GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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In silico cancer potential of 2-pyrrolidinones from marine origin

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GSC Biological and Pharmaceutical Sciences, 2025, 30(03), 099-111

Publication history: Received on 26 January 2025; revised on 03 March 2025; accepted on 05 March 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.30.3.0093

Abstract

2-pyrrolidinones present a great variability of biological activities, particularly those of marine origin have given rise to a great diversity of these, so from them, through studies of structural similarity, molecular docking and ADMETx analysis, the potential carcinogenic activity of a library of 33 2-pyrrolidines from various marine organisms was found. Derived from this study, several compounds, such as Cephalimysins M, Cephalimysins N, Amycolactam and Spongialactam A, were shown to be excellent candidates against cancer, via JAK2, JAK3, PDE10A, MAPK14, PDE4A, PDE4B and EGFR, functioning at a mono or multi-target level, without negatively affecting the central nervous system and with low possible toxic effects.

Keywords: 2-pyrrolidinones; Cancer potential activity; Marine organisms; *In silico* studies

1. Introduction

Among the numerous classes of natural products isolated from marine organisms, structures that contain 2-pyrrolidinones ring system are a fascinating group of molecules that possess diverse pharmacological activities such as anticancer, antibacterial, antifungal, and anticonvulsant [1]. In addition, these structures can be characterized as simple heterocycles or more complex systems, possibly containing long chains of fused polycyclic skeletons. For example; L-tenuazonic acid, Dysidamide B [2], Smenamide A [3], Salinosporamide A [4], Miclosclerodermis A [5], Dolastatin 15 [6], etc (Figure 1).

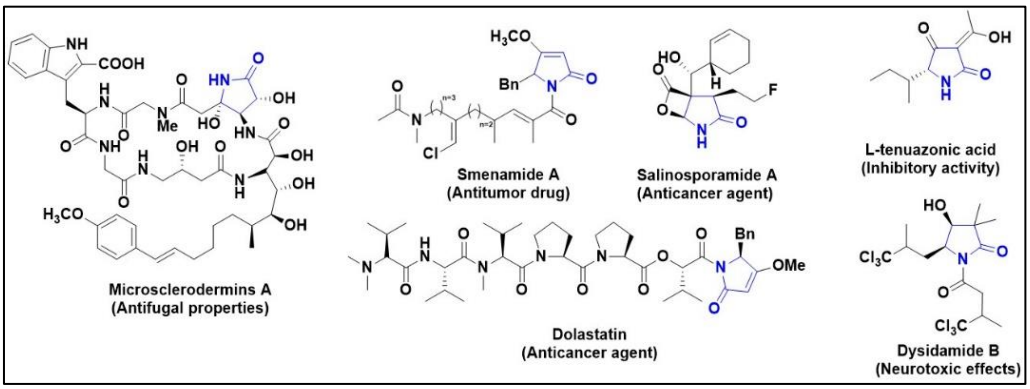

Figure 1 The structure of 2-pyrrolidonones from marina origin possesses diverse pharmacological activities

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Due to the importance of natural products isolated from marine organisms containing 2-pyrrolidine heterocycle, because is of interest to outline these structures towards biological application, at this point, the bioinformatics tools that allow to predict different biological activities towards a set of natural products [7–9], through prediction of structural similarity [10] and subsequent molecular coupling in the selected targets towards different pathologies, and biological systems, such as neurodegenerative diseases [8,11], infections [12,13], cancer [14], among others. This is why it is reported an *in silico* study on the 33 selected 2-pyrrolidinones as a cancer potential activity isolated from diverse marine organisms. To this end, the chosen molecules are depicted in Figure 2.

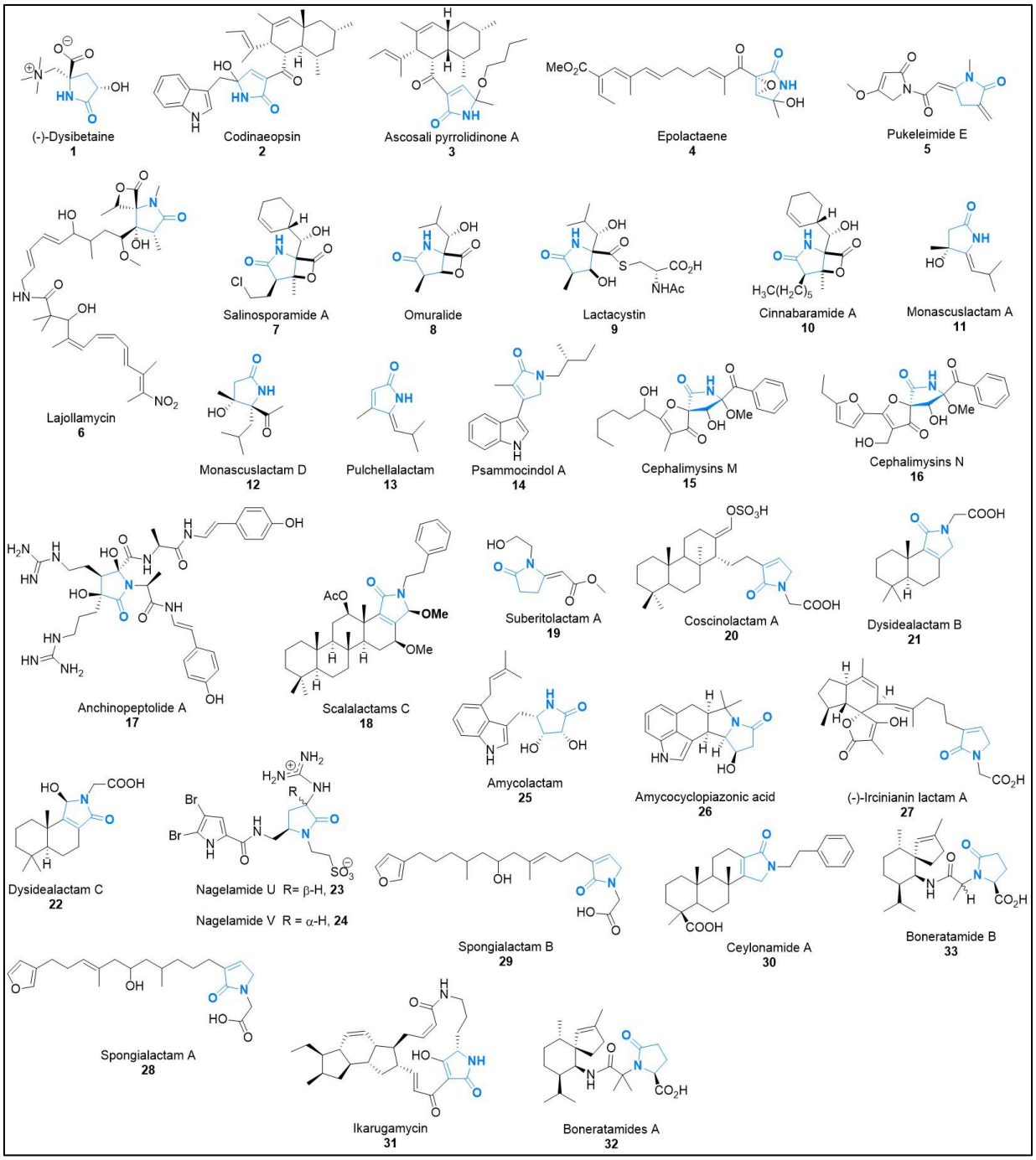

Figure 2. 2-pyrrolidinones selected molecules isolated from marine organisms for *in silico* studies [15–33]

2. Material and methods

2.1. Studies of similar structures

From the 33 2-pyrrolidinone structures obtained from a bibliographic review, their SMILE codes were generated and, using the SwissTargetPrediction platform [10], a cumulative frequency diagram for p≠0 was obtained as an inclusion criterion, according to the previously reported protocol [8]. For the selection of molecular targets, a bibliographic review of the molecular targets obtained with a frequency higher than the average was carried out and related to different types of cancer [34] as the object of study.

2.2. Molecular Docking studies

Ligand and reference drug preparation was performed in two stages. In the first stage, the structures drawn in 2D Sketcher were minimized for a water solvent system in the macromodel module; the second stage was performed in the LigPrep module at physiological pH conditions, preserving the original stereochemistry reported for each 2-pyrrolidinone.

Protein preparation for docking used, JAK1 (4EHZ) [35], JAK2 (3KRR) [36], JAK3 (1YVJ) [37], MAPK14 (6ZWP) [38], KDR (6GQO) [39], EGFR (8A2A) [40], PDE4A (2QYK) [41], PDE4B (4MYQ) [42], PDE10A (6IJH) [43] crystals obtained from the protein data bank, using Baricitinib [44], Fedratinib [45], Tofacitinib [46], Skepinone-L [47], Sorafenib [48], Erlotinib [49], PDE4i [50], Pentoxifylline [51], Dipyridamole [52] as the reference drug, respectively. Subsequently, the preparation was carried out at pH 7.4, hydrogen bonds were optimized, and the structure was minimized with OPLS4 as a force field in the protein preparation module [53]. Molecular docking was performed in the Glide module [54] with an SP level of accuracy, allowing free rotation of the amino acids in the catalytic site as a flexible docking of protein and ligand according to the previously reported protocol [55].

2.3. ADMETx Studies

From the minimized structures and brought to physiological conditions, an ADMETx prediction analysis was performed with the QikProp module [56] of the Schrodinger platform.

3. Results and discussion

Structural similarity analysis shows a wide variety of proteins with which 2-pyrrolidinones can interact (Figure 3), showing their great pharmacological potential, finding proteins associated with pathologies where metabolic and hormonal deregulation is present (HSD11B1, AR, CA2, NR3C1, HMGCR), proteins associated with neurodegenerative diseases (PSEN2, ADORA1, PARP1, CNR1/2, FABP4, LRRK2) and highlighting proteins associated with proliferative diseases such as cancer (red sticks), of which the JAK1, JAK2 and JAK3 subgroup can be identified, associated with the regulation of proliferation via STAT activation, in this same vein MAPK14 is also presented, the second subgroup of interest is the EGFR and KDR pathway associated with the viability of tumor cells and the third associated with phosphodiesterase PDE4 and PDE10.

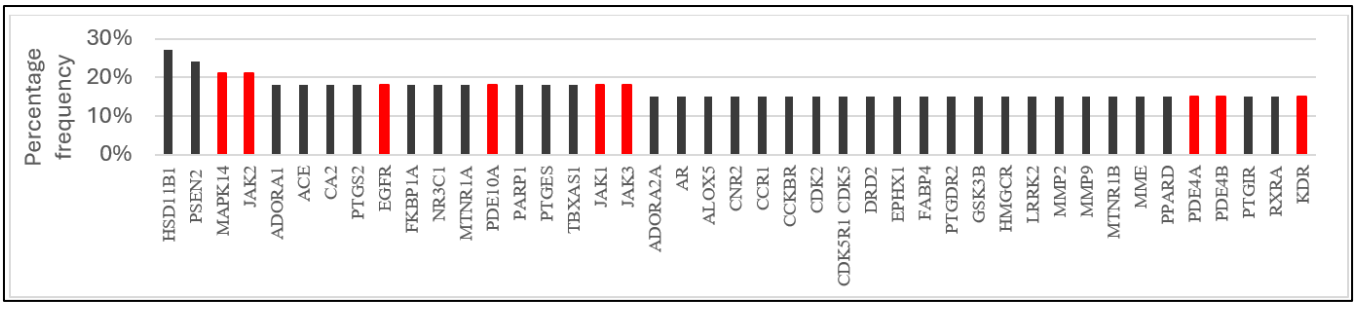

Figure 3 Diagram of percentage frequency protein of 2-pyrrolidinones from marine origin by SwissTargetPrediction

Cancer as a pathology is quite broad, especially the type of cancer; the selected targets are present in more than one type of cancer (Table 1), highlighting the potential, converging in breast, cervical, endometrial, gastric, and lung cancer, demonstrating the broad potential of these derivatives. However, the possible interaction is not sufficient to determine good treatment options for this group from reference drugs; through molecular docking calculations, it is possible to determine if they are better than these.

Table 1 Diseases, inhibitors to Cancer protein related to 2-pyrrolidinones from marine origin by SwissTargetPrediction

Target protein	Common name	UniProt ID	Cancer type related by docking analyses	Inhibitors	[Ref.]
Tyrosine-protein kinase JAK1	JAK1	P23458	Breast cancer, endometrial cancer	Baricitinib,	[44,57]
Tyrosine-protein kinase JAK2	JAK2	O60674	Colon cancer, pancreatic cancer, cervical cancer	Fedratinib	[45,58,59]
Tyrosine-protein kinase JAK3	JAK3	P52333	Glioblastoma, leukemia	Tofacitinib	[46,60–62]
MAP kinase p38α	MAPK14	Q16539	Endometrial cancer, gastric cancer	Skepinone-L	[47,63,64]
Vascular endothelial growth factor receptor 2	KDR	P35968	Gastric cancer, breast cancer	Sorafenib	[48,65,66]
Epidermal growth factor receptor erbB1	EGFR	P00533	Non-small cell lung cancer	Erlotinib	[49,67]
Phosphodiesterase 4A	PDE4A	P27815	Ovarian cancer, thyroid carcinoma	PDE4Ai	[50,68,69]
Phosphodiesterase 4B	PDE4B	Q07343	Gastric cancer,	Pentoxifylline	[51,70]
Phosphodiesterase 10A	PDE10A	Q9Y233	Ovarian cancer	Dipyridamole	[52,71]

Molecular docking results demonstrate degrees of interaction in all pathways (Table 2); however, when compared with experimental inhibitors, the JAK2, JAK3, MAPK14, EGFR, PDE4A/B, and PDE10A pathways become of greater interest. This is because, for JAK1 and KDR, none of the compounds surpasses any reference drug. Regarding coupling, 2-pyrrolidinones can be divided into two groups: those that are selective to a type of protein and those that are multitarget. In the first group, they have 2, 4, 10, 15, and 20 that present a better coupling than Dipyridamole, the reference drug inhibitor of this protein. In terms of a multitarget, 13, 16, 19, 24, and 25 stand out, which surpass the reference drug in two targets, in three targets, 5, 17, and 28 in four targets, 14, 23, and 29 in five targets, highlighting the multitarget potential of these compounds. The JAK2 and PDE10A pathway stands out, where a greater amount of pyrrolidinones surpass the reference drug. A second trend of study for these molecules is that the pyrrolidinone group is exposed to favor exposure, given that this group generates dominant interactions in the catalytic sites of each enzyme studied.

Table 2 Docking Score of 2-pyrrolidinones in protein selected related to cancer.

Compound	JAK1	JAK2	JAK3	MAPK14	EGFR	KDR	PDE4A	PDE4B	PDE10A
1	-5.101	-4.479	-4.419	-5.068	-6.294	-5.212	-4.890	-4.939	-4.934
2	-5.239	-4.388	-6.620	N.I.	N.I.	N.I.	-5.870	N.I.	-6.846
3	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
4	-6.899	-5.289	-6.897	-7.003	-7.892	-5.542	-5.880	-5.822	-6.043
5	-5.491	-6.777	-7.195	-7.671	-7.368	-7.763	-6.306	-7.075	-7.210
6	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
7	-6.004	-5.078	-5.439	-6.992	-6.713	-5.703	-5.189	-6.053	-5.432
8	-4.911	-4.724	-5.487	-5.742	-6.459	-6.502	-4.720	-6.031	-3.949
9	-6.392	-4.471	-4.893	N.I.	N.I.	-2.788	-3.370	N.I.	-3.228
10	-4.399	-4.890	-5.762	-6.202	-4.775	-5.566	-5.452	-5.646	-6.082
11	-5.327	-4.923	-6.196	-5.686	-6.041	-4.847	-6.266	-4.777	-5.392
12	-5.430	-5.080	-5.556	-5.261	-6.615	-5.516	-4.647	-4.009	-5.222
13	-5.626	-5.667	-5.890	-5.861	-5.877	-6.327	-5.506	-6.156	-6.500

14	-6.318	-4.688	-7.213	-8.790	-8.109	-9.434	-6.430	-8.049	-7.293
15	-3.327	-4.905	-6.745	-4.767	-3.865	-5.506	-4.755	-7.178	-7.505
16	-4.629	-3.457	-6.224	-2.430	-5.120	-4.426	-5.221	-8.458	-7.198
17	-5.991	-7.086	-10.578	-5.819	-7.422	-6.174	-9.615	N.I.	-10.106
18	N.I.	N.I.	-5.440	N.I.	-5.397	N.I.	-4.916	N.I.	-4.825
19	-5.174	-5.367	-5.589	-5.374	-6.307	-5.559	-5.261	-7.010	-6.298
20	N.I.	-4.758	-4.023	-5.435	N.I.	-5.744	-6.130	N.I.	-6.426
21	-2.859	-3.301	-4.041	-4.420	-2.169	-3.653	-4.765	N.I.	-2.849
22	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
23	-6.965	-6.219	-7.862	-6.559	-8.760	-5.542	-5.618	-7.812	-6.346
24	-7.326	-6.876	-6.736	-4.271	-7.234	-7.055	-5.298	-7.580	-6.487
25	-6.525	-5.456	-6.604	-4.879	-6.933	-5.578	-6.197	-6.877	-6.314
26	-5.462	-4.211	-5.513	N.I.	-4.494	-5.383	-4.784	N.I.	-4.818
27	-2.570	-3.397	-2.046	-2.208	-2.739	-3.769	-6.412	N.I.	-3.369
28	-6.587	-6.132	-6.806	-8.595	-7.628	-7.161	-7.788	-7.603	-8.105
29	-6.796	-6.226	-6.017	-8.438	-8.729	-8.996	-7.667	-7.377	-6.668
30	-3.436	-3.961	-6.680	-5.504	-7.127	-7.461	-5.258	N.I.	-4.627
31	-2.520	-2.212	-3.817	N.I.	-1.988	-4.257	-5.134	N.I.	-4.280
32	N.I.	-4.188	-4.791	N.I.	N.I.	N.I.	-5.249	N.I.	-4.519
33	N.I.	-4.948	-4.129	N.I.	N.I.	N.I.	N.I.	N.I.	-5.158
Reference*	-7.344	-5.344	-7.785	-7.289	-8.055	-11.581	-6.415	-7.808	-5.579

* References: Baricitinib (JAK1), Fedratinib (JAK2), Tofacitinib (JAK3), Skepinone-L (MAPK14), Sorafenib (KDR), Erlotinib (EGFR), PDE4Ai (PDE4A), Pentoxifylline (PDE4B), Dipyridamole (PDE10A)
Ni. Not interaction encounter in catalytic site

The molecules with the highest interaction are 23 and 29 (Figure 4), being in JAK2, PDE10A and EGFR for both molecules; in JAK2 we can denote that the 2-pyrrolidinone nucleus acts through polar interaction towards Arg980 and Asn859 like the reference inhibitor, for PDE10A, they predominate equally by interactions by hydrogen bridge through the hydrated site with Asp674 and Tyr524, for 23. In contrast, in 29, the interaction is direct with Ser573 and Asn572, denoting the polar substituent in both molecules, which facilitates the coupling, particularly in 23 by forming a bridge exited with the Mg of the catalytic site.

For EGFR, the 2-pyrridinonic nucleus participates through a negative charge type interaction towards the electrophilic sites of the structure. In this case, it is the substituents that favor the coupling towards Glu749 and Ser752 respectively, as well as the reference inhibitor where the lipophilic site is occupied by these molecules to avoid this pathway. Regarding the differences between 23 and 29 concerning the molecular targets, 29 is for MAPK14 and PDE4A, while 23 results in PDE4B and JAK3.

For MAPK14, 23 docks at the same site as the reference inhibitor, changing in that 2-pyrrolidinone is dominated by negative charge interactions, contrary to the reference inhibitor, which is hydrophobic, which explains the increase in docking by 23 as well as the interaction with Met109, Glu71 and Arg67 by hydrogen bonding.

For 23 in PDE4A, polar interactions predominate at the terminal chain of the substituent, while they are hydrophobic where 2-pyrrolidinone is, as well as the aromatic ring on the part of the reference inhibitor, increasing the docking due to the formation of hydrogen bonds at the hydrated site towards Try371 and Asp530. For the case of 29 in PDE4B the 2-pyrrolidinone nucleus forms the hydrogen bond with Gln615 like the reference, improving given the guanidinium substituent with hydrogen bond interactions with Thr579 and Asn567.

Finally, for the case of 29 with JAK3 the hydrophobic site couples with the 2-pyrrolidinone region but it is the polar substituents that favor the formation of hydrogen bonds with Cys909, Leu828, Leu905, Asp967, Asn954 and Arg953, the latter being the one repeated with the reference inhibitor, explaining the increase in coupling.

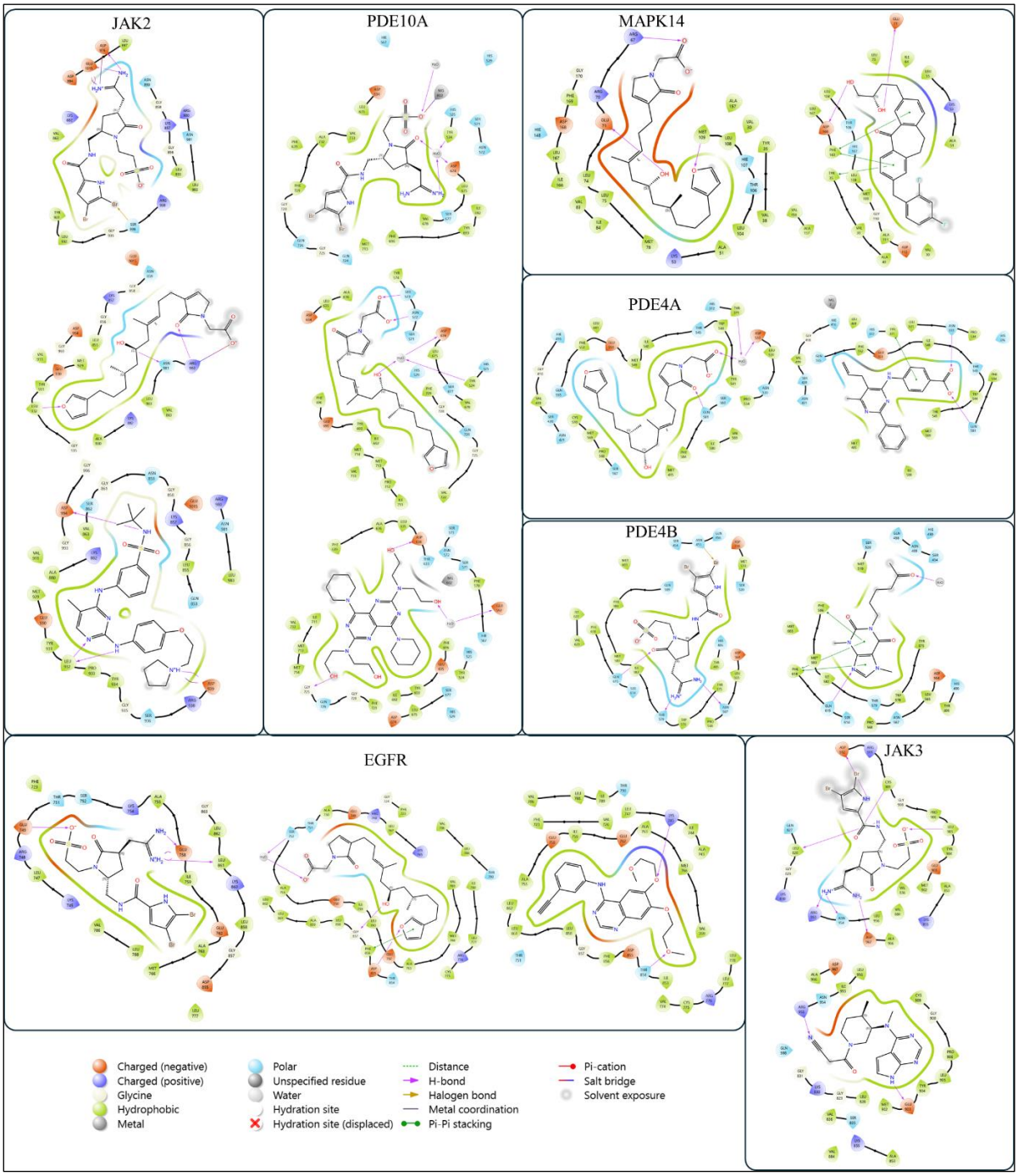

Figure 4 2D interaction of Nagelamide U (23) and 29-Spongialactam B (29) in proteins with *in silico* potential and drug references for each

In terms of JAK2 and PDE10A with an anticancer potential by pyrrolidinones, Figure 5 shows the couplings by the compounds with the greatest potential in these molecular targets, where it stands out the versatility of the substituents in the 2-pyrrolidinone ring, from small substituents to larger substituents, depending on their polarity. In the case of JAK2, in the molecules with small substituents, the nucleus is placed near Ser936 to occupy the active site of this pathway, as in the case of 5, 17 and 19, while for large and polar substituents the ring moves to the polar region and increases the hydrogen bond formation with Ser936, Asp939, Asn859 and Arg980 as a common denominator of interaction towards the catalytic site of JAK2.

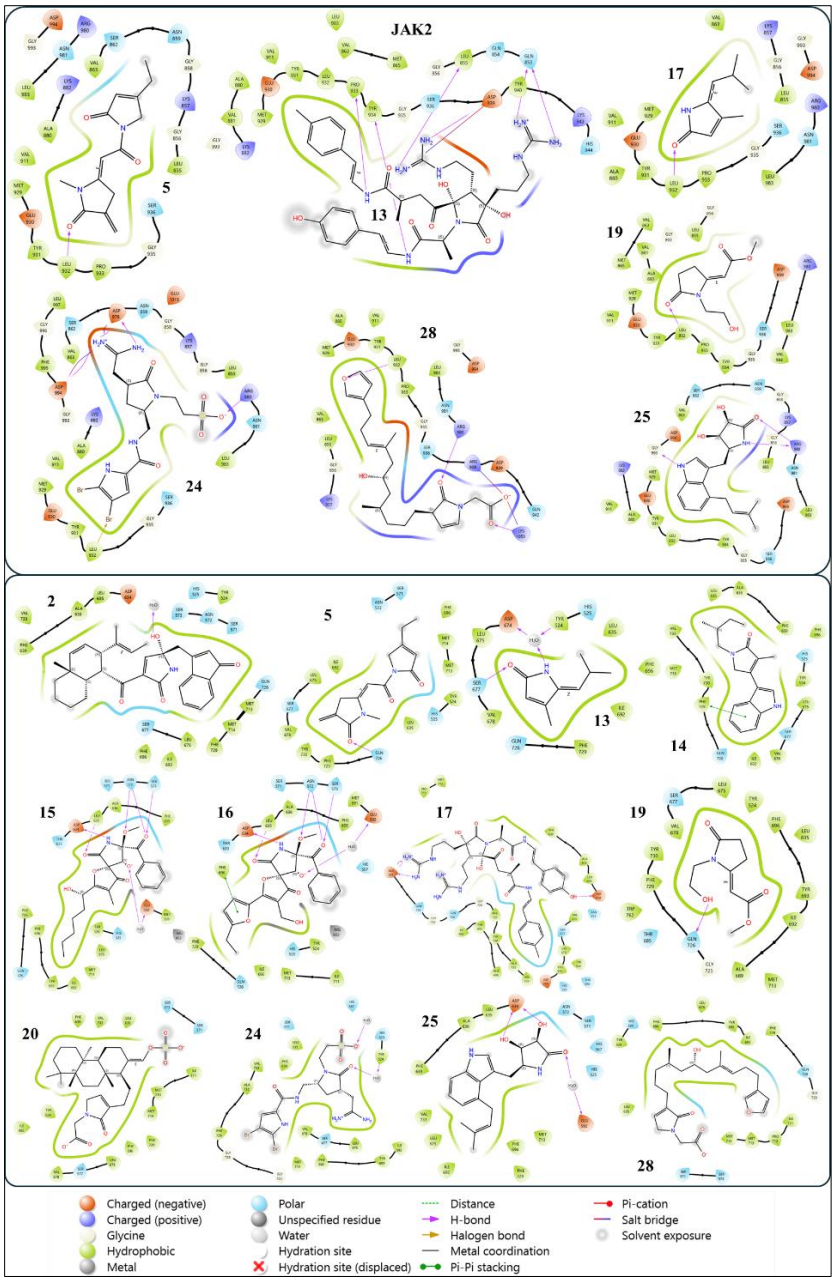

Figure 5 Best 2-pyrrolidinones 2D interactions in JAK2 and PDE10A

For the analysis on PDE10A it can be observed that for small molecules the 2-pyrrolidine cycle gives to the formation of hydrogen bonds with Asp674, as well as interactions of a hydrophobic nature. In contrast, for large molecules, it depends on the type of substituent for the cases of 2, 20, and 28, which are of a hydrophobic nature. In contrast, the interactions increase for those with polar chain groups, given the formation of hydrogen bonds with Asn572 and Ser573. Denoting that the 2-pyrrolidine ring is an excellent structural ring for the formation of proliferation-regulating compounds in cancer, given the deregulation that can be generated by these pathways.

Finally, it is important to know the ADMETx properties for biological potential to determine its viability against pathologies such as cancer. Table 3 shows the results of the molecules with the highest coupling, both mono-target and multi-target, the pharmacokinetic profile established by the prediction of ADMETx properties of this group of molecules shows some with properties in and out to a great extent within or little of the recommended intervale, such as 2, 4, 5, 10, 13, 14, 17, 19-21, 23 and 24; and molecules in which all the properties analyzed are within the recommended range and with the best possible results, being 15, 16, 25, 28, 29; using this analysis as a selection criterion, the latter type of molecule is of great interest, in which the predicted value of the Linpinski's Rules Violations is 0, and consequently the predicted values of each individual parameters, molecular weight, QPlogPo/w, hydrogen bond donor/acceptor, are also

within the recommended intervale; the number of reactive functional groups that can produce reactivity and toxicity is 0, which indicates that the 2-pyrrolidinic ring is not recognized as a toxicophore.

Table 3 ADMETx predictions by selected 2-pyrrolidinones with high anticancer potential

Compound	CNS	#rtvFG	HOA	MW	QPlogPo /w	HBD/A	Lipinski's Rule Violations	#metab	QPlog HERG	Jm
2	-2	0	1	471.595	5.209	1.0/6.25	1	6	-5.732	0.000
4	-2	5	3	389.447	2.256	1.0/8.25	0	6	-3.993	0.002
5	-2	1	3	260.292	1.408	0.0/6.0	0	3	-4.757	0.042
10	-2	1	3	335.442	2.304	0.25/6.45	0	4	-3.286	0.500
13	0	0	3	151.208	1.738	1.0/2.5	0	2	-3.437	0.297
14	0	0	3	282.385	4.116	1.0/3.0	0	2	-4.978	0.039
15	-2	0	3	417.458	1.612	1.0/9.4	0	3	-3.248	0.126
16	-2	0	3	427.41	1.66	0.0/8.9	0	4	-4.064	0.219
17	-2	0	1	719.839	0.653	13.0/16.25	3	9	-6.659	0.000
19	-2	1	2	199.206	0.036	1.0/6.7	0	3	-3.634	1.831
20	-2	0	1	537.71	4.265	2.0/9.5	1	4	-1.107	0.000
21	-1	0	3	291.389	2.869	1.0/5.0	0	3	-0.883	0.000
23	-2	0	2	529.203	0.116	6.0/11.0	2	3	-1.852	0.000
24	-2	0	1	529.203	0.102	6.0/11.0	2	6	-3.240	0.550
25	-2	0	3	314.383	1.28	4.0/5.9	0	8	-3.597	0.007
28	-2	0	3	403.517	4.523	2.0/7.2	0	8	-4.014	0.005
29	-2	0	3	403.517	4.598	2.0/7.2	0	6	-5.732	0.000

CNS, Predicted central nervous system activity on a −2 (inactive) to +2 (active) scale. #rtvFG, Number of reactive functional groups, HOA, Predicted qualitative human oral absorption, MW, Molecular weight of the molecule, QPlogPo/w, Predicted octanol/water partition coefficient., HB D/A, Estimated number of hydrogen bonds that would be donated/ accepted by the solute to water molecules in an aqueous solution, #metab, Number of likely metabolic reactions, QPlogHERG, Predicted IC50 value for blockage of HERG K+ channels. Jm, Predicted maximum transdermal transport rate.

The predicted qualitative human oral absorption is the highest with a value of 3, and finally, the predictive central nervous system (CNS) activity is -2, again being the best value within the range, indicating that the compounds are central nervous system inactive, making them excellent candidates against cancer without presenting adverse effects on the central nervous system. Regarding to selectivity of the selected compounds, only one compound is selective for one protein, and most of them are multi-target type; being compound 15 is selective for one target, compounds 16 and 25 in two targets, not having a compound in three targets, compound 28 in four targets and compound 29 in five targets, making these structures excellent templates for structural optimization towards the design and synthesis of new 2-pyrrolidine derivatives against cancer.

4. Conclusion

33 2-pyrrolidinones isolated from marine organisms were *in silico* studied and showed great pharmacological potential, highlighting proteins associated with proliferative diseases such as cancer. The 2-pyrrolidine unit is an excellent structural ring for forming proliferation-regulating compounds in cancer, given the deregulation these pathways can generate from small substituents to larger substituents, depending on their polarity.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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