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Computational Screening, Synthesis and Characterization of Serotonin 5-HT_{2A} Receptor with Novel Phenothiazine Derivatives Toward Schizophrenia.

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Abstract: This research glance into synthesis of novel phenothiazine derivatives and their computational screening of serotonin 5-HT2A receptor towards schizophrenia with reference medicine Risperidone which is second generation antagonist (SGAs). Schizophrenia is a life-threatening and long-running mental disorder. It can result patient misreading of the actual life. This situation aften come from combination of symptoms which can differ greatly in impact and intensity on day-to-day life. Derivatives of phenothiazine (PTZ) are a class of compounds that have received recognition for their therapeutic properties. The parent molecule, PTZ and its derivatives have diverse pharmacological properties like antiemetic, antipsychotic, antihistamine. In this work many types of PTZ derivatives were synthesized and compared with Risperidone (SGAs) medicine via molecular docking. Four compounds (Lig-8, 10, 11 & 12) showed auspicious binding affinity towards schizophrenia.

Key words: Molecular docking, Phenothiazine, Schizophrenia, SGAs, FGAs.

Introduction: Phenothiazine (PTZ) derivatives are a class of chemically synthesized compounds that have received recognition for their medicinal properties. The parent molecule, PTZ and its derivatives have diverse pharmacological properties such as antipsychotic, antihistamine, antiemetic. The most widely known remedial application of PTZ is in the treatment of schizophrenia and other psychiatric disorders. PTZ derivatives, such as thioridazine, were among the FGAs (first generation of antipsychotics) drugs, revolutionizing the treatment of mental illnesses. These drugs antagonize dopamine receptors in the brain, specifically the D2 receptor, which helps alleviate symptoms of psychosis, including delusions and hallucinations. Some other neurological PTZ derivatives drugs, such as fluphenazine, prochlorperazine and chlorpromazine are also useful in the treatment of mental disorders. Drugs based on PTZ derivatives are basically FGAs and act by blocking D2-dopamine receptors. Risperidone is a SGAs (second generation antipsychotics) and act by antagonizes the 5-HT2A receptors and D2- dopamine receptors. The serotonin antagonism plays a key role in the reducing anxiety and improving mood.

1. Schizophrenia:

Schizophrenia is chronic, severe psychological disorder. In this disorder it affects the thinking capacity it also affects behavior and feeling ability so it leads to misperception of the real life. This situation often outcome in a combination of symptoms which can differ greatly in impact and intensity on daily life. "Schizophrenia affects approximately 24 million people or 1 in 300 people throughout the world. Schizophrenia is consistently associated with significant misery and detriment in personal, family, social, academic, vocational, and other important field of life"[2].

1.1. Genesis of schizophrenia:

It is very difficult to decide main cause of this disorder, because it come from amalgamation of environmental, social and genetical factors, also another factor like stress, infections, deformity in neurotransmitters. A family history can lead the risk of developing the symptoms of schizophrenia.

1.2. Recognition and therapy of schizophrenia:

Schizophrenia is mostly recognized by a psychiatric via monitoring psychological tests and clinical counselling. Antipsychotic drugs are used to balance the positive symptoms like hallucinations and delusions. Cognitive-Behavioral Therapy (CBT) can help to upgrade the situation, stress and communication skills.

FGAs, target & aftertaste; Thioridazine, Chlorpromazine, Haloperidol & Fluphenazine are representative antipsychotics and they pick out Dopamine receptors. The aftertaste of these drug are Extrapyramidal symptoms (EPS), coolness and cardiovascular effects.

SGAs, target & aftertaste; Aripiprazole, Risperidone, Clozapine & Olanzapine are representative antipsychotics and they pick out D2 dopamine & serotonin (5-HT2A) receptors. From their customary aftertaste of these drug are Extrapyramidal symptoms (EPS), metabolite, neuroleptic malignant syndrome (NMS) & coolness.

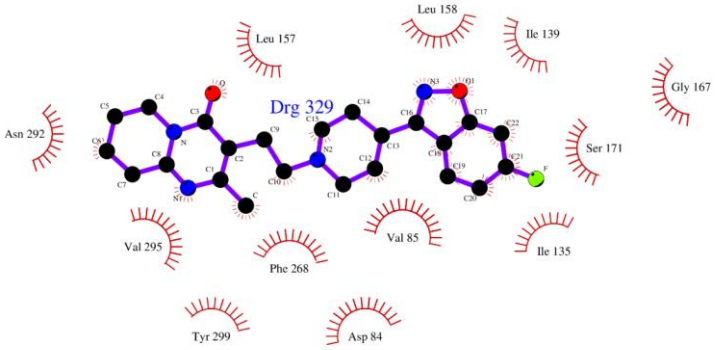
2. Objectives:

As schizophrenia is a mental disorder. It leads to misunderstanding of the real life. There are many 1^{sts} and 2nd generation antipsychotic medicine are obtainable which are playing pivotal role in the living healthy life of people who are hurt from psychological disorders like schizophrenia. Risperidone is a second-generation medicine which display some common side effects; light-headedness, malignancy, jerk and agitation. There are numerous drugs already reported which are based on phenothiazine derivative and these medicines are helpful in the therapy of schizophrenia and other brain sickness. The phenothiazine-based drugs are mainly First-Generation Antipsychotics (FGAs) which inhibit dopamine receptors. The main objective of this research is to bloom novel drug molecule based on phenothiazine which inhibit the 5- hydroxy tryptamine receptor 2A (5-HT2A) with slighter side effects. In this research Risperidone was used as recommended drug for the occurrence of new drug which based on PTZ derivatives. "Drug pick out the serotonin 2A receptor (5-HT2AR), including 2nd generation antipsychotics (SGAs) that also pick out the dopamine D2R (D2 receptor). These drugs often fabricate acute side effects due to non-selective binding to other aminergic receptors. Here, in this literature the structures of human 5-HT2AR in complex with the SGAs (second-generation antipsychotics), zotepine and risperidone. These antipsychotics successfully maintain the inactive geometry

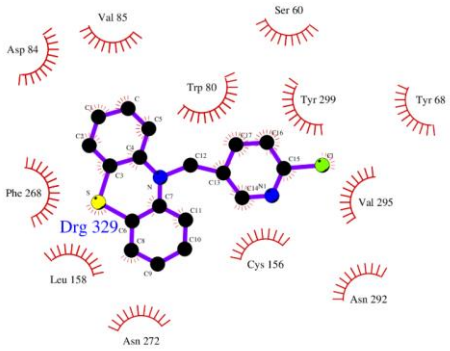
with the residues at the bottom of the ligand-binding pocket by forming direct contacts, the movements of which are pivotal for receptor activation. 5-HT2AR and 5-HT2CR are systemically similar but possesses a special side-extended pocket near the Ortho steric binding site"[3].

3. Results and Conversation:

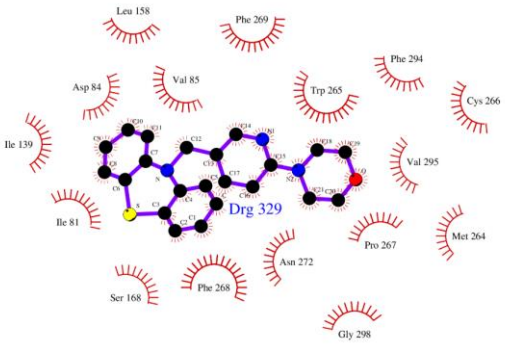
3.1 Computational studies: Virtual screening was performed by using docking server Par Dock+. Target protein (PDB id: 6A93) was prepared by the pymol and used in PDBQT format. Ligands were designed using Chem draw and converted in 3D format with the help of Chem draw 3D and save as SDF format with minimized energy. Target receptor (PDBQT format) and ligands (SDF format) were uploaded in docking server to obtain result. Out of 12 novel PTZ derivatives, four (Lig_8, 10, 11 and 12) derivatives were showed good binding score with reference medicine Risperidone.



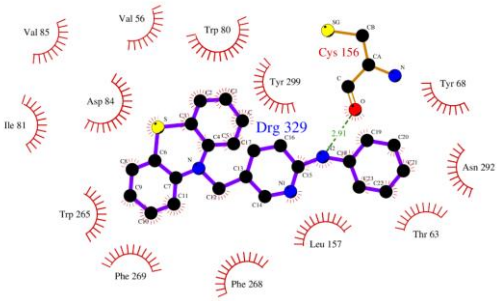
Risperidone: Reference medicine.



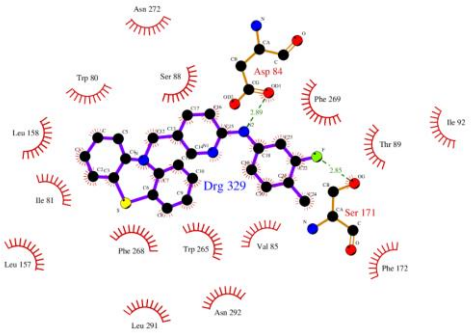
Lig-6



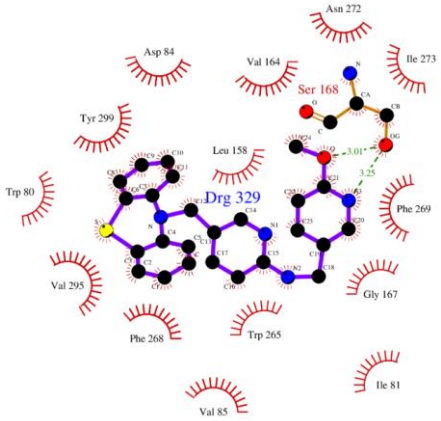
Lig-7



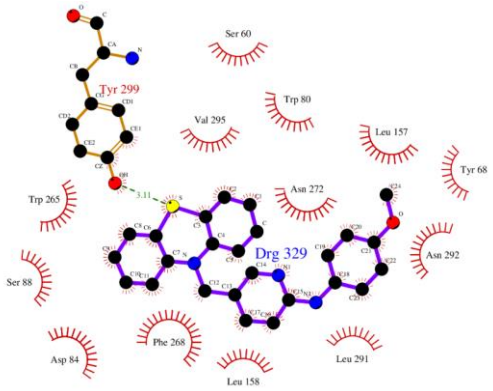
Lig-8:



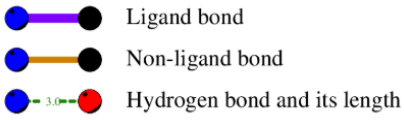
Lig-10



Lig-11



Lig-12



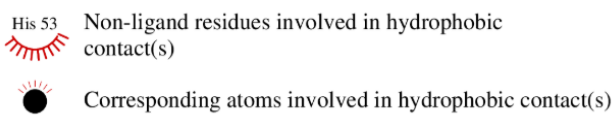
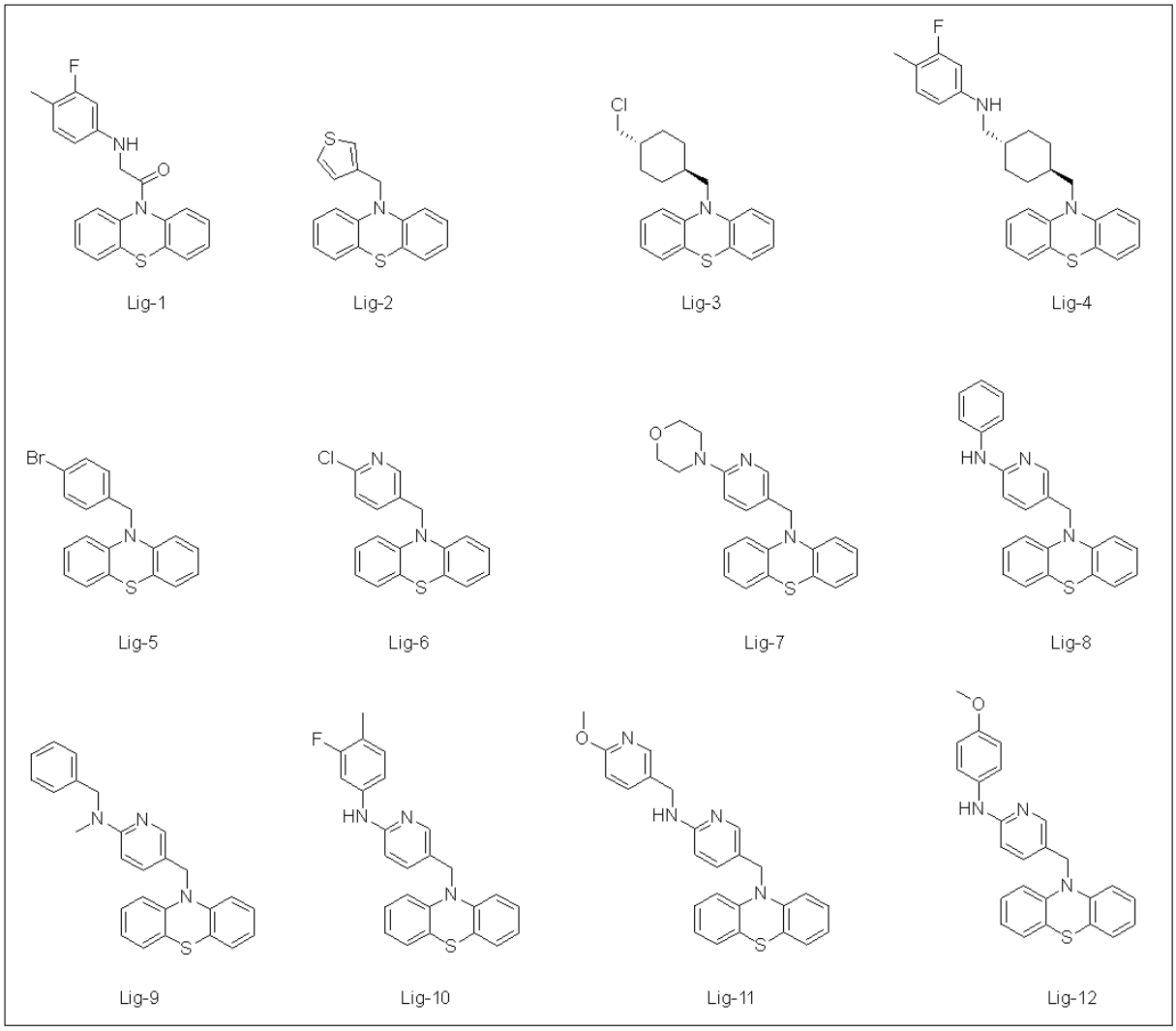


Table-1:

Compound Name	Target Receptor	Docking Score (kcal/mol)	Hydrogen Bonds
Risperidone	PDB id: 6A93	-10.88	**1**
Lig-1	〃	**-9.47**	3
Lig-2	〃	**-8.08**	0
Lig-3	〃	**-9.55**	1
Lig-4	〃	**-11.55**	2
Lig-5	〃	**-8.98**	0
Lig-6	〃	**-9.06**	0
Lig-7	〃	**-10.65**	0
Lig-8	〃	**-10.25**	1
Lig-9	〃	**-10.76**	0
Lig-10	〃	**-11.01**	2
Lig-11	〃	**-11.48**	2
Lig-12	〃	**-10.93**	1

Conclusion: Computational screening of 12 novel derivatives of phenothiazine was performed. Out of twelve derivatives six were shortlisted and synthesized. Four compounds (Lig-8, 10, 11 & 12) were showed better docking score with reference medicine Risperidone. Further in-vivo study is required to corelate with computational screening result.



5. Experimental:

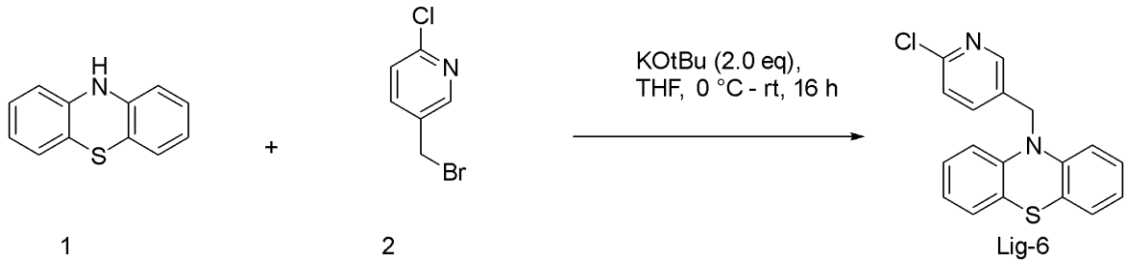
5.1 Chemistry:

All solvent, chemical and catalyst were purchased from Chempure, RCP, Spectrochem, GLR, TCI & Aldrich. Progress of each reaction was monitored by thin layer chromatography (TLC), purified by flash column chromatography and characterized by 1H-NMR, LCMS.

5.2 Synthesis of 10-((6-chloropyridin-3-yl)methyl)-10H-phenothiazine (Lig-6).

To s stirred solution of 10H-phenothiazine (1, 10.0 g, 50.18 mmol) in THF (150 mL), was added potassium tert-butoxide (11.26 g, 100.37 mmol) at 0 °C and stirred for 10 minutes. 5-(bromomethyl)-2-chloropyridine (2, 12.43 g, 60.22 mmol) was added at same temperature then the reaction was warm up to rt and stirred for 16 hours. After completion, the reaction mixture was poured into ice cold water (250 mL) and extracted with ethyl acetate (3 x 100 mL). Combined organic layer was washed with water (100 mL), brine (100 mL), dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to get crude. The crude product was purified by flash column chromatography (0 – 20% ethyl acetate in heptane) to get 10-((2-chloropyridin-4-yl)methyl)-10H-phenothiazine (Lig-6, 12.50 g, yield 72.8%) as tan solid. ^{1}H NMR (400 MHz, DMSO-D6) δ 8.43 (d, J = 1.72 Hz, 1H), 7.55 (dd, J = 2.12 Hz & 8.16 Hz, 1H), 7.47 (d, J = 8.16

Hz, 1H), 7.19 (dd J = 7.52 Hz, 2H), 7.12 (t, J = 7.36 Hz, 2H), 6.95 (t, J = 6.56 Hz, 2H), 6.88 (d, J = 8.52 Hz, 2H), 5.22 (s, 2H). LCMS-ESI (m/z): [M+1] 324.80.

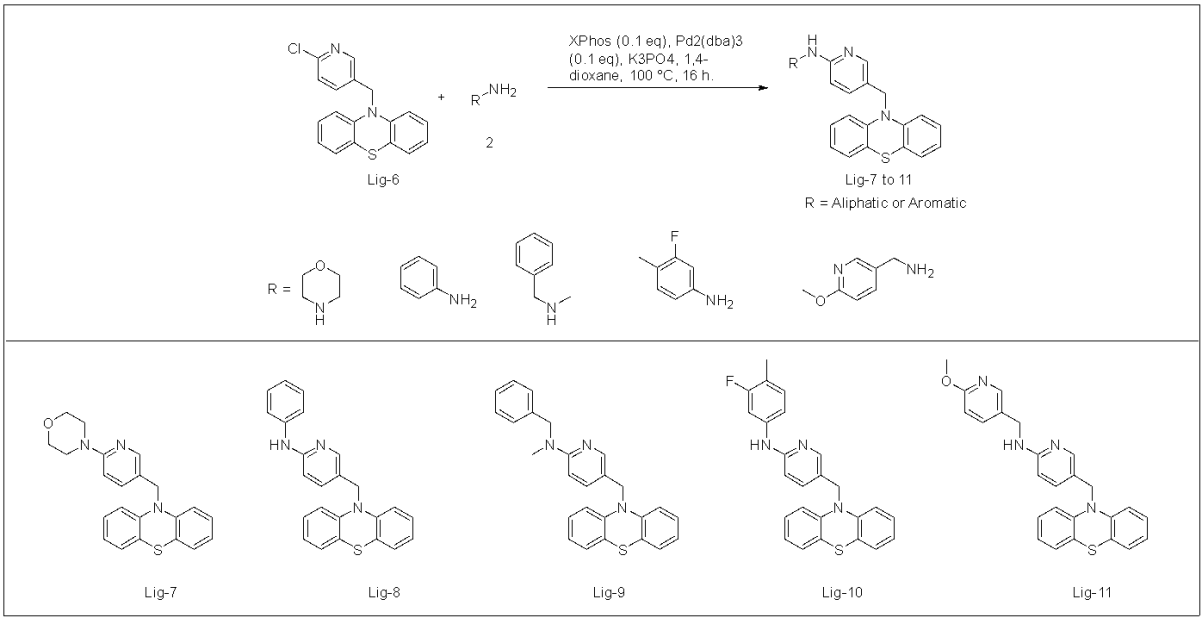


1 2 Lig-6

Table- 2:

SM-1(1 eq)	SM-2 (1.2eq)	Base (2.5 eq)	Solvent (10 V)	Temp	Time	Yield
1	2	DIPEA	DMF	90 °C	16 h	NR
1	2	K2CO3	DMF	80 °C	16 h	10%
1	2	KOtBu	DMSO	rt	16 h	25%
1	2	KOtBu	DMSO	60 °C	16 h	30%
1	2	Cs2CO3	DMF	80 °C	16 h	15%
1	2	NaH	DMF	rt	16 h	40%
1	2	KOtBu	THF	rt	16 h	75%

Synthesis of Lig-7,8,9,10 and 11.



General procedure:

To a stirred solution of Lig-6 (0.5 mmol, 1 eq) and 2 (0.6 mmol, 1.2 eq) in 1,4-dioxane were added K3PO4 (1.5 mmol, 3 eq). Nitrogen was purged for 2 minutes. Pd2(dba)3 (0.05 mmol, 0.1 eq) and XPhos (0.05 mmol, 0.1 eq) were added. Nitrogen was purged for another 2 minutes then the reaction was heated at 100 °C for 16 h. Upon completion, the reaction mixture was poured into ice cold water and extracted with ethyl acetate (2 – 3 times). Organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to get crude. The crude was purified by flash column chromatography to afford Lig-7 to 11.

Table 3:

Lig-6(1 eq)	SM-2(1.2eq)	Base (2.5 eq)	Catalyst (0.1 eq)	Ligand (0.1 eq)	Solvent (10 V)	Temp.	Time	Yield
Lig-6	2	K2CO3	Pd(OAc)2	XPhos	Toluene	100 °C	16 h	NR
Lig-6	2	Cs2CO3	Pd(OAc)2	XPhos	Toluene	100 °C	16 h	NR
Cpd-6	2	K3PO4	Pd2(dba)3	XPhos	Toluene	100 °C	16 h	40%
Cpd-	2	K3PO4	Pd2(dba)3	XPhos	Dioxane	100 °C	16 h	70%
Cpd-6	2	K3PO4	Pd2(dba)3	Xanth Phos	Dioxane	100 °C	16 h	50%

4-(5-((10H-phenothiazin-10-yl)methyl)pyridin-2-yl)morpholine (Lig-7). ^{1}H NMR (400 MHz, DMSO-D6) δ 8.12 (s, 1H), 7.46 (d, J = 7.04 Hz, 1H), 7.16 – 7.09 (m, 4H), 6.93 – 6.87 (m, 4H), 6.77 (d, J = 8.54 Hz, 1H), 5.02 (s, 2H), 3.65 (s, 4H), 3.37 (s, 4H). LCMS-ESI (m/z): [M+1] 375.95.

5-((10H-phenothiazin-10-yl)methyl)-N-phenylpyridin-2-amine (Lig-8). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.15 (s, 1H), 7.63 (d, J = 7.42 Hz, 2H), 7.48 (d, J = 8.04 Hz, 1H), 7.22 (t, J = 7.21 Hz, 2H), 7.18 – 7.10 (m, 4H), 6.95 – 6.91 (m, 4H), 6.85 (t, J = 7.20 Hz, 1H), 6.78 (d, J = 8.40 Hz, 1H), 5.05 (s, 2H). LCMS-ESI (m/z): [M+1] 381.58.

5-((10H-phenothiazin-10-yl)methyl)-N-benzyl-N-methylpyridin-2-amine (Lig-9). ^{1}H NMR (400 MHz, DMSO-D6) δ 8.09 (s, 1H), 7.40 (d, J = 8.83 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.22 – 7.09 (m, 7H), 6.92 – 6.86 (m, 4H), 6.59 (d, J = 8.84 Hz, 1H), 5.00 (s, 2H), 4.73 (s, 2H), 2.97 (s, 3H). LCMS-ESI (m/z): [M+1] 409-60.

5-((10H-phenothiazin-10-yl)methyl)-N-(3-fluoro-4-methylphenyl)pyridin-2-amine (Lig-10). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.95 (s, 1H), 8.11 (s, 1H), 7.52 – 7.45 (m, 3H), 7.17 – 7.10 (m, 4H), 7.01 – 6.90 (m, 5H), 6.73 (d, J = 8.82 Hz, 1H), 5.04 (s, 2H), 2.19 (s, 3H). LCMS-ESI (m/z): [M+1] 413.57.

5-((10H-phenothiazin-10-yl)methyl)-N-((6-methoxypyridin-3-yl)methyl)pyridin-2-amine (Lig-11). ^{1}H NMR (400 MHz, DMSO-D6) δ 8.09 (s, 1H), 7.97 (s, 1H), 7.74 – 7.62 (m, 1H), 7.28 (d, J = 8.42 Hz, 1H), 7.15 – 7.08 (m, 4H), 6.94 – 6.87 (m, 5H), 6.74 (d, J = 8.36 Hz, 1H), 6.43 (8.64 Hz, 1H), 4.95 (s, 2H), 4.33 (d, J = 5.56 Hz, 2H), 3.80 (s, 3H). LCMS-ESI (m/z): [M+1] 426.60.

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