

SUPPLEMENTARY MATERIAL TO
**Theoretical study of molecular structure, reactivity, and molecular
docking of almotriptan and its metabolite**

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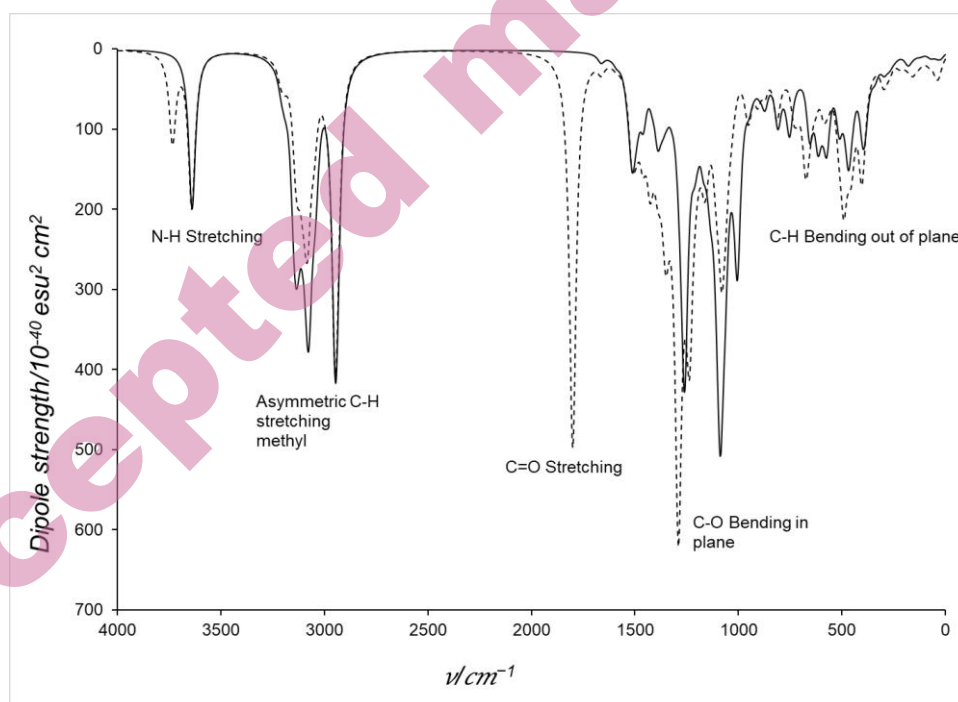


Fig S-1. Theoretical IR spectrum of Almo-I (solid line) and Almo-II (dashed line) in the aqueous medium obtained at the B3LYP / DGDZVP level of theory.

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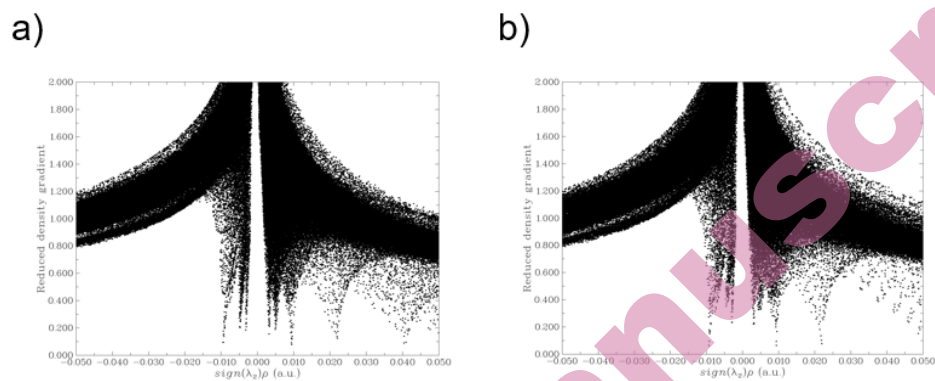


Fig S-2. Reduced density gradient vs $\text{sign}(\lambda_2)\rho$ for a) Almo-I and b) Almo-II.

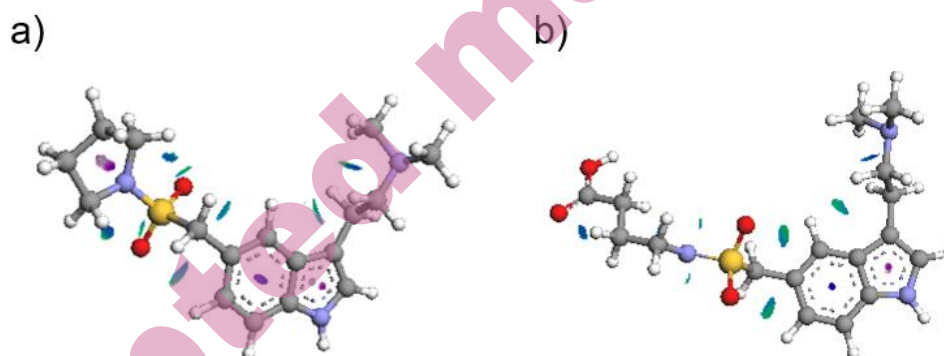


Fig S-3. NCI isosurfaces with $\rho=0.2$ for a) Almo-I and b) Almo-II in the aqueous phase.

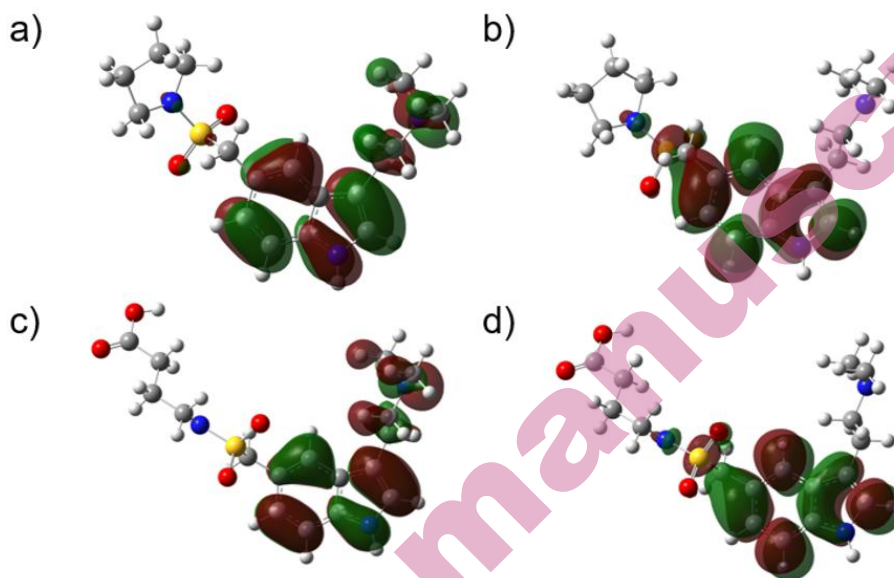


Fig S-4. HOMO-LUMO molecular orbital distribution of Almo-I and Almo-II, obtained at the B3LYP / DGDZVP level of theory in aqueous phase, employing the PCM solvation model. In all cases, the isosurfaces were generated at $0.08 \text{ e} / \text{u.a.}^3$.

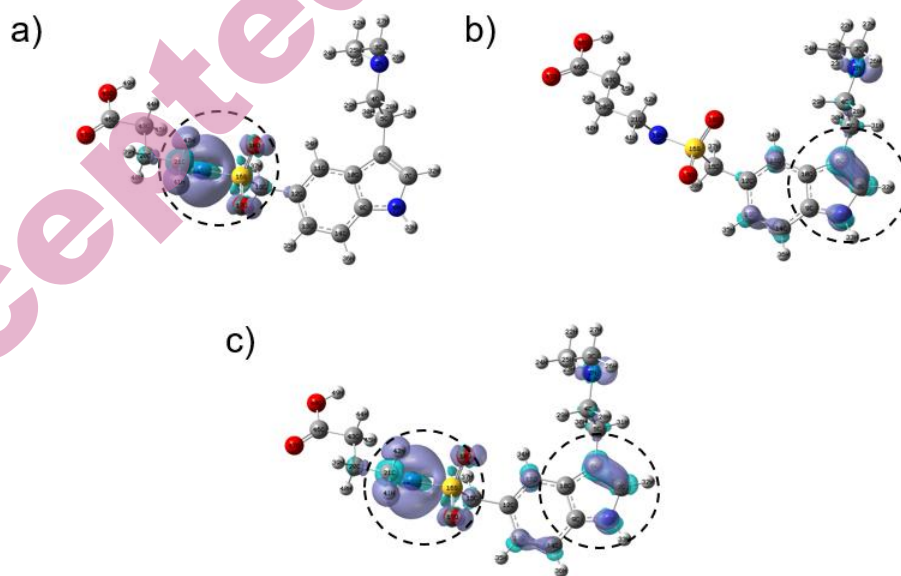


Fig. S-5. Fukui function isosurfaces for Almo-II, calculated according to Eqs. (10)–(12) at the B3LYP / DGDZVP level of theory using the PCM solvation model. The isosurfaces correspond to: (a) nucleophilic, (b) electrophilic, and (c) radical attacks. In all cases, the isosurfaces were generated at $0.004 \text{ e} \cdot \text{bohr}^{-3}$, and the dashed line highlights the most reactive regions of the molecule.

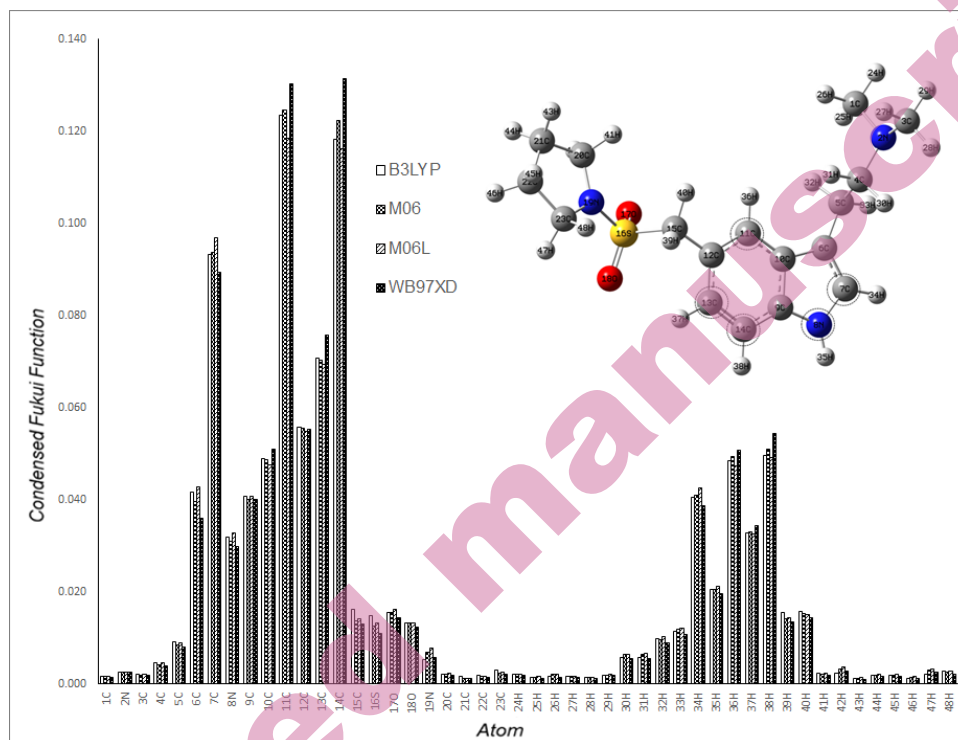


Fig S-6. Values of the condensed Fukui function for nucleophilic attacks on Almo-I at the x / DGDZVP level of theory (where X=B3LYP,^{26,27} M06,²⁸ M06L,²⁹ and ωB97XD³⁰) in the aqueous phase using Hirshfeld population analysis and equations (13)-(15).

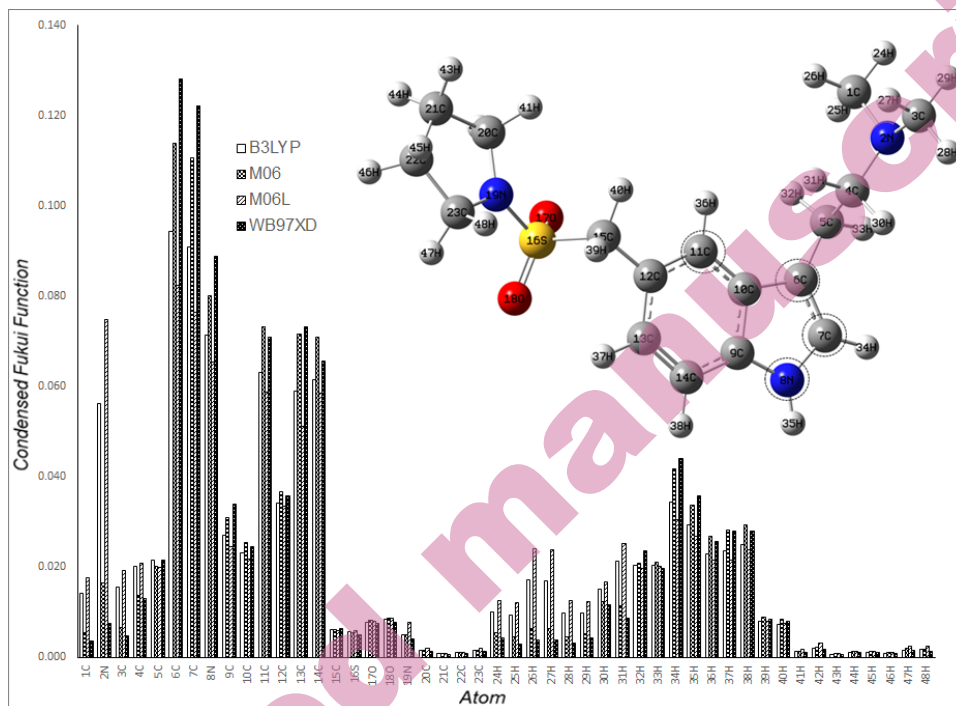


Fig S-7. Values of the condensed Fukui function for electrophilic attacks on Almo-I at the x / DGDZVP level of theory (where X=B3LYP,^{26,27} M06,²⁸ M06L,²⁹ and ω B97XD³⁰) in the aqueous phase using Hirshfeld population analysis and equations (13)-(15).

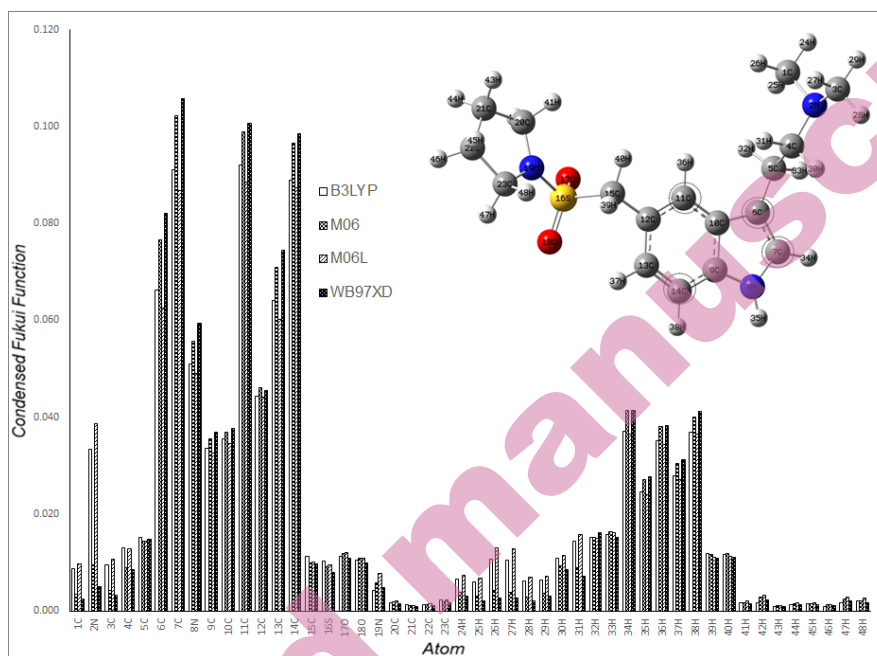


Fig S-8. Values of the condensed Fukui function for free radical attacks on Almo-I at the x / DGDZVP level of theory (where X=B3LYP,^{26,27} M06,²⁸ M06L,²⁹ and ω B97XD³⁰) in the aqueous phase using Hirshfeld population analysis and equations (13)-(15).

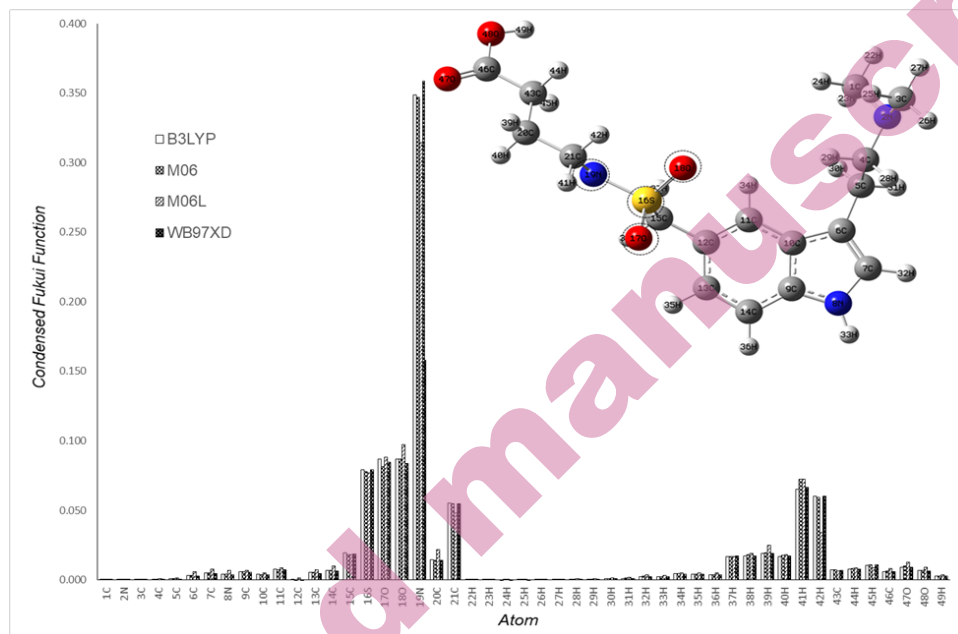


Fig S-9. Values of the condensed Fukui function for nucleophilic attacks on Almo-II at the x / DGDZVP level of theory (where X=B3LYP,^{26,27} M06,²⁸ M06L,²⁹ and ω B97XD³⁰) in the aqueous phase using Hirshfeld population analysis and equations (13)-(15).

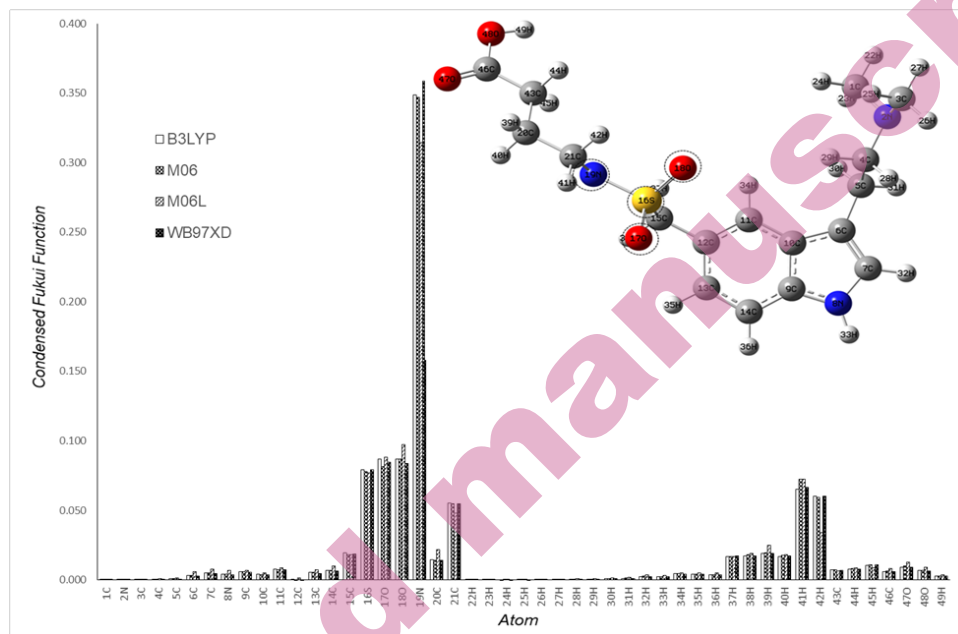


Fig S-10. Values of the condensed Fukui function for electrophilic attacks on Almo-II at the x / DGDZVP level of theory (where X=B3LYP,^{26,27} M06,²⁸ M06L,²⁹ and ω B97XD³⁰) in the aqueous phase using Hirshfeld population analysis and equations (13)-(15).

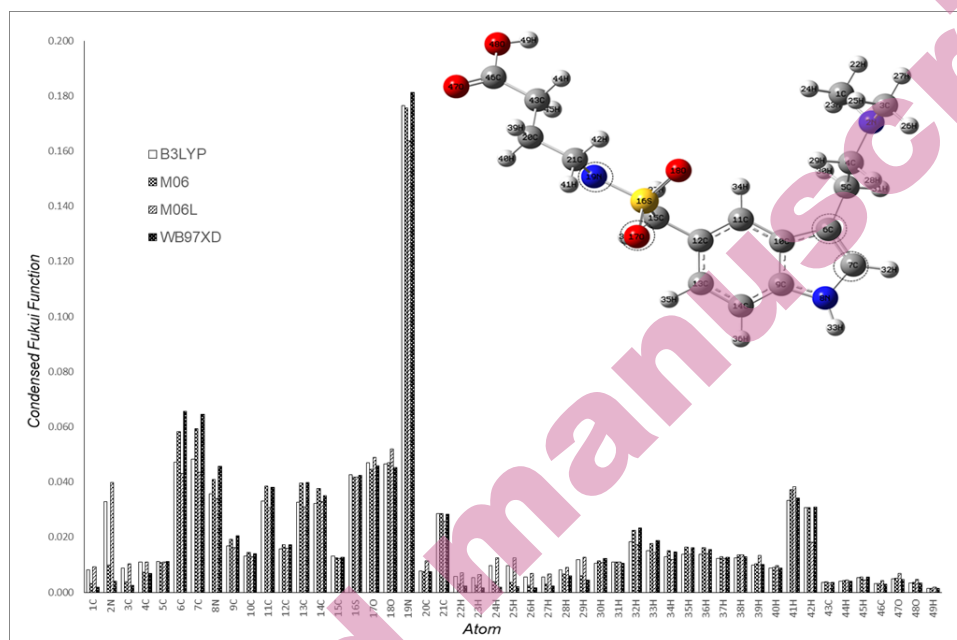


Fig S-11. Values of the condensed Fukui function for free radical attacks on Almo-II at the x / DGDZVP level of theory (where X=B3LYP,^{26,27} M06,²⁸ M06L,²⁹ and ω B97XD³⁰) in the aqueous phase using Hirshfeld population analysis and equations (13)-(15).

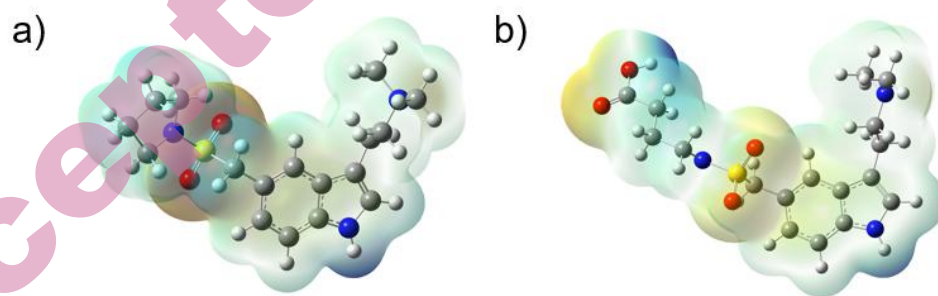
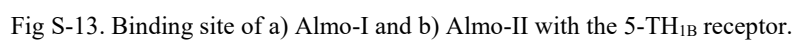
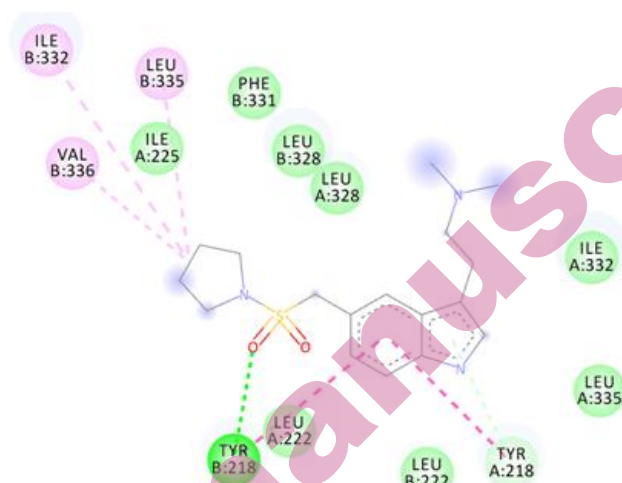


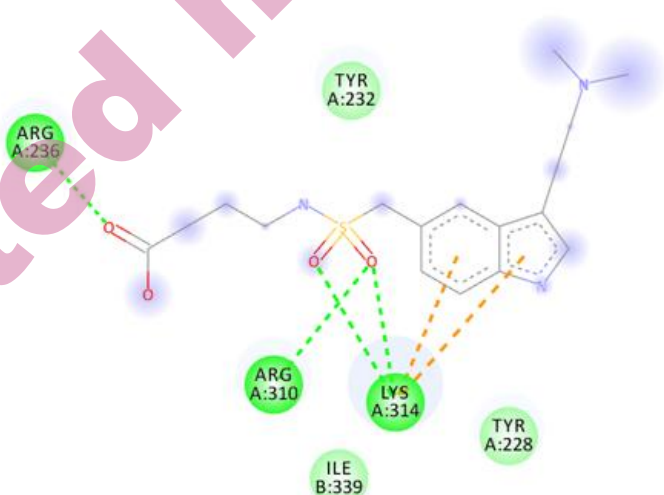
Fig S-12. Electrostatic potential mapping, evaluated at the B3LYP / DGDZVP level of theory using the PCM solvation model, over an electron density isosurface (value=0.002 e / u.a.³) for a) Almo-I and b) Almo-II.



a)



b)

**Interactions**

Van der Waals

Conventional
Hydrogen Bond

π-Cation



π-π Stacked



Alkil

Fig S-14. Two-dimensional interactions map predicted of a) Almo-I and b) Almo-II with the 5-TH_{1B} receptor obtained from the molecular docking.

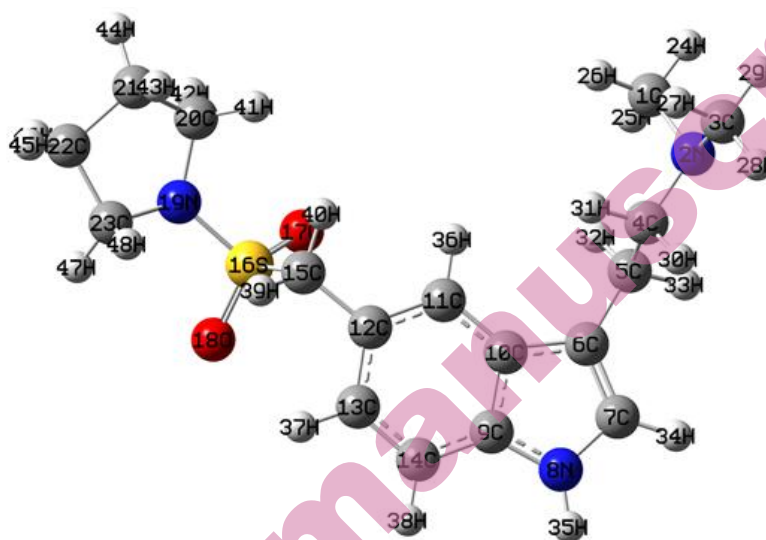
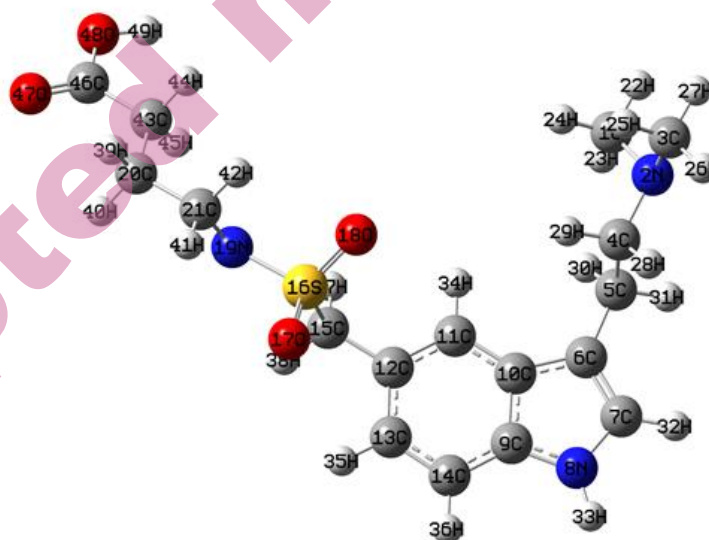


Fig S-15. Atom numbering schemes of Almo-I and Almo-II used in the Fukui function analysis.

Table S-1. Cartesian coordinates (Å) of the optimized structure of Almo-I at the B3LYP / DGDZVP level of theory in aqueous phase.

Atom	Element	X / Å	Y / Å	Z / Å
1	C	-3.86607	3.43341	0.710649
2	N	-4.80062	2.537226	0.023973
3	C	-5.35703	3.200775	-1.15846
4	C	-4.17802	1.258663	-0.34879
5	C	-3.87604	0.345734	0.857261
6	C	-3.33119	-0.99743	0.448484
7	C	-4.02394	-2.18822	0.404992
8	N	-3.19895	-3.20822	-0.04253
9	C	-1.94409	-2.69619	-0.29305
10	C	-1.98909	-1.30128	0.003916
11	C	-0.82126	-0.53263	-0.164
12	C	0.349013	-1.14482	-0.61998
13	C	0.360247	-2.53427	-0.91337
14	C	-0.77639	-3.32164	-0.75538
15	C	1.604242	-0.33524	-0.80086
16	S	2.694171	-0.37325	0.688538
17	O	1.969348	0.273587	1.799153
18	O	3.178712	-1.7566	0.860409
19	N	4.016757	0.567354	0.360585
20	C	3.903704	2.058123	0.35128
21	C	4.935282	2.492822	-0.70409
22	C	5.947635	1.335069	-0.73624
23	C	5.066136	0.090327	-0.5813
24	H	-4.37713	4.367	0.967217
25	H	-3.51064	2.98474	1.64177
26	H	-2.98424	3.685068	0.090798
27	H	-4.58801	3.456563	-1.91186
28	H	-6.09818	2.552136	-1.63659
29	H	-5.85813	4.12783	-0.86068
30	H	-4.87726	0.729405	-1.00539
31	H	-3.25316	1.42056	-0.93513
32	H	-3.16169	0.835185	1.528861
33	H	-4.80228	0.211385	1.426647
34	H	-5.05469	-2.39476	0.664902
35	H	-3.47249	-4.17748	-0.14086
36	H	-0.827	0.532393	0.05685
37	H	1.278292	-2.99283	-1.27141
38	H	-0.7562	-4.38365	-0.98663
39	H	2.228354	-0.70947	-1.61601
40	H	1.393923	0.723263	-0.9705
41	H	2.892187	2.390882	0.103319
42	H	4.149638	2.437557	1.347313
43	H	4.451026	2.592426	-1.68098
44	H	5.391687	3.453166	-0.45181
45	H	6.532907	1.303386	-1.65861

Atom	Element	X / Å	Y / Å	Z / Å
46	H	6.640978	1.407127	0.108212
47	H	5.591579	-0.76508	-0.15393
48	H	4.640148	-0.20442	-1.54917

Table S-2. Cartesian coordinates (Å) of the optimized structure of Almo-II at the B3LYP / DGDZVP level of theory in aqueous phase.

Atom	Element	X / Å	Y / Å	Z / Å
1	C	3.192148	4.121723	-0.641646
2	N	4.202776	3.538969	0.245321
3	C	4.171706	4.204948	1.550537
4	C	4.037065	2.087042	0.404588
5	C	4.405522	1.281514	-0.858263
6	C	4.322039	-0.206117	-0.640209
7	C	5.374826	-1.064953	-0.409177
8	N	4.909642	-2.357863	-0.226377
9	C	3.536888	-2.363569	-0.338001
10	C	3.128245	-1.020928	-0.598657
11	C	1.758044	-0.749391	-0.770333
12	C	0.832592	-1.792857	-0.679676
13	C	1.269146	-3.11811	-0.416508
14	C	2.617308	-3.419067	-0.247236
15	C	-0.635166	-1.515963	-0.853919
16	S	-1.436156	-1.099219	0.738852
17	O	-1.418877	-2.274	1.63499
18	O	-0.898112	0.177847	1.251955
19	N	-3.036809	-0.838318	0.210913
20	C	-5.361367	-0.232677	0.732233
21	C	-3.955788	-0.488163	1.281791
22	H	3.360298	5.200031	-0.728733
23	H	3.263585	3.694196	-1.645053
24	H	2.160522	3.964554	-0.272731
25	H	3.208659	4.073473	2.079299
26	H	4.967225	3.809737	2.190582
27	H	4.341179	5.279073	1.421388
28	H	4.70132	1.76533	1.214082
29	H	3.006826	1.833977	0.720715
30	H	3.748153	1.561772	-1.689015
31	H	5.423653	1.555154	-1.156034
32	H	6.436192	-0.855436	-0.362457
33	H	5.491825	-3.167681	-0.055702
34	H	1.418568	0.263267	-0.975543
35	H	0.53455	-3.916631	-0.352005
36	H	2.942482	-4.438367	-0.05528
37	H	-0.836035	-0.65368	-1.49337
38	H	-1.193723	-2.378289	-1.224722

Atom	Element	X / Å	Y / Å	Z / Å
39	H	-6.031775	-0.072325	1.581861
40	H	-5.713526	-1.127334	0.210685
41	H	-3.978086	-1.309065	2.015538
42	H	-3.574419	0.38864	1.828341
43	C	-5.413623	0.975276	-0.206521
44	H	-5.066016	1.880381	0.308017
45	H	-4.737139	0.829936	-1.057531
46	C	-6.803477	1.250743	-0.750165
47	O	-7.801096	0.603991	-0.489822
48	O	-6.911414	2.313145	-1.592837
49	H	-6.045757	2.742731	-1.720295