Synthesis and Antimicrobial Activity of Some Novel Thiophene Carbohydrazide Derivatives

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ABSTRACT
The present paper describes the synthesis and antibacterial activity of fifteen novel (E)-N’-benzylidene-3-methoxy-4(4-nitrophenyl)thiophene) benzohydrazide derivatives (5a-m) from commercially available methyl-4-bromo-3-methoxythiophene-2-carboxylate as starting material. The (E)-N’-benzylidene-3-methoxy-4(4-nitrophenyl)thiophene) benzohydrazide derivatives 5a-m have been screened against gram positive and gram negative bacterial strains. It is observed that within the series of 5a-m, compounds incorporated with the fluorine substituent’s exhibited excellent antibacterial activity and the compounds 5g, 5h having benzo[b]furan and 3,4,5-trimethoxy substituent’s exhibited equipotent activity, while the remaining compounds having substituent’s viz., methoxy (-OMe) and tertiarybutyl group (-C(CH₃)₃) displayed moderate antibacterial activity.

Keywords: Thiophene benzohydrazide, Hydrazones, Antibacterial activity, Synthesis.

INTRODUCTION
The thiophenes bearing aryl substituents are known to be present in several bioactive molecules and are used as precursors of materials. Certain aryl thiophenes have been patented as herbicides [1] or for fungicidal [2] and others have antileishmanial and antifungal activities [3]. Highly substituted thiophene derivatives are important heterocyclic found in numerous biologically active and natural compounds [4-9]. A novel class of thiophene derivatives as antagonists of the human glucagon receptor has been discovered [10]. During literature survey, several articles have been found with good therapeutic activities of 3-arylthiophene derivatives.
Some of them display anthelmintic activity against Haemonchus contortus [11], HLADM activities [12]. It has also been reported that compounds containing hydrazide-hydrazone moiety possess good analgesic, anti-inflammatory [13-18] and antimicrobial activities [19-22].

In addition, hydrazone moiety plays an important key role in heterocyclic chemistry [23-29]. Among the hydrazides, 2-thienohydrazides have attracted considerable attention due to the biological activity of the 2-thiophene moiety which has been widely recognized and practically applied in several drugs [30-32], herbicides [33] and fungicides [34,35]. Thiophenecarboxylic hydrazides were tested for antituberculous activity [36] and found to show β –adrenergic blocking activities [37]. The fast resistance of bacteria against antibiotics has become a widespread medical problem. Treatment options for these infections are often limited, especially in debilitated and immune compromised patients. The dramatically rising incidence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists.

Encouraged by these reported activities and with the aim of searching for new, broad spectrum and more potent antimicrobial compounds which can improve the current chemotherapeutic treatments, thirteen new (E)-N’-benzylidene-3-methoxy-4(4-nitrophenyl)thiophene)benzohydrazide derivatives were synthesized and evaluated against antibacterial activity.

**MATERIALS AND METHODS**

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and spots were visualized with UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point (mp) determinations were performed by using Mel-temp apparatus and are uncorrected. $^1$H NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals were reported as s (singlet), d (doublet), dd (doblet of doblet), t (triplet), q (quartet), m (multiplet) and coupling
constants in Hz. The mass spectra were recorded on Agilent ion trap MS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer.

**Synthesis of methyl 3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxylate (3)**

To a mixture of methyl 4-bromo-3-methoxythiophene-2-carboxylate (1.0 g, 3.54 mmol), 2M sodium carbonate (0.56 g, 5.32 mmol), Pd(PPh₃)₄ (0.01 mmol) in 50% toluene : water (10 mL) was added 4-nitrophenyl boronic acid (0.61 g, 3.54 mmol) and stirred at reflux temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with ethylacetate and evaporated under reduced pressure to obtain the crude compound 3, which was purified by column chromatography (silica gel: 60 – 120 mesh, eluent: 5% ethylacetate / petether) to afford compound 3 as a yellow solid. Yield: 75%; m.p 119-120 °C. IR (KBr): υmax 3401, 3114, 3004, 2936, 2848, 1718, 1595, 1511, 1439, 1417, 1389, 1344, 1280, 12292, 1198, 1078, 1047, 975, 948, 851, 822, 793, 747, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.31 (d, J = 1.8 Hz, 1H), 8.27 (dd, J = 3.9 Hz, 1.8 Hz, 2H), 7.90 (dd, J = 2.1 Hz, 1.8 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H). ESI-MS: m/z, 294.0 (M+1).

**Synthesis of 3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (4)**

To a solution of compound 3 (1.5 g, 5.95 mmol) in ethanol (15.0 mL) was added hydrazine hydrate (24 mmol) and heated to reflux for 3 h. After completion of the reaction, ethanol was concentrated under reduced pressure to obtain crude compound 3. The crude compound was slurried in n-Hexane, filtered at the vaccum pump and dried to obtain compound 4. Pale yellow solid, Yield: 80%; m.p 132-133 °C. IR (KBr): υmax 3480, 3413, 3073, 3102, 2932, 2850, 1653, 1595, 1543, 1511, 1455, 1427, 1343, 1227, 1184, 1158, 1109, 1013, 1034, 944, 921, 859, 846, 788, 764, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 9.06 (br.s, 1H), 8.30 (d, J = 8.8 Hz, 2H), 8.07 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 4.57 (br.s, 2H), 3.65 (s, 3H). ESI-MS: m/z, 293.8 (M+1).

**General Experimental Procedure for the Synthesis of Hydrazone derivatives (5a-5m)**

To a stirred solution of compound 4 (100 mg, 0.40 mmol) in ethanol was added corresponding benzaldehydes (1.0 mmol) and refluxed for 1 h. The reaction medium was poured into water and extracted with ethylacetate. The organic layer was washed with water followed by brine solution, dried over anhydrous sodiumsulphate, filtered and concentrated under reduced pressure, to obtain the pure compounds. Yields of the products varied between 78 and 92%.
Synthesis of (E)-N’-(4-fluorobenzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5a)

Yield: 80%; M.p: 115-116 °C; IR (KBr): \( \nu_{\text{max}} \) 3444, 3281, 3092, 3018, 2946, 2886, 1698, 1671, 1627, 1597, 1544, 1511, 1506, 1497, 1455, 1424, 1412, 1364, 1346, 1293, 1277, 1227, 1212, 1151, 1129, 1107, 1094, 1054, 1030, 1008, 941, 925, 906, 877, 856, 841, 828, 793, 785, 773, 765, 744, 715, 694, 661, 624, 593, 575, 530, 502, 470, 450 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 11.84 (11.30\(^*\), s, 1H), 8.48 (8.02\(^*\), s, 1H), 8.33 (d, \( J = 7.6 \) Hz, 2H), 8.23 (s, 1H), 7.93 (d, \( J = 8.8 \) Hz, 2H), 7.81-7.78 (m, 2H), 7.34-7.30 (m, 2H), 3.75 (s, 3H); ESI-MS: m/z, 400.1 (M+1).

Synthesis of (E)-N’-(2,4-difluorobenzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5b)

Yield: 78%; M.p: 121-123 °C; IR (KBr): \( \nu_{\text{max}} \) 3443, 3287, 3097, 3063, 2859, 1665, 1618, 1596, 1516, 1497, 1457, 1426, 1345, 1307, 1291, 1278, 1223, 1206, 1161, 1140, 1107, 1087, 1054, 1031, 942, 928, 911, 881, 764, 747, 728, 717, 659, 613, 594, 543, 478, 447 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 11.92 (* 11.49, s, 1H), 8.68 (* 8.33, s, 1H), 8.33 (d, \( J = 7.8 \) Hz, 2H), 8.24 (s, 1H), 7.95 (s, 2H), 7.93 (s, 2H), 7.40 (br.t, \( J = 7.6 \) Hz, 1H), 7.23 (t, \( J = 7.8 \) Hz, 1H), 3.75 (s, 3H); ESI-MS: m/z, 418.0 (M+1).

Synthesis of (E)-N’-(4-(trifluoromethyl)benzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5c)

Yield: 82%; M.p: 118-119 °C; IR (KBr): \( \nu_{\text{max}} \) 3443, 3290, 3099, 3045, 2940, 2888, 2850, 1671, 1597, 1543, 1517, 1498, 1426, 1349, 1323, 1311, 1276, 1222, 1204, 1159, 1106, 1064, 1029, 1011, 929, 907, 875, 857, 829, 791, 783, 763, 714, 695, 669, 623, 577, 540, 516, 500, 456 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 12.02 (* 11.46, s, 1H), 8.56 (* 8.30, s, 1H), 8.33 (d, \( J = 7.8 \) Hz, 2H), 8.25 (s, 1H), 7.96 (s, 2H), 7.94 (s, 2H), 7.82 (d, \( J = 8.4 \) Hz, 2H), 3.77 (s, 3H); ESI-MS: m/z, 450.0 (M+1).

Synthesis of (E)-N’-(3-(trifluoromethyl)benzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5d)

Yield: 85%; M.p: 136-137 °C; IR (KBr): \( \nu_{\text{max}} \) 3443, 3278, 3162, 3101, 2964, 2940, 1650, 1598, 1514, 1455, 1419, 1345, 1295, 1281, 1244, 1218, 1124, 1116, 1096, 1069, 954, 944, 935, 919, 857, 812, 799, 764, 716, 693, 657, 628, 561, 545, 457, 443 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 12.02 (11.47\(^*\), s, 1H), 8.57 (* 8.30, s, 1H), 8.33 (d, \( J = 7.8 \) Hz, 2H), 8.25 (s, 1H), 8.04 (t, \( J = 7.7 \) Hz, 2H).
Yield: 90%; M.p: 129-130 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 11.88 (11.79\textsuperscript{*}, s, 1H), 8.84 (s, 2H), 8.32 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 10.2 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.84-7.76 (m, 2H), 7.67-7.62 (m, 1H), 3.78 (s, 3H); ESI-MS: m/z, 450.1 (M+1).

Synthesis of (E)-N’-(4-(trifluoromethoxy)benzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxyhydrazide (5e)

Yield: 92%; M.p: 134-135 °C; IR (KBr): \nu_{\text{max}} 3477, 3293, 3095, 2939, 2850, 1653, 1599, 1545, 1517, 1507, 1496, 1455, 1421, 1370, 1349, 1294, 1263, 1217, 1200, 1163, 1124, 1106, 1055, 1034, 1015, 944, 935, 919, 911, 883, 858, 845, 813, 803, 778, 764, 746, 717, 693, 675, 663, 588, 544, 455 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): δ 11.92 (*11.36, s, 1H), 8.51 (*8.24, s, 1H), 8.33 (d, J = 7.2 Hz, 1H), 8.24 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 3.75 (s, 3H); ESI-MS: m/z, 466.0 (M+1).

Synthesis of (E)-N’-(3,4,5-trimethoxy benzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxyhydrazide (5g)

Yield: 88%; M.p: 125-126 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 11.48 (s, 1H), 8.54 (s, 1H), 8.33 (d, J = 8.7 Hz, 2H), 8.24 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 7.2 Hz, 2H), 7.44 -7.28 (m, 3H), 3.76 (s, 3H); ESI-MS: m/z, 422.1 (M+1).

Synthesis of (E)-N’-(2,5-dimethoxybenzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxyhydrazide (5i)

Yield: 84%; M.p: 140-141 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 11.76 (11.39\textsuperscript{*}, s, 1H), 8.72 (8.07\textsuperscript{*}, s, 1H), 8.19-8.31 (m, 3H), 7.88-7.93 (m, 2H), 7.38 (brs, 1H), 7.01-7.06 (m, 2H), 3.81 (s, 6H), 3.74 (s, 3H); ESI-MS: m/z, 442.0 (M+1).
Synthesis of (E)-N’-(2,4-dimethoxybenzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5j)

Yield: 79%; M.p: 136-137 °C; 1H NMR (400 MHz, CDCl3): δ 11.76 (11.2*, s, 1H), 8.60 (s, 1H), 8.40 (d, J = 8.0 Hz, 2H), 8.02 (s, 1H), 7.9 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.8 Hz, 1H), 6.70 (s, 2H), 4.80 (s, 6H), 3.74 (s, 3H); ESI-MS: m/z, 442.0 (M+1).

Synthesis of (E)-N’-(4-ethoxy-3-methoxybenzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5k)

Yield: 83%; M.p: 146-147 °C; 1H NMR (400 MHz, CDCl3): δ 11.72 (11.21*, s, 1H), 8.34-8.22 (m, 1H), 8.09 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.34 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 7.5 Hz, 1H), 4.05 (q, J = 6.9 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 1.23 (t, J = 6.8 Hz, 3H); ESI-MS: m/z, 456.1 (M+1).

Synthesis of (E)-N’-(3-methoxy-4-propoxy-benzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5l)

Yield: 86%; M.p: 142-143 °C; 1H NMR (400 MHz, CDCl3): δ 11.71 (11.15*, s, 1H), 8.34-8.20 (m, 2H), 7.92 (d, J = 8.7 Hz, 2H), 7.34 (s, 1H), 7.18 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 3.94 (t, J = 8.6 Hz, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 1.71-1.68 (m, 2H), 0.96 (t, J = 8.8 Hz, 3H); ESI-MS: m/z, 470.1 (M+1).

Synthesis of (E)-N’-(4-(tert-butylbenzylidene)-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide (5m)

Yield: 85%; M.p: 138-139 °C; 1H NMR (400 MHz, CDCl3): δ 11.8 (11.24*, s, 1H), 8.05 (8.05*, s, 1H), 8.4 (d, J = 8.8 Hz, 2H), 8.30 (s, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.5 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 1.90 (s, 9H); ESI-MS: m/z, 438.2 (M+1).

**BIOLOGICAL ASSAY**

The newly synthesized (E)-N’-benzylidene-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide derivatives 5a–m, were dissolved in dimethylsulphoxide at 25 μg/mL concentration and tested against two Gram negative strains viz., i) *Escherichia coli* (MTCC 443), (ii) *Pseudomonas aeruginosa* (MTCC 424) and two Gram positive strains viz., (iii) *Staphylococcus aureus* (MTCC 96) strains iv) *Streptococcus pyogenes* (MTCC 442) using agar disc diffusion method according to the literature protocol [38-40]. The composition of nutrient agar medium was Yeast extract (5 g), NaCl (10 g), Bactotryptone (10 g), final pH 7.4. After 18 h
the exponentially growing cultures of the four bacteria in nutrient broth at 37 °C were diluted in sterile broth. From each of these diluted cultures, 1mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 x 10^6 cell/ml. The plates were set at room temperature and later dried at 37 °C for 20h. Paper discs (6mm, punched from whatmann no 1 paper) were ultraviolet sterilized and used for the assays. Discs were soaked in different concentration of the test solution and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. The plates were incubated at 37 °C in an inverted fashion. Activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control. All the samples were taken in triplicates.

RESULTS AND DISCUSSIONS
The newly synthesized N'-benzylidene-3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide 5a – m described in this paper were prepared according to the synthetic Scheme 1. The suzuki reaction of methyl 4-bromo-3-methoxythiophene-2-carboxylate with 4-nitrophenyl boronic acid 2 resulted in the formation of methyl 3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxylate 3 was carried out using Pd(PPh₃)₄ in presence of aqueous 2M sodium carbonate and toluene : water as solvent at reflux temperature for 12 h. The reaction of methyl 3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxylate 3 with hydrazine hydrate in ethanol at reflux for 3 h afforded 3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide 4. The target compounds 5a- m were synthesized by reacting 3-methoxy-4-(4-nitrophenyl)thiophene-2-carbohydrazide 3 with various aryl aldehydes a-m. The structures of the synthesized compounds were confirmed by ^1H NMR, Mass and IR spectral data. The singlet due to the azomethine (-CH=N) group appeared at δ values between 8.01 - 8.81 ppm in all the compounds. The -CONH proton appearing as singlet resonated at δ values between 11.4 and 11.8 ppm. Also, the protons of -CONH and -CH=N exhibited two separate signals in ^1HNMR spectra in between 11.40 - 11.80 ppm and 8.07 - 8.72 ppm respectively due to the nitrogen inversion. All the other aromatic protons were observed at expected regions. The ^1H NMR data for the derivatives 5a – m are in agreement with the assigned structures. The mass spectra of compounds showed (M+1) peaks, in agreement with their molecular formula.
ANTIMICROBIAL ACTIVITY

The preliminary antibacterial activity results (Table 1) indicated that the newly synthesized (E)-N’-benzylidene-3-methoxy-4(4-nitrophenyl)thiophene-benzyldrazide 5a-m, showed varying degree of zone of inhibition against the tested microorganisms. Among the series it is observed that compounds 5a to 5f exhibited excellent antibacterial activity while the compounds 5g, 5h showed equipotent activity and the remaining compounds 5i to 5m displayed moderate antibacterial activity against all the tested bacterial strains viz., *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. It is observed that within the compounds 5a-5m, compounds incorporated with the fluorine substituent’s exhibited excellent antibacterial activity where as the compounds embedded with benzo[b]furan and 3,4,5-trimethoxy substituent’s exhibited equipotent activity, while the remaining compounds having substituent’s methoxy and tertiary butyl group displayed moderate antibacterial activity. From the above varying pattern of antibacterial activity, it can be suggested that by substituting R with an appropriate group in the basic scaffold of 3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxylic acid 4 may lead to a promising antibacterial agent.

![Chemical structure](image)

**Scheme-1**: (E)-N’-benzylidene-3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxylic acid (5a-5m)

**Reagents and Conditions**: a) Pd(PPh₃)₄, 2M Na₂CO₃, Toluene:water, reflux, 12 h; b) NH₂NH₂·H₂O, ethanol, reflux, 3 h; c) Benzaldehydes a-m, ethanol, reflux, 1 h
### Table-1: Results of Antibacterial Activity of Compounds 5a–m

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<th>Compound No.</th>
<th>( R )</th>
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<th>Gram positive</th>
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<td>P.aeruginosa MTCC 424</td>
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**CONCLUSION**

In conclusion, the present paper describes the synthesis and antibacterial activity of thirteen new \((E)-N’-benzylidene-3-methoxy-4-(4-nitrophenyl)thiophene)benzohydrazide from commercially available 4-nitrophenyl boronic acid and methyl 4-bromo-3-methoxythiophene-2-carboxylate as
starting material in three steps and was screened against four bacterial strains such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. It is observed that compounds incorporated with the fluorine substituent’s exhibited excellent antibacterial activity while the compounds having benzo[b]furan and 3,4,5-trimethoxy substituent’s exhibited equipotent activity, while the remaining compounds having substituents methoxy’s and tertiary group displayed moderate antibacterial activity.

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**REFERENCE**


