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SYNTHESIS OF NEW SERIES OF THIENYL ACRYLATE DERIVATIVES VIA BAYLIS-HILLMAN REACTION AND EVALUATION OF ANTIMICROBIAL ACTIVITY

Anand Sivadas [1, 3] *, Maneesh Paul Satyaseela [2], Thirunavukkarasu Bharani [2], Sampath Kumar Upparapalli [1] and Narayanan Subbaraya [3]

Department of Synthetic chemistry, Orchid Chemicals and Pharmaceutical Ltd., Research and Development [1], Shollinganallur, Chennai, Tamil Nadu, India
Department of Microbiology, New Dug Discovery, Orchid Research Laboratories Ltd., New Drug Discovery [2], Shollinganallur, Chennai, Tamil Nadu, India.
Department of Chemistry, Presidency College [3], Chennai, Tamil Nadu, India

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Correspondence to Author:

Anand Sivadas

Research Scientist-II, Department of Synthetic chemistry, Orchid Chemicals and pharmaceutical Ltd, Research and development, Shollinganallur, Chennai , Tamil Nadu, India

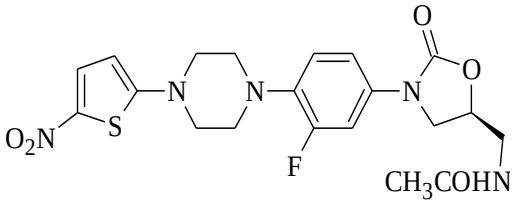
ABSTRACT

A series of new Thienyl acrylate compounds were synthesized via Baylis-Hillman reaction and tested to demonstrate *in vitro* antimicrobial activity. Some of these compounds exhibited a very good activity against Gram positive strains. The structure of these newly synthesized compounds were conformed by ^{1}H NMR, IR, Mass and Elemental analysis, some of them were also confirmed by ^{13}C NMR.

INTRODUCTION: A dramatic increase in microorganisms resistant to multiple antimicrobial agents is a serious problem worldwide, especially the gram positive bacteria which triggered a clear need for the discovery of new antibacterials rather than analogs of the existing ones [1-3]. Traditionally, small molecules have been a reliable source for discovering novel biologically active compounds. Although a lot of work has been done on the heterocycles, they remained an active area of research [4-6]. In this context, thiophene nucleus represents a very important field in drug discovery, which is present in many natural and synthetic products with a wide range of pharmacological activities [7-11]. Studies on thiophene like compounds have served as a feasible field of research in the perusal of biologically active compounds (**Fig. 1**) [12-15].

Consequently, there continues to be interest in developing new biologically active compounds. In our continuous endeavor to develop new and potent antibacterial molecules, we decided to study thiophene as our basic structure and investigate the activity by introducing substituent like quinoline, which is known to possess pharmacological activity [16-23]. Quinolines and their derivatives occur in numerous natural products. Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as being general synthetic building blocks [24-25].

In particular hydroxyquinoline at 8th position well known as oxyquinoline has wide variety of uses and its medicinal and agricultural significances were discovered before the start of current century. 8-hydroxy quinoline and its derivatives have been found to show diverse biological activities such as antibacterial, antimalarial, antipneumococcic, fungicidal, antiseptic, antituberculotic, antineoplastic, amebacidal, pesticidal, antihelmintic and ant diuretic activities like Chlorquinaldol, Clioquinol and nitroxoline. Its derivatives benzoquine, 8-hydroxy quinoline citrate and 8-hydroxy quinoline sulfate are employed as antiseptic and disinfectants.



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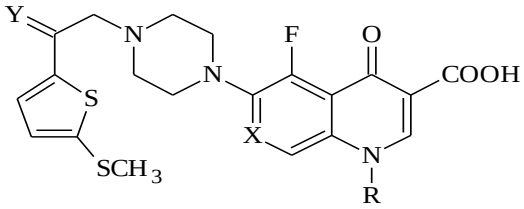

X = CH, N

Y = O, NOH, NOMe, NOBn

R= cyclopropyl, ethyl

B

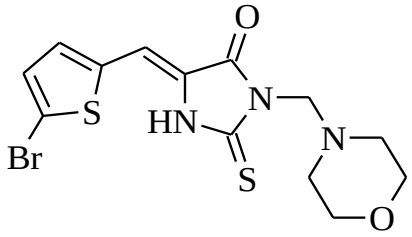

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FIG. 1: STRUCTURE OF KNOWN COMPOUNDS CONTAINING THIOPHENE

We have prepared a library of thienyl acrylate compounds via Baylis-Hillman reaction, which have been evaluated for their *in vitro* antibacterial and anti fungal activity. The Baylis-Hillman reaction [26-32] has attracted the attention of organic chemists for preparing synthetically useful multifunctional molecules which have been successfully employed in various syntheses.

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 spectrometer 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 (4a-b):

Methyl (2E)-2-(bromomethyl)-3-(2-thienyl) acrylate (4a): Thiophene-2-carboxaldehyde **1a** (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 **3a**.

To the crude **3a,** 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.pt. 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.

Methyl (2E)- 2- (bromomethyl)- 3- (5- bromo- 2- thienyl) acrylate (4b): Yield- 6.5 g (73 %); m.pt. 80°C; I.R (KBr pellets cm^{-1}) υ 1708, 1606, 1411, 1253, 1207, 771; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1H), δ 7.26 (s, 1H), δ 7.21 (d, J = 5.72 Hz, 1H), δ 4.50 (s, 2H), δ 3.86 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.15, 135.88, 135.38, 134.26, 127.27, 122.63, 52.51, 27.86.

General Synthetic procedure for synthesis of 6-18:

Methyl (2*E*) - 2- {[(2-methylquinolin- 8- yl) oxy] methyl}- 3- (2- thienyl) acrylate(6): Compound **4a** (0.006 mole) was treated with 8-hydroxy-2-methyl quinoline (0.006 mole) in the presence of K_2CO_3 in dry dimethyl formamide 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 yellow solid. Yield- 1.23g (82 %); m.pt. 165°C. I.R (KBr pellets cm^{-1}): υ 1710, 1617, 1209, 1101, 983, 740 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.23 (s, 2H), δ 8.21 (d, J = 8.4 Hz, 1H), δ 7.83 (d, J = 4.96 Hz, 1H), δ 7.70 (d, J = 3.44 Hz, 2H), δ 7.52- δ 7.45 (m, 1H), δ 7.42 - δ 7.34 (m, 1H), δ 7.19 (t, 1H), δ 5.10 (s, 2H), δ 3.80 (s, 3H), δ 2.59 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6 + TFA-d): δ 167.31, 148.68, 146.25, 139.01, 136.81, 135.72, 133.47, 129.89, 128.51, 125.36, 121.55, 121.18, 117.36, 114.77, 113.55, 109.74, 65.18, 52.50, 21.03.Mass (m/z) = 340 (M^+); Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13. Found: C, 67.20; H, 5.04; N, 4.11.

Methyl (2*E*)- 3- (5- bromo- 2- thienyl)- 2- {[(2- methylquinolin- 8- yl) oxy] methyl} acrylate (7): Yield- 1.2 g (82 %). m.pt. 176°C; I.R (KBr pellets cm^{-1}) υ 1691, 1614, 1261, 1209, 1099, 831, 752 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.22 (d, J = 8.4 Hz, 1H), δ 8.15 (s, 1H), δ 7.57 (d, J = 3.88 Hz, 1H), δ 7.54 (d, J = 8.0 Hz, 1H), δ 7.49 (d, J = 7.52 Hz, 1H), δ 7.45 (t, 1H), δ 7.35 (t, 2H), δ 5.10 (s, 2H), δ 3.79 (s, 3H), δ 2.60 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6 + TFA-*d*): δ 166.69, 148.54, 145.34, 138.12, 137.70, 136.14, 131.63, 129.39, 128.11, 125.07, 121.76, 120.89, 118.93, 117.18, 114.22, 113.35, 64.87, 52.41, 21.03. Mass (m/z) = 420 (M^{2+}). Anal. Calcd for $C_{19}H_{16}BrNO_3S$: C, 54.55; H, 3.86; N, 3.35. Found: C, 54.53; H, 3.85; N, 3.33.

Methyl (2*E*) - 3- (5- bromo- 2- thienyl)- 2- [(quinolin- 8- yloxy) methyl] acrylate (8): Yield-1.05 g (80 %). m.p. 161 °C. I.R (KBr pellets cm^{-1}): υ 1693, 1616, 1261, 1209, 1101, 757 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.80 (t, 1H), δ 8.36 (d, J = 8.2 Hz, 1H), δ 8.16 (s, 1H), δ 7.61- δ 7.55 (m, 3H), δ 7.42 (t, 2H), δ 7.31 (d, J = 3.88 Hz, 1H), δ 5.10 (s, 2H), δ 3.79 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6 + TFA-*d*): δ 166.70, 149.06, 146.01, 145.54, 138.15, 137.69, 136.16, 131.68, 130.18, 129.98, 129.84, 122.99, 121.83, 121.10, 120.89, 119.02, 117.27, 113.83, 113.44, 109.62, 64.49, 52.45. Mass (m/z) = 406 (M^{2+}). Anal. Calcd for $C_{18}H_{14}BrNO_3S$: C, 53.48; H, 3.49; N, 3.46. Found: C, 53.45; H, 3.47; N, 3.45.

Methyl (2*E*) - 2- [(quinolin- 8- yloxy) methyl] - 3- (2- thienyl) acrylate (9): Yield- 1.0 g (78 %). m.pt. 160°C. I.R (KBr pellets cm^{-1}): υ 1714, 1617, 1207, 1099, 981, 738 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.79 (d, J = 3.96 Hz, 1H), δ 8.33 (d, J = 8.28 Hz, 1H), δ 8.25 (s, 1H), δ 7.81 (d, J = 4.88 Hz, 1H), δ 7.66 (d, J = 3.4 Hz, 1H), δ 7.56- δ 7.52 (m, 3H), δ 7.41 (t, 1H), δ 7.18 (t, 1H), δ 5.15 (s, 2H), δ 3.79 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167.0, 154.10, 148.90, 139.62, 137.72, 136.44, 135.69, 135.05, 133.20, 128.99, 127.93, 126.75, 122.30, 121.81, 119.92, 109.44, 63.09, 52.18. Mass (m/z) = 326 (M^+). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.45; H, 4.65; N, 4.29.

Ethyl (2*E*) - 2- [(quinolin- 8- yl) oxy) methyl] - 3- (2- thienyl) acrylate (10): Yield- 1.0 g (81 %). m.pt. 148.5°C. I.R (KBr pellets cm^{-1}): υ 1683, 1613, 1280, 1212, 1098, 795, 713 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (t, 1H), δ 8.21 (s, 1H), δ 8.15 (d, J = 7.92 Hz, 1H), δ 7.52- δ 7.39 (m, 5H), δ 7.26 (t, 1H), δ 7.04 (t, 1H), δ 5.26 (s, 2H), δ 4.31 (t, 2H), δ 1.33 (t, 3H). Mass (m/z) = 340 (M^+). Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13. Found: C, 67.22; H, 5.03; N, 4.12.

Propyl (2*E*) - 2- [(quinolin- 8- yloxy) methyl] - 3- (2- thienyl) acrylate (11): Yield- 1.1 g (78 %). m.pt. 121°C. I.R (KBr pellets cm^{-1}): υ 1682, 1615, 1465, 1282, 1215, 1100, 986, 943, 821, 711 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (t, 1H), δ 8.21 (s, 1H), δ 8.14 (d, J = 8.24 Hz, 1H), δ 7.52- δ 7.38 (m, 5H), δ 7.26 (t, 1H), δ 7.04 (t, 1H), δ 5.26 (s, 2H), δ 4.19 (t, 2H), δ 1.73 (s, 3H), δ 0.97 (t, 3H). Mass (m/z) = 354.0 (M^+). Anal. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96. Found: C, 67.96; H, 5.41; N, 3.95.

Cyclopentyl (2*E*) - 2- [(quinolin- 8- yl) oxy) methyl] - 3- (2- thienyl) acrylate (12): Yield- 1.2 g (76 %). m.pt. 116°C. I.R (KBr pellets cm^{-1}): υ 1682, 1616, 1465, 1283, 1215, 1100, 986, 944, 821, 711ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (t, 1H), δ 8.14 (s, 1H), δ 8.12 (s, J = 1.56 Hz, 1H), δ 7.51- δ 7.38 (m, 5H), δ 7.26 (t, 1H), δ 7.04 (t, 1H), δ 5.30 (q, 1H), δ 5.25 (s, 2H), δ 1.89 (t, 2H), δ 1.76 (m, 2H), δ 1.66 (s, 2H), δ 1.60 (t, 2H). Mass (m/z) = 380 (M^+). Anal. Calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69. Found: C, 69.60; H, 5.56; N, 3.68.

Benzyl (2*E*) - 2- [(quinolin- 8- yloxy) methyl] - 3- (2- thienyl) acrylate (13): Yield- 1.25 g (84 %). m.pt. 99.5°C. I.R (KBr pellets cm^{-1}): υ 1694, 1617, 1206, 1099, 982, 741, 693 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (t, 1H), δ 8.24 (s, 1H), δ 8.15 (d, J = 8.2 Hz, 1H), δ 7.49- δ 7.21 (m, 11H), δ 7.04 (t, 1H), δ

5.29 (s, 4H). Mass (m/z) = 402 (M^+). Anal. Calcd for $C_{24}H_{19}NO_3S$: C, 71.80; H, 4.77; N, 3.49. Found: C, 71.78; H, 4.76; N, 3.49.

4-Trifluoromethylbenzyl (2*E*) - 2- [(quinolin- 8-yl) oxy) methyl] - 3-(2-thienyl) acrylate (14): Yield- 1.05 g (70 %). m.pt. 117°C. I.R (KBr pellets cm^{-1}): υ 1689, 1620, 1329, 1212, 1102, 1067, 984, 694 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (t, 1H), δ 8.25 (s, 1H), δ 8.15 (d, J = 1.68 Hz, 1H), δ 7.61- δ 7.40 (m, 9H), δ 7.26 (t, 1H), δ 7.06 (t, 1H), δ 5.30 (s, 4H). Mass (m/z) = 470 (M^+). Anal. Calcd for $C_{25}H_{18}F_3NO_3S$: C, 63.96; H, 3.86; N, 2.98. Found: C, 63.95; H, 3.85; N, 2.97.

Methyl (2*E*) - 2- {[(5, 7- dichloroquinolin- 8-yl) oxy] methyl} - 3- (2- thienyl) acrylate (15): Yield- 1.1 g (78 %). m.pt. 137°C. I.R (KBr pellets cm^{-1}): υ 3430, 2944, 1715, 1619, 1502, 1308, 1206, 1094, 989, 778, 738 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.04 (d, J = 0.8 Hz, 1H), δ 9.02 (t, 1H), δ 8.62 (d, J = 8.8 Hz, 1H), δ 8.32 (s, 1H), δ 7.85- δ 7.81 (m, 2H), δ 7.68 (d, J = 3.4 Hz, 1H), δ 7.62 (d, J = 8.88 Hz, 1H), δ 7.20 (t, 1H), δ 5.30 (s, 2H), δ 3.81 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166.91, 159.63, 150.28, 138.68, 138.63, 137.58, 136.28, 135.77, 133.72, 131.78, 128.14, 127.71, 124.86, 122.10, 121.11, 107.52, 64.36, 52.40. Mass (m/z) = 394 (M). Anal. Calcd for $C_{18}H_{13}Cl_2NO_3S$: C, 54.83; H, 3.32; N, 3.55. Found: C, 54.84; H, 3.30; N, 3.55.

Methyl (2*E*) - 2- {[(5-chloro- 7- iodoquinolin- 8-yl) oxy] methyl} - 3- (2- thienyl) acrylate (16): Yield- 0.9 g (72%), m.pt. 124.5°C. I.R (KBr pellets cm^{-1}): υ 3381, 2944, 1703, 1617, 1570, 1330, 1219, 1084, 938, 780, 710 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.05 (d, J = 2.76 Hz, 1H), δ 8.56 (d, J = 8.56 Hz, 1H), δ 8.09 (s, 1H), δ 8.0 (s, 1H), δ 7.86 (d, J = 4.76 Hz, 1H), δ 7.81- δ 7.76 (m, 2H), δ 7.22 (t, 1H), δ 5.59 (s, 2H), δ 3.66 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167.09, 155.26, 150.47, 141.22, 136.42, 136.17, 134.86, 134.59, 133.06, 132.15, 128.07, 127.79, 124.85, 124.19, 123.01, 91.13, 69.28, 52.07 Mass (m/z) = 486 (M^+). Anal. Calcd for $C_{18}H_{13}ClINO_3S$: C, 44.51, H, 2.70; N, 2.88. Found: C, 44.49, H, 2.68; N, 2.86.

Methyl (2*E*) - 2- {[(5, 7- dichloro- 2- methylquinolin- 8- yl) oxy] methyl} - 3- (2-thienyl) acrylate (17): Yield- 1.0 g (80 %). m.pt. 147°C. I.R (KBr pellets cm^{-1}): υ 3387, 2949, 1705, 1616, 1493, 1314, 1251, 1089, 945, 792, 709 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.42 (s, 1H), δ 7.97- δ 7.83 (m, 4H), δ 7.64 (s, 1H), δ 7.22 (s, 1H), δ 5.55 (s, 2H), δ 3.63 (s, 3H), δ 2.74 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167.14, 159.95, 149.91, 142.48, 136.44, 136.28, 134.56, 134.17, 133.05, 132.23, 128.29, 126.37, 125.60, 123.76, 119.33, 97.97, 68.91, 52.29, 25.03. Mass (m/z) = 408 (M). Anal. Calcd for $C_{19}H_{15}Cl_2NO_3S$: C, 55.89; H, 3.70; N, 3.43. Found: C, 55.86; H, 3.69; N, 3.42.

Methyl (2*E*) - 2 - {[(5- nitroquinolin - 8- yl) oxy] methyl} – 3 - (2- thienyl) acrylate (18): Yield- 1.1 g (70 %), m.pt. 154°C. I.R.: (KBr pellets cm^{-1}): υ 3435, 1705, 1611, 1433, 1283, 1117, 942, 710 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.09 (t, 1H), δ 8.58 (t, 1H), δ 7.99 (s, 1H), δ 7.91 (s, 1H), δ 7.85- δ 7.82 (m, 2H), δ 7.79- δ 7.75 (m, 2H), δ 7.21- δ 7.18 (m, 1H), δ 5.57 (s, 2H), δ 3.60 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167.12, 151.09, 136.43, 136.38, 134.72, 133.87, 133.04, 132.26, 131.78, 130.19, 128.46, 127.98, 127.34, 126.56, 123.93, 123.02, 69.13, 51.89. Mass (m/z) = 371 (M^+). Anal. Calcd for $C_{18}H_{14}N_2O_5S$: C, 58.37; H, 3.81; N, 7.56. Found: C, 58.36; H, 3.81; N, 7.55.

General Synthetic procedure for synthesis of 19-20:

(2*E*) - 2- {[(2-methylquinolin-8-yl) oxy] methyl} - 3- (2- thienyl) acrylic acid (19): Compound **6** (0.006 mole), 4N NaOH solution (0.006 mole) and methanol were stirred at room temperature for 15 h and the reaction was monitored by TLC. Solvent was completely distilled out and solid precipitates out when pH of the reaction was adjusted to 6-7 to obtain yellow solid Yield- 1.3g (86 %). m.p. 196 °C.

I.R (KBr pellets cm^{-1}): υ 3370, 1702, 1625, 1428, 1265, 838, 698 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.22 (s, 1H), δ 8.21 (d, J = 8.5 Hz, 2H), δ 7.80 (d, J = 4.84 Hz, 1H), δ 7.65 (d, J = 3.16 Hz, 1H), δ 7.58- δ 7.45 (m, 4H), δ 7.19 (t, 1H), δ 5.18 (s, 2H), δ 2.73 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167.18, 156.93, 148.63, 145.15, 143.61, 137.12, 136.15, 126.85, 125.79 (2C), 125.44, 124.72, 123.79, 122.46, 116.75, 24.54. Mass (m/z) = 326 (M^+). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.42; H, 4.64; N, 4.29.

(2*E*) - 2- [(quinolin- 8- yloxy) methyl] - 3- (2- thienyl) acrylic acid (20): Yield- 1.25 g (85 %). m.pt. 198°C. I.R (KBr pellets cm^{-1}): υ 3330, 1681, 1504, 1201, 1105, 823, 719 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.79 (t, 1H), δ 8.33 (d, J = 8.24 Hz, 1H), δ 8.20 (s, 1H), δ 7.76 (d, J = 4.88 Hz, 1H), δ 7.60 (d, J = 3.0 Hz, 1H), δ 7.56- δ 7.51 (m, 3H), δ 7.40 (dd, J = 3.12, 5.48 Hz, 1H), δ 7.16 (t, 1H), δ 5.12 (s, 2H). ^{13}C NMR (300 MHz, DMSO-d_6 + TFA-*d*): δ 168.17, 148.86, 146.96, 145.28, 138.34, 136.84, 135.20, 133.02, 130.53, 129.90, 128.86, 123.08, 122.19, 120.71, 117.19, 114.22, 64.85. Mass (m/z) = 312 (M^+). Anal. Calcd for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. Found: C, 65.55; H, 4.21; N, 4.50.

General Synthetic procedure for synthesis of 21-22:

(2*E*)- *N*- benzyl- 2 - [(quinolin- 8- yl) oxy) methyl] – 3 - (2- thienyl) acrylamide (21): Compound **20** (0.006 mole), benzyl 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- 1.1 g (68 %). m.pt. 135°C. I.R (KBr pellets cm^{-1}): υ 1657, 1603, 1499, 1378, 1102, 979, 820, 706, 699 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.88 (s, 1H), δ 8.20 (s, 1H), δ 8.16 (t, 2H), δ 7.60- δ 7.44 (m, 3H), δ 7.52 (t, 3H), δ 7.41 (d, J = 6.88 Hz, 3H), δ 7.32 (d, J = 4.8 Hz, 1H), δ 7.29 (t, 1H), δ 7.15 (t, 1H), δ 5.3 (s, 2H), δ 4.7 (d, J = 5.6 Hz, 2H). Mass (m/z) = 401 (M^+). Anal. Calcd for $C_{24}H_{20}N_2O_2S$: C, 71.98; H, 5.03; N, 6.99. Found: 71.96; H, 5.01; N, 6.98.

(2*E*) - *N*- butyl - 2- [(quinolin-8-yloxy) methyl] - 3- (2- thienyl) acrylamide (22): Yield-1.05 g (64 %). m.pt. 110°C. I.R (KBr pellets cm^{-1}): υ 1655, 1600, 1500, 1375, 1242, 1102, 978, 820, 705 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.91 (t, 1H), δ 8.24 (t, 1H), δ 8.11 (s, 1H), δ 7.60- δ 7.44 (m, 4H), δ 7.37 (d, J = 3.52 Hz, 1H), δ 7.26 (s, 1H), δ 7.13 (dd, J = 3.72, 5.0 Hz, 1H), δ 5.32 (s, 2H), δ 3.52 (q, 2H), δ 1.66 (q, 2H), δ 1.42 (q, 2H), δ 0.92 (t, 3H). Mass (m/z) 367 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.64. Found: C, 68.80; H, 6.03; N, 7.63.

RESULTS AND DISCUSSION:

Chemistry: As per Scheme-1, Baylis-Hillman reaction was carried out using 1, 4-diazabicyclo [2.2.2] octane (DABCO) as catalyst without any solvent using thiophene-2-carboxaldehyde **1a** and methyl acrylate **2** as the starting compound for the synthesis of thienyl acrylates [33]. The structure of this intermediate was confirmed by I.R and NMR spectral analysis. The sharp absorption at 1716 cm^{-1}, 1631 cm^{-1}, and 1438 cm^{-1} in the I.R spectrum showed that compound **3a** to be α, β-unsaturated ester.

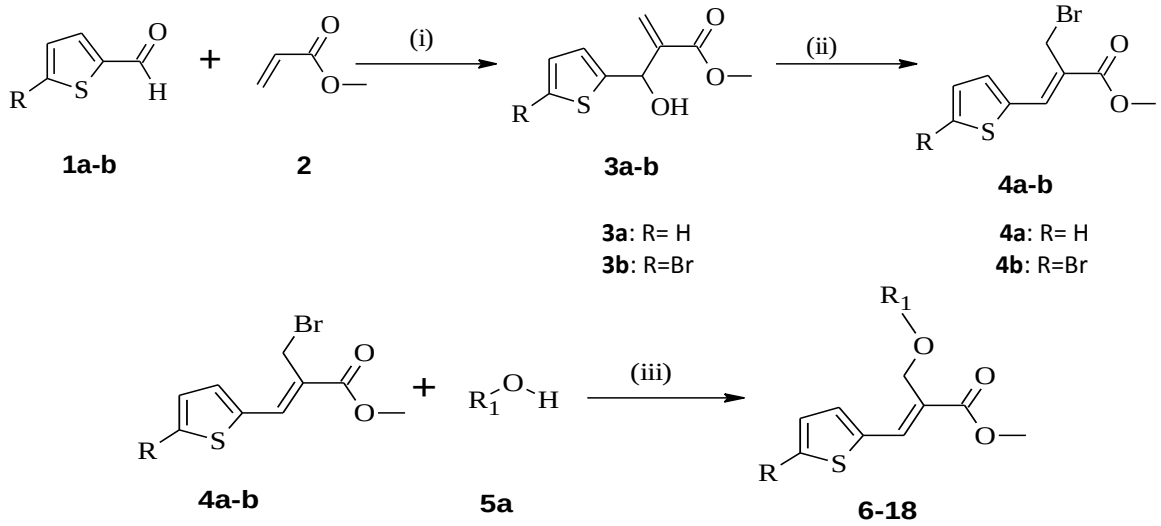
The broad absorption at 3448 cm^{-1} in the I.R spectrum showed the presence of hydroxyl group. Three singlets at δ 5.7, δ 5.9 and δ 6.3 each integrating for one proton in the ^{1}H NMR spectrum correspond to two vinylic protons and the single hydroxy methylene proton. The appearance of singlet at δ 5.7 is due to the presence of a hydroxy methylene group and the deshielding is due to its presence adjacent to vinylic group. Signals corresponding to thiophenylic protons appear around δ 6.9 and δ 7.7 and the 3-carbomethoxy

protons as singlet at δ 3.7. The compound **3a** is thus confirmed by the above spectral data. The hydroxy compound **3a** was converted to thienyl bromo ester **4a** by treatment with 47% Hydrobromic acid in the presence of concentrated sulphuric acid in Methylene dichloride at room temperature according the reported procedure [34]. It was purified in hexane solvent to afford a low melting solid, which was the key intermediate in synthesizing the title compounds. The conversion of alcohol to bromide is evident from the appearance of absorption at 723 cm^{-1} and disappearance of broad absorption around 3448 cm^{-1} in the I.R spectrum.

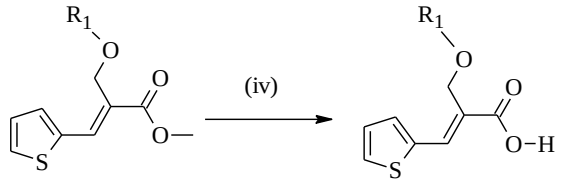
In ^{1}H NMR spectrum, a singlet at δ 4.58 for two protons indicates the proton at the bromo methyl group and the vinylic protons appear much deshielded at δ 8.03. From the above data, the compound **4a** is structurally confirmed. The above synthesized bromo ester **4a** was treated with various hydroxyl quinoline compounds in presence of K_2CO_3 in dry dimethyl formamide to afford a series of esters (compounds **6** to **23**) at ambient temperature according the reported procedure [35-36]. Completion of the reaction was judged by TLC and the isolation of products involves simple workup. Crude product obtained was further purified by simple recrystalization methods. Ether formation is evident from the absorption at 1209 cm^{-1} and 1101 cm^{-1} (compound 6) and the oxymethylene protons appeared as singlet integrating for two protons at δ 5.10.

The vinyl proton of the α, β -unsaturated system were deshielded significantly and appeared as a singlet at δ 8.23. In the ^{13}C NMR spectrum, a signal at δ 167.31 correspond to the carbonyl, with the oxymethylene and methoxy carbons appearing at δ 52.50 and δ 21.03 respectively. The mass spectrum of 6 showed a molecular ion peak at m/z 340.0 (M^{+}), which further confirms the compound. The structures of the new compounds **6-22** are presented in **Table 1**.

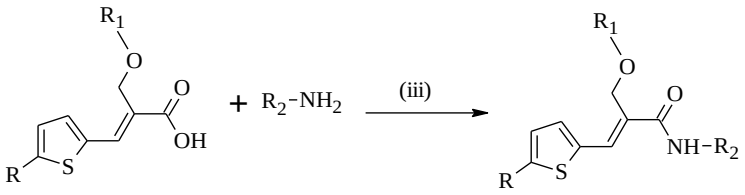
SCHEME 1



R= H, Br
R_1= 8-hydroxy quinoline
2-methyl-8-hydroxy quinoline
5, 7 dichloro-8-hydroxy quinoline
5, 7 dichloro-2-methyl-8-hydroxy quinoline
5-chloro-7-Iodo-8-hydroxy quinoline
5-nitro 8-hydroxy quinoline



6, 9 **19, 20**

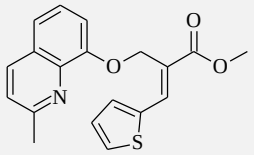
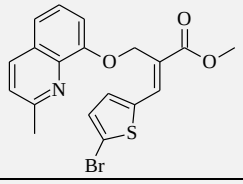


20 **5b** **21-22**

R_2= Benzyl amine
Butyl amine
Methyl amine

Reagents and Condition: (i) DABCO, room temperature, 80 h (ii) Hydrobromic acid, Concentrated sulphuric acid, Methylene dichloride, 5-10°C, 3 h (iii) K_2CO_3, Dimethyl formamide, room temperature, 1 h (iv) NaOH, Methanol, room temperature, 8 h (v) HOBt, EDC.HCl, Triethyl amine, Dimethyl formamide, room temperature, 10 h.

TABLE 1: STRUCTURAL FORMULAE OF THE SYNTHESIZED COMPOUNDS, 6-23

Comp. No	Structure
6	
7	
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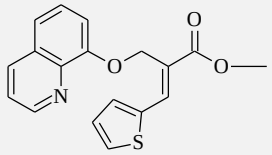
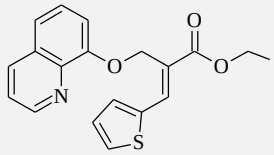
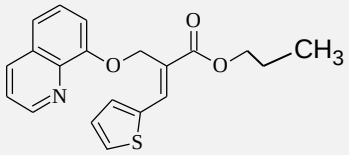
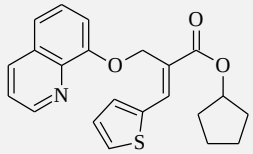
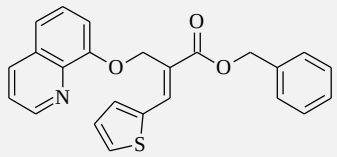
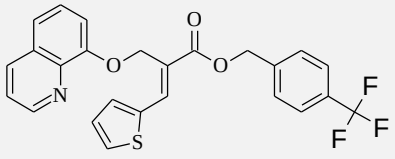
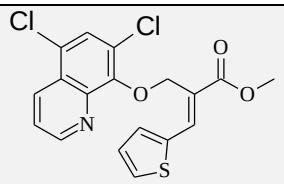
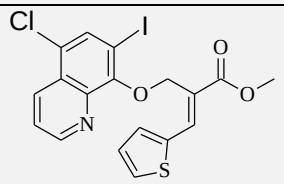
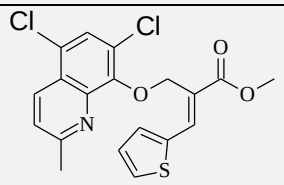
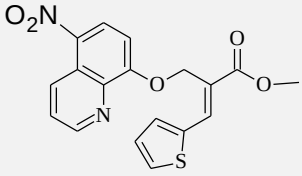
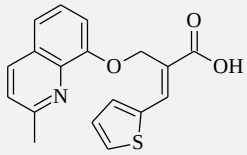
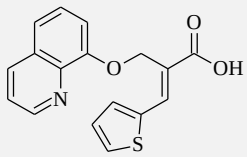
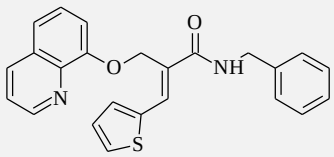
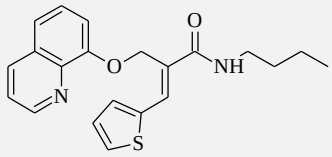
9	
10	
11	
12	
13	
14	

15	
16	
17	
18	
19	
20	
21	
22	

Pharmacology:

***In vitro* antimicrobial activity**: Initial screening of antimicrobial susceptibility testing was carried out for all the seventeen synthesized compounds by agar well diffusion method as recommended by the CLSI [37]. Briefly, bacterial & yeast cultures were grown to exponential phase concentration adjusted at recommended McFarland and plated by pour-plate method into the 150 mm Petri dishes and allowed to settle. Four representative bacterial isolates namely *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *B. subtilis* ATCC 6633, and one fungal *Candida albicans* ATCC 90028 were used for screening. Wells were bored into the inoculated plate and the test compounds dissolved in DMSO were dispensed in the wells at three concentrations (10, 100 and 1000 µg/mL), allowed for complete diffusion and the plates were incubated at 37˚C overnight.

Three antibacterial agents and one fungal (cefepime, amikacin, linezolid & fluconazole) were used as internal assay standards and 100% DMSO was used as a control. The zones of inhibition were measured using the digital Vernier's calipers. Further, the short-listed compounds were subjected to the determination of MIC by agar dilution method as per the CLSI guidelines [37]. Briefly, the selected bacterial strains were: Gram negative isolates of *E. coli* ATCC 25922, NCTC 13353, ATCC BAA200, *P. aeruginosa* ATCC 27853, *K. pneumoniae* ATCC 700603, ATCC 51503, *E. cloacae* 2160 P99+; and Gram positive strains *S. aureus* ATCC 25923, ATCC 43300, *B. subtilis* ATCC 6633 and fungal *Candida albicans* ATCC 90028.

The inoculum was prepared from 3- 5 well isolated bacterial colonies in 0.9 % NaCl such that the final inoculum spot contained 1 x 10^4 CFU of bacteria when seeded onto agar plates containing different concentrations of the antimicrobial agents by a Multipoint Inoculator. The plates were incubated at 35˚C for 18-20 h in an ambient atmosphere for bacterial strains and 48 h for fugal strains. MIC was recorded as the lowest concentration that inhibited visible growth of the inoculated culture.

The observations indicated that all the seventeen compounds screened for antibacterial activity exhibited a moderate to very good activity, but against the fungal strains all the compounds showed no activity (**Table 2**)**.** The compounds which showed significant activity in the preliminary screening were further tested for antibacterial and antifungal activity by agar dilution method for determining the MIC as per CLSI guidelines and their results are tabulated (**Table 3**). Compounds in series which contain chloro/nitro displayed very good antibacterial activity against all the strains. Compound 18 was highly active against *B. subtilis* ATCC 6633 (MIC = 1 µg/mL), *S. aureus* ATCC 43300 (MIC = 2 µg/mL) and *S. aureus* ATCC 25923 (MIC = 4 µg/mL), compound 15 and 16 were also active against *B. subtilis* ATCC 6633 (MIC = 2 µg/mL), *S. aureus* ATCC 43300 (MIC = 2 µg/mL) and *S. aureus* ATCC 25923 (MIC = 4 µg/mL). Compound 17 was highly active against *B. subtilis* ATCC 6633 (MIC = 2 µg/mL), and *S. aureus* ATCC 25923 (MIC = 4 µg/mL). Compounds 6, 9, 10 and 20 were also highly active against *S. aureus* ATCC 25923 (MIC = 4 µg/mL).

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

Comp. No	*S. aureus* ATCC 25923			*B. subtilis* ATCC 6633			*E. coli* ATCC 25922			*P. aeruginosa* ATCC 27853		
	1000 µg	100 µg	10 µg	1000 µg	100 µg	10 µg	1000 µg	100 µg	10 µg	1000 µg	100 µg	10 µg
6	25.56	24.1	23.15	27.23	26.33	24.5	10.9	nz	nz	11.56	7.15	nz
7	19.35	18.36	8.54	18.2	14.32	nz[#]	nz	nz	nz	9.35	nz	nz
8	15.85	14.99	12.04	nz	13.15	nz	nz	nz	nz	4.99	nz	nz
9	27.31	25.28	24.85	28.54	27.63	26.98	8.91	nz	nz	9.28	nz	nz
10	26.84	25.11	23.48	27.59	26.55	25.28	6.32	nz	nz	10.01	4.06	nz
11	23.96	16.96	12.66	nz	8.66	nz	nz	nz	nz	nz	nz	nz
12	12.39	8.24	nz	nz	nz	nz	7.32	nz	nz	14.24	nz	nz
13	12.39	11.6	nz	nz	nz	nz	nz	nz	nz	11.6	nz	nz
14	20.05	21.16	12.13	nz	16.5	nz	nz	nz	nz	nz	nz	nz
15	29.24	29.15	28.54	28.93	27.78	27.10	10.3	7.62	nz	21.16	12.13	nz
16	29.54	28.95	28.24	27.68	26.54	26.32	18.3	11.2	nz	20.01	6.06	nz
17	28.64	27.32	27.10	27.10	26.28	25.32	9.82	nz	nz	14.99	8.04	nz
18	29.94	28.94	28.69	28.94	27.93	27.58	19.6	15.2	nz	23.96	12.66	nz
19	22.56	20.81	18.32	24.65	22.18	20.23	nz	nz	nz	9.56	nz	nz
20	27.31	25.28	24.85	nz	nz	nz	4.85	nz	nz	9.28	nz	nz
21	20.35	18.66	12.10	16.82	15.18	13.28	nz	nz	nz	6.12	nz	nz
22	14.96	12.47	10.78	16.86	13.15	11.31	nz	nz	nz	nz	nz	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	

[#] nz: no zone of inhibition

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

Compound No.	*S. aureus* *ATCC* 25923	*S. aureus* ATCC 43300	*B. subtilis* ATCC 6633
6	16	32	4
9	4	8	2
10	4	8	8
15	4	2	2
16	4	2	2
17	4	16	4
18	4	2	1
19	16	32	4
20	4	8	8
Linezolid	4	2	1
Amikacin	2	128	0.5
Cefepime	2	32	2

[a] Agar dilution method used to determine the MIC

CONCLUSION: In conclusion, from an SAR standpoint, we observe that, of all compounds tested (6-23 of table 1), the highest antimicrobial activity occurs in compound 15, 16 and 18 when the molecule possesses the choro substiuents in position 5 and 7, the choro and iodo substiuents in position 5 and 7 and nitro substituents in position 5. Hence it is concluded that there is ample scope for further developing this field.

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