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NOTE

Synthesis and Pharmacological Activities of Some Schiff Bases Derived from N,N′-Bis(4-ethoxyphenyl)malonamide

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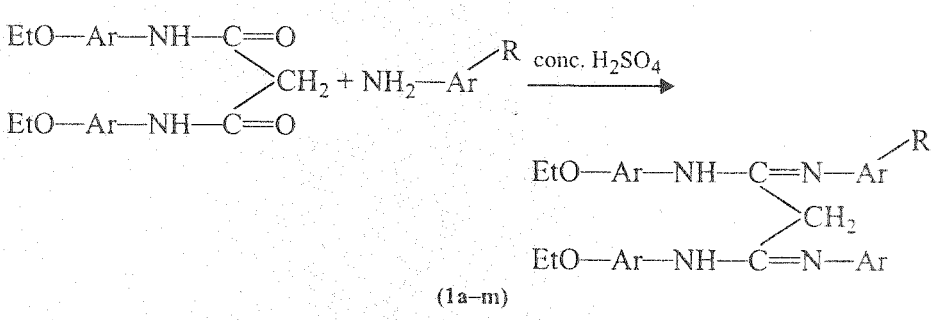
Series of the Schiff Bases (**1a–m**) of N,N'-bis(4-ethoxyphenyl) malonamide (**1**) are synthesized by the condensation reaction between compound **1** and substituted aromatic amines. Compound **1** is obtained by condensation of 4-ethoxy aniline and diethylmalonate. The resulting compounds are characterized by spectral data and evaluated for antihistaminic activity. Most of the compounds have shown interesting biological activity.

Key Words: Synthesis, Schiff bases, N,N′-Bis(4-ethoxyphenyl) - malonamide, Antihistaminic activity.

A variety of Schiff bases[1–4] were reported to possess interesting activities like anti-tubercular, bacteriostatic, anticancer activities. The synthesis of starting material N,N′-bis(4-ethoxyphenyl)malonamide were synthesized by reported method[5] in 62–68% yield. Thirteen different substituted anilines reacted with N,N′-bis(4-ethoxyphenyl) malonamide in presence of conc. H_2SO_4 and produced the new compounds **1a–m.**

Synthesis of Schiff bases

A mixture of N,N′-bis(4-ethoxyphenyl)malonamide (0.01 M) with 4-nitroaniline (0.01 M) and catalytic amount of conc. H_2SO_4 (about 1 mL) in ethyl alcohol (50 mL) was taken in a round bottom flask with air condenser heated for 1.5 h. The product separated was cooled, filtered, washed with ethyl alcohol and recrystallized from 95% ethanol to yield bright yellow coloured crystalline compound; yield 83%, m.p. 111°C. Similar procedure was employed in the preparation of other compounds **(Scheme-1).**



(1a–m)

R: **(1a)** = H, **(1b)** = 2-methoxy, **(1c)** = 4-methoxy, **(1d)** = 2-chloro, **(1e)** = 3-chloro, **(1f)** = 4-chloro, **(1g)** = 2-nitro, **(1h)** = 3-nitro, **(1i)** = 4-nitro, **(1j)** = 2-methyl, **(1k)** = 3-methyl, **(1l)** = 4-methyl, **(1m)** = 4-ethoxy

Scheme-1

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The formation of the starting compound N,N′-bis(4-ethoxyphenyl)malonamide has been clearly indicated by the characteristic IR spectra which show absorption band in 3274–3089 cm^{-1} region arising from the asymmetric and symmetric stretching vibration of the two N—H bands (2° amino groups), respectively. Further, the presence of a sharp band at 1666 cm^{-1} is due to ν(C=O) group.

The formations of the Schiff bases **(1a–m)** were confirmed by the difference in m.p. and characteristics of IR peaks at 1660–1600 ν(C=N *str.*) and 1170–1110 cm^{-1} ν(N—H *str.*).

(1c): ^{1}H NMR (DMSO-d_6) (δ ppm): 7.30 (1H, —NH—), 9.76–9.26 (8H, arom.), 8.43 (8H, arom.), 4.70–4.26 (3H, —OCH_3) and 2.33 (3H, —CH_3). **(1j):** 7.13 (8H, arom.), 8.86 (8H, arom.), 11.8 (1H, —NH), 3.46 (2H, —CH_2) and 2.33 (3H, —CH_3).

Antimicrobial activity: All the synthesized compounds **(1a–m)** were evaluated for their antimicrobial activity by disc diffusion method[6] at a concentration of 100 μg/mL. Bacterial cultures used for the study were *S. aureus*, *B. subtilis*, *S. typhi*, *P. vulgaris*, *E. coli* and *P. aeruginosa*. The activity was compared with streptomycin (100 μg/mL) as standard compound (Table-1).

TABLE-1
PHYSICAL AND ANTIMICROBIAL DATA OF COMPOUNDS (1a–m)

Comp. No.	R	m.p.	Zone of inhibition (in mm)					
			S. aureus	*B. subtilis*	*S. typhi*	*P. vulgasis*	*E. coli*	*P. aeruginosa*
1a	H	90	23	21	32	31	25	30
1b	2-Methoxy	102	29	22	—	10	28	29
1c	4-Methoxy	106	33	32	17	14	31	29
1d	2-Chloro	101	33	32	17	14	31	23
1e	3-Chloro	107	—	15	30	27	35	36
1f	4-Chloro	115	11	19	19	25	23	24
1g	2-Nitro	104	21	30	29	28	35	15
1h	3-Nitro	107	34	35	20	25	29	28
1i	4-Nitro	111	33	20	19	27	35	36
1j	2-Methyl	102	16	13	07	14	22	25
1k	3-Methyl	113	29	28	25	15	35	15
1l	4-Methyl	115	07	19	23	22	20	14
1m	4-Ethoxy	120	20	19	29	28	31	—
	Streptomycin		55	49	45	52	65	42

Antihistaminic activity: Compounds **1h, 1c, 1g, 1j** and **1m** were subjected to antihistaminic activity. Degranulation of mast cell was done as reported[7]. Male wistar rats were sacrificed by stunning and the peritoneal cavity was lavaged with 10 mL of tyrode solution. The lavaged fluid was collected and centrifuged at 2000 rpm for 5 min. The pellet was separated, washed with tyrode solution and finally resuspended in 1 mL tyrode solution. 0.1 mL of this lavaged fluid was transferred to 8 tubes (in duplicate). The lavaged fluid was then subjected to the following treatment schedule.

The cells were added with test drug and then incubated for 10 min at 37°C.

Compound 48/80 (0.1 mL, 10 μg/mL) was added to each test tube except test tube no. 1. After further incubation for 10 min at 37°C. 0.1 mL of 10% toluidine blue was added and examined under microscope. A minimum of 100 cells Counted for intact and disrupted mast cells and from it % protection from degranulation was calculated.

Rat's peritoneal mast cells (10 cells/mL) were pre-incubated in presence of test materials (100 μg/mL) and standard drug Ketotifen (10 min at 37°C). Compound 48/80 (10 μg/mL) was added and cells further incubated for 20 min at 37°C. The reaction was stopped by putting the tubes in ice. Cells were centrifuged (400 × g for 5 min) and histamine was measured in supernatant according to Shore *et al.*[8]. (Tables 2 and 3).

TABLE-2
EFFECT OF PURE COMPOUND ON COMPOUND 48/80 INDUCED RAT PERITONEAL MAST CELL DEREGULATION

Compd. No.	Treatment	Protection from deregulation (%)
Control cells	(Cells + 100 μg/mL) + 48/80	85
1b	(Cells + 100 μg/mL) + 48/80	82
1c	(Cells + 100 μg/mL) + 48/80	8
1g	(Cells + 100 μg/mL) + 48/80	35
1j	(Cells + 100 μg/mL) + 48/80	76
1m	(Cells + 100 μg/mL) + 48/80	58

TABLE-3
EFFECT OF PURE COMPOUND ON COMPOUND 48/80 INDUCED RAT PERITONEAL MAST CELL DEREGULATION

Comp. No.	Test concentration (μg/mL/105 cells)	Effect (%)
Ketotifen (known mast cell stabilizer drug)	100 μg	85.56
1b	100 μg	29.70
1c	100 μg	12.10
1g	100 μg	8.15
1j	100 μg	27.80
1m	100 μg	7.80

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