

Supplementary material for the article:

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Synthesis of novel 5-HT1A arylpiperazine ligands: Binding data and computer-aided analysis of pharmacological potency

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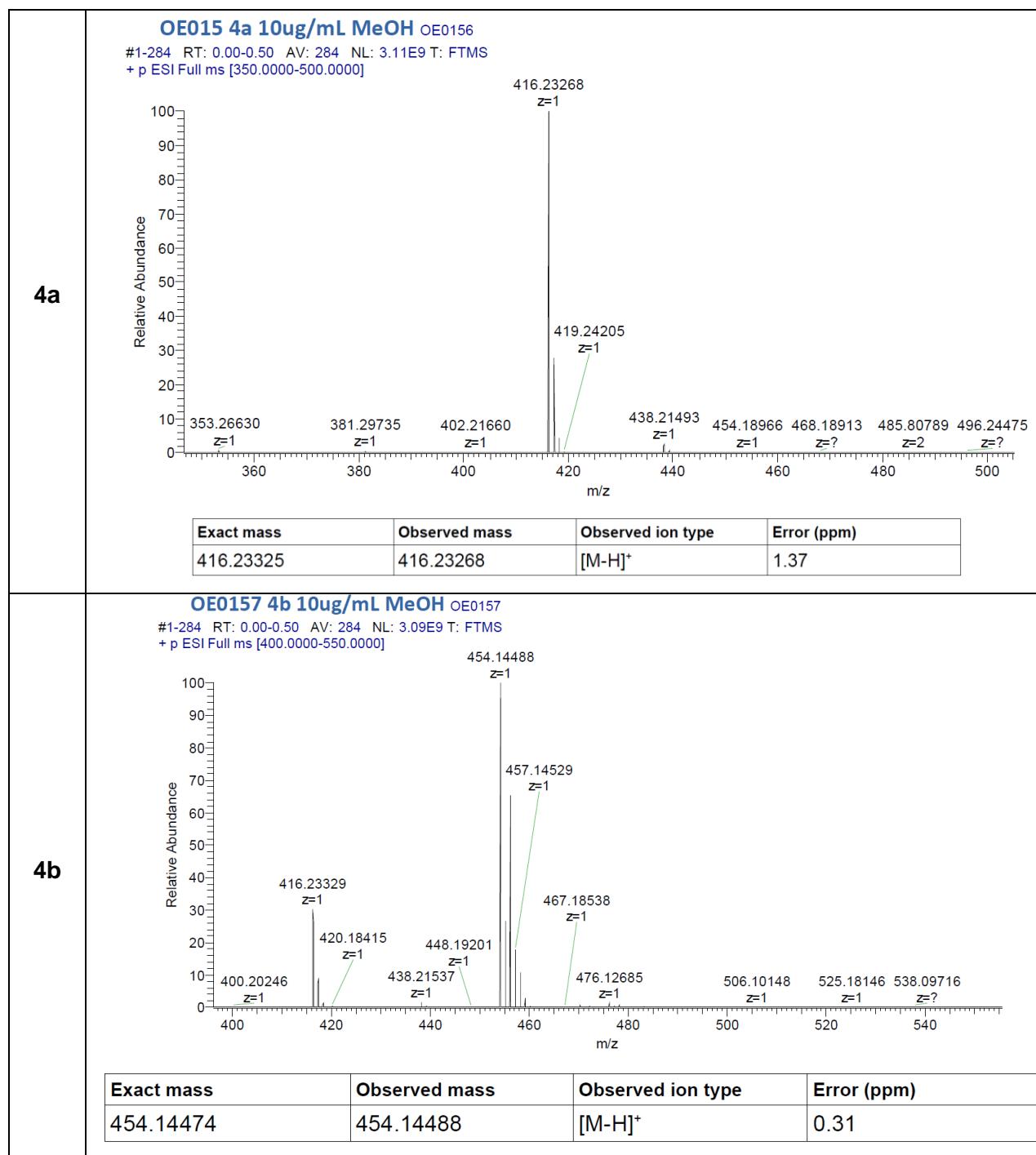
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(deanad@chem.bg.ac.rs)

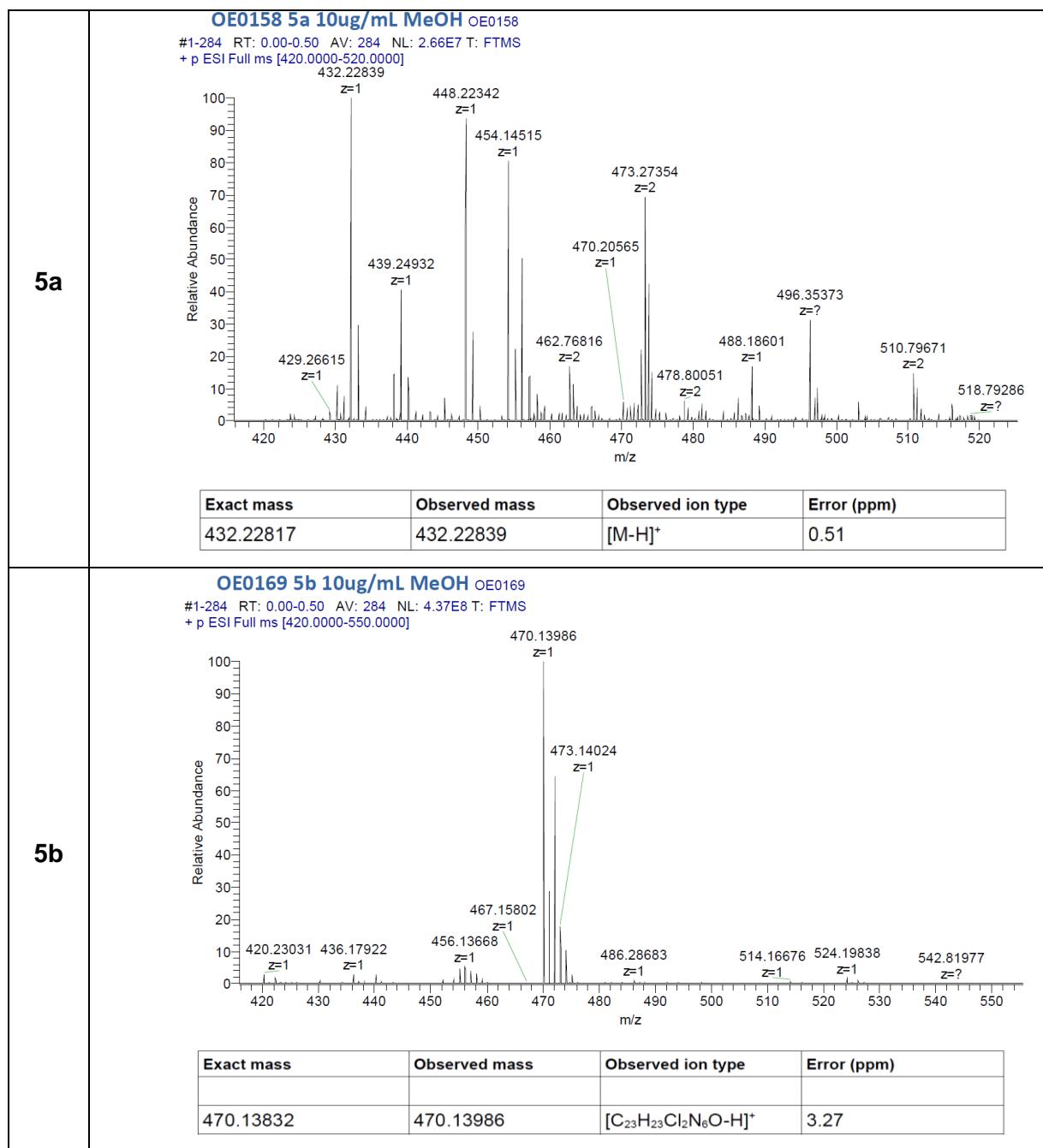
* Corresponding author: Deana B. Andrić, email: deanad@chem.bg.ac.rs

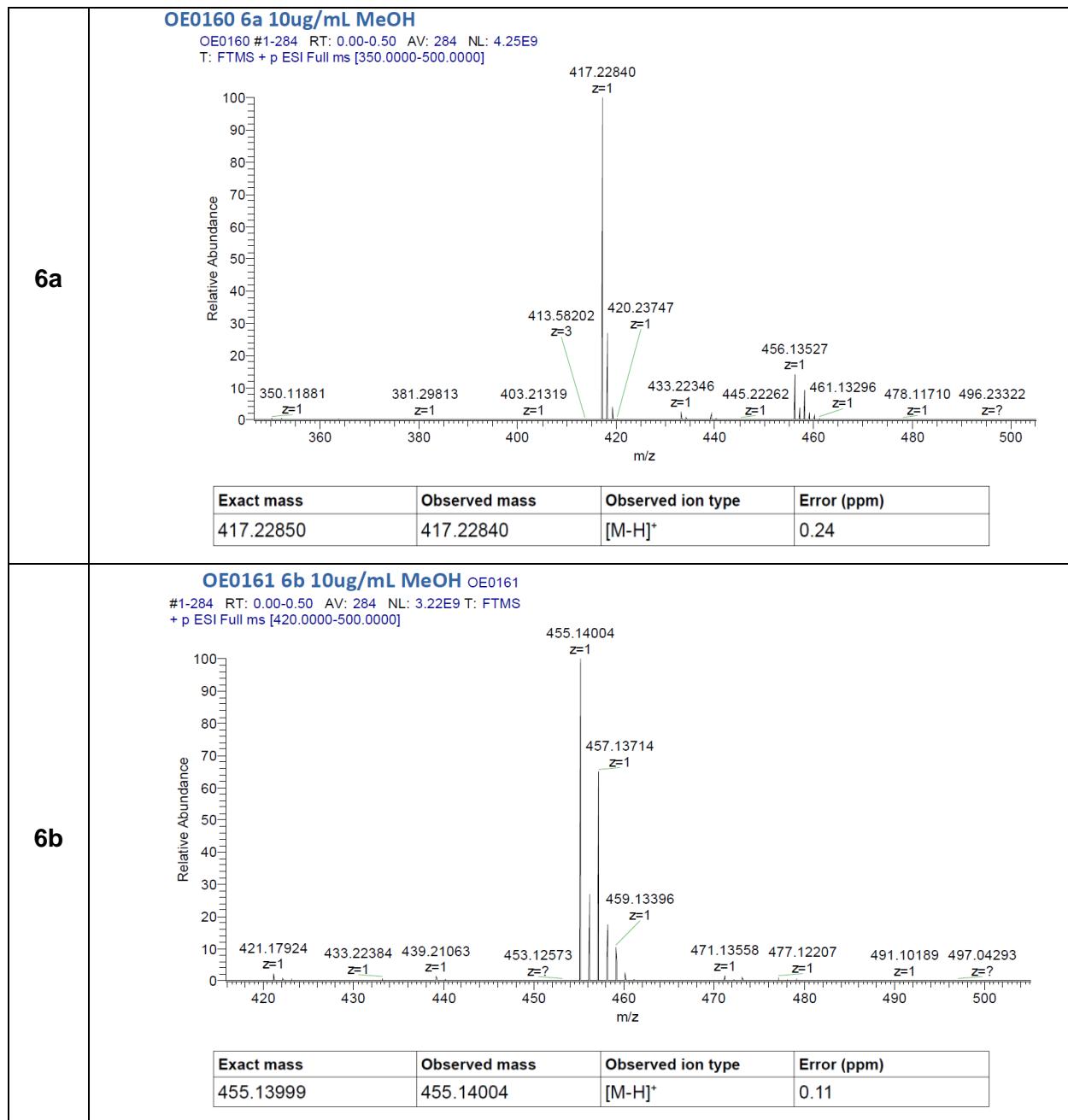
Table of contents:

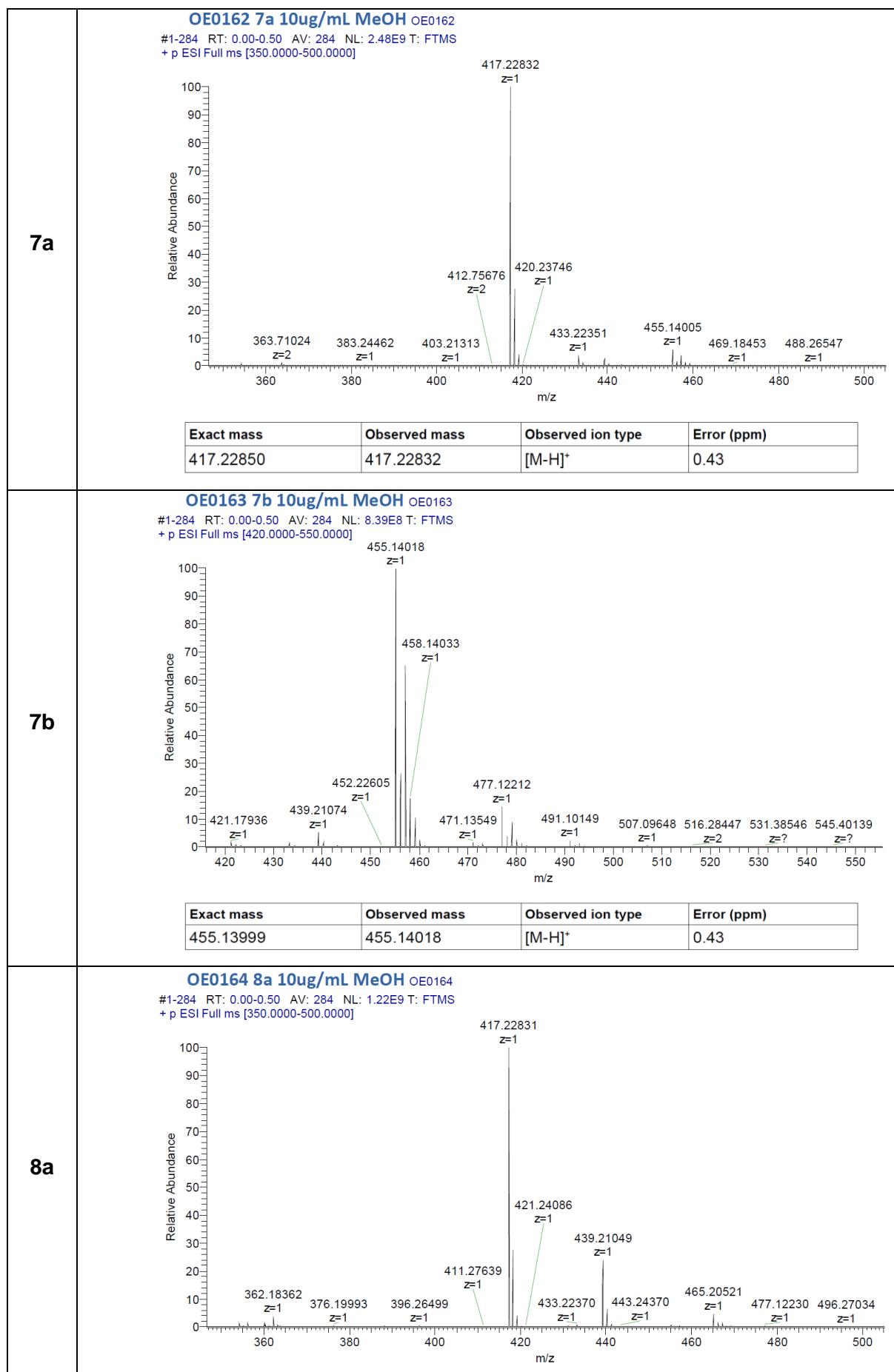
1. Fig. S1: HRMS spectra for newly synthesized ligands (4a,b-10a,b)	Page 2
2. Fig. S2: Diagram representing the increase in affinity compared to: the parent compound and to aripiprazole.....	Page 9
3. Fig. S3: Predicted ADME profiles for tested compounds.....	Page 10
4. Fig. S4: Predicted Toxicity profiles for tested compounds	Page 21
5. Fig. S5: 3D model of docked ligands into 5HT1A receptor	Page 32
6. Fig. S6: Predicted metabolites for selected substances	Page 33
7. Fig. S7: Predicted ADMET profiles for predicted metabolites.....	Page 36
8. Fig. S8: 2D schematics of docked metabolites into 5HT1A receptor.....	Page 41

Fig. S1 HRMS spectra for newly synthesized ligands (4a,b-10a,b).

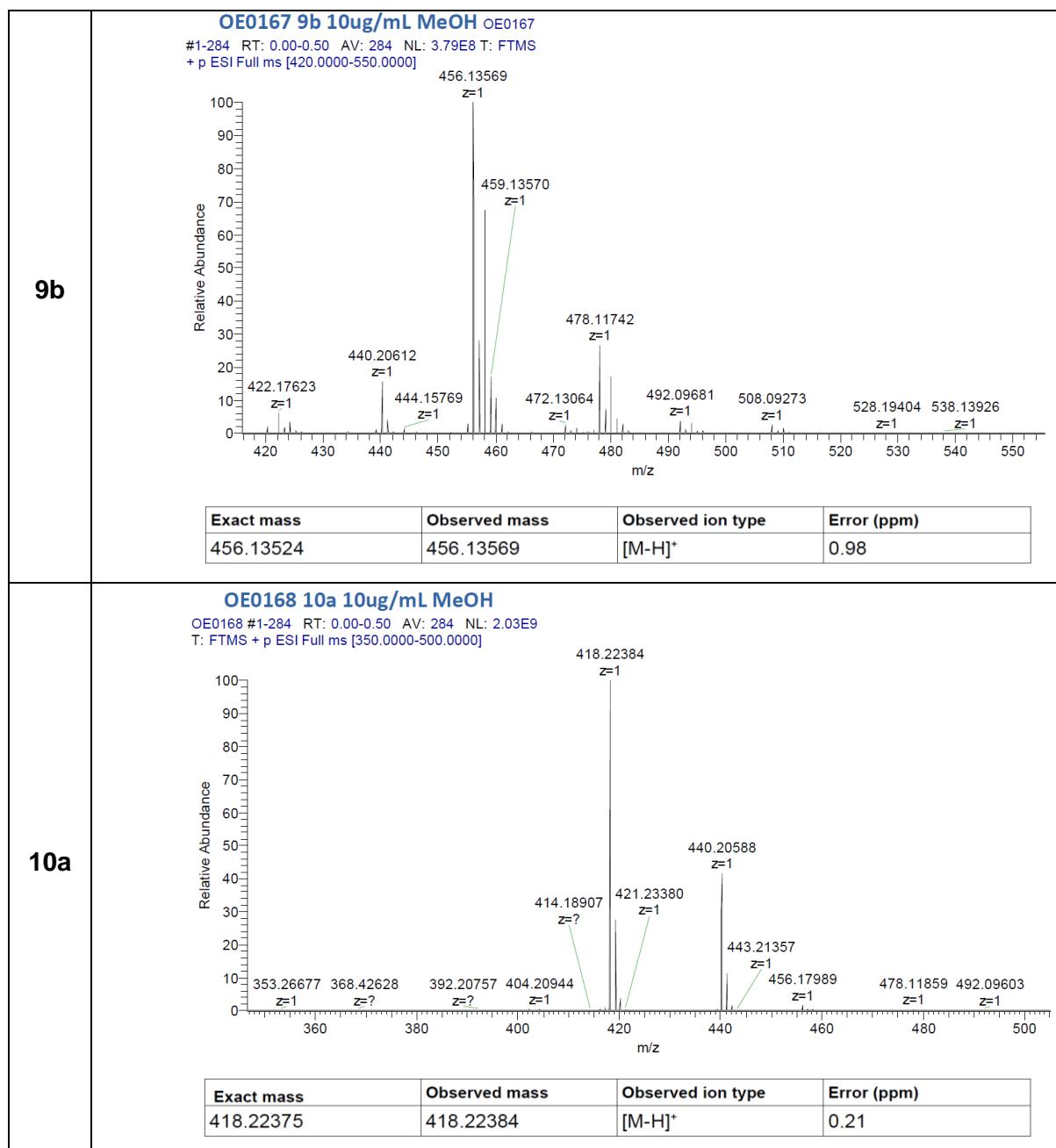








		Exact mass	Observed mass	Observed ion type	Error (ppm)	
		417.22850	417.22831	[M-H] ⁺	0.45	
	8b	OE0165 8b 10ug/mL MeOH OE0165 #1-284 RT: 0.00-0.50 AV: 284 NL: 1.09E9 T: FTMS +p ESI Full ms [420.0000-550.0000] <p>Relative Abundance</p> <p>m/z</p>				
	9a	OE0166 9a 10ug/mL MeOH OE0166 #1-284 RT: 0.00-0.50 AV: 284 NL: 1.32E9 T: FTMS +p ESI Full ms [350.0000-500.0000] <p>Relative Abundance</p> <p>m/z</p>				
		Exact mass	Observed mass	Observed ion type	Error (ppm)	
		455.13999	455.14032	[M-H] ⁺	0.72	
		Exact mass	Observed mass	Observed ion type	Error (ppm)	
		418.22375	418.22381	[M-H] ⁺	0.51	



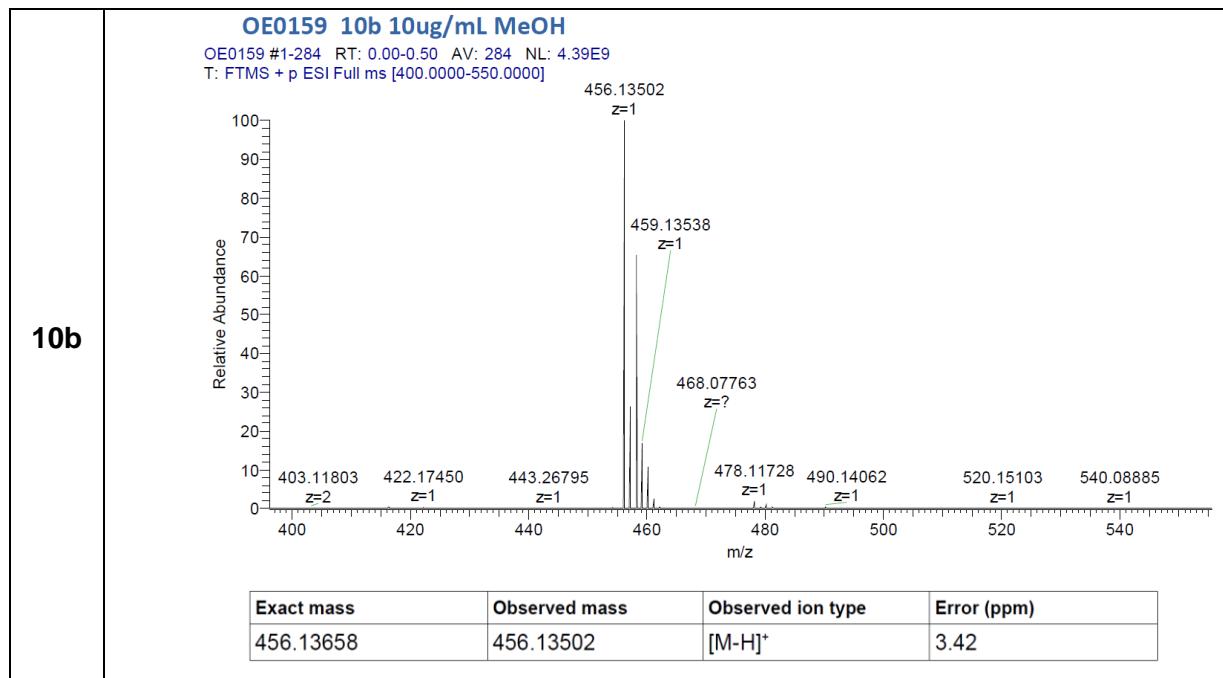


Fig. S2 Diagram representing the increase in affinity compared to: the parent compound and to aripiprazole.

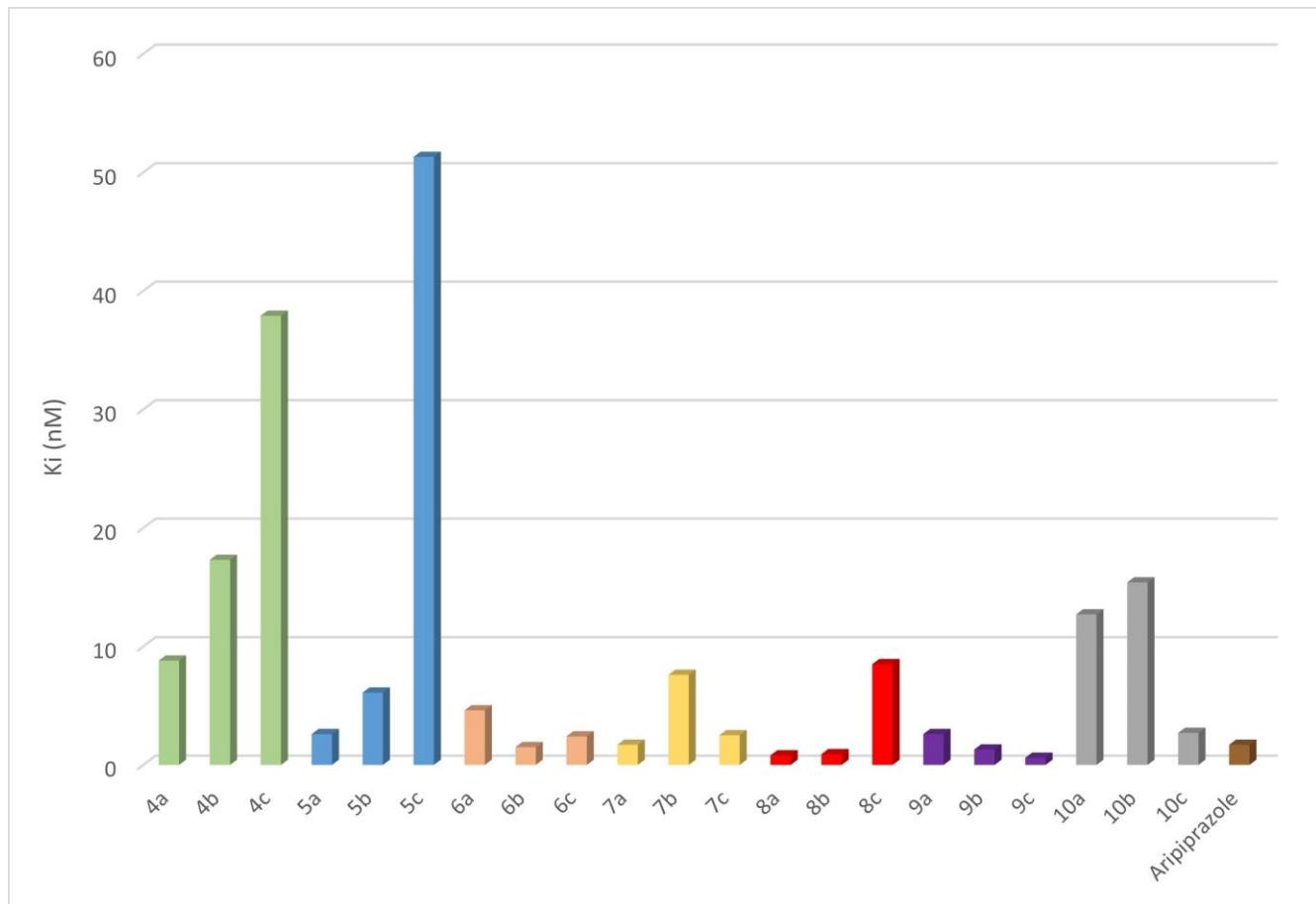
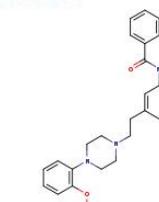
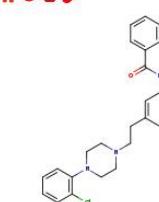
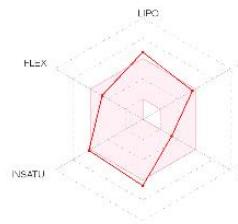
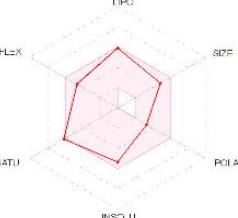


Fig. S3 Predicted ADME profiles for tested substances (Table 1).

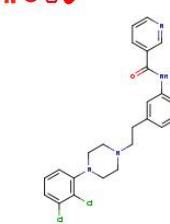
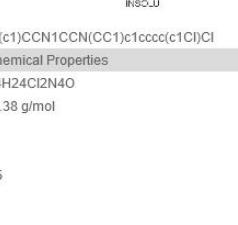
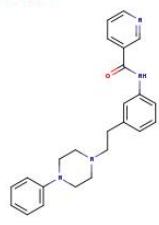
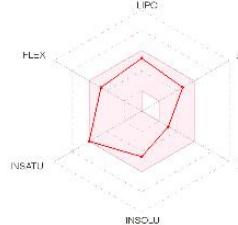
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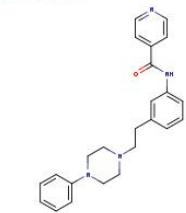
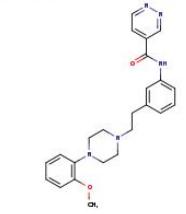
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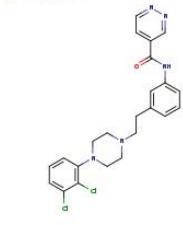
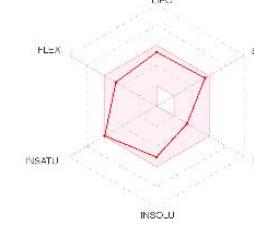
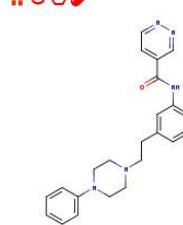
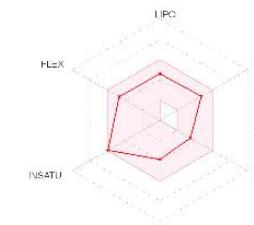
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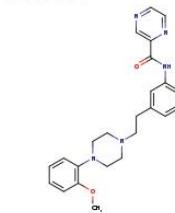
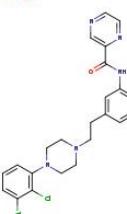
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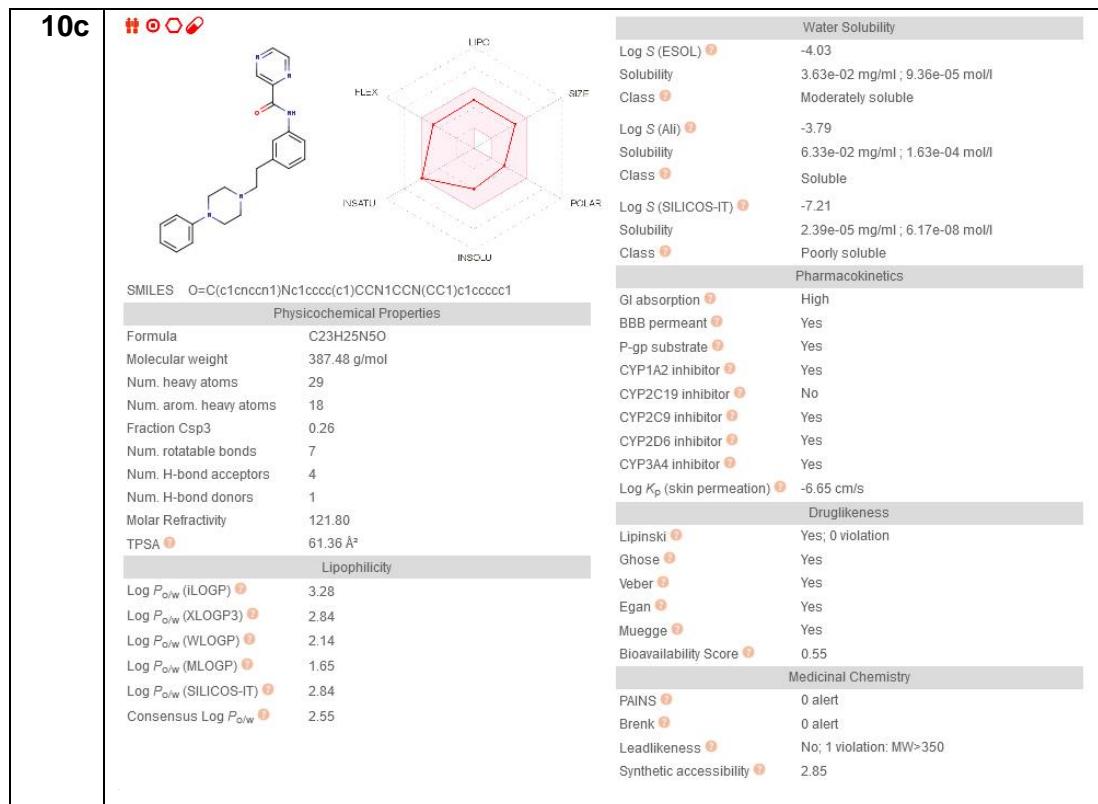
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Criteria for violation of:

Lipinski

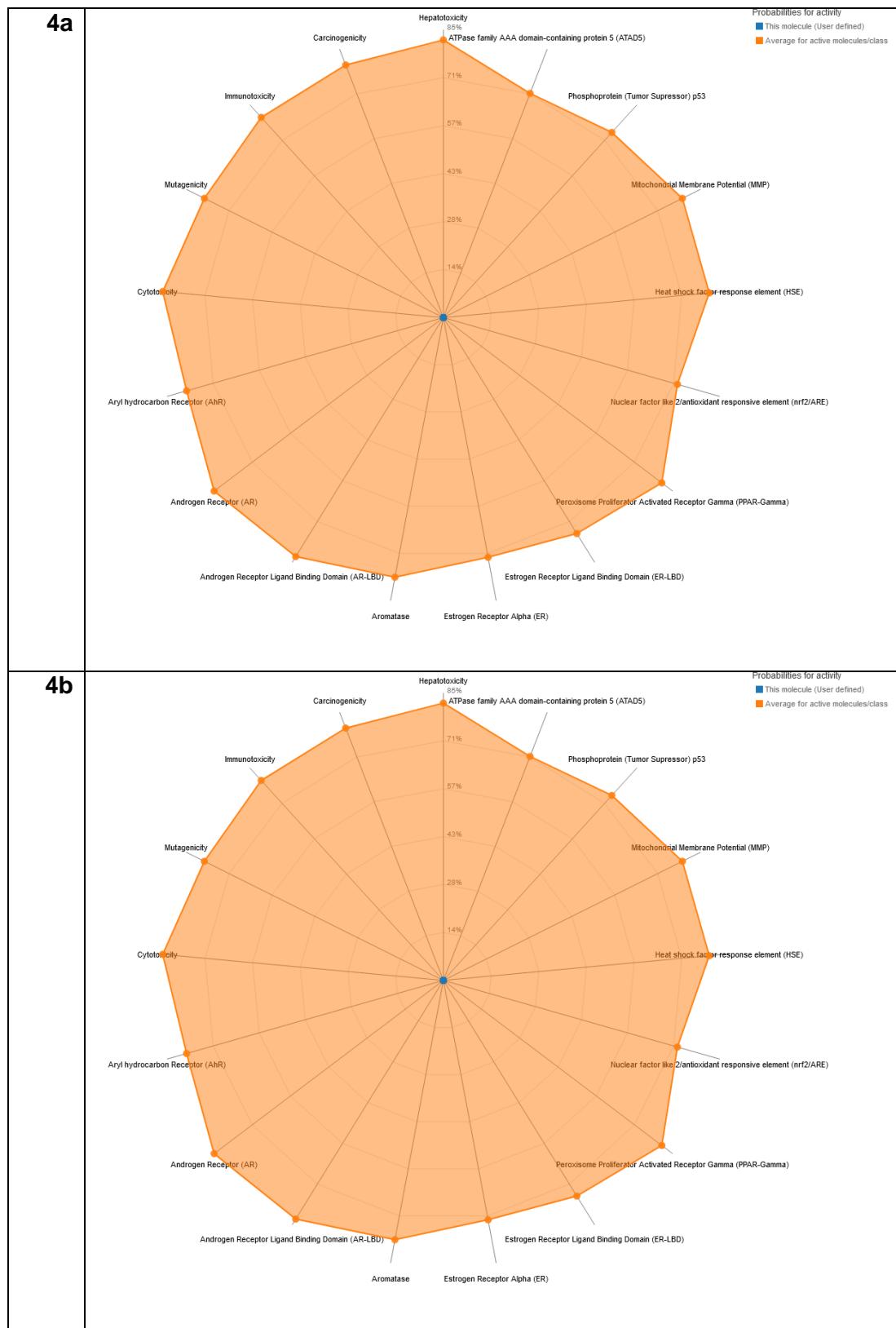
MW <= 500
MLOGP <= 4.15
N or O <= 10
NH or OH <= 5

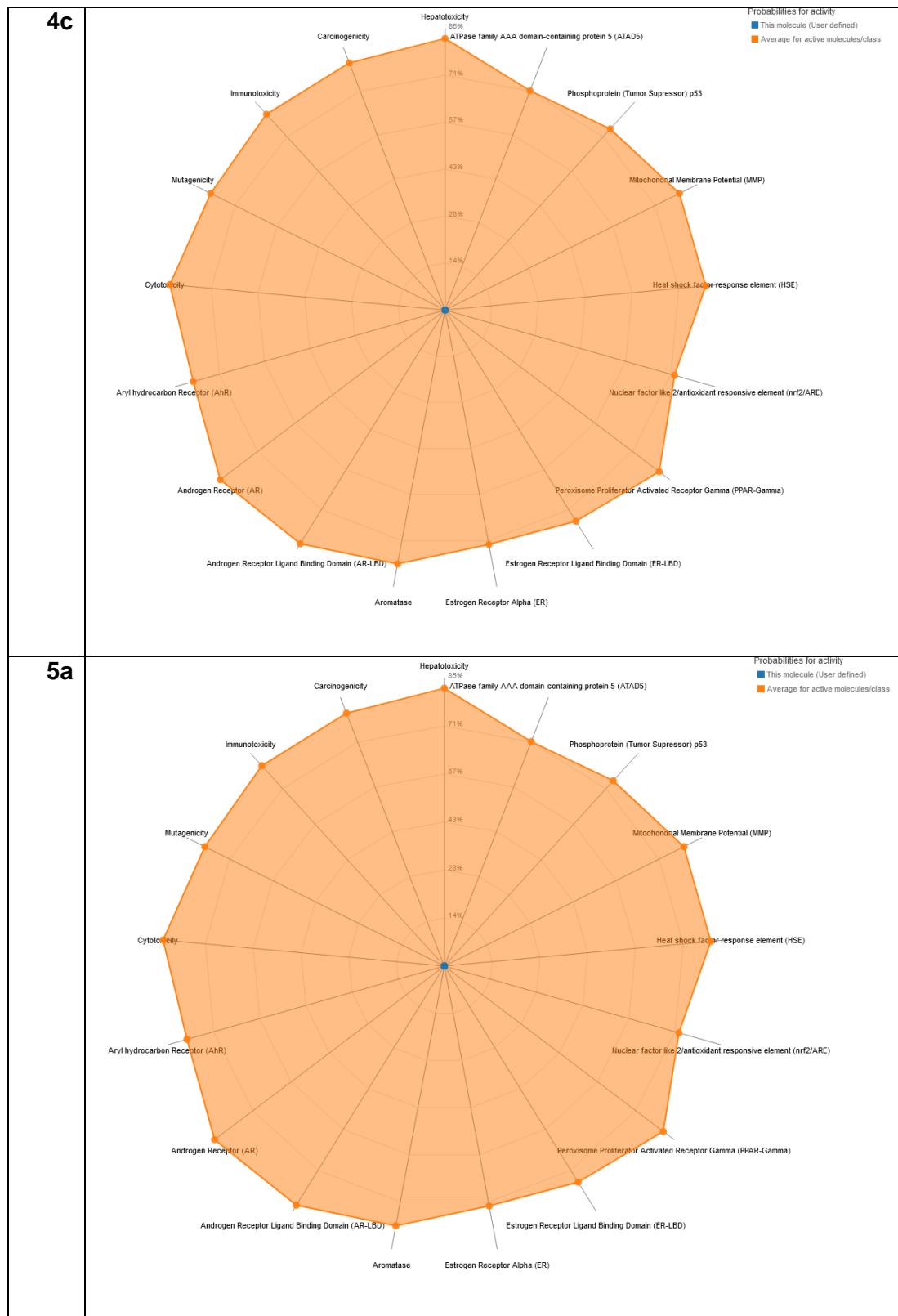
Ghose

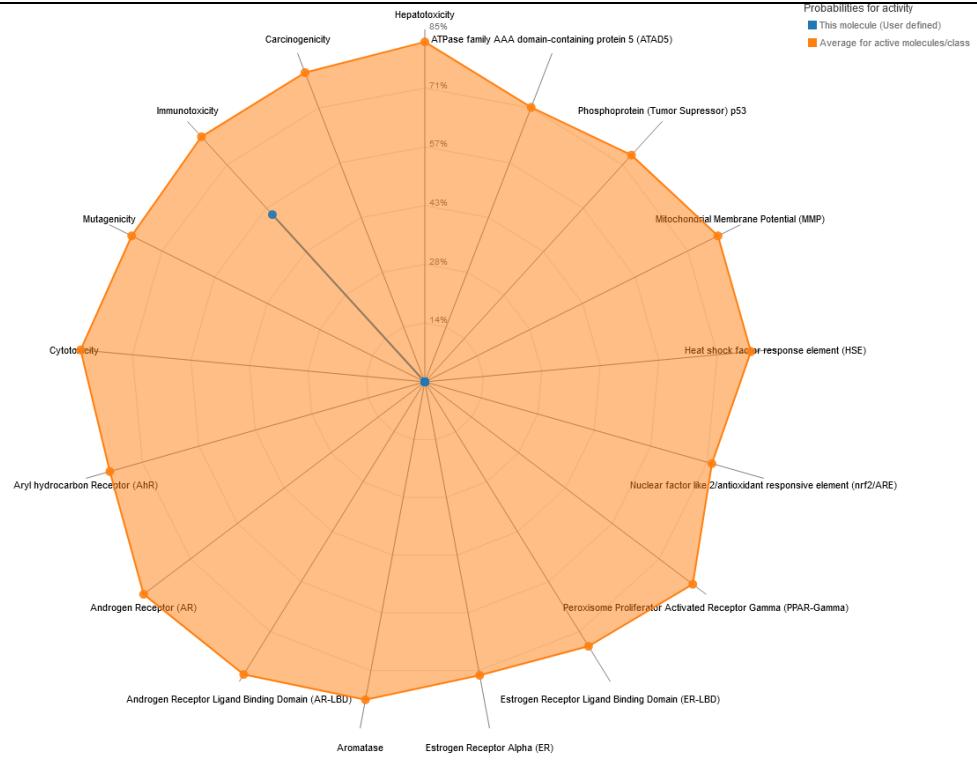
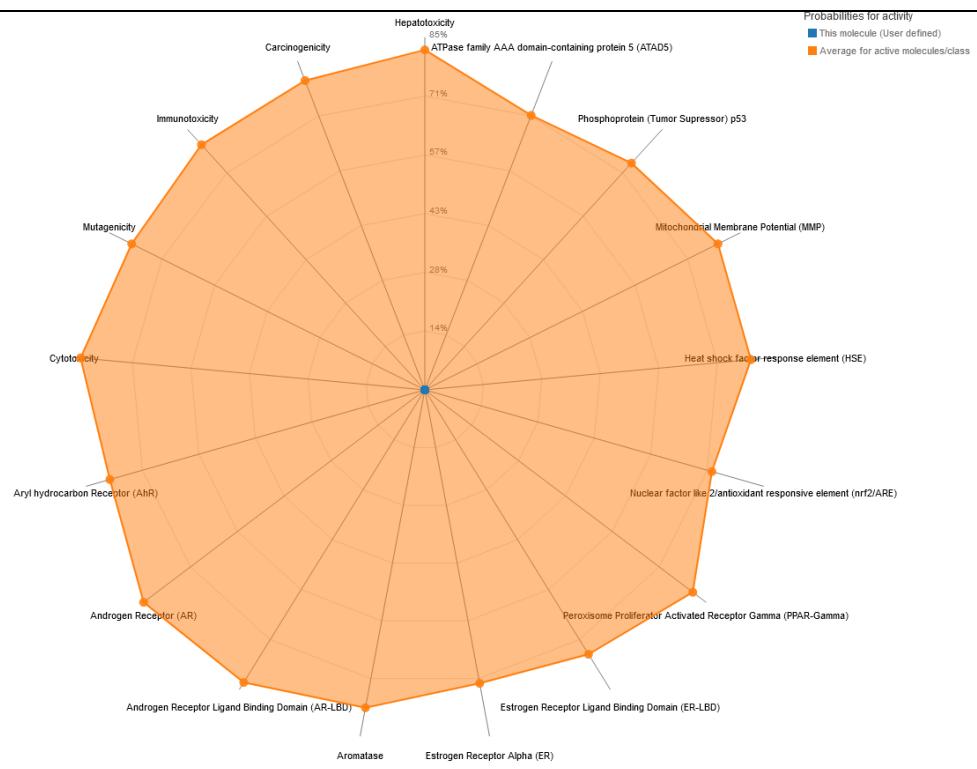
160<=MW<=480
-0.4<= WLOGP <= 5.6
40<= MR <= 130
20 <= atoms <=70

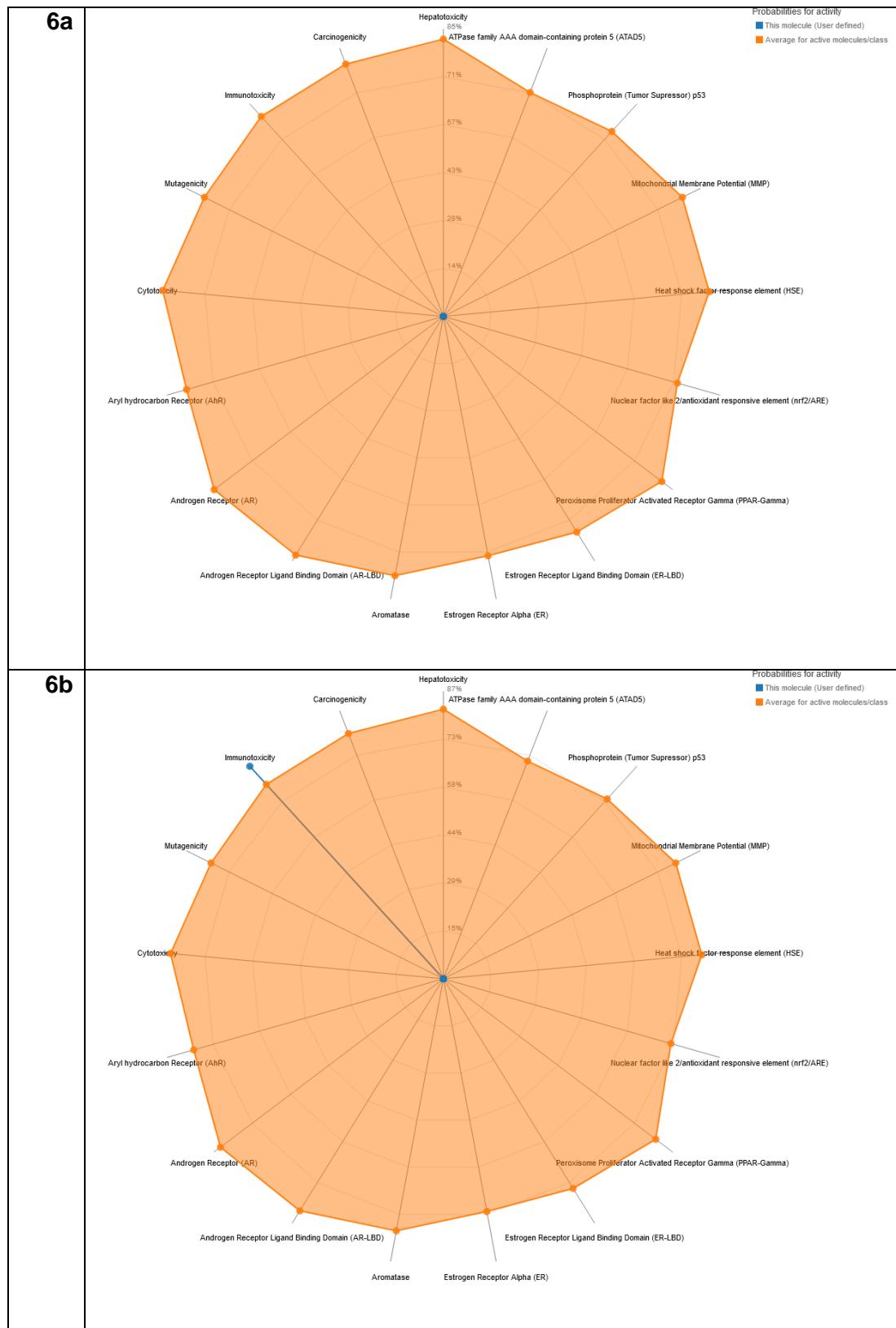
Muegge

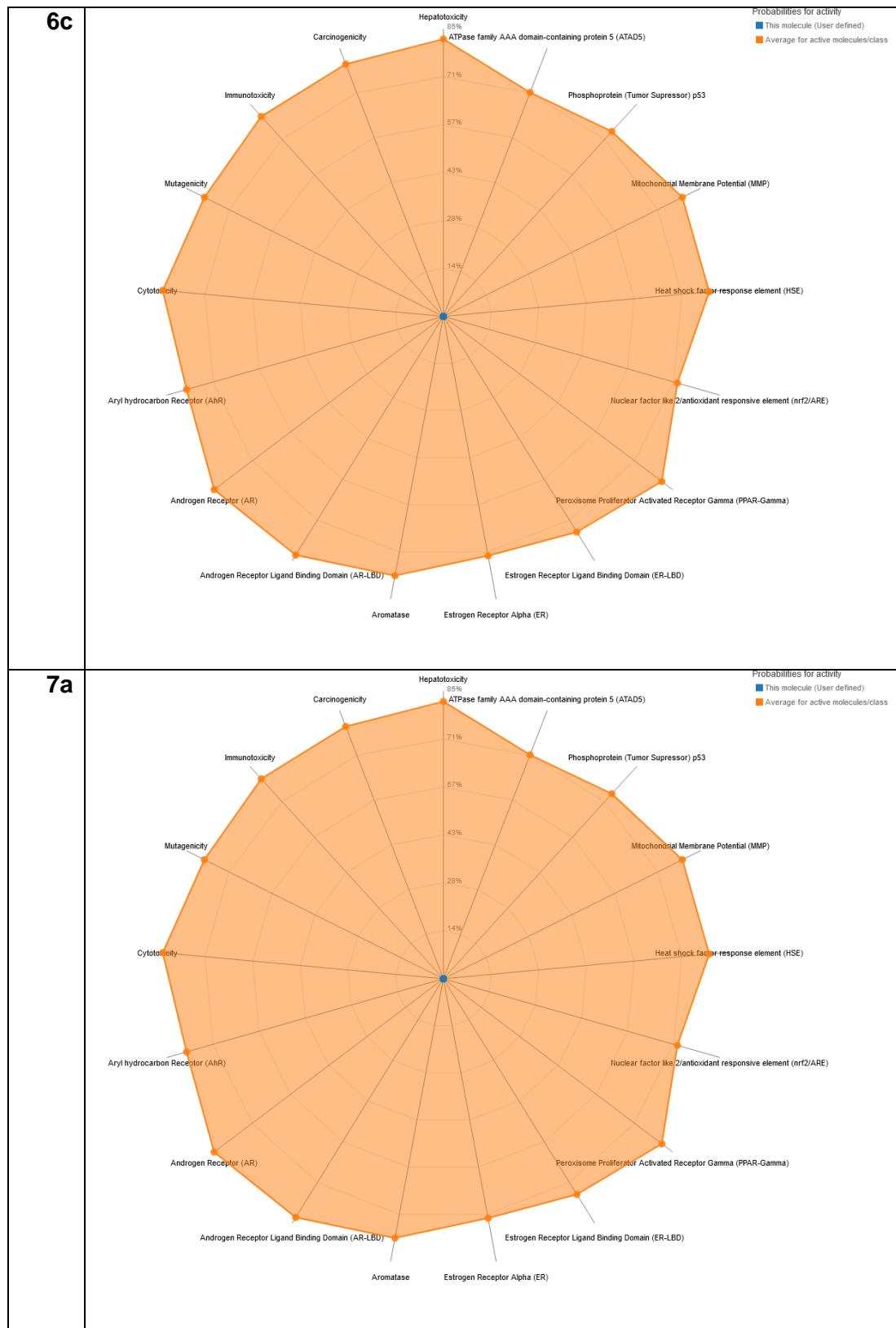
200 <= MW <= 600
-2 <= XLOGP <= 5
TPSA <= 150
Num. rings <= 7
Num. carbon > 4
Num. heteroatoms > 1
Num. rotatable bonds <= 15
H-bond acc. <= 10
H-bond don. <= 5

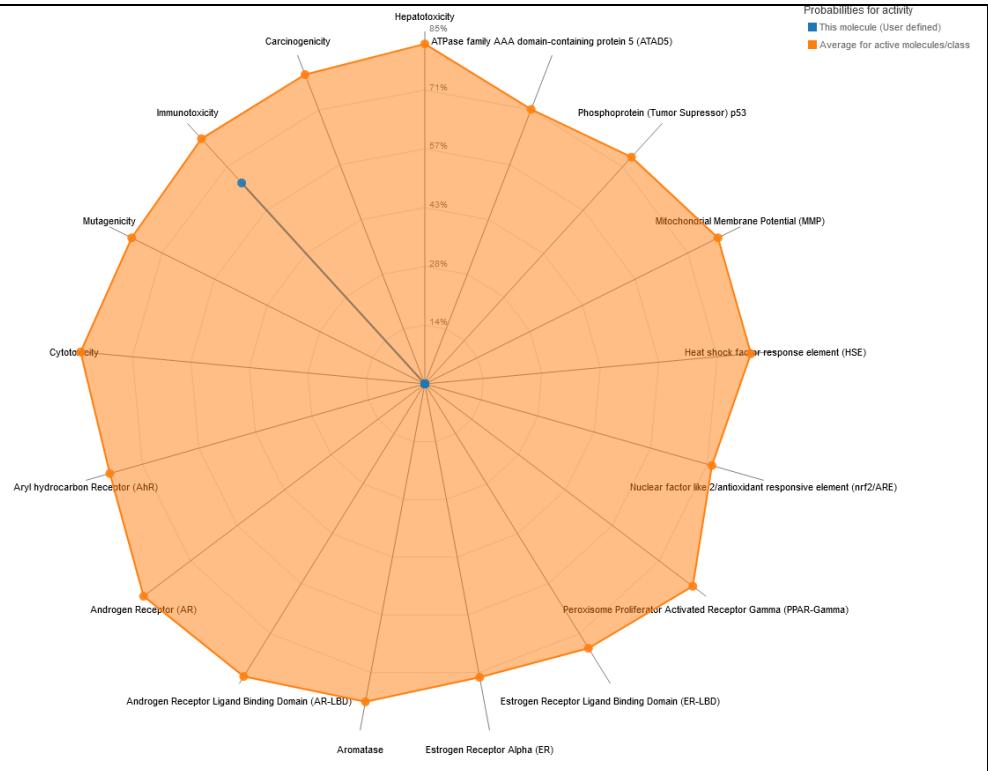
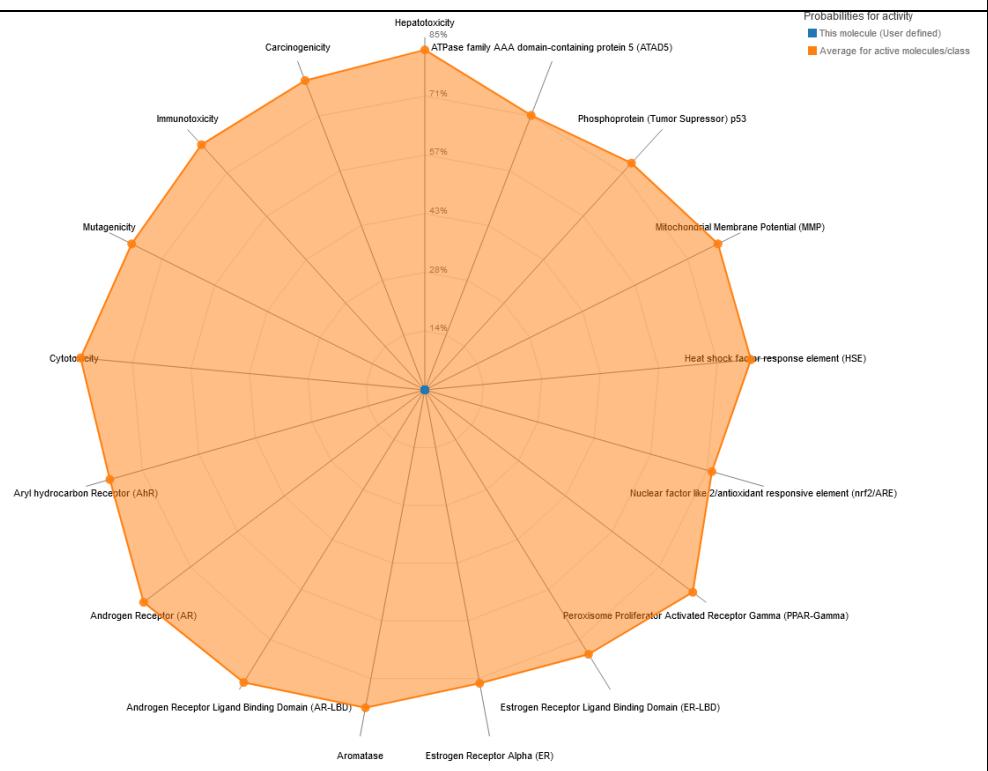
Fig. S4 Predicted Toxicity profiles for tested compounds (Table 1).

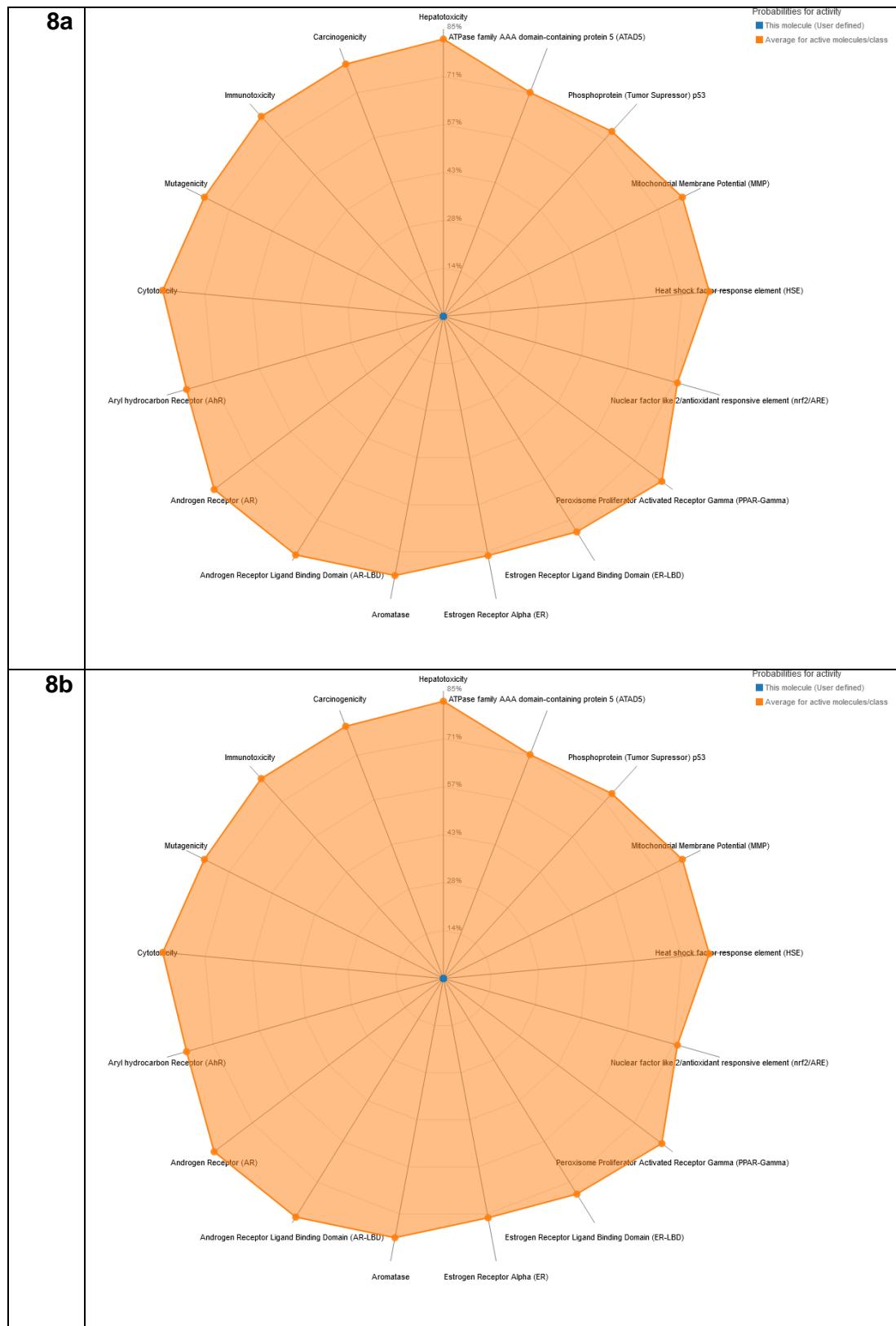


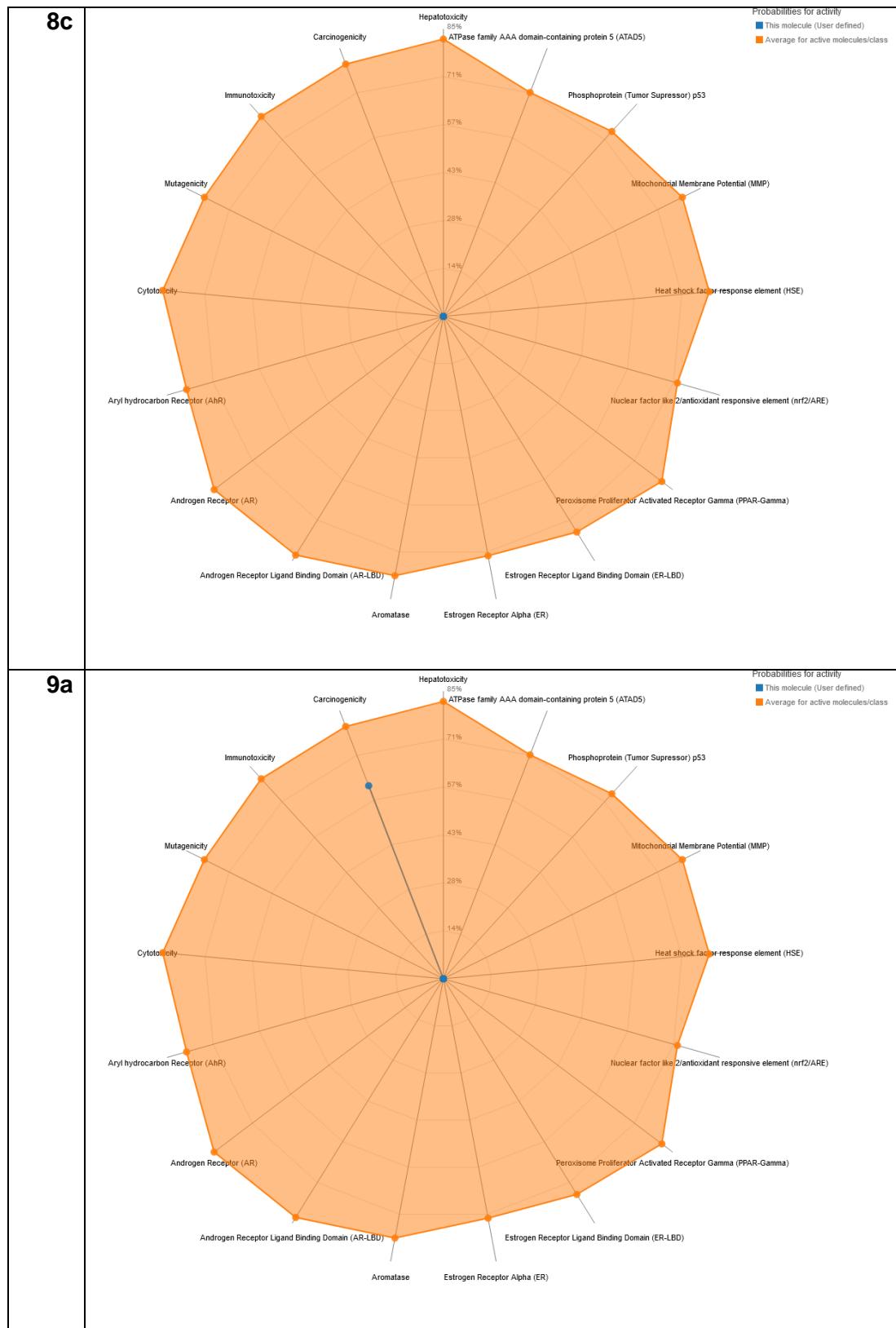
5b**5c**

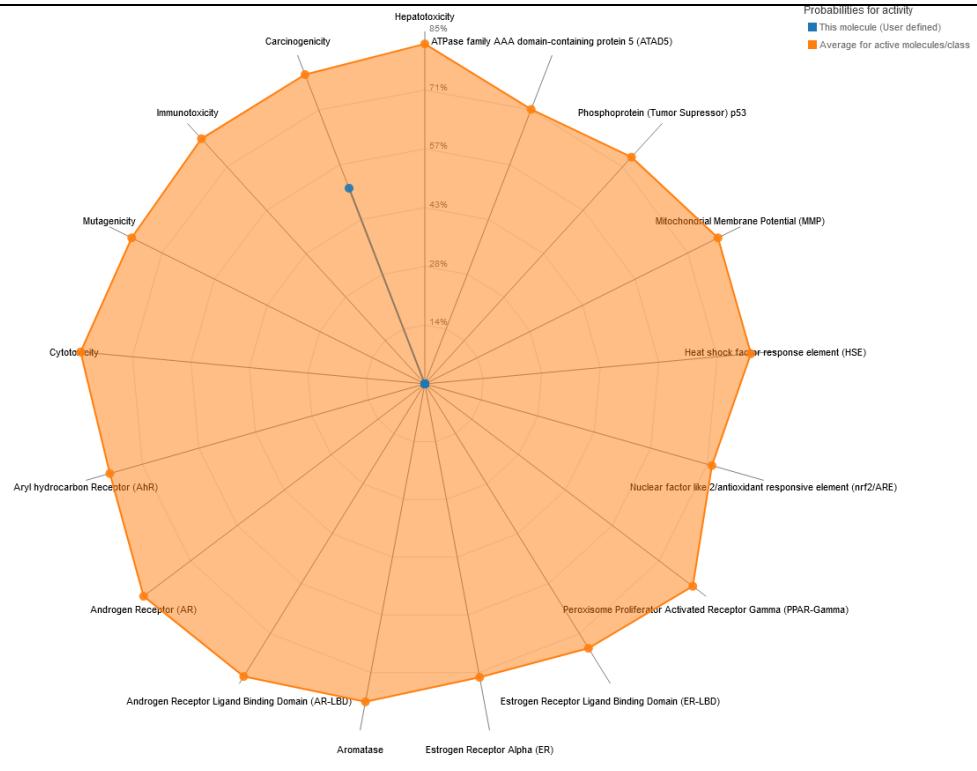
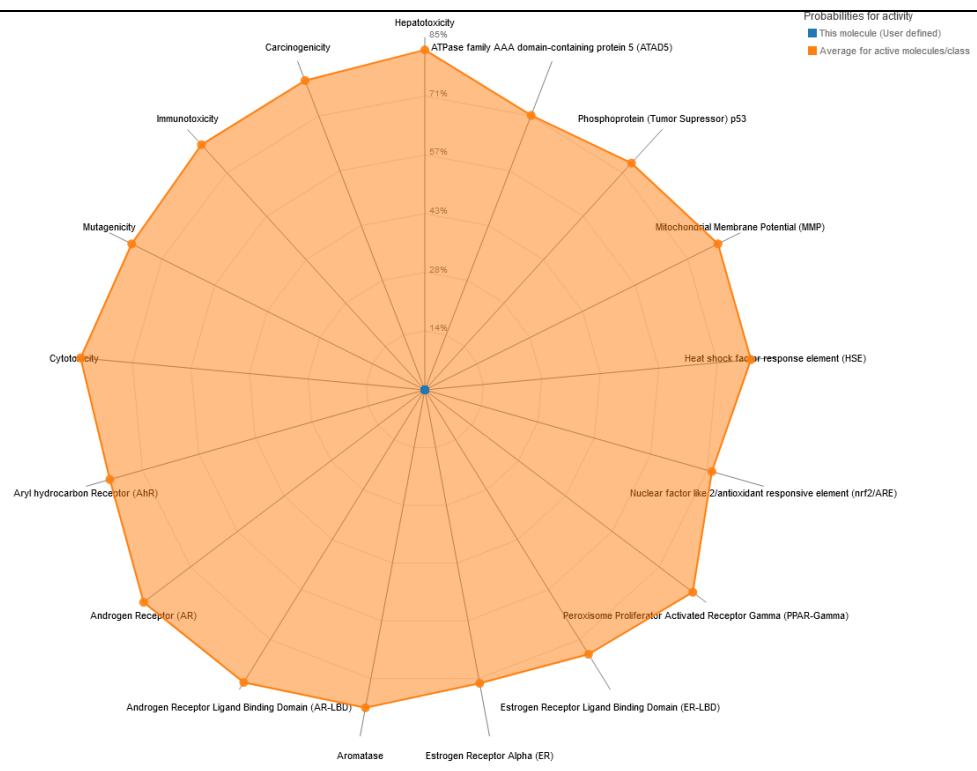




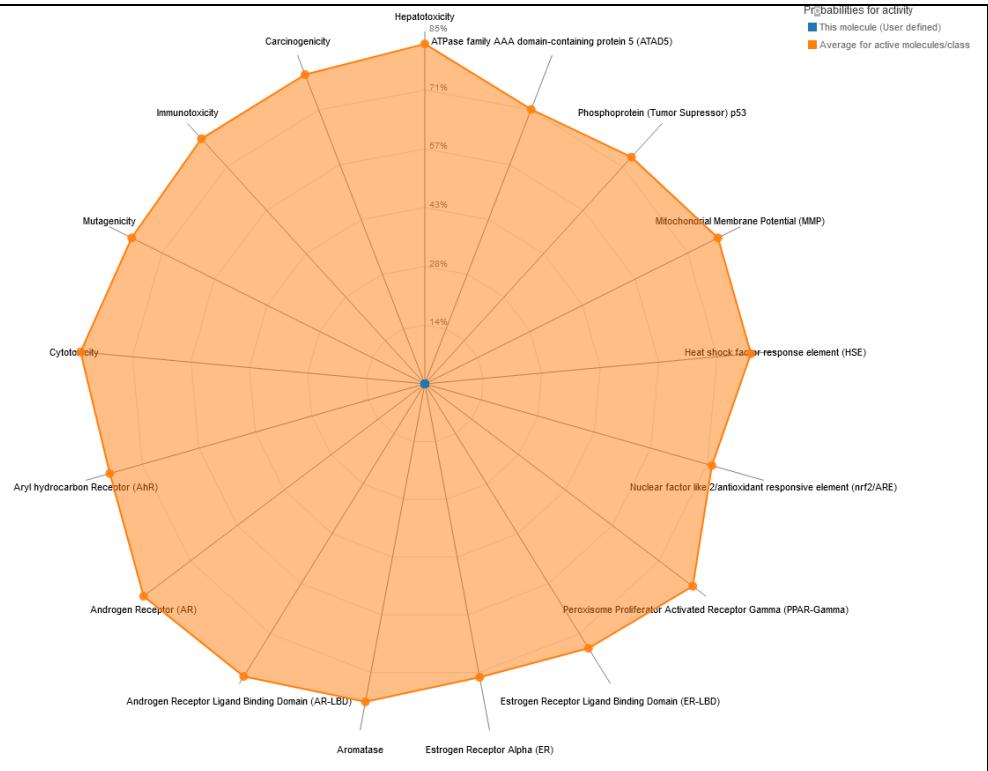
7b**7c**



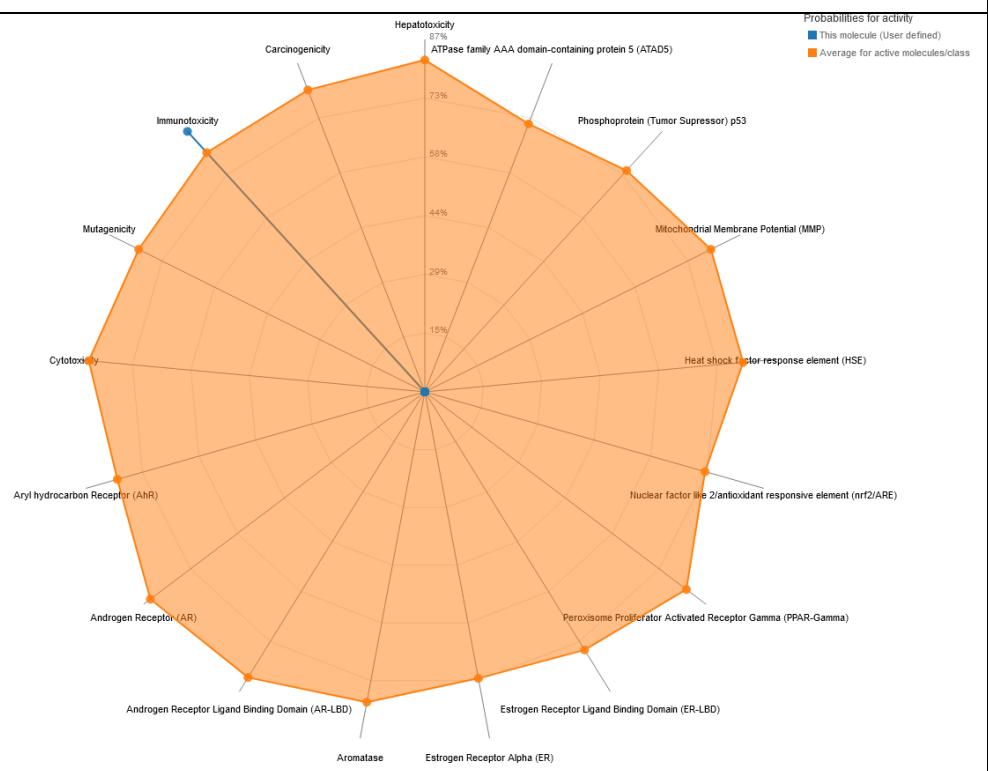


9b**9c**

10a



10b



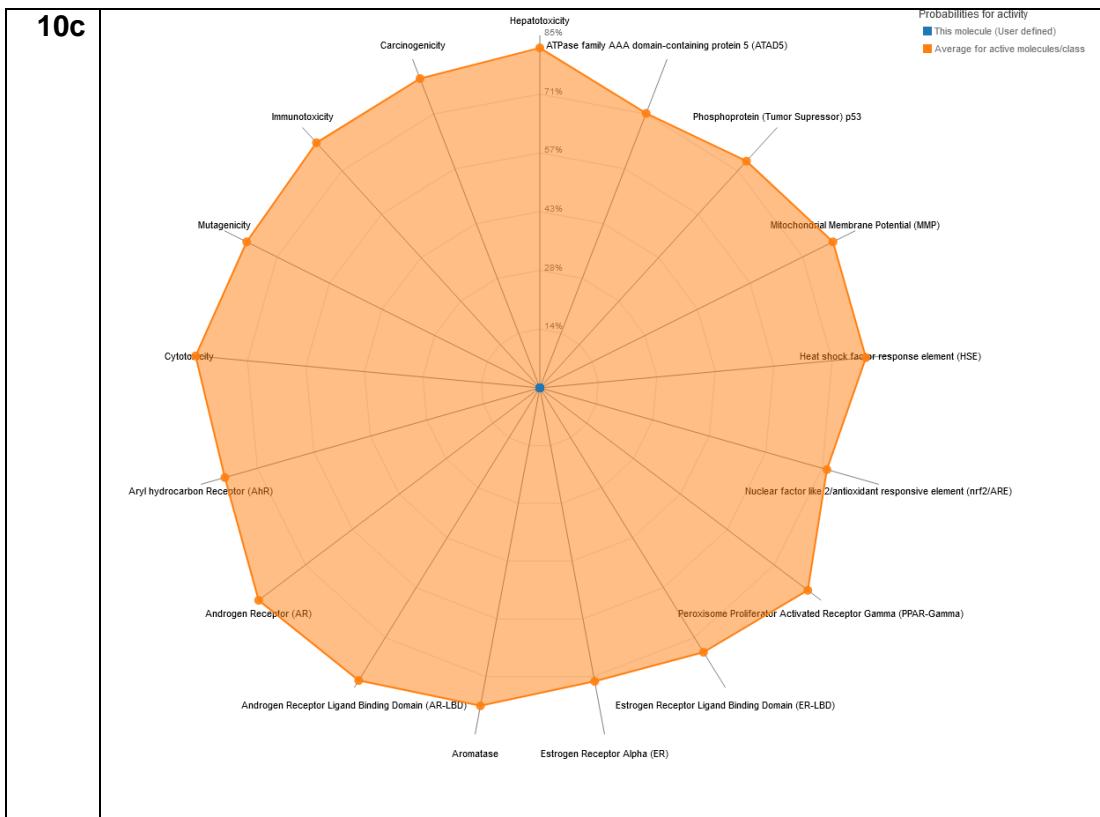


Fig. S5 3D model of docked ligands (Table 2) into 5HT1A receptor.

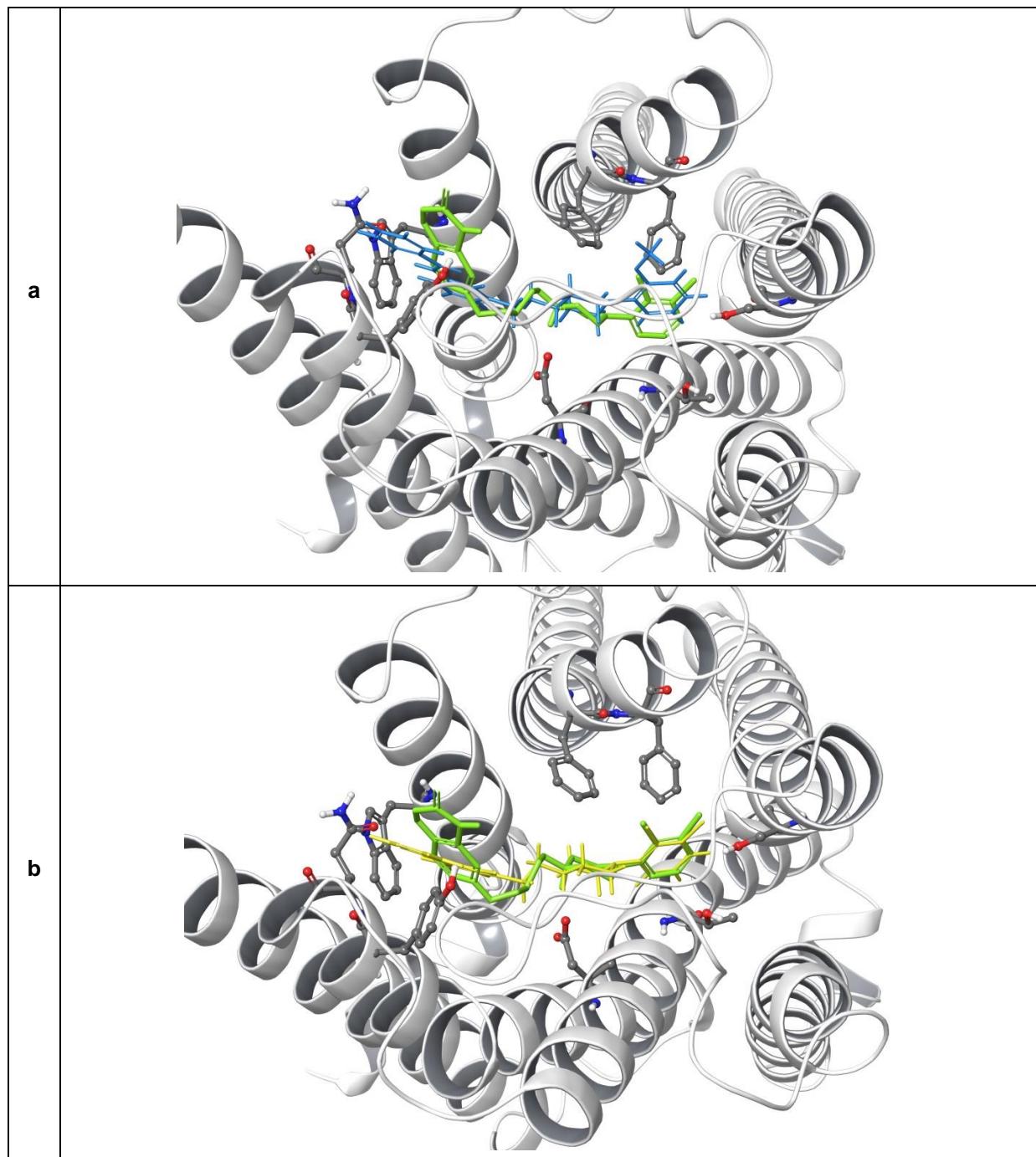
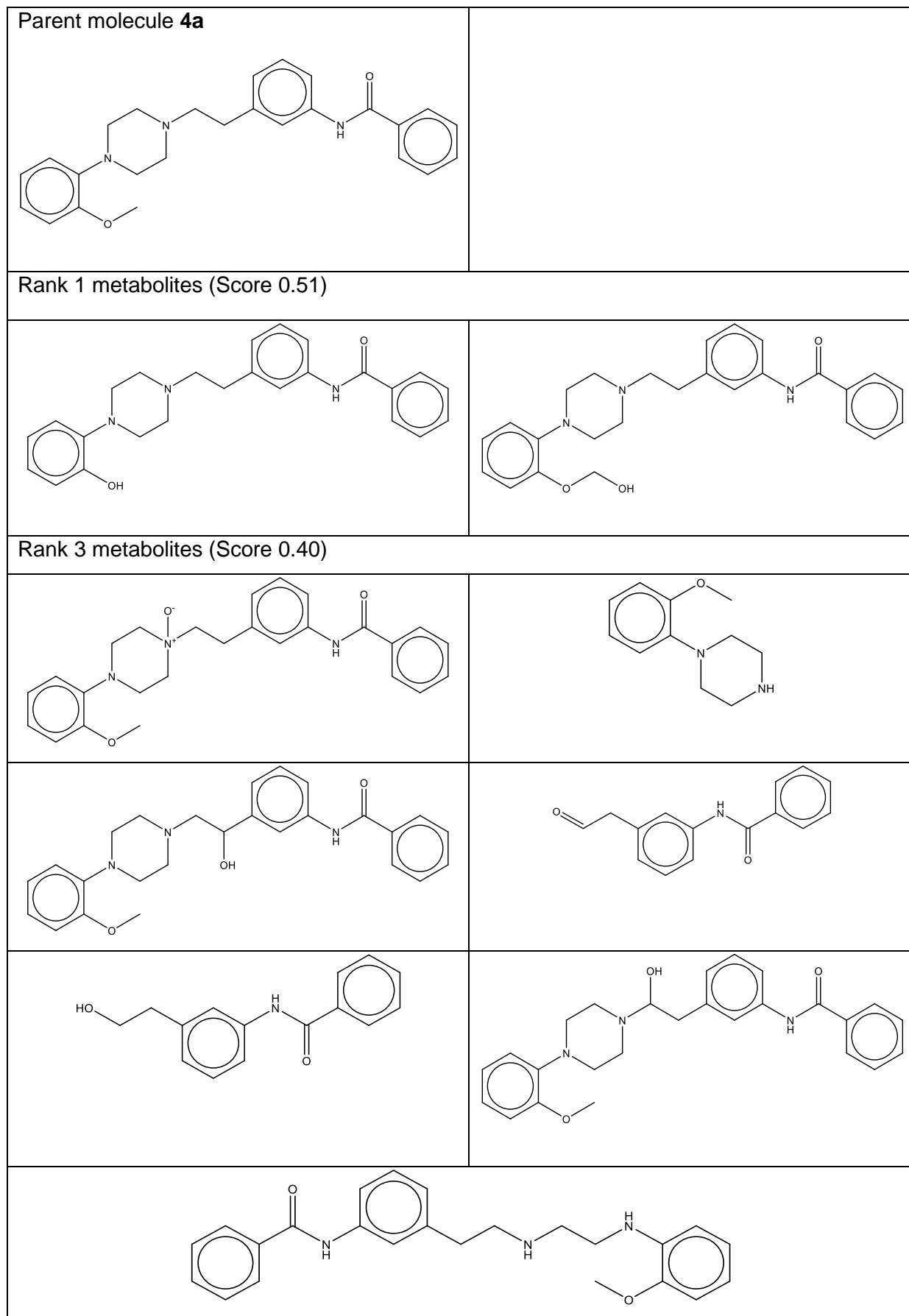
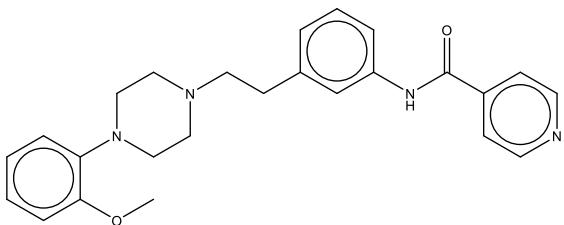
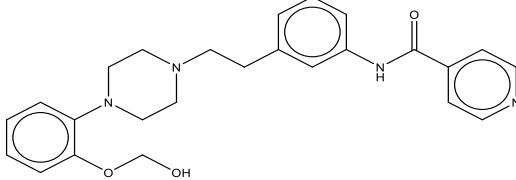
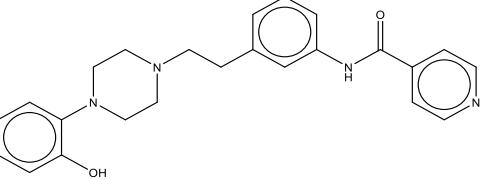
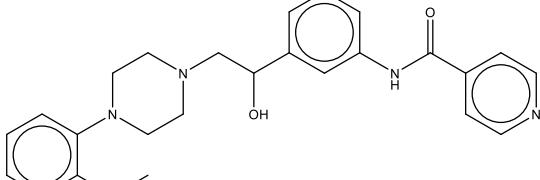
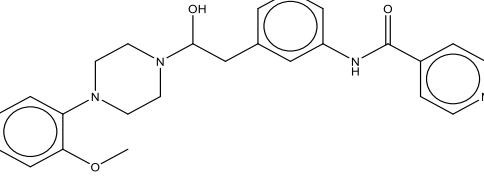
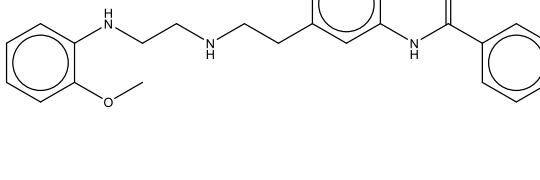
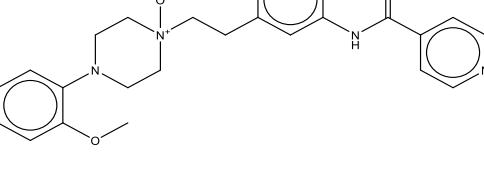
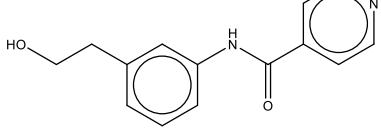
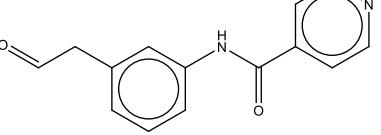
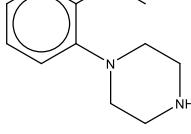


Fig. S5 Superposition of: a) ligand **4a** (blue) and aripiprazole (green), docked into 5HT1A receptor; b) ligand **8b** (yellow) and aripiprazole (green), docked into 5HT1A receptor. Only key amino acid residues are shown for clarity.

Fig. S6 Predicted metabolites (Table 3) for selected substances (Table 2).



Parent molecule 8a		
Rank 1 metabolites (Score 0.54)		
		
Rank 3 metabolites (Score 0.44)		
		
		
		
		

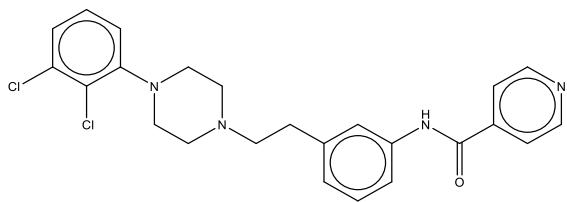
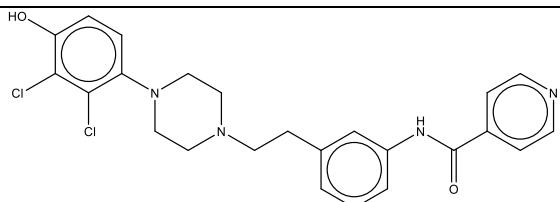
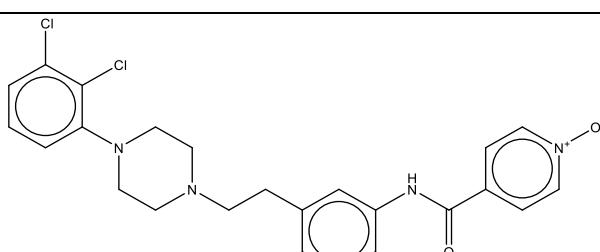
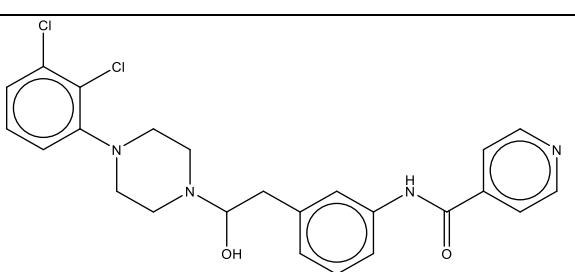
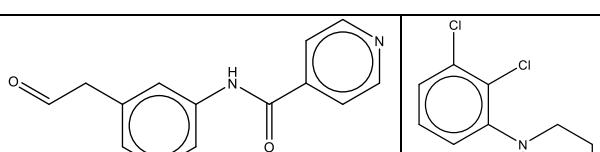
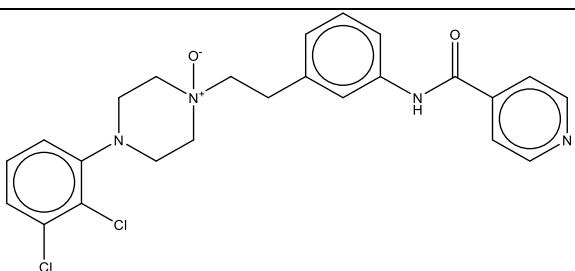
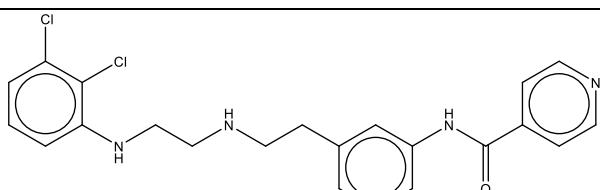
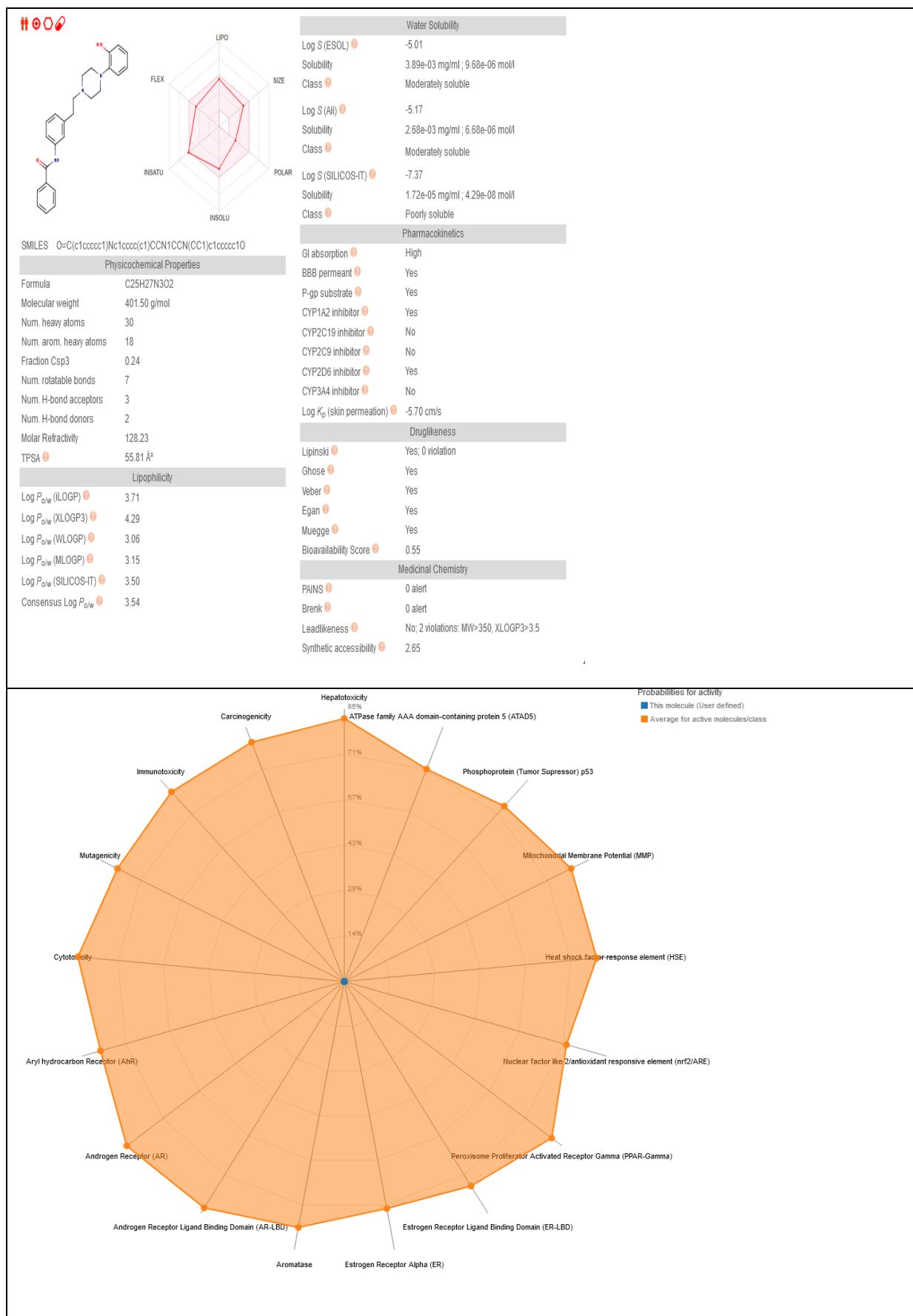
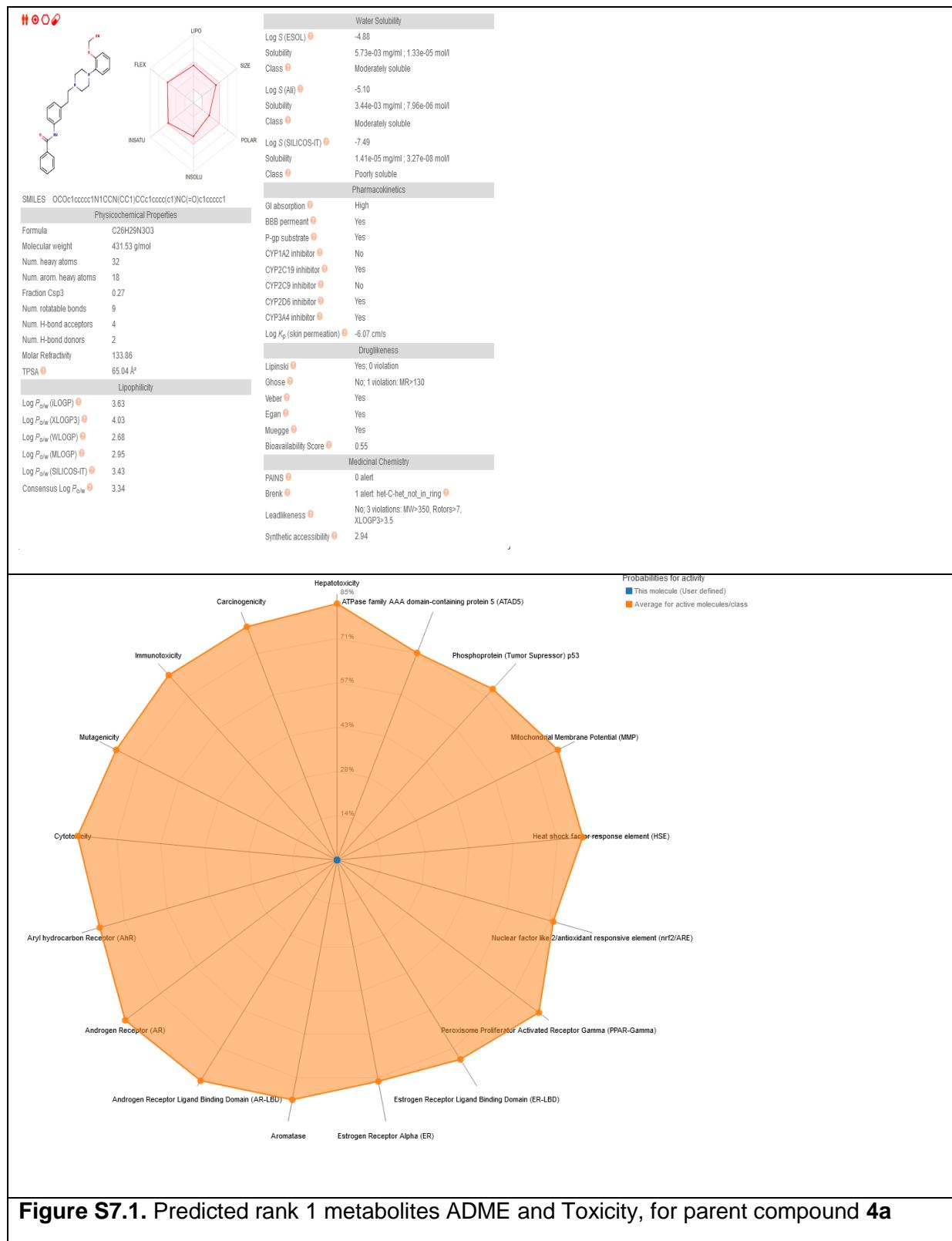
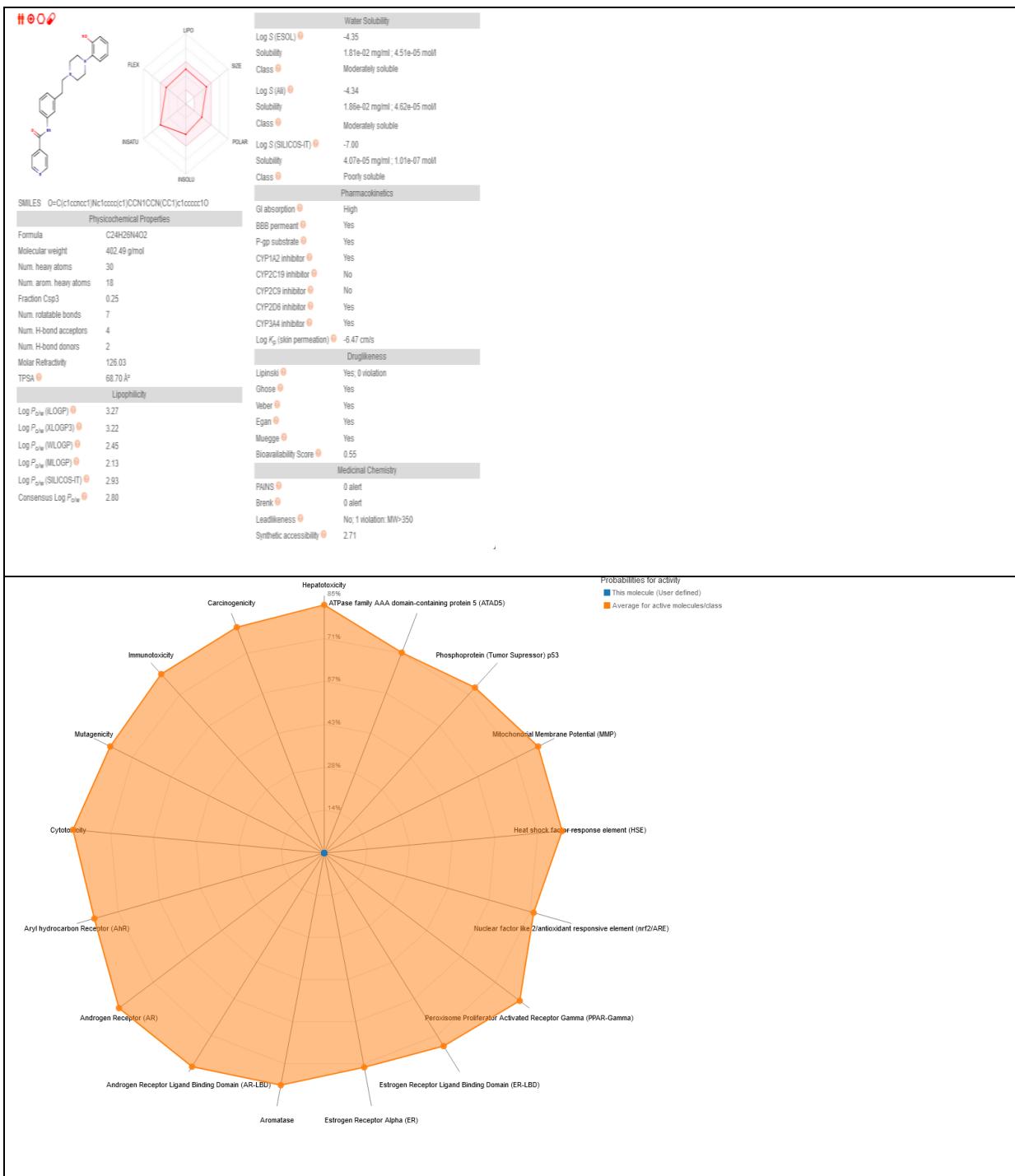
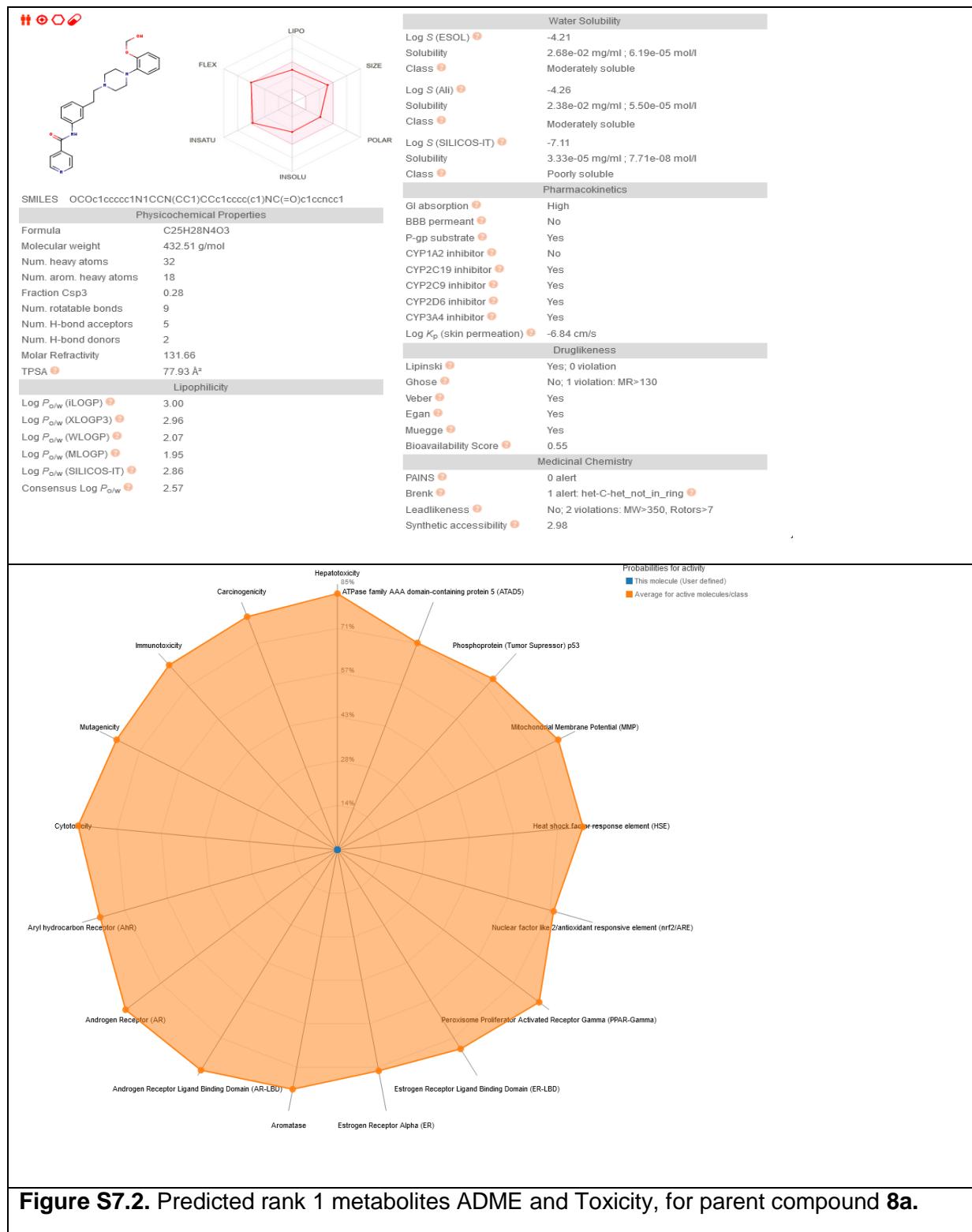
Parent molecule 8b**Rank 1 metabolite (Score 2.77)****Rank 2 metabolite (Score 2.04)****Rank 3 metabolites (Score 1.97)**

Fig. S7 Predicted ADMET profiles for predicted metabolites (Table 3).









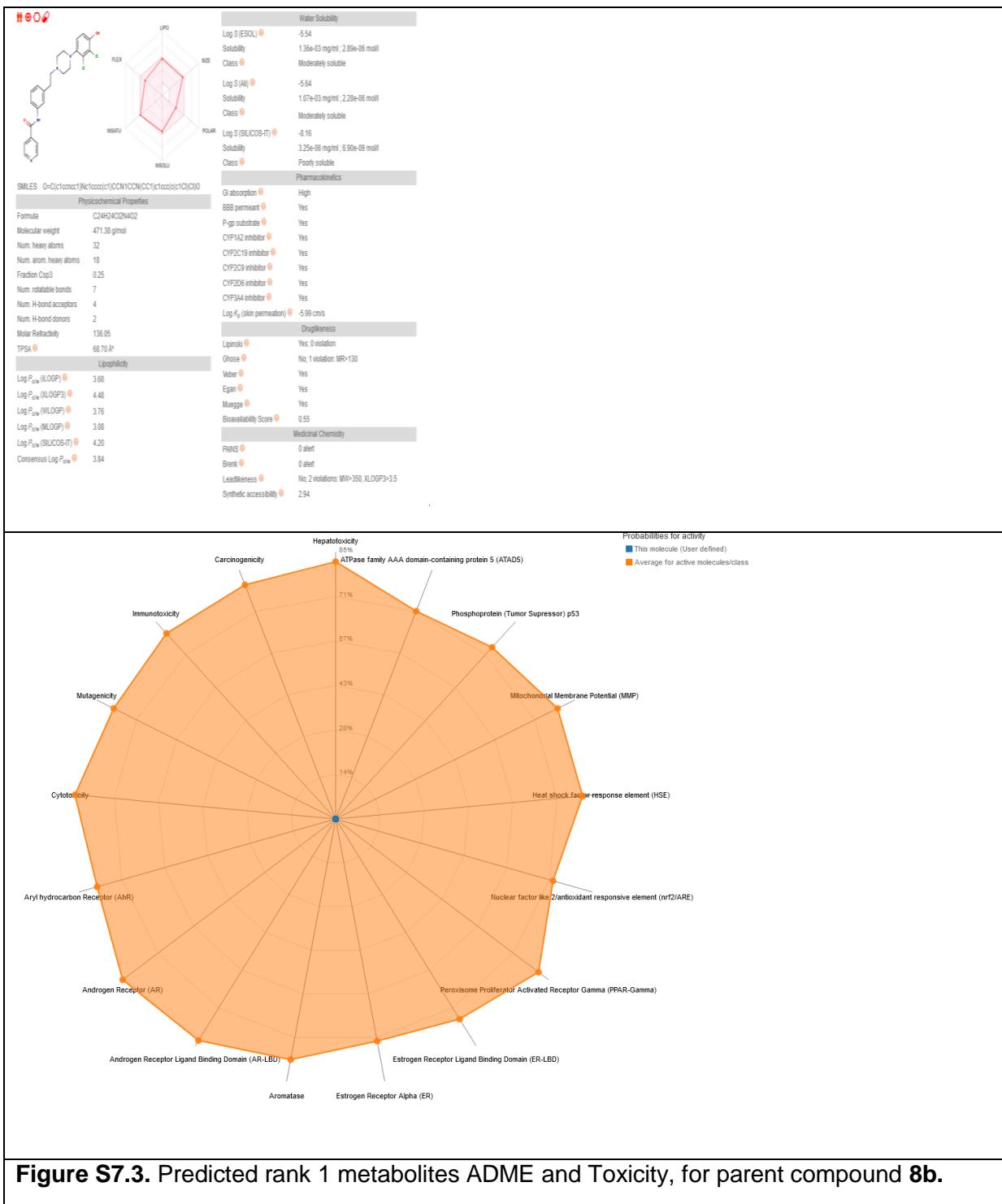


Fig. S8 2D schematics of docked metabolites (Table 3) into 5HT1A receptor.

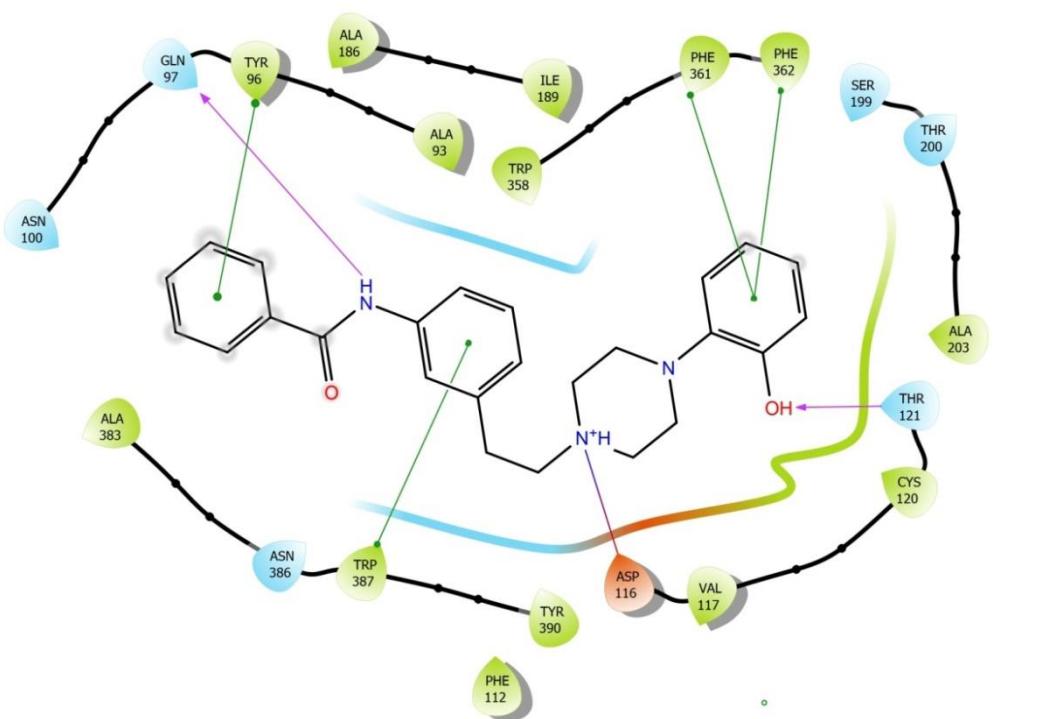


Figure S8.1. 2D docking schematics of **4a** metabolite 1. Aromatic interactions are presented as green lines, hydrogen bonds and salt bridge are purple. Only key amino acid residues are shown for clarity.

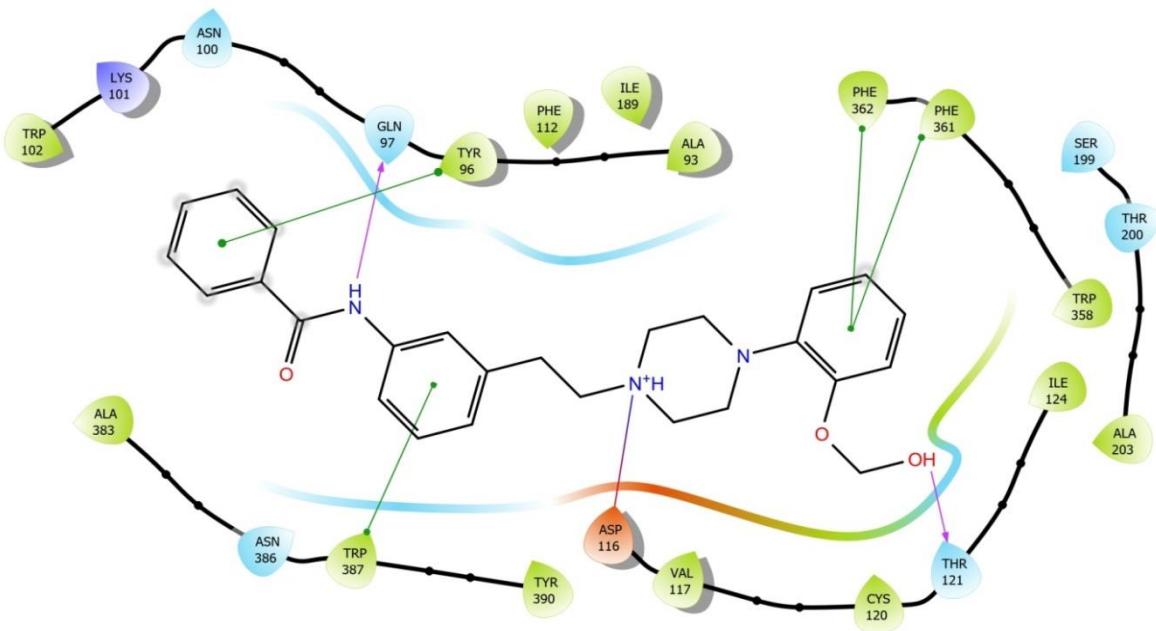


Figure S8.2. 2D docking schematics of **4a** metabolite 2. Aromatic interactions are presented as green lines, hydrogen bonds and salt bridge are purple. Only key amino acid residues are shown for clarity.

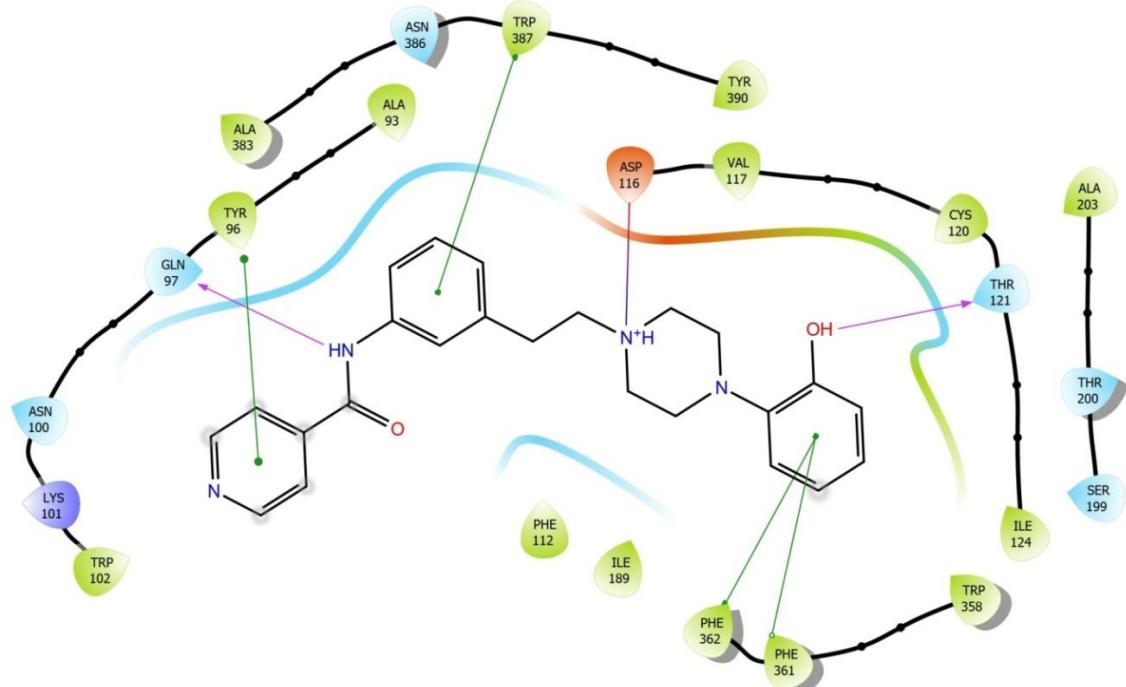


Figure S8.3. 2D docking schematics of **8a** metabolite 1. Aromatic interactions are presented as green lines, hydrogen bonds and salt bridge are purple. Only key amino acid residues are shown for clarity.