

# Design, Synthesis and Anti-Depressant Activity of Some Novel Coumarin Derivatives

## Abstract

The present research work deals with the synthesis, characterization and to evaluate the synthesized compound for antidepressant activity of a series of coumarin derivatives. Basic coumarin is prepared by Perkin reaction, which further reacted with aryl thiourea by cyclization reaction leads to produce 3-(2-(phenylaminothiazol-4-yl)-2H-chromen-2-one. Totally twelve compounds, were synthesized by conventional method and their purity was determined by TLC and they were characterized by IR and NMR spectroscopic methods. 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 three Compounds (A<sub>4</sub>, A<sub>5</sub> and A<sub>9</sub>) showed significant antidepressant activity comparing with control drug imipramine and some compound shows mild antidepressant activity. These results are useful for the further investigation in the future.

**Keywords:** Antidepressant activity; Coumarin; Despair swims test; Perkin reaction; Sprague dawley rat

## Research Article

Volume 2 Issue 4 - 2016

**Nachiket S Dighe\*<sup>1</sup>, Dhananjay L Tambe<sup>1</sup>,  
Amol S Dighe<sup>1</sup>, Deepak S Musmade<sup>2</sup> and  
Sunil A Nirmal<sup>3</sup>**

<sup>1</sup>Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, India

<sup>2</sup>Department of Pharmaceutical Chemistry, SRES's, Sanjivani College of Pharmaceutical Education & Research, India

<sup>3</sup>Department of Pharmacognosy, Pravara Rural College of Pharmacy, India

**\*Corresponding author:** Nachiket S Dighe, Associate Professor & HOD, Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, A/P-Loni Bk, Taluka-Rahata, Dist-Ahmednagar 413736, India (MS), Tel: 09890215729; 07720058490; Email: nachiket1111@rediffmail.com

**Received:** May 18, 2016 | **Published:** June 03, 2016

## Introduction

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration. Depressive episode involves symptoms such as depressed mood, loss of interest and enjoyment, and increased fatigability. Depression is a major psychiatric disorder affecting nearly 21% of the world population and imposes a substantial health burden on society [1,2]. 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. Antidepressants are the drugs used to treat depression thereby elevates mood and modifies the behavior. The discovery of antidepressants could be described as a 'lucky accident'. During the 1950s, while carrying out trials on a new medication for tuberculosis (TB), researchers noticed that the medication also had a mood improving effect. Half a century ago, antidepressants were discovered by serendipity. There is much more area in which the research and development for antidepressant drugs is done. But till the glob required the development of new antidepressants which have greater efficacy, absence of side effects, lack of toxicity in over dose and earlier onset of action [3].

The forced swim test is a rodent behavioral test used for evaluation of antidepressant drugs, antidepressant efficacy of new compounds, and experimental manipulations that are aimed

at rendering or preventing depressive-like states. Decrease in the duration of immobility which denotes the antidepressant activity majorly [4].

There are many coumarin and its analogs are very important chemical synthons of pharmacological acceptations and pharmaceutical use. They possess a variety of biological activities including antibacterial [5], anti-clotting and anti-thrombotic, anti-inflammatory, anti-carcinogenic [6], anti-HIV activities, hepatoprotective, antidepressant and antiplatelet aggregation activities [7]. Coumarin shows antidepressant activity by various mechanisms such as MAO inhibitors, triple reuptake inhibitor [8]. But there are much further investigation in future may be done for coumarin as antidepressant.

## Materials and Methods

### Chemistry

Loba Chemie is a manufacturer of Laboratory Reagents and Fine Chemicals for industrial use. Monitoring of reactions is done by TLC using silica gel G. The melting point was determined by using Kjeldahl flask containing liquid paraffin. FTIR-spectrophotometer (JASCO) is used for IR spectra recording using KBr pellets. BRUKER AVANCE II 400 NMR spectrometer is used for 1H NMR spectral determination in DMSO using tetra methyl silane (TMS) as internal reference.

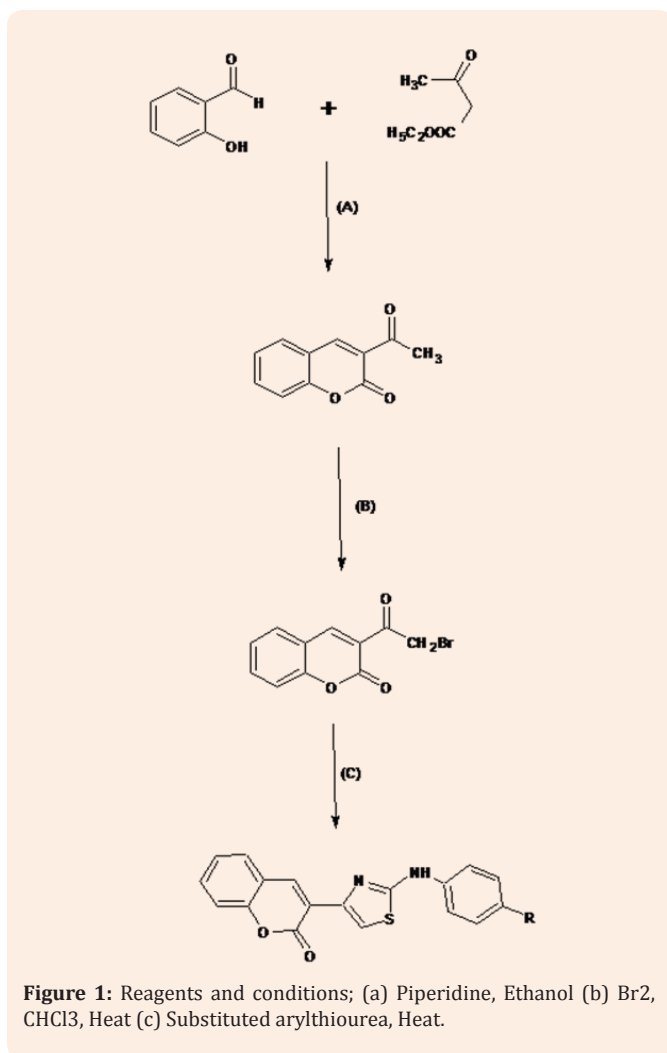
### Procedure for scheme

**Synthesis of 3-Acetyl-2H-Chromen-2-one:** A mixture of salicylaldehyde (0.5mol) and ethyl acetoacetate (0.5mol) was

stirred and cooled. To this mixture 0.5-1ml of piperidine was added with shaking. The mixture was maintained at freezing temperature for 30-45 minutes resulting in a yellow colored solid mass, which was separated out. It was recrystallized from ethanol to get the target compound (I).

**Synthesis of 3-(Bromoacetyl)-2H-Chromen-2-one:** To a solution of compound (I) (0.25mol) in 200 ml of alcohol free chloroform, bromine (0.25ml) in 25ml of chloroform was added with intermittent shaking. The mixture was warmed to decompose an addition product. The mixture was heated for 20min, cooled and filtered to get a solid mass which on washing with ether gave the desired product. It was recrystallized from acetic acid to give colorless needles (II).

**Synthesis of 3-(2-Arylamino-1, 3-Thiazol-4-yl)-2- Chromenone [A<sub>1-A12</sub>]:** A suspension of compound (II) (0.1mol) in 175mL of hot ethanol was heated with arylthiourea (0.1mol), giving a clear solution that soon deposited as crystals. It was filtered, washed with ethanol and then boiled with water containing sodium acetate which yielded the target compound. The product obtained was recrystallized with ethanol (III) (Figure 1).



## Pharmacology

Rat-Sprague Dawley having weight 220-255gm and are 8-12 weeks old, was obtained from National Institute of Bioscience, Pune. They were housed in autoclaved polypropylene cages in groups of 2-3 rats per cage and kept in a room maintained at 19 to 25°C and humidity 45 to 65 % with a 12-h light/dark cycle. They were allowed to acclimatize for four days before the experiments and were given free access to Standard sterilized extruded rodent diet was provided *ad libitum*, Reverse Osmosis water treated with UV light was provided *ad libitum* in autoclaved polypropylene bottles and Autoclaved corn cob was used as bedding material.

Standard operating procedures of the Prado Pvt. Ltd. are referred as present study with the guidelines provided by the CPCSEA was published in The Gazette of India, December 15, 1998. Prior approval of the Institutional Animal Ethics Committee (IAEC) was obtained before initiation of the study (IAEC-13-002).

## Antidepressant activity (forced swim test in rat)

Porsolt et al. [9] is a founder of Behavioral despair or forced swim test (FST) as a model to test antidepressant activity [9,10]. It was recommended that mice when forced to swim in blocked space from where they cannot bypassing are induced to a unique action of immobility [11]. This behavior follows a state of despair which can be reduced by certain agents which are therapeutically competent in human abasement. The behavioral despair test is occupied to assess the antidepressant activity of synthesized compound. Sprague-Dawley rats of 200-27 gm in a faction of two each were used and on the first day of the analysis, (pretest session), rats were personally placed in a circular recipient (Plexiglass cylinder) of dimensions (diameter, 10cm; height, 25cm) containing 10 cm of water 25°C. The animals were left to swim for 6min before being detached, dried and returned to their cages. The experiment was repeated 24 h later, in 5min swim session (test session). The synthesized compounds (25mg, kg<sup>-1</sup>), and imipramine, as a reference antidepressant drug (25mg, kg<sup>-1</sup>) 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, 1hr prior to the test. Control animals received 0.5% aqueous solution of Na CMC (Corboxy Methyl Cellulose). This test was performed after 1hr, 5hrs and 24hrs of dose administration. For individual animal video recording was made. Then, the rats were dropped individually into the Plexi glass cylinder and left in the water for 6min. After the first 2min 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 5min of the 6min test session.

## QSAR methodology

All molecules were drawn in Chem draw ultra 8.0module in Chemoffice 2004 software and imported into TSAR software. Charges were derived using Charge 2-Derive charges option and optimized by using Cosmic-optimize 3D option in the structure menu of the project table. Substituents were defined and descriptors were calculated for whole molecule as well as for the Substituent's. Several equations were generated correlating

both Log (% Immobility) with physicochemical parameters (descriptors) by multiple linear regression analysis (MLR) method. Data was standardized by range and leave one out method was used for cross validation. Models were excluded if correlation was exceeding 0.9 for more rigorous analysis. Correlation matrix was generated to find any Intercorrelation between the descriptors. Intercorrelation between the descriptors in the final equation is less than 0.2 [11].

## Result and Discussion

### Chemistry

The molecular formula, melting points and yields of the compounds were given in Table 1. The compounds were pure by checking melting points of the synthesized compounds; chemical methods were reliable for the synthesis of the compounds giving yield value of the compounds (Figure 1).

### Spectral data of the synthesized compounds (A1-A12)

A<sub>1</sub>: FTIR (KBr Disc cm<sup>-1</sup>) = 3029(Ar-CH str.), 1700(-C=O str.), 1505(-C=N str), 1235(-C-N str). <sup>1</sup>H-NMR(ppm) = 12.00(1H of -COOH); 6.80-7.40(8H of phenyl); 5.0(1H of -NH).

A<sub>2</sub>: FTIR(KBr Disc cm<sup>-1</sup>) = 3424(Ar-CH str.), 1702(-C=O str.), 1575(-C=N str), 247(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(9H of phenyl); 5.0(1H of -NH).

A<sub>3</sub>: FTIR(KBr Disc cm<sup>-1</sup>) = 3452(Ar-CH str.), 1699(-C=O str.), 1576.52(-C=N str), 1273(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.85-7.55(8H of Phenyl); 5.0(1H of -NH).

A<sub>4</sub>: FTIR(KBr Disc cm<sup>-1</sup>) = 3504.99(Ar-CH str.), 1735.62(-C=O str.), 1578.45(-C=N str), 1272.79(-C-N str). <sup>1</sup>H-NMR(ppm) = 7.00-7.80(8H of phenyl); 5.0(1H of -NH); 4.0(2H of -NH<sub>2</sub>).

A<sub>5</sub>: FTIR (KBr Disc cm<sup>-1</sup>) = 3438.46(Ar-CH str.), 1738.51(-C=O str.), 1589.06(-C=N str), 1278.57(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.90-7.60(8H of phenyl); 5.0(1H of -NH).

A<sub>6</sub>: FTIR(KBr Disc cm<sup>-1</sup>) = 3516.56(Ar-CH str.), 1743.33(-C=O str.), 1575.56(-C=N str), 1272.79(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(8H of phenyl); 5.0(1H of -NH); 4.0(1H of -OH).

A<sub>7</sub>: FTIR(KBr Disc cm<sup>-1</sup>) = 3057.58 (Ar-CH str.), 1700.91 (-C=O str.), 1578.45 (-C=N str), 1222.65 (-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(8H of phenyl); 5.0(1H of -NH).

A<sub>8</sub>: FTIR(KBr Disc cm<sup>-1</sup>) = 3329.5(Ar-CH str.), 1700.91(-C=O str.), 1552.66(-C=N str), 1376.93(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(8H of phenyl); 5.0(1H of -NH).

A<sub>9</sub>: FTIR (KBr Disc cm<sup>-1</sup>) = 2945.73(Ar-CH str.), 1701.87(-C=O str.), 1577.49(-C=N str), 1272.79(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(8H of phenyl); 5.0(1H of -NH).

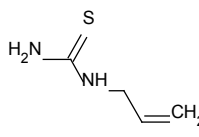
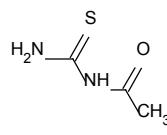
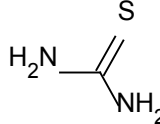
A<sub>10</sub>: FTIR (KBr Disc cm<sup>-1</sup>) = 3448.10 (Ar-CH str.), 1699.94(-C=O str.), 1590.02(-C=N str), 1271.82(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(8H of phenyl); 6.20-6.40(2H of CH=CH); 5.0(2H of -NH); 4.5(2H of NH<sub>2</sub>).

A<sub>11</sub>: FTIR(KBr Disc cm<sup>-1</sup>) = 3306.36(Ar-CH str.), 1810.83(-C=O str.), 1467.56(-C=N str), 1272.79(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(8H of phenyl); 5.0(2H of -NH); 4.5(2H of NH<sub>2</sub>); 0.8-1.4(3H of CH<sub>3</sub>).

A<sub>12</sub>: FTIR (KBr Disc cm<sup>-1</sup>) = 3374.82(Ar-CH str.), 1811.79(-C=O

str.), 1500.35(-C=N str), 1271.82(-C-N str). <sup>1</sup>H-NMR(ppm) = 6.80-7.40(8H of phenyl); 5.0(2H of -NH); 4.5(2H of NH<sub>2</sub>).

**Table 1:** Synthesis of 3-(2-Arylamino-1, 3-Thiazol-4-yl)-2- Chromen-one [A<sub>1</sub>-A<sub>12</sub>].

Compound Code	R
A <sub>1</sub>	COOH
A <sub>2</sub>	H
A <sub>3</sub>	NO <sub>2</sub>
A <sub>4</sub>	NH <sub>2</sub>
A <sub>5</sub>	Cl
A <sub>6</sub>	OH
A <sub>7</sub>	Br
A <sub>8</sub>	NO <sub>2</sub>
A <sub>9</sub>	Cl
A <sub>10</sub>	
A <sub>11</sub>	
A <sub>12</sub>	

### Antidepressant activity

The test is despair swim test and a Sprague-Dawley rats are used to antidepressant activity study for all the integrate compounds. Standard control Imipramine was used. At the last four minutes of the period the animals show more strong levels of paralysis. With the synthesized compounds three Compounds (A<sub>4</sub>, A<sub>5</sub> and A<sub>7</sub>) showed powerful antidepressant activity with reference to standard control imipramine (Table 2) (Figure 2). The results were taken as a triplicate and average of each was calculated.

### QSAR

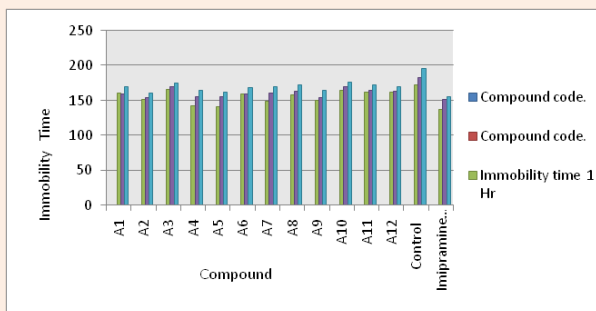
Intercorrelation between the captions in the final equations is less than 0.2. Best equations correlating Log (% Immobility) with descriptors for series (A<sub>1</sub>-A<sub>12</sub>) generated are conferred in Table 3 (Figure 3).

**Table 2:** Analytical & physicochemical data of the synthesized compounds (A<sub>1</sub>-A<sub>12</sub>).

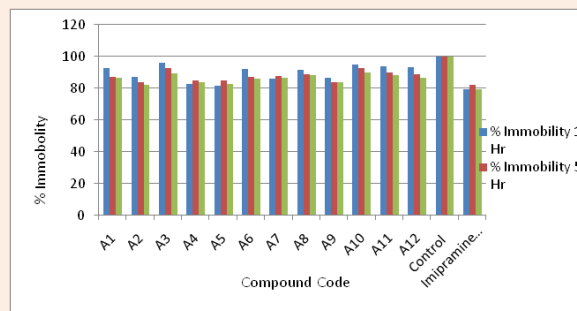
Compound	Mol. Formula	Mol. Wt.	M.P°C	Yield %	Elemental analyses Found (Cal.)			
					C	H	N	S
A <sub>1</sub>	C <sub>19</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub> S	364	220-230	80	62.63(62.15)	3.29(2.98)	7.69(7.45)	8.79(8.47)
A <sub>2</sub>	C <sub>18</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> S	319	235-237	75	67.71(67.38)	3.44(3.18)	8.77(8.56)	10.03(9.78)
A <sub>3</sub>	C <sub>18</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> S	365	205-207	67	59.17(58.86)	3.01(2.89)	11.5(11.18)	8.76(8.49)
A <sub>4</sub>	C <sub>18</sub> H <sub>12</sub> N <sub>3</sub> O <sub>2</sub> S	334	260-270	80	64.67(64.38)	3.59(3.29)	12.57(12.21)	9.58(9.23)
A <sub>5</sub>	C <sub>18</sub> H <sub>9</sub> C <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S	388	210-215	78	55.67(55.31)	2.31(1.98)	7.21(6.85)	8.24(7.89)
A <sub>6</sub>	C <sub>18</sub> H <sub>11</sub> N <sub>2</sub> O <sub>3</sub> S	335	265-267	69	64.47(64.21)	3.28(2.89)	8.35(8.04)	9.55(9.25)
A <sub>7</sub>	C <sub>18</sub> H <sub>10</sub> BrN <sub>2</sub> O <sub>2</sub> S	398	230-233	72	54.27(53.98)	2.51(2.18)	7.03(6.85)	8.04(7.85)
A <sub>8</sub>	C <sub>18</sub> H <sub>9</sub> N <sub>4</sub> O <sub>6</sub> S	309	270-275	65	69.9(69.57)	2.91(2.58)	18.12(17.89)	10.35(10.08)
A <sub>9</sub>	C <sub>18</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S	388	190-200	71	55.67(55.28)	2.31(1.98)	7.21(6.98)	8.24(7.96)
A <sub>10</sub>	C <sub>15</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> S	283	234-236	69	63.6(63.28)	3.88(3.76)	9.89(9.69)	11.3(10.92)
A <sub>11</sub>	C <sub>14</sub> H <sub>9</sub> N <sub>2</sub> O <sub>3</sub> S	285	240-242	62	58.94(58.68)	3.18(2.94)	9.82(9.68)	11.22(10.98)
A <sub>12</sub>	C <sub>12</sub> H <sub>7</sub> N <sub>2</sub> O <sub>2</sub> S	243	262-264	70	59.25(58.98)	2.88(2.67)	11.52(11.24)	13.16(12.94)

**Table 3:** Antidepressant activities of the compounds.

Compound code	Immobility time(±SD)			% Immobility (±SD)		
	1 Hr	5 Hr	24 Hr	1 Hr	5 Hr	24 Hr
A <sub>1</sub>	160.5±0.23	159.5±0.31	169.5±0.12	93.02±0.16	87.39±0.09	86.92±0.38
A <sub>2</sub>	150.5±0.16	153±0.18	160.5±0.08	87.50±0.12	83.83±0.23	82.30±0.09
A <sub>3</sub>	165±0.12	169.5±0.19	174±0.27	95.93±0.10	92.87±0.18	89.23±0.29
A <sub>4</sub>	142.5±0.34	155±0.27	163.5±0.41	82.84±0.09	84.93±0.06	83.84±0.10
A <sub>5</sub>	140.5±0.11	155.5±0.08	161.5±0.19	81.68±0.21	85.20±0.27	82.82±0.29
A <sub>6</sub>	159±0.27	159.5±0.3	168±0.62	92.44±0.11	87.39±0.17	86.15±0.18
A <sub>7</sub>	148.5±0.26	160.5±0.28	169.5±0.09	86.33±0.27	87.94±0.29	86.92±0.30
A <sub>8</sub>	157.5±0.17	162.5±0.19	172±0.21	91.56±0.29	89.04±0.06	88.20±0.13
A <sub>9</sub>	149.5±0.33	153.5±0.28	163.5±0.45	86.91±0.39	84.10±0.29	83.84±0.28
A <sub>10</sub>	163.5±0.18	169.5±0.14	175.5±0.46	95.05±0.26	92.87±0.23	90.0±0.38
A <sub>11</sub>	161.5±0.06	164.5±0.50	172±0.08	93.89±0.1	90.13±0.2	88.20±0.16
A <sub>12</sub>	161±0.21	162.5±0.32	169.5±0.39	93.60±0.24	89.04±0.25	86.92±0.3
Control	172±0.28	182.5±0.29	195±0.4	100±0.11	100±0.26	100±0.36
Imipramine (std.)	136.5±0.07	150.5±0.10	154.5±0.06	79.36±0.09	82.49±0.67	79.26±0.24



**Figure 2:** Antidepressant-like effects of Coumarin derivatives test compounds in FST Data are presented as compared to control group. (Compounds code Vs Immobility time).



**Figure 3:** Antidepressant-like effects of Coumarin derivatives test compounds in FST Data are presented as compared to control group. (Compounds code Vs % Immobility).

### Significance of the terms -

N= No. of Molecules,

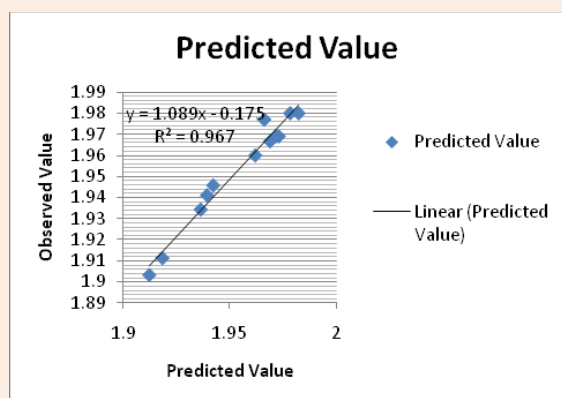
s = standard error --- less is better,

r = correlation coefficient - higher is better > 0.7,

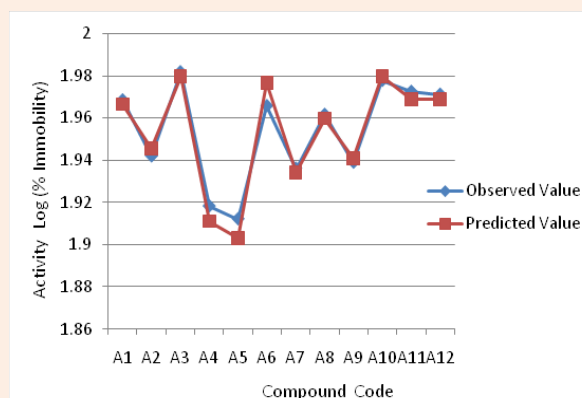
$r^2_{cv}$  = cross validated  $r^2$  - higher is better > 0.5,

F Value = higher is better

Observed and predicted data and graphs are conferred in Table 4 & 5 (Figure 4a & 4b) and Graph I for Series



**Figure 4a:** Correlation graph.



**Figure 4b:** Histogram of observed and predicted log (% Immobility) data for 12 compounds.

**Table 4a:** Equations generated between Log (% Immobility) and descriptors.

Sr. No.	Equation	N	S	r	$r^2$	$r^2_{cv}$	F
Series (A <sub>1</sub> -A <sub>12</sub> )	$Y = -0.199 \cdot X_3 - 0.229 \cdot X_1 - 1.553 \cdot X_2 - 12.575$	12	0.06438	0.9835	0.9674	0.9503	8.14

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)

**Table 4b:** Observed and predicted log (% Immobility) value data for 12 compounds.

Compound No.	Observed Value	Predicted Value	Residual Value
A <sub>1</sub>	1.96857	1.96658	0.00199
A <sub>2</sub>	1.94200	1.94568	-0.00368
A <sub>3</sub>	1.98195	1.97986	0.00209
A <sub>4</sub>	1.91824	1.91123	0.00701
A <sub>5</sub>	1.91211	1.90321	0.0089
A <sub>6</sub>	1.96585	1.97684	-0.01099
A <sub>7</sub>	1.936116	1.93424	0.001876
A <sub>8</sub>	1.96170	1.95987	0.00183
A <sub>9</sub>	1.93906	1.94102	-0.00196
A <sub>10</sub>	1.97795	1.97988	-0.00193
A <sub>11</sub>	1.97261	1.96892	0.00369
A <sub>12</sub>	1.97127	1.96892	0.00235

## Discussion

The range of demographic interpretation of the equations is accepted. Less deviation with the correlation coefficient is high. The residual value for each sequence also is less indicating good guessing power of models. From equation it is observed that two electronic specification Dipole Moment Z Component (Whole Molecule) and VAMP HOMO (Whole Molecule) as well as one static parameter Inertia Moment 2 Length (Whole Molecule) contribute (-0.227, -1.469 and -0.414 respectively) negatively for the action so electron eliminate and less heavy groups may upgrade the activity (%1 Immobility). Synthetic method and scientific applications of coumarins for the treatment of several defects were seriously discussed.

## Conclusion

In the present research, attempt has been made to present synthetic strategies, reactions, in the structural skeleton of the compounds for their antidepressant activity. At dose (25mg/kg) the compounds shows good antidepressant activity. The compounds codes (A<sub>4</sub>, A<sub>5</sub> and A<sub>9</sub>) showed excellent activity. Lastly, the boost result of the antidepressant activity showed by these compounds may be of significant for further structural alteration to the chief compound and next level studies in the desire of finding a new great antidepressant instruction.

## References

- Nemeroff CB (2007) The burden of severe depression: a review of diagnostic challenges and treatment alternatives. *J Psychiatr Res* 41(3-4): 189-206.
- Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, et al. (2014) A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *Am J Clin Nutr* 99(1): 181-197.
- Eleni P (1997) Development of new antidepressants. *Advances in Psychiatric treatment* 3: 46-51.
- Porsolt RD, Brossard G, Hautbois C, Roux S (2010) Rodent models of depression: Forced swim and tail suspension behavioral despair tests in rats and mice. *Curr Protoc Neurosci* 8(8).
- Murray RDH, Mendez J, Brown SA (1982) *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*, John Wiley & Sons, New York, USA.
- Jung K, Park YJ, Ryu JS (2008) Scandium(III) Triflate-Catalyzed Coumarin Synthesis. *An International Journal for Rapid Communication of Synthetic Organic Chemistry* 38(24): 4395-4406.
- Chen KS, Ko FN, Teng CM, Wu YC (1996) Antiplatelet and vasorelaxing actions of some benzylisoquinoline and phenanthrene alkaloids. *J Nat Prod* 59(5): 531-534.
- Huong DT, Huong L, Choi HC, Rho TC, Lee HS, et al. (1999) *Arch Pharm Res* 22(3): 324-326.
- Porsolt RD, Anton G, Blavet N, Jalfre M (1978) Behavioural despair in rats: a new model sensitive to antidepressive treatments. *Eur J Pharmacol* 47(4): 379-391.
- Porsolt RD, Bertin A, Jalfre M (1977) Behavioural despair in mice: A primary screening test for antidepressants. *Arch Int Pharmacodyn* 229(2): 327-336.
- Mogilaiah K, Vidya K, Kumara T, Shiva K (2009) Synthesis and antibacterial activity of 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles. *Indian Journal of Chemistry* 48(2): 282-285.