfonic Acid, end-capped silica	High
SCX	SiO ₂	Silicycle R60530B	Arylsulfonic Acid, non-capped silica	High
SCX, capped	SiO ₂	Silicycle R60430B	Arylsulfonic acid, end-capped silica	High

ZrO ₂ H ₂ SO ₄	ZrO ₂	Alfa Aesar	Sulfuric Acid	Low (20% conversion, refluxed heptane, 0.5 h)
Phos-Cat1	SiO ₂	Carbosynth	Phosphoric Acid	Medium (74% conversion, refluxed heptane, 1 h)
Al ₂ O ₃ acidic	Al ₂ O ₃	Alfa Aesar	Al-OH	VERY LOW
NaHSO ₄	Hydrosulfate	Aldrich	HSO ₄ ⁻	VERY LOW

It is noteworthy that zirconium sulfuric acid, known to possess some superacidity properties, showed low activity along with somewhat more active phosphoric acid functionalized silica. In certain embodiments, the acidically enriched solid support particles are not Al₂O₃ acidic or NaHSO₄.

5 In certain embodiments, the acidically enriched solid support particles are not ZrO₂ H₂SO₄.

Example 6

Conversion of CBD to (-)-Δ⁸-THC and (-)-Δ⁹-THC Using Aluminosilicates

10 It was further discovered that some aluminosilicates and aluminophosphosilicates act as very efficient catalysts of the CBD-to-THC conversion at loads of 10-50 %. The tested materials are listed in Table 3. In these embodiments, it was essential to have the catalyst in the H⁺ form. When in the salt form (shown for Zeolite Y), the materials were found to be inactive.

15

Table 4. Aluminosilicate and Aluminophosphosilicate Tested for Catalytic CBD Conversion

Catalyst	Si/Al Ratio	Largest Pore Size, Å	Activity
ZSM-5	15:1	10	Low (7% conversion, 30 min reflux heptane)
Zeolite Y	5:1	12	High
Zeolite Y (Na ⁺)	5:1	12	Inactive
Zeolite Beta	360:1	12	High
SAPO-34	1:4	8	Inactive
SAPO-11	1:8	10	High

In certain embodiments, the acidically enriched solid support particles are not SAPO-34. In

20 certain embodiments, the acidically enriched solid support particles are not ZSM-5.

The reaction proceeds with high conversion outcomes in refluxed heptane over a period of 1 h. Surprisingly, the transformation is significantly accelerated when conducted in the melt, without any solvent. Using aluminosilicates helps to stabilize THC-9 vs. THC-8 reaction products. In only 5 minutes time, the conversion rate was already about 80% with THC-9/THC-8 ratio of 2:1. The outcomes of catalytic transformations in different reaction conditions for the most active materials, *i.e.*, Zeolite Y, SAPO-11 and Zeolite Beta are summarized in the Tables 5-7.

Table 5. Reaction Products of CBD-to-THC Conversion Catalyzed by Aluminophosphosilicate SAPO-11

Composition of Reaction Products	Reaction Conditions (Time, Temperature, Solvent)				
	5 min, Reflux Heptane	30 min, Reflux Heptane	60 min, Reflux Hexane	5 min, Reflux Hexane	5 min, 100°C Solid
CBD, %	72	27	2	20	2
THC-9, %	21	43	45	46	31
THC-8, %	2	14	23	22	35

Table 6. Reaction Products of CBD-to-THC Conversion Catalyzed by Aluminosilicate Zeolite Y

Composition of Reaction Products	Reaction Conditions (Time, Temperature, Solvent)				
	5 min, Reflux Heptane	60 min, Reflux Heptane	5 min, 100°C, Solid	15 min, 100°C, Solid	30 min, 100°C, Solid
CBD, %	68	8	19	4	1
THC-9, %	22	47	47	42	36
THC-8, %	2	23	23	36	44

Table 7. Reaction Products of CBD-to-THC Conversion Catalyzed by Aluminosilicate Zeolite Beta

Composition of Reaction Products	Reaction Conditions (Time, Temperature, Solvent)			
	5 min, Refl. Heptane	60 min, Refl. Heptane	5 min, 100°C, Solid	15 min, 100°C, Solid
CBD, %	55	12	64	53
THC-9, %	27	49	22	27
THC-8, %	3	12	2	3

References

- 5 1. Y. Gaoni and R. Mecholaum, Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish, *J. Am. Chem. Soc.*, 1964. Vol. 86, pp. 1646-1647.
2. Y. Gaoni and R. Mecholaum, Hashish-VII. The Isomerization of Cannabidiol to Tetrahydrocannabinols, *Tetrahedron*, 1966. Vol. 22, pp. 1481-1488.
3. Y. Gaoni, R. Mechoulam, Concerning the Isomerization of delta-1 to delta-6-
10 tetrahydrocannabinol. *J. Am. Chem. Soc.*, 1966, Vol. 88, pp.5673-5675.
4. G.R.B. Webster, L.P. Sarna, R. Mechoulam, Conversion of CBD to Delta8-THC and Delta9-THC, US Patent Appl. 10/469,928.
5. M. Kidwai, R. Chauhan and S. Bhatnagar, Nafion-H: A Versatile Catalyst for Organic Synthesis, *Current Organic Chemistry*, 2015, 19, pp.72-98.
- 15 6. R. J. Razdan, H. C. Dalzell, G.R. Handrick, Hashish, A Simple One-Step Synthesis of (-)-delta1-Tetracannabinol (THC) from p-Mentha-2,8-dien-1-ol and Olivetol, *J. Am. Chem. Soc.* 1974, Vol. 96, pp. 5860-5866.
7. P. Gupta, S. Paul, Solid Acids: Green Alternatives for Acid Catalysis, *Catalysis Today*, 2014, Part B, Vol. 236, pp. 153-214.
- 20 8. L. Hanus, S. M. Meyer, E. Munoz, O. Taglialatela-Scafati and G. Appendino, Phytocannabinoids: a Unified Critical Inventory, *Nat. Prod. Rep.*, 2016, Vol. 33(12), pp.1357-1392.
9. L.E. Hollister, Structure-Activity Relationships in Man of Cannabis Constituents and Homologs and Metabolites of delta-9-Tetrahydrocannabinol, *Pharmacology*,
25 1974, Vol. 11, pp. 3-11.
10. Y. H. Choi, A. Hazelkamp, A.M.G. Peltenburg-Looman, M. Frederich, C. Erkelens, A.W.M. Lefebr, R. Verpoorte, NMR Assignments of the Major Cannabinoids and Cannabiflavonoids Isolated from Flowers of Cannabis Sativa, *Phytochem. Anal.* 2004, Vol.15, pp.545-554.
- 30 11. E. C. Taylor, K. Lenard, Y. Shvo, Active Constituents of Hashish. Synthesis of *dl*- Δ^6 -3,4-*trans*-Tetrahydrocannabinol, *J. Am. Chem. Soc.*, 1966, pp.367-370.
12. T. Y. Oshidome, Z. D. Ang, and B. A. Morrow, Infrared Spectra of Silica Reacted with Gaseous BF₃ and Analyses of the Reaction, *Anal. Sc.* 2001, Vol. 17 Suppl., pp.

i1085-1088.

13. Hazekamp, R. Simons, A. Peltenburg-Looman, M. Sengers, R. van Zweden, R. Verpoorte, Preparative Isolation of Cannabinoids from Cannabis Sativa by Centrifugal Partition Chromatography, *J. Liq. Chrom. & Rel. Technol.* 2004, Vol. 27, pp. 2421-2439.

5 14. H. Y. Luo, J. D. Lewis, and Y. Roman-Leshkov, Lewis Acid Zeolites for Biomass Conversion: Perspectives and Challenges on Reactivity, Synthesis, and Stability, *Ann. Rev. Chem. Biochem. Eng.*, 2016.

15. R. H. Vekariya and H. D. Patel, Alumina Sulfuric Acid (ASA), Tungstate Sulfuric Acid (TSA), Molybdate Sulfuric acid (MSA) and Xanthan Sulfuric Acid (XSA) as
10 Solid and Heterogeneous Catalysts in Green Organic Synthesis: a Review, *ARKIVOC*, 2016, pp.70-96.

16. H. Sharghi, M. H. Sarvari and R. Eskandari, Alumina Sulfuric Acid as a Novel Heterogeneous System for Esterification of Carboxylic Acids in Solvent Free Conditions, *J. Chem. Res.*, 2005, pp.488-491

15 17. A.D. Sawant, D. G. Raut, A. R. Deorukhkar, U. V. Desai, M. M. Salunkhe, Silica supported orthophosphoric acid ($H_3PO_4 \cdot SiO_2$): a green, heterogeneous catalyst for solvent-free oxathioacetalization of aldehydes, *Green Chem. Let. Rev.*, 2011, Vol. 4, No. 3, pp. 235-240.

18. X. Zhang, Y. Zhao, S. Xu, Y. Yang, J. Liu, Y. Wei, Q Yang, Polystyrene Sulphonic Acid Resins with Enhanced Acid Strength via Macromolecular Self-Assembly within Confined Nanospace, *Nature Com.*, 2014.

19. P. Wang, Y. Zhao, J. Liu, Versatile Design and Synthesis of Mesoporous Sulfonic Acid Catalysts, *Sc. Bull.* 2018, 63, pp.252-266.

20. Zhou J, Wang Y, Guo X, et al. Etherification of Glycerol with Isobutene on
25 Sulfonated Graphene: Reaction and Separation. *Green Chem.* 2014, Vol. 16, pp. 4669–79.

Incorporation By Reference

The entire contents of all patents, published patent applications and other references
30 cited herein are hereby expressly incorporated herein in their entireties by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents were considered to be within the scope of this invention and are covered by the following claims. Moreover, any numerical or alphabetical ranges provided herein are
5 intended to include both the upper and lower value of those ranges. In addition, any listing or grouping is intended, at least in one embodiment, to represent a shorthand or convenient manner of listing independent embodiments; as such, each member of the list should be considered a separate embodiment.

CLAIMS

What is claimed is:

1. A material-efficient method for conversion of cannabidiol (CBD) to
5 tetrahydrocannabinol (THC) comprising the step of:
introducing CBD to acidically enriched solid support particles to create a CBD-
activated accelerated conversion environment,
such that THC is produced.
- 10 2. The material-efficient method of claim 1, wherein the solid support particles are
selected from the group consisting of acidically enriched resin beads, acidically enriched
functionalized silica gel, acidically enriched zirconium oxide, acidically enriched aluminosilicate
zeolites, acidically enriched aluminophosphosilicate zeolites, and any combination thereof.
- 15 3. The material-efficient method of claim 1 or 2, further comprising the step of heating
said CBD-activated accelerated conversion environment.
4. The material-efficient method of claim 3, wherein the accelerated conversion
environment is heated to less than or equal to 100 °C.
- 20 5. The material-efficient method of any one of claims 1, 2, 3, or 4, wherein the step of
introducing the CBD to the acidically enriched solid support particles is through solvent
dissolution of the CBD to create the CBD-activated accelerated conversion environment.
- 25 6. The material-efficient method of any one of claims 1, 2, 3, or 4, wherein the step of
introducing the CBD to the acidically enriched solid support particles is through solvent-free
direct melt of the CBD to create the CBD-activated accelerated conversion environment.
- 30 7. The material-efficient method of any one of claims 1, 2, 3, 4, 5, or 6, further
comprising the step of extraction of the solid support particles.

8. The material-efficient method of any one of claims 1, 2, 3, 4, 5, 6, or 7, wherein the THC produced in the accelerated conversion environment is selected from the group consisting of THC-9, THC-8, and any combination thereof.

5 9. The material-efficient method of claim 8, wherein the THC is selectively produced in the accelerated conversion environment.

10 10. The material-efficient method of claim 8 or 9, wherein the THC produced in the accelerated conversion environment has a THC-9 bias.

11. The material-efficient method of claim 8 or 9, wherein the THC produced in the accelerated conversion environment has a THC-8 bias.

15 12. The material-efficient method of any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11, wherein the THC produced in the accelerated conversion environment is produced with enhanced conversion efficiency of the CBD with greater than 75% efficiency.

20 13. The material-efficient method of any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein the THC produced in the accelerated conversion environment is greater than 80% pure.

25 14. The material-efficient method of any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, wherein the THC produced in the accelerated conversion environment is produced at an enhanced rate.

15 15. The material-efficient method of any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14, wherein the THC produced in the accelerated conversion environment is 500 g or greater.

30 16. A tunable material-efficient method for conversion of cannabidiol (CBD) to tetrahydrocannabinol (THC) comprising the step of:

introducing CBD to acidically enriched solid support particles to create a CBD-activated accelerated conversion environment,
such that THC is selectively produced in the accelerated conversion environment.

- 5 17. A solvent-free method for conversion of cannabidiol (CBD) to tetrahydrocannabinol (THC) comprising the step of:

introducing CBD to acidically enriched solid support particles through direct melt of the CBD to create a CBD-activated accelerated conversion environment,
such that THC is produced.

10

18. A tetrahydrocannabinol (THC) production device comprising:

a vessel for containing acidically enriched solid support particles; and

a plurality of CBD-activated acidically enriched solid support particles

positioned inside the vessel, wherein THC is produced from the CBD-activated acidically

- 15 enriched solid support particles.

19. The THC production device of claim 18, wherein the vessel is selected from the group consisting of a reaction vessel, a collection vessel, a column, a vape device, a cartridge for a vape device, a smoking device, a skin applicator, a syringe, and any combination thereof.

20

20. The THC production device of claim 18 or 19, wherein the vessel is selected for commercial production of THC

21. The THC production device of claim 18 or 19, wherein the vessel is selected for
25 personal use production of THC

22. The THC production device of any one of claim 18, 19, 20 or 21, further comprising a heating source suitable to control the temperature of vessel.

- 30 23. The THC production device of claim 22, wherein the heating source is a heating jacket.

24. The THC production device of any one of claim 18, 19, 20, 21, 22, or 23, further comprising a means for extraction of the THC from the acidically enriched solid support particles in the vessel.

5 25. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, or 24, wherein the solid support particles are selected from the group consisting of acidically enriched resin beads, acidically enriched functionalized silica gel, acidically enriched zirconium oxide, acidically enriched aluminosilicate zeolites, acidically enriched aluminophosphosilicate zeolites, and any combination thereof.

10

26. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, 24, or 25, wherein the THC produced in the accelerated conversion environment is selected from the group consisting of THC-9, THC-8, and any combination thereof.

15

27. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, 24, 25, or 26, wherein the THC may be selectively produced in the accelerated conversion environment.

20

28. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27, wherein 500 g or greater of THC may be produced in a single use of the device.

29. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28, wherein the THC is produced with enhanced conversion efficiency of the CBD with greater than 75% efficiency.

25

30. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29, wherein the THC produced is greater than 80% pure.

30

31. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, wherein the THC is produced at an enhanced rate.

32. The THC production device of any one of claim 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or 31, further comprising a second vessel.

33. A tunable tetrahydrocannabinol (THC) production device comprising:

5 a vessel for containing acidically enriched solid support particles; and
 a plurality of acidically enriched solid support particles positioned inside the vessel, wherein THC is produced from the CBD-activated acidically enriched solid support particles.

10 34. The tunable THC production device of claim 33, wherein the vessel comprises a first column.

35. The tunable THC production device of claim 34, further comprises at least one additional column comprising a second plurality of acidically enriched solid support particles
15 different from the first column.

36. A tetrahydrocannabinol (THC) production personal use device comprising
 a vessel for containing acidically enriched solid support particles, wherein the vessel is designed for personal use; and
20 a plurality of acidically enriched solid support particles positioned inside the vessel, wherein THC is produced from the CBD-activated acidically enriched solid support particles.

37. The THC production personal use device of claim 36, wherein the vessel is a vaping
25 device.

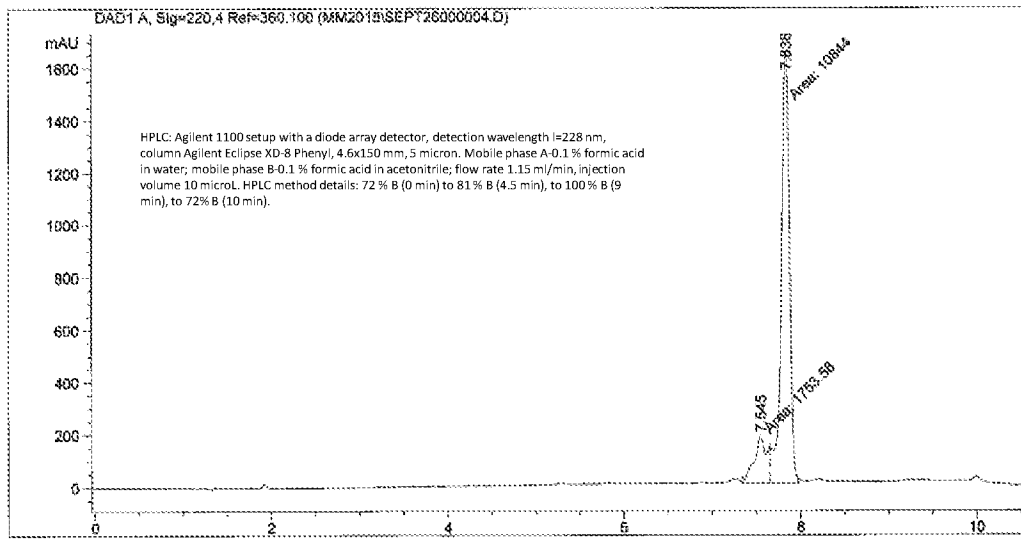
38. The THC production personal use device of claim 36 or 37, wherein the vessel comprises an extraction means to extract the THC from the acidically enriched solid support particles.

30 39. The THC production personal use device of any one of claim 36, 37, or 38, wherein the device is tunable to selectively produce THC.

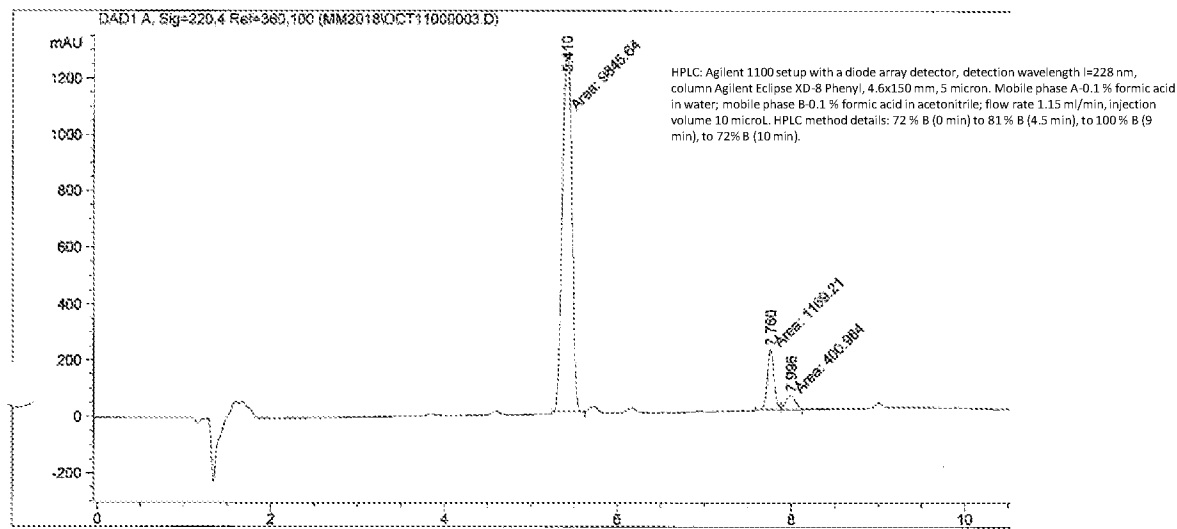
40. The THC production personal use device of claim 39, wherein the device is programmed with a selected reaction time to selectively produce THC.

- 5 41. The THC production personal use device of claim 39 or 40, wherein the device is suitable for medical precision dosing of THC.

Fig. 1



Panel A



Panel B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2020/013418

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/35; B01J 35/02; C07C 37/68 (2020.01)

CPC - A61K 31/35; A61K 36/185; B01J 35/026; C07C 37/68; C07D 311/80 (2020.02)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 131/328; 424/725; 514/453; 549/390 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0210860 A1 (ERLER et al) 19 August 2010 (19.08.2010) entire document	1-4, 16
X	US 2004/0049059 A1 (MUELLER) 11 March 2004 (11.03.2004) entire document	18-21, 33, 34
Y		36-38
Y	US 2016/0211693 A1 (JJ 206 LLC) 21 July 2016 (21.07.2016) entire document	36-38
A	US 2019/0276420 A1 (SOCATI TECHNOLOGIES) 12 September 2019 (12.09.2019) entire document	1-4, 16-21, 33-38
A	US 2008/0221339 A1 (WEBSTER et al) 11 September 2008 (11.09.2008) entire document	1-4, 16-21, 33-38

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 February 2020

Date of mailing of the international search report

24 MAR 2020

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2020/013418

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-15, 22-32, 39-41
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.