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Original Article

COMPARISON OF BIOPHARMACEUTICAL PARAMETERS OF CANNABINOIDS AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS BY QSAR METHOD

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ABSTRACT

Objective: To prove the benefits of biopharmaceutical parameters of cannabinoids over NSAIDs using quantitative structure and activity relationships (QSAR).

Methods: The topological indices of Wiener (W) and Balaban (J) were calculated using the previously developed original program ChemicDescript (certificate no. 2003612305).

Results: It was shown that the calculated topological indices were in one-to-one correspondence with such biopharmaceutical parameters as the constants of equilibrium binding to cannabinoid receptors CB1 and CB2, toxicity, and lipophilicity. For example, it was shown that when the Wiener index changes from 480 to 530 LogK increases from 1.0 to 3.5. The LD50-W/J and logP-W/J diagrams demonstrate that cannabinoids are less toxic and more lipophilic than NSAIDs. Cannabidiol and cannabinol, having close values of their topological indices and insignificant psychoactivity, have the highest LD50 values, i.e. they are the least toxic. Moreover, for synthetic cannabinoids–nabilone and THJ-2201–the Wiener index is approximately 2 times higher than for plant analogues.

Conclusion: In connection with the successful promotion of cannabinoid analgesics in the global pharmaceutical market, the results obtained are important for demonstrating their advantages over NSAIDs in terms of toxicity and lipophilicity. The results demonstrate the possibility of predicting the cannabinoid receptor binding energy of synthetic and newly identified plant cannabinoids, as well as assessing their toxicity and lipophilicity.

Keywords: Cannabinoids, NSAIDs, Toxicity, Lipophilicity, Wiener and Balaban topological indices

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INTRODUCTION

It is known that long-term use or overdose of NSAIDs cause adverse side effects: gastropathy, hepatotoxicity, nephrotoxicity, severe allergies, asthma [1, 2]. The frequency of side effects caused by NSAIDs contributes to the active search for new drugs for pain relief. The possible alternative to NSAIDs can be drugs based on non-psychoactive plant cannabinoids, which have successfully established themselves on the world market [3]. Cannabinoid-based drugs have been developed and registered in the US, Canada, Australia and the European Union. Epidiolex (GW Pharmaceuticals, UK), Bedrocan (Bedrocan International, Canada, the Netherlands), Sativex (GW Pharmaceuticals, UK) and other drugs are used to treat pain, epilepsy, and several orphan diseases [4, 5].

But in the conditions of strict drug control in many countries, research involving cannabinoids is not possible. Various methods of modeling ligand-receptor interactions, such as molecular docking [6] or Quantitative Structure Activity Relationship (QSAR) [7, 8], are effective tools for predicting the pharmacological properties and toxicity of plant and synthetic cannabinoids.

Previously, the QSAR method was used to evaluate the values of cannabinoid affinity constants for CB1 and CB2 receptors [10]. But the comparative assessment of the biopharmaceutical parameters of large groups of cannabinoids and NSAIDs has not previously been carried out.

In the article, for the first time, a comparative analysis of lipophilicity and toxicity of cannabinoids and NSAIDs was carried out. The authors considered statistically significant values of LD50, and octanol-water distribution constants (LogP) accumulated in the reference literature based on studies in different laboratories around the world. The non-standard QSAR modeling approach chosen is based on the use of the original ChemicDescript program developed earlier (certificate no. 2003612305).

The goal of the work is to prove the benefits of biopharmaceutical parameters of cannabinoids over NSAIDs using quantitative structure and activity relationships.

MATERIALS AND METHODS

Two groups of analgesics were studied using the QSAR-modeling method [10]: the first-generation NSAIDs (paracetamol, dipyrone (analgin), ibuprofen, diclofenac, aspirin) and plant cannabinoids (non-psychoactive: cannabinol, cannabidiol; psychoactive: plant Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC), as well as their synthetic analogues–nabilone and THJ-2201 (fig. 1 and 2). For both groups of analgesics, the Wiener (W) and Balaban (J) topological indices were calculated (using the ChemicDescript software developed earlier, certificate No. 2003612305). The comparative evaluation of the values of topological indices with toxicity (LD50, mouse, per os/ intraperitoneal) and lipophilicity logP (logarithm of the octanol/water partition coefficient) was carried out on the basis of correlation diagrams "LD50-W/J" and "logP-W/J".

RESULTS AND DISCUSSION

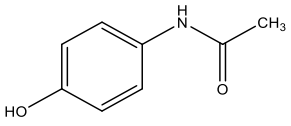
The biopharmaceutical characteristics of substances reflect the extent to which the L (ligand) (cannabinoid or NSAID molecule) binds to the corresponding R (receptor). Differences in the structures of molecules, numerically characterized by topological indices, should correlate with such biopharmaceutical indicators as the dissociation constant for the L•R complex, toxic dose LD50, and lipophilicity of the molecule (logP).

Cannabinoids with varying degrees of psychoactivity have different affinities for CB1 and CB2 receptors. This affinity is characterized by the values of the equilibrium constants for the decomposition of cannabinoid complexes with the receptor (table 1). For example, for Δ^9-THC, which has the highest psychoactivity among plant cannabinoids, the dissociation of the Δ^9-THC•CB1 and Δ^9-THC•CB2 complexes is

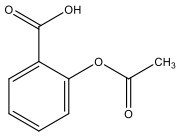
characterized by low equilibrium constants of the same order [11], which indicates the strength of the bond with both receptors:

Δ^9-THC•CB1 ↔ Δ^9-THC+CB1 K_{CB1}= 40.7±1.7 nmol

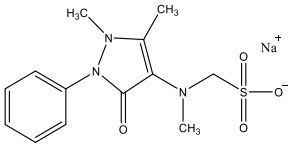
Δ^9-THC•CB2 ↔ Δ^9-THC+CB2 K_{CB2}= 36.4±10 nmol



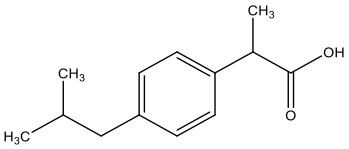
Paracetamol



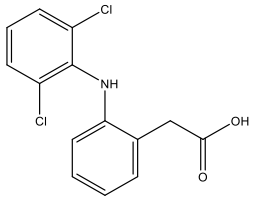
Aspirin



Dipyrone (analgin)

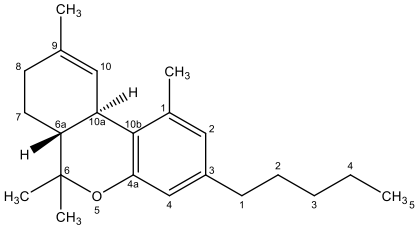


Ibuprofen

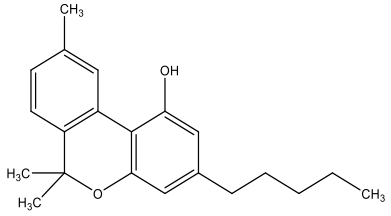


Diclofenac

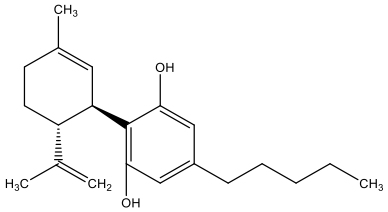
Fig. 1: Structural formulas of pharmaceutical substances of the NSAID group



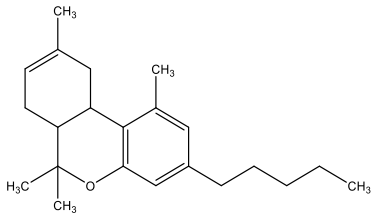
Δ⁹-THC



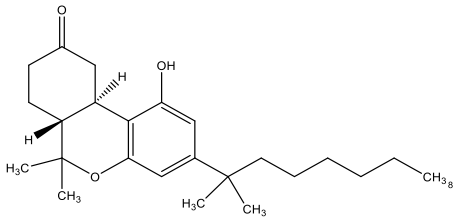
Cannabinol



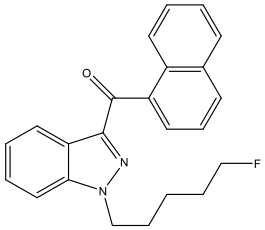
Cannabidiol



Δ⁸-THC



Nabilon



THJ-2201

Fig. 2: Structural formulas of plant cannabinoids and their synthetic analogues

Table 1: Dissociation constants for the "cannabiniod-receptor" complexes [5, 12] and calculation of the Wiener (W) topological index

No.	Cannabinoid	Dissociation constants for the L•R complexes, nmol		Wiener topological index
		CB1	CB2	
1	Cannabinol	13.0	16.0	479.5
2	Δ^9-THC	40.7; 22.0; 53.3	36.4; 47.0; 75.5	495.3
3	Δ^8-THC	47.6	39.3	503.5
4	Cannabidiol	4350.0	2860.0	528.8
5	Nabilone	2.2	1.8	828.0

As can be seen from table 1, the decrease in the bond strength of plant cannabinoids to receptors, reflecting changes in the structure of the molecules, is quantified by an increasing Wiener index. An exception is the synthetic cannabinoid nabilone, which has a high affinity for receptors and the highest Wiener index in the presented group of compounds. The appearance of a carbonyl group in the structure of nabilone, a decrease in the aromaticity of its molecule, and the racemic form of the drug caused a violation of the pattern identified for the cannabinoids of plant origin.

Binding to cannabinoid receptors has mainly been studied for Δ^9-THC, which has the highest psychoactivity among plant cannabinoids [10]. The values of dissociation constants for the Δ^9-THC•CB1 and Δ^9-THC•CB2 complexes obtained by different authors are within the same order of magnitude. On the contrary, the geometric stereoisomers of Δ^9-THC differ significantly in the strength of binding to the CB receptors. For example, the dissociation constant, determined using the [^{3}H] CP55940 radioactive label for (-)-Δ^9-(trans)-THC equals (22±13) nmol, while

its value for (-)-Δ^9-(cis)-THC is one order of magnitude higher: (228±45) nmol.

Unlike previous studies, the Wiener index allows estimation of affinity constants for both types of cannabinoid receptors, and not just for the CB1 receptor [10]. The lgK-W diagram (fig. 3) allows predicting the values of dissociation constants of the ligand-receptor interaction products for other natural cannabinoids, for example, for non-psychoactive 2-COOH-THC (plant precursor of Δ9-THC) and 11-COOH-THC (final product of the Δ9-THC biotransformation in the human body). The calculated Wiener indices for 2-COOH-THC (W=674) and 11-COOH-THC (W=638) indicate a weak bond to cannabinoid receptors CB1 and CB2.

The values of dissociation constants should exceed the value known for cannabidiol from the literature by one order of magnitude (table 1).

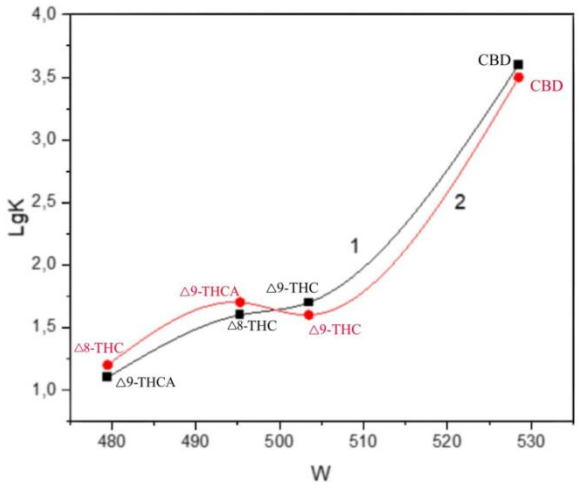


Fig. 3: Dependence of the dissociation constant of cannabinoid complexes with CB1 (1) and CB2 (2) receptors on the Wiener index

The topological indices for both groups of analgesics showed one-to-one correspondences with median lethal doses LD50 (mouse, oral) and LD50 (mouse, intraperitoneal). At the same time, cannabinoids and NSAIDs were grouped in different regions of the diagram (fig. 4). It was a matter of interest to demonstrate the possibility of using the diagram for a compound that was different in its chemical structure from both plant cannabinoids and NSAIDs. For this purpose, a designer drug with a high affinity for cannabinoid receptors, THJ-2201, was selected (fig. 2). Its position on the diagram turned out to be close to the synthetic cannabinoid nabilone, which allows suggesting that the search for compounds with identical pharmacological properties/toxicity should be based on the calculation of topological indices and not only on the basic structure of Δ^9-THC with the introduction of various substituents.

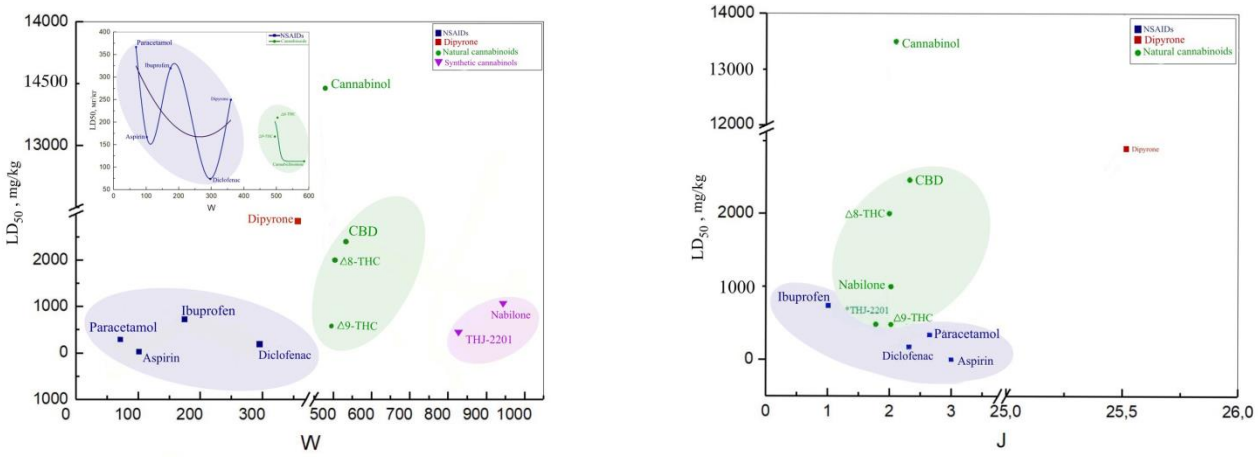


Fig. 4: One-to-one correspondence of the Wiener and Balaban indices for median lethal doses LD50 (mouse, per os). *Insert:* LD50 (mouse, intraperitoneal)

Thus, plant and synthetic cannabinoids show less toxicity than most NSAIDs considered. For synthetic cannabinoids–nabilone and THJ-2201–the Wiener index is approximately 2 times higher than for plant analogues. Cannabidiol and cannabinol, having close values of their topological indices and insignificant psychoactivity, have the highest LD50 values, i.e. they are the least toxic. For the Δ^8-THC and Δ^9-THC positional isomers–in terms of the position of the double bond–the differences in toxicity and topological indices are insignificant.

Since the number of separated and identified plant cannabinoids is growing from year to year [12, 13], the results obtained allow for the assessment of toxicity of these "new" compounds using the LD50-W and LD50-J diagrams. For example, there are no data in the literature on the toxicity of 2-COOH-THC and 11-COOH-THC. Based on the obtained diagrams and calculated values of the topological indices, the predicted LD50 values for 2-COOH-THC should be within the range of 1800-2000 mg/kg, and for 11-COOH-THC–2000-2100 mg/kg (mouse, per os).

A similar approach can be applied to evaluate the lipophilicity (logP) of newly separated plant cannabinoids once their chemical structures have been identified. One-to-one correspondences between the lipophilicity (logP) and the Wiener and Balaban topological indices indicate that the two groups of analgesic substances, as in the case of correlation with toxicity, occupy different regions in the diagram (fig. 5).

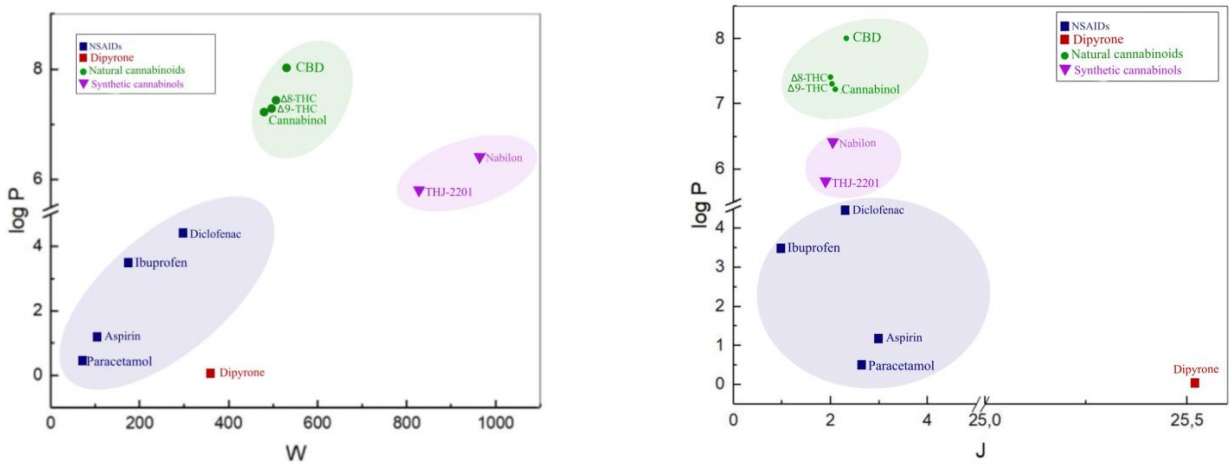


Fig. 5: One-to-one correspondence of the Wiener and Balaban indices to lipophilicity (logP)

Extension of the group of cannabinoids (tetrahydrocannabivarin, cannabigerol, cannabichromene, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol, cannabidivarin) with their synthetic analogues (JWH-015, JWH-018, JWH-019, JWH-020, JWH-022, JWH-122, JWH-210, AM-2201, MAM-2201) confirmed the conclusions about their higher lipophilicity compared to NSAIDs and opioid analgesics (fig. 6).

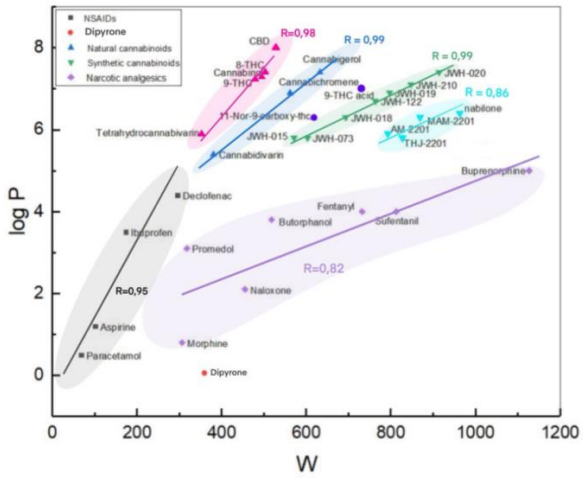


Fig. 6: One-to-one correspondences of lipophilicity (logP) to Wiener index

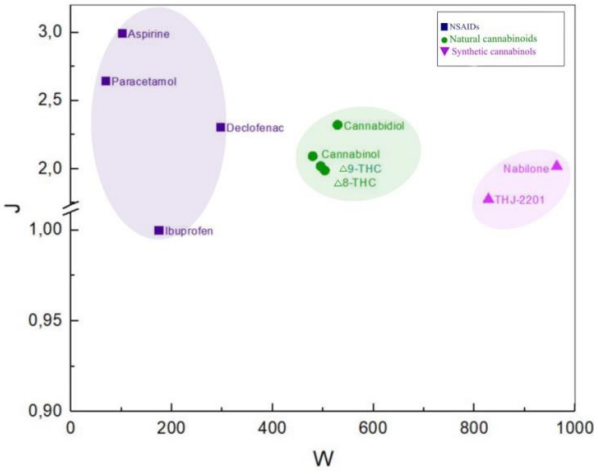


Fig. 7: One-to-one correspondence of the Wiener and Balaban indices for cannabinoid analgesics and NSAIDs, the regions of "existence" of the two groups of analgesics are located far from each other in the entire range of topological indices

The high lipophilicity of cannabinoids implies their easy penetration through lipophilic cell membranes. The higher bioavailability of cannabinoids allows the use of a lower therapeutic dose compared to other analgesics. Correlation lines of the same type of chemical structures make it possible to predict the lipophilicity of new herbal and synthetic analgesics.

The independence of correlation studies with the use of the selected topological indices is confirmed by the diagram "Wiener index–Balaban index" for two groups of analgesics (fig. 7).

CONCLUSION

In connection with the successful promotion of cannabinoid analgesics in the global pharmaceutical market, the results obtained are important for demonstrating their advantages over NSAIDs in terms of toxicity and lipophilicity. The QSAR approach opens up the possibility of predicting the cannabinoid receptor binding energy of synthetic and newly identified plant cannabinoids, as well as assessing their toxicity and lipophilicity.

FUNDING

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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