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Modulator compound for captive induced breeding in *Monopterus cuchia* through molecular modeling and Dynamics

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Abstract
The Insilco experiment was conducted to find out small drug or ligand which can able to bind Gonadotropin releasing hormone receptor of *Monopterus cuchia*. GnRH receptor are G protein coupled receptor for this purpose ligand selected on basis of GPCR ligand, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor, Enzyme inhibitor activity. Compound selected based on ADMET property. In this present Study modified protocol followed which help us to find compound which is less toxic or nontoxic to fish as our target organism is fish.

Keywords: *Monopterus cuchia*, GPCR ligand, ADMET property, GnRH receptor

Introduction
Research works on artificial propagation of *M. cuchia* is infancy stage. Begum *et al*. (2018) made an attempt to breed *M. cuchia* in three habitats such as cistern, hapa and pond with different hormones *viz* [1]. Carp Pituitary Extract (cPGE), Cuchia Pituitary Gland, Ovaprim and Pregnyl in different doses. Miah, *et al*. (2015) conducted an experiment on the breeding biology and induced breeding status of freshwater mud eel, M. cuchia [2]. They experiment with the different doses of different inducing agents like pituitary gland (PG), human chorionic gonadotropin (HCG), Gonadotropin releasing hormone (GnRH) and Ovuline a synthetic hormone in different environmental conditions. They opined that the artificial breeding of freshwater mud eel, M. cuchia was not yet succeeded through inducing agents in captive conditions, rather the inducing agent showed negative impacts on fecundity and ovarian tissues). No culture system has yet been developed in India and till now no successful Artificial breeding was observed through inducing agent (Shuvra, T. M., 2011) [3]. This Insilco analysis to find out new potent molecule which will help in captive breeding.

Material and methods
As know deep inside of gonadotropin releasing hormone receptor and their interaction with different ligand amino acid sequence of receptors were downloaded from closely related species *Monopterus albus*. *M. albus* Gonadotropin-releasing hormone receptor 1 (GnRH-R1) and Gonadotropin-releasing hormone receptor 2 (GnRH-R2) having NCBI Accession number Gene Bank: ARS88253.1 and Gene Bank: ARS88254.1 respectively. The three dimensional structure were generated from GPCR –Itasser web server [4] and their anylysis were done. The homology modelling was carried out using- ITASSER GPCR which is a programmed homology modelling server. To view the structure of modeled molecules Chimera 2.0 were used [5]. Physiochemical properties were calculated using Protparam tool which gives details about molecular weight, theoretical Pi, amino acid composition etc Table1. These structure were used for screening purpose from ZINC data base [6]. The results are summarized in table 2 and table 3.Bioactivity of ligands were calculated from molinspiraton [7]. Admet SAR [8] and Swiss ADME [9] is used for toxicity, Pharmacokinetics, Lipophilicity, Drug likeness test. Mouse Tox server [10] is used for Prediction of small molecules cytotoxic effect to NIH/3T

cells through Enalos Cloud Platform.

Results and Discussion

For R1 receptor: The formula is C2137H3337N555O577S28 and Total number of atoms are 6634.Extinction coefficients are in units of M-1 cm-1, at 280 nm measured in water. Ext. coefficient value is 77765 at Abs 0.1% (=1 g/l) 1.657, assuming all pairs of Cys residues form cystines. Ext. coefficient 76890 at Abs 0.1% (=1 g/l) 1.638, assuming all Cys residues are reduced. Estimated half-life- The estimated half-life is 30 hours (mammalian reticulocytes, in vitro), >20 hours (yeast, in vivo),>10 hours (Escherichia coli, in vivo).

For R2 receptor: The Formula is C1944H2993N523O500 S26 and total number of atoms are 5986.Extinction coefficients: Extinction coefficients are in units of M-1 cm-1, at 280 nm measured in water. Ext. Coefficient 72140 at Abs 0.1% (=1 g/l) 1.696, assuming all pairs of Cys residues form cystines and Ext. coefficient 71390 At Abs 0.1% (=1 g/l) 1.679, assuming all Cys residues are reduced. Estimated half-life: The estimated half-life is 30 hours (mammalian reticulocytes, in vitro), >20 hours (yeast, in vivo),>10 hours (Escherichia coli, in vivo). Table 1 represent the physicochemical property of the GnRH-R1 and GnRH-R2 receptors having amino acid length 414 and 376 respectively. The isoelectric point is the pH at which a molecule does not carry net electrical charge or we can say that it is electrically neutral in their statistical mean. As we know that pH below their PI, proteins carry a net positive charge; above their PI they carry a net negative charge so in case of R1 if the pH is below 9.07 it will show the positive charge and above it shows the negative charge. Similarly below 9.17 R2 receptor shows positive and above this it will show negative charge. The Extinction coefficient (EC) calculated at 280nm wavelength. The calculated extinction coefficient values indicates us the quantitative values of protein-protein and protein-ligand interactions in solution as this values is high in our receptor study so we can conclude that the ligand which is indicated in Table 2 and Table 3 will shows the strong interaction [11]. Their G protein coupled receptor ligand score is varies from 0.016 to -0.039.

Table 1: Physicochemical properties of receptors

Accession number	Length	Molecular Weight	PI Isoelectric point	(-) R Negative charged Residue	(+) R Positive charged Residue	Extinction coefficient	Instability index	Aliphatic index	Grand average of hydropathicity (GRAVY):
ARS88253.1	414	46934.06	9.07	25	37	77765	42.22	103.16	0.370
ARS88254.1	376	42524.91	9.17	18	29	72140	46.91	101.17	0.340

Table 2: Bioactivity of ligands against receptor 1

Serial No.	ZINC ID Name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	ZINC39946944	-0.039	-0.062	-0.137	-0.292	0.006	-0.227
2	ZINC13220126	-0.362	-0.803	-0.616	-0.575	-0.493	-0.407
3	ZINC39321642	0.016	-0.120	-0.226	-0.343	0.034	0.035

Table 3: Bioactivity of ligands against receptor 2

Serial No.	ZINC ID	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	ZINC43799595	0.794	0.521	0.366	-1.117	0.033	0.952
2.	ZINC03871615	0.934	0.531	0.673	-0.963	0.305	1.013
3.	ZINC39946944	-0.039	-0.062	-0.137	-0.292	0.006	0.227

There is no difference between protein half-life in receptor R1 and R2. For receptor R1 the based ligand selected on the basis of non-toxicity in fishes. Molecular weight 436.14 g/mol, Num. heavy atoms 28 Num. arom. heavy atoms 0,Fraction Csp30.30,Num. rotatable bonds-9, Num. H-bond acceptors-15, Num. H-bond donors 1, Molar Refractivity 6.09,TPSA260.18 Å, having pharmacokinetics value GI absorption Low, BBB- No, P-gp substrate Yes,CYP1A2 inhibitor No,CYP2C19 inhibitor No,CYP2C9 inhibitor No, CYP2D6 inhibitor No, CYP3A4 inhibitor No, Log Kp (skin permeation) value -12.26 cm/s. The Lipophilic values are Log Po/w (iLOGP) -1.12,Log Po/w (XLOGP3) -4.65, Log Po/w (WLOGP) -1.12, Log Po/w (MLOGP) -4.14,Log Po/w (SILICOS-IT) -2.41 and Consensus Log Po/w -2.69. The Drug likeness Lipinski- Yes; 1 violation: Nor O>10 Ghose-No; 1 violation: WLOGP<-0.4, Veber -No; 1 violation: TPSA>140, Egan-No; 1 violation: TPSA>131.6, Muegge -No; 3 violations: XLOGP3<-2, TPSA>150, H-acc>10and Bioavailability Score -0.11. For R2 based ligand having Physicochemical Properties like as Molecular weight582.05 g/mol, Num. heavy atoms 32, Num. arom. heavy atoms 9, Fraction Csp3 0.50, Num. rotatable bonds 8, Num. H-bond acceptors 16, Num. H-bond donors 3, Molar Refractivity 96.98, TPSA 319.88 Å². The Pharmacokinetics values are GI absorption Low, BBB per meant No, P-gp substrate Yes, CYP1A2 inhibitor No, CYP2C19 inhibitor No, CYP2C9 inhibitor No, CYP2D6 inhibitor No, CYP3A4 inhibitor No, Log Kp (skin permeation) -13.18 cm/s. The Drug likeness Lipinski -No; 2 violations: MW>500, NorO>10, Ghose -No; 1 violation: MW>480, Veber -No; 1 violation: TPSA>140, Egan No; 1 violation: TPSA>131.6, Muegge -No; 3 violations: XLOGP3<-2, TPSA>150, H-acc>10, Bioavailability Score 0.11. Mouse Tox which is Mouse Embryonic Fibroblast Prediction result shows Prediction (Class) – inactive and Prediction–unreliable. These two compound can acts as modulator for *Monopterus cuchia* GnRH receptors.

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