An efficient one pot synthesis and antimicrobial activity of novel S-alkylisothiosemicarbazone and imidazolidinone derivatives of pyrazole carbaldehyde

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S-Alkylisothiosemicarbazone and imidazolidinone derivatives were synthesised from pyrazole 4-carbaldehyde in a one pot reaction. The synthesised compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. Most of the synthesised compounds showed antimicrobial activity against *S. Aureus, B. subtilis, E. coli, P. aeruginos, A. Niger* and *C. albicans.*

Keywords: one pot, S-alkylisothiosemicarbazone, imidazolidinone, ethyl chloroacetate, alkyl bromides, pyrazole 4-carbaldehyde

Pyrazole, imidazolidinone and isothiosemicarbazone derivatives show varied biological activities and are therefore of considerable interest for drug discovery. On this basis, we have studied the design and synthesis of new molecules which combine the nucleus of pyrazole and thiazolidinone as well as pyrazole and isothiosemicarbazone in one molecular framework in anticipation that such compounds might show enhanced biological activity.[1–12] The literature revealed that pyrazole derivatives of barbituric acid, thiobarbituric acid, some activated nitriles, and acetophenones showed antimicrobial activities.[13] In continuation of our work[14–17] on the synthesis of new derivatives with a combination of different heterocyclic rings as possible antimicrobial agents, we report here the synthesis of some new S-alkyl isothiosemicarbazone and imidazolidinone derivatives of pyrazole carbaldehyde. From substituted acetophenones **1a–e** the intermediate pyrazole carbaldehydes **2a–e** were synthesised by known literature methods.[18,19] Two different series of pyrazole aldehyde derivatives (**3a–j** and **4a–k**) were synthesised and screened for their antimicrobial activity.

Experimental

Chemicals were purchased from Aldrich Chemical Co. Reactions were monitored and purity of the products was checked by TLC using Merck 60 F-254 silica gel plates with visualisation by UV light. Melting points were determined on a Buchi Melting Point B-545 apparatus. The IR spectra of the compounds were recorded on a Nicolet 6700 FT-IR spectrometry using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker spectrometer at 300 MHz and 75 MHz (^{13}C NMR) in $CDCl_3$. Chemical shifts were recorded in parts ppm downfield from tetramethylsilane. Mass spectra were recorded using a MS-3200Q. CHN Analysis was done on an HOSLI CH- analyser. Column chromatography was performed on silica gel (230–400 mesh) supplied by Acme Chemical Co. The chemicals and solvents used were laboratory grade and were purified as per literature methods.

Antimicrobial activity

For antibacterial activity the solid media used for the study were Muller-Hinton agar (Hi media) MHA of the following composition, beef infusion (300 g L^{-1}), casein acid hydrolysate (17.5 g L^{-1}), starch (1.5 g mL^{-1}), agar-agar (17 g L^{-1}) and sterilised distilled water (1000 mL) adjusted to pH 7.4. and soyabean casein digest agar (SCDA; casein enzymatic hydrolysate (17.0 g L^{-1}), papain digest of soyabean 3.0 (g L^{-1}), NaCl 5.0 (g L^{-1}), dipotassium phosphate (2.5 g L^{-1}) and distilled water (1000 mL), adjusted to pH 7.3) were used for biological assays.

For antifungal activity the solid media used for the study were potato dextrose agar (Hi media) of the following composition potato (250 g), dextrose (10g), agar-agar (20g), sterilised distilled water (100 mL) adjusted to pH 7.3.

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Test microorganisms

All the synthesised compounds were screened for their *in vitro* antibacterial activity against the standard strains *B. subtilis* (2250), *S. aureus* (2079), *E. coli* (2109) and *P. aeruginosa* (2036) and for their antifungal activity against *C. albicans* (3471) and *A. niger* (545). All the strains were obtained from the microbial type culture collection (MTCC) at the NCIM, Pune, India.

Primary screening

The antibacterial activity of all the newly synthesised compounds was estimated by the agar-well diffusion assay technique.[20] A 24 h old bacterial culture of all test microorganisms were used as the inoculum, which was adjusted to 0.5 McFarland standard (1.5×10^8 CFU/mL). The stock solutions of all test compounds (100 μg mL^{-1}) were prepared by dissolving 100 μg of the test compound in DMSO (1 mL). Chloramphenicol and DMSO were used as positive and negative controls, respectively.

20 mL of molten and cooled MHA and 320 μl of each test bacterial culture were mixed (separate flasks were used for each bacterial culture) and poured in sterilised and labelled Petri plates. The wells of 6 mm were punched in the solidified Petri plates, aseptically. 50 μL from stock solutions of all compounds as well as controls were added to each well of labelled Petri plates and incubated at 35 °C for 24 h. The diameter of the zone of growth inhibition around each well was measured after incubation using a Vernier caliper.

For the antifungal activity, sliced potatoes were placed with 500 mL of distilled water in a pan and boiled for 30 min until a spoon could pierce them. The mixture was then filtered while hot and broth was again placed in a pan with the rest of the distilled water. Dextrose was dissolved in distilled water and weighed agar was added to the broth and heated to boiling. The medium thus obtained was sterilised in a pressure cooker for 30 min. The sterilised medium (15 mL) was pipetted out into flat Petri plates. When it solidified, 15 mL of warm seeded agar was applied over it. The seeded agar was made by cooling the medium to 40 °C and then adding a spore suspension to the seeded medium. The spores were obtained from 10 days culture of *C. albicans* and *A. niger* species. The final inoculum size was adjusted to 1×10^6 spore mL^{-1}. Nystatin and DMSO were used as positive and negative controls, respectively.

Before the solidification of agar, the plate was tilted to ensure that coverage was even. These Petri plates were then put into the refrigerator upside down to prevent condensation of moisture. A concentration 100 μg mL^{-1} of the synthesised compounds were prepared by dissolving the required quantity of compounds in DMSO. Sterilised Whatman filter paper number 541 discs were prepared by cutting 6 mm diameter with a cork borer and were spread individually with a needle and planted upon the chilled seeded medium. The culture plates were then incubated for 24 to 72 h at 37 °C and the inhibition zone around each disc was measured from the centre of the disc. The diameter of growth inhibition zone was calculated by a Vernier caliper.

Synthesis of pyrazole 4-carbaldehyde (**2a–e**)

The compounds **2a–e** were synthesised from different substituted acetophenones **1a–e** using literature protocol[18,19] as shown in Scheme 1.

Synthesis of isothiosemicarbazone derivatives (**3a–j**)
A suspension of thiosemicarbazide (5 mmol) and alkyl bromide (5 mmol) in ethanol (20 mL) was refluxed until the solid was completely dissolved. To this, aldehyde (5 mmol) was added and the heating was continued for 1 h. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 4:6). After completion, the reaction mixture was cooled at room temperature and poured into ice-cold water. The solid product obtained was filtered, washed with water and purified by column chromatography.

Synthesis of imidazolidinone derivatives (**4a–k**)
A mixture of (5 mmol) of pyrazole carbaldehyde, thiosemicarbazide (5 mmol), ethyl chloroacetate (5 mmol), alkyl bromide (5 mmol) and triethyl amine (two drops) was refluxed in ethanol (20 mL) for about 30 minutes. The reaction was monitored by TLC (ethyl acetate: hexane, 3:7). After completion, the reaction mixture was cooled and poured into crushed ice. The precipitate obtained was filtered, washed with water and purified by column chromatography.

1-((1,3-Diphenyl-1H-pyrazol-4-yl)methyleneamino)-2-butylisothiourea (**3a**): M.p. 121 °C, yield: 75%, IR (cm^{-1}): 3200 (NH_2), 3020 (Aromatic CH), 1615 (C=N), 1600, 1500, 1228, 504, 754, 705. ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.3 (s, 1H, pyrazolyl H), 9.1 (bs, 2H, NH_2), 8.5 (s, 1H, CH=N), 7.3–7.9 (m, 9H), 3.3 (t, *J* = 6.8 Hz, 2H, S–CH_2), 1.7 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), 0.9 (t, *J* = 7.1 Hz, 3H,CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.5 (N=C-S), 150.35 (CH=N), 150.6, 140.43, 130 (2C), 131.245, 129.10 (2C), 130.03 (2C), 125.54, 125.05, 123.03, 119.54 (2C), 117.142, 22.569 (S–CH_2), 16.684 (CH2), 16, 15.657. MS (EI, 70 eV): *m/z* (%) = 377 (M^+, 100), 378 (M+1, 42). Anal. Calcd for $C_{21}H_{23}N_5S$, C, 66.81; H, 6.14; N, 18.55. Found: C, 66.75; H, 6.20; N, 18.50%.

1-((1-Phenyl-3-(4-methyl-phenyl)-1H-pyrazol-4-yl)methyleneamino)-2-ethyl isothio urea (**3b**): M.p. 113 °C, yield: 65%, IR (cm^{-1}): 3200–3210 (NH_2), 3010 (Aromatic CH), 1616 (C=N), 1600, 1510, 1235, 510, 750, 708. ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.8 (bs, 2H, NH_2), 9.3 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 7.6 (d, 2H, *J* = 8.1 Hz), 7.9 (d, 2H, *J* = 8.1 Hz), 7.3–7.8 (m, 5H), 3.1 (q, *J* = 7.1 Hz, 2H, S–CH_2), 1.3 (t, 3H, *J* = 7.1 Hz, CH_3), 2.4 (s, 3H, Ar-CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.021 (C=S), 150 (CH=N), 151.01, 139.01, 128.6 (2C), 131, 127.11 (2C), 129 (2C), 125, 123.8, 122.5, 118 (2C), 117.142, 22.50 (S–CH_2), 14 (CH_3), 23.380 (CH_3-Ar). MS (EI, 70 eV): *m/z* (%) = 363 (M^+, 100), 364 (M+1, 27). Anal. Calcd for $C_{20}H_{21}N_5S$ C, 66.09; H, 5.82; N, 19.27. Found: C, 66.15; H, 5.75; N, 19.35%.

1-((1-Phenyl-3-(4-methyl-phenyl)-1H-pyrazol-4-yl)methyleneamino)-2-butylisothio urea (**3c**): M.p. 141 °C, yield: 68%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.3 (s, 1H, pyrazolyl H), 9.2 (bs, 2H, NH_2), 8.5 (s, 1H, CH=N), 7.6 (d, 2H, *J* =8.1 Hz), 7.9 (d, 2H, *J* = 8.1 Hz), 7.3–7.8 (m, 5H), 3.3 (t, 2H, *J* = 7.1 Hz, S–CH_2), 2.4 (s, 3H, Ar-CH_3), 1.7 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), 0.9 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.462 (C=S), 150 (CH=N), 151.07, 139, 128.87 (2C), 131, 127.82 (2C), 129 (2C), 125.5, 122.852, 122.663, 118.87 (2C), 116.60, 23.45 (CH_3-Ar), 22.05 (S–CH_2), 15.80 (CH_3), 14.87 (CH_2), 12 (CH_2). MS (EI, 70 eV): *m/z* (%) = 391 (M^+, 100), 392 (M+1, 32). Anal. Calcd for $C_{22}H_{25}N_5S$, C, 67.49; H, 6.44; N, 17.89. Found: C, 67.60; H, 6.35; N, 17.79%.

1-((3-(4-Chlorophenyl)1-phenyl-1H-pyrazol-4-yl)methyleneamino)-2-heptylisothio urea (**3d**): M.p. 190 °C, yield: 77%, IR (cm^{-1}): 3220 (NH_2), 3015 (Aromatic CH), 1610 (C=N), 1500, 1235, 510, 705. ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.6 (bs, 2H, NH_2), 9.3 (s, 1H, pyrazolyl H), 8.5 (s, 1H, CH=N), 7.7 (d, 2H, *J* = 8.3 Hz), 7.8 (d, 2H, *J* = 8.3 Hz), 7.3–7.7 (m, 5H), 3.4 (t, 2H, *J* = 7.1 Hz, S–CH_2), 1.4–1.7 (m, 10 H, 5CH_2), 0.9 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162 (C=S), 149.8 (CH=N), 150.51, 139, 131 (2C), 131.5, 129.91 (2C), 129.04 (2C), 127, 126.05, 122.05, 119 (2C), 117, 22.62 (S–CH_2), 15.71 (CH_2), 15.05 (CH_2), 14.02, 13.5, 13, 12.11. MS (EI, 70 eV): *m/z* (%) = 453 (M^+, 100), 454 (M+1, 20), 455 (M+2, 35). Anal. Calcd for $C_{24}H_{28}ClN_5S$ C, 63.49; H, 6.22; N, 15.42. Found: C, 63.34; H, 6.35; N, 15.39%.

1-((3-(4-Chlorophenyl)1-phenyl-1H-pyrazol-4-yl)methyleneamino)-2-butylisothio urea (**3e**): M.p. 225 °C, yield: 69%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.6 (bs, 2H, NH_2), 9.3 (s, 1H, pyrazolyl H), 8.5 (s, 1H, CH=N), 7.7 (d, 2H, *J* = 8.3 Hz), 7.8 (d, 2H, *J* = 8.3 Hz), 7.4–7.7 (m, 5H), 3.4 (t, 2H, *J* = 7.1 Hz, S–CH_2), 1.7 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), 0.9 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162 (C=S), 150.05 (CH=N), 150.8, 139, 131 (2C), 131.52, 130 (2C), 129.64 (2C), 127.01, 125.94, 123.05, 119.431 (2C), 117, 22.011 (S–CH_2), 15.0 (CH_3), 12.5 (CH_2), 13.41 (CH_2). MS (EI, 70 eV): *m/z* (%) = 411 (M^+, 100), 413 (M+2, 33), 412 (M+1, 20) Anal. Calcd for $C_{21}H_{22}ClN_5S$ C, 61.23; H, 5.38; N, 17.00. Found: C, 61.15; H, 5.43; N, 17.26%.

1-((3-(4-Nitrophenyl)1-phenyl-1H-pyrazol-4-yl)methyleneamino)-2-ethylisothio urea (**3f**): M.p. 176 °C, yield: 80%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.8 (bs, 2H, NH_2), 9.3 (s, 1H, pyrazolyl H), 8.5 (s, 1H, CH=N), 8.38 (d, 2H, *J* = 8.2 Hz), 8.03 (d, 2H, *J* = 8.2 Hz), 7.4–7.7 (m, 5H), 3.4 (q, 2H, *J* = 7.1 Hz, S–CH_2), 1.3 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.62 (C=S), 150.540 (CH=N), 150.767, 139.335, 133.749 (2C), 131.542, 130.01 (2C), 129, 128.421, 128.121 (2C), 122.896, 119.431 (2C), 117.142, 22.85 (S–CH_2), 15.61 (CH_3) Anal. Calcd for $C_{19}H_{18}N_6O_2S$ C, 57.85; H, 4.60; N, 21.31. Found: C, 57.79; H, 4.72; N, 21.25%.

1-((3-(4-Nitrophenyl)1-phenyl-1H-pyrazol-4-yl)methyleneamino)-2-propylisothiourea (**3g**): M.p. 180 °C, yield: 83%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.8 (bs, 2H, NH_2), 9.4 (s, 1H, pyrazolyl H), 8.6 (s, 1H, CH=N), 8.38 (d, 2H, *J* = 8.2 Hz), 8.03 (d, 2H, *J* = 8.2 Hz), 7.4–7.7 (m, 5H), 3.4 (t, 2H, *J* = 7.1 Hz,S–CH_2), 1.7 (m, 2H, CH_2), 1.0 (t, 3H, *J* = 7.1 Hz,CH_3). ^{13}C NMR, δ (75 MHz, $CDCl_3$): 162 (C=S), 150.45 (CH=N), 150.92, 140, 134.10 (2C), 131.624, 130.52 (2C), 129.2, 128.54, 128 (2C), 123.01, 119.132 (2C), 117.142, 22.58 (S–CH_2), 14.50 (CH_3), 13.54 (CH_2) MS (EI, 70 eV): *m/z* (%) = 408 (M^+, 100), 409 (M+1, 25). Anal. Calcd for $C_{20}H_{20}N_6O_2S$, C, 58.81; H, 4.94; N, 20.57. Found: C, 58.75; H, 4.86; N, 20.45%.

1-((3-(4-Nitrophenyl)1-phenyl-1H-pyrazol-4-yl)methyleneamino)-2-butylisothiourea (**3h**): M.p. 192 °C, yield: 78%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.5 (bs, 2H, NH_2), 9.4 (s, 1H, pyrazolyl H), 8.6 (s, 1H, CH=N), 8.38 (d, 2H, *J* = 8.2 Hz), 8.03 (d, 2H, *J* = 8.2 Hz), 7.4–7.7 (m, 5H), 3.3 (t,2H, *J* = 7.1 Hz, S–CH_2), 1.6 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), 0.9 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.62 (C=S), 150.540 (CH=N), 150.767, 139.335, 133.749 (2C), 131.542, 130.01 (2C), 129, 128.421, 128.121 (2C), 122.896, 119.431 (2C), 117.142, 22.11 (S–CH_2), 14 (CH_3), 13.21 (CH_2), 12.35 (CH_2) Anal. Calcd for $C_{21}H_{22}N_6O_2S$ C, 59.70; H, 5.25; N, 19.89. Found: C, 59.65; H, 5.15; N, 19.78%.

1-((3-(4-Bromophenyl)1-phenyl-1H-pyrazol-4-yl)methyleneamino)-2-ethylisothiourea (**3i**): M.p. 178 °C, yield: 72%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.85 (bs, 2H, NH_2), 9.3 (s, 1H, pyrazolyl H), 8.45 (s, 1H, CH=N), 7.9 (d, 2H, *J* = 8.3 Hz), 7.8 (d, 2H, *J* = 8.3 Hz), 7.3–8.2 (m, 5H, ArH), 3.4 (q,2H, *J* = 7.1 Hz, S–CH_2), 1.3 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.784 (C=S), 150.018 (CH=N), 150.767, 139.335, 131.749 (2C), 131.245, 130.360 (2C), 129.551 (2C), 127.689, 127.353, 122.896, 119.431 (2C), 117.142, 22.11 (S–CH_2), 15 (CH_3). MS (EI, 70 eV): *m/z* (%) = 427 (M^+, 100), 429 (M+2, 100) 428 (M+1, 21). Anal. Calcd for $C_{19}H_{18}BrN_5S$, C, 53.28; H, 4.24, N, 16.35. Found: C, 53.38; H, 4.29; N, 16.31%.

1-((3-(3,5-Bis(trifluoromethyl)phenyl-1H-pyrazol-4-yl)methyleneamino)-2-ethylisothiourea (**3j**): M.p. 182 °C, yield: 69%, ^{1}HNMR δ (300 MHz, $CDCl_3$): 9.85 (bs, 2H, NH_2), 9.3 (s, 1H, pyrazolyl H), 8.45 (s, 1H, CH=N), 8.3 (s, 2H, ArH), 7.9 (s, 1H, ArH), 7.4–7.8 (m, 5H, ArH phenyl), 3.4 (q, 2H, *J* = 7.1 Hz, S–CH_2), 1.3 (t,3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.95 (N=C-S), 150.305 (CH=N), 149, 139.5, 135, [133.122, 132.682, 132.242, 131.794 (q, 2C, *J* = 33 Hz)], 130.15 (2C), 128.9, 128.544 (2C), 127.680, 123, 120.1 (2C), 117.524, [125.135, 121.51, 117.88, 114.252 (q, 2C *J* = 272 Hz)], 22.356 (S–CH_2), 15.241 (CH_3). MS (EI, 70 eV): *m/z* (%) = 485 (M^+, 100), 487 (M+2, 10) 486 (M+1, 15). Anal. Calcd for $C_{21}H_{17}F_6N_5S$: C, 51.96; H, 3.53; N, 14.43. Found: C, 51.90; H, 3.59; N, 14.49%.

3-((3,5-Bis(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazol-4-yl)methyleneamino)-1-ethyl-2-thioimidazolidin-4-one (**4a**): M.p. 125 °C, yield: 70%, IR (cm^{-1}): 3015 (Aromatic CH), 1610 (C=N), 1680 (C=O), 1055 (C=S), 1230, 500. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 8.3 (s, 2H, ArH), 7.9 (s, 1H, ArH), 7.4–7.8 (m, 5H, ArH phenyl), 3.9 (q, 2H, *J* = 7.1 Hz, CH_2-**N**), 3.7 (s, 2H, CH2, imidazolidinone ring), 1.1 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 171.95 (C=S), 163.17 (C=O), 149.805 (CH=N), 149.561,139.106, 134.771, [133.254, 132.809, 132.364, 131.919 (q, 2C, *J* = 33 Hz)], 129.658 (2C), 128.864, 128.544 (2C), 127.735, 122.9, 119.508 (2C), 117.524, [125.06, 121.435, 117.809, 114.182 (q, 2C, *J* = 272 Hz], 38.743 (CH_2 imidazolidinone ring), 33.05 (N–CH_2), 29.53. MS (EI, 70 eV): *m/z* (%) = 525 (M^+, 100), 527 (M+1, 27). Anal. Calcd for $C_{23}H_{17}F_6N_5OS$: C, 52.57; H, 3.26; N, 13.33. Found: C, 52.48; H, 3.68; N, 13.25%.

3-((3,5-Bis(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazol-4-yl) methyleneamino)-1-isopropyl-2-thioimidazolidin-4-one (**4b**): M.p. 220 °C, yield: 69%, IR (cm^{-1}): 3010 (Aromatic CH), 1600 (C=N), 1685 (C=O), 1055 (C=S), 500. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 8.3 (s, 2H, ArH), 7.9 (s, 1H, ArH), 7.4–7.8 (m, 5H, ArH phenyl), 4.8–4.85 (m, 1H, CH–N), 3.7 (s, 2H, CH_2 imidazolidinone ring), 1.5 (d, 6H, *J* = 6.8 Hz, 2CH_3).

^{13}C NMR δ (75 MHz, $CDCl_3$): 171.9 (C=S), 163.15 (C=O), 149.70 (CH=N), 149.52, 139.02, 134.62,[133.254, 132.809, 132.364, 131.919 (q, 2C, *J* = 33 Hz)], 129.66 (2C), 128.745, 128.40 (2C), 127.691, 122.85, 119.48 (2C), 117.420, [125.06, 121.435, 117.809, 114.182 (q, 2C, *J* = 272 Hz)], 38.83 (CH_2 imidazolidinone ring), 32.121 (N–CH), 28.15 ($2CH_3$). MS (EI, 70 eV): *m/z* (%) = 539 (M^+, 100), 540 (M+1, 32) Anal. Calcd for $C_{24}H_{19}F_6N_5OS$: C, 53.43; H, 3.55; N, 12.98. Found: C, 53.31; H, 3.65; N, 12.89%.

3-((3,5-Bis(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazol-4-yl) methyleneamino)-1-propyl-2-thioimidazolidin-4-one (**4c**): M.p. 180 °C, yield: 72%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.48 (s, 1H, pyrazolyl H), 8.46 (s, 1H, CH=N), 8.3 (s, 2H, ArH), 7.9 (s, 1H, ArH), 7.4–7.8 (m, 5H, ArH phenyl), 3.8 (t, 2H, *J* = 7.4 Hz, N–CH_2), 3.7 (s, 2H, CH_2 imidazolidinone ring), 1.8 (m, 2H, CH_2), 0.9 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 171.80 (C=S), 163.2 (C=O), 149.791 (CH=N), 149.432, 139.11, 134.651, [133.254, 132.809, 132.364, 131.919 (q, 2C,*J* = 33 Hz)], 129.4 (2C), 128.912, 128.624 (2C), 127.660, 122.6, 119.81 (2C), 117.5, [(125.06, 121.435, 117.809, 114.182, q, 2C, *J* = 272 Hz], 38.5 (imidazolidinone ring), 31.1 (N–CH_2), 25.05 (CH_2), 23.16 (CH_3). MS (EI, 70 eV): *m/z* (%) = 539 (M^+, 100), 540 (M+1, 32). Anal. Calcd for $C_{24}H_{19}F_6N_5OS$: C, 53.43; H, 3.55; N, 12.98. Found: C, 53.34; H, 3.40; N, 13.01%.

3-((3,5-Bis(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazol-4-yl) methyleneamino)-1-hexyl-2-thioimidazolidin-4-one (**4d**): M.p. 118 °C, yield: 71%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.48 (s, 1H, pyrazolyl H), 8.46 (s, 1H, CH=N), 8.3 (s, 2H, ArH), 7.9 (s, 1H, ArH), 7.4–7.8 (m, 5H, ArH phenyl), 3.8 (t, 2H, *J* = 7.1 Hz, N–CH_2), 3.7 (s, 2H, CH_2 imidazolidinone ring), 1.7 (m, 2H, CH_2), 1.3 (m, 6H, $3CH_2$), 0.9 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 171.95 (C=S), 163.17 (C=O), 149.805 (CH=N), 149.561, 139.106, 134.771, [(133.254, 132.809, 132.364, 131.919 q, 2C, *J* = 33 Hz)] 129.5 (2C), 128.9, 128.6 (2C), 127.71, 122.50, 119.410 (2C), 116.9, [(125.06, 121.435, 117.809, 114.182, q, 2C, *J* = 272 Hz)], 38.91 (CH_2 imidazolidinone ring), 32.01 (N–CH_2), 24.45 (CH_2), 20.92, 17.6, 15.09, 12.15. Anal. Calcd for $C_{27}H_{25}F_6N_5OS$: C, 55.76; H, 4.33; N, 12.04. Found: C, 55.68; H, 4.28; N, 12.40%.

3-((3-(4-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methyleneamino)-1-ethyl-2-thioimidazolidin-4-one (**4e**): M.p. 160 °C, yield: 71%, IR (cm^{-1}): 3010 (Aromatic CH), 1600 (C=N), 1685 (C=O), 1050 (C=S), 1350, 1535 (NO_2). ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.6 (s, 1H, pyrazolyl H), 8.5 (s, 1H, CH=N), 8.34 (d, 2H, *J* = 8.2 Hz), 8.06 (d, 2H, *J* = 8.2 Hz), 7.3–7.8 (m, 5H, ArH), 3.9 (q, 2H, 7.1 Hz, N–CH_2), 3.7 (s, 2H, CH_2 imidazolidinone ring), 1.1 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 171.95 (C=S), 162.5 (C=O), 152 (CH=N), 150.87, 139.7, 134.12 (2C), 130.6, 130.21 (2C), 129.8, 128.6, 128.350 (2C), 123, 118.61 (2C), 117, 38.6 (CH_2 imidazolidinone ring), 32.51 (N–CH_2), 28 (CH_3). MS (EI, 70 eV): *m/z* (%) = 434 (M^+, 100), 435 (M+1, 30). Anal. Calcd for $C_{21}H_{18}N_6O_3S$: C, 58.05; H, 4.18; N, 19.34. Found: C, 58.15; H, 4.09; N, 19.42%.

3-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methyleneamino)-1-propyl-2-thioimidazolidin-4-one (**4f**): M.p. 190 °C, yield: 68%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 7.8 (d, 2H, *J* = 8.6 Hz), 7.7 (d, 2H, *J* = 8.6 Hz), 7.3–7.6 (m, 5H, ArH), 3.8 (s, 2H, CH_2 imidazolidinone ring), 1.8 (m, 2H, CH_2), 0.9 (t, 3H, *J* = 7.1 Hz, CH_3), 3.9 (q, 2H, *J* = 7.1 Hz, N–CH_2). ^{13}C NMR δ (75 MHz, $CDCl_3$): 171.784 (C=S), 162.183 (C=O), 152.018 (CH=N), 150.767, 139.335, 131.749 (2C), 131.245, 130.360 (2C), 129.551 (2C), 127.689, 127.353, 122.896, 119.431 (2C), 117.142, 38.583 (CH_2 imidazolidinone ring), 32.569 (N–CH_2), 29.187 (CH_2), 26.542 (CH_3). MS (EI, 70 eV): *m/z* (%) = 481 (M^+, 100), 483 (M+2, 98), 482 (M+1). Anal. Calcd for $C_{22}H_{20}BrN_5OS$: C, 54.78; H, 4.18; N, 14.52. Found: C, 54.60; H, 4.28; N, 14.48%.

3-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methyleneamino)-1-ethyl-2-thioimidazolidin -4-one (**4g**): M.p. 171 °C, yield: 72%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 7.8 (d, 2H, *J* = 8.6 Hz), 7.7 (d, 2H, *J* = 8.6 Hz), 7.3–7.6 (m, 5H, ArH), 3.8 s (s, 2H, CH_2 imidazolidinone ring), 3.9 (q, 2 H, *J* = 7.1 Hz, N–CH_2), 1.3 (t, 3 H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 171.8 (C=S), 162.10 (C=O), 152 (CH=N), 150.7, 139, 131.6 (2C), 132, 131.60 (2C), 128.9 (2C), 127.6, 127, 123.1, 118.89 (2C), 116, 37.80 (CH_2 imidazolidinone ring), 32.01 (N–CH_2), 28.78 (CH_3). Anal. Calcd for $C_{21}H_{18}BrN_5OS$: C, 53.85; H, 3.87; N, 14.95. Found: C, 53.78; H, 3.79; N, 14.87%.

3-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methyleneamino)-1-Hexyl-2-thioimidazolidin -4-one (**4h**): M.p. 140 °C, yield: 73%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 7.8 (d, 2H, *J* = 8.6 Hz), 7.7 (d, 2H, *J* = 8.6 Hz), 7.3–7.6 (m, 5H, ArH), 3.8 (s, 2H, CH_2 imidazolidinone ring), 3.9 (t, 2H, *J* = 6.8 Hz, CH_2-N), 1.3–1.7 (m, 8H, 4 CH_2), 0.9 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 171.6 (C=S), 162 (C=O), 151 (CH=N), 150.69, 140.1, 130.9 (2C), 131.33, 130 (2C), 128.85 (2C), 127.8, 127, 123.01, 119.56 (2C), 116, 38.60 (CH_2 imidazolidinone ring), 33.619 (N–CH_2), 28.95 (CH_2), 25.61 (CH_2), 23, 22.5, 16.01. MS (EI, 70 eV): *m/z* (%) = 523 (M^+, 100), 525 (M+2, 97), 524 (M+1, 21). Anal. Calcd for $C_{25}H_{26}BrN_5OS$: C, 57.25; H, 5; N, 13.35. Found: C, 57.10; H, 4.95; N, 13.1%.

3-((1,3-Diphenyl-1H-pyrazol-4-yl)methyleneamino)-1-ethyl-2-thioimidazolidin-4-one (**4i**): M.p. 136 °C, yield: 64%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 7.3–7.9 (m, 5H, ArH), 3.8 s (s, 2H, CH_2 imidazolidinone ring), 3.9 (q, 2H, *J* = 7.1 Hz, N–CH_2), 1.3 (t, 3H, *J* = 7 Hz, CH_3).^{13}C NMR δ (75 MHz, $CDCl_3$): 170 (C=S), 162 (C=O), 152.01 (CH=N), 150.5, 140, 132.05 (2C), 131.5, 128.12 (2C), 129.810 (2C), 127, 123, 122.5, 118.6 (2C), 117, 38.05 (CH_2 imidazolidinone ring), 32.5 (N–CH_2), 29 (CH_3). MS (EI, 70 eV): *m/z* (%) = 389 (M^+, 100), 390 (M+1, 23). Anal. Calcd for $C_{21}H_{19}N_5OS$: C, 64.76; H, 4.92; N, 17.98. Found: C, 64.70; H, 4.89; N, 17.90%.

3-((1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl)methyleneamino)-1-ethyl-2-thioimidazolidin-4-one (**4j**): M.p. 173 °C, yield: 69%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 7.6 (d, 2H, *J* = 8.3 Hz), 7.9 (d, 2H, *J* = 8.3 Hz), 7.3–7.8 (m, 5H, ArH), 3.8 (s, 2H, CH_2 imidazolidinone ring), 3.9 (q, 2H, *J* = 7.1 Hz, N–CH_2), 1.3 (t, 3H, *J* = 7 Hz, CH_3), 2.3 (s, 3H, CH_3, Ar-CH_3).^{13}C NMR δ (75 MHz, $CDCl_3$): 170 (C=S), 161 (C=O), 152.05 (CH=N), 151, 139.5, 129 (2C), 130.85, 129 (2C), 129.70 (2C), 124.85, 122.77, 123.01, 119 (2C), 118.01, 38.5 (CH_2 imidazolidinone ring), 32.7 (N–CH_2), 25.5 (CH_3), 24.420 (CH_3-Ar). MS (EI, 70 eV): *m/z* (%) = 403.05 (M^+, 100), 404.11 (M+1, 23). Anal. Calcd for $C_{22}H_{21}N_5OS$: C, 65.49; H, 5.25; N, 17.36. Found: C, 65.40; H, 5.21; N, 17.30%.

3-((3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methyleneamino)-1-ethyl-2-thioimidazolidin -4-one (**4k**): M.p. 185 °C, yield: 72%, ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.5 (s, 1H, pyrazolyl H), 8.4 (s, 1H, CH=N), 7.7 (d, 2H, *J* = 8.4 Hz), 7.6 (d, 2H, *J* = 8.4 Hz), 7.3–7.5 (m, 5H, ArH), 3.8 (s, 2H, CH_2 imidazolidinone ring), 3.9 (q, 2H, *J* = 7.1 Hz, N–CH_2), 1.3 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$): 170 (C=S), 162.89 (C=O), 151 (CH=N), 150.5, 140, 132 (2C), 131.7, 128.8 (2C), 129.6 (2C), 127, 126.6, 122.8, 118.8 (2C), 117.142, 37.78 (CH_2 imidazolidinone ring), 32.5 (N–CH_2), 29.760 (CH_3).MS (EI, 70 eV): *m/z* (%) = 423.05 (M^+, 100), 425.11 (M+1, 25). Anal. Calcd for $C_{21}H_{18}ClN_5OS$: C, 59.50; H, 4.28; N, 16.52. Found: C, 59.59; H, 4.21; N, 16.59%.

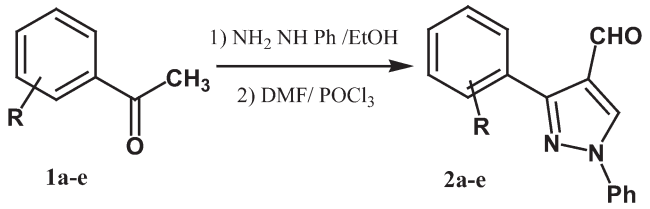
Results and discussion

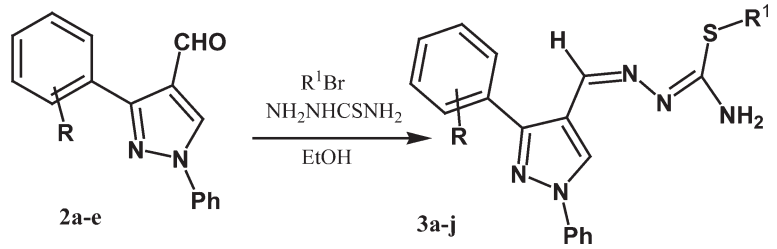
The synthesis of target isothiosemicarbazones (**3a–j**) is depicted in Scheme 1. Treatment of thiosemicarbazide with the appropriate alkyl bromide in ethanol gave alkyl isothiosemicarbazide salt intermediates which were then condensed with pyrazole carbaldehyde to afford compounds **3a–j**. One pot reaction of pyrazole carbaldehyde, thiosemicarbazide, ethyl chloroacetate and alkyl bromide afforded imidazolidinone derivatives **4a–k** (Scheme 2).

The IR and ^{1}H NMR spectra of compounds (**3a–j**) were consistent with the assigned structures. The ^{1}H NMR spectra of these compounds showed a singlet at 8.5–8.6 ppm for the CH=N proton, while NH_2 protons appeared at 9.5–9.8 ppm as a broad singlet. In IR spectra, the bands in the region of 3450–3100 cm^{-1} are due to NH_2. The typical bands of ν(C=N) and ν(C=C) appeared between 1680 and 1565 cm^{-1} while the C–H stretching band appeared at 705–710 cm^{-1}. The ^{1}H NMR spectra of compounds (**4a–k**) showed a singlet at 8.4–8.6 ppm for the CH=N proton while CH_2 protons of the imidazolidinone ring appeared between 3.7 and 3.9 ppm. In the IR spectra of compounds (**4a–k**), the C=N and C=C stretching bands appeared in the region 1550–1650 cm^{-1} while C=O of amide and C=S stretching band appeared in the range of 1670–1685 cm^{-1} and 1050–1055 cm^{-1} respectively.

Antimicrobial screening

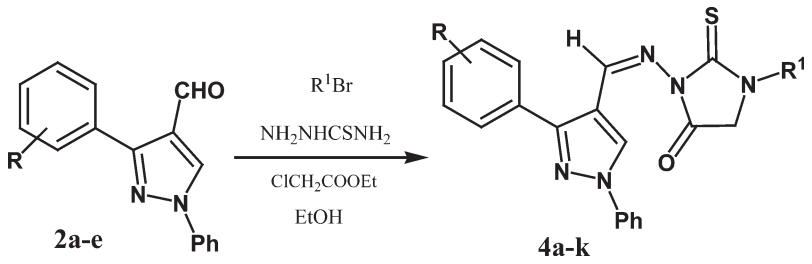
All the compounds synthesised were tested for antibacterial activity against *B. subtilis* (2250), *S. aureus* (2079), *E. coli* (2109) and *P. aeruginosa* (2036) and antifungal activity against *C. albicans* (3471) and *A. niger* (545) at 100 μg mL^{-1} in DMSO,





Scheme 1 Synthesis of S-alkyl isothiosemicarbazone derivatives.

Compd	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**
R	H	4-CH_3	4-CH_3	4-Cl	4-Cl	4-NO_2	4-NO_2	4-NO_2	4-Br	3,5-Bis CF_3
R^1	n-Butyl	Et	n-Butyl	n-Heptyl	n-Butyl	Et	n-Propyl	n-Butyl	Et	Et



Scheme 2 Synthesis of imidazolidinone derivatives.

Compd	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**
R	3,5-Bis CF_3	3,5-Bis CF_3	3,5-Bis CF_3	3,5-Bis CF_3	4-NO_2	4-Br	4-Br	4-Br	H	4-CH_3	4-Cl
R^1	Et	Isopropyl	n-Propyl	n-Hexyl	Et	n-Propyl	Et	n-Hexyl	Et	Et	Et

Table 1 Antimicrobial activity of synthesised compounds **(3a–j** and **4a–k)**

Compound	*S. aureus*	*E. coli*	*B. subtilis*	*P. aeruginosa*	*A. niger*	*C. albicans*
3a	20.2	–	18	16.6	–	14.8
3b	22.1	20.2	–	16	16	8
3c	22	20.1	–	15	16.4	7.9
3d	16.3	17	15.4	–	12.4	–
3e	16	17.4	15	8	12	–
3f	14.5	15	–	10	10.5	11
3g	14.5	15.1	–	10.3	10	10.8
3h	14.6	12	–	9.9	9.9	10.9
3i	18	11.2	–	7.9	12	–
3j	13.1	12	9	7.6	–	–
4a	10	9.5	–	10	–	–
4b	10.1	10.5	8.9	–	–	–
4c	9.5	11	–	8.6	–	–
4d	8.9	10	8.0	10	–	–
4e	11	–	9	7.9	9.5	8.6
4f	15.4	14.9.	–	12	11.5	–
4g	15	15.1	–	11.8	12	–
4h	15	–	14.3	13.8	11.8	–
4i	16	–	14.4	–	16	10
4j	18	–	16.7	16.5	15.6	8
4k	15	12	–	13.4	13.8	9.1
Nystatin	NA	NA	NA	NA	21.12	21.96
Chloramphenicol	32.8	29.14	30.11	24.68	NA	NA

Zone diameter of growth inhibition in mm.
NA, not applicable; –, inactive. Chloramphenicol (100 μg/disc) and Nystatin (100 μg/disc) were used as reference; synthesised compounds (100 μg/disc)

using agar diffusion method. Known antibiotics Chloramphenicol and Nystatin were used for comparison. Most of the compounds were found to be active against gram positive and gram negative bacteria as well as both the fungi species as shown in Table 1. Both isothiosemicarbazone (**3a–j**) and imidazolidinone derivatives (**4a–k**) showed enhanced antimicrobial activity with an electron donating group (CH_3) on the phenyl ring as compared to electron withdrawing groups (Cl, Br, NO_2 and CF_3).

Conclusions

In the present work we have successfully synthesised new S-alkyl isothiosemicarbazone and imidazolidinone derivatives. Most of the synthesised compounds showed good biological activity against bacteria like *B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa* and against fungi like *C. albicans* and *A. niger*. Based on the results, it can be concluded that these new pyrazole aldehyde derivatives could serve as lead molecules for further development of new antimicrobial agents.

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