SYNTHESIS AND EVALUATION OF ANTIDEPRESSANT ACTIVITY OF COUMARINE DERIVATIVES

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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.

Keywords: - Antidepressant activity, Coumarin, Despair swims test, Perkin reaction, and Sprague Dawley Rat.

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Introduction [1-3]

The present research work is a Bonafide novel work for the synthesis of 3-(2- (phenylaminothiazol-4-yl)-2H-chromen-2-one. 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 twelve 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 by using open capillary method. The structures of the synthesized compounds were established by using IR, 1 H NMR and CHN analysis. The synthesized compounds were screened for their antidepressant activity. 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 4, A 5 and A 9) showed better activity. The synthesized compounds were also subjected for QSAR analysis the results found were in the range of less than 0.2 hence are acceptable. 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

Material and Methods:

Antidepressant Activity [2-3]

Behavioral despair was proposed as a model to test for antidepressant activity by Porzelt 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 behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression.

Procedure

Behavioral despair or forced swim test (FST) was proposed as a model to test antidepressant activity by Porzelt 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 (carboxyl 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 (Carboxyl 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.

Table 1: Antidepressant activity data of the compounds synthesized compounds.

Compound Code	Immobility time			% Immobility		
	1 Hr	5 Hr	24 Hr	1 Hr	5 Hr	24 Hr
A1	160.5	159.5	169.5	93.02	87.39	86.92
A2	150.5	153	160.5	87.50	83.83	82.30
A3	165	169.5	174	95.93	92.87	89.23
A4	142.5	155	163.5	82.84	84.93	83.84
A5	140.5	155.5	161.5	81.68	85.20	82.82
A6	159	159.5	168	92.44	87.39	86.15
A7	148.5	160.5	169.5	86.33	87.94	86.92
A8	157.5	162.5	172	91.56	89.04	88.20
A9	149.5	153.5	163.5	86.91	84.10	83.84
A10	163.5	169.5	175.5	95.05	92.87	90.0
A11	161.5	164.5	172	93.89	90.13	88.20
A12	161	162.5	169.5	93.60	89.04	86.92
Control	172	182.5	195	100	100	100
Imipramine (std.)	136.5	150.5	154.5	79.36	82.49	79.26

Antidepressant-like effects of 3-(2-(phenylaminothiazol-4-yl)-2H-chromen-2-one derivatives test compounds in FST Data are presented as compared to control group. (Compounds code Vs Immobility time).

Procedure for Scheme

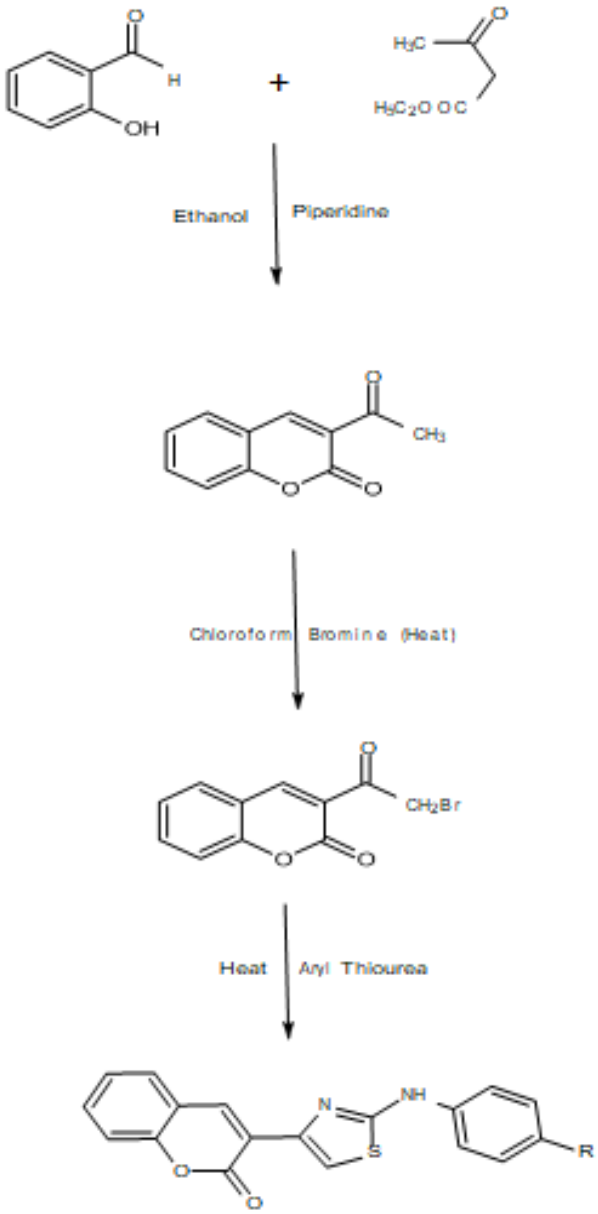
Synthesis of 3-Acetyl-2H-Chromen-2-one

A mixture of salicylaldehyde (0.5 ml) and ethyl acetoacetate (0.5 ml) was stirred and cooled. To this mixture 0.5-1 ml 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-(Bromo acetyl)-2H-Chromen-2-One

To a solution of compound (I) (0.25 ml) in 200 ml of alcohol-free chloroform, bromine (0.25 mol) in 25 ml of chloroform was added with intermittent shaking. The mixture was warmed to decompose an addition product. The mixture was heated for 20 min, 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)

Scheme:



Synthesis of 3-(2-Arylamino-1, 3-Thiazol-4-yl)-2- Chroman-one [A1-A12]

A suspension of compound (2) (0.1 moL) 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)

Table no. 2: Analytical & Physicochemical data of the synthesized compounds (A1-A12)

Comp.	Mol. Formula	Mol. Wt.	M.P. ° C	Yield %	Elemental analyses Calculated			
					C	H	N	S
A1	C19H12N2O4S	364	220-230	80	62.63	3.29	7.69	8.79
A2	C18H11N2O2S	319	235-237	75	67.71	3.44	8.77	10.03
A3	C18H11N3O4S	365	205-207	67	59.17	3.01	11.50	8.76
A4	C18H12N3O2S	334	260-270	80	64.67	3.59	12.57	9.58

A5	C18H9Cl2N2O2S	388	210-215	78	55.67	2.31	7.21	8.24
A6	C18H11N2O3S	335	265-267	69	64.47	3.28	8.35	9.55
A7	C18H10BrN2O2S	398	230-233	72	54.27	2.51	7.03	8.04
A8	C18H9N4O6S	309	270-275	65	69.90	2.91	18.12	10.35
A9	C18H9Cl2N2O2S	388	190-200	71	55.67	2.31	7.21	8.24
A10	C15H11N2O2S	283	234-236	69	63.60	3.88	9.89	11.30
A11	C14H9N2O3S	285	240-242	62	58.94	3.18	9.82	11.22
A12	C12H7N2O2S	243	262-264	70	59.25	2.88	11.52	13.16

Spectral Data

- **Infrared Spectra:**

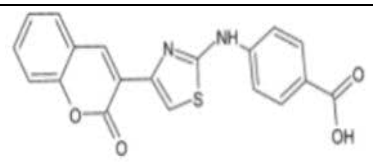
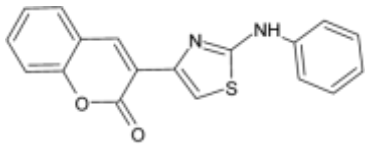
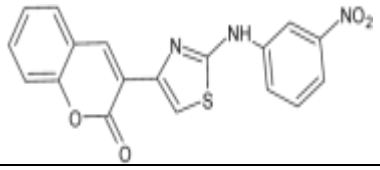
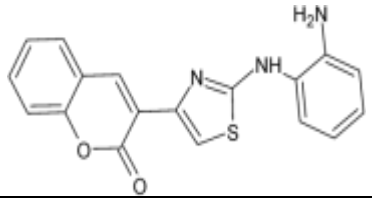
The peaks in IR spectrum gave an idea about the probable structure of the compound. IR region ranges between 4000-650 cm^{-1}. The derivatives including intermediates were recorded on Beckmann Microlambert 600 spectrometer, which showed different vibration levels of molecules by using potassium bromide (KBr) pellet technique.

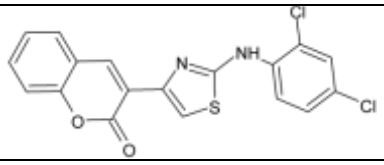
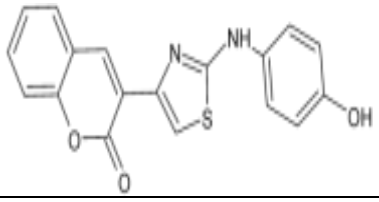
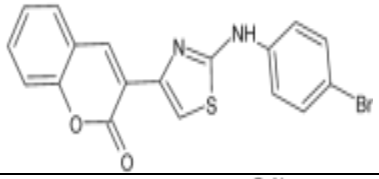
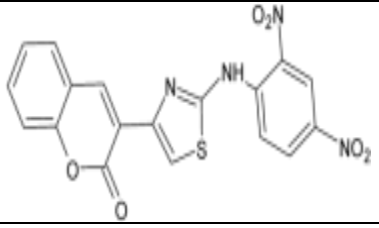
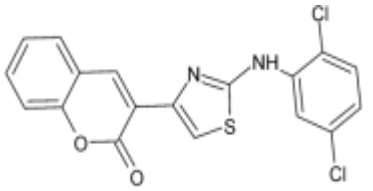
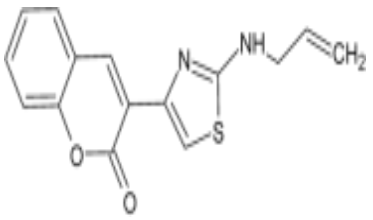
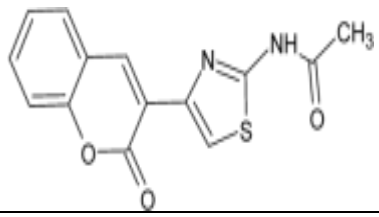
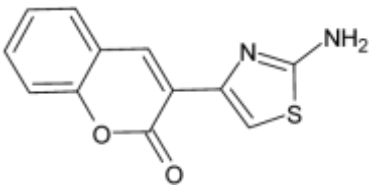
- **^{1}H-NMR Spectra:**

NMR Spectroscopy enables us to record differences in magnetic properties of the various magnetic nuclei present and to deduce in the large measure about the position of these nuclei within the molecule. We can deduce how many different kinds of environment are there in the molecules and also which atoms are present in neighboring groups. The proton NMR spectra, enables us to know different chemical and magnetic environments corresponding to protons in molecules.

^{1}H-NMR of the title compounds were recorded on sophisticated multinuclear FT NMR spectrometer model Bruker 500, DMSO-d6 as internal standards. The instrument is equipped with a Gyro magnet of field strength 9.4T. Its ^{1}H frequency is 5400 MHz the chemical shift data were expressed as δ-values related to TMS.

Table no.3: Infra-Red / ^{1}H-NMR spectral study of the synthesized compounds. (A1-A13)

Sr. No.	Comp. Name	Structure	I R	N M R
1.	**A1**		3029(Ar-CH str.), 170(-C=O str.), 1505 (-C=N str), 1235 (-C-N str),	7.20-7.42 (coumarin), 10.22 (aromatic C-NH), 12.74 (carboxylic acid)
2.	**A2**		3424(Ar-CHstr.), 1702(-C=Ostr.), 1575 (-C=N str), 1247 (-C-N str),	
3.	**A3**		3452(Ar-CHstr.), 1699(-C=O str.), 1576.52 (-C=N str),1273 (-C-N str),	7.20-7.42 (coumarin), 10.22(aromatic C-NH), 7.41(thiazol) 7.26-7.64 (1-benzene)
4.	**A4**		3504.99 (Ar-CHstr.), 1735.62 (-C=Ostr.), 1578.45 (-C=Nstr), 1272.79 (-C-N str),	7.20-7.42(coumarin), 7.41(thiazol) 5.19 (aromatic C-NH), 6.38-7.26 (1-benzene)
5.	**A5**		3438.46 (Ar-CHstr.),	7.41(thiazol) 10.22(aromatic

			1738.51 (-C=O str.), 1589.06 (-C=N str), 1278.57(-C-Nstr),	C-NH), 7.26-7.28 (1-benzene) 7.20-7.42 (coumarin),
6.	**A6**		3516.56 (Ar-CH str.), 1743.33 (-C=O str.), 1575.56(-C=N str), 1272.79 (-C-N str),	
7.	**A7**		3057.58 (Ar-CH str.), 1700.91 (-C=O str.), 1578.45 (-C=N str), 1222.65 (-C-N str)	
8.	**A8**		3329.5 (Ar-CH str.), 1700.91 (-C=O str.), 1552.66 (-C=N str), 1376.93 (-C-Nstr),	
9.	**A9**		2945.73 (Ar-CH str.), 1701.87 (-C=O str.), 1577.49 (-C=N str), 1272.79 (-C-N str),	7.20-7.42 (coumarin), 10.22 (aromatic C-NH), 8.56(thiazol) 7.09-7.26 (1-benzene)
10.	**A10**		3448.10 (Ar-CH str.), 1699.94 (-C=O str.), 1590.02 (-C=N str), 1271.82 (-C-N str),	
11.	**A11**		3306.36 (Ar-CH str.), 1810.83 (-C=O str.), 1467.56 (-C=N str), 1272.79 (-C-Nstr),	
12	**A12**		3374.82 (AR-CH str.), 1811.79 (-C=O str.), 1500.35 (-C=N str), 1271.82 (-C-N str),	

Result and 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 4, A 5 and A 9) showed significant antidepressant activity comparing with standard control imipramine

Fig.: Antidepressant Activity (Forced Swim Test in Rat) of synthesized compounds.

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