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Synthesis and Biological Evaluation of Some Novel Chromene-2-one Derivatives for Antipsychotic Activity

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ABSTRACT

Various Chromene -2- one derivatives (1a-1f) were synthesized and evaluated for antipsychotic activity. All the synthesized compounds showed antipsychotic activity with muscle relaxant property. The compound 1d, N-(Fluoro benzothiazol-2-yl)-(4-Methyl-2-oxo-chromene-7-yloxy) acetamide has been found to have significant atypical behaviour.

Keywords: Schizophrenia, Dopaminergic antagonist, Stereotype, Catalepsy.

INTRODUCTION

Schizophrenia is a psychotic disorder characterized by positive symptoms such as hallucinations and disorganized thought, and negative symptoms such as apathy and social withdrawal. This socially and economically debilitating disease is fairly common & is striking approximately 1% of the population. [1]. Classical or typical antipsychotic drugs antagonizing central dopaminergic receptors have been used for several decades in the treatment of psychiatric disorders, e.g. schizophrenia [2]. Although these drugs can reduce the positive symptoms of schizophrenia, they unfortunately often induce extrapyramidal motoric side effects and are furthermore often not able to ameliorate the negative symptoms of schizophrenia. The antipsychotic action has been suggested to be due to blockade of the mesocorticolimbic dopaminergic system, while the motoric side effects are believed to be due to antagonism of dopaminergic receptors in the nonlimbic nigro-striatal dopamine system of the brain [3]. While a diversified group of the so

called atypical antipsychotic drugs express increased effectiveness in negative, affective and cognitive symptoms, including efficacy in patients resistant to standard therapy. Atypical antipsychotic drugs also have a low incidence of extrapyramidal side effects and prolactinaemia but may produce other undesirable side effects (e.g. agranulocytosis), that limit their clinical use [4].

Chromene-2-one & its derivatives are known to possess diverse biological activities such as antibacterial [5], antifungal [6], antineoplastic [7], antitubercular [8] & anthelmintic [9]. Recently it has been reported that Chromene-2-one derivatives possess selective dopamine D_4 antagonistic activity [10] & 2-piperazinylbenzothiazoles possess high affinity for 5-HT_{1A} & 5-HT_3 receptors [11]. In this direction our efforts were devoted to combine Chromene-2-one nucleus with different benzothiazole derivatives to obtain compounds having affinities for both dopamine and 5-HT receptors.

EXPERIMENTAL SECTION

Synthetic part

In present work all synthetic reactions were monitored by TLC. All the synthesized compounds (1a-1f) were characterized by analytical and spectroscopic methods. Melting points (Table-1) were determined on Veego melting point apparatus, model no-MPI by open capillary method and are uncorrected. The FTIR spectra (Table-1) were recorded on Jasco FTIR instrument model no-5300, using KBr pellets. ^{1}H-NMR spectra (Table-2) were recorded on BRUKER AVANCE II 400 NMR spectrometer at 400 MHz, for which $CDCl_3$ was used as solvent and TMS as internal standard. Mass spectra (Table-1) were recorded on Micromass Q-Tof Micro, Mass spectrometer.

General procedure for synthesis of Chromene-2-one nucleus, (step-I)

The method of Pechmann and Duisburg was followed for the synthesis of Chromeme-2-one nucleus [12].

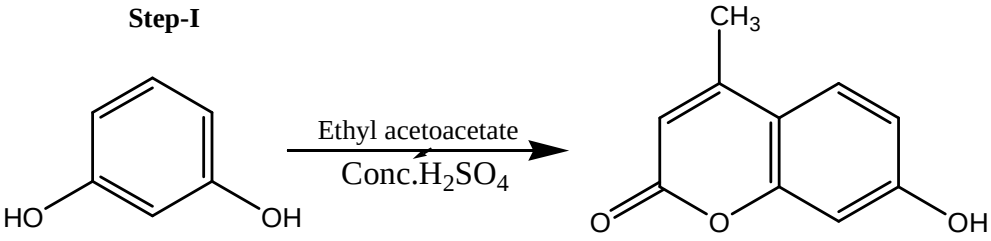
General procedure for synthesis of 6-Substituted 2-aminobenzothiazole derivatives,(step-II)

0.06 moles of aniline derivative & 0.06 moles of potassium thiocyanate were added to 150 ml of glacial acetic acid (previously cooled to 5°C). The mixture was placed in freezing mixture of ice & salt and mechanically stirred, while bromine (0.02 moles of bromine in 10 ml glacial acetic acid) was added from a dropping funnel at such a rate that temperature does not rise beyond 0-5°C. After addition of bromine (105 min), the solution was stirred for an additional 2 hours at 0-10°C. The residue was filtered and dissolved in hot water (150 ml). The resulting solution was filtered and filtrate was neutralized with ammonia solution to pH 6.0. The precipitate was collected and crystallized with ethanol [13].

General procedure for synthesis of 6-Substituted (1'-chloroacetyl)-2-aminobenzothiazole derivatives, (step-III)

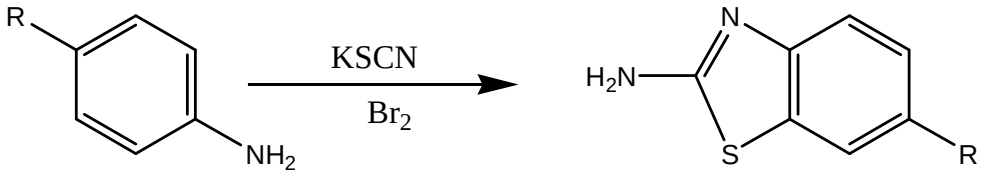
To a stirred solution of 6-substituted 2-aminobenzothiazole (0.05 moles) and triethylamine (0.05 moles) in dry benzene (50 ml), chloroacetyl chloride (0.05 moles) was added drop wise to an ice-cold condition. The reaction mixture was stirred for about 6 hours and the separated amine hydro chloride was filtered off. The filtrate was refluxed on a water-bath for about 4 hr, concentrated at reduced pressure and the separated solid was purified over the column of silica gel using chloroform as an eluant. The product was crystallized from ethanol [14].

Step-I



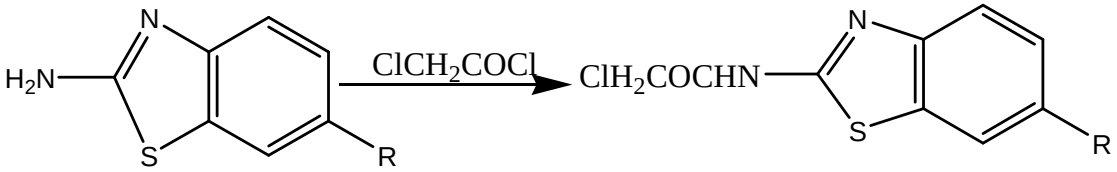
Resorcinol — Chromene-2-one nucleus

Step-II



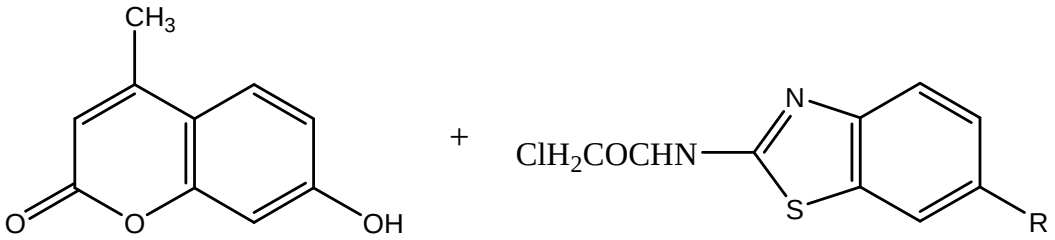
Aniline derivative — 6-Substituted 2-aminobenzothiazole derivative

Step-III

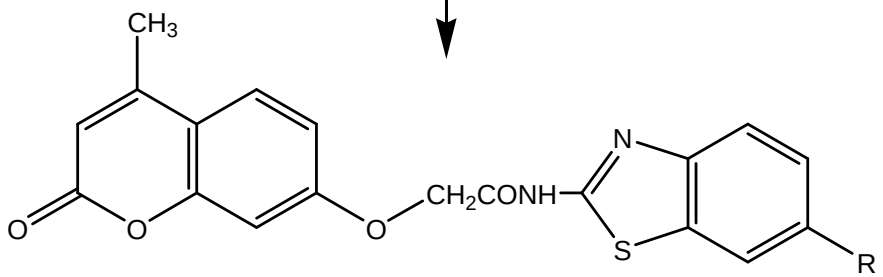


6-Substituted 2-aminobenzothiazole derivative — 6-Substituted 2-aminobenzothiazole derivative

Step-IV



Chromene-2-one nucleus — 6-Substituted 2-aminobenzothiazole derivative



N-(6-substituted benzothiazol-2-yl)-(4-methyl-2-oxo-chromene-7-yloxy) acetamide

General procedure for synthesis of N-(6-substituted benzothiazol-2-yl)-(4-methyl-2-oxo-chromene-7-yloxy) acetamide derivatives (1a-1f), (step-IV)

0.01 mole of chromene-2-one nucleus and 0.01 mole of 6-Substituted (1'-chloroacetyl)-2-aminobenzothiazole derivatives were added to round bottom flask containing 30 ml of acetonitrile. 0.01 mole of anhydrous potassium carbonate was added to reaction mixture and refluxed for 38 hours, then solvent was removed under vacuum and residue was dissolved in dichloromethane. Dichloromethane layer was washed with water to remove potassium carbonate and then washed with 5% w/v sodium hydroxide solution to remove the unreacted material. Dichloromethane layer was again washed with water and then anhydrous sodium sulphate was added to remove water and this layer was kept overnight to collect crude product which was crystallized from ethanol.

Table-1: Physicochemical parameters and IR spectral data of synthesized compounds (1a-1f)

Compound	-R	Yield (%)	M.P. (°C)	R_f value	IR (KBr disc, cm^{-1})	Mass Spectra (m/z)
1a	-H	57	124*	0.458	1742, 3060, 1575, 3120, 1610	359.6
1b	-Br	53	134*	0.523	1740, 3085, 1564, 3130, 1624	438.8
1c	-Cl	44	128*	0.621	1740, 3060, 1566, 3135, 1635, 762	394.4
1d	-F	53	138*	0.592	1744, 3068, 1570, 3132, 1640, 1195	377.9
1e	$-OCH_3$	48	116*	0.487	1742, 3065, 1560, 3140, 1640, 1242	389
1f	$-OC_2H_5$	50	122*	0.436	1739, 3070, 1572, 3128, 1644, 1246	403

*(Benzene: Ethyl acetate: 3:2)

Table-2: ^{1}H-NMR spectral data

Compound	^{1}H-NMR (δ, 400MHz, $CDCl_3$)
1a	δ 6.53 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.90 (t, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 8.1 (s, -NH), δ 4.80 (d, Methylene-CH_2), δ 7.52 (m, Benzothiazole (-CH)), δ 8.12 (m, Benzothiazole (-CH)), δ 8.22
1b	(m, Benzothiazole (-CH)) δ 6.53 (t, Benzene (-CH)), δ 7.14 (t, Benzene (-CH)), δ 5.95 (t, Benzene (-CH)), δ 1.74 (d, $-CH_3$), δ 8.1 (s, -NH), δ 4.84 (d, Methylene-CH_2), δ 7.70 (m, Benzothiazole (-CH)), δ 8.10 (m, Benzothiazole (-CH)), δ 8.29 (m, Benzothiazole (-CH))
1c	δ 6.54 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.92 (t, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 8.0 (s, -NH), δ 4.82 (d, Methylene-CH_2), δ 7.56 (m, Benzothiazole (-CH)), δ 8.11 (m, Benzothiazole (-CH)), δ 8.20 (m, Benzothiazole (-CH))
1d	δ 6.53 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.90 (t, Benzene (-CH)), δ 1.71

	(d, -CH_3), δ 8.1 (s, -NH), δ 4.80 (d, Methylene-CH_2), δ 7.82 (m, Benzothiazole (-CH)), δ 7.24 (m, Benzothiazole (-CH)), δ 8.21 (m, Benzothiazole (-CH))
1e	δ 6.56 (t, Benzene (-CH)), δ 7.15 (t, Benzene (-CH)), δ 5.93 (t, Benzene (-CH)), δ 1.71 (d, -CH_3), δ 8.1 (s, -NH), δ 4.83 (d, Methylene-CH_2), δ 7.62 (m, Benzothiazole (-CH)), δ 7.06 (m, Benzothiazole (-CH)), δ 8.12 (m, Benzothiazole (-CH)), δ 3.71 (d, -OCH_3)
1f	δ 6.53 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.90 (t, Benzene (-CH)), δ 1.71 (d, -CH_3), δ 8.1 (s, -NH), δ 4.80 (d, Methylene-CH_2), δ 7.64 (m, Benzothiazole (-CH)), δ 8.10 (m, Benzothiazole (-CH)), δ 8.23 (m, Benzothiazole (-CH)), δ 1.33 (s, Ethoxy-CH_3), δ 3.88 (d, Ethoxy-CH_2)

Pharmacological Studies

All the experiments were performed as per CPCSEA guidelines, with the permission of Animal ethical committee (Registration no. 931/ac/06/ CPCSEA). Swiss albino rats (male or female, body weight: 80-120 gm) maintained under hygienic laboratory conditions were fasted for 24 hours before experimentation. All the synthesized compounds were administered through intra peritoneal (i.p.) route. Haloperidol (1mg/kg) and Risperidone (1mg/kg) were used as standard drugs.

Determination of minimum effective dose [ED_{min}]: Swiss albino rats were divided into six groups, having six animals in each group (n=6). Minimum dose [ED_{min}] required for preventing the apomorphine induced climbing response & 5-HTP induced head twitches response was recorded.

Apomorphine induced behaviour: During this experiment, animals were pretreated with standard drug (1mg/kg) or test compound (15mg/kg), 30 minutes before treatment with apomorphine (4mg/kg) [15]. Inhibition of apomorphine induced climbing behavior was recorded. All the results were statistically evaluated using student's t-test. Results are shown in table: 3.

5-HTP induced behaviour: During this experiment, animals were pretreated with standard drug or test compound, 30 minutes before treatment with 5-HTP (50mg/kg) [15]. Inhibition of 5-HTP induced head twitches were recorded at 10 min time interval. All the results were statistically evaluated using student's t-test. Results are shown in table: 4.

Conditioned avoidance response using Pole climbing apparatus: Before experiment rats were trained by a shock treatment of 30 seconds duration to climb the pole. The conditioning stimulus was a buzzer. During this experiment, animals were treated with standard drug or test compound. After 30 minutes the animals were observed [16, 17]. All the results were statistically evaluated using student's t-test. Results are shown in table: 5.

Rota rod experiment: Before experiment rats were trained by placing them on a scraped rotating rod (25 rpm) of the Rota rod assembly to remain there on the rod at least for 3 minutes. After 30 minutes of treatment with standard drug or test compound, time of fall from the rotating rod for animals was observed [16, 17]. All the results were statistically evaluated using student's t-test. Results are shown in table: 5.

Catalepsy test: Synthesized compounds were evaluated in catalepsy test model at 3 cm level [16, 17].

Table-3: Inhibition of Apomorphine induced climbing behaviour (D_2 antagonism)

Compound	Dose	Time spent* (min)	Time spent (%)	% Inhibition
Control	-	28.76 (2.76)	95.86	-
Haloperidol	1 mg/kg	0.00	0.00	100
Risperidone	1 mg/kg	0.00	0.00	100
Compound 1a	15 mg/kg	0.00	0.00	100
Compound 1b	15 mg/kg	0.00	0.00	100
Compound 1c	15 mg/kg	0.00	0.00	100
Compound 1d	15 mg/kg	0.00	0.00	100
Compound 1e	15 mg/kg	16.94(1.26)	56.46	41.09
Compound 1f	15 mg/kg	18.96(1.44)	63.20	34.07

***** The value in parenthesis indicates standard deviation (n=6, p* <0.05)

Table-4: Inhibition of 5-HTP induced head twitches (5-HT antagonism, %)

Compound	Dose	Observation at interval of (min)					
		5	15	25	35	45	55
Control	-	0.00	0.00	0.00	0.00	0.00	0.00
Haloperidol	1 mg/kg	34.7	46.8	52.2	28.9	32.1	26.7
Risperidone	1 mg/kg	48.9	77.9	72.4	88.6	97.4	92.5
Compound 1a	15 mg/kg	38.8	28.6	55.6	66.4	46.9	43.4
Compound 1b	15 mg/kg	34.5	42.1	48.7	52.4	49.6	54.2
Compound 1c	15 mg/kg	32.8	36.6	38.8	46.8	68.8	76.4
Compound 1d	15 mg/kg	56.8	72.8	77.9	82.7	84.8	92.3
Compound 1e	15 mg/kg	38.5	35.4	37.6	45.3	44.8	42.3
Compound 1f	15 mg/kg	42.5	44.6	43.1	42.2	28.9	28.8

(n=6, p* <0.05)

Table-5: Pole climbing and Rota rod Experiment

Compound	Pole climbing experiment	Rota rod experiment
	Time taken for pole climbing (seconds)	Time of fall from rod* (seconds)
Normal control	18	150 (2.46)
Haloperidol	Unable to climb	02(1.21)
Risperidone	Unable to climb	03(1.32)
Compound 1a	Unable to climb	05(1.44)
Compound 1b	Unable to climb	04(1.33)
Compound 1c	Unable to climb	03(1.24)
Compound 1d	Unable to climb	04(1.28)
Compound 1e	Unable to climb	05(1.28)
Compound 1f	Unable to climb	06(1.34)

***** The value in parenthesis indicates standard deviation (n=6, p* <0.05)

SUMMARY AND CONCLUSION

All the synthesized compounds were in conformity with the structure envisaged on the basis of spectral data. The minimum effective dose [ED_{min}] for title compounds was recorded as 15 mg/kg. All compounds showed inhibition of apomorphine and 5-HTP induced behavior confirming that targeted compounds have both dopamine and 5-HT receptor blocking activity, with the Fluoro derivative (1d) showing more inhibitory action for 5-HT receptors. All compounds also showed negative catalepsy test even at 3 cm level. During Rota rod experiment all compounds showed muscle relaxant property while the standard drugs showed rigidity of muscles. The present investigation also indicates that the synthesized compounds have promising antipsychotic effect and are more effective than Haloperidol but less effective than Risperidone in blocking 5-HT receptors.

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