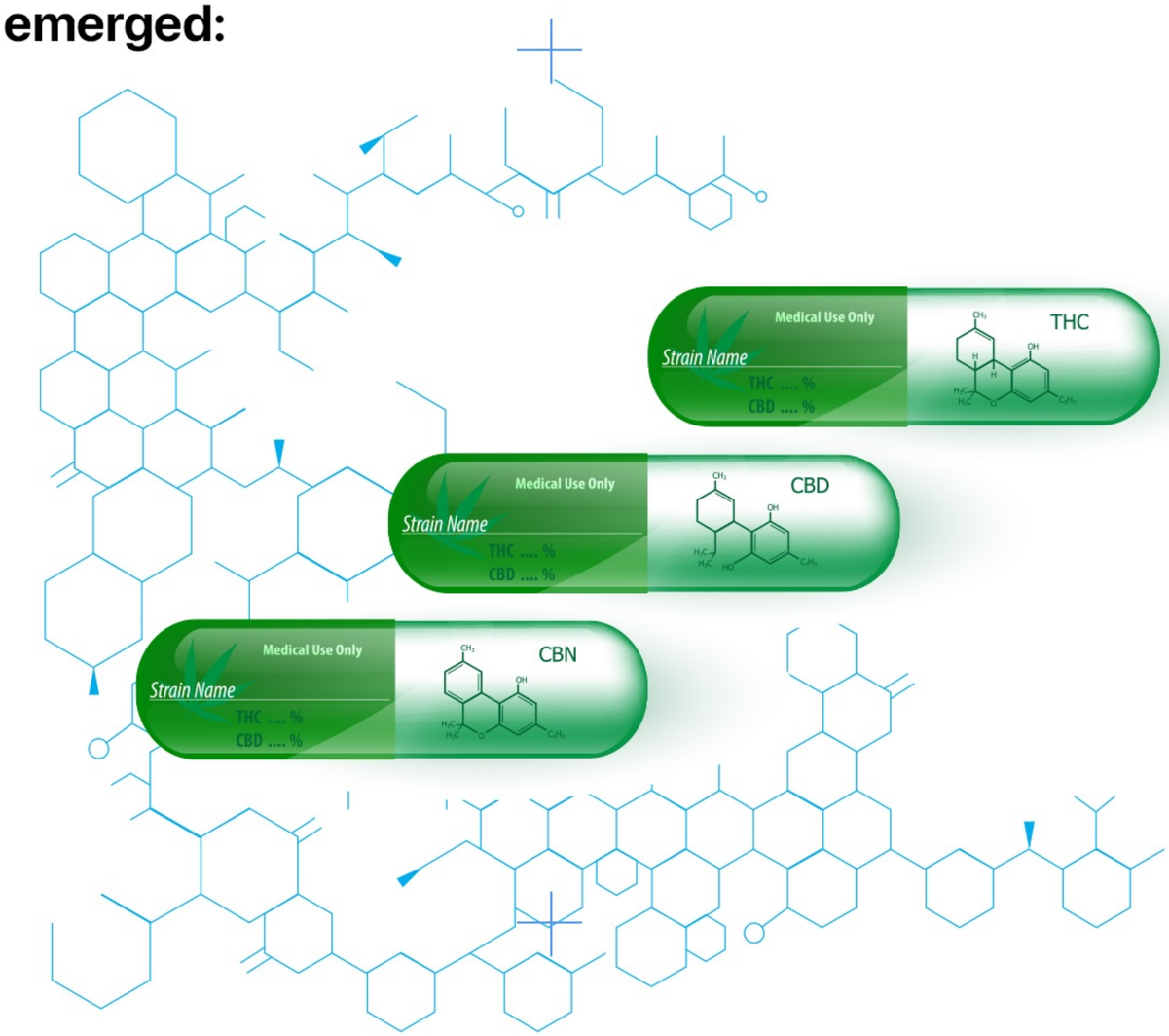
Cannabis and Cannabinoid Drug Development
Evaluating Botanical Versus Single Molecule Approaches

© PREPAIRE LABS LIMITED 2022

INTRODUCTION

Accumulating evidence suggests that the endocannabinoid system is a promising target for the treatment of a variety of health conditions.
Two paths of cannabinoid drug development have emerged:

- One approach is focused on developing medications that are directly derived from the cannabis plant.
- The another utilizes a single molecule approach whereby individual phytocannabinoids or novel cannabinoids with therapeutic potential are identified and synthesized for pharmaceutical development.



Cannabis has a long history of use in medicine, dating back thousands of years, and has been used historically to treat a variety of ailments such as **asthma**, **depression**, **epilepsy**, **fatigue**, **glaucoma**, **insomnia**, **migraine**, **nausea**, **pain**, **rheumatism** and **tetanus**.

A wide-spread political movement in the early 20th century resulted in prohibition of cannabis use throughout the developed world. Subsequent to this prohibition, western medical practices transitioned from reliance on botanical extracts and tinctures to a pharmacopeia predominantly comprised of single molecule therapeutics and the establishment of rigid regulations regarding the review and approval of new medications in a highly competitive and lucrative drug marketplace. In the time since cannabis prohibition, a lot has been discovered with regards to the chemical constituents of the cannabis plant and their pharmacology.

Researchers in Israel identified Δ9-Tetrahydrocannabinol (Δ9-THC) as the primary psychoactive agent in the cannabis plant in the mid-1960s. This discovery led to extensive research on cannabinoids in the 1970s, which also coincided with renewed interest in potential therapeutic effects of cannabinoids. In 1985, a synthetic formulation of THC (dronabinol) and a synthetic analog of THC (nabilone) were approved by the U.S. Food and Drug Administration for the treatment of nausea and vomiting associated with cancer chemotherapy. They were subsequently also approved for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS)

© PREPAIRE LABS LIMITED 2022

This progression followed the established model of western medicine in which individual chemical constituents of plants historically used in medicine are isolated and then developed into proprietary medications. In 1996, however, a twist in this saga began when the U.S. state of California legalized the medicinal use of botanical cannabis by its residents.

Over the past 20 years, an increasing number of countries, states, and territories have followed suit, legalizing the medicinal use of cannabis for a variety of health conditions. This is important because it is a unique example in medicine where:

A new medication is introduced to the market via legislation rather than through formal drug development practices.

We see a reversal of the trend towards single molecule drug development in favor of the use of raw botanical products.

Both cannabis and isolated cannabinoids hold tremendous therapeutic promise. There are several popular misconceptions (detailed below) associated with the two approaches that require better public education as cannabinoid medicines becomes more commonplace.

Cannabis Vs Cannabinoids

This section provides an important background with respect to important definitions, nomenclature, and pharmacology. The cannabis plant has been shown to be chemically rich, with 565 known constituents belonging to 23 classes of compounds.
The most recognized class of compounds in cannabis are the namesake cannabinoids. 120 different phytocannabinoids, plant-derived molecules unique to cannabis, have been identified in the cannabis plant, many of which directly modulate the endogenous cannabinoid system.
These naturally occurring cannabinoids are distributed among 10 subclasses including:

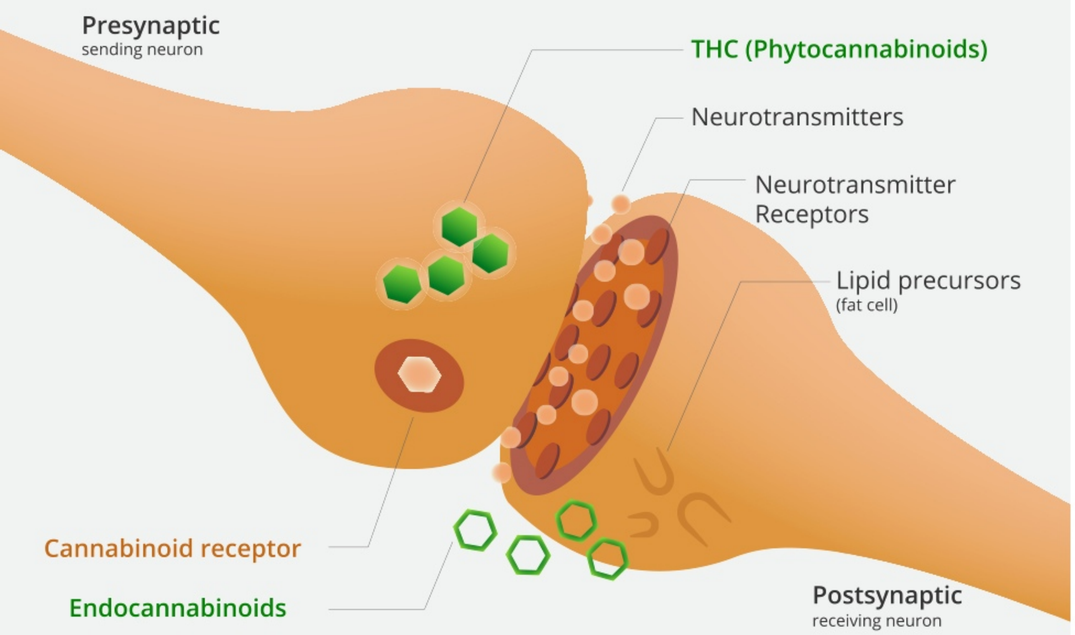
- **Δ9**
- **Δ8-THC**
- **Cannabidiol (CBD)**
- **Cannabigerol (CBG)**
- **Cannabinol (CBttN)**
- **Cannabinodiol (CBND)**
- **Cannabielsoin (CBE)**
- **Cannabicyclol (CBL)**
- **Cannabitriol (CBT)**
- **Miscellaneous type (30 known)**

prepaire

FULL SPECTRUM
(Everything from source plant)

BROAD SPECTRUM
(Everything except THC)

© PREPAIRE LABS LIMITED 2022



PHYTOCANNABINOIDS

Cannabinol

Cannabidiol

Tetrahydrocannabinol

Cannabigerol

Cannabichromene

Tetrahydrocannabivarin

ENDOCANNABINOIDS

Amandamide

2-Arachidonoylglycerol

prepaire

THC is produced as an acid (Δ9-Tetrahydrocannabinolic acid, Δ9-THCA) in the glandular trichomes of the leaves and inflorescence bracts of the plant and undergoes decarboxylation with age or heating to form Δ9-THC. THC is typically the most abundant chemical constituent of the cannabis flower, and is by far the most studied and well-understood cannabinoid. Cannabinoids are not the only active components of cannabis. Other constituents that might contribute in some way to the effects of cannabis include:

- **Terpenes (120 known)**
- **Nitrogenous compounds (33 known)**
- **Amino acids (18 known)**
- **Proteins, enzymes and glycoproteins (11)**
- **Sugars and related compounds (34)**
- **Hydrocarbons (50 known)**
- **Simple alcohols (7 known)**
- **Simple aldehydes (12 known)**
- **Simple ketones (13 known)**
- **Simple acids (20 known)**
- **Fatty acids (27 known)**
- **Simple esters and lactones (13 known)**
- **Steroids (15 known)**
- **Non-cannabinoid phenols (25 known)**
- **Flavonoids (27 known)**
- **Vitamins (1 known)**
- **Pigments (2 known)**
- **Elements (9 known)**
- **Phenanthrenes (4 known)**
- **Spiroindans (2 known)**
- **Xanthones (1 known)**
- **Biphenyls (1 known**

In addition to plant-derived phytocannabinoids, hundreds of exogenous synthetic cannabinoids have been synthesized and characterized. These include pharmaceutical-grade synthetically derived substances that are chemically identical to the phytocannabinoids found naturally in the cannabis plant (e.g. dronabinol, an oral formulation of synthetically derived Δ9-THC, and ZYN002, a transdermal synthetic CBD gel produced by Zynerba Pharmaceuticals), in addition to novel molecules not found in nature (e.g., WIN 55,212–2, JWH-018, AM-2201, AMB-FUBINACA).

There are two common misconceptions related to synthetic versus naturally occurring phytocannabinoids. One is that there are differences in the effects of a single molecule phytocannabinoid (e.g. CBD) based on whether it is synthetic versus plant derived.

© PREPAIRE LABS LIMITED 2022

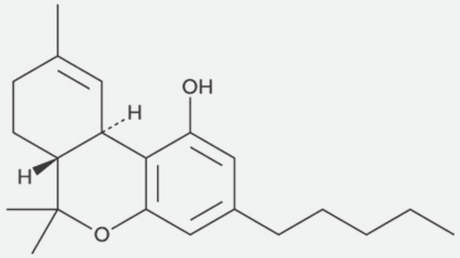
This should not be the case as chemistry is an exact science with respect to chemical composition and structure. The circumstances under which this could be true with respect to botanical cannabinoid products versus synthetic products would be limited to cases in which one of the two substances contains impurities that contribute to the overall pharmacological or toxicological effect, or due to inappropriate designation of synthetically derived isomers as being true replications of naturally derived cannabinoids. In these cases, the differences would be due to impure extraction of botanically sourced cannabinoids or missteps in the synthesis of the cannabinoid.

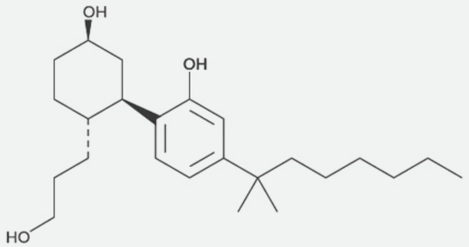
A common misconception is that synthetic cannabinoids not found naturally in cannabis are more harmful than phytocannabinoids. This largely stems from the ongoing problems associated with illicit sales of synthetic CB1 full agonists.

The potential harm associated with any newly synthesized drug is directly tied to its pharmacological effects (pharmacology, receptor specificity and affinity, potency) in the body. Indeed, one advantage of pursuing drug development of botanical cannabis or synthesized phytocannabinoids is that the cannabis plant has a very well established and positive safety profile.

Both phytocannabinoids and synthetic cannabinoids can directly impact the endocannabinoid system via a variety of pharmacological mechanisms, including agonism, antagonism, and allosteric modulation. Though 120 phytocannabinoids have been identified, they are finite and somewhat limited with respect to pharmacological interaction with the endocannabinoid system. Because of this, there are clear advantages of focusing on single molecule synthetic cannabinoid drug development, simply due to the fact that medicinal chemists are able to systematically modify known cannabinoid molecules in order to target very specific pharmacological effects.

This type of "fine tuning" has the potential to yield medications that have a very specific mechanism of action (e.g. full agonism of CB1 receptors outside the CNS), which might both improve therapeutic efficacy and reduce adverse effects compared with phytocannabinoids such as THC, which is neither selective to a specific cannabinoid receptor subtype nor limited with respect to crossing the blood-brain barrier.



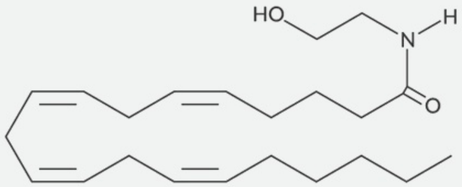


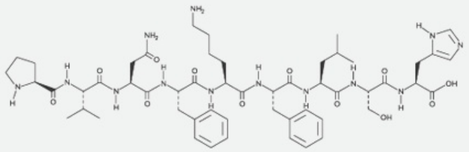
Classical Dibenzopyran Derivatives

- Δ^9-THC
- HU-210

Nonclassical Bicyclic and Tricyclic A-THC Analogs

- (–)-CP 55,940



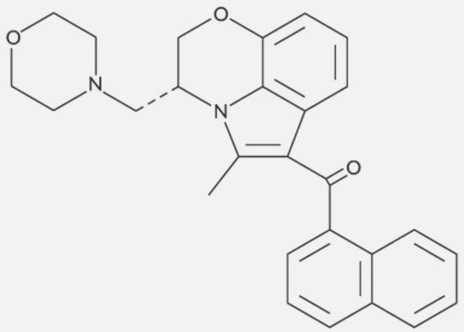


Eicosanoids

- AEA
- 2-AG

Peptides

- Hemopressin



Aminoalkylindoles

- (+)-WIN 55,212-2
- JWH 018

© PREPAIRE LABS LIMITED 2022

Quality control and experimental design considerations

Quality control for synthetically derived, single molecule medications is much easier, and is the norm for the pharmaceutical industry. There are clear standards to follow and established methods for manufacturing, testing, and quality control from start to finish. Single molecule medications also have major advantages in clinical testing. In single molecule studies, the study drug represents only one independent variable and one direct effect being tested. The simplicity of design makes it easier to ensure that clinical trials are well powered to find effects, and interpretation of results is relatively straightforward and concise. Identification of target molecules, especially novel synthetic molecules is one of the advantages of using the Prepaire HAiLO platform.

Cannabinoid Signaling: Pharmacotherapeutic Development

Active compounds found in plants of the Cannabis genus as well as endogenous analogs of these substances, and a myriad of synthetic analogs can influence a wide range of biological processes by engaging G protein-coupled receptors (GPCRs) of the endocannabinoid system. This system also includes the enzymes involved in endocannabinoid synthesis, transporters that enable cellular uptake/release, and enzymes that initiate endocannabinoid degradation. Many additional receptors including GPR18, GPR55, and GPR119, peroxisome proliferator-activated receptors (PPARs), and several members of the transient receptor potential (TRP) ion channel superfamily are also closely associated. Parts of this system are present in virtually every cell type of the human body, situating them to influence varied physiological processes

LIGANDS	
Endocannabinoids	AEA, 2-AG, Noladin, NADA, O-AEA, LPI
Phytocannabinoids	Δ^9-THC, CBD, and over 150 others
Synthetic Cannabinoids	(+)-WIN 55,212-2, HU-210, (–)-CP 55,940, JWH 018, etc.
RECEPTORS	
Classical	CB_1 and CB_2
Related Metabotropic	GPR18, GPR55, GPR119
Related Nuclear	PPARα, PPARγ, PPARδ
Related Ionotropic	TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, TRPM8
METABOLIC ENZYMES AND TRANSPORTERS	
Synthesis	NAPE-PLD, DAGLα, DAGLβ, PTPN22
Cellular uptake/release	Endocannabinoid membrane transporter
Degradation	FAAH, MAGL, COX-2
Intracellular transport	FABPs

Figure 1. Cannabinoid system overview

© PREPAIRE LABS LIMITED 2022

Cannabinoid Receptor Distribution and Mechanism of Action

The mechanism of actions of cannabinoids are becoming more realized with the understanding of the expression and distribution of the cannabinoid receptors CB1 and CB2 CB1 receptors, though predominant in the brain, are also expressed in the spleen, lung, thymus, heart, and vasculature. In the CNS, they are most highly expressed by the axons and presynaptic termini of neurons in the amygdala, hippocampus, cortex, basal ganglia, and cerebellum. They are strongly associated with GABAergic (inhibitory) and glutamergic (excitatory) neurons, where they mediate inhibition of ongoing release of inhibitory and excitatory neurotransmitters.

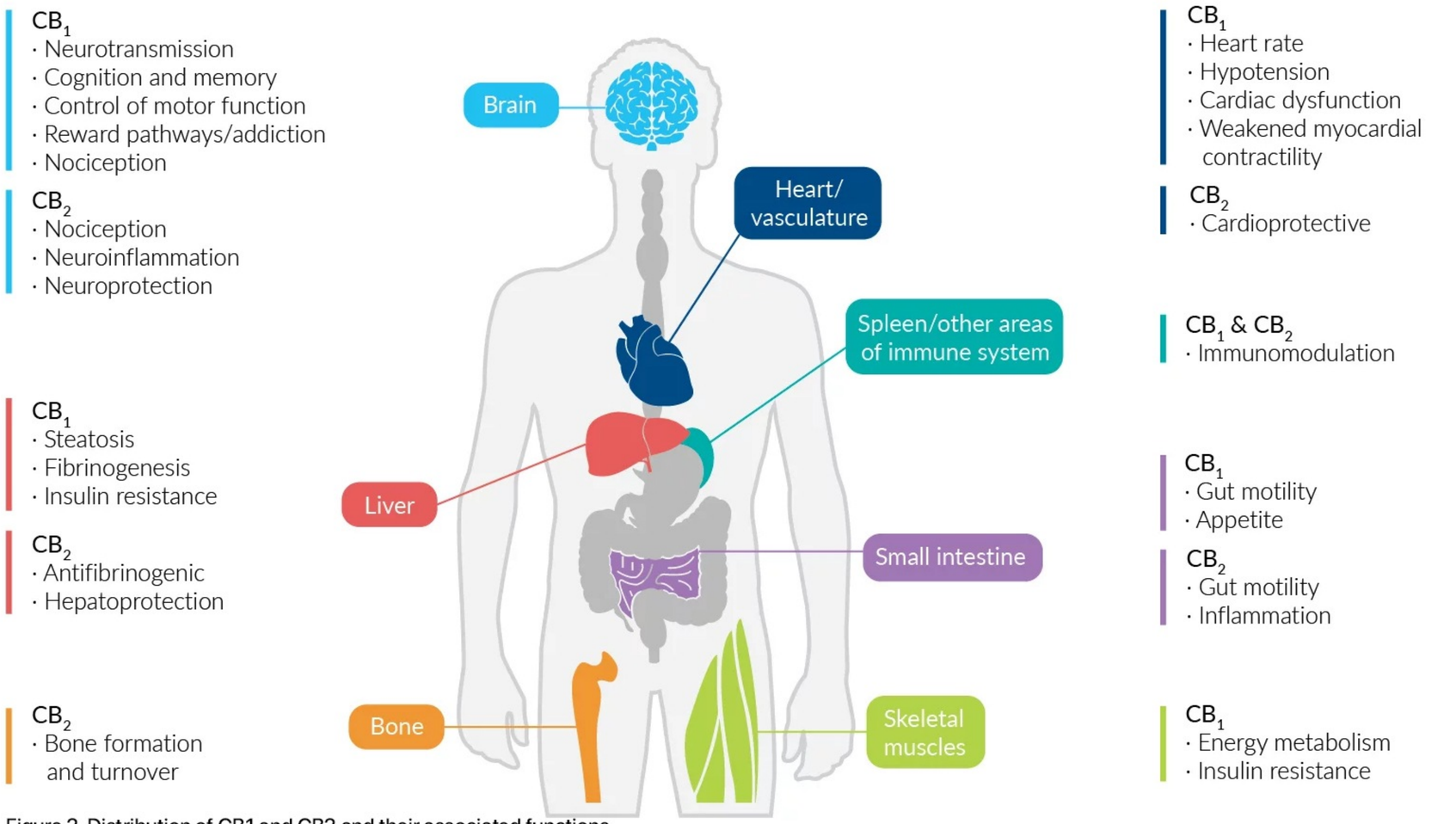


Figure 2. Distribution of CB1 and CB2 and their associated functions.

CB1 receptors are coupled to Gi/Go proteins in a manner that leads to the inhibition of adenylate cyclase activity, activation of the β-arrestin pathway, regulation of L-, N- and P- or Q-type Ca2+ channels and G protein-regulated A-type and inwardly rectifying K+ channels, initiation of intracellular Ca2+transients, stimulation of MAPK, and/or induction of immediate early gene expression. These receptors can also signal through Gs proteins, working in opposition to stimulate adenylate cyclase activity, causing a rise in intracellular cAMP levels. Under certain circumstances, CB1 can also couple to Gq. In a form of biased agonism, the actual ligand determines the signaling preference among these possible second messenger pathways.

© PREPAIRE LABS LIMITED 2022

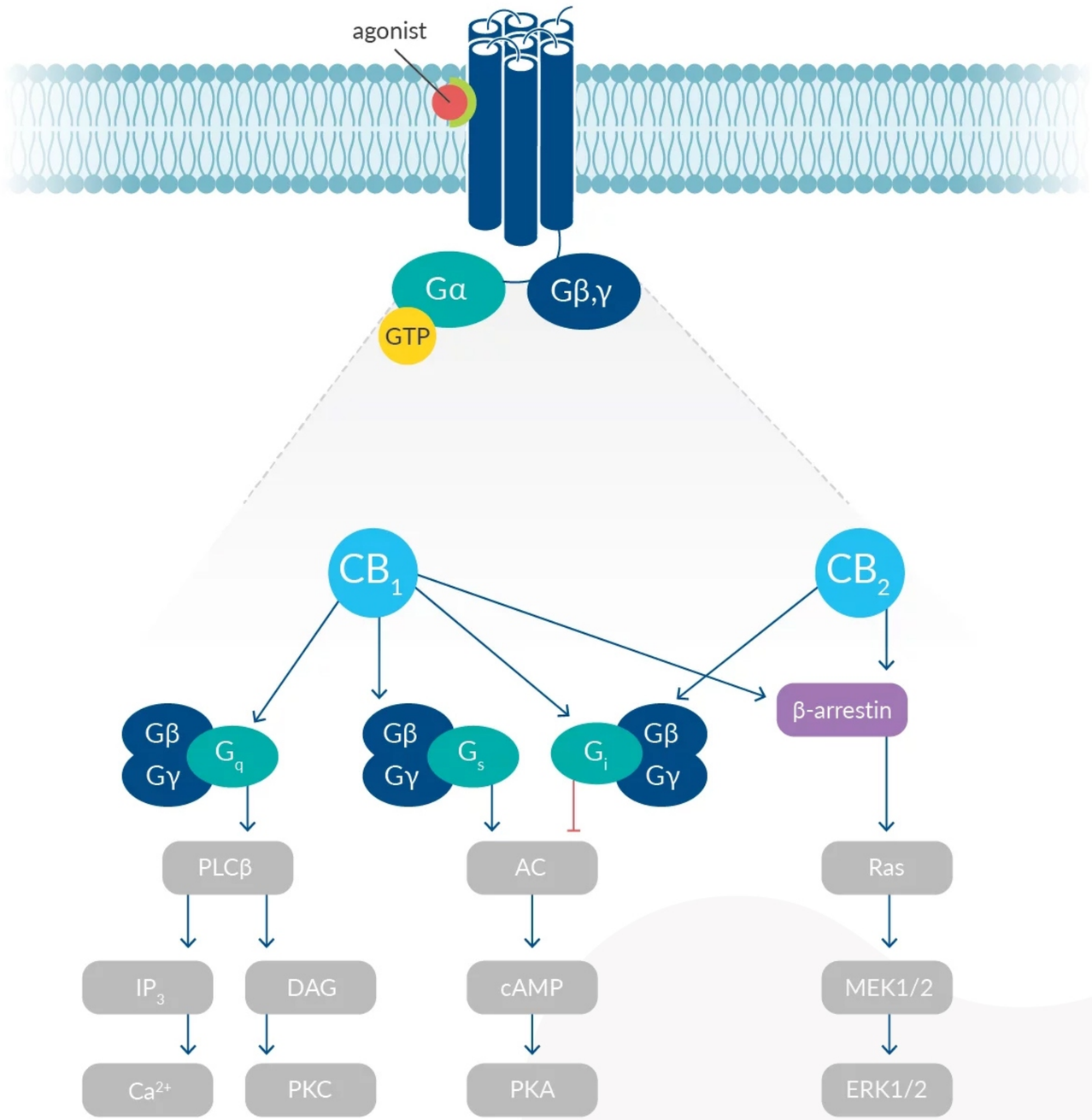
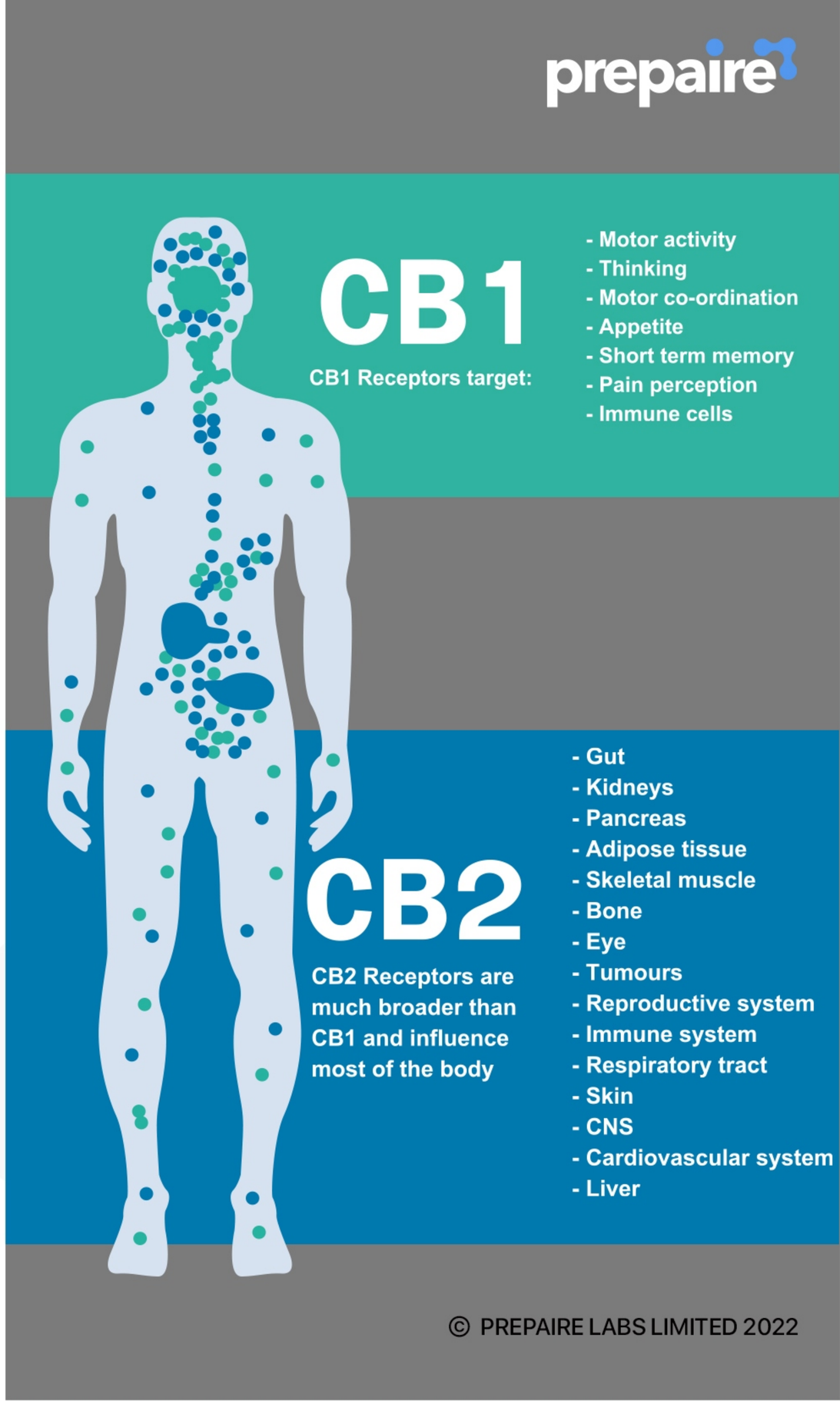


Figure 3. G protein coupling of cannabinoid receptors.

Ligand binding to the receptor occurs through lateral insertion via the lipid bilayer rather than directly from solution. CB1 receptors also possess one or more allosteric sites wherein some ligands interact to enhance or inhibit CB1 receptor activation by direct agonists. Some CB1 receptors form heteromers with dopamine D2 receptors, μ-opioid receptors, and orexin-1 receptors, which can affect CB1 receptor activation by agonists adding to the complexity of cannabinoid signaling.



© PREPAIRE LABS LIMITED 2022

CB2 receptors are most abundant in tissues with immune function both outside of the brain, such as spleen, tonsils, bone marrow, pancreas, peripheral blood leukocytes, and inside of the brain in astrocytes and microglia. They function to modulate immune cell migration and cytokine release, but also have roles in cardiovascular and respiratory systems, bone, the gastrointestinal tract, liver, and the reproductive system.

CB2 receptors couple to Gi/o proteins to signal a response through inhibition of cAMP production, MAPK activation, and immediate early gene expression. No modulation of ion channels or alterations of intracellular Ca2+ has been observed in host cells expressing CB2 receptors.

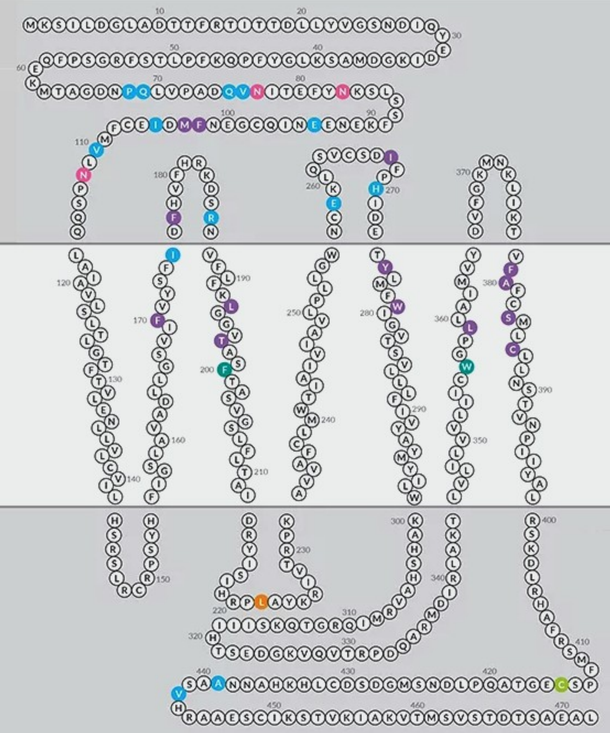
Cannabinoid Receptor Distribution and Mechanism of Action

Much of the understanding of how ligands physically activate and inactivate CB receptors comes from structural observation of binding with agonists and antagonists wherein the C-terminal intracellular helix adopts an active or inactive conformation.

The intracellular loop 2, particularly residue L222, of both CB1and CB2 receptors plays a critical role in Gi and Gs protein coupling and specificity, making the inhibition versus activation of adenylate cyclase ligand specific.

The first crystal structure of the human CB1 receptor in complex with a tight binding antagonist was successfully resolved in 2016. Since then, three more crystal structures and two cryo-electron microscopic (cryo-EM) structures of CB1 have been obtained and reported. Comparisons between the agonist- and antagonist-bound CB1 complexes show notable structural rearrangements around an extended twin molecular toggle switch (F200 and W356), whose activation leads to G protein binding and plasticity in the orthosteric binding pocket that can accommodate a variety of ligands with different shapes and sizes. F200 functions as a latch to restrict the movement of W356 and locks CB1 in the inactive state unable to bind G proteins.

The first crystal structure of CB2 bound to high-affinity synthetic antagonist was reported in 2019, and both the crystal structure and cryo-EM structure of agonist-bound CB2 was revealed in 2020. The N-terminal sequence has different behaviors between the two receptors. Compared to CB1, CB2 only experiences minor conformational changes upon agonist binding. With antagonist bound, CB1 conforms to a V-shaped loop that inserts into the cannabinoid binding pocket.



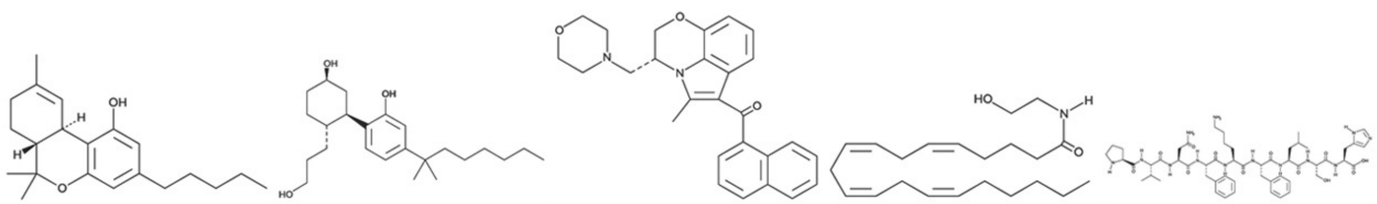
© PREPAIRE LABS LIMITED 2022

However, this portion of CB2 remains extended and does not interact with the pocket, instead hovering over it with no direct contact during antagonist binding. Also, there is only a single toggle switch residue (W258) for CB2. Interestingly, the antagonist-binding motif in CB2 looks similar to the agonist-binding motif in CB1, providing a structural basis for the fact that CB2 antagonists are often CB1 agonists.

These structural differences also define ligand preference in that CB1 requires the polycyclic core of a potential ligand to have an alkyl chain of five or more carbons, while CB2 recognizes much smaller compounds.

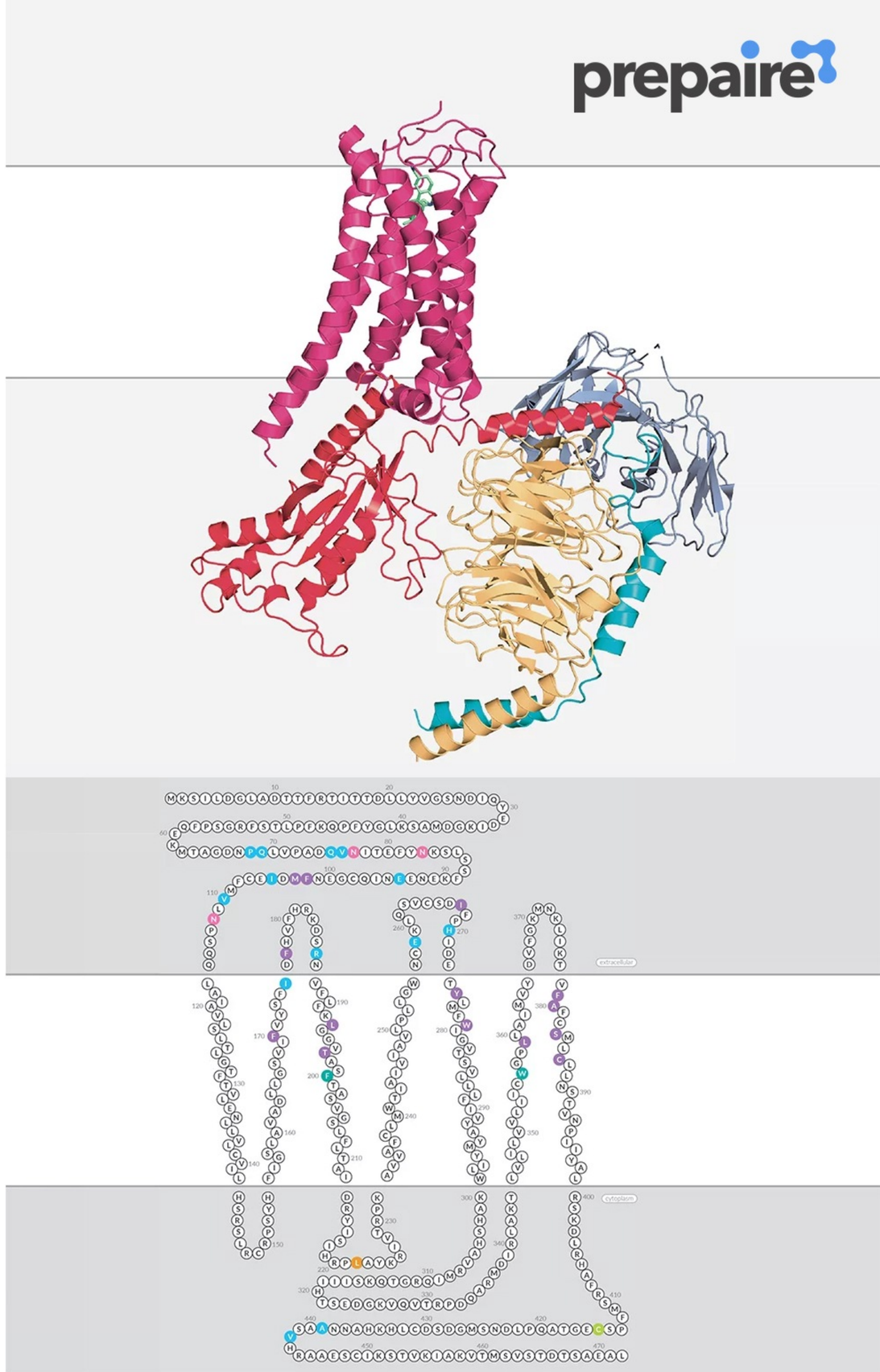
Receptor Pharmacology

Cannabinoid receptor ligands can be classified into four main chemical groups: classical, nonclassical, aminoalkylindole, and eicosanoid. The classical group contains dibenzopyran derivatives, the most well-known of which are Δ9-THC and HU-210, a synthetic analog of Δ8-THC. In 2019, the novel phytocannbinoid Δ9-THCP was isolated from Cannabis and shown to bind to both CB1 and CB2. Its affinity for CB1 as well as cannabimimetic activity attributed to its elongated alkyl side chain is significantly higher than that of Δ9-THC. The nonclassical group consists of bicyclic and tricyclic analogs of Δ9-THC that lack a pyran ring, such as (–)-CP 55,940. Aminoalkylindoles (represented by (+)-WIN 55,212-2) and eicosanoids (comprised of endocannabinoids) have structures that are distinctly different from classical and nonclassical cannabinoid receptor agonists and also from each other. A fifth chemical classification has also emerged: peptide-like compounds. The endogenous peptide hemopressin, its derivatives RVD-Hpα and VD-Hpα, and the novel Pep19 have all been shown to function as ligands of cannabinoid receptors.



Classical Dibenzopyran Derivatives	Nonclassical Bicyclic and Tricyclic Δ⁹-THC Analogs	Aminoalkylindoles	Eicosanoids	Peptides
· Δ⁹-THC · HU-210	· (–)-CP 55,940	· (+)-WIN 55,212-2 · JWH 018	· AEA · 2-AG	· Hemopressin

Figure 3. G protein coupling of cannabinoid receptors.



© PREPAIRE LABS LIMITED 2022

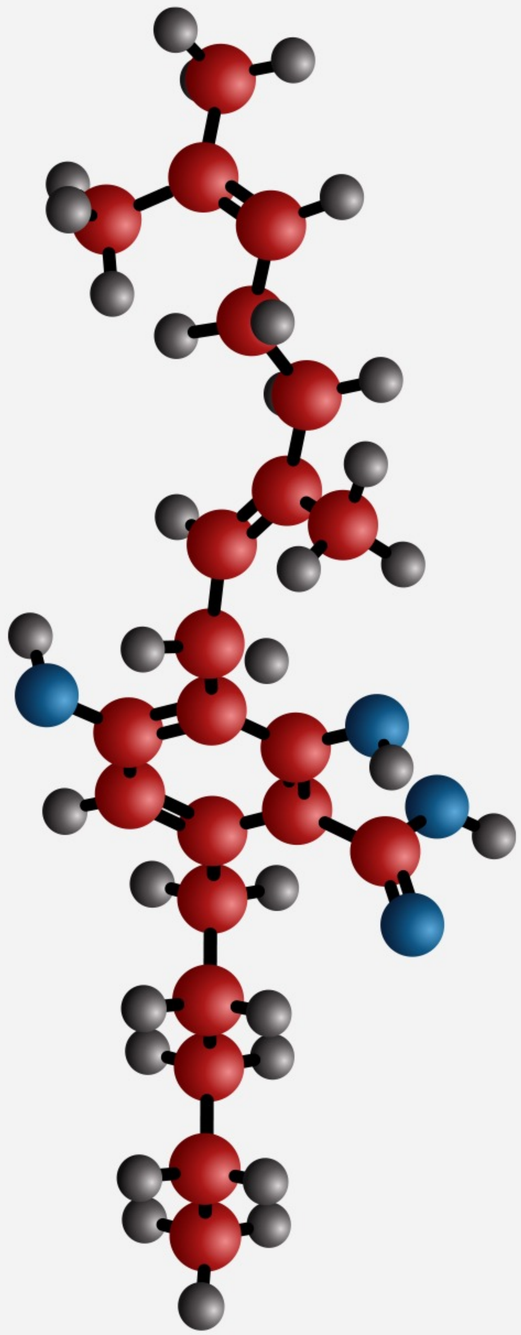
Competitive antagonists that display significant CB1-selectivity include rimonabant, AM251, AM281, LY320135, and taranabant. These compounds all work as inverse agonists, eliciting responses in some CB1 receptor-containing tissues that are contradictory from those induced by a CB1 receptor agonist. NESS 0327and AM4113, which are structural analogs of rimonabant, behave as neutral antagonists in that they lack any detectable ability to induce signs of inverse agonism at the CB1 receptor.
The CB2-selective inverse agonists most often used as experimental tools include AM630 and SR 144528. A neutral antagonist that selectively targets the CB2 receptor has yet to be developed.

There is interest not only in directly acting cannabinoid receptor agonists and antagonists, but also in compounds that can affect the activity of the endocannabinoid system indirectly by allosterically modulating endocannabinoid-induced activation of cannabinoid receptors or by altering the concentration of endocannabinoids at their receptors through effects on endocannabinoid production. Some cannabinoid receptor agonists and antagonists can also activate or block non-CB1/CB2 GPCRs, ligand- and voltage-gated ion channels, and/or nuclear receptors (PPAR receptors). They do, however, target these channels or receptors at different potencies than that which can activate or block CB1 and/or CB2 receptors. tt

For example, arachidonoyl ethanolamide (anandamide) can activate T-type voltage-gated calcium channels, voltage-gated KV3.1 and KV4.3 potassium channels, calcium-activated (BK) potassium channels, NMDA receptors, TRPV receptors, glycine receptors, and allosteric sites on serotonin 5-HT3, and nicotinic acetylcholine receptors. Cannabidiol (CBD), which has weak CB1 and CB2 antagonistic effects and behaves as a negative allosteric modulator of CB1, can act as a FAAH inhibitor, TRPV1 agonist, adenosine A2A agonist, PPARγ activator, 5-HT1a agonist, and GPR55 antagonist. The combinatorial actions of these compounds on various receptors and channels likely endow their ultimate functions.

Pharmacotherapeutic Implications

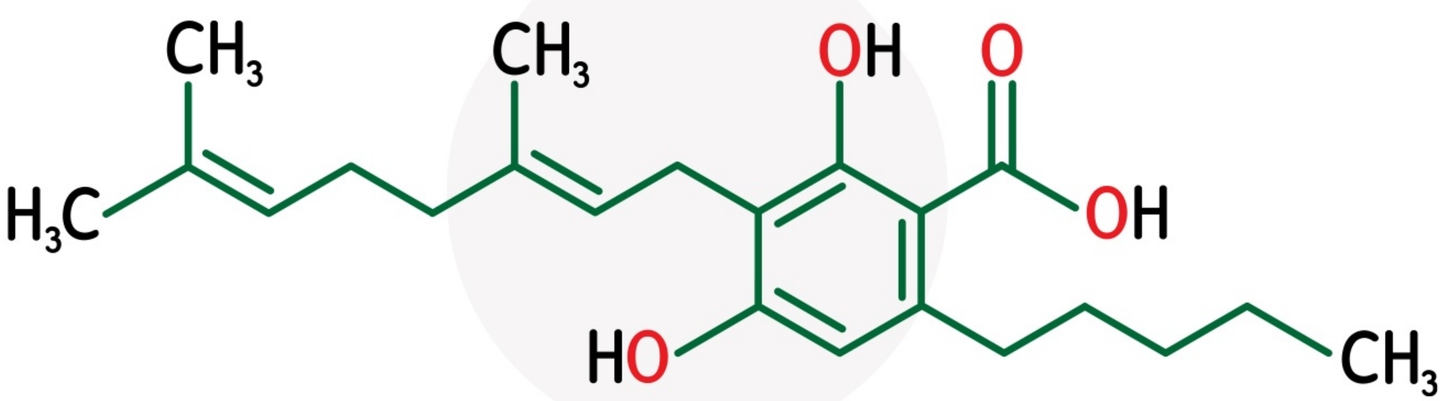
Cannabinoid receptor modulation is involved in cognition, memory, anxiety, control of appetite, emesis, motor behavior, sensory, autonomic and neuroendocrine responses, immune responses, and inflammatory effects as well as liver injury and hepatocellular carcinoma. The pharmacologic regulation of CB1 has been proposed as a promising therapeutic strategy for pain, inflammation, obesity, neurodegenerative disorders, and cancer. Meanwhile, CB2 has been explored as a therapeutic target for immune modulators, pain management, osteoporosis, and the treatment of liver diseases. Indeed, the endocannabinoid system functions as a gatekeeper of the immune system, regulating cytokine release and immune cell migration, which has implications in preventing the onset of pathological immune responses through the regulation of inflammation, autoimmunity, antitumor, and antipathogen immune responses.

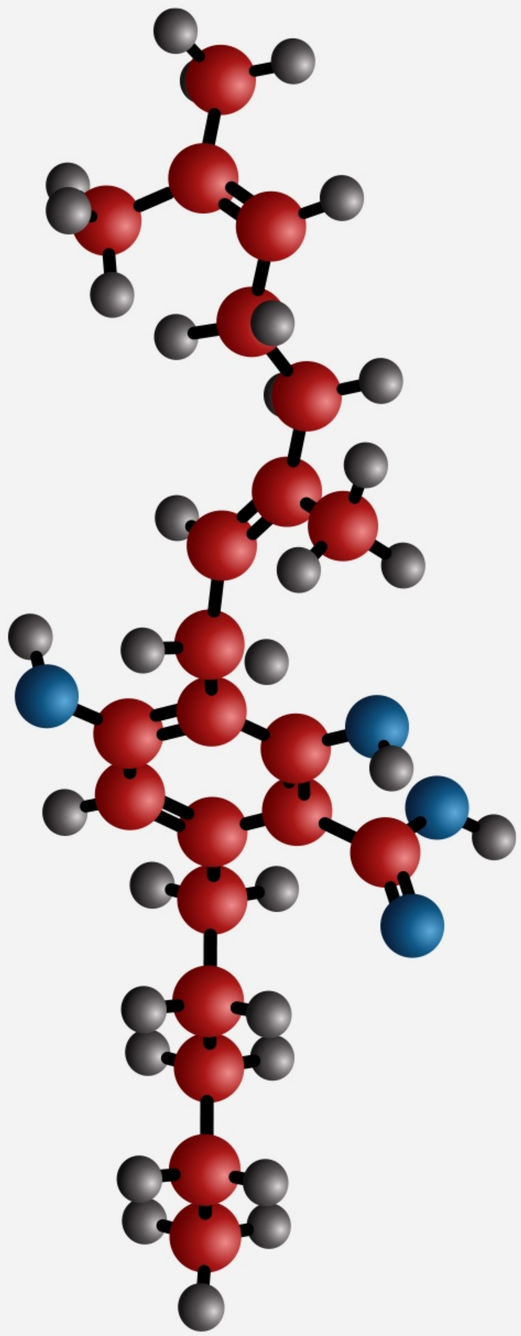


© PREPAIRE LABS LIMITED 2022

Many in vitro and in vivo studies aimed at exploiting the putative therapeutic potential of cannabinoids have largely focused on isolating Δ9-THC and CBD and the need to develop appropriate formulations to separate any psychoactive effects from therapeutic benefits. This has led to the establishment of the first Δ9-THC-containing and CBD-containing FDA-approved therapeutics. Dronabinol (Marinol®, Syndros®) is a Δ9-THC formulation used as an appetite stimulant and anti-emetic that the FDA has only approved for use in HIV/AIDS-induced anorexia and chemotherapy-induced nausea and vomiting. Several countries have approved the use of nabiximols (Sativex®), a 1:1 combination of Δ9-THC and CBD, for the treatment of pain and/or spasticity in multiple sclerosis. The synthetic THC mimic nabilone (Cesamet®), which has therapeutic use as an antiemetic and as an adjunct analgesic for neuropathic pain, is in a phase III clinical trial for treating non-motor symptoms in Parkinson's disease.

Epidiolex®, a prescription oral solution of CBD, is being used to treat seizures associated with certain forms of epilepsy and tuberous sclerosis complex. However, the Cannabis plant contains more than 100 different cannabinoids, including numerous secondary cannabinoid metabolites as well as terpenes and flavonoids that likely contribute synergistically to its therapeutic benefits.
Due to this entourage effect, focus will need to shift to these other Cannabis components in order to fully understand which components have pharmacotherapeutic potential.
Attention has also focused on anandamide analogs including arachidonoyl 2′ chloroethylamide and arachidonoyl cyclopropylamide, CB1-selective agonists that have been shown to have antidepressant and antinociceptive effects as well as the ability to potentiate anticonvulsant drugs in animal models of epilepsy. CB2-selective agonists are a keen focus in the field of therapeutic uses since specific modulation of CB2 may avoid the CNS-related side effects known to occur with CB1-selective agonists. With recent revelation of the ligand-bound, cryo-EM structure of the active CB2 receptor in complex with Gi-protein, new ligands rationally designed to interact with CB2 as selective agonists will be on the horizon.





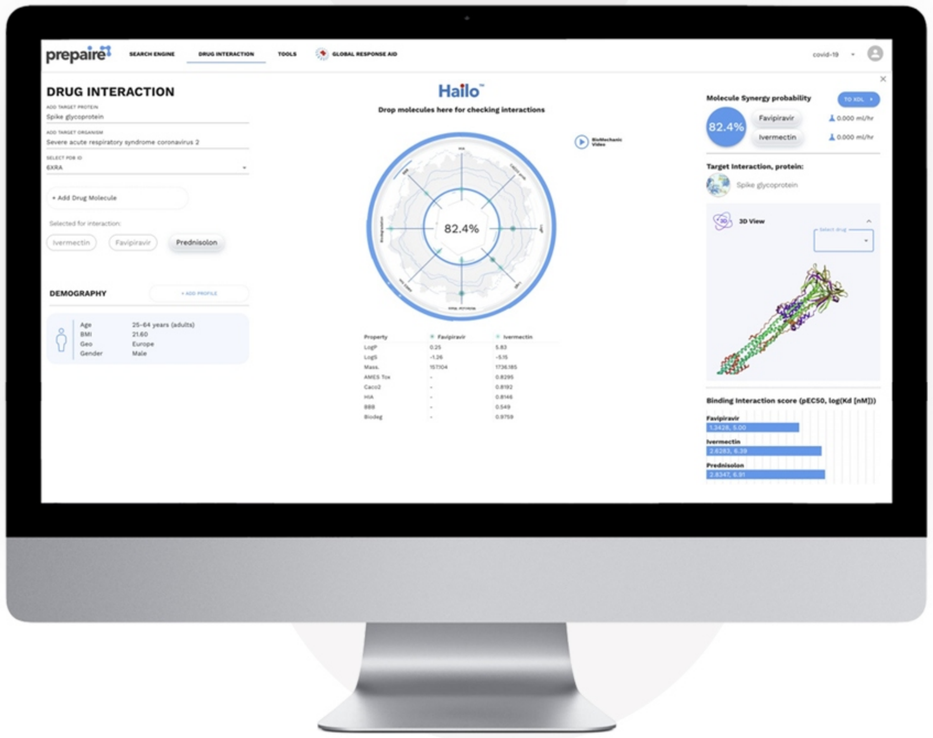
© PREPAIRE LABS LIMITED 2022

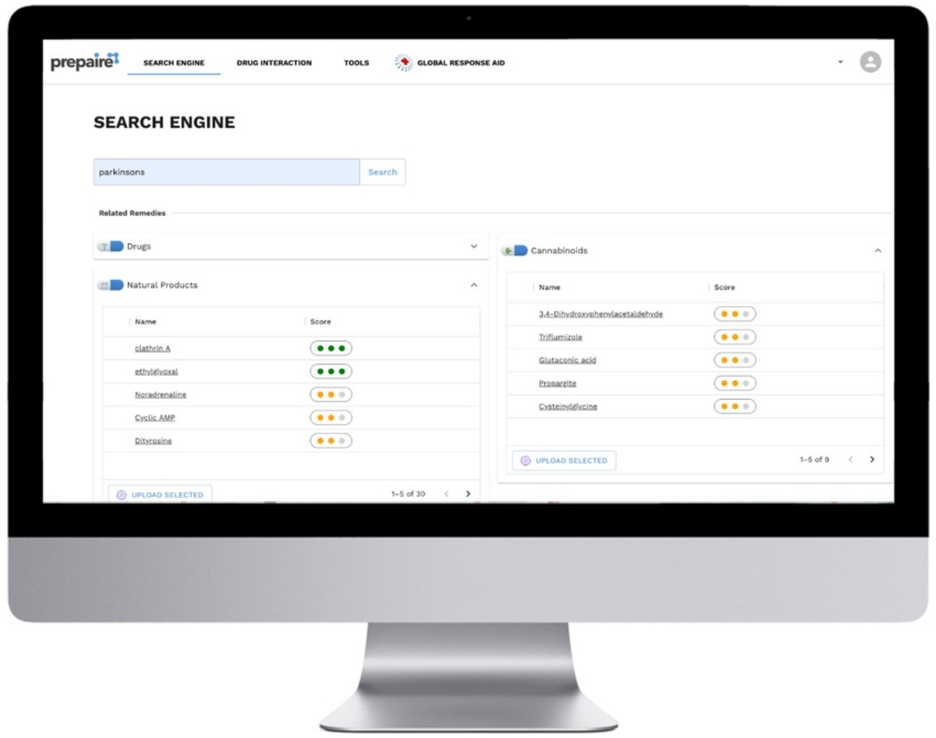
Synthetic routes

In addition to the increasing interest, research into medicinal cannabis is also becoming easier. Countries around the world are beginning to relax regulations for cannabis use in medical situations, leading to fewer restrictions for researchers looking to investigate its potential applications. Conversely, for pharmaceutical developers the lack of standardised protocols makes cannabinoid-based drug development challenging to manage as many countries have their own specific rules on the import and export of certain cannabinoids. While there have been improvements to the standardisation of regulations, country-to-country harmonisation is still far from a reality.

For a potential cannabinoid active pharmaceutical ingredient (API) to navigate the complex and often confusing regulatory minefield, manufacturers must understand and meet strict quality controls on purity and consistency. For instance, drugs using CBD as the API must ensure they meet extremely low THC thresholds and avoid the psychoactive side-effects. This becomes vital in applications such as paediatrics, where healthcare professionals must be assured that these side effects will not occur. To ensure regulations are kept to, and to safeguard the health of potential cannabis product consumers, the industry is increasingly looking to apply optimised, synthetic routes to manufacture cannabinoids. Compared to cannabinoid extraction from plant products, these methods provide a greater level of control over every available parameter, helping to improve the yields of products while avoiding any impurities and contamination.

Prepaire Discovery





© PREPAIRE LABS LIMITED 2022

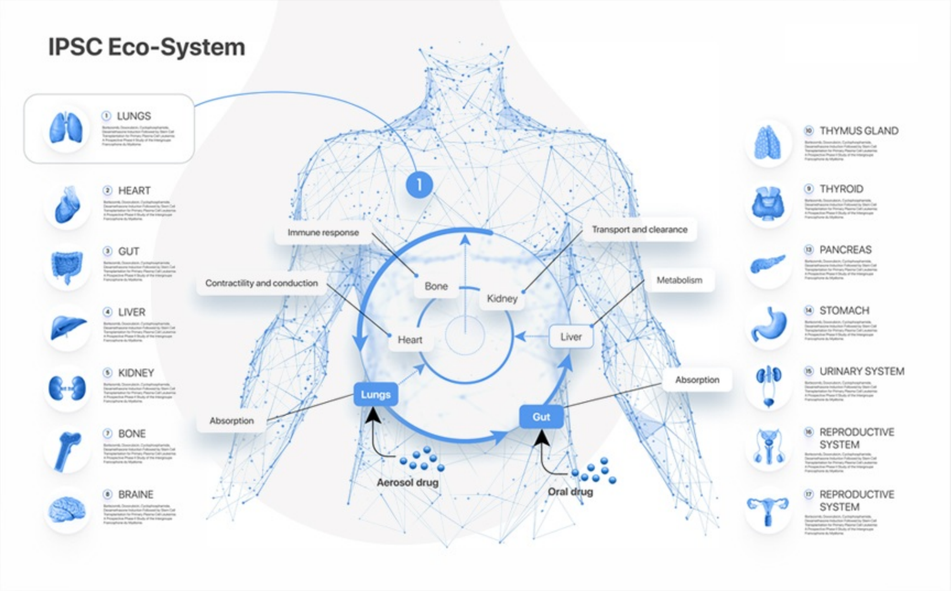
Prepaire™ is an in-silico to in-vitro fully integrated one stop shop for discovery, repurposing and personalized medicine.
The platform, or as we call it, the Operating-System, integrates:

- AI synthetic chemistry, binding autonomous drug discovery and repurposing
- Automated drug and vaccine production, to "print" any drug molecule directly in the lab
- Genome sequencing and creation of in-silico digital twins
- IPSC (Induced pluripotent stem cells) to directly test the drugs or vaccines on human analogues / organelles based on the specific characteristic of a demographic or a population
- Test drugs for specific populations/demographics
- Remove red tapes and material transfer between different locations, saving time and errors
- Repurpose libraries in a fraction of time and cost
- Improve Clinical trial outcomes and costs
- Reduce adverse effects and negative interactions

Validation

Our human iPSC-based solutions are physiologically relevant and enable reproducible high-throughput efficacy and safety screenings with highly translational results. The full process for the project is managed by the same specialized scientific team at Ncardia, our world-leding partners, which allows us to successfully implement de-risking strategies that smooth the transition from each step to the next and deliver robust outcomes efficiently.

Established cell models and custom disease models recapitulate the profile of human biology in vitro and bring higher predictability to the early phases of drug discovery. We ensure the efficiency of our models for consistent screening from beginning to end.



© PREPAIRE LABS LIMITED 2022

We’ve developed standard large-scale manufacturing procedures for many different cell types in at-scale batches. Our procedures are designed to scale up in the shortest possible time frame and wittth minimal batch-to-batch variability.

Deep roots

With the growing requirement for Good Manufacturing Practice (GMP) grade material within the pharmaceutical sector, drug developers are increasingly seeking out experienced partners in the development and manufacture of cannabinoids. Prepaire’s involvement with pharmaceutical cannabinoids started this year when helping a customer develop new therapy against CWA.

Working with cannabinoids is very complex as the APIs produced can be challenging to work with. For example, in some cases the API oxidizes quickly and is prone to impurities. To support the launch, Prepaire is investing in advanced chemical computers also referred to as AutoMedic ™ devices. They will be equipped with fluid chromatography and other modalities to achieve the high purity needed to prevent THC from oxidising readily.

Through the cannabinoid expertise generated, we will be able to develop a novel synthetic method for producing ultra-pure free-flowing CBD powder. To gain FDA approval, you need to produce a very pure product, which requires the right equipment and a significant amount of technical know-how.

As well as developing a validated process for cannabidiol synthesis, we will create reference standards for our cannabinoids, which help our customers understand what they are getting, and gives them the confidence to use our APIs in their formulations.

Beyond THC and CBD, there are well over one hundred different cannabinoids within the cannabis plant, and pharma companies are interested in assessing the therapeutic potential of a number of these. In response, we are planning to expand our portfolio to include other synthetic cannabinoids.

© PREPAIRE LABS LIMITED 2022

iPSC Cultivation

prepaire

Induced pluripotent stem cells (iPSCs) can self-renew indefinitely in culture and differentiate into all specialized cell types including gametes. iPSCs do not exist naturally and are instead generated ("induced" or "reprogrammed") in culture from somatic and blood cells through ectopic co-expression of defined pluripotency factors.

Since they can be generated from any healthy person or patient, iPSCs are considered a valuable resource for regenerative medicine to replace diseased or damaged tissues. In addition, this re-programming technology has provided a powerful tool to study mechanisms of cell fate decisions and to model human diseases, enabling the discovery and repurposing of drugs in screening formats and thus help identify and treat life-threatening diseases.

The production of iPSCs is complex and requires a lot of precision and hygiene throughout each step of the process, it is thus heavily automated.

PROCESS SET UP IPSC PROGRAMMING

Includes:

- Enclosure
- Inter-process Robotics
- Automated reprogramming
- Gantry robot
- Photometer
- Cell harvesting device
- Microscopes
- Incubator
- Industrial Freezer
- Cell counting device
- Camera station
- Appurtenances

Suppliers: HiTec Zang (Germany)
Medicom (UAE)

© PREPAIRE LABS LIMITED 2022

Prepaire is Launching their universal drug discovery operating-system with the the AutoMedic™ platform

AutoMedic™ Machine

Automatic Therapeutic Printer

Prepaire is an autonomous drug discovery and production O/S AutoMedic™ is a universal chemical synthesis robot that uses high-level formulae abstraction of chemical synthesis.
It can perform organic covalent chemistry, and also mechanical bond chemistry by digitalising complex chemical molecular formulas and translating these into executable computer code. Once executed, the AutoMedic™ makes use of various reagents for the production of infinite new molecules . This means that we can explore and create new molecules in search of new and repurposed drugs, which is a game changer for new drug discovery and whereas the design and production of a new treatment molecule might traditionally take months or even years - the AutoMedic™ can achieve this in up to 24 hours (including stability testing). Our goal is to advance the AutoMedic™ machines to near real-time production.

Prototype Version

© PREPAIRE LABS LIMITED 2022

Appurtenances

Listed below are some of the necessary appurtenances and consumables needed to support I mentioned capital equipment (the list is non-exhaustive)

Class III Biosafety Cabinets x 4

Incubator x 2

Pipettors (numerous)

Industrial Vacuum flask/aspiration device (numerous)

Water bath (37°C) x 3

Low-speed centrifuge (clinical grade, for spinning cells) x 2

6 x Phase–contrast microscopes

Refrigerator (4°C)

Freezer (–20°C, non-defrosting)

Low-temperature freezer (–70 to –85°C)

Cryogenic freezer (storage below –140°C, usually liquid nitrogen)

Flow cytometer

Fluorescence microscope

Confocal microscope

Vacuum supply

Water faucets x 6

Sinks x 6

IT closet

Back-up generator

Alarm system

Other considerations.

Protective (compliant) clothing

Interior finishes

Vinyl flooring

Nonporous ceilings

Washable, impermeable paint and coatings

Impermeable bench-tops and furniture

Quality Control

The laboratory should be designed, equipped, staffed, cGMP approved and operated in a manner that allows for the production of reliable and reproducible experimental results. While the research laboratory must operate with enough flexibility to allow discovery to take place, establishing standard operating procedures and a quality control system can provide the foundation on which new discoveries can take place.

The dynamic nature of biomedical research and the cost of laboratory construction have resulted in the prevalent use of modular design that allows reconfiguration of the laboratory as needed while keeping construction costs to a minimum.

© PREPAIRE LABS LIMITED 2022

 © PREPAIRE LABS LTD 2022 | CONFIDENTIAL

With the explosion of 'omics' sciences, the amount of data available has dramatically increased from several MB to the average 10TB of data for typical proteomics analyses.

Moreover, high-throughput omics analyses (from gene sequencing to peptidomics) have resulted in better knowledge about pathophysiology, pathway analysis, and treatment development. This has resulted in more scientific papers being published every year on topics related to life sciences.

It is this concurrence of numerical data and text data that is currently driving the machine learning revolution in healthcare beyond their traditional application in medical imaging.

In this context, natural language processing (NLP) presents a huge potential for the life-sciences field, given the industry's reliance on text-based data in the form of scientific papers, clinical records, clinical study reports and so on.

This data proliferation is creating a wealth of opportunities for life science companies seeking to advance drug development and gain deep insights at all development stages – from target discovery to the development and delivery of therapeutics in the clinic.

Our platform accelerates the drug development process by integrating disease models spanning in-vitro cellular systems, in-silico machine learning models, and **Prepaire** models.

These models, combined with robotic chemical systems capable of navigating a chemical space based on learned general associations between molecular structures and reactivity, it is possible to identify and predict a range of high yield and highly efficient chemical reactions and products that ultimately lead to the discovery of new molecules or new uses for already existing molecules that can eventually become new speciality treatments.

We use artificial intelligence with DL in all accessible formats, including neural, GANs, NLP, supervised, semi-supervised and unsupervised learning to build procedures and pipelines that will become key enablers for medical compliance and clinical approval whilst ensuring IP protection throughout the whole drug discovery process.

NVIDIA DGX SUPERPOD

Flexible, high-density compute reference architecture

- Integrated AI infrastructure built on DGX A100
- Mellanox AI network fabric
- Best of Breed Storage Partners Reference Architectures
- NVIDIA Validated and Tested
- 20 node Scalable Unit
- Advice /Support from NVIDIA DGxperts

© PREPAIRE LABS LIMITED 2022

Future of synthetic cannabinoids

The future for cannabis-based therapeutics is very bright. And with new players in the field, it is vital to ensure that partnerships with established forces are forged. At Prepaire, we believe that strong particle engineering and manufacturing solutions will play a crucial role in further developing the industry. With the right scientific expertise and manufacturing capabilities, we can ensure the development of therapeutics that will help forge a better, innovative tomorrow.

Natural vs synthetic CBD

Key differences:
Generally, synthetic CBD is produced to contain more specific yielding pure CBD molecules, while natural CBD extracts often come with other naturally occurring compounds, like cannabinoids, terpenes, and flavonoids. Because of their composition, which includes other compounds, cannabinoids and terpenes can also bind to one or more cannabinoid receptors. This can therefore alter the therapeutic effect of natural CBD.

Regarding their affinity, synthetic CBD is often designed to have a high affinity for receptors, resulting in lasting effects. In comparison, natural CBD is considered to be more gentle, with a moderate affinity for receptors. This affinity can also be short-lasting and overpowered by other compounds or modulators.

Our cannabinoid specialists have developed new, synthetic routes to five different cannabinoids, including CBDA, CBGA, and three metabolites. In addition, we have also identified a novel, scalable, synthetic route to CBD. With these routes, we can help you deliver the best possible product in the shortest timeframe.

At Prepaire we offer

Consistent support, from pre-clinical to market authorisation to commercial supply; for both drug substances and cannabinoid drug products

Capabilities to handle various stages of synthetic and naturally derived cannabinoids

Purifying plant extracts to produce the desired cannabinoid substance

Drug product development for a wide range of dosage forms with cannabinoid product (liquids, solids, semi-solids, inhalation)

GMP compliant manufacturing capacity for cannabinoids

We're utilising our scientific and manufacturing expertise to develop and commercialise ultra-pure synthetic cannabinoids that meet the quality requirements demanded by the pharmaceutical industry.

prepaire

© PREPAIRE LABS LIMITED 2022