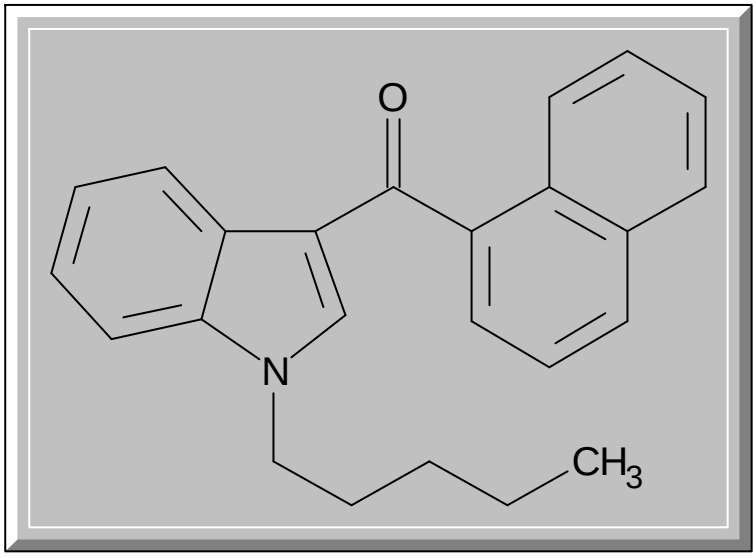
Molecular and Pharmacological Review of Cannabimimetics

Peter Rösner, Giselher Fritschi



Posener Str. 18
D 24161 Altenholz
Tel. 0049 (0)431-30034843
Fax: 0049 (0)431-32723
www.Chemograph.de
https://db12.designer-drugs.de
p.roesner@designer-drugs.de
g.fritschi@designer-drugs.de

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1. Introduction

The last decade has seen a dramatic increase of new designer drugs on the illegal market. In 2008 C. Steup[1] and Auwärter et al.[2] reported a representative of a new class of synthetic designer drugs with cannabimimetic effects sold as spice and herbal blends.
The detected naphthalen-1-yl-(1-pentylindol-3-yl)methanone JWH-018[3] acts as a full agonist at the CB_1 and CB_2 receptor and produces effects similar to Δ9-tetrahydrocannabinol (THC).
Due to the propagation by internet an increasing number of synthetic cannabimimetics flooded the market[4] getting popular under the name 'legal highs' as legal alternatives to cannabis[5]. The proliferation of cannabimimetics is unprecedented in the annals of designer drugs and today synthetic cannabinoids belong to the major abused drug class in many countries[6].
Following the first compounds derived from 3-naphthoylindole meanwhile other N-alkyl derivatives of naphthylmethylindoles, benzoylindoles, pyridinoylindoles, naphthoylpyrroles, indole-3-carboxylic acid derivatives, cyclopropylcarbonylindoles, adamantylindoles, phenyl-acetylindoles, cyclohexylphenols, phenylamino-1-benzoxazin-4-ones, 1,3-thiazol-2-ylidene-carboxamides, dibenzopyrans, 1,4-dihydroquinoline-3-carboxamide, naphthylmethylindenes and 1,2-dihydropyrazol-3-ylidene-benzamides entered the illegal market in high numbers.

As a consequence a tremendous diversity of cannabimimetic designer drugs must be considered and their occurrence on the illegal market is to be visualized especially because

many of them are described in the scientific literature. However neither the metabolism nor the toxicology of synthetic cannabinoids has been extensively studied, therefore serious health risks are involved with the use of synthetic cannabinoids[7].

The rapid rising number (roughly 5-10 times more in the last ten years) of unknown compounds confronts the forensic scientists and law enforcement agencies with a nearly insolvable problem. Between seizure, first analysis and a more detailed analysis and interpretation of the results can elapse weeks. Even with the support of more powerful instrumentation it is often not possible to keep pace. The next step: frequently updating local[8] or internet based[9] mass spectral libraries with reliable data used by the analytical community is costly in terms of labor and high price.

This situation was motive to evaluate the literature and generate a collection of molecular and basic pharmacological data for a convenient survey of the numerous compounds acting at cannabinoid receptors.

1.1 Cannabinoid receptor type statements

The cannabinoid receptor activity was named according the International Union of Pharmacology[10] and the database of the IUPHAR Committee on Receptor Nomenclature and Drug Classification[11,12] .
Cannabinoid receptor types are termed by the abbreviations CB_1 and CB_2 denoted by the order of their discovery. Two cannabinoid receptor types CB_1 and CB_2 have been discovered to date[13]. CB1 receptors are widely distributed in the human body[14] but with a high density in the central nervous system (CNS). The central CB1 receptor is associated with psychotropic effects including hallucinations euphoria sedation and cognitive dysfunction.
The CB2 receptor is almost exclusively distributed in the periphery[15] and predominantly in cells and tissues of the immune system and explains the immune modulating effects of cannabinoids.

Cannabimimetic

The term “Cannabimimetic” characterizes a ligand (chemical compound) that binds to a cannabinoid receptor and triggers a response in the cell. The ligand acts as cannabinoid receptor agonist**.**
In the case of entries without specified receptor affinities the term „Cannabimimetic “ does not imply any experimentally verified cannabinoid receptor activity. The selection of these compounds is based only on their structural similarity to cannabinoid lead substances.

Cannabinoid antagonist

A cannabinoid antagonist prevents the action of a cannabinoid receptor agonist (cannabimimetic). It binds to a cannabinoid receptor but due to the lacking intrinsic activity (efficacy) it does not change the response of the cell.

Inverse cannabinoid agonist

An inverse cannabinoid agonist binds to a cannabinoid receptor and causes the opposite action of an agonist. The inverse cannabinoid agonist therefore decreases the response of the cell.

Synthetic cannabinoid

Synthetic compounds cited in literature without abovementioned specifications are summarized under the term "Synthetic cannabinoid".

Cannabimimetic Designer Drugs

These are "Synthetic cannabinoids" as abovementioned. They have been seized as clandestine drugs or discussed for possible use in the drug scene. Like above there are no substantial data available in respect to their effect. These compounds have no valid pharmacological definition of the receptor and affinity values**.**
If necessary the term "Cannabimimetic designer drug**"** is specified in greater detail:
Derivative of cannabimimetic designer drug
Metabolite of cannabimimetic designer drug
Artifact of cannabimimetic designer drug
Metabolite/artifact of cannabimimetic designer drug
Precursor of cannabimimetic designer drug

Natural cannabinoid, Cannabis sativa ingredient

These indications describe the natural provenance of compounds or a structural very close relationship to these. If reasonable additional self-explaining comments like **"**Endogenous cannabimimetic" or **"**Cannabimimetic analog" are used.

1.2 Receptor affinity statements

Starting with the intention to support the analytical work of our colleagues in drug enforcement agencies and legal medicines we built up a library including emerging drugs on the illegal market and structurally similar compounds acting at cannabinoid receptors.
During the collecting process we were overwhelmed by the enormous number of potential compounds[16], so we had to cut back to compounds with a K_i binding affinity[17] of about <= 1000 nM at least at one cannabinoid receptor type CB_1 or CB_2[18].

The binding affinity K_i can be measured at isolated CB1 and CB2 receptors with a predetermined concentration of radiolabelled CP 55,490 by a competitive binding assay using the Cheng-Prusoff[19] equation:

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{K_d}}$$

IC50 is the concentration of a ligand which displaces 50% of the radiolabelled ligand used, K_d is the dissociation constant for the unlabeled ligand and [L] is the concentration of the radioactive ligand. The lower the K_i value of a ligand, the more tightly it bounds to the receptor.

A low Ki value is essential but not sufficient to produce a pharmacological effect, because the resulting effect is determined by the binding affinity and additionally by the efficacy (intrinsic activity) of a ligand. Efficacy specifies the maximal pharmacological effect a bound ligand can have inside the cell[20]. The efficacy describes if a substance is an (full) agonist (efficacy=100) or a (silent) antagonist (efficacy=0). Inverse cannabinoid agonists have a negative

efficacy (efficacy<0). Whether compounds act as a full agonists, partial agonists or antagonists can be measured by the cAMP (Cyclic Adenosine 5'-Monophosphate) and GTP (Guanosine 5'-triphosphate) levels with in vitro functional assays.

1.3 Blood–brain barrier

A central physiological action is determined by the ability of an agent to reach the brain receptors[21]. The blood–brain barrier hinders many hydrophilic agents to enter the brain. Compounds having a high lipophility rapidly cross the blood–brain barrier. The lipophility of compounds can be specified by the octanol/water partition coefficients. The receptor binding affinity and efficacy as well as lipophility are crucial for the physiological action of compounds acting at central receptors.

Lipophilic compounds with high CB_1 affinity (< 100 nM) would prove attractive to illicit users.
Though meanwhile the number of entries increased to more than 2000 we are aware offering information only of a selection of known cannabimimetics.
The listed receptor affinities (RA:) were gathered from the original literature without any value evaluation because the data were often gained using different competitive based binding assays and varying experimental conditions. Therefore the cited affinity values can vary considerably. The data should be applied with care using the mentioned literature and if possible further supplementary information**.**

1.4 Presentations

1.4.1 Name and structure listing

The listing is sorted alphabetically by the name following the prefix "INN:". The naming of the "INN:" entry was done in the order: Codes, Acronyms, International non-proprietary names or chemical names.

The scientific literature extensively uses codes and acronyms to name designer drugs like cannabimimetics to avoid the inconvenient use of chemical names or international non-proprietary names. Therefore we conceded codes and acronyms to be the first choice on naming compounds with considerable concerns in respect to an unequivocal definition.

An entry of the of name and structure list exist of entry index written in bigger fonts near the structural formula and the following optional information designated by an abbreviation:

Term	**Abbreviation**
1) Codes, international non-proprietary name	INN:
2) Chemical name	IUPAC:
3) Synonym	SYN:
4) Literature	LIT:
5) CAS-number	CAS:
6) Kovats retention index	RI:
7) Legal classification	LC:
8) Cannabimimetic receptor type	CRT:

9) Receptor affinity RA:
10) Comment COM:
11) Mass by most abundant isotopes MM:
12) Molecular weight MW:
13) Structural formula
14) Empirical formula
15) Entry index

“INN:” also specifies codes and acronyms as abbreviations for chemical compounds. Chemical names were formulated according to the rules of the International Union of Pure and Applied Chemistry (IUPAC).

INN:JWH-018
IUPAC:Naphthalen-1-yl(1-pentylindol-3-yl)methanone
SYN:AM-678
LIT:Aung M.M., Griffin G., Huffman J.W. Drug Alcohol Dependence 60 133-140 (2000)
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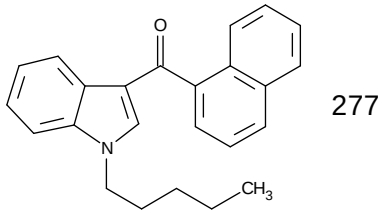

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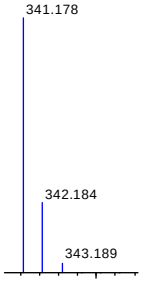

CRT:Cannabimimetic (CB1, CB2), designer drug RA:CB1 9.0 (nM), CB2 2.9 (nM) *CAS:209414-07-3* LC:GE II RI: 3127 (SE-30)
MM:341.17796 MW:341.45276 $C_{24}H_{23}NO$

At the right side of the structural formula a graphical representation of the theoretical molecular ion pattern is given, which is useful for mass spectral measurements and helps to deduce empirical formulas.

1.4.2 Theoretical mass listing by most abundant isotopes

The listing of theoretical masses by most abundant isotopes is useful to select possible compounds by measured values of nominal or accurate molecular ion masses. Dependent on the mass accuracy of the instrument the variety of possible compounds can be restricted and in an ideal case a single empirical formula can be deduced. The offer of structures can be compared with a measured electron impact mass spectrum and helps to specify the course of further analytical efforts.

The theoretical mass listing calculated on the basis of most abundant isotopes is sorted by increasing masses and includes an entry index (see name and structure listing). As additional information the empirical formula and names are presented.

Mass by most abundant isotopes	**Index**	**Empirical formula**	**Acronym/International non-proprietary Name**

247.19361	1	$C_{16}H_{25}NO$	A-1
310.17150	6	$C_{16}H_{26}N_2O_2S$	A-836,339
339.21983	5	$C_{22}H_{29}NO_2$	A-834,735
349.24056	8	$C_{24}H_{31}NO$	AB-001
352.25146	9	$C_{23}H_{32}N_2O$	AB-005
354.23073	4	$C_{22}H_{30}N_2O_2$	A-796,260
368.16485	10	$C_{20}H_{21}FN_4O_2$	AB-FUBINACA
395.28243	2	$C_{26}H_{37}NO_2$	A-40174
433.24171	3	$C_{28}H_{32}FNO_2$	A-41988

1.4.3 List of synonyms

The literature uses extensively codes and acronyms to name designer drugs and cannabimimetics very often applying different codes and acronyms to name the very same compound. This fact complicates the searching of these compounds in the literature and the internet. Therefore a list with records of all occurred synonyms was generated. An entry in the list of synonyms usually begins with a code or acronym followed by a sequence of denominations for the same compound.
If no code or acronym exist the international non-proprietary name or in minor priority the exact chemical name is used.

AKB-48	APINACA
AKB-48 N-(5-fluoropentyl)	5F-APINACA, 5F-AKB-48
AM-1172	AM1172
AM-2232	(1-(4-Cyanobutyl)-3-(naphthalen-1-oyl)indole)
AM-356	Methanandamide

1.5 Acronyms of origins and author

A	Abbott
AM	Alexandros Makriyannis
AZ	AstraZeneca
AZD	AstraZeneca Development
Bay	Bayer AG
CE	Pfizer
CP	Pfizer (CyclohexylPhenols)
EA	Edgewood Arsenal
GSK	GlaxoSmithKline
HU	Hebrew University of Jerusalem
JHU	Johns Hopkins University
JWH	John W. Huffman
KDS	Kadmus Pharmaceutical Inc.
LY	Eli Lilly
RCS	Research Chemical Suppliers
SR	Romano Silvestri

UP	Paolo Urbani
X	Hoffmann- La-Roche

1.6 Literature

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1.7 Acknowledgements

The “Molecular and Pharmacological Index of Cannabimimetics” contains now more than 2000 compounds. Because of the large data amount errors cannot be excluded and no legal responsibility can be accepted for any inaccuracies of statements, data, illustrations, procedural details or other items.