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Supplementary Material

Local Intersection Volume (LIV) Descriptors: 3D-QSAR Models for PGI_2 Receptor Ligands

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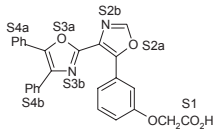
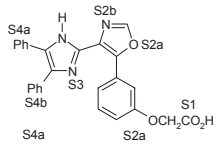
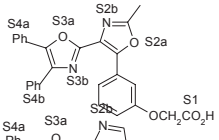
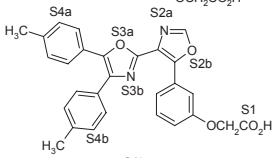
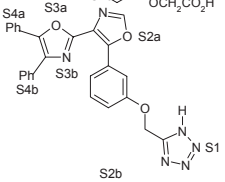
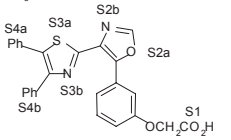
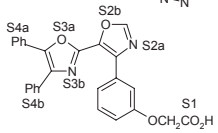
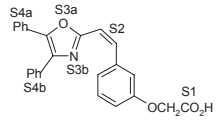
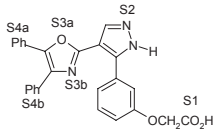
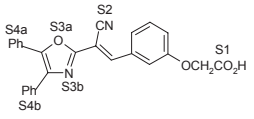
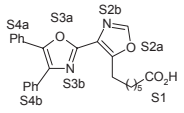
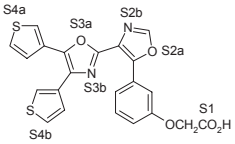
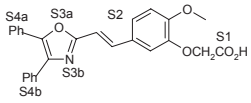
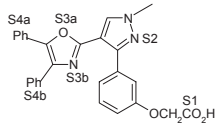
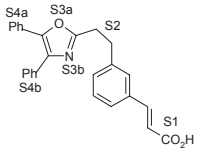
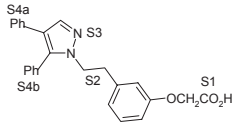
Table 1. Structures of the 43 aromatic heterocyclic derivatives (2-44) used in this work and their pIC_{50} values[4-8]

compound[a]	Structure	pIC_{50}	compound[a]	Structure	pIC_{50}
2		7.57	**3**		7.52
4		7.30	**5**		7.00
6		6.89	**7**		6.82
8		6.80	**9**		6.74
10		6.74	***11***		6.60
12		6.38	**13**		6.35
14		6.30	***15***		6.19
16		6.18	**17**		6.12

* e-mail: magaly@iq.ufrj.br

Table 1. (cont.)

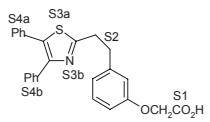
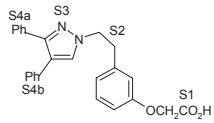
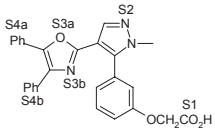
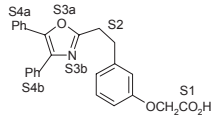
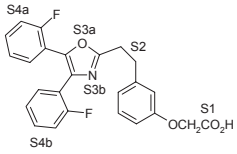
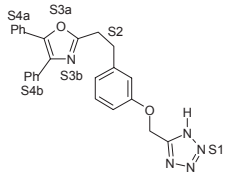
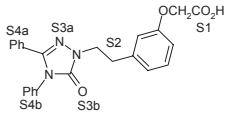
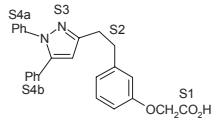
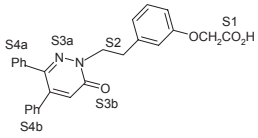
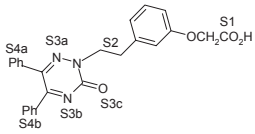
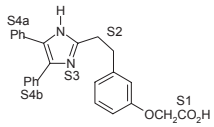
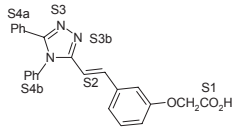
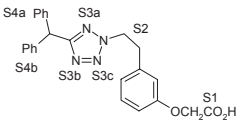
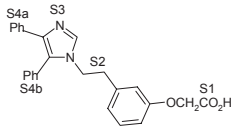
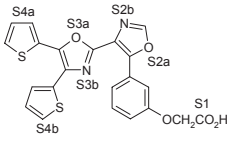
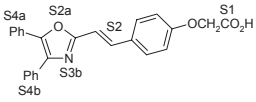
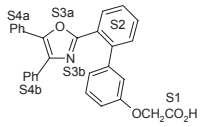
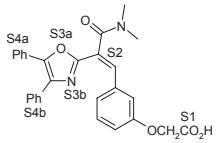
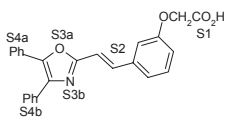
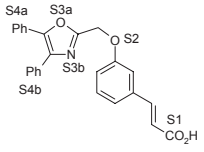
compound[a]	Structure	pIC_{50}	compound[a]	Structure	pIC_{50}
18		6.07	***19***		6.06
20		5.97	***21***		5.90
22		5.85	***23***		5.82
24		5.80	**25**		5.78
26		5.72	**27**		5.68
28		5.54	**29**		5.52
30		5.44	***31***		5.30
32		5.13	**33**		5.00
34		4.95	**35**		4.91
36		4.89	**37**		4.85

Table 1. (cont.)

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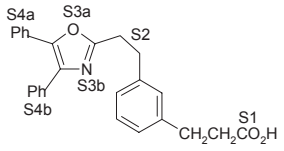
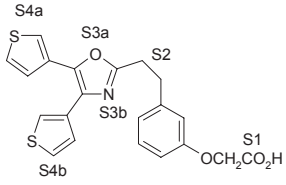
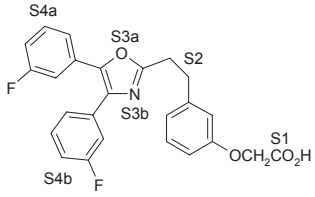
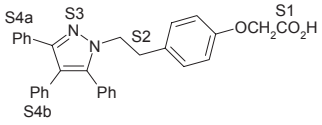
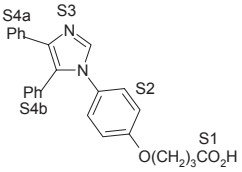
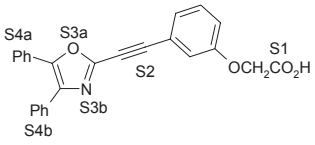
38		4.80	***39***		4.77
40		4.75	**41**		4.61
42		4.53	**43**		4.22

[a] Compounds from the test set are underlined.

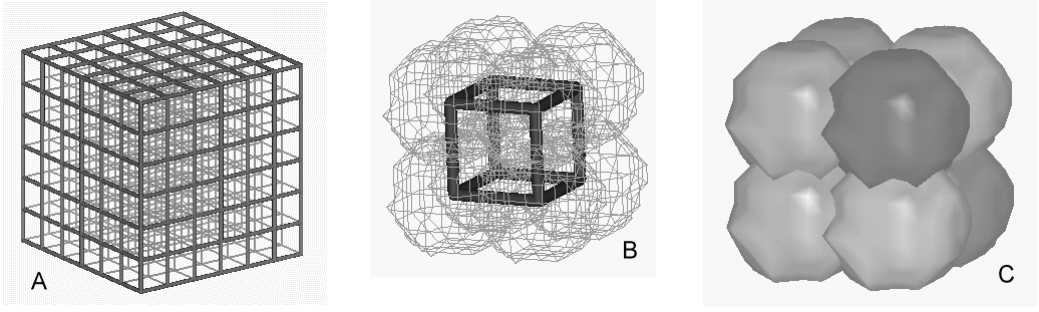


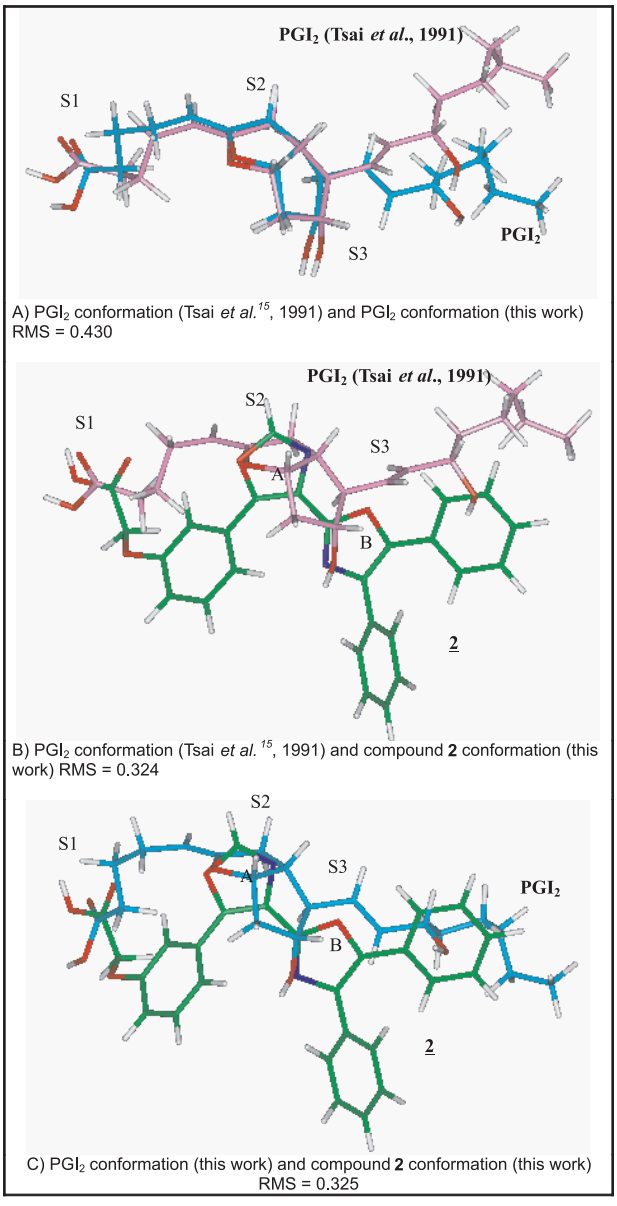
Figure 2. The grid matrix of hard spheres (A) composed by carbon atoms subdivided in cubic unitary cells of 1.5 Å of length (B), and the associated carbon atoms volumes (C) used to calculate the LIVs.

The PGI_2 reference conformation selection [19] (Methods, Step 3)

The PGI_2 conformational analysis was performed as described on Step 3 of Methods section. The PGI_2 conformation selected as the reference conformation is the one that has the lowest RMS value (RMS = 0.325) derived from the superposition of the PGI_2 and compound **2** conformations generated by the analysis using three atoms. This means a common conformation, and probably a bioactive one. The three atoms used for the superposition were selected according to structure-activity relationship (SAR) studies[5,20] in which the pharmacophoric groups were labeled as S1 (carbon atom of carboxylic acid group), S2 (oxygen atom of the endocyclic ring), and S3 (oxygen atom of the hydroxyl group binding at C11).

The PGI_2 reference conformation selected is in agreement with the conformation found by Tsai and co-workers (1991).[15] We reproduced the PGI_2 conformation from their work, and performed a superposition with the PGI_2 reference conformation selected for our work, using the same three atoms from the pharmacophoric groups described above. The RMS value observed were equal to 0.430, as may be seen in Figure A of Scheme 1.

We also observed from superposition the similarity between compound **2** conformation and both PGI_2 conformations, *i.e.*, PGI_2 Tsai and co-workers (1991) conformation and our PGI_2 conformation. The RMS values are 0.324 (Figure B, Scheme 1) and 0.325 (Figure C, Scheme 1). For PGI_2 conformations we used the same three atoms from the pharmacophoric groups described above for the superposition; and for compound **2** conformation we used as S2 atom the oxygen atom of the heterocyclic ring A, and as S3 atom the nitrogen atom of the heterocyclic B. These results point out the high degree of similarity among the selected conformations.



A) PGI_2 conformation (Tsai *et al.*[15], 1991) and PGI_2 conformation (this work) RMS = 0.430

B) PGI_2 conformation (Tsai *et al.*[15], 1991) and compound **2** conformation (this work) RMS = 0.324

C) PGI_2 conformation (this work) and compound **2** conformation (this work) RMS = 0.325

Scheme 1.

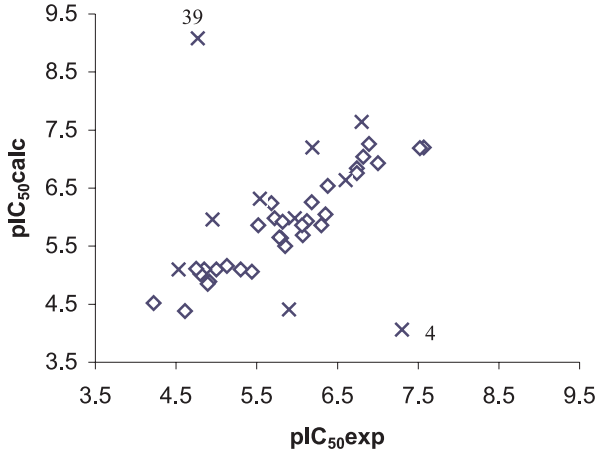


Figure 3. Experimental versus calculated (30 training compounds, ◊) and predicted (12 test compounds, ×) values (pIC_{50}) for the 42 aromatic heterocyclic compounds. The corresponding structures are indicated in Table 1.

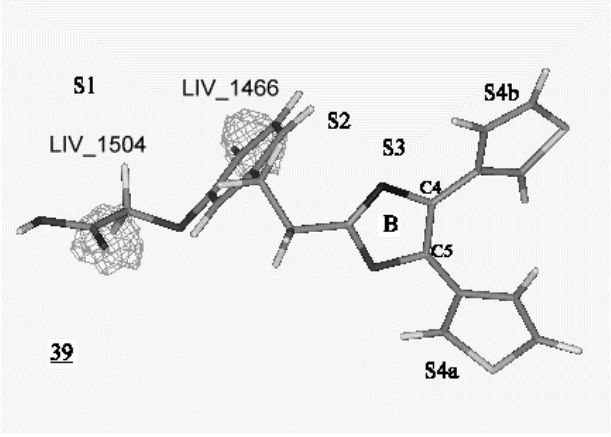


Figure 6. Graphical representation of the LIV-3D-QSAR Model 2 for compound **39** LIV_1466 and LIV_1504 correspond to positive (gray) contributions for the activity. Nitrogen atom in blue, oxygen atoms in red and sulfur atoms in yellow.