Original Article

Analysis of Interaction between Twenty-Seven Pyrimidinone Derivatives with XIAP Using a Theoretical Model

Abstract

For several years, several drugs have been used to treat different types of cancer; however, some of these drugs can cause side effects, such as high blood pressure, liver damage, and erectile dysfunction. In the search for new therapeutic alternatives, some compounds have been developed for the treatment of this clinical pathology; however, the interaction of these drugs with some biomolecules involved in the development of cancer is very unclear. Analyzing this data, this investigation aimed to evaluate the possible theoretical interaction of some pyrimidinone derivatives (compounds 1 to 27) on the X-linked inhibitor of apoptosis protein (XIAP) involved in cancer using the Docking model. The results showed that some pyrimidinone derivatives (1-6, 10, 11, 14, 15, 22-24, 26, and 27) could interact with the XIAP protein surface. In conclusion, these data suggest that some pyrimidinone derivatives can produce changes in the biological activity of XIAP. Therefore, these pyrimidinone derivatives could be good candidates to treat cancer.

Keywords: *Cancer, Pyrimidinone derivatives, XIAP, Docking*

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Introduction

Several data indicate that cancer is one of the main causes of death worldwide, which translates into a decreased life expectancy of the population.[1-9] This clinical pathology has been increasing in both developed and developing countries due to various factors involved such as aging and population growth.[10-13] In addition, some biomolecular signaling systems are activated to produce cancer; for example, there are some studies indicating that X-linked inhibitors of apoptosis protein (XIAP) may regulate cell death signaling pathways through the binding and inhibition of caspases.[14-16] In addition, other data suggest that XIAP may be involved in the development of several types of cancer.[17-23] In this way, some drugs have been developed; for example, a study showed that Clioquinol (5-chloro-7-iodo-8-quinolinol) induces cytoplasmic clearance of the X-linked inhibitor of apoptosis protein (XIAP) translated as a decrease of prostate cancer.[24] Other data showed that compound (3S,6S,9R,10aR)-6-((S)-2-(Methylamino)propanamido)-5-oxo 9-(2-phenylacetami-do)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)decahydropyrrolo [1,2-a]azocine-3-carboxamide decreases the growth of cancer cells (MDA-MB-231) through XIAP inhibition.[25] Besides, a report displayed the synthesis of a series of benzodiazepinones as XIAP selective inhibitors for the treatment of cancer using an in vitro model.[26] In addition, a study carried out on human gastric cancer cell lines AGS (adenocarcinoma), KATO-III (signet-ring cell carcinoma), and NCI-N87 (gastric carcinoma) showed that Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) can decrease the expression of XIAP translated as cell cycle arrest at the S and G2/M phases and apoptosis.[27] Furthermore, a study showed that embelin acts as an inhibitor of XIAP using human prostate cancer cell lines (PC-3, LNCap, CL-1, DU-145).[27] Other data show that some diazabicyclic derivatives inhibit the expression of XIAP using some cancer cell lines such as MDA-MB-231 and SK-OV-3.[28] All these data suggest that some drugs can decrease the expression of XIAP, which translates as changes in the growth of some cancer cells; however, there is little information in the literature on the interaction of pyrimidinone with XIAP protein.

Perhaps this is due to the diverse experimental designs that focus on multiple

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molecular mechanisms involved in cancer. Analyzing this hypothesis, the objective of this study was to evaluate the interaction of twenty-seven pyrimidinone derivatives with XIAP using a theoretical model.

Materials and Methods

Twenty-seven pyrimidinone derivatives previously reported in PubChem.[29] **(Figure 1)** were used to evaluate the possible interaction with X-linked inhibitor of apoptosis protein (XIAP) as follows:

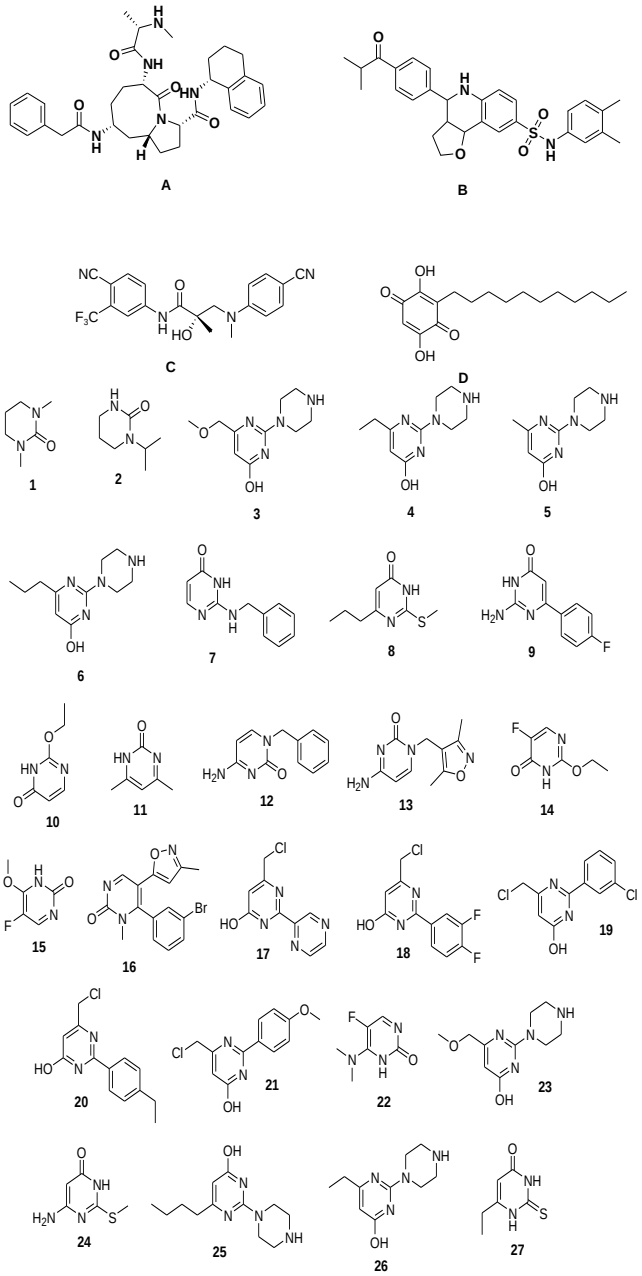

Figure 1. Chemical structure of XIAP inhibitors (A, B, and C) and pyrimidinone derivatives (1-27)

A = (3*S*,6*S*,9*R*,10*AR*)-6-((*S*)-2-(Methylamino)propanamido)-5-oxo-9-(2-phenylacetami- do)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)decahydropyrrolo[1,2-a]azo-cine-3-car-boxamide.[25]
B = *N*-(3,4-Dimethylphenyl)-4-(4-isobutyrylphenyl)-2,3,3a,4,5,9bhexahydrofuro [3,2-c]quinoline-8-sulfonamide.[30]
C = (*S*)-N-(4-cyano-3-(trifluoromethyl)phenyl)-3-((4-cyanophenyl)(methyl)amino)-2-hydroxy-2-methylpropanamide).[31]
1 = 1,3-Dimethyl-3,4,5,6,-tetrahydro-2(1H)-pyrimidinone
2 = 1-isopropyltetrahydro-2(1H)-pyrimidinone
3 = 2-(1,4-Diazepan-1-yl)-6-(methoxymethyl)-4(3H)-pyrimidinone
4 = 2-(1,4-Diazepan-1-yl)-6-ethyl-4(3H)-pyrimidinone
5 = 2-(1,4-Diazepan-1-yl)-6-methyl-4(3H)-pyrimidinone
6 = 2-(1,4-Diazepan-1-yl)-6-propyl-4(3H)-pyrimidinone
7= 2-(Benzylamino)-4(3H)-Pyrimidinone
8= 2-(Methylsulfanyl)-6-propyl-4(3H)-pyrimidinone
9= 2-Amino-6-(4-fluorophenyl)-4(3H)-pyrimidinone
10= 2-ethoxy-4(3H)-pyrimidinone
11= 4,6-Dimethyl-2(1H)-Pyrimidinone
12= 4-Amino-1-benzyl-2(1H)-pyrimidinone
13= 4-Amino-1-[(3,5-dimethyl-4-isoxazolyl)methyl]-2(1H)-pyrimidinone
14= 5-Fluoro-2-ethoxy-4(1H)pyrimidinone
15= 5-Fluoro-6-methoxy-2(1H)-pyrimidinone
16= 6-(3-Bromophenyl)-1-methyl-5-(3-methyl-5-isoxazolyl)-2(1H)-pyrimidinone
17= 6-(Chloromethyl)-2-(2-pyrazinyl)-4(3H)-pyrimidinone
18= 6-(Chloromethyl)-2-(3,4-difluorophenyl)-4(3H)-pyrimidinone
19= 6-(Chloromethyl)-2-(3-chlorophenyl)-4(3H)-pyrimidinone
20= 6-(Chloromethyl)-2-(4-ethylphenyl)-4(3H)-pyrimidinone
21= 6-(Chloromethyl)-2-(4-methoxyphenyl)-4(3H)-pyrimidinone
22= 6-(Dimethylamino)-5-fluoro-2(1H)-pyrimidinone
23= 6-(Methoxymethyl)-2-(1-piperazinyl)-4(3H)-pyrimidinone
24= 6-Amino-2-(methylsulfanyl)-4(3H)-pyrimidinone
25= 6-Butyl-2-(1-piperazinyl)-4(3H)-pyrimidinone
26= 6-Ethyl-2-(1-piperazinyl)-4(3H)-pyrimidinone
27= 6-Ethyl-2-thioxo-2,3-dihydro-4(1H)-pyrimidinone

Ligand-protein evaluation

The interaction of twenty-seven pyrimidinone derivatives with XIAP was evaluated using 4ic2[32] protein as a theoretical model using some XIAO inhibitors (compounds A, B, and C)[25, 30, 31] as control. In addition, binding energy involved in the interaction of pyrimidinone derivatives with the 4ic2 protein surface was evaluated using DockingServer software.[33]

Pharmacokinetics parameter

Pharmacokinetic parameters were determined using the SwissADME software.[34]

Toxicity evaluation

The possible toxicity produced by pyrimidinone derivatives (2, 5, 9, 11, 13, and 15) was determined using the GUSAR software.[35]

Results and Discussion

The literature reports are indicating that some compounds can produce changes in the biological activity of XIAP,[24-27] resulting in a decrease in the growth of cancer cells. However, there are data on the interaction of pyrimidinone derivatives with XIAP, which translates into insufficient information on the effect that these compounds could produce on cancer cells.

Protein-ligand analysis

This study aimed to evaluate the interaction of twenty-seven pyrimidinone derivatives with XIAP using 4ic2 protein and compounds A, B, and C **(Figure 1)** as theoretical tools in a Docking model.[33] The results showed in **Table 1** and Figure that different amino acid residues are involved in the interaction of pyrimidinone derivatives with XIAP; this data suggest that this interaction is due to different functional

groups involved in the chemical structure of each pyrimidinone derivative **(Table 1, Figures 2 and 3)**.

Table 1. Aminoacid residues are involved in the interaction of pyrimidinone derivates with the 4ic2-protein surface

Compound	Aminoacid residues
A	Glu_{447}; Lys_{448}; Lys_{451}; Asn_{457}; Ile_{458}; Leu_{468}; Met_{483}; Ile_{494}; Met_{496}
B	Leu_{444}; Glu_{447}; Lys_{448}; Lys_{451}; Ile_{458}; Leu_{468}; Met_{496}
C	Lys_{448}; Ile_{458}; Leu_{468}; Met_{483}; Ile_{494}; Phe_{495}; Met_{496}
1	Lys_{448}; Asn_{457}; Ile_{458}; Leu_{468}; Ile_{494}; Met_{496}
2	Lys_{448}; Asn_{457}; Ile_{458}; Ile_{494}; Met_{496}
3	Leu_{444}; Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}; Met_{496}
4	Leu_{444}; Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}; Met_{496}
5	Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}; Met_{496}
6	Leu_{444}; Glu_{447}; Lys_{448}; Ile_{458}; Met_{496}
7	Lys_{448}; Ile_{458}; Ala_{459}; Leu_{468}; Ile_{494}; Phe_{495}; Met_{496}
8	Lys_{448}; Ile_{458}; Leu_{468}; Ile_{494}; Met_{496}
9	Leu_{444}; Glu_{447}; Lys_{448}; Ile_{458}; Ile_{494}; Met_{496}
10	Lys_{448}; Ile_{458}; Ala_{459}; Ile_{494}; Met_{496}
11	Ile_{458}; Ala_{459}; Ile_{494}; Phe_{495}; Met_{496}
12	Lys_{448}; Asn_{457};Ile_{458}; Ala_{459}; Ile_{494}; Phe_{495}; Met_{496}
13	Glu_{447}; Ile_{458}; Gly_{466}; His_{467}; Leu_{468}
14	Lys_{448}; Ile_{458}; Ile_{494}; Met_{496}
15	Lys_{448}; Ile_{458}; Ala_{459}; Ile_{494}; Met_{496}
16	Leu_{444}; Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}; Met_{496}
17	Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}; Ile_{494}; Met_{496}
18	Lys_{448}; Asn_{457}; Ile_{458}; Leu_{468}; Ile_{494}; Phe_{495}; Met_{496}
19	Asn_{457}; Ile_{458}; Ala_{459}; Ile_{494}; Phe_{495}; Met_{496}
20	Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}; Ile_{494}; Met_{496}
21	Glu_{447}; Lys_{448}; Ile_{458}; Ala_{459}; Leu_{468}; Ile_{494}; Met_{496}
22	Lys_{448}; Asn_{457}; Ile_{458}; Ala_{459}; Ile_{494}; Met_{496}
23	Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}
24	Lys_{448}; Asn_{457}; Ile_{458}; Leu_{468}; Ile_{494}; Met_{496}
25	Leu_{444}; Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}
26	Leu_{444}; Glu_{447}; Lys_{448}; Ile_{458}; Leu_{468}; Met_{496}
27	Glu_{447}; Lys_{448}; Ile_{458}

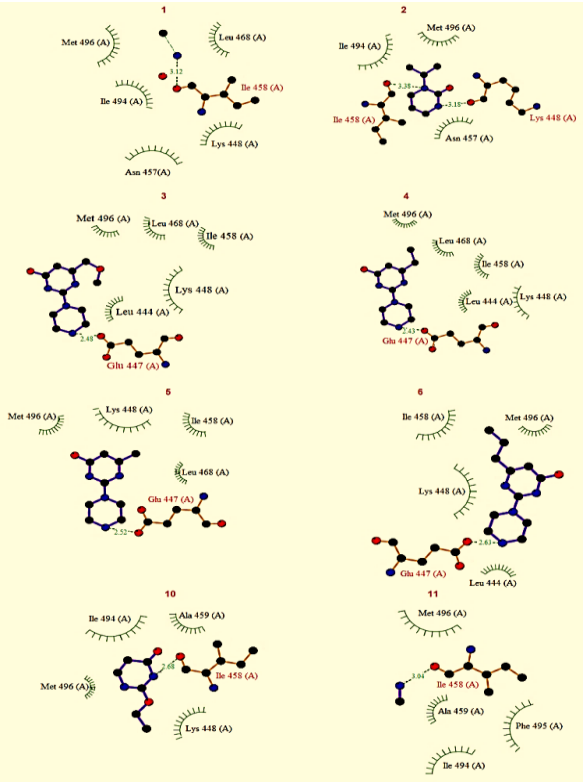

Figure 2. The scheme showed different amino acid residues involved in the interaction of some pyrimidinone derivatives (1-6, 10, and 11) with a 4ic2-protein surface using DockingServer software.[30]

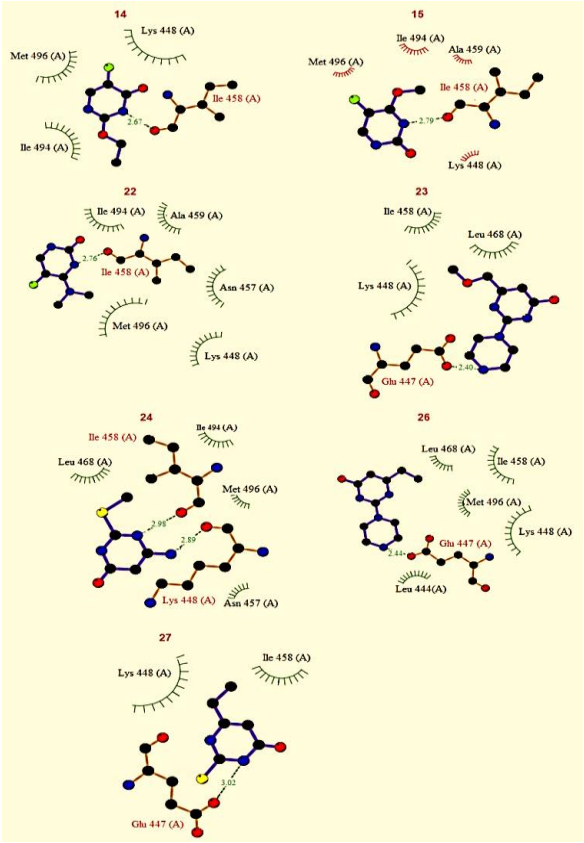

Figure 3. Interaction of pyrimidinone derivatives (14, 15, 22, 23, 24, 26, and 27) with the 4ic2-protein surface involves several amino acid residues involved. Scheme visualized with the DockingServer software.[30]

Binding energies

Some studies indicate that the ligand-protein interaction may depend on the energy levels such as the binding free energy, Electrostatic energy, total intermolecular energy, and Van der Waals forces.[34] Analyzing these data, in this study, several thermodynamic factors involved in the interaction of pyrimidinone-derivatives with 4ic2 protein surface were evaluated using some XIAO-inhibitors such as compounds A, B, and C as controls. The results showed differences in the energy levels involved in the interaction of pyrimidinone derivatives with the 4ic2 protein surface compared with the controls **(Table 2)**. Other results show that inhibition constant (Ki) pyrimidinone-derivatives (2, 3, 4, 6, 22, 24, and 26) was lower, compared with the controls (A, B, and C). In addition, the Ki for pyrimidinone-derivatives 1, 5, 10, 11, 14, 15, 23, and 27 were lower compared with the controls A and C. This phenomenon suggests that pyrimidinone derivatives such as 1-6, 10, 11, 14, 15, 22-22-24, 25, and 27 could inhibit the biological activity of XIAO protein translated as a possible decrease in prostate cancer levels.

Table 2. Thermodynamic parameters involved in the interaction of pyrimidinone derivates with the 4ic2-protein surface.

Compound	I	II	II	IV	V	VI
A	-6.88	9.04	-8.41	-0.14	-8.55	860.34
B	-7.79	1.94	-6.75	-0.73	-7.48	725.16
C	-5.60	78.24	-7.53	+0.05	-7.48	745.32
1	-3.15	4.92	-3.09	-0.06	-3.15	380.46
2	-3.94	1.30	-4.15	-0.09	-4.24	440.55
3	-3.89	1.40	-3.71	-0.93	-4.64	490.22
4	-3.92	1.35	-3.60	-1.00	-4.60	489.58
5	-3.64	2.13	-3.05	-0.89	-3.94	462.71
6	-3.88	1.43	-3.84	-0.92	-4.75	519.73
7	-5.20	153.39	-5.73	-0.06	-5.79	545.63
8	-4.17	873.21	-5.06	-0.02	-5.08	489.01
9	-4.98	222.21	-5.13	-0.15	-5.28	495.88
10	-3.33	3.65	-3.81	-0.10	-3.91	437.03
11	-3.51	2.68	-3.45	-0.06	-3.51	350.85
12	-4.97	227.23	-5.75	-0.12	-5.87	526.51
13	-4.16	886.57	-4.99	-0.05	-5.04	462.63
14	-3.52	2.62	-4.12	+0.01	-4.11	430.46
15	-3.68	2.01	-3.87	-0.10	-3.98	389.157
16	-5.40	109.27	-5.69	-0.18	-5.87	596.089
17	-4.47	533.28	-4.86	-0.35	-5.22	536.748
18	-5.46	100.33	-5.87	-0.34	-6.21	546.824
19	-5.22	148.08	-5.95	-0.06	-6.00	596.423
20	-5.32	126.81	-6.14	-0.22	-6.36	610.769
21	-4.58	436.01	-5.80	+0.04	-5.76	615.318
22	-3.76	1.74	-3.91	-0.15	-4.06	432.66
23	-3.65	2.10	-3.53	-1.01	-4.53	513.375
24	-3.79	1.66	-4.35	-0.04	-4.39	436.637
25	-4.49	507.65	-4.52	-1.03	-5.55	551.579
26	-4.00	1.17	-3.62	-0.99	-4.61	488.779
27	-3.66	2.09	-3.87	-0.09	-3.96	419.721

I = Free Energy of Binding (kcal/mol)
II = Inhibition Constant, Ki (mM)
III = Vander Waals forces + H-bond + desolv Energy (kcal/mol)
IV = Electrostatic Energy (kcal/mol)
V = Total Intermolecular Energy (kcal/mol)
VI = Interaction Surface

Pharmacokinetic analysis

In the literature, there are methods to predict some pharmacokinetic parameters for different drugs, such as PK/PD,[36] MONOLIX,[37] CXTMAIN,[38] and SwissADME.[39] In this research, some pharmacokinetic factors involved in pyrimidinone derivatives were evaluated using SwissADME software **(Table 3)**. The results showed differences in gastrointestinal absorption and metabolism (involving different types of cytochrome P450 systems) of pyrimidinone derivatives compared with the controls. This data suggest that the pharmacokinetics of pyrimidinone derivatives could depend on their chemical structure.

Table 3. Pharmacokinetic parameters for pyrimidinone derivatives

Compound	i	ii	iii	iv	v	vi	vii	viii	ix
A	High	No	Yes	No	Yes	No	Yes	Yes	4.59
B	High	No	Yes	No	Yes	No	Yes	Yes	2.92
C	High	No	Yes	No	No	No	No	Yes	2.68
1	Low	No	No	No	No	No	No	No	0.33
2	High	No	No	No	No	No	No	No	0.73
3	High	No	Yes	No	No	No	No	No	0.11
4	High	No	Yes	No	No	No	No	No	0.72
5	High	No	Yes	No	No	No	No	No	0.43
6	High	No	Yes	No	No	No	No	No	1.04
10	High	No	No	No	No	No	No	No	0.65
11	High	No	No	No	No	No	No	No	0.73
14	High	Yes	No	No	No	No	No	No	0.95
15	High	No	No	No	No	No	No	No	0.56
22	High	No	No	No	No	No	No	No	0.61
23	High	No	Yes	No	No	No	No	No	0.11

24	High	No	No	No	No	No	No	No	0.23
26	High	No	Yes	No	No	No	No	No	0.72
27	High	No	No	No	No	No	No	No	1.24

i = GI absorption
ii = BBB permeant
iii = P-GP substrate
iv = CYP1A2 inhibitor
v = CYP2C19 inhibitor
vi = CYP2C9 inhibitor
vii = CYP2D6 inhibitor
viii = CYP3A4 inhibitor
ix = Consensus Log $P_{O/W}$

Toxicity analysis

Some data in the literature indicate that several pyrimidinone derivatives can produce toxicity in different biological models.[40-43] Analyzing these data, the possible toxicity produced by some pyrimidinone derivatives (2, 5, 9, 11, 13, and 15) was evaluated using the GUSAR software.[35] The results showed that compounds A, B, and C require higher doses to produce toxicity (LD50) through the intraperitoneal route compared to pyrimidinone derivatives; however, pyrimidinone derivatives could produce different toxicity degrees through intravenous, oral, and subcutaneous routes compared with the controls. These data suggest that the toxicity could depend on the dose and routes of administration of each pyrimidinone derivative.

Table 4. Theorethical toxicity produced by compouns A,B,C, and pyrimidinone derivatives (1-6, 10, 11, 14, 15 22-24 26 and 27) using the Gussar software.

Compound	IP LD50 (mg/kg)	IV LD50 (mg/kg)	Oral LD50 (mg/kg)	SC LD50 (mg/kg)
A	959.00	58.74	1265.00	79.10
B	689.10	46.93	1943.00	396.00
C	757.70	82.31	974.40	695.40
1	126.40	33.69	797.20	169.20
2	137.70	89.46	871.30	151.60
3	94.22	128.40	1196.00	611.90
4	93.290	104.30	1854.00	563.60
5	55.75	125.40	1925.00	159.10
6	78.37	64.300	1071.00	583.40
10	346.40	139.80	3856.00	463.20
11	218.10	105.30	3451.00	287.80
14	369.60	226.20	804.20	466.10
15	465.00	307.30	591.20	377.80
22	194.20	169.20	651.40	277.40
23	94.22	128.40	1196.00	611.90
24	298.70	255.50	658.80	604.90
26	93.29	104.30	1854.00	563.60
27	232.80	103.90	944.50	496.20

IP = Intraperitoneal.
IV = Intravenous.
Oral = Oral.
SC = Subcutaneous.

Conclusion

Theoretical analyzes on the interaction of pyrimidinone derivatives with the 4ic2 protein surface suggest that pyrimidinone derivatives 1-6, 10, 11, 14, 15, 22-24, 26, and 27 might have a higher affinity for XIAP translated as greater XIAP inhibition compared with the controls. These data suggest that pyrimidinone derivatives could be good candidates to treat cancer through XIAP inhibition.

Acknowledgments

None.

Conflict of interest

None.

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None.

Ethics statement

This study developed out following the rules of professional ethics involved in the pharmacochemical research laboratory of the Autonomous University of Campeche.

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