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Synthesis and screening of some novel 7-Hydroxy 4-Methyl Coumarin derivatives for antipsychotic activity

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Abstract

Coumarin derivatives have shown dopaminergic antagonistic activity. In this direction our efforts were devoted to combine 7-Hydroxy-4-Methyl coumarin nucleus with different secondary amines through two carbon spacing to obtain compounds having affinities for both dopamine and 5-HT receptors. All synthesized compounds were evaluated for antipsychotic activity and have shown dopaminergic and 5-HT receptor blocking action.

Keywords: Schizophrenia, Dopaminergic antagonist, Catalepsy

Introduction

The psychoses are among most severe psychiatric disorders and are affecting perhaps 1% of the population at some age. Classical or typical antipsychotic drugs, antagonizing central dopaminergic receptors, have been used for several decades in the treatment of psychiatric disorders. Unfortunately, these drugs often induce extra pyramidal motor disturbances and are further often not able to ameliorate the negative symptoms of schizophrenia. 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 extra pyramidal side effects and prolactinaemia but may produce other undesirable side effects (e.g. agranulocytosis), that limit their clinical use. Despite the introduction of atypical neuroleptics, there is still a strong need for compounds which induce fewer side effects and, equally importantly, also address the negative symptoms and cognitive deficits of schizophrenia more efficiently[1].

7-Hydroxy-4-methyl coumarin derivatives possess diverse biological properties such as neuroleptic, antibacterial, antitubercular, antifungal, antineoplastic, anti HIV, and antihelmintic[2]. It has been evidenced from literature survey that coumarin derivatives have shown dopaminergic antagonistic activity[3]. Therefore in present work 7-Hydroxy-4-Methyl coumarin nucleus was combined with different secondary amines through two carbon spacing to obtain targeted compounds, expected to have affinities for both dopamine and 5-HT receptors.

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Experimental Section

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.

General procedure for synthesis of 7-Hydroxy-4-Methyl coumarin nucleus (step-I)

A beaker containing 100 ml of concentrated sulphuric acid was kept in an ice-bath, added with solution of resorcinol (0.1 moles) and ethyl aceto acetate (0.1 moles), with continuous stirring for two hours, maintaining the temperature below 10 ºC. The reaction mixture was kept at room temperature for 18 hrs and then poured onto the mixture of 200g of crushed ice and 300 ml of distilled water, with vigorous stirring. The white precipitate formed was collected by vacuum filtration, washed with 350 ml of cold water, dissolved in 150 ml of 5% w/v sodium hydroxide solution and filtered. The filtrate was added with 55 ml of concentrated sulphuric acid with vigorous stirring until the solution was acidic. The crude 7-Hydroxy-4-methyl Coumarin was collected by filtration, washed with cold water, dried, and purified by recrystallization from ethanol [4,5].

General procedure for synthesis of 7-(2-chloroethoxy)-4-Methyl coumarin derivatives (step-II)

3g of 7-Hydroxy-4-methyl Coumarin and 2.47 ml of 1-Bromo-2-chloro ethane were added to round bottom flask containing 30ml of acetonitrile. 0.01 moles of anhydrous potassium carbonate was added to reaction mixture and refluxed for 30 hrs. The solvent was removed under vacuum and residue was dissolved in dichloromethane. Dichloromethane layer was washed with water and then with 5% w/v sodium hydroxide solution, and added with anhydrous sodium sulphate, and kept overnight. The crude 7-(2-chloroethoxy) 4-methyl Coumarin formed was collected and purified by recrystallization from ethanol[8].

General procedure for synthesis of 7-(2-(N,N-Dialkyl)aminoethoxy)-4-Methyl coumarin derivatives (step-III)

0.05 moles of 7-chloro ethoxy-4-methyl Coumarin and 0.1 moles of Dialkylamine were added to round bottom flask containing 30ml of acetone. 0.01 moles of anhydrous potassium carbonate was added to reaction mixture and refluxed for 26 hrs. The solvent was removed under vacuum and residue was dissolved in dichloromethane. Dichloromethane layer was washed with water, added with anhydrous sodium sulphate and kept overnight. The crude product was collected and purified by recrystallization from chloroform[9].

Pharmacological Studies

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.

Apomorphine induced behavior: During this experiment, animals were pretreated with standard drug (1mg/kg) or test compound (15mg/kg), 30 minutes before treatment with apomorphine (4mg/kg). [6,10]

5-HTP induced behavior: During this experiment, animals were pretreated with standard drug or test compound, 30 minutes before treatment with 5-HTP (50mg/kg). [7,11]

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.[11,12,13]

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.[12]

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Catalepsy test: Synthesized compounds were evaluated in catalepsy test model at 3 cm level.[11,12]

Scheme of Synthesis for compounds (1a-1f)

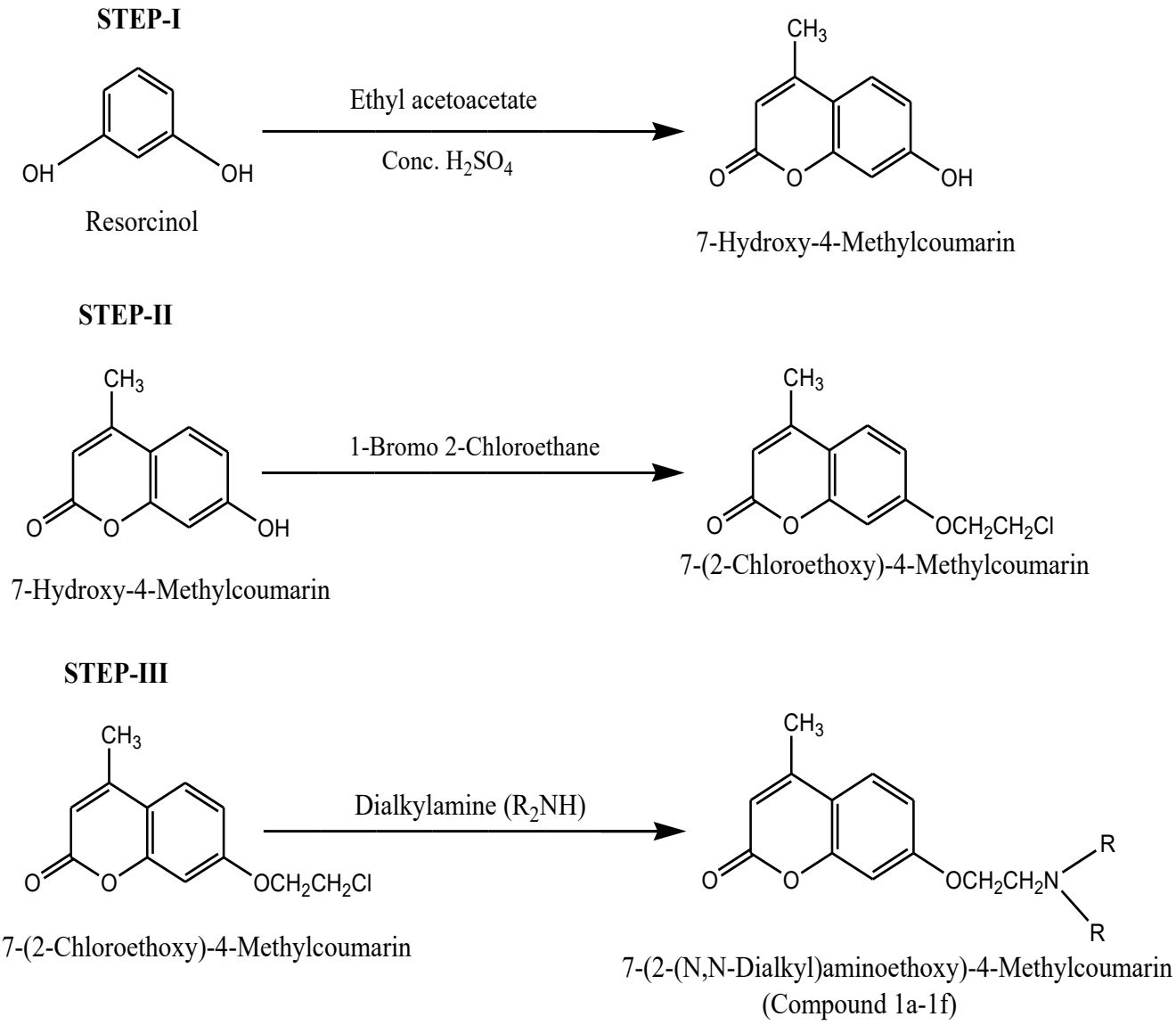

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Table-1: Physicochemical parameters and IR spectral data of synthesized compounds (1a-1f)

Compd	-R	Yield (%)	M.P. (°C)	R_f value	IR (KBr disc, cm^{-1})
1a	$-CH_3$	47	86	0.250*	1724, 1366, 1151, 1253
1b	$-C_2H_5$	42	89	0.517*	1744, 1366, 1151, 1253
1c	$-CH(CH_3)_2$	37	96	0.431*	1714, 1370, 1146, 1241
1d	$-(CH_2)_2CH_3$	45	95	0.427*	1712, 1366, 1151, 1253
1e	$-(CH_2)_3CH_3$	48	99	0.411*	1732, 1374, 1159, 1257
1f	$-C_6H_5$	35	107	0.672*	1730, 1371, 1155, 1255

*(Benzene: Ethyl acetate: 2:3)

ISSN 0976-7126

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

Compd	^{1}H-NMR (δ, 400MHz, $CDCl_3$)
1a	δ 6.53 (t, Benzene (-CH)), δ 7.16 (q, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 2.27 (d, $-NCH_3$), δ 2.78 (t, Ethylene-CH_2), δ 4.04 (t, Ethylene-CH_2)
1b	δ 6.50 (t, Benzene (-CH)), δ 7.26 (q, Benzene (-CH)), δ 1.75 (d, $-CH_3$), δ 1.01 (m, Ethyl-CH_2), δ 2.41 (t, Ethyl-CH_3), δ 2.98 (t, Ethylene-CH_2), δ 4.07 (t, Ethylene-CH_2)
1c	δ 6.55 (t, Benzene (-CH)), δ 7.23 (q, Benzene (-CH)), δ 1.73 (d, $-CH_3$), δ 2.97 (m, Isopropyl-CH), δ 1.05 (t, Isopropyl-CH_3), δ 2.82 (t, Ethylene-CH_2), δ 4.01 (t, Ethylene-CH_2)
1d	δ 6.50 (t, Benzene (-CH)), δ 7.20 (q, Benzene (-CH)), δ 1.70 (d, $-CH_3$), δ 2.37 (t, Propyl-CH_2), δ 1.43 (m, Propyl-CH_2), δ 0.98 (t, Propyl-CH_3), δ 2.82 (t, Ethylene-CH_2), δ 4.01 (t, Ethylene-CH_2)
1e	δ 6.55 (t, Benzene (-CH)), δ 7.20 (q, Benzene (-CH)), δ 1.72 (d, $-CH_3$), δ 2.36 (t, Butyl-CH_2), δ 1.39 (m, Butyl-CH_2), δ 1.33 (m, Butyl-CH_2), δ 0.96 (t, Butyl-CH_3), δ 2.76 (t, Ethylene-CH_2), δ 4.04 (t, Ethylene-CH_2)
1f	δ 6.52 (t, Benzene (-CH)), δ 7.20 (q, Benzene (-CH)), δ 1.73 (d, $-CH_3$), δ 6.42 (m, Benzene-CH), δ 6.58 (m, Benzene-CH), δ 7.07 (m, Benzene-CH), δ 2.8 (t, Ethylene-CH_2), δ 4.10 (t, Ethylene-CH_2)

Summary and conclusion

All the synthesized compounds were in conformity with the structure envisaged on the basis of spectral data. All compounds showed inhibition of apomorphine and 5-HTP induced behavior confirming that targeted compounds have both dopamine and 5-HT receptor blocking activity. 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. Therefore present study indicates that the synthesized compounds possess antipsychotic activity with muscle relaxation and depression property and are devoid of the major extra pyramidal side effects like rigidity. The present investigation also indicates that the synthesized compounds have promising antipsychotic effect and are more effective than Haloperidol but less than Risperidone in blocking 5-HT receptors.

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