IJPSR (2017), Vol. 8, Issue 5 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 14 October, 2016; received in revised form, 14 December, 2016; accepted, 31 December, 2016; published 01 May, 2017

SCHIZOPHRENIA: A LOOK FORWARD WITH ZINC06025953

Rituraj * and K. K. Srivastava

Department of Chemistry, Vinoba Bhave University, Hazaribag, Jharkhand, India.

Keywords:

Phosphodiesterase, PDE10A, pyp-1, Schizophrenia, ZINC06025953

Correspondence to Author:
Rituraj

Department of Chemistry,
VBU, Hazaribag, Jharkhand, India.

Email: rituraj.msc@gmail.com

ABSTRACT: Phosphodiesterase PDE10A is an enzyme that has established connection earlier with schizophrenic condition, schizophrenia is well known severely chronic and disabling disease worldwide today. Unfortunately, there is no concrete evidence till day to point out as a single cause of this disease. However, in a recent work a research team of Merck Research Group recognized earlier pyp-1 as an effective drug like lead(DLL) after a long term "*in vitro*" experimentations, to inhibit phosphodiesterase PDE10A to control the schizophrenic conditions. Herein we carry forward this work to "in silico" way to find similar/more efficient molecules in "ZINC" DL (Drug Like) molecular structure bank (zincdocking.org) in consideration with pyp-1 as a standard molecular structure for our work, docking has been performed with separated DL (Drug Like) molecular structures as similar to "pyp-1", using similarity measures "tanimoto" binding efficacy and drug properties are computed out and analyzed, the outcomes of that work has been reported. The ZINC06025953 molecular structure pointed out that it may acts as a potential drug like lead(DLL), it all on that of the computation ground. Further, need the herein virtual laboratory work an experimental verification, for that synthesis and drug ability check out, off course in a real laboratory equipped with adequate facilities.

INTRODUCTION: Psychiatric disorders such as depression, anxiety and a severely major one schizophrenia are leading causes of disability in humans, on another hand Pathogenesis of psychiatric disorders remain challenging and elusive, drug discovery is still ambiguous and very complicated till day along the globe. In 1999, phosphodiesterase (PDE10A) is identified as a promising target for the treatment of schizophrenia [1], it well established earlier that it intervene in the various cellular responses that regulated by the second messengers like cAMP and cGMP in the medium spiny neurons of the mammalian striatum, which involved in cognitive function in coordination to the proper body movement and individual motivation. Striatum (part of basal ganglia) also believed to integrate signaling from the midbrain dopaminergic and cortical glutamatergic pathways. In schizophrenic conditions patients display dysfunction in these signaling pathways, abnormal striatal output has been implicated in the pathophysiology of the disease [2, 3, 4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(5).2122-33

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (5).2122-33

It has hypothesized that inhibition of PDE10A will increase the intracellular levels of cGMP (cyclic guanosine monophosphate) and cAMP (cyclic adenosine monophosphate), thereby increasing striatal output and restoring behavioral inhibition [5]. Disturbances of the basal ganglia processes is heavily involved in schizophrenia. Phosphodiesterase 10A (PDE10A) is a basal ganglia specific hydrolase, which plays an essential

role in regulating cAMP/PKA (protein kinase A) and cGMP/PKG (protein kinase G) signaling cascades by controlling the magnitude, duration and cellular location of cAMP/cGMP elevation [6]. Biochemical and behavioral data indicate that PDE10A inhibition activates cAMP/PKA signaling in the basal ganglia process, leading to the potentiation of dopamine D_1 receptor signaling, and concomitant inhibition of dopamine D_2 receptor signaling. Across mammalian species PDE10A is potentially expressed in the striatum the main recipient of dopaminergic afferents from the substantia nigra. Due to its high striatal expression PDE10A inhibitors are regarded as therapeutic approach in the treatment of disease related to striatal dysfunction such as Schizophrenia [7, 8, 9].

The antipsychotic-like effect of PDE10A inhibitors has been proven in animal models. Preclinical evidence in a range of animal models suggests that a PDE10A inhibitor could provide efficacy on positive, cognitive and negative symptoms of schizophrenia and PDE10A inhibitors are currently being evaluated in clinical trials for the treatment of schizophrenia. Today about 20 pharmaceuticals companies have running discovery program to identification of potential PDE10A inhibitor [1], success of identification of seven compounds by different pharmaceutical companies presently undergoing human trials. Schizophrenia remains an enigma though enhanced understanding of the cause, consequence, and potential treatments are bringing out today much light to the subject but till day considering as a lifelong mental disorder with nobody known to cure, and psychiatric practitioner worldwide believed that 1% world population affected by this severe chronic disease and it prevail in all type of classified communities. Presently a dozen no. of drug compounds is known as efficient treatment, despite these recognized drugs are prescribed for treatment but typical and atypical antipsychotic treat only the positive symptoms of the disease and have little bit limited efficacy and tolerability resulting in high rates of discontinuation among patients, it's make psychotherapist's job more challengeable.

MATERIALS AND METHODS: Recently a research team of Merck Research Laboratories successfully identified a novel class of pyrazolopyrimidine to potentially active against PDE10A inhibition. This research team investigated out that PyP-1(best "pyrazolopyrimidine" identified by that team)) [1] exhibits subnanomolar potency towards PDE10A (Ki = 0.23 nM), excellent pharmacokinetic (PK) and physicochemical properties, and a clean off-target profile of PyP-1 after a big span experimentation [1]. PyP-1 displays dose-dependent efficacy in numerous pharmacodynamics (PD) assays that measure potential for anti-psychotic activity and cognitive improvement [1], so on this all ground we start our work with using "in silico" utilities to search for as similar to PyP-1 in a freely accessible drug like structural bank ZINCdocking.org, herein work we investigate through 180,000,000 DL molecular structures and finally left with few in hand, a long span computation performed and on the outcomes of that, considering, our reporting molecules may be a better one than pyp-1 as potentially active against PDE10A as inhibitor for treatment for Schizophrenia. We're coming these molecular structures in front of scientific community for further investigation by any methodological approach including "in silico".

During the past decade, increasing numbers of complex structures were solved by the development of high throughput X-ray crystallographic technique [10] and NMR[11] methods and it grounding the basis for "in silico" technique to get it in the proper now days shape as a very valuable intervening technique in a total drug evaluation strategy to employed and very honestly it got a respectable space in concerning communities as a big comprehensive strategic tool to intermediate in drug designing workout, getting much viable by day.

We're initiate our work with rcsb.org.in with a download of "5DH5", it reported in recent time, it was a crystallographic structure of pyp-1 with "in vitro" experiments in Homo sapiens phosphodiesterase PDE10A. Ramachandran plot of 5DH5 taken, it in Fig. 1(a) clearly showing that the maximum residues are in the core region (red colored) placed, very few residues are in the allowed region (dark yellow colored) and only two of the residues showing to place in disallowed region, nevertheless much fairer crystallographic structures was in our hand.

A close look on interaction pattern for pyp-1 with phosphodiesterase PDE10A bring out facts that it coordinated in two different regions in phosphodiesterase "PDE10A", inspection pointed out that it was a homodimeric protein and in both chains have a similar kind of location where a molecule of pyp-1 has interactionally placed in each protein chain, these binding location after here referred as "1" and "2". In both binding location pyp-1 bind up with very same efficacy, interactions are in common frame (**Fig 1. (b)** and **(c**) but the pyp-1 is in different conformation in these binding locations.

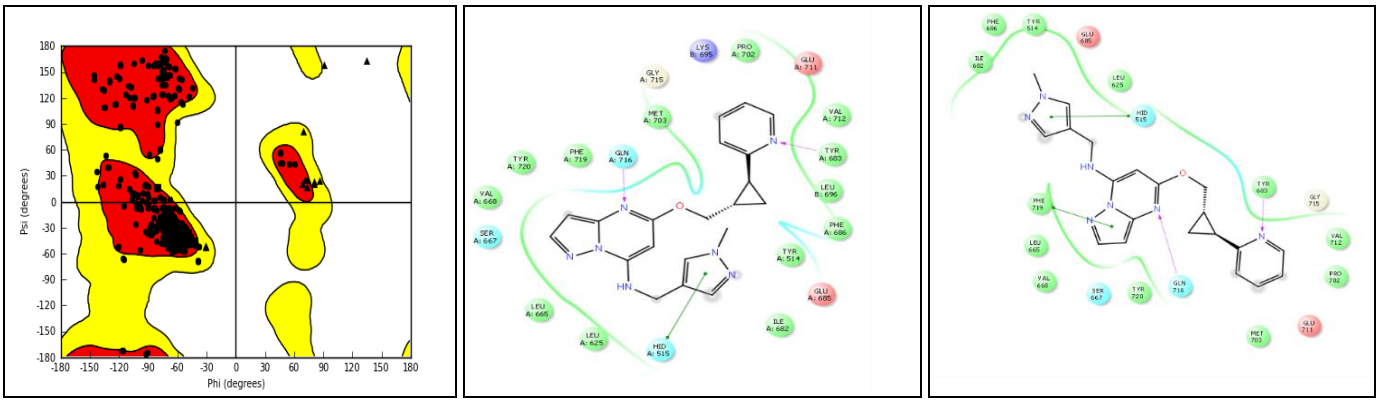


FIG. 1 (a) RAMACHANDRAN PLOT FOR "5DH5", BINDING INTERACTIONS OF PYP-1 IN (b) REGION "1" AND (c) IN REGION "2" IN PHOSPHODIESTERASE PDE10A

RESULTS AND DISCUSSION: The potential energy (PRIME MM-GBSA) of pyp-1 in region "1" is calculated (OPLS3) out to -1683.994 and for region "2" it is -1738.587 i.e. in location "2" pyp-1 was better placed in energy stability terms, it's may due to various reasons. The pyp-1 has three important interactions, pyrazole ring has π-π stacking with Histidine (515), it is common in both regions, however in region "2" an extra π-π stacking of pyrazole ring of pyrazolopyrimidine (pyp-1) with phenylalanine (719) makes it more efficient binding region, pyp-1 acts as two H-bond acceptor in both region, pyridine ring for tyrosine (683) and pyrimidine (pyp-1, pyrazolopyrimidine) for Glycine (716).

Above mentioned interactions, as a consideration, that are important for recognizing as similar pyp-1like molecular structures identification. We prepared the protein PDB 5DH5 with glide program in protein preparation wizard the tool is very important to raw data of protein PDB file to came it in condition to molecular docking, in protein preparation panel in maestro 5DH5 first preprocessed with default settings and this job added the Hydrogen atoms to PDB, assign bond order in protein, create zero bond order with metal atoms and disulfide bridges between individual cysteine units, after job completion came with a message "missing side chains in the protein" we ran further to add the missing side chain and after the job came with a message of position alteration of a particular amino acid which was resolved in next steps, we take a Ramachandran plot at this stage, the plot (**Fig 1(a)** prevails that PDB is as usual).

In a second stage of protein preparation wizard(review and modify) we have two homodimer chains A and B, both pyp-1 binding location were near to two adjacent metal (Mg^{2+}, Zn^{2+}) coordination sites in each chain of 5DH5, we in this stage deleted the 33 water molecules among the total of 43 water molecules present in 5DH5, which are either Hydrogen bonded or non-Hydrogen bonded with the amino acid both chains, we remains untouched a total 10 water molecules which are all present in hex dentate co-ordination sphere around two separate Mg^{2+} atoms (one ligand in them is ASP:554 of chain A and chain B in location "1" and "2"), two Zn^{2+} ions are also present adjacent to Mg^{2+} coordination sphere, which coordinated in square pyramidal coordination sphere one of them ligand i.e. a water molecule is common as a ligand to both metal coordination sphere it's both lone pair directed towards different metals (here Mg^{2+} & Zn^{2+}) to coordinating it, so it's in a role as a bi-dentate bridge to both metals coordination sites, these two metals at four coordination sites are very important

for PDE10A quaternary and tertiary structural concerns, it's there a great impact on the nearby active site where pyp-1 bind up in the cavity, when we checked with deleting both Zn^{2+} and remain with two Mg^{2+} ions the docking score sank up by two unit against when it included in the same job. We generate the state for pyp-1 in binding cavity and we stood with the original state. And in the third stage (refinement) of protein preparation wizard first we run optimization job, its take about 2 minutes in 4.0 GHz Machine (Octa Core) and after completion, run for minimization job, minimization run take about 5 minutes to complete, it utilizes OPLS3 force field and with setting; converge heavy metals to RMSD 0.30Å. Grid were generated in both "1" and "2" centrally defined location as ligand selection with partial charge of ligand included. We considered pyp-1 as a standard molecular drug lead's structure and using "tanimoto" similarity measure we separated out DL molecular structures in DL molecular structure file downloaded from free accessible zincdocking.org with setting to identification of 1% similar to pyp-1, in a general such drug like molecular structure file have 140,000 structures in an average and we have performed similarity search with 131 such drug structure files (.sdf). After such jobs we left first about 183,000 DL molecular structures which were structurally very similar to pyp-1.

The job separated out 1% DL molecular structures which were best in similarity measure to pyp-1. Extracted such DL molecular structures are our raw structures for docking analysis, we prepared such extracted DL molecules in "ligprep" wizard. The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures, and optimize the structures. Many of the steps are optional and are controlled by selecting options in the LigPrep panel or by specifying command-line options in maestro. With prepared ligand and previously generated grid for binding region of pyp-1 in "1" and "2" region in phosphodiesterase PDE10A, at this instance docking was the next step for our work concerns, with each prepared ligand file (131 such prepared ligand file which were .mae typed) we performed docking job first in "SP"(simple precession) mode in "Glide docking" with included ligand partial charge, ligand sampling unaltered and remain default "flexible" with included input ring conformation and other remaining settings were as default, 131 docking job performed. The analysis of job result manually separated out good scoring molecules which are generally better than pyp-1 in docking score, and these DL molecular structures are separated out and saved separately in a .mae file, and in this stage need to perform with extra precision docking calculation mode i.e. XP docking. Previously separated ligand in an .mae file again prepared in ligand preparation wizard, in this wizard ionized state ligand generation are also available using "ionizer" but we haven't much concerned with ionized ligand in present context, so only utilized "epik" for ligand preparation job and not go for "ionizer"(an another tool in ligprep job setting). In the next step docking performed in "maestro" with "glide" in "XP (extra precision) mode", setting included "include input ring conformation" and "reward intramolecular Hydrogen bonds".

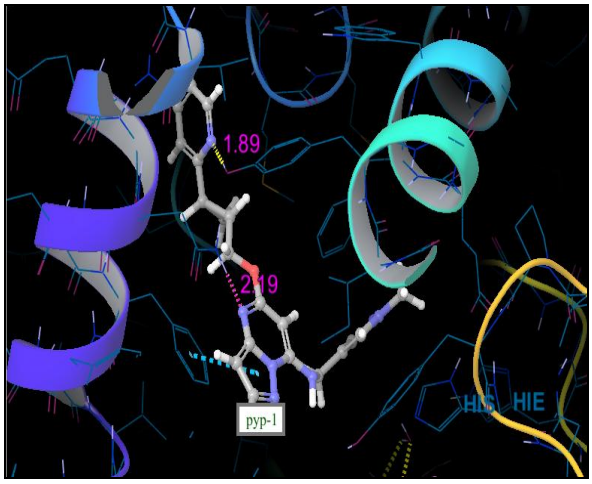
Docking performed in both regions "1" and "2" of binding pyp-1 in PDE10A the result is much improved due to included various extra terms in XP docking mode. In performing final XP docking job, during the generating grid we used some constraints these are listed in table 1.1, in our work have been given priorities of such interactions in our investigation, and docking performed with above constraints and finally stacked with around 2000 molecules which have XP docking score much competing or in instead, better than pyp-1. With these separated molecules quikprop Job performed, the result with the docking score and others properties **(**Table- 5DH5- "1" and Table- 5DH5- "2" for corresponding location i.e "1" and "2" to binding of "pyp-1" in "5DH5") cut further molecules to report i.e. requirement of properties in required limit, such as CNS activity, lipophilicity, and other important medicinal parameters also remove various structures in this context as a DLL consideration.

In both tables the DLL are in require limit of drug properties, the docking score which reflects binding efficacy are much better than the pyp-1 in the docking score, in location "1" for pyp-1it is at -9.79 and for location "2" it for that at -8.759, the difference between the DS in location "1" and "2" is around 1 unit, so some difference in binding

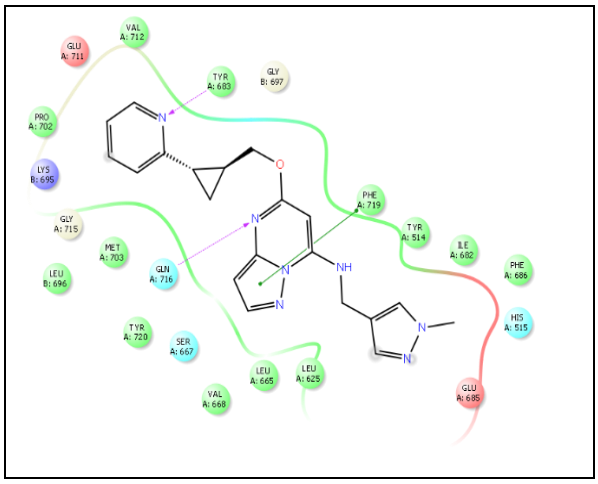
ability. In table: 5DH5- "1" the DS for ZINC71524592 was at the highest and it was at -13.21 which is 3.5 unit more than DS of pyp-1 at the same location. The various computed out medicinal properties are also in the required limit but the lipophilic nature of ZINC71524592

TABLE 1: USED CONSTRAINTS FOR GRID GENERATION FOR REGION "1" AND FOR REGION "2" FOR PYP-1 IN "PDE10A"

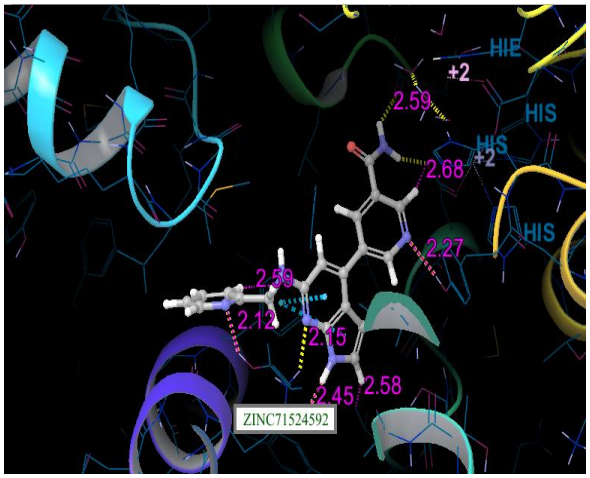
S no.	Interacting Amino Acid(PDE10A) with pyp-1	Receptor Constraint Type	Ligand Feature
1	Chain A: TYR: 683, Chain B:TYR:683	H-bond	Acceptor
2	Chain A: GLN: 716, Chain B:TYR:683	H-bond	Acceptor



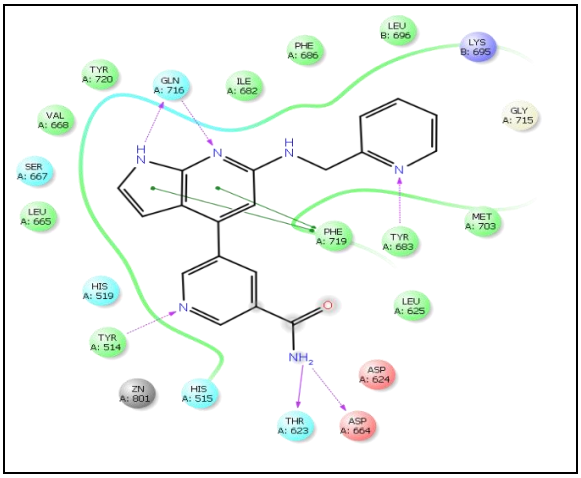
(a)



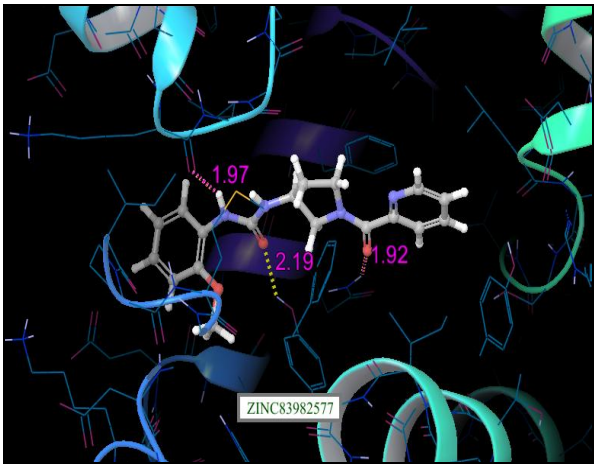
(1)



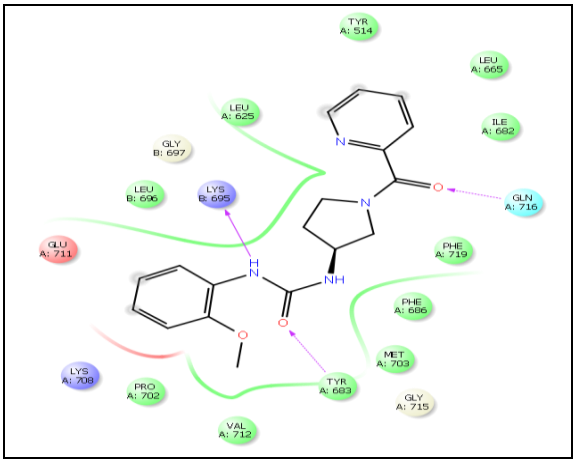
(b)



(2)



(c)



(3)

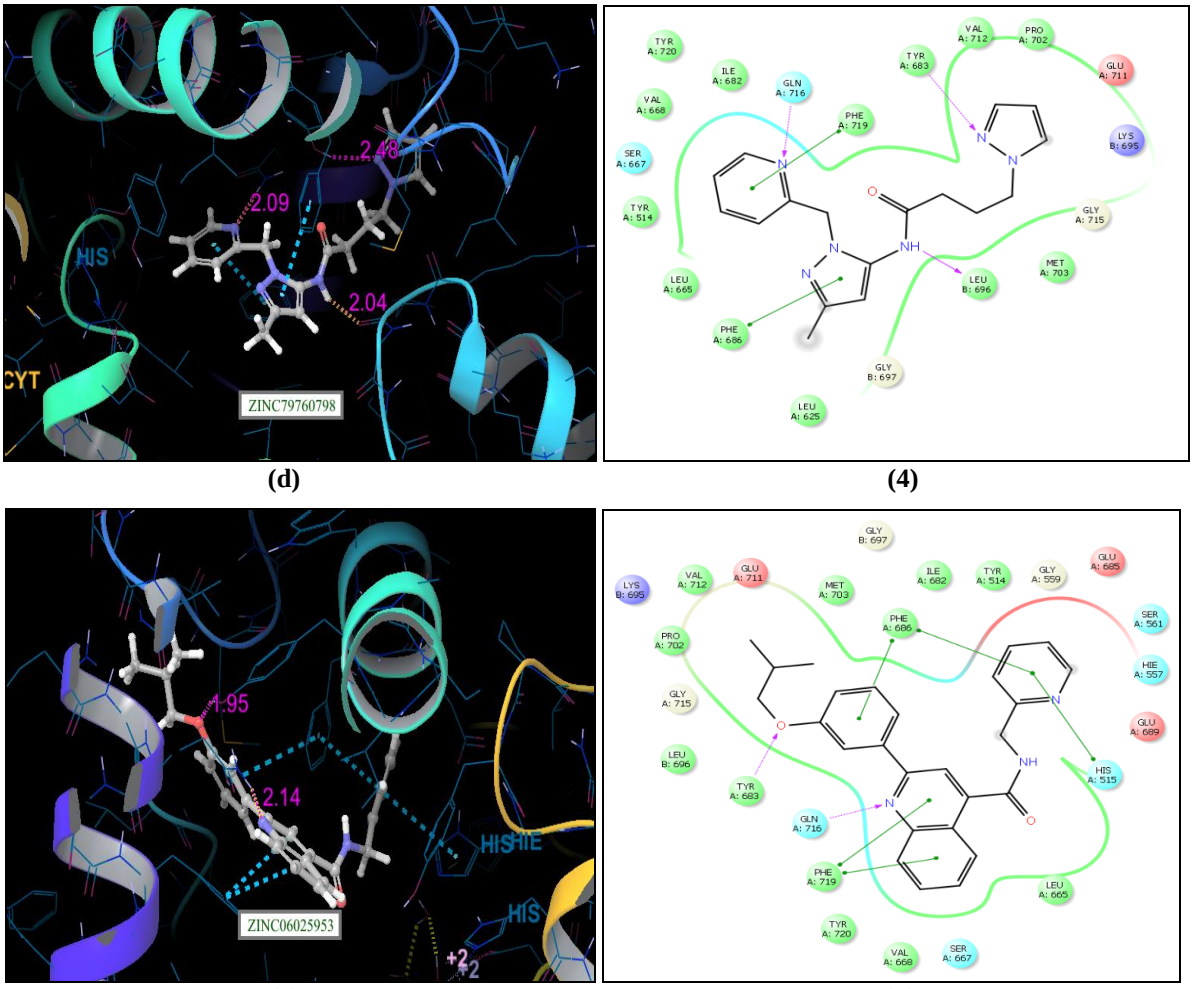


FIG. 2: IMAGES OF pyp-1(a,1), ZINC71524592(b,2), ZINC83982577(c,3), ZINC79760798(d,4) & ZINC06025953(e,5) IN DOCKED POSITION IN REGION "1" OF HOMODIMERIC PHOSPHODIESTERASE PDE10A (5DH5) AND ITS CORRESPONDING INTERACTION DIAGRAMS.

have some concerns, its far distant to pyp-1 which we have found in XP visualizer panel it at -7.1 for pyp-1 but for ZINC71524592 it was only at -6.2. On another hand, the QMDCK and QCaco values are also not too much appreciable in this venture, higher values for these terms are generally better for DLL recognition. Nevertheless interaction pattern for ZINC71524592 is much more efficient, the two interactions which we consider previous as a constraint for docking (it was always a mandatory interaction requirement during docking calculation and afterwards pose generation) in context to pyp-1 it has various other interactions including H-bonding, π-π stacking with neighboring amino acids, make it energetically most favorable in binding location in our investigation, in region "2" it also bind up with closer efficiency with a fair docking score of -11.92. The 2nd and 3rd listed molecules ZINC83982577 and ZINC79760798 respectively are binding efficiently in region "1" but it region "2" these are loose some effectiveness in binding with docking score 4.34 and 5.23 unit less than corresponding for region "1" respectively, so it efficient only in a single site binding. But, the ZINC06025953 is the most attainable molecule (in our view), it binds up in both locations "1" and "2" very efficiently with very fair docking score of -12.38 and -10.7 respectively for these locations, almost all computed medicinal properties associated with this molecule are very fair, lipophilic nature is very important in DLL cosideration, its "Lip" score at -7.9, easily understandable it can travel through lipid bilayer smoothly with lesser opposing resistance than pyp-1(-7.1). The computed QPBB of ZINC06025953 is -0.74 that value for pyp-1 is -0.82 so very close to each other, "QMDCK", "QCaco", "QHERG" & "QKhsa" are very appreciable in DLL context, Predicted aqueous solubility, a very important check point in drug development procedure, herein

"QlogS", for ZINC06025953(-7.912), somewhat better computed score against pyp-1(-6.898). Metabolite for ZINC06025953 is calculated out to 4 instead 3 for pyp-1, both pyp-1 and ZINC06025953 have value -1 for CNS activity so both have same proportionate activity in this regard various properties which is no reported here due to written-space limitation concerns, are also very favorable.

The H-bonding interactions, in the interaction diagram for ZINC06025953 **(Fig:2(5))** the two important interactions i.e. with TYR: 683 and GLN:716 in both locations "1"and "2" are very efficiently maintained and no other extra H-bonding interaction are present with ZINC06025953 in both locations in the phosphodiesterase, one hydrogen bond has some weakening effect but another has almost same scale strengthening itself, a mutual exchange effect so overall H-bonding stabilization maintained. On the another hand π-π stacking with ZINC06025953 has a big promotion and got very strange multi channels stacking phenomena, and in this regard, the interaction diagram (**Fig. 2(5))** clearly showing that the pyp-1 stacking with PHE:719 is strictly maintained with ZINC06025953 and complex networking of π-π stacking make a big relief to energy stabilization in both locations, conclusively π-π stacking gave a direction to look much better to its favor. Nevertheless, other molecules may have good impact as a DLL consideration, scientific bodies need to look it well and also too ahead.

TABLE 2: 5DH5- "1"

Title	DS	lip	CNS	dHB	aHB	QlogS	QHERG	QCaco	QBB	QMDCK	QKp	metab	QKhsa	PHOAbs
ZINC71524592	-13.21	-6.2	-2	4	6.5	-4.298	-6.325	122	-1.751	50	-3.402	5	-0.031	75.779
ZINC83982577	-12.48	-6.0	-1	2	6.75	-4.614	-5.204	746	-0.773	529	-1.818	3	-0.152	92.821
ZINC79760798	-12.41	-6.3	-1	1	6	-5.066	-6.714	1521	-0.783	778	-1.154	4	0.197	100
ZINC06025953	-12.38	-7.9	-1	1	5.25	-7.912	-7.912	1952	-0.74	1019	-0.492	3	1.096	100
ZINC58054025	-12.3	-6.5	-2	2	7.25	-6.04	-7.168	955	-1.008	471	-1.526	4	0.35	100
ZINC84432266	-12.27	-5.5	-1	2	7	-4.747	-4.909	581	-0.953	447	-2.241	2	-0.122	91.011
ZINC79865442	-12.1	-5.4	-1	3	6.2	-4.282	-5.097	889	-0.951	490	-1.509	5	-0.295	93.587
ZINC79817785	-12.1	-6.6	-1	2	5.45	-4.812	-4.948	996	-0.721	1375	-1.311	4	0.071	100
ZINC91202695	-11.82	-6.8	-1	2	4.5	-5.638	-5.501	1008	-0.726	717	-1.415	3	0.293	100
ZINC79864804	-11.8	-5.8	-1	2	5.5	-5.158	-5.103	913	-0.862	589	-1.695	3	0.054	100
ZINC73962721	-11.73	-6.1	-2	3	7.5	-3.62	-4.657	127	-1.713	78	-3.158	3	-0.39	73.527
ZINC41482372	-11.67	-5.1	-2	2	6.5	-5.238	-4.601	186	-1.678	138	-3.074	4	-0.181	80.608
ZINC14535744	-11.53	-7.5	-1	1	7.5	-7.789	-7.441	1287	-0.872	650	-1.152	4	1.003	100
ZINC77590749	-11.52	-6.3	-2	2	5.5	-4.74	-4.981	430	-1.104	389	-1.978	6	0.191	94.008
ZINC79865891	-11.45	-5.5	-2	2	5.5	-4.792	-3.44	283	-1.254	302	-2.413	4	-0.045	87.435
ZINC33170440	-11.45	-6.9	-1	1	8.5	-5.784	-7.472	1001	-0.987	495	-1.273	3	0.183	100
ZINC65393661	-11.34	-5.6	-1	2	7.2	-4.561	-5.89	630	-0.87	300	-2.154	3	0.101	93.152
ZINC77888860	-11.33	-6.5	-1	1	6.25	-5.56	-6.737	1552	-0.713	795	-1.214	4	0.356	100
ZINC65913172	-11.32	-6.8	-2	3	6.75	-5.234	-6.787	277	-1.369	279	-2.536	4	0.116	88.315
ZINC32943989	-11.27	-6.9	-1	1	9	-4.86	-6.071	1112	-0.707	837	-1.951	4	-0.076	100
ZINC73962719	-11.21	-6.2	-2	3	7.5	-3.799	-4.864	111	-1.822	70	-3.243	3	-0.376	72.613
ZINC41481907	-11.12	-6.3	-2	1	7	-5.508	-7.07	391	-1.333	179	-1.952	3	0.014	90.304
ZINC41493316	-11.1	-6.1	-2	1	7	-5.424	-6.695	371	-1.228	302	-2.219	4	-0.058	89.352
ZINC09183656	-11.08	-6.1	-2	1	7.5	-4.12	-6.498	300	-1.137	135	-2.74	1	-0.152	82.758
ZINC84333505	-11.08	-5.7	-1	2	7	-4.61	-3.668	575	-0.931	623	-1.752	3	-0.268	91.607
ZINC91164251	-11.07	-6.2	-2	2	7.75	-5.198	-6.914	952	-1.06	469	-1.581	5	0.04	100
ZINC41493317	-11.05	-6.2	-2	1	7	-5.413	-6.708	376	-1.226	301	-2.198	4	-0.06	89.44
ZINC19238436	-11.01	-6.7	-1	0	9	-2.398	-3.94	646	-0.702	478	-2.306	5	-0.868	85.946
ZINC92814406	-10.96	-6.6	-1	2	7.5	-5.484	-6.444	1049	-0.818	521	-1.738	3	0.294	100
ZINC55119912	-10.95	-6.0	-2	1	9.2	-3.1	-5.086	498	-1.078	233	-2.702	4	-0.433	85.025
ZINC03830321	-10.94	-6.2	-1	0	6	-5.182	-6.646	1056	-0.821	524	-1.61	3	0.241	100
ZINC48326837	-10.91	-6.6	-1	1	7.5	-5.062	-6.893	811	-0.96	394	-1.355	6	0.252	100
ZINC73088440	-10.91	-5.9	-2	1	8	-5.133	-6.975	290	-1.48	129	-2.286	4	-0.213	84.441
ZINC19688613	-10.9	-7.0	-2	2	7.5	-5.948	-6.836	272	-1.377	121	-2.86	4	0.387	89.145
ZINC78690369	-10.9	-5.8	-1	3	4.95	-3.843	-4.613	991	-0.737	629	-1.546	3	-0.229	94.828
ZINC78459239	-10.9	-6.3	-1	1	8.2	-5.302	-6.326	1366	-0.888	693	-1.769	6	0.028	100
ZINC72420945	-10.86	-6.4	-1	2	5	-6.785	-7.244	1243	-0.809	625	-1.333	2	0.75	100
ZINC83982579	-10.86	-5.9	-1	2	6.75	-4.764	-5.162	867	-0.741	558	-1.776	3	-0.149	94.113
ZINC72867974	-10.85	-6.4	-2	0	6.5	-4.151	-6.737	469	-1.085	218	-2.096	3	-0.105	91.497
ZINC78459239	-10.84	-6.1	-1	1	8.2	-4.992	-6.119	1428	-0.832	727	-1.73	6	-0.003	100
ZINC55483225	-10.82	-6.3	-1	2	7	-3.651	-5.176	752	-0.834	623	-1.208	4	-0.266	93.668
ZINC18079701	-10.81	-7.0	-2	2	9.25	-5.682	-6.923	728	-1.07	351	-1.656	4	0.279	100

ZINC81476230	-10.79	-6.2	-1	2	6.7	-4.645	-5.039	713	-0.901	616	-1.61	4	0.015	96.519
ZINC89818453	-10.79	-6.3	-2	1	6	-5.738	-6.002	641	-1.117	306	-2.392	5	0.108	94.389
ZINC08597819	-10.78	-7.4	-1	1	7	-8.789	-7.156	1233	-0.802	620	-1.705	4	1.306	100
ZINC52796850	-10.78	-5.6	-2	3	6	-4.53	-5.178	425	-1.058	275	-2.308	2	-0.168	86.815
ZINC41493316	-10.77	-5.8	-2	1	7	-7.16	-8.267	409	-1.478	339	-1.811	4	0.119	93.724
ZINC19016551	-10.77	-6.1	-2	1	8.5	-4.426	-5.134	264	-1.153	240	-2.554	3	-0.204	83.735
ZINC32943990	-10.75	-6.8	-1	1	9	-4.823	-6.04	1121	-0.7	842	-1.949	4	-0.081	100
ZINC73088440	-10.74	-6.2	-2	1	8	-5.138	-6.967	246	-1.556	109	-2.425	4	-0.209	82.93
ZINC95476095	-10.74	-5.8	-1	1	7.5	-4.261	-6.148	755	-0.876	365	-2.174	2	-0.114	92.54
ZINC78477213	-10.73	-6.4	-2	1	5.25	-5.452	-4.913	483	-1.15	368	-1.823	5	0.091	93.934
ZINC05381205	-10.73	-6.6	-2	0.5	7.5	-5.208	-6.066	543	-1.118	256	-2.516	5	0.225	95.199
ZINC43574137	-10.71	-5.7	-1	2	6	-4.571	-4.843	493	-0.864	356	-2.385	4	-0.06	89.12
ZINC04078897	-10.7	-5.9	-1	1	6	-3.93	-5	604	-0.835	435	-1.659	3	-0.142	92.25
ZINC55391865	-10.69	-6.3	-1	2	7.5	-4.883	-6.594	784	-0.843	691	-1.875	5	-0.026	95.461
ZINC41493357	-10.65	-5.7	-2	2	6.5	-5.075	-5.613	196	-1.443	131	-2.179	4	-0.153	82.114
ZINC06786491	-10.65	-5.6	-2	1	7	-4.673	-6.413	578	-1.078	273	-2.168	2	0.057	93.174
ZINC84279708	-10.62	-5.6	-2	1	8	-5.483	-6.066	267	-1.289	209	-3.219	4	-0.194	82.422
ZINC41255012	-10.58	-6.6	-2	1	5.5	-5.506	-5.297	562	-1.038	400	-1.844	5	0.299	100
ZINC19016553	-10.56	-6.3	-2	1	8.5	-4.46	-5.204	225	-1.239	204	-2.663	3	-0.198	82.36
ZINC12761470	-10.55	-6.3	-2	3	6.5	-3.638	-5.058	201	-1.354	213	-2.593	4	-0.384	78.663
ZINC19118877	-10.54	-5.7	-1	1	7.25	-5.773	-6.501	1557	-0.774	798	-1.301	5	0.403	100
ZINC57483627	-10.54	-5.9	-1	1	6	-4.893	-4.699	735	-0.764	591	-1.923	3	0.16	100
ZINC04841284	-10.53	-5.6	-2	1	6.5	-4.653	-5.807	496	-1.121	232	-2.646	2	0.091	90.934
ZINC19016551	-10.52	-6.6	-2	1	8.5	-4.385	-5.122	217	-1.251	193	-2.729	3	-0.214	81.682
ZINC78477210	-10.49	-6.3	-2	1	5.25	-5.327	-4.921	455	-1.161	358	-1.833	5	0.069	93.104
ZINC68819219	-10.49	-7.0	-1	1	6.5	-6.311	-6.813	842	-0.804	673	-1.889	2	0.515	100
ZINC76450999	-10.48	-6.2	-1	2	5.5	-5.342	-5.873	677	-0.921	324	-2.446	3	0.411	100
ZINC72914610	-10.47	-6.2	-2	1	6.95	-5.585	-5.928	425	-1.52	196	-2.854	7	0.289	93.91
ZINC47596286	-10.46	-6.0	-2	3	5.5	-4.931	-6.278	403	-1.137	348	-1.35	4	0.117	93.302
ZINC78669119	-10.45	-6.1	-2	2	7.5	-6.346	-6.704	264	-1.601	198	-2.532	5	0.171	89.493
ZINC19016553	-10.45	-6.3	-2	1	8.5	-4.359	-5.113	208	-1.263	187	-2.753	3	-0.213	81.321
ZINC79803294	-10.42	-5.9	-1	1	8.5	-5.31	-6.591	1097	-0.824	547	-2.059	4	-0.054	100
ZINC72868130	-10.41	-5.7	-2	0	4	-5.1	-6.67	747	-1.081	360	-1.907	2	0.297	100
ZINC11859384	-10.41	-5.9	-2	1	8.5	-4.005	-6.054	292	-1.264	132	-3.165	3	-0.187	82.149
ZINC38519990	-10.39	-5.8	-2	2	7.25	-5.642	-6.415	508	-1.146	238	-2.595	6	0.274	93.433
ZINC72914610	-10.39	-5.9	-2	1	6.95	-5.557	-5.874	547	-1.379	257	-2.641	7	0.301	96.492
ZINC53164694	-10.38	-6.4	-1	2	6.25	-5.338	-6.443	1394	-0.729	1016	-1.292	5	0.302	100
ZINC41493424	-10.38	-6.0	-2	1	7	-4.834	-6.481	578	-1.26	273	-1.834	4	-0.208	91.33
ZINC40520781	-10.38	-6.3	-1	1	7.5	-2.968	-4.794	401	-0.859	397	-2.17	7	-0.487	83.392
ZINC04151781	-10.36	-5.7	-1	1	7	-3.69	-6.113	429	-0.916	198	-2.509	1	-0.197	85.146
ZINC08188257	-10.35	-6.4	-1	2	6.25	-4.839	-6.733	1307	-0.75	661	-1.132	2	0.182	100
ZINC33311756	-10.34	-5.7	-1	1	6.75	-5.36	-6.067	1286	-0.774	649	-1.719	2	0.331	100
ZINC76114861	-10.33	-6.5	-2	2	5.45	-4.076	-4.847	732	-1.005	487	-1.564	5	-0.146	94.579
ZINC56208597	-10.33	-6.7	-2	1	7	-6.254	-7.309	936	-1.059	460	-1.267	4	0.53	100
ZINC79857825	-10.32	-6.3	-2	1	7	-5.579	-6.004	740	-1.082	357	-2.394	2	0.315	100
ZINC12760838	-10.31	-6.2	-1	2	6.25	-5.197	-6.358	1076	-0.779	791	-1.634	5	0.239	100
ZINC19238436	-10.29	-6.4	-1	0	9	-2.77	-4.275	580	-0.784	447	-2.36	5	-0.812	85.738
ZINC81258678	-10.29	-5.8	-1	0	6.5	-4.919	-6.921	917	-0.823	450	-1.595	4	0.098	100
ZINC76786285	-10.27	-6.8	-2	3	6	-5.967	-5.206	281	-1.537	181	-2.375	5	0.023	87.874
ZINC68819995	-10.27	-6.4	-1	1	6.5	-5.442	-6.194	934	-0.74	762	-2.22	3	0.273	100
ZINC76786285	-10.26	-6.3	-2	3	6	-5.801	-4.925	248	-1.557	155	-2.556	5	0.03	86.517
ZINC68817560	-10.25	-6.6	-1	1	6.5	-6.623	-6.96	813	-0.969	395	-1.999	3	0.594	100
ZINC66506999	-10.25	-6.0	-2	1	7	-5.051	-6.2	655	-1.067	565	-1.863	4	-0.169	93.847
ZINC81339135	-10.23	-6.7	-2	1	8.5	-4.566	-6.56	455	-1.226	211	-2.377	0	-0.129	88.862
ZINC68820222	-10.19	-6.3	-1	1	6.5	-5.408	-6.639	786	-0.731	940	-1.972	0	0.161	100
ZINC21895962	-10.18	-6.0	-1	1	5.5	-4.089	-4.974	819	-0.724	715	-1.395	3	-0.019	100
ZINC68817669	-10.18	-6.3	-1	1	6.5	-6.806	-6.947	818	-0.783	982	-1.977	2	0.559	100
ZINC69848553	-10.18	-5.8	-2	2	6	-4.665	-5.382	321	-1.09	273	-2.259	2	0.04	87.887
ZINC38520209	-10.18	-6.0	-2	2	6.75	-5.863	-6.262	469	-1.047	360	-2.645	5	0.392	95.085
ZINC22355181	-10.17	-7.5	-1	2	6.25	-5.448	-7.081	1163	-0.922	582	-1.136	3	0.306	100
ZINC01358659	-10.16	-6.0	-2	2	7.75	-4.649	-6.929	544	-1.145	256	-1.97	3	-0.069	90.771
ZINC27986318	-10.15	-6.1	-2	3	6	-4.422	-5.672	366	-1.177	299	-1.811	4	-0.078	88.837
ZINC38519989	-10.15	-6.1	-2	2	7.25	-5.842	-6.542	478	-1.205	223	-2.643	6	0.302	93.301
ZINC31604194	-10.14	-6.6	-1	1	6.5	-4.235	-5.064	564	-0.803	574	-1.791	7	-0.021	93.483
ZINC45991607	-10.11	-6.6	-1	1	5	-5.229	-5.4	764	-0.789	675	-1.322	5	0.365	100
ZINC78874051	-10.11	-6.0	-1	2	5.5	-4.571	-6.364	788	-0.959	382	-2.051	4	0.046	94.821
ZINC55291564	-10.09	-6.3	-1	1	6.25	-4.944	-6.62	1263	-0.703	945	-1.311	3	0.136	100

ZINC44894878	-10.07	-5.7	-1	1	5.5	-3.786	-4.877	714	-0.725	599	-1.626	3	-0.14	93.6
ZINC53766644	-10.06	-6.2	-1	2	6.5	-4.18	-6.337	819	-0.857	398	-1.692	5	-0.003	95.074
ZINC32000789	-10.06	-5.8	-1	1	6.5	-3.869	-4.809	744	-0.707	558	-1.879	2	-0.266	91.592
ZINC19749422	-10.05	-6.5	-2	2	7.5	-4.544	-5.651	342	-1.308	273	-1.895	4	-0.14	88.154
ZINC79134856	-10.03	-6.0	-1	1	6.75	-4.987	-7.069	999	-0.849	494	-1.351	2	0.128	100
ZINC77590749	-10	-5.6	-2	2	5.5	-5.135	-5.155	526	-1.081	444	-1.888	6	0.21	96.086
ZINC73334882	-9.99	-6.0	-2	2	8.2	-4.501	-6.811	347	-1.429	157	-2.357	2	-0.138	85.951
ZINC63489149	-9.98	-5.8	-2	2	7	-4.464	-5.598	458	-1.016	312	-2.938	5	-0.044	87.807
ZINC68817560	-9.98	-6.5	-1	1	6.5	-6.601	-6.979	901	-0.921	442	-1.917	3	0.574	100
ZINC04676345	-9.98	-7.1	-1	1	6.5	-4.129	-5.794	849	-0.77	735	-0.663	6	-0.037	100
ZINC04151782	-9.98	-5.7	-1	1	6.5	-4.491	-6.244	479	-0.794	406	-2.477	1	-0.007	89.762
ZINC68818157	-9.94	-6.6	-1	1	8.2	-4.786	-6.83	1061	-0.893	527	-1.436	3	-0.041	100
ZINC41492549	-9.94	-6.3	-1	0	6.75	-4.948	-6.205	826	-0.894	759	-1.776	7	-0.247	100
ZINC58326761	-9.94	-6.7	-2	2	7.5	-4.524	-6.784	344	-1.261	156	-2.426	2	-0.056	85.848
ZINC80363211	-9.92	-5.8	-2	2	7.5	-5.383	-5.77	516	-1.042	242	-3.037	3	0.203	91.248
ZINC78798430	-9.92	-5.7	-1	2	5	-4.011	-4.506	454	-0.854	322	-2.504	4	-0.129	87.051
ZINC66274588	-9.92	-6.6	-1	1	7	-5.293	-6.601	1221	-0.886	614	-1.398	2	0.243	100
ZINC41492549	-9.91	-6.6	-1	0	6.75	-5.399	-6.678	817	-0.963	748	-1.691	7	-0.199	100
ZINC80007760	-9.91	-6.6	-2	1	5.75	-5.917	-7.462	915	-1.121	449	-1.36	4	0.358	100
ZINC68818157	-9.9	-6.7	-1	1	8.2	-4.884	-6.896	969	-0.948	478	-1.506	3	-0.025	100
ZINC41493545	-9.9	-5.6	-1	0	6	-5.09	-6.492	910	-0.883	795	-1.58	6	-0.185	100
ZINC81827249	-9.9	-6.1	-1	2	6	-6.254	-6.667	805	-0.91	669	-2.057	4	0.456	100
ZINC76908263	-9.87	-6.4	-2	3	7	-3.574	-3.454	137	-1.217	196	-2.851	5	-0.353	75.291
ZINC71753490	-9.86	-6.3	-2	1	8	-4.913	-6.581	733	-1.122	353	-1.789	6	0.07	100
ZINC74399612	-9.86	-6.7	-1	1	5.25	-5.98	-6.372	1704	-0.711	880	-1.22	4	0.649	100
ZINC68819383	-9.86	-6.0	-1	1	7.5	-4.738	-6.511	480	-0.967	568	-2.489	1	-0.066	90.82
ZINC68820521	-9.86	-6.3	-1	1	7.25	-4.919	-6.679	914	-0.9	449	-1.743	1	0.058	100
ZINC38520209	-9.85	-5.8	-1	2	6.75	-5.918	-6.277	519	-0.999	405	-2.556	5	0.41	96.314
ZINC73334882	-9.84	-6.1	-2	2	8.2	-4.483	-6.76	306	-1.482	137	-2.478	2	-0.134	84.768
ZINC23021154	-9.84	-6.9	-1	2	7	-5.524	-6.726	1162	-0.762	582	-1.411	3	0.358	100
ZINC73334833	-9.83	-6.0	-2	1	8.5	-4.381	-6.211	539	-1.122	253	-2.713	3	-0.242	87.574
ZINC42195692	-9.83	-5.8	-2	1	8	-4.918	-6.017	544	-1.136	256	-2.614	3	0.045	92.057
ZINC41128109	-9.83	-5.9	-1	1	6.5	-3.771	-4.999	852	-0.802	592	-1.504	4	-0.34	93.159
ZINC80363211	-9.83	-5.6	-2	2	7.5	-5.392	-5.766	500	-1.056	234	-3.063	3	0.208	91.022
ZINC76778637	-9.83	-5.9	-1	1	7	-4.885	-5.855	788	-0.883	382	-2.461	2	0.095	95.218
ZINC68818152	-9.82	-6.6	-1	1	8.2	-4.861	-6.83	894	-0.979	438	-1.588	3	-0.015	100
ZINC75531727	-9.81	-6.5	-1	1	6.5	-5.349	-6.531	1122	-0.717	560	-1.673	5	0.3	100
ZINC43976747	-9.8	-6.2	-1	3	5	-5.211	-5.856	668	-0.973	520	-1.112	3	0.26	100
ZINC81060640	-9.79	-6.0	-2	1	6.5	-5.796	-6.75	477	-1.298	222	-2.211	2	0.04	88.311
PYP-1	-9.79	-7.1	-1	1	5	-6.898	-7.193	1406	-0.82	715	-1.234	4	0.793	100

(**D.S.**(Docking Score, kcal/mol), **Lip**(Lipophilicity), **CNS**(Predicted central nervous system activity on a, # –2 (inactive) to +2 (active) scale), **dHB** Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer, #0.0 – 6.0), **aHB** Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer, #2.0 – 20.0, **QPlogS** Predicted aqueous solubility, log S. S in mol dm^{-3} is the concentration of the solute in a saturated solution that is in equilibrium with the crystalline solid, #–6.5 – 0.5, **QHERG** (Predicted IC50 value for blockage of HERG K+ channels, #concern below –5), **QCaco** Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gut-blood barrier. QikProp predictions are for non-active transport, #<25 poor, >500 great, **QPBB**(Predicted brain/blood partition coefficient, #–3.0 – 1.2, **QMDCK**(Predicted apparent MDCK cell permeability in nm/sec, # <25 poor, >500 great), **QKp** (Predicted skin permeability, log *K*p, # –8.0 – –1.0, **metab** (Number of likely metabolic reactions, # 1 – 8), **QKhsa**(Prediction of binding to human serum albumin, # –1.5 – 1.5), **PHOAbs**(Predicted human oral absorption on 0 to 100% scale, # >80% is high, <25% is poor, "#" indicates Range or recommended values

TABLE 3: 5DH5- "2"

Title	DS	Lip	CNS	dHB	aHB	QPlogS	QHERG	QCaco	QPBB	QMDCK	QKp	metab	QKhsa	PHOAbs
ZINC71524592	-11.96	-5.72	-2	4	6.5	-4.463	-6.544	106	-1.874	43	-3.494	5	-0.034	74.56
ZINC06025953	-10.7	-6.53	-1	1	5.25	-8.153	-8.139	1945	-0.764	1015	-0.441	3	1.113	100
ZINC72867974	-10.59	-5.43	-2	0	6.5	-4.08	-6.613	433	-1.104	200	-2.196	3	-0.105	90.67
ZINC65492531	-10.45	-6.87	-2	2	7	-7.143	-8.515	1084	-1.01	540	-0.354	2	0.812	100
ZINC32943989	-10.44	-5.77	-1	1	9	-4.992	-6.149	816	-0.869	598	-2.205	4	-0.052	95.8
ZINC03830321	-10.4	-5.76	-1	0	6	-4.282	-5.861	755	-0.866	365	-1.988	3	0.127	100
ZINC78459239	-10.13	-5.49	-2	1	8.2	-5.154	-6.191	822	-1.128	400	-2.213	6	0.02	96.77
ZINC71405828	-10.11	-6.03	-2	1	8	-6.467	-6.899	391	-1.556	179	-2.188	7	0.196	93.64
ZINC21895838	-10.09	-5.77	-1	1	8	-3.332	-4.456	657	-0.595	575	-2.026	4	-0.403	88.33
ZINC79804048	-9.947	-4.98	-1	2	4.7	-6.173	-5.933	1205	-0.857	808	-1.126	3	0.298	100
ZINC19016553	-9.882	-6.11	-2	1	8.5	-4.551	-5.231	201	-1.32	177	-2.798	3	-0.189	81.34
ZINC41493545	-9.833	-5.12	-1	0	6	-5.103	-6.483	877	-0.9	766	-1.62	6	-0.181	100
ZINC89818453	-9.812	-4.99	-2	1	6	-5.824	-6.092	601	-1.163	285	-2.43	5	0.117	93.93

ZINC41492549	-9.802	-5.85	-1	0	6.75	-4.84	-6.254	879	-0.86	812	-1.669	7	-0.281	100
ZINC19016553	-9.788	-5.81	-2	1	8.5	-4.61	-5.303	234	-1.248	209	-2.632	3	-0.177	83.04
ZINC19016551	-9.778	-5.61	-2	1	8.5	-4.511	-5.223	212	-1.282	189	-2.731	3	-0.193	81.84
ZINC19696099	-9.756	-6.14	-1	1	8	-3.996	-3.682	422	-0.712	1044	-1.552	6	-0.275	90.89
ZINC94019282	-9.667	-5.67	-2	1	7.5	-6.821	-6.5	637	-1.181	304	-2.533	5	0.587	100
ZINC65381010	-9.645	-4.57	-2	1	6	-3.912	-3.539	78	-1.153	40	-3.072	5	-0.136	77.39
ZINC12318585	-9.643	-5.17	-2	1	10.25	-3.986	-5.597	271	-1.395	216	-2.047	3	-0.448	83.46
ZINC71753490	-9.635	-6.02	-2	1	8	-5.112	-6.689	782	-1.117	379	-1.752	6	0.093	100
ZINC04078897	-9.632	-5.19	-1	1	6	-3.223	-4.773	334	-0.942	314	-1.959	3	-0.156	86.75
ZINC81476230	-9.615	-5.59	-1	2	6.7	-4.968	-5.25	681	-0.954	594	-1.634	4	0.061	96.83
ZINC19016551	-9.589	-5.8	-2	1	8.5	-4.402	-5.105	276	-1.121	250	-2.503	3	-0.201	84.22
ZINC19285784	-9.589	-4.84	-2	2	8.5	-3.194	-2.53	199	-1.192	258	-2.746	6	-0.419	79.18
ZINC44448318	-9.554	-5.12	-1	0	8.5	-2.852	-4.344	1043	-0.349	868	-1.803	2	-0.68	92.14
ZINC09183656	-9.544	-5.14	-2	1	7.5	-4.174	-6.576	320	-1.12	144	-2.665	1	-0.147	83.49
ZINC19238436	-9.522	-4.93	-1	0	9	-2.565	-4.062	663	-0.712	486	-2.284	5	-0.844	86.5
ZINC79804048	-9.51	-5.56	-1	2	4.7	-5.68	-5.586	1271	-0.792	827	-1.11	3	0.235	100
ZINC14530839	-9.46	-5.47	-1	1	8.25	-6.089	-5.441	974	-0.732	798	-1.258	6	0.428	100
ZINC71746869	-9.451	-5.78	-1	1	7.5	-4.727	-4.508	599	-0.968	510	-2.062	5	0.067	95.762
ZINC23021154	-9.427	-5.58	-1	2	7	-5.343	-6.545	1156	-0.739	578	-1.428	3	0.351	100
ZINC45991607	-9.426	-6.2	-1	1	5	-5.196	-5.49	609	-0.871	584	-1.438	5	0.379	100
ZINC41493545	-9.417	-5	-1	0	6	-4.908	-6.354	812	-0.915	703	-1.689	6	-0.214	100
ZINC14533852	-9.41	-5.6	-1	1	9	-5.598	-5.437	636	-0.939	509	-1.602	5	0.203	100
ZINC72420945	-9.409	-5.49	-1	2	5	-6.814	-7.271	1202	-0.829	603	-1.353	2	0.754	100
ZINC49458134	-9.399	-4.74	-2	0	7.5	-4.409	-6.327	394	-1.288	319	-2.424	6	-0.553	86.37
ZINC38519989	-9.37	-5.23	-2	2	7.25	-5.792	-6.482	420	-1.261	193	-2.769	6	0.298	91.94
ZINC41128109	-9.327	-5.05	-1	1	6.5	-3.681	-5.001	937	-0.73	697	-1.372	4	-0.334	94.27
ZINC55391865	-9.316	-5.36	-1	2	7.5	-4.829	-6.553	787	-0.832	691	-1.866	5	-0.029	95.45
ZINC45991613	-9.29	-6.34	-1	1	4.5	-6.411	-5.628	710	-0.815	706	-1.334	5	0.817	94.45
ZINC09790011	-9.283	-4.83	-2	0	11.5	-3.358	-4.853	109	-1.685	183	-3.584	3	-1.01	71.3
ZINC73962719	-9.266	-4.65	-2	3	7.5	-3.766	-4.884	99	-1.866	64	-3.307	3	-0.37	71.66
ZINC67605106	-9.259	-4.9	-1	2	6	-5.26	-6.713	1376	-0.795	698	-1.051	3	0.362	100
ZINC08164150	-9.254	-5.15	-2	2	8.75	-4.657	-6.809	318	-1.525	145	-2.326	3	-0.083	86.72
ZINC19239889	-9.247	-4.5	-2	1	8	-3.986	-4.628	211	-1.172	157	-3.292	4	-0.355	77.39
ZINC55119912	-9.239	-5.1	-1	1	9.2	-3.939	-5.859	853	-0.946	417	-2.117	4	-0.313	92.39
ZINC49458610	-9.239	-5.33	-2	0	6.75	-4.153	-6.041	745	-1.003	359	-1.725	5	-0.351	93.95
ZINC19289085	-9.232	-4.38	-1	0	8	-3.463	-5.859	550	-0.834	259	-2.909	2	-0.538	85.37
ZINC72914610	-9.228	-4.92	-2	1	6.95	-5.547	-5.876	459	-1.467	213	-2.785	7	0.299	94.78
ZINC32943990	-9.221	-5.42	-1	1	9	-4.728	-5.87	721	-0.897	521	-2.393	4	-0.089	93.91
ZINC31817586	-9.218	-4.83	-2	1	6.5	-5.2	-5.917	482	-1.031	225	-2.838	2	0.27	92.39
ZINC36705568	-9.199	-4.58	-2	2	8.5	-4.785	-5.653	150	-1.801	63	-4.073	5	-0.098	76.22
ZINC04841284	-9.197	-5.2	-2	1	6.5	-4.93	-6.098	573	-1.09	271	-2.436	2	0.161	94.3
ZINC36705569	-9.187	-4.58	-2	2	8.5	-5.052	-5.84	150	-1.866	63	-4.08	5	-0.072	76.65
ZINC11859384	-9.171	-4.96	-2	1	8.5	-3.975	-6.028	291	-1.26	131	-3.17	3	-0.191	82.04
ZINC04676345	-9.163	-6.48	-1	1	6.5	-4.397	-5.969	826	-0.813	707	-0.693	6	-0.007	100
ZINC79805548	-9.155	-4.9	-2	2	7	-3.205	-3.024	205	-1.093	256	-2.645	3	-0.454	77.98
ZINC60673419	-9.12	-4.81	-1	2	6	-5.785	-6.638	1105	-0.761	984	-1.546	1	0.382	100
ZINC27062239	-9.115	-5	-1	1	7.5	-3.051	-5.022	514	-0.919	375	-1.847	4	-0.594	84.8
ZINC66274588	-9.105	-5.57	-2	1	7	-5.402	-6.583	772	-1.125	374	-1.848	2	0.258	100
ZINC36705569	-9.092	-4.15	-2	2	8.5	-4.892	-5.75	210	-1.664	91	-3.789	5	-0.095	79.55
ZINC41481907	-9.087	-4.4	-2	1	7	-5.439	-6.999	405	-1.307	186	-1.942	3	0.004	90.44
ZINC19289086	-9.071	-4.22	-1	0	8	-3.472	-5.868	560	-0.826	264	-2.891	2	-0.537	85.57
ZINC72628717	-9.07	-4.68	-1	2	6	-5.276	-6.247	1112	-0.704	989	-1.582	1	0.313	100
ZINC84563233	-9.06	-5.58	-1	2	6	-5.833	-6.735	1114	-0.76	995	-1.482	3	0.393	100
ZINC04675632	-9.049	-4.6	-2	3	9	-0.669	-1.202	29	-1.721	62	-3.873	6	-1.366	48.02
ZINC04865833	-9.035	-5.55	-2	0.25	6.25	-5.973	-6.025	386	-1.345	266	-2.987	5	0.425	95.28
ZINC21001571	-9.026	-4.57	-2	1	7	-4.549	-6.78	365	-1.229	166	-2.364	4	-0.004	87.85
ZINC78459239	-9.023	-5.42	-2	1	8.2	-5.213	-6.266	828	-1.138	403	-2.202	6	0.014	96.79
ZINC73088440	-8.999	-4.18	-2	1	8	-5.133	-6.963	250	-1.55	110	-2.419	4	-0.213	83
ZINC72013940	-8.993	-6.05	-1	1	5.5	-7.341	-6.279	1145	-0.905	855	-1.616	7	0.698	100
ZINC38519990	-8.992	-5.19	-2	2	7.25	-5.707	-6.417	499	-1.159	233	-2.623	6	0.292	93.49
ZINC40387597	-8.977	-5.33	-2	0.25	8	-4.217	-6.772	355	-1.222	161	-2.329	4	-0.162	87.34
ZINC73088440	-8.969	-4.76	-2	1	8	-5.099	-6.944	244	-1.556	107	-2.439	4	-0.218	82.68
ZINC78477213	-8.965	-5.22	-2	1	5.25	-5.773	-5.01	739	-1.024	496	-1.547	5	0.096	100
ZINC41493317	-8.954	-4.2	-2	1	7	-5.439	-6.733	397	-1.204	325	-2.156	4	-0.063	89.95
ZINC76457629	-8.951	-4.96	-1	1	7.5	-4.073	-5.037	783	-0.809	585	-1.495	5	-0.229	94.41
ZINC41493250	-8.95	-4.24	-2	1	7	-4.832	-6.06	515	-1.163	488	-2.191	5	-0.279	89.95
ZINC19696099	-8.942	-5.58	-1	1	8	-4.458	-3.846	508	-0.688	1139	-1.429	6	-0.205	93.58

ZINC06063284	-8.937	-5.29	-2	1	7	-6.876	-5.886	194	-1.635	125	-3.534	5	0.422	88.01
ZINC20783155	-8.934	-5.66	-2	1	9	-5.939	-6.823	858	-1.049	419	-1.818	6	0.26	100
ZINC53766644	-8.919	-5.47	-1	2	6.5	-4.322	-6.538	919	-0.83	451	-1.555	5	0.002	96.39
ZINC41493422	-8.919	-4.19	-2	1	7	-4.809	-6.136	495	-1.215	402	-2.184	5	-0.275	89.44
ZINC44970498	-8.909	-4.73	-1	1	6.5	-4.858	-4.315	706	-0.8	477	-2.473	3	-0.015	93.51
ZINC72459023	-8.908	-5.34	-1	1	5.5	-4.252	-5.06	783	-0.72	754	-1.391	1	0.059	100
ZINC19285784	-8.908	-5.28	-2	2	8.5	-4.345	-3.391	182	-1.398	245	-2.752	6	-0.291	80.64
ZINC77590749	-8.898	-5.31	-2	2	5.5	-5.796	-5.312	716	-1.077	467	-1.811	6	0.237	100
ZINC77888860	-8.88	-4.79	-1	1	6.25	-5.476	-6.632	1425	-0.744	725	-1.309	4	0.353	100
ZINC41493316	-8.875	-4.75	-2	1	7	-5.364	-6.655	363	-1.232	295	-2.246	4	-0.071	88.94
ZINC70003792	-8.863	-4.2	-2	2	8	-3.773	-5.131	209	-1.391	91	-3.776	3	-0.238	77.02
ZINC41493316	-8.859	-4.22	-2	1	7	-5.256	-6.552	406	-1.163	337	-2.179	4	-0.095	89.63
ZINC66506999	-8.85	-4.24	-2	1	7	-5.08	-6.212	591	-1.121	505	-1.965	4	-0.169	92.84
ZINC81314543	-8.848	-4.99	-2	2	7.5	-4.325	-6.764	255	-1.505	113	-2.714	2	-0.17	81.71
ZINC19238436	-8.841	-4.72	-2	0	9	-1.992	-4.095	251	-1.004	246	-2.831	5	-0.854	77.66
ZINC38520105	-8.822	-5.07	-2	2	6.75	-7.188	-6.586	482	-1.23	374	-2.706	6	0.69	100
ZINC60673419	-8.815	-4.95	-1	2	6	-5.581	-6.479	1032	-0.776	888	-1.619	1	0.361	100
ZINC64062433	-8.814	-4.42	-2	2	7	-6.432	-6.275	271	-1.225	413	-2.992	5	0.136	88.16
ZINC19582190	-8.804	-5.48	-1	1	8	-4.772	-5.299	328	-0.979	249	-2.476	5	-0.078	86.3
ZINC41493424	-8.794	-4.22	-2	1	7	-4.666	-6.352	417	-1.383	192	-2.104	4	-0.225	87.92
ZINC01358659	-8.791	-4.61	-2	2	7.75	-4.678	-6.98	633	-1.074	302	-1.813	3	-0.062	92.39
ZINC72147139	-8.786	-5.48	-2	4	7	-4.965	-6.702	67	-2.15	40	-3.832	2	0.015	72.25
ZINC04151782	-8.781	-4.29	-1	1	6.5	-4.459	-6.202	483	-0.785	407	-2.474	1	-0.006	89.82
ZINC72914610	-8.779	-5.63	-2	1	6.95	-5.668	-6.004	619	-1.34	294	-2.518	7	0.3	100
ZINC42195692	-8.761	-4.99	-2	1	8	-4.944	-6.021	543	-1.138	255	-2.617	3	0.053	92.15
ZINC72868130	-8.761	-4.7	-2	0	4	-4.418	-6.191	728	-1.001	351	-1.93	2	0.2	100
PYP-1	-8.759	-6.15	-1	1	5	-6.61	-6.899	1060	-0.931	527	-1.541	4	0.768	100

CONCLUSION: Synthesis of ZINC06025953 (i.e. 2-(3-isobutoxyphenyl) - N - (pyridin-2 ylmethyl) quinoline-4-carboxamide) is a need and above facts to verified in real manner be in demand conclusively.

ACKNOWLEDGEMENTS: The authors wish to thank with proud and privilege to Will Richard, Raghu Rangaswamy and Vinod Dewarjee of Schrodinger Ltd. for providing the Schrodinger Suite Software and its training.

Note: This research article only for academic purposes, authors not interested for any financial beneficiary.

REFERENCES:

1. Izzat T. Raheem John D. Schreier Joy Fuerst Liza Gantert, Eric D. Hostetler, Sarah Huszar, Aniket Joshi, Monika Kandebo, Somang H. Kim, Jing Li, Bennett Maf, Georgia McGaughey, Sujata Sharma, William D. Shipe, Jason Uslaner, George H. Vandeveer, Youwei Yan, John J. Renger, Sean M. Smith, Paul J. Coleman, Christopher D. Cox "Discovery of pyrazolopyrimidine phosphodiesterase 10A inhibitors for the treatment of schizophrenia" Bioorganic & Medicinal Chemistry Letters 2016; 26 126–132.
2. Thomas A. Chappie, Christopher J. Helal, and Xinjun Hou Current Landscape of Phosphodiesterase 10A (PDE10A) Inhibition; J. Med. Chem., 2012. 55 (17), pp 7299–7331.
3. Jun Kunitomo, MasatoYoshikawa, Makoto Fushimi, Akira Kawada, John F. Quinn, Hideyuki Oki, Hironori Kokubo, Mitsuyo Kondo, Kosuke Nakashima, NaomiKamiguchi, Kazunori Suzuki, Haruhide Kimura, and Takahiko Taniguchi; Discovery of 1-[2-Fluoro-4-(1H-pyrazol-1-yl) phenyl]-5-methoxy - 3 - (1-phenyl-1H-pyrazol-5-yl) pyridazin-4(1H)-one (TAK-063), a Highly Potent, Selective, and Orally Active Phosphodiesterase 10A (PDE10A) Inhibitor; J. Med. Chem., 2014; 57 (22), pp 9627–9643.
4. Fujishige K, Kotera J, Michibata H, Yuasa K, Takebayashi S, Okumura K, Omori K "Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A)". J Biol Chem Jul 1999: 274 (26). 18438-45
5. Simpson, E. H Kellendonk, C.; Kandel, E. A possible role for the striatum in the pathogenesis of the cognitive symptoms of schizophrenia Neuron; 2010; 65(5), 585-96.
6. Kehler J. Nielsen J., "PDE10A inhibitors: novel therapeutic drugs for Schizophrenia" Curr Pharm Des 2011; 17 (2):137-50
7. Marques TR, Natesan S, Niccolini F, Politis M, Gunn RN, Searle GE, Howes O, Rabiner EA, Kapur S; Phosphodiesterase 10A in Schizophrenia: A PET Study Using [(11)C]IMA107 Am J Psychiatry, 2016; Jul 1;173(7):714-21.
8. William D. Shipe, Steven S. Sharik, James C. Barrow, Georgia B. McGaughey, Cory R. Theberge, Jason M. Uslaner, Youwei Yan, John J. Renger, Sean M. Smith§, Paul J. Coleman, and Christopher D. Cox Discovery and Optimization of a Series of Pyrimidine-Based Phosphodiesterase 10A (PDE10A) Inhibitors through Fragment Screening, Structure-Based Design, and Parallel Synthesis; J. Med. Chem., 2015; 58 (19), pp 7888–7894.
9. Izzat T. Raheem, John D. Schreier, Joy Fuerst, Liza Gantert, Eric D. Hostetler, Sarah Huszar, Aniket Joshi, Monika Kandebo, SomangH. Kim, Jing Li, Bennett Ma, Georgia Mc Gaughey, Sujata Sharma, William D. Shipe, Jason Uslaner, George H. Vandeveer, Youwei Yan, John J. Renger, Sean M. Smith, Paul J. Coleman, Christopher D. Discovery of pyrazolopyrimidine phosphodiesterase 10A inhibitors for the treatment of schizophrenia, Cox

Bioorganic & Medicinal Chemistry Letters 2016; 26 (1), 126-132.

10. Rituraj, K. K. Srivastava, Shubha Srivastava & Tanweer Alam; An in silico approach to identify new anti-hiv integrase inhibitor like leads by docking studies; IJPSR, 2015;Vol. 6(10): 4484-4490.
11. Peter M. Njogu Eric M. Guantai Elumalai Pavadaiand Kelly Chibale ACS Computer-Aided Drug Discovery Approaches against the Tropical Infectious Diseases Malaria, Tuberculosis, Trypanosomiasis, and Leishmaniasis; Infect. Dis., 2016; 2 (1), pp 8–31.

How to cite this article:
Rituraj and Srivastava KK: Schizophrenia: A Look Forward With Zinc06025953. Int J Pharm Sci Res 2017; 8(5): 2122-33.doi: 10.13040/IJPSR.0975-8232.8(5).2122-33.