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In silico approach of 2,5-Diketopiperazines from marine organisms to neurodegenerative diseases

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Abstract

In this paper we present an *in silico* studies of new biological active of 2,5-Diketopiperazines candidates, from Marine Organisms to neurodegenerative diseases particular for the neurodegenerative central nervous system to Alzheimer's, Huntington and Parkinson's diseases. A total of 35 DKPs were studied, by structural similarity analysis obtained MAO-A/B, β/γ-Secretase, COX-1/2 enzymes targets obtained, to continue molecular docking studies compared to endogenous substrates and reference inhibitors, finding a multitarget potential to increase dopamine levels and decrease β-amyloid and PGE2 levels, which makes them excellent molecules for studies against neurodegenerative diseases. DKP4, DKP23 and DKP25 as inhibitors of the 6 enzymes and DKP15, DKP19, DKP21, DKP26 and DKP33 for β-Secretease specifically, the rest with multitarget potential, denoting that the DKP ring serves as a base to generate multitarget or unitarget compounds through modifications in substituents. Finally, DKPs present low bioaccumulation in the body, no toxicity, high feasibility of crossing hematoencephalic membrane and activity on the CNS, which makes them an interesting set of molecules for the search for alternatives against neurodegenerative diseases.

Keyword: 2,5-Diketopiperazines; Neurodegenerative diseases; *In silico*; MAO-A/B; β/γ-Secretease; COX-1/2

1. Introduction

Marine organisms are a great source of natural products, ranging from terpenes, steroids, flavonoids to alkaloids, standing out in this last group for the versatility of reported derivatives, with diverse biological activities, a group of particular interest are 2,5-Diketopiperazines (DKPs), figure 1, that are a cyclic peptide known, commonly biosynthesized from amino acids by different organisms, including mammals, and are secondary functional metabolites or side products of terminal peptide cleavage [1–7]. DKPs cyclic structures have been detected in numerous natural resources. Usually, extracted from marine microorganisms, sea stars, sponges, tunicates, and red algae. Their interest has been constantly increased due to biological activities inhibition of plasminogen activator inhibitor and alteration of cardiovascular and blood-clotting functions. Also has activities as an antitumor, antiviral, antifungal, antibacterial, and antihyperglycemic agent and affinities for calcium channels an opioid, GABAergic, serotoninergic 5-HTiA, and cytotoxin receptors [8].

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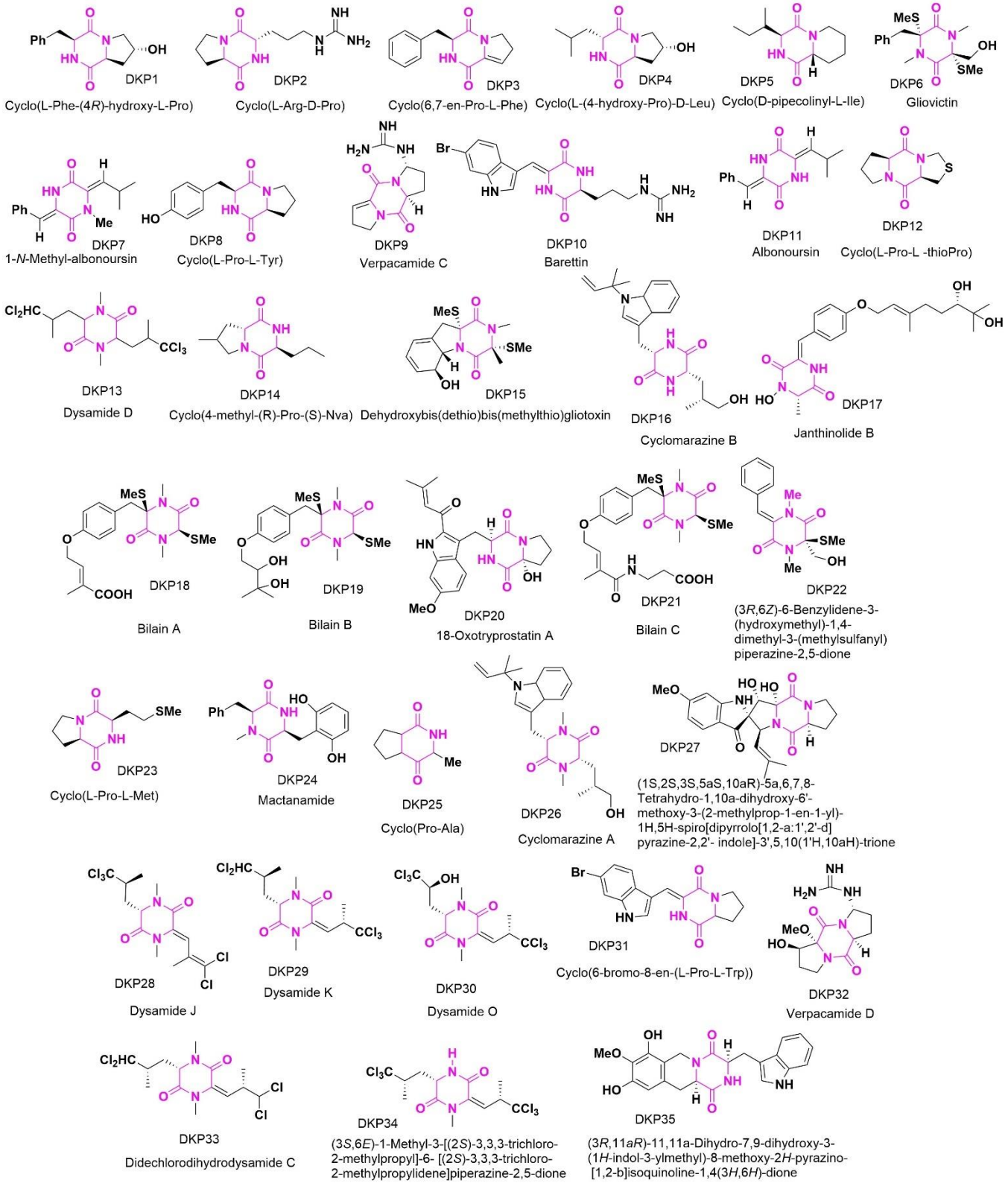

Figure 1 2,5-Diketopiperazines (DKPs) reported isolated in marine organism.

Natural DKPs are dipeptides biosynthetically assembled by either nonribosomal peptide synthetases (NRPSs) or the more recently discovered cyclodipeptide synthases (CDPs), with structural diversity achieved through choice of amino acid precursor, and subsequent formation of heterocycles, prenylation, oxidation, dimerization etc. [9] Therefore, their peculiar heterocyclic system constitutes a rich source of new biologically active compounds and is considered ideal for the development of new therapeutic agents [10]. From a lot of isolated DKPs their biological activity has not been

studied until now, their total synthesis has not been developed, and only their structure has been elucidated by spectroscopy studies. Therefore, there *in silico* studies are crucial for developing new biological active candidates, particular for the neurodegenerative central nervous system.

2. Material and methods

2.1. Studies of Similar Structures

From the metabolites reported in the literature, the targets were obtained using the SwissTargetPrediction platform (STP). In this way, the construction of the frequency diagram was possible, according to the methodology previously reported for performing a frequency analysis on a set of metabolites from studies [11,12].

2.2. Molecular Docking Studies

References and 2,5-diketopiperazines were drawn in 2D Sketcher to minimize Macromodel [13] conformers with OPSL4 and brought to physiological conditions in LigPrep [14]. The proteins were obtained from the Protein Data Bank and coded as 2Z5Y [15] for MAO-A, 2V60 [16] for MAO-B, 6C2I [17] for β-secretase, 4R12 [18] for γ-secretase, 3N8Z [19] for COX1 and 5KIR [20] for COX2. Proteins were prepared using Protein Preparation Wizard [21] according to the methodology. Molecular docking was performed on the Glide [22] module with flexibility at the site and using the ligands according to the reported protocol [12,23].

2.3. ADMETx Studies

The prediction of ADME properties was carried out with minimized structures using the QikProp module [24].

3. Result and Discussion

The structural core of the 2,5-Diketopiperazines presents a great similarity with drugs reported in the literature, which gives it a potential for diverse biological activity. Through structural similarity analysis in STP, proteins of different types were detected (Figure 2). That can be associated in various groups, highlighting metabolism, cell proliferation and particularly a group associated with neurotransmitters (orange sticks) both in their production and degradation.

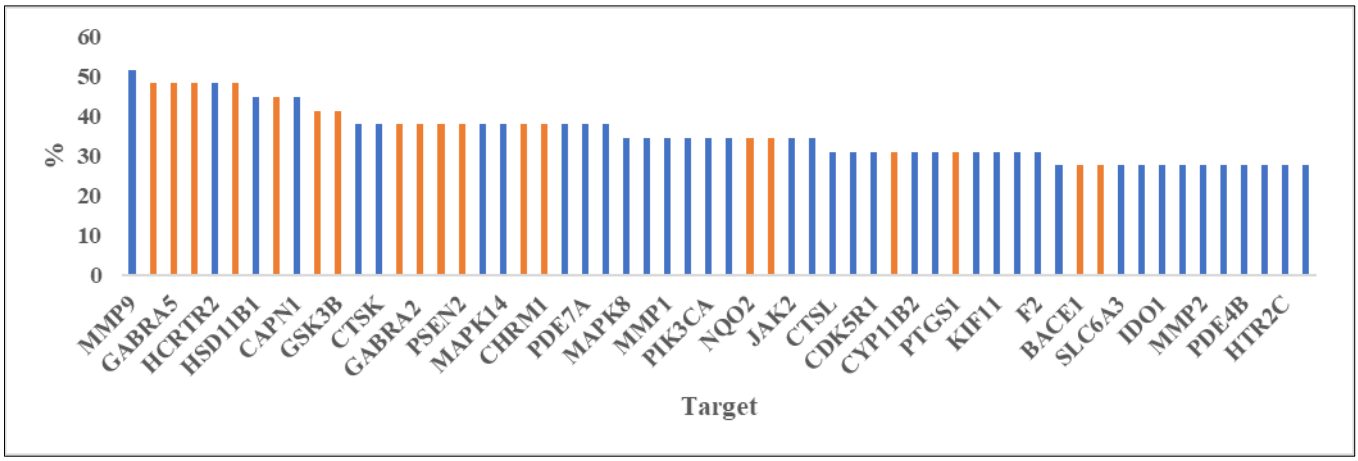

Figure 2 Diagram of percentage frequency targets of DKPs in STP.

From the analysis of structural similarity, focused on CNS, the enzymes that are related to the regulation of neurotransmitter levels stand out. Table 1 shows the relationship of these with different neurodegenerative diseases, highlighting Epilepsy, Parkinson's, Alzheimer's, and Huntington's disease. These enzymes are responsible for the regulation of dopamine (MAO-A/B) as well as the formation of the amyloid peptide (β/γ-Secretease) and prostaglandin E2 (COX-1/2), giving a multifaceted regimen according to the effect levels and selectivity of the protein inhibition, denoting the potential of DKPs derivatives against neurodegenerative diseases.

Table 1 CNS targets related to DKPs. Diseases, tissues and inhibitors reported

Target protein	UniProt code	Disease	Tissues	Inhibitors	[Ref.]
Monoamine oxidase B (MAOB)	P27338	Parkinson's disease, Alzheimer's disease.	Liver, brain, myocardium, many tissues	Selegiline, Safinamide, rasagiline.	[25,26]
Monoamine oxidase A (MAOA)	P21397	Alzheimer's disease, Parkinson's disease, depression.	Brain, placenta, guts, liver	Harmine, ladostigil, resveratrol.	[27,28]
Phosphodiesterase 10A (PDE10A)	Q9Y233	Parkinson's disease, psychosis, schizophrenia, Huntington's disease.	Brain, heart.	CPL500036, papaverine, TAK-063	[29–32]
Glycogen synthase kinase-3 beta (GSK3B)	P49841	Alzheimer's disease, Huntington's disease, multiple sclerosis, gliosis.	Brain, many tissues.	Tideglusib, LY2090314, SB216763, TDZD-8	[33–35]
γ-secretase (PSEN2)	P49810	Alzheimer's disease.	Brain, many tissues.	Semagacestat, E2012, BMS-708163, GSI-953	[36–38]
β-secretase (BACE1)	P56817	Alzheimer's disease.	Brain, endocrine tissue, pancreas, muscle tissue, lymphoid tissue	Verubecestat, lanabecestat, umibecestat, elenbecestat	[39,40]
Phosphodiesterase 7A (PDE7A)	Q13946	Parkinson's disease, Alzheimer's disease, Huntington's disease.	Brain, alveolar tissue, immune tissues.	Dipyridamole, SCH51866, S14, TC3.6, VP1.15, BRL-50481	[41]
Quinone reductase 2 (NQO2)	P16083	Alzheimer's disease.	Brain	S29434, M-11	[42–44]
Cyclooxygenase-1 (PTGS1)	P23219	Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jakob disease	Endothelium, platelets, renal collecting tubules	Resveratrol	[45–47]
Cyclooxygenase-2 (PTGS2)	P35354	Epilepsy, schizophrenia.	Brain, kidney, gastrointestinal tract, may tissues	Celecoxib, refecoxib, Nimesulide, NS-398	[48–50]
Phosphodiesterase 4B (PDE4B)	Q07343	Alzheimer's disease, schizophrenia, multiple schlerosis.	Heart, brain, skeletal muscle and lung	Rolipram, roflumilast, cilomilast.	[51,52]
Dipeptidyl peptidase IV (DPP4)	P27487	Parkinson's disease, Parkinson's disease	Adipose tissue, liver, gut, lung, kidney	Linagliptin, sitagliptin, saxagliptin.	[53,54]

The results of molecular docking with the selected enzymes (Table 2) demonstrate the aforementioned latent potential of the DKPs, in purple the better than reference inhibitors and in green better than the endogenous substrates, observing multitarget inhibition by the DKPs, particularly DKP4, DKP23 and DKP25 have the potential to inhibit all the enzymes under study, proposing an increase in dopamine levels and a decrease in β-amyloids and PGG2, proposing a decrease in the progression of neurodegenerative diseases. DKP8 and DKP11 inhibit the secretase and COX pathways selectively. DKP13 inhibits COX only, while DKP16, DKP20, DKP24, DKP32 and DKP35 inhibit only secretases. For specific inhibition only DKP15, DKP19, DKP21, DKP26 and DKP33 β-Secretease, the rest of the DKPs present inhibitions in at least two

enzymes except for DKP6, DKP18, DKP27, DKP28, DKP29, DKP30 and DKP34, which do not present the possibility of inhibition with any enzyme.

Table 2 Docking score (kcal/mol) of DKPs in neurodegenerative diseases enzyme related

Compound	MAOA	MAOB	β-Secretease	γ-Secretease	COX-1	COX-2
DKP1	-	-7.600	-6.183	-4.031	-8.018	-7.636
DKP2	-6.784	-5.959	-5.251	-4.678	-6.053	-6.525
DKP3	-4.255	-7.121	-5.287	-4.419	-8.183	-7.485
DKP4	-6.938	-7.378	-5.990	-4.655	-7.614	-7.182
DKP5	-6.868	-7.928	-5.130	-6.328	-7.178	-7.374
DKP6	-	-	-4.466	-3.701	-	-
DKP7	-5.817	-7.172	-5.181	-3.663	-7.736	-7.430
DKP8	-5.085	-5.748	-5.754	-5.069	-6.977	-7.481
DKP9	-6.370	-	-4.667	-5.921	-7.834	-7.968
DKP10	-6.134	-7.931	-5.372	-6.450	-4.429	-4.483
DKP11	-5.335	-6.167	-4.787	-4.481	-7.439	-7.344
DKP12	-7.869	-7.931	-5.506	-	-8.108	-7.348
DKP13	-4.782	-	-4.184	-2.816	-7.005	-7.455
DKP14	-6.035	-5.912	-5.158	-4.678	-7.159	-6.828
DKP15	-	-	-4.780	-4.035	-	-
DKP16	-	-	-6.142	-4.660	-	-
DKP17	-5.676	-	-5.333	-5.337	-	-7.573
DKP18	-2.531	-	-4.079	-3.365	-	-
DKP19	-4.935	-	-5.751	-3.874	-	-5.851
DKP20	-	-	-6.549	-6.612	-	-
DKP21	-3.836	-	-5.214	-3.599	-	-
DKP22	-	-	-4.781	-5.968	-	-7.382
DKP23	-7.113	-6.513	-5.647	-5.988	-7.274	-6.988
DKP24	-	-	-5.377	-5.714	-	-
DKP25	-7.118	-7.252	-5.456	-4.972	-7.083	-7.621
DKP26	-	-	-6.093	-2.821	-	-
DKP27	-	-	-4.307	-3.617	-	-
DKP28	-	-	-4.192	-2.872	-	-
DKP29	-	-	-4.003	-2.604	-	-
DKP30	-	-	-4.107	-3.513	-	-
DKP31	-	-8.993	-5.266	-4.418	-7.935	-6.078
DKP32	-	-	-5.288	-4.557	-	-4.885
DKP33	-5.861	-	-4.796	-4.241	-	-
DKP34	-	-6.121	-4.081	-3.419	-	-6.146

DKP35	-	-	-5.739	-4.727	-	-
Substrate*	-5.958	-6.204	-	-	-6.244	-6.509
Inhibitor**	-6.916	-9.208	−4.755	−4.358	-5.666	-7.385

* MAOA: dopamine, MAOB: dopamine, COX-1: arachidonic acid, COX-2: arachidonic acid.

** MAOA: Harmine, MAOB: Safinamide, β-Secretease: EJ7, γ-Secretease: Semagacestat, COX1: ASA, COX2: diclofenac.

The next relevant point is the relationship of the 2,5 diketopiperazinic ring with respect to the coupling in each of the active sites. In Figure 3 we can see the best candidates for MAO-A/B, where it can be noted that the key amino acids They are Asn181, Phe202, Met350 and Phe352, which are interacting with the main ring via amphipathic interaction, having a polar and a nonpolar region dividing the ring into two factions, in addition the insertion of a 3rd ring increases the interaction, as well as sulfur derivatives with the MAOA; while for MAOB, the active site environment is mostly lipophilic, resulting in better interactions by the DKPs derivatives with aromatic rings and the tricyclic sulfur system, denoting particular polar interactions by the NH groups of the substituents and the DKP ring.

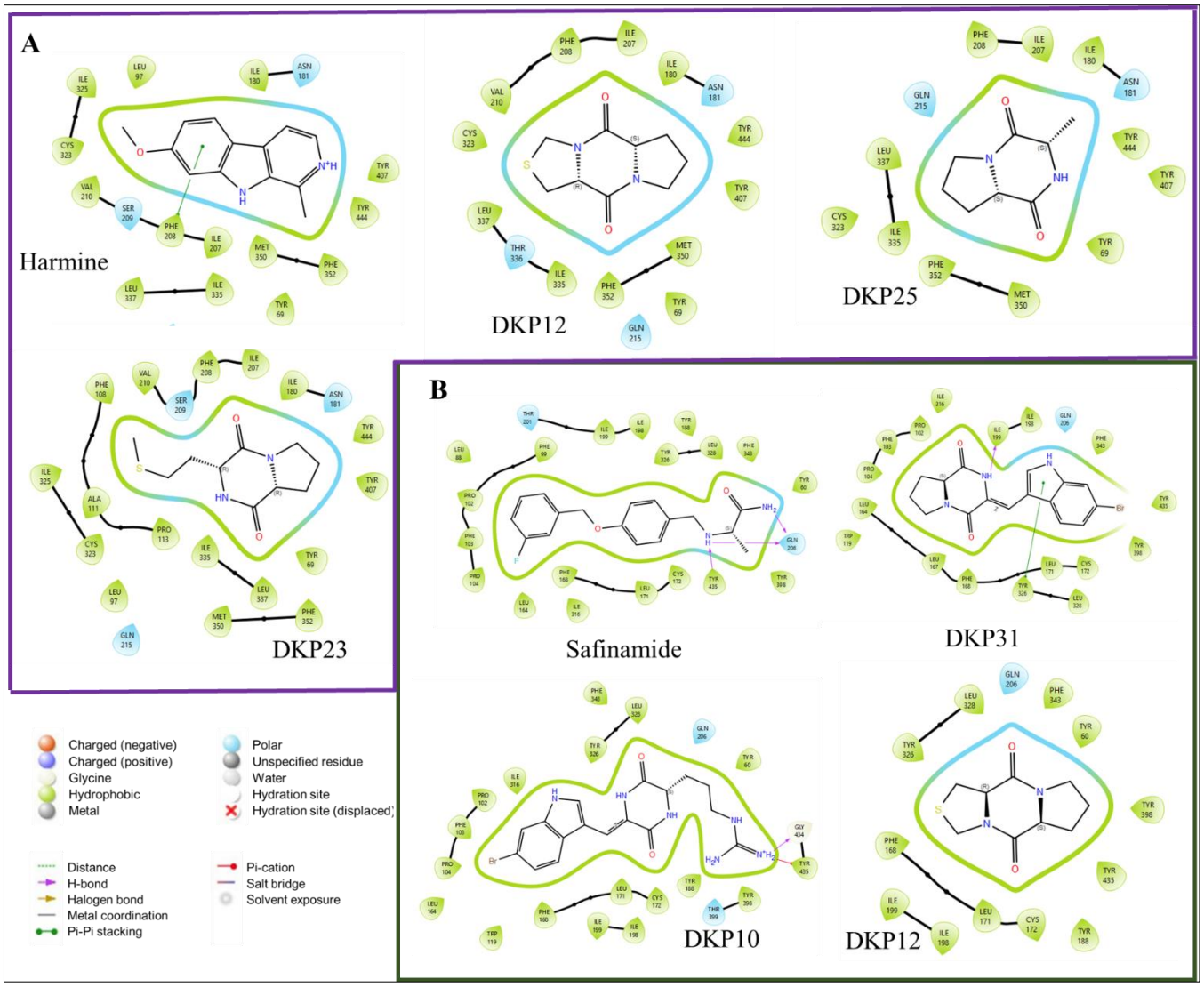

Figure 3 References and best DKPs in a) MAOA and b) MAOB catalytic site.

For the secretase system in Figure 4, it is observed that the sites are highly polar in both cases, governing the interactions by hydrogen bonding and π-π staking to stabilize and favor couplings, on the part of the DKP ring it forms a hydrogen bond. with Gln72, Ash31 and Thr71, characteristic of the aminopeptidase site of β-secretase, however the polar substituents are those that have a superior effect on coupling, mainly with the anchoring site of the enzyme. For γ-

secretase, the DKP ring presents hydrogen bond coupling by the carbonyls, giving the greatest coupling contribution to the cleavage site for the formation of β-amyloids, however in the same way as in β-secretase are the substituents that give stability to the coupling, particularly as they are of the aromatic type or guanidinium type, which agrees with the commercial inhibitors that exist for these enzymes.

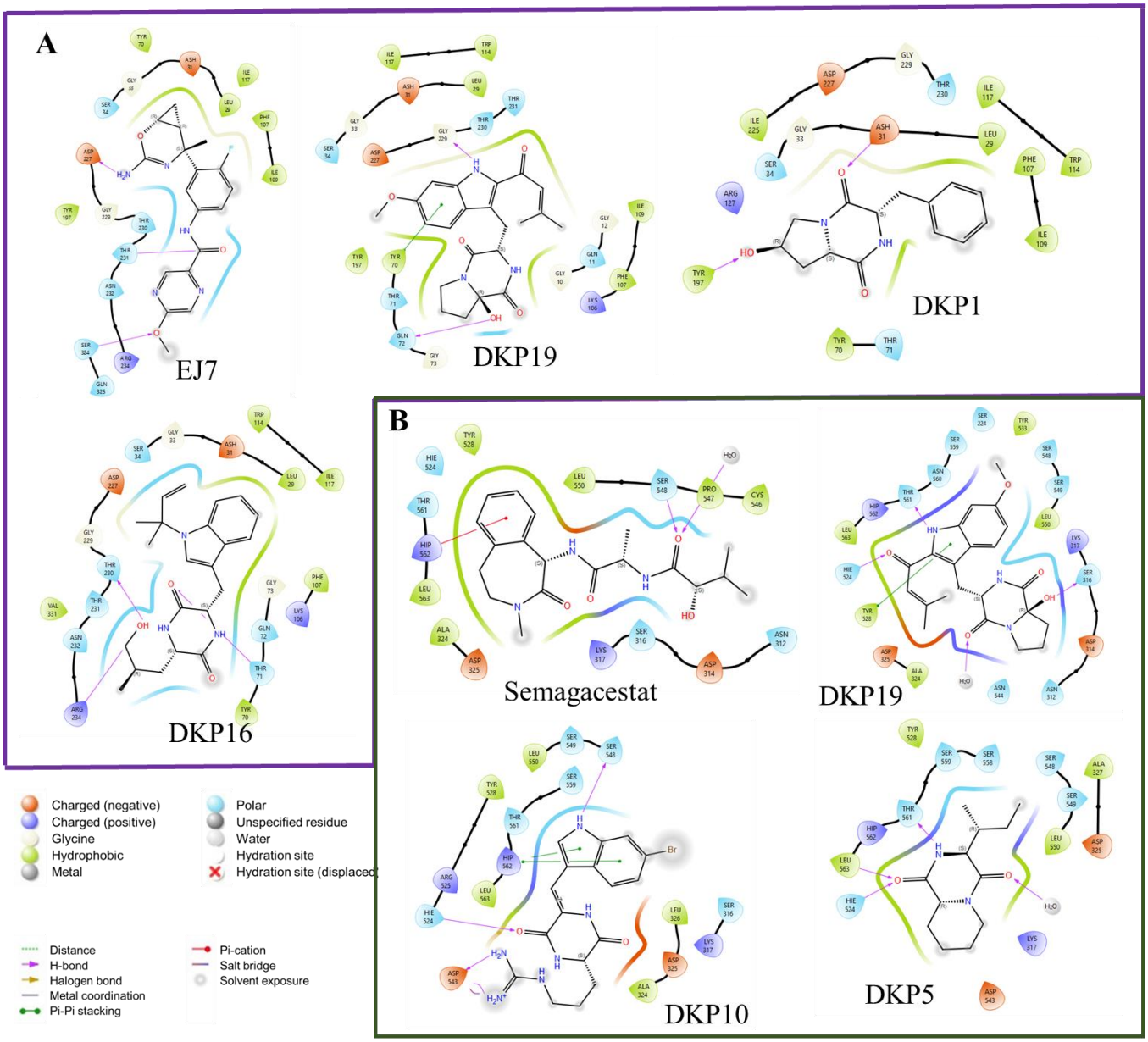

Figure 4 References and DKPs in a) β-Secretase and b) γ-Secretase catalytic site

In contrast, for COX-1/2, Figure 5 shows that it is the smaller DKPs that present greater activity, given the size of the active site, forming interactions with Ser353 and Ser530, characteristics of the mechanism. of COX1, and aromatic substitutions of a ring and of guanidinium allow increasing the coupling as well as sulfur, maintaining a low total volume on the part of the DKPs; For COX2, the same effect is observed: tricyclic DKPs with small substituents are better suited to the active site, in this case forming interactions with Arg120 and Ser353 and Ser530, given the great similarity between the two enzymes in the catalytic site. , hence the little selectivity between these.

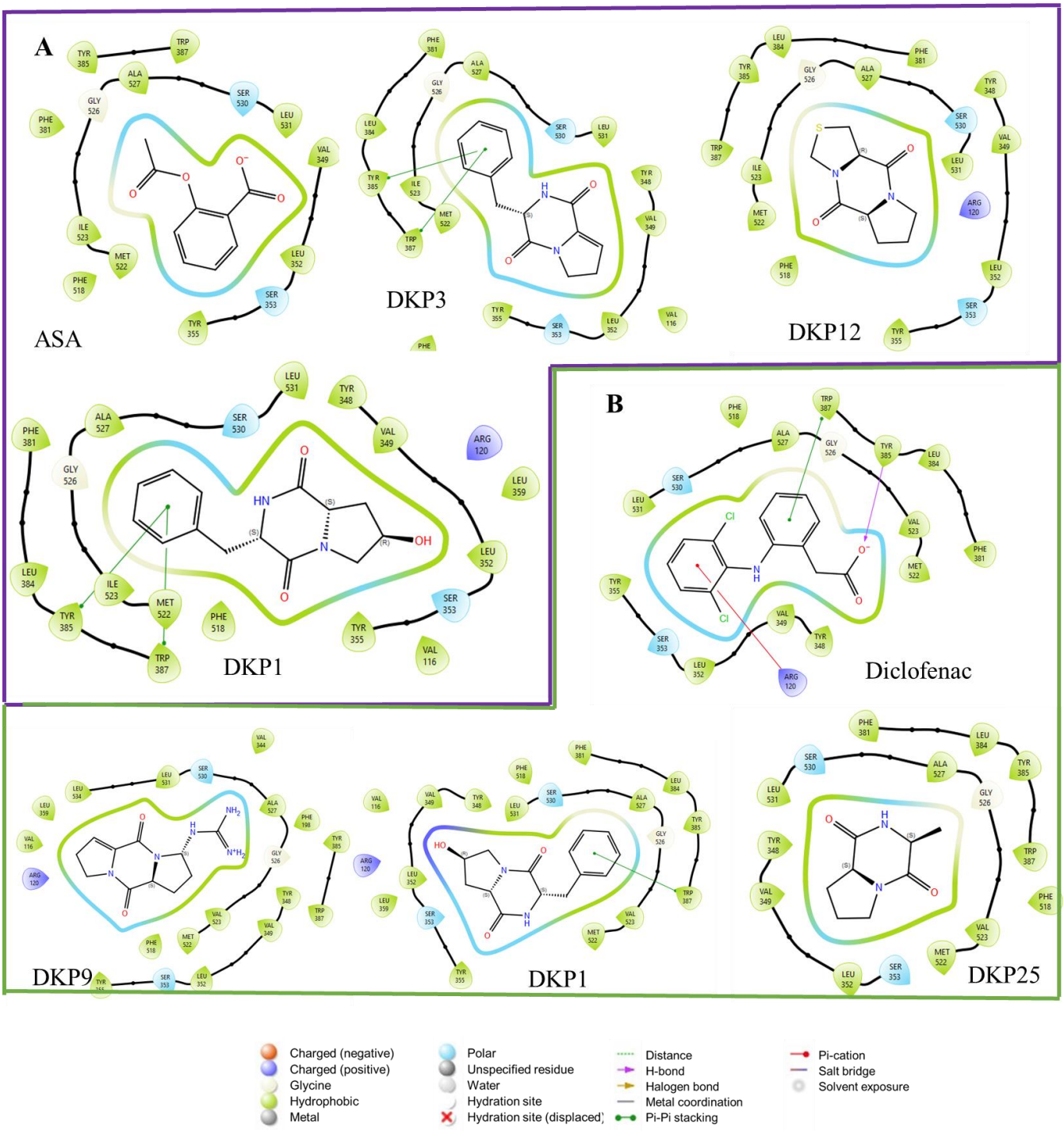

Figure 5 References and DKPs in a) COX-1 and b) COX-2 catalytic site

Finally, to highlight the global potential of the DKPs, their ADMETx properties were analyzed. Table 3 shows the most relevant properties; It can be seen in the column that the molecular weight is within the admissible ranges of 130 to 725 g/mol for each of the molecules studied; The generation of hydrogen bonds remains mostly within the suggested ranges for both donor and acceptor atoms with the ranges of 0 to 6 and 2 to 20 respectively, with the exception of structures DKP10 and DKP12 with a number of donors of hydrogen bond of 7; The octanol/water partition coefficient shows the diversity that exists among the molecules studied, with a range of -1.787 to 4.647, being within the recommended values of -2 to 6.5, the lower limit being molecules with hydrophilic properties and the upper limit being hydrophobic. Skin permeability is an important factor to predict one of the routes of drug excretion and possible bioaccumulation. The recommended range is between -8 and -1, in which all structures are within; It is also important to evaluate the possible number of metabolic reactions that can be carried out within the organism, what is expected

for this parameter are minimum values of 1 and 2, and with a recommended maximum of 8, the structures that meet the minimum values with DKP1, DKP2, DKP4, DKP5, DKP8, DKP10, DKP12, DKP14, DKP16, DKP17, DKP19, DKP23, DKP24, DKP25, DKP27, DKP32 and DKP35.

Table 3 ADMETx prediction for DKPs in Qikprop

Structure	[1]CNS	Molecular weight	[2]HB D/A	[3]logPo/w	[4]logBB	[5]PMDCK	[6]logKp	[7]#met	Linpinski´s rule
DKP1	-2	260.292	2.0/7.2	-0.413	-1.153	123.484	-3.549	4	0
DKP2	-2	253.303	5.0/7.5	-1.787	-2.089	15.172	-7.759	3	0
DKP3	0	242.277	1.0/5.5	1.472	-0.305	535.196	-2.523	3	0
DKP4	-2	226.275	2.0/7.2	-1.088	-1	135.798	-4.177	3	0
DKP5	0	224.302	1.0/5.5	0.197	-0.426	579.032	-3.14	2	0
DKP6	-1	354.481	0.0/7.7	0.914	-0.122	2837.62	-1.421	2	0
DKP7	0	270.33	1.0/5.5	2.547	-0.66	511.842	-2.291	1	0
DKP8	-2	260.292	2.0/6.25	-0.118	-1.202	114.549	-3.756	4	0
DKP9	-2	249.272	3.0/7.0	-0.098	-1.278	50.238	-6.962	3	0
DKP10	-2	419.28	7.0/7.0	0.881	-2.54	19.118	-7.54	2	1
DKP11	-2	256.304	2.0/5.0	2.201	-1.083	227.487	-2.912	1	0
DKP12	1	212.266	7.0/6.5	-1.106	0.021	1582.61	-3.051	2	0
DKP13	1	426.597	0.0/6.0	2.997	0.404	10000	-2.323	2	0
DKP14	0	210.275	1.0/5.5	-0.149	-0.491	453.883	-3.33	2	0
DKP15	-1	340.455	1.0/8.7	0.445	-0.16	1573.765	-2.202	3	0
DKP16	-2	383.489	3.0/6.7	1.282	-1.175	122.326	-3.296	4	0
DKP17	-2	418.489	4.0/9.9	2.163	-2.559	40.075	-3.701	7	0
DKP18	-2	438.556	1.0/9.75	1.979	-1.273	91.987	-3.079	5	0
DKP19	-2	509.634	1.0/11.25	2.506	-2.24	27.722	-3.561	6	1
DKP20	-2	411.457	3.0/9.0	1.204	-1.402	156.083	-3.311	6	0
DKP21	-2	442.587	2.0/10.2	1.625	-1.075	672.299	-2.351	5	0
DKP22	0	306.379	0.0/7.2	1.501	-0.517	746.71	-2.347	1	0
DKP23	0	228.309	1.0/6.0	-0.029	-0.391	977.715	-3.059	2	0
DKP24	-1	340.378	3.0/7.0	0.823	-0.993	177.372	-2.743	6	0
DKP25	0	168.195	1.0/5.5	-1.131	-0.331	417.221	-3.588	2	0
DKP26	-1	411.543	1.0/7.7	2.1	-0.86	377.337	-2.446	4	0
DKP27	1	441.483	2.0/11.2	0.114	-0.613	52.302	-5.404	6	0
DKP28	1	422.565	0.0/6.0	4.076	0.372	10000	-2.343	2	0
DKP29	2	424.581	0.0/6.0	4.487	0.493	10000	-2.103	2	0
DKP30	0	460.999	1.0/7.7	3.799	0.226	10000	-2.645	3	0
DKP31	0	360.209	2.0/5.5	2.462	-0.613	702.013	-3.116	1	0
DKP32	-2	297.313	3.0/8.45	-1.343	-1.48	41.527	-7.068	3	0
DKP33	1	390.136	0.0/6.0	3.558	0.139	10000	-2.376	2	0

DKP34	1	445	1.0/5.5	4.647	0.31	10000	-2.634	2	0
DKP35	-1	403.48	2.0/6.25	2.401	-0.836	293.585	-2.753	8	0

[1]CNS (Central Nervous System activity), [2]HB D/A (Hydrogen bonds donor/acceptor), [3]logPo/w (Predicted octanol/water partition coeffitient), [4]logBB (Predicted brain/blood partition coefficient), [5]PMDCK (Predicted MDCK cell permeability), [6]logKp (Predicted skin permeability), [7]#met (number of likely metabolic reactions)

Because the focus of these molecules is related to mental illnesses, it is important to emphasize parameters such as the CNS column, which predicts activity in the central nervous system, where a total of 7 molecules stand out among all those studied, with high activity in the central nervous system, showing values of 1 and 2, these being the most active and the least active from -2 to 0; The predictions related to the partition coefficient to overcome the blood-brain barrier of drugs administered orally, logBB, show mostly negative values, these being those that have a lower capacity to cross said barrier, giving an indication that the structures are of interest. with positive values such as 12, 13, 28, 29, 30, 33 and 34; The PMDCK parameter refers to the permeability of molecules in the blood-brain barrier with non-active transport in the MDCK cell model. The expected values in this parameter for this study must be greater than 500, for good permeability, which is met. in structures DKP3, DKP5, DKP6, DKP7, DKP12, DKP13, DKP15, DKP21, DKP22, DKP23, DKP28, DKP29, DKP30, DKP31, DKP33 and DKP34. Lipinski's rule is the number of violations made to the parameters that make a molecule like a drug. Those that do not violate any rules are the most interesting. The parameters or rules to comply with are molecular weight < 500, coefficient of octanol/water partition < 5, hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10, most molecules do not break any rules except for DKP10 and DKP19.

4. Conclusion

In silico studies revealed that DKPs could be excellent candidates for neurodegenerative diseases particular for the neurodegenerative central nervous system to Alzheimer's, Huntington and Parkinson's diseases. In particular, DKP4, DKP23 and DKP25 showed a brilliant activity as inhibitors of the 6 enzymes and DKP15, DKP19, DKP21, DKP26 and DKP33 for β-Secretease. Therefore, synthesis and *in vitro* evaluation of these DKPs products is currently underway in our laboratory, and the results will be reported in due course.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Rigogliuso S, Campora S, Notarbartolo M, Ghersi G. Recovery of Bioactive Compounds from Marine Organisms: Focus on the Future Perspectives for Pharmacological, Biomedical and Regenerative Medicine Applications of Marine Collagen. Molecules 2023, 28:1152. https://doi.org/10.3390/molecules28031152.

[2] Chen N, Zhang S, Javeed A, Jian C, Liu Y, Sun J, et al. Structures and Anti-Allergic Activities of Natural Products from Marine Organisms. Marine Drugs 2023, 21:152. https://doi.org/10.3390/md21030152.

[3] Avhad AB, Bhangale CJ. Marine natural products and derivatives. RPS Pharmacy and Pharmacology Reports 2023, 2:rqad008. https://doi.org/10.1093/rpsppr/rqad008.

[4] Carroll AR, Copp BR, Davis RA, Keyzers RA, Prinsep MR. Marine natural products. Nat Prod Rep 2023, 40:275–325. https://doi.org/10.1039/D2NP00083K.

[5] Zhang M, Zhang Q, Zhang Q, Cui X, Zhu L. Promising Antiparasitic Natural and Synthetic Products from Marine Invertebrates and Microorganisms. Marine Drugs 2023, 21:84. https://doi.org/10.3390/md21020084.

[6] Thawabteh AM, Swaileh Z, Ammar M, Jaghama W, Yousef M, Karaman R, et al. Antifungal and Antibacterial Activities of Isolated Marine Compounds. Toxins 2023, 15:93. https://doi.org/10.3390/toxins15020093.

[7] Li X, Xu J, Wang P, Ding W. Novel indole diketopiperazine stereoisomers from a marine-derived fungus Aspergillus sp. Mycology 2023, 14:1–10. https://doi.org/10.1080/21501203.2022.2069173.

[8] Martins MB, Carvalho I. Diketopiperazines: biological activity and synthesis. Tetrahedron 2007, 63:9923–32. https://doi.org/10.1016/j.tet.2007.04.105.

[9] Raju R, Piggott AM, Conte M, Aalbersberg WGL, Feussner K, Capon RJ. Naseseazines A and B: A New Dimeric Diketopiperazine Framework from a Marine-Derived Actinomycete, Streptomyces sp. Org Lett 2009, 11:3862–5. https://doi.org/10.1021/ol901466r.

[10] McCleland K, Milne PJ, Lucieto FR, Frost C, Brauns SC, Van De Venter M, et al. An investigation into the biological activity of the selected histidine-containing diketopiperazines cyclo(His-Phe) and cyclo(His-Tyr). Journal of Pharmacy and Pharmacology 2004, 56:1143–53. https://doi.org/10.1211/0022357044139.

[11] Daina A, Michielin O, Zoete V. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Research 2019, 47:W357–64. https://doi.org/10.1093/nar/gkz382.

[12] Suárez-González E, Sandoval-Ramírez J, Flores-Hernández J, Carrasco-Carballo A. Ginkgo biloba: Antioxidant Activity and In Silico Central Nervous System Potential. Current Issues in Molecular Biology 2023, 45:9674–91. https://doi.org/10.3390/cimb45120604.

[13] Schrödinger, L. Schrödinger Release 2022-4: MacroModel. EE UU: New York, NY, USA 2021.

[14] Schrödinger, L. Schrödinger Release 2022-4: LigPrep. EE UU: New York, NY, USA 2021.

[15] Son S-Y, Ma J, Kondou Y, Yoshimura M, Yamashita E, Tsukihara T. Structure of human monoamine oxidase A at 2.2-Å resolution: The control of opening the entry for substrates/inhibitors. Proceedings of the National Academy of Sciences 2008, 105:5739–44. https://doi.org/10.1073/pnas.0710626105.

[16] Binda C, Wang J, Pisani L, Caccia C, Carotti A, Salvati P, et al. Structures of Human Monoamine Oxidase B Complexes with Selective Noncovalent Inhibitors: Safinamide and Coumarin Analogs. J Med Chem 2007, 50:5848–52. https://doi.org/10.1021/jm070677y.

[17] Low JD, Bartberger MD, Cheng Y, Whittington D, Xue Q, Wood S, et al. Diastereoselective synthesis of fused cyclopropyl-3-amino-2,4-oxazine β-amyloid cleaving enzyme (BACE) inhibitors and their biological evaluation. Bioorganic & Medicinal Chemistry Letters 2018, 28:1111–5. https://doi.org/10.1016/j.bmcl.2018.01.056.

[18] Xie T, Yan C, Zhou R, Zhao Y, Sun L, Yang G, et al. Crystal structure of the γ-secretase component nicastrin. Proceedings of the National Academy of Sciences 2014, 111:13349–54. https://doi.org/10.1073/pnas.1414837111.

[19] Sidhu RS, Lee JY, Yuan C, Smith WL. Comparison of Cyclooxygenase-1 Crystal Structures: Cross-Talk between Monomers Comprising Cyclooxygenase-1 Homodimers,. Biochemistry 2010, 49:7069–79. https://doi.org/10.1021/bi1003298.

[20] Orlando BJ, Malkowski MG. Crystal structure of rofecoxib bound to human cyclooxygenase-2. Acta Cryst F 2016, 72:772–6. https://doi.org/10.1107/S2053230X16014230.

[21] Schrödinger, L. Schrödinger Release 2022-4: Schrödinger KNIME Extensions. EE UU: New York, NY, USA 2021.

[22] Schrödinger, L. Schrödinger Release 2022-4: Glide. EE UU: New York, NY, USA 2021.

[23] Galeana-Ascencio RA, Mendieta L, Limon DI, Gnecco D, Terán JL, Orea ML, et al. β-Secretase-1: In Silico Drug Reposition for Alzheimer's Disease. International Journal of Molecular Sciences 2023, 24:8164. https://doi.org/10.3390/ijms24098164.

[24] Schrödinger, L. Schrödinger Release 2022-4: QikProp. EE UU: New York, NY, USA 2021.

[25] Teo KC, Ho S-L. Monoamine oxidase-B (MAO-B) inhibitors: implications for disease-modification in Parkinson's disease. Transl Neurodegener 2013, 2:19. https://doi.org/10.1186/2047-9158-2-19.

[26] Heger J, Hirschhäuser C, Bornbaum J, Sydykov A, Dempfle A, Schneider A, et al. Cardiomyocytes-specific deletion of monoamine oxidase B reduces irreversible myocardial ischemia/reperfusion injury. Free Radical Biology and Medicine 2021, 165:14–23. https://doi.org/10.1016/j.freeradbiomed.2021.01.020.

[27] Manzoor S, Hoda N. A comprehensive review of monoamine oxidase inhibitors as Anti-Alzheimer's disease agents: A review. European Journal of Medicinal Chemistry 2020, 206:112787. https://doi.org/10.1016/j.ejmech.2020.112787.

[28] Happe K. Monoamine Oxidase Inhibitors. xPharm: The Comprehensive Pharmacology Reference, Elsevier, 2007, p. 1–3. https://doi.org/10.1016/B978-008055232-3.61002-5.

[29] Bhat A, Tan V, Heng B, Chow S, Basappa S, Essa MM, et al. Papaverine, a Phosphodiesterase 10A Inhibitor, Ameliorates Quinolinic Acid-Induced Synaptotoxicity in Human Cortical Neurons. Neurotox Res 2021, 39:1238–50. https://doi.org/10.1007/s12640-021-00368-4.

[30] Sharma B, Bhattacherjee D, Zyryanov GV, Purohit R. An insight from computational approach to explore novel, high-affinity phosphodiesterase 10A inhibitors for neurological disorders. Journal of Biomolecular Structure and Dynamics 2023, 41:9424–36. https://doi.org/10.1080/07391102.2022.2141895.

[31] Birjandi SZ, Abduljawad N, Nair S, Dehghani M, Suzuki K, Kimura H, et al. Phosphodiesterase 10A Inhibition Leads to Brain Region-Specific Recovery Based on Stroke Type. Transl Stroke Res 2021, 12:303–15. https://doi.org/10.1007/s12975-020-00819-8.

[32] Lenda T, Ossowska K, Berghauzen-Maciejewska K, Matłoka M, Pieczykolan J, Wieczorek M, et al. Antiparkinsonian-like effects of CPL500036, a novel selective inhibitor of phosphodiesterase 10A, in the unilateral rat model of Parkinson's disease. European Journal of Pharmacology 2021, 910:174460. https://doi.org/10.1016/j.ejphar.2021.174460.

[33] Sahin I, Eturi A, De Souza A, Pamarthy S, Tavora F, Giles FJ, et al. Glycogen synthase kinase-3 beta inhibitors as novel cancer treatments and modulators of antitumor immune responses. Cancer Biology & Therapy 2019, 20:1047–56. https://doi.org/10.1080/15384047.2019.1595283.

[34] Noori T, Dehpour AR, Sureda A, Fakhri S, Sobarzo-Sanchez E, Farzaei MH, et al. The role of glycogen synthase kinase 3 beta in multiple sclerosis. Biomedicine & Pharmacotherapy 2020, 132:110874. https://doi.org/10.1016/j.biopha.2020.110874.

[35] Yu H, Xiong M, Zhang Z. The role of glycogen synthase kinase 3 beta in neurodegenerative diseases. Front Mol Neurosci 2023, 16:1209703. https://doi.org/10.3389/fnmol.2023.1209703.

[36] Golde TE, Koo EH, Felsenstein KM, Osborne BA, Miele L. γ-Secretase inhibitors and modulators. Biochimica et Biophysica Acta (BBA) - Biomembranes 2013, 1828:2898–907. https://doi.org/10.1016/j.bbamem.2013.06.005.

[37] Kimberly WT, Wolfe MS. Identity and function of γ-secretase. J of Neuroscience Research 2003, 74:353–60. https://doi.org/10.1002/jnr.10736.

[38] Panza F, Frisardi V, Imbimbo BP, Capurso C, Logroscino G, Sancarlo D, et al. REVIEW: γ-Secretase Inhibitors for the Treatment of Alzheimer's Disease: The Current State. CNS Neuroscience & Therapeutics 2010, 16:272–84. https://doi.org/10.1111/j.1755-5949.2010.00164.x.

[39] Selkoe D. β-secretase inhibitors for Alzheimer's disease: heading in the wrong direction? The Lancet Neurology 2019, 18:624–6. https://doi.org/10.1016/S1474-4422(19)30202-9.

[40] Taylor HA, Przemylska L, Clavane EM, Meakin PJ. BACE1: More than just a β-secretase. Obesity Reviews 2022, 23:e13430. https://doi.org/10.1111/obr.13430.

[41] Zorn A, Baillie G. Phosphodiesterase 7 as a therapeutic target – Where are we now? Cellular Signalling 2023, 108:110689. https://doi.org/10.1016/j.cellsig.2023.110689.

[42] Gould NL, Scherer GR, Carvalho S, Shurrush K, Kayyal H, Edry E, et al. Specific quinone reductase 2 inhibitors reduce metabolic burden and reverse Alzheimer's disease phenotype in mice. J Clin Invest 2023, 133. https://doi.org/10.1172/JCI162120.

[43] Boutin JA, Bouillaud F, Janda E, Gacsalyi I, Guillaumet G, Hirsch EC, et al. S29434, a Quinone Reductase 2 Inhibitor: Main Biochemical and Cellular Characterization. Mol Pharmacol 2019, 95:269–85. https://doi.org/10.1124/mol.118.114231.

[44] Voronin MV, Kadnikov IA, Zainullina LF, Logvinov IO, Verbovaya ER, Antipova TA, et al. Neuroprotective Properties of Quinone Reductase 2 Inhibitor M-11, a 2-Mercaptobenzimidazole Derivative. International Journal of Molecular Sciences 2021, 22:13061. https://doi.org/10.3390/ijms222313061.

[45] Cacabelos R, Torrellas C. Pharmacoepigenomics. Medical Epigenetics, Elsevier, 2016, p. 585–617. https://doi.org/10.1016/B978-0-12-803239-8.00032-6.

[46] Zurier RB. Prostaglandins, Leukotrienes, and Related Compounds. Kelley and Firestein's Textbook of Rheumatology, Elsevier, 2017, p. 366-383.e3. https://doi.org/10.1016/B978-0-323-31696-5.00024-3.

[47] Choi S-H, Aid S, Bosetti F. The distinct roles of cyclooxygenase-1 and -2 in neuroinflammation: implications for translational research. Trends in Pharmacological Sciences 2009, 30:174–81. https://doi.org/10.1016/j.tips.2009.01.002.

[48] Rawat C, Kukal S, Dahiya UR, Kukreti R. Cyclooxygenase-2 (COX-2) inhibitors: future therapeutic strategies for epilepsy management. Journal of Neuroinflammation 2019, 16:197. https://doi.org/10.1186/s12974-019-1592-3.

[49] Kirkby NS, Chan MV, Zaiss AK, Garcia-Vaz E, Jiao J, Berglund LM, et al. Systematic study of constitutive cyclooxygenase-2 expression: Role of NF-κB and NFAT transcriptional pathways. Proc Natl Acad Sci USA 2016, 113:434–9. https://doi.org/10.1073/pnas.1517642113.

[50] Yang X, Li M, Jiang J, Hu X, Qing Y, Sun L, et al. Dysregulation of phospholipase and cyclooxygenase expression is involved in Schizophrenia. eBioMedicine 2021, 64. https://doi.org/10.1016/j.ebiom.2021.103239.

[51] Christensen SB, DeWolf WE, Ryan MD, Torphy TJ. 13 - Molecular Aspects of Inhibitor Interaction with PDE4. In: Schudt C, Dent G, Rabe KF, editors. Phosphodiesterase Inhibitors, San Diego: Academic Press, 1996, p. 185–207. https://doi.org/10.1016/B978-012210720-7/50015-0.

[52] Azam MA, Tripuraneni NS. Selective Phosphodiesterase 4B Inhibitors: A Review. Sci Pharm 2014, 82:453–81. https://doi.org/10.3797/scipharm.1404-08.

[53] Dipeptidyl Peptidase IV - an overview | ScienceDirect Topics n.d. https://www.sciencedirect.com/topics/medicine-and-dentistry/dipeptidyl-peptidase-iv (accessed December 10, 2023).

[54] Ikeda Y, Nagase N, Tsuji A, Kitagishi Y, Matsuda S. Neuroprotection by dipeptidyl-peptidase-4 inhibitors and glucagon-like peptide-1 analogs via the modulation of AKT-signaling pathway in Alzheimer's disease. World J Biol Chem 2021, 12:104–13. https://doi.org/10.4331/wjbc.v12.i6.104.