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COMPUTATIONAL MODELING OF COMPOUNDS THAT INTERACT WITH OPIOID AND CANNABINOID RECEPTORS

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ABSTRACT

The present study was designed to investigate the structure-activity relationship between cannabinoid and opioid ligands with models of cannabinoid and opioid receptors. There are differences in the mechanisms of pain control for these two types of receptors, but targeting the creation of compounds that bind to both opioid and cannabinoid receptors lead to more effective solving of this problem. This will lead to the development of new and improved strategies to prevent opiate addiction and its consequences.

Keywords: computational modelling, drug design, structure-activity relationship, opioid receptor, cannabinoid receptor.

INTRODUCTION

The endocannabinoid system, comprising the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), their endogenous ligands (endocannabinoids), and the proteins that regulate endocannabinoid biosynthesis and degradation, controls several physiological and pathological functions [1]. Cannabinoid receptors are activated by Δ9-THC, the psychoactive component of Cannabis sativa, leading to analgesia, inhibition of nausea, lowering of intraocular pressure, appetite stimulation, antiemetic activity, and bronchial dilation [2]. Endogenous ligands to these receptors include arachidonoylethanolamide (anandamide) [3], 2-arachidonoylglycerol (2-AG) [4] and 2-arachidonoyl ether (noladin ether) [5], the latter having a high affinity for CB1 receptors but binding only weakly to CB2.

Opioids have been used to treat pain for years. In addition, they successfully deal with all related disorders. To reduce the side effects of the action of opioids, a large number of their analogues have been obtained, while at the same time their effect is also aimed at the treatment of other diseases - diarrhea, cough, postoperative pain and cancer [6].

The opioid and cannabinoid systems have substantially similar effects and signalling mechanisms. This suggests a possible interaction between them. Before the discovery of cannabinoid receptors, it was thought that cannabinoids probably exerted their effects through opioid receptors. Although Δ9-THC interacts competitively with μ- and δ-opioid receptors, IC50 values indicate that its effect is due to the combined interaction with both types of receptors - opioid and cannabinoid [7].

The purpose of the present study is to analyze the

docking results of some selective cannabinoid ligands docked with μ-opioid receptor (MOR) and δ-opioid receptor (DOR).

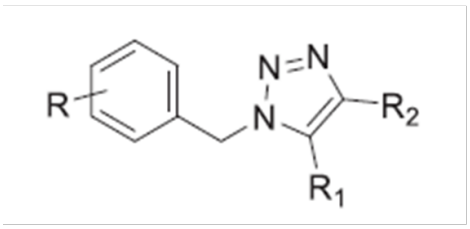
EXPERIMENTAL

The crystal structures of the investigated compounds were obtained from the RCSB Protein Data Bank[8]: cannabinoid receptor type 1 (PDBid: 5tgz), μ-opioid receptor (PDBid: 4dkl) and δ-opioid receptor (PDBid: 4ej4). This study used 18 ligands whose structures are presented in Fig. 1. The 1,2,3-Triazole derivatives were synthesized as a selective cannabinoid receptor agonist [9]. Ligand preparation was done with Avogadro: an open-source molecular builder and visualization tool [10]. Docking studies were performed by using GOLD 5.2 (Genetic Optimization for Ligand Docking) [11], run on the Scientific LINUX 5.5 operating system. For generation Figures, Molegro Molecular Viewer [12] was used. Graph Pad Prism statistical software was used to determine Pearson's correlation coefficient (https://www.graphpad.com).

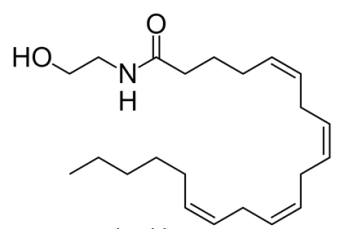
RESULTS AND DISCUSSION

The study used 18 compounds that were synthesized to interact with the CB1 receptor. Docking of these compounds with CB1, MOR and DOR were carried out. The docking results are presented in Table 1.

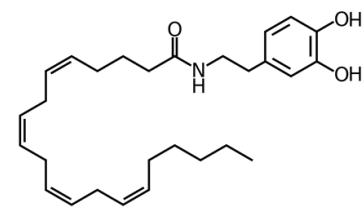
There is a correlation (Pearson R = 0.63, p = 0.005) between the total energy values of the complexes of the ligands with CB1 and those of MOR. This could lead to a combination of the effects of both types of receptors and, accordingly, achieve a stronger pain-relieving effect. Typically, in the search for ligands interacting with MOR, various analogues of opioid peptides are used. However, peptides, as is known, are not stable in biological conditions as a result of their rapid degradation under the action of peptidases. This



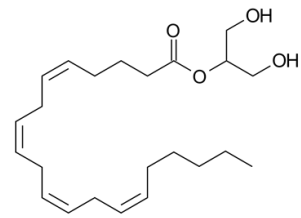
T1 R=2,6-dichloro; R_1=-CO_2tBu; R_2=CO_2tBu
T2 R=4-fluoro; R_1=CO_2tBu; R_2=CO_2tBu
T3 R=3-fluoro; R_1 =CO_2CH_3; R_2 = CO_2CH_3
T4 R=4-fluoro; R_1 = CO_2CH_3; R_2 = CO_2CH_3
T5 R=3-fluoro; R_1 =H; R_2 = CO_2CH_3
T6 R=3-fluoro; R_1 =H; R_2 = CO_2CH_3
T7 R=3-fluoro; R_1 =$CONHNH_2$; R_2 = $CONHNH_2$
T8 R=2,3,4,5,6-pentamethyl; R_1 = CO_2tBu; R_2 = CO_2tBu
T9 R=2,3,4,5,6-pentamethyl; R_1 = CO_2CH_3; R_2 = CO_2CH_3
T10 R=2,6-dichloro; R_1 =- $CONHNH_2$; R_2 = $CONHNH_2$
T11 R=2,6-dichloro; R_1 =- CO_2CH_3; R_2 = CO_2CH_3



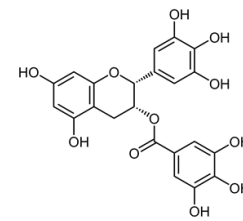
Anandamide



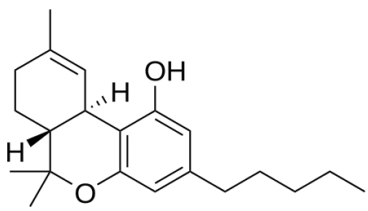
Arachidonyl dopamine



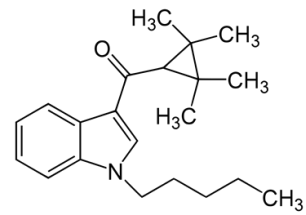
Arachidonylglycerol



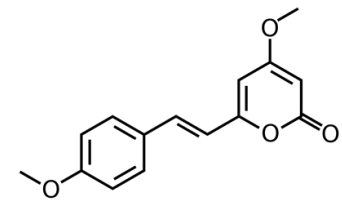
Epigallocatechin Gallate



Tetrahydrocannabinol



UR-144



Yangonin

Fig. 1. Structures of the ligands used in the study.

Table 1. Scoring functions and total energies of selected ligands with CB1, MOR and DOR.

Ligands	CB1		MOR		DOR	
	Score	Total energy	Score	Total energy	Score	Total energy
Anandamide	26.75	-90.569	34.73	-122.226	32.50	-100.661
Arachidonyl dopamine	27.89	-97.194	38.94	-144.657	36,60	-101.841
Arachidonylglycerol	23.05	-69.335	31.62	-100.388	34.61	-98.394
Epigallocatechin Gallate	7.20	-57.076	28.53	-110.215	26.96	-112.242
T1	19.77	-57.682	29.18	-97.619	38.19	-81.968
T2	18.04	-69.244	30.08	-86.102	30.96	-106.282
T3	16.04	-67.864	23.99	-82.133	22.34	-83.833
T4	15.66	-55.770	24.19	-73.583	22.74	-76.664
T5	16.89	-60.931	23.83	-82.979	23.61	-90.196
T6	17.16	-56.141	23.64	-77.900	23.95	-84.702
T7	16.31	-73.240	23.60	-66.374	23.16	-70.682
T8	24.00	-67.130	33.02	-93.003	32.76	-81.073
T9	18.94	-53.041	29.39	-81.696	27.42	-82.862
T10	20.93	-52.568	30.98	-83.694	31.42	-82.273
T11	16.87	-55.351	26.46	-88.692	25.65	-94.987
Tetrahydrocannabinol	26.97	-62.533	32.07	-84.739	33.52	-81.827
UR-144	26.04	-81.786	33.67	-96.371	34.49	-103.858
Yangonin	19.77	-53.635	28.06	-101.710	28.37	-109.250

problem can be successfully solved with the use of similar types of compounds that will not undergo such biotransformations and, accordingly, will have a higher bioavailability [13 - 17].

Examining the docking data of the compounds (Table 2) with the three types of receptors, several key points can be noted. The core residue of the CB1 sequence is Asn366. None of the tested compounds interacted with it. However, the main ligands of this receptor, anandamide (endogenous) and tetrahydrocannabinol (exogenous), interact with the nearest Tyr365 and thus produce the desired effect. T5 and T11 do not interact with any amino acid residue and therefore could not lead to appropriate conformational changes in the receptor structure. However, T5 binds to the appropriate amino acid residues in DOR (Asp128 and Tyr129) and MOR (Tyr148) and its analgesic effect is likely to be due to its interaction with opioid receptors.

The compounds with the lowest total energy of formation with the corresponding receptor complex interact with the important amino acid residues in the binding centre of the receptor. The more interactions the ligand has with the receptor, the lower the total energy of the complex. However, the type of interactions (strength and amino acid residue) determines the nature of the effect - agonistic or antagonistic. Often binding too strongly to the receptor leads to its blocking and the corresponding compound will exhibit an antagonistic effect.

Table 2. Interactions of the ligands with the respective receptor.

Ligands	CB1 interactions	DOR	MOR
Anandamide	Val364, Tyr365, Lys370, Ile375	Lys108, Tyr109, Asp128, His278	Gln124, Asp147, Asn150, Trp293, Ile296, His297, Tyr326
Arachidonyl dopamine	Ala361, Val364, Tyr365, Ile375	Gln105, Lys108, Tyr109, Tyr129, Trp274, Ile277, Tyr308	Asp147, Tyr148, Leu219, Lys233, Ile296, Tyr326
Arachidonylglycerol	Leu360, Ala361, Val364, Tyr365, Gly369	Gln105, Lys108, Tyr109, Met132, Val281	Asp147, Tyr148, Ile296, Gly325
Epigallocatechin Gallate	Val364, Tyr365, Phe368, Gly369	Gln105, Lys108, Asp128, Tyr129, Asn131, Lys214, Ile277, Ile304, Gly307, Tyr308	Gln124, Asp147, Tyr148, Asn150, Trp293, Ile322, Gly325, Tyr326
T1	Ile375, Cys382	Leu125, Tyr129, Ile277	Tyr148, Lys233, Val236, Ile322
T2	Ala361, Tyr365	Tyr129, Lys214, Val217, Val281	Tyr148, Lys233, Val236, Trp326
T3	Ile 375	Asp128, Tyr129, Ile277, Tyr308	Tyr148, Lys233, Ile296
T4	Pro358, Tyr365, Ile375	Tyr129, Tyr274, Tyr308	Tyr148, Lys233
T5		Asp128, Tyr129, Trp274	Tyr148, Ile296
T6	Pro358, Tyr365, Ile375	Asp128, Tyr129	Tyr148, Tyr326
T7	Tyr365	Tyr129, Ile277, Gly307, Tyr308	Tyr148, Lys233
T8	Ile375, Phe381	Tyr129, His278	Lys233, His297, Trp318, Ile322
T9	Val378	Tyr129, Ile277	Tyr148, Lys233, Ile296, His297
T10	Tyr365, Val378	Gln105, Tyr109, Tyr129, Ile277, His278, Ile304	Gln124, Tyr128, Ile296, Trp318, His319, Tyr326
T11		Tyr129, Trp274, Ile304	Tyr148, Lys233, Ile296, Trp318, Ile322
Tetrahydrocannabinol	Tyr365, Ile375, Val378	Asp128, Val281, Leu300, Ile304, Tyr308	Asp147, Ile296
UR-144	Leu374	Tyr129, Trp274, Ile277	Tyr148, His297, Val236
Yangonin	Pro358, Ile375	Tyr129, Lys214	Tyr148, Val236, Val300

CONCLUSIONS

The research done shows that a more in-depth study of the effects of different compounds is needed in view of the fact that, in addition to the desired effect, they could have an effect on other receptors, for example. With the help of docking, this type of research is easily carried out, and the interactions of a given compound with a large array of receptors can be studied. In addition to unwanted effects, many positive interactions can be found that lead to a more complex treatment of a particular problem, for example, pain in our case.

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