molecules

MDPI

Supplementary Material

Mollusc Derived Brominated Indoles for the Selective Inhibition of Cyclooxygenase: A Computational Expedition

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Table S1. Summary of nonbonding interactions analysis for Cyclooxygenase-1 (PDB ID: 3N8X), for the reference molecule aspirin and four *D. orbita* compounds.

Compounds Name	Hydrogen Bond				Hydrophobic Bond				Electrostatic Bond (EB) / Halogen Bond (HB) / Other Bond (OB)			
	Bonding type	Protein	Ligand	Distance	Bonding type	Protein	Ligand	Distance	Bonding type	Protein	Ligand	Distance
		Interacting amino acids	Interacting atoms or ring			Interacting amino acids	Interacting atoms or ring			Interacting amino acids	Interacting atoms or ring	
Aspirin	Conventional	Arg-120	H…O	2.04	Pi-Alkyl	Leu-352	X	5.07				
	Conventional	Arg-120	H…O	2.44		Ile-523	X	4.70				
	Carbon Hydrogen	Ser-530	H…O	2.97		Ala-527	X	4.49				
Tyrindoxyl Sulfate	Conventional	Arg-120	H…O	2.41	Amide Pistacked	Gly-526	X1	4.47	Attractive Charge	Arg-120	H…O (EB)	2.13
	Carbon Hydrogen	Arg-120	H…O	2.13		Ala-527	X1	4.47				
	Salt Bridge	Ser-353	H…O	2.76	Alkyl	Ile-523	X3	3.83	Pi-Sulfur	His-90	X3 (OB)	5.87
					Pi-Alkyl	Leu-352	X2	5.04				
						Ile-523	X2	4.56				
						Ala-527	X2	4.27				
Tyrindoleninone	Carbon Hydrogen	Ile-523	H…O	2.73	Amide Pistacked	Gly-526	X1	4.87	Pi-Sulfur	Met-522	X1 (OB)	5.98
						Ala-527	X4	4.87				
						Gly-526	X4	3.96				
						Ala-527	X1	3.96				
					Alkyl	Ile-523	X3	4.77				
					Pi-Alkyl	Tyr-355	X3	4.19				
						Val-349	X4	5.21				
						Leu-352	X4	4.82				
						Ala-527	X4	3.93				
						Leu-352	X1	5.18				
						Ala-527	X1	4.71				
6-Bromoisatin					Amide Pistacked	Gly-526	X5	3.88				
						Ala-527	X1	3.88				
						Gly-526	X1	4.97				
						Ala-527	X5	4.97				
					Pi-Alkyl	Leu-352	X5	5.17				
						Ala-527	X5	4.38				
						Val-349	X1	5.05				
						Leu-352	X1	5.04				
						Ala-527	X1	3.71				
6,6′ dibromoindirubin	Carbon Hydrogen	Ser-353	H…O	2.59	Amide Pistacked	Gly-526	X6	4.83	Attractive charge	Arg-120	N-H…O (EB)	5.41
						Ala-527	X1	4.83				
						Gly-526	X1	3.96				
						Ala-527	X6	3.96				
	Pi-donor Hydrogen	Tyr-355	H…O	2.59	Alkyl	Leu-384	Br	4.86	Pi-Anion	Tyr-355	O (EB)	4.20
					Pi-Alkyl	Phe-381	Br					
						Tyr-385	Br					
						Trp-387	Br					
						Val-349	X6					
						Ala-527	X6					
6,6′ dibromoindirubin (Continue)					Pi-Alkyl	Val-349	X6					
						Leu-352	X6					
						Ile-523	X6					
						Ala-527	X6					
						Val-349	X1					
						Leu-359	X1					
						Ala-527	X1					
						Leu-531	X1					
						Leu-352	X1					

Ala-527	X1

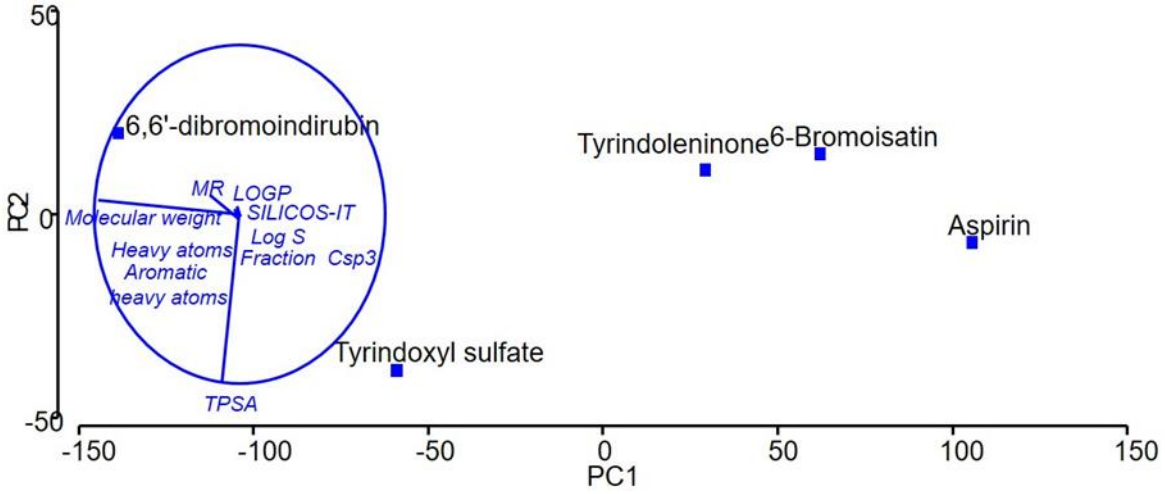
Here, X, X1, X2, X3 indicates that, X = Benzene, X1 = 6-Bromo benzene, X2 =Indole-3-ol, X3 = (Methylthio)methane, X4 = Indole-3-one, X5 = Indoline-2,3-dione, X6 = Indolin-2-one.

Table S2. Summary of nonbonding interactions analysis for Cyclooxygenase-2 (PDB ID: 5IKR), for the reference molecule aspirin and four *D. orbita* compounds.

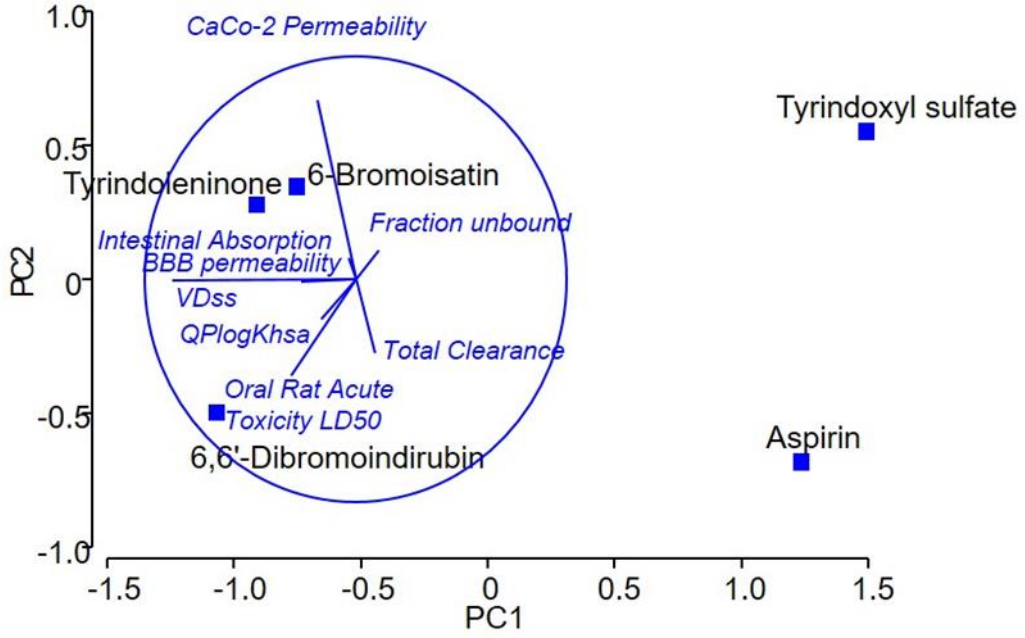
Compounds Name	Hydrogen Bond				Hydrophobic Bond				Electrostatic Bond (EB) / Halogen Bond (HB) / Other Bond (OB)			
		Protein	Ligand	Dis - tance		Protein	Ligand	Distance		Protein	Ligand	Distance
	Bonding Type	Inter-acting Amino Acids	Interact-ing Atoms or Rings		Bonding Type	Interact-ing Amino Acids	Interacting Atoms or Rings		Bonding Type	Inter-acting Amino Acids	Interact-ing Atoms or Rings	
Aspirin	Conventional Hydrogen	Tyr-385	H…O	1.79	Amide Pi-stacked	Gly-526	X	3.76				
		Ser-530	H…O	1.83		Ala-527	X	3.76				
					Pi-Alkyl	Leu-352	X	5.13				
						Ala-527	X	4.82				
Tyrindoxyl Sulfate	Conventional Hydrogen	Tyr-385	H…O	2.11	Pi-Alkyl	Val-349	X2	5.03	Pi-Sulfur	Trp-387	X3 (OB)	5.72
		Ser-530	H…O	2.22						Trp-387	O (OB)	5.83
						Leu-352	X2	4.85				
	Carbon Hydrogen	Ser-530	H…O	2.82		Val-523	X1	5.38				
		Ser-530	H…O	2.50								
		Ser-530	H…O	2.93		Ala-527	X1	3.57				
						Val-349	X	4.25				
						Ala-527	X	3.47				
						Leu-531	X	4.12				
Tyrindoleni-none	Conventional Hydrogen	Ser-530	H…O	2.10	Amide Pi-stacked Alkyl	Gly-526	X1	4.12	Halogen	Met-522	Br	3.12
						Ala-527	X4	4.12				
						Gly-526	X4	3.80				
						Ala-527	X1	3.80				
	Hydrogen	Ser-530	H…O	2.71	Alkyl	Ala-527	X3	3.63				
						Val-349	X3	4.39				
						Leu-531	X3	3.72				
					Pi-Alkyl	Val-349	X4	5.15				
						Leu-352	X4	4.83				
						Ala-527	X4	3.92				
						Leu-352	X1	5.17				
						Ala-527	X1	5.14				
6-Bromoisatin	Conventional Hydrogen	Ser-530	H…O	2.12	Amide Pi-stacked	Gly-526	X1	4.12	Halogen	Met-522	Br	3.13
						Ala-527	X4	4.12				
	Carbon Hydrogen	Ser-530	H…O	2.70		Gly-526	X4	3.80				
						Ala-527	X1	3.80				
					Pi-Alkyl	Val-349	X5	5.10				
						Leu-352	X5	4.78				
						Ala-527	X5	3.92				
						Leu-352	X1	5.14				
						Ala-527	X1	5.10				
6,6′dibromoindi-rubin	Carbon Hydrogen	Ser-530	H…O	2.92	Pi-pi T shaped	Tyr-355	X1	4.74				
	Pi-donor Hydrogen	Arg-120	H…O	3.00	Amide pi-stacked	Gly-526	X6	4.95				
						Ala-527	X6	4.95				
						Gly-526	X1	4.06				
						Ala-527	X1	4.06				
					Alkyl	Leu-352	Br	5.09				
						Met-522	Br	4.95				
					Pi-Alkyl	Trp-387	Br	5.22				
						Phe-518	Br	4.46				
						Val-116	X6	4.86				

	Val-349	X6	5.35
	Leu-359	X6	4.98
	Ala-527	X6	4.93
	Leu-531	X6	4.71
	Val-349	X6	4.32
	Leu-352	X1	4.81
	Ala-527	X1	3.97

Here, X, X1, X2, X3 indicates that, X = Benzene, X1 = 6-Bromo benzene, X2 =Indole-3-ol, X3 = (Methylthio)methane, X4 = Indole-3-one, X5 = Indoline-2,3-dione, X6 = Indolin-2-one.



a)



b)

Figure S1. Principle coordinate ordination showing the difference in **a**) physicochemical properties and **b**) pharmacokinetic properties of the brominated indoles from *Dicathais orbita.*