SUPPORTING INFORMATION

A Multilevel Strategy for the Exploration of the Conformational Flexibility of Small Molecules

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Figure S1. Population distribution for the active torsions of the (*top*) N1H and (bottom) N3H tautomers of neutral histamine in gas phase (gray) and in water (black).

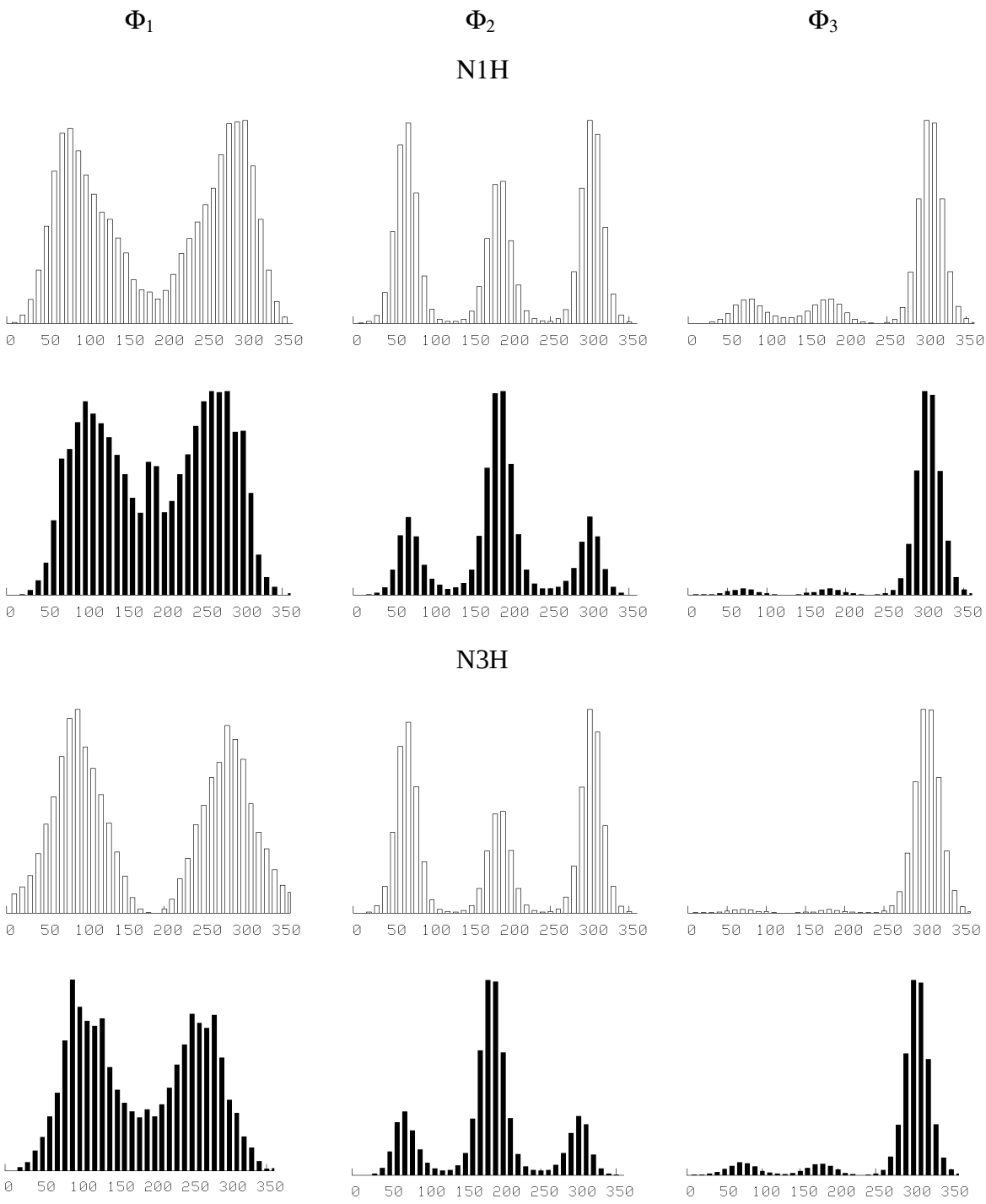
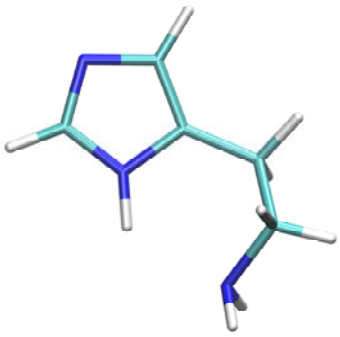
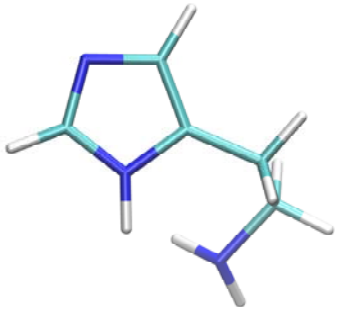


Figure S2. Minimum energy structures of the main conformational wells found for neutral histamine in the gas phase from multilevel calculations. The values of the torsional angles ϕ_1, ϕ_2 and ϕ_3 determined from B3LYP/6-31G(d) geometry optimizations are given for each structure (including the specular conformation). We have used the nomenclature adopted in ref. 42. G-X denotes the new conformer not described in ref. 42.

N1-H tautomer

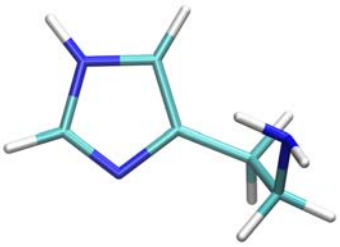


G-Iva: (43, 295, 174) and (317, 65, 70)

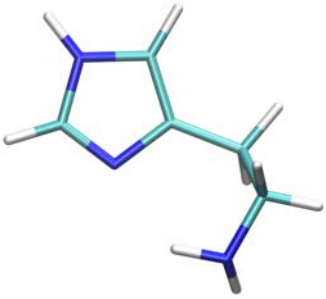


G-X (67, 305, 90) and (294, 54, 154)

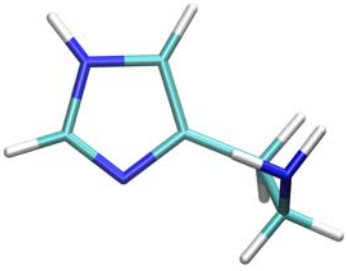
N3-H tautomer



G-Ib: (71, 66, 181) and (289, 294, 63)



G-Vc: (59, 294, 297) and (301, 66, 310)



G-Ic: (65, 63, 294) and (295, 298, 294)

Figure S3. Energy profile (kcal/mol) for the rotation around torsion that enables the conversion of the conformer of N1H tautomer characterized by torsional angles ϕ_1, ϕ_2 and ϕ_3 of 80, 300 and 80 degrees to the most stable conformer G-Iva.

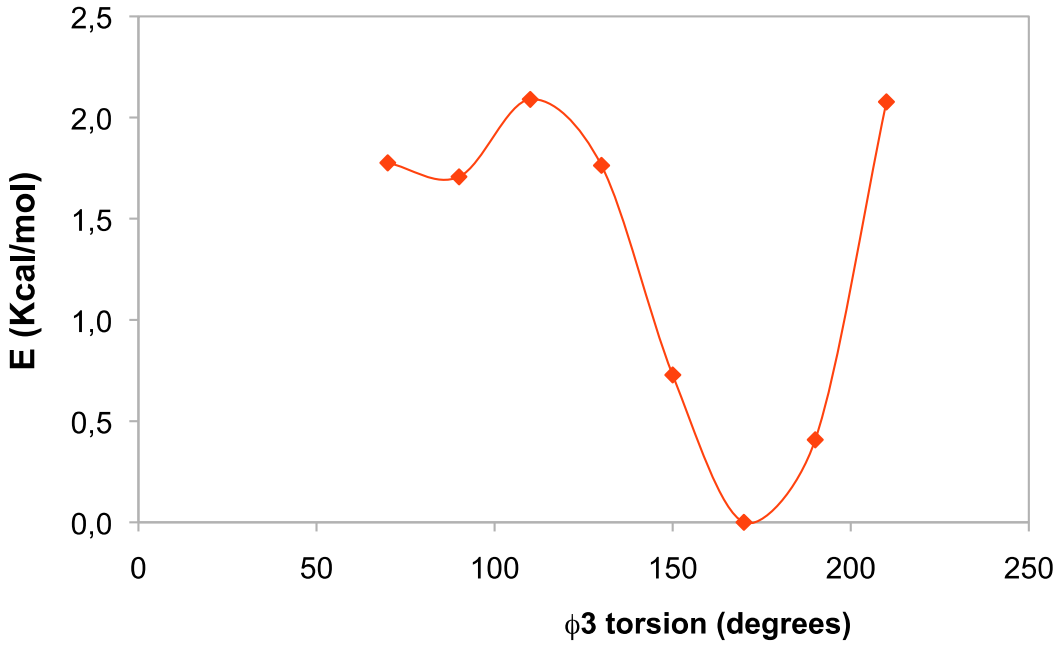


Figure S4. Minimum energy structures of the three main conformational wells found for nevirapine (shown as green-coloured sticks). (*top*) Superposition of the global minimum (i.e., the bioactive conformation) and the conformation found in the X-ray structure (shown as gray-coloured sticks). (*bottom*) Representation of the other two conformations found in the conformational sampling. They are mirror images and are disfavored by 5 kcal/mol with regard to the global minimum.

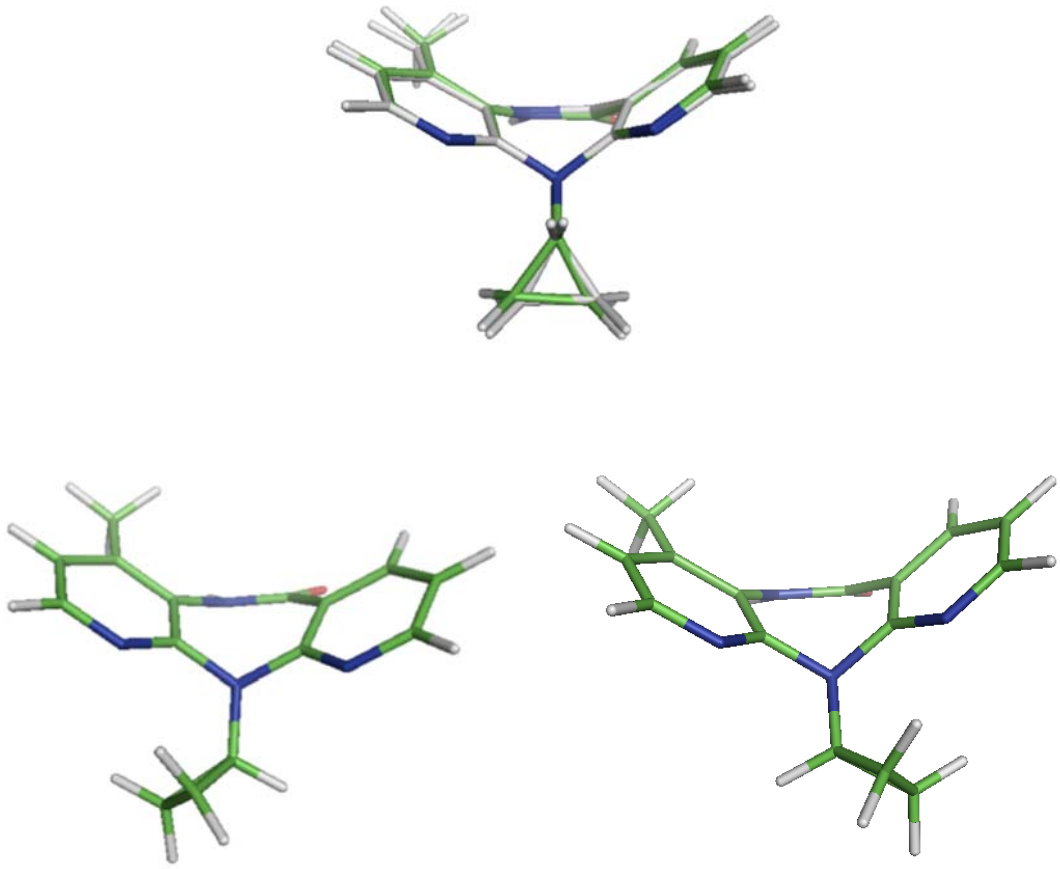


Table S1. Normalized distribution of conformational wells found using the multilevel strategy for neutral histamine in water. Values are given considering the flexibility around the three active torsions of the ethylamine side chain and the two tautomeric forms. Only those conformations with a total contribution equal or larger than 2% are indicated.

N1H				**N3H**			
ϕ_1	ϕ_2	ϕ_3	**%**	ϕ_1	ϕ_2	ϕ_3	**%**
Trans conformers (ϕ_2)							
70	179	69	2	71	181	303	5
69	182	177	2	72	180	68	3
71	180	303	3	69	183	178	7
290	181	177	2	214	181	178	2
291	178	69	2	292	177	68	7
289	180	303	3	289	179	303	5
Gauche conformers (ϕ_2)							
42	296	174	5	75	64	304	4
75	66	180	2	72	67	182	3
78	63	304	2	285	296	302	4
79	296	305	2	288	293	64	4
281	64	300	2				
285	62	167	2				
318	64	71	11				
282	297	302	3				
285	294	66	2				