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Supplementary Information

The Correlation Between Electronic Structure and Antimalarial Activity of Tetrahydropyridines

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Logistic fits to obtain IC_{50} values

Figures S1-S4 show the logistic fits performed for all the compounds in order to obtain IC_{50} values. The fits were performed considering the activity reported by Misra *et al.* for distinct concentrations:[1] *(i)* 10, 5, 2.5 and 1.25 μg mL^{-1} for all the set of molecules and *(ii)* 0.78, 0.39, 0.19, 0.09, and 0.05 μg mL^{-1} only for the compounds that had presented 100% of efficiency at higher concentrations. In the following fits, we had employed logarithmic scales for very active compounds in order to better present the adjusted curve, linear scales were used for the others derivatives. The fits and graphics were performed with the aid of QtiPlot computational package.[2]

Energy evaluation

Figures S5-S7 present the result of total energy evaluation of each molecule. This study aimed to select low energy structures for subsequent RMSD-AP comparison. Red colored lines represent the most stable conformer (C1) and yellow lines (C2) define structures with relatively low energy, in relation to C1 (which difference does not exceed $k_B T_{300}$, or ca. 25 meV).

RMSD-AP study

Table S1 presents the RMSD-AP values obtained for each molecule (Mol). Such comparisons were performed by considering the atomic positions' deviation of each conformer, C2 (for which $E_T^{C2} = E_{T(min)} \leq k_B T_{300}$), in relation to the most stable structure, C1 (where $E_T^{C1} = E_{T(min)}$). Just the position of heavy atoms were considered in these evaluations (all hydrogens atoms were disregarded). The analyses were performed with the aid of Qmol computational package.[3]

For molecules **6**, **9**, **11**, and **12** just one stable conformer was obtained. In other words, there are no structures close in energy to the conformer C1. In these cases RMSD study was not necessary. On the other hand, all the conformers associated to the molecules **15** and **16** have shown similar energies, being necessary to evaluate all of them. Despite of it, as can be seen, all the structures have shown to be quite similar to each other (presenting very low RMSD-AP values).

It is important to note that all RMSD-AP values are bellow 2 Å, in such way that just one structure was considered in the single point calculations, based in our RMSD-AP cutoff value.

Equivalent linear regression

In addition to the result presented in the main text, multiple linear analyses also provide the following equivalent equation:

$$\frac{1}{IC_{50}} = -335.046 + (193.519 \times \mathrm{BO}_{28\text{-}29}) - (29.068 \times \mathrm{CHAR}^{\mathrm{MP}}_{32}) - (608.968 \times \mathrm{CHAR}^{\mathrm{MP}}_{29}) \quad \text{(S1)}$$

As can be seen, not just the electronic descriptors involved are equivalent to those observed in equation 3, but the obtained coefficients are also quite similar. This

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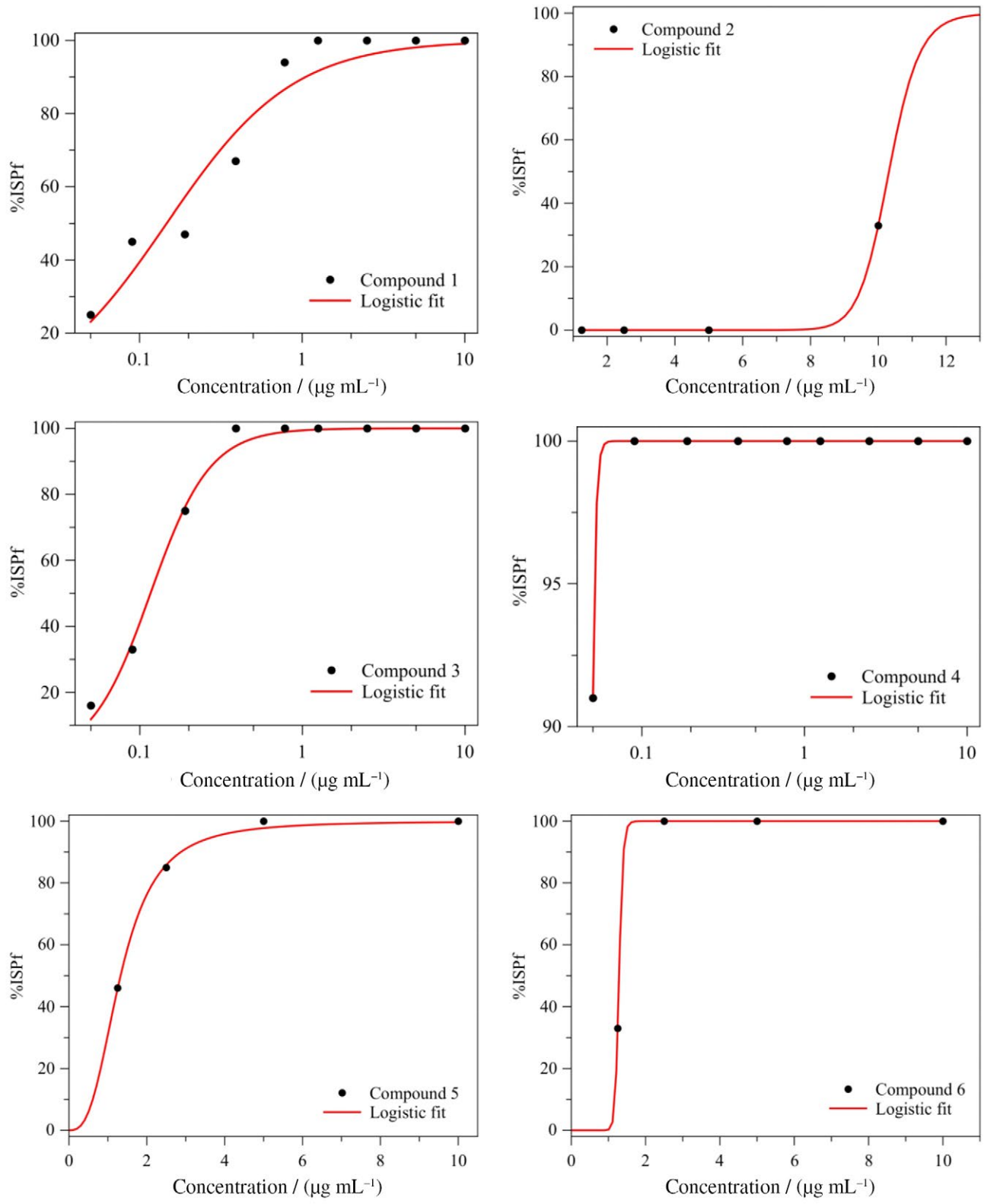


Figure S1. Logistic fits performed in order to obtain IC_{50} values: compounds from **01** to **06**.

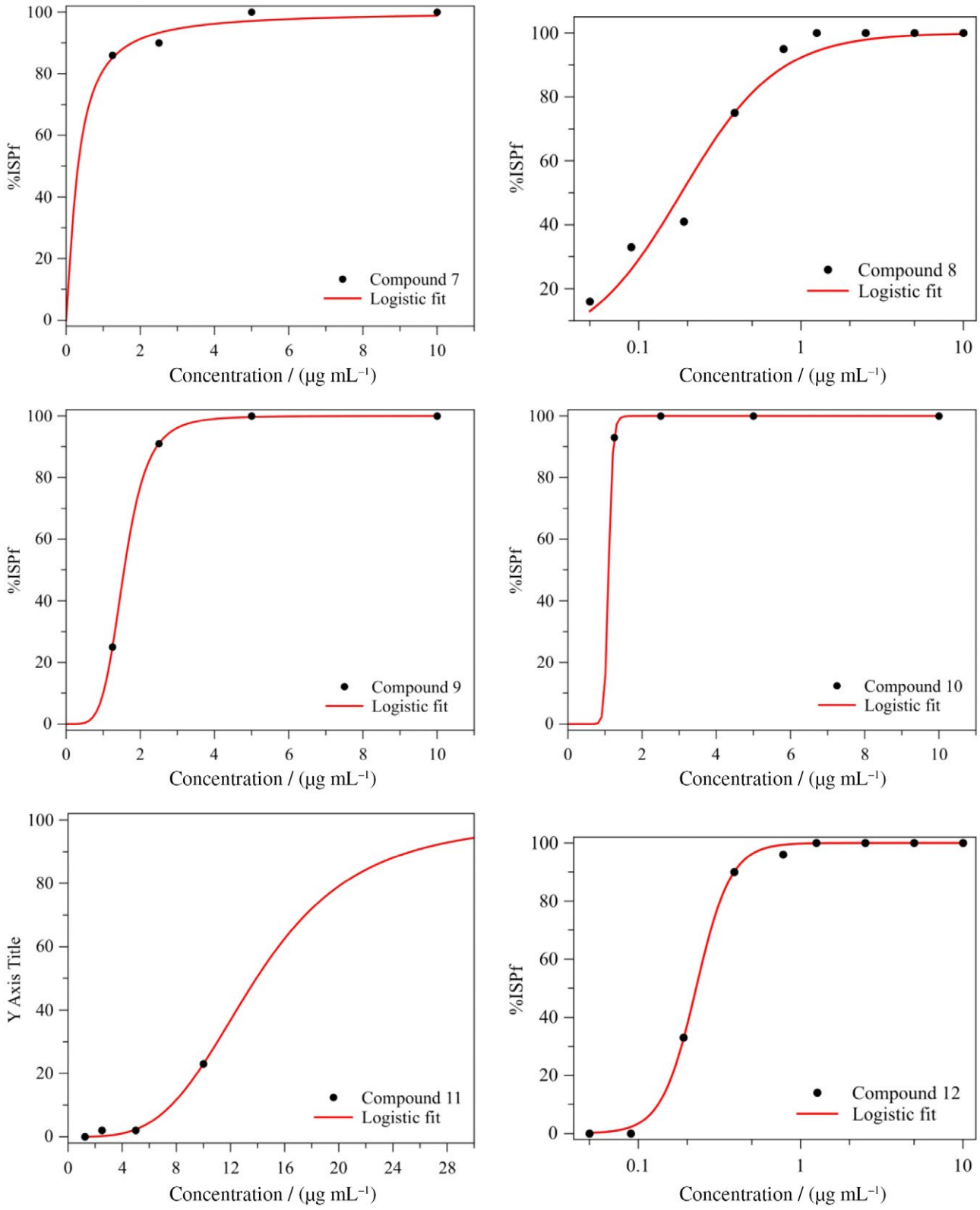


Figure S2. Logistic fits performed in order to obtain IC_{50} values: compounds from **07** to **12**.

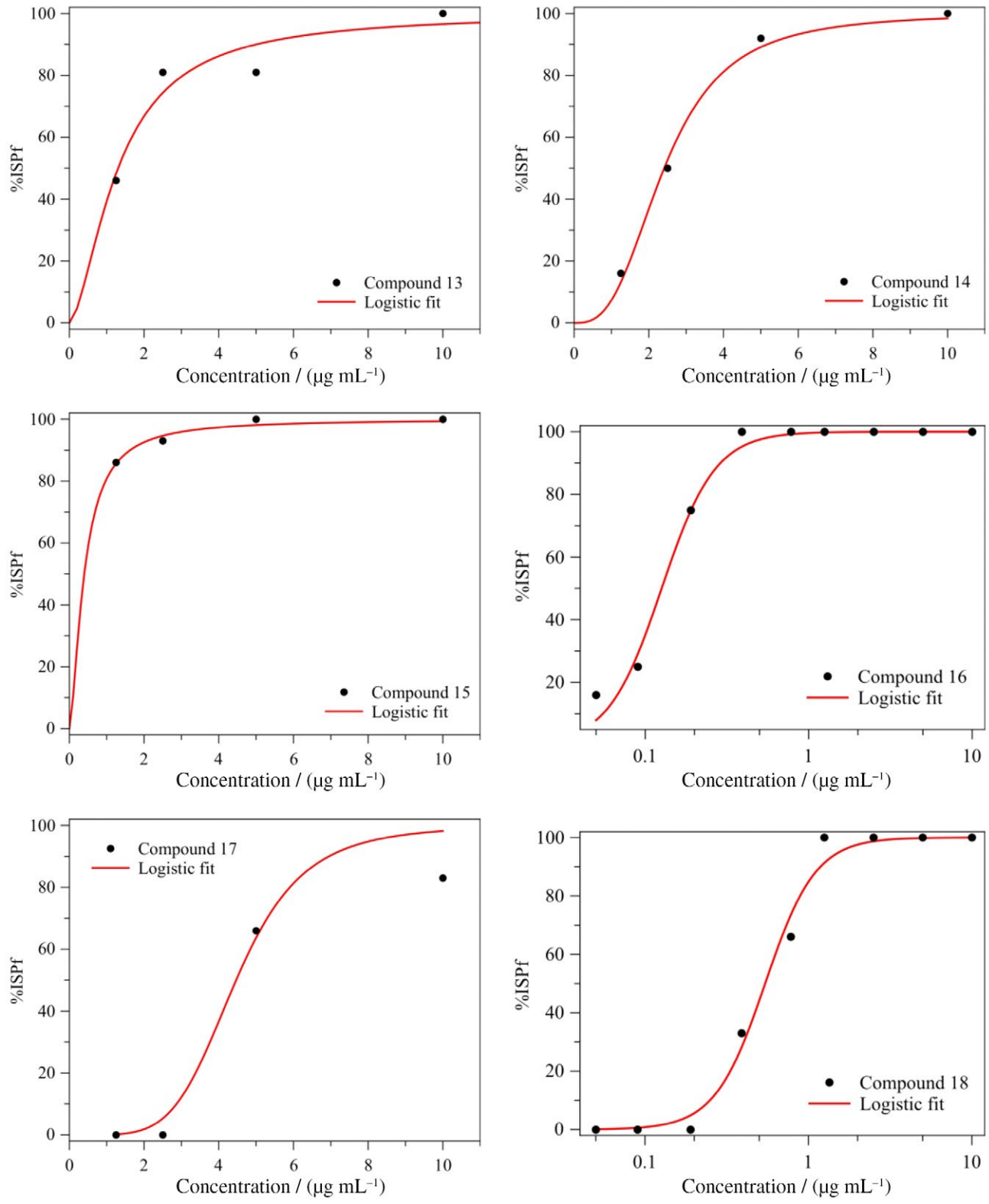


Figure S3. Logistic fits performed in order to obtain IC_{50} values: compounds from **13** to **18**.

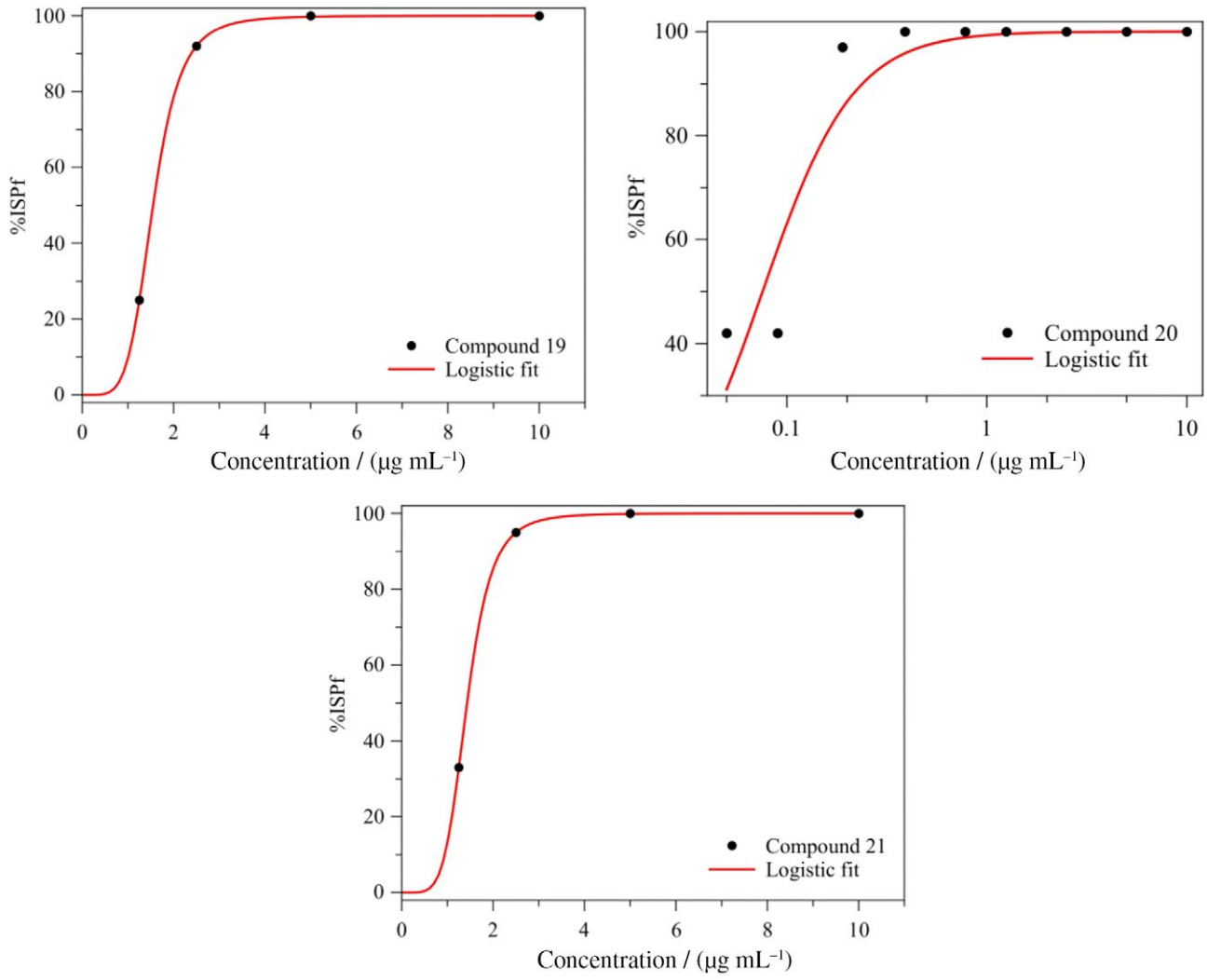
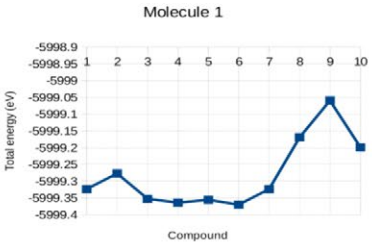


Figure S4. Logistic fits performed in order to obtain IC_{50} values: compounds from **19** to **21**.

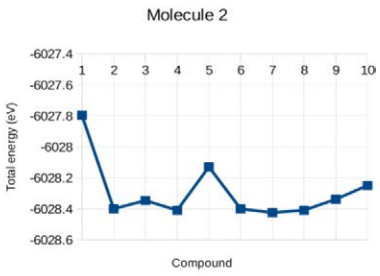
Molecule 1.

Compound	Total energy (eV)
1	-5999.32337
2	-5999.27688
3	-5999.35245
4	-5999.36393
5	-5999.35557
6	-5999.36993
7	-5999.32337
8	-5999.16892
9	-5999.05942
10	-5999.19890



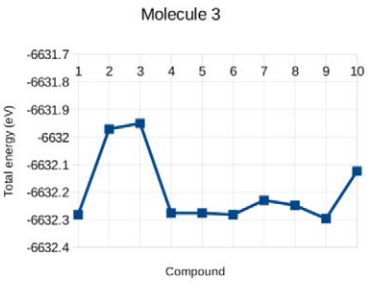
Molecule 2.

Compound	Total energy (eV)
1	-6027.79567
2	-6028.39863
3	-6028.34497
4	-6028.40793
5	-6028.12840
6	-6028.39863
7	-6028.42272
8	-6028.40793
9	-6028.33642
10	-6028.24797



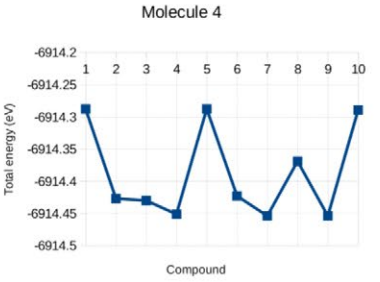
Molecule 3.

Compound	Total energy (eV)
1	-6632.28068
2	-6631.96983
3	-6631.94904
4	-6632.27488
5	-6632.27488
6	-6632.28068
7	-6632.22831
8	-6632.24685
9	-6632.29495
10	-6632.12245



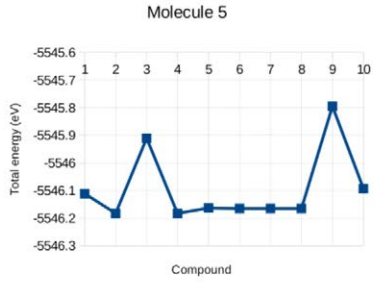
Molecule 4.

Compound	Total energy (eV)
1	-6914.28734
2	-6914.42677
3	-6914.42979
4	-6914.45114
5	-6914.28735
6	-6914.42264
7	-6914.45378
8	-6914.36880
9	-6914.45378
10	-6914.28895



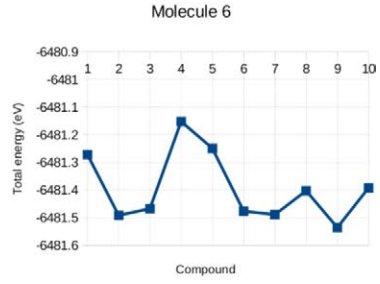
Molecule 5.

Compound	Total energy (eV)
1	-5546.11129
2	-5546.18295
3	-5545.91050
4	-5546.18295
5	-5546.16320
6	-5546.16515
7	-5546.16515
8	-5546.16515
9	-5545.79475
10	-5546.09314



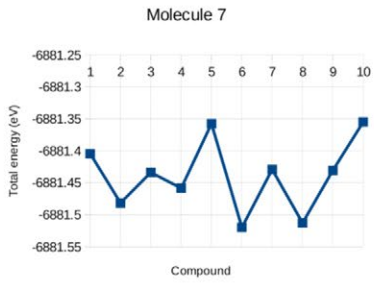
Molecule 6.

Compound	Total energy (eV)
1	-6481.27188
2	-6481.49175
3	-6481.46759
4	-6481.15216
5	-6481.24923
6	-6481.47667
7	-6481.48876
8	-6481.40275
9	-6481.53568
10	-6481.39230



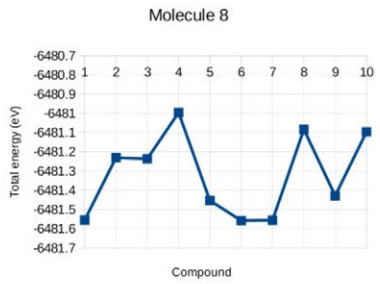
Molecule 7.

Compound	Total energy (eV)
1	-6881.40461
2	-6881.48165
3	-6881.43389
4	-6881.45843
5	-6881.35749
6	-6881.51994
7	-6881.42920
8	-6881.51291
9	-6881.43062
10	-6881.35482



Molecule 8.

Compound	Total energy (eV)
1	-6481.55626
2	-6481.23138
3	-6481.23700
4	-6480.99683
5	-6481.45440
6	-6481.55862
7	-6481.55656
8	-6481.08457
9	-6481.42934
10	-6481.09664



Molecule 9.

Compound	Total energy (eV)
1	-6428.37267
2	-6428.09574
3	-6428.35480
4	-6428.15582
5	-6428.35480
6	-6428.44687
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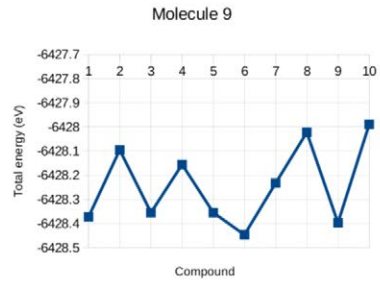
8	-6428.02282
9	-6428.39756
10	-6427.98926



Molecule 10.

Compound	Total energy (eV)
1	-6514.40938
2	-6514.45342
3	-6514.43106
4	-6514.34540
5	-6514.43904
6	-6514.34191
7	-6514.34724
8	-6514.13586
9	-6514.16310
10	-6514.26682

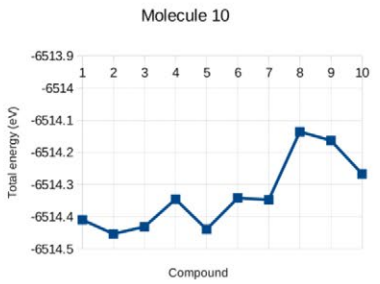
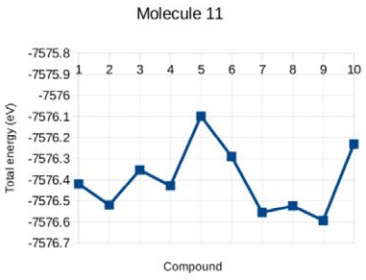


Figure S5. Energy evaluation of molecule conformers after geometry optimization (part 1).

Molecule 11.

Compound	Total energy (eV)
1	-7576.41988
2	-7576.51931
3	-7576.35342
4	-7576.42836
5	-7576.09869
6	-7576.28985
7	-7576.55505
8	-7576.52427
9	-7576.59330
10	-7576.23051



Molecule 12.

Compound	Total energy (eV)
1	-5117.11093
2	-5116.83334
3	-5117.11093
4	-5117.11093
5	-5117.11093
6	-5117.11093
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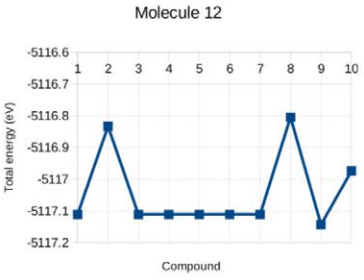
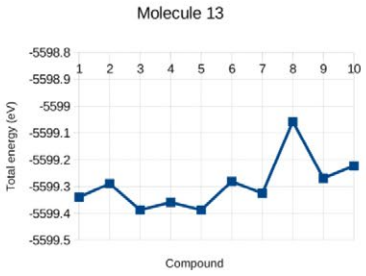
8	-5116.80494
9	-5117.14335
10	-5116.97455



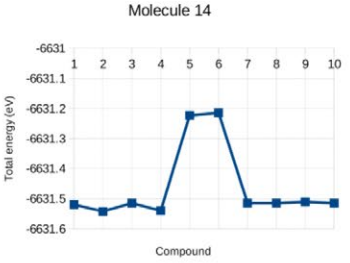
Molecule 13.

Compound	Total energy (eV)
1	-5599.33974
2	-5599.28917
3	-5599.38715
4	-5599.35861
5	-5599.38716
6	-5599.28058
7	-5599.32521
8	-5599.05750
9	-5599.26891
10	-5599.22296



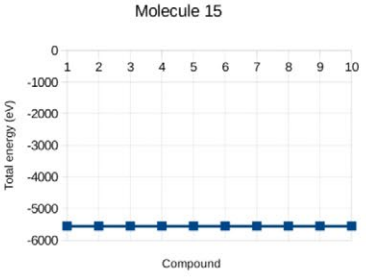
Molecule 14.

Compound	Total energy (eV)
1	-6631.51951
2	-6631.54250
3	-6631.51465
4	-6631.54002
5	-6631.22317
6	-6631.21412
7	-6631.51465
8	-6631.51465
9	-6631.51063
10	-6631.51465



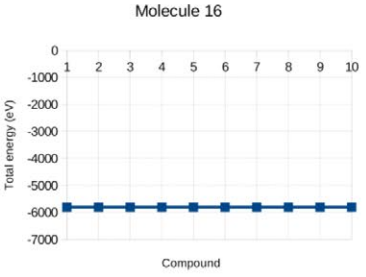
Molecule 15.

Compound	Total energy (eV)
1	-5553.49405
2	-5553.49405
3	-5553.49405
4	-5553.49405
5	-5553.49405
6	-5553.49405
7	-5553.49405
8	-5553.49405
9	-5553.49405
10	-5553.49405



Molecule 16.

Compound	Total energy (eV)
1	-5803.52465
2	-5803.52465
3	-5803.52465
4	-5803.52465
5	-5803.52465
6	-5803.52465
7	-5803.52465
8	-5803.52465
9	-5803.52465
10	-5803.52465



Molecule 17.

Compound	Total energy (eV)
1	-6231.51464
2	-6231.51269
3	-6231.31301
4	-6231.46591
5	-6231.46971
6	-6231.45836
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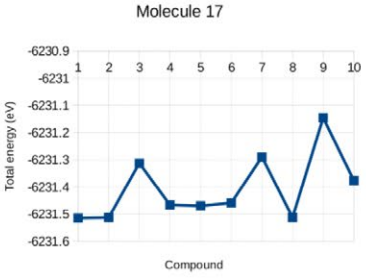
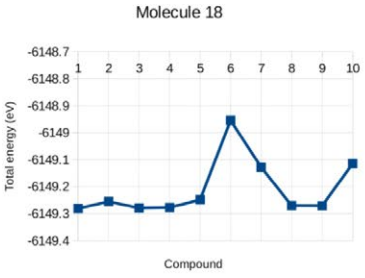
8	-6231.51252
9	-6231.14551
10	-6231.37647



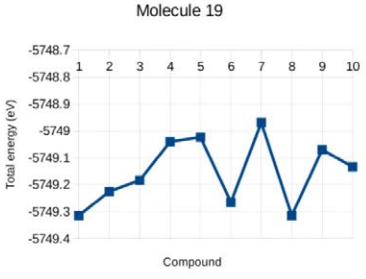
Molecule 18.

Compound	Total energy (eV)
1	-6149.28122
2	-6149.25494
3	-6149.27927
4	-6149.27740
5	-6149.24830
6	-6148.95413
7	-6149.12822
8	-6149.27013
9	-6149.27078
10	-6149.11468



Molecule 19.

Compound	Total energy (eV)
1	-5749.31420
2	-5749.22561
3	-5749.18357
4	-5749.04049
5	-5749.02363
6	-5749.26521
7	-5748.96932
8	-5749.31420
9	-5749.07010
10	-5749.13373



Molecule 20.

Compound	Total energy (eV)
1	-5353.47566
2	-5353.77345
3	-5353.75880
4	-5353.75880
5	-5353.74539
6	-5353.74302
7	-5353.44228
8	-5353.52266
9	-5353.44710
10	-5353.61514

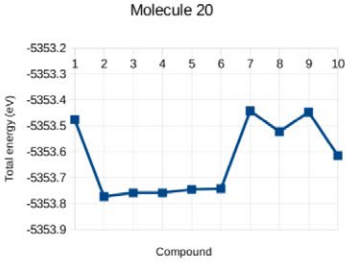


Figure S6. Energy evaluation of molecule conformers after geometry optimization (part 2).

Molecule 21.

Compound	Total energy (eV)
1	-6428.33381
2	-6428.42938
3	-6428.43001
4	-6428.41838
5	-6428.32110
6	-6428.32109
7	-6428.26516
8	-6428.04105
9	-6428.10680
10	-6428.27232

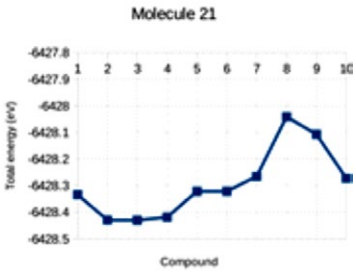


Figure S7. Energy evaluation of molecule conformers after geometry optimization (part 3).

Table S1. Data coming from RMSD-AP evaluation

Mol.	C1	C2	RMSD (Å)
1	6	3	1.401
	6	4	1.140
	6	5	0.000
2	7	2	1.147
	7	4	0.948
	7	6	1.510
	7	8	1.080
3	9	1	1.214
	9	4	1.618
	9	5	1.412
	9	6	1.221
4	9	3	1.414
	9	4	0.383
	9	7	0.758
	7	9	0.758
	7	3	1.200
	7	4	0.849
5	2	4	0.876
	2	5	1.408
	2	6	1.508
	2	7	1.502
	2	8	1.503
	4	2	0.076
	4	5	1.499
	4	6	1.402
	4	7	1.410
	4	8	1.410
6	9	–	–

Mol.	C1	C2	RMSD (Å)
7	6	8	0.975
8	6	1	1.177
	6	7	0.352
9	6	–	–
10	2	3	1.499
	2	5	0.682
11	9	–	–
12	9	–	–
13	5	3	0.136
14	4	1	1.613
	4	2	0.513
15	1	2	0.002
	1	3	0.001
	1	4	0.002
	1	5	0.002
	1	6	0.002
	1	7	0.003
	1	8	0.002
	1	9	0.002
	1	10	0.002
	2	3	0.002
	2	4	0.004
	2	5	0.004
	2	6	0.004
	2	7	0.003
	2	8	0.002
	2	9	0.001
	2	10	0.002

Mol.	C1	C2	RMSD (Å)
15	3	4	0.002
	3	5	0.003
	3	6	0.002
	3	7	0.003
	3	8	0.002
	3	9	0.002
	3	10	0.002
	4	5	0.001
	4	6	0.001
	4	7	0.005
	4	8	0.004
	4	9	0.003
	4	10	0.004
	5	6	0.001
	5	7	0.005
	5	8	0.004
	5	9	0.003
	5	10	0.004
	6	7	0.005
	6	8	0.004
	6	9	0.003
	6	10	0.003
	7	8	0.002
	7	9	0.003
	7	10	0.002
	8	9	0.002
	8	10	0.002
	9	10	0.002

Mol.	C1	C2	RMSD (Å)
16	1	2	0.002
	1	3	0.001
	1	4	0.002
	1	5	0.001
	1	6	0.004
	1	7	0.003
	1	8	0.004
	1	9	0.002
	1	10	0.005
	2	3	0.003
	2	4	0.004
	2	5	0.003
	2	6	0.004
	2	7	0.002
	2	8	0.003
	2	9	0.002
	2	10	0.004
	3	4	0.002
	3	5	0.002
	3	6	0.005
	3	7	0.004
	3	8	0.005
	3	9	0.003
	3	10	0.006
	4	5	0.002
	4	6	0.006
	4	7	0.005
	4	8	0.006

Mol.	C1	C2	RMSD (Å)
16	4	9	0.004
	4	10	0.007
	5	6	0.004
	5	7	0.004
	5	8	0.004
	5	9	0.003
	5	10	0.005
	6	7	0.002
	6	8	0.002
	6	9	0.003
	6	10	0.003
	7	8	0.001
	7	9	0.002
	7	10	0.002
	8	9	0.003
	8	10	0.002
	9	10	0.003
17	1	2	1.602
	1	8	0.485
18	1	3	0.541
	1	4	1.094
	1	8	0.826
	1	9	0.887
19	1	8	0.810
20	2	3	1.544
	2	4	1.546
21	3	2	0.506
	3	4	0.888

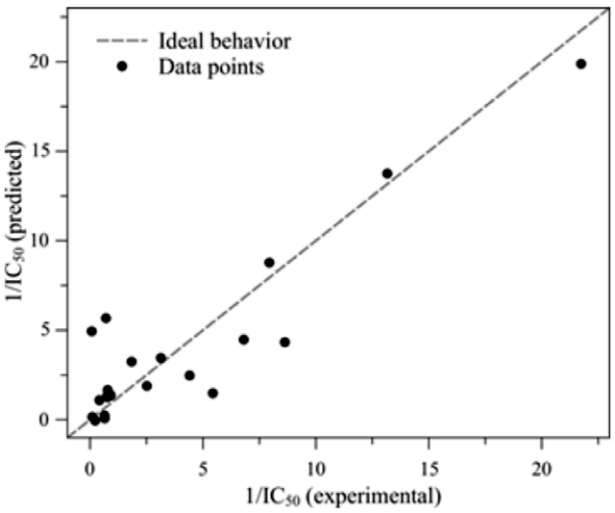


Figure S8. Comparison between 1 / IC_{50} values predicted by equation S1 and experimental data.

feature indicates that equation S1 and equation 3 carry the same physical information. Figure S8 present a comparison between experimental and predicted $1/IC_{50}$ values (by equation S1); it is equivalent to Figure 2 of the manuscript.

Relationship between the total energy and number of electrons in THP derivatives

Figure S9 shows the relationship between E_T and the number of electrons present in THP derivatives. Active and non-active compounds are distinguished by distinct points.

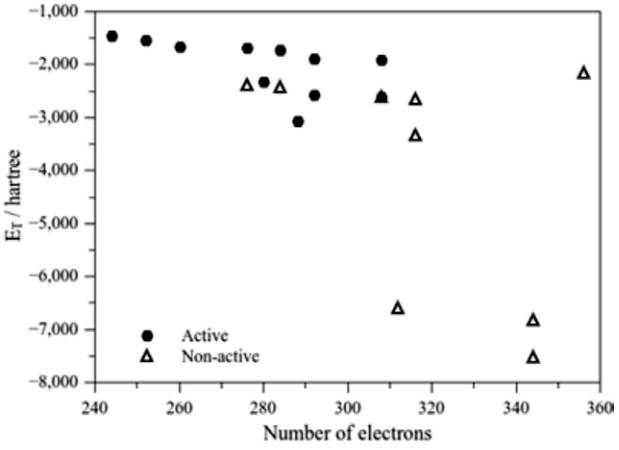


Figure S9. Relationship between total energy and number of electrons of THP derivatives.

Relationship between the hydrophobic parameter log P and IC_{50}

Figure S10 shows the linear dependence between the hydrophobic parameter and log (IC_{50}) associated to THP derivatives. The line represents the linear fit, which statistical information is presented in Table S2. The values of log P were obtained with the aid of ALOGPS 2.1 program,[4,5] implemented in the Virtual Computational Chemistry Laboratory.[6]

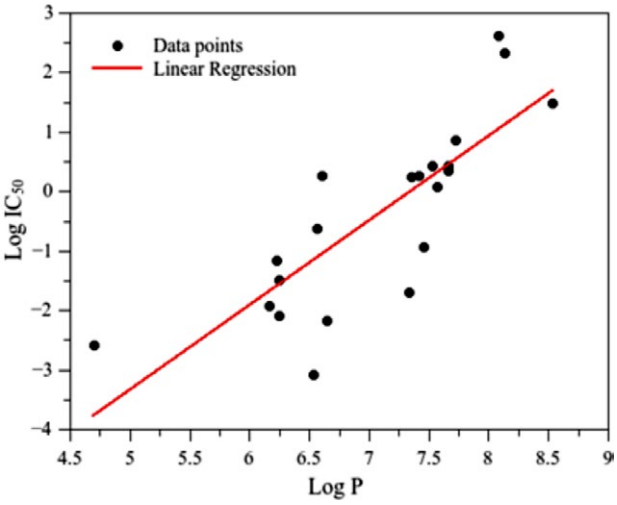


Figure S10. Relationship between log (P) and log (IC_{50}) obtained for THP derivatives.

Table S2. Regression equation data

Equation: Log (IC_{50}) = A_0 + A_1*Log (P)		
Parameter	Value	Error
A_0	–4.53	0.74
A_1	0.62	0.10
Correlation	0.79	–

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