

**Mapeamento de Interações Intermoleculares de Inibidores de Segunda Geração da mTOR:
Evidências Computacionais para o Desenho de Novos Ligantes**

Mapping Intermolecular Interactions of Second-Generation mTOR Inhibitors: Computational
Evidence for the Design of New Ligands

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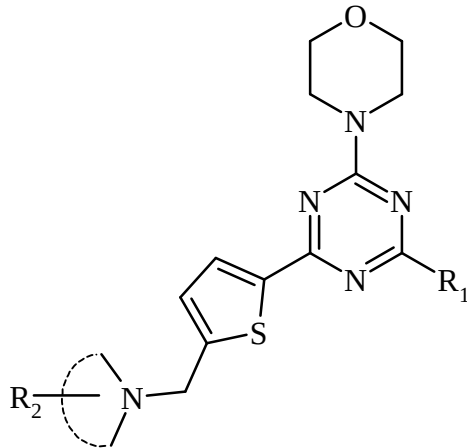
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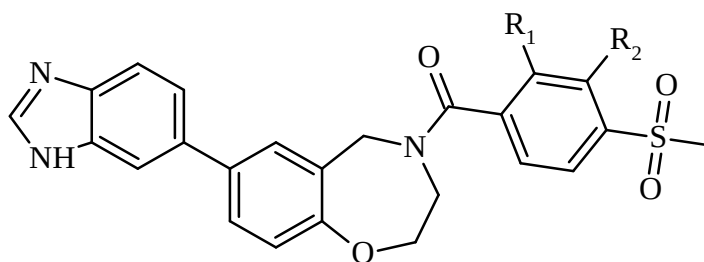
1. Estruturas e Dados de Atividade Biológica (IC₅₀) dos Compostos de Referência

Tabela S1. Ligantes com valores experimentais de IC₅₀ por Zhang *et al* (2020)¹



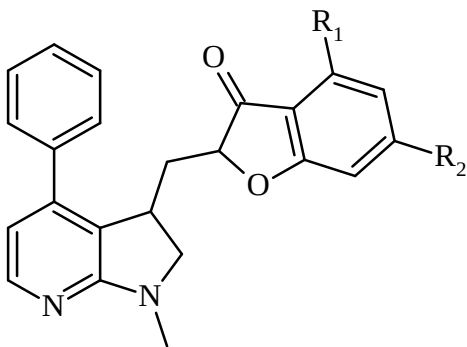
Identificação	Composto	R ₁	R ₂	IC ₅₀ (nM)
A	11c			> 1000
	11e			485
	11g			439
	12c			864
	12e			183
	12g			195
	13c			483
	13e			69
	13g			48

Tabela S2. Ligantes com valores experimentais de IC₅₀ por Takeuchi *et al* (2013)²



Identificação	Composto	R ₁	R ₂	IC ₅₀ (nM)
B	16	H	H	4,4
	18	Me	H	5,7
	19	Et	H	5,2
	20	n-Pr	H	28
	21	NHEt	H	204
	22	Cl	H	23,2
	23	Br	H	5,2
	24	H	Me	6,6
	25	Me	F	1,4
	26	Et	F	2,9

Tabela S3. Ligantes com valores experimentais de IC₅₀ por Tsou *et al* (2010)³



Identificação	Composto	R ₁	R ₂	IC ₅₀ (nM)
C	9a	OH	OH	0,46
	9b	OH	H	3,45
D	9k	-	-	0,0016

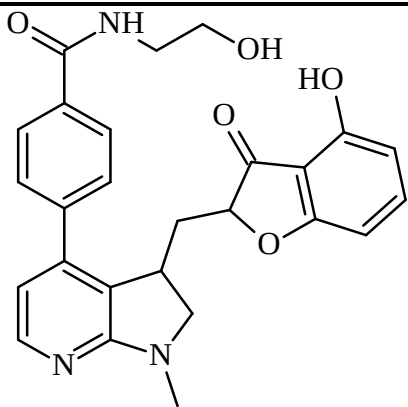
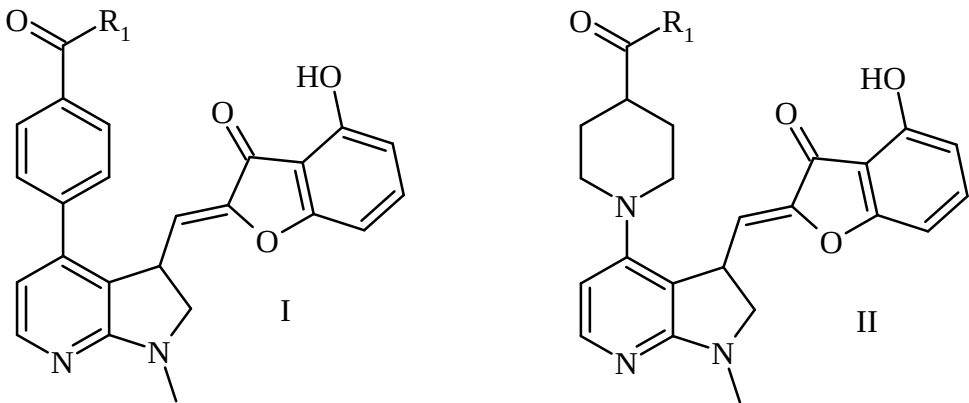


Tabela S4. Ligantes com valores experimentais de IC₅₀ por Tsou *et al* (2010)³ (continuação) corrigir insaturação



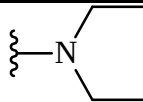
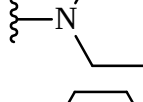
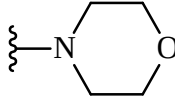
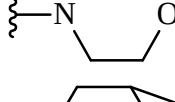
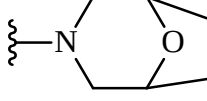
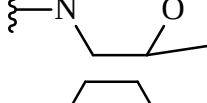
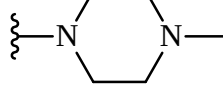
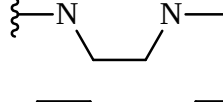
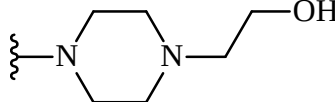
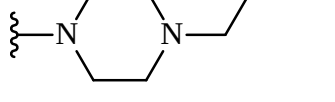
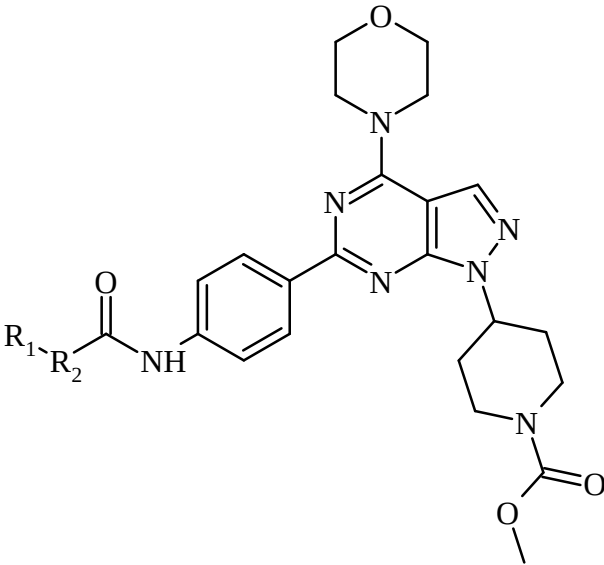
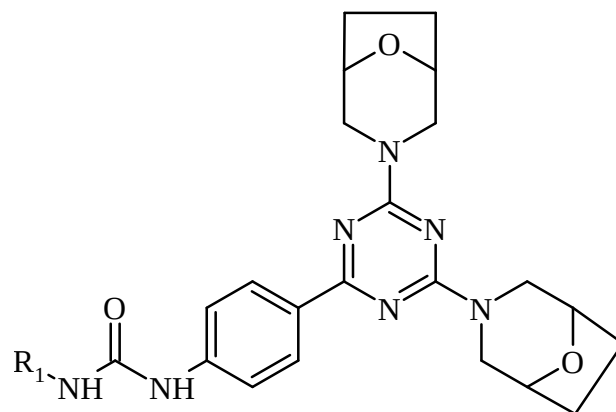
Identificação	Composto	R ₁	Estrutura	IC ₅₀ (nM)
E	9d		I	0,55
	10d		II	0,67
	9e		I	0,50
	10e		II	1,40
	9f		I	0,56
	10f		II	2,00
	9g		I	1,00
	10g		II	3,10
	9h		I	0,39
	10h		II	1,85

Tabela S5. Ligantes com valores experimentais de IC₅₀ por Zask *et al* (2009)⁴



Identificação	Composto	R ₁	R ₂	IC ₅₀ (nM)
F	19	-CH ₃	O	4,3
	20	-CH ₃ CH ₂ OH	O	1,0
	21	-Et	NH	0,32
	22	-CH ₂ CH ₂ F	NH	0,61
	23	-CH(CH ₃) ₂	NH	0,45
	24		NH	0,20
	25		NH	0,30
	27		NH	0,34
	28		NH	0,08

Tabela S6. Ligantes com valores experimentais de IC₅₀ por Zask *et al* (2010)⁵



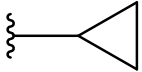
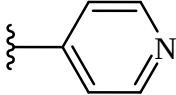
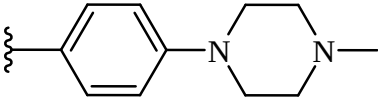
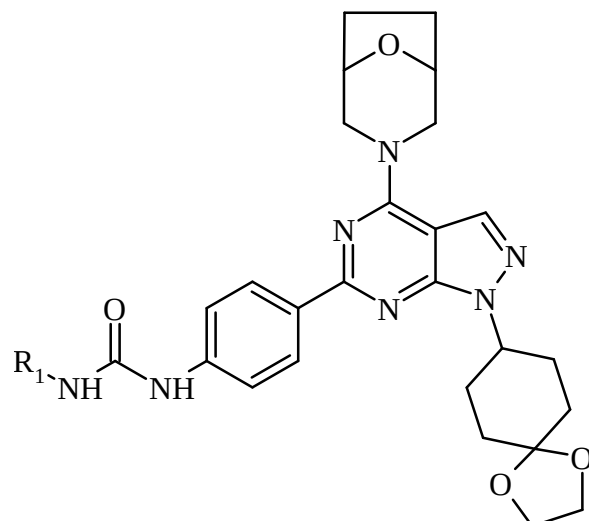
Identificação	Composto	R ₁	IC ₅₀ (nM)
G	9	-Me	2,5
	10	-Et	2,8
	11		2,6
	12		0,50
	13		1,7

Tabela S7. Ligantes com valores experimentais de IC₅₀ por Curran *et al* (2010)⁶



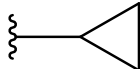
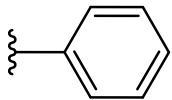
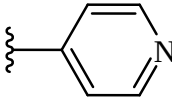
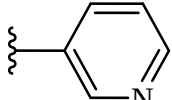
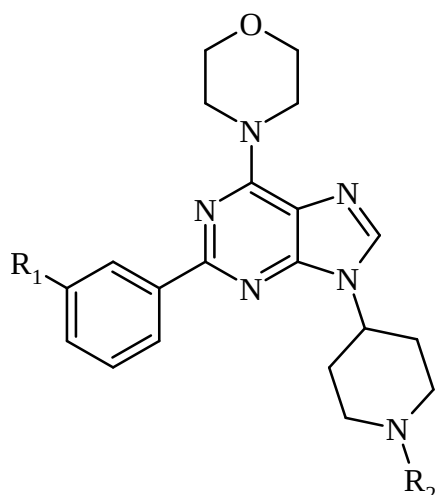
Identificação	Composto	R ₁	IC ₅₀ (nM)
H	8b	-Et	0,26
	8c	-CH ₂ CH ₂ F	0,22
	8d		0,22
	8e		0,16
	8f		0,12
	8g		0,12

Tabela S8. Ligantes com valores experimentais de IC₅₀ por Venkatesan *et al* (2010)⁷



Identificação	Composto	R ₁	R ₂	IC ₅₀ (nM)
I	14	-OH	H	1650
	15	-OH	H	950
	16	-OH	Benzil	140
	20	-OH		51
	22	-CH ₂ OH	H	7200
	24	-CH ₂ OH		310

2. Parâmetros de Energia Calculados pelo Ancoramento Molecular

Tabela S9. Energias inter e intramoleculares

Ligante	Energia Intermolecular	Energia Intramolecular	Torções
4JT6	-137,527	20,5518	2
A11C	-147,357	11,3992	5
A11E	-170,985	16,9524	5
A11G	-180,103	15,4817	6
A12C	-154,902	19,3177	5
A12E	-152,959	17,5913	5
A12G	-165,597	19,058	6
A13C	-145,084	11,6575	5

A13E	-153,853	19,3185	5
A13G	-164,8	22,6223	6
B16	-151,013	15,8318	3
B18	-162,668	20,8283	3
B19	-155,122	10,8732	4
B20	-142,328	9,04439	5
B21	-124,041	9,55618	5
B22	-147,137	10,9749	3
B23	-148,465	10,103	3
B24	-166,304	15,3044	3
B25	-163,338	20,8695	3
B26	-157,167	19,5267	4
C9A	-139,381	-3,94147	3
C9B	-154,007	13,427	3
D	-132,768	-26,5924	6
E10DB	-155,943	2,09715	6
E10EB	-135,918	-15,8462	4
E10FB	-151,717	8,7324	4
E10GB	-157,02	14,5827	4
E10HB	-168,784	18,767	6
E9DA	-163,139	-3,39488	6
E9EA	-164,95	1,51535	4
E9FA	-176,933	96,598	4
E9GA	-165,841	2,06759	4
E9HA	-169,299	6,97565	6
F19	-158,53	17,2705	8
F20	-160,356	12,2322	10
F21	-166,506	12,4004	9
F22	-181,884	19,3804	10
F23	-170,473	10,0652	9
F24	-181,248	19,9667	9
F25	-189,846	18,6882	9
F27	-174,164	16,7749	10
F28	-201,103	17,5694	10
G10	-167,04	15,76	8
G11	-165,917	29,9925	8
G12	-190,909	36,7461	8
G13	-201,426	10,1	9
G9	-164,024	17,68	7
H8B	-164,378	5,86234	8
H8C	-168,327	9,05335	9
H8D	-189,065	16,8096	8
H8E	-172,552	-2,08638	8
H8F	-196,189	21,0612	8
H8G	-191,4	18,6127	8
I14	-141,795	15,737	4

I15	-141,683	13,761	4
I16	-148,832	20,0224	5
I20	-161,115	6,56183	8
I22	-134,963	13,3058	5
I24	-154,682	17,8366	6

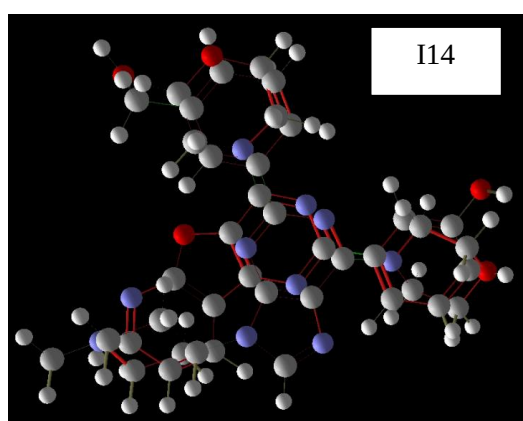
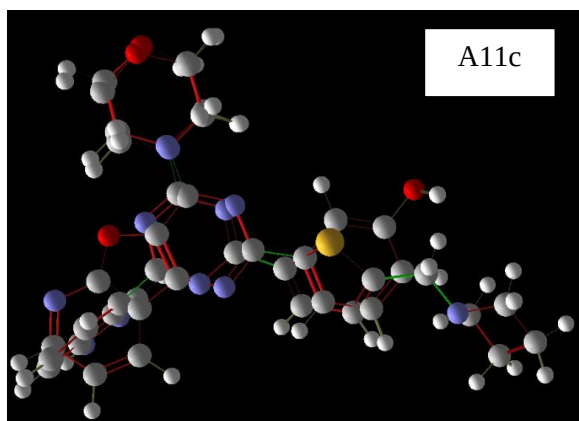
Tabela S10. Número de átomos pesados, peso molecular, eficiência do ligante e pontuação do ancoramento

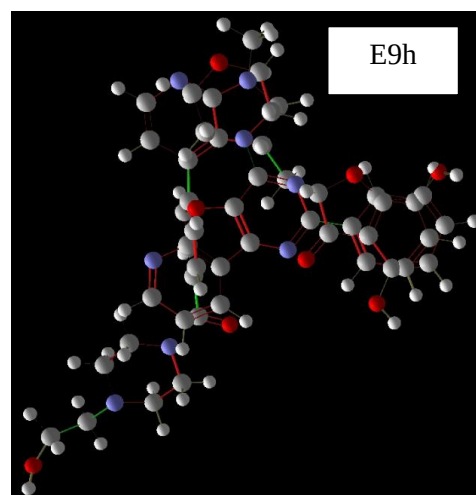
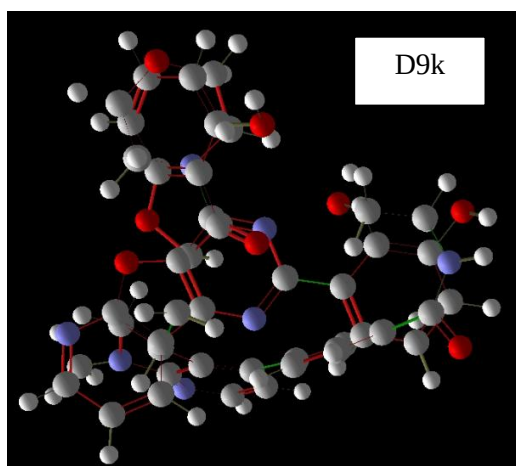
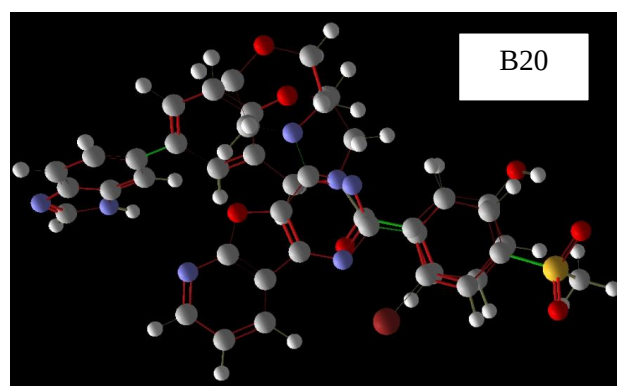
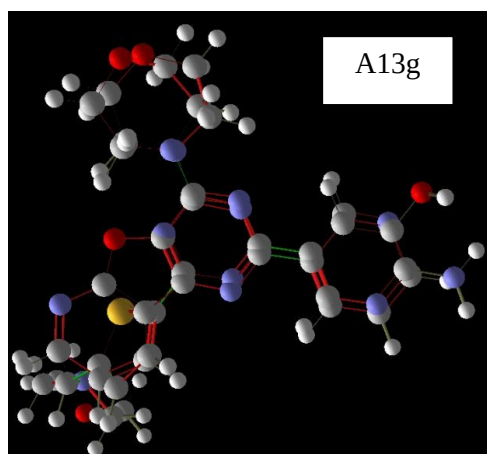
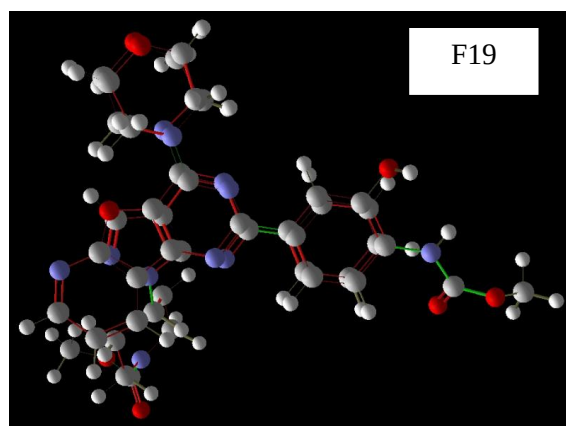
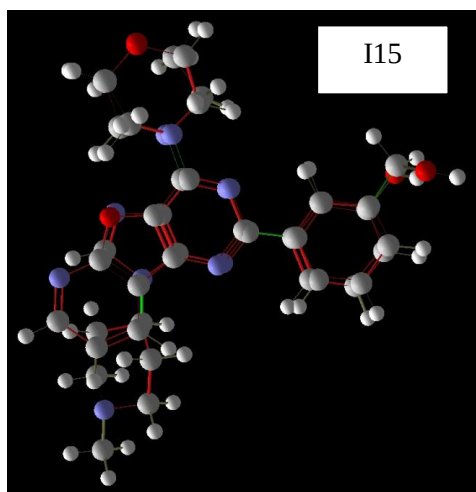
Ligante	Átomos pesados	Peso molecular (Da)	Eficiência do Ligante 1	Pontuação do Ancoramento
4JT6	26	348,355	-4,49906	-121,133
A11C	32	447,556	-4,24868	9864,17
A11E	33	463,555	-4,66765	9847,46
A11G	37	540,661	-4,44923	9834,7
A12C	30	423,531	-4,51949	9861,02
A12E	31	439,531	-4,3667	9865,79
A12G	35	516,636	-4,18682	9850,3
A13C	30	424,523	-4,44754	9867,72
A13E	31	440,522	-4,33982	9866,85
A13G	35	517,628	-4,06221	9857,88
B16	32	447,506	-4,22443	9867,11
B18	33	461,533	-4,29817	9857,06
B19	34	475,559	-4,2426	9854,42
B20	35	489,586	-3,80809	9863,05
B21	35	490,574	-3,27099	9884,03
B22	33	481,951	-4,12613	9862,19
B23	33	526,402	-4,19278	9859,93
B24	33	461,533	-4,57575	9848,16
B25	34	479,523	-4,19024	9854,89
B26	35	493,55	-3,93258	9864,73
C9A	29	388,416	-4,94217	-145,54
C9B	28	372,417	-5,02072	-140,849
D	34	459,494	-4,68706	-163,864
E10DB	35	478,583	-4,39559	9845,97
E10EB	36	492,567	-4,21567	9850,26
E10FB	38	518,604	-3,76276	9855,73
E10GB	37	505,609	-3,84966	9854,18
E10HB	39	535,635	-3,84659	9843,78
E9DA	35	471,548	-4,75811	9833,34
E9EA	36	485,531	-4,53986	9835,46
E9FA	38	511,568	21,5701	10818,7
E9GA	37	498,573	-4,42632	9833,15
E9HA	39	528,599	-4,16215	9835,54
F19	36	495,531	-3,92387	9855,74



F20	38	525,557	-3,89799	9847,86
F21	37	508,573	-4,16501	9835,85
F22	38	526,563	-4,27642	9832,48
F23	38	522,599	-4,22127	9833,11
F24	41	557,604	-3,9337	9826,07
F25	41	557,604	-4,17457	9819,05
F27	48	653,774	-3,27893	9838,47
F28	43	586,642	-4,26822	9805,44
G10	35	479,575	24,2492	10848,2
G11	36	491,585	-3,77567	9860,22
G12	39	530,621	-3,95289	9846,62
G13	46	625,764	17,8625	10821,6
G9	34	465,548	25,1075	10854
H8B	40	547,649	-3,96289	9839,73
H8C	41	565,639	-3,88472	9837,31
H8D	41	559,659	-4,20134	9827,13
H8E	44	595,691	-3,96905	9825,93
H8F	44	596,679	-3,98019	9817,12
H8G	44	596,679	-3,92699	9823,43
I14	30	408,497	-4,20194	9875,47
I15	30	408,497	-4,26405	9871,73
I16	35	470,566	-3,68027	9871,96
I20	38	515,607	-4,0672	9843,06
I22	31	422,523	-3,92443	9877,96
I24	36	485,581	-3,80126	9860,95

3. Sobreposição das Poses do Ancoramento Molecular





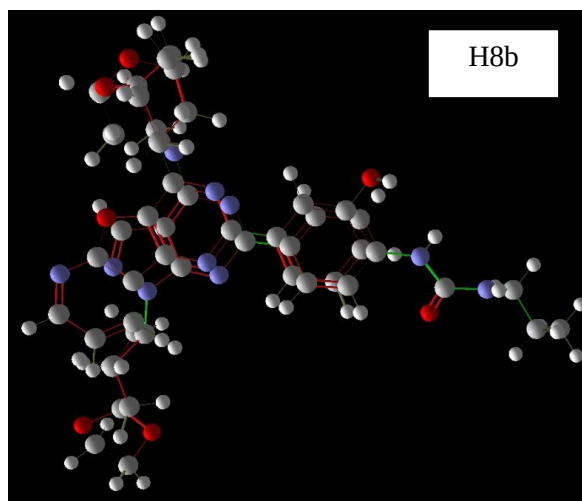
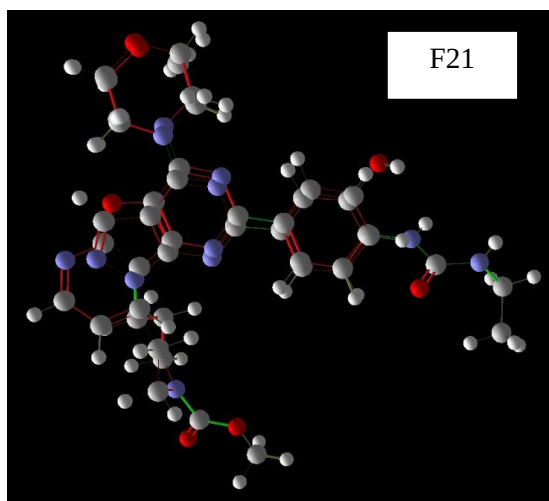
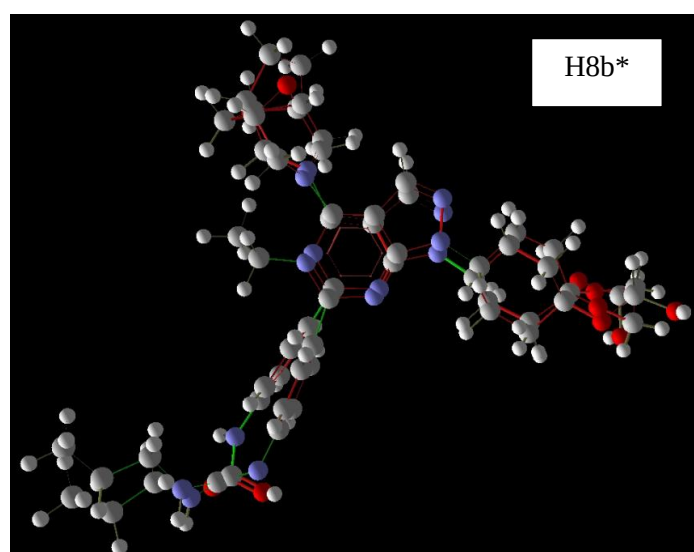
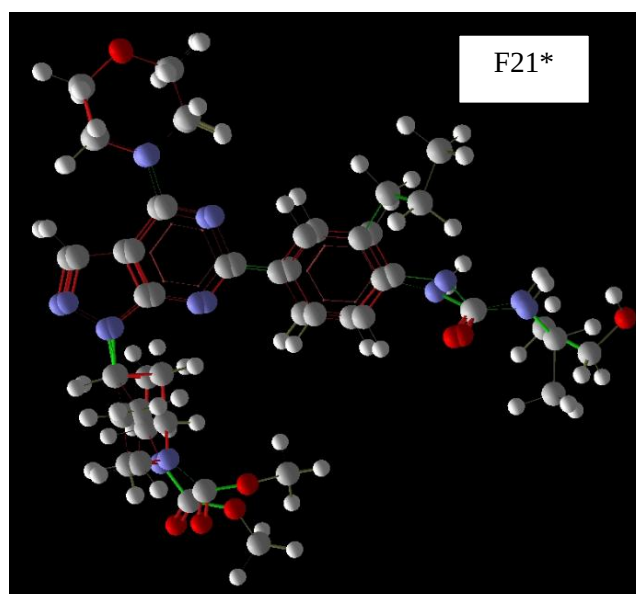


Figura S1. Imagens das poses obtidas para os ligantes A11c, I14, I15, F19, A13g, B20, D9k, E9h, F21 e H8b, sobrepostas ao composto PI-103



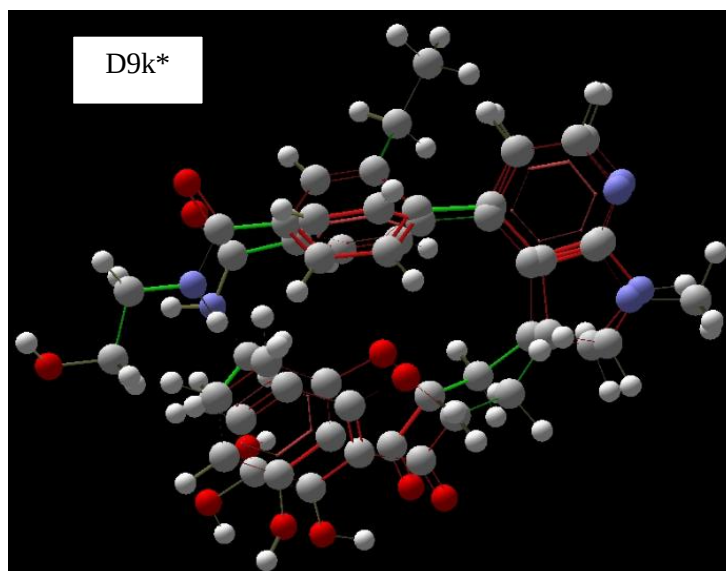


Figura S2. Imagens das poses obtidas para os ligantes F21*, H8b* e D9k*

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