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Potent Antimicrobial Agents of 8-Aza-bicyclo[3.2.1]octyl hydrazide Derivatives: Synthesis and Biological Evaluation

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A facile synthesis of 8-aza-bicyclo[3.2.1]octyl hydrazide derivatives **4(a-m)** can be achieved by modified Mannich reaction. Novelty of this research involves one pot synthesis of new modified Mannich based triazole derivatives using aromatic aldehydes and active hydrogen containing amides in the presence of ammonia and primary amine. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Among all the compounds which are screened for antibacterial and antifungal activities, hydrogen containing thiosemicarbazide moiety and 4,4-diflorocyclohexane carboxylic hydrazide has shown better activity against four bacterial strains and two fungal strains.

Keywords: Mannich reaction, Triazoles, Hydrazides, Biological activity.

INTRODUCTION

The protection of carbonyl groups plays an important role in drug design chemistry. The most common method for the preparation of Mannich bases are the reaction of aldehydes with active hydrogen containing amide moieties such as semicarbazide, thiosemicarbazide and 4,4-difluorocyclohexane carboxylic acid hydrazide in the presence of acid or base as catalyst with secondary amine [1-5]. The examples of clinically useful Mannich bases which consist of amino alkyl chain are cocaine, fluoxetine, atropine, ethacrynic acid, procyclidine and so forth.

Mannich bases also known to play a vital role in the development of synthetic pharmaceutical chemistry. Mannich reactions are widely used for the construction of nitrogen containing compounds. These bases have important biological applications such as antifungal [6], antimicrobial [7-13], anticonvulsant [14,15], antitumor [16], antiepileptic activity [17], anti-inflammatory, analgesic [18], antimalarial [19] and antioxidant activity [20].

EXPERIMENTAL

All the compounds used in the synthesis are of analytical grade. The melting points of the compounds were determined in open head capillary in paraffin bath and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm^{-1} by FT-IR Perkin spectrophotometer. ^{1}H NMR spectra were recorded on Bruker FT NMR (400Hz) spectro photometer in DMSO-d_6.The values of the chemical shift are expressed in δ ppm as a unit. Mass spectral data were obtained by using a network mass selective detector (Agilent). All the compounds were checked for purity by thin layer chromatography (TLC).

***in vitro* Antibacterial screening:** The compounds **(4a-4m)** were evaluated for their *in vitro* antibacterial activity against *Escherichia coli* (MTCC No. 42), *Pseudomonas aeruginosa* (MTCC No. 1034), *Staphylococcus aureus* (MTCC No.3160), *Bacillus megaterium* (MTCC No. 6544) by disc diffusion method [21,22]. It was performed using a LBS agar medium. Each compound and standard were used at a concentration of 100 µg/mL in DMSO. The zone of inhibition was measured after 24 h incubation at 37 ºC.

***in vitro* Antifungal screening:** The compounds **4a-4m** were evaluated for their *in vitro* antifungal activity against *Candia albicans* (MTCC No: 3017) and *Rizopus microsporus* var. oligosporus: (MTCC No: 2785) using disc diffusion method with culture media, which provides all essential nutrients for

the growth of microorganisms. Potassium dextrose agar (PDA) medium is used for fungal strains. Each compound and standard were used at a concentration of 100 µg/mL in DMSO. The zone of inhibition was measured after 24h incubation at 37 ºC.

General procedure for the synthesis of N-{[3-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-substituted phenyl methyl}acid hydrazides (4a-m): To an aqueous solution of active hydrogen containing amide, few drops of aqueous ammonia solution (1 eq.) and secondary amine (1 eq.) were added in drops in an ice-cold solution under constant stirring for dissolution. Aromatic aldehydes dissolved in methanol, added dropwise to the above mixture and stirring was continued for 2 h. The formation of compounds were observed within 30 min. Reaction was monitored by TLC, after completion of reaction, the product was filtered and washed with distilled water and dried at 45-50 ºC (**Scheme-I**).

Spectral data

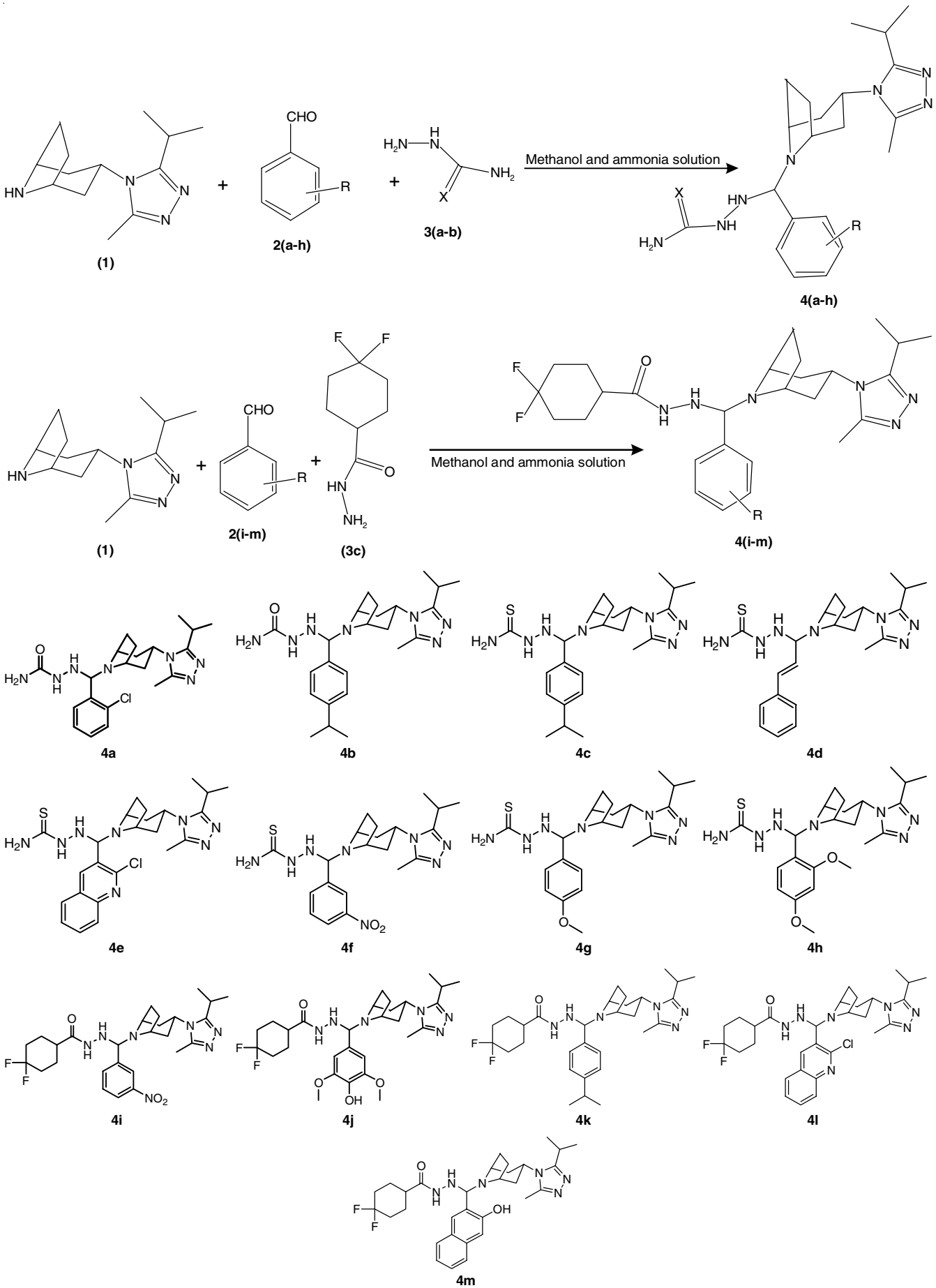
N′-{2-Chlorophenyl)-[3-(3-isopropyl-5-methyl-[1,2,4]-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}hydrazine carboxamide (4a): White solid, yield: 75.85 %, m.p. 230-232 ºC. IR (KBr, ν_{max}, cm^{-1}): 3464, 3242, 3151, 3060, 2987, 1722, 1654, 1591, 1510, 1415, 1344, 1278, 1219, 1157, 1093, 1051, 1033, 918, 852, 736, 627. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.49 (s, 2H, -NH_2, D_2O exchangeable), 8.26 (s, 1H, chiral proton), 8.15-8.18 (m, 1H, Ar-H, J_1 = 6.023 Hz, J_2 = 3.51 Hz), 7.47-7.49 (m, 1H, Ar-H, J_1 = 5.27 Hz, J_2 = 3.26 Hz, J = 7.027 Hz),7.368-7.397 (m, 2H, Ar-H, J_2 = 3.514Hz, J_2 = 6.023 Hz), 6.589 (br, s, 2H, -2NH), 3.789 (s, 3H,-CH_3), 3.46 (m, 1H, H_a), 3.31-3.36 (1H, m, J = 9.53 Hz), 2.668-2.677 (m, 2H, J = 1.757 Hz), 2.326-2.335 (m, 2H, J = 1.757 Hz), 1.88-1.97 (m, 4H, J_1 = 1.225 Hz, J_2 = 2.008 Hz), 1.253-1.236 (d, 6H, 2 × CH_3, J = 7.027 Hz); ^{13}C NMR: 8.1 (CH_3), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 36.6 (2 × CH_2), 52.7 (2 × CH), 65.2 (1CH, adjacent to arom. ring), 126.3, 128.4, 128.6, 130.4, 136.7, 137.3 (6C-arom. ring), 158.8 (-C=O, amide), 163.7 (2C, imine (C=N)). Mass: *m/z*: 429 (M-2), 391 ((M-2)-isopropyl), 414 ((M-2)-NH_3), 301, 309, 279.

N′-{4-Propane-2-yl-phenyl)-[3-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}-hydrazine carboxamide (4b): White solid, yield: 79.82 %, m.p. 215-217 ºC. IR (KBr, ν_{max}, cm^{-1}):3458, 3344, 3068, 2951, 2864, 1683, 1643, 1597, 1508, 1438, 1357, 1286, 1234, 1134, 1087, 958, 933, 829, 754. ^{1}H NMR (DMSO-d_6, 400 MHz):δ10.18 (s, 1H, -NH), 7.804 (s, 1H, -chiral proton) 7.632-7.611 (d, 2H, Ar-H, J = 8.282 Hz), 7.24-7.261 (d, 2H, Ar-H, J = 8.282 Hz), 6.451 (s, 2H, -NH_2, D_2O-exchangeable), 4.236 (s,1H,-NH-), 3.991-4.017 (m, 2H, J_1 = 5.52 Hz, J_2 = 4.768 Hz), 3.779-3.805 (m, 1H, H_a, J_1 = 5.52 Hz, J_2 = 4.517 Hz), 3.338 (s, 3H, -CH_3), 2.86-2.929 (m, 6H, J_1 = 6.776 Hz, J_2 = 7.027 Hz), 2.669-2.677 (m, 2H, J = 1.757 Hz), 2.326-2.336 (m, 2H, J_1 = 1.757 Hz, J_2 = 2.008 Hz), 1.193-1.210 (d, 12H, J = 6.776 Hz); ^{13}C NMR: δ 8.1 (CH_3), 24.4 (4 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 31.7 (1CH), 36.6 (2 × CH_2), 52.7 (2 × CH), 74.3 (1CH, adjacent to arom. ring), 126, 128.7, 128.6, 133.4, 147.2 (4C-arom. ring), 158.8 (C=O, amide), 163.7 (2C, imine (C=N)). Mass (*m/z*): 412 (M-N_2H_2), 427, 434, 441 (M+2).

N′-{4-Propane-2-yl-phenyl)-[3-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}-hydrazine carbothiamide (4c): White solid, yield: 67.27 %, m.p. 150-152 ºC. IR (KBr, ν_{max}, cm^{-1}): 3414, 3277, 3153, 3138, 2972, 2954, 1587, 1531, 1469, 1365, 1280, 1228, 1180, 1141, 1078, 1053, 1014, 954, 931, 873, 821, 711. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.38 (s, 2H, -NH_2), 8.178 (s, 1H, NH), 7.944 (s, 1H, NH), D_2O-exchangeable protons, 8.034 (s, 1H, chiral proton), 7.70-7.72 (d, 2H, Ar-H, J = 8.031 Hz) 7.284-7.305 (d, 2H, Ar-H, J = 8.282 Hz), 2.664-2.682 (m, 2H, J_1 = 1.757 Hz, J_2 = 2.008 Hz), 2.326-2.336 (m, 2H, J_1 = 1.757 Hz, J_2 = 2.008Hz, -$CH(CH_3)_2$, 2.863-2.963 (m, 4H, J_1 = 6.776 Hz, J_2 = 13.803 Hz), 3.36 (m, 1H, H_a), 3.78 (s, 3H, -CH_3), 1.199-1.232 (d, 12H, 4 × CH_3, J = 6.776 Hz), 1.422-1.51 (m, 4H). ^{13}C NMR: δ 8.1 (CH_3), 24.4 (4 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 31.7 (1CH), 36.6 (2 × CH_2), 52.7 (2 × CH), 75 (1CH, adjacent to arom. ring), 126, 128.7, 128.6, 133.4, 147.2 (4C-arom. ring), 163.7 (2C, imine(C=N)), 186 (-C=S). Mass (*m/z*): 456.2 (M+1), 439 (M-NH_2), 412 (M-isopropyl), 395.29 (M-$CSNH_2$), 365 (M-CSN_3H_3).

N′-{(2*E*)-3-phenyl-prop-2-en-1-yl)-[3-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-methyl}hydrazine carbothiamide (4d): Pale brown solid, yield: 82.21 %, m.p. 208-210 ºC. IR (KBr, ν_{max}, cm^{-1}): 3456, 3344, 3140, 3080, 2980, 1710, 1670, 1645, 1589, 1512, 1421, 1298, 1253, 1178, 1139, 974, 740, 684. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.207 (s, 2H, NH_2), 7.674-7.694 (d, 1H, chiral proton, J = 8.031 Hz), 7.519- 7.537 (d, 2H, Ar-H, J = 7.278 Hz), 7.352-7.389 (t, 2H, Ar-H, J = 7.278 Hz, 7.529 Hz), 7.724-7.310 (t, 1H, ArH, J = 7.278 Hz), 6.864-6.88 (d, 2H, CH=CH, J = 6.274 Hz), 6.294 (s, 2H, 2 × NH), 3.783-3.723 (m, 1H, -$CH(CH_3)_2$), 3.438-3.471 (m, 1H, H_a, J = 6.776 Hz), 3.32 (s, 3H, -CH_3), 2.672-2.676 (m, 2H, J = 1.757 Hz), 2.325-2.334 (m, J = 1.757 Hz), 1.728-1.742 (m, 2H, J_1 = 2.008 Hz, J_2 = 1.25Hz), 1.534-1.537 (m, 2H, J = 1.25 Hz), ^{13}C NMR: δ 8.1 (CH_3), 24.4 (2 × CH_3), 28.5 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 36.7 (2 × CH_2), 53.2 (2 × CH), 74.4 (1CH, adjacent to arom. ring), 127.4, 123.3 (2C, vinyl group), 126.2, 127.7, 128.4, 134.9, (4C-arom. ring), 163.7 (2C, imine (C=N)), 186 (-C=S). Mass (*m/z*): 440.25 (M+1), 396.20 (M-isopropyl), 379.52 (M-$CSNH_2$).

N′-{(2-Chloro-quinolin-3-yl)-[3,3-isopropyl-5-methyl)-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-(3-nitrophenyl)methyl]hydrazine carbothiamide (4e): Yellow solid, yield: 75.0 %, m.p. 222-225 ºC. IR (KBr, ν_{max}, cm^{-1}): 3460, 3342, 3143, 3072, 2980, 1651, 1597, 1525, 1490, 1448, 1352, 1274, 1211, 1184, 1128, 1105, 1045, 960, 931, 844, 813, 758, 686. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.063 (s, 1H, -NH), 11.83 (s, 2H, -NH_2), 11.654 (s, 1H, -NH) D_2O-exchangeable protons, 8.52-8.50 (d, 1H, chiral proton), 8.023-7.959 (dd, 2H, J_1 = 8.03 Hz, J_2 = 8.28 Hz), 7.84-7.87 (t, 1H, Ar-H, J = 7.278 Hz), 7.732-7.69 (t, 1H, Ar-H, J = 7.27 Hz),4.136-4.175 (m, 1H, H_a, J = 5.27 Hz), 3.48 (s, 3H, -CH_3), 3.28 (m, 1H, J = 5.27 Hz), 2.353 (m, 2H), 1.868(m, 4H), 1.446 (m, 4H), 1.25-1.26 (d, 6H, J = 6.77 Hz, 2 × CH_3). ^{13}C NMR: δ 8.1 (1C, CH_3), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 36.6 (2 × CH_2), 52.7 (2 × CH), 66.3 (1CH, adjacent to arom. ring), 126, 126.3, 126.8, 127.6, 129.2, 130.9, 135.9, 146.8,



Scheme-I: Synthetic route of compounds **4(a-m)**

157.7 (9C-quinoline ring)), 163.7 (2C, imine (C=N)), 186 (-C=S). Mass (*m/z*): 499, 461.8 (M-Cl), 437.8 (M-$CSNH_2$), 279.2.

N′-{(3-Nitro phenyl)-[3-(3-isopropyl-5-methyl[1,2,4]-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}hydrazine carbothiamide (4f): Cream solid, yield: 69.0 %, m.p. 232-234 ºC. IR (KBr, ν_{max}, cm^{-1}): 3392, 3226, 3153, 3030, 2980, 1600, 1525,1471, 1346, 1294, 1226, 1163, 1105, 1068, 937, 887, 842, 815, 732, 705, 673. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.704 (s, 1H, -NH), 11.513 (s, 1H, -NH) D_2O-exchangeable protons, 8.518-8.509 (t, 1H, Ar-H, J_1 = 1.757 Hz, J_2 = 2.008 Hz), 8.457-8.447 (t, 1H, Ar-H, J_1 = 1.757 Hz, J_2 = 2.008 Hz), 8.16-8.18 (d, 1H, Ar-H, J = 7.78 Hz), 8.311-8.32 (d, 1H, chiral proton J = 3.514 Hz), 7.706-7.755 (dt, 1H, Ar-H, J_1 = 8.031Hz, J_2 = 4.015 Hz, J_3 = 7.780 Hz) 4.084-4.124 (m, 1H, -$CH(CH_3)_2$), 3.334 (s, 3H, CH_3), 3.67(m, 1H, H_a, J = 5.270 Hz), 2.408 (m, 2H, J = 10.79 Hz), 1.602-2.110 (m, 8H, J = 4.015 Hz, 1.234-1.250 (d, 6H, -2 × CH_3, J = 6.776 Hz). ^{13}C NMR: δ 8.1 (CH_3), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 36.6 (2 × CH_2), 52.7 (2 × CH), 74 (1CH, adjacent to arom. ring), 122.1, 124.1, 129.1, 135.1, 137.2, 148.1 (6C-arom. ring), 163.7 (2C, imine (C=N)), 186 (-C=S). Mass (*m/z*): 459.22 (M+1), 415.49 (M-isopropyl), 414.8 [(M+2)-NO_2], 398.25 (M-$CSNH_2$).

N′-{(3-Methoxyphenyl)-[3-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}-hydrazine carbothiamide (4g): White shiny solid, yield: 79.65 %, m.p. 158-160 ºC. IR (KBr, ν_{max}, cm^{-1}): 3392, 3157, 3034, 2980, 1595, 1541, 1508, 1465, 1444, 1415, 1377, 1294, 1249, 1161, 1101, 1051, 1024, 952, 927, 883, 819, 690. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.2 (s, 1H,-NH), 7.804 (s, 1H, -chiral proton), 7.632-7.611 (d, 2H, Ar-H, J = 8.282 Hz), 7.24-7.26 (d, 2H, Ar-H, J = 8.282 Hz), 6.451 (s, 2H, -NH_2, D2O-exchangeable), 4.36 (s,1H, -NH-), 3.991-4.017 (m, 1H , J_1 = 5.27 Hz, J_2 = 4.768 Hz), 3.779-3.805 (m, 1H, H_a, J_1 = 5.52 Hz, J_2 = 4.517 Hz), 3.75 (s, 3H, -OCH_3), 3.34 (s, 3H, CH_3), 2.86-2.929 (m, 6H, J_1 = 6.776 Hz, J_2 = 7.027 Hz), 2.669-2.677 (m, 2H, J = 1.757 Hz, 2.326-2.336 (m, 2H, J_1 = 1.757 Hz, J_2 = 2.008 Hz), 1.193-1.210 (d, 6H, J = 6.776 Hz). ^{13}C NMR: δ 8.1 (CH_3), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH) isopropyl), 31.8 (1CH), 36.6 (2 × CH_2), 52.7 (2 × CH), 56 (1C, OCH_3), 75 (1CH, adjacent to arom. ring), 113.8, 128.6, 130, 160.5 (4C-arom. ring), 163.7 (2C, imine (C=N)), 186(-C=S). Mass (*m/z*): 441.25 (M+1), 413.58 (M-OCH_3), 383.6 (M-$CSNH_2$).

N′-{(2,4-Dimethoxy-phenyl)-[3-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}-hydrazine carbothiamide (4h): Pale yellow solid, yield: 78.24 %, m.p. 193-195 ºC. IR (KBr, ν_{max}, cm^{-1}): 3448, 3340, 3257, 3120, 2972, 1685, 1589, 1527, 1504, 1450, 1421, 1365, 1319, 1269, 1207, 1166, 1109, 1024, 939, 813, 738. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.53 (s, 2H, 2 × NH), 8.665 (s, 2H, -NH-), 8.065 (s, 1H, chiral proton), 7.77-7.78 (s, Ar-H, 1H, J = 8.69 Hz), 6.54-6.56 (dd, 1H, J = 6.4 Hz), 6.452-6.448 (d, 1H, J = 2.136 Hz), 3.85 (s, 6H, -OCH_3), 3.73 (m, 1H, J = 5.27 Hz), 3.23-3.28 (m, 1H, -$CH(CH_3)_2$), 2.74 (s, 3H, -CH_3), 2.35 (m, 2H), 1.59-2.17 (m, 8H), 1.29 (d, 6H, -2× CH_3, J = 6.77 Hz). ^{13}C NMR: δ 8.1 (CH_3), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 36.6 (2 × CH_2), 52.7 (2 × C H), 56 (2C, 2 × OCH_3), 65.1 (1CH, adjacent to arom. ring), 99.4, 106.1, 161.5, 163.5 (4C-arom. ring), 163.7 (2C, imine (C=N)), 186 (-C=S). Mass (*m/z*) : 474.26 (M+1), 431.5 (M-isopropyl), 443.61 (M-OCH_3), 441.65 (M-N_2H_2).

4,4-Difluoro-cyclohexanecarboxylic acid N′-{[3-3-isopropyl-5-methyl)[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]-oct-8-yl]-(3-nitro phenyl)methyl]hydrazide (4i): Off white solid, yield: 76.34 %, m.p. 187-189 ºC. IR (KBr, ν_{max}, cm^{-1}): 3456, 3346, 3217, 3066, 2974, 2864, 1670, 1595, 1521, 1408, 1348, 1232, 1178, 1141, 1103, 968, 904, 813, 738, 678. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.704 (s, 1H, -NH), 11.513 (s, 1H, NH) D_2O-exchangeable protons, 8.518-8.509 (t, 1H, Ar-H, J_1 = 1.757 Hz, J_2 = 2.008 Hz), 8.457-8.447 (t, 1H, Ar-H, J_1 = 1.757 Hz, J_2 = 2.008 Hz), 8.16-8.18 (d, 1H, Ar-H, J = 7.78 Hz), 8.31-8.32 (d, 1H, chiral proton J = 3.514 Hz), 7.706-7.755 (dt, 1H, Ar-H, J_1 = 8.031 Hz, J_2 = 4.015 Hz, J_3 = 7.780 Hz), 4.084-4.124 (m, 1H, -$CH(CH_3)_2$), 3.334 (s, 3H, CH_3), 3.162-3.175 (d, 1H, H_a, J = 5.270 Hz), 2.408 (m, 2H, J = 10.79 Hz), 2.335-2.326 (m, 1H, J_1 = 1.757 Hz, J_2 = 2.008 Hz, cyclohexyl, CH-), 1.602-2.110 (m, 16H, J = 13.803 Hz, J_2 = 4.015 Hz, J_3 = 13.30 Hz), 1.234-1.250 (d, 6H, -2 × CH_3, J = 6.776 Hz). ^{13}C NMR: δ 8.1 (CH_3), 14.2 (2 × CH_2), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 34.4 (2 × CH_2), 36.6 (2 × CH_2), 42 (1CH-difluoro cyclohexyl ring), 52.7 (2 × CH), 73.8 (1CH, adjacent to arom. ring), 108.3 (1C-geminal fluoro carbon), 122.1, 124.1, 129.1, 135.1, 137.2, 148.1 (6C-arom. ring), 163.7 (2C, imine (C=N), 177.9 (-C=O). Mass (*m/z*): 546.2 (M+1), 503.5 (M-isopropyl), 500.63 (M-NO_2), 369.46, 399.24.

4,4-Difluoro-cyclohexanecarboxylic acid N′-{4-hydroxy-3,5-dimethoxy-phenyl)methyl]-[3,3-isopropyl-5-methyl)-[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]hydrazide (4j): Dark brown solid, yield: 88.20 %, m.p. 130-132 ºC. IR (KBr, ν_{max}, cm^{-1}): 3342, 3213, 3032, 2974, 2881, 1683, 1585, 1506, 1454, 1421, 1369, 1319, 1276, 1242, 1213, 1163, 1109, 991, 945, 837, 717, 682, 578. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.665 (s, 2H, -NH-), 8.065 (s, 1H, chiral proton), 7.77-7.78 (s, Ar-H, 1H, J = 8.69 Hz), 6.54-6.56 (dd, 1H, J = 6.4 Hz), 5.1 (s, 1H, -OH), 3.85 (s, 6H, -OCH_3), 3.73 (m, 1H, J = 5.27 Hz), 3.23-3.28 (m, 1H, -$CH(CH_3)_2$), 2.74 (s, 3H, -CH_3), 2.35 (m, 3H), 1.597-2.17 (m, 16H), 1.29 (d, 6H, 2 × CH_3, J = 6.7776 Hz). ^{13}C NMR: δ 8.1 (CH_3), 14.2 (2 × CH_2), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 34.4 (2 × CH_2), 36.6 (2 × CH_2), 42 (1CH-difluoro cyclohexyl ring), 52.7 (2 × CH), 56.3 (2 × OCH_3), 75.4 (1CH, adjacent to arom. ring), 108.3 (1C-geminal fluoro carbon), 108.3, 127, 130.9, 149.9 (4C-arom. ring), 163.7 (2C, imine (C=N), 177.9 (C=O).Mass (*m/z*): 577.32 (M+1), 546.31 (M-OCH_3), 430.27, 370.24.

4,4-Difluoro-cyclohexanecarboxylic acid N′-{[3,3-isopropyl-5-methyl)[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]-oct-8-yl]-(4-isopropyl phenyl)methyl]hydrazide (4k): White solid, yield: 78 %, m.p. 118-120 ºC. IR (KBr, ν_{max}, cm^{-1}): 3344, 3057, 2978, 2885, 1654, 1606, 1573, 1508, 1367, 1267, 1211, 1111, 1058, 1035, 1012, 954, 835, 785, 680, 582. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.665 (s, 2H, NH), 8.065 (s, 1H, chiral proton), 6.54-6.56 (dd, 2H, J = 6.4 Hz), 6.77-6.81 (dd, 2H, J = 6.4 Hz), 3.73 (m, 1H, J = 5.27 Hz), 3.23-3.28 (m, 1H, -CH-$(CH_3)_2$), 2.74 (s, 3H, -CH_3), 2.35 (m, 3H), 1.597-2.17 (m, 16H), 1.29 (d, 12H, 4 × CH_3, J = 6.77 Hz). ^{13}C NMR: δ 8.1 (CH_3), 14.2 (2 × CH_2), 24.4 (4 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-

isopropyl), 31.8 (1CH), 34.4 (2 × CH_2), 36.6 (2 × CH_2), 42 (1CH-difluoro cyclohexyl ring), 52.7 (2 × CH), 74.8 (1CH, adjacent to arom. ring), 108.3 (1C-geminal fluoro carbon), 126, 128.7, 133.5, 147.2 (4C-arom. ring), 163.7 (2C, imine (C=N)), 177.9 (-C=O). Mass (*m/z*): 543.7 (M+1), 500.63 (M-isopropyl), 424.27, 396.30.

4,4-Difluoro-cyclohexanecarboxylic acid N′-{(2-chloro-quinolin-3-yl)-[3-(3-isopropyl-5-methyl)[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl-methyl]}hydrazide (4l): Pale yellow solid, yield: 76.25 %, m.p. 240-242 ºC. IR (KBr, ν_{max}, cm^{-1}): 3342, 3116, 3012, 2972, 2872, 1668, 1591, 1514, 1398, 1328, 1265, 1224, 1111, 1051, 950, 904, 831, 798, 781, 754. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.54 (s, 2H, NH) D_2O-exchangeable protons, 8.52-8.50 (d, 1H, chiral proton), 8.023-7.959 (dd, 2H, J_1 = 8.03 Hz, J_2 = 8.28 Hz), 7.84-7.87 (t, 1H, Ar-H, *J* = 7.278 Hz), 7.732-7.695 (t, 1H, Ar-H, *J* = 7.278 Hz), 4.136-4.175 (m, 1H, H_a, *J* = 5.27 Hz), 3.48 (s, 3H, -CH_3), 3.28 (m, 1H, *J* = 5.27 Hz), 2.353 (m, 3H), 2.1-1.97 (m, 8H, 4 × CH_2, cyclohexane), 1.868 (m, 4H), 1.446 (m, 4H), 1.25-1.26 (d, 6H, *J* = 6.776 Hz, 2 × CH_3). ^{13}C NMR: δ 8.1 (CH_3), 14.2 (2 × CH_2), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 34.4 (2 × CH_2), 36.6 (2 × CH_2), 42 (1CH-difluoro cyclohexyl ring), 52.7 (2 × CH), 66.1 (1CH, adjacent to arom. ring), 108.3 (1C-geminal fluoro carbon), 126, 128.7, 133.5, 147.2 (4C-arom. ring), 126, 126.3, 126.8, 127.6, 129.2, 130.9, 135.9, 146.8, 157.7 (9C-quinoline ring)), 163.7 (2C, imine (C=N)), 177.9 (-C=O). Mass (*m/e*): 586.5 (M+1), 588.5 (M+3), 543.2 (M-isopropyl), 439.23.

4,4-Difluoro-cyclohexanecarboxylicacid N′-{(3-hydroxy-naphthlen-2-yl)-[3-(3-isopropyl-5-methyl)[1,2,4]triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl-methyl]}hydrazide (4m): Brown solid, yield: 78.56 %, m.p. 182-184 ºC. IR (KBr, ν_{max}, cm^{-1}): 3448, 3342, 3219, 3055, 2951, 2868, 1658, 1620, 1575, 1544, 1516, 1398, 1367, 1311, 1276, 1240, 1207, 1182, 1109, 1035, 1010, 941, 848, 813, 738, 642. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.75 (s, 2H, NH) D_2O-exchangeable protons, 8.52-8.50 (d, 1H, chiral proton), 8.11 (s, 1H, Ar-H), 8.023-7.959 (dd, 2H, J_1 = 8.03 Hz, J_2 = 8.28 Hz), 7.84-7.87 (t, 1H, Ar-H, *J* = 7.278 Hz), 7.732-7.695 (t, 1H, Ar-H, *J* = 7.27 Hz), 5.0 (s, 1H, -OH), 4.136-4.175 (m, 1H, H_a, *J* = 5.27 Hz), 3.48 (s, 3H, -CH_3), 3.28 (m, 1H, *J* = 5.27 Hz), 2.353 (m, 3H), 2.1-1.97 (m, 8H, 4 × CH_2, cyclohexane), 1.868 (m, 4H), 1.446 (m, 4H), 1.25-1.26 (d, 6H, *J* = 6.776 Hz, 2 × CH_3). ^{13}C NMR: δ 8.1 (CH_3), 14.2 (2 × CH_2), 24.4 (2 × CH_3), 28.4 (2 × CH_2), 26.3 (1CH)-isopropyl), 31.8 (1CH), 34.4 (2 × CH_2), 36.6 (2 × CH_2), 42 (1CH-difluoro cyclohexyl ring), 52.7 (2 × CH), 65 (1CH, adjacent to arom. ring), 108.3 (1C-geminal fluoro carbon), 108.6, 123.3, 125.3, 125.8, 126.9, 127.1, 128.5, 128.8, 132.5, 155.2 (10C-arom. ring), 163.7 (2C, imine (C=N)), 177.9 (C=O). Mass (*m/e*): 567.32 (M+1), 524.61, 424.28, 420.55.

RESULTS AND DISCUSSION

8-Aza-bicyclo[3.2.1]octyl hydrazide derivatives **4(a-m)** were synthesized by using modified Mannich reaction and characterized by IR, NMR and mass spectral data. In general, IR absorption band of 1º amine and 2º amines of N-H absorption bands observed in the region 3460-3130 cm^{-1}. 1º amine N-H stretching absorption frequency appeared as doublet at 3460 and 3342 cm^{-1} for asymmetric and symmetric stretching frequencies. For 2º amine, the absorption band appears as singlet at 3200-3143 cm^{-1}. The peaks at 3080-3030 cm^{-1} appeared for aromatic -C-H stretching. At 2980-2850 cm^{-1} methyl C-H stretching absorption was observed. The peak at 1691-1659 cm^{-1} caused primarily by imine (C=N), it is conjugation with C=C in aromatic ring so it shifts to higher absorption frequency. The out of plane N-H wagging is responsible for broad band in the region 844-813 cm^{-1}. The bands at 1597.06-1525 cm^{-1} are due to the absorption frequency of C=C and N-H bending vibrations and at 1600-1597 cm^{-1} absorption is due to C=S. The peaks at 1274 and 1128-1105 cm^{-1} for C-N and C-O stretching frequencies, respectively. The band at 1354 cm^{-1} is attributed for N-N absorption band while at 1045 cm^{-1} for C=S and 758.02 cm^{-1} for C-Cl stretching absorption band.

^{1}H NMR spectra of compounds **4(a-m)** revealed that the chemical shift of chiral proton deshielding to down field in the region at δ 7.5-8.5 ppm as doublet due to the chiral proton attached to aromatic ring and electronegativity of nitrogen atom on both sides. So it deshields to higher δ value than expected and for NH protons appeared as singlet in the region δ 12.063-11.654 ppm., *i.e*. one NH proton at δ 12.063, two hydrogens of NH_2 at δ 11.83 and for one NH proton at δ 11.654 ppm, these protons are D_2O exchangeable. The two protons of aromatic ring appeared as doublet of doublet at δ 7.59 ppm, it's J_1 = 8.03 Hz and J_2 = 8.28 Hz. One aromatic proton appeared as triplet at δ 7.84-7.87 ppm and its coupling constant is *J* = 7.278 Hz. The other peak at δ 7.732-7.695 appeared as triplet and it's coupling constant is *J* = 7.278 Hz. The axial proton at azabicyclo[3.2.1] octane ring appeared as multiplet at δ 4.136-4.175 ppm having coupling constant *J* = 5.27 Hz. At 3.48 ppm, three hydrogen's of methyl group appeared as singlet and at δ 3.18 appeared as multiplet. The peaks at δ 2.353 appeared as multiplet and at δ 1.868 and 1.446 appeared as multiplet of 4 × CH_2 groups of azabicyclic ring. The six protons of 2 × CH_3 groups of isopropyl appeared as doublet with lower intensity with coupling constant *J* = 6.776Hz. ^{13}C NMR spectra of most compounds have characteristic C=O signals appeared at around δ 158-177.9 ppm, N=CH δ 163.7-164 ppm, at δ 108.3 ppm 1C-geminal fluoro carbon and C=S at δ 186 ppm.

The synthesized compounds **4(a-m)** have been evaluated for their *in vitro* antimicrobial activities using four bacterial and two fungal strains. Ciprofloxacin and nystatin have been used as standard drugs for bacteria and fungi. It is revealed that N-{[3-(3-isopropyl-5-methyl-[1,2,4]triazol-4-yl)-8-azabicyclo-[3.2.1]oct-8-yl]-substituted phenyl-methyl}acid hydrazides and carboxythiamides **4(a-m)** showed significant antimicrobial activities (Table-1). The compounds **4f**, **4h**, **4i**, **4j**, **4l** and **4m** exhibited high antibacterial activity while compounds **4a**, **4d**, **4f**, **4g**, **4h** and **4i** exhibited high antifungal activity.

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TABLE-1
DATA OF ANTIMICROBIAL ACTIVITY OF COMPOUNDS **4(a-m)**

Compound	Zone of inhibition (mm)					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	Staphylococcus aureus	*Streptococcus faecalis*	*Escherichia coli*	*Psedomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*
4a	20	25	22	21	20	23
4b	16	25	21	19	21	19
4c	23	24	24	19	20	18
4d	24	22	23	21	21	22
4e	18	23	19	22	18	19
4f	23	27	25	22	22	23
4g	20	19	20	24	21	21
4h	27	20	24	25	21	23
4i	22	21	25	20	20	21
4j	22	22	21	23	18	20
4k	19	19	20	19	22	19
4l	20	26	20	18	17	23
4m	21	26	24	20	19	22
Standard	25	30	28	26	22	24
Std. drug	Ciprofloxacin (antibacterial)				Nystatin (antifungal)	

CONFLICT OF INTEREST

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

REFERENCES

1. S. Bala, N. Sharma, A. Kajal, S. Kamboj and V. Saini, *Int. J. Med. Chem.*, **Article ID 191072** (2014); https://doi.org/10.1155/2014/191072.
2. H.C. Yao and P. Resnick, *J. Org. Chem.*, **30**, 2832 (1965); https://doi.org/10.1021/jo01019a504.
3. R. Fusco and F. Sannicolo, *J. Org. Chem.*, **46**, 90 (1981); https://doi.org/10.1021/jo00314a019.
4. T. Iida and F.C. Chang, *J. Org. Chem.*, **46**, 2786 (1981); https://doi.org/10.1021/jo00326a037.
5. R.L. Frank and R.R. Phillips, *J. Am. Chem. Soc.*, **71**, 2804 (1949); https://doi.org/10.1021/ja01176a060.
6. Y. Koltin, *Annu. Rep. Med. Chem.*, **25**, 141 (1990).
7. A.J. Abdul Nasser, A. Idhayadhulla, R.S. Kumar and J. Selvin, *J. Indian Heterocycl. Chem.*, **18**, 399 (2009).
8. A. Idhayadhulla, R.S. Kumar, A.J. Abdul Nasser, J. Selvin and A. Manilal, *Arab. J. Chem.*, **7**, 994 (2014); https://doi.org/10.1016/j.arabjc.2010.12.025.
9. S. Fandakli, H.B. Serapbasoglu, A.D. Meltemyolal and A.K.G. Sengul, *Turk. J. Chem.*, **36**, 567 (2012); https://doi.org/10.3906/kim-1103-23.
10. S.G. Subramaniapillai, *J. Chem. Sci.*, **125**, 467 (2013); https://doi.org/10.1007/s12039-013-0405-y.
11. T. Plech, M. Wujec, M. Majewska, U. Kosikowska and A. Malm, *Med. Chem. Res.*, **22**, 2531 (2013); https://doi.org/10.1007/s00044-012-0248-y.
12. H. Bayrak, A. Demirbas, S.A. Karaoglu and N. Demirbas, *Eur. J. Med. Chem.*, **44**, 1057 (2009); https://doi.org/10.1016/j.ejmech.2008.06.019.
13. L. Popiolek, A. Biernasiuk, K. Paruch, P. Patrejko and M. Wujec, *Phosphorus, Sulfur, Silicon Rel. Elem.*, **192**, 880 (2017); https://doi.org/10.1080/10426507.2017.1290629.
14. M. Sivakami, B. Natarajan and M. Vijayachandrasekar, *Chem. Sci. Transac.*, **3**, 1110 (2014); https://doi.org/10.7598/cst2014.837.
15. M.M. Alam, S. Nazreen, S. Haider, S. Shafi, M.S. Yar, H. Hamid and M.S. Alam, *Arch. Pharm.*, **345**, 203 (2012); https://doi.org/10.1002/ardp.201100128.
16. J. Chen, X.Y. Sun, K.Y. Chai, J.S. Lee, M.S. Song and Z.S. Quan, *Bioorg. Med. Chem.*, **15**, 6775 (2007); https://doi.org/10.1016/j.bmc.2007.08.004.
17. V. Vrdoljak, I. Dilovic, M. Rubcic, S. Kraljevic Pavelic, M. Kralj, D. Matkovic-Calogovic, I. Piantanida, P. Novak, A. Rozman and M. Cindric, *Eur. J. Med. Chem.*, **45**, 38 (2010); https://doi.org/10.1016/j.ejmech.2009.09.021.
18. M. Köksal, N. Gökhan, E. Küpeli, E. Yesilada and H. Erdogan, *Arch. Pharm. Res.*, **30**, 419 (2007); https://doi.org/10.1007/BF02980214.
19. D. Sharma, D. Chetia and M. Rudrapal, *Asian J. Chem.*, **28**, 782 (2016); https://doi.org/10.14233/ajchem.2016.19478.
20. R. Seth, S. Arora, S. Jain and N. Jain, *J. Pharm. Technol. Res. Manage.*, **3**, 57 (2015); https://doi.org/10.15415/jptrm.2015.31005.
21. S.J. Haycock-Lewandowski, A. Wilder and J. Åhman, *J. Org. Process. Res. Dev.*, **12**, 1094 (2008); https://doi.org/10.1021/op8000614.
22. T.L. Viveka, M. Saba, S.N.T. Sunitha, Y. Aparna and L.N. Sharada, *World J. Pharm. Pharm. Sci.*, **4**, 1087 (2016).