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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME SCHIFF'S BASES OF SULPHAMIDO COUMARIN

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ABSTRACT

Some new Schiff's base of methyl sulphamido-7-hydroxy-4-methyl coumarin were synthesized and the anti nociceptive and *in vitro* anti-inflammatory activities were evaluated. The Mannich reaction between 7-hydroxy-4-methyl coumarin, sulphanilamide and formaldehyde gives 7-hydroxy-4-methyl-8[sulphamidomethyl] coumarin **(1)**. The compound **(1)** with various aromatic aldehydes gives Schiff's base **(2a-2g)**. All the synthesized compounds were characterized by spectral analysis. The *in vitro* anti-inflammatory activity was carried by HRBC membrane stabilization method and the antinociceptive activity was carried by Writhing reflux method and hot plate method. All the compounds shows significant anti-inflammatory and anti-nociceptive activity.

Key words : Schiff's base, Mannich reaction, Anti-inflammatory, Anti-nociceptive.

INTRODUCTION

Various substituted coumarins are known for their antibacterial[1], analgesic[2,3], anti-inflammatory[4-5] and antioxidant[6] activities. Literature review reveals that introduction of amino methyl group in coumarin gives rise to biological active compounds Coumarin, Mannich base[7,8], sulphonamide[9] and Schiff's base[10,11] have also been reported to have diverse biological properties. Considering the biological potential of coumarin and sulphonamide herein, the synthesis of some of these derivatives are reported and evaluated for *invitro* anti-inflammatory[12] and *in vivo* anti-nociceptive activities[13].

EXPERIMENTAL

Melting points were determined in Veego Digital melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer FTIR spectrometer using KBr. ^{1}H-

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NMR spectra were recorded on Mitz-FTNMR. The chemical shifts were reported as parts per million downfield from tetramethyl silane. The purity of the compound was checked by TLC using precoated silica gel G plate.

Synthesis of 7-hydroxy-4-methyl 8-(sulphamido methyl) coumarin (Mannich reaction) (1)

A solution of sulphanilamide (0.01M in 10 mL ethanol) was added slowly into warm solution of 7-hydroxy-4-methyl coumarin (0.01M in 20 mL ethanol) and 0.01M of formaldehyde and kept overnight in refrigerator. The product obtained was collected; recrystallized with ethanol. [Yield : 98%; m. p. 120^0C; IR(KBr, cm^{-1}) 3445, 3320 (NH_2), 3100(ArC-H), 1600(ArC=C), 1667(ArC=O), 1158(C-O), 3400(OH), 985 (ArCH), 2974(CH), 1175(SO_2NH) cm^{-1}; ^{1}H-NMR (δ) 6.58-8.2(m, 11H, Aromatic); 8.1 (s, 1H, N=CH); 2.1 (s, 1H, NH); 1.71 (s, 3H, CH_3); 4.42 (s, 2H, CH_2); 3.7 (d, 1H, CH); 5.0 (s, 1H, OH).

General method of synthesis of Schiff's base (2a-2g)

An equimolar mixture of compound (1) and various substituted aldehydes were refluxed for 1-2 hrs at 100^0C. After cooling, it was poured into a beaker containing 20 mL ethanol. The product separated out was recrystallized with ethanol.

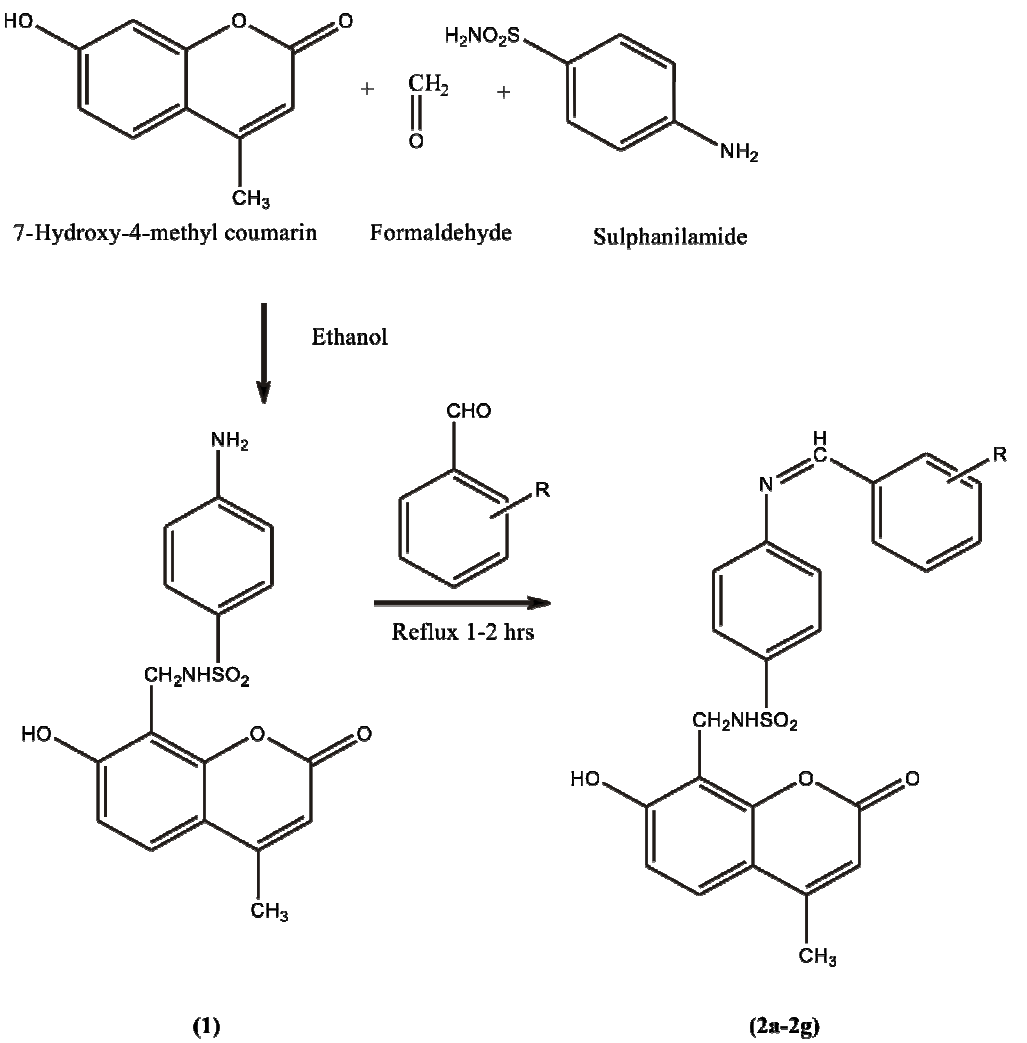
Physical and spectral data

2a : Yellowish white crystal; Yield 85%; M. P. 194^0C; IR(KBr, cm^{-1}) 3442(NH), 3100(ArC-H), 1608(ArC=C), 1667(C=O), 1158(C-O), 3403(OH), 985(ArCH), 2974(CH), 1175(SO_2NH), 1676(C=N) cm^{-1}; ^{1}H-NMR(δ) 6.37-7.9 (m, 10H, Aromatic); 8.9(s, 1H, N=CH); 2.0(s, 1H, NH); 1.72(s, 3H, CH_3); 4.38(s, 2H, CH_2); 3.7(d, 1H, CH); 5.2(s, 1H, OH).

2b : Yellow crystal, Yield 57%; M. P. 56ºC; IR(KBr, cm^{-1}) 3448(NH), 3104 (ArC-H), 1600(ArC=C), 1657(C=O), 1138(C-O), 3369(OH), 989(ArCH), 2984(CH), 1136 (SO_2NH), 1606(C=N) cm^{-1}; ^{1}H-NMR(δ) 6.37-7.9 (m, 9H, Aromatic); 3.20(s, 3H, OCH_3); 5.2(s, 2H, OH); 8.3(s, 1H, N=CH); 2.0(s, 1H, NH); 1.79(s, 3H, CH_3); 4.48(s, 2H, CH_2); 3.1(d, 1H, CH).

2c : Pale yellow crystal, Yield 81%; M. P. 97^0C; IR(KBr, cm^{-1}) 3451(NH), 3108(ArC-H), 1609(ArC=C), 1669(C=O), 1132(C-O), 3406(OH), 965(ArCH), 2976(CH), 1135(SO_2NH), 1609(C=N) cm^{-1}; ^{1}H-NMR(δ) 6.22-8.1(m, 10H, Aromatic); 8.9(s, 1H, N=CH); 2.85(s, 6H, $N(CH_3)_2$); 2.0(s, 1H, NH); 1.75(s, 3H, CH_3); 4.31(s, 2H, CH_2); 3.1(d,

1H, CH); 5.5(s, 1H, OH).



Reaction scheme

2d : Pale yellow crystal, Yield 84%; M. P. 122^0C; IR(KBr, cm^{-1}) 3449(NH), 3113(ArC-H), 1603(ArC=C), 1627(C=O), 1104(C-O), 3435(OH), 982(ArCH), 2994(CH), 1152(SO_2NH), 1661(C=N) cm^{-1}; ^{1}H-NMR(δ) 6.22-8.1(m, 10H, Aromatic); 8.6(s, 1H, N=CH); 2.2(s, 1H, NH); 1.63(s, 3H, CH_3); 4.23(s, 2H, CH_2); 3.3(d, 1H, CH); 5.5(s, 2H, OH).

2e : Yellowish white crystal; Yield 57%; M. P. 63^0C; IR(KBr, cm^{-1}) 3446(NH), 3110(ArC-H), 1602(ArC=C), 1653(C=O), 1174 (C-O), 3418(OH), 983(ArCH), 2989(CH), 1132 (SO_2NH), 1667(C=N) cm^{-1}; ^{1}H-NMR(δ) 6.32-8.8(m, 10H, Aromatic); 8.4(s, 1H, N=CH); 2.1(s, 1H, NH); 1.56(s, 3H, CH_3); 4.25(s, 2H, CH_2); 3.6(d, 1H, CH); 5.9(s, 1H, OH).

2f : White crystal; Yield 62%; M. P. 74^0C; IR(KBr, cm^{-1}) 3450(NH), 3112(ArC-H), 1605(ArC=C), 1637(C=O), 1142(C-O), 3442(OH), 986(ArCH), 2985(CH), 1139(SO_2NH), 1669(C=N) cm^{-1}; ^{1}H-NMR(δ)) 6.25-8.9(m, 10H, Aromatic); 8.5(s, 1H, N=CH); 2.5(s, 1H, NH); 1.47(s, 3H, CH_3); 4.26(s, 2H, CH_2); 3.8(d, 1H, CH); 5.3(s, 2H, OH).

2g : Pure white crystal; Yield 48%; M. P. 84^0C; IR(KBr, cm^{-1}) 3440(NH), 3101(ArC-H), 1606(ArC=C), 1647(C=O), 1162(C-O), 3412(OH), 982(ArCH), 2988(CH), 1169(SO_2NH), 1610(C=N) cm^{-1}; ^{1}H-NMR(δ)) 6.37-8.8(m, 10H, Aromatic); 8.2(s, 1H, N=CH); 2.5(s, 1H, NH); 1.60(s, 3H, CH_3); 4.42(s, 2H, CH_2); 3.8(d, 1H, CH); 5.1(s, 1H, OH).

Anti-inflammatory activity

The *in vitro* anti-inflammatory activity was carried for all the synthesized compounds **(2a-2g)** using HRBC membrane stabilization method. Diclofenac sodium (1 mg/mL) was used as standard. The reaction mixture containing 1 mg/mL of test solution or standard solution, 2 mL of 0.25% hypotonic saline, 1 mL of phosphate buffer (0.15M, pH 7.4) and 0.5 mL of HRBC in normal saline was incubated at 56^0C for 30 min and centrifuged. The absorbance of supernatant was read at 560 nm with suitable blank. The stabilization percentage was calculated (Table 1).

Anti-nociceptive activity

This activity was carried out by thermal and chemical methods.

Acetic acid induced Writhing method (Chemical method)

The anti-nociceptive activities of the compounds were carried out in Swiss albino mice using acetic acid induced writhing method. The animals (25-30 g) were divided into ten groups. Each group consists of five animals. One group served as a negative control (received vehicle), second group served as a positive control (received indomethacin 100 mg/mL) and the remaining groups were treated with synthesized compounds **(2a-2g)** 50 mg/mL in DMF, intraperitonially. Acetic acid solution (15 mg/mL) at the dose of 300

mg/kg body weight was injected intraperitonially and the number of writhes was counted for a period of 30 minutes. A significant reduction in the number of writhes by drug treatments as compared to vehicle control animals was considered positive anti-nociceptive response. The percentage inhibition of writhing was then calculated and are given in the Table 1.

Table 1. Anti-inflammatory and anti-nociceptive activity of synthesied compounds (2a-2g)

Comp. code	R	Anti-inflammatory activity %of stabilization (Mean±SEM)	% of anti-nociceptive activity	
			Writhing reflux method (Mean±SEM)	Hot plate method (Mean±SEM)
2a	-H	81.26 ± 1.3	71.40 ± 0.5	66.20 ± 0.5
2b	4-OH, 3-OCH_3	81.14 ± 1.1	83.60 ± 0.9	60.80 ± 0.3
2c	4-$N(CH_3)_2$	80.13 ± 1.0	79.50 ± 0.6	63.60 ± 0.8
2d	2-OH	62.92 ± 0.9	66.62 ± 0.3	58.10 ± 0.9
2e	2-NO_2	80.08 ± 1.2	79.52 ± 0.5	50.30 ± 1.2
2f	4-OH	80.30 ± 0.7	70.82 ± 0.4	53.40 ± 1.0
2g	3-NO_2	78.64 ± 0.8	72.70 ± 0.8	48.20 ± 0.9
Standard	-	82.29 ± 0.1	98.78 ± 0.5	93.40 ± 0.6

Eddy's hot plate method (Thermal method)

All the synthesized compounds were screened for anti-nociceptive activity by Eddy's hot plate method. Swiss albino mice (25-30 g) were divided into ten groups with five in each. Groups I served as a control and groups II received pentazocin 5 mg/kg, served as a standard. The remaining groups received the synthesized compounds **(2a-2g)** at a dose of 20 mg/kg in DMF. Thirty minutes after intraperitonial administration of the standard and test compounds, animal were individually placed on a hot plate (maintained at 55 ± 2ºC) and the response such as paw licking or jump response, whichever first appeared

were noted. A cut off period of 15 sec. was maintained to prevent the damage or lesion to animal paw. The anti-nociceptive activity was expressed in terms of percentage inhibition and are reported in the Table 1.

RESULTS AND DISCUSSION

The Mannich reaction between 7-hydroxy 4-methyl coumarin, formaldehyde and sulphanilamide gives the compound **(1)**. The stretching at 3509, 1136 and 1597 cm^{-1} shows the presence of aromatic amino group and SO_2-NH in the compound **(1)**. The characteristic signal between 1.5-1.9 in the entire compound may be due to $–CH_2$ proton. The imino stretching between1660 to 1676 cm^{-1} confirm the Schiff base formation. All the compounds were screened for *in vitro* anti-inflammatory and *in vivo* anti-nociceptive activities. The compounds showed a significant *in vitro* anti-inflammatory activity except the compound **(2d)**. Among all the compounds **(2b)**, **(2c)** and **(2f)** exhibited significant anti-inflammatory and analgesic activity.

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