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

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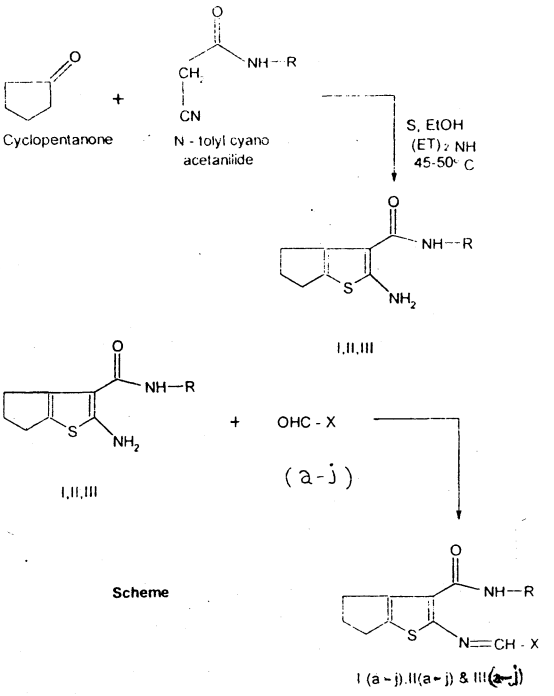
2-Amino-3-(N-tolyl carboxamido)-4,5-trimethelene thiophenes **(I–III)** were synthesized by Gewald reaction. Later, the compounds **I–III** were treated with ten different substituted aryl aldehydes to yield thirty new Schiff bases **(Ia–j to IIIa–j)** . The compounds were characterized by spectral data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

Key Words: Synthesis, Characterization, Antibacterial activity, Schiff bases

INTRODUCTION

Various derivatives of thiophenes[1–4] and Schiff bases[5–8] were reported to exhibit interesting biological activities like antitubercular, bacteriostatic and antifungal activities. These observations stimulated us with a presumption that Schiff bases of



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thiophenes **(I–III)** would produce new compounds of better antibacterial activity. Hence an attempt was made by us to synthesize thirty new thiophene schiff bases for antibacterial studies **(Scheme).**

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 DPX 200, 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 Schiff Bases

Synthesis of Schiff Base of 2-Amino-3-(N-*o*-Tolyl Carboxamido)-4,5-Trimethelene Thiophene (Ia): The starting compound 2-amino-3-(N-tolyl carboxamido)-4,5-dimethyl thiophenes **(I–III)** were synthesized by already reported procedure[9]. Later to the compound 2-amino-3-(N-*o*-tolyl carboxamido)-4, 5-trimethelene thiophene **(I)** (2.72 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 recrystallized from DMF : H_2O mixture (5 : 1) to yield bright yellow coloured crystalline compound. Yield 86%, m.p. 206°C. The other compounds reported in Table–1 were prepared in the same manner.

The formation of the starting compound 2-amino-3-(N-tolyl carboxamido)-4,5-dimethyl thiophene **(I–III)** was confirmed by the presence of specific IR peaks at 1618 cm^{-1} ν(—CONH—), 2858–2731 cm^{-1} ν(—S—CH—), 3282 cm^{-1} ν(—NH—) and 3458 cm^{-1} ν(—NH_2).

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

Ib: = 8.5 (s, 1H, —CH =), 8.0 (d, 1H, —NH—), 7.2–7.8 (m, 8H, arom), 4.0 (m, 3H, —OCH_3 arom), 3.0 (s, 3H, —CH_3 arom), 2.5 (m, 6H, trimethelenic protons)

Ig: = 8.5 (s, 1H, —CH =), 8.0 (d, 1H —NH—), 7.2–7.8 (m, 8H, arom), 2.25–3.25 (d, 6H, —CH_3 arom), 2.5 (m, 6H, trimethelenic protons).

Ij: = 8.5 (s, 1H, —CH =), 8.0 (d, 1H, —NH—), 7.2–7.8 (m, 8H, arom), 3.25 (t, 3H, —CH_3 arom), 2.5 (m, 6H, trimethelenic protons).

IIc: = 8.5 (s, 1H, —CH =), 7.75 (d, 1H, —NH—), 6.75–7.5 (m, 7H, arom), 4.0 (d, 6H), OCH_3 arom), 3.25 (t, 3H, —CH_3 arom), 2.5 (m, 6H, trimethelenic protons)

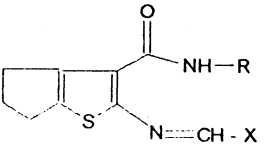
IId: = 8.5 (s, 1H, —CH =), 7.75 (d, 1H, —NH—), 6.75–7.5 (m, 6H, arom), 4.0 (d, 9H, OCH_3 arom), 3.25 (t, 3H, —CH_3 arom), 2.5 (m, 6H, trimethelenic protons).

IIh: = 8.25 (s, 1H, —CH =), 7.5 (d, 1H, —NH—), 6.75–7.75 (m, 8H, arom), 3.25 (m, 9H, —CH_3 arom), 2.5 (m, 6H, trimethelenic protons).

IIIa: = 8.5 (d, 2H, —CH = and —OH protons), 7.25–7.4 (m, 8H, Ar—H), 2.5 (m, 6H, trimethelenic protons), 1.75 (t. 3H, —CH_3 Arom).

IIIf: = 8.5 (s, 1H, —CH =), 8.0 (d, 1H, —NH—), 7.2–8.0 (M, 8H, arom), 2.5 (m, 6H, trimethelenic protons), 2.5 (m, 6H, trimethelenic protons), 1.75 (t, 3H, —CH_3 arom).

IIIi: = 8.5 (s, 2H, —CH = and —OH protons), 8.0 (d, 1H, —NH—), 7.2–8.0 (m, 7H, arom), 4.0 (s, 3H, OCH_3 arom), 3.25 (t, 3H, —CH_3 arom), 2.5 (m, 6H, trimethelenic protons).



I (a - j), II(a - j) & III(a - j)

TABLE-1
PHYSICAL & ANTIBACTERIAL DATA OF COMPOUNDS **Ia–j, IIsa–j and IIIa–j**

Compound No.	R	X	m.p. (°C)	Zone of inhibition in mm			
				S.a	*S. e*	*E.c*	*S.t*
I a	*o*-tolyl	-2 hydroxy phenyl	206	14	16	NA	NA
I b	*o*-tolyl	-4 methoxy phenyl	178	NA	NA	NA	NA
I c	*o*-tolyl	-3,4-dimethoxy phenyl	136	NA	NA	NA	NA
I d	*o*-tolyl	-3,4,5-trimethoxy phenyl	146	12	14	NA	NA
I e	*o*-tolyl	-2-nitrophenyl	186	NA	NA	NA	NA
I f	*o*-tolyl	-3-nitrophenyl	196	NA	NA	NA	NA
I g	*o*-tolyl	-4-methylphenyl	140	NA	NA	NA	NA
I h	*o*-tolyl	-4-dimethyl aminophenyl	152	NA	NA	NA	NA
I i	*o*-tolyl	-3-methoxy-4-hydroxyphenyl	208	NA	NA	NA	NA
I j	*o*-tolyl	-4-chloro phenyl	164	17	18	NA	NA
II a	*m*-tolyl	-2-hydroxy phenyl	188	15	17	NA	NA
II b	*m*-tolyl	-4-methoxy phenyl	156	NA	NA	NA	NA
II c	*m*-tolyl	-3,4-dimethoxy phenyl	152	NA	NA	NA	NA
II d	*m*-tolyl	-3,4,5-trimethoxy phenyl	146	14	14	NA	NA
II e	*m*-tolyl	-2-nitro phenyl	204	NA	NA	NA	NA
II f	*m*-tolyl	-3-nitro phenyl	202	NA	NA	NA	NA
II g	*m*-tolyl	-4-methylphenyl	186	NA	NA	NA	NA
II h	*m*-tolyl	-4-dimethyl amino phenyl	200	NA	NA	NA	NA
II i	*m*-tolyl	-3-methoxy-4-hydroxy phenyl	172	NA	NA	NA	NA
II j	*m*-tolyl	-4-chlorophenyl	178	16	17	NA	NA
III a	*p*-tolyl	-2-hydroxy phenyl	202	20	22	NA	NA
III b	*p*-tolyl	-4-methoxy phenyl	162	NA	NA	NA	NA
III c	*p*-tolyl	-3,4-dimethoxy phenyl	180	NA	NA	NA	NA
III d	*p*-tolyl	-3,4,5- trimethoxy phenyl	148	16	17	NA	NA
III e	*p*-tolyl	-2-nitro phenyl	152	NA	NA	NA	NA
III f	*p*-tolyl	-3-nitro phenyl	192	NA	NA	NA	NA
III g	*p*-tolyl	-4-methyl phenyl	204	NA	NA	NA	NA
III h	*p*-tolyl	-4-dimethyl amino phenyl	172	NA	NA	NA	NA
III i	*p*-tolyl	-3-methoxy-4-hydroxy phenyl	156	NA	NA	NA	NA
III j	*p*-tolyl	-4-chloro phenyl	194	18	20	NA	NA
Ampicillin	—	—	—	38	29	28	26

S.a = *S. aureus*, S.e. = *S. epidermidis*, E.c. = *E. coli*, S.t. = *S. typhi*, NA = Not active

Antibacterial activity: The *in vitro* antibacterial activity of the synthesized compound **(I a–j to IIIa–j)** was determined by cup-plate 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. From the antibacterial screening results it was observed that nine compounds were exhibiting interesting activities, however not on par with that of the standard employed. The compound **Ia IIa** and **IIIa** having 2-hydroxy phenyl substituent, compounds **Id, IId, IIId** having 3, 4, 5-trimethoxy phenyl substituent and compounds **Ij, IIIj** possessing 4-chlorophenyl substituent at **X** were exhibiting antibacterial activity against gram positive organisms only, and no activity against gram negative organisms. It was observed that the active compounds exhibited a better activity against *S. epidermidis* than *S. aureus*.

It is also interesting to note that the compounds **IIIa, IIId & IIIj** containing *p*-tolyl substituent at third position 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 09 compounds were found to possess moderate antibacterial activity when compared to the standard.

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