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Studies of 5-aryl-4-(1*H*-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one Derivatives

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Abstract: Novel series of heterocyclic compounds 2-aryl-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid derivatives (**4a–h**) and 5-aryl-4-(1*H*-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl) pyrrolidin-2-one derivatives (**5a–h**) have been synthesized by condensation of Schiff bases arylidine-[4-(2-naphthalenyl)thiazolyl]-2-amines (**3a–h**) with succinic anhydride. Synthesized heterocyclic compounds were duly characterized by physico chemical parameters, ^{1}H-NMR, ^{13}C-NMR and FT–IR spectral features. Schiff bases **3a–h** have been synthesized from 4-(naphthalen-2-yl)thiazol-2-amine **1** and various aromatic aldehydes **2a–h**. All novel synthesized compounds **4a–h** and **5a–h** were evaluated for their antibacterial activity against various Gram positive bacterial strains e.g. *Bacillus subtilis* [BS] and *Staphylococcus aureus* [SA] and Gram negative bacterial strains e.g. *Salmonella typhimurium* [ST] and *Escherichia coli* [EC]. Growth inhibition was compared with the standard drug ciprofloxacin. Antifungal activity was also carried out against different fungal strains e.g. *Penicillium expansum* [PE], *Botryodiplodia theobromae* [BT], *Nigrospora sp*. [NS], *Trichothesium sp*. [TS]. The antifungal drug, Ketoconazole was used as a positive control. Compounds **4a–h** found less active as compare to compound **5a–h.**

Keywords: heterocyclic compounds; thiazole; benzimidazole; pyrrolidin-2-one

1. INTRODUCTION

Tremendous work has been carried out in the synthesis and development of heterocyclic compounds due to their important biological properties. 2-Aminothiazoles and their derivatives have been used as pioneers for the synthesis of biologically active molecules [1-4]. Some of these compounds possess anthelmintic activity, such as thiabedazole. Sulphathiazole possesses antibiotic activity. Nizatidine [5] compound possesses the thiazole moiety, which has clinical uses as an antiulcer drug. Farnetiaole has significant immunosuppressant activity, while fentiasac has clinical use as an anti-inflammatory agent [5]. Recent research indicates that some of 2-aminothiazoline derivatives are inhibitors of enzymes such as kinurenine-3-hydroxylase [6] or possess inhibitory activity against the enzyme cyclin-dependent kinase [7]. On the other hand, benzimidazole consists of benzene and imidazole and its derivatives have wide variety of biological activities, in addition to that the benzimidazole have played a very important role in the development of theory in heterocyclic chemistry and also extensively in organic synthesis [8]. 2-substituted benzimidazole derivatives are found to be pharmacologically more potent and hence the design and synthesis of 2-substituted benzimidazoles are the potential area of research [9]. Benzimidazole derivatives have played an important role in medicinal chemistry. In addition, they have been studied broadly [10-15] because of their ready accessibility and broad spectrum of biological activities. One of the authors had already synthesized the Schiff bases **3a–h** [16]**.**

When Schiff bases **3a–h** was reacted with succinic anhydride, it undergoes a cycloaddition reaction. The formal cycloaddition process of imines and succinic anhydrides was first demonstrated by Castagnoli [17]. Favorable substrates for this reaction have substituent, such as an aromatic ring, capable of stabilizing an enolate intermediate formed from iminolysis of the anhydride [18-20]. The reaction of anhydride with dienophiles can be accelerated by

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deprotonation of the anhydride to form a dienolate anion [21] and finally converted to γ-lactams. Furthermore one-step synthesis of complex nitrogen heterocycles from imines with maleic anhydrides [22] and imines with succinic anhydrides [23] were carried out by Shaw and his research group. This prompted us to carry out our study by introducing thiazole and benzimidazole segments together. Herein we report the reaction of Schiff bases **3a–h** with succinic anhydride to produce compound **4a–h** and subsequently benzo[d]imidazol derivatives **5a–h** with benzene-1,2-diamine. This work has not attracted any attention. Figure 1 summarizes our synthetic approach to the various phases of this work, viz., (i) synthesis of 2-aryl-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid derivatives **4a–h** from compounds **3a–h** and succinic anhydride (ii) subsequent reaction of **4a–h** with benzene-1,2-diamine to the obtained compounds **5a–h** i.e. 5-aryl-4-(1H-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one derivatives. Compounds **4a–h** and **5a–h** were evaluated for their antibacterial activity against Gram–positive and Gram–negative bacterial strains. Antifungal activity was also carried out against different fungal strains.

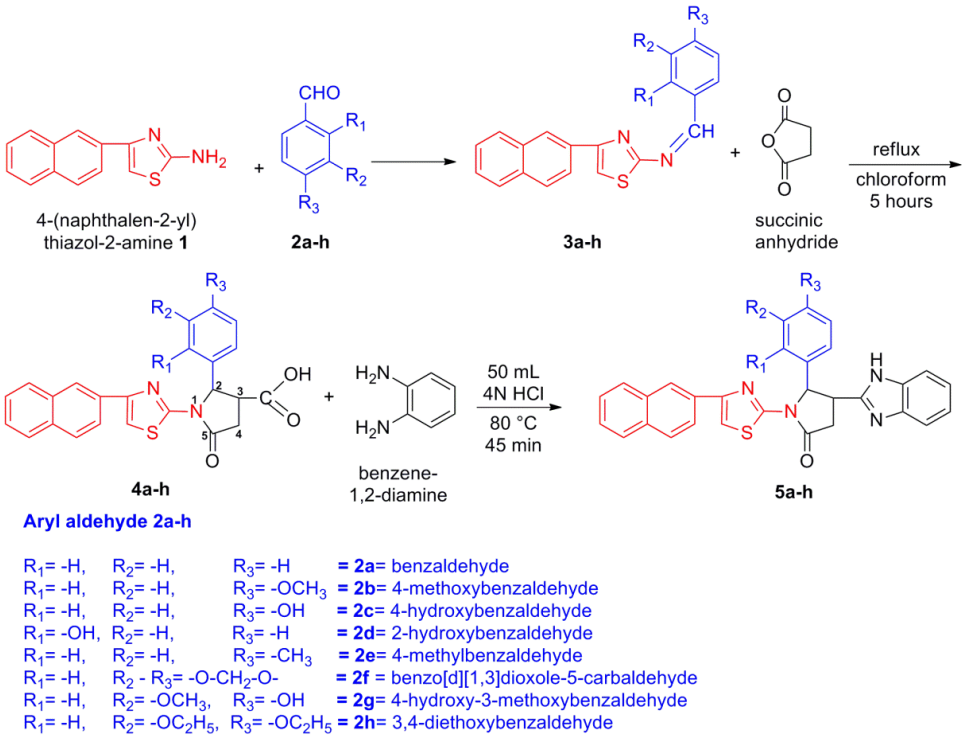

Figure 1. Synthesis of compounds 4a–h and 5a–h.

2. MATERIAL AND METHODS

All common reagents and solvents were used of analytical grade and were used without further purification. Alumina-supported pre-coated silica gel 60 F_{254} thin layer chromatography (TLC) plates were purchased from the E. Merck (India) Limited, Mumbai and were used to check purity of compounds and, to study the progress of the reaction whereby TLC plates were illuminated under Ultraviolet light (254 nm), evaluated in I_2 vapors and visualized by spraying with Draggendorff's reagent. Infrared spectra (FT–IR) were obtained from KBr pellets in the range of 4000–400 cm^{-1} with a Perkin Elmer spectrum GX spectrophotometer (FT–IR) instrument. ^{1}H-NMR and ^{13}C-NMR spectra were acquired at 400 MHz on a Bruker NMR spectrometer using DMSO–d_6 (residual peak at δ ~2.5 or ~ 39.5 ppm, 300 °K) as a solvent as well as TMS an internal reference standard. Micro analytical (C, N, H) data was obtained by using a Perkin–Elmer 2400 CHN elemental analyzer. The melting point was checked by the standard open capillary method.

Synthesis of 2-aryl-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid derivatives (4a–h)

An equimolar ratio of compounds **3a–h** (0.1 mole) and succinic anhydride (0.1 mole) were refluxed for about 5 hours in 30 mL of chloroform. The resultant reaction mixture was allowed to stand for 2 days. The precipitate formed was checked by TLC monitoring. Thus obtained products were filtered, washed, and recrystallized from ethanol to give pure 2-aryl-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid derivatives. The products were designated as 4a–h and characterized by elemental, FT-IR, and NMR analyses.

4a: 1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxo-2-phenylpyrrolidine-3-carboxylic acid: Yield was 70%; M. Mol. wt. 414.48 g; Melting Point: 186–187 ˚C (uncorrected); Elemental analysis calculated for $C_{24}H_{18}N_2O_3S$: C 69.55, H 4.38, N 6.76, S 7.74% found: C 69.4, H 4.3, N 6.7, S 7.7%; ^{1}H NMR (δ ppm): 11.95 (s, 1H, –COOH), 8.17–6.40 (m, 13H, aromatic + thiazole ring), 5.63 (d, 2H, C_4H), 4.45 (d, 1H, C_2H), 4.18 (q, 1H, C_3H); ^{13}C NMR (δ ppm): 170 (–C=O), 167 (–COOH), 107–142 (aromatic carbon), 36, 48, 51 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3512 (–COOH), 3024, 1729 (C=O pyrrole-2-one), 1716 (–COOH), 1609, 1517 (aromatic C–H), 1687, 1594 (thiazole ring), 720 (C–S–C thiazole).

4b: 2-(4-methoxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carbo xylic acid: Yield was 68%; Mol. wt. 444.50 g; Melting Point: 183–184 ˚C (uncorrected); Elemental analysis calculated for $C_{25}H_{20}N_2O_4S$: C 67.55, H 4.54, N 6.30, S 7.21% found: C 67.4, H 4.5, N 6.2, S 7.1%; ^{1}H NMR (δ ppm): 11.92 (s, 1H, –COOH), 8.13–6.45 (m, 12H, aromatic + thiazole ring), 5.68 (d, 2H, C_4H), 4.47 (d, 1H, C_2H), 4.15 (q, 1H, C_3H), 2.36 (s, 3H, –OCH_3); ^{13}C NMR (δ ppm): 169 (–C=O), 165 (–COOH), 138–102 (aromatic carbon), 46 (–OCH_3), 38, 47, 53 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3505 (–COOH), 3030, 1600, 1500 (aromatic C–H), 2820,1250 (–OCH_3), 1728 (C=O pyrrole-2-one), 1710 (–COOH), 1690, 1597 (thiazole ring), 712 (C–S–C thiazole).

4c: 2-(4-hydroxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid: Yield was 70%; Mol. wt. 430.48 g; Melting Point: 194–195 ˚C (uncorrected); Elemental analysis calculated for $C_{24}H_{18}N_2O_4S$: C 66.96, H 4.21, N 6.51, S 7.45% found: C 66.9, H 4.1, N 6.4, S 7.3%; ^{1}H NMR (δ ppm): 11.90 (s, 1H, –COOH), 9.32 (s, 1H, –OH), 8.19–6.42 (m, 12H, aromatic + thiazole ring), 5.55 (d, 2H, C_4H), 4.41 (d, 1H, C_2H), 4.21 (q, 1H, C_3H); ^{13}C NMR (δ ppm): 168 (–C=O), 164 (–COOH), 136-101 (aromatic carbon), 52, 48, 38 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3511 (–COOH), 3448 (O–H), 3036, 1605, 1508 (aromatic C–H), 1725 (C=O pyrrole-2-one), 1709 (–COOH), 1692, 1591 (thiazole ring), 711 (C–S–C thiazole).

4d: 2-(2-hydroxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid: Yield was 70%; Mol. wt. 430.48 g; Melting Point: 198–199 ˚C (uncorrected); Elemental analysis calculated for $C_{24}H_{18}N_2O_4S$: C 66.96, H 4.21, N 6.51, S 7.45% found: C 66.9, H 4.1, N 6.4, S 7.4%; ^{1}H NMR (δ ppm): 11.87 (s, 1H, –COOH), 9.32 (s, 1H, –OH), 8.14-6.47 (m, 12H, aromatic + thiazole ring), 5.65 (d, 2H, C_4H), 4.43 (d, 1H, C_2H), 4.11 (q, 1H, C_3H); ^{13}C NMR (δ ppm): 169 (–C=O), 166 (–COOH), 137–102 (aromatic carbon), 52, 46, 37 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3508 (–COOH), 3456 (O–H), 3030, 1602, 1505 (aromatic C–H), 1728 (C=O pyrrole-2-one), 1711 (–COOH), 1693, 1592 (thiazole ring), 713 (C–S–C thiazole).

4e: 1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxo-2-(p-tolyl)pyrrolidine-3-carboxylic acid: Yield was 75%; Mol. wt. 428.50 g; Melting Point: 180–181 ˚C (uncorrected); Elemental analysis calculated for $C_{25}H_{20}N_2O_3S$: C 70.07, H 4.70, N 6.54, S 7.48% found: C 70.0, H 4.6, N 6.4, S 7.4%; ^{1}H NMR (δ ppm): 11.88 (s, 1H, COOH), 8.17-6.44 (m, 12H, aromatic + thiazole ring), 5.61 (d, 2H, C_4H), 4.40 (d, 1H, C_2H), 4.18 (q, 1H, C_3H), 2.38 (s, 3H, CH_3); ^{13}C NMR (δ ppm): 167 (–C=O), 163 (–COOH), 136–101 (aromatic carbon), 29 (–CH_3), 55, 47, 37 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3508 (–COOH), 3035, 1603, 1509 (aromatic C–H), 2950,1370 (–CH_3), 1726 (C=O pyrrole-2-one), 1707 (–COOH), 1697, 1593 (thiazole ring), 712 (C–S–C thiazole).

4f: 2-(benzo[d][1,3]dioxol-5-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid: Yield was 70%; Mol. wt. 458.49 g; Melting Point: 177–178 ˚C (uncorrected); Elemental analysis calculated for $C_{25}H_{18}N_2O_5S$: C 65.49, H 3.96, N 6.11, S 6.99% found: C 65.4, H 3.9, N 6.0, S 6.9%; ^{1}H NMR (δ ppm): 11.96 (s, 1H, COOH), 8.18-6.48 (m, 11H, aromatic + thiazole ring), 6.09 (s, 2H, OCH_2O), 5.62 (d, 2H, C_4H), 4.43 (d, 1H, C_2H), 4.18 (q, 1H, C_3H); ^{13}C NMR (δ ppm): 168 (–C=O), 165 (–COOH), 136–103 (aromatic carbon), 102 (OCH_2O), 53, 45, 36 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3512 (–COOH), 3037, 1602, 1511 (aromatic C–H), 2880 (–OCH_2O), 1722 (C=O pyrrole-2-one), 1710 (–COOH), 1695, 1592 (thiazole ring), 712 (C–S–C thiazole).

4g: 2-(4-hydroxy-3-methoxyphenyl)-1-(4-

(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid: Yield was 65%; Mol. wt. 460.50 g; Melting Point: 202–203 ˚C (uncorrected); Elemental analysis calculated for $C_{25}H_{20}N_2O_5S$: C 65.20, H 4.38, N 6.08, S 6.96% found: C 65.1, H 4.2, N 6.0, S 6.8%; ^{1}H NMR (δ ppm): 11.87 (s, 1H, COOH), 9.38 (s, 1H, –OH), 8.10-6.48 (m, 11H, aromatic + thiazole ring), 5.72 (d, 2H, C_4H), 4.51 (d, 1H, C_2H), 4.12 (q, 1H, C_3H), 2.36 (s, 3H, -OCH_3); ^{13}C NMR (δ ppm): 167 (–C=O), 164 (–COOH), 138–104 (aromatic carbon), 46 (-OCH_3), 53, 47, 38 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3511 (–COOH), 3448 (O–H), 3035, 1604, 1502 (aromatic C–H), 2820,1250 (–OCH_3), 1724 (C=O pyrrole-2-one), 1711 (–COOH), 1698, 1593 (thiazole ring), 710 (C–S–C thiazole).

4h: 2-(3,4-diethoxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid: Yield was 65%; Mol. wt. 502.58 g; Melting Point: 200–201 ˚C (uncorrected); Elemental analysis calculated for $C_{28}H_{26}N_2O_5S$: C 66.91, H 5.21, N 5.57, S 6.38% found: C 66.8, H 5.1, N 5.4, S 6.2%; ^{1}H NMR (δ ppm): 11.87 (s, 1H, COOH), 8.10-6.41 (m, 11H, aromatic + thiazole ring), 5.60 (d, 2H, C_4H), 4.52 (d, 1H, C_2H), 4.11 (q, 1H, C_3H), 2.36 (q, 4H, –OCH_2), 1.87 (t, 6H, –CH_3); ^{13}C NMR (δ ppm): 169 (–C=O), 165 (–COOH), 135–103 (aromatic carbon), 51 (–OCH_2), 42 (–CH_3), 50, 47, 36 (carbon of pyrrole-2-one ring); IR (KBr, cm^{-1}): 3505 (–COOH), 3039, 1604, 1503 (aromatic C–H), 2930, 1450 (–OCH_2), 1724 (C=O pyrrole-2-one), 1711 (–COOH), 1699, 1595 (thiazole ring), 710 (C–S–C thiazole).

Synthesis of 5-aryl-4-(1H-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl) thiazol-2-yl) pyrrolidin-2-one derivatives (5a-h)

Benzene-1,2-diamine dihydrochloride (0.1 mole) was condensed with an equimolar amount of compounds **4a–h** for about 5 hours in 50 mL 4N HCl with a magnetic stirrer at 80 ˚C. The resultant reaction mixture was allowed to stand for 45 min, make the cooled reaction mixture distinctly basic by gradual addition of conc. ammonia solution. Thus obtained products were filtered, washed with cold water, and recrystallized from ethanol to obtain pure 5-aryl-4-(1H-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl) pyrrolidin-2-one derivatives. The products were designated as 5a–h and characterized by elemental, IR and NMR analyses.

5a: 4-(1H-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-phenylpyrrolidin -2-one: Yield was 60%; Mol. wt. 486.59 g; Melting Point: 235–237 ˚C (uncorrected); Elemental analysis calculated for $C_{30}H_{22}N_4OS$: C 74.05, H 4.56, N 11.51, S 6.59% found: C 74.0, H 4.5, N 11.4, S 6.5%; ^{1}H NMR (δ ppm): 10.81 (s, 1H, NH of benzimidazole), 7.89–6.43 (m, 17H, aromatic + thiazole ring), 5.54 (d, 2H, C_3H), 4.60 (d, 1H, C_5H), 3.42 (q, 1H, C_4H); ^{13}C NMR (δ ppm): 170 (pyrrolidin-2-one), 164 (benzimidazole), 148–105 (aromatic carbon), 57, 48, 39 (carbon of pyrrole-2-one ring); FT-IR (KBr, cm^{-1}): 3674 (–N–H of Benzimidazole), 1728 (–C=O of pyrrole-2-one), 1682 (–C=N of benzimidazole), 1289 (–C–N of benzimidazole), 717 (C–S–C thiazole).

5b: 4-(1H-benzo[d]imidazol-2-yl)-5-(4-methoxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl) pyrrolidin-2-one: Yield was 60%; Mol. wt. 516.61 g; Melting Point: 210–211 ˚C (uncorrected); Elemental analysis calculated for $C_{31}H_{24}N_4O_2S$: C 72.07, H 4.68, N 10.85, S 6.21% found: C 72.0, H 4.6, N 10.8, S 6.1%; ^{1}H NMR (δ ppm): 10.86 (s, 1H, NH of benzimidazole), 7.86–6.48 (m, 16H, aromatic + thiazole ring), 5.57 (d, 2H, C_3H), 4.62 (d, 1H, C_5H), 3.38 (q, 1H, C_4H), 2.36 (s, 3H, -OCH_3); ^{13}C NMR (δ ppm): 171 (pyrrolidin-2-one), 162 (benzimidazole), 145–102 (aromatic carbon), 57, 49, 42 (carbon of pyrrole-2-one ring), 46 (-OCH_3); IR (KBr, cm^{-1}): 3678 (–N–H of Benzimidazole), 2820,1250 (–OCH_3), 1721 (–C=O of pyrrole-2-one), 1680 (–C=N of benzimidazole), 1287 (–C–N of benzimidazole), 721 (C–S–C thiazole).

5c: 4-(1H-benzo[d]imidazol-2-yl)-5-(4-hydroxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl) pyrrolidin-2-one: Yield was 55%; Mol. wt. 502.59 g; Melting Point: 215–217 ˚C (uncorrected); Elemental analysis calculated for $C_{30}H_{22}N_4O_2S$: C 71.69, H 4.41, N 11.15, S 6.38% found: C 71.6, H 4.3, N 11.1, S 6.3%; ^{1}H NMR (δ ppm): 10.76 (s, 1H, NH of benzimidazole), 9.32 (s, 1H, –OH), 7.89–6.43 (m, 16H, aromatic + thiazole ring), 5.62 (d, 2H, C_3H), 4.69 (d, 1H, C_5H), 3.34 (q, 1H, C_4H); ^{13}C NMR (δ ppm): 170 (pyrrolidin-2-one),164 (benzimidazole), 140–104 (aromatic carbon), 42, 47, 56 (carbon of pyrrole-2-one ring); FT-IR (KBr, cm^{-1}): 3670 (–N–H of benzimidazole), 3450 (O–H), 1724 (–C=O of pyrrole-2-one), 1683 (–C=N of benzimidazole), 1286 (–C–N of benzimidazole), 720 (C–S–C thiazole).

5d: 4-(1H-benzo[d]imidazol-2-yl)-5-(2-hydroxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl) pyrrolidin-2-one: Yield was 55%; Mol. wt. 502.59 g; Melting Point: 208–209 ˚C (uncorrected); Elemental analysis calculated for $C_{30}H_{22}N_4O_2S$: C 71.69, H 4.41,

N 11.15, S 6.38% found: C 71.6, H 4.3, N 11.1, S 6.3%; ^{1}H NMR (δ ppm): 10.80 (s, 1H, NH of benzimidazole), 9.30 (s, 1H, -OH), 7.83–6.40 (m, 16H, aromatic + thiazole ring), 5.53 (d, 2H, C_3H), 4.60 (d, 1H, C_5H), 3.34 (q, 1H, C_4H); ^{13}C NMR (δ ppm): 173 (pyrrolidin-2-one), 161 (benzimidazole), 144–102 (aromatic carbon), 56, 48, 44 (carbon of pyrrole-2-one ring); FT-IR (KBr, cm^{-1}): 3675 (–N–H of benzimidazole), 3455 (O–H), 1720 (–C=O of pyrrole-2-one), 1686 (–C=N of benzimidazole), 1283 (–C–N of benzimidazole), 718 (C–S–C thiazole).

5e: 4-(1H-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-(p-tolyl) pyrrolidin-2-one: Yield was 60%; Mol. wt. 500.61 g; Melting Point: 205–207 ˚C (uncorrected); Elemental analysis calculated for $C_{31}H_{24}N_4OS$: C 74.38, H 4.83, N 11.19, S 6.41% found: C 74.3, H 4.7, N 11.1, S 6.3%; ^{1}H NMR (δ ppm): 10.89 (s, 1H, NH of benzimidazole), 7.89–6.49 (m, 16H, aromatic + thiazole ring), 5.60 (d, 2H, C_3H), 4.67 (d, 1H, C_5H), 3.40 (q, 1H, C_4H), 2.36 (s, 3H, -CH_3); ^{13}C NMR (δ ppm): 173 (pyrrolidin-2-one), 160 (benzimidazole), 142–101 (aromatic carbon), 56, 47, 41 (carbon of pyrrole-2-one ring), 30 (-CH_3); FT-IR (KBr, cm^{-1}): 3679 (–N–H of benzimidazole), 2950,1370 (–CH_3), 1723 (–C=O of pyrrole-2-one), 1685 (–C=N of benzimidazole), 1286 (–C–N of benzimidazole), 720 (C–S–C thiazole).

5f: 5-(benzo[d][1,3]dioxol-5-yl)-4-(1H-benzo[d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one: Yield was 65%; Mol. wt. 530.60 g; Melting Point: 208–210 ˚C (uncorrected); Elemental analysis calculated for $C_{31}H_{22}N_4O_3S$: C 70.17, H 4.18, N 10.56, S 6.04% found: C 70.1, H 4.1, N 10.5, S 6.0%; ^{1}H NMR (δ ppm): 10.86 (s, 1H, NH of benzimidazole), 7.82–6.50 (m, 16H, aromatic + thiazole ring), 6.09 (s, 2H, OCH_2O), 5.55 (d, 2H, C_3H), 4.66 (d, 1H, C_5H), 3.34 (q, 1H, C_4H); ^{13}C NMR (δ ppm): 145–109 (aromatic carbon), 162 (benzimidazole), 171 (pyrrolidin-2-one), 102 (OCH_2-O), 55, 49, 42 (carbon of pyrrole-2-one ring); FT-IR (KBr, cm^{-1}): 3680 (–N–H of benzimidazole), 2886 (–OCH_2O), 1725 (–C=O of pyrrole-2-one), 1685 (–C=N of benzimidazole), 1283 (–C–N of benzimidazole), 723 (C–S–C thiazole).

5g: 4-(1H-benzo[d]imidazol-2-yl)-5-(4-hydroxy-3-methoxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one: Yield was 55%; Mol. wt. 532.61 g; Melting Point: 203–205 ˚C (uncorrected); Elemental analysis calculated for $C_{31}H_{24}N_4O_3S$: C 69.91, H 4.54, N 10.52, S 6.02% found: C 69.8, H 4.5, N 10.5, S 6.0%; ^{1}H NMR (δ ppm): 10.89 (s, 1H, NH of benzimidazole), 9.39 (s, 1H, –OH), 7.80–6.43 (m, 15H, aromatic + thiazole ring), 5.62 (d, 2H, C_3H), 4.69 (d, 1H, C_5H), 3.37 (q, 1H, C_4H), 2.39 (s, 3H, -OCH_3); ^{13}C NMR (δ ppm): 170 (pyrrolidin-2-one), 162 (benzimidazole), 143–106 (aromatic carbon), 45 (–OCH_3), 54, 46, 40 (carbon of pyrrole-2-one ring); FT-IR (KBr, cm^{-1}): 3672 (–N–H of benzimidazole), 3441 (O–H), 2827,1256 (–OCH_3), 1725 (–C=O of pyrrole-2-one), 1687 (–C=N of benzimidazole), 1283 (–C–N of benzimidazole), 724 (C–S–C thiazole).

5h: 4-(1H-benzo[d]imidazol-2-yl)-5-(3,4-diethoxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl) pyrrolidin-2-one: Yield was 50%; Mol. wt. 574.69 g; Melting Point: 214–215 ˚C (uncorrected); Elemental analysis calculated for $C_{34}H_{30}N_4O_3S$: C 71.06, H 5.26, N 9.75, S 5.58% found: C 71.0, H 5.2, N 9.7, S 5.5%; ^{1}H NMR (δ ppm): 10.82 (s, 1H, NH of benzimidazole), 7.89–6.42 (m, 15H, aromatic + thiazole ring), 5.51 (d, 2H, C_3H), 4.60 (d, 1H, C_5H), 3.34 (q, 1H, C_4H), 2.39 (q, 4H, –OCH_2), 1.89 (t, 6H, –CH_3); ^{13}C NMR (δ ppm): 173 (pyrrolidin-2-one), 161 (benzimidazole), 140–106 (aromatic carbon), 58, 47, 42 (carbon of pyrrole-2-one ring), 50 (–OCH_2), 41 (–CH_3); FT-IR (KBr, cm^{-1}): 3674 (–N–H of benzimidazole), 2936, 1453 (–OCH_2), 1723 (–C=O of pyrrole-2-one), 1682 (–C=N of benzimidazole), 1289 (–C–N of benzimidazole), 723 (C–S–C thiazole).

Biological activity

Antibacterial activity (in vitro)

Compounds **4a–h** and **5a–h** were screened for in vitro antibacterial activity against Gram-positive bacterial strains (*Bacillus subtilis* [BS] and *Staphylococcus aureus* [SA]) and Gram-negative bacterial strains (*Salmonella typhimurium* [ST] and *Escherichia coli* [EC]) utilizing the agar diffusion assay [24-25]. The wells were dug in the media with the help of a sterile metallic borer. A recommended concentration (100 µL) of the test sample (1 mg/mL in DMSO) was introduced in the respective wells. Other wells were supplemented with DMSO and reference antibacterial drug, ciprofloxacin, was served as negative and positive controls, respectively. The plates were incubated immediately at 37˚C for 24 hours. The activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard drug. In order to clarify any participating role of DMSO in the biological screening, separate studies were carried out with the solutions alone of DMSO

and they showed no activity against any bacterial strains.

Antifungal activity (in vitro)

Compounds **4a–h** and **5a–h** were also examined for antifungal activity against different fungal strains, i.e. *Penicillium expansum* [PE], *Botryodiplodia theobromae* [BT], *Nigrospora sp.* [NS], *Trichothesium sp.* [TS]. The antifungal drug, ketoconazole was used as a positive control. Antifungal screening for compounds **4a–h** and **5a–h** and positive control was performed at a recommended concentration. The fungal strains were grown and maintained on potato dextrose agar plates. The cultures of the fungi were purified by single spore isolation technique. Each compound **4a–h** and **5a–h** in DMSO solution was prepared for testing against spore germination of each fungus. The fungal culture plates were inoculated and incubated at 25± 2˚C for 48 h. The plates were then observed and the diameters of the zone of inhibition (in mm) were measured. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where, X = Area of colony in control plate and Y = Area of colony in test plate.

3. RESULTS AND DISCUSSION

Synthesis of compounds 4a–h and 5a–h

To the best of our knowledge, compounds **4a–h** and **5a–h** have not been reported previously. The characterization of the reaction product provided the first unambiguous proof of the successful synthesis of 2-aryl-1-(4-(naphthalen-2-yl) thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid derivatives. Elemental analyses of all compounds were in good agreement with proposed structures. The structures of all compounds were consistent with the FT–IR, ^{1}H NMR and ^{13}C NMR. The FT-IR spectrum of **4a–h** showed the most relevant peaks of naphthalene ring, thiazole ring, other than typical absorptions arising from the band at 3490 cm^{-1} and 1709 cm^{-1} for carboxylic acid and 1720 cm^{-1} for C=O pyrrole-2-one [26]. In the ^{1}H NMR spectroscopy, the signals in the range of 6.4–8.2 ppm were ascribed to the protons of the aromatic naphthalene, thiazole & benzene rings. The singlet at 11.8–11.9 ppm was ascribed to the protons of carboxylic -OH group, which was further confirmed by ^{13}C NMR value i.e. 169 attributed to carboxylic carbon. The expected structure was thus clearly verified by the spectroscopic analysis which indicated moreover the absence of any detectable impurity, particularly of the two reagents used to prepare **4a–h**.

Structures of the analogs **5a–h** were consistent with the elemental analyses, FT–IR, ^{1}H NMR and ^{13}C NMR. FT–IR Spectral features provide valuable information. The FT-IR spectra of compounds **5a–h** showed important changes with respect to those of the compounds **4a–h**, which clearly confirmed that the reaction had taken place with good yields. Considerable differences to be expected were observed. The band at about 3510 cm^{-1} and 1710 cm^{-1} corresponding to –OH and C=O groups of carboxylic acid respectively in **4a–h** were virtually disappeared from the spectra of **5a–h**. Compounds **5a–h** exhibit bands near 3670 cm^{-1}, 1680 cm^{-1} and 1290 cm^{-1} indicating the formation of benzimidazole derivatives. The singlet at about 10.8 ppm was ascribed to the protons of benzimidazole. Furthermore, the ^{13}C NMR value at about 160-165 ppm indicated that benzimidazole formation was taken place successfully. The expected structures of the compounds 5-aryl-4-(1H-benzo [d]imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one derivatives 5a–h were clearly verified by the spectroscopic analysis.

Biological activity

Antibacterial activity

Based on the data from the antibacterial studies against both Gram–positive and Gram–negative bacterial strains (Figure 2), the following observations can be made. All compounds **4a–h** and **5a–h** exhibited antibacterial activity against both Gram–positive and Gram–negative bacterial strains with zones of inhibition (ZOI) ranging from 20 mm to 41 mm (Figure 2). Among the analogs **5a–h**, compound **5f** ($ZOI_{[BS]}$ = 40 mm, $ZOI_{[SA]}$ = 38 mm, $ZOI_{[ST]}$ = 41 mm, $ZOI_{[EC]}$ = 39 mm) was identified as a potent antibacterial agent against all Gram-positive and Gram-negative bacterial strains. Compound **5g** ($ZOI_{[BS]}$ = 39 mm, $ZOI_{[SA]}$ = 36 mm, $ZOI_{[ST]}$ = 39 mm, $ZOI_{[EC]}$ = 38 mm) and compound **5h** ($ZOI_{[BS]}$ = 37 mm, $ZOI_{[SA]}$ = 34 mm, $ZOI_{[ST]}$ = 38 mm, $ZOI_{[EC]}$ = 36 mm) had good antibacterial activity against bacterial strains. Compound 5b ($ZOI_{[BS]}$ = 35 mm, $ZOI_{[SA]}$ = 34 mm, $ZOI_{[ST]}$ = 37 mm, $ZOI_{[EC]}$ = 35 mm)

and compound **5e** ($ZOI_{[BS]}$ = 34 mm, $ZOI_{[SA]}$ = 33 mm, $ZOI_{[ST]}$ = 36 mm, $ZOI_{[EC]}$ = 33 mm) also had comparable antibacterial activity against bacterial strains. Compounds **5c**, **5d,** and **5a** exhibited moderate antibacterial activity (Figure 3).

Among the analogs **4a–h**, compound **4f** ($ZOI_{[BS]}$ = 28 mm, $ZOI_{[SA]}$ = 28 mm, $ZOI_{[ST]}$ = 30 mm, $ZOI_{[EC]}$ = 27 mm), compound **4g** ($ZOI_{[BS]}$ = 27 mm, $ZOI_{[SA]}$ = 27 mm, $ZOI_{[ST]}$ = 28 mm, $ZOI_{[EC]}$ = 25 mm) and compound **4h** ($ZOI_{[BS]}$ = 25 mm, $ZOI_{[SA]}$ = 25 mm, $ZOI_{[ST]}$ = 26 mm, $ZOI_{[EC]}$ = 27 mm) had good antibacterial activity against bacterial strains. Compounds **4b, 4c, 4d, 4e,** and **4a** exhibited less antibacterial activity (Figure 3). Compounds **4a–h** exhibited less antibacterial activity as compared to standard antibiotic drug, ciprofloxacin ($ZOI_{[BS]}$ = 45 mm, $ZOI_{[SA]}$ = 43 mm, $ZOI_{[ST]}$ = 47 mm, $ZOI_{[EC]}$ = 45 mm).

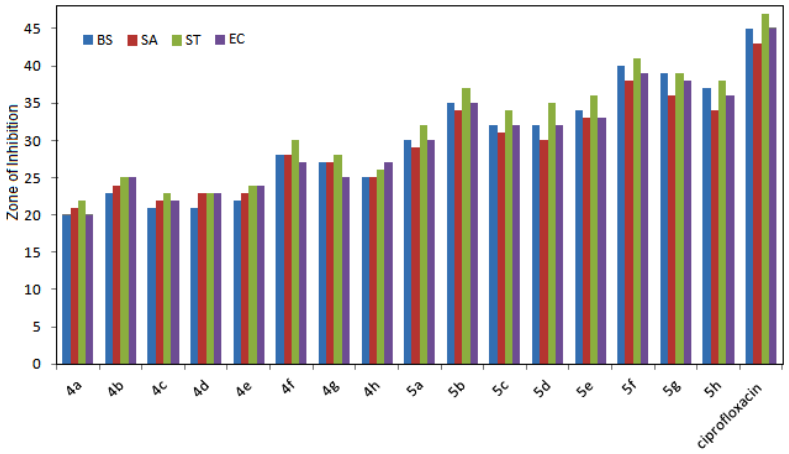

Figure 2. Antibacterial activity of compounds **4a–h** and **5a–h.**

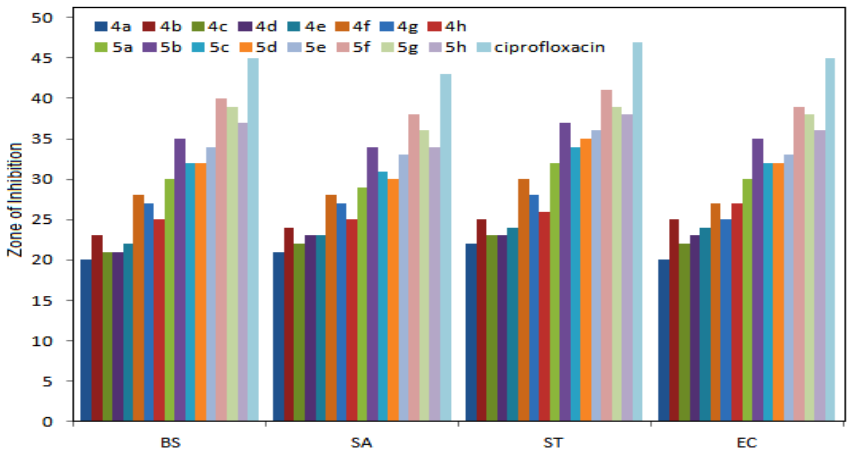

Figure 3. Comparative antibacterial activity of compounds **4a–h** and **5a–h.**

Antifungal activity

Based on the screening data from the antifungal studies (Figure 4), the following observations can be made. All compounds **4a–h** and **5a–h** exhibited antifungal activity against different fungal strains (Figure 5). Among the analogs **5a–h**, compound **5f** ($ZOI_{[PE]}$ = 35 mm, $ZOI_{[BT]}$ = 32 mm, $ZOI_{[NS]}$ = 36 mm, $ZOI_{[TS]}$ = 38 mm) was found more active against all fungal strains. Compound **5g** ($ZOI_{[PE]}$ = 34 mm, $ZOI_{[BT]}$ = 31 mm, $ZOI_{[NS]}$ = 36 mm, $ZOI_{[TS]}$ = 36 mm), compound **5h** ($ZOI_{[PE]}$ = 33 mm, $ZOI_{[BT]}$ = 31 mm, $ZOI_{[NS]}$ = 35 mm, $ZOI_{[TS]}$ = 34 mm) and compound **5b** ($ZOI_{[PE]}$ = 32 mm, $ZOI_{[BT]}$ = 28 mm, $ZOI_{[NS]}$ = 33 mm, $ZOI_{[TS]}$ = 32 mm) also had good antifungal activity against fungal strains. Compounds **5a, 5c, 5d,** and **5e** exhibited moderate antifungal activity.

Compounds **4a–h** were found less active as

compare to compound **5a–h**. In this analogs, compound **4f** ($ZOI_{[PE]}$ = 27 mm, $ZOI_{[BT]}$ = 28 mm, $ZOI_{[NS]}$ = 28 mm, $ZOI_{[TS]}$ = 28 mm), **4g** ($ZOI_{[PE]}$ = 26 mm, $ZOI_{[BT]}$ = 27 mm, $ZOI_{[NS]}$ = 26 mm, $ZOI_{[TS]}$ = 27 mm) and **4h** ($ZOI_{[PE]}$ = 25 mm, $ZOI_{[BT]}$ = 25 mm, $ZOI_{[NS]}$ = 26 mm, $ZOI_{[TS]}$ = 27 mm) were found more antifungal activity in this series. While compound **4a, 4b, 4c, 4d,** and **4e** were exhibited less antifungal activity. All compounds **4a–h** and **5a–h** exhibited less antifungal activity as compare to standard antifungal drug, ketoconazole ($ZOI_{[PE]}$ = 40 mm, $ZOI_{[BT]}$ = 38 mm, $ZOI_{[NS]}$ = 42 mm, $ZOI_{[TS]}$ = 43 mm)

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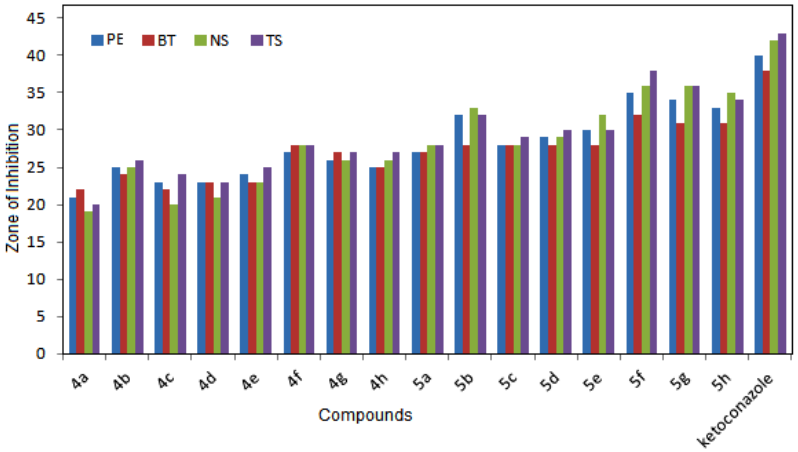

Figure 4. Antifungal activity of compounds **4a–h** and **5a–h.**

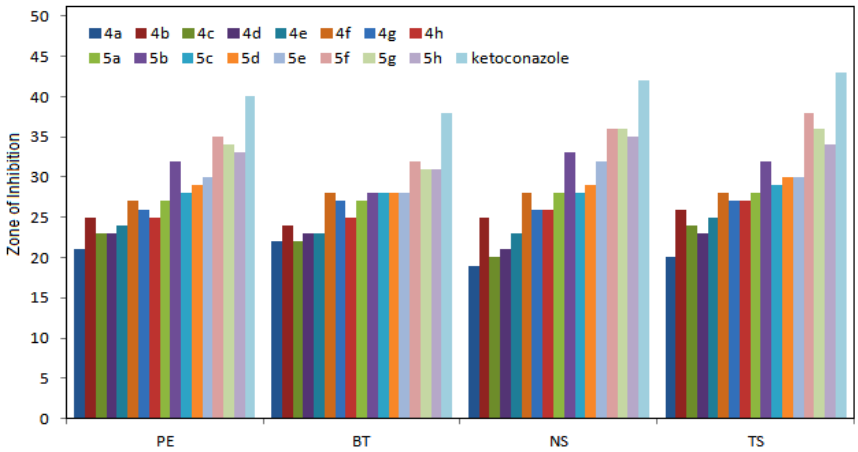

Figure 5. Comparative Antifungal activity of compounds **4a–h** and **5a–h.**

4. CONCLUSION

Novel series of heterocyclic compounds 2-aryl-1-(4-(naphthalen-2-yl)thiazol-2-yl)-5-oxopyrrolidine-3-carboxylic acid derivatives (4a–h) and 5-aryl-4-(1H-benzo[d] imidazol-2-yl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one derivatives (5a–h) have been duly synthesized. Antibacterial activities were studied against gram positive and gram negative bacteria and antifungal activities of all the compounds were studied against various fungi.

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