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Microwave Assisted Synthesis of Some 2-Amino-3-(p-Fluorocarboxanilido)-6-Methyl piperidino[4,3-b] Thiophenes and Their Antibacterial Evaluation

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***Abstract*—Synthesis of a series of 2-substituted-3-(p-fluorocarboxanilido)-6-methyl piperidino (4, 3-b) thiophenes has been carried out by microwave irradiation method. The microwave methods effectively reduced the reaction time from 3-4 h (conventional method) to a few minutes (1.0-1.5 min). Highest yield improvement of about 82% was observed for compound IIIc. All the compounds were characterized by using spectral and analytical techniques. All the compounds were screened for their antibacterial activity and showed moderate to significant activities.**

Keywords-Piperidino thiophenes, Gewald reaction, Microwave irradiation

I. INTRODUCTION

Infectious diseases are one of the leading causes of death worldwide, during the past few decades. New infectious diseases have appeared and old ones, thought to be controlled have reemerged [1] and thus, despite of many significant developments in the antimicrobial therapy, many problems are still to be solved for most of the antimicrobial drugs available [2]. Hence, discovery of novel antimicrobial agents with better pharmacological profile is still highly desirable. Thiophenes are reported to possess a number of significant and diverse biological activities such as antifungal [3, 4], analgesic [5], anti-inflammatory [6-8], antibacterial [9], antioxidant [10], antitumor [11], local anesthetic [12] and antimicrobial activities [13,14].

During our synthetic studies, it was observed that the conventional synthesis of 2-substituted-3-(p-fluorocarboxanilido)-6-methyl piperidino (4, 3-*b*) thiophene required a reaction time of about 3-4 h with poor yields (highest yield was 58% for compound (IIIc) [15]. On the other hand microwave assisted organic reactions have emerged as a new 'lead' in organic synthesis with important advantages like highly acclerated rate of reaction alongwith improvement in yield and quality of products [16]. Thus keeping in view these advantages of these techniques, and immense biological importance of thiophenes, and as a part of our ongoing programme on design and discovery of novel pharmacotherapeutic and antimicrobial and agents [17-21], it was felt worthwhile to study the reaction under microwave irradiation with the aim of decreasing the reaction time and increasing the yield and to screen the target compounds for antibacterial activity.

II. EXPERIMENTAL

A. Chemistry

All reagents, solvents and catalyst were of analytical grade and used directly. The purity of synthesized compounds was ascertained by thin layer chromatography on silica gel G in various solvent systems using iodine vapors as detecting agents. All the melting points reported were determined in open capillaries using Veego VMP-1 melting point apparatus expressed in ^{o}C and are uncorrected. The IR spectra of the compounds were recorded on Perkin-Elmer Infra Red-283 FTIR spectrometer in KBr phase and are expressed in cm^{-1}. ^{1}H NMR spectra recorded on Brucker 300 MHz NMR spectrometer (chemical shift in δ ppm) using TMS as internal standard.

Synthesis of 2-amino-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene

B. Reported method

A mixture of p-fluorocyano acetanilide (I) (0.04mol), N-methyl piperidin-4-one (0.04mol), ammonium acetate (2g) and glacial acetic acid (2ml) in benzene (100ml) was refluxed for 6 h. The intermediate crude product obtained was immediately processed by reacting with sulfur (1.28 g) in alcohol (30 ml) at 45-50 ^{0}C adding diethyl amine (4 ml) drop wise with continuous stirring for 3h to yield 2-amino-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene. Synthesis of Schiff bases (IIIa-IIIm) was carried out by reacting a mixture of 2-amino-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene

(II) (0.05mol) and appropriately substituted aryl aldehyde (0.05mol) in ethanol (in presence of catalytic amount of glacial acetic acid) by heating under reflux for 3-4 h. The solid product obtained was filtered washed with ethanol, dried and recrystallized [15].

C. Microwave method

A mixture of 2-amino-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene (II) (0.05mol) and appropriately substituted aryl aldehyde (0.05mol) in ethanol was placed in a conical flask, which was covered with a glass funnel. A petri dish containing few ice pieces was kept on the funnel to prevent excess evaporation of the solvent. The reaction mixture was irradiated with microwaves at different microwave intensities for different durations by following the pulse heating approach (irradiation in 15 seconds increments). A beaker containing water was also kept in the oven to serve as 'heating sink'. To check the completion of reaction, a TLC was run and finally the reaction mixture was processed in a manner similar to the conventional procedure. The authenticity of product was confirmed by physical (melting point, mixed melting point, Co-TLC), chemical and spectral analysis by comparison with samples obtained in conventional manner. Spectral data of synthesized compounds is presented in following text.

***2-[(4-Hydroxybenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIa). IR [v, cm-1, KBr]**: 3315 (OH); 3239 (-NH-); 2938 (CH-Ar); 1669 (C=O); 1539 (-N=CH); 1170 (C-F); 820 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 10.93 (s, 1H, NH); 8.91(s, 1H,N=CH) 8.28 (d, 1H, CH); 7.65 (q, 2H,CH); 7.50 (t, 1H, CH); 7.40 (t, H, CH); 7.10 (t, 1H, CH); 5.14 (s, 1H, OH); 3.62 (s, 2H, CH2); 3.22 (t, 2H, CH2); 2.78 (t, 2H, CH2); 2.52 (s, 3H, CH3).

***2-[(2-Nitrobenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIb). IR [v, cm-1, KBr]:** 3310 (-NH-); 1653 (C=O); 1521 (-N=CH); 1538,1320 (NO_2); 1212 (C-F); 837 (C-N). **^{1}H NMR [300 MHz, δ, ppm]** 10.94 (s, 1H, NH); 8.89(s, 1H, N=CH); 8.51 (d, 1H, CH); 7.76(q, 2H,CH); 7.61 (d, 1H, CH); 7.55 (t, 1H, CH); 7.41 (t, 1H, CH); 7.12 (q, 2H, CH); 3.62 (s, 2H, CH_2); 3.23 (t, 2H, CH_2); 2.73 (t, 2H, CH_2); 2.56 (s, 3H, CH_3).

***2-[(3-Nitrobenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene (IIIc)*. IR [v, cm-1, KBr]**: 3310 (-NH-); 1658 (C=O); 1521 (-N=CH); 1532,1365 (NO_2); 1211 (C-F) 839 (C-N). **^{1}H NMR [300 MHz, δ, ppm]** 10.43 (s, 1H, NH); 8.32(s, 1H,N=CH); 8.28 (d, 1H, CH); 7.75 (q, 2H,CH); 7.48 (t, 1H, CH); 7.20 (t, H, CH); 7.04 (t, 1H, CH); 3.78 (s, 2H, CH2); 3.32 (t, 2H, CH2); 2.69 (t, 2H, CH2); 2.53 (s, 3H, CH3).

***2-[(2-Hydroxybenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIId). IR [v, cm-1, KBr]**: 3315 (OH); 3239 (-NH-); 2938 (CH-Ar); 1669 (C=O); 1539 (-N=CH); 1170 (C-F); 820 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 10.54 (s, 1H, NH); 8.69 (s, 1H,N=CH); 8.52 (d, 1H, CH); 7.70 (q, 2H,CH); 7.62 (t, 1H, CH); 7.38 (t, H, CH); 7.18 (t, 1H, CH); 3.62 (s, 2H, CH2); 5.02 (s, 1H, OH); 3.68 (s, 2H, CH2); 3.43 (t, 2H, CH2); 2.73 (t, 2H, CH2); 2.62 (s, 3H, CH3).

***2-[(2-Chlorobenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIe). IR [v, cm-1, KBr]:** 3254 (-NH-); 2929 (CH-Ar); 1672 (C=O); 1540 (-N=CH); 1225 (C-F); 829 (CN); 780 (C-Cl). **^{1}H NMR [300 MHz, δ, ppm]** 10.93 (s, 1H, NH); 8.91(s, 1H, N=CH); 8.28 (d, 1H, CH); 7.73 (q, 2H,CH); 7.59 (d, 1H, CH); 7.50 (t, 1H, CH); 7.40 (t, 1H, CH); 7.10 (q, 2H, CH); 3.62 (s, 2H, CH_2); 3.22 (t, 2H, CH_2); 2.78 (t, 2H, CH_2); 2.52 (s, 3H, CH_3).

***2-[(4-Hydroxy-3-methoxybenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIf). IR [v, cm-1, KBr]:** 3278 (OH); 3226 (-NH-); 2935 (CH-Ar); 1669 (C=O); 1538 (-N=CH); 1222 (C-F); 831 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 11.10 (S, 1H, NH); 8.80 (s, 1H, CH); 7.65 (q, 2H, CH); 7.46 (s, 1H, CH); 7.38 (d, 2H, CH); 7.02 (q, 2H, CH); 4.90 (s, 1H, OH); 4.0 (s, 3H, OCH3); 3.71 (t, 2H, CH2); 3.23 (t, 2H, CH2); 2.74 (t, 2H, CH2); 2.51 (s, 3H, CH3).

***2-[(4-Methoxybenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIg). IR [v, cm-1, KBr]:** 3249 (-NH-); 1669 (C=O); 1522 (-N=CH); 1222 (C-F); 828 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 10.75 (s, 1H, NH); 8.95(s, 1H,N=CH); 8.49 (d, 1H, CH); 7.82 (q, 2H,CH); 7.60 (t, 1H, CH); 7.44 (t, H, CH); 7.20 (t, 1H, CH); 4.1 (s, 3H, OCH3); 3.73 (s, 2H, CH2); 3.42 (t, 2H, CH2); 2.61 (t, 2H, CH2); 2.32 (s, 3H, CH3).

***2-[(3,4-Dimethoxybenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIh). IR [v, cm-1, KBr]:** 3260 (-NH-); 2941 (CH-Ar); 1672 (C=O); 1540 (-N=CH); 1225 (C-F); 825 (CN). **^{1}H NMR [300 MHz]** δ, ppm, 11.10 (s, 1H, NH); 8.38 (s, 1H, CH); 7.65 (q, 2H, CH); 7.46 (s, 1H, CH); 7.38 (d, 2H, CH); 7.02 (q, 2H, CH); 4.0 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_2); 3.62 (t, 2H, CH_2); 3.23 (t, 2H, CH_2); 2.74 (t, 2H, CH_2); 2.51 (s, 3H, CH_3).

***2-[(4-Dimethylaminebenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIi). IR [v, cm-1, KBr]:** 3232 (-NH-); 2924 (CH-Ar); 1664 (C=O); 1526 (-N=CH); 1181 (C-F); 823 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 11.42 (s, 1H, NH); 8.30 (s, 1H, CH); 7.76 (d, 2H, CH); 7.65 (q, 2H, CH); 7.08 (q, 2H, CH); 6.76 (d, 2H, CH); 3.68 (s, 2H, CH_2); 3.27 (t, 2H, CH_2); 2.83 (t, 2H, CH_2); 3.11 (s, 6H, N $(CH_3)_2$); 2.54 (s, 3H, N-CH_3).

***2-[(3,4,5-Trimethoxybenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIj). IR [v, cm-1, KBr]:** 3249 (-NH-); 2922 (CH-Ar); 1669 (C=O); 1521 (-N=CH); 1227 (C-F); 825 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 11.18 (S, 1H, NH); 8.45 (s, 1H, CH); 7.72 (q, 2H, CH); 7.66 (s, 1H, CH); 7.31 (s, 1H, CH); 7.22 (q, 2H, CH); 4.12 (s, 3 H, OCH3;); 4.0 (s, 3H, OCH3); 3.90 (s, 3H, OCH2); 3.64 (t, 2H, CH2); 3.38 (t, 2H, CH2); 2.74 (t, 2H, CH2); 2.40 (s, 3H, CH3).

***2-[(4-Chlorobenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIk). IR [v, cm-1, KBr]:** 3260 (-NH-); 1669 (C=O); 1540 (-N=CH); 1225 (C-F); 825 (CN); 772 (C-Cl). **^{1}H NMR [300 MHz, δ, ppm]** 10.62 (s, 1H, NH); 8.72 (s, 1H,N=CH) 8.16 (d, 1H, CH); 7.76 (q, 2H,CH); 7.50 (t, 1H, CH); 7.30 (t, H, CH); 7.11 (t, 1H, CH); 3.55 (s, 2H, CH2); 3.29 (t, 2H, CH2); 2.74 (t, 2H, CH2); 2.63 (s, 3H, CH3).

***2-[(Benzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIl). IR [v, cm-1, KBr]:** 3238 (-NH-); 2936 (CH-Ar); 1669 (C=O); 1508 (-N=CH); 1216 (C-F); 847 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 10.98 (s, 1H, NH); 8.20(s, 1H,N=CH) 8.03 (d, 1H, CH); 7.81 (q, 2H,CH); 7.52 (t, 1H, CH); 7.47 (t, 2H, CH); 7.11 (t, 1H, CH); 3.82 (s, 2H, CH2); 3.54 (t, 2H, CH2); 2.91 (t, 2H, CH2); 2.69 (s, 3H, CH3).

***2-[(4-Methylbenzylidene)-amino]-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-b) thiophene* (IIIm). IR [v, cm-1, KBr]:** 3232 (-NH-); 2933 (CH-Ar); 1667 (C=O); 1538 (-N=CH); 1208 (C-F); 845 (CN). **^{1}H NMR [300 MHz, δ, ppm]** 10.55(s, 1H, NH); 8.35(s, 1H,N=CH) 8.21 (d, 1H, CH); 7.85 (q, 2H,CH); 7.60 (t, 1H, CH); 7.35 (t, H, CH); 7.15 (t, 1H, CH); 3.72 (s, 2H, CH2); 3.31 (s, 3H, CH3); 3.22 (t, 2H, CH2); 2.88 (t, 2H, CH2); 2.70 (s, 3H, CH3).

III. ANTIBACTERIAL SCREENING

All the synthesized compounds were screened for antibacterial activity by agar cup plate method at a

concentration 50 µg/0.1mL using two Gram positive and two Gram negative bacteria. The zone of inhibition was measured in mm and reported in Table-/ The activity was compared with streptomycin (50 µg/0.1mL) as standard.

IV. Results And Discussion

A new microwave procedure for rapid and efficient synthesis of 2-substituted-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-*b*) thiophene has been devised. With respect to the conventional method, the microwave method effectively reduced the reaction time from 4-5 hours to a few minutes (0.5-1.5 min). Highest yield improvement of about 82% was observed for compound IIIc, when compared with conventional method as sown in Table 1. All the compounds were characterized by using spectral and analytical data, which was in full agreement with the proposed structures. The compounds were evaluated for their antibacterial potential. The compound IIIf with 3-methoxy, 4-hydroxy substitution was found to be the most active antibacterial compound among the series and compound IIIk with chloro substitution at position 4 showed good activity against *Klebsiella* and *Escherichia coli* only and moderate activity against gram positive organisms. Results are summarized in Table-2.

Considering the fact that microwave method can find applications in chemical laboratories for rapid, cost effective and eco-friendly synthesis of similar compounds. Therefore, further research to improve synthetic procedure and yield of this series is in progress in our laboratory.

V. Conclusion

A series of 2-substituted-3-(p-fluorocarboxanilido)-6-methyl piperidino (4,3-*b*) thiophene have been synthesized employing microwave irradiation method. The compounds were evaluated for their antimicrobial activities and the compound 3f and 3k have shown significant activities.

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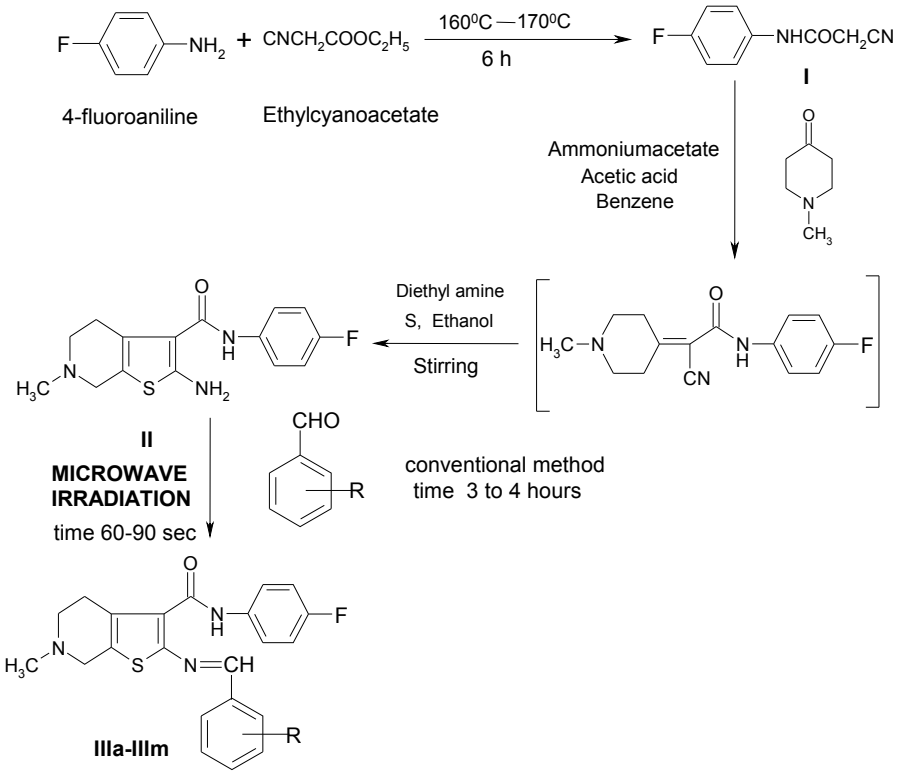

Figure 1. Synthesis of substituted-3-(p-fluorocarboxanilido)-6-methyl piperidino (4, 3-b) thiophenes

TABLE I. PHYSICAL DATA, COMPARATIVE REACTION TIME AND PERCENTAGE YIELD OF THE 2-SUBSTITUTED AMINO-3-(P-FLUOROCARBOXANILIDO)-6-METHYL PIPERIDINO[4,3-B]THIOPENE BY CONVENTIONAL AND MICROWAVE METHODS.

Compound	R	Reaction Time		Yield *(%)		Rf Value		Melting Point	
		Conventional (h)	Microwave (s)	Conventional	Microwave	Reported	Microwave (s)	Reported	Microwave
IIIa	4-Hydroxy	3.45	75	51	74	0.61	0.63	61	59-60
IIIb	2-Nitro	3.30	60	53	76	0.43	0.45	54	52-54
IIIc	3-Nitro	4.00	90	58	82	0.48	0.46	52	50-51
IIId	2-Hydroxy	3.30	60	42	69	0.35	0.38	54	52-54
IIIe	2-Chloro	3.40	75	55	79	0.78	0.76	48	45-47
IIIf	4-Hydroxy, 3-Methoxy	3.00	60	48	71	0.72	0.70	58	56-58
IIIg	4-Methoxy	3.15	60	46	72	0.64	0.61	52	50-52
IIIh	3,4-di-Methoxy	3.00	60	52	77	0.63	0.65	61	58-60
IIIi	4-N(Me)2	3.30	75	45	70	0.57	0.57	65	63-65
IIIj	3,4,5-tri-Methoxy	3.45	75	48	75	0.52	0.53	63	60-62
IIIk	4-Chloro	4.00	90	52	78	0.42	0.42	42	40-41
IIIl	H	3.15	60	55	81	0.69	0.68	60	60-61
IIIm	4-Me	3.30	90	48	73	0.58	0.56	52	50-51

*Results average of three readings

TABLE II. ANTIBACTERIAL ACTIVITIES OF TARGET COMPOUNDS

Compound	Microorganisms and Inhibition Zones (mm)			
	Klebsiella	*E. coli*	*S. aureus*	*S. citrus*
IIIa	**10**	**4**	**12**	**-**
IIIb	**4**	**-**	**-**	**4**
IIIc	**-**	**-**	**12**	**10**
IIId	**8**	**-**	**10**	**-**
IIIe	**10**	**12**	**-**	**8**
IIIf	**20**	**28**	**22**	**21**
IIIg	**8**	**10**	**10**	**-**
IIIh	**9**	**14**	**8**	**15**
IIIi	**16**	**14**	**19**	**17**
IIIj	**13**	**22**	**14**	**9**
IIIk	**21**	**28**	**13**	**11**
IIIl	**-**	**12**	**10**	**8**
IIIm	**-**	**8**	**-**	**8**
Standard	**24**	**31**	**24**	**23**