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Research Article

Synthesis and in vitro Evaluation of Novel Thiophene Derivatives

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ABSTRACT

sulfur-containing heterocycles used to create a wide variety of sophisticated compounds with a wide range of biological functions, they are valuable analogs for medicinal chemists. Synthesis novel thiophene derivative by Schiff base were validated by FTIR, MS and 1H-NMR. The produced compounds were additionally assessed for their in vitro biological potentials, specifically antimicrobial activity against chosen microbial species utilizing tube dilution method. Antimicrobial screening outcomes revealed that compound S1 emerged as the most effective antibacterial agent against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Salmonella typhi, with an MIC value of 0. 87 µM/ml.

INTRODUCTION

Heterocyclic compounds are widely found in nature and possess diverse synthetic utility and biological activity, which encourages new strategies for medicinal chemists to devise and coordinate the search for innovative drugs [1]. Thiophene and its derivatives have demonstrated considerable importance in the pharmaceutical arena due to their various biological and clinical uses[2]. Serious infections that pose a life threat have risen due to the growing resistance of microbial agents, which is primarily attributed to multi-drug resistance in both Gram-positive and Gram-negative pathogenic bacteria [3]. Therefore, there is an urgent necessity to develop effective, potent, and innovative antimicrobial agents with superior pharmacodynamic and pharmacokinetic properties [4]. Recently, thiophene and its derivatives have drawn the attention of researchers in broadening their potential in the domain of antioxidants [5]. The primary objective of antioxidants is to counteract free radicals to avert several oxidative diseases such as autoimmune, cardiovascular, and neurovascular disorders[6]. Thiophene derivatives demonstrate impressive applications across various fields. In the medical sector, thiophene

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derivatives exhibit antimicrobial [7] analgesic and anti-inflammatory [8] antihypertensive [9] and antitumor effects [10] while they are also utilized as corrosion inhibitors for metals [11] and in the production of light-emitting diodes within material science [12].

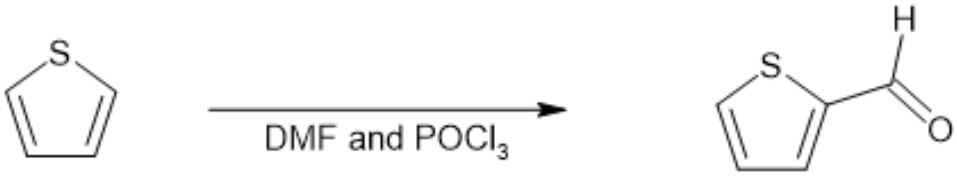
MATERIALS AND METHODS

Labtech melting point equipment was utilized to assess melting points through an open glass capillary technique. Thin layer chromatography (TLC) was employed to monitor the progression of the reaction utilizing commercial silica gel plates (Merck), Silica gel F254 on aluminum sheets. 1H NMR spectra were obtained using a Bruker Avance 400 NMR spectrometer in an appropriate chloroform solvent and are presented in parts per million (δ, ppm) downfield from tetramethyl silane (internal standard). 1H NMR data are provided as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) along with the number of protons. Infrared (IR) spectra were recorded on a Bruker FTIR spectrometer using the KBr pellet technique and are presented in cm−1. The mass spectra of the derived compounds were conducted on a Waters Micromass Q-ToF Micro instrument via mass spectrometer.

Synthesis-

Synthesis of thiophene-2-carbaldehyde

thiophene and N, and dinethylformamide (DMF) is put into reaction flask, drips POCl3 generation cationoid reaction and obtains 2 thiophene carboxaldehyde The reaction mixture will be stirred at 80°C until the conversion was complete (monitored by TLC, 1−4.5 hrs). After being cooled to room temperature, it will be treated with 5% sodium thiosulfate (20 ml) and extracted with *dichloromethane/methanol* (10:1, 10 ml × 4). The combined organic layer was dried over anhydrous sodium sulfate and will be made concentrated. The given residue will be purified through silica gel column chromatography using a mixture of ethyl acetate and petroleum ether as eluent to afford the corresponding thiophene-2-carbaldehyde.[1]



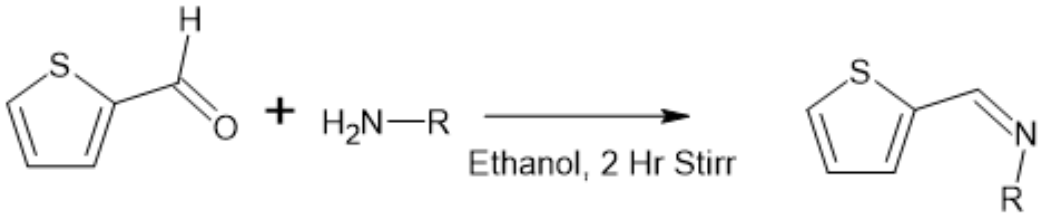
Step-2 Conventional Method

In RBF thiophene-2-carbaldehyde (1.0 mmol) and primary amine in ethanol heat for 4 hr. A few drops of 10% NaOH were added to adjust the pH and the reaction mixture then refluxed with stirring for two hours and the obtained precipitate was collected by filtration through Buchnner funnel, recrystallized from methanol, and dried at room temperature to afford yellow needles. [2]

Green route method

To a solution of 1.08 gm of primary amine (0.01 mole) in 10 ml of water, 1.22 gm thiophene-2-carbaldehyde (0.01 mole) was added. The resulting mixture was then stirred for 10 min at room temperature. The yellow precipitate formed was filtered, washed with water, and dried to afford yellow needles The Schiff's bases obtained by both conventionaland green route methods are subjected to point determination and obtain but the yields are highly varying, i.e. 52% yield in

conventional method and 97% yield in the green route method.[3,4]



R=aniline, 4 chloro aniline, 4- amino pyridine, 4-nitro aniline , 2- nitro aniline , 2-amino benzoic acid, 2 amino tolulene, 4- amino tolulene, 4-hydroxy aniline, 2-hydroxy aniline

Evaluation of antimicrobial activity

The stock solutions were prepared in DMSO having 100 µg/ml concentrations for standard and test drugs. Fresh pure cultures were used to prepare the bacterial and fungal inoculums. In the test-tubes containing serial dilutions (50, 25, 12.5, 6.25 and 3.12 µg/ml) of test and standard compounds in nutrient broth and Sabouraud dextrose broth, 100 µl of inoculum was added. After that it was incubated at 37 ± 1 °C for 24 h (bacteria), at 25 ± 1 °C for 7 days (*A. niger*) and at 37 ± 1 °C for 48 h (*C. albicans*). Antimicrobial screening results were recorded in terms of lowest concentration of test substances which inhibited the growth of microorganisms i.e. MIC.

Analytical Data

Compound S1: (*Z*)-*N*-phenyl-1-(thiophen-2-yl)methanimine: M. p: 96–97 °C; yield: 84.71%; IR (KBr pellets, cm^{-1}): 2977 (C–H str.), 1582 (C=C str.), 1657 (C=N str.), 1698 (C=O str., carbonyl), 1267 (C–O–C str.), 665.53 (C–S–C str., thiophene ring), 822 (C–Cl str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 7.28–7.50 (m, 3H, Ar–H), 8.12 (s, 1H, CH=N), 4.33 (q, 2H, CH_2), 1.39 (t, 3H, CH_3), 2.74 (t, 2H, CH_2 cyclo), 1.67 (q, 2H, CH_2 cyclo); ^{13}C NMR (75 MHz, $CDCl_3$) d 166.74, 163.75, 123.90, 122.84, 106.61, 51.20, 39.17, 32.08, 29.37, 27.50, 22.43; MS ES + (ToF): m/z 383 [M^++1].

Compound S2: (*Z*)-*N*-(4-chlorophenyl)-1-(thiophen-2-yl)methanimine: M. p: 122–124 °C; yield: 75%; IR (KBr pellets, cm^{-1}): 2970 (C–H str.), 1555 (C=C str.), 1598 (C=N str.), 1707 (C=O str., carbonyl), 1269 (C–O–C str.), 682 (C–S–C str., thiophene ring), 592 (C–Br str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 7.28–7.78 (m, 3H, Ar–H), 9.99 (s, 1H, CH=N), 4.35 (q, 2H, CH_2), 1.40 (t, 3H, CH_3), 2.71 (t, 2H, CH_2 cyclo), 1.84 (q, 2H, CH_2 cyclo); ^{13}C NMR (75 MHz, $CDCl_3$) d 165.80, 161.50, 127.46, 121.60, 106.16, 51.20, 30.20, 29.39; MS ES + (ToF): m/z 393 [M^++1].

Compound S3: (*Z*)-*N*-(pyridin-4-yl)-1-(thiophen-2-yl)methanimine: M. p: 87–89 °C; yield: 82.22%; IR (KBr pellets, cm^{-1}): 2988 (C–H str.), 1599 (C=C str.), 1648 (C=N str.), 1686 (C=O str., carbonyl), 1272 (C–O–C str.), 697 (C–S–C str., thiophene ring), 1550, 1352 (N–O str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 8.04–8.93 (m, 3H, Ar–H), 10.12 (s, 1H, CH=N), 4.36 (q, 2H, CH_2), 1.31 (t, 3H, CH_3), 2.57 (t, 2H, CH_2 cyclo), 1.67 (q, 2H, CH_2 cyclo); ^{13}C NMR (101 MHz, $CDCl_3$) d 165.94, 160.53, 128.07, 122.37, 106.00, 50.97, 32.04, 29.75, 29.26, 29.90; MS ES + (ToF): m/z 359.41 [M^++1].

Compound S4: 4-{(*Z*)-[(thiophen-2-yl)methylidene]amino}benzoic acid: M. p: 95–98 °C; yield: 72.67%; IR (KBr pellets, cm^{-1}): 2934

(C–H str.), 1600 (C=C str.), 1657 (C=N str.), 1693 (C=O str., carbonyl), 1252 (C–O–C str.), 647 (C–S–C str., thiophene ring), 2842 (O–CH_3 str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 6.84–7.33 (m, 3H, Ar–H), 3.76 (s, 3H, CH_3 methoxy), 9.75 (s, 1H, CH=N), 4.36 (q, 2H, CH_2), 1.35 (t, 3H, CH_3), 2.68 (t, 2H, CH_2 cyclo), 1.84 (q, 2H, CH_2 cyclo); ^{13}C NMR (101 MHz, $CDCl_3$) d 166.84, 161.63, 127.77, 120.37, 107.00, 50.90, 41.04, 28.75, 29.20, 28.81; MS ES + (ToF): m/z 344.4 [M^++1].

Compound S5: 2-{(*Z*)-[(thiophen-2-yl)methylidene]amino}benzoic acid: M. p: 98–100 °C; yield: 78.86%; IR (KBr pellets, cm^{-1}): 2985 (C–H str.), 1575 (C=C str.), 1649 (C=N str.), 1736 (C=O str., carbonyl), 1274 (C–O–C str.), 639 (C–S–C str., thiophene ring), 1333 (C–N str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 6.60–7.38 (m, 3H, Ar–H), 3.94 (q, 2H, N-CH_2), 1.25 (t, 3H, N-CH_3), 9.05 (s, 1H, CH=N), 4.29 (q, 2H, CH_2), 1.34 (t, 3H, CH_3), 2.53 (t, 2H, CH_2 cyclo), 1.58 (q, 2H, CH_2 cyclo); ^{13}C NMR (101 MHz, $CDCl_3$) d 165.50, 163.45, 129.90, 106.26, 106.82, 93.93, 74.51, 50.23, 32.24, 29.48, 22.45, 20.76, 15.11; MS ES + (ToF): m/z 385.53 [M^++1].

Compound S6: (*Z*)-*N*-(2-nitrophenyl)-1-(thiophen-2-yl)methanimine: M. p: 95–97 °C; yield: 82.43%; IR (KBr pellets, cm^{-1}): 2985 (C–H str.), 1597 (C=C str.), 1645 (C=N str.), 1792 (C=O str., carbonyl), 1273 (C–O–C str.), 632 (C–S–C str., thiophene ring), 3403 (O–H str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 7.02–7.05 (m, 3H, Ar–H), 3.76 (s, 3H, CH_3 methoxy), 5.07 (s, 1H, OH alcohol), 9.86 (s, 1H, CH=N), 4.26 (q, 2H, CH_2), 1.34 (t, 3H, CH_3), 2.53 (t, 2H, CH_2 cyclo), 1.78 (q, 2H, CH_2 cyclo); ^{13}C NMR (75 MHz, $CDCl_3$) d 165.90, 164.48, 131.27, 125.37, 116.11, 54.00, 39.06, 36.17, 30.82, 39.79, 20.83, 14.26; MS ES + (ToF): m/z 362 [M^++1].

Compound S7: (*Z*)-*N*-(4-nitrophenyl)-1-(thiophen-2-yl)methanimine: M. p: 97–99 °C; yield: 83.67%; IR (KBr pellets, cm^{-1}): 2985 (C–H str.), 1574 (C=C str.), 1597 (C=N str.), 1648 (C=O str., carbonyl), 1274 (C–O–C str.), 639 (C–S–C str., thiophene ring), 2854 (O–CH_3 str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 6.87–7.11 (m, 3H, Ar–H), 3.73 (s, 3H, CH_3 methoxy) 9.02 (s, 1H, CH=N), 4.26 (q, 2H, CH_2), 1.49 (t, 3H, CH_3), 2.53 (t, 2H, CH_2 cyclo), 1.67 (q, 2H, CH_2 cyclo); ^{13}C NMR (101 MHz, $CDCl_3$) d 166.48, 163.45, 129.97, 107.25, 105.80, 94.93, 75.51, 55.23, 36.24, 29.48, 22.35, 19.76, 14.11; MS ES + (ToF): m/z 374 [M^++1].

Compound S8: (*Z*)-*N*-(4-methylphenyl)-1-(thiophen-2-yl)methanimine: M. p: 94–95 °C; Yield: 87.62%; IR (KBr pellets, cm^{-1}): 2985 (C–H str.), 1596 (C=C str.), 1646 (C=N str.), 1696 (C=O str., carbonyl), 1274 (C–O–C str.), 639 (C–S–C str., thiophene ring), 607 (C–Br str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 7.64–7.86 (m, 3H, Ar–H), 8.34 (s, 1H, CH=N), 4.81 (q, 2H, CH_2), 1.52 (t, 3H, CH_3), 2.51 (t, 2H, CH_2 cyclo), 1.88 (q, 2H, CH_2 cyclo); ^{13}C NMR (75 MHz, $CDCl_3$) d 165.80, 161.48, 127.24, 121.35, 106.08, 51.00, 32.06, 31.16, 29.95, 29.68, 29.50, 29.88, 25.83, 15.26; MS ES + (ToF): m/z 393 [M^++1].

Compound S9: 4-{(*Z*)-[(thiophen-2-yl)methylidene]amino}phenol: M. p: 87–88 °C; yield: 85.63%; IR (KBr pellets, cm^{-1}): 2977 (C–H str.), 1582 (C=C str.), 1657 (C=N str.), 1698 (C=O str., carbonyl), 1267 (C–O–C str.), 665 (C–S–C str., thiophene ring), 822 (C–Cl str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 7.17–7.74 (m, 3H, Ar–H), 10.09 (s, 1H, CH=N), 4.48 (q, 2H, CH_2), 1.32 (t, 3H, CH_3), 2.40 (t, 2H, CH_2 cyclo), 1.69 (q, 2H, CH_2 cyclo); ^{13}C NMR (75 MHz, $CDCl_3$) d 166.89, 161.47, 128.27, 122.37, 107.12, 51.01, 32.06, 31.17, 29.84, 29.80, 29.78, 29.68, 29.49, 29.08, 23.83, 14.26; MS ES + (ToF): m/z 349 [M^++1].

Compound S10: 2-{(*Z*)-[(thiophen-2-yl)methylidene]amino}phenol: M. p: 94–97 °C; yield: 79.80%; IR (KBr pellets, cm^{-1}): 2983 (C–H str.), 1592 (C=C str.), 1649 (C=N str.), 1699 (C=O str., carbonyl), 1268 (C–O–C str.), 696 (C–S–C str., thiophene ring), 1533, 1344 (N–O str., aromatic); ^{1}H NMR ($CDCl_3$, δppm): 7.64–8.24 (m, 3H, Ar–H), 10.27 (s, 1H, CH=N), 4.60 (q, 2H, CH_2), 1.38 (t, 3H, CH_3), 2.51 (t, 2H, CH_2 cyclo), 1.63 (q, 2H, CH_2 cyclo);); ^{13}C NMR (75 MHz, $CDCl_3$) d 166.90, 164.48, 131.27, 125.37, 116.11, 54.00, 34.06, 36.17, 30.82, 39.80, 20.93, 15.26; MS ES + (ToF): m/z 359 [M^{+}+1].

RESULT

All the compounds synthesized from the second scheme (A-1 to A-10) were tested for antibacterial activity at a concentration of 100µg/ml, using DMF as a control against Bacillus subtilis, Bacillus pumilus, Escherichia coli, and Pseudomonas aeruginosa through the disc diffusion method. It was noted that all the compounds exhibited sensitivity to the gram-positive bacteria. Compounds S-1 showed sensitivity to gram-negative bacteria. However, the compounds did not show significant activity when compared to Ciprofloxacin, but they can be regarded as lead molecules for the further development of more potent and selective derivatives. Since compounds S-4 and S-6 were sensitive to both types of bacteria (gram-positive and gram-negative), they can be viewed as lead molecules for subsequent development as potential antibacterial agents to combat resistance. For the compounds from the second scheme, we designed and synthesized indole-fused coumarin derivatives as possible antibacterial agents. The current investigation revealed that compound S-9 was effective against gram-positive, gram-negative, and both types of fungal strains. From a structural perspective, compound S-4 contains an aldehyde functional group within the indole nucleus. Consequently, based on this study, we concluded that compound S-4 serves as a lead molecule for further development of potential antibacterial and antifungal agents.

CONCLUSION-

In summary, we can conclude that new thiophene derivatives were created with various donor or acceptor groups on the aromatic rings. Compound S1 exhibited the greatest activity
against multiple Gram positive and Gram negative bacterial strains.

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