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Synthesis, Characterization and Biological Screening of Some New Condensed N-Methyl Piperidino Thiophenes

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The synthesis of 2-amino-3-furfuryl carboxamido-6-N-methyl piperidino thiophene (**2**) was synthesized *via* a multi-component condensation between sulphur, N-methyl piperidin-4-one and furfuryl cyanoacetamide adapting Gewald reaction. Later the compound (**2**) was condensed with different substituted aryl aldehydes to yield 11 new Schiff bases (**3a-3k**) of this series and in second series the compound (**2**) was reacted with freshly prepared acid chlorides to form 4 new title compounds (**3l-3p**). All the 15 compounds were characterized by spectral data and were screened for antibacterial activity. Some of the compounds exhibited promising activity.

Key Words: Synthesis, Gewald reaction, Schiff bases, Amides, Antibacterial activity.

INTRODUCTION

A number of thiophenes and Schiff bases[1-4] were reported to possess different biological activities like antitubercular, antifungal, analgesis, anti-inflammatory, antimicrobial activities[5-7]. These findings prompted us to synthesize some new Schiff bases and amides from the starting compound 2-amino-3-furfuryl carboxamido-6-N-methyl piperidino thiophene (**2**). All the Schiff bases are bright coloured crystalline solids where as the amides were amorphous.

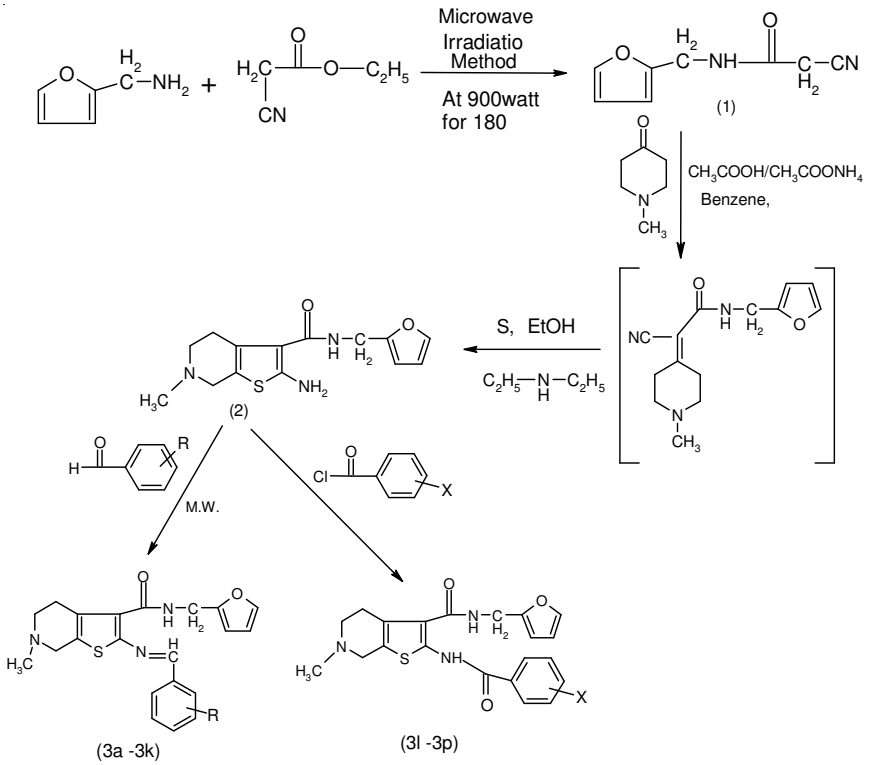
The new title compounds were synthesized with a presumption to obtain potent antibacterial agents.

EXPERIMENTAL

2-Amino-3-furfuryl carboxamido-6-N-methyl piperidino thiophene (2): The initial compound furfuryl cyanoacetamide (**1**) was prepared by heating furfuryl amine (55 mL, 0.56 M) and ethyl cyanoacetate (70 mL, 0.63 M) in microwave oven at 900 watt for 180 s. In the next step the furfuryl cyanoacetamide (6.56 g, 0.04 M) was refluxed with N-methyl piperidin-4-one (4.6 mL, 0.04 M) with an arrangement for continuous

separation of water, by Dean-stark apparatus for 8 h. The intermediate so formed was immediately cyclized by using sulphur in alkaline medium to yield the starting compound **2** which was crystallized from methanol.

General method for the synthesis of 2-[(substituted benzylidene) amino]-3-furfuryl carboxamido-6-N-methyl piperidino thiophenes (Schiff bases) (3a-3k): (Microwave assisted method): A mixture of 2-amino-3-furfuryl carboxamido-6-N-methyl piperidino thiophene (0.005 M) (**2**) and various substituted aromatic aldehydes (0.005 M) in 20 mL of isopropyl alcohol along with catalytic amount of glacial acetic acid (2 mL) was taken in conical flask and placed in microwave oven for 60 s at 900 watt. The reaction mixture was allowed to cool. Solid obtained was filtered washed with isopropyl alcohol and recrystallised with DMF:water mixture (5:1).



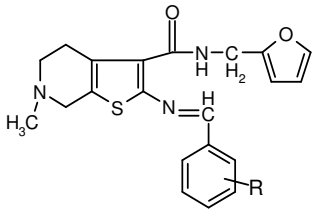
Scheme

General method for the synthesis of 2-(substituted benzamido)-3-furfuryl carboxamido-6-N-methyl piperidino thiophenes: (3l-3p): A mixture of 2-amino-3-furfuryl carboxamido-6-N-methyl piperidino

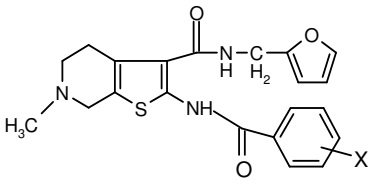
thiophene (1.5 g, 0.005 M) (**2**) in pyridine (25 mL). To this mixture, the freshly prepared acid chloride (0.005 M) was added with continuous stirring. Stirring was continued for 1 h on a magnetic stirrer. The product obtained was poured in to ice cold water. The precipitate obtained is filtered and washed with ice-cold water to remove excess of pyridine. The crude product was recrystallized from suitable solvents.

All the synthesized compounds (**3a-3k)** and (**3l-3p**) were screened for antibacterial activity by agar cup-plate method at a concentration of 50 µg/ 0.1 mL using 02 gram+ve and 02 gram-ve bacteria. The zone of inhibition was measured in mm and reported in Table-1. The activity was compared with streptomycin (50 µg/0.1 mL) as standard.

TABLE-1
PHYSICAL AND ANTIBACTERIAL DATA OF COMPOUNDS **3a** to **3p**



(3a -3k)



(3l -3p)

Compd. no.	X/R	m.p. (ºC)	Recrystallization solvent	Zone of inhibition (mm)			
				K	EC	SA	SC
3a	3,4,5-Trimethoxy	174	DMF:Water (5:1)	12	20	14	10
3b	3,4-Dimethoxy	163	DMF:Water (5:1)	8	12	10	14
3c	2-Nitro	169	DMF:Water (5:1)	–	–	4	–
3d	3-Nitro	189	DMF:Water (5:1)	–	–	12	9
3e	2-Chloro	181	DMF:Water (5:1)	9	9	–	6
3f	4-Hydroxy	193	DMF:Water (5:1)	7	–	9	–
3g	3-Methoxy-4-Hydroxy	179	DMF:Water (5:1)	18	26	22	20
3h	2-Hydroxy	166	DMF:Water (5:1)	–	6	8	–
3i	4-Methoxy	131	DMF:Water (5:1)	7	8	9	–
3j	4-Dimethyl amino	119	DMF:Water (5:1)	12	16	18	16
3k	4-Chloro	175	DMF:Water (5:1)	–	10	–	7
3l	4-Chloro	211	Ethyl acetate	20	24	10	9
3m	H	71	Ethyl acetate	–	10	8	7
3n	4-Amino	173	DMF:Water (5:1)	–	7	8	–
3p	2-Bromo	191	DMF:Water (5:1)	12	9	7	16
Standard	Streptomycin			25	30	24	22

K = *Klebsiella*, EC = *E. coli*, SA = *S. aureus*, SC = *S. citrus*

RESULTS AND DISCUSSION

All the compounds of the first series are bright coloured solids. Melting points are uncorrected, IR (KBr) was recorded on Perkin Elemer spectrum RX_1, ^1H NMR spectra were recorded on Bruker-Avance 700 MHz and the chemical shift values are in δ (ppm), Maldi GC-MS was used to record mass spectra.

The formation of furfuryl cyanoacetamide (**1**) was confirmed by the presence of specific IR peaks at 3293 cm^{-1} ν(-NH-); 3159 cm^{-1} ν(Ar-CH); 2929 cm^{-1} ν(Ali-CH); 2250 cm^{-1} ν(-CN); 1652 cm^{-1} ν(C=O); 1559 cm^{-1} ν(NH-bend); 1202 cm^{-1} ν(-CO).

The formation of 2-amino-3-furfuryl carboxamido-6-N-methyl piperidino thiophene (**2**) was confirmed by presence of specific IR peaks at 3461, 3364 cm^{-1} ν(-NH_2); 3217 cm^{-1} ν(-NH-); 3140 cm^{-1} ν(Ar-CH); 1627 cm^{-1} ν(C=O); 1526 cm^{-1} δ(NH-bend); 1600-1475 cm^{-1} ν(Ar-C=C); 690, 738 cm^{-1} (mono substituted); 1202 cm^{-1} ν(C-O); 824 cm^{-1} ν(C-N); 690 cm^{-1} ν(S-C).

The formations of new Schiff bases (**3a-3k**) were confirmed by the difference in melting points, R_f values and specific IR peaks. The IR spectrum of the compound **2** shows distinct peaks of primary amino group at 3364 and 3217 cm^{-1} and where as that of derivatives **3a** to **3k** have no primary amino group peak instead peaks for imine group at 1539 itself is sufficient to explain the formation of the new derivatives.

^1H NMR spectra in (DMSO) of the following representative compounds

3a = δ (ppm) 9.09 (t, 1H, -NH-); 8.52 (s, 1H, -N=CH); 7.54 (d, 1H, Ar-H); 7.27 (s, 2H, Ar-2H); 6.37 (t, 1H, Ar-H); 6.36 (d, 1H, Ar-H); 4.54 (d, 2H, CH_2); 3.78 (s, 9 H, Ar-H); 3.73 (s, 2H, -CH_2-); 2.88 (t, 2H, -CH_2); 2.74 (t, 2H, -CH_2-); 2.49 (s, 1H, N-CH_3).

3c = δ (ppm) 8.78 (t, 1H, -NH-); 8.70 (s, 1H, N=CH); 8.12(d, 1H, Ar-H); 7.94 (d, 1H, Ar-H); 7.80(m, 2H, Ar-H); 7.62 (d, 1H, Ar-H) 6.42 (t, 1H, Ar-H); 6.34 (d, 1H, Ar-H); 4.49 (d, 2H, CH_2); 3.54 (s, 2H, -CH_2-); 2.77 (t, 2H, -CH_2); 2.63 (t, 2H, -CH_2-); 2.36 (s, 1H, N-CH_3).

3e = δ (ppm) 8.85 (t, 1H, -NH-); 8.70 (s,1H, N=CH); 7.83(d, 1H, Ar-H); 7.62(d, 1H, Ar-H); 7.55 (m, 2H, Ar-H); 7.43 (t, 1H, Ar-H); 6.44 (t, 1H, Ar-H); 6.36 (d, 1H, Ar-H); 4.49 (d, 2H, CH_2); 3.49 (s, 2H, -CH_2-); 2.78 (t, 2H, -CH_2); 2.63 (t, 2H, -CH_2-); 2.33 (s, 1H, N-CH_3).

3g = δ (ppm) 10.05 (s, 1H, -OH); 9.24 (t, 1H, -NH-); 8.42 (s, 1H, N=CH); 7.5(s, 1H, Ar-H); 7.45 (s, 1H, Ar-H); 7.26(d, 1H, Ar-H); 6.87 (d, 1H, Ar-H); 6.40 (t, 1H, Ar-H); 6.32 (d, 1H, Ar-H); 4.53 (d, 2H, CH_2); 3.75 (s, Ar-H); 3.54 (s, 2H, -CH_2-); 2.88 (t, 2H, -CH_2); 2.65 (t, 2H, -CH_2-); 2.07 (s, 1H, N-CH_3).

Mass spectra of 3e showed m/z peak at 413: The formations of compounds (**3l-3p**) were confirmed by difference in melting points, R_f values and IR spectra. The IR spectra of the compound **2** shows distinct peaks of primary amino group at 3364 and 3217 cm^{-1} and where as that of derivatives **3l** to **3p** have no primary amino group peak instead peaks for secondary amine at 3310 cm^{-1} itself is sufficient to explain the formation of the new derivatives.

^{1}H NMR in ($CDCl_3$) of the compound: 3m = δ (ppm) 8.10 (t, 1H, NH); 8.08 (d, 1H, Ar-H); 7.5 (m, 5H, Ar-H); 7.48(s, 1H, NH); 6.34(t, 1H, Ar-H); 6.32 (d, 1H, Ar-H); 4.65 (d, 2H, CH_2); 4.18 (s, 2H, -CH_2-); 3.33 (t, 2H, -CH_2); 3.25 (t, 2H, -CH_2-); 2.17 (s, 1H, N-CH_3).

Finally out of 15 compounds screened for antibacterial activities. The compound **3g** named 2-[(3-methoxy-4-hydroxy benzylidene)amino]-3-furfuryl carboxamido-6-N-methyl piperidino thiophene was found to be the most active antibacterial compound among the series and compound with *p*-chloro (**3l**) named 2-(4-chloro benzamido)-3-furfuryl carboxamido-6-N-methyl piperidino thiophene showed good activity against *Klebsiella* and *Escherichia coli* only and moderate activity against gram positive organisms. Compound **3g** showed considerable antibacterial activity among the two series compared to the standard.

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