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Synthesis, characterization and antimicrobial activity of some thiophene derivatives.

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ABSTRACT

We have synthesized a series of new thiophenes with various substitutions at 2-amino position[2]. The starting material 2-amino-3-carboxamido-4, 5, 6, 7-tetramethylene thiophene was synthesized as per literature method which were derivatised into Schiff bases by reacting with various substituted aromatic aldehydes. The synthesized new compounds were characterized by mp, TLC, UV, IR, NMR and Mass spectrum. The synthesized compounds were screened for their antibacterial activity against two gram positive and two gram negative bacteria and antifungal screening against two fungi using Ampicillin and Miconazole nitrate.

Key words: Schiff bases, 2-amino-3-carboxamido-4, 5, 6, 7-tetramethylene thiophene, Antibacterial, Antifungal, Ampicillin and Miconazole nitrate

INTRODUCTION

OBJECTIVE: A new series of some thiophene derivatives were designed to meet the structural requirement of antimicrobial drugs which has been known to possess a broad spectrum of biological activities drugs ranging from antibacterial, antifungal, anti-inflammatory[1], anti pyretic to CNS depressants The therapeutic importance of these rings prompted us to develop selective molecules in which a substituent could be arranged in a pharmacophore pattern to display higher pharmacological activities

PRINCIPLE CONCLUSION

In conclusion among all the compounds tested, 2-[(4'-methylbenzylidene) imino]-3-Carboxamido-4, 5, 6, 7-tetramethylene thiophene) was found to be most active against both Gram-positive and Gram-negative bacteria among the series comparable to standard.Thiophene has exhibited an array of biological activities ranging from antibacterial, antifungal, analgesic to anti-inflammatory activity. Among the antimicrobial agents thiophene derivatives are known to have a promising activity. Few to name are Cephalothin (I), Cephalorodine (II) and Cefoxitin (III). In the current literature survey, it has been observed that drug designed by molecular modification is more rational and productive foundation of new drug, consequently the need to synthesize new molecule as potential medicinal agent is more relevant today. So far various new thiophenes have been synthesized and screened in our laboratories for antimicrobial activity[3]. The enthusiastic results prompted us to continue the investigation. So, an attempt was made to synthesize new substituted thiophene as anti-bacterial agents adapting Gewald reaction[4]. Hence the synthesis of "2-amino-3-carboxamido-4, 5, 6, 7-tetra methylenethiophene" was carried out. The different derivatives of the parent compound were achieved by using different aryl aldehyde to obtain a series of Schiff Bases [5], [6], [7].

Experimental:

a. Synthesis

The synthesis of Schiff bases of thiophene was carried out in four steps.

Step I: Synthesis of Cyanoacetamide :

Ethylcyanoacetate treated with ammonia under cold condensation to form cyanoacetamide.

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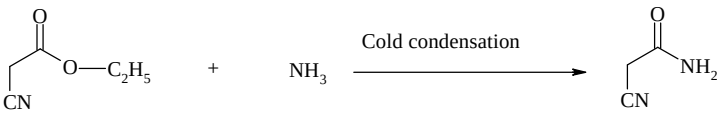
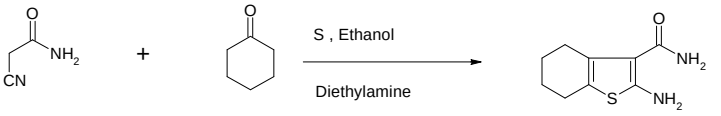
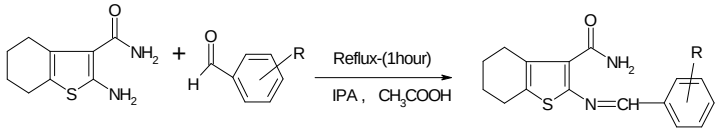


Ethylcyanoacetate **Ammonia** **Cyanoacetamide (1)**

Step II: Synthesis of 2-amino-3-carboxamido-4,5,6,7-tetramethylene thiophene: cyanoacetamide treated with cyclohexanone in the presence of sulfur and diethylamine to form 2-amino-3-carbaxamido-4,5,6,7-tetramethylene thiophene.

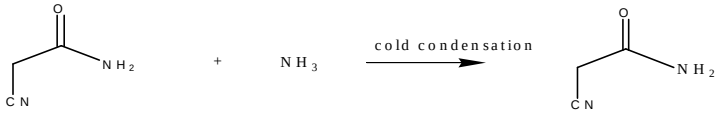


Cyanoacetamide **Cyclohexanone** **(2)**



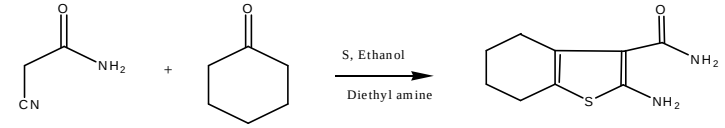
(2) 2-amino-3-carboxamido -4,5,6,7-tetramethylene thiophene (2) **(a-i) Various substituted aromatic aldehydes** **(2a-i)**

Step-1:



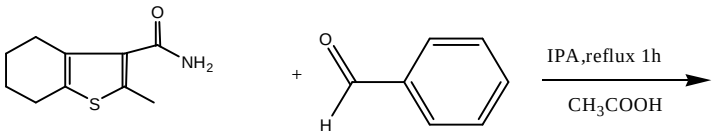
Ethylcyanoacetate Ammonia Cyanoacetamide

Step-2 :

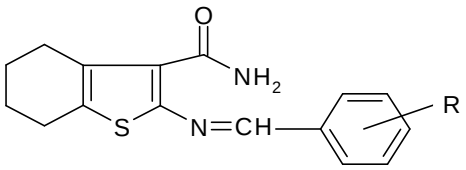


Cyanoacetamide Cyclohexanone 2-amino3-carboxamido tetra methylene thiophene

Step-3 :



2-substituted benzylidine imino-carboxamido-4,5,6,7-tetramethylene thiophenes (2a-i)



2-amino 3-carbaxamido-4,5,6,7 tetra methylene Benzaldehyde

MATERIAL AND METHODS:

The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel and visualized using iodine vapour. Melting points are determined in one end open capillary tubes and were uncorrected. All the synthesised compounds were characterised by spectral (IR, NMR (^{1}H), Mass) and elemental analysis. Melting points were determined in open capillaries with electrical melting point apparatus and are uncorrected. The IR spectra were obtained with Perkin Elmer spectrophotometer.

The 1H NMR spectra were recorded on a Bruker (300MHz) spectrometer using tetramethylsilane as an internal standard. All the new compounds gave satisfactory analytical results.

Experimental:

Synthesis of 2-amino-3-carboxamido-4,5,6,7-tetramethylene thiophene :

A mixture of Cyanoacetamide (3.2gm, 0.04 Mol), (4.0ml, 0.04 Mol) of Cyclohexanone , Sulphur (1.28gm, 0.04 Mol) and 30 ml of Ethanol was taken in conical flask. The above mixture was stirred at 45-50 ºC. Once the temperature was attained, 4ml of Diethylamine was added dropwise until Sulphur completely went in.The reaction mixture was kept overnight in refrigerator. The obtained crystals was filtered , dried and recrystsllized with Ethanol.

Synthesis of 2-substituted benzylidine imino-3- carboxamido-4,5,6,7-tera methylene thiophene (Schiff bases) (2a-i):

A mixture of the starting compound (SPR-2) (0.005 Mol) and the required aryl aldehydes (0.005 Mol) in isopropyl alcohol (30 ml) and catalytic amount of glacial acetic acid (2 ml) was subjected to reflux for 1 hour. Then cooled to room temperature. The solid separated was filtered, washed with isopropyl alcohol and recrystallized with following mentioned solvents. The structures of the products wereconfirmed by IR, 1H-NMR and 13C-NMR spectroscopy.

4-Chloro benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophenes (2a) :

mp 172-186^{0}C ; IR (KBr, cm-1) 3053, 1776, 1705, 1588, 1494, 1456, 1385 and 1122; 1HNMR(DMSO-d6) δ (ppm): 7.35-7.55 (5H, m, Ar-H) and7.84-7.94 (4H, m, Ar-H).

2-nitro benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophenes (2b) :

mp 175-180^{0}C ; IR (KBr, cm-1) 3337.6cm^{-1} at N-H str,3019 cm^{-1}at aromatic C-H bending, 1623 cm^{-1} at C=O functional group. 1HNMR(DMSO-d6) δ (ppm): 7.35-7.55 (5H, m, Ar-H) and7.84-7.94 (4H, m, Ar-H).

3-nitro benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophenes (2c):

mp 200-201oC (202-203oC, Bacon *et al.*, 1973); IR (KBr,cm-1) 3093, 1789, 1716, 1604, 1523, 1484, 1376 and 1103;1H-NMR (CDCl3) δ (ppm): 7.24-7.97 (8H, m, Ar-H) and8.19 (1H, d, *J* = 8.2 Hz, Ar-H); 13C-NMR (CDCl3) δ (ppm):122.3, 122.8, 123.8, 130.5, 131.5, 133.5, 133.6, 134.8,147.5 and 166.8.

4-hydroxy benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophene (2d):

mp 250-252oC (250oC, Bacon *et al.*, 1973); IR (KBr, cm-1)3475, 3381, 3240, 1710, 1630, 1465 and 1178; 1H-NMRDMSO-d6) δ (ppm): 5.34 (2H, s, br, NH2), 6.63 (2H, d, *J* =7.6 Hz, Ar-H), 6.98 (2H, d, *J* = 6.5 Hz, Ar-H) and 7.88 (4Hs, br, Ar-H); 13C-NMR (DMSO-d6) δ (ppm): 113.5, 119.5,123.1, 128.2, 131.5, 134.5, 148.8 and 167.6

4-methyl benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophene (2e):

mp 166-172oC (Pebalk *et al.*, 1982); IR (KBr, cm-1) 3378,3340, 3220, 3097, 3077, 1760, 1635, 1469, 1438, 1330and 1120; 1H-NMR (DMSO-d6) δ (ppm): 5.05 (2H, NH2, s,br), 6.03 (2H, s, br,NH2), 6.48 (1H, m, br, Ar-H), 7.11 (2H,s, br, Ar-H) and 7.79 (4H, m, br, Ar-H); 13C-NMR (DMSOd6)δ (ppm): 106.5, 110.3, 119.8, 122.0, 124.5, 132.5,133.7, 145.5, 148.8 and 167.9.

2-bromo benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophene 2f:

mp 166-172oC (Pebalk *et al.*, 1982); IR (KBr, cm-1) 3378,3340, 3220, 3097, 3077, 1760, 1635, 1469, 1438, 1330and 1120; 1H-NMR (DMSO-d6) δ (ppm): 5.05 (2H, NH2, s,br), 6.03 (2H, s, br, NH2), 6.48 (1H, m, br, Ar-H), 7.11 (2H,s, br, Ar-H) and 7.79 (4H, m, br, Ar-H); 13C-NMR (DMSOd6) δ (ppm): 106.5, 110.3, 119.8, 122.0, 124.5, 132.5,133.7, 145.5, 148.8 and 167.9.

3,4,5-trimethoxybenzylideneimino-3-carboxamido-4,5,6,7-tetramethylene thiophenes 2g:

mp 198-200oC (194-195oC, Sherrill *et al.*, 1928); IR (KBr,cm-1) 3062, 1789, 1743, 1712, 1612, 1465, 1087 and 720;1H-NMR (CDCl3) δ (ppm): 7.36-7.49 (4H, m, Ar-H) and7.74-7.98 (4H, m, Ar-H); 13C-NMR (CDCl3) δ (ppm): 123.8,127.7, 129.3, 131.3, 132.4, 132.8, 134.6 and 166.8.

3,4,-dimethoxy benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophenes (2h) :

mp 152-156oC (155oC, Chattaway *et al.*, 1916); IR (KBr,cm-1) 3090, 1790, 1752, 1720, 1614, 1494, 1108 and 714;1H-NMR (CDCl3) δ (ppm): 7.20-7.41 (2H, m, Ar-H), 7.56(1H, m, Ar-H) and 7.75-7.97 (4H, m, Ar-H); 13C-NMR(CDCl3) δ (ppm): 124.0, 128.1, 128.3, 130.4, 131.4), 131.7,134.1, 134.6, 136.0 and 166.4.

2-chloro benzylidene imino-3-carboxamido-4,5,6,7-tetramethylene thiophenes (2i) :

mp 170-172oC (172-173oC, Bacon *et al.*, 1973); IR (KBr,cm-1) 3089, 1762, 1708, 1612, 1427 and 1076; 1H-NMR(DMSO-d6) δ (ppm): 7.50 (2H, m, Ar-H), 7.61-7.71 (2H, m,Ar-H) and 7.87-7.99 (4H, m, Ar-H); 13C-NMR (DMSO-d6) d(ppm): 121.1, 123.5, 126.5, 130.0, 130.7, 130.8, 131.4,133.4, 134.8 and 166.6.

Table 1: Various substitution of the synthesized thiophenes

Compound	R
2a	4-Cl
2b	2-NO_2
2c	3-NO_2
2d	4-OH
2e	4-CH_3
2f	2-Br
2g	3,4,5—$(OCH_3)_3$
2e	
2h	3,4-$(OCH_3)_2$
2i	2-Cl

Table 2: Physio-chemical data of the synthesised Schiff bases

Compound	Molecular Formula	Molecular Weight	m.p (ºc)	Yield (%)	R_f Value
2a	$C_{17}H_{17}ClN_2OS$	332.85	172-173	70	0.89
2b	$C_{17}H_{19}N_3O_3S$	345.42	175-176	68	0.94
2c	$C_{17}H_{19}N_3O_3S$	345.42	177-178	62	0.85
2d	$C_{17}H_{18}N_2O_2S$	314.40	170-171	52	0.88
2e	$C_{18}H_{20}N_2OS$	312.43	178-179	56	0.88
2f	$C_{17}H_{17}N_2BrOS$	377.3	173-174	50	0.86
2g	$C_{20}H_{24}N_2O_4S$	388.48	171-172	60	0.94
2h	$C_{19}H_{22}N_2O_3S$	358.45	182-183	74	0.95
2i	$C_{17}H_{17}ClN_2OS$	380.47	176-177	51	0.96

Dose concentration: 50 ìg/0.1 ml
NA : No activity.
Control : DMSO (Dimethyl sulfoxide).
Medium : Sabouraud's Agar.
Method : Agar diffusion method.

RESULTS AND DISCUSSION

The steps for the synthesis of novel substituted thiophene analogue were prepared by the literature. In our current study the antibacterial activity was analysed by the agar dilution method. Here responses of organisms to the synthesized compounds were measured and compared with the response of the standard reference drugs. The standard reference drug used were Ampicillin and Miconazole.

The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel and visualized using iodine vapour. Melting points are determined in one end open capillary tubes and were uncorrected. All the synthesised compounds were characterised by spectral (IR, NMR (^{1}H), Mass) and elemental analysis.

Antibacterial activity:

All the test compounds i.e., 2a-i showed a varied degree of antibacterial activity against the test organisms employed. However, among this series of compounds 2e shows similar and high activity against *K.pneumoniae*, *S.aureus* whereas the test compounds 2a, 2f, 2g, 2i exhibited no activity against *E.coli* and *K.pneumoniae*. Among the test compounds employed 2f,2g,2c were having relatively mild activities against *S.aureus* The compound 2a,2b were relatively less active against *S.aureus* .

Table 3: Anti bacterial activity for synthesized compounds

Comp. Code	R	Zone of Inhibition (mm). *S .aureus*	*B. subtilis*	*E. coli*	*K. pneumoniae*
2a	4 – Chloro	02	05	NA	NA
2b	2 –Nitro	03	04	02	03
2c	3 –Nitro	05	04	05	06
2d	4 –Hydroxy	06	05	06	07
2e	4 –Methyl	07	09	07	10
2f	2- bromo	05	02	NA	NA
2g	3,4,5 - trimethoxy	05	05	NA	NA
2h	3,4 – dimethoxy	06	03	02	07
2i	2 –Chloro	07	05	NA	NA
Ampicillin	-	**11**	**13**	**16**	**12**

Dose concentration: 50 µg / 0.1 ml
NA : No Activity.
Control : DMSO (Dimethyl sulfoxide).
Medium : Nutrient Agar.
Method : Agar diffusion method.

Antifungal activity:

It could be evidenced from the results of present investigation that irrespective of their nature, none of the test compounds are comparable with the standard i.e., Miconazole in their antifungal activity. Antifungal activity among the test compounds is presented in table24. Among the newly synthesized Schiff bases 2a exhibited high activity against *Aspergillus niger*. Among the test compounds i.e.,2b,2c,2i were showing relatively moderate activity against A*spergillus niger,* whereas 2a and 2c mild activity against C*andida albicans.*

Anti Fungal Activity data for synthesized compounds (2a-i)

Table 4 : Anti fungal activity for synthesized compounds

Comp code.	R	zone of inhibition (mm). *A.niger*	*C. albicans*
2a	4 –Chloro	12	3
2b	2-Nitro	08	01
2c	3-Nitro	09	NA
2d	4-Hydroxy	06	03
2e	4-Methyl	02	NA
2f	2- bromo	NA	NA
2g	3,4,5-Tri methoxy	06	NA
2h	3,4-Dimethoxy	07	NA
2i	2-Chloro	08	NA
Miconazole	-	**19**	**16**

Dose concentration: 50 µg/0.1 ml
NA : No activity.
Control : DMSO (Dimethyl sulfoxide).
Medium : Sabouraud's Agar.
Method : Agar diffusion method.

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