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Full Length Article

Design, synthesis, spectroscopic characterization and anti-psychotic investigation of some novel Azo dye/Schiff base/Chalcone derivatives

Chandravadivelu Gopi [a,b], Vedula Girija Sastry [c], Magharla Dasaratha Dhanaraju [a,*]

[a] Research Lab, GIET School of Pharmacy, Rajahmundry, Andhra Pradesh 533296, India
[b] School of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh 533003, India
[c] A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh 530017, India

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ABSTRACT

The purpose of the study is to design, synthesise and assess the antipsychotic activity of a set of the novel (5-(10-(3-*N*, *N*-Dimethylamino) propyl)-10*H*-phenothiazine-3-yl)-1,3,4-thiadiazo-2-yl) Azodye/Schiff base/Chalcone derivatives. The newly synthesised compound structure was characterised by FT-IR, ^{1}H NMR, Mass spectroscopy and elemental analysis. Each compound has been shown an excellent anti-psychotic activity in a haloperidol-induced catalepsy metallic bar test. The results found are firmly similar to docking study. Among the synthesised derivatives, compound 2-Amino-6-(3-hydroxy-4-methyl phenyl) pyrimidine-4-yl) (7-chloro-10-(3-(*N*, *N*-dimethylamino) propyl)-10*H*-phenothiazine-3-yl) methanone (**GC8**) exhibiting high potency of catalepsy induction. Therefore, the derivative of GC8 has been considered that a potent anti-psychotic agent among the synthesised compounds.

1. Introduction

Dopamine receptors are responsible for several functions such as fine motor control, emotion, learning, cognition, pleasure, sensation, motivation, memory and modulation of neuroendocrine behaviour, movements etc., [1]. Some changes in the role of dopaminergic receptor actions are generated many diseases like parkinsonism, psychomotor, schizophrenia, neurodegeneration, drug abuse, delusions and hallucinations etc., [2]. These receptors are mainly divided into D1-5. They belong to the class of G-protein-coupled-receptors [3,4]. Here, D1 and D5 receptors are known as D1 family associates, whereas D2, D3 and D4 receptors are known as D2 family associates [5]. Both families coupled with G-protein and retard the adenylyl cyclase [6,7]. With the knowledge of some evidence state that the possibility of the existence of D6 and D7 dopamine receptors, but such a type of receptor has not been sturdily documented. Generally, these receptors bind to the plasma membrane as a homodimer, heterodimers or higher-order oligomers etc., [8]. It has been targeted for different psychotic illnesses and also be considered in some non-psychotic disorders [9]. Drugs used to treat the psychotic problem are known as antipsychotic agents (or neuroleptic) is majorly classified into two types. Earlier antipsychotic drugs are called as typical or classical antipsychotic agents, whereas; currently available drugs are recognised as a second generation or atypical antipsychotic agents. Both the type of the antipsychotic agent is having a tendency to obstruct receptors in brain's dopamine pathways [10]. Most of the antipsychotic agents are having substantial side effects, such as dysphoria, parkinsonism, tardive dyskinesia, galactorrhea, sedation, irritability, hyperprolactinaemia, sexual functioning disorder and symptoms of ADHD, depression, narcolepsy, anxiety, improved appetite, obesity threat, paranoia, aggression, psychomotor agitation, diabetes mellitus (Type 2), akathisia, extrapyramidal symptoms and menstrual trouble [11]. Therefore, identification of a novel antagonist of dopamine receptor is needed to treat nervous diseases effectively. In recent years, there has been an immense awareness among the scientists toward the design of new drugs, which consumes less time, highly potent and lower cost to prepare an effective drug molecule against various health problems. Rapid and high throughput method of drug discovery is an only way to improve the therapeutic value of drugs in the animal model. Molecular docking is a one among the method to measure the biological activity of the proposed molecule with the targeted receptor rapidly using Molegro Virtual Docker (MVD). With the support of MVD, we found a bunch of novel compounds known as potent dopamine pathway inhibitors and bearing least side effect due to the presence of trusted thiadiazole and phenothiazine nucleus as part of the molecular structure. This study stated that easy way for the synthesis of novel Azo dye/Schiff bases/Chalcone

* Corresponding author.
E-mail address: mddhanaraju@yahoo.com (M.D. Dhanaraju).

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2314-808X/

derivatives and their antipsychotic activity by using virtual docking and a metallic bar test. The synthesised compound structure was characterised by FT-IR, ^{1}H NMR, mass spectroscopy and elemental analysis.

2. Materials and method

2.1. Molecular docking

Virtual screening has been playing an important role in drug discovery processes which deal with a quick search of chemical structures likely to have more chemical binding to the drug target (protein or enzyme) from large libraries. MVD is a powerful docking tool used to detect the binding ability lies between the ligand and receptor. Before we start the docking process, the human dopamine D2 receptor template was collected from the protein bank as mentioned in Fig. 1. A setup of 26 different ligands was built in ChemDraw (Table 1), and the 2D structure was converted to the 3D structure using molegro virtual software [12]. The best 3D structure of ligand was selected from energy minimization through molecular objective functions and modeller score in MVD [13,14]. The properties of each ligand such as absorption, distribution, metabolism and excretion were also studied. The best conformation was selected and used to predict the strength of the bond between the receptor and ligand. The result reveals that around 10 compounds (Table 2) out of 26 are capable of making a perfect binding to the active site of the receptor amino acid. It also helped us to find out the order of prioritising molecules to synthesise from the bunch of the molecule based on moledock score, rerank score and hydrogen bond binding energy with DA. The docking study pathway was presented in Fig. 2.

2.2. Chemistry

The raw materials and solvents were purchased from Ranbaxy, Sigma-Alrich, Ranchem companies. The melting points of prepared analogues were recorded in open capillary tube method on an Electrothermal 9100 melting point apparatus and are uncorrected. Functional group of synthesised compound was confirmed by using Fourier transform infrared spectroscopy (FT-IR) between the ranges from 4000 cm^{-1} to 400 cm^{-1}. The number of proton present in the analogues was recorded on the Bruker ^{1}H NMR spectroscopy from chemical shift (δ) and the molecular mass of the compound was analysed by the Shimadzu mass spectroscopy. The element analysis was performed on Perkin Elmer 2400 CHN elemental analyser.

2.2.1. Synthesis of 4-(Phenylamino)benzoic acid (Scheme-I)

Aniline (0.1 mol, 9.3 ml), para chloro benzoic acid (0.1 mol, 15.6 g), potassium carbonate (0.01 mol, 1.38 g) and 0.63 g of copper wire were dissolved in 30 ml of *N, N*-dimethylformamide (DMF) contained round bottom flask of about 250 ml capacity. The mixture was allowed to agitate for 30 min at 20–25 °C. The flask was fitted with a reflux condenser and heated at 80 °C for 4 h with occasional shaking. The crude 4-(Phenylamino) benzoic acid was filtered, washed with little cold water and crystallized from ethanol.

2.2.2. Synthesis of 10H-Phenothiazine 3-carboxylic acid

An ethanolic solution of 4-(Phenylamino) benzoic acid (0.01 mol, 2.13 g) was added dropwise to a mixture of sulphur (0.01 mol, 0.32 g) and iodine (0.01 mol, 1.26 g). Shake the mixture until it became a solution. Placed the solution in a round bottom flask of about 250 capacities and fitted with the reflux condenser. The mixture was subjected to reflux on a water bath around 3 h with occasional shaking. The crude 10*H*-Phenothiazine 3-carboxylic acid was separated with a vacuum pump, washed with a small portion of cold water and re-crystallized from ethanol.

2.2.3. Synthesis of 5-(10-(3-(N,N-Dimethylamino)propyl-10H-phenothiazine-3-yl)-1,3,4-thiadiazole-2-amine

10*H*-Phenothiazine 3-carboxylic acid (0.01 mol, 2.43 g) and thiosemicarbazide (0.01 mol, 0.75 g) were dissolved in 60 ml of phosphorus oxychloride with the stirring duration of 10 min. The contents were placed in a distillation flask fitted with the reflux condenser. The flask was heated on a water bath for around 4 h. The reflux was detached from reflux condenser and added dropwise 3-Chloro-*N, N*-dimethyl propanamine (0.01 mol, 1.21 ml), sodium hydride (0.01 mol, 0.24 g) in DMF. Again, the reaction mixture was warmed for 3 h in a water bath. The hot solution was cooled to room temperature and separated crude product was

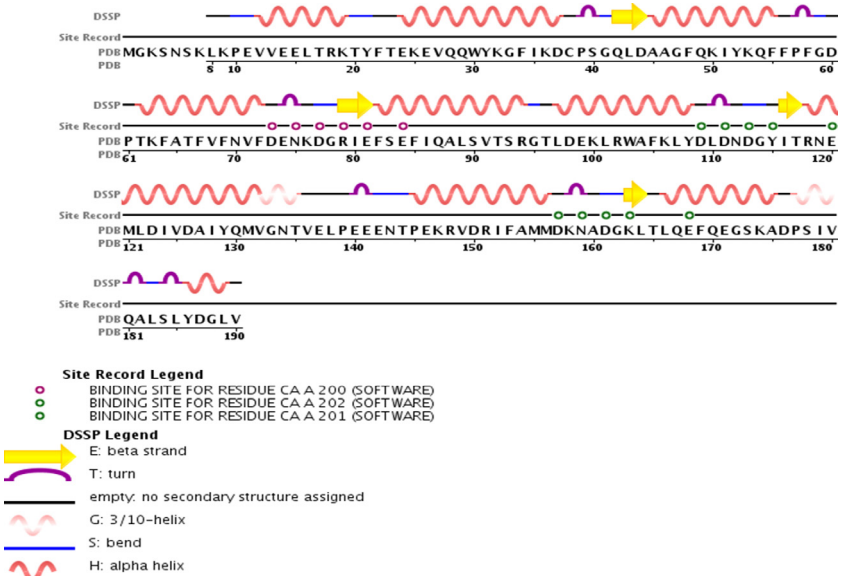


Fig. 1. Dopamine D2 Receptor (DA) pdb format structure from protein data bank.

Table 1
Structure and name of proposed molecules (ligand).

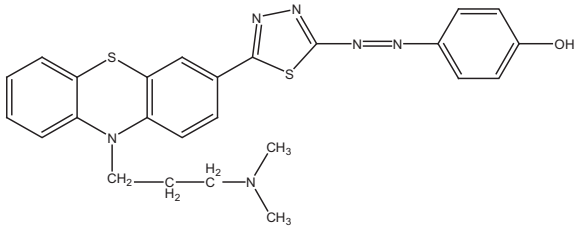
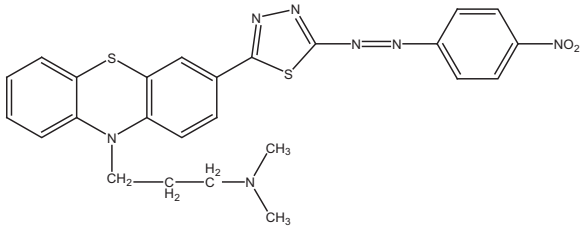
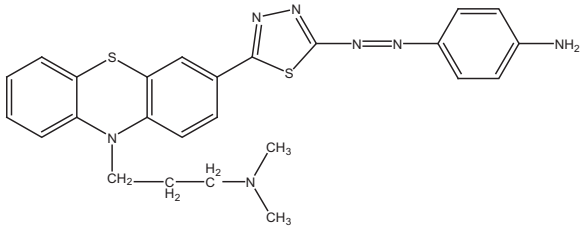
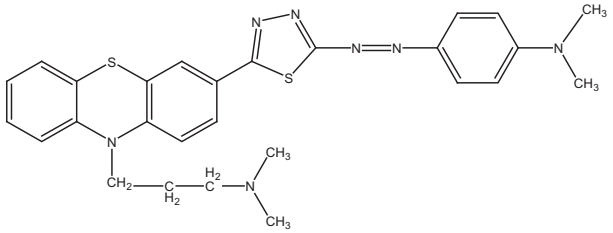
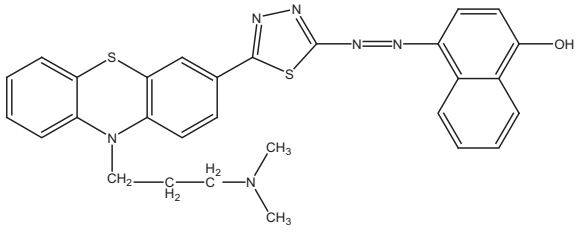
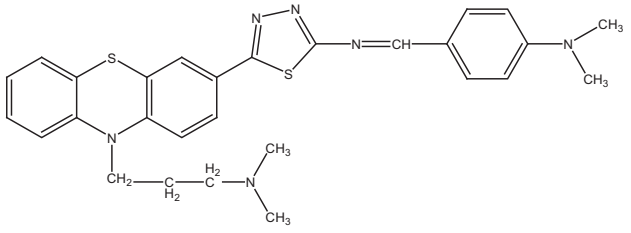
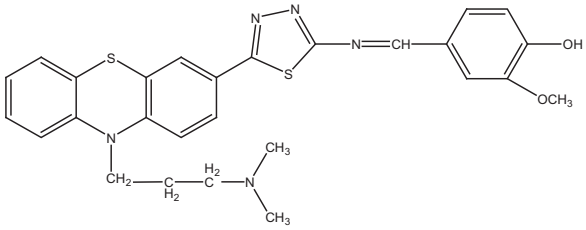
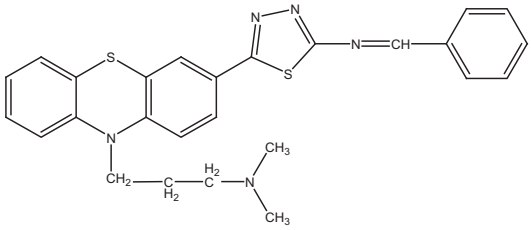
Compound	Structure
1	 4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)phenol
2	 4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)-3-nitrobenzylidene
3	 4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)benzenamine
4	 4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)*N*,*N*-dimethylbenzenamine
5	 4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)naphthalene-1-ol
6	 *N*-(4(*N*,*N*-Dimethylamino)benzylidene)-5-(10-(3-*N*,*N*-dimethylamino)poropyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-amine

Table 1 (*continued*)

Compound	Structure
7	
	4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-ylimino)methyl)-2-methoxyphenol
8	
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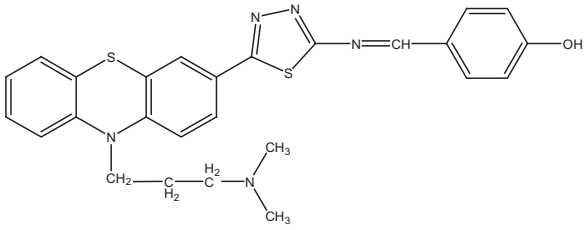
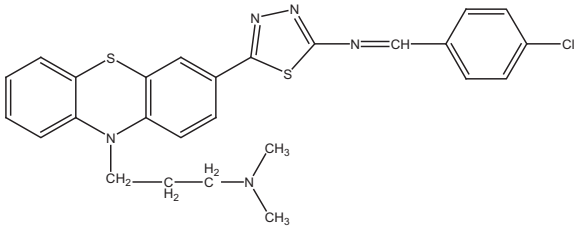
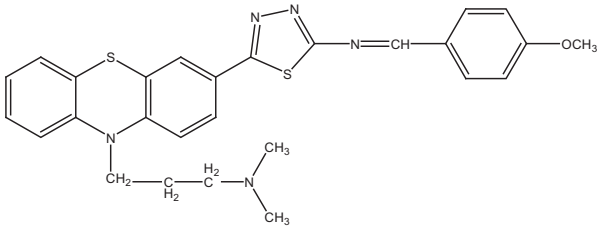
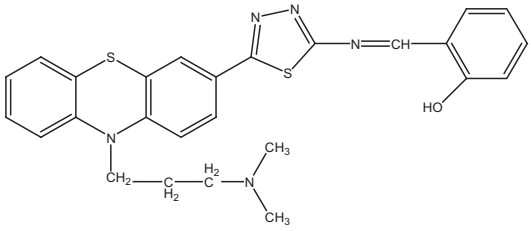
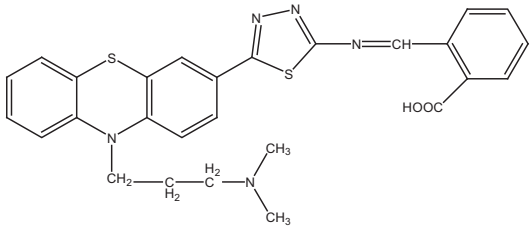
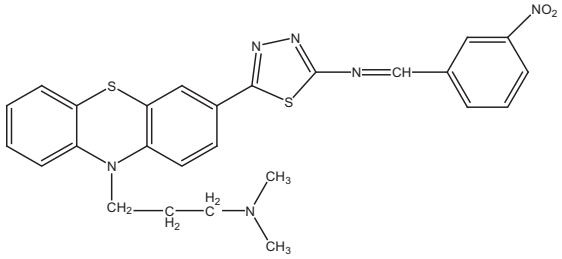
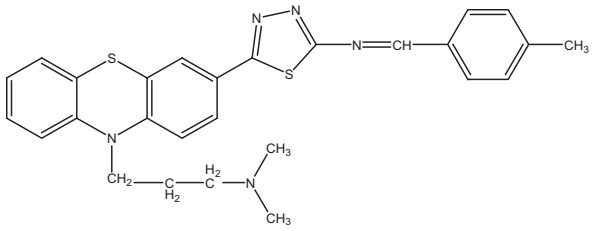
9	
	4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-ylimino)methyl)phenol
10	
	N-(4-Chlorobenzylidene)-5-(10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-amine
11	
	N-(4-Methoxybenzylidene)-5-(10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-amine
12	
	2-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-ylimino)methyl)phenol

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure
13	
	2-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-ylimino)methyl)benzoic acid
14	
	N-(3-Nitrobenzylidene)-5-(10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-amine
15	
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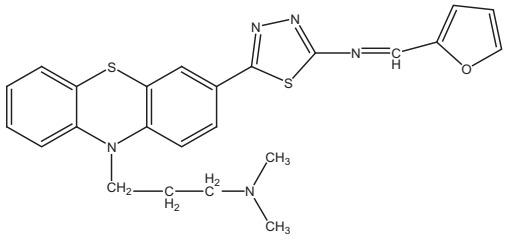
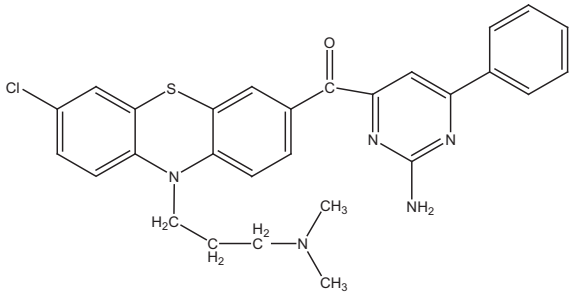
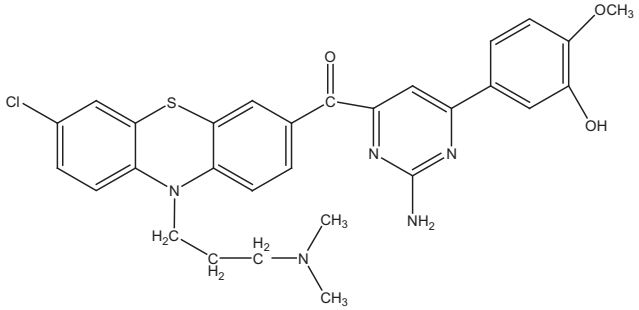
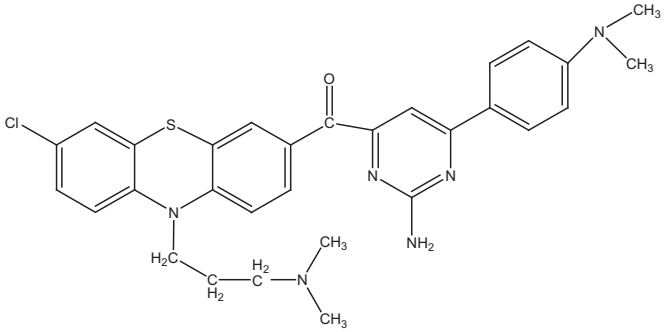
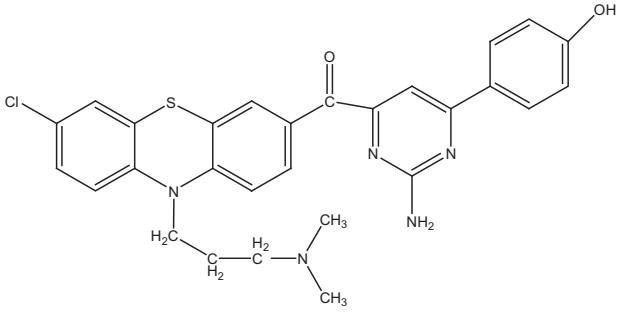
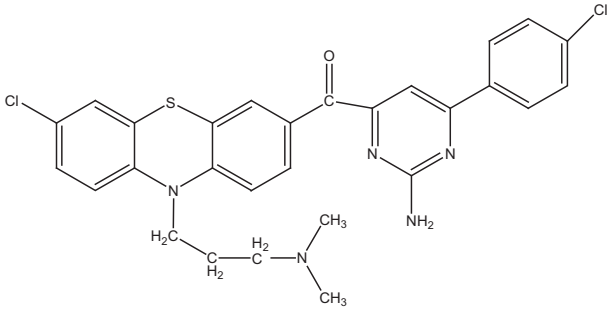
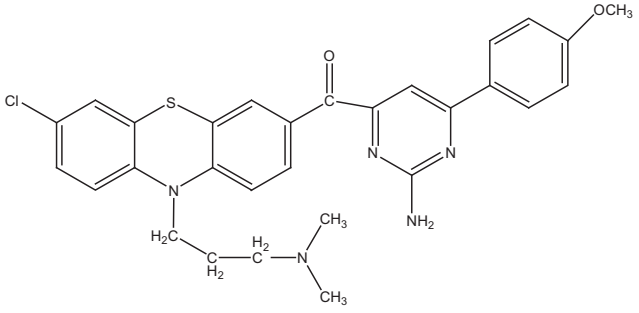
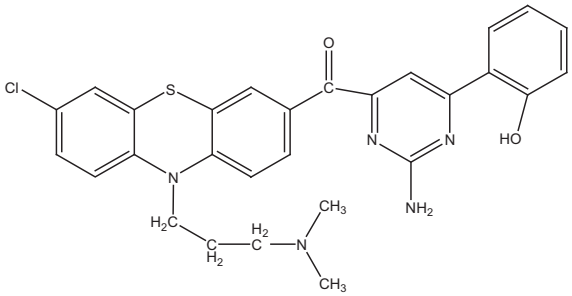
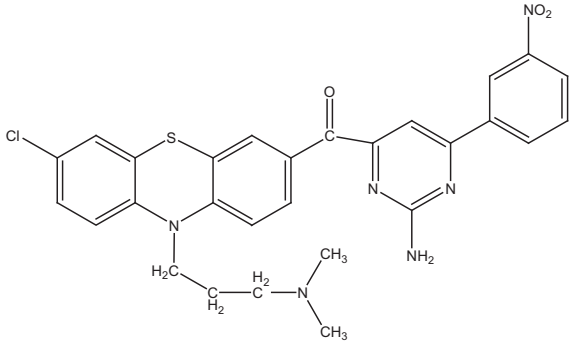
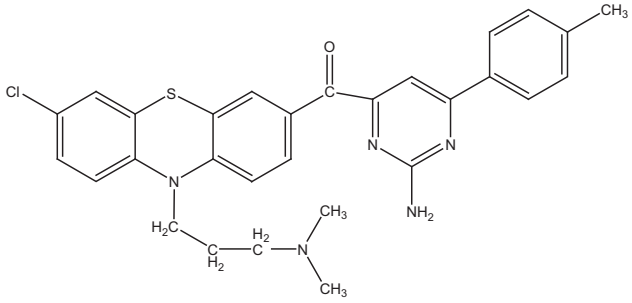
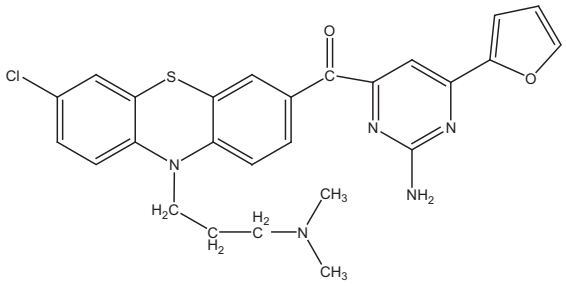
16	
	5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-*N*-(furan-2-ylmethylene)-1,3,4-thiadiazole-2-amine
17	
	2-Amino-6-phenylpyrimidine-4yl)(7-chloro-10-(3(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone
18	
	2-Amino-6-(3-hydroxyl-4methoxyphenyl)pyrimidine-4yl)(7-chloro-10-(3(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone

Table 1 (*continued*)

Compound	Structure
19	 2-Amino-6-(4-dimethylamino)phenyl)pyrimidine-4yl)(7-chloro-10-(3(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone
20	 2-Amino-6-(4-hydroxyphenyl)pyrimidine-4yl)(7-chloro-10-(3(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone
21	 2-Amino-6-(4-chloroyphenyl)pyrimidine-4yl)(7-chloro-10-(3(dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone
22	 2-Amino-6-(4-methoxyphenyl)pyrimidine-4yl)(7-chloro-10-(3(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone
23	 2-Amino-6-(2-hydroxyphenyl)pyrimidine-4yl)(7-chloro-10-(3(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure
24	 2-Amino-6-(3-nitrophenyl)pyrimidine-4yl)(7-chloro-10-(3(*N,N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone
25	 2-Amino-6-*p*-tolylpyrimidine-4yl)(7-chloro-10-(3(*N,N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone
26	 2-Amino-6-(furan-2-yl)pyrimidine-4yl)(7-chloro-10-(3(*N,N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)methanone

filtered, washed with a small quantity of water and re-crystallized from ethyl acetate.

2.2.4. General procedure for preparation of varies Azo dye: ***(GC1-GC2)***

5-(10-(3-(*N,N*-Dimethylamino) propyl-10*H*-phenothiazine-3-yl)-1,3,4-thiadiazole-2-amine (0.01 mol, 3.83 g), sodium nitrite (0.01 mol, 0.68 g) and Con. HCl (0.1 mol, 3.6 ml) were placed in a 50 ml Erlenmeyer flask, immerse the flask in an ice bath and maintained the temperature below 0–5 °C. Diazotization took place and formation of phenyl diazonium chlorde. Coupling reagents were allowed to interact with phenyl diazonium chloride at 4 °C. The separated azo dye was filtered, washed thoroughly with a small portion of cold water and re-crystallized from ethyl acetate and n-hexane.

2.2.5. General procedure for preparation of various Schiff base: ***(GC3–GC7)***

An equimolar mixture of aromatic aldehydes (0.01 mol) and 5-(10-(3-(*N,N*-Dimethylamino)propyl-10*H*-phenothiazine-3-yl)-1,3, 4-thiadiazole-2-amine (0.01 mol, 3.83 g) were added gradually to 10 ml of GAA contained two-necked round bottom flask. Then it was refluxed at 80 °C for 6 h with constant stirring. The precipitated solid was filtered, washed with 50 ml of water and re-crystallized from ethanol. The azo dye and Schiff base compounds were synthesised according to the reported procedure [15] (Fig. 3).

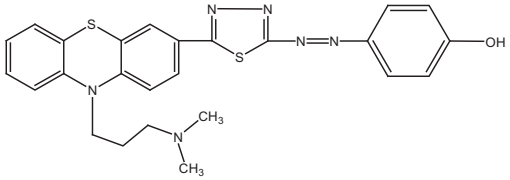
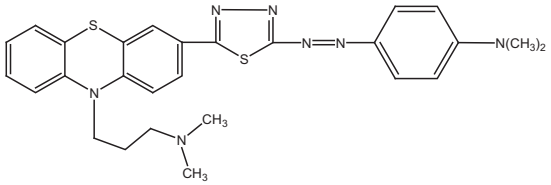
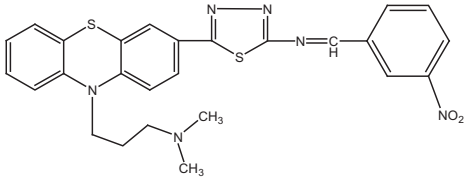
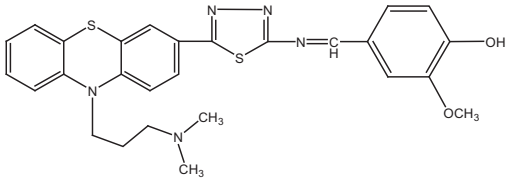
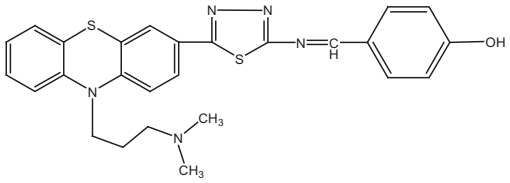
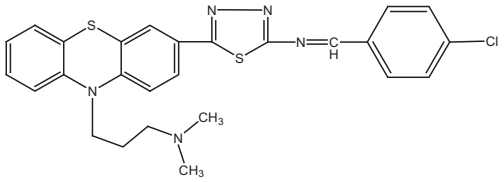
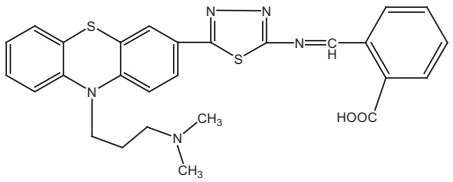
2.2.6. Synthesis of 1-(4-(4-Chlorophenylamino)phenyl)ethanone (Scheme II)

4-Chlorobenzene amine (0.01 mol, 1.27 g), *p*-chloroacetophenone (0.01 mol, 1.54 g), potassium carbonate (0.01 mol, 1.38 g) and 0.63 g of copper wire were dissolved in 30 ml of DMF contained round bottom flask of about 250 ml capacity. The mixture was stirred for 30 min. The flask was fitted with a reflux condenser and heated at 80 °C for 4 h with occasional shaking. The crude 4-(Phenylamino) benzoic acid was filtered, washed with little cold water and crystallized from ethyl acetate [16].

2.2.7. Synthesis of 1-(7-Chloro-10H-Phenothiazine-3-yl)ethanone

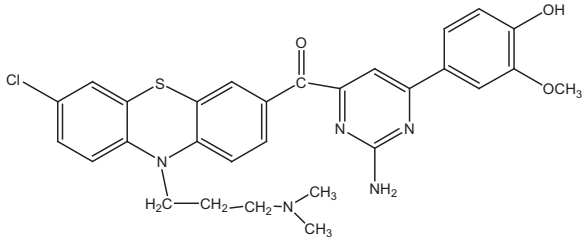
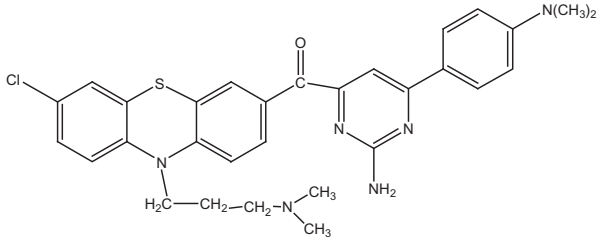
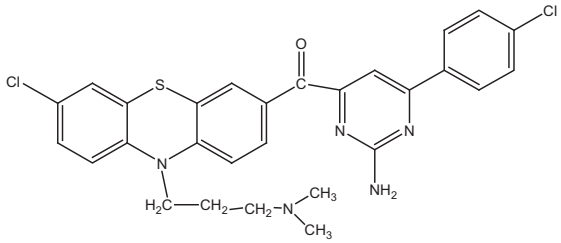
To a solution of 1-(4-(4(Chlorobenzeneamino) phenyl) ethanone (0.01 mol, 2.45 g) in rectified spirit, sulphur (0.01 mol, 0.3 g) and iodine (0.01 mol, 1.26 g) were placed in a two-necked flask fitted with a reflux condenser. The mixture was subjected to reflux on a water bath around 3 h with occasional shaking. The separated 1-(7-Chloro-10*H*-Phenothiazine-3-yl) ethanone was filtered, washed with distilled water, dried and crystallized from acetone [17].

Table 2
Structure and name of synthesised compounds.

Compound name	Structure of synthesised compounds
GC1	 (E)-4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl phenol
GC2	 (E)-4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)-*N*,*N*-dimethylbenzenamine
GC3	 *N*-(3-Nitrobenzylidene)-5-(10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-amine
GC4	 4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-ylimino)methyl)-2-methoxyphenol
GC5	 4-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-ylimino)methyl)phenol
GC6	 *N*-(4-Chlorobenzylidene)-5-(10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-amine
GC7	 2-((5-(10-(3-(*N*,*N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-ylimino)methyl)benzoic acid

(*continued on next page*)

Table 2 (*continued*)

Compound name	Structure of synthesised compounds
GC8	 2-Amino-6-(4-hydroxy-3-methoxyphenyl)pyrimidine-4-yl)(7-chloro-10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3-yl) methanone
GC9	 2-Amino-6-(4-(*N*,*N*-dimethylamino)phenyl)pyrimidine-4-yl)(7-chloro-10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3-yl) methanone.
GC10	 2-Amino-6-(4-chlorophenyl)pyrimidine-4-yl)(7-chloro-10-(3-(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3-yl) methanone

2.2.8. Synthesis of 1-(7-Chloro-10-(3(N,N-dimethylamino)propyl)-10H-phenothiazine-3-yl) ethanone

A mixture of 1-(7-Chloro-10*H*-Phenothiazine-3-yl) ethanone (0.01 mol, 2.75 g), 3-Chloro *N, N*-dimethyl propanamine (0.01 mol, 1.21 ml), sodium hydride (0.01 mol, 0.239 g) in DMF was kept in a reflux condenser and heated on a water bath at 80 °C for 3 h. The resulting solution was cooled and separated 1-(7-Chloro-10-(3(*N*,*N*-dimethylamino)propyl)-10*H*-phenothiazine-3-yl) ethanone and washed with small quantities of cold water and re-crystallized from ethyl acetate [18,19].

*2.2.9. General procedure for preparation of Chalcone derivatives (**GC8–GC10**)*

Dissolve 1-(7-Chloro-10-(3(*N*,*N*-Dimethylamino)-10*H*-phenothiazine-3-yl)ethanone (0.01 mol, 3.60 g) and aromatic aldehyde (0.01 mol) in a 20 ml ethyl alcohol contained 10% potassium hydroxide, stirring with a glass rod for 7 h or until it became a clear solution. Guanidine (0.01 mol, 0.59 g) in *N, N*-dimethylformamide was added and stirred. Then the mixture was refluxed for 2 h with continuous stirring. The hot solution was cooled to room temperature and the separated compound was filtered, washed with a portion of cold water and re-crystallized from ethyl alcohol and ethyl acetate [20,21] (Fig. 4).

2.3. X-ray crystallography

X-ray crystallography is a tool used to investigate the three-dimensional picture of the atomic and molecular structure of a crystal by using X-ray light, which has wavelengths of 1 angstrom (10^{-8} cm). The beam of X-ray strikes a crystal and causes the diffraction of light into specific directions, fed into the computer and using a mathematical equation to calculate the position of every atom in the crystallized molecule.

3. Results

3.1. Molecular docking

Each ligand potency has been identified from moldock score (Table 3), rerank score (Table 4) and hydrogen bonding score (Table 5) after successful interaction with DA. The potent anti-psychotic agents are perfectly docked to a hydrophobic and the hydrophilic center of the target (DA) and were exhibiting excellent score as compared to standard drugs. The key amino-acids responsible for the binding site of DA were found to be Asp 123, Lue110, Asp 111, Asp 109, Asn 112, Thr 66, Asn 70 Lys 76, Glu 74, Arg 79, Asn 75 and Glu 84 residues etc., Each compound had shown a significant affinity towards DA due to the formation of a salt bridge between the ligand and some hydrophobic amino acid residue (Asp111 and Asp123), hydrogen bond formation with hydrophilic amino acid (Asn112, Glu74) and π-π interaction with some hydrophobic amino acid residue (Phe67). Here, compound **GC8** and **GC2** had exhibited admirable moldock score as compared to other derivatives due to presence of electron releasing groups such as OH, OCH_3 and $N(CH_3)_2$ etc., The overall decreasing order of dopamine-inhibiting action of the entire synthesised analogues

Fig. 2. Different steps involved in docking process.

was found to **GC8 > GC2 > GC1 > GC7 > GC3 > GC5 > GC4 > GC9 > GC6 > GC10**. The interaction of each ligand and DA was shown in Fig. 5.

3.2. X-ray crystallography determination and refinement

Diffraction data of the compound GC8 were collected from 8031 reflections using X calibur CCD diffractometer equipped with area detector and graphite monochromator (λ = 0.71835). The dimension of the crystal employed for data collection was 0.28 × 0.28 × 0.25 mm at 30% probability with selected bond length and bond angle. The refinement was carried out by full-matrix least squares using SHELXL 97 [22]. The complete detail of data collections, condition and different parameters of refinement process were furnished in Table 6. The ORTEP view of the crystal, bond length and bond angle were shown in Fig. 6 and Table 7.

3.3. Spectral data

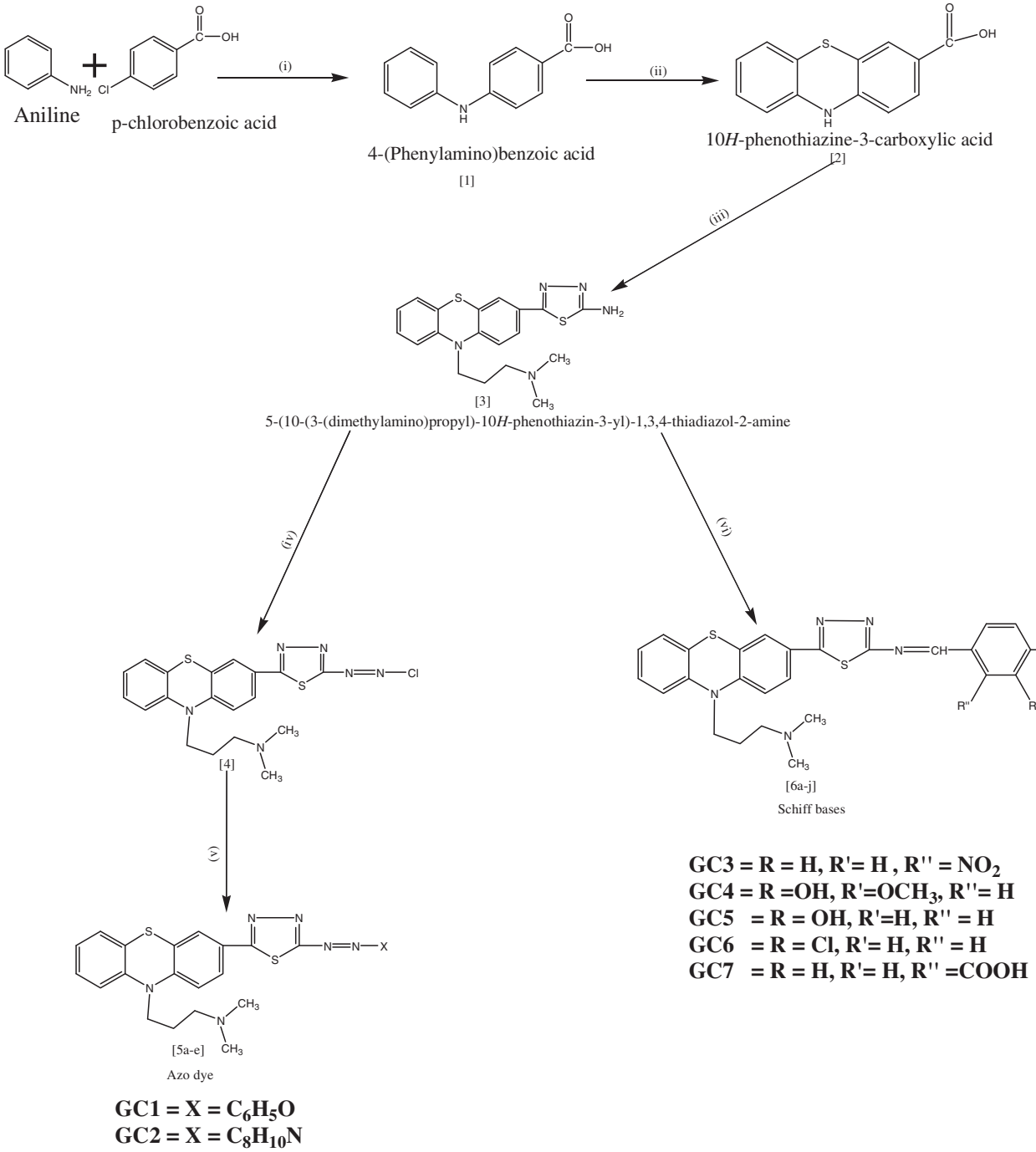
3.3.1. Preparation of azo dye and Schiff base derivative: ***(GC1-GC7)*** *[15]*

3.3.1.1. Preparation of 2-Amino-6-(3-hydroxy-4-methylphenyl) pyrimidine-4-yl)(7-chloro-10-(3-(N,N-dimethylamino)propyl)-10H-phenothiazine-3-yl)methanone: ***(GC8)***. Molecular formula – $C_{29}H_{28}ClN_5O_3S$; Yield (86%); M.P – 217 °C; IR (νmax, cm^{-1}): 3045 (Ar-H str), 1426(Ar-C str), 1503 (C═N), 1167(C—N), 1663(C═O), 3405 (OH), 1245 (OCH_3), 3492 (NH_2), Cl (6 2 3); ^1H NMR ($CDCl_3$, δppm, 500 MHz): δ1.30–1.62 (q, 2H, CH_2-H, *J* = 13.6 Hz), δ2.52–2.64(s, 6H, $N(CH_3)_2$), δ2.67–2.85 (t, 2H, CH_2-H, *J* = 4.7 Hz), δ2.91–3.18(t, 2H, CH_2-H, *J* = 7.8 Hz), δ3.71–3.78(s, 3H, OCH_3-H), δ4.15–4.28(s, 2H, NH_2-H), δ5.10–5.27(s, 1H, OH-H) δ6.46–6.63(t, 1H, Ar-H, *J* = 15.8 Hz), δ6.72–6.79(s, 1H, Ar-H), δ6.85–6.94(s, 1H, Ar-H), δ6.97–7.08(s, 1H, Ar-H), δ7.09–7.22(m, 2H, Ar-H), δ7.43–7.48(s, 1H, Ar-H), δ7.53–7.60(s, 1H, Ar-H), δ8.06–8.15(s, 1H, Ar-H), δ8.20–8.37(s, 1H, Ar-H); Mass(*m*/*z*)-561(38) [M^+], 563(15)[M^++2], 489 (42), 345 (100), 203 (55), 85 (50), 58 (37); Anal. Calcd for $C_{29}H_{28}ClN_5O_3S$ (561): C, 61.97; H, 5.02; N, 12.46; S, 5.70; O, 8.54; Cl, 6.31. Found: C, 61.82; H, 5.14; N, 12.26%.

3.3.1.2. Preparation of 2-Amino-6-(4-methylphenyl) pyrimidine-4-yl) (7-chloro-10-(3-(N,N-dimethylamino)propyl)-10H-phenothiazine-3-yl)methanone: ***(GC9)***. Molecular formula – $C_{30}H_{31}ClN_6OS$; Yield (79%); M.P – 222 °C; IR (νmax, cm^{-1}): 3093 (Ar-H str), 1452(Ar-H ben), 1514 (C═N), 1240(C—N), 1670(C═O), 3426 (NH_2), Cl (6 1 2); ^1H NMR ($CDCl_3$, δppm, 500 MHz): δ1.27–1.48 (q, 2H, CH_2-H, *J* = 15.1 Hz), δ2.53–2.71(s, 6H, $N(CH_3)_2$), δ2.72–2.85 (t, 2H, CH_2-H, *J* = 9.8 Hz), δ2.87–2.95(s, 6H, $N(CH_3)_2$), δ3.00–3.22(t, 2H, CH_2-H, *J* = 9.8 Hz), δ4.15–4.29(s, 2H, NH_2-H), δ6.42–6.58(m, 3H, Ar-H), δ6.59–6.87(m, 2H, Ar-H), δ6.88–7.00(t, 1H, Ar-H, *J* = 15.1 Hz), δ7.06–7.21 (d, 2H, Ar-H, *J* = 15.5 Hz), δ7.23–7.31(s, 1H, Ar-H), δ7.37–7.44(s, 1H, Ar-H), δ7.46–7.63(d, 1H, Ar-H, *J* = 16.8 Hz); Mass (*m*/*z*)-558 (40) [M^+], 560(15) [M^++2], 528(22), 514 (33), 345 (1 0 0), 203 (53), 197 (49), 59 (33); Anal. Calcd for $C_{30}H_{31}ClN_6OS$ (5 5 8): C, 64.44; H, 5.59; N, 15.03; S, 5.73; O, 2.86; Cl, 6.35. Found: C, 64.38; H, 5.62; N, 15.10%.

3.3.1.3. Preparation of 2-Amino-6-(4-chlorophenyl) pyrimidine-4-yl) 10-(3-(N,N-dimethylamino) propyl)-10H-phenothiazine-3-yl)methanone: ***(GC10)***. Molecular formula – $C_{28}H_{25}Cl_2N_5OS$; Yield (71%); M.P – 217 °C; IR (νmax, cm^{-1}): 3187 (Ar-H str), 1473(Ar-H ben), 1514 (C═N), 1257(C—N), 1665(C═O), 3436 (NH_2), Cl (7 3 5); ^1H NMR ($CDCl_3$, δppm, 500 MHz): δ1.20–1.44 (q, 2H, CH_2-H, *J* = 14.8 Hz), δ2.47–2.62(s, 6H, $N(CH_3)_2$), δ2.64–2.82 (t, 2H, CH_2-H, *J* = 10.1 Hz), δ2.83–3.02(t, 2H, CH_2-H, *J* = 10.5 Hz), δ4.12–4.29(s, 2H, NH_2-H) δ6.52–6.67(d, 2H, Ar-H, *J* = 13.2 Hz), δ6.70–6.91(t, 2H, Ar-H, *J* = 8.1 Hz), δ6.94–7.20(m, 1H, Ar-H), δ7.22–7.34(t, 1H, Ar-H, *J* = 9.6 Hz), δ7.37–7.52(m, 2H, Ar-H), δ7.54–7.64(m, 2H, Ar-H), δ7.68–7.82(d, 1H, Ar-H, *J* = 15.1 Hz); Mass (*m*/*z*)-549 (56) [M^+], 551(19)[M^++2], 505 (1 0 0), 476 (31), 317 (61), 203 (42), 59 (29); Anal. Calcd for $C_{28}H_{25}Cl_2N_5OS$ (5 4 9): C, 61.09; H, 4.58; N, 12.72; S, 5.82; O, 2.91; Cl, 12.88. Found: C, 61.15; H, 4.46; N, 12.80%. FT-IR, ^{1}H NMR and Mass spectroscopy of compound GC8 was shown in Figs. 7–9.

3.3.1.4. Mass fragmentation of compound ***(GC8)***. The mass spectral decomposition mode of the prepared 2-Amino-6-(3-hydroxy-4-methyl phenyl) pyrimidine-4-yl) (7-chloro-10-(3-(*N,N*-dimethylamino) propyl)-10*H*-phenothiazine-3-yl)methanone (GC8) has been investigated by electrospray ionization mass spectrometry (ESI-MS). The mass spectrum of compound GC8 showed the molecular ion (M^+)/(molecular isotope ion (M^++2) peaks (*m*/*z*) at 561/563 corresponding to the molecular formula of $C_{29}H_{28}ClN_5O_3S$ (Fig. 10). The molecular ion of *m*/*z* 561 has been fragmented and gives a peak at 488 *m*/*z*. The peak at *m*/*z* 488 underwent fragmentation and produced a daughter ion at *m*/*z* 345.It further loss of the certain group of atoms such as $C_6H_{11}ClS$, C_7H_3NO and C_2H_4 to give a peak at *m*/*z* 203, 85 and 56 respectively. The ESI mass spectral fragmentation pathway of compound GC8 was discussed with typical example and other chalcone derivatives displayed similar mass spectral fragmentation pattern.



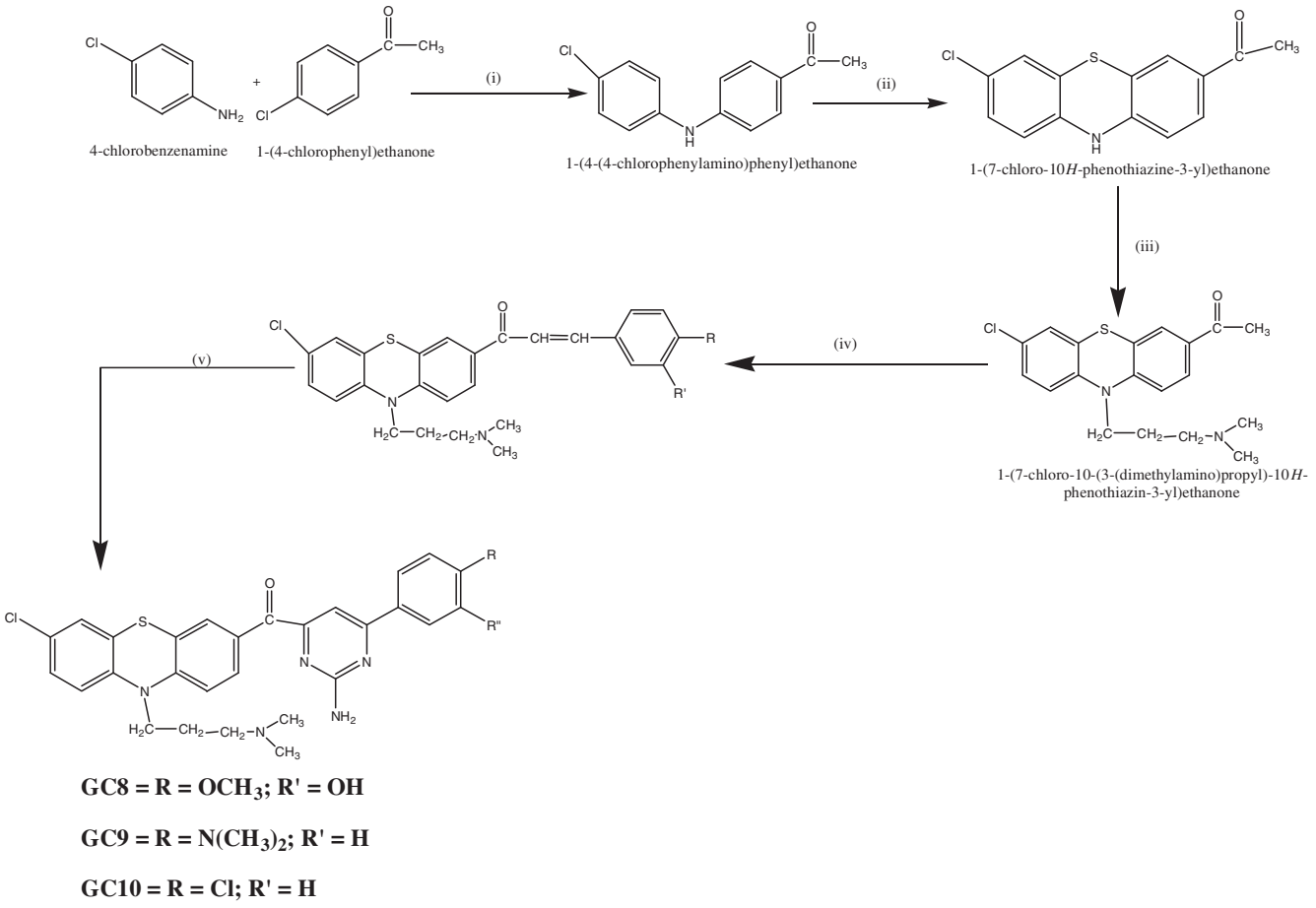
Reagent and condition: (i) potassium carbonate, copper wire, DMF, 4 hours reflux (ii) Sulphur, iodine, 3 hours reflux (iii) Thiosemicarbazide, phosphorus oxychloride, 3 chloro-N,N-dimethyl propanamine, sodium hydride, DMF, 7 hours reflux (iv& v) Sodium nitrite, Con HCl, coupling reagents, 0-5°C(vi) Aromatic aldehyd, glacial acetic acid, 6 hours reflux

Fig. 3. Synthesis of novel series of Azodye **(GC1–GC2)** and Schiff bases **(GC3–GC7)** derivatives.

4. Biological evaluation

4.1. Catalepsy test

Catalepsy is defined as the inability of an animal to correct its abnormal posture after a particular period of time [23]. It can accurately predict by haloperidol-induced catalepsy metallic bar test [24]. To test the catalepsy, Wistar rats of either sex with an average weight of 200–225 g were selected, grouped (standard, test and control) and placed into different cages. Before starting the experiment protocol has been approved by the institutional animal ethics committee at GIET School of pharmacy, Rajahmundry, India (GSP/PY/04/2015). Each group maintained six animals under standard lab conditions. Haloperidol was administered 1 mg/kg, IP route to induce catalepsy in standard group of animals. Synthesised compounds (7.5 mg/kg and 15 mg/kg) were also given simultaneously to test group of animals. The animal front paws had been placed on a metallic bar, which elevated at 10 cm above the base of the cage. If the animal maintained abnormal posture more than 30 s called as catalepsy. The response observed at the various intervals like 0, 30, 60, 120, 180 and 240 min etc.,



Reagent and condition: (i) Potassium carbonate, copper wire, DMF, 4 hours reflux (ii) Sulphur, iodine, 3 hours reflux (iii) Thi osemicarbazide, phosphorus oxychloride, 3 chloro-N,N-dimethyl propanamine, sodium hydride, DMF, 7 hours reflux (iv) Aromatic aldehyd, ethanol, potassium hydroxide, 7 hours stirring, (v) Gu anidine, 2 hours reflux,

Fig. 4. Synthesis of novel series of Chalcone (**GC8**–**GC10**) derivatives.

Table 3
In-silico docking analysis of GC1–GC10 on dopamine D2 receptor (DA) ranking based on MolDock Score.

Name	Ligand	MolDock Score	Re rank Score	HBond
GC8	**GC8**	**−131.74**	**−100.047**	**−9.19985**
GC2	GC2	−125.962	−88.3381	0
GC1	GC1	−125.306	−92.3564	−4.97835
GC7	GC7	−120.894	−95.0643	−1.31705
GC3	GC3	−120.529	−88.0914	−3.40765
GC5	GC5	−116.655	−87.1045	−1.27654
GC4	GC4	−116.105	−81.3478	−3.67334
GC9	GC9	−115.915	−86.9129	−4.2662
Paliperidone	**Paliperidone**	**−115.616**	**−78.6045**	**−4.77099**
Pimozide	**Pimozide**	**−112.327**	**−74.7795**	**−3.38109**
Amisulpride	**Amisulpride**	**−107.705**	**−73.6292**	**−3.59328**
GC6	GC6	−106.161	−58.463	−3.2839
GC10	GC10	−104.659	−76.7722	−0.533093
Risperidone	**Risperidone**	**−100.451**	**−70.9697**	**0**
Aripiprazole	**Aripiprazole**	**−98.0063**	**−59.924**	**0**
Chlorpromazine	**Chlorpromazine**	**−88.7884**	**−63.6353**	**−2.24238**
Haloperidol	**Haloperidol**	**−71.0573**	**−44.1023**	**−4.09793**
Clozapine	**Clozapine**	**−70.8065**	**−30.9689**	**−1.42074**

Bold values indicate the comparison of Compound GC8 MVD Score (Moldock score, Rerank score and HBond) VS Commercial anti-psychotic agents.

4.2. Catalepsy score

The cataleptic score of test, standard and control batch of Wister rats had taken at the interval of 30, 60, 120, 180 and 240 min. The score is significantly increased with the standard and test compounds in between 60 min and 120 min and the highest catalepsy score was achieved after 120 min of administration of standard and test compounds. This evidence proves that our test compounds were the severely block the dopaminergic neurotransmission in the striatum effectively to show anti-psychotic activity. Among the synthesised analogues, compound 2-Amino-6-(3-hydroxy-4-methylphenyl) pyrimidin-4-yl) (7-chloro-10-(3-(*N, N*-

Table 4
In-silico docking analysis of GC1–GC10 on dopamine D2 receptor (DA) ranking based on Rerank score.

Name	Ligand	MolDock Score	Rerank Score	HBond
GC8	**GC8**	**−131.74**	**−100.047**	**−9.19985**
GC7	GC7	−120.894	−95.0643	−1.31705
GC1	GC1	−125.306	−92.3564	−4.97835
GC2	GC2	−125.962	−88.3381	0
GC3	GC3	−120.529	−88.0914	−3.40765
GC5	GC5	−116.655	−87.1045	−1.27654
GC9	GC9	−115.915	−86.9129	−4.2662
GC4	GC4	−116.105	−81.3478	−3.67334
Paliperidone	**Paliperidone**	**−115.616**	**−78.6045**	**−4.77099**
GC10	GC10	−104.659	−76.7722	−0.533093
Pimozide	**Pimozide**	**−112.327**	**−74.7795**	**−3.38109**
Amisulpride	**Amisulpride**	**−107.705**	**−73.6292**	**−3.59328**
Risperidone	**Risperidone**	**−100.451**	**−70.9697**	**0**
GC6	GC6	−95.1296	−67.8326	−3.04164
Chlorpromazine	**Chlorpromazine**	**−88.7884**	**−63.6353**	**−2.24238**
Aripiprazole	**Aripiprazole**	**−98.0063**	**−59.924**	**0**
Haloperidol	**Haloperidol**	**−71.0573**	**−44.1023**	**−4.09793**
Clozapine	**Clozapine**	**−63.4029**	**−42.8125**	**0**

Bold values indicate the comparison of Compound GC8 MVD Score (Moldock score, Rerank score and HBond) VS Commercial anti-psychotic agents.

Table 5
In-silico docking analysis of GC1–GC10 on human dopamine D2 receptor (DA) ranking based on H bond.

Name	Ligand	MolDock Score	Rerank Score	*HBond*
GC8	**GC8**	**−119.655**	**−90.0228**	**−09.19985**
GC1	GC1	−125.306	−92.3564	−4.97835
Paliperidone	**Paliperidone**	**−115.616**	**−78.6045**	**−4.77099**
GC9	GC9	−115.915	−86.9129	−4.2662
Haloperidol	**Haloperidol**	**−71.0573**	**−44.1023**	**−4.09793**
GC4	GC4	−105.318	−72.9724	−3.70795
Amisulpride	**Amisulpride**	**−107.705**	**−73.6292**	**−3.59328**
GC3	GC3	−120.529	−88.0914	−3.40765
Pimozide	**Pimozide**	**−112.327**	**−74.7795**	**−3.38109**
GC6	GC6	−106.161	−58.463	−3.2839
GC10	GC10	−97.4928	−74.954	−3.17228
GC5	GC5	−108.666	−79.2343	−2.3231
Chlorpromazine	**Chlorpromazine**	**−88.7884**	**−63.6353**	**−2.24238**
Aripiprazole	**Aripiprazole**	**−85.4159**	**−40.5995**	**−2.02837**
Clozapine	**Clozapine**	**−70.8065**	**−30.9689**	**−1.42074**
GC7	GC7	−116.268	−82.2282	−1.37673
GC2	GC2	−114.849	−25.4314	−0.90971
Risperidone	**Risperidone**	**−87.1754**	**−56.9585**	**−0.13061**

Bold values indicate the comparison of Compound GC8 MVD Score (Moldock score, Rerank score and HBond) VS Commercial anti-psychotic agents.

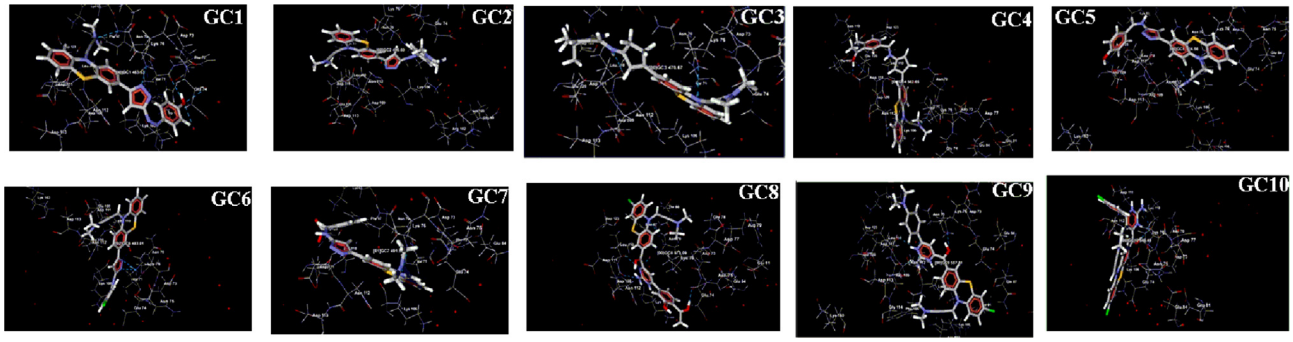


Fig. 5. Interaction between synthesised compounds and human Dopamine D2 receptor (DA).

dimethylamino) propyl)-10*H*-phenothiazin-3-yl) methanone **(GC8)** induced the highest catalepsy period at the various time intervals such as 60, 120, 180 and 240 min. Compound GC8 (7.5 mg/kg and 15 mg/kg) significantly reduces the level of normal dopamine and generated catalepsy as similar to that of haloperidol treated animals with the percentage of 17.3%,41.6%,37.0%,35.8% and 39.5%, 57.1%, 54.0%, 51.8% respectively at various time interval such as 60, 120, 180 and 240 min. Effects of behavioural assessment in haloperidol/synthesised compound administered rat by metallic bar test were shown in Table 8 and Fig. 11.

5. Discussion

The route of prepared analogues was depicted in the synthetic scheme (Figs. 1 & 2) outlines the preparation part of the synthesised analogues. The Azodye compounds were prepared by

Table 6
Crystal data and structural refinement for compound **GC8**.

Identification code	Compound **GC8**
Empirical formula	$C_{29}H_{28}ClN_5O_3S$
Formula weight	561
Crystal system	Monoclinic
Crystal size (mm)	0.28 × 0.28 × 0.25
Temperature (K)	296
Space group	P 21/n
Wave length (A°)	0.71835
Volume (A^{o3})	1687.46 (12)
Absorption coefficient (mm^{-1})	0.058
F (ooo)	1017
Z	4
Calculated density (Mg/m^3)	1.572
Theta range for data collection	2.81°–29.47°
Index range	$-9 \le h \le 13$ $-12 \le k \le 14$ $-14 \le l \le 10$
Measured reflections	8031
Independent/observed reflections	3185
Data/restraints/parameters	13352/1/528
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.168
Final R indices [I > 2 σ (I)]	R1 = 0.0548, ωR2 = 0.1428
R indices [all data]	R1 = 0.0149, ωR2 = 0.1784
Extinction coefficient	0.03819 (12)
Largest diff. Peak and hole ($e{\cdot}Å^3$)	0.314/−0.232

Table 7
Bond distances and bond angle of **GC8** compound.

Bond distances (Å)		Bond angle (°)	
C10A-C13A	1.562(3)	C10A-C13A-C14A	113.7(2)
C13A-C14A	1.507(8)	C22A-O03A-C24A	117.5(8)
C13A-O01A	1.236(5)	C20A-C21A-O02A	119.7(2)
C21A-O02A	1.427(5)	N01A-C25A-C26A	124.2(3)
C22A-O03A	1.473(2)	C25A-C26A-C27A	116.4(5)
O03A-C24A	1.412(3)	C26A-C27A-N05A	126.8(3)
N01A-C25A	1.406(2)	C27A-N05A-C28A	124.1(8)
C25A-C26A	1.519(3)	C27A-N05A-C29A	127.4(5)
C26A-C27A	1.502(5)	N05A-C28A-C29A	121.4(5)
C27A-N05A	1.418(6)		
N05A-C28A	1.424(3)		
N05A-C29A	1.405(2)		

performing an interaction between 5-(10-(3-(*N*,*N*-Dimethylamino) propyl-10*H*-phenothiazine-3-yl)-1,3,4-thiadiazole-2-amine, sodium nitrite, Con. HCl and the different coupling reagents. The Schiff base derivatives were prepared by condensation of 5-(10-(3-(*N*,*N*-Dimethylamino) propyl-10*H*-phenothiazine-3-yl)-1,3,4-th iadiazole-2-amine and different aromatic aldehydes. The derivatives of Chalcone were prepared from Claisen-Schmidt condensation reaction between 1-(7-Chloro-10-(3-(*N*,*N*-dimethylamino)-10*H*-Phenothiazine-3-yl) ethanone, different aldehyde and quanidine. The FT-IR and ^{1}H NMR spectrum of synthetic analogues were shown peaks due to different groups present in the analogues. In FT-IR spectrum, strong bands at the region of 704, 735, 623, 612, 1502, 1306, 1210, 1245, 3457, 3364, 3414, 3405, 1725, 2854, 3436, 3492, 3426, 1663, 1670, 1665 cm^{-1} could be attributed to the chloro, nitro, methoxy, hydroxyl, carboxylic, amino and carbonyl group respectively. The aryl ring was raised stretching peak in between 3187–3016 cm^{-1} and 1473–1403 cm^{-1}. A strong absorption peak at 1662–1649 cm^{-1} is due to the presence of the azomethine group (—C═NH). The number of proton present in the synthetic compounds was identified by ^{1}H NMR spectroscopy from the chemical shift. The spectra showed a quintet at δ 1.20–1.90 ppm corresponding to methylene proton (CH_2), a triplet at δ 2.52–3.47 ppm corresponding to methylene proton (CH_2), a singlet at δ 2.24–2.71 ppm corresponding to *N*,*N*-dimethyl amine proton (*N*-$(CH3)_2$); a singlet at δ 3.64–3.70 ppm corresponding to a methoxy proton (OCH_3); a singlet at δ 4.11–4.28 ppm corresponding to amine proton (NH_2); a singlet at δ 4.95–5.27 ppm corresponding to hydroxyl proton (OH)); a singlet at δ 6.72–8.37 ppm corresponding to aromatic protons(Ar-H); a doublet at δ 6.42–8.62 ppm corresponding to aromatic protons (Ar-H); a triplet at δ 6.46–8.23 ppm corresponding to aromatic protons (Ar-H); a multiplet at δ 6.25–7.65 ppm corresponding to aromatic protons (Ar-H) and a singlet at δ 7.94–8.71 ppm corresponding to azomethine proton (C═NH), a singlet at δ 10.95–11.05 ppm corresponding to a carboxylic acid proton (COOH). The synthesised compound molecular mass was confirmed by the Shimadzu mass spectrometer. The result of the antipsychotic activity of synthetic compounds was depicted in Table 8. It indicates catalepsy time of experimental animals after administration of haloperidol/synthesised compounds at the interval of 30, 60, 120, 180 and 240 min. Compound with electron donating groups on aryl ring showed remarkable antipsychotic activity over the unsubstituted and electron withdrawing group oriented compound.

6. Conclusion

The study stated that easy way of synthesis of novel Azodye/Schiff base/Chalcone derivatives and act as a powerful template for making a potent antipsychotic agent through molecular

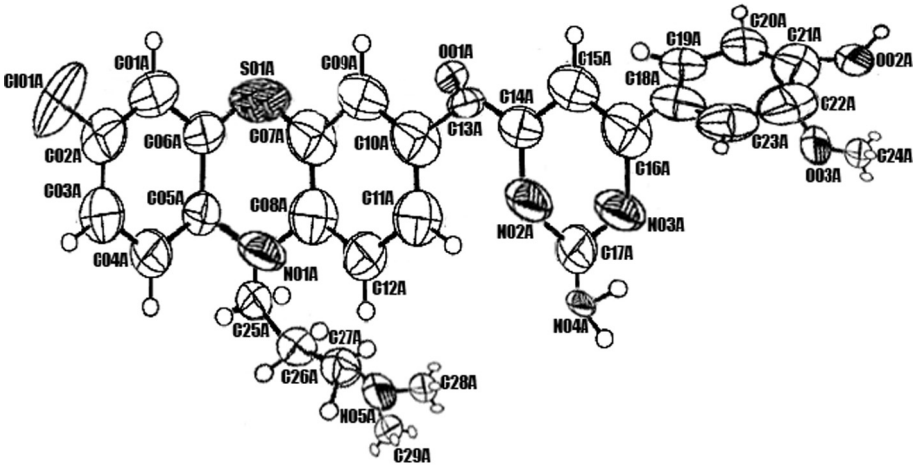


Fig. 6. Compound **GC8** ORTEP view at 30% probability level.

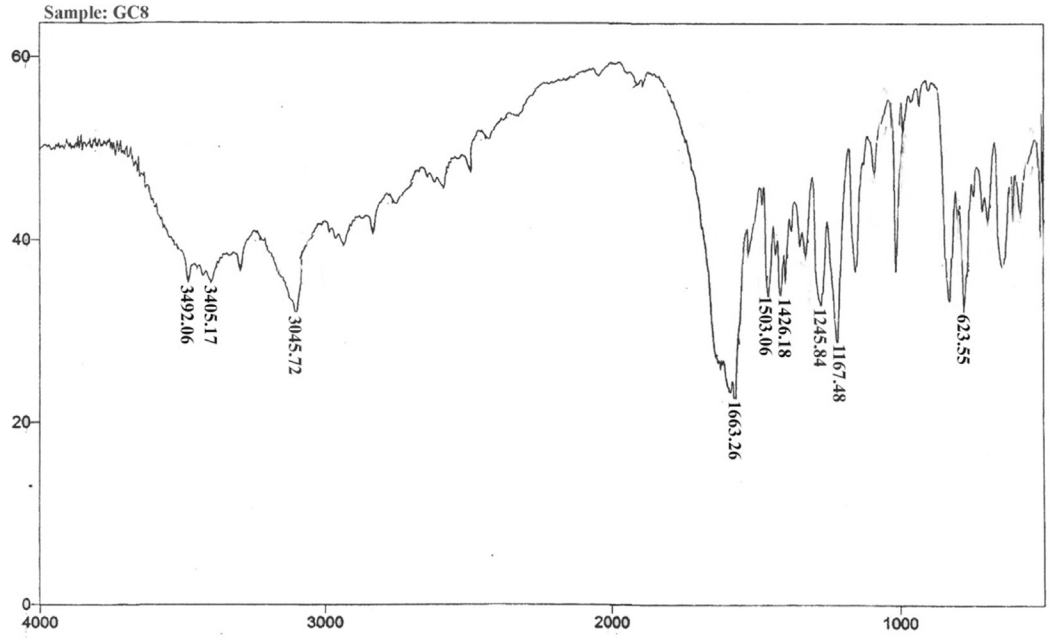


Fig. 7. FT-IR spectrum of synthesised compound (**GC8**).

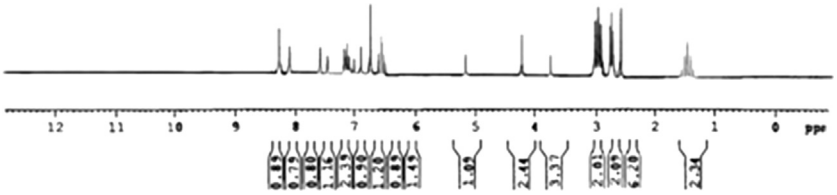


Fig. 8. ^{1}H NMR spectrum of synthesised compound (**GC8**).

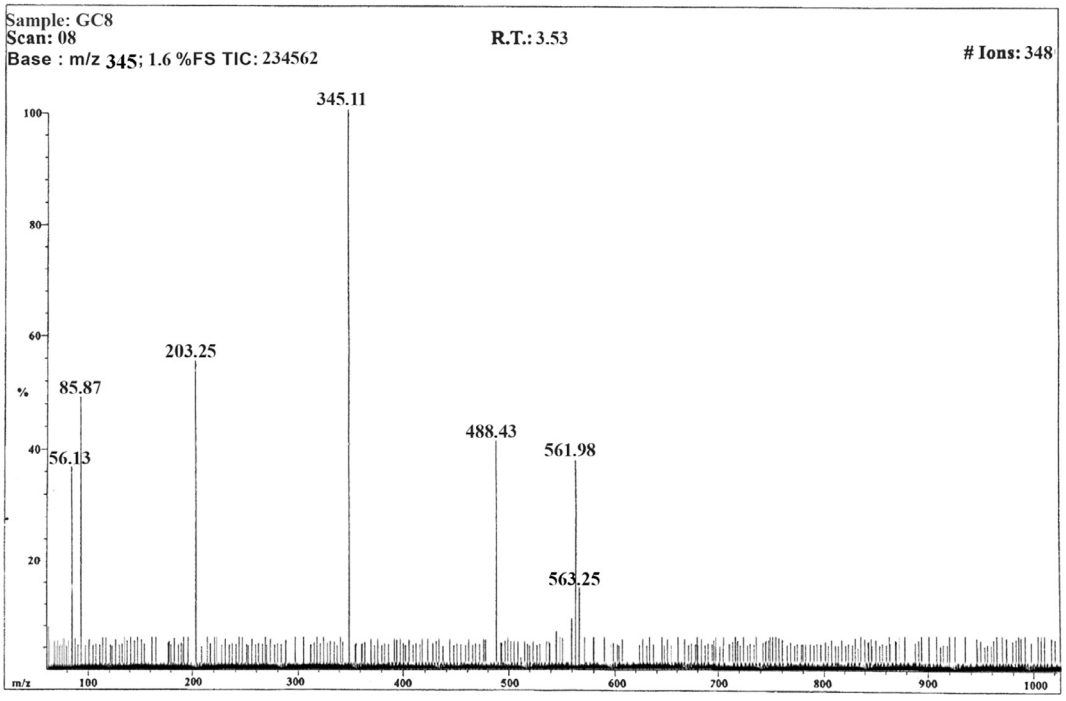


Fig. 9. Mass spectrum of synthesised compound (**GC8**).

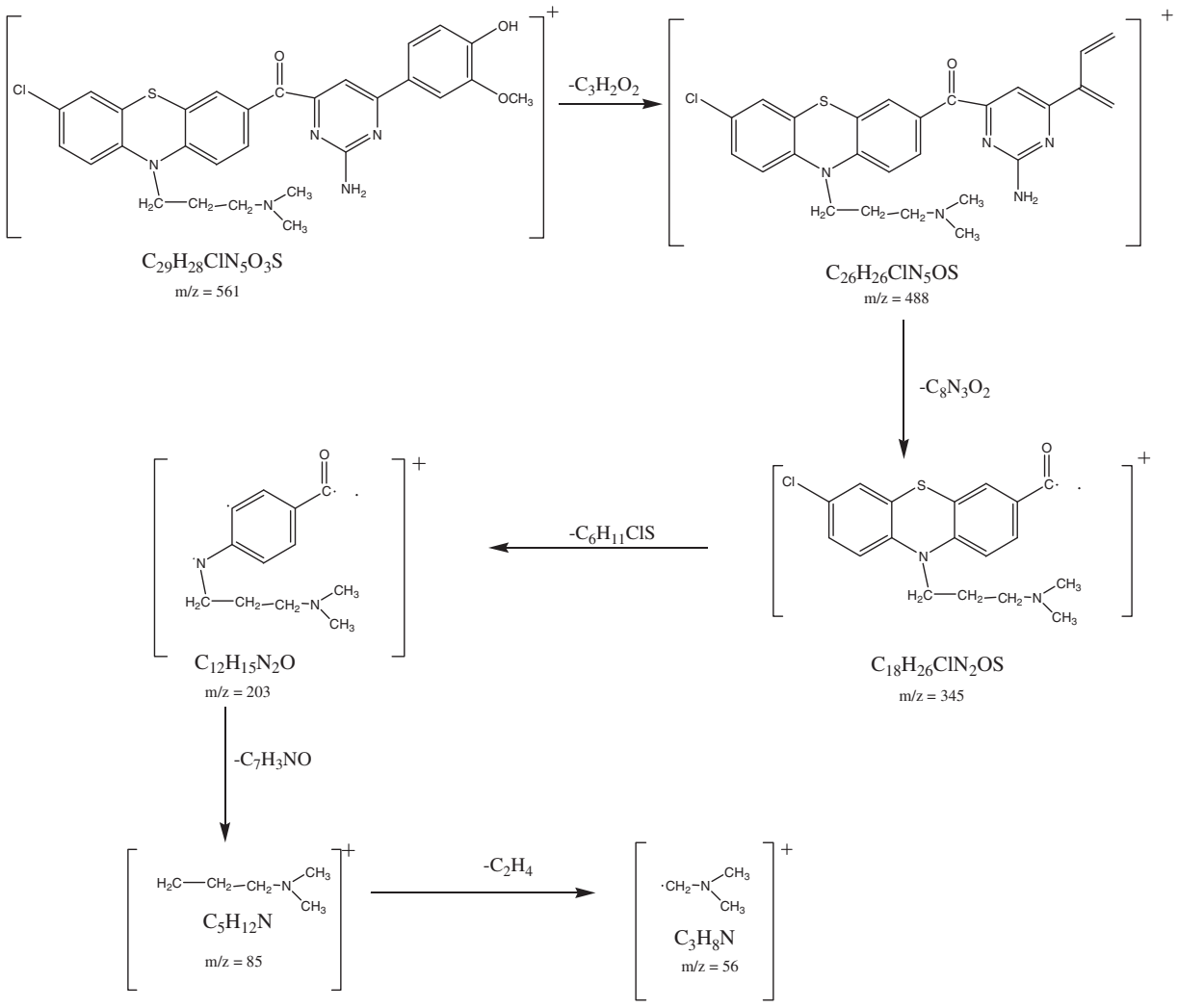


Fig. 10. Positive ion ESI mass spectrum of compound **GC8**.

Table 8
Effect of anti-psychotic activity of synthesised compounds in Wistar rats.

Drug treatment	30 min		60 min		120 min		180 min		240 min	
	7.5 mg	15 mg	7.5 mg	15 mg	7.5 mg	15 mg	7.5 mg	15 mg	7.5 mg	15 mg
GC1	69.773 ± 0.417	39.452 ± 0.364	125.035 ± 2.754*	89.864 ± 3.045*	101.052 ± 4.013**	74.156 ± 3.572**	87.164 ± 3.027*	65.821 ± 5.174*	54.264 ± 3.842	41.742 ± 2.845
GC2	68.502 ± 0.182	37.371 ± 0.742	121.271 ± 2.471*	88.428 ± 3.062**	99.863 ± 3.372*	73.095 ± 3.026**	86.653 ± 3.853*	64.749 ± 4.028**	53.054 ± 3.026*	40.162 ± 2.063*
GC3	73.975 ± 0.174	43.771 ± 0.165	128.656 ± 2.874*	97.112 ± 3.853*	114.658 ± 3.629**	82.367 ± 3.952**	95.452 ± 2.967*	73.672 ± 3.453*	59.386 ± 3.652	46.755 ± 2.425
GC4	76.917 ± 0.152	46.911 ± 0.167	131.372 ± 2.110**	102.115 ± 2.088*	123.094 ± 2.654*	91.576 ± 3.081**	105.424 ± 2.113*	83.163 ± 2.113*	69.243 ± 2.671	51.022 ± 2.537
GC5	75.834 ± 0.174	44.829 ± 0.056	129.763 ± 2.387**	99.156 ± 3.056*	118.214 ± 2.764**	86.548 ± 3.542	99.401 ± 2.273**	80.172 ± 2.942*	63.052 ± 2.621*	49.014 ± 2.210
GC6	80.151 ± 0.212	49.832 ± 0.547	135.022 ± 2.985*	113.201 ± 2.914**	136.167 ± 2.097*	99.017 ± 4.943**	119.265 ± 2.267**	93.134 ± 2.324*	76.136 ± 2.567	58.263 ± 2.374
GC7	71.801 ± 0.482	41.743 ± 0.548	126.548 ± 2.631**	94.176 ± 3.642*	109.372 ± 3.065**	77.843 ± 3.127**	91.864 ± 3.547*	69.658 ± 4.153*	56.761 ± 3.052	42.751 ± 2.092
GC8	66.512 ± 0.154	36.163 ± 0.127	119.275 ± 2.053*	87.146 ± 3.267**	98.175 ± 3.953**	72.356 ± 3.093**	85.182 ± 3.163*	62.651 ± 4.028**	52.614 ± 3.031*	39.761 ± 2.165*
GC9	78.247 ± 0.763	47.927 ± 0.131	133.037 ± 2.243**	107.258 ± 2.932*	130.113 ± 2.871**	97.036 ± 4.022**	112.253 ± 2.372**	88.108 ± 2.076*	72.861 ± 2.325*	55.763 ± 2.121

(*continued on next page*)

Table 8 (*continued*)

Drug treatment	30 min		60 min		120 min		180 min		240 min	
	7.5 mg	15 mg	7.5 mg	15 mg	7.5 mg	15 mg	7.5 mg	15 mg	7.5 mg	15 mg
GC10	82.351 ± 0.178	51.942 ± 0.512	137.022 ± 2.985*	121.534 ± 2.354**	141.132 ± 2.127*	103.017 ± 4.943**	124.224 ± 2.065*	96.104 ± 2.322*	77.133 ± 2.431	61.244 ± 2.021
Haloperidol (1 g)	85.742 ± 0.546**		144.654 ± 3.172**		168.159 ± 3.572**		135.438 ± 4.743**		81.852 ± 5.563**	
Blank	0.0 ± 0.0		0.0 ± 0.0		0.0 ± 0.0		0.0 ± 0.0		0.0 ± 0.0	

** P < .05.
* P < 0.01as compared to blank and standard respectively. Statistical analysis – One way ANOVA.

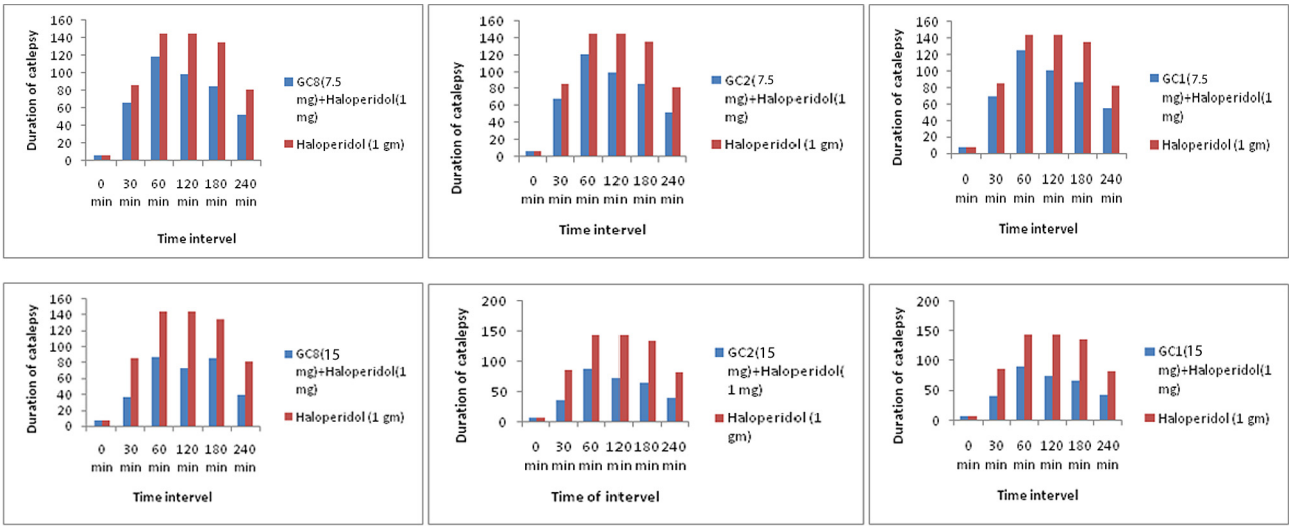


Fig. 11. Effects of synthesised compounds (**GC8**, **GC2** and **GC1**) induced catalepsy in Wistar rats.

docking and haloperidol-induced catalepsy metallic bar test. Most of the compounds were perfectly docked to a hydrophobic and hydrophilic centre of the human dopamine D2 receptor with the support of key amino-acids like Asp 123, Leu110, Asp 111, Asp 109, Asn 112, Thr 66, Asn 70 Lys 76, Glu 74, Arg 79, Asn 75 and Glu 84 etc., these amino acid residues are allowing the molecules to bind firmly with human dopamine D2 receptor by forming a salt bridge, hydrogen bond and π-π interaction with the ligand. Therefore, the binding energy of each ligand lies between the ranges of 09.19985–0.533093 kcal/moles (Table 4). In addition to that each compound had been shown an excellent anti-psychotic activity in a haloperidol-induced catalepsy metallic bar test. The results found are firmly similar to docking study. Among the various analogues, compound **GC8** and **GC2** were bound more effectively to the receptor through electron donating groups such as OH, OCH_3 and N $(CH_3)_2$ present in the part of the molecular structure and offered excellent antipsychotic activity. Therefore, there is a need for further study of the above-mentioned compounds for the development of the novel atypical antipsychotic agent.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ejbas.2017.10.003.

References

[1] Qian Y, Chen M, Forssberg H, Diaz Heijtz R. Genetic variation in dopamine-related gene expression influences motor skill learning in mice. Genes Brain Behav 2013;12:604–14.
[2] Song J, Kim J. Degeneration of dopaminergic neurons due to metabolic alterations and parkinson's disease. Front Aging Neurosci 2016;8:1–11.
[3] Bradley SJ, Tobin AB. Design of next-generation g protein–coupled receptor drugs: linking novel pharmacology and *in vivo* animal models. Annu Rev Pharmacol Toxicol 2016;56:535–59.
[4] Gurevich EV, Gainetdinov RR, Gurevich VV. G protein-coupled receptor kinases as regulators of dopamine receptor functions. Pharmacol Res 2016;111:1–16.
[5] Lanzenka MF, Legakis LP, Negus SS. Opposing effects of dopamine D1- and D2-like agonists on intracranial self-stimulation in male rats. Exp Clin Psychopharmacol 2016;24. 193-05.
[6] Cho DI, Min C, Jung KS, Cheong SY, Zheng M, Cheong SJ, et al. The *N*-terminal region of the dopamine D_2 receptor, a rhodopsin-like GPCR, regulates correct integration into the plasma membrane and endocytic routes. Br J Pharmacol 2012;166:659–75.
[7] Dreyer JK. Three mechanisms by which striatal denervation causes breakdown of dopamine signaling. J Neuro Sci 2014;34:12444–56.
[8] Meng XY, Mezei M, Cui M. Computational approaches for modeling gpcr dimerization. Curr Pharm Biotechnol 2014;15. 996-06.
[9] Kumar S, Wahi SK, Singh R. Synthesis and preliminary pharmacological evaluation of 2-[4-(aryl substituted) piperazin-1-yl]-N-phenylacetamides: potential antipsychotics. Trop J Pharm Res 2011;10:265–72.
[10] Jaszczyszyn A, Gsiorowski K, Swiatek P, Malinka W, Cieoelik-Boczula K, Petrus J, et al. Chemical structure of phenothiazines and their biological activity. Pharmacol Rep 2012;64:16–23.
[11] Mao YM, Zhang MD. Augmentation with antidepressants in schizophrenia treatment: benefit or risk. Neuropsychiatr Dis Treat 2015;11:701–13.
[12] Singh SP, Deb CR, Ahmed SU, Saratchandra Y, Konwar BK. Molecular docking simulation analysis of the interaction of dietary flavonols with heat shock protein 90. J Biomed Res 2016;30:67–74.
[13] Korb O, Ten BT, Victor Paul Raj FR, Keil M, Exner TE. Are predefined decoy sets of ligand poses able to quantify scoring function accuracy. J Comput Aided Mol Des 2012;26:185–97.
[14] Cen G, Herold JM, Kireev D. Assessment of free energy predictors for ligand binding to a methyllysine histone code reader. J Comput Chem 2012;33:659–66.
[15] Gopi C, Sastry VG, Dhanaraju MD. Synthesis, spectroscopic characterization, X-ray crystallography, structural activity relationship and antimicrobial activity

of some novel 4- (5-(10-(3-N,N-dimethylamino) propyl)-10H-phenothiazine-3-yl) -1,3,4-thiadiazole-2yl) Azo dye/Schiff base derivatives. Future J Pharma Sci 2017. xx: 1-11.
[16] Kumar R, Singh M, Prasad DN, Silakari OM, Sharma S. Synthesis and chemical characterization of 9-anilinoacridines. Chem Sci Trans 2013;2:246–50.
[17] Satyanarayana B, Muralikrishna P, Kumar DR, Ramachandran D. Preparation and biological evaluation of phenothiazine derivatives. J Chem Pharma Res 2013;5:262–6.
[18] Pooja M, Suroor AK, Surajpal V, Ozair A. Synthesis, characterization and antimicrobial activity of new thiadiazole derivative. Bull Korean Chem Soc 2010;31:2345–50.
[19] Morak-Mlodawska B, Pluta K, Zimecki M, Jelen M, Artym J, Kocieba M. Synthesis and selected immunological properties of 10-substituted 1,8-diazaphenothiazines. Med Chem Res 2015;24:1408–18.
[20] Kumar N, Drabu S, Shalini K. Synthesis and pharmacological screening of 4,6-substituted di-(phenyl) pyrimidin-2-amine. Arab J Chem 2017;10:S877–80.
[21] Kant R, Kumar D, Agarwa D, Gupta RD, Tilak R, Awasthi SK, Agarwal A. Synthesis of newer 1,2,3-triazole linked chalcone and flavone hybrid compounds and evaluation of their antimicrobial and cytotoxic activities. Eur J Med Chem 2016;113:34–49.
[22] Ganapayya B, Jayarama A, Sankolli R, Hathwar VR, Dharmaprakash SM. Synthesis, growth, and characterization of a new NLO material3-(2,3-dimethoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one. J Mol Struct 2012;1007:175–8.
[23] Bhattacharjee N, Paul R, Giri A, Borah A. Chronic exposure of homocysteine in mice contributes to dopamine loss by enhancing oxidative stress in nigrostriatum and produces behavioral phenotypes of Parkinson's disease. Biochem Biophys Rep 2016;6:47–53.
[24] Nishchal BS, Rai S, Prabhu MN, Ullal SD, Rajeswari S, Gopalakrishna HN. Effect of Tribulus terrestris on Haloperidol-induced Catalepsy in Mice. Indian J Pharm Sci 2014;76:564–7.