Synthesis of Sulfonated Dihydrofuropyrazoles Derivatives as Antimicrobial Active Agents

VENKATA SWAMY TANGETI* and K.V.V. SATYANARAYANA

Department of Chemistry, Dr. Sarvepalli Radha Krishnan Government Arts College (Pondicherry University), Yanam-533464, India

*Corresponding author: E-mail: swamychempcu@gmail.com

A series of sulfonated dihydrofuropyrazole derivatives was prepared from one pot multi component condensation of sulfonated β-keto ester, aromatic aldehyde, hydrazine, pyridinium ylide in presence of piperidine catalyst under ethanol solvent conditions and subsequent oxidation of SPh group with MCPBA. All the synthesized compounds were characterized by analytical and spectral techniques and screened in vitro for antimicrobial activity. The activity data revealed that most of the compounds exhibited good to significant activities. Compounds 6b, 6i, 6j, 6k, 6m, 6n exhibited good and broad spectrum activity towards all the tested bacterial strains.

Keywords: Sulfonated dihydrofuropyrazole, Phenylthio β-keto ester, Blaise reaction, Antimicrobial activity.

INTRODUCTION

Sulfones are important class of organo sulfur compounds, whose chemistry has been explored due to their wide range of applications in chemistry and pharmacy. Sulfone group is a potential unit for different therapeutic targets in medicinal chemistry. Sulfoxide bearing heterocycles were used to treat bacterial and some fungal infections. These are effectively killed the bacteria and fungi by interfering with metabolic reactions [1]. These are widely used as antimicrobial agents, antidiabetic agents, diuretics, anticonvulsants, antiretroviral and Hepatitis-C antiviral agents. Several researches revealed that the broad spectrum antimicrobial activity of sulfone containing heterocycles entities [2-10]. Recently, Kudruavtsev et al [11] reported that the sulfone bearing pyrrolidine derivatives inhibits Staphylococcus aureus sortase SrtA isoform, irreversibly by modification of enzyme cys 184.

In accordance with the increasing need to develop new and simple methods to prepare this biologically active sulfoxide bearing heterocyclic compounds [12-17]. Since few years onwards, our laboratory actively engaged with synthesis of different biologically active nitrogen and oxygen heterocyclic molecules by employing green chemical multicomponent approaches [18-24]. In the continuation of these efforts recently our group has developed novel methodology for synthesis of dihydrofuropyrazoles from one pot multicomponent condensation of β-ketoester, aromatic aldehyde, hydrazine, pyridinium ylied and NEt3 as a catalyst [25]. This reaction inspired us to synthesize SO2 group containing dihydrofuropyrazoles by using sulfur bearing β-keto ester through Blaise approach, in order to explore their antimicrobial activity.

EXPERIMENTAL

The progression of all the reactions was monitored by TLC using a solution of hexanes (60-80 °C boiling mixture) and ethyl acetate as eluent. 1H NMR spectra (400 MHz) and 13C NMR (100 MHz) and DEPT-135 spectra were recorded for (CDCl3 and CDCl3 + CCl4; 1:1) solutions on a Bruker-400 spectrometer with tetramethylsilane (TMS) as internal standard; J values are in Hz. Number of hydrogen’s attached to each carbon was determined from DEPT spectra and are given next to the corresponding 13C NMR spectral data. IR spectra were recorded as KBr pellets on a Nicolet-6700 spectrometer. Melting points were recorded using open-ended capillary tubes on VEEGO VMP-DS instrument. High resolution mass spectra were recorded on a Waters Q-TOF micro mass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use.

General procedure for synthesis of (4R,5R)-ethyl 4-phenyl-3-(2-(phenylthio)ethyl)-4,5-dihydro-1H-furo[2,3-
c) Pyrazole-5-carboxylate (5a-q): Mixture of ethyl 3-oxo-5-(phenylthio)pentanoate (1) (385 mg, 0.153 mmol), hydrazine hydrate (2) (81 mg, 0.153 mmol), benzaldehyde (3a) (172 mg, 0.153 mmol), 1-(2-ethoxy-2-oxoethyl)pyridiniumylide (4) (272 mg, 0.153 mmol), 0.1 equivalents of trimethylamine (16 mg, 0.015 mmol) were refluxed in EtOH (5 mL). The solid residue was purified by column chromatography on silica-gel (hexane-ethyl acetate). 4:6 (Scheme-I). Analytical samples were obtained from the recrystallization in EtOH. 5a: Yellow colour solid. Yield 85%. Yellow colour solid; Yield 93 %, m.p.: 145.2 ºC, IR (KBr, νmax, cm⁻¹): 3321, 3256, 3028, 3002, 2995, 1789, 1636, 1622, 1518, 1221, 1180, 1082, 960, 882, 766; 1H NMR (400 MHz, CDCl3) δ 12.58 (br s, 1H), 7.40 (m, 10H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.58 (t, J = 8.2 Hz, 2H), 3.11 (t, J = 8.2 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 171.5, 163.7, 143.4, 140.2, 136.4, 129.3, 128.9, 128.6, 127.7, 125.9, 125.1, 113.4, 87.6, 61.6, 41.7, 35.6, 29.6, 14.2 ppm; HRMS (ESI, m/z): 417.1249 calc. for C22H22N2O5S (M+Na) found: 417.1247. Analysis calc. for C22H22N2O5S: C, 61.96; H, 5.20; N, 6.57; S, 7.52; Found C, 61.94; H, 5.17; N, 6.54; S, 7.50.

(4R,5R)-Ethyl 4-(4-chlorophenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6b): Light yellow colour crystalline solid; Yield 93 %, m.p.: 165.1 ºC, IR (KBr, νmax, cm⁻¹): 3331, 3218, 3017, 2982, 1760, 1616, 1584, 1485, 1317, 1051, 1016, 967, 751; 1H NMR (400 MHz, CDCl3) δ 12.56 (br s, 1H), 7.86 (d, J = 7.8 Hz, 2H), 7.63-7.60 (m, 3H), 7.46 (d, J = 7.4 Hz, 2H), 7.23 (d, J = 7.4 Hz, 2H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.58 (t, J = 8.2 Hz, 2H), 3.09 (t, J = 8.2 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 172.8, 164.1, 143.6, 138.9, 137.2, 135.6, 133.7, 129.7, 128.9, 128.3, 126.7, 125.9, 113.4, 87.6, 62.8, 61.3, 41.5, 19.3, 14.1 ppm; HRMS (ESI, m/z): 449.1147 calc. for C23H20N2O5S (M+Na) found: 449.1145. Analysis calc. for C23H20N2O5S: C, 61.96; H, 5.20; N, 6.57; S, 7.52; Found C, 61.94; H, 5.17; N, 6.54; S, 7.50.

**General procedure for synthesis of (4R,5R)-Ethyl 4-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (5a):** To a stirred solution of (4R,5R)-ethyl 4-phenyl-3-(2-(phenylthio)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (5a) (272 mg, 0.692 mmol) in CHCl3 (10 mL) at −40 ºC was added 50-60 % m-CPBA (0.61 g, 1.8 mmol) in CHCl3 (10 mL) drop-wise via addition funnel. This solution was stirred at −40 ºC for 12 h and then was allowed to warm to 0 ºC in the refrigerator overnight. Then, the solution was cooled to −40 ºC over 1 h and was filtered to remove any m-CPBA. The filtrate was washed with 2 M NaOH (3 × 25 mL), brine (25 mL) and was dried with Na2SO4. Organic layer was concentrated by rotavaporation. Pure yellow colour crystalline solid was obtained by recrystallization from EtOH (Scheme-II). Light yellow colour crystalline solid; Yield 91 %, m.p.: 160.5 ºC, IR (KBr, νmax, cm⁻¹): 3351, 3215, 3014, 2998, 1762, 1616, 1584, 1485, 1371, 1143, 1016, 966, 764; 1H NMR (400 MHz, CDCl3) δ 12.68 (br s, 1H), 7.86 (d, J = 7.8 Hz, 2H), 7.63-7.60 (m, 3H), 4.27-4.36 (m, 3H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.58 (t, J = 8.2 Hz, 2H), 3.11 (t, J = 8.2 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 172.8, 163.9, 143.6, 140.2, 138.6, 129.7, 128.3, 128.1, 127.6, 125.9, 113.4, 87.6, 62.8, 61.3, 41.5, 19.3, 14.1 ppm; HRMS (ESI, m/z): 449.1147 calc. for C23H20N2O5S (M+Na) found: 449.1145. Analysis calc. for C23H20N2O5S: C, 61.96; H, 5.20; N, 6.57; S, 7.52; Found C, 61.94; H, 5.17; N, 6.54; S, 7.50.

**Scheme-I:** One pot multicomponent synthesis of phenylthioethyldihydrofuropyrazole derivatives (5a-p)
carboxylate (6e): Light yellow colour crystalline solid; Yield 91 %, m.p.: 170.1 °C, IR (KBr, νmax, cm−1): 3324, 3210, 3012, 2987, 1761, 1622, 1584, 1483, 1304, 1126, 1013, 956, 768; 1H NMR (400 MHz, CDCl3) δ 12.67 (br s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.60-7.56 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.82 (s, 3H), 3.58 (t, J = 8.2 Hz, 2H), 3.11 (t, J = 8.2 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 172.6, 164.1, 157.7, 143.8, 138.9, 133.6, 132.5, 16 + 29.7, 128.6, 128.3, 114.2, 113.2, 87.4, 41.7, 19.4, 14.1 ppm; HRMS (ESI, m/z): 479.1253 calcd. for C23H24N2O6S (M+Na) found: 479.1251. Analysis calcd. for C23H24N2O6S: C, 60.51; H, 5.30; N, 6.14; S, 7.02; Found C, 60.49; H, 5.28; N, 6.11; S, 7.00.

(4R,5R)-Ethyl 4-(4-nitrophenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6f): Light yellow colour crystalline solid; Yield 93 %, m.p.: 169.7 °C, IR (KBr, νmax, cm−1): 3329, 3212, 3002, 2987, 1762, 1619, 1581, 1483, 1366, 1311, 1144, 1025, 966, 825, 779; 1H NMR (400 MHz, CDCl3) δ 12.51 (br s, 1H), 8.21 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.63-7.55 (m, 5H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.82 (s, 3H), 3.58 (t, J = 8.2 Hz, 2H), 3.11 (t, J = 8.2 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 172.6, 163.7, 146.2, 145.1, 143.8, 138.9, 133.6, 129.6, 128.4, 128.1, 123.8, 123.8, 123.8, 113.4, 87.2, 62.7, 61.6, 41.8, 19.4, 14.1 ppm; HRMS (ESI, m/z): 494.0998 calcd. for C22H21N3O7S (M+Na) found: 494.0996. Analysis calcd. for C22H21N3O7S: C, 56.04; H, 4.49; N, 8.91; S, 6.80; Found C, 56.02; H, 4.47; N, 8.59; S, 6.76.

Scheme-II: Oxidative synthesis of sulfonyl dihydrofuropyrazole derivatives

(4R,5R)-Ethyl 4-(4-hydroxyphenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6g): Light yellow colour crystalline solid; Yield 93 %, m.p.: 169.7 °C, IR (KBr, νmax, cm−1): 3329, 3212, 3002, 2987, 1762, 1619, 1581, 1483, 1366, 1311, 1144, 1025, 966, 825, 779; 1H NMR (400 MHz, CDCl3) δ 12.51 (br s, 1H), 8.21 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.63-7.55 (m, 5H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.82 (s, 3H), 3.58 (t, J = 8.2 Hz, 2H), 3.11 (t, J = 8.2 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 172.6, 163.7, 146.2, 145.1, 143.8, 138.9, 133.6, 129.6, 128.4, 128.1, 123.8, 123.8, 123.8, 113.4, 87.2, 62.7, 61.6, 41.8, 19.4, 14.1 ppm; HRMS (ESI, m/z): 494.0998 calcd. for C22H21N3O7S (M+Na) found: 494.0996. Analysis calcd. for C22H21N3O7S: C, 56.04; H, 4.49; N, 8.91; S, 6.80; Found C, 56.02; H, 4.47; N, 8.59; S, 6.76.

Scheme-II: Oxidative synthesis of sulfonyl dihydrofuropyrazole derivatives

Vol. 31, No. 4 (2019) Synthesis of Sulfonated Dihydrofuropyrazoles Derivatives as Antimicrobial Active Agents 775
(4<sup>R</sup>5R)-Ethyl 3-(2-(phenylsulfonyl)ethyl)-4-(pyridin-2-yl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6h): Light yellow colour crystalline solid; Yield 94 %, m.p.: 174.3 °C, IR (KBr, ν<sub>max</sub>, cm<sup>−1</sup>): 3344, 3232, 3012, 2974, 1624, 1615, 1577, 1577, 1438, 1387, 1335, 129.1, 128.3, 113.5, 87.6, 62.8, 61.6, 41.8, 19.5, 14.1 ppm; HRMS (ESI, m/z): 465.1096 calcd. for C<sub>23</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S (M+Na) found: 465.1091. Analysis calcd. for C<sub>23</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S: C, 59.00; H, 5.01; N, 6.33; S, 7.25; Found C, 59.70; H, 5.00; N, 6.32; S, 7.21.

(4<sup>R</sup>5R)-Ethyl 4-(4-fluorophenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6i): Light yellow colour crystalline solid; Yield 89 %, m.p.: 160.9 °C, IR (KBr, ν<sub>max</sub>, cm<sup>−1</sup>): 3325, 3206, 3012, 2974, 1624, 1614, 1582, 1483, 1324, 1141, 1027, 955, 849, 764; 1<sup>H</sup>NMR (400 MHz, CDCl<sub>3</sub>) δ 12.54 (br s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.60-7.53 (m, 3H), 7.24-7.20 (m, 4H), 5.29 (d, J = 4.2 Hz, 1H), 3.58 (t, J = 7.6 Hz, 2H), 3.10 (t, J = 7.8 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3ppm); 13<sup>C</sup>NMR (100 MHz, CDCl<sub>3</sub>) δ 172.8, 163.8, 148.3, 143.9, 138.4, 136.1, 133.7, 129.7, 128.2, 122.6, 121.9, 113.4, 87.2, 62.8, 61.6, 41.7, 19.4, 14.2 ppm; HRMS (ESI, m/z): 450.1100 calcd. for C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>S (M+Na) found: 450.1098. Analysis calcd. for C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>S: C, 59.00; H, 4.95; N, 9.83; S, 7.50; Found C, 58.97; H, 4.92; N, 9.80; S, 7.46.

(4<sup>R</sup>5R)-Ethyl 4-(3,5-dimethylphenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6m): Light yellow colour crystalline solid; Yield 92 %, m.p.: 162.8 °C, IR (KBr, ν<sub>max</sub>, cm<sup>−1</sup>): 3344, 3208, 3011, 2985, 1672, 1616, 1583, 1484, 1304, 1158, 912, 948, 862, 764; 1<sup>H</sup>NMR (400 MHz, CDCl<sub>3</sub>) δ 12.44 (br s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.65-7.62 (m, 3H), 7.52 (s, 2H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.58 (t, J = 7.8 Hz, 2H), 3.10 (t, J = 7.8 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3ppm); 13<sup>C</sup>NMR (100 MHz, CDCl<sub>3</sub>) δ 172.8, 163.5, 143.8, 139.2, 138.3, 135.6, 135.4, 133.4, 129.6, 128.2, 113.6, 86.8, 62.7, 61.6, 31.5, 19.7, 14.1 ppm; HRMS (ESI, m/z): 550.9978 calcd. for C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>8</sub>S(M+Na) found: 550.9975. Analysis calcd. for C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>8</sub>S: C, 59.87; H, 3.95; N, 5.29; S, 6.05; Found C, 49.85; H, 3.35; N, 5.26; S, 6.02.

(4<sup>R</sup>5R)-Ethyl 4-(3,5-dimethylphenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6n): Light yellow colour crystalline solid; Yield 87 %, m.p.: 180.5 °C, IR (KBr, ν<sub>max</sub>, cm<sup>−1</sup>): 3348, 3213, 3021, 1762, 1618, 1589, 1481, 1327, 1147, 1012, 959, 844, 768; 1<sup>H</sup>NMR (400 MHz, CDCl<sub>3</sub>) δ 12.69 (br s, 1H), 7.86-7.83 (m, 3H), 7.66-7.59 (m, 4H), 7.18 (d, J = 8.2 Hz, 1H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.6 Hz, 2H), 3.10 (t, J = 7.6 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H),
1.29 (t, \( J = 7.8 \) Hz, 3H) ppm; \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 172.3, 163.2, 143.3, 138.7, 136.9, 133.6, 129.7, 128.5, 128.4, 128.3, 128.2, 126.5, 124.4, 124.3, 123.0, 113.4., 87.3, 62.8, 61.6, 39.2, 19.4, 14.1 ppm; HRMS (ESI, \( m/z \)) 585.0895 calcd. for C\(_{24}\)H\(_{20}\)N\(_2\)O\(_5\)S (M+Na) found: 585.0766. Analysis calcd. for C\(_{24}\)H\(_{20}\)N\(_2\)O\(_5\)S: C, 57.68; H, 4.84; N, 6.73; S, 5.41. Synthesis of phenylthio \( \beta \)-keto ester (4) synthesized by employing Blaise reaction (Scheme-III). According to the Blaise reaction protocol acrylonitrile (1), thiophenol (2), ethyl-bromo acetate (3) treated with zinc and TMSCl provided phenylthio \( \beta \)-keto ester [26,27]. In the reaction protocol when equimolar amounts mixture of phenylthio \( \beta \)-ketoester, aromatic aldehyde, hydrazine, pyridinium ylide and NaEt (0.1 eq.) as a catalyst were refluxed in EtOH solvent provide sulfonyl pyranopyrazole (5a-p) with 89 % yield.

Starting material phenylthio \( \beta \)-keto ester (4) synthesized using the synthesis of phenylthio \( \beta \)-keto ester by blaise reaction (Scheme-III). According to the Blaise reaction protocol acrylonitrile (1), thiophenol (2), ethyl-bromo acetate (3) treated with zinc and TMSCl provided phenylthio \( \beta \)-keto ester [26,27].

In the reaction protocol when equimolar amounts mixture of phenylthio \( \beta \)-ketoester, aromatic aldehyde, hydrazine, pyridinium ylide and NaEt (0.1 eq.) as a catalyst were refluxed in EtOH solvent provide sulfonyl pyranopyrazole (5a-p) with 89 % yield.

**RESULTS AND DISCUSSION**

The structure of the compounds was characterized by \(^1\)H and \(^13\)C NMR, MS, and spectral and elemental analyses. IR spectrum of compound 6a shows displayed four characteristic absorption peaks approximately at 3351 and 3152 cm\(^{-1}\) \((\nu_{NH})\), 1762 cm\(^{-1}\) \((\nu_{CO})\), 1213 cm\(^{-1}\) \((\nu_{SO})\), and 1050 cm\(^{-1}\) \((\nu_{C-O})\). Two strong bands at 1426 and 1182 cm\(^{-1}\) which belongs to asymmetric SO\(_2\); symmetric and symmetric SO\(_2\); stretching. \(^1\)H NMR spectrum of 6a shows \( \delta \) 3.58 and \( \delta \) 3.11 two triplets for two CH\(_2\). C12, C22 groups between furanopyrazole and phenyl sulfonyl groups and one broad singlet appear at \( \delta \) 12.51 ppm for NH group (Fig. 1). The two protons at 4,5-position of dihydrofuran ring display two doublets at 5.41 and 5.11 ppm with the vicinal coupling constant \( J = 4.6 \) and 4.6 Hz, respectively. It has been documented that in cis-2,3-dihydrofuran the vicinal coupling constant of the two methine protons \( J = 7-10 \) Hz, while in trans-2,3-dihydrofuran vicinal coupling constant \( J = 4-7 \) Hz. So we concluded that thermodynamically stable trans isomer of 2, 3-dihydrofuran derivative was formed on pyrazolone moity [28]. \(^1\)C NMR shows 17 signals unequivocally. C12, C22 are disappeared at \( \delta \) 62.8, \( \delta \) 19.3. Finally structure can be confirmed by the HRMS spectrum of compound 6a showed a peak at \( m/z \) 449.1145 (M+Na\(^+\)), which is in good agreement with the molecular weight of the compound. Similarly, compounds 6a-p was synthesized and characterized.

**Pharmacology**

**Antibacterial activity:** The synthesized derivatives (6a-p) were screened in vitro for antibacterial activity against two Gram-positive bacteria (Staphylococcus epidermidis MTCC 6880 and Bacillus subtilis MTCC 441) and two Gram-negative bacteria (Escherichia coli MTCC 16521 and Pseudomonas aeruginosa MTCC 8230). The antibacterial activity of synthesized under the reaction conditions is given in Table 1. The minimum inhibitory concentrations (MICs) values of the synthesized derivatives (6a-p) were 31.25 to 125.0 μg/mL against bacterial strains. The MICs values of the synthesized derivatives (6a-p) against Gram-positive bacteria were lower than thoseiver microorganisms. The lowest inhibition was observed for Bacillus subtilis, and the highest was observed for Staphylococcus epidermidis. The MICs values of the synthesized derivatives (6a-p) against Gram-negative bacteria were lower than those of Gram-positive bacteria. The lowest inhibition was observed for Escherichia coli, and the highest was observed for Pseudomonas aeruginosa. The MICs values of the synthesized derivatives (6a-p) against Gram-negative bacteria were lower than those of Gram-positive bacteria. The lowest inhibition was observed for Escherichia coli, and the highest was observed for Pseudomonas aeruginosa.
aeruginosa MTCC 424) following standard serial dilution method [29]. Ciprolfloxacin was used as standard drug and the minimum inhibitory concentrations (MIC) in µM/mL are listed in Table-1. As evident from the antibacterial evaluation data some of the synthesized compounds exhibited good to significant activity with MIC value ranging from 0.0141 to 0.0256 µM/mL.

In case of Gram-positive bacteria B. subtilis and S. epidermidis, the insertion of electron withdrawing group like –F, –CF₃, –NO₂ on aromatic ring A enhances the activity while the electron releasing group decreases the same. In case of P. vulgaris insertion of halogen groups Cl, F, Br on ring A enhances the activity. Compound 6n contains two CF₃ groups on ring A exhibited highest activity with MIC value 0.0219 µM/mL. Compounds 6i, 6j, 6k, 6m and 6n shows better activity against E. coli, P. vulgaris with MIC value 0.0212 due to the presence of –F, –CF₃ groups on the aromatic ring A. Compounds 6b, 6h, 6i, 6j, 6m, 6n exhibiting promising activity against of B. subtilis and S. epidermidis with MIC values 0.0141-0.0256.

**Antifungal activity:** All the synthesized sulfonated dihydrofuryropyrazole (6a-p) were also tested in vitro for antifungal activity against five fungal strains viz. A. flavus, M. purpureous, A. niger, P. citrinum, C. albicans following standard serial dilution method [29]. Fluconazole was used as reference and MICs (MIC in µM/mL) are presented in Table-1. The activity data revealed that most of the compounds exhibited good to high antifungal activity. Compounds 6b, 6i, 6j, 6k, 6m and 6n exhibited good potency with MIC value ranging 0.0219-0.0310 µM/mL compared to fluconazole (MIC = 0.0102 µM/mL) against A. niger. Two –CF₃ substituted on ring of sulfonated furyropyrazole (6n) was found to be most active and exhibited better activity among all the synthesized compounds with MIC values in the range of 0.0219-0.0438.

**Conclusion**

We have synthesized a number of sulfonated dihydrofuropyrazole derivatives from one pot multicomponent condensation of sulfonated β-keto ester, aromatic aldehyde, hydrazine, pyridinium ylide in presence of piperidine catalyst under ethanol solvent condition. Antimicrobial studies reveals that among the newly synthesized derivatives F and two CF₃ group substituted derivatives 6i, 6m and 6n shows broad spectrum antibacterial and antifungal activity.

**ACKNOWLEDGEMENTS**

One of the authors, VST thanks to IICT Hyderabad and University of Hyderabad, Hyderabad, India for recording NMR and mass Spectra, and also to University of Madras, Chennai, India for the biological evolution of samples.

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interests regarding the publication of this article.

---

**TABLE-1**

<table>
<thead>
<tr>
<th>Compd.</th>
<th>B. subtilis</th>
<th>S. epidermidis</th>
<th>E. coli</th>
<th>P. vulgaris</th>
<th>A. flavus</th>
<th>M. purpureous</th>
<th>A. niger</th>
<th>P. citrinum</th>
<th>C. albicans</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>0.0422</td>
<td>0.0422</td>
<td>0.0844</td>
<td>0.0422</td>
<td>0.0924</td>
<td>0.0924</td>
<td>0.0462</td>
<td>0.0462</td>
<td>0.0462</td>
</tr>
<tr>
<td>6b</td>
<td>0.0221</td>
<td>0.0221</td>
<td>0.0342</td>
<td>0.0342</td>
<td>0.0620</td>
<td>0.0620</td>
<td>0.0310</td>
<td>0.0310</td>
<td>0.0310</td>
</tr>
<tr>
<td>6c</td>
<td>0.0256</td>
<td>0.0256</td>
<td>0.0562</td>
<td>0.0562</td>
<td>0.0960</td>
<td>0.0960</td>
<td>0.0480</td>
<td>0.0480</td>
<td>0.0480</td>
</tr>
<tr>
<td>6d</td>
<td>0.1246</td>
<td>0.0623</td>
<td>0.0623</td>
<td>0.0623</td>
<td>0.0944</td>
<td>0.0944</td>
<td>0.0472</td>
<td>0.0472</td>
<td>0.0472</td>
</tr>
<tr>
<td>6e</td>
<td>0.0344</td>
<td>0.0688</td>
<td>0.0344</td>
<td>0.0688</td>
<td>0.0650</td>
<td>0.0650</td>
<td>0.0325</td>
<td>0.0325</td>
<td>0.0325</td>
</tr>
<tr>
<td>6f</td>
<td>0.1220</td>
<td>0.1220</td>
<td>0.0610</td>
<td>0.0610</td>
<td>0.1022</td>
<td>0.1022</td>
<td>0.0511</td>
<td>0.0511</td>
<td>0.0511</td>
</tr>
<tr>
<td>6g</td>
<td>0.0422</td>
<td>0.0422</td>
<td>0.0844</td>
<td>0.0422</td>
<td>0.1006</td>
<td>0.1006</td>
<td>0.0503</td>
<td>0.0503</td>
<td>0.0503</td>
</tr>
<tr>
<td>6h</td>
<td>0.0256</td>
<td>0.0256</td>
<td>0.0512</td>
<td>0.0512</td>
<td>0.1084</td>
<td>0.1084</td>
<td>0.0542</td>
<td>0.0542</td>
<td>0.0542</td>
</tr>
<tr>
<td>6i</td>
<td>0.0212</td>
<td>0.0212</td>
<td>0.0212</td>
<td>0.0212</td>
<td>0.0570</td>
<td>0.0570</td>
<td>0.0285</td>
<td>0.0285</td>
<td>0.0285</td>
</tr>
<tr>
<td>6j</td>
<td>0.0198</td>
<td>0.0198</td>
<td>0.0198</td>
<td>0.0198</td>
<td>0.0530</td>
<td>0.0530</td>
<td>0.0265</td>
<td>0.0265</td>
<td>0.0265</td>
</tr>
<tr>
<td>6k</td>
<td>0.0311</td>
<td>0.0611</td>
<td>0.0611</td>
<td>0.0611</td>
<td>0.0584</td>
<td>0.0584</td>
<td>0.0292</td>
<td>0.0292</td>
<td>0.0292</td>
</tr>
<tr>
<td>6l</td>
<td>0.0422</td>
<td>0.0422</td>
<td>0.0844</td>
<td>0.0422</td>
<td>0.0608</td>
<td>0.0608</td>
<td>0.0304</td>
<td>0.0304</td>
<td>0.0304</td>
</tr>
<tr>
<td>6m</td>
<td>0.0343</td>
<td>0.0343</td>
<td>0.0343</td>
<td>0.0686</td>
<td>0.0450</td>
<td>0.0450</td>
<td>0.0225</td>
<td>0.0225</td>
<td>0.0225</td>
</tr>
<tr>
<td>6n</td>
<td>0.0141</td>
<td>0.0141</td>
<td>0.0282</td>
<td>0.0282</td>
<td>0.0438</td>
<td>0.0438</td>
<td>0.0219</td>
<td>0.0219</td>
<td>0.0219</td>
</tr>
<tr>
<td>6o</td>
<td>0.0502</td>
<td>0.0502</td>
<td>0.0502</td>
<td>0.1004</td>
<td>0.0804</td>
<td>0.0804</td>
<td>0.0402</td>
<td>0.0402</td>
<td>0.0402</td>
</tr>
<tr>
<td>6p</td>
<td>0.0633</td>
<td>0.1266</td>
<td>0.0633</td>
<td>0.0633</td>
<td>0.0848</td>
<td>0.0848</td>
<td>0.0424</td>
<td>0.0424</td>
<td>0.0424</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.0047</td>
<td>0.0047</td>
<td>0.0047</td>
<td>0.0047</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.0051</td>
<td>0.0051</td>
<td>0.0051</td>
<td>0.0051</td>
<td>0.0102</td>
</tr>
</tbody>
</table>
REFERENCES


