Journal of Organic and Pharmaceutical Chemistry

Opinion

OPEN ACCESS
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UDC 615.214:544

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Balancing Physicochemical Properties between the Molecules of Mercy (Non-Addictive Drugs) and the Molecules of Mysticism (Often Addictive Drugs)

Abstract

The fundamental physicochemical features of drugs acting on the central nervous system (CNS) determine their ability to penetrate the blood-brain barrier (BBB) and be active against the CNS activities. In this paper, we study two well-known groups of drugs used or prescribed by physicists to treat CNS disorders. One group of drugs belongs to pain killers (the Molecules of Mercy), and the other group belongs to the mind-changers (the Molecules of Mysticism). These two groups of CNS drugs differ in a number of physicochemical parameters: molecular weight, lipophilicity, hydrogen bound acceptor count, hydrogen bond donor count, polar surface area, polarizability, flexibility, bioavailability, and their behavior (agreement or disagreement) related to specific structural conditions, in particular the Lipinski's rule, Ghose filter, Veber's rule, Multi-Drug Data Report (MDDR) criteria. In the study of 41 well-known drugs that affect the CNS (both approved or illegal), it has been found that painkillers that do not cause addiction have a physicochemical profile other than those of mind-changer drugs that are very often addictive.

The features of physicochemical parameters associated with the profiles of "pain killer" and "mind-changer" drugs are discussed.

Keywords: CNS-drugs discovery; pain killers; mind-changers; physicochemical properties; therapeutic drugs

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Балансування фізико-хімічних властивостей між молекулами милосердя (неадиктивними препаратами) і молекулами містицизму (часто адиктивними препаратами)

Анотація

Фундаментальні фізико-хімічні характеристики лікарських засобів, що діють на центральну нервову систему (ЦНС), визначають їхню здатність проникати через гематоенцефалічний бар'єр (ГЕБ) і проявляти активність щодо ЦНС. У цій роботі досліджено дві відомі групи препаратів, які застосовують для лікування розладів ЦНС. Перша група належить до анальгетиків (молекули милосердя), а друга – до психоактивних речовин (молекули містицизму). Ці дві групи лікарських засобів відрізняються за деякими фізико-хімічними параметрами: молекулярною масою, ліпофільністю, кількістю акцепторів і донорів водневого зв'язку, площею полярної поверхні, поляризованістю, «гнучкістю», біодоступністю, а також за відповідністю або невідповідністю певним структурним критеріям, зокрема правилу Ліпінські, фільтру Гоуза, правилу Вебера та критеріям Multi-Drug Data Report (MDDR). У ході дослідження 41 добре відомого лікарського засобу, що впливають на ЦНС (як затверджених, так і нелегальних), було виявлено, що анальгетики, які не викликають залежності, мають фізико-хімічний профіль, відмінний від профілю психоактивних речовин, які часто є адиктивними. У статті розглянуто особливості фізико-хімічних параметрів, пов'язані з профілями «анальгетичних препаратів» та «психоактивних препаратів».

Ключові слова: розробка препаратів для ЦНС; анальгетики; психоактивні препарати; фізико-хімічні властивості; терапевтичні препарати

Citation: Kraus, J.-L. Balancing Physicochemical Properties between Molecules of the Mercy (Non-Addictive Drugs) and Molecules of Mysticism (Often Addictive Drugs) *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 3–10.
https://doi.org/10.24959/ophcj.25.321860
Received: *17 October 2024*; **Revised:** *30 January 2025*; **Accepted:** *5 February 2025*

Funding: CNRS-Aix Marseille-University and Marseille Institute for Biology of Development (IBDM) are greatly acknowledged for the facilities offered and financial support.
Conflict of interest: The author has no conflict of interest to declare.
Ethics approval and consent to participate: This article does not contain any studies involving patients or animals as test objects.

■ Introduction

At all times, throughout his evolution and development, man has sought to protect himself against pain, whether physical or psychological. At first, he was looking for plants or natural compounds for this purpose. Then, taking care of the health and well-being, a person was seeking for new flavors, new tastes, new antibacterial drugs and new hormone regulators. Throughout this time, man has been creating a pharmacopoeia that contains several thousand molecules with a wide variety of chemical structures. Some of these molecules are of natural origin, while most of them are obtained as a result of chemical synthesis. Today, in order to cure specific pathologies or disorders, medical professionals have to make difficult choices between thousands of possible therapeutic molecules.

In their book, "Organic Molecules in Action" (1973), *Murray Goodman* and *Frank Morehouse* [1] have proposed to classify the pharmacopeial constitutive molecules into several classes of compounds, which represent millions of combinations between carbon, hydrogen, oxygen, sulfur, and other atoms upon which life itself is based:

- the Molecules of the code of life (nucleic acid and proteins);
- the Giant molecules (polymers);
- the Molecules of Mercy (pain killers or pain relievers);
- the Molecules of Mysticism (mind-changers);
- the Molecules of Might (germ killers);
- the Molecules of the steroid family (hormonal modulators);
- the Molecules of Growth and Health (vitamins);
- the Molecules of Senses (taste, odor, attraction).

Among these different classes of molecules, the Molecules of Mercy (pain relievers or pain killers) and the Molecules of Mysticism appeared of particular interest since both classes act at the Central Nervous System level (CNS), which requires crossing the blood-brain barrier (BBB).

This article will focus on these two groups of drugs, emphasizing their physicochemical properties that enable them to act as pain killers or as mind changers. From medicinal and chemical perspectives, the ability to design efficient pain reliever drugs in reducing their psychedelic side effect (mind changers) could be of high interest.

■ Materials and methods

The drugs included in this study are approved by the Food and Drug Administration (FDA) or have received approval from the European Medicines Agency (EMA). Some of these drugs are approved, others are banned, and some are obsolete molecules that have been replaced. However, all the drugs mentioned in this manuscript have been tested on patients for their effects on the CNS and are registered in the DrugBank database available at www.drugbank.com. According to literature recommendations, CNS drugs mentioned in this study are classified into two groups of drugs – *pain killers* (drugs of Mercy) and *mind-changers* (drugs of Mysticism) [1].

The group of Pain killers (*Molecules of Mercy*)

Pain killers or pain reliever molecules (Molecules of Mercy) are used to alleviate the common human aches and pains. Their action is often mediated through the prostaglandin production. The prostaglandin change is generally very low in uninflamed tissues, but increases immediately in acute inflammation [2]. Nevertheless, some compounds like capsaicin, codeine, and buprenorphine, listed below, do not act through the inhibition of prostaglandin effects.

The branded names of the drugs included in this group of painkillers, which refer to the international non-proprietary names (INN), are the following: Salicylic acid, Codeine, Buprenorphine, Methadone, Nalorphine, Celecoxib, Ibuprofen, Naproxen, Paracetamol, Pregabalin, Diclofenac, Oxycodone, Carbamazepine, Amitriptyline, Capsaicin, Meloxicam, Prednisolone, Meperidine, Butalbital, Naltrexone, Gabapentin, Morphine and Fentanyl[§].

[§] **Note**: it should be underlined that in this study Fentanyl and Morphine have been considered as Pain Killers, as well as Mind Changers.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

The group of Mind-Changer Drugs (*Molecules of Mysticism*)

These molecules affect mental processes and fall under the classification of hallucinogenic or psychotomimetic drugs. They alter thinking, perception, and mood [3]. The international nonproprietary names of drugs belonging to the group of mind changers are as follows: Heroin, Cocaine, Ergotamine, LSD, Mescaline, Amphetamine, Psylocibin, Nikethamide, Serotonin, Epinephrine, Phenylethylamine, Methamphetamine, Bufotenine, Tetrahydrocannabinol, Methylphenidate (Ritalin), Cathinone, Morphine, and Fentanyl[§].

This study does not include prescribed drugs available to treat mental illness. Antidepressants used to treat depression, anxiety, and some types of personality disorders, or antipsychotic drugs to treat schizophrenia and bipolar disorders, as well as to restore the chemical balance of the brain are not mentioned [4]. The study presented includes only modern medicines, natural or synthetic, which are known to be active against the CNS as pain relievers or mind changers.

■ Results

Physical and chemical properties of the drugs studied (pain killers and mind-changers)

In the broad sense, moderately lipophilic drugs cross the BBB, by passive diffusion, and the hydrogen bonding properties of drugs can significantly influence their CNS uptake profile. Polar molecules are generally poor CNS drugs unless they undergo active transport across the CNS. Other properties (size, molecular weight, partition coefficient, molecular flexibility (rotational bonding), solubility, polar surface, polarizability, bioavailability) are also factors that can affect the transport of an organic molecule to cross the BBB [5, 6].

Pain killers and mind-changers possess tremendous chemical diversity and yet reach their target(s) in the brain. The question is, "*What physical and medicinal-chemical characteristics do they possess to induce their various activities: pain killers for the molecules of Mercy and mind changers for the molecules of Mysticism?*"

The most known molecules belonging to the group of the Molecules of Mysticism are the cannabinoids (hashish, marihuana) extracted from *Cannabis sativa*, which are the oldest and most broadly occurring hallucinogens. Cannabis ranks second after opium as the most widely used mind-altering drug today. The most active ingredient of cannabinoids is Δ^9-tetrahydrocannabinol (THC). In the late 1960s, researchers learned that there were specific areas in the brain controlling pain [7–9]. As for psychedelic drugs, hallucinogenic compounds, such as Δ^1-Tetrahydrocannabinol, Psylocibin, and LSD, exert their primary effects through activating serotonin 5-HT_{2A} receptors found predominantly in cortical regions [10]. The question that arises at the level of chemical structures and physicochemical properties is, "*How can the molecules of the group of pain killers be differentiated from those of mind-changers, taking into account that these two groups of compounds must penetrate the blood-brain barrier to reach their targets at the CNS level?*"

To answer this question, 23 drugs (US FDA approved or/and European marketing authorization) most prescribed for the treatment of pain (the Molecules of Mercy) and 18 molecules of well-known psychedelic drugs used for recreational purposes (the Molecules of Mysticism) and/or for mental disorders are included in this study. The physicochemical characteristics of these 41 molecules could be found in DrugBank Online data, offered to the public as a free-to-access resource [11]. For each drug, 11 representative structural physicochemical parameters were considered: Molecular weight (MW), Chemical formula, Water solubility (mg mL^{-1}), log *P*, log *S*, Hydrogen acceptor count, Hydrogen donor count, Rotatable bond count, Polar surface area ($Å^2$), Polarizability ($Å^3$), Bioavailability.

Table 1 and **Table 2** show the values of the physicochemical parameters for each drug belonging to both groups of drugs: 23 Molecules of Mercy (pain killers) and 19 Molecules of Mysticism (mind-changers), as well as their compliance with the Lipinski's rule (Rule of five), Ghose filter, Veber's rule, and MDDR-like rule.

Notes to the descriptors that appear in **Tables 1** and **2** are given below:

MW – the molecular weight in g mol^{-1}. **Water Solubility** in mg mL^{-1}. **Log*P*** – the octanol-water partition coefficient [12]. **Log*S*** – the common solubility unit corresponding to the 10-based logarithm of the water solubility of a molecule measured in mol L^{-1}. $\mathbf{H_A}$ – the number of hydrogen bond acceptors. $\mathbf{H_D}$ – the number of hydrogen bond donors. **Rotatable bonds** – the number of single bonds which can freely rotate around their axis [13]. **Bioavailability** – representing the fraction (F) of the administered dose

Table 1. Molecules of Mercy (pain killers)

№	Generic names	MW	Chemical formula	Water solubility,[a] mg mL^{-1}	Log *P*[a]	Log *S*[a]	H_A[a]	H_D[a]	Rotatable bonds[a]	Bioavailability[a]	Polar surface area[a]	Polarizability[a]	Lipinskis rule[b] (Rule of five)	Ghose rule[b]	Vebers rule[b]	MDDR-like rule[b]
1	Salicylic acid	180	$C_9H_8O_4$	10	1.2	-	3	1	3	1	63.6	7.1	Yes	Yes	No	No
2	Codeine	299	$C_{18}H_{21}NO_3$	0.57	1.24	-2.7	4	1	1	1	41.93	31.9	Yes	Yes	No	No
3	Buprenorphine	467	$C_{29}H_{41}NO_4$	0.017	4.53	-4.4	5	2	5	1	65.07	53.35	Yes	No	No	No
4	Methadone	309	$C_{21}H_{27}NO$	0.006	4.14	-4.7	2	0	7	1	20.31	36.28	Yes	No	No	No
5	Nalorphine	311	$C_{19}H_{21}NO_3$	1.36	1.55	-2.4	4	2	2	1	52.93	33.3	Yes	Yes	No	No
6	Celecoxib	381	$C_{17}H_{14}F_3N_3O_2S$	0.005	3.99	-2.7	3	1	4	1	59.3	26.67	Yes	Yes	No	No
7	Ibuprofen	206	$C_{13}H_{18}O_2$	0.070.	3.5	-3.5	2	1	4	1	37.3	23.76	Yes	Yes	Yes	No
8	Naproxen	260	$C_{14}H_{14}O_3$	0.051	3.29	-3.6	3	3	1	1	46.53	24.8	Yes	Yes	No	No
9	Paracetamol	151	$C_8H_9NO_2$	4.15	0.51	-1.16	2	2	1	1	49.33	15.52	Yes	No	No	No
10	Pregabalin	159	$C_8H_{17}NO_2$	11.3	-1.4	-1.2	3	2	5	1	66.32	18.08	Yes	No	No	No
11	Diclofenac	296	$C_{14}H_{11}Cl_2N_20$	0.0045	4.98	-4.8	3	2	4	1	49.33	27.93	Yes	Yes	No	No
12	Oxycodone	315	$C_{18}H_{21}NO_4$	5.59.	1.04	-1.8	5	1	1	1	59	32.79	Yes	Yes	No	No
13	Carbamazepine	236	$C_{15}H_{12}N_2O$	0.152	2.1	-3.2	1	1	0	1	46.33	25	Yes	Yes	No	No
14	Amitriptyline	277	$C_{20}H_{23}N$	0.0045	5.1	-4.8	1	0	3	1	3.24	33.74	Yes	Yes	No	No
15	Capsaicin	305	$C_{14}H_{27}NO_3$		3.75	-	3	2	9	1	58.56	36.32	Yes	Yes	No	No
16	Meloxicam	351	$C_{14}H_{13}N_3O_4S_2$	0.154	2.28	-3.4	5	4	2	1	99.6	34.25	Yes	Yes	No	No
17	Prednisolone	360	$C_{21}H_{28}O_{50}$	0.2390	1.66	-3.2	5	3	2	4	94.83	38.69	Yes	Yes	No	No
18	Meperidine	247	$C_{15}H_{21}NO_2$	1.11	2.9	-2.4	2	0	4	1	29.54	28.09	Yes	Yes	No	No
19	Butalbital	224	$C_{11}H_{16}N_2O_3$	2.23.	1.47	-2	3	2	4	1	75.27	22.43	Yes	Yes	No	No
20	Naltrexone	341	$C_{20}H_{23}NO_4$	3.07	2.07	-2	5	2	2	1	70	36.03	Yes	Yes	No	No
21	Gabapentin	171	$C_9H_{17}NO_2$	4.34	- 1.9	-1.6	3	2	3	1	63.32	18.92	Yes	Yes	No	No
22	Morphine	285	$C_{17}H_{19}NO_3$	0.149	0.9	-1.4	4	2	0	1	52.93	29.94	Yes	Yes	No	No
23	Fentanyl	336	$C_{22}H_{28}N_2O$	0.024	4.12	-4.2	2	0	6	1	23.55	30.89	Yes	Yes	Yes	Yes

Notes: [a] Reported Values (Water solubility, log *P*, log *S*, H_A, H_D, Rotatable bonds, Bioavailability, Polar surface area, Polarizability) are **predicted values** through the ALOGPS 2.1 program; [b] Answers (Yes or Not) associated with the rules of Five, Ghose filter, Veber and MDDR-like, are **given according to DrugBank** database recommendations.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Table 2. Molecules of Mysticism (mind-changers)

№	Generic names	MW	Chemical formula	Water solubility, [a] mg mL^{-1}	Log *P*[a]	Log *S*[a]	H_A[a]	H_D[a]	Rotatable bonds[a]	Bioavailability[a]	Polar surface area [a]	Polarizability[a]	Lipinski's rule[b] (Rule of five)	Ghose rule[b]	Veber`s rule[b]	MDDR-like rule[b]
1	Heroin	369	$C_{21}H_{23}NO_5$	0.266	2.3	-3.1	4	0	0	1	65.07	38.19	Yes	Yes	No	No
2	Cocaine	303	$C_{17}H_{21}NO_4$	5.03	1.97	-1 8	3	0	5	1	55.84	32.02	Yes	Yes	No	No
3	Ergotamine	581	$C_{33}H_{35}N_5O_5$	0.233	2.95	-3.4	6	3	4	1	118.21	62.23	No	No	No	No
4	LSD	323	$C_{20}H_{25}N_3O$	0.27	3.3	-	2	1	3	1	39.34	37.54	Yes	Yes	Yes	No
5	Mescaline	211	$C_{11}H_{17}NO_3$	1.0	0.78	-	4	2	2	1	-	-	Yes	-	-	
6	Amphetamine	135	$C_9H_{13}N$	1.74	1.85	-1.9	1	1	2	1	26.02	16.17	Yes	No	Yes	No
7	Psylocibin	284	$C_{12}H_{17}N_2O_4P$	-	1.24	-	4	3	5	1	85.79	-	Yes	-	No	No
8	Nikethamide	178	$C_{10}H_{14}N_2O$	109.0	0.83	-0.21	2	0	3	1	33.2	19.56	Yes	Yes	Yes	No
9	Serotonin	176	$C_{10}H_{12}N_2O$	2.5	0.56	-1.8	2	3	2	1	62.04	19.31	Yes	Yes	No	No
10	Epinephrine	183	$C_9H_{13}NO_3$	0.1	-0.82	-0.99	4	4	3	1	77.72	19.04	Yes	No	No	No
11	Phenethylamine	121	$C_8H_{11}N$	2.19	1.41	-1.7	1	1	2	1	2602	14.36	Yes	No	Yes	No
12	Methamphetamine	149	$C_{10}H_{15}N$	0.928	2.23	-2.2	1	1	3	1	12.03	18.04	Yes	No	Yes	No
13	Bufotenine	204	$C_{12}H_{16}N_2O$	3.2	2.04	-1.8	2	2	3	1	39.26	23.29	Yes	Yes	Yes	No
14	Tetrahydrocannabinol	314	$C_{21}H_{30}O_2$	0.0026	7.29	-5.1	2	1	4	1	29.46	38.96	No	No	Yes	No
15	Methylphenidate	233	$C_{14}H_{19}NO_2$	0.182	1.47	-2.1	2	1	4	1	38.33	25.91	Yes	Yes	Yes	No
16	Cathinone	149	$C_9H_{11}NO$	2.46	0.51	-1.8	2	1	2	1	43.09	16.28	Yes	No	No	No
22	Morphine	285	$C_{17}H_{19}NO_3$	0.149	0.9	-1.4	4	2	0	1	52.93	29.94	Yes	Yes	No	No
23	Fentanyl	336	$C_{22}H_{28}N_2O$	0.024	4.12	-4.2	2	0	6	1	23.55	39.89	Yes	Yes	Yes	Yes

Notes: [a] Reported Values (Water solubility, log *P*, log *S*, H_A, H_D, Rotatable bonds, Bioavailability, Polar surface area, Polarizability) are **predicted values** through the ALOGPS 2.1 program; [b] Answers (Yes or Not) associated with the rules of Five, Ghose filter, Veber and MDDR-like, are **given according to DrugBank** database recommendations.

of a xenobiotic that reaches the systemic circulation, measured on a continuous range from 0 to 1 [14]. **Polar Surface Area** (PSA) – defined as the surface sum over all polar atoms or molecules, primarily oxygen and nitrogen, including also their attached hydrogen atoms [15, 16]. **Polarizability** – determines the response of the susceptibility of a molecule to an approaching charge. Larger molecules, atoms, or ions are more polarizable than smaller objects. Polarizability is expressed as the polarizability volume with units in $Å^3 = 10^{-24}$ cm^3 [17, 18]. **Rule of Five** (Lipinski's rule) – not more than 5 hydrogen bond donors; not more than 10 hydrogen bond acceptors; the molecular mass less than 500 Da [19]. **Ghose Filter** – the partition coefficient Log*P* from −0.4 to +5.6; the molecular refractivity from 40 to 130; the molecular weight from 180 to 480; the number of atoms from 20 to 70 (includes H-bond donors [e.g., OHs and NHs] and H-bond acceptors [e.g., Ns and Os]) [20]. **Veber's rule** – 10 or fewer rotatable bonds and the polar surface area equal to or less than 140 $Å^2$ or 12 or fewer H-bond donors and acceptors [21]. **MDDR-like rule** – the rule-of-five test cannot be used to discriminate between drugs and non-drugs. Descriptors used for the MDDR-like rule are the number of rings, the number of rigid bonds, and the number of rotatable bonds. The probability of finding a "druglike" compound is higher in the ranges: No. of rings ≥ 3, No. of rigid bonds ≥ 18, No. of rotatable bonds ≥ 6, while the probability of finding a 'nondrug-like' compound is higher in the ranges: No. of rings ≤ 2, No. of rigid bonds ≤ 17, No. of rotatable bonds ≤ 5 [22, 23].

Table 3. The average values of all the physicochemical values related to both groups of drugs

No.	Physicochemical properties	The Molecules of Mysticism (mind-changers)	The Molecules of Mercy (pain killers)
1	MW	263.8	192.88
2	Solubility (mg/ml)	4.37	0.96
3	Log *P*	2.28	1.55
4	Log *S*	-1.3	-2.17
5	H_A	2.56 (between 2 and 3)	3.2 (between 3 and 4)
6	H_D	1.2 (between 1 and 2)	1.3 (between 1 and 2)
7	Rotatable bonds	3	3
8	Polar Surface Area	30.58	54.14
9	Polarizability	29.01	31.51
10	Bioavailability	1	1
11	Rule of Five	Yes (18/18)	Yes (23/23)
12	Ghose Filter	Yes (9/17)	Yes (19/23)
13	Veber's rule	Yes (9/17)	Yes (2/23)
14	MDDR-like rule	Yes (2/18)	Yes (0/23)

Note: Values provided in **Table 3** correspond to the mean ones calculated based on data from **Tables 1** and **2**

Table 3 shows the average values of all the physicochemical parameters listed in **Tables 1** and **2** related to both groups of drugs: *Pain killers* and *Mind-changers*.

Discussion

A careful analysis of the reported values allows us to determine what are the physicochemical properties that support the ability of these CNS drugs to act as pain killers or pain relievers and what are the physicochemical parameters that induce a mind-changer effect (psychedelic activity) in this group of drugs. Let us first recall that all the values of the physicochemical parameters considered came from the same database, the Drug Bank, which is accessible freely online.

All the molecules cited in this manuscript are used in clinical practice, mainly as pain killers, and are therefore approved by the FDA; other substances in the group of mind-changers are used in clinical practice, while others are classified as prohibited and non-commercial. It is known that all the molecules analyzed act at the CNS level, which means that all these drugs must penetrate the blood-brain barrier. The analysis of the physicochemical parameters associated with each of the two groups – pain killers and mind-changer compounds – reveals differences in the average values of certain parameters.

As can be seen from **Table 3**, the molecular weight, solubility, Log *P,* and log *S* values for the mind changer drugs are lower than for pain killers. On the contrary, the values of polarizability, polar surface area, hydrogen acceptor count, and hydrogen donor count of the pain killers are higher than those of the mind-changer drugs.

From the results presented in **Table 3**, the following conclusions can be drawn:

- most of the drugs belonging to both groups, the Molecules of Mercy or the Molecules of Mysticism, corresponded to the *Lipinski's rule* as indicated in **Tables 1** and **2**;
- 9 of 23 compounds of the Mysticism group satisfy the *Veber's rule*, while only 2 of 23 compounds of the Mercy group satisfy this rule;
- the majority of the drugs (19/21) related to drugs of Mercy comply with the *Ghose filter*

ISSN 2308-8303 (Print) / 2518-1548 (Online)

rule, while only half of drugs of Mysticism comply with this rule;

- most of the drugs of these two groups do not support the *MDDR-like rules*.

Based on the data presented in **Tables 1**, **2**, and **3**, the development and synthesis of molecules for the treatment of pain in the CNS, in particular for end-of-life care, requires a targeted approach. Chemists developing new pain killers or improving existing ones through molecular modifications should ensure that the physicochemical properties of these molecules meet the criteria set out in **Table 3**.

For Molecules of Mercy (pain killers), these new structures will represent pharmacological profiles that would limit the side effects often associated with taking active painkiller ingredients (morphine and related analogs), mainly addiction effects. As indicated in **Table 3**, mind-changing drugs that act on the psyche (anxiety, depression) present physicochemical criteria significantly different from those of more specific molecules to combat pain.

■ Conclusion

When designing new CNS drugs, it is necessary to maintain a balance between physical and chemical requirements and achieve the best compromises in properties depending on the target therapeutic effect – pain killers or mind-changers. While all CNS drugs (41 compounds), pain killers, and mind-changers involved in this study comply well with the Lipinski's rule, it can be noted that pain killers mostly comply with the Ghose filter conditions, but do not satisfy the Veber's rule. In contrast, only half of the mind-changer drugs agree with the Veber's rule and satisfy the Ghose filter conditions. This observation indicates that other physicochemical parameters, such as polar surface area, polarizability, and flexibility, are important parameters that can be manipulated by medicinal chemists involved in the CNS drug design in order to modulate or improve the pharmacological effect of a new CNS drug depending on the desired target effect: pain reliever or mind changer activities. Of course, since we have focused only on approved or natural, well-known drugs that ensure the BBB penetration, the conclusions presented are restrictive. They could only be applied to drugs that satisfied the condition of the BBB penetration in order to orient the desired effect to the pain reliever effect rather than the mind changer effect. These results can be of interest since addictive psychedelic effects are often associated with the use of pain reliever drugs.

■ Acknowledgments

CNRS-Aix Marseille University and Marseille Institute for Biology of Development (IBDM), director Dr. L. Kodjabachian, are greatly acknowledged for the facilities offered and financial support.

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ISSN 2308-8303 (Print) / 2518-1548 (Online)