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DESIGN SYNTHESIS AND EVALUATION OF ANTI-DEPRESSANT ACTIVITY OF SOME NEW DERIVATIVES OF PHENOTHIAZINE

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ABSTRACT

This study was aimed at the synthesis of fused Phenothiazine derivatives containing heterocyclic moiety. The synthesized compounds were tested for their preliminary tests, physical constants, TLC, IR, ^{1}H-NMR Spectra and CHN analysis confirmed the structures of the final compounds. Antidepressant activity of all the synthesized compounds was evaluated by despair swim test by using *Sprague Dawley Rats.* Standard drug Imipramine was used as the control. In the despair swim test, all the synthesized derivatives showed antidepressant activity. Among them four Compounds (A_1, A_8, B_1 and B_8) showed significant antidepressant activity comparing with control drug imipramine. These results are useful for the further investigation in the future.

KEYWORDS: Antidepressant activities, Despair swim test, Phenothiazine and *Sprague Dawley Rats.*

1. INTRODUCTION

Depression is a significant contributor to the global burden of disease and affects people in all communities across the world. Today, depression is estimated to affect 350 million people. The World Mental Health Survey conducted in 17 countries found that on average about 1 in 20 people reported having an episode of depression in the previous year. Depressive disorders often start at a young age; they reduce people's functioning and often are recurring. For these reasons, depression is the leading cause of disability worldwide in terms of total years lost due to disability. The demand for curbing depression and other mental health conditions is on the rise globally.

A depressant, or central depressant, is a drug or endogenous compound that lowers neurotransmission levels, which is to depress or reduce arousal or stimulation, in various areas of the brain.[1]

10 *H*-phenothiazine Heterocyclic compounds plays important role in medicinal chemistry, nitrogen containing heterocyclic with a sulfur atom are considered as an important class of compounds in medicinal chemistry because of their interesting diversified biological application.[3-7] 10H-Phenothiazine (PTZ) is a tricyclic aromatic compound linked via bridges of sulfur and nitrogen. In this ring system it consists of two benzene rings Ortho fused to 1, 4 – thiazine ring. It is also called as Dibenzothiazine, Thiodiphenylamine. [8-10] Phenothiazine derivatives are very useful precursors for the development of molecules of biological interest. [12-13] Phenothiazine derivatives are considered to be important chemical synthons of various physiological significances and pharmaceutical utilities. They possess a variety of biological activity including anti-imlamatory, antitubercular, anticonvalscent, antimicrobial and antidepressant activities.

2. MATERIALS AND METHODS

The chemicals which are used in this study were supplied by E. Merck and LOBA Co. All the reactions were monitored by TLC using silica gel G. The melting point determinations were done by using in open glass capillary using Kjeldahl flask containing liquid paraffin. IR spectra were recorded on the (JASCO) FTIR-Spectrophotometer using KBr pellets. 1HNMR spectra were recorded on BRUKER AVANCE II 400 NMR spectrometer in DMSO using tetra methyl silane (TMS) as internal reference.

Procedure for Scheme

Synthesis of 4-(Cyclohexylidene) Benzoic acid

0.01mole of Para amino benzoic acid (PABA) was reflux with 0.01mole of Cyclohexanone in 250ml RBF. After which the resulting reaction mixture was kept in ice cold water. The resulting precipitate was collected, dried and recrystallized from ethanol.

Synthesis of ethyl 4-(cyclohexylidene amino) benzoate

0.01mole of above compound was reflux with 5 ml of an ethanol for 1 hour. After which the resulting reaction mixture was allow to cool in ice bath and add few drops of conc. H_2SO_4. The resulting precipitate was collected and dried.

Synthesis of 4-(cyclohexylidene amino) benzohydrazine

0.01mole of above compound was reflux with 0.01mole of hydrazine hydrate for 2 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried and recrystallized from ethanol.

Synthesis of 10H-phenothiazine-3-carbohydrazine

0.01mole of above compound was reflux with 0.01mole of sulphur powder for 2 hour at 260-290^{0}c. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried and recrystallized from ethanol.

Synthesis of N'-[(E)-substituted phenyl methylidene]-10h-phenothiazine-2-carbohydrazide

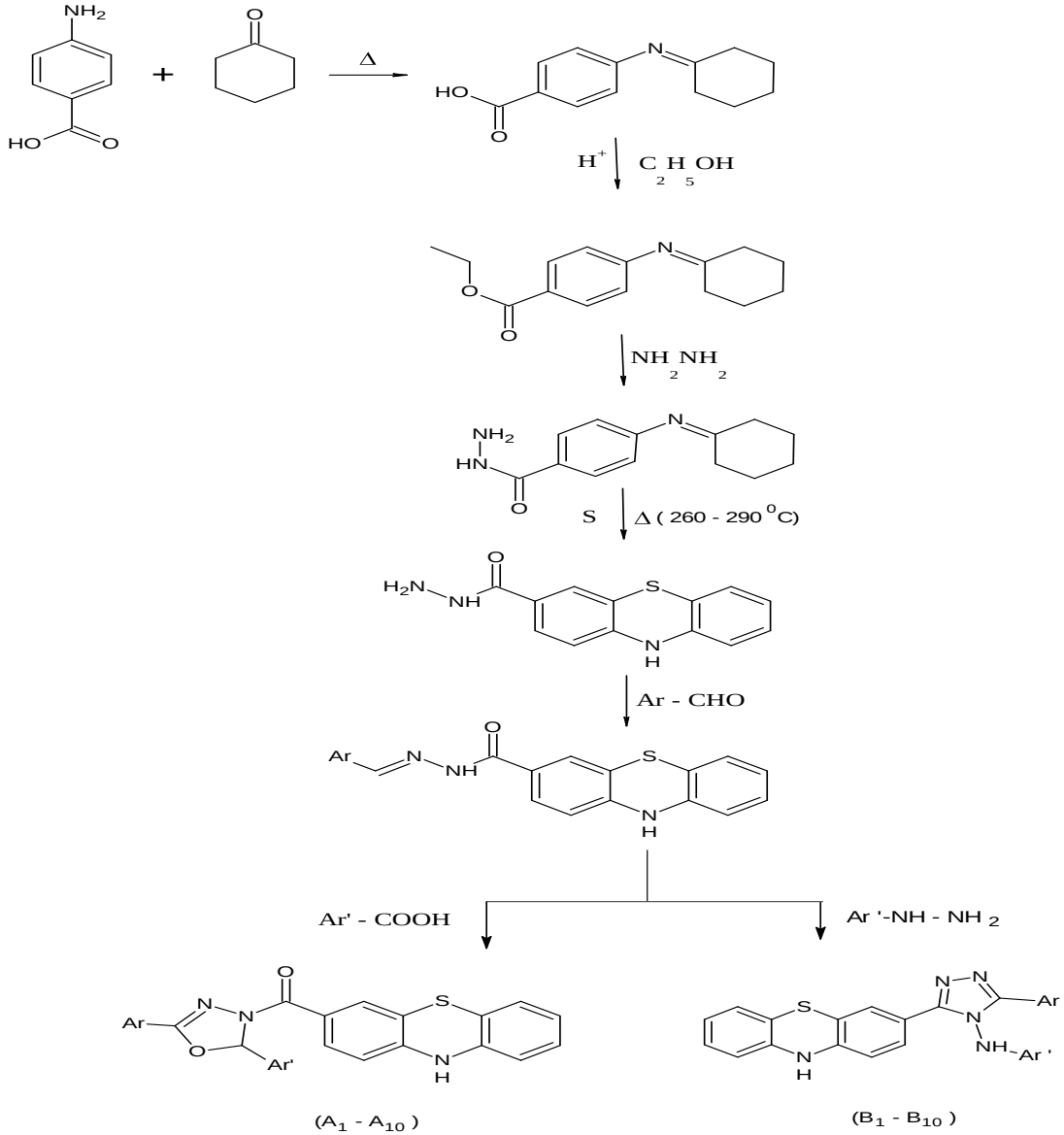
0.01mole of above compound was reflux with 0.01mole of substituted aromatic aldehyde for 2 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried and recrystallized from ethanol. (Compound E).

Synthesis of (2,5-disubtituted-1,3,4-oxadiazol-3(2H)-yl)(10Hphenothiazin-2-yl) methanone

0.01mole of above compound was reflux with 0.01mole of aromatic acid for 3 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried and recrystallized from ethanol. (A_1-A_{10}).

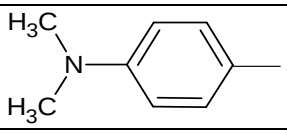
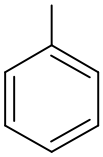
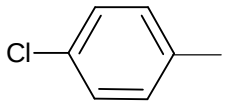
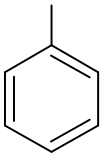
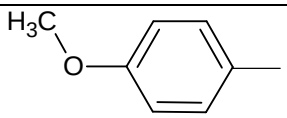
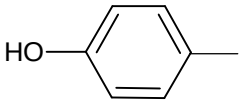
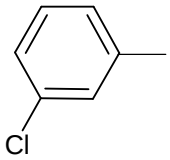
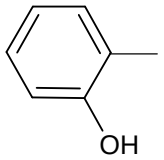
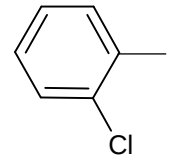
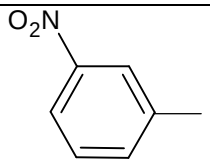
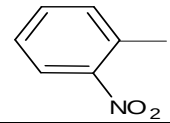
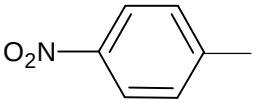
Synthesis of 3-(10H-phenothiazin-2-yl)-N,5-diphenyl-4H-1,2,4-triazol-4-amine

0.01mole of compound of 5th step was reflux with 0.01mole of phenylhydrazine for 3 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried and recrystallized from ethanol. (B_1-B_{10}).



Scheme.

Table 1: FOR COMPOUNDS A_1-A_{10}

Comp. Code	Ar	Ar'	Comp. Code	Ar	Ar'
A_1			A_6		
A_2			A_7		
A_3			A_8		
A_4			A_9		
A_5			A_{10}		

3. ANTIDEPRESSANT ACTIVITY[14-17]

Behavioural despair was proposed as a model to test for antidepressant activity by Porsolt et al. (1977, 1978). It was suggested that mice or rats forced to swim in a restricted space from which they cannot escape are induced to a characteristic behaviour of immobility. This behaviour reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression.

Behavioral despair or forced swim test (FST) was proposed as a model to test antidepressant activity by Porsolt et al. (1977) It was suggested that mice or rats when forced to swim in restricted space from where they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression. The behavioral despair test is employed to assess the antidepressant activity of synthesized derivatives. Sprague-Dawley rats of 200-270 gm in a group of two each were used and on the first day of the experiment (pretest session), rats were individually placed in a cylindrical recipient (Plexiglass cylinder) of dimensions (diameter, 10 cm; height, 25 cm) containing 10 cm of water 25°C. The animals were left to swim for 6 min before being removed, dried and returned to their cages. The procedure was repeated 24 h later, in 5 min swim session (test session). The synthesized compounds (25 mg kg-1) and imipramine, as a reference antidepressant drug (25 mg kg-1) were suspended in a 0.5% aqueous solution of Na CMC (Corboxy Methyl Cellulose). The drugs were given by gavage in a standard volume of 10ml/kg body weight, 1 h prior to the test. Control animals received 0.5% aqueous solution of Na CMC (Corboxy Methyl Cellulose). This test was performed after 1 hr, 5 hrs and 24 hrs of dose administration. For individual animal video recording was made. Then, the rats were dropped individually into the Plexiglass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. An immobility time is the time spent by rat floating in water without struggling, making only those moment necessary to keep the head above the water. The total duration of immobility was recorded during the last 5 min of the 6 min test session.

3.2 EVALUATION

Duration of immobility is measured in controls and animals treated with various doses of a test drug or standard. Antidepressant drugs, but also stimulants like amphetamine and caffeine, reduce duration of immobility. Dose-responses can be evaluated.

Table 2: Antidepressant activity data of the compounds synthesized compounds.(A_1-A_{10}).

Compound code.	Immobility time (sec.)			% Immobility		
	1 Hr	5 Hr	24 Hr	1 Hr	5 Hr	24 Hr
A_1	152.5	162	162.5	88.66	88.76	83.33
A_2	166.5	171	167.5	96.80	93.69	85.89
A_3	160.5	164	173	93.31	89.88	88.71
A_4	162	161.5	171	94.18	88.49	87.69
A_5	163.5	164	172.5	95.05	89.86	88.46
A_6	154.5	161	166	89.82	88.21	85.12
A_7	145	155.5	167.5	84.30	85.20	85.89
A_8	149	151	157.5	86.62	82.73	80.76
A_9	162.5	163	165	94.47	89.31	84.61
A_{10}	151	157.5	161	87.79	86.30	82.56
Control	172	182.5	195	100	100	100
Imipramine std.	136.5	150.5	154.5	79.41	82.49	79.26

Table 3: Antidepressant activity data of the compounds synthesized compounds.(B_1-B_{10}).

Compound code.	Immobility time (sec.)			% Immobility		
	1 Hr	5 Hr	24 Hr	1 Hr	5 Hr	24 Hr
B_1	161.5	161.5	171	94.15	88.56	87.82
B_2	157.5	161	168.5	91.56	88.21	86.41
B_3	175	174.5	183.5	101.84	95.58	94.01
B_4	142.5	156	163.5	82.84	85.47	83.84
B_5	144	158.5	163.5	83.72	86.84	83.84
B_6	164	164	173	95.34	89.86	88.71
B_7	145.5	158	167.5	84.59	86.57	85.89
B_8	160.5	163.5	173	93.34	89.90	88.74
B_9	169.5	178.5	184	98.54	97.80	94.35
B_{10}	151.5	156	165	88.08	85.47	84.61
Control	172	182.5	195	100	100	100
Imipramine std.	136.5	150.5	154.5	79.41	82.49	79.26

3.3 RESULT AND DISCUSSION

The synthesized of new compound where structures, yields and melting points have been given in the (Table 1). Melting points of the synthesized compounds were sharp indicating that the compounds were pure; the yield value of the compounds also suggested that the chemical methods were reliable for the synthesis of the compound. All spectral data were in accordance with assumed structure. All the synthesized compounds were subjected anti-depressant activity study by despair swim test. The imipramine was used as standard control.

Table 4: Analytical & Physicochemical data of the synthesized compounds (A_1-A_{10}).

Comp.	Mol. Formula	Mol. Wt.	M.P.°C	Yield %	Elemental analysis Found		
					C	H	N
A_1	$C_{29}H_{24}N_4O_2S$	492	350-355	65	70.71	4.91	11.37
A_2	$C_{28}H_{21}ClN_3O_3S$	479	310-315	62	70.13	4.41	8.76
A_3	$C_{27}H1_8ClN_3O_3S$	483	363-365	65	67.01	4.11	9.03
A_4	$C_{27}H_{18}ClN_3O_3S$	483	365-370	52	67.01	3.75	8.68
A_5	$C_{27}H_{18}N_4O_4S$	494	352-355	60	65.58	3.67	11.33
A_6	$C_{27}H_{18}ClN_3O_3S$	483	365-370	52	67.01	3.75	8.68
A_7	$C_{27}H_{19}N_3O_3S$	465	320-325	70	69.66	4.11	9.03
A_8	$C_{27}H_{19}N_3O_3S$	465	345-350	60	69.66	4.11	9.03
A_9	$C_{27}H_{18}N_4O_4S$	494	352-355	60	65.58	3.67	11.33
A_{10}	$C_{27}H_{18}N_4O_4S$	494	360-365	65	65.58	3.67	11.33

Table 5: Analytical & Physicochemical data of the synthesized compounds (B_1-B_{10}).

Comp.	Mol. Formula	Mol. Wt.	M.P. °C	Yield %	Elemental analysis Found		
					C	H	N
B_1	$C_{28}H_{24}N_6S$	476	350-355	60	70.50	5.00	17.59
B_2	$C_{27}H_{21}N_5OS$	463	325-330	65	69.90	4.52	15.8
B_3	$C_{27}H_{18}ClN_3O_3S$	467	363-365	55	66.67	6.84	14.93
B_4	$C_{27}H_{18}ClN_3O_3S$	467	363-365	55	66.67	6.84	14.93
B_5	$C_{26}H_{18}N_6O_2S$	478	352-355	60	65.18	3.73	17.15
B_6	$C_{26}H_{18}ClN_5OS$	467	365-370	52	66.67	6.84	14.93
B_7	$C_{26}H_{19}N_5OS$	459	320-325	62	69.42	4.20	15.53
B_8	$C_{26}H_{19}N_5OS$	449	345-350	60	69.42	4.20	15.53
B_9	$C_{26}H_{18}N_6O_2S$	478	352-355	60	65.18	3.73	17.15
B_{10}	$C_{26}H_{18}N_6O_2S$	476	350-355	65	70.15	5.00	17.59

4. SPECTRAL DATA OF SYNTHESIZED COMPOUNDS A_1-A_{10} and B_1-B_{10}

A_1: FT-IR (KBr disc) cm^{-1}: 3010.23 (Ar-CH str.), 1605.11 (-C=O str.),1510.32 (-C=N str.), 1250.36 (-C-N str.), 3250.23 (-N-H str.), 1320.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.4-7.65(14H phenyl), 3.06 (3H –CH_3), 8.90 (1H NH phenothiazine).

A_2: FT-IR (KBr disc) cm^{-1}: 3050.23 (Ar-CH str.),1615.11 (-C=O str.),1520.32 (-C=N str.), 1240.36 (-C-N str.), 3240.23 (-N-H str.), 1330.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 3.83 (3H – CH3), 7.60 (1H NH phenothiazine), 7.26 (1-C=O).

A_3: FT-IR (KBr disc) cm^{-1}: 850.22 (-C-Cl str.), 3015.23 (Ar-CH str.),1685.11 (-C=O str.),1510.32 (-C=N str.), 1250.36 (-C-N str.),3260.23 (-N-H str.), 1350.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7..21 (phenothiazine 1-C(=O)N, 7.26 -7.38 14H phenyl.

A_4: FT-IR (KBr disc) cm^{-1}: 3100.25 (Ar-CH str.), 830.23(-C-Cl str.),1635.12 (-C=O str.),1490.2 (-C=N str.), 1270.16 (-C-N str),3270.23 (-N-H str.), 1340.33 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.60 (phenothiazine 1-C(=O)N), 7.36-7.52- (14H phenyl).

A_5: FT-IR (KBr disc) cm^{-1}: 1255.36 (-N-O str.),3110.23 (Ar-CH str.),1615.11 (-C=O str.),1510.32 (-C=N str.), 1260.36 (-C-N str.),3250.23 (-N-H str.), 1370 (-N-O str.),1320.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.60 phenothiazine (1-C(=O)N, 7.21-7.52 (14H phenyl).

A_6: FT-IR (KBr disc) cm^{-1}: 3050.23 (Ar-CH str.),1605.11 (-C=O str.),1520.32 (-C=N str.), 1240.36 (-C-N str.), 3250.23 (-N-H str.), 1320.32 (-C-O str.),945.20 (-C-Cl str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.60 (phenothiazine 1-C(=O)N), 7.21-7.52 (14H phenyl).

A_7: FT-IR (KBr disc) cm^{-1}: 3650.21 (-OH str.), 3010.23 (Ar-CH str.),1615.11 (-C=O str.),1500.32 (-C=N str.), 1250.36 (-C-N str.),3250.23 (-N-H str.), 1320.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.20 (phenothiazine 1-C(=O)N, 7.38-7.54 (14H phenyl), 6.85 (1H-OH).

A_8: FT-IR (KBr disc) cm^{-1}: 3020.23 (Ar-CH str.), 3600.23 (-OH str.), 1715.11 (-C=O str.),1510.32 (-C=N str.), 1250.36 (-C-N str.), 3270.23 (-N-H str.), 1320.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.85-8.21(14H phenyl), 8.50 (1H NH phenothiazine), 11.82 (1H – OH).

A_9: FT-IR (KBr disc) cm^{-1}: 3010.23 (Ar-CH str.),1680.11 (-C=O str.),1540.32 (-C=N str.), 1260.36 (-C-N str.),1340 (-N-O str.), 3250.23 (-N-H str.), 1320.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.60 (phenothiazine), 7.21-8.15- (14 H phenyl), 7.36- (H-C*C-H, H-C*C*C-H, H-C*CH*H-C).

A_{10}: FT-IR (KBr disc) cm^{-1}: 3010.23 (Ar-CH str.),1680.11 (-C=O str.),1540.32 (-C=N str.), 1260.36 (-C-N str.),1340 (-N-O str.), 3250.23 (-N-H str.), 1320.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.60 (phenothiazine), 7.21-8.15- (14 H phenyl), 7.36- (H-C*C-H, H-C*C*C-H, H-C*CH*H-C).

B_1: FT-IR (KBr disc) cm^{-1}: 3010.23 (Ar-CH str.), 1510.32 (-C=N str), 1234.36 (-C-N str),3250 (-N-H str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.6-7.65(15H phenyl), 3.06 (3H –CH_3), 8.80 (1H NH phenothiazine).

B_2: FT-IR (KBr disc) cm^{-1}: 3020.23 (Ar-CH str.), 1525.32 (-C=N str), 1234.36 (-C-N str),3260 (-N-H str.), 1320.32 (-C-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.13 (1H NH pheothiazine), 7.20 (benzene), 3.83 (3H-CH_3).

B_3: FT-IR (KBr disc) cm^{-1}: 3050.23 (Ar-CH str.), 860.22 (-C-Cl str.), 1510.32 (-C=N str), 1234.36 (-C-N str),3270 (-N-H str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.63-7.21 (14 H phenyl), 8.01- (1H NH phenothiazine), 4.30 (1H ArNH).

B_4: FT-IR (KBr disc) cm^{-1}: 3040.23 (Ar-CH str.), 1500.32 (-C=N str), 840.23(-C-Cl str.), 1234.36 (-C-N str),3260 (-N-H str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.63-7.21 (14 H phenyl), 8.01- (1H NH phenothiazine), 4.30 (1H ArNH).

B_5: FT-IR (KBr disc) cm^{-1}: 3070.23 (Ar-CH str.), 1510.32 (-C=N str), 1234.36 (-C-N str), 3280 (-N-H str.),

1255.36 (-N-O str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.63-7.21 (14H phenyl), 8.0-8.05 (2H-CH), 8.86 (1H NH phenothiazine), 4.3 (1H NH).

B_6: FT-IR (KBr disc) cm^{-1}: 3010.23 (Ar-CH str.), 1500.32 (-C=N str), 945.20 (-C-Cl str.), 1234.36 (-C-N str),3250 (-N-H str.), **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.4-7.2 (8H –phenyl), 8.50 (1H NH phenothiazine), 4.2 (1H NH).

B_7: FT-IR (KBr disc) cm^{-1}: 3040.23 (Ar-CH str.), 3650 (-OH str.), 1510.32 (-C=N str), 1234.36 (-C-N str), 3260 (-N-H str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.63-7.21 (14H phenyl), 8.11- 1H NH phenothiazine, 4.0 (1H NH), 5.35 (H-CO).

B_8: FT-IR (KBr disc) cm^{-1}: 3010.23 (Ar-CH str.), 3610 (-OH str.), 1520.32 (-C=N str), 1234.36 (-C-N str), 3260 (-N-H str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.63-7.21 (14H phenyl), 8.11- 1H NH phenothiazine, 4.0 (1H NH), 5.35 (H-CO).

B_9: FT-IR (KBr disc) cm^{-1}: 3040.23 (Ar-CH str.), 1510.32 (-C=N str), 1234.36 (-C-N str), 1320 (-N-O str.),3250 (-N-H str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.63-7.71 (15H phenyl), 8.21 (1H NH phenothiazine), 4.2 (1H NH).

B_{10}: FT-IR (KBr disc) cm^{-1}: 3010.23 (Ar-CH str.), 1510.32 (-C=N str), 1330 (-N-O str.),1234.36 (-C-N str),3250 (-N-H str.). **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 6.63-7.71 (15H phenyl), 8.21 (1H NH phenothiazine), 4.2 (1H NH).

5. QSAR

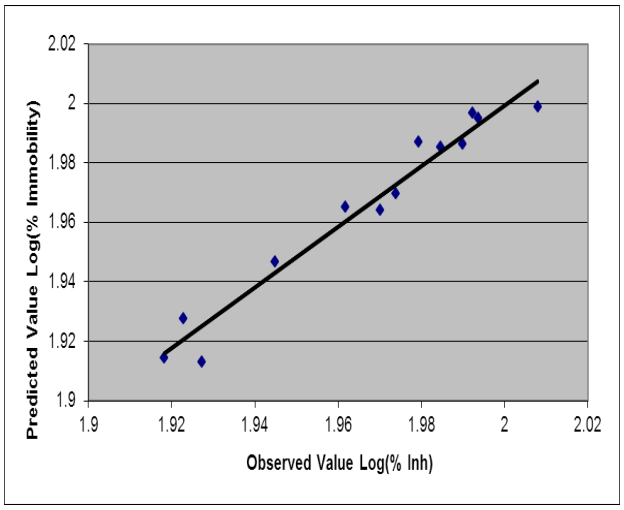
Intercorrelation between the descriptors in the final equations is less than 0.2. Best Equations correlating Log (% Immobility) with descriptors for series (A_1-A_{10} & B_1-B_{10}) generated are presented in Table no. 6.

Table 6: Equations generated between Log (% Immobility) and descriptors.

Sr. No.	Equation	N	S	R	r^2	r^2_{cv}	F
series series (A_1-A_{10} and B_1-B_{10})	Y = -0.199 *X3 - 0.229 * X1 - 1.553 * X2 - 12.575	20	0.361	0.838	0.702	0.538	14.17

Where
Y = Log (% Immobility)
X1: ClogP -
X2 = VAMP HOMO (Whole Molecule)
X3 = Dipole Moment Z Component (Whole Molecule)
X4 = Inertia Moment 2 Length (Whole Molecule)
Significance of the terms –
N= No. of Molecules
s = standard error --- less is better
r = correlation coefficient – higher is better > 0.7,
r^2cv = cross validated r^2 - higher is better > 0.5,
F Value = higher is better

Observed and predicted data and graphs are presented in Table no. 8.3.2 and Fig.9.3.1 for Series.



(**a).**

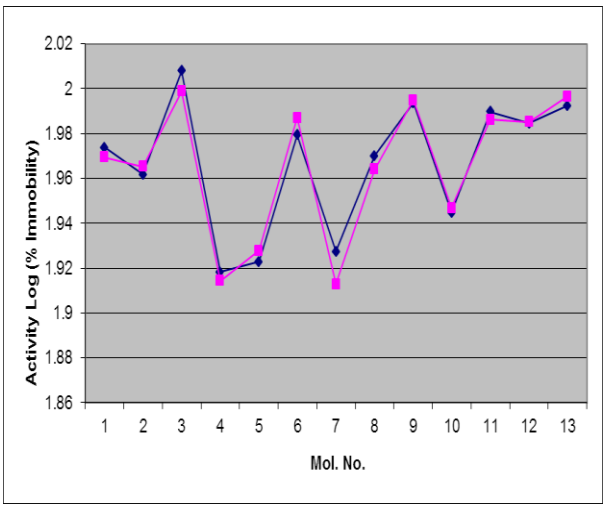


Fig 2: b) Discussion.

Fig 1: a) Correlation graph and b) Histogram of observed and predicted log (% Immobility) data for 13 compounds.

Statistical evaluation of the equations is in accepted range. The correlation coefficient is high with less standard error. The residual value and residual variance for each series also is less indicating good predictive power of models. From equation it is observed that two electronic parameters Dipole Moment Z Component (Whole Molecule) and VAMP HOMO (Whole Molecule) as well as one steric parameter Inertia Moment 2 Length (Whole Molecule) contribute (-0.227, – 1.469 and – 0.414 respectively) negatively for the activity so electron withdrawing and less bulky groups may enhance the activity (%1 Inh).

Table 7: Observed and predicted log (% Immobility) value data for 20 compounds.

Comp. No.	Observed Value	Predicted Value	Residual Value	Residual Variance
A1	1.821448	1.820758	0.00069	0.0043
A2	1.835881	1.843681	-0.0078	0.0027
A3	1.806451	1.805551	0.0009	0.0090
A4	1.828724	1.818924	0.0098	0.0009
A5	1.821448	1.814184	0.007264	0.0049
A6	1.806451	1.810851	-0.0044	0.0070
A7	1.821448	1.819752	0.001696	0.0044
A8	1.821448	1.812048	0.0094	0.0060
A9	1.821448	1.830548	-0.0091	0.0313
A10	1.821448	1.830548	-0.0091	0.0313
B1	1.828724	1.836242	-0.00752	0.0019
B2	1.813981	1.813581	0.0004	0.0035
B3	1.821448	1.813648	0.0078	0.0006
B4	1.798789	1.802989	-0.0042	0.0403
B5	1.813981	1.823181	-0.0092	0.0122
B6	1.798789	1.7921	0.006689	0.0273
B7	1.821448	1.825678	-0.00423	0.0135
B8	1.806451	1.813899	-0.00745	0.0049
B9	1.798789	1.79345	0.005339	0.0324
B10	1.798789	1.79345	0.005339	0.0324

6. DISCUSSION

All the synthesized compounds were subjected to antidepressant activity study on Sprague-Dawley rats by despair swim test. Imipramine was used as standard control. The animals show more stable levels of immobility during the last four minutes of the session. The results showed that all the compounds showed antidepressant activity. Among them three Compounds (A_1, A_8 and B_1, B_8) showed significant antidepressant activity comparing with standard control imipramine.

7. CONCLUSION

The present research work is a bonafide novel for the synthesis of phenothiazine. The extensive literature review suggests the utilization of these heterocycles as a lead in treatment of wide variety of diseases and disorders. The method of synthesis of these heterocycles starting from different substrate had been established. Around twenty newer derivatives of mentioned heterocycles were synthesized. The purity of synthesized compounds was checked with the help of TLC. The physical constants (M.P.) of the synthesized compounds were determined using open capillary method. The structures of the synthesized compounds were established by using IR, ^{1}H NMR and CHN analysis. We investigated the importance of functional group substitutions, in the structural framework of the compounds for their antidepressant activity. All compounds showed significant antidepressant activity at dose (25 mg/kg). The compounds (A_7, A_8, B_7 and B_8) showed better activity. Finally, the encouraging result of the antidepressant activity displayed by these compounds may be of interest for further structural modifications to the lead compound and next level studies in the hope of finding a new potent antidepressant prescription. From these studies, it is clear that further works needed to be done in the future for the development of clinically useful agents.

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