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THEORETICAL INTERACTION OF PURINE AND ITS DERIVATIVES WITH HUMAN ECTO-5´-NUCLEOTIDASE, ASSOCIATED TO SOME PHYSICOCHEMICAL PROPERTIES

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ABSTRACT

Several purine analogs have been synthesized as anticancer agents; nevertheless, the physicochemical properties involved in the coupling of purine analogs with some biomolecules, such as human ecto-5'-nucleotidase (CD73), are not clear. The aim of this investigation was to design some pharmacophores to predict the possible interaction of purine and its analogues using a theoretical model. Besides, some physicochemical parameters such as HBD (hydrogen bond donor), HBA (hydrogen bond acceptor), HOMO (highest occupied molecular orbital), and LUMO (lowest unoccupied molecular orbital) were analyzed using Spartan software. On the other hand, to predict the interaction of purine and its derivative with CD73 and the inhibition constant, 4hdf protein was used as a theoretical tool. Besides, compound adenosine, AB-680, OP-5244, and PSD-12379 were used as controls in the DockingServer program. The results displayed several pharmacophore models for compounds 1-27, which involve different HBA or HBD groups. Other data shows different amino acid residues involved in the coupling of purine and its derivatives with the 4h2f protein surface compared with the controls. Besides, the Ki value for compound 4 was similar to the OP-5244 drug; however, the purine derivatives 4, 5, 6, 8, and 17 were lower compared with adenosine, AB-680, and PSD-12379. This phenomenon could depend on the difference in the chemical structure of the purine analogues compared to the controls, which may result in the interaction with different types of amino acids involved in the 4H2F protein surface. In this way, compound 4 could interact with Asn_{499} via H-bond and Phe_{417} and Phe_{500} through hydrophobic bond.

KEYWORDS. Purine, derivatives, HOMO, LUMO.

INTRODUCTION

For several years, there has been increased interest in developing different purine derivatives, both in the fields of pharmacy and organic chemistry. [i-v] For example, a series of 2,6,9-trisubstituted purine analogs were developed as antitumor agents.[vi] Another study showed the preparation of 6-[4-(4-Trifluorophenyl)piperazin-1-yl]-9-cyclopentyl-9H-purine with biological activity against Huh7 (a cell line composed of epithelial-like, tumorigenic cells).[vii] Besides, the compound 6-Chloro-9-{[1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl]methyl}-9H-purine was synthesized as an anticancer agent against CFPAC-1 (pancreatic carcinoma cells).[viii] Other reports displayed the synthesis of a purine derivative from 8-hydrazino-1,3,7-trimethyl-3,7-dihydropurine-2,6-dione[ix] with biological activity on HCT-15 (colon cancer cells). Further, a study showed the preparation of another anticancer agent, such as 6-(2-substituted ethyl amino) purine analog, through the removal of the acetyl groups of an acetylated ribofuranose-purine derivative with NaOMe.[x]

On the other hand, some theoretical methods have been used to predict the chemical interaction of different purine derivatives with some biomolecules; in this way, 2.4.2.3. The compound 8-((1-hydroxynaphthalen-2-yl)diazenyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione was synthesized from 8-Amino-1,3-dimethyl-3,4,5,7-tetrahydro-1H-purine-2,6-dione and its theoretical activity as an inhibitor of aurora kinase was determined using MOE 2015.10 software.[xi] Besides, a study shows the reaction of 7-benzyl-8-bromo-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione and 6-aminouracil to form the compound 7-benzyl-8- (2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione which could act as an anticancer agent through PI3Kγ (Activated phosphoinositide 3-kinase delta syndrome) using the MOE 2010.10 program.[xii] Other studies on the synthesis of 1, 3, 4-oxadiazole-purine derivatives and their anticancer activity using computational models such as the PASS prediction program.[xiii] In addition, some purine amide, hydroxamate, and amidoxime were prepared as non-small cell lung cancer agents; additionally, in this study, a pharmacohore model for phenyl- and 8-oxopurine derivatives was prepared.[xiv] All these experimental and theoretical data indicate that several purine derivatives can decrease the biological activity of some cancer strains; however, their chemical interaction with some biomolecules responsible for cancer development is not clear. Therefore, the objective of this investigation was to evaluate the possible interaction of twenty-two purine analogs (Figure 1) with human ecto-5'-nucleotidase (CD73; which is involved in cancer cell growth) and some physicochemical properties of these compounds using some theoretical models.

2. MATERIALS AND METHODS

Figure 1 show chemical structure of purine (27) and its analogs (2-26) which were used to determine some physicochemical properties involved in the interaction with human ecto-5'-nucleotidase as follows:

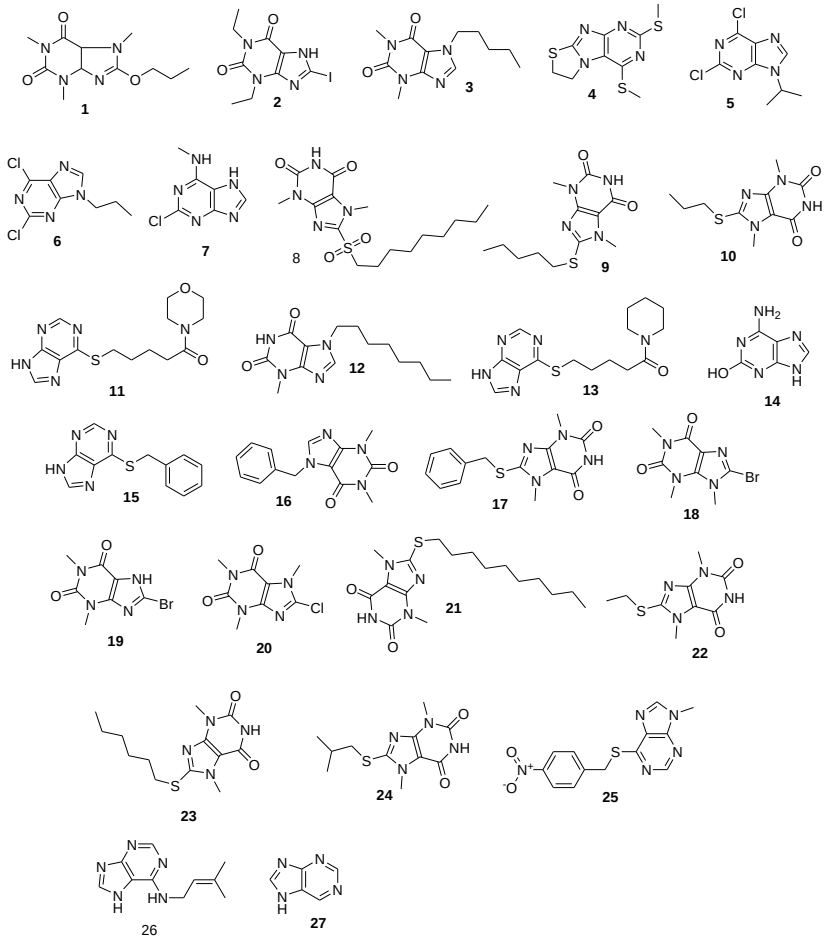


Figure 1. Chemical structure of purine (27) and its analogs (2-26).

1 = 1,3,7-Trimethyl-8-propoxy-3,4,5,7-tetrahydro-purine-2,6-dione
2 = 1,3-Diethyl-8-Iodo-3,7-dihydro-purine-2,6-dione
3 = 1,3-Dimethyl-7-pentyl-3,7-dihydro-1H-purine-2,6-dione
4 = 2,4-Bis(methylsulfanyl)-6,7-dihydro[1,3]thiazolo[2,3-F]purine
5 = 2,6-Dichloro-9-(1-methylethyl)-9H-purine
6 = 2,6-dichloro-9-propyl-9H-purine
7 = 2-Chloro-6(methylamino)purine
8 = 3,7-Dimethyl-8-nonylsulfonyl-3,7-dihydro-purine-2,6-dione
9 = 3,7-Dimethyl-8-pentylsulfanyl-3,7-dihydro-purine-2,6-dione
10 = 3,7-Dimethyl-8-propylsulfanyl-3,7-dihydro-purine-2,6-dione
11 = 6-((5-(4-Morpholinyl)-5-oxopentyl)thio)-9H-purine
12 = 3-Methyl-7-octyl-3,7-dihydro-purine-2,6-dione
13 = 6-((5-oxo-5-(1-piperidinyl)pentyl)thio)-9H-purine
14 = 6-Amino-9H-purin-2-ol
15 = 6-Benzylsulfanyl-9H-purine
16 = 7-Benzyl-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione
17 = 8-Benzylsulfanyl-3,7-dimethyl-3,7-dihydro-purine-2,6-dione
18 = 8-Bromo-1,3,9-trimethyl-3,9-dihydro-1H-purine-2,6-dione
19 = 8-Bromo-1,3-dimethyl-3,9-dihydro-purine-2,6-dione
20 = 8-Chloro-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione
21 = 8-Decylsulfanyl-3,7-dimethyl-3,7-dihydro-purine-2,6-dione
22 = 8-Ethylsulfanyl-3,7-dimethyl-3,7-dihydro-purine-2,6-dione
23 = 8-Hexylsulfanyl-3,7-dimethyl-3,7-dihydro-purine-2,6-dione
24 = 8-Isobutylsulfanyl-3,7-dimethyl-3,7-dihydro-purine-2,6-dione
25 = 9-methyl-6-[(4-nitrobenzyl)sulfanyl]-9H-purine
26 = N-(3-methylbut-2-enyl)-7H-purin-6-amine
27 = Purine

2.1 Pharmacophore model.

3D pharmacophore model for purine and their derivatives (1 to 30) was evaluated using LigandScout 4.08 software.[xv-xvii]

2.2 Physicochemical properties

HOMO, LUMO, dipole moment (μ) were determinate using Spartan´16 (v.2.7).[xviii-xx] Besides, LogPO/W, TPSA (topological polar surface area) and MR (molar refractory) for purine analogs was carried out using SwissAdme.[xxi-xxiii]

2.2 Protein-Ligand

Coupling of purine analogs (1 to30) with Human ecto-5'-nucleotidase, was determined using 4h2f protein (PDB: https://doi.org/10.2210/pdb4H2F/pdb)[xxiv] as chemical tool. Furthermore, the compounds such as adenosine, AB-680 ([[(2R,3S,4R,5R)-5-[6-chloro-4-[[(1S)-1-(2-fluorophenyl)ethyl]amino]pyrazolo[3,4-b]pyridin-1-yl]-3,4-dihydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl]methylphosphonic acid), Op-5244 ([(2R)-2-[[(2R,3S,4R,5R)-5-[6-chloro-4-(cyclopentylamino)pyrazolo[3,4-d]pyrimidin-1-yl]-3,4-dihydroxyoxolan-2-yl]methoxy]-1-hydroxy-3-methoxypropan-2-yl]phosphonic acid), and Psb-12379 ([[(2R,3S,4R,5R)-5-[6-(benzylamino)purin-9-yl]-3,4-dihydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl]methyl-phosphonic acid) were used as controls in DockingServer program.[xxv]

RESULTS AN DISCUSSION

In the literature, there are several studies indicating that the interaction of some purine derivatives with different biomolecules can produce a decrease in cancer cell growth, and this phenomenon may be due to the physicochemical properties of each purine analog.[xxvi-xxviii] Analyzing these data, the aim of this study was to determine the possibility that some physicochemical parameters could condition the coupling of purine and its analogues with human ecto-5'-nucleotidase (CD73) as follows:

Pharmacophore design

For several years, some computational methods have been used to design different purine analogues; For example, a pharmacophore was designed to characterize the possible interaction of purine derivatives with an ATPase enzyme using LigandScout program.[xxvix] Another study displayed the synthesis and design of a pharmacophore for 2,6,9-trisubstituted purine derivatives and their role as anticancer agents using molecular operating environment software.[xxx] Analyzing these data in this research, several pharmacophore models for purine and its derivatives were developed using the LigandScout 4.08 software. The results (Table 1, and Figures 2 and 3) displayed different functional groups involved in the chemical structure of purine and its analogs, which could act as hydrogen-bonded acceptors (HBA) and hydrogen-bonded donors (HBD). This phenomenon could be translated as a possible interaction of purine and its analogs with some biomolecules, such as proteins and enzymes, resulting in changes in its biological activity.

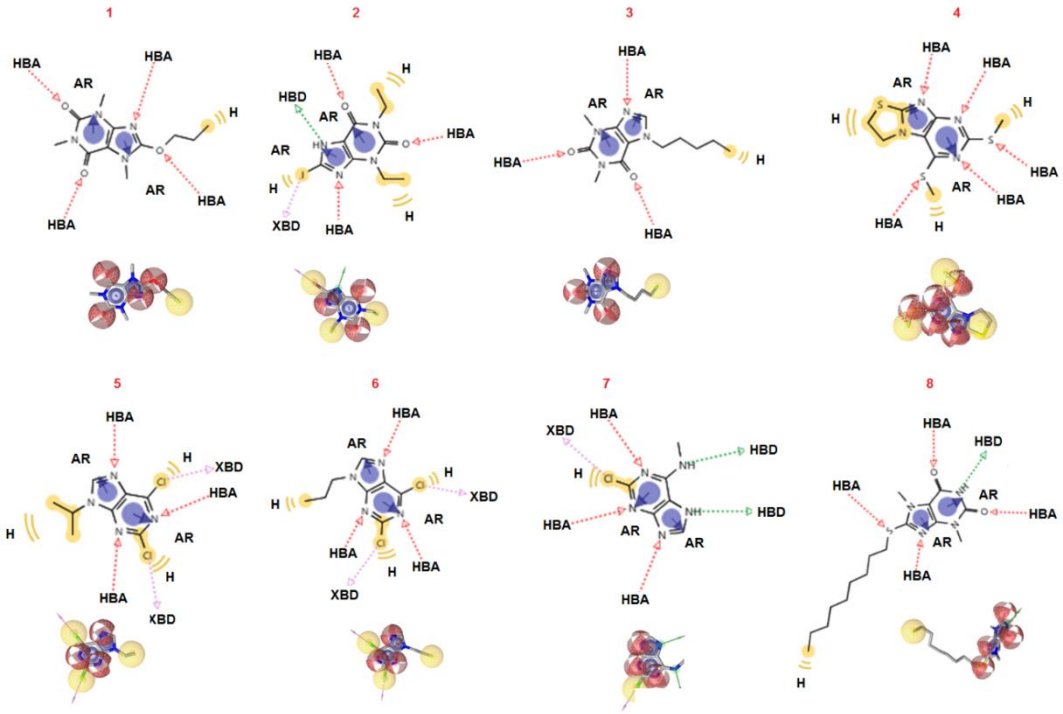


Figure 2. Pharmacophores from purine derivatives (1-8) visualized with LigandScout 4.08 program. HBA = Hydrogen bond acceptors (red); HBD = Hydrogen bond donors (green).

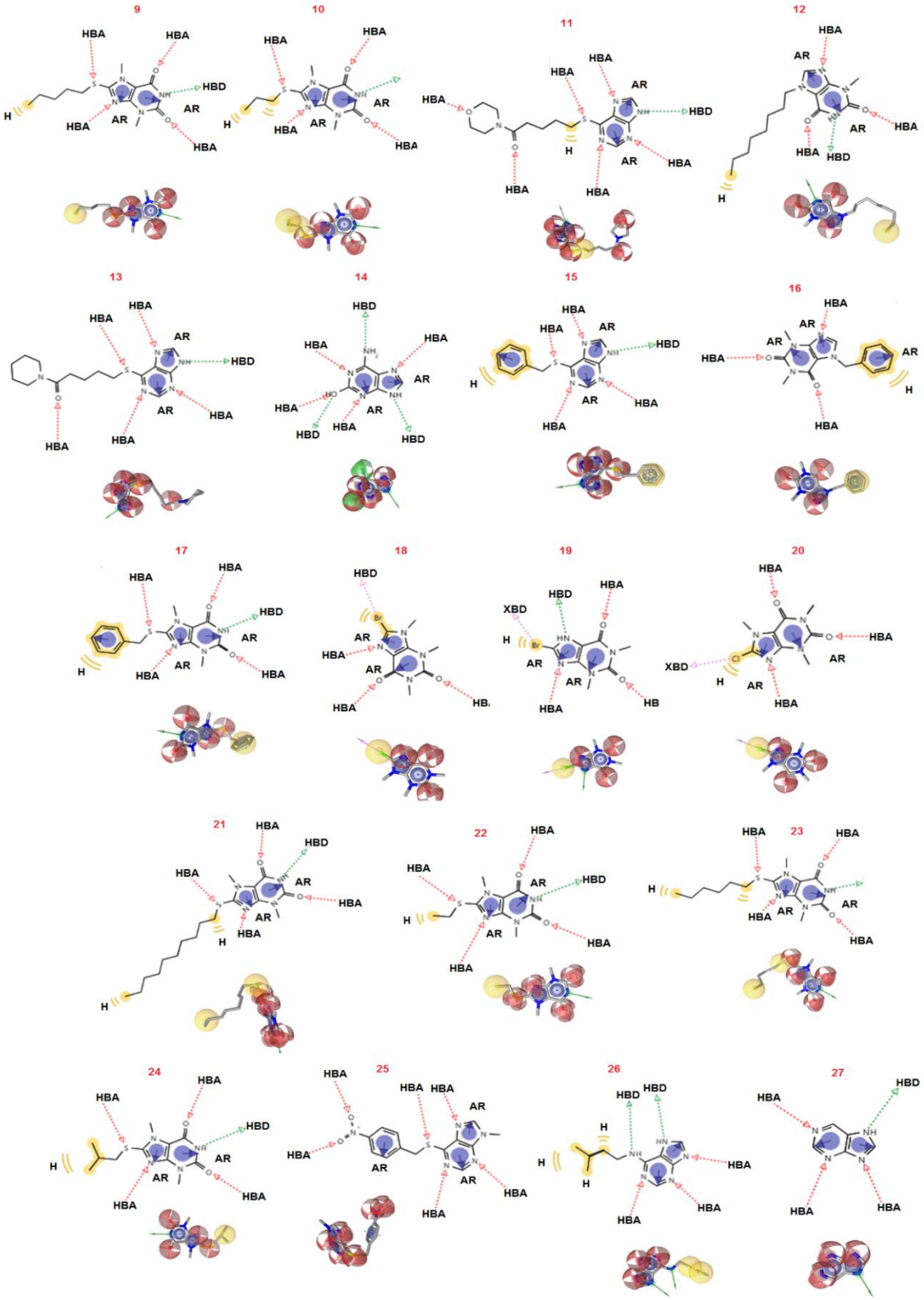


Figure 3. Pharmacophores from purine (27) and its analogs (9-26) visualized with LigandScout 4.08 program.

Physicochemical parameters

Other studies suggest that molecular orbitals HOMO and LUMO could be associated with the reactivity of some molecules, which could be translated as differences in the biological

activity of each compound.[xxxi, xxxii] Analyzing these data, in this investigation, both molecular orbitals HOMO and LUMO for purine and its analogs were determined; the results (Table 1 and Figure 4-7) displayed different HOMO and LUMO values for each compound, which could be associated with different functional groups bound to purine and its analogs. Besides, HOMO-LUMO gap values were determinate for purine and its derivatives; the results displayed a higher value for purine (12.04) compared with its derivatives 1-26; however, values for purine analogs 1-24, and 26 were >11 in comparison with compound 25.

Table 1. Physicochemical properties of purine (27) and its derivatives (1-26)

Compound	Homo	Lumo	HBD	HBA	Homo-Lumo gap energy	MR (cm^3)	MV (cm^3)	PSA	μ (g/cm^3)
1	-8.16	3.42	0	7	11.58	65.4 ± 0.5	187.3 ± 7.0	42.82	4.94
2	-8.67	2.39	0	5	11.06	62.2 ± 0.3	180.1 ± 3.0	49.48	3.18
3	-8.48	3.10	0	6	11.58	68.81 ± 0.5	197.8 ± 7.0	36.94	4.73
4	-8.20	2.38	0	7	10.58	72.55 ± 0.5	158.6 ± 7.0	21.10	6.25
5	-9.47	1.77	0	4	11.24	56.26 ± 0.5	146.1 ± 7.0	23.78	6.04
6	-9.46	1.78	0	4	11.24	56.44 ± 0.5	147.0 ± 7.0	29.93	6.18
7	-9.33	2.29	1	4	11.62	47.30 ± 0.3	112.9 ± 3.0	47.87	7.96
8	-8.14	3.03	1	7	11.17	95.10 ± 0.5	276.3 ± 7.0	47.90	5.55
9	-8.15	3.03	1	7	11.18	75.72 ± 0.5	206.2 ± 7.0	47.90	5.46
10	-8.17	3.01	1	7	11.18	66.51 ± 0.5	174.0 ± 7.0	47.90	5.31
11	-9.03	2.08	0	7	11.11	85.01 ± 0.4	234.4 ± 5.0	58.17	2.47
12	-8.57	3.03	1	6	11.60	77.32 ± 0.5	224.8 ± 7.0	48.81	3.03
13	-8.64	2.42	0	6	11.06	87.90 ± 0.4	244.5 ± 5.0	49.83	5.10
14	-8.51	3.20	2	5	11.71	38.92 ± 0.3	82.2 ± 3.0	80.01	3.20
15	-8.59	2.43	0	10	11.02	68.98 ± 0.4	173.0 ± 5.0	34.34	2.40
16	-8.47	3.12	0	6	11.59	75.67 ± 0.5	202.3 ± 7.0	36.90	4.93
17	-8.19	2.96	1	7	11.15	82.58 ± 0.5	210.8 ± 7.0	47.88	5.35
18	-8.53	3.54	0	6	12.07	57.93 ± 0.5	145.9 ± 8.0	38.02	7.71
19	-8.78	2.64	0	5	11.42	50.84 ± 0.3	139.0 ± 3.0	49.61	2.88
20	-8.73	2.71|	0	6	11.44	54.98 ± 0.5	142.7 ± 7.0	36.93	2.77
21	-8.14	3.03	1	7	11.17	98.77 ± 0.5	286.7 ± 7.0	42.90	5.54
22	-8.19	3.00	1	7	11.19	61.90 ± 0.5	157.9 ± 7.0	47.90	5.15
23	-8.15	3.03	1	7	11.18	80.33 ± 0.5	222.3 ± 7.0	47.90	6.47
24	-8.15	3.01	1	7	11.16	70.93 ± 0.5	189.3 ± 7.0	47.90	5.38
25	-8.92	0.14	0	8	9.06	81.21 ± 0.5	200.3 ± 7.0	63.22	10.23
26	-9.16	2.70	1	4	11.86	60.84 ± 0.3	160.4 ± 3.0	47.30	6.97
27	-9.73	2.31	0	3	12.04	32.80 ± 0.3	81.5 ± 3.0	35.28	6.32

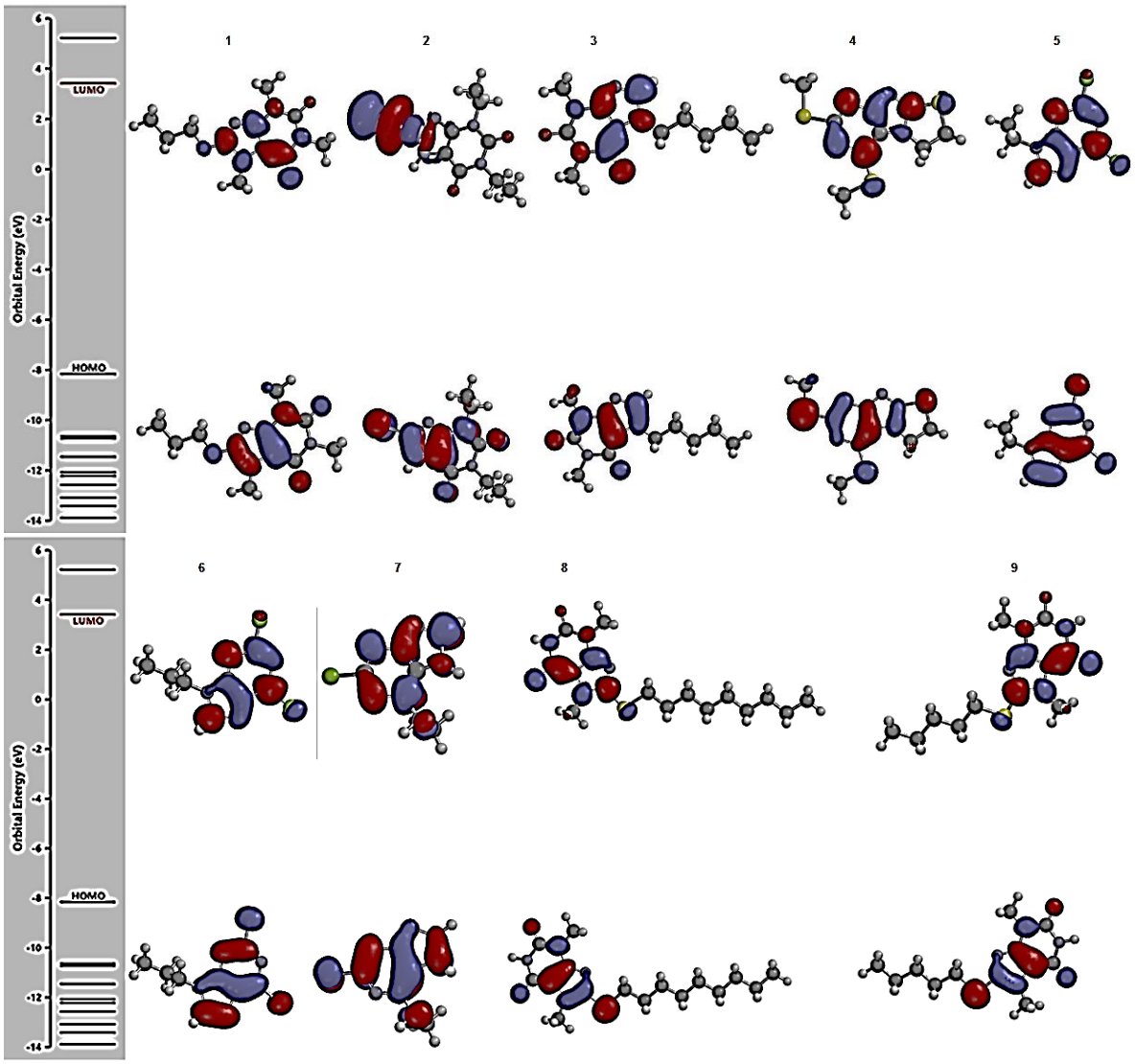
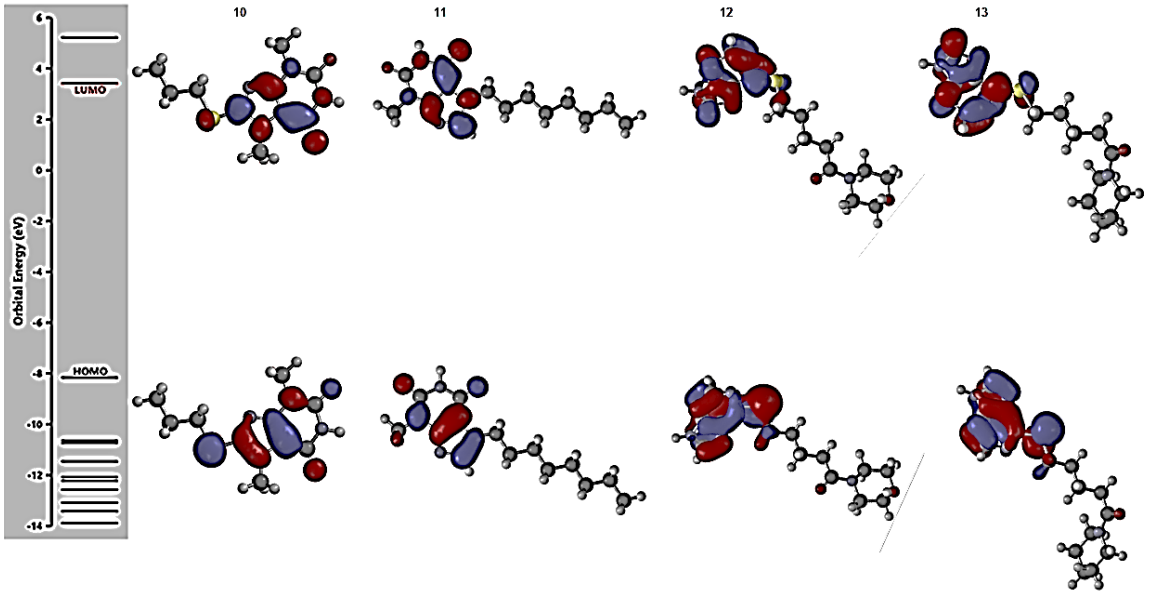


Figure 4. HOMO and LUMO orbitals for purine derivatives (1-9). Visualized with Sartan-16.0 program



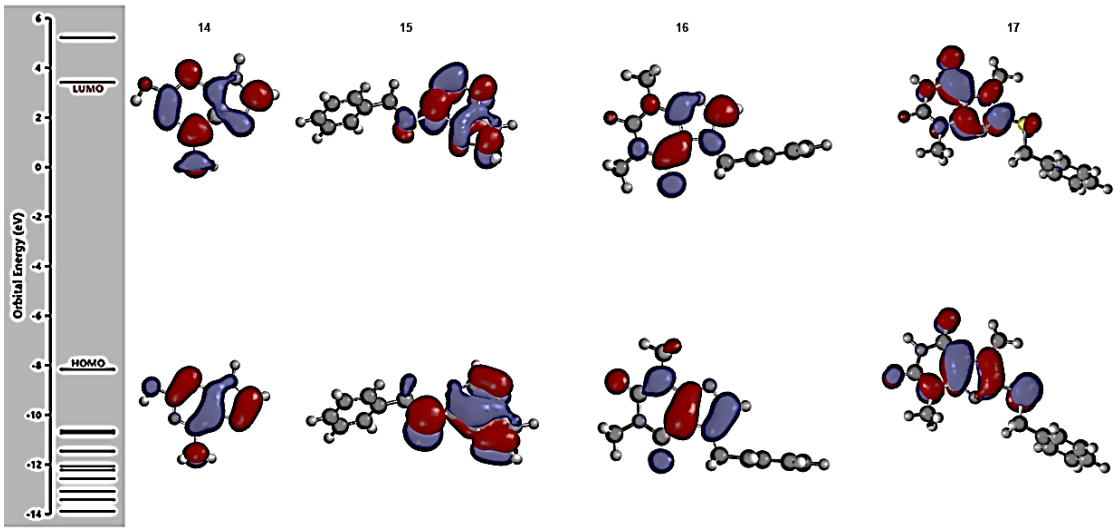
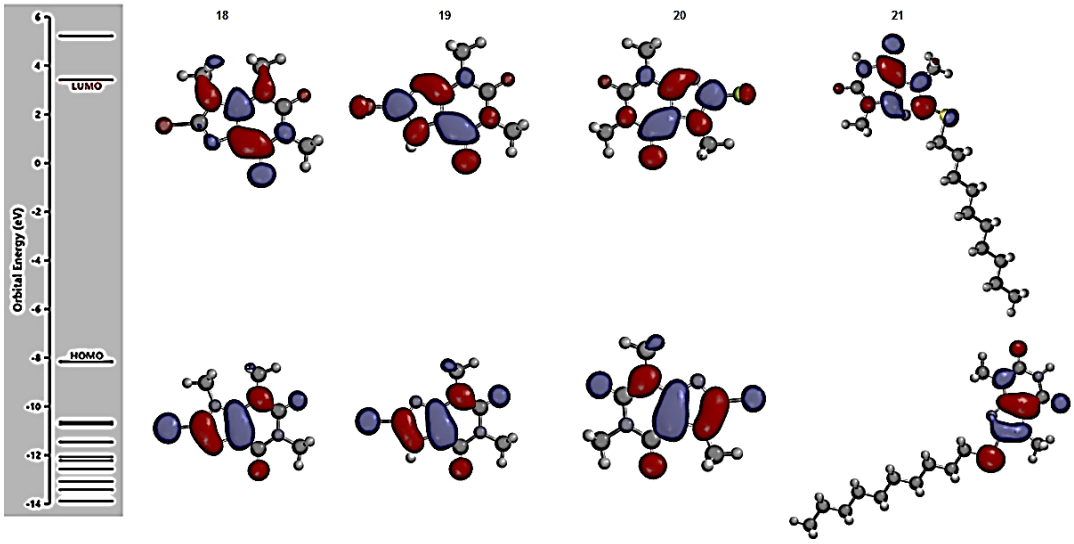


Figure 5. Visualization of HOMO and LUMO orbitals for purine derivatives (10-17) using Sartan-16.0 program.



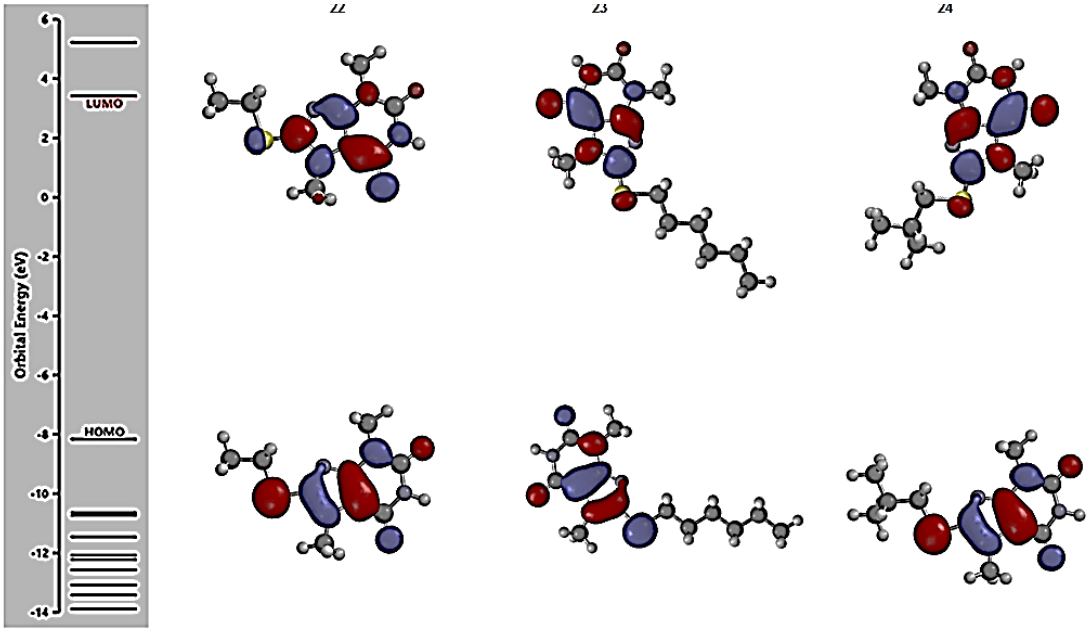


Figure 6. HOMO and LUMO orbitals for purine derivatives (18-24). Visualized with Sartan-16.0 program.

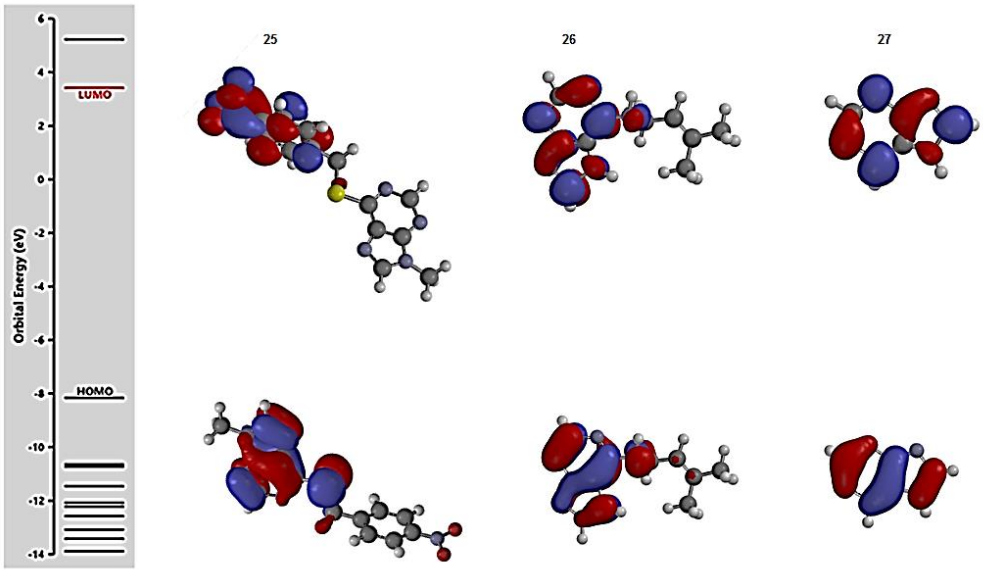


Figure 7. Visualization of HOMO and LUMO orbitals for purine (27) and its derivatives (25 and 26) using Sartan-16.0 program.

Ligand-protein complex formation

There are some reports which suggest that different purine analogs may interact with several biomolecules involved in some cancer strains; for example, a study showed the interaction of 6-mer capto-2-(methylthio)purin-8-one with the alpha-crystallin B chain (a protein that in humans is encoded by the CRYAB gene) using the Molecular Operating Environment.[xxxiii] This study suggests that methylthio side group may interact with the protein surface; in addition, the nitrogen groups of the imidazolidine ring form an H-bond with Tyr_{122}. Other studies displayed the synthesis of 9-(quinolin-6-ylmethyl)-2-[1-((1R,4R)-4-hydroxy-cyclo-hexyl)-1H-pyrazol-4-yl]-9H-purine which was docked with Met receptor tyrosine kinase using Surflex-Dock program/Sybyl 7.3 soft.[xxxiv] This study suggests that the quinoline moiety engaged the hinge region with a single typical hydrogen bond between the N of quinoline and

the backbone carbonyl of Met_{1160}. All these data indicate that different theoretical methods can be used to predict the interaction of some purine derivatives with several biomolecules; however, the coupling of purine derivatives with human ecto-5'-nucleotidase (CD73) is not clear. Analyzing these data, in this research, the possible interaction of purine and its derivatives with CD73 (a biomolecule involved in cancer growth)[xxxv,xxxvi] were determined using 4h2f protein as a theoretical tool. Furthermore, some compounds, such as adenosine, AB-680, OP-5244, and PSD-12379, were used as controls in the DockingServer program. The results showed (Table 2) different amino acid residues in the interaction of purine and its derivatives with the 4h2f protein surface compared with the controls. This data could be due to differences in chemical structure, which can be translated as differences in lipophilicity degree (Table 1). However, it is important to mention that other studies suggest that several thermodynamic parameters could condition the interaction of some compounds with different biomolecules.

Table 2. Aminoacid residues involved in the coupling of purine (27) and its derivatives (1-26) with 4h2f protein surface.

Compound	**Aminoacid Residues**
Adenosine	Asn_{390}; Phe_{417}; Pro_{498}; Phe_{500}
AB-680	Asn_{390}; Arg_{395}; Pro_{416}; Phe_{417}; Phe_{500}; Asp_{506}
OP-5244	Arg_{354}; Asn_{390}; Arg_{395}; Leu_{415}; Phe_{417}; Pro_{498}; Phe_{417}; Asp_{524}
PSD-12379	Val_{52}; Phe_{417}; Phe_{417};
1	Asn_{390}; Leu_{415}; Phe_{417}; Pro_{498}; Phe_{500}; Asp_{524}
2	Asn_{390}; Gly_{392}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
3	Asn_{390}; Leu_{415}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
4	Leu_{389}; Asn_{390}; Leu_{415}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}
5	Asn_{390}; Arg_{395}; Phe_{417}; Phe_{500}; Asp_{506}
6	Asn_{390}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}
7	Asn_{390}; Phe_{417}; Pro_{498}; Phe_{500}
8	Asn_{390}; Leu_{415}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
9	Asn_{390}; Leu_{415}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
10	Leu_{389}; Asn_{390}; Leu_{415}; Phe_{417}; Phe_{421}; Pro_{498}; Phe_{500}; Asp_{524}
11	Val_{52}; Asn_{390}; Phe_{417}; Pro_{498}; Phe_{500}
12	Arg_{354}; Asn_{390}; Arg_{395}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
13	Asn_{390}; Phe_{417}; Asn_{499}; Phe_{500}; Asn_{503}
14	Leu_{389}; Asn_{390}; Gly_{393}; Leu_{415}; Pro_{416}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
15	Asn_{390}; Phe_{417}; Phe_{421}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
16	Asn_{390}; Leu_{415}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
17	Asn_{390}; Phe_{417}; Phe_{421}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{506}; Asp_{524}
18	Asn_{390}; Gly_{392}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}
19	Asn_{390}; Gly_{392}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}
20	Asn_{390}; Gly_{392}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}
21	Asn_{390}; Phe_{417}; Asn_{499}; Phe_{500}; Asn_{503}
22	Asn_{390}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
23	Arg_{354}; Asn_{390}; Arg_{395}; Phe_{417}; Asn_{499}; Phe_{500}
24	Leu_{389}; Asn_{390}; Leu_{415}; Phe_{417}; Pro_{498}; Phe_{500}; Asp_{524}
25	Val_{52}; Asn_{390}; Phe_{417}; Asn_{499}; Phe_{500}
26	Ser_{49}; Leu_{415}; Phe_{417}; Thr_{420}; Phe_{421}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}
27	Gly_{393}; Leu_{415}; Pro_{416}; Phe_{417}; Pro_{498}; Asn_{499}; Phe_{500}; Asp_{524}

Thermodynamic parameters

The molecular interaction of several drugs that act as ligands with some biomolecules involves different thermodynamic parameters for ligand-protein complex formation; for example, some studies indicate that different types of energies, such as free energy of binding, electrostatic energy, total intermolecular energy, Vander Waals (vdW) + hydrogen bond (H-bond), + desolvation energy, are involved in protein-ligand complex formation.[xxxvii] Analyzing this data, in this research some thermodynamic parameters involved in the coupling of purine and its analogs with 4h2f protein surface were determined using DockingServer software. The results (Table 3) displayed differences in the energy levels involved in the possible purine-protein complex formation. Other data indicate that the inhibition constant (Ki) value for compound 4 was similar to OP-5244 drug; however, purine derivatives 4, 5, 6, 8, and 17 were lower compared with adenosine, AB-680, and PSD-12379. This phenomenon could depend on the difference in the chemical structure of the purine analogues compared to the controls, which may result in the interaction with different types of amino acids involved in 4h2f protein surface. In this way, compound 4 could interact with Asn_{499} via H-bond and Phe_{417} and Phe_{500} through hydrophobic-bond (Figure 8).

Table 3. Thermodynamic parameters involved in the coupling of compounds adenosine, AB-680, OP-5244, PSD-12379, purine (1) and its derivatives (1-26) with 4h2f protein surface.

Compound	**A**	**B**	**C**	**D**	**E**	**F**
Adenosine	-6.45	18.70	-5.49	-0.03	-5.52	506.05
AB-680	-5.62	76.23	-4.35	0.03	-4.32	546.55
OP-5244	-7.52	3.06	-8.05	-0.53	-8.58	749.55
PSD-12379	-4.29	717.13	-3.29	0.52	-2.77	497.21
1	-6.26	25.64	-6.97	-0.02	-6.99	566.16
2	-5.21	151.03	-5.89	0.02	-5.87	513.48
3	-5.70	66.09	-6.65	-0.01	-6.66	595.16
4	-7.37	3.97	-7.47	-0.49	-7.96	568.27
5	-6.36	9.35	-7.16	-0.00	-7.16	562.79
6	-6.61	14.31	-7.16	-0.02	-7.18	567.11
7	-5.15	166.53	-6.52	-0.04	-5.45	486.82
8	-6.84	9.76	-9.05	-0.01	-9.06	652.78
9	-5.70	66.09	-6.85	-0.01	-6.66	5.95.16
10	-6.42	19.83	-7.25	-0.02	-7.27	581.50
11	-4.36	640.68	-5.84	-0.03	-5.87	620.77
12	-5.34	121.45	-7.24	0.02	-7.21	666.93
13	-5.91	46.51	-7.06	-0.04	-7.11	684.72
14	-4.70	361.01	-4.99	-0.18	-5.17	400.92
15	-5.81	55.33	-6.68	-0.00	-6-69	560.32
16	-6.04	37.58	-7.14	-0.02	-7.16	579.15
17	-6.91	8.57	-7.80	0.00	-7.79	659.35
18	-5.83	53.48	-5.82	0.00	-5.83	478.00
19	-5.83	53.48	-5.82	0.00	-5.83	478.00
20	-6.68	12.66	-6.68	0.00	-6.68	538.40
21	-4.89	262.18	-7.65	0.00	-7.65	766.01
22	-5.49	94.13	-6.59	0.05	-6.54	539.17
23	-5.46	98.72	-7.16	0.05	-7.11	654.24
24	-6.33	22.79	-7.12	-0.01	-7.12	594.50

25	-6.24	28.57	-7.00	-0.03	-7.03	643.22
26	-5.75	60.53	-5.14	-1.65	-6.79	543.92
27	-4.70	358.25	-3.89	-0.81	-4.70	344.72

A = Est: Free Energy of Binding (kcal/mol); **B** = Inhibition Constant, Ki (mM); **C** = vdW + Hbond + desolv Energy (kcal/mol); **D** = Electrostatic Energy (kcal/mol); **E** = Total Intermolec. Energy (kcal/mol); **F** = Interact. Surface.

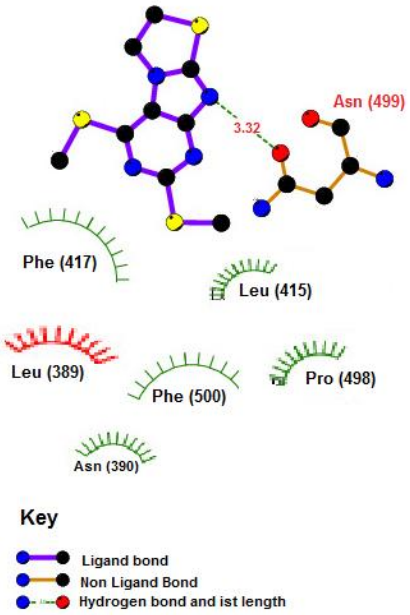


Figure 8. Interaction of purine derivative (4) with 4h2f protein surface. Visualization with Docking program

CONCLUSIONS

This theoretical study indicates that some physicochemical parameters could be involved in the coupling of purine and its derivatives with human ecto-5´-nucleotidase (CD73), such as different functional groups (which may act as hydrogen-bonded acceptors or hydrogen-bonded donors), and some thermodynamic parameters could condition the biological activity of CD73. Besides, other data indicate that inhibition constant of purine derivatives 4, 5, 6, 8, and 17 was lower compared with adenosine, AB-680, and PSD-12379. These data suggest that these compounds could be considered good anticancer agents; however, it is important to mention that other types of biological experiments could be carried out to confirm this hypothesis.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interests regarding the publication of the paper in this study

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