Supplementary Material

Quantum mechanical, molecular docking, molecular dynamics, ADMET and antiproliferative activity on *Trypanosoma cruzi* (Y strain) of chalcone (*E*)-1-(2-hydroxy-3,4,6-trimethoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one derived from natural product

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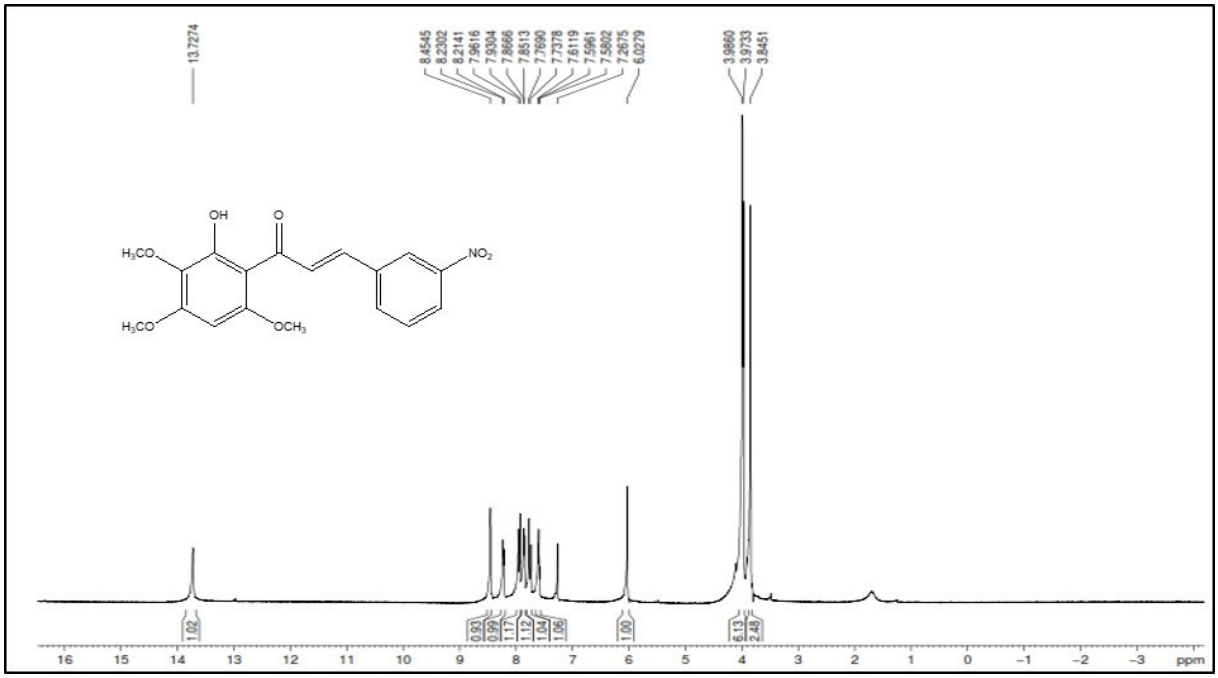

Figure S1. ^{1}H NMR Spectrum ($CDCl_3$, 500 MHz) of chalcone CPN_3NO_2.

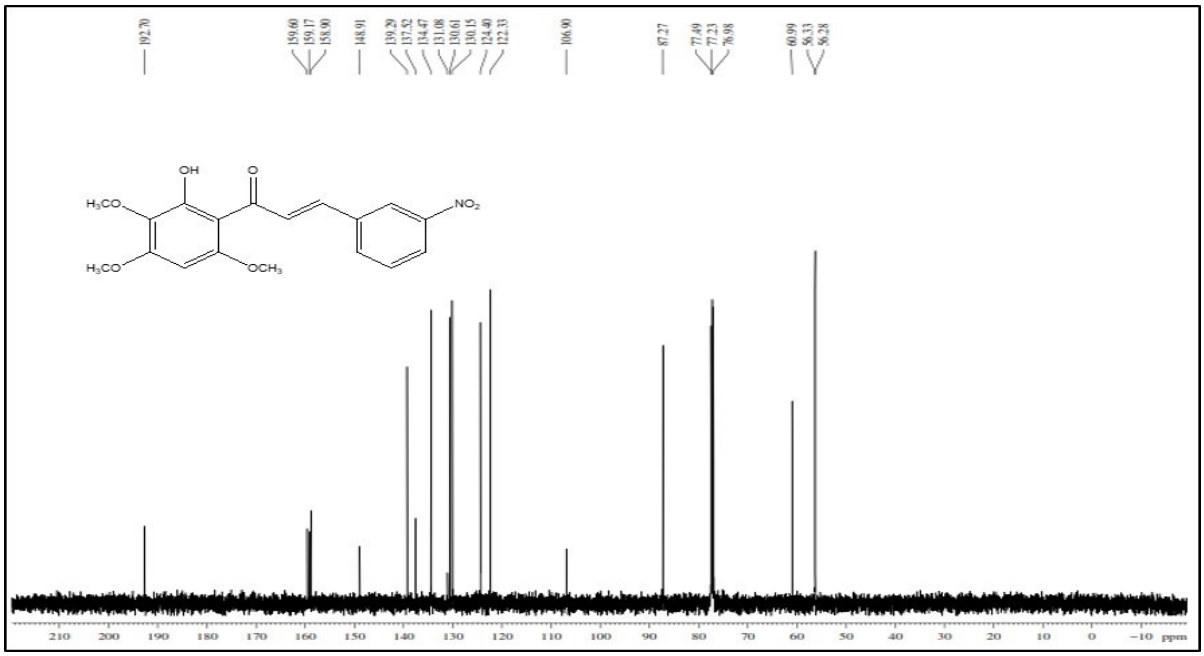

Figure S2. ^{13}C-NMR Spectrum ($CDCl_3$, 125 MHz) of chalcone CPN_3NO_2.

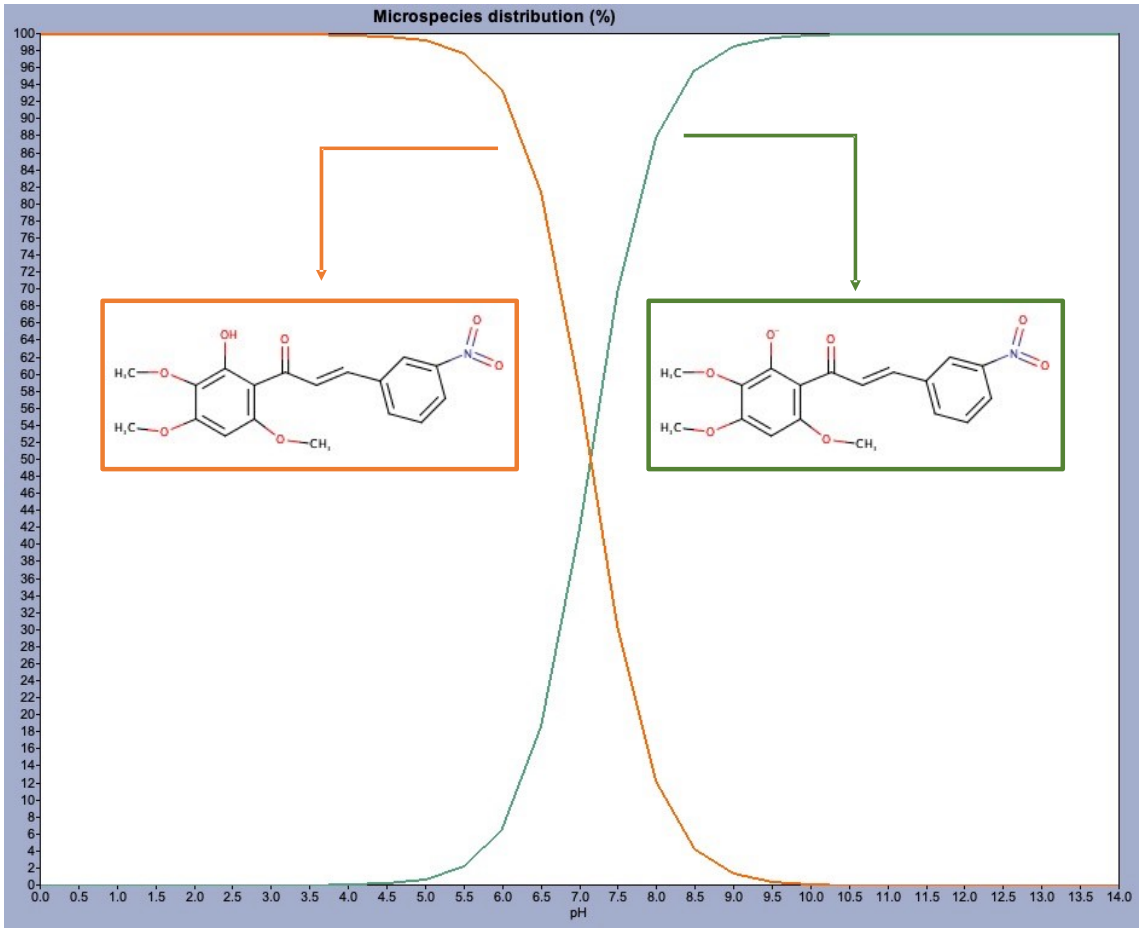

Figure S3. Macrospecies distribution (%) as a function of pH for CPN_3NO_2.

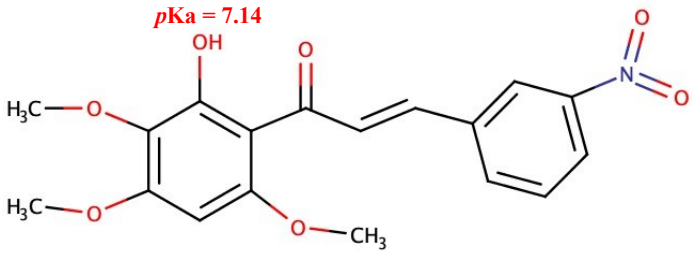

Figure S4. pKa value for the hydroxyl group of the CPN_3NO_2.

Tabela S1. Geometric parameters (bond lengths and bond angles) of the optimized structure of CPN3NO2.

Bond lengths	Calc. (Å)	Bond lengths	Calc. (Å)	Bond lengths	Calc. (Å)	Bond lengths	Calc. (Å)
R(1-2)	1.402	R(7-13)	1.433	R(15-22)	1.094	R(34-41)	1.483
R(1-6)	1.397	R(8-25)	0.999	R(15-23)	1.089	R(36-38)	1.39
R(1-7)	1.367	R(10-14)	1.424	R(15-24)	1.094	R(36-39)	1.083
R(2-3)	1.438	R(11-26)	1.251	R(27-28)	1.344	R(38-40)	1.081
R(2-8)	1.334	R(11-27)	1.483	R(27-29)	1.077	R(41-42)	1.224
R(3-4)	1.427	R(12-15)	1.425	R(28-30)	1.086	R(41-43)	1.225
R(3-11)	1.47	R(13-16)	1.09	R(28-31)	1.464	R(25-26)	1.566
R(4-5)	1.388	R(13-17)	1.092	R(31-32)	1.403		
R(4-12)	1.363	R(13-18)	1.095	R(31-33)	1.406		
R(5-6)	1.405	R(14-19)	1.095	R(32-34)	1.385		
R(5-9)	1.077	R(14-20)	1.095	R(32-35)	1.08		
R(6-10)	1.351	R(14-21)	1.088	R(33-36)	1.393		

Bond angles	Calc. (°)	Bond angles	Calc. (°)	Bond angles	Calc. (°)	Bond angles	Calc. (°)
A(2-1-6)	119.1	A(4-5-6)	120.4	A(12-15-23)	105.6	A(31-32-34)	119.5
A(2-1-7)	120.9	A(4-5-9)	120.1	A(12-15-24)	111.1	A(31-32-35)	121.7
A(1-2-3)	121.9	A(4-12-15)	119.8	A(16-13-17)	109.6	A(31-33-36)	121.5
A(1-2-8)	116.3	A(6-5-9)	119.6	A(16-13-18)	109.4	A(31-33-37)	118.9
A(6-1-7)	119.8	A(5-6-10)	123.4	A(17-13-18)	110.1	A(34-32-35)	118.8
A(1-6-5)	120.6	A(6-10-14)	119.5	A(19-14-20)	109.8	A(32-34-38)	122.7
A(1-6-10)	116	A(7-13-16)	106	A(19-14-21)	109.3	A(32-34-41)	118.5
A(1-7-13)	115.6	A(7-13-17)	111	A(20-14-21)	109.3	A(36-33-37)	119.6
A(3-2-8)	121.7	A(7-13-18)	110.6	A(22-15-23)	109.3	A(33-36-38)	120.3
A(2-3-4)	116.5	A(8-25-26)	149.8	A(22-15-24)	109.9	A(33-36-39)	120
A(2-3-11)	117.5	A(10-14-19)	111.5	A(23-15-24)	109.4	A(38-34-41)	118.8
A(2-8-25)	106.2	A(10-14-20)	111.4	A(28-27-29)	121.9	A(34-38-36)	117.9
A(4-3-11)	126.1	A(10-14-21)	105.5	A(27-28-30)	117.4	A(34-38-40)	119.9
A(3-4-5)	121.5	A(26-11-27)	117.7	A(27-28-31)	126.6	A(34-41-42)	117.6
A(3-4-12)	117.5	A(11-26-25)	104	A(30-28-31)	116.1	A(34-41-43)	117.8
A(3-11-26)	119.9	A(11-27-28)	120.1	A(28-31-32)	122.8	A(38-36-39)	119.7
A(3-11-27)	122.4	A(11-27-	117.9	A(28-31-	119.1	A(36-38-	122.1

		29)		33)		40)	
A(5-4-12)	121	A(12-15-22)	111.4	A(32-31-33)	118	A(42-41-43)	124.6

Tabela S2. The Condensed Fukui functions for the nucleophilic attack (f^{+}), electrophilic attack(f^{-}), radical attack (f^{o}), the dual descriptor (Δf) calculated forthe title chalcone at B3LYP/6-311++G(d,p) computational level using the Hirshfeld charge population.

	f+		***f-***		***f°***		***Δf***
1(C)	0.013613		0.109342		0.061478		-0.09573
2(C)	0.016307		0.035639		0.025973		-0.01933
3(C)	0.002137		0.030139		0.016138		-0.028
4(C)	0.013089		0.054716		0.033902		-0.04163
5(C)	0.014723		0.041083		0.027903		-0.02636
6(C)	0.027024		0.037254		0.032139		-0.01023
7(O)	0.009408		0.064398		0.036903		-0.05499
8(O)	0.024531		0.053046		0.038789		-0.02852
9(H)	0.01061		0.023207		0.016909		-0.0126
10(O)	0.018258		0.041442		0.02985		-0.02318
11(C)	0.05172		0.008857		0.030289		0.042863
12(O)	-0.00163		0.055501		0.026933		-0.05714
13(C)	0.006409		0.026191		0.0163		-0.01978
14(C)	0.008047		0.018094		0.01307		-0.01005
15(C)	0.005329		0.017546		0.011437		-0.01222
16(H)	0.011585		0.027579		0.019582		-0.01599
17(H)	0.00255		0.017473		0.010012		-0.01492
18(H)	0.006068		0.022765		0.014417		-0.0167
19(H)	0.006656		0.016983		0.01182		-0.01033
20(H)	0.007125		0.017216		0.01217		-0.01009
21(H)	0.012085		0.021708		0.016896		-0.00962
22(H)	0.007947		0.017713		0.01283		-0.00977
23(H)	0.002355		0.021176		0.011765		-0.01882
24(H)	0.010374		0.017688		0.014031		-0.00731
25(H)	0.010252		0.019245		0.014748		-0.00899
26(O)	0.054204		0.028533		0.041368		0.025671
27(C)	0.0438		-0.00904		0.017381		0.052838
28(C)	0.042022		0.031891		0.036956		0.010131
29(H)	0.015341		-7E-05		0.007635		0.015411
30(H)	0.020203		0.012666		0.016435		0.007537
31(C)	0.024637		-0.00055		0.012045		0.025185
32(C)	0.012634		0.005022		0.008828		0.007612
33(C)	0.05926		0.012957		0.036109		0.046302

34(C)	0.021542		0.008256		0.014899		0.013286
35(H)	0.01131		-0.00188		0.004716		0.013187
36(C)	0.034295		0.014738		0.024516		0.019556
37(H)	0.029239		0.007232		0.018236		0.022007
38(C)	0.065385		0.023799		0.044592		0.041586
39(H)	0.026802		0.011805		0.019303		0.014997
40(H)	0.03333		0.0127		0.023015		0.02063
41(N)	0.046424		0.002672		0.024548		0.043752
42(O)	0.082641		0.021066		0.051854		0.061575
43(O)	0.080361		0.002194		0.041278		0.078167

Table S3. Affinity energy and RMSD values of the complexes formed after docking simulations against the Cruzain enzyme

Complex	Parameters			
	Energy (kcal/mol)	Ki	pKi	RMSD (Å)
CPAB-cruzain	-6.9	8.704×10^{-5}	5.06	1.976
BZN-cruzain	-6.0	3.979×10^{-5}	4.40	1.728
KB2-cruzain*	-5.6	7.818×10^{-5}	4.11	1.590

*ligand co-cristalized (redocking); BZN: benznidazol; KB2: (3S)-3-(4-{(1S)-1,2-dimethyl-1-[(quinolin-6-ylmethyl)amino]propyl}-1H-1,2,3-triazol-1-yl)heptan-2-one.

Table S4. Interactions between CPAB, CPAC, BZN and KB2 with cruzin

Binder	Receiver	Interaction	Distance (Å)
CPN3NO2	Trp 184 A	Hydrofobic	3.47
	Trp 184 A	Hydrofobic	3.59
	Trp 184 A	Hydrofobic	3.75
	Trp 184 A	Hydrofobic	3.82
	Gln 19A	H-Bond	2.98
	Trp 184 A	H-Bond	2.31
BZN	Trp 184A	Hydrofobic	3.52
	Trp 184A	Hydrofobic	3.78
	Trp 184A	Hydrofobic	3.67
	Trp 188A	Hydrofobic	3.99
	Gln 21A	H-Bond	3.54
	Trp 184A	π-stacking	4.54
KB2*	Leu 67A	Hydrofobic	3.88
	Leu 67A	Hydrofobic	3.59
	Gln 19A	H-Bond	2.28
	Cys 25A	H-Bond	2.18
	Gly 66A	H-Bond	1.87
	Gly 66A	H-Bond	2.27

*ligand co-cristalized (redocking); BZN: Benznidazol; KB2: (3S)-3-(4-{(1S)-1,2-dimethyl-1-[(quinolin-6-ylmethyl)amino]propyl}-1H-1,2,3-triazol-1-yl)heptan-2-one.