IJPSR (2011), Vol. 2, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 January, 2011; received in revised form 08 February, 2011; accepted 21 March, 2011

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL THIOPHENE ACRYLATE DERIVATIVES

Anand Sivadas*[1, 2] and Narayanan Subbaraya [2]

Department of Synthetic chemistry, Orchid Chemicals and pharmaceutical Ltd, Research and Development [1], Shollinganallur, Chennai, Tamil Nadu, India
Department of Chemistry, Presidency College [2], Chennai, Tamil Nadu, India

Keywords:

Thiophene,
Antimicrobial activity,
Baylis-Hillman,
Heterocycles

Correspondence to Author:

Anand Sivadas

Department of Synthetic chemistry, Orchid Chemicals and Pharmaceutical Ltd, Research and development, Shollinganallur, Chennai, Tamil Nadu, India

ABSTRACT

This study deals with the synthesis and evaluation of antimicrobial activity of some novel Thiophene acrylate compounds. Totally fourteen compounds have been synthesized with different heterocyclic moieties on the Thiophene acrylate in order to study their influence on the antimicrobial activity. These compounds demonstrated potent to weak antibacterial activity against Gram-positive bacteria.

INTRODUCTION: Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Nitrogen and sulfur heterocyclic system families are very interesting due to their versatile pharmacological activities, such as antitumor, diuretics, fungicides, bactericides, antihelmintic, anti- allergic, anti-ulcer and local analgesic [1-3], especially in the sense of design of new drugs.

Although a number of drugs are available in the market, thirst for discovering new antimicrobial drugs with better pharmacokinetic profile, and lesser toxicity has become main objectives in the field of medicinal chemistry due to fast development of microbial resistance towards the existing molecules. Studies on thiophene-like compounds have served as a feasible field of research in the perusal of biologically active compounds [4-7].

These observations lead us to study thiophene acrylates as our basic structure and investigate the activity by introducing substituents like heterocyclic moieties, which are known to possess pharmacological activity like pyridine, pyrimidine, coumarins, pyrone, indanone, tetralone, and tyrosine [8-15].

MATERIALS AND METHODS: All the chemicals and reagents were procured from Sigma Aldrich lab grade source. All the solvents used were from commercial sources and redistilled before use. All melting points were determined on a Buchi apparatus and are uncorrected. The I.R spectra (in KBr pellets) were recorded on a JASCO spectrophotometer and frequencies are expressed in cm^{-1}. Mass spectra (CG/MS) were recorded on an Agilent MSD VL mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400 spectrometer operating at 400 MHz. The chemical shifts are reported in ppm (δ) relative to TMS. Proton and carbon spectra were typically obtained at room temperature. The purity of the compounds was checked by TLC on silica gel plates using ethyl acetate: hexane or methylene dichloride: methanol as eluent and spots were developed in ultraviolet.

General Synthetic procedure for synthesis of 4: Methyl (2E) - 2- (bromomethyl)- 3- (2-thienyl) acrylate (4): Thiophene-2carboxaldehyde **1** (0.04 mole), methyl acrylate **2** (0.14 mole), 1,4-diazabicyclo [2.2.2] octane (DABCO) (0.04 mole) were stirred at room temperature for 72 h and the reaction was monitored by TLC. Ethyl acetate was used to dilute the reaction mixture after the completion of the reaction and washed successively with 2N Hydrochloric acid, aqueous sodium bicarbonate solution and water. The organic layer was dried over anhydrous sodium sulphate and the solvent was evaporated to get crude hydroxy compound **3**.

To the crude **3,** 47% Hydrobromic acid (0.285 mole) and concentrated sulphuric acid (0.13 mole) were added and stirred in methylene dichloride at 0-10°C for 3 h. The reaction mixture was extracted in methylene dichloride and washed with sodium bicarbonate solution and water. It was then dried, solvent evaporated to get the residue, to obtain a yellow solid which was recrystallized from n-hexane. Yield- 9 g (78 %). m.p. 52°C. I.R (KBr pellets cm^{-1}): υ 1710, 1602, 1415, 1214, 1201, 723. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (s, 1H), δ 7.64 (d, J = 5 Hz, 1H), δ 7.47 (d, J = 3.6 Hz, 1H), δ 7.18 (dd, J = 3.96, 5.08 Hz, 1H), δ 4.59 (s, 2H), δ 3.87 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.02, 136.11, 135.78, 135.28, 133.96, 128.27, 123.57, 52.43, 27.91.

General Synthetic procedure for synthesis of 6-17: Methyl (2E)- 2- [(pyridin- 3- yloxy) methyl]- 3- (2-thienyl) acrylate 6: Compound **4** (0.006 mole) was treated with 3-hydroxy pyridine (0.006 mole) in the presence of potassium carbonate in dry

dimethylformamide for 1 h at room temperature. Water was added to the reaction mixture which precipitates out the solid was filtered and purified in methanol to get pure compound as brown solid. Yield- 0.95 g (56 %). m.p. 80°C. I.R (KBr pellets cm^{-1}): υ 1710, 1617, 1423, 1276, 1234, 1207, 730 ppm. ^{1}H NMR (DMSO-*d_6*, 400 MHz): δ 8.37 (d, J = 2.72 Hz, 1H), δ 8.23 (d, J = 4.56 Hz, 1H), δ 8.20 (s, 1H), δ 7.90 (d, J = 4.76 Hz, 1H), δ 7.64 (d, J = 4.56 Hz, 1H), δ 7.54- δ 7.51 (m, 1H), δ 7.40- δ 7.37 (m, 1H), δ 7.22 (t, 1H), δ 5.04 (s, 2H), δ 3.8 (s, 3H). ^{13}C NMR (300 MHz, DMSO-*d_6*): δ 166.82, 154.48, 142.07, 137.74 (2C), 136.15, 135.42, 133.38, 128.02, 124.19, 121.68, 121.11, 62.71, 52.22. Mass (m/z) = 276.1 (M^+).

Methyl (2E) - 2- {[(6-methylpyridin- 2- yl) oxy] methyl} - 3- (2-thienyl) acrylate7: Yield- 0.92 g (58 %). m.p. 98°C. I.R (KBr pellets cm^{-1}): υ 1708, 1616, 1450, 1263, 1228, 1199, 713 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.09 (s, 1H), δ 7.87 (d, J = 5.04 Hz, 1H), δ 7.61 (dd, J = 3.16, 8.0 Hz, 2H), δ 7.21 (dd, J = 3.84, 14.88 Hz, 1H), δ 6.87 (d, J = 7.16 Hz, 1H), δ 6.62 (d, J = 8.2 Hz, 1H), δ 5.19 (s, 2H), δ 3.77 (s, 3H), δ 2.39 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167.11, 162.26, 155.64, 139.39, 136.66, 136.44, 134.92, 132.85, 127.85, 122.92, 116.10, 107.33, 60.13, 52.07, 23.69. Mass (m/z) = 290.0 (M^+).

Methyl (2E) - 2- {[(5- nitropyridin- 2- yl) oxy] methyl} - 3- (2-thienyl) acrylate 8: Yield- 0.84 g (56 %). m.p. 141°C. I.R (KBr pellets cm^{-1}): υ 1710, 1670, 1440, 1265, 1201, 1103, 713 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (d, J = 3.0 Hz, 1H), δ 8.15 (t, 2H), δ 7.95 (d, J = 5.08 Hz, 1H), δ 7.71 (d, J = 3.72 Hz, 1H), δ 7.25 (t, 1H), δ 6.49 (d, J = 10.04 Hz, 1H), δ 5.15 (s, 2H), δ 3.69 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.45, 160.91, 141.20, 136.32, 135.97, 135.57, 133.38, 132.67, 129.59, 127.96, 119.96, 118.09, 52.13, 47.67. Mass (m/z) = 321.0 (M^+).

Methyl (2E) - 2- [(pyrimidin- 4- yloxy) methyl]- 3- (2- thienyl) acrylate 9: Yield- 0.92 g (61 %). m.p. 134°C. I.R (KBr pellets cm^{-1}): υ 1702, 1664, 1421, 1284, 1211, 1095, 738 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.35 (s, 1H), δ 8.07 (s, 1H), δ 7.93 - δ 7.88 (m, 2H), δ 7.68 (d, J = 4.96 Hz, 1H), δ 7.24 (t, 1H), δ 6.40 (t, 1H), δ 5.0 (s, 2H), δ 3.7 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.54, 160.16, 153.48, 152.14, 136.17 (2C), 135.31, 132.44, 127.90, 120.27, 114.62, 52.05, 44.27. Mass (m/z) = 277.1 (M^+).

Methyl (2E) - 2- [(quinazolin- 4- yloxy) methyl]- 3- (2-thienyl) acrylate 10: Yield- 1.05 g (70 %). m.p. 127°C. I.R (KBr pellets cm^{-1}): υ 1695, 1606, 1282, 1214, 1103, 941, 777 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.32 (s, 1H), δ 8.12- δ 8.10 (m, 2H), δ 8.06 (s, 1H), δ 7.94 (d, J = 5.0 Hz, 1H), δ 7.84 (dd, J = 8.32, 15.32 Hz, 1H), δ 7.72 (d, J = 3.44 Hz, 1H), δ 7.68 (d, J = 8.04 Hz, 1H), δ 7.56- δ 7.52 (m, 1H), δ 7.25 (dd, J = 3.72, 4.96 Hz, 1H), δ 5.12 (s, 2H), δ 3.67 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.64, 160.19, 147.79, 147.66, 136.32, 135.76, 135.31, 134.28, 132.29, 127.81, 127.04, 126.97, 125.91, 121.35, 121.02, 52.02, 44.30. Mass (m/z) = 327.1 (M^+).

Methyl (2E) - 2- {[(2- oxo- 2H- chromen-7- yl) oxy] methyl} - 3- (2-thienyl) acrylate 11: Yield- 1.25 g (80 %). m.p. 186°C. I.R (KBr pellets cm^{-1}): υ 1724, 1608, 1199, 1122, 998, 835, 723 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.22 (s, 1H), δ 8.03 (d, J = 9.52 Hz, 1H), δ 7.90 (d, J = 5.08 Hz, 1H), δ 7.68 (d, J = 8.64, 15.48 Hz, 2H), δ 7.23- δ 7.18 (m, 2H), δ 7.04 (dd, J = 2.4, 8.64 Hz, 1H), δ 6.34 (d, J = 9.44 Hz, 1H), δ 5.07 (s, 2H), δ 3.79 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.87, 161.46, 160.26, 155.41, 144.28, 138.03, 136.22, 135.62, 133.59, 129.63, 128.12, 121.39, 112.81, 112.77, 112.72, 101.42, 63.32, 52.34. Mass (m/z) = 343.1 (M^+).

Methyl (2E) - 2- {[(2- oxo- 2H- chromen- 4- yl) oxy] methyl} - 3- (2- thienyl) acrylate 12: Yield- 1.1 g (74 %). m.p. 149°C. I.R (KBr pellets cm^{-1}): υ 1724, 1619, 1238, 1207, 1103, 927, 881, 769 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.32 (s, 1H), δ 7.91 (d,

J = 4.92 Hz, 1H), δ 7.70- δ 7.63 (m, 3H), δ 7.44 (d, J = 8.64 Hz, 1H), δ 7.31 (t, 1H), δ 7.24 (t, 1H), δ 6.21 (s, 1H), δ 5.21 (s, 2H), δ 3.81 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.61, 164.67, 161.39, 152.69, 138.89, 136.06, 135.95, 133.95, 132.77, 128.19, 124.20, 122.72, 120.06, 116.43, 114.85, 91.33, 64.40, 52.36. Mass (m/z) = 343.1 (M^+).

Methyl (2E) - 2- {[(6-methyl- 2- oxo- 2H- chromen- 4- yl) oxy] methyl}- 3- (2- thienyl) acrylate 13: Yield- 1.0 g (74 %). m.p. 120°C. I.R (KBr pellets cm^{-1}): υ 1704, 1687, 1272, 1205, 1103, 941, 811, 719 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.32 (s, 1H), δ 7.91 (d, J = 4.92 Hz, 1H), δ 7.69 (d, J = 3.28 Hz, 1H), δ 7.45 (d, J = 13.84 Hz, 2H), δ 7.33 (d, J = 8.4 Hz, 1H), δ 7.24 (dd, J = 3.72, 4.88 Hz, 1H), δ 6.18 (s, 1H), δ 5.19 (s, 2H), δ 3.81 (s, 3H), δ 2.30 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.60, 164.70, 161.52, 150.85, 138.95, 136.04, 135.07, 134.90, 133.95, 133.63, 128.20, 122.04, 120.06, 116.27, 114.53, 91.25, 64.41, 52.35, 20.18. Mass (m/z) = 357.1 (M^+).

Methyl (2E) - 2- {[(2-methyl- 4- oxo- 4H- pyran- 3- yl) oxy] methyl}- 3- (2- thienyl) acrylate 14: Yield- 0.95 g (66 %). m.p. 63°C. I.R (KBr pellets cm^{-1}): υ 1702, 1643, 1617, 1267, 1211, 1170, 968, 825, 742 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.05 (d, J = 5.6 Hz, 1H), δ 7.99 (s, 1H), δ 7.94 (d, J = 4.96 Hz, 1H), δ 7.87 (d, J = 3.48 Hz, 1H), δ 7.25 (dd, J = 3.84, 4.76 Hz, 1H), δ 6.36 (d, J = 5.69 Hz, 1H), δ 5.05 (s, 2H), δ 3.72 (s, 3H), δ 2.17 (s, 3H).^{13}C NMR (300 MHz, DMSO-d_6): δ 173.87, 167.13, 158.98, 154.94, 143.74, 136.45, 136.24, 134.55, 132.48, 128.37, 123.49, 116.25, 65.44, 51.98, 14.30. Mass (m/z) = 307.1 (M^+).

Methyl (2E) - 2- {[(3-oxo- 2, 3- dihydro- 1H- inden- 5- yl) oxy] methyl}- 3- (2- thienyl) acrylate 15: Yield- 1.05g (70 %). m.p. 150°C. I.R (KBr pellets cm^{-1}): υ 1712, 1702, 1619, 1274, 1205, 998, 836, 730 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.18 (s, 1H), δ 7.88 (d, J = 4.96 Hz, 1H), δ 7.63 (d, J = 3.4 Hz, 1H), δ 7.53 (d, J = 8.26 Hz, 1H), δ 7.32 (dd, J = 2.52, 8.36 Hz, 1H), δ 7.24 (d, J = 2.44 Hz, 1H), δ 7.21 (dd, J = 3.8, 5.08 Hz, 1H), δ 5.0 (s, 2H), δ 3.78 (s, 3H), δ 3.06 (t, 2H), δ 2.69 (t, 2H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 206.05, 166.95, 157.89, 148.29, 137.96, 137.66, 136.55, 135.43, 133.46, 128.03 (2C), 123.72, 121.99, 105.66, 62.86, 52.29, 36.62, 24.73. Mass (m/z) = 346.1 (M^+) + NH_3 adduct.

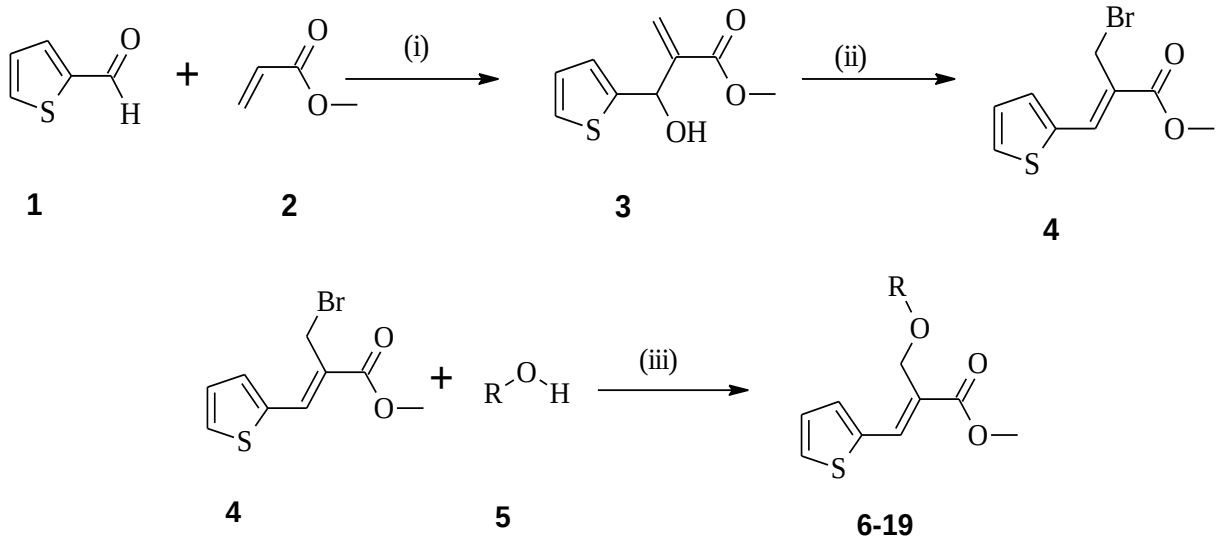
Methyl (2E) - 2- {[(6-oxo- 5, 6, 7, 8- tetrahydro naphthalen- 2- yl) oxy] methyl} - 3- (2-thienyl) acrylate 16: Yield- 0.96 g (69 %). m.p. 147°C. I.R (KBr pellets cm^{-1}): υ 1700, 1617, 1234, 1213, 1018, 709 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.21 (s, 1H), δ 7.89 (d, J = 5.08 Hz, 1H), δ 7.64 (d, J = 3.28 Hz, 1H), δ 7.54 (dd, J = 1.0, 7.68 Hz, 1H), δ 7.43 (t, 1H), δ 7.41 (t, 1H), δ 7.22 (dd, J = 3.72, 5.0 Hz, 1H), δ 5.02 (s, 2H), δ 3.79 (s, 3H), δ 2.72 (t, 2H), δ 2.51 (t, 2H), δ 1.98 (p, 2H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 197.56, 166.99, 155.52, 137.72, 136.36, 135.43, 133.47 (2C), 133.24, 128.08, 126.97, 122.14, 118.31, 116.07, 63.14, 52.30, 38.17, 22.35, 21.96. Mass (m/z) = 343.1 (M^+).

Synthetic procedure for (2S) - 2- amino- 3- (4- {[(2E)- 2- (methoxycarbonyl)- 3- (2- thienyl) prop- 2- en- 1- yl]oxy} phenyl) propanoic acid 17: Compound **4** (0.006 mole) was treated with L-Tyrosine boc (0.006 mole) in the presence of K_2CO_3 in dry DMF for 1 h at rt. Water was added to the reaction mixture which precipitates out the solid was filtered and purified in methanol. Boc was deprotected using HCl and purified by methanol to obtain white solid. Yield- 0.95 g (75 %). m.p. 182°C. I.R (KBr pellets cm^{-1}): υ 3336, 1747, 1614, 1515, 1247, 1205, 1106, 715 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.43 (s, 1H), δ 8.40 (s, 3H), δ 8.11 (s, 1H), δ 7.96 (d, J = 4.84 Hz, 1H), δ 7.62 (d, J = 3.36 Hz, 1H), δ 7.26 (t, 1H), δ 6.99 (d, J = 8.32 Hz, 2H), δ 6.68 (d, J = 8.36 Hz, 2H), δ 5.20 (dd, J = 12.2, 12.24 Hz, 2H), δ 4.28 (t, 1H), δ 3.77 (s, 3H), δ 2.98- δ 2.95 (m, 2H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 169.08, 166.43, 156.62, 137.72, 135.90, 135.43, 133.03, 130.34 (2C), 128.24, 124.03, 120.45, 115.27 (2C),

60.16, 53.25, 52.22, 34.98. Mass (m/z) = 362.0 (M^+).

Synthetic procedure for (2E) - 2- [4- (2S) - (2- amino- 2- benzyloxycarbonyl- ethyl) - phenoxy methyl]- 3- thiophen- 2- yl- acrylic acid methyl ester 18: Compound **17** (0.006 mole) was treated with benzyl chloride (0.006 mole) potassium carbonate in dry dimethylformamide for 10 h at room temperature. Water was added to the reaction mixture which precipitates out the solid was filtered and purified in methanol to obtain pale yellow solid. Yield- 0.65 g (60 %). m.p. 153°C. I.R (KBr pellets cm^{-1}): υ 1743, 1704, 1243, 1207, 1108, 728 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.13 (s, 3H), δ 7.96 (d, J = 4.84 Hz, 1H), δ 7.63 (d, J = 3.2 Hz, 1H), δ 7.44- δ 7.33 (m, 4H), δ 7.26 (t, 2H), δ 7.16- δ 7.10 (m, 2H) δ 6.97- δ 6.89 (m, 2H), δ 5.18 (d, J = 2.88 Hz, 2H), δ 5.07 (d, J = 7.44 Hz, 2H), δ 4.35 (t, 1H), δ 3.77 (s, 3H), δ 3.04 (dd, J = 7.64, 7.88 Hz, 2H)). ^{13}C NMR (300 MHz, DMSO-d_6): δ 169.07, 168.91, 166.90, 157.48, 137.68, 136.29, 135.12, 134.79, 133.16, 130.60, 130.48, 128.34 (2C), 127.55, 126.44, 122.21, 120.47, 115.32, 114.69, 114.49, 69.07, 66.83, 53.30, 52.20, 35.02. Mass (m/z) = 452.0 (M^+).

Synthetic procedure for (2E) - 2- [4- (2S)- (2- amino- 2- butyl carbomyl- ethyl) - phenoxymethyl]- 3- thiophen- 2- yl- acrylic acid 19: Compound **17** (0.006 mole), butyl amine (0.006 mole), Hydroxybenzotriazole (HOBt) (0.001 mole), 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC.HCl) (0.01 mole), Triethyl amine (0.05 mole) in dry dimethyl formamide were stirred for 10 h at room temperature. Water was added to the reaction mixture which precipitates out the solid was filtered and purified in methanol to obtain white solid. Yield- 0.5 g (60 %). m.p. 179°C. I.R (KBr pellets cm^{-1}): υ 1710, 1658, 1619, 1207, 1008, 719 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.29 (s, 1H), δ 8.16 (s, 1H), δ 8.09 (s, 2H), δ 7.89 (d, J = 4.72 Hz, 1H), δ 7.62 (d, J = 3.24 Hz, 1H), δ 7.22 (t, 1H) δ 7.17 (d, J = 8.28 Hz, 2H), δ 7.0 (d, J = 8.32 Hz, 2H), δ 4.94 (s, 2H), δ 3.88 - δ 3.86 (m, 1H), δ 3.77 (s, 3H), δ 3.13 (m, 1H), δ 2.99- δ 2.95 (m, 3H), δ 1.30- δ 1.28 (m, 2H), δ 1.20- δ 1.17 (m, 2H), δ 0.85 (t, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167.51, 166.88, 157.34, 137.30, 136.29, 135.10, 133.08, 130.53 (2C), 128.0, 127.18, 122.23, 114.38 (2C), 62.22, 53.59, 52.16, 38.15, 36.16, 30.69, 19.31, 13.49. Mass (m/z) = 417.1 (M^+).



SCHEME 1

Reagents and Condition: (i) DABCO, room temperature, 80 h (ii) Hydrobromic acid, concentrated sulphuric acid, methylene chloride, 5-10 °C, 3 h (iii) sodium carbonate, methanol, room temperature, 1 h

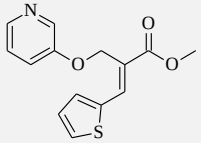
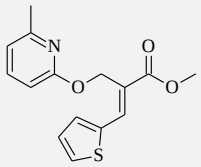
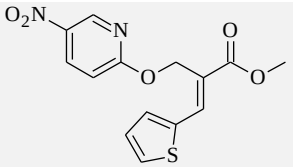
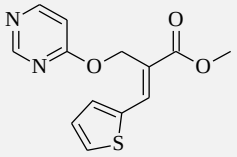
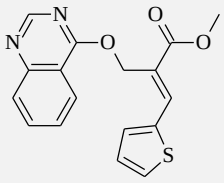
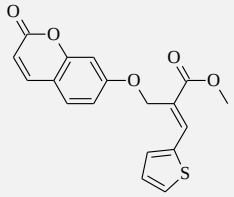
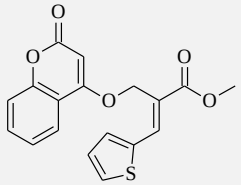
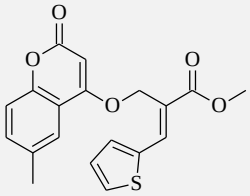
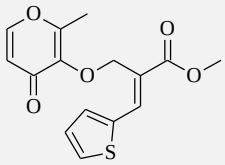
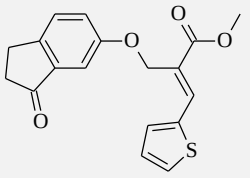
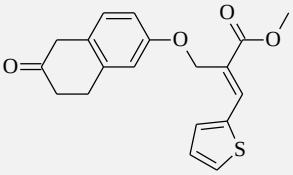
RESULTS AND DISCUSSION:

Chemistry: Compound **3** was prepared using thiophene-2-carboxaldehyde **1** and methyl acrylate **2** as starting material without any solvent and DABCO as catalyst according the reported procedure [16]. The hydroxy compound **3** was converted to thienyl bromo ester **4** by treatment with 47% Hydrobromic acid in the presence of concentrated sulphuric acid in methylene dichloride at room temperature according the reported procedure [17].

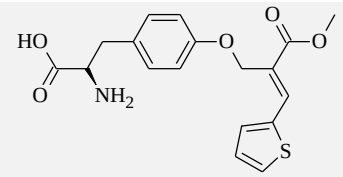
The above synthesized bromo ester **4** was treated with various heterocyclic compounds in presence of sodium carbonate and methanol to afford a series of esters at room temperature according the reported procedure [18-19].

Compounds **6-19** were prepared as per the **scheme 1** and their structures are presented in **Table 1**. The structures of all the compounds were confirmed by their spectral analysis, which are presented in the experimental section.

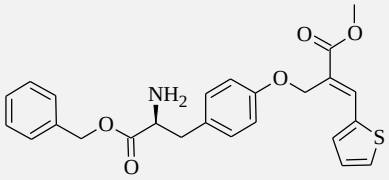
TABLE 1: STRUCTURAL FORMULAE OF THE SYNTHESIZED COMPOUNDS, 6-19

Compound Number	Structure
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	

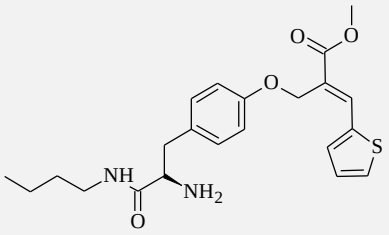
17



18



19



Pharmacology: Antimicrobial activity of all the fourteen compounds synthesized was assayed by agar well diffusion method as recommended by The Clinical and Laboratory Standards Institute (CLSI) [20] against four representative bacterial, and one fungal isolate namely *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *B. subtilis* ATCC 6633, and *Candida albicans* ATCC 90028. Bacterial cultures were grown to exponential phase and plated by pour-plate method into the 150 mm Petri dishes and allowed to settle. Wells were bored into the inoculated plate and the test compounds were dispensed in the wells at three concentrations such as 10 μg, 100 μg and 1000 μg per well respectively and allowed for complete diffusion.

Three antibacterial agents (Cefepime, Amikacin & Linezolid) were used as internal assay standards and 100% DMSO was used as a control. The plates were incubated for 24 hours at 37°C. The zones of inhibition were measured using the digital Vernier's calipers. The preliminary results of antimicrobial activities indicated that only six compounds out of fourteen compounds exhibited a moderate to good activity against bacterial strains, while other compounds did not exert any antibacterial activity. All the fourteen compounds tested against fungi did not show any antifungal activity. The disc concentration and their zone of inhibition of the tested compounds were tabulated as per CLSI and is presented in **Table 2.**

TABLE 2: ANTIMICROBIAL ACTIVITIES OF THE NEWLY SYNTHESIZED COMPOUNDS (ZONE OF INHIBITION IN mm)

Compound	*S. aureus* ATCC 25923			*B. subtilis* ATCC 6633			*E. coli* ATCC 25922			*P. aeruginosa* ATCC 27853		
	1000μg	100 μg	10μg	1000μg	100μg	10μg	1000μg	100μg	10μg	1000μg	100μg	10μg
6	12.63	9.55	nz[#]	15.6	11.6	nz	6.78	nz	nz	4.56	nz	nz
8	11.48	7.64	nz	9.86	8.63	nz	7.22	nz	nz	6.85	nz	nz
9	18.95	16.56	15.8	11.20	10.2	9.37	9.8	6.53	nz	10.6	8.7	nz
17	20.63	18.2	9.88	14.63	13.3	12.18	11.6	nz	nz	9.56	7.52	nz
18	22.47	20.55	19.8	19.65	18.9	17.63	7.8	3.36	nz	8.32	5.66	nz
19	25.68	24.92	24.0	26.62	25.9	25.62	15.3	11.6	nz	11.6	9.78	nz
Linezolid		30.16			30.53			nz			nz	
Amikacin		25.42			35.13			25.23			26.37	
Cefepime		28.21			37.6			31.47			26.69	

Compounds which showed significant activity in the preliminary screening were further tested for antibacterial activity by agar dilution method for MIC as per the CLSI against the clinical isolates of *S. aureus* ATCC 25923, *S. aureus* ATCC 43300, *B. subtilis* ATCC 6633, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *K. pneumoniae* ATCC 700603, *K. pneumoniae* ATCC 51503, *E. cloacae* 2160 P99+, *E. coli* J53 R6206, *E. coli* NCTC 13353 and *E. coli* ATCC BAA 200. All the six compounds tested showed only Gram positive activity **Table 3**.

TABLE 3: MINIMUM INHIBITORY CONCENTRATION (MIC, μg/ml) OF SELECTED COMPOUNDS AGAINST GRAM POSITIVE BACTERIAL STRAINS [a]

Compound	S. *aureus* ATCC 25923	S. *aureus* ATCC 43300	B. *subtilis* ATCC 6633
	MIC μg/mL	MIC μg/mL	MIC μg/mL
6	64	256	256
8	128	64	128
9	16	8	4
17	64	64	32
18	32	64	128
19	8	4	4
Linezolid	4	2	1
Amikacin	2	128	0.5
Cefepime	2	32	2

[a] Disc diffusion method used to determine the MIC

CONCLUSION: In conclusion, we have reported the synthesis of fifteen new thiophene acrylate compounds and evaluated their antibacterial activity. Among the compounds that exhibit antibacterial activity against Gram positive bacteria, compounds containing tyrosine in the molecular structure showed better antibacterial activity compared to the other molecules. We conclude that further improvement of the scaffold of compound **19** would pave the path for identifying a Gram-positive antibacterial compound.

ACKNOWLEDGEMENTS: We are thankful to the management of Orchid Chemicals and Pharmaceutical Ltd for the excellent support to perform the research project. We are also thankful for the kind support from the Staff of Orchid Chemicals and Pharmaceuticals Ltd in recording the spectral data and studying the biological activity of the synthesized thiophene derivatives.

REFERENCES:

1. Singh A K and Lown J W: Anti Cancer Drug Des 2000; 15: 265.
2. Kucukbay H, Durmaz R, Okuyucu N and Gunal S, Folia: Micobiology 2003; 48: 679.
3. Kucukbay H, Durmaz R, Okuyucu N, Gunal S and Kazaz C: Arzneimittelforschung 2004; 54: 64.
4. AL-Obaid A M, EI-Subbagh H J, Khodair A I and El-Mazar M M A: Anticancer Drugs 1996; 7: 873.
5. Alireza Foroumadi, Mehdi Oboudiat, Saeed Emami, Alireza Karimollah, Lotfollah Saghaee, Mohammad Hassan Moshafi and Abbas Shafiee: Bioorganic and Medicinal Chemical Letters 2006; 14: 3421.
6. Sonali Rudra, Fnu Sangita, Arti Gujrati, Manisha Pandya, Pragya Bhateja, Tarun Mathur, Smita Singhal, Ashok Rattan, Mohammed Salman and Biswajit Das: Bioorg Bioorganic and Medicinal Chemical Letters 2007; 17: 4778.
7. Ryuichi Kimura, Takahiro Yabuuchi and Masakatsu hisaki: Chemical and pharmaceutical bulletin 1962; 10(12): 1226.
8. Yeong Woo Jo, Weon Bin Im, Jae Keol Rhee, Mi Ja Shim, Won Bae Kim, Eung Chil Choi: Bioorganic and Medicinal Chemical Letters 2004; 12: 5909
9. Chandrasekaran S and Nagarajan S: II Farmaco 2005; 60: 279.
10. Sam J and Advani G G: Journal of Pharmaceutical Science 2006; 54: 753.
11. Daniel Dube, Marc Blouin, Christine Brideau, Chi-Chung Chan, Sylvie Desmarais, Diane Ethier, Jean-Pierre Falgueyret, Richard Friesen W, Mario Girard, Yves Girard, Jocelyne Guay, Denis Riendeau, Philip Tagari and Robert Young N: Bioorganic and Medicinal Chemical Letters 1998; 8: 1255.
12. Allen F H, Kennard O, Watson D G, Brammer L, Orpen A G and Taylor R:J. Chem. Soc. Perkin Trans 1987; 2: S1–19.
13. Allen Jr G R, Baker B R, Dornbush A C, Joseph J P, Kissman H M and Weiss M J: J. Med. Pharm. Chem. 1960; 2: 391.
14. 14. El-Agrody A M, Abd El-Latif M S, El-Hady N A, Fakery A H and Bedair A H: Molecules 2001; 6: 519.
15. Pratibha S and Shreeya P: Indian J. Chemistry 1999; 38B: 1139.
16. Yu C et al: Journal of organic chemistry 2001; 66: 5413.
17. Bucholz R and Hoffmann H M R: Helv Chim Acta 1991; 74: 1213.
18. Rajan Y C, Kanakam C C, Selvam S P and Murugaesan K: Tetrahedron Letters 2007; 48: 8562.
19. Rajan Y C and Kanakam C C: Tetrahedron Letters: 2008; 49: 3023.
20. Performance standards for antimicrobial susceptibility testing: Eighteenth information supplement 2008; Vol. 28 No. 1: M 100-S18.