## **Supplementary Information**

**Fig. S1.** Sequence alignment of the serotonin<sub>1A</sub> receptor in invertebrates. Sequences of the serotonin<sub>1A</sub> receptor were obtained from NCBI (http://www.ncbi.nlm.nih.gov/) database. The sequence alignment of the serotonin<sub>1A</sub> receptor was carried out with ClustalX (version 2.0.11) and the alignments were viewed using Jalview (version 2.4).

**Fig. S2.** Sequence alignment of the serotonin<sub>1A</sub> receptor in vertebrates. Sequences of serotonin<sub>1A</sub> receptor were obtained from NCBI (http://www.ncbi.nlm.nih.gov/) database. Sequence alignment of the serotonin<sub>1A</sub> receptor was carried out with ClustalX (version 2.0.11) and alignments were viewed using Jalview (version 2.4).

**Fig. S3.** Validation of models of the serotonin<sub>1A</sub> receptor in the absence and presence of cholesterol, using the ProSA-web service. Panels (a) and (c) show results for models of the serotonin<sub>1A</sub> receptor in the absence and presence of cholesterol. The z-scores of the models are highlighted as large dots. Panels (b) and (d) are the energy plots for receptor models in the absence and presence of cholesterol. Residue energies averaged over a sliding window are plotted as a function of the central residue in the window. Window sizes of 10 and 40 are used.

**Fig. S4.** Clustering analysis of docked poses of serotonin to the serotonin<sub>1A</sub> receptor in the absence and presence of cholesterol using AutoDock. Panels (a) and (b) show the cluster for serotonin docked to the serotonin<sub>1A</sub> receptor in the absence and presence of cholesterol. RMSD used for the clustering was 2 Å.

## ClustalX Multiple Sequence Alignment of the Serotonin<sub>1A</sub> Receptor in Invertebrates



## ClustalX Multiple Sequence Alignment of the Serotonin<sub>1A</sub> Receptor in Vertebrates



## ClustalX Multiple Sequence Alignment of the Serotonin<sub>1A</sub> Receptor in Vertebrates

NP_001116793.1   D.rerio-1A_a NP_001139238.1   D.rerio-1A_b ACN86308.1   0.heta 042385.1   F.rubripes-1A 042384.1   F.rubripes-1B AAP83427.1   0.mossambicus NP_001079299.1 X.laevis XP_00156318.1 0.anatinus XP_00156318.1 0.anatinus XP_00156318.1 0.anatinus XP_00136318.2 1 M.domestica NP_03234.2 M.musculus NP_03234.2 M.musculus NP_036717.1   R.norvegicus AAP12466.1   V.vulpes NP_001075251.1   E.caballus XP_001083407.1   M.mulatta EAA94490.1   G.gorilla EAA94488.1   H.sapiens	- EVOKTWERSVEP - ELEKNWKSAVEF KP - AA ESG - WTRREFKAN-SP DAVGAEWKROVEFRF - LP DTOAKSWKRSVEFRF - LP DTOAKSWKRSVEFRF - LE DTOAKSWKRSVEFRF - LE DTOAKSWKRSVEFRF - LE DTOAKSWKRSVEFRF - LE DTOAKSWKRSVEFRF - LE PTOSEN EPCOREWRCAAL PTOSED - SKORWERSAENRAVOTP CPGGENRQPGSKAGOPLC EJGREWRQPGSKAGOPLC EJGREWRQOTENVTTAFF ESGGRWELGVESKAGGAL ESGGRWELGVESKAGGAL ESGGRWELGVESKAGGAL SSGRWELG	IANGALKNSDDGSSFITEVQSI UNGAIKHAEDGESSEITEVNSN UNGALKHVEEGESLEIIEVNSN UNGAVRHGEEMESLEIIEVNSN UNGAVRHGEGSJLEIIEVNSN UNGAVRHGEGSJLEIIEVNSN UNGAVRHGEGSJLEIIEVNSN UNGAVRGGDGALEIIEVNSN UNGAVRGGDDGALEVIEVNNGN TNGAVRGGDDALEVIEVNNGN TNGAVRGDDGALEVIEVNNGN TNGAVRGDDGALEVIEVNNGN TNGAVRGDDGALEVIEVNNGN ANGAVGGDDGALEVIEVNNGN ANGAVGGDDGALEVIEVNNGN ANGAVGGDDGALEVIEVNNGN ANGAVGGDDGALEVIEVNNGN ANGAVGGDDGALEVIEVNNGN ANGAVGGDDGALEVIEVNNGN ANGAVGGDDGALEVIEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNGN ANGAVGDDGALEVNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	: :* - KNHLEJEP NNPQP-CI - KNHLEJEP NTPQSSCO - KTHLPLP NTPQSSCO - KTHLPLP NTPQSSCO - KTHLPLP NTPQSVP-LI - KOHLFLP NTPGSVP-LI - KOHLFLP RGCPOPPDP - KOHLFLP RGCPOPPDP - KOHLFLP RGCPOPPDP - KOHLFLP RGCPOPPDP - KOHLFLPBEAGAICGPAS - KHLPLPGEAGAICGPAS - KHLPLPGEAGAICGPAS - KHLPLPGEAGAICGPAS - KHLPLPGEAGFTCAAAS - KHLPLPGEAGFTCAAAS - KHLPLPGEAGFTCAAAS - KHLPLPGEAGFTCAAAS - KHLPLPGEAGFTCAAAS - KHLPLPGEAGFTCAAAS - KHLPLPGEAGFTCAAAS	E NRNERNTEAKK VALARERKTVKT E NRHENTEAKK VALARERKTVKT E TIMBER SGAKK IALARERKTVKT E SRHEKATARK KALARERKTVKT SRHEKATEAKK IALARERKTVKT ALKNDEATEAKK VALARERKTVKT E RANERNTEAKK VALARERKTVKT E RANERNTEAKK MALARERKTVKT E KNEN AEAKK MALAREKTVKT E KNEN AEAKK MALARERKTVKT E KNEN AEAKK MALAREKTVKT E KNEN AEAKK MALARERKTVKT E KNEN AEAKK MALAREKTVKT E KNEN AEAKK MALAREKTVKT	GIINGTFICWLPFFVALVLP GIINGTFICWLPFFVALVLP GIINGTFICWLPFFVALVLP GIINGTFICWLPFFVALVLP GIINGTFILWLPFFVALVLP	COD-CPMPENLGAVINULGYSNELLA COD-CPMPENLGAVINULGYSNELLA CAENCYMPENLGAVINULGYSNELLA CAENCYMPENLGAVINULGYSNELLA COESCHMPHLFDIINULGYSNELLA COESCHMPHLFDIINULGYSNELLA CESCHMPELGAVINULGYSNELLA CESCHMPELGAVINULGYSNELLA CESCHMPELGAIINULGYSNELLA CESCHMPELGAIINULGYSNELLA CESCHMPELGAIINULGYSNELLA CESCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA CESSCHMPELGAIINULGYSNELLA	PUIXAYPNK 381   PIIXAYPNK 386   PIIXAYPNK 386   PIIXAYPNK 406   PIIXAYPNK 399   PIXAYPNK 399   PIXAYPNK 391   PIXAYPNK 395   PIXAYPNK 395   PUIXAYPNK 405   PUIXAYPNK 405
	ور واللواقين	والأحدي					
NP_001116793.1   D.rerio-1A_a NP_001139238.1   D.rerio-1A_b ACN86308.1   0.beta 042385.1   F.rubripes-1A 042385.1   F.rubripes-1B AAP83427.1   0.mosSambicus NP_001079299.1 X.laevis XP_001360318.1 0.antinus XP_001360318.1 0.antinus XP_001360318.1 0.antinus XP_001360318.1 0.antinus NP_03274.2   M.nucculus NP_03274.2   M.nucculus NP_036717.1   C.familiaris AAP12466.1   V.vulpes NP_001075251.1   S.caballus XP_0010535.2   B.taurus XP_001083407.1   M.mulatta EAR394490.1   C.gor111a EAR394490.1   C.gor11a EAR394490.1   M.sapiens	DFOMAFKKIIKCHCC DFOSAFKKIIKCHCRF DFOSAFKKIIKCHCRF DFOSAFKIIKCHCRF DFOSAFKIIKCHCRF DFOSAFKIIKCHCRG DFOSAFKIIKCHCRG DFOSAFKIIKCHCCG DFOSAFKKIIKCKFCC DFOMAFKKIIKCKFCR DFOMAFKKIIKCKFCR DFOMAFKKIIKCKFCR DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC DFOMAFKKIIKCKFCC	396 403 423 416 416 416 410 411 421 421 422 423 423 422 422 422 422 422 422 422					



**Fig. S3** Paila *et al.* 



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**Fig. S4** Paila *et al.*