

### Supplementary Files:

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Compound	Docking Score (Kcal/mol)	Re-rank score	Log P	RMSD	Torsions	HB	Molecular weight
Biliverdin	32135	446.2	2,5	0	10	-6.60	582.65
Bilirubin	2124	345.3	2.9	0	10	-4.43	584.66
Lumirubin	-114.0	-89.6	1.4	0	3	-6.84	218.25
FICZ	-125.7	-95.6	4.3	0	1	0	282.30
KA	-81.42	-72.56	1.3	0	0	-4.98	189.17
QA	-87.80	-74.86	0.2	0	2	-8.65	167.12

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Abbreviations: FICZ (6-Formylindolo[3,2-b]carbazole), KA (kynurenic acid), P (partition coefficient), QA (quinolinic acid), RMSD (root mean square deviation), torsion (flexibility of ligand) HB (hydrogen bonds)

**Table S1:** Docking of biliverdin, bilirubin, lumirubin and other compounds to the NMDA receptor.

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Compound	Docking Score (Kcal/mol)	Re-rank score	Log P	RMSD	Torsions	HB	Molecular weight
Biliverdin	3163	398.5	2.5	0	10	-9.07	582.65
Bilirubin	2164	413.8	2.9	0	10	-5.95	584.66
Lumirubin	-93.6	-62.6	1.4	0	3	-1.84	218.25
FICZ	-95.7	-65.6	4.3	0	1	-3.09	282.30
KA	-61.1	-54.67	1.3	0	0	-3.20	189.17
QA	-65.4	-53.46	0.2	0	2	-6.22	167.12

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Abbreviations: FICZ (6-Formylindolo[3,2-b]carbazole), KA (kynurenic acid), P (partition coefficient), QA (quinolinic acid), RMSD (root mean square deviation), torsion (flexibility of ligand) HB (hydrogen bonds)

**Table S2:** Docking of biliverdin, bilirubin, lumirubin and other compounds to the GABA<sub>A</sub> receptor.

Compound	Docking Score (Kcal/mol)	Re-rank score	Log P	RMSD	Torsions	HB	Molecular weight
Biliverdin	3162	390.9	2.5	0	10	-10.60	582.65
Bilirubin	2148	371.5	2.9	0	10	-9.49	584.66
Lumirubin	-96.8	-71.6	1.4	0	3	-6.65	218.25
FICZ	-97.9	-61.5	4.3	0	1	-0.42	282.30
KA	-65.7	-60.5	1.3	0	0	-5.11	189.17
QA	-71.7	-58.4	0.2	0	2	-6.35	167.12

Abbreviations: FICZ (6-Formylindolo[3,2-b]carbazole), KA (kynurenic acid), P (partition coefficient), QA (quinolinic acid), RMSD (root mean square deviation), torsion (flexibility of ligand) HB (hydrogen bonds)

**Table S3:** Docking of biliverdin, bilirubin, lumirubin and other compounds to the GABA<sub>B</sub> receptor.

Compound	Docking Score (Kcal/mol)	Re-rank score	Log P	RMSD	Torsions	HB	Molecular weight
Biliverdin	3158	648.3	2.5	0	10	-3.26	582.65
Bilirubin	2155	818.3	2.9	0	10	-9.21	584.66
Lumirubin	-96.8	-96.5	1.4	0	3	-6.62	218.25
FICZ	-109.9	-13.8	4.3	0	1	-0.99	282.30
KA	-104.1	-93.2	1.3	0	0	-12.37	189.17
QA	-87.2	-75.9	0.2	0	2	-13.89	167.12

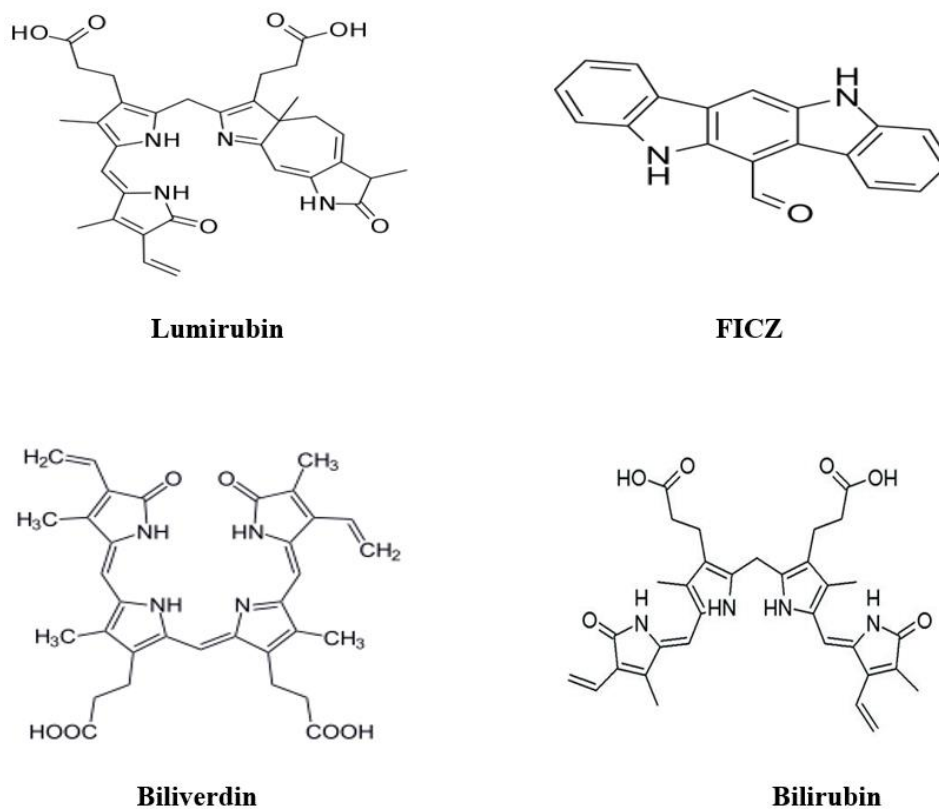
Abbreviations: FICZ (6-Formylindolo[3,2-b]carbazole), KA (kynurenic acid), P (partition coefficient), QA (quinolinic acid), RMSD (root mean square deviation), torsion (flexibility of ligand) HB (hydrogen bonds)

**Table S4:** Docking of biliverdin, bilirubin, lumirubin and other compounds to the kainate receptor.

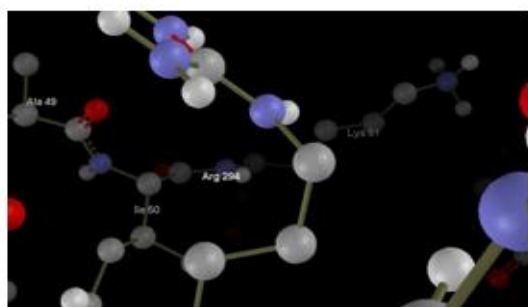
Enzyme	Docking Score (Kcal/mol)	Re-rank score	Log P	RMSD	Torsions	HB	Molecular weight
<b>TDO:</b>							
Bilirubin	2119	554.8	2.9	0	10	-7.53	584.662
Lumirubin	-99.0	-72.1	1.4	0	3	-3.51	218.252
<b>IDO 1:</b>							
Bilirubin	2120	440.4		0	10	-8.19	
Lumirubin	-122.7	-98.5		0	3	-2.17	
<b>KMO:</b>							
Bilirubin	2124	364.3		0	10	-9.65	
Lumirubin	-107.4	-82.4		0	3	-4.27	
<b>KAT II:</b>							
Bilirubin	2142	369.6		0	10	-8.61	
Lumirubin	-98.8	-80.6		0	3	-12.15	

Abbreviations: P (partition coefficient), QA (quinolinic acid), RMSD (root mean square deviation), torsion (flexibility of ligand) HB (hydrogen bonds)

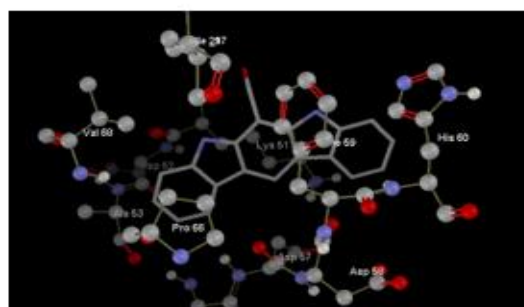
**Table S5:** Docking of bilirubin and lumirubin to key enzymes of the kynurenine pathway.



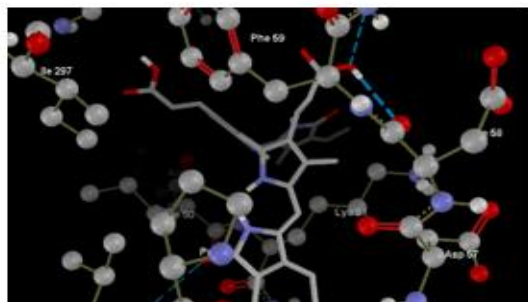
**Figure S1:** Chemical structures of lumirubin, biliverdin and bilirubin.



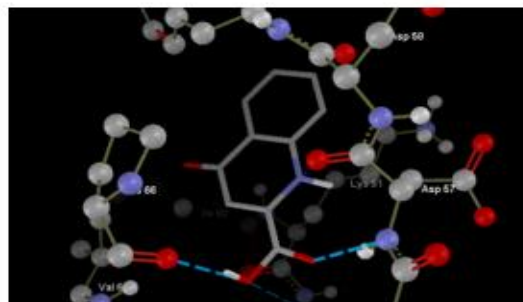
**Biliverdin-NMDA**



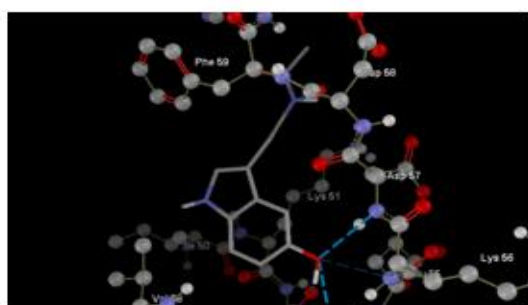
**FICZ-NMDA**



**Bilirubin-NMDA**



**KA-NMDA**

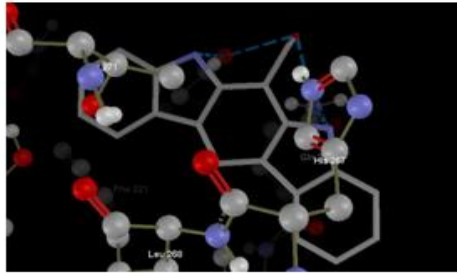


**Lumirubin-NMDA**

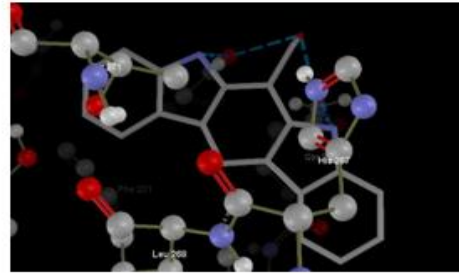


**QA-NMDA**

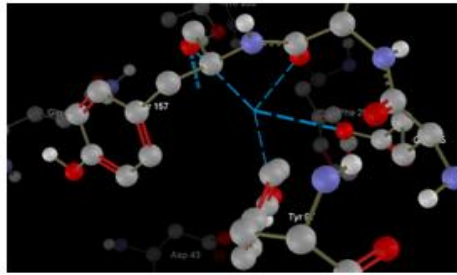
**Figure S2:** Docking of biliverdin, bilirubin, lumirubin and others to the NMDA receptor. Amino acid residues at the NMDA A chain active site and those binding the ligands were as follows: biliverdin (Arg294, Gly296, Ile297, Asp295) and (Gly296) respectively; bilirubin (Lys51, Asp57, Ile297, Phe59) and (Asp57); lumirubin (Asp57, 58, Phe59, Lys51, Ile50, Lys56) and (Asp57); FICZ (Ile297, Val51, Pro66, Asp57,58, Ala53, Val68) and (Asp57, His60); KA (Lys51, Asp57,58, Pro66, Val68, Phe59) and (Asp57); QA (Lys56, Val68, Pro66, Asp52,57, Ala53) and (Asp57, Val68).



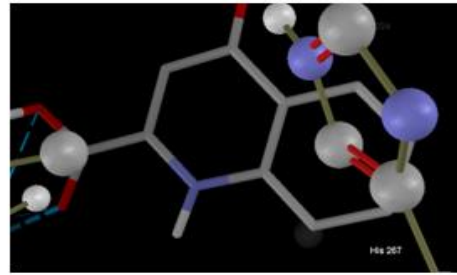
**Biliverdin-GABA<sub>A</sub>**



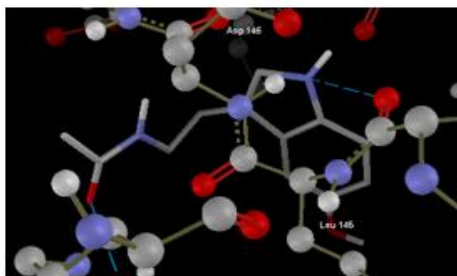
**FICZ-GABA<sub>A</sub>**



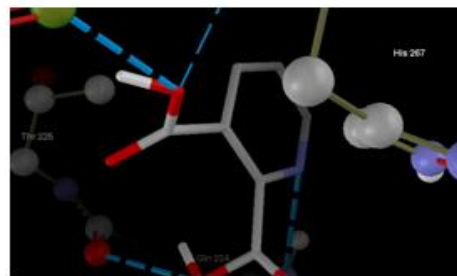
**Bilirubin-GABA<sub>A</sub>**



**KA-GABA<sub>A</sub>**

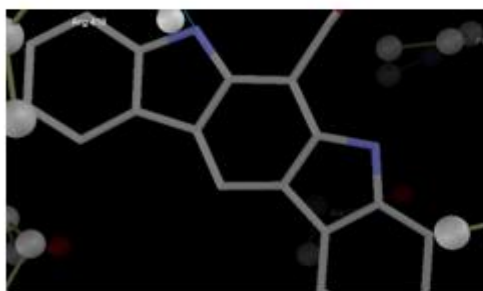


**Lumirubin-GABA<sub>A</sub>**



**QA-GABA<sub>A</sub>**

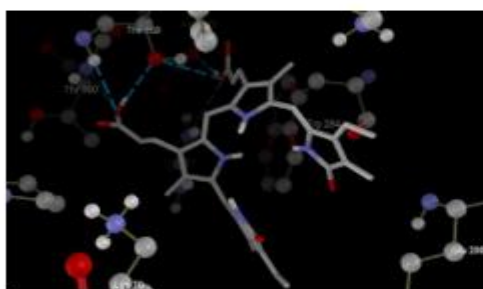
**Figure S3:** Docking of biliverdin, bilirubin, lumirubin and others to the GABA<sub>A</sub> receptor. Amino acid residues at the GABA<sub>A</sub> active site and those binding the ligands were as follows: biliverdin (Gln64, Asp43) and (none) respectively; bilirubin ( Tyr157, Ser156, Glu155, Gln64, Phe200, Tyr97) and (Tyr97, Phe200); lumirubin (Arg142, Glu147, Leu145, Asp146, Lys215) and (Leu145, Arg142); FICZ (His267, Phe221, Leu268, Thr271, Gln224, Tyr220) and (Tyr220, Gln224, His267); KA (His267, Gln224, Tyr220, Leu268) and (Thr271); QA (Ile264, Gln224, His267, Thr225) and (Leu268, Gln224).



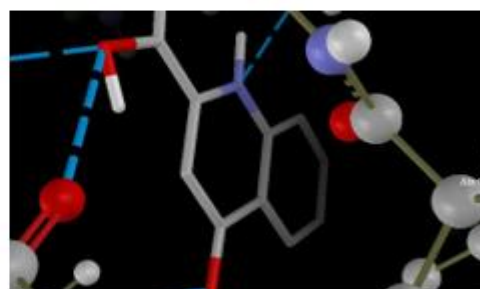
**Biliverdin-GABA<sub>B</sub>**



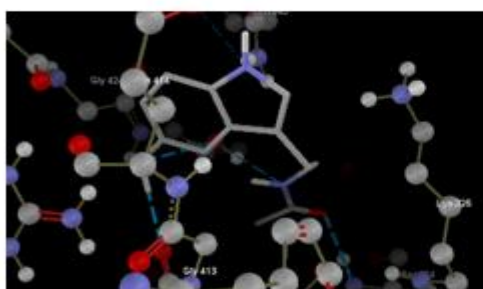
**FICZ-GABA<sub>B</sub>**



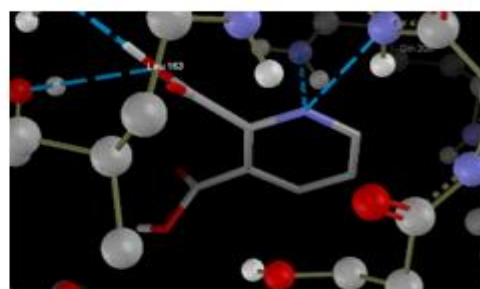
**Bilirubin-GABA<sub>B</sub>**



**KA-GABA<sub>B</sub>**

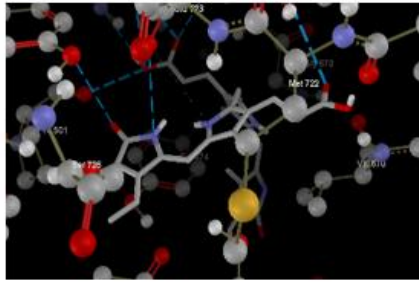


**Lumirubin-GABA<sub>B</sub>**

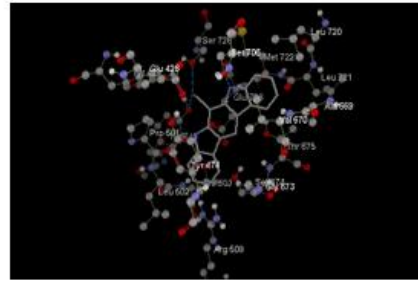


**QA-GABA<sub>B</sub>**

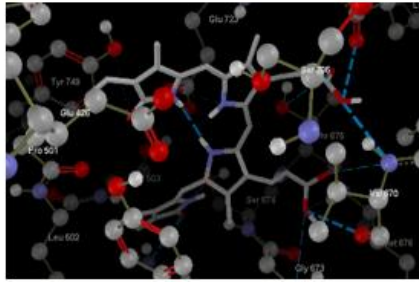
**Figure S4:** Docking of biliverdin, bilirubin, lumirubin and others to the GABA<sub>B</sub> receptor. Amino acid residues at the GABA<sub>B</sub> active site and those binding the ligands were as follows: biliverdin (Arg418, Asn419, Glu421, Asn180, Ala181) and (Ser178, Asn419, Arg418) respectively; bilirubin (Thr159,160, Trp284, Phe354, Lys353, Asp179) and (Thr159,160, Arg207); lumirubin (Gly413,424, Gln414, Thr425, Val445, Ser323, Arg422, Glu320) and (Thr425, Ser324); FICZ (Arg418, Ala181, Glu421, Tyr442) and (Arg418); KA (Ala158, Thr159, Trp284, Arg207, Lys70) and (Lys70, Thr159); QA (Gln206, Leu163, Ser173, Thr160, Val162, Pro163) and (Tyr169, Val162, Gln206).



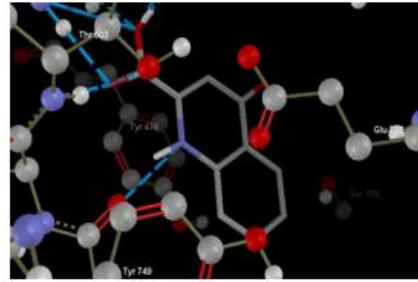
**Biliverdin-Kainate**



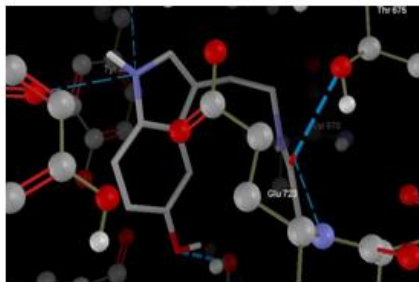
**FICZ-Kainate**



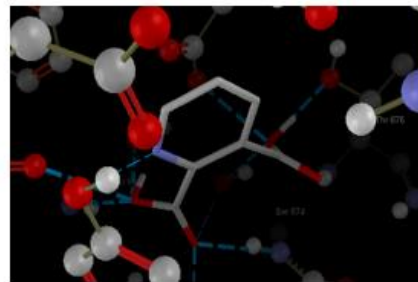
**Bilirubin-Kainate**



**KA-Kainate**



**Lumirubin-Kainate**



**QA-Kainate**

**Figure S5:** Docking of biliverdin, bilirubin, lumirubin and others to the kainate receptor. Amino acid residues at the kainate active site and those binding the ligands were as follows: biliverdin (Ser726, Met722, Glu723, Tyr474) and (Thr503,675); bilirubin (Glu723, Ser706,674, Val670, Gly673, Glu426, Pro501) and (Val670, Thr675, Tyr749); lumirubin (Glu723, Ser706, Met722, Tyr474, Val670) and (Tyr749, Glu723, Thr503); FICZ (Arg508, Leu502, Thr503, Tyr474, Gly673, Glu426, Tyr429) and (Tyr749, Ser726); KA (Tyr474,749, Thr503, Glu723, Leu502) and (Arg508, Ser674); QA (Ser674, Thr675, Glu723, Tyr474, Thr503) and (Tyr474, Ser674,675, Arg508).