ISSN: 2456-9909 (Online)

International Journal of Research in AYUSH and Pharmaceutical Sciences

Research Article

SYNTHESIS, ANTIMICROBIAL ACTIVITY OF SOME NOVEL SUBSTITUTED THIOPHENE DERIVATIVES

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Keywords:
Cyclohexanone, acetaldehyde, cyanoacetamide malanonitrile.

ABSTRACT

Various novel substituted thiophene derivatives were prepared by Gewald method using cyclohexanone/acetaldehyde treated with elemental sulphur and active nitriles like ethylcyanoacetate, cyanoacetamide and malanonitrile in presence of base morpholine and solvent ethanol to give corresponding titled compounds in good yields. The synthesized compounds were characterized by physical properties and spectral studies (IR, ^{1}H-NMR& mass) and tested for antimicrobial activity.

INTRODUCTION

Thiophene is the backbone of several important products including dyes pharmaceuticals[1] and agrochemicals[2]. The synthesis and properties of these compounds were reviewed in 1999 by Sabinis et al.[3] and more recently by Puterová et al.[4].

2-Aminothiophenes are important five-membered heterocyclic building blocks in organic synthesis and the chemistry of these small molecules is still developing based on the discovery of cyclization by Gewald[5,6]. Currently, the biological actions of 2-aminothiophenes or their 2-*N*-substituted analogues are still being investigated because of their various mechanisms of action and broad spectrum of applications with remarkable potency[7]. Various biological activities of 2-aminothiophene derivatives are analgesic[8], anti-inflammatory[9], antioxidant & antibacterial[10], antiproliferative[11], antimicrobial[12], anti-leishmanial[13], anticonvulsant[14].

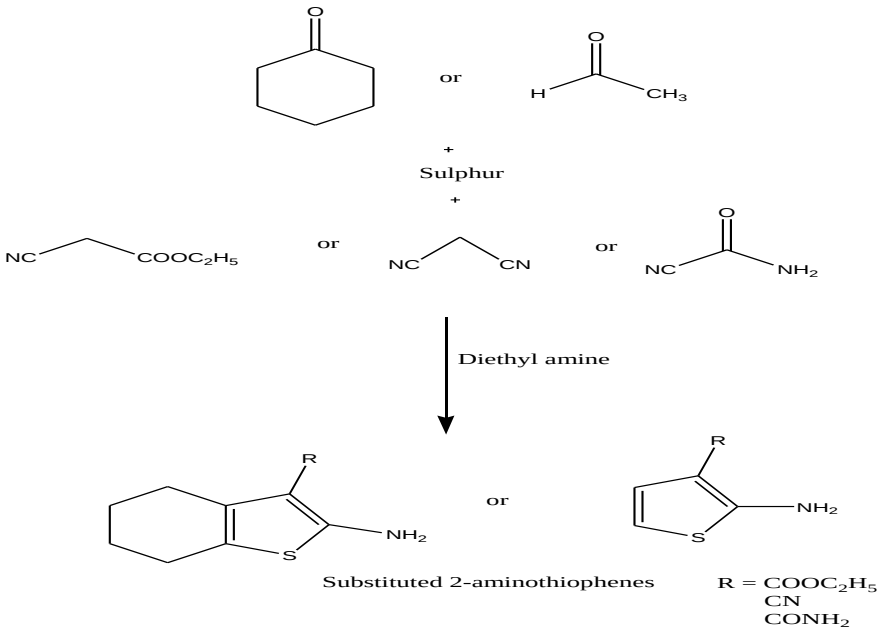
Therefore, it seems promising to synthesize some new substituted thiophene derivatives using compounds like cyclohexanone /acetaldehyde, sulphur, ethyl cyanoacetate, cyanoacetamide & malanonitrile.

Substituted thiophene derivatives possess numerous activities. As part of ongoing studies in developing new anti-microbials, we report the synthesis of a new class of structurally novel derivatives with interesting anti-microbial properties.

MATERIALS AND METHODS

Materials and reagents were obtained from commercial suppliers (Merck grade) and were used without further purification. Melting points were determined by using electrical melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC using Silica Gel G (Merck). IR spectra were recorded in KBr discs on a Bruker analyzer. ^{1}H-NMR &^{13} C-NMR spectra were recorded on a Bruker (400 MHz) spectrometer (chemical shifts in γ, ppm) in DMSO using TMS as internal standard. The mass spectra of the compounds recorded on Agilent LC-MSD-1200 mass spectrometer.

Experimental work



General procedure for synthesis of novel substituted thiophene derivatives[15]

Cyclohexanone (0.01 mol) or acetaldehyde (0.01 mol), ethyl cyanoacetate (0.01 mol) or cyanoacetamide (0.01 mol) or malanonitrile (0.01 mol) and sulphur (0.01 mol) in 20 ml of ethanol were taken in round bottomed flask and warmed with stirring meanwhile 4 ml of morpholine was added dropwise until sulphur went into solution completely. After completion of reaction the solid gets separated out. The resultant precipitate was filtered, air dried and purified by recrystallization from 95% ethanol to get pure product.

Physical characterization of the synthesized Compounds

Melting points were determined by open ended capillary tube and are uncorrected. Purity of the compounds was identified by the TLC by using silica gel-G as stationary phase. Physical characterization data of all the synthesized compounds were given in Table 1.

Table 1: Physical characterization data of the synthesized compounds

Compound	Molecular formula	Molecular weight (gm)	Melting point (˚C)	% yield	R_f value
1a	$C_{11}H_{15}O_2NS$	225	92	72	0.70
1b	$C_9H_{10}N_2S$	178	160	60	0.30
1c	$C_9H_{12}N_2SO$	196	110	55	0.45
2a	$C_7H_9O_2NS$	171	125	80	0.85
2b	$C_5H_4N_2S$	124	210	75	0.72
2c	$C_5H_6N_2SO$	142	130	72	0.6

Spectral Data

Ethyl-2-amino-4,5,6,7-tetrahydrobenzo [*b*]thiophene-3-carboxylate (1a)

IR [KBr, cm^{-1}]: 3405.52 (NH stretch), 1646.72 (C=O of ester group), 780.88 (C-S stretch), 1594.72 (C=C stretch). H^1 NMR [400 MHz, DMSO-d_6] δ:1.62 (4H, s, $C\underline{H_2}$ of cyclohexane), 2.55 (4H, s, $C\underline{H_2}$ of cyclohexane), 4.29 (2H, q, $C\underline{H_2}$), 1.30 (3H, t, $C\underline{H_3}$), 4 (2H, s, NH_2). ^{13}C-NMR [400 MHz, DMSO-d_6] δ: 160, 158.8, 138.5, 128.4, 112.6, 60.9, 25, 23.5, 23.5, 19.9, 14.1. ESI-MS: m/z (M^+): 226.

2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (1b)

IR [KBr, cm^{-1}]: 3445.08 (NH stretch), 762.52 (C-S stretch), 1619.76 (CN stretch), 1519.63 (C=C stretch). H^1 NMR [400 MHz, DMSO-d_6] δ: 1.62 (4H, s, $C\underline{H_2}$ of cyclohexane), 2.55 (4H, s, $C\underline{H_2}$ of cyclohexane), 4 (2H, s, NH_2). ^{13}C-NMR [400 MHz, DMSO-d_6] δ : 141, 136, 135, 115.3, 82.5, 24.5, 23.5, 23.0, 19.4. ESI-MS: m/z (M^+): 179.

2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (1c)

IR[KBr, cm^{-1}]: 3406.43 (NH stretch), 2927.23 (Amide NH stretch), 621.85 (C-S stretch), 1635.40 (C=O of Amide group). H^1 NMR [400 MHz, DMSO-d_6] δ: 1.62 (4H, s, CH_2 of cyclohexane), 2.55 (4H, s, CH_2 of cyclohexane), 6 (2H, s, NH_2-C=O), 4 (2H, s, NH_2). ^{13}C-NMR [400 MHz, DMSO-d_6] δ : 168.1, 163.6, 139.5, 125.2, 115.7, 24.6, 23.5, 23.1, 19.5. ESI-MS: m/z (M^+): 197.

Ethyl-2-aminothiophene-3-carboxylate (2a)

IR [KBr, cm^{-1}]: 3515.52 (NH stretch), 1636.72 (C=O of ester group), 785.33 (C-S stretch), 1574.72 (C=C stretch). H^1 NMR [400 MHz, DMSO-d_6] δ: 6.98 (1H, d, CH at 4th position), 6.30 (1H, d, CH at 5th position), 4.29 (2H, q, CH_2), 4 (2H, s, NH_2), 1.30 (3H, t, CH_3). ^{13}C-NMR [400 MHz, DMSO-d_6] δ: 134, 161.1,160, 126.8, 123.6, 60.9, 14.1. ESI-MS: m/z (M^+):172.

2-aminothiophene-3-carbonitrile (2b)

IR [KBr, cm^{-1}]: 3316.59 (NH stretch), 618.90 (C-S stretch), 1620.46 (CN stretch), 1567.01 (C=C stretch). H^1 NMR [400 MHz, DMSO-d_6] δ: 6.71 (1H, d, CH at 4th position), 6.50 (1H, d, CH at 5th position), 4 (2H, s, NH_2). ^{13}C-NMR [400 MHz, DMSO-d_6] δ: 137, 129.3, 129, 115.3, 111. ESI-MS: m/z (M^+): 125.

2–aminothiphene-3-carboxamide (2c):

IR [KBr, cm^{-1}]: 3460.74 (NH stretch), 3409.86 (Amide NH stretch), 780.52 (C-S stretch), 1680.60 (C=O of Amide group). H^1 NMR [400 MHz, DMSO-d_6] δ: 6.96 (1H, d, CH at 4th position), 6.38 (1H, d, CH at 5th position), 6 (2H, s, NH_2), 4 (2H, s, NH_2). ^{13}C-NMR [400 MHz, DMSO-d_6] δ: 168.1, 165.9, 132.2, 127.8, 120.4. ESI-MS: m/z (M^+): 143.

Antimicrobial activity[16-18]

In the present work the antimicrobial activity was tested by cup plate method. The antimicrobial activity of novel substituted 2-aminothiophenes were tested and compared with the standard Streptomycin. The concentration of different test solutions is 100 µg/ml compared with standard solution at a concentration of 100 µg/ml. Acetone, chloroform were used as a solvent.

Test organisms: *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus.*

Procedure

The Mueller Hinton Agar medium was inoculated at 1% level with 18 hrs old cultures of the above mentioned test organisms and were transferred into sterile petri dishes. The medium in the plates was allowed to set at room temperature for about 10 min and they were set to solidify in a refrigerator for 30 min. After that cylinders were made in the medium. The test solutions which were prepared in acetone and chloroform along with the standard solution of Streptomycin were placed in their respective cylinders. The plates thus prepared were left to stand in a refrigerator for about 1hr to allow the test solution for diffusion. Then incubation of the above plates was done for 24 hrs at 37^{0}C. The plates were examined for zones of inhibition and the inhibition zone diameters were measured.

RESULTS AND DISCUSSION

The present study aimed to synthesize novel substituted thiophene derivatives using the appropriate synthetic procedure i.e. reaction of cyclohexanone/acetaldehyde, sulphur and ethyl cyanoacetate, cyanoacetamide and malanonitrile in presence of morpholine and ethanol. The progress of the reaction was monitored by TLC. The obtained precipitate was filtered and dried.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr discs on a Bruker (300 FT-IR). Thin layer chromatography was performed on silica gel G (Merck). ^{1}H-NMR ^{13} C-NMR spectra were recorded on a Bruker 400 spectrometer operating at 400.13MHz in DMSO. The mass spectra of the compounds recorded on Agilent LC-MSD. Various title compounds were tested for antimicrobial activity against *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus* by using cup plate method with reference to the standard Streptomycin. After 24 hrs of incubation, zone of inhibition was measured (Table 2) and compare the antimicrobial activity of synthesized compounds (1a-2c) with standard (Fig. 2).

CONCLUSION

Cyclohexanone / acetaldehyde treated with sulphur and active nitriles to give corresponding titled compounds (1a-2c) in good yields. Synthesized compounds were characterized by physical data (Molecular formula, Molecular weight, Melting point and R_f value) and spectral data (IR spectra, H^1 NMR, ^{13}C-NMR & mass spectra). Further titled compounds (1a-2c) tested for antimicrobial activity. All the synthesized compounds possess good antimicrobial activity against *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus* with respect to standard. Specifically 1a compound possess good antimicrobial activity against *Bacillus cereus* whereas 1c compound shows very good antimicrobial activity against *Bacillus cereus*, *Staphylococcus aureus.*

ACKNOWLEDGMENTS

The authors are thankful to the Management of V. V. Institute of Pharmaceutical Sciences, Gudlavalleru, Andhra Pradesh, India for providing necessary facilities to carry out the research work.

Table 2: Anti-microbial activity results

S. No.	Name of organism	Average zone of inhibition (mm)						
		Standard (100 µg/ml)	1a (100 µg/ml)	1 b (100 µg/ml)	1 c (100 µg/ml)	2a (100 µg/ml))	2 b (100 µg/ml)	2 c (100 µg/ml)
1.	E. coli	10.8	10.6	10.5	10.8	9.4	10.2	9.5
2.	B. cereus	10.5	**20**	10.6	**20.1**	10.5	10.4	10.3
3.	S. aureus	10.4	10.2	10.7	**20**	10.3	10.6	10.4

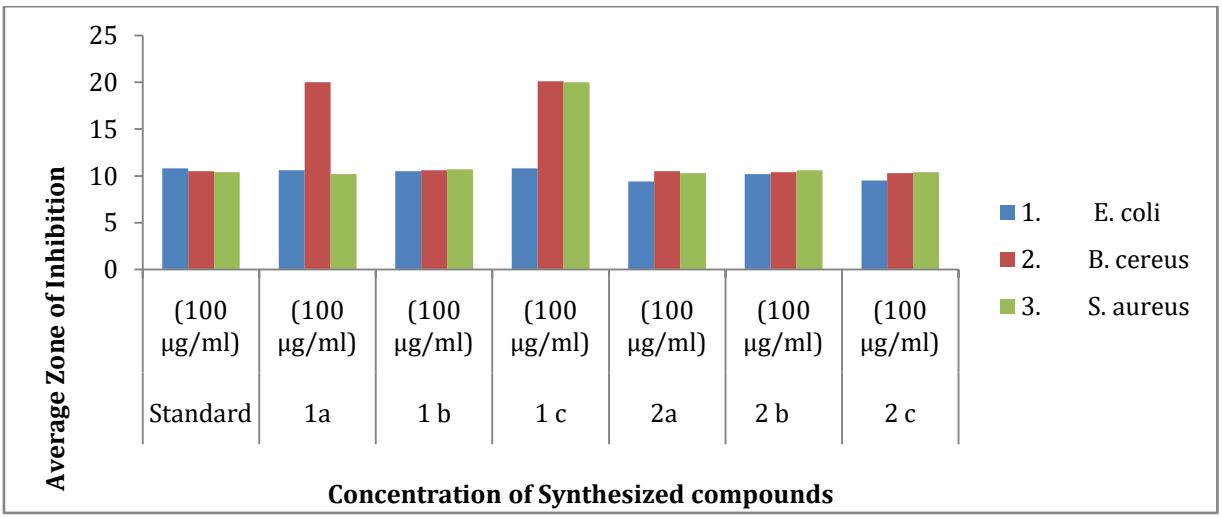


Fig. 2: Comparative antimicrobial activity of synthesized compounds

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Cite this article as:
B.Satya Sree, A.Lakshmana Rao, M.L.N.T.Amaleswari, M.Udaykiran, M.Sasikala, N.Teja. Synthesis, Antimicrobial Activity of Some Novel Substituted Thiophene Derivatives. International Journal of Research in AYUSH and Pharmaceutical Sciences, 2019;3(12):380-384.
Source of support: Nil, Conflict of interest: None Declared

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