Synthesis of Sulfonated Dihydrofuropyrazoles Derivatives as Antimicrobial Active Agents

VENKATA SWAMY TANGETI* and K.V.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

Received: 30 July 2018;

Accepted: 14 October 2018;

Published online: 27 February 2019;

AJC-19284

A series of sulfonyl 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, Kudruvatsav *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 ylide and NEt_3 as a catalyst [25]. This reaction inspired us to synthesize SO_2 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 ^{13}C NMR (100 MHz) and DEPT-135 spectra were recorded for (CDCl_3 and $\text{CDCl}_3 + \text{CCl}_4$; 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 ^{13}C 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 (4*R*,5*R*)-ethyl 4-phenyl-3-(2-(phenylthio)ethyl)-4,5-dihydro-1*H*-furo[2,3-

c]pyrazole-5-carboxylate (5a-q): Mixture of ethyl 3-oxo-5-(phenylthio)pentanoate (**1**) (385 mg, 0.153 mmol), hydrazine (**2**) (81 mg, 0.153), 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 (5mL). 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 °C, IR (KBr, $\nu_{\max}$, cm^{-1}): 3321, 3265, 3028, 3002, 2995, 1789, 1636, 1622, 1518, 1221, 1180, 1082, 960, 882, 766; ^1H NMR (400 MHz, CDCl_3) 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; ^{13}C NMR (100 MHz, CDCl_3) 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 calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$ (M+Na) found: 417.1247. Analysis calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$: C, 66.98; H, 5.62; N, 7.10; S, 8.13; Found C, 66.94; H, 5.60; N, 7.08; S, 8.11.

General procedure for synthesis of (4R,5R)-Ethyl 4-phenyl-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6a): 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 CHCl_3 (10 mL) at -40°C was added 50-60 % *m*-CPBA (0.61 g, 1.8 mmol) in CHCl_3 (10 mL) drop-wise *via* addition funnel. This solution was stirred at -40°C for 12 h and then was allowed to warm to 0°C in the refrigerator overnight. Then, the solution was cooled to -40°C over 1 h and was filtered to remove any excess *m*-CPBA. The filtrate was washed with 2 M NaOH (3 $\times$ 25 mL), brine (25 mL) and was dried with Na_2SO_4 . Organic layer was concentrated by rotaevaporation. Pure yellow colour crystalline solid was obtained by recrystallization from EtOH (**Scheme-II**). Light yellow colour crystalline solid; Yield 91 %, m.p.: 160.5°C , IR (KBr, $\nu_{\max}$, cm^{-1}): 3351, 3215, 3014, 2998, 1762, 1616, 1584, 1485, 1371, 1143, 1016, 966, 764; ^1H NMR (400 MHz, CDCl_3) δ 12.68 (br s, 1H), 7.86 (d, $J = 7.8$ Hz, 2H), 7.63-7.60 (m, 3H), 7.42-7.36 (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; ^{13}C NMR (100 MHz, CDCl_3) 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 calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$ (M+Na) found: 449.1145. Analysis calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$: 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°C , IR (KBr, $\nu_{\max}$, cm^{-1}): 3331, 3218, 3017, 2982, 1760, 1616, 1584, 1485, 1317, 1051, 1016, 967, 751; ^1H NMR (400 MHz, CDCl_3) 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, 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), 3.58 (t, $J = 8.2$ Hz, 2H), 3.09 (t, $J = 8.2$ Hz, 2H), 1.29 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.8, 163.6, 143.5, 138.7, 138.1, 133.6, 131.4, 129.1, 128.6, 128.2, 113.45, 87.2, 62.7, 61.5, 41.7, 19.2, 14.1 ppm; HRMS (ESI, m/z): 483.0757 calcd. for $\text{C}_{22}\text{H}_{21}\text{ClN}_2\text{O}_5\text{S}$ (M+Na) found: 483.0755. Analysis calcd. for $\text{C}_{22}\text{H}_{21}\text{ClN}_2\text{O}_5\text{S}$: C, 57.33; H, 4.59; N, 6.08; S, 6.96; Found C, 57.32; H, 4.58; N, 6.05; S, 6.93. 483.0757.

(4R,5R)-Ethyl 4-(4-bromophenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6c): Light yellow colour crystalline solid; Yield 92 %, m.p.: 171.3°C , IR (KBr, $\nu_{\max}$, cm^{-1}): 3344, 3201, 3005, 1769, 1626, 1614, 1580, 1445, 1312, 1148, 1011, 965, 823, 764; ^1H NMR (400 MHz, CDCl_3) δ 12.46 (br s, 1H), 7.92 (d, $J = 7.8$ Hz, 2H), 7.86 (d, $J = 8.4$ Hz, 7.58-7.54 (m, 3H), 7.19 (d, $J = 8.2$ Hz, 2H), 7.529 (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; ^{13}C NMR (100 MHz, CDCl_3) δ 172.3, 163.7, 143.6, 139.1, 138.6, 133.6, 131.4, 129.9, 129.7, 128.1, 120.4, 114.6, 87.6, 62.5, 61.6, 41.2, 19.4, 14.1 ppm; HRMS (ESI, m/z): 527.0252 calcd. for $\text{C}_{22}\text{H}_{21}\text{BrN}_2\text{O}_5\text{S}$ (M+Na) found: 527.0250. Analysis calcd. for $\text{C}_{22}\text{H}_{21}\text{BrN}_2\text{O}_5\text{S}$: C, 52.28; H, 4.19; Br, 15.81; N, 5.54; S, 6.34; Found C, 52.25; H, 4.17; Br, 15.79; N, 5.52; S, 6.31.

(4R,5R)-Ethyl 3-(2-(phenylsulfonyl)ethyl)-4-*p*-tolyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6d): Light yellow colour crystalline solid; Yield 90 %, m.p.: 168.4°C , IR (KBr, $\nu_{\max}$, cm^{-1}): 3347, 3212, 3005, 1761, 1621, 1580, 1484, 1325, 1141, 1026, 954, 827, 763; ^1H NMR (400 MHz, CDCl_3) δ 12.67 (br s, 1H), 7.86 (d, $J = 8.2$ Hz, 2H), 7.60-7.56 (m, 3H), 7.18 (d, $J = 8.2$ Hz, 2H), 7.14 (J = 8.2 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), 2.34 (s, 3H), 1.29 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.3, 164.1, 143.6, 138.9, 137.2, 135.6, 133.7, 129.7, 128.9, 128.3, 127.6, 113.4, 87.3, 62.8, 61.5, 41.6, 21.4, 19.3, 14.2 ppm; HRMS (ESI, m/z): 463.1304 calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ (M+Na) found: 463.1302. Analysis calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$: C, 62.71; H, 5.49; N, 6.36; S, 7.28; Found C, 62.71; H, 5.49; N, 6.36; S, 7.28.

(4R,5R)-Ethyl 4-(4-methoxyphenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-

Scheme-I: One pot multicomponent synthesis of phenylthioethyldihydrofuropyrazole derivatives (**5a-p**)

Scheme-II: Oxidative synthesis of sulfonyl dihydrofuro-pyrazole derivatives

carboxylate (6e): Light yellow colour crystalline solid; Yield 91 %, m.p.: 170.1°C , IR (KBr, ν_{max} , cm^{-1}): 3324, 3210, 3012, 2987, 1761, 1622, 1584, 1483, 1304, 1126, 1013, 956, 768; ^1H NMR (400 MHz, CDCl_3) 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; ^{13}C NMR (100 MHz, CDCl_3) 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, 62.6, 61.3, 55.8, 41.7, 19.4, 14.1 ppm; HRMS (ESI, m/z): 479.1253 calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$ ($\text{M}+\text{Na}$) found: 479.1251. Analysis calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$: 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, ν_{max} , cm^{-1}): 3329, 3212, 3002, 2987, 1762, 1619, 1581, 1483, 1366, 1311, 1144, 1025, 966, 825, 779; ^1H NMR (400 MHz, CDCl_3) 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; ^{13}C NMR (100 MHz, CDCl_3) δ 172.6, 163.7, 146.2, 145.1, 143.8, 138.9, 133.6, 129.6, 128.4, 128.1, 123.8, 128.1, 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 $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_7\text{S}$ ($\text{M}+\text{Na}$) found: 494.0996. Analysis calcd. for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_7\text{S}$: 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.

(4R,5R)-Ethyl 4-(4-hydroxyphenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate

xylate (6g): Light yellow colour crystalline solid; Yield 88 %, m.p.: 174.2 °C, IR (KBr, $\nu_{\max}$, cm^{-1}): 3328, 3204, 3015, 2982, 1762, 1632, 1611, 1580, 1485, 1334, 1148, 1012, 961, 768; ^1H NMR (400 MHz, CDCl_3) δ 12.58 (br s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.63-7.58 (m, 3H), 7.12 (d, J = 7.6 Hz, 2H), 6.70 (d, J = 7.6 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; ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 163.6, 157.7, 143.8, 138.7, 133.5, 129.7, 129.2, 128.3, 115.5, 113.4, 87.6, 62.8, 61.6, 41.8, 19.5, 14.1 ppm; HRMS (ESI, m/z): 465.1096 calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6\text{S}$ (M+Na) found: 465.1091. Analysis calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6\text{S}$: C, 59.72; H, 5.01; N, 6.33; S, 7.25; Found C, 59.70; H, 5.00; N, 6.32; S, 7.21.

(4S,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, $\nu_{\max}$, cm^{-1}): 3344, 3232, 3012, 1762, 1624, 1615, 1577, 1483, 1323, 1141, 1012, 966, 855, 778; ^1H NMR (400 MHz, CDCl_3) δ 12.65 (br s, 1H), 8.45 (d, J = 8.6 Hz, 1H), 7.60-7.57 (m, 4H), 7.24-7.21 (m, 2H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (q, J = 7.8 Hz, 2H), 3.58 (t, J = 7.8 Hz, 2H), 3.12 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.8, 163.8, 163.3, 148.5, 143.4, 138.9, 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 $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_5\text{S}$ (M+Na) found: 450.1098. Analysis calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_5\text{S}$: 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.

(4R,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, $\nu_{\max}$, cm^{-1}): 3325, 3206, 3012, 2984, 1762, 1614, 1582, 1483, 1324, 1141, 1027, 955, 849, 764; ^1H NMR (400 MHz, CDCl_3) 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), 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, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 163.8, 160.5, 143.6, 138.3, 135.7, 133.6, 129.5, 129.3, 128.7, 115.4, 113.1, 87.6, 62.8, 61.2, 41.7, 19.5, 14.1 ppm; HRMS (ESI, m/z): 467.1053 calcd. for $\text{C}_{22}\text{H}_{21}\text{FN}_2\text{O}_5\text{S}$ (M+Na) found: 467.1050. Analysis calcd. for $\text{C}_{22}\text{H}_{21}\text{FN}_2\text{O}_5\text{S}$: C, 59.45; H, 4.76; N, 6.30; S, 7.21; Found C, 59.42; H, 4.74; N, 6.28; S, 7.19.

(4R,5R)-Ethyl 3-(2-(phenylsulfonyl)ethyl)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6j): Light yellow colour crystalline solid; Yield 90 %, m.p.: 166.5 °C, IR (KBr, $\nu_{\max}$, cm^{-1}): 3337, 3229, 3026, 2998, 1761, 1612, 1568, 1482, 1310, 1139, 1018, 966, 819, 751; ^1H NMR (400 MHz, CDCl_3) δ 12.65 (br s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.72-7.65 (m, 5H), 7.22 (d, J = 7.6 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 = 7.8 Hz, 2H), 3.10 (t, J = 7.8 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 173.3, 163.9, 143.1, 142.8, 138.2, 133.5, 129.5, 128.3, 128.0, 127.9, 125.1, 124.3, 113.5, 87.3, 62.6, 61.3, 41.7, 19.4, 14.1 ppm; HRMS (ESI, m/z): 517.1021 calcd. for $\text{C}_{23}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_5\text{S}$ (M+Na) found: 517.1019. Analysis calcd. for $\text{C}_{23}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_5\text{S}$:

C, 55.87; H, 4.28; N, 5.67; S, 6.48; Found C, 55.85; H, 4.26; N, 5.64; S, 6.47.

(4S,5R)-Ethyl 4-(2,4-dichlorophenyl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6k): Light yellow colour crystalline solid; Yield 88 %, m.p.: 166.2 °C, IR (KBr, $\nu_{\max}$, cm^{-1}): 3351, 3218, 3014, 2998, 1762, 1621, 1584, 1485, 1311, 1143, 1016, 951, 827, 766; ^1H NMR (400 MHz, CDCl_3) δ 12.79 (br s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.62-7.58 (m, 4H), 7.32 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 7.2 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), 3.58 (t, J = 7.8 Hz, 2H), 3.10 (t, J = 7.8 Hz, 2H), 1.29 (t, J = 7.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.2, 163.9, 143.2, 138.6, 134.5, 133.8, 132.9, 131.0, 130.2, 130.1, 129.7, 128.3, 126.5, 113.2, 86.5, 62.5, 61.2, 36.2, 19.2, 14.1 ppm; HRMS (ESI, m/z): 517.0368 calcd. for $\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_5\text{S}$ (M+Na) found: 517.0366. Analysis calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$: C, 53.34; H, 4.07; N, 5.65; S, 6.47; Found C, 53.32; H, 4.05; N, 5.62; S, 6.46.

(4S,5R)-Ethyl 3-(2-(phenylsulfonyl)ethyl)-4-(2,4,6-trichlorophenyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate (6l): Light yellow colour crystalline solid; Yield 91 %, m.p.: 178.1 °C, IR (KBr, $\nu_{\max}$, cm^{-1}): 3345, 3242, 3021, 2981, 1762, 1616, 1583, 1484, 1304, 1158, 1012, 948, 862, 764; ^1H NMR (400 MHz, CDCl_3) 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, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.8, 163.5, 143.8, 139.2, 138.3, 135.6, 134.5, 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 $\text{C}_{22}\text{H}_{19}\text{Cl}_3\text{N}_2\text{O}_5\text{S}$ (M+Na) found: 550.9975. Analysis calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_5\text{S}$: C, 49.87; H, 3.61; N, 5.29; S, 6.05; Found C, 49.85; H, 3.59; N, 5.26; S, 6.02.

(4R,5R)-Ethyl 4-(3,5-dimethoxyphenyl)-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, $\nu_{\max}$, cm^{-1}): 3344, 3208, 3011, 2985, 1762, 1616, 1580, 1482, 1305, 1148, 1017, 959, 817, 764; ^1H NMR (400 MHz, CDCl_3) δ 12.51 (br s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.68-7.65 (m, 3H), 6.68 (s, 1H), 6.19 (s, 1H), 5.29 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.21 (d, J = 7.8 Hz, 2H), 3.83 (s, 6H), 3.58 (t, J = 7.8 Hz, 2H), 3.11 (d, J = 7.8 Hz, 2H), 1.29 (t, J = 8.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 163.7, 161.6, 143.8, 142.2, 138.9, 133.7, 129.7, 128.3, 113.4, 104.1, 97.6, 87.6, 62.8, 61.5, 55.8, 42.3, 19.4, 14.1 ppm; HRMS (ESI, m/z): 509.1358 calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_7\text{S}$ (M+Na) found: 509.1355. Analysis calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_7\text{S}$: C, 59.25; H, 5.39; N, 5.76; S, 6.59; Found C, 59.22; H, 5.36; N, 5.74; S, 6.56.

(4R,5R)-Ethyl 4-(2,4-bis(trifluoromethyl)phenyl)-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, $\nu_{\max}$, cm^{-1}): 3348, 3213, 3021, 1762, 1618, 1589, 1481, 1327, 1147, 1012, 959, 844, 768; ^1H NMR (400 MHz, CDCl_3) 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), 3.58 (t, J = 7.6 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H),

1.29 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 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 $\text{C}_{24}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_5\text{S}$ ($\text{M}+\text{Na}$) found: 585.0890. Analysis calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_5\text{SF}_6$: C, 51.25; H, 3.58; N, 4.98; S, 5.70; Found C, 51.23; H, 3.56; N, 4.94; S, 5.66.

(4*R*,5*R*)-Ethyl 3-(2-(phenylsulfonyl)ethyl)-4-(2,4,5-tris(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-furo[2,3-*c*]pyrazole-5-carboxylate (6*o*): Light yellow colour crystalline solid; Yield 86 %, m.p.: 191.8 °C, IR (KBr, ν_{max} , cm^{-1}): 3249, 3147, 3002, 2999, 2254, 1789, 1680, 1622, 1502, 1208, 1180, 1073, 963, 870, 751; ^1H NMR (400 MHz, CDCl_3) δ 12.59 (br s, 1H), 7.86 (d, $J = 8.4$ Hz, 2H), 7.65-7.61 (m, 4H), 7.41 (s, 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), 3.58 (t, $J = 8.2$ Hz, 2H), 3.11 (t, $J = 7.6$ Hz, 2H), 1.29 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.3, 163.7, 143.8, 138.6, 137.4, 133.7, 130.1, 129.7, 128.3, 127.1, 126.3, 124.3, 123.7, 123.6, 123.3, 121.4, 113.4, 87.3, 62.8, 61.6, 39.5, 19.4, 14.1 ppm; HRMS (ESI, m/z): 653.0769 calcd. for $\text{C}_{25}\text{H}_{19}\text{F}_9\text{N}_2\text{O}_5\text{S}$ ($\text{M}+\text{Na}$) found: 653.0766. Analysis calcd. for $\text{C}_{25}\text{H}_{19}\text{N}_2\text{O}_5\text{SF}_9$: C, 47.63; H, 3.04; N, 4.44; S, 5.09; Found C, 47.62; H, 3.02; N, 4.41; S, 5.05.

(4*R*,5*R*)-Ethyl 4-(furan-2-yl)-3-(2-(phenylsulfonyl)ethyl)-4,5-dihydro-1*H*-furo[2,3-*c*]pyrazole-5-carboxylate (6*p*): Light yellow colour crystalline solid; Yield 91 %, m.p.: 180.4 °C, IR (KBr, ν_{max} , cm^{-1}): 3346, 3322, 3012, 3002, 2984, 1789, 1680, 1622, 1509, 1209, 1180, 1072, 961, 877, 744; ^1H NMR (400 MHz, CDCl_3) δ 12.54 (br s, 1H), 7.86 (d, $J = 7.8$ Hz, 2H), 7.65-7.62 (m, 4H), 6.45 (m, 1H), 6.12 (d, $J = 8.4$ 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), 3.58 (t, $J = 7.6$ Hz, 2H), 3.11 (t, $J = 7.6$ Hz, 2H), 1.29 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ ppm; HRMS (ESI, m/z): 439.0940 calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_6\text{S}$ ($\text{M}+\text{Na}$) found: 439.0938. Analysis calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_6\text{S}$: C, 57.68; H, 4.84; N, 6.73; S, 7.70; Found C, 57.65; H, 4.82; N, 6.72; S, 7.67.

(4*R*,5*R*)-Ethyl 3-(2-(phenylsulfonyl)ethyl)-4-(thiophen-2-yl)-4,5-dihydro-1*H*-furo[2,3-*c*]pyrazole-5-carboxylate (6*q*): Light yellow colour crystalline solid; Yield 92 %, m.p.: 178.2 °C, IR (KBr, ν_{max} , cm^{-1}): 3361, 3256, 3129, 3015, 2987, 1793, 1687, 1622, 1511, 1212, 1185, 1061, 948, 875, 759; ^1H NMR (400 MHz, CDCl_3) δ 12.69 (br s, 1H), 7.86 (d, $J = 7.8$ Hz, 2H), 7.65-7.62 (m, 3H), 7.40 (d, $J = 8.9$ Hz, 1H), 6.93 (t, $J = 8.2$ Hz, 1H), 6.83 (t, $J = 8.2$ 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), 3.58 (t, $J = 7.6$ Hz, 2H), 3.11 (t, $J = 7.6$ Hz, 2H), 1.29 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 163.3, 149.7, 143.1, 138.9, 133.7, 129.7, 128.3, 127.0, 126.7, 125.5, 113.4, 87.5, 62.8, 61.6, 40.9, 19.0, 14.1 ppm; HRMS (ESI, m/z): 455.0711 calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_5\text{S}_2$ ($\text{M}+\text{Na}$) found: 455.0708. Analysis calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_5\text{S}_2$: C, 55.54; H, 4.66; N, 6.48; S, 14.83; Found C, 55.51; H, 4.65; N, 6.44; S, 14.80.

RESULTS AND DISCUSSION

Starting material phenylthio β -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 β -keto ester [**26,27**].

In the reaction protocol when equimolar amounts mixture of phenylthio β -keto ester, aromatic aldehyde, hydrazine, pyridinium ylide and NEt_3 (0.1 eq.) as a catalyst were refluxed in EtOH solvent provide sulfonyl pyranopyrazole (**5a-p**) with 89 % yield.

In compounds **5a-p** sulfur was oxidized by treating with *m*-CPBA provides sulfonated pyranopyrazoles (**6a-p**). To a stirred solution of (4*R*,5*R*)-ethyl 4-phenyl-3-(2-(phenylthio)-ethyl)-4,5-dihydro-1*H*-furo[2,3-*c*]pyrazole-5-carboxylate (**5a**) (1 eq.) in CHCl_3 (10 mL) at -40°C was added 50-60 % *m*-CPBA (3 eq.) in CHCl_3 (10 mL) dropwise *via* addition funnel. This solution was stirred at -40°C for 12 h and then was allowed to warm to 0°C in the refrigerator overnight provided the sulfonyl dihydrofuro-pyrazole derivatives.

The structure of the compounds was characterized by ^1H and ^{13}C NMR, MS and IR spectra and elemental analysis. IR spectrum of compound **6a** shows displayed four characteristic absorption peaks approximately at 3351 and 3152 cm^{-1} ($-\text{NH}-$), 1762 cm^{-1} (ester $-\text{C}=\text{O}$), 1143 and 1371 cm^{-1} ($-\text{SO}_2-$), 1050 cm^{-1} ($\text{C}-\text{O}-\text{C}$). Two strong bands at 1426 and 1182 cm^{-1} which belongs to asymmetric SO_2 stretching and symmetric SO_2 stretching. ^1H NMR spectra of **6a** shows δ 3.58 and δ 3.11 two triplets for two CH_2 (C12, C22) groups between furo-pyrazole and phenyl sulfonyl groups and one broad singlet appear at δ 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 moiety [**28**]. ^{13}C NMR shows 17 signals unequivocally. C12, C22 are appeared at δ 62.8, δ 19.3. Finally structure can be confirmed by the HRMS spectrum of compound **6a** showed a peak at m/z 449.1145 ($\text{M}+\text{Na}$)*, 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*

Scheme-III: Synthesis of phenylthio β -keto ester by blaise reaction

Fig. 1. Structure of sulfonated dihydrofuro-pyrazole

aeruginosa MTCC 424) following standard serial dilution method [29]. Ciprofloxacin was used as standard drug and the minimum inhibitory concentrations (MIC) in $\mu\text{M/mL}$ 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 $\mu\text{M/mL}$.

In case of Gram-positive bacteria *B. subtilis* and *S. epidermidis*, the insertion of electron withdrawing group like $-\text{F}$, $-\text{CF}_3$, $-\text{NO}_2$ 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 CF_3 groups on ring A exhibited highest activity with MIC value 0.0211 $\mu\text{M/mL}$. Compounds **6i**, **6j**, **6m**, **6n** shows better activity against *E. coli*, *P. vulgaris* with MIC value 0.0212 due to the presence of $-\text{F}$, $-\text{CF}_3$ 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 dihydrofuro-pyrazole (**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 $\mu\text{M/mL}$) 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 $\mu\text{M/mL}$ compared to fluconazole (MIC = 0.0102 $\mu\text{M/mL}$) against *A. niger*. Two $-\text{CF}_3$ substituted on ring of sulfonated furo-pyrazole (**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 dihydrofuro-pyrazole 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 CF_3 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
in vitro ANTIBACTERIAL AND ANTIFUNGAL SCREENING OF COMPOUNDS **6a-p** (MIC in $\mu\text{M/mL}$)

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

REFERENCES

1. D. Muñoz-Torrero, A.A. Mangoni, C. Guillou, S. Collina, J.J. Vanden Eynde, J. Rautio, G.M. Keseru, C. Hulme, K. Chibale, F.J. Luque, R. Karaman, M. Gütschow, H. Liu and R. Ragno, *Molecules*, **22**, 743 (2017); <https://doi.org/10.3390/molecules22050743>.
2. E. Low, B. Kim, C. Francavilla, T.P. Shiau, E.D. Turtle, D.J.R. O'Mahony, N. Alvarez, A. Houchin, P. Xu, M. Zuck, C. Celeri, M.B. Anderson, R.R. Najafi and R.K. Jain, *Bioorg. Med. Chem. Lett.*, **21**, 3682 (2011); <https://doi.org/10.1016/j.bmcl.2011.04.084>.
3. V.S. Pilyugin, S.L. Kuznetsova, Y.E. Sapozhnikov, G.E. Chikisheva, G.V. Kiseleva, T.P. Vorob'eva, E.V. Klimakova, N.A. Sapozhnikova, R.D. Davletov and Z.B. Galeeva, *Russ. J. Gen. Chem.*, **78**, 446 (2008); <https://doi.org/10.1134/S1070363208030195>.
4. Y. Dixit, R. Dixit, N. Gautam and D.C. Gautam, *E-J. Chem.*, **5**(s1), 1063 (2008); <https://doi.org/10.1155/2008/809419>.
5. L.V. Kumar, P.J. Naik, M. Naveen, T. Chandrasekhar, A.B. Reddy and N. Penchalaiah, *Indian J. Chem.*, **53B**, 208 (2014).
6. A.B.V.K. Kumar, K.S.V.K. Rao, M.S. Chandra, M.C.S. Subha and Y.L. Choi, *J. Korean Soc. Appl. Biol. Chem.*, **52**, 34 (2009); <https://doi.org/10.3839/jksabc.2009.006>.
7. A. Wani and S. Mahajan, *Am. J. Pharm. Tech. Res.*, **4**, 1058 (2014).
8. B. Guruswamy, R.K. Arul, M.V.S.R.K. Chaitan and S.S.P.K. Darsi, *Eur. J. Chem.*, **4**, 329 (2013); <https://doi.org/10.5155/eurjchem.4.4.329-335.792>.
9. S. Barbuceanu, G.L. Almajan, I. Saramet, C. Draghici, R. Socoteanu and F. Barbuceanu, *J. Serb. Chem. Soc.*, **74**, 1041 (2009); <https://doi.org/10.2298/JSC0910041B>.
10. S. Soni, M. Seth and P. Sah, *Res. J. Pharm. Biol. Chem. Sci.*, **3**, 898 (2012).
11. K.V. Kudryavtsev, M.L. Bentley and D.G. McCafferty, *Bioorg. Med. Chem.*, **17**, 2886 (2009); <https://doi.org/10.1016/j.bmc.2009.02.008>.
12. H. Otten, *J. Antimicrob. Chemother.*, **17**, 689 (1986); <https://doi.org/10.1093/jac/17.6.689>.
13. G. Scherthaner, A. Grimaldi, U. Di Mario, J. Drzewoski, P. Kempler, M. Kvapil, A. Novials, R. Rottiers, G.E.H.M. Rutten and K.M. Shaw, *Eur. J. Clin. Invest.*, **34**, 535 (2004); <https://doi.org/10.1111/j.1365-2362.2004.01381.x>.
14. C. Reviriego, *Drugs Future*, **37**, 247 (2012); <https://doi.org/10.1358/dof.2012.037.04.1789350>.
15. M.J. Yelland, C.J. Nikles, N. McNairn, C.B. Del Mar, P.J. Schluter and R.M. Brown, *Rheumatology*, **46**, 135 (2007); <https://doi.org/10.1093/rheumatology/kei195>.
16. S.G. Kang and J.J. Kim, *Ther. Adv. Urol.*, **5**, 101 (2013); <https://doi.org/10.1177/1756287212470019>.
17. C.L. Lawrence, P. Proks, G.C. Rodrigo, P. Jones, Y. Hayabuchi, N.B. Standen and F.M. Ashcroft, *Diabetologia*, **44**, 1019 (2001); <https://doi.org/10.1007/s001250100595>.
18. V.S. Tangeti, R. Varma K, G.V. Siva Prasad and K.V.V.V. Satyanarayana, *Synth. Commun.*, **46**, 613 (2016); <https://doi.org/10.1080/00397911.2016.1159696>.
19. S.V.H.S. Bhaskaruni, S.Maddila, K.K. Gangu and S.B. Jonnalagadda, *Arab. J. Chem.*, (2017); <https://doi.org/10.1016/j.arabjc.2017.09.016>.
20. M.S. Singh and S. Chowdhury, *RSC Adv.*, **2**, 4547 (2012); <https://doi.org/10.1039/C2RA01056A>.
21. V.S. Tangeti, B.H. Reddy and P. Sombabu, *Der Pharma Chemica*, **9**, 1 (2017).
22. M. Hossain and A.K. Nanda, *Sci. J. Chem.*, **6**, 83 (2018); <https://doi.org/10.11648/j.sjc.20180605.12>.
23. V.S. Tangeti, K.R. Babu, D. Vasundhara, K.V.V.V. Satyanarayana, H. Mylapalli and K.S.P. Kumar, *Curr. Org. Synth.*, **15**, 267 (2018); <https://doi.org/10.2174/1570179414666171011161836>.
24. V.S. Tangeti, K.R. Babu, G.V.S. Prasad and P. Venkata Rao, *J. Indian Chem. Soc.*, **15**, 823 (2018).
25. V.S. Tangeti, G.V. Siva Prasad, J. Panda, K.R. Varma and K.R. Varma, *Synth. Commun.*, **46**, 878 (2016); <https://doi.org/10.1080/00397911.2016.1174781>.
26. H. Prakash Rao, S. Rafi and K. Padmavathy, *Lett. Org. Chem.*, **5**, 527 (2008); <https://doi.org/10.2174/157017808785982121>.
27. H.S.P. Rao and N. Muthanna, *Synlett*, **27**, 2014 (2016); <https://doi.org/10.1055/s-0035-1561662>.
28. S.M. Rajesh, S. Perumal, J.C. Menéndez, S. Pandian and R. Murugesan, *Tetrahedron*, **68**, 5631 (2012); <https://doi.org/10.1016/j.tet.2012.04.058>.
29. J.G. Cappuccino and N. Sherman, Cultivation of Microorganisms: Nutritional and Physical Requirements, and Enumeration of Microbial Population. In: Microbiology – A Laboratory Manual, Addison Wesley Longman Inc.: Harlow, edn 4, p. 263 (1999).