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Synthesis, Characterization and Antibacterial Activity of Some Schiff Bases of 2-Amino-3-(N-Tolyl Carboxamido)-4,5-Pentamethylene Thiophenes

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2-Amino-3-(N-tolyl carboxamido)-4,5-pentamethylene thiophenes **(I–III)** were synthesized by Gewald reaction. Later, the compounds **I–III** were treated with ten different substituted arylaldehydes to yield thirty new Schiff bases **(Ia–j** to **IIIa–j)**. The compounds were characterized by spectral data and were screened for antibacterial activity. Some of these Schiff bases exhibited interesting activity.

Key Words: Synthesis, Thiophenes, Schiff bases, Antibacterial activity.

INTRODUCTION

A number of thiophenes[1–4] and Schiff bases[5–8] were reported to possess different biological activities like antitubercular, bacteriostatic and antifungal activities. These observations stimulated us with a presumption that Schiff bases of thiophenes **(I–III)** would produce new compounds of better antibacterial activity. Hence an attempt was made to synthesize thirty new thiophene Schiff bases for antibacterial studies.

EXPERIMENTAL

All the compounds are bright coloured solids. Melting points are uncorrected. The UV spectra were recorded on Shimadzu 1601 spectrometer, IR (KBr) were recorded on FT-IR 8201. ^{1}H NMR spectra were recorded on Brucker AMX 400. The chemical shift values are in δ (ppm). Elemental analyses were within ±0.4% of their calculated values.

General Method for the Synthesis of the New Schiff Bases

Synthesis of Schiff Base of 2-Amino-3-(N-*o*-Tolyl Carboxamido)-4,5-Pentamethylene Thiophene (Ia): The starting compounds 2-amino-3-(N-tolyl carboxamido)-4,5-pentamethylene thiophenes **(I–III)** were synthesized by already reported procedure[9]. Later to the compound 2-amino-3-(N-*o*-tolyl carboxamido)-4,5-pentamethylene thiophene **(I)** (3.0 g, 0.01 M) in ethanol (40 mL) was added salicylaldehyde (1.22 g, 0.01 M) and catalytic amount of glacial acetic acid (1 mL). The product separated out on warming was cooled, filtered, washed with ethanol, dried and recrystallised from DMF : water mixture (5 : 1) to yield bright yellow coloured crystalline compound. Yield 90%, m.p. 212°C. The other compounds reported in Table-1 were prepared in the same manner.

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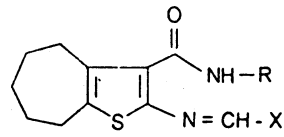


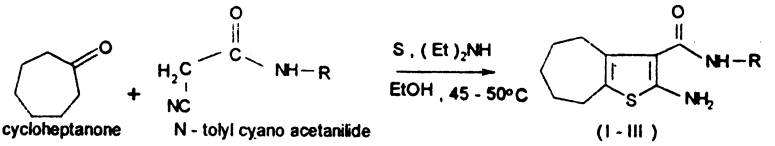
{ Ia-j to IIIa-j }

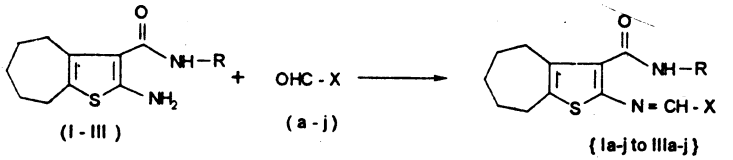
TABLE-1
PHYSICAL & ANTIBACTERIAL DATA OF COMPOUNDS **1a–j** to **IIIa–j**

Compd. No.	R	X	m.p. (°C)	Recrystalization solvent	Zone of inhibition (mm)			
					S.a.	*S.e.*	*E.c.*	*S.t.*
Ia	*o*-tolyl	-2-hydroxy phenyl	212	DMF : Water	15	14	NA	NA
Ib	*o*-tolyl	-4-methoxy phenyl	120	DMF : Water	NA	NA	NA	NA
Ic	*o*-tolyl	-3,4-dimethoxy phenyl	126	DMF : Water	NA	NA	NA	NA
Id	*o*-tolyl	-3,4,5-trimethoxy phenyl	122	Ethanol	14	17	NA	NA
Ie	*o*-tolyl	-2-nitro phenyl	168	DMF : Water	NA	NA	NA	NA
If	*o*-tolyl	-3-nitro phenyl	122	DMF : Water	NA	NA	NA	NA
Ig	*o*-tolyl	-4-methyl phenyl	118	DMF : Water	NA	NA	NA	NA
Ih	*o*-tolyl	-4-dimethyl amino phenyl	128	DMF : Water	NA	NA	NA	NA
Ii	*o*-tolyl	-3-methoxy-4 hydroxy phenyl	158	DMF : Water	NA	NA	NA	NA
Ij	*o*-tolyl	-4-chloro phenyl	166	DMF : Water	16	14	NA	NA
IIa	*m*-tolyl	-2-hydroxy phenyl	190	DMF : Water	16	15	NA	NA
IIb	*m*-tolyl	-4-methoxy phenyl	124	DMF : Water	NA	NA	NA	NA
IIc	*m*-tolyl	-3,4-dimethoxy phenyl	146	DMF : Water	NA	NA	NA	NA
IId	*m*-tolyl	-3,4,5-trimethoxy phenyl	138	Ethanol	15	16	NA	NA
IIe	*m*-tolyl	-2-nitro phenyl	202	DMF : Water	NA	NA	NA	NA
IIf	*m*-tolyl	-3-nitro phenyl	184	DMF : Water	NA	NA	NA	NA
IIg	*m*-tolyl	-4-methyl phenyl	120	DMF : Water	NA	NA	NA	NA
IIh	*m*-tolyl	-4-dimethyl amino phenyl	164	DMF : Water	NA	NA	NA	NA
IIi	*m*-tolyl	-3-methoxy-4-hydroxy phenyl	162	DMF : Water	NA	NA	NA	NA
IIj	*m*-tolyl	-4-chloro phenyl	172	DMF : Water	18	17	NA	NA
IIIa	*p*-tolyl	-2-hydroxy phenyl	228	DMF : Water	21	16	NA	NA
IIIb	*p*-tolyl	-4-methoxy phenyl	186	DMF : Water	NA	NA	NA	NA
IIIc	*p*-tolyl	-3,4-dimethoxy phenyl	174	DMF : Water	NA	NA	NA	NA
IIId	*p*-tolyl	-3,4,5-trimethoxy phenyl	170	Ethanol	16	19	NA	NA
IIIe	*p*-tolyl	-2-nitro phenyl	216	DMF : Water	NA	NA	NA	NA
IIIf	*p*-tolyl	-3-nitro phenyl	208	DMF : Water	NA	NA	NA	NA
IIIg	*p*-tolyl	-4-methyl phenyl	206	DMF : Water	NA	NA	NA	NA
IIIh	*p*-tolyl	-4-dimethyl amino phenyl	190	DMF : Water	NA	NA	NA	NA
IIIi	*p*-tolyl	-3-methoxy-4-hydroxy phenyl	172	DMF : Water	NA	NA	NA	NA
IIIj	*p*-tolyl	-4-chloro phenyl	194	DMF : Water	24	21	NA	NA
Ampicillin		—	—	—	38	32	28	25

S.a. = S. aureus, S.e. = S. epidermidis, E.c. = E. coli, S.t. = S. typhi

All the synthesized compounds (**Ia–j** to **IIIa–j**) were screendfor their antibacterial activity by cup diffusion method[10] at a concentration of 50 μg/mL using two gram +ve and two gram –ve bacteria. The zone of inhibition was measured in mm and reported in Table-1. The activity was compared with ampicillin (50 μg/mL) as standard.





Scheme-1

RESULTS AND DISCUSSION

The formation of the starting compounds 2-amino-3-(N-tolyl carboxamido)-4,5-pentamethylene thiophenes (**I–III**) was confirmed by the presence of specific IR peaks at 750 cm^{-1} due to *o*-tolyl group, 780 cm^{-1} due to *m*-tolyl group, 830 cm^{-1} due to *p*-tolyl group, 1618 cm^{-1} (—CONH—), 2858–2731 cm^{-1} (—S—CH—), 3282 cm^{-1} (—NH—), 3458 cm^{-1} ($—NH_2$).

The formation and the purity of the new Schiff bases (**Ia–j** to **IIIa–j**) were confirmed by the difference in m.p., R_f values and specific IR peaks between 609 cm^{-1} (C—Cl aromatic), 750–740 cm^{-1} (*o*-tolyl $—CH_3$ group), 830–810 cm^{-1} (*p*-methyl aromatic), 1307 cm^{-1} (—OH aromatic), 1370–1330 cm^{-1} ($—NO_2$ aromatic), 1660–1640 cm^{-1} (—CH=N— of Schiff's bases), 2860–2840 cm^{-1} ($—OCH_3$). ^1H NMR spectra are as follows:

Ib = 10.0 (s, 1H, —CH—), 8.4 (d, 1H, —NH—), 6.9–8.0 (m, 8H, Arom), 3.9 (s, 3H, $—OCH_3$ Arom), 2.8 and 3.2 (t, 4H, dimethylenic protons of cycloheptane ring), 2.3 (s, 3H, $—CH_3$ Arom), 1.7–1.9 (m, 6H, trimethylenic protons of cycloheptane ring).

Ih = 10.4 (s, 1H, —CH=), 8.4 (d, 1H, —NH—), 6.6–8.0 (m, 8H, Arom), 2.8 and 3.3 (t, 4H, dimethylenic protons of cycloheptane ring), 3.1 (s, 6H, $—N(CH_3)_2$ Arom), 2.3 (s, 3H, $—CH_3$ Arom), 1.7–1.9 (m, 6H, trimethylenic protons of cycloheptane ring).

IIc = 10.4 (s, 1H, —CH=), 8.4 (d, 1H, —NH—), 6.75–7.25 (m, 7H, Arom), 3.8–4 (d, 6H, $—OCH_3$ Arom), 2.75 and 3.25 (t, 4H, dimethylenic protons of cycloheptane ring), 2.4 (s, 3H, $—CH_3$ Arom), 1.6–1.9 (m, 6H, trimethylenic protons of cycloheptane ring).

IIf = 10.5 (s, 1H, —CH=), 8.7 (d, 1H, —NH—), 6.9–8.5 (m, 8H, Arom), 2.8–3.3 (t, 4H, dimethylenic protons of cycloheptane ring), 2.4 (s, 3H, $—CH_3$ Arom), 1.6–1.9 (m, 6H, trimethylenic protons of cycloheptane ring).

IIIg = 10.5 (s, 1H, —CH=), 8.5 (d, 1H, —NH—), 7.2–7.8 (m, 8H, Arom), 2.8–3.4 (t, 4H, dimethylenic protons of cycloheptane ring), 2.3–2.5 (s, 6H, —CH_3 Arom), 1.6–1.9 (m, 6H, trimethylenic protons of cycloheptane ring).

IIIj = 10.1 (s, 1H, —CH=), 8.5 (d, 1H, —NH—), 7.2–7.8 (m, 8H, Arom), 2.8–3.3 (t, 4H, dimethylenic protons of cycloheptane ring), 2.4 (s, 6H, —CH_3 Arom), 1.6–1.9 (m, 6H, trimethylenic protons of cycloheptane ring).

A comparative study of MIC values (Table-1) of these compounds reveals that nine compounds were exhibiting interesting antibacterial activities, however not on par with that of standard employed.

The three compounds of three series having 2-hydroxy phenyl substituent, 3,4,5-trimethoxy phenyl substituent and 4-chloro phenyl substituent at X were exhibiting antibacterial activity against gram positive organisms only, and no activity against gram negative organisms.

It is also interesting to note that the compounds **IIIa, IIId** and **IIIj** containing *p*-tolyl substituent at R of thiophene showed a better antibacterial activity than the active compounds of series **I** and **II.**

Finally out of the 30 compounds screened for antibacterial activity 21 compounds were possessing least antibacterial activity and nine compounds were found to possess moderate antibacterial activity when compared to the standard and no compounds were active against the two gram negative organisms used.

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