

Supporting Information

Computational Insights into β -Carboline Inhibition of Monoamine Oxidase A

*Alja Prah,^{1,2} Tanja Gavranic,^{1,3} Andrej Perdih,^{1,3} Marija Sollner Dolenc,³ Janez Mavri^{*1}*

¹ Theory Department, National Institute of Chemistry, Slovenia

² Networking Infrastructure Centre, Jožef Stefan Institute, Slovenia

³ University of Ljubljana, Faculty of Pharmacy, Slovenia

** Correspondence: janez.mavri@ki.si*

Table S1. Parameters and atom types for compound 1.

Name	Atom type	Charge	Name	Atom type	Charge
N1	NB	-0.627167	C10	CA	-0.258372
C1	CA	0.277849	C11	CA	-0.044640
N2	NA	-0.659257	H1	HA	0.074191
C2	CA	0.346683	H2	HA	0.138254
C3	CA	-0.524251	H3	HA	0.155958
C4	C56B	0.314435	H4	HA	0.160158
C5	C56B	-0.004619	H5	HA	0.181165
C6	C56B	0.433887	H6	HA	0.058143
C7	CA	-0.375403	H7	HA	0.206540
C8	C56B	-0.165691	H8	H	0.421296
C9	CA	-0.109160			

Table S2. Parameters and atom types for compound 2.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CA	-0.124700	C12	CT	-0.185016
N1	NAP	0.034460	H1	HC	0.154979
C2	CA	-0.070145	H2	HC	0.154979
N2	NA	-0.624408	H3	HC	0.154979
C3	CA	-0.248609	H4	HA	0.181944
C4	C56B	0.146988	H5	HA	0.173293
C5	C56B	0.198083	H6	HA	0.161804
C6	C56B	0.397271	H7	HA	0.200980
C7	CA	-0.355814	H8	HA	0.200813
C8	C56B	-0.067840	H9	HA	0.215975
C9	CA	-0.148086	H10	HA	0.214076
C10	CA	-0.201283	H11	H	0.440122
C11	CA	-0.004845			

The chemical structure of compound 2 is a complex polycyclic system. It features a central nitrogen atom (N2) bonded to two carbon atoms (C5 and C6). Carbon C5 is part of a five-membered ring containing carbons C1, C2, and C3, which is further connected to a six-membered ring containing carbons C4, C8, and C9. The six-membered ring is fused to a five-membered ring containing carbons C10, C11, and C12. Various hydrogen atoms (H1 to H11) are shown bonded to the carbon atoms, and some carbons have specific atom types assigned (e.g., CA, CT, HC, HA).

Table S3. Parameters and atom types for compound 3.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CT	-0.523721	C11	CA	-0.233281
N1	NB	-0.658430	C12	CA	-0.065902
C2	CA	0.595521	H1	HA	0.177082
N2	NA	-0.541782	H2	HA	0.136823
C3	CA	0.240226	H3	HA	0.164965
C4	CA	-0.435624	H4	HA	0.174390
C5	C56B	0.176056	H5	HA	0.097254
C6	C56B	-0.090646	H6	HA	0.179458
C7	C56B	0.373985	H7	HC	0.139919
C8	CA	-0.375332	H8	HC	0.139919
C9	C56B	-0.029445	H9	HC	0.139919
C10	CA	-0.177414	H10	H	0.396061

The chemical structure of compound 3 is a complex polycyclic system. It features a central nitrogen atom (N2) bonded to two carbon atoms (C5 and C6). Carbon C5 is part of a five-membered ring containing carbons C1, C2, and C3, which is further connected to a six-membered ring containing carbons C4, C9, and C10. The six-membered ring is fused to a five-membered ring containing carbons C11, C12, and C7. Various hydrogen atoms (H1 to H9) are shown bonded to the carbon atoms, and some carbons have specific atom types assigned (e.g., CA, CT, HC, HA).

Table S4. Parameters and atom types for compound 4.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CA	0.314960	C13	CT	-0.369953
N1	NAP	-0.005213	H1	HA	0.190157
C2	CA	-0.130805	H2	HA	0.181759
N2	NA	-0.509171	H3	HA	0.197921
C3	CA	-0.244798	H4	HA	0.159727
C4	C56B	0.078153	H5	HC	0.144194
C5	C56B	-0.030148	H6	HA	0.211289
C6	C56B	0.360353	H7	HA	0.226637
C7	CA	-0.374663	H8	HC	0.144194
C8	C56B	0.019461	H9	HC	0.144194
C9	CA	-0.190045	H10	HC	0.146419
C10	CA	-0.188390	H11	HC	0.146419
C11	CA	-0.012521	H12	HC	0.146419
C12	CT	-0.164595	H13	H	0.408045

The chemical structure of compound 4 is a complex organic molecule. It features a central nitrogen atom (N2) double-bonded to carbon C5 and single-bonded to carbon C6. Carbon C6 is also double-bonded to nitrogen N1, which is single-bonded to carbon C1. Carbon C1 is single-bonded to carbon C3, which is double-bonded to carbon C2. Carbon C2 is single-bonded to carbon C4, which is single-bonded to carbon C8. Carbon C8 is single-bonded to carbon C9, which is single-bonded to carbon C10. Carbon C10 is single-bonded to carbon C11, which is double-bonded to carbon C7. Carbon C7 is single-bonded to carbon C6. Carbon C11 is single-bonded to hydrogen H4. Carbon C9 is single-bonded to hydrogen H1. Carbon C8 is single-bonded to hydrogen H2. Carbon C4 is single-bonded to hydrogen H6. Carbon C3 is single-bonded to hydrogen H7. Carbon C1 is single-bonded to hydrogen H5. Carbon C13 is single-bonded to hydrogen H8. Carbon C12 is single-bonded to hydrogen H9. Carbon C1 is single-bonded to carbon C12, which is single-bonded to hydrogen H10. Carbon C12 is also single-bonded to hydrogen H11.

Table S5. Parameters and atom types for compound 5.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CA	0.293121	H1	HA	0.166798
N1	NAP	-0.023254	H2	HA	0.180803
C2	CA	-0.133842	H3	HA	0.158483
N2	NA	-0.056208	H4	HA	0.183084
C3	CA	-0.195988	H5	HC	0.146197
C4	C56B	0.069653	H6	HA	0.214972
C5	C56B	-0.077079	H7	HA	0.203382
C6	C56B	0.181622	H8	HC	0.120573
C7	CA	-0.291303	H9	HC	0.120573
C8	C56B	0.025576	H10	HC	0.120573
C9	CA	-0.172491	H11	HC	0.146197
C10	CA	-0.179275	H12	HC	0.146197
C11	CA	-0.027107	H13	HC	0.146986
C12	CT	-0.163345	H14	HC	0.146986
C13	CT	-0.195627	H15	HC	0.146986
C14	CT	-0.403242			

The diagram shows the chemical structure of compound 5. It consists of a central five-membered ring (C1-C5) fused to a six-membered ring (C2-C7). A nitrogen atom (N2) is attached to C6 and C7. Another nitrogen atom (N1) is attached to C1 and C12. Double bonds are present between C3=C2, C9=C8, C11=C7, and C5=C6. Various hydrogen atoms (H1-H15) are shown bonded to the carbon atoms.

Table S6. Parameters and atom types for compound 6.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CT	-0.357709	C12	CA	0.548725
N1	NB	-0.681270	C13	CT	0.027979
O1	OS	-0.383457	H1	HA	0.080821
C2	CA	0.621389	H2	HA	0.204471
N2	NA	-0.455290	H3	HA	0.192071
C3	CA	0.294448	H4	HA	0.161627
C4	CA	-0.536078	H5	HA	0.194987
C5	C56B	0.363125	H6	HC	0.093373
C6	C56B	-0.225204	H7	HC	0.093373
C7	C56B	0.312346	H8	HC	0.093373
C8	CA	-0.498308	H9	H	0.372831
C9	C56B	-0.210456	H10	HC	0.062240
C10	CA	-0.024785	H11	HC	0.062240
C11	CA	-0.469101	H12	HC	0.062240

The chemical structure of compound 6 is a complex molecule with the following atom mapping:

- Carbon Atoms:** C1 (N), C2 (C), C3 (C), C4 (C), C5 (C), C6 (C), C7 (C), C8 (C), C9 (C), C10 (C), C11 (C), C12 (C), C13 (C).
- Hydrogen Atoms:** H1 (C1), H2 (C4), H3 (C11), H4 (C10), H5 (C8), H6 (C1), H7 (C1), H8 (C1), H9 (C6), H10 (C13), H11 (C13), H12 (C11).
- Other Atoms:** O1 (Sulfur atom).

The structure features a central five-membered ring (C7-C8-C9-C5-C6) fused to a six-membered ring (C10-C11-C12-C13-O1). There are also two double bonds: one between C4 and C3, and another between C7 and C8. A triple bond is present between C2 and C3.

Table S7. Parameters and atom types for compound 7.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CA	0.297264	H1	HC	0.144399
N1	NAP	-0.035333	H2	HC	0.144399
C2	CA	-0.134899	H3	HC	0.144399
N2	NA	-0.508775	H4	HC	0.083733
C3	CA	-0.145909	H5	HC	0.083733
C4	C56B	0.100178	H6	HC	0.083733
C5	C56B	-0.051447	H7	HA	0.186213
C6	C56B	0.454071	H8	HA	0.199258
C7	CA	-0.646777	H9	HA	0.247531
C8	C56B	-0.160466	H10	HA	0.218259
C9	CA	-0.131442	H11	HA	0.216955
C10	CA	-0.358781	O1	OS	-0.369729
C11	CA	0.628524	H12	HC	0.151850
C12	CT	-0.181445	H13	HC	0.151850
C13	CT	-0.381808	H14	HC	0.151850
C14	CT	0.002102	H15	H	0.416511

The chemical structure of compound 7 is a complex organic molecule. It features a central nitrogen atom (N1) with a positive charge (+) and a double bond to another nitrogen atom (N2). N2 is also bonded to two carbon atoms (C6 and C7), which are part of a five-membered ring. This ring includes a carbonyl group (C11-O1-C10) and a double bond between C8 and C4. The molecule also contains a six-membered ring with double bonds between C3 and C2, and between C5 and C1. Various methyl groups (C12, C13, C14) and hydrogen atoms (H1-H15) are attached to the carbon framework.

Table S8. Parameters and atom types for compound 8.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CA	0.274315	H2	HC	0.035193
N1	NAP	0.091401	H3	HC	0.035193
C2	CA	-0.139962	H4	HA	0.244872
N2	NA	0.077014	H5	HA	0.195140
C3	CA	-0.235150	H6	HA	0.217880
C4	C56B	0.115165	H7	HA	0.226170
C5	C56B	-0.143271	H8	HA	0.203693
C6	C56B	0.186189	H9	HC	0.143710
C7	CA	-0.486059	H10	HC	0.149475
C8	C56B	-0.032649	H11	HC	0.149475
C9	CA	-0.153367	H12	HC	0.149475
C10	CA	-0.353112	H13	HC	0.143710
C11	CA	0.529660	H14	HC	0.143710
C12	CT	-0.286091	O1	OS	-0.402910
C13	CT	0.128488	H15	HC	0.150805
C14	CT	-0.307855	H16	HC	0.150805
C15	CT	-0.387110	H17	HC	0.150805
H1	HC	0.035193			

The chemical structure of compound 8 is a complex polycyclic system. It features a central iminium nitrogen atom (N1+) bonded to two carbons (C1 and C12) and an oxygen atom (O1). The N1+ carbon is also bonded to a hydrogen atom (H15) and another carbon (C1), which is further bonded to a hydrogen atom (H14). The O1 carbon is bonded to a methyl group (C13) and a hydrogen atom (H1). The structure includes several double bonds: between C9 and C10, between C4 and C5, between C3 and C2, between C6 and C7, and between C8 and C9. There are also single bonds between C10 and C11, C11 and C7, C12 and C13, and C14 and H12. Various hydrogen atoms are labeled with subscripts (e.g., H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17) to indicate their positions relative to the carbons.

Table S9. Parameters and atom types for compound 9.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CT	-0.474064	C13	CT	0.481459
N1	NI	-0.730741	H1	HA	0.163041
O1	OS	-0.387008	H2	HA	0.190115
C2	CD	0.695351	H3	HA	0.197476
N2	NA	-0.442773	H4	HA	-0.044034
C3	C5B	0.116397	H5	HA	0.090443
C4	C5A	-0.214237	H6	HA	0.090443
C5	C56A	0.288777	H7	HA	-0.044034
C6	CA	-0.501025	H8	HA	0.121525
C7	C56B	-0.153271	H9	HA	0.121525
C8	CA	-0.048741	H10	HA	0.121525
C9	CA	-0.461798	H11	H	0.370836
C10	CA	0.541308	H12	HC	0.056286
C11	CT	0.043539	H13	HC	0.056286
C12	CT	-0.300895	H14	HC	0.056286

The diagram shows the chemical structure of compound 9. It consists of a central five-membered ring (C7-C5-N2-C4-C3) fused to a six-membered ring (C8-C9-C10-C6-C5-N2). A three-membered ring (C12-C13-N1) is attached to the five-membered ring at C13. A four-membered ring (C11-O1-C10-C6) is attached to the six-membered ring at C10. Various hydrogen atoms (H1-H14) are shown bonded to the carbon atoms.

Table S10. Parameters and atom types for compound 10.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CT	-0.456900	H1	HA	0.194599
N1	NI	-0.710167	H2	HC	0.047052
C2	CD	0.671601	H3	HA	0.168913
N2	NA	-0.458449	H4	HA	0.181209
C3	CT	0.445969	H5	HC	0.047052
C4	CT	-0.294499	H6	HC	0.047052
C5	C5B	0.087881	H7	HC	0.087832
C6	C5A	-0.156832	H8	HC	0.087832
C7	C56A	0.169326	H9	HC	-0.034114
C8	CA	-0.186125	H10	HC	-0.034114
C9	C56B	-0.042593	O1	OS	-0.391438
C10	CA	-0.356187	H11	HC	0.118760
C11	CA	0.427084	H12	HC	0.118760
C12	CA	-0.338720	H13	HC	0.118760
C13	CT	0.070257	H14	H	0.370199

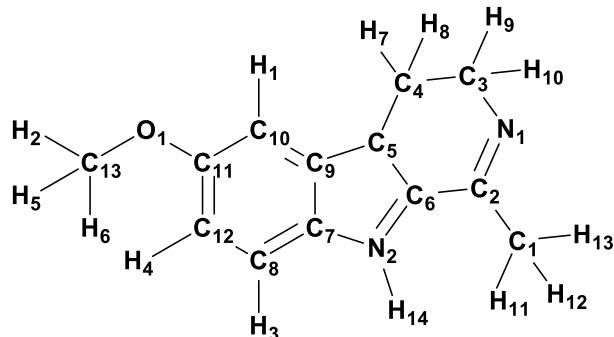


Table S11. Parameters and atom types for compound 11.

Name	Atom type	Charge	Name	Atom type	Charge
C1	CM	0.406343	H2	HC	0.072194
N1	NE	-0.183108	H3	HC	0.072194
C2	CT	-0.027202	H4	HC	0.123986
N2	NIP	-0.431395	H5	HC	0.123986
C3	CT	-0.187076	H6	HC	0.123986
C4	CM	0.119921	H7	HC	0.190101
C5	CM	-0.174237	H8	HC	0.191122
C6	CG	0.216533	H9	HC	0.188536
C7	CM	-0.230202	H10	HC	0.101415
C8	CM	-0.007605	H11	HC	0.101415
C9	CM	-0.381159	H12	HC	0.124900
C10	CM	0.446756	H13	HC	0.124900
C11	CM	-0.218144	O1	OS	-0.375086
C12	CT	-0.138609	H14	HC	0.136566
C13	CT	0.031355	H15	HC	0.136566
C14	CT	-0.281383	H16	HC	0.136566
H1	HC	0.072194	H17	H	0.393672

Figure S1. RMSD graph for compound 1.

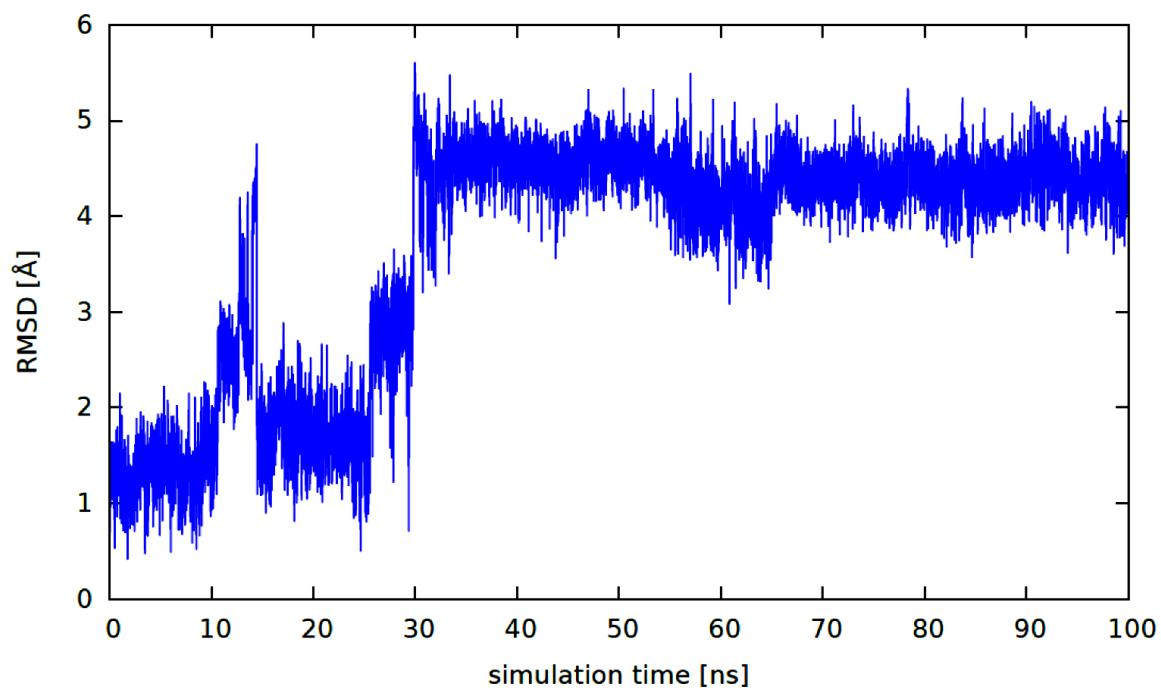


Figure S2. RMSD graph for compound 2.

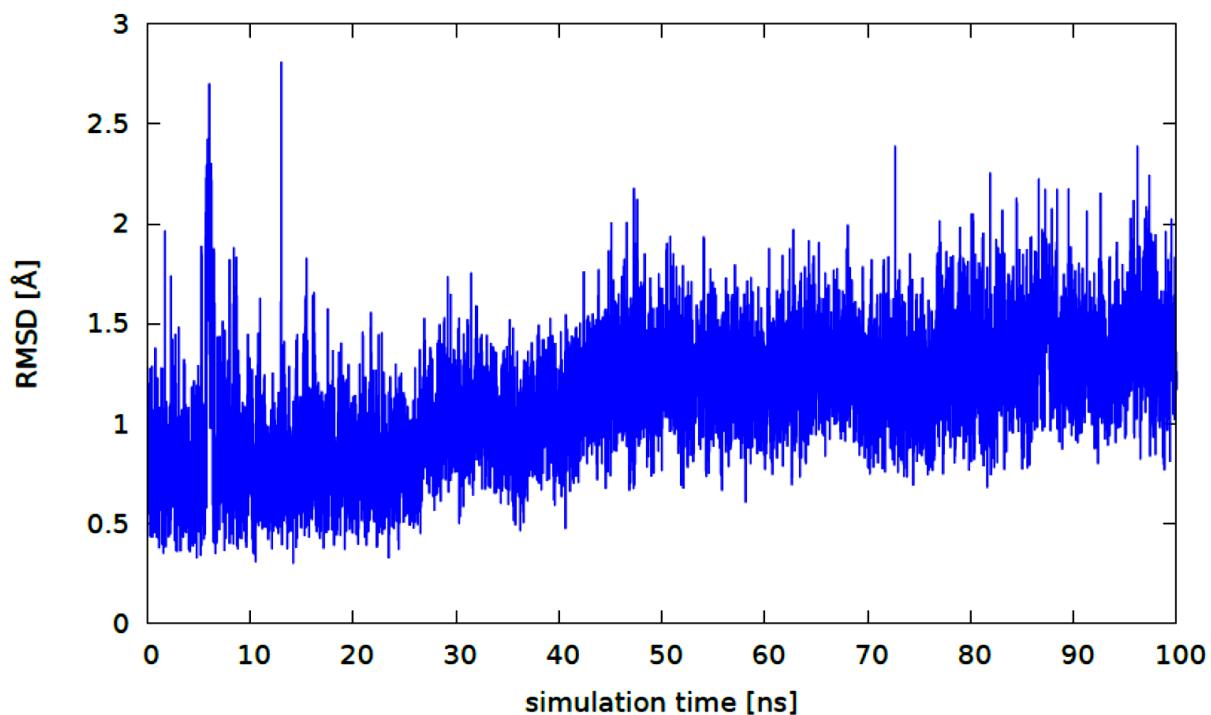


Figure S3. RMSD graph for compound 3.

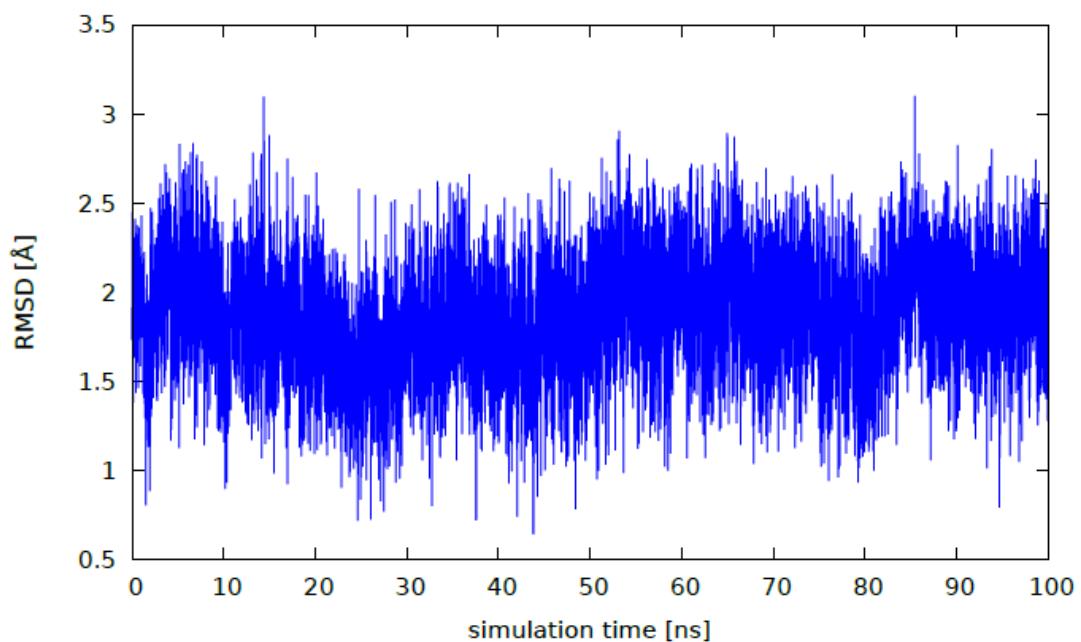


Figure S4. RMSD graph for compound 4.

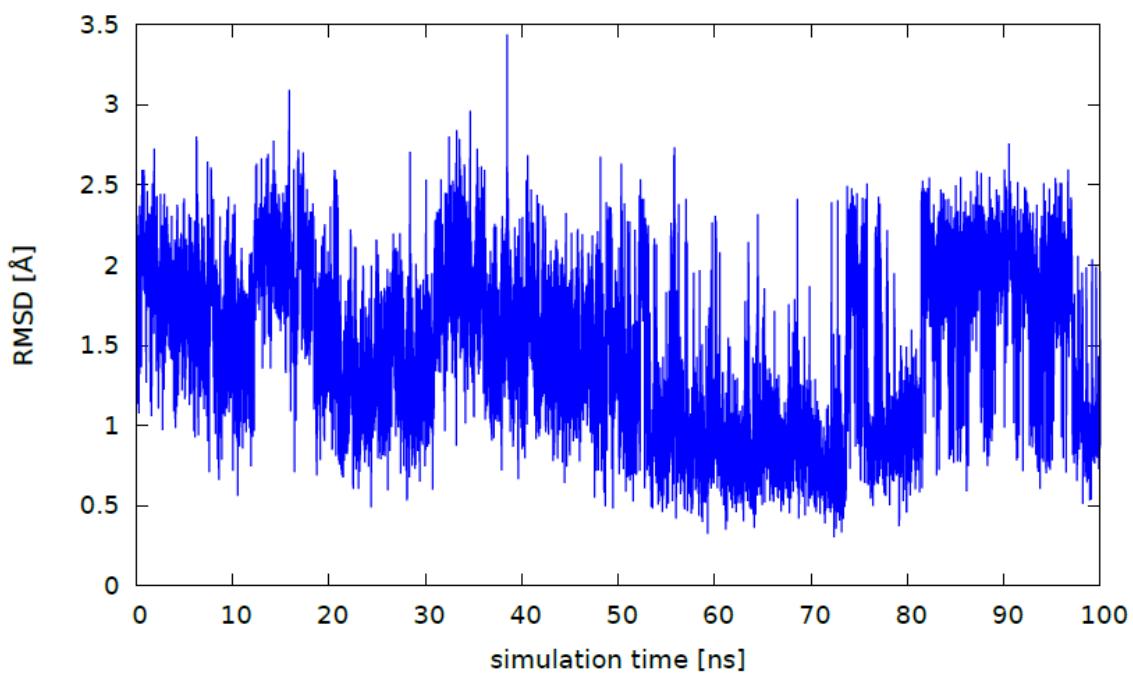


Figure S5. RMSD graph for compound 5.

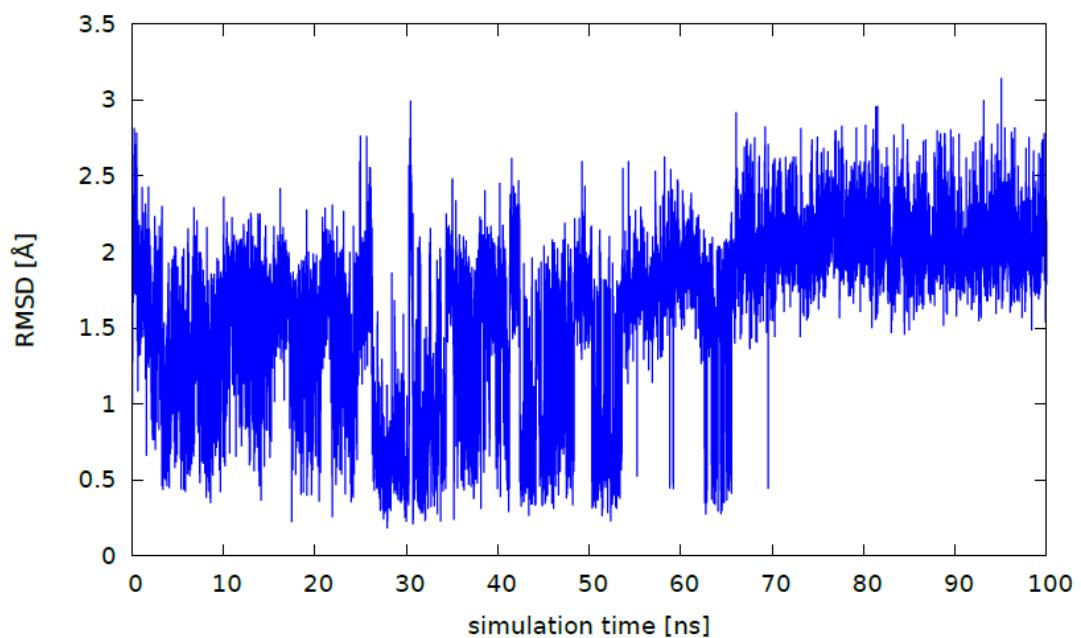


Figure S6. RMSD graph for compound 6.

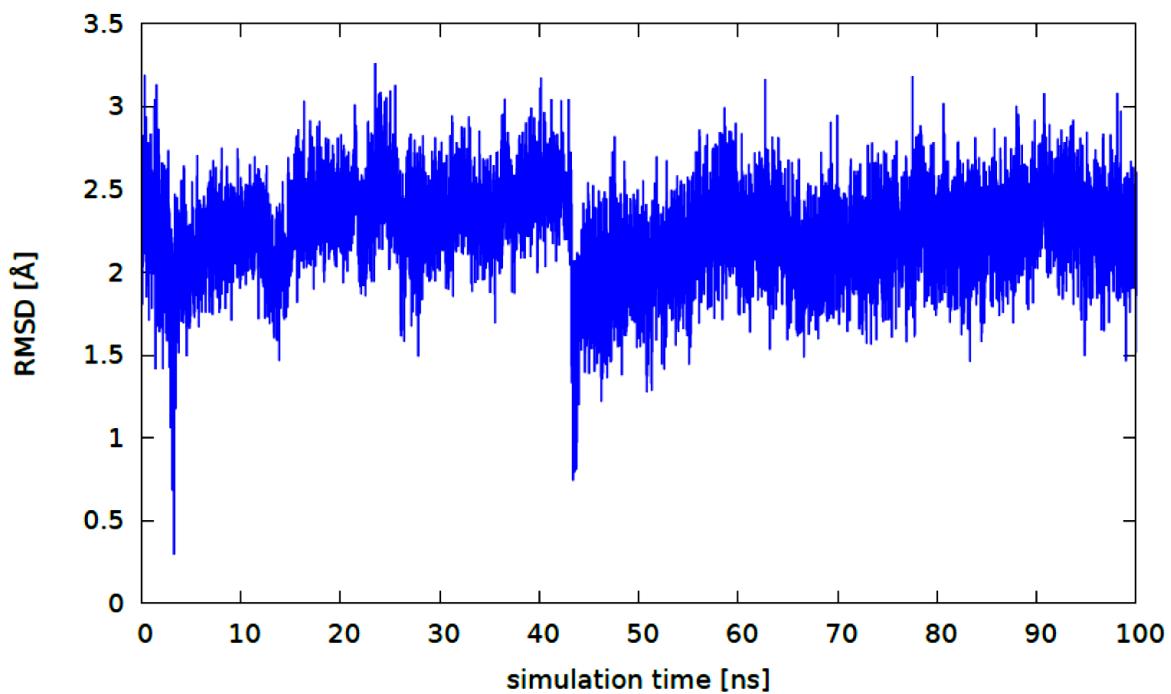


Figure S7. RMSD graph for compound 7.

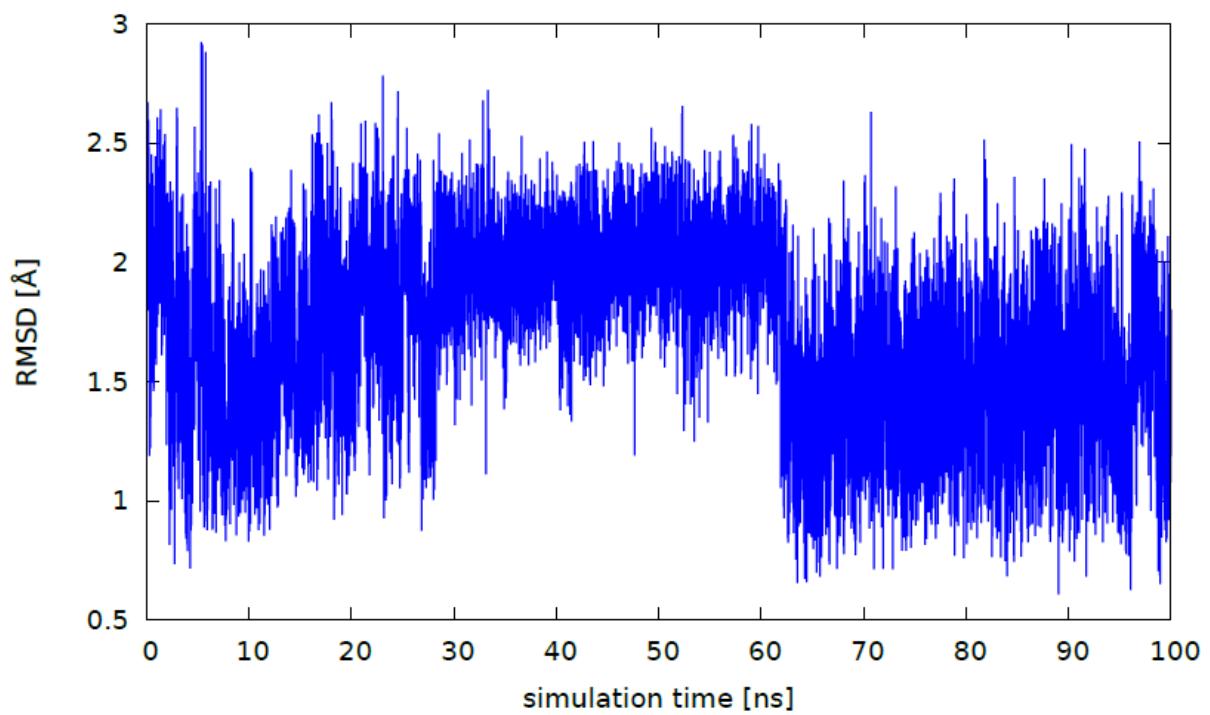


Figure S8. RMSD graph for compound 8.

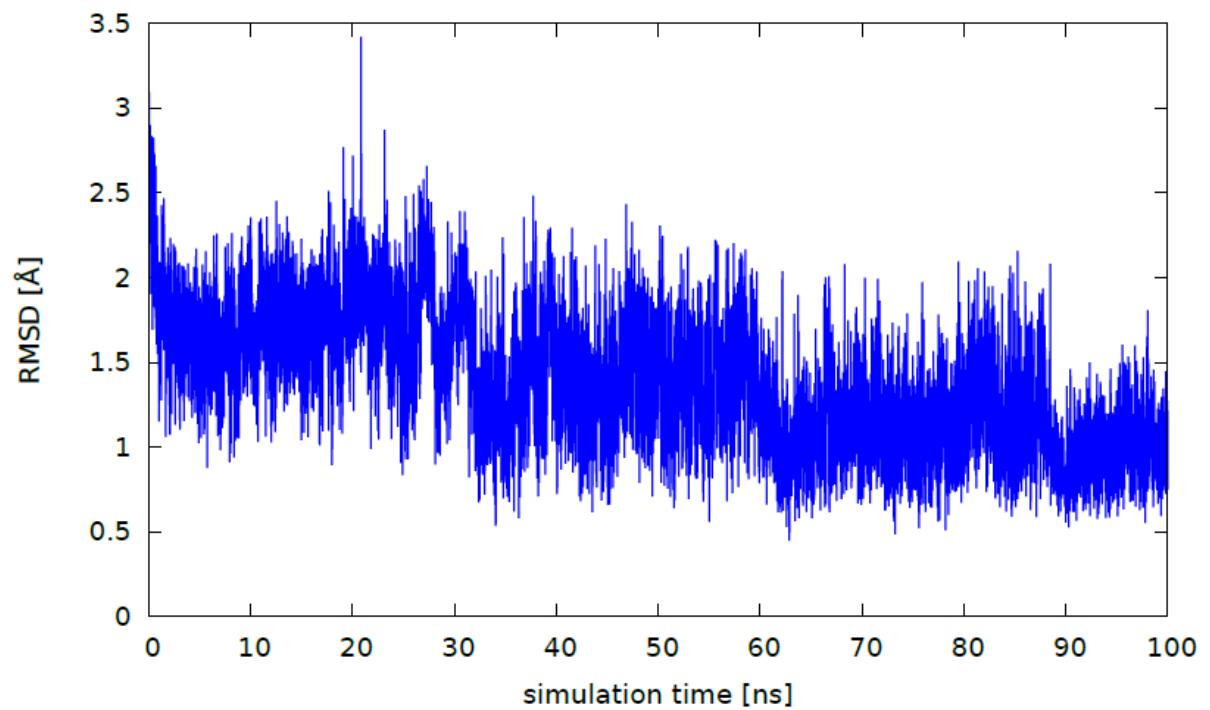


Figure S9. RMSD graph for compound 9.

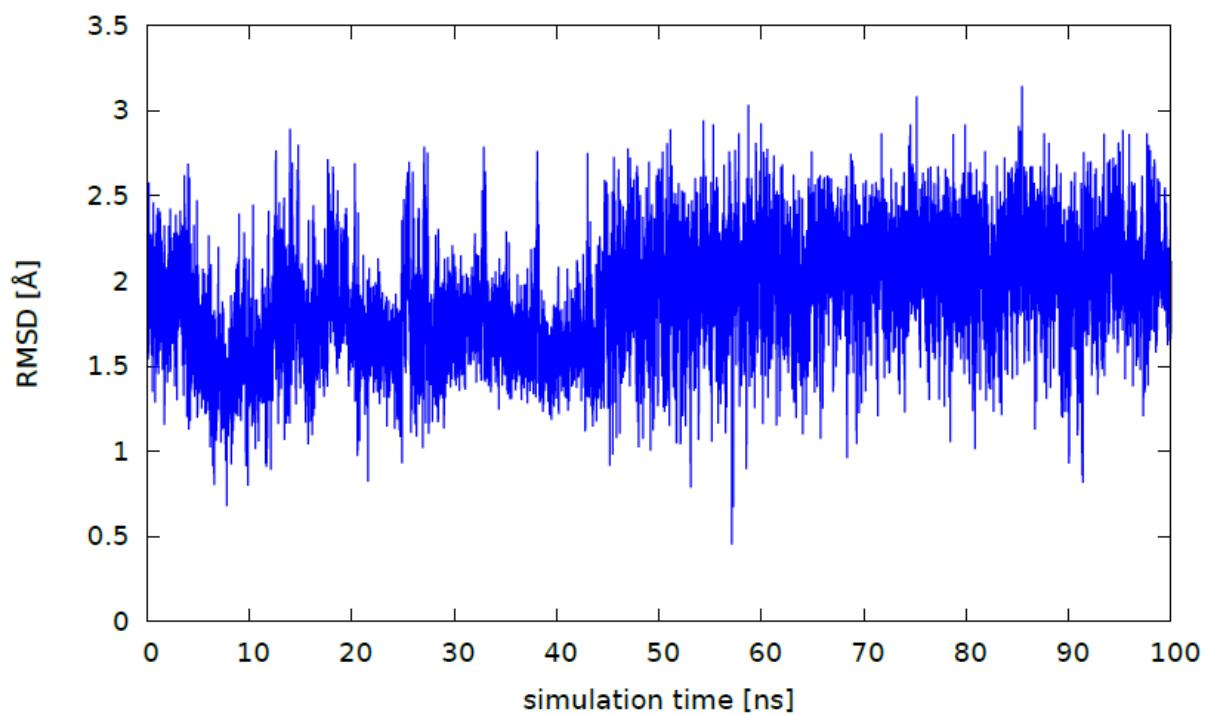


Figure S10. RMSD graph for compound 10.

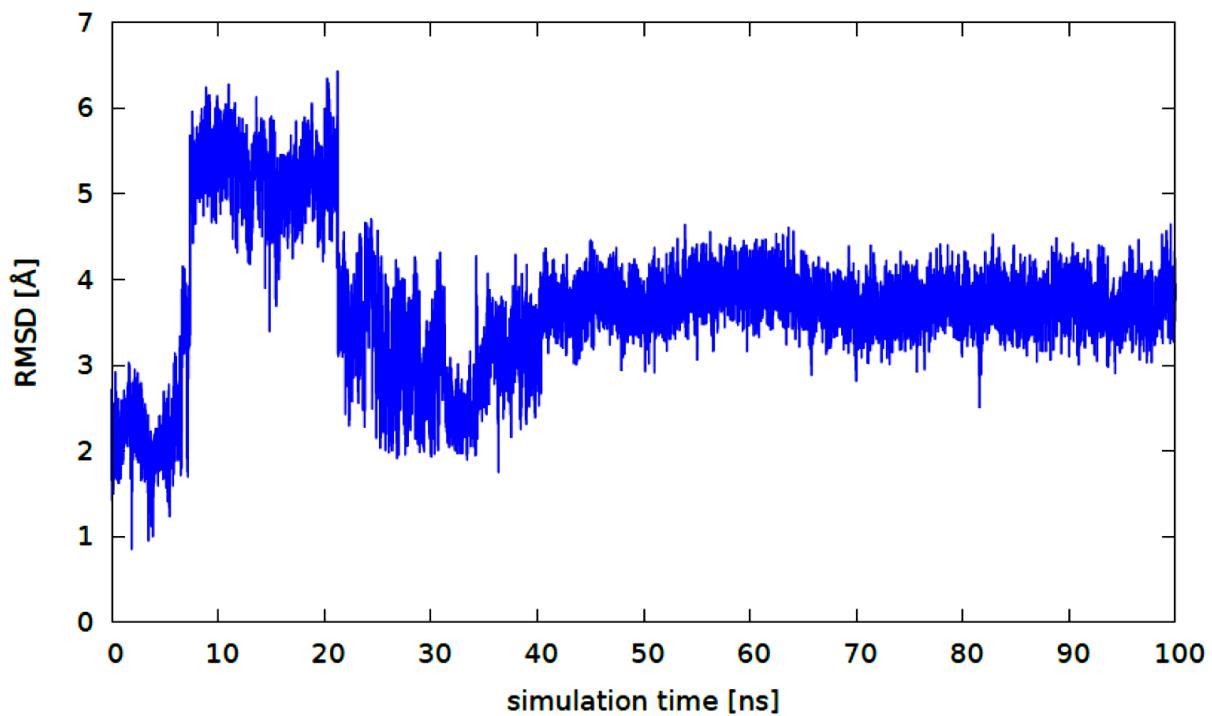


Figure S11. RMSD graph for compound 11.

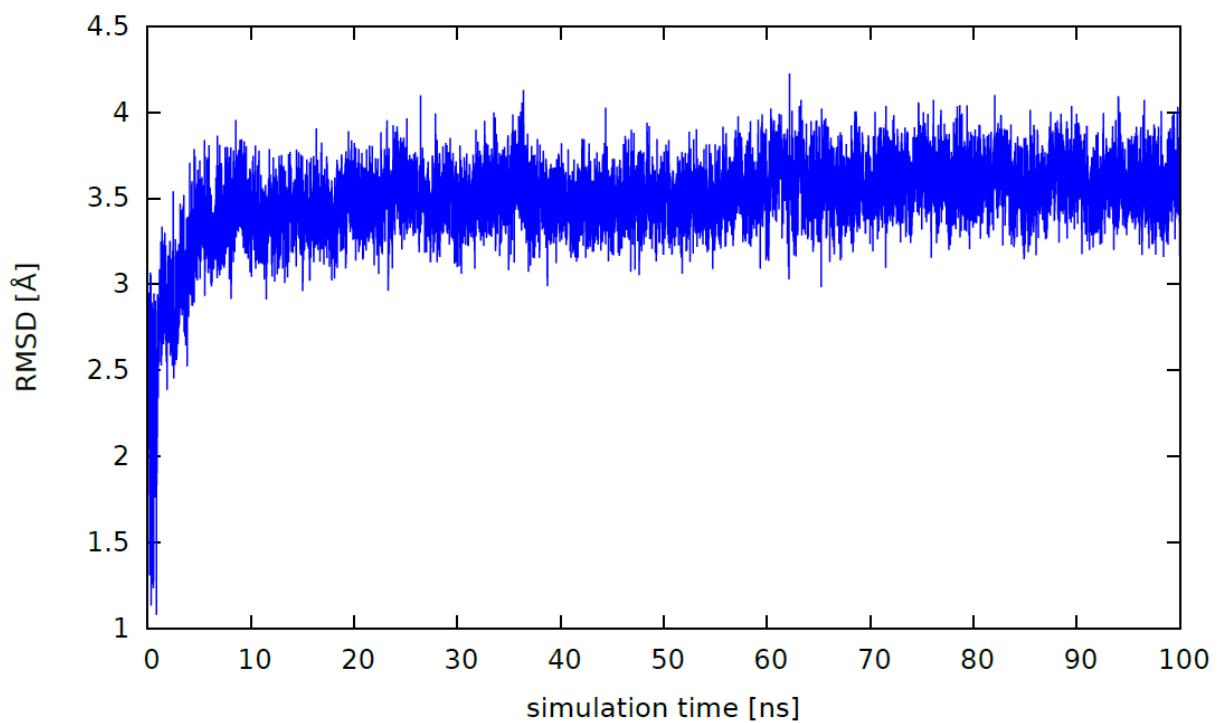


Figure S12. Overview of the interaction pattern obtained with dynophore analysis for compounds 2-5.
 Calculated percentage of the occurrence of a dynamic pharmacophore element on the basis of all frames broken into element-interacting amino acids pairs.

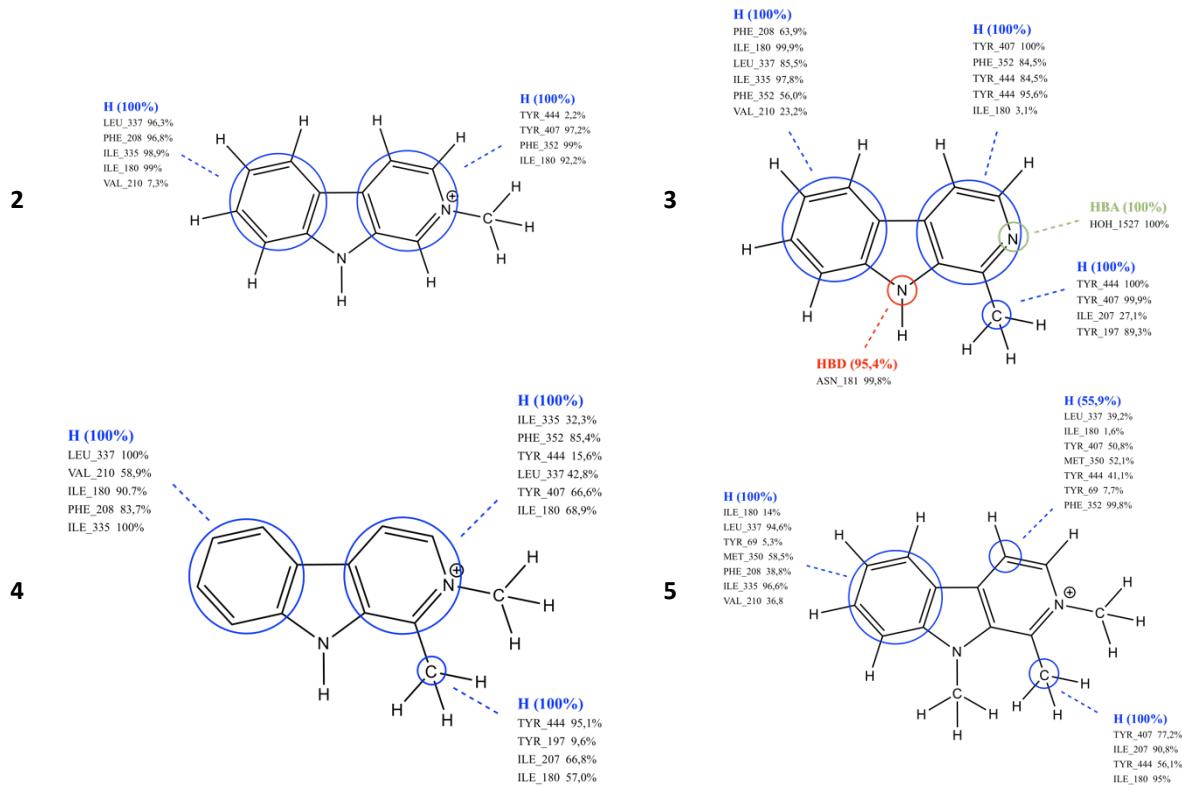


Figure S13. Overview of the interaction pattern obtained with dynophore analysis for compounds 7-9.
 Calculated percentage of the occurrence of a dynamic pharmacophore element on the basis of all frames broken into element-interacting amino acids pairs.

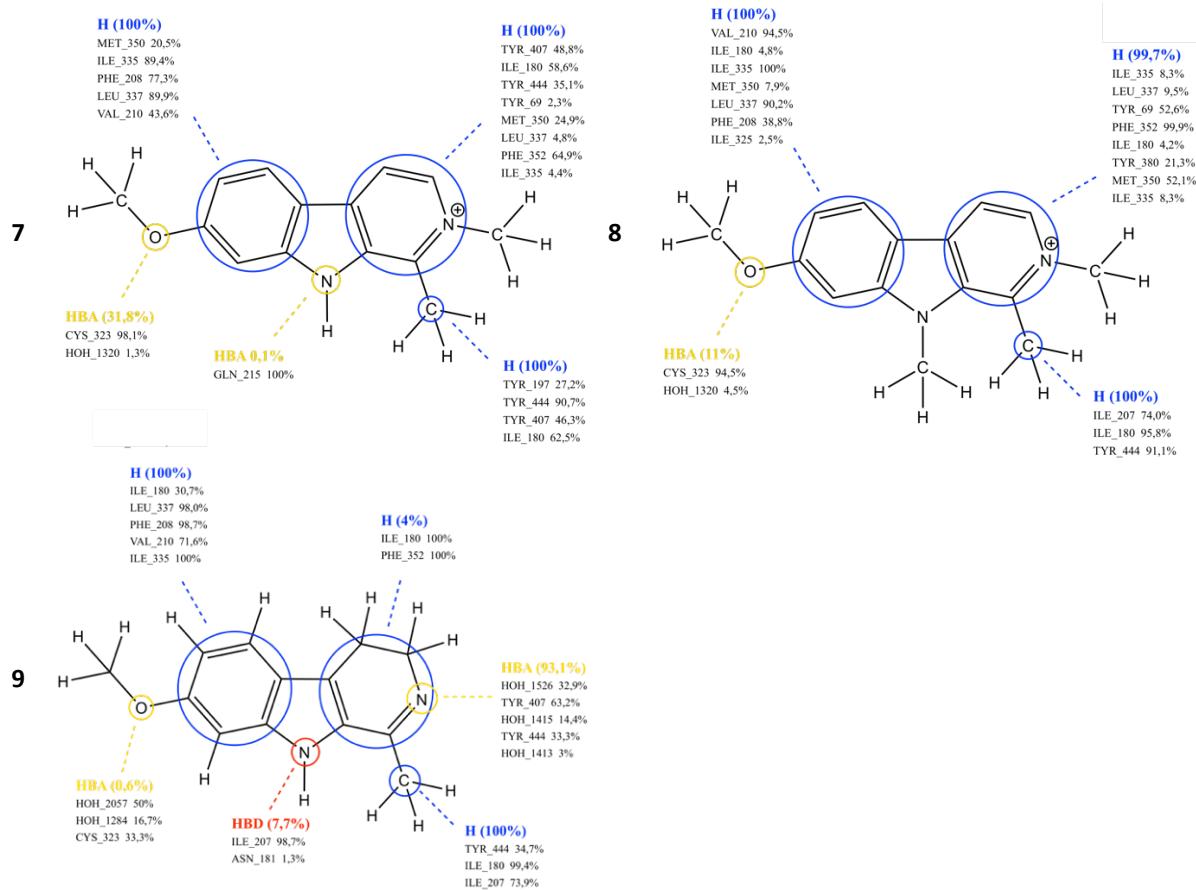


Figure S14. Comparison between X-ray binding pose of harmine (compound 6, in silver) with the determined binding modes using scoring functions ChemScore (in green), GoldScore (in violet) and ChemPLP (in red).

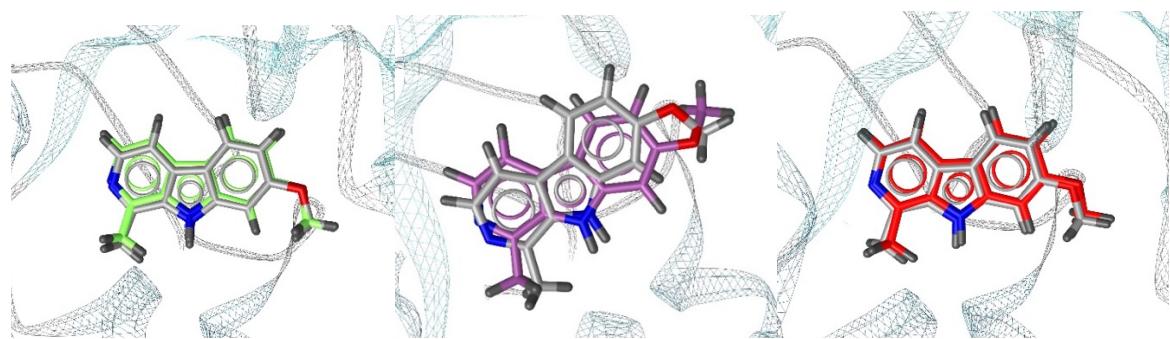
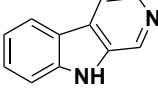
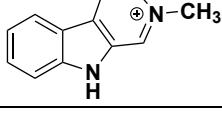
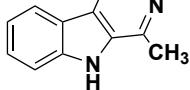
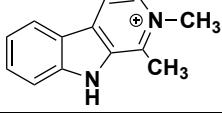
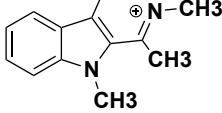
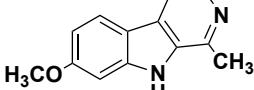
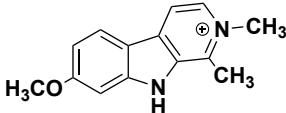
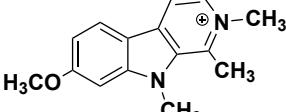
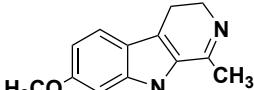
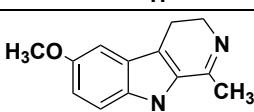
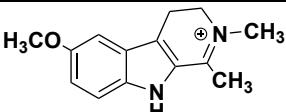


Table S12. The average number of water molecules present in the MAO-A active site (i.e., within 5 Å of the pertinent compound) during the molecular dynamics simulation, with standard deviations also provided.

Compound	Structure	Average num. of water molecules	ST. DEV.
1		6.1	2.1
2		7.4	1.1
3		4.3	0.9
4		3.4	1.0
5		4.9	0.9
6		4.9	0.9
7		6.2	1.1
8		4.3	0.9
9		2.5	0.6
10		6.1	1.3
11		5.2	1.6