SYNTHESIS AND MOLECULAR DOCKING STUDIES OF NOVEL PYRIDINE-THIAZOLE-HYDRAZONE CONJUGATES AS ANTIMICROBIAL AND ANTIOXIDANT AGENTS

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In the investigation, a series of new pyridyl and thiazolyl clubbed hydrazone derivatives have been synthesized. The newly synthesized compounds were evaluated for their in vitro antimicrobial and antioxidant activities. Some among the compounds have shown excellent antimicrobial activity against both bacterial and fungal pathogens. Two compounds among the series have exhibited excellent antioxidant activity. Furthermore, a molecular docking study has been performed against *DNA gyrase* to know the binding modes of these molecules and recorded good binding affinity. The ADME study has also been performed for predicting the pharmacokinetic profile, which expressed good oral drug-like behaviour.

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INTRODUCTION

Antibiotic resistance has to turn out to be one of the major issues of global health. The various medical treatments such as cancer chemotherapy, organ, transplantation, major surgery and diabetes management have become difficult without effective antimicrobial agents.[1] The available antimicrobial agents in the market have several drawbacks, including toxicity, low effectiveness, and environmental issues. Therefore, the exploration and progress of high-efficient antimicrobial agents with a different mode of action is of prime importance.[2]

The incorporation of two or more bioactive pharmacophores in a hybrid architecture is one of the important technique used in the new drug discovery.[3-7] Thiazole pharmacophore linked with different pharmacophores for the construction of new bioactive compounds has gained much consideration in current years.[8,9] The thiazole comprising molecules are reported to have encouraging α-glucosidase inhibiting,[10] antioxidant,[11] anti-inflammatory,[12] anti-Candida[13] and antifungal[14] activities. The pyridine nucleus is widespread in many naturally occurring bioactive products and is tremendously useful for the development of new bioactive synthetic compounds. Pyridine derivatives are known for biological activities such as antimicrobial,[15] anticancer,[16] anti-inflammatory, analgesic,[17]protein kinase inhibitor,[18]and antitubercularactivities.[19] Pyridine-thiazole clubbed molecules are designed with extensive applications in medicinal chemistry.[20,21] Compounds containing a *N*-acylhydrazone (NAH) pharmacophore have shown to possess anticancer, anti-HIV, antimicrobial,[22] antibacterial, antitubercular,[23] antioxidant,[24] anti-proliferative,[25] analgesic,[26] anti-inflammatory,[27] and anthelmintic activities.[28] Its significance and persistent presence in bioactive molecules have attracted many researchers towards the NAH moiety.[29-32] The representative bioactive hydrazones reported in the literature are shown in Figure 1.

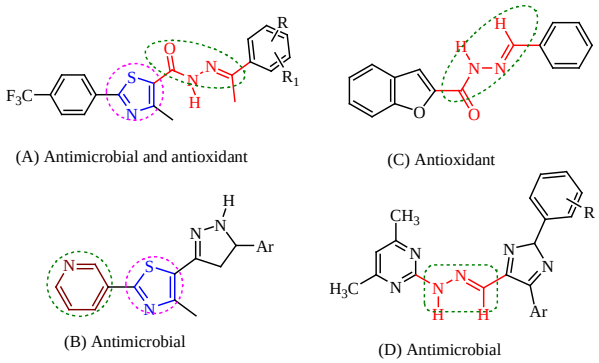


Figure 1. Some bioactive hydrazones.

In continuation, of our efforts to synthesize hydrazone derivatives having medicinal properties activities,[33-36] we have synthesized new hydrazone derivatives starting from ethionamide. The synthesized compounds were evaluated for their in vitro antimicrobial and antioxidant activities.

EXPERIMENTAL

The commercially available chemicals and reagents were used directly without further purification. The IR spectra (Neat) were recorded on Bruker FTIR spectrometer.The ^{1}H and ^{13}C NMR spectra were recorded on Bruker NMR (400 MHz) spectrometer. The chemical shifts were reported

in parts per million (ppm). TMS is used as a reference. The coupling constants (*J*) are reported in Hertz (Hz).

Procedure for the synthesis of ethyl 2-(2-ethylpyridin-4-yl)thiazole-4-carboxylate (3).

The mixture of 2-ethylpyridine-4-carbothioamide (**1**) (1.0 mmol) and ethyl bromopyruvate (**2**) (1.3 mmol) was refluxed in ethanol. The progress of the reaction was monitored by TLC. After completion of the reaction in 4 h, the ethanol was evaporated under a vacuum. The residue obtained was dissolved in ethyl acetate (50 mL) and neutralized by ammonia solution. The organic layer was washed with brine and dried over anhydrous sodium sulphate. The ethyl acetate was evaporated under vacuum and the obtained product was purified by column chromatography using ethyl acetate and petroleum ether to furnish ethyl 2-(2-ethylpyridin-4-yl)thiazole-4-carboxylate (**3**) as a thick oil. Yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.20 (t, *J* = 6.4 Hz, 3H, CH_3), 1.28 (t, *J* = 8.0 Hz, 3H, CH_3), 2.75 (q, *J* = 6.4 Hz, 2H, CH_2), 4.30 (q, *J* = 8.0 Hz, 2H, O-CH_2), 7.49 (s, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 8.14 (s, 1H, Thiazolyl-H), 8.47 (s, 1H, Ar-H).

Procedure for the synthesis of 2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (4).

Compound **3** (1.0 mmol) and excess of hydrazine hydrate (3.0 mmol) were refluxed in ethanol. The progress of reaction was monitored by TLC. After completion of the reaction, the ethanol was evaporated under reduced pressure. The obtained residue was poured in ice-cold water. The solid obtained was filtered, washed with water and crystallized with ethanol to furnish 2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide(**4**). Yield: 75 %, mp: 97-99 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.28 (t, *J* = 7.2 Hz, 3H, CH_3), 2.84 (q, *J* = 7.2 Hz, 2H, CH_2), 4.63 (bs, 2H, NH_2), 7.80 (d, *J* = 4.1 Hz, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 8.41 (s, 1H, Thiazolyl-H), 8.62 (d, *J* = 4.1 Hz, 1H, Ar-H), 9.88 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 13.69, 30.64, 117.85, 118.45, 125.04, 139.47, 150.02, 150.10, 159.62, 164.19, 164.91.

General procedure for the synthesis of substituted (*E*)-*N*'-benzylidene-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide derivatives (6a-l)

The mixture of aromatic aldehydes (**5a-l**) (1.0 mmol) and **4** (1.0 mmol) was dissolved in diisopropyl-ethyl ammonium acetate (DIPEAc) (5 mL) and stirred at room temperature for 30 min. Then, the reaction mixture was poured on cold water. The solid obtained was filtered and washed with cold water. The products obtained were crystallized with ethanol to furnish the correspondingsubstituted (*E*)-*N*'-benzylidene-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (**6a-l**) with 82-95 % yields.

(*E*)-*N*'-(3-Bromobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide(6a)

Yield 84%, m.p. 138-140 °C. IR (Neat) : 3265, 3103, 2976, 2906, 1663, 1589, 1539, 1487, 1418, 1357, 1265, 1215, 1177, 1039, 929, 840, 791, 655 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.30 (t, *J* = 6.4 Hz, 3H, CH_3), 2.88 (q, *J* = 6.4 Hz, 2H, CH_2), 7.45 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.66 (dd, *J* = 8.2 & 4.1 Hz, 1H, Ar-H), 7.75 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.88 (dd, *J* = 4.1 & 4.1 Hz, 1H, Ar-H), 7.94 (s, 2H, Ar-H), 8.62 (s, 1H, Thiazolyl-H), 8.67 (d, *J* = 4.1 Hz, 1H, Ar-H), 12.00 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 13.80, 30.69, 118.04, 118.64, 122.26, 126.48, 127.78, 129.18, 131.16, 132.83, 136.73, 139.36, 147.29, 149.60, 150.22, 156.88, 164.28, 165.37. HRMS (ESI)$^+$ calcd. for $C_{18}H_{15}BrN_4OS$ $[M+H]^+$ 415.0150. Found 415.0127.

(*E*)-2-(2-Ethylpyridin-4-yl)-*N*'-(4-fluorobenzylidene)thiazole-4-carbohydrazide (6b)

Yield: 87 %, m.p. 122-124 °C. IR (Neat): 3237, 3042, 2913, 2898, 2807, 1669, 1588, 1517, 1470, 1402, 1366, 1275, 1240, 1167, 1039, 959, 908, 821, 713, 661 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.30 (t, *J* = 7.5 Hz, 3H, CH_3), 2.85 (q, *J* = 7.5 Hz, 2H, CH_2), 7.32 (t, *J* = 8.3 Hz, 2H, Ar-H), 7.80-7.83 (m, 2H, Ar-H), 7.87 (dd, *J* = 3.9 & 3.9 Hz, 1H, Ar-H), 7.94 (s, 1H, Thiazolyl-H), 8.65 (s, 2H), 8.67 (d, *J* = 8.3 Hz, 1H), 11.88 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 13.82, 30.71, 115.94, 116.16, 118.04, 118.64, 127.54, 129.43, 129.52, 130.87, 139.39, 147.97, 149.74, 150.22, 156.77, 162.04, 164.31, 165.33. HRMS (ESI)$^+$ calcd. for $C_{18}H_{15}FN_4OS$ $[M+H]^+$ 355.0951. Found 355.1028.

(*E*)-*N*'-(4-Chlorobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (6c).

Yield 83 %, m.p. 160-162 °C. IR (Neat): 3131, 3052, 2969, 2916, 1670, 1597, 1536, 1487, 1408, 1356, 1228, 1177, 1096, 1058, 1025, 977, 897, 828, 786, 705, 659 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.30 (t, *J* = 5.2 Hz, 3H, CH_3), 2.87 (q, *J* = 5.2 Hz, 2H, CH_2), 7.54 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.77 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.88 (dd, *J* = 4.2 & 4.2 Hz, 1H, Ar-H), 7.94 (s, 1H, Thiazolyl-H), 8.65 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.67 (d, *J* = 4.2 Hz, 1H, Ar-H), 11.93 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 13.81, 30.69, 118.03, 118.14, 118.63, 127.65, 128.89, 129.06, 133.21, 134.74, 139.37, 147.76, 149.67, 150.21, 156.79, 161.46, 164.37, 165.35.

(*E*)-*N*'-(4-Bromobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (6d).

Yield 95 %, m.p. 168-170 °C. IR (Neat): 3223, 3055, 2969, 1669, 1596, 1536, 1483, 1408, 1353, 1229, 1113, 1060, 1010, 897, 827, 709, 661 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.39 (t, *J* = 5.2 Hz, 3H, CH_3), 2.94 (q, *J* = 5.2 Hz, 2H, CH_2), 7.54 (d, *J* = 4.3 Hz, 2H, Ar-H), 7.63 (dd, *J* = 4.3 & 4.3 Hz, 1H, Ar-H), 7.67-7.69 (m, 3H, Ar-H &Thiazolyl-H), 8.37 (d, *J* = 8.2 Hz, 2H, Ar-H), 8.66 (d, *J* = 4.2 Hz, 1H, Ar-H), 10.41 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.00, 31.63, 117.96, 118.88, 125.19, 126.21, 129.32, 132.14, 132.61, 139.70, 147.86, 149.96, 150.45, 156.86, 165.19, 166.44. HRMS (ESI)$^+$ calcd. for $C_{18}H_{15}BrN_4OS$ $[M+H]^+$ 415.0150. Found 415.0231.

(*E*)-2-(2-Ethylpyridin-4-yl)-*N*'-(3-nitrobenzylidene)thiazole-4-carbohydrazide (6e).

Yield 92 %, m.p. 126-128 °C. IR (Neat): 3289, 3118, 3053, 2959, 2917, 2855, 1654, 1595, 1518, 1343, 1222, 1059, 944, 882, 802, 734, 671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.39 (t, *J* = 6.3 Hz, 3H, CH_3), 2.94 (q, *J* = 6.3 Hz, 2H, CH_2), 7.59-7.64 (m, 2H, Ar-H), 7.69 (s, 1H, Ar-H), 8.82 (d, *J* = 8 Hz, 1H, Ar-H), 8.25 (dd, *J* = 4.3 & 4.3 Hz, 1H, Ar-H), 8.40 (s, 1H, Thiazolyl-H), 8.56 (s, 1H, Ar-H), 8.59 (s, 1H, Ar-H), 8.67 (d, *J* = 8.2 Hz, 1H, Ar-H), 10.57 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.99, 31.63, 117.96, 118.87, 122.75, 125.07, 126.54, 129.95, 133.02, 135.70, 139.62, 146.42, 148.75, 149.72, 150.47, 157.07, 165.23, 166.61.

(*E*)-2-(2-Ethylpyridin-4-yl)-*N*'-(2-nitrobenzylidene)thiazole-4-carbohydrazide (6f)

Yield 90 %, m.p. 154-156 °C. IR (Neat): 3277, 3114, 3029, 2967, 2905, 2798, 1664, 1597, 1521, 1349, 1237, 1041, 928, 865, 755, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, *J* = 6.2 Hz, 3H, CH_3), 2.93 (q, *J* = 6.2 Hz, 2H, CH_2), 7.53-7.58 (m, 1H, Ar-H), 7.63-7.68 (m, 2H, Ar-H), 7.70 (d, *J* = 3.8 Hz, 1H, Ar-H), 8.05 (t, *J* = 7.9 Hz, 1H, Ar-H), 8.35 (t, *J* = 7.9 Hz, 1H, Ar-H), 8.41 (d, *J* = 3.8 Hz, 1H, Ar-H), 8.65 (t, *J* = 7.9 Hz, 1H, Ar-H), 8.91 (s, 1H, Thiazolyl-H), 10.74 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.04, 31.58, 118.01, 118.88, 124.91, 126.61, 128.74, 129.50, 130.84, 133.82, 139.58, 144.02, 148.20, 149.64, 150.42, 157.04, 165.20, 166.57. HRMS $(ESI)^+$ calcd. for $C_{18}H_{15}N_5O_3S$ $[M+H]^+$ 382.0896. Found 382.0973.

(*E*)-*N*'-(3-Chlorobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (6g)

Yield 88 %, mp: 140-142 °C. IR (Neat): 3193, 3043, 2973, 2897, 2831, 1667, 1597, 1528, 1468, 1418, 1349, 1270, 1224, 1180, 1106, 1061, 966, 902, 834, 790, 710, 692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 1.30 (t, *J* = 6.1 Hz, 3H, CH_3), 2.87 (q, *J* = 6.1 Hz, 2H, CH_2), 7.51 (d, *J* = 4.3 Hz, 1H, Ar-H), 7.53 (d, *J* = 4.3 Hz, 1H,Ar-H), 7.70-7.72 (m, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.87 (dd, *J* = 4.3 & 4.3 Hz, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 8.63 (s, 1H, Thiazolyl-H), 8.67 (s, 1H, Ar-H), 8.68 (s, 1H, Ar-H), 12.00 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 13.81, 30.70, 118.04, 118.64, 126.06, 126.35, 127.78, 129.95, 130.90, 133.74, 136.51, 139.37, 147.20, 149.60, 150.22, 156.89, 164.31, 165.37.

(*E*)-*N*'-(2-Bromobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (6h)

Yield 82 %, m.p. 162-164 °C. IR (Neat): 3225, 3121, 3052, 2966, 2919, 2855, 1667, 1595, 1534, 1483, 1407, 1353, 1269, 1227, 1179, 1111, 1061, 1017, 974, 896, 826, 786, 705, 657 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.39 (t, *J* = 6.3 Hz, 3H, CH_3), 2.94 (q, *J* = 6.3 Hz, 2H, CH_3), 7.55 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.63 (dd, *J* = 4.4 & 4.4 Hz, 1H, Ar-H), 7.66-7.69 (m, 3H, Ar-H, &Thiazolyl- H), 8.37 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.67 (d, *J* = 4.4 Hz, 1H, Ar-H), 10.41 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.00, 31.63, 117.97, 118.88, 125.20, 126.21, 129.32, 132.14, 132.61, 139.70, 147.86, 149.96, 150.45, 156.87, 165.19, 166.45. HRMS $(ESI)^+$ calcd. for $C_{18}H_{15}BrN_4OS$ $[M+H]^+$ 415.0150. Found 415.0230.

(*E*)-*N*'-(2-Chlorobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (6i)

Yield 93 %, m.p. 128-130 °C. IR (Neat): 3140, 3017, 2951, 2918, 1665, 1589, 1533, 1485, 1427, 1343, 1214, 1159, 1115, 1037, 891, 815, 778, 653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.39 (t, *J* = 5.5 Hz, 3H, CH_3), 2.95 (q, *J* = 5.5 Hz, 2H, CH_2), 7.30-7.37 (m, 2H, Ar-H), 7.38-7.42 (m, 1H, Ar-H), 7.66 (dd, *J* = 3.8 & 3.8 Hz, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 8.25 (dd, *J* = 4.0 & 4.0 Hz, 1H, Ar-H), 8.41 (s, 1H, Thiazolyl-H), 8.68 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.76 (s, 1H, Ar-H), 10.52 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.03, 31.62, 118.03, 118.95, 126.36, 127.30, 128.28, 129.91, 131.09, 131.71, 134.54, 139.73, 145.36, 149.93, 150.44, 156.90, 165.20, 166.50. HRMS $(ESI)^+$ calcd. for $C_{18}H_{15}ClN_4OS$ $[M+H]^+$ 371.8559. Found 371.0731.

(*E*)-2-(2-Ethylpyridin-4-yl)-*N*'-(4-nitrobenzylidene)thiazole-4-carbohydrazide (6j)

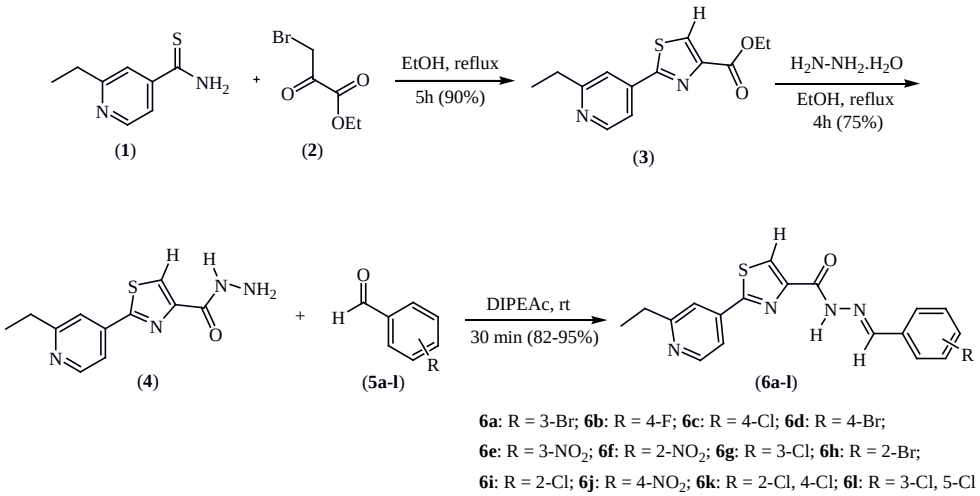
Yield 80 %, m.p. 188-190 °C. IR (Neat): 3255, 3081, 2978, 2905, 2851, 1667, 1562, 1523, 1367, 1217, 1047, 956, 867, 814, 754, 661 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.40 (t, *J* = 6.3 Hz, 3H, CH_3), 2.95 (q, *J* = 6.3 Hz, 2H, CH_2), 7.64 (dd, *J* = 4.2 & 4.2 Hz, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.99 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.29 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.42 (s, 1H, Thiazolyl-H), 8.57 (s, 1H, Ar-H), 8.68 (d, *J* = 4.2 Hz, 1H, Ar-H), 10.56 (s, 1H, Amido-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.01, 31.65, 117.97, 118.89, 124.21, 126.68, 128.47, 139.62, 139.80, 146.20, 148.94, 149.65, 150.51, 157.05, 165.27, 166.70.

(*E*)-*N*'-(2,4-Dichlorobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (6k)

Yield 87 %, m.p. 144-146 °C. IR (Neat): 3247, 2993, 2944, 2831, 1662, 1598, 1522, 1489, 1418, 1349, 1265, 1214, 1183, 1058, 971, 841, 776, 722, 656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.38 (t, *J* = 7.1 Hz, 3H, CH_3), 2.94 (q, *J* = 7.1 Hz, 2H, CH_2), 7.30 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.41 (t, *J* = 4.5 Hz, 1H, Ar-H), 7.65 (d, *J* = 4.5 Hz, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 8.19 (dd, *J* = 4.5 & 4.5 Hz, 1H, Ar-H), 8.41 (s, 1H, Thiazolyl-H), 8.66 (d, *J* = 4.5 Hz, 1H, Ar-H), 8.69 (s, 1H, Ar-H), 10.57 (s, 1H, Amido- NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.03, 31.59, 118.01, 118.95, 126.54, 127.86, 129.03, 129.71, 129.76, 134.93, 137.06, 139.69, 144.24, 149.76, 150.42, 156.94, 165.20, 166.53.

(*E*)-*N*'-(3,5-Dichlorobenzylidene)-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide (6l).

Yield 85 %, m.p. 174-176 °C; IR (Neat): 3244, 3082, 3021, 2954, 2871, 1668, 1561, 1547, 1491, 1417, 1359, 1268, 1233, 1188, 1056, 1003, 917, 849, 812, 780 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.38 (t, *J* = 6.1 Hz, 3H, CH_3), 2.94 (q, *J* = 6.1 Hz, 2H, CH_2), 7.48 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.62 (d, *J* = 4.3 Hz, 2H, Ar-H), 7.68 (s, 1H, Ar-H), 7.91



Scheme 1. Synthesis of (*E*)-*N*'-benzylidene-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide derivatives.

(s, 1H, Thiazolyl-H), 8.37 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.67 (d, *J* = 4.3 Hz, 1H, Ar-H), 10.45 (s, 1H, Amido-NH) ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.00, 31.63, 117.96, 118.88, 126.39, 126.90, 129.30, 130.91, 133.41, 133.76, 134.77, 139.65, 146.44, 149.80, 150.45, 156.92, 165.20, 166.52.

RESULTS AND DISCUSSIONS

The reaction sequence followed for the synthesis of target compounds has been depicted in **Scheme 1**. In the first step, 2-ethylpyridine-4-carbothioamide (**1**) (1.0 mmol) and ethyl bromopyruvate (**2**) (1.3 mmol) were refluxed in ethanol to obtain ethyl 2-(2-ethylpyridin-4-yl)thiazole-4-carboxylate (**3**) with 90 % yield. Then, ethyl 2-(2-ethylpyridin-4-yl)thiazole-4-carboxylate (**3**) (1.0 mmol) and excess of hydrazine hydrate (3.0 mmol) was refluxed in ethanol to furnish the important intermediate 2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide(**4**) with 75 % yield. The condensation of various substituted aromatic aldehydes (**5a-l**) with 2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide(**4**) furnished the corresponding substituted (*E*)-*N*'-benzylidene-2-(2-ethylpyridin-4-yl)thiazole-4-carbohydrazide(**6a-l**) with 82-95 % yields. Diisopropyl-ethyl ammonium acetate (DIPEAc) is used as solvent and catalyst in the condensation reaction.[37]

The structures of the newly synthesized compounds were assigned by their IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. In the IR spectrum, the peaks in the range of 1660 to 1670 cm^{-1} was observed, which confirms the presence of hydrazone carbonyl. The C=N stretching band appears in the range of 1590 to 1600 cm^{-1}. The band at 3150-3210 cm^{-1} is assigned for the N-H stretching. The ^{1}H NMR spectrum of these compounds have displayed a triplet-quartet pattern for ethyl substituent at δ 1.30-1.40 and 2.85-2.95. The amide N-H signal has appeared in the range of δ 10.41 to 12.00. The characteristic signal at δ 166 ppm in the ^{13}C NMR spectrum, confirms the presence of the carbonyl group (*N*-acylhydrazone). Finally, the HRMS data strengthen the structure assigned to newly synthesized compounds.

Antioxidant Activity

Free radicals are considered to be an important performers in physiological mechanisms.[38,39] The radical reacts comprehensively with nearly every kind of biomolecules seen in the living cell and may deviate the cells from their normal physiological roles. Antioxidants are the substances capable of scavenging free radicals. The antioxidant properties of the hydrazones (**6a-l**) were calculated by 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging method.[40,41]

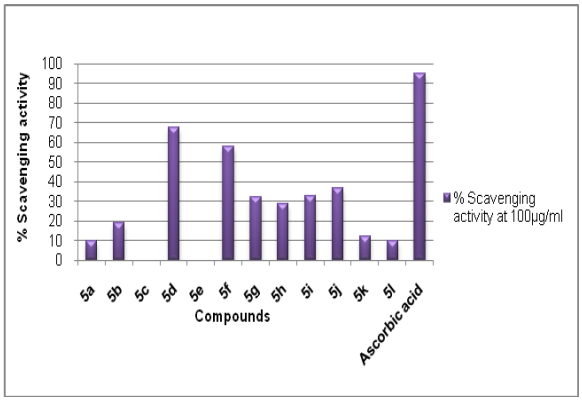


Figure 2. DPPH scavenging activity (%) of hydrazone derivatives (**6a-l**).

Ascorbic acid was used as a reference for antioxidant assay. According to the results obtained from the DPPH test, the best performing hydrazones were **6d** (67 %) and **6f** (57 %). The moderate antioxidant activity (10-36 %) was shown by hydrazones **6g**, **6h**, **6i** and **6j** (Figure 2). Free radical scavenging activity was measured in terms of percent inhibition.

Antimicrobial Activity

The agar well diffusion method was used for screening of the antimicrobial activity of the hydrazone derivatives (**6a-l**).[42]

Table 1. Antimicrobial activity of hydrazone derivatives (**6a-l**).

S.No.	Pathogens	Compounds											Standard
		6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	
1	*S. typhi*	23	-	-	05	-	-	-	-	12	-	-	-	33
2	*E. aerogenes*	17	12	-	-	05	-	-	09	05	-	-	06	33
3	*B. subtilis*	26	12	-	-	-	-	05	-	06	-	07	-	32
4	*B. cereus*	18	06	-	-	-	09	-	-	07	-	-	-	33
5	*P. aeruginosa*	18	06	-	-	-	07	-	-	10	-	-	08	32
6	*S. abony*	16	07	-	-	-	05	-	-	06	-	-	-	32
7	*E. coli*	-	09	-	-		-	-	-	-	-	08	-	29
8	*S. aureus*	16	08	-	05	-	-	06	-	-	-	05	-	29
9	*S. boydii*	18	08	-	-	-	-	-	-	06	-	-	-	34
10	*C. albicans*	06	05	08	-	07	-	-	-	15	-	-	-	30
11	*S. cerevisiae*	15	10	10	-	-	-	-	05	05	-	-	-	30
12	*A. niger*	15	05	-	-	-	-	-	-	-	-	-	05	30

- = no activity

Table 2. MIC value of most potent hydrazone derivatives **6a**, **6b** and **6i** (µg mL^{-1}).

S.No.	Pathogens	Compounds			Ceftazidime	Fluconazole
		6a	6b	6i		
1	*B. subtilis*	40 ± 0.35	85 ± 0.35	150 ± 1.50	24 ± 0.65	NA
2	*B. cereus*	65 ± 1.20	95 ± 1.60	135 ± 0.90	35 ± 1.35	NA
3	*E. aerogenes*	60 ± 0.40	110 ± 1.30	280 ± 2.30	30 ± 0.55	NA
4	*S. cerevisiae*	120 ± 0.85	170 ± 1.10	310 ± 0.80	NA	20 ± 0.80
5	*C. albicans*	90 ± 0.45	215 ± 1.40	190 ± 1.12	NA	30 ± 1.50

NA = Not available

Both the Gram-positive and Gram-negative bacterial pathogens were used for evaluating antibacterial activity. *Staphylococcus aureus* ATCC 6538, *Bacillus megaterium* ATCC 2326, *Bacillus subtilis* ATCC 6633 were Gram-positive pathogens used in this study. *Escherichia coli* ATCC8739, *Salmonella typhi* ATCC9207, *Shigella boydii* ATCC 12034, *Enterobacter aerogenes* ATCC13048, *Pseudomonas aeruginosa*ATCC9027 and *Salmonella abony* NCTC6017 were the Gram-negative pathogens used. Antifungal activity of synthesized compounds was determined against *Aspergillusniger*ATCC 16404, *Saccharomyces cereviseae*ATCC 9763, and *Candida albicans* ATCC10231 fungal pathogens. Ceftazidime and fluconazole were used as antibacterial and antifungal standard reference compounds, respectively. The hydrazone derivatives**6a**, **6b**, and **6i**were displayed remarkable antibacterial and antifungal activity against almost all pathogens. The zones were measured and recorded by using the scale in millimeter (Table 1).

The MIC values were calculated for the most active hydrazones. The hydrazones **6a**, **6b** and **6i** were found effective against many pathogens; hence these hydrazones were selected for MIC determination studies. The MIC was determined against *B. subtilis*, *E. aerogenes* and *C. albicans.*It was determined by using the method and rules of the Clinical and Laboratory Standard Institute (CLSI).[43]All experiments were performed in triplicates and results are expressed as mean ± SD in µg mL^{-1} (Table 2).

Molecular Docking Study

A molecular docking was performed to predict the molecular mechanism of action of hydrazone derivatives (**6a-l**).[44,45] The crystal structure of the *DNA gyrase* (PDB ID1QX1) was used for docking analysis. All the hydrazone derivatives showed excellent binding potential with *DNA gyrase*, which indicates the antimicrobial potential of hydrazone derivatives. Hydrazone **6a** has shown hydrogen bonding interaction with ARG342, and VdW interactions with ARG630, GLU634, GLY178, ARG342, LEU345 (Figure 3). Hydrazone **6b** has displayed hydrogen bonding interactions with ARG342, hydrophobic interaction with MET27, VAL31 and VdW interactions with GLU634, ALA637, MET27, VAL31, GLY341, ARG342, PRO343 (Figure 4). While hydrazone **6i** has shown hydrogen bonding interactions with ARG630, hydrophobic interaction with ARG342 and VdW interactions with GLU627, ARG630, GLU634, ARG342, PRO343, LYS344 (Figure 5).

ADME Prediction

The hydrazone derivatives (**6a-l**) were scrutinized for ADME prediction using Swiss ADME portal.46All the hydrazone derivatives were displayed excellent ADME parameters with low Lipinski violation, which is needed for the oral absorption of drug molecules, and the outcomes are summarized in Table 3.

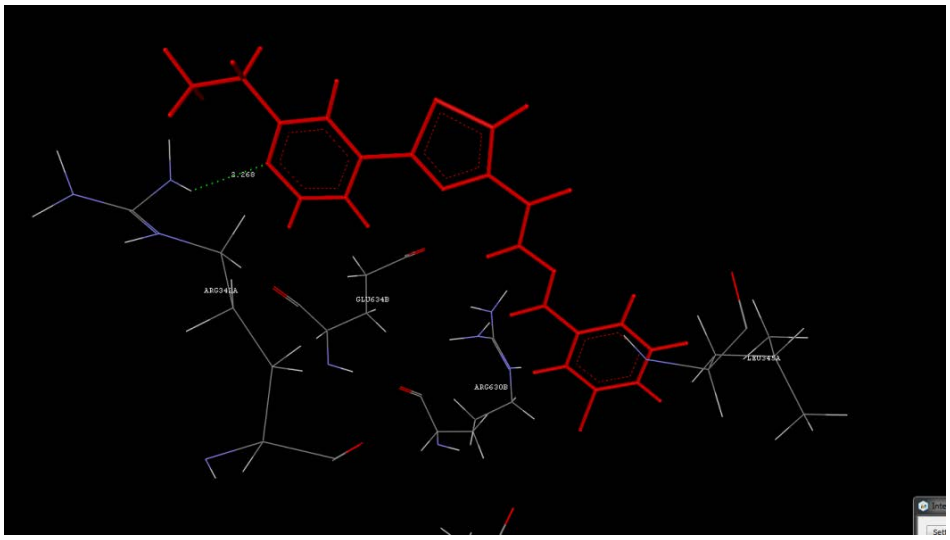


Figure 3. Binding mode of hydrazone **6a** into the active site of DNA gyrase.

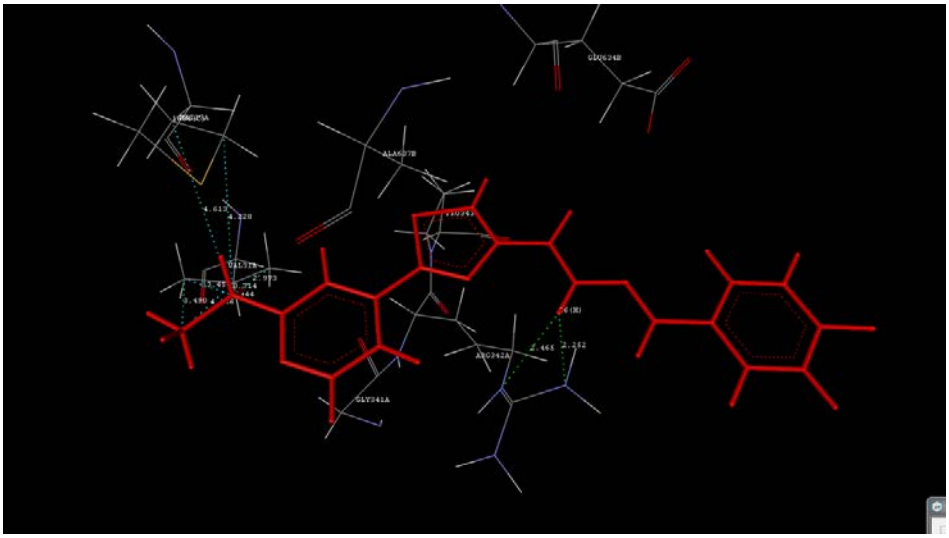


Figure 4. Binding mode of hydrazone **6b** into the active site of DNA gyrase.

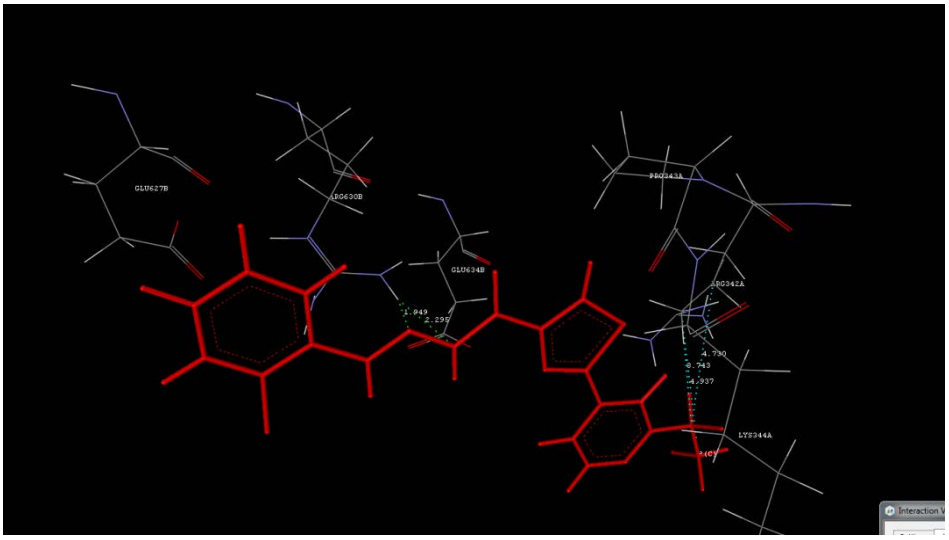


Figure 5. Binding mode of hydrazone **6i** into the active site of DNA gyrase.

Table 3. Pharmacokinetic parameters of hydrazone derivatives (**6a-l**).

Entry	Mol. Wt.	Rotatable bonds	H-bond acceptors	H-bond donors	LOG P	Bioavailability Score
6a	414.32	6	3	1	3.93	0.55
6b	353.41	6	4	1	3.65	0.55
6c	369.87	6	3	1	3.81	0.55
6d	414.32	6	3	1	3.9	0.55
6e	380.42	7	5	1	3.23	0.55
6f	380.42	7	5	1	3.18	0.55
6g	369.87	6	3	1	3.78	0.55
6h	414.32	6	3	1	3.93	0.55
6i	369.87	6	3	1	3.83	0.55
6j	380.42	7	5	1	3.24	0.55
6k	404.31	6	3	1	4.04	0.55
6l	404.31	6	3	1	3.94	0.55

CONCLUSION

In conclusion, a series of new pyridyl and thiazolyl clubbed hydrazone derivatives (**6a-l**) were synthesized starting from ethionamide. All the newly synthesized hydrazone derivatives were screened for their *in vitro* antimicrobial activity. The hydrazone derivatives **6a**, **6b** and **6i** have displayed excellent antimicrobial activities. Antioxidant potential of synthesized hydrazone derivatives has also been evaluated by DPPH scavenging method. The hydrazone derivatives **6d** and **6f** have shown good antioxidant activity. A molecular docking study was performed to investigate the binding modes of these molecules by using *DNA gyrase*. These compounds were showed excellent binding potential, which indicates the antimicrobial potential of synthesized hydrazone derivatives.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

The supporting information of this article containing ^{1}H NMR, ^{13}C NMR and HRMS spectrums of new compounds are available for the authorized users.

REFERENCES

[1]Nalawade, J., Shinde, A., Chavan, A., Patil, S., Suryavanshi, M., Modak, M., Choudhari, P., Bobade, V. D., Mhaske, P. C., Synthesis of new thiazolyl-pyrazolyl-1,2,3-triazole derivatives as potential antimicrobial agents, *Eur. J. Med. Chem.*, **2019**, *179*, 649-659. DOI: 10.1016/j.ejmech.2019.06.074

[2]Lopes, S. M. M., Novais, J. S., Costa, D. C. S., Castro, H. C., Figueiredo, A. M. S., Ferreira, V. F., Pinho E Melo,T. M. V. D., da Silva, F. C., Hetero-Diels-Alder reactions of novel 3-triazolyl-nitrosoalkenes as an approach to functionalized 1,2,3-triazoles with antibacterial profile, *Eur. J. Med. Chem.*, **2018**, *143*, 1010-1020.DOI:10.1016/j.ejmech.2017.11.052

[3]Beruve, G., An overview of molecular hybrids in drug discovery, *Expert Opin. Drug Discov.*, **2016**, *11*, 281-305.DOI: 10.1517/17460441.2016

[4]Abhale, Y. K., Shinde, A. D., Deshmukh,K. K., Nawale, L., Sarkar, D., Choudhari, P. B., Kumbhar, S. S., Mhaske, P. C., Synthesis, antimycobacterial screening and molecular docking studies of 4-aryl-4′-methyl-2′-aryl-2, 5′-bisthiazole derivatives, *Med. Chem. Res.*, **2017**, *26*, 2889-2899. DOI:10.1007/s00044-017-1955-1

[5]Lima, C. H. S., Henriques, M. G. M. O., Candea, A. L. P., Lourenco, M. C. S,Bezerra, F. A. F. M., Ferreira, M. L., Kaiser, C. R., de Souza, M. V. N., Synthesis and antimycobacterial evaluation of *N*′-(*E*)-heteroaromatic-pyrazine-2-carbohydrazide derivatives, *Med. Chem.*, **2011**, ***7***, 245-249.DOI:1573-4064/11

[6]Ajani, O. O., Obafemi, C. A., Nwinyi, O. C., Akinpelu, D. A., Microwave assisted synthesis and antimicrobial activity of 2-quinoxalinone-3-hydrazone derivatives, *Bioorg. Med. Chem.*, **2010**, *18*, 214-221.DOI:10.1016/j.bmc.2009.10.064

[7]Sriram, D., Yogeeswari, P., Madhu, K., Synthesis and in vitro and in vivo antimycobacterial activity of isonicotinoyl hydrazones, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 4502-4505.DOI:10.1016/j.bmcl.2005.07.011

[8]Dhumal, S. T., Deshmukh, A. R., Khillare, L. D., Arkile, M., Sarkar, D., Mane, R. A., Synthesis and antitubercular activity of new thiazolidinones with pyrazinyl and thiazolyl scaffolds, *J. Heterocycl. Chem.*, **2017**, *54*, 125-130.DOI: 10.1002/jhet.2552

[9]Nalawade, J., Mhaske, P. C., Shinde, A., Patil, S. V., Choudhari, P. B., Bobade, V. D., Synthesis, characterization, and antimicrobial screening of 4″-methyl-2,2″-diaryl-4,2′:4′,5″-terthiazole derivatives, *J. Heterocycl. Chem.*, **2018**, *55*, 1366-1374.DOI: 10.1002/jhet.3170

[10]Khan, K. M., Qurban, S., Salar, U., Taha, M., Hussain, S., Perveen, S., Hameed, A., Ismail, N. H., Riaz, M., Wadood, A., Synthesis, *in vitro* *α*-glucosidase inhibitory activity and molecular docking studies of new thiazole derivatives, *Bioorg. Chem.*,**2016**, *68*, 245-258. DOI: 10.1016/j.bioorg.2016.08.010

[11]Ummadi, N., Gundala, S., Venkatapuram, P., Adivireddy, P., Synthesis and antioxidant activity of a new class of pyrazolylindoles, thiazolyl pyrazolylindoles, *Med. Chem. Res.*, **2017**, *26*, 1574-1584.DOI:10.1007/s00044-017-1827-8

[12]Bharti, S. K., Singh, S. K., Design, synthesis and biological evaluation of some novel benzylidene-2-(4-phenylthiazol-2-yl) hydrazines as potential anti-inflammatory agents, *Med. Chem. Res.*, **2014**, *23*, 1004-1015.DOI: 10.1007/s00044-013-0708-z

[13]Carradori, S., Secci, D., Bolasco, A., Rivanera, D., Mari, E., Zicari, A., Lotti, L. V., Bizzarri, B., Synthesis and cytotoxicity of novel (thiazol-2-yl)hydrazine derivatives as promising anti-*Candida* agents, *Eur. J. Med. Chem.*, **2013**, *65*, 102-111.DOI:10.1016/j.ejmech.2013.04.042

[14]Kauthale, S., Tekale, S., Damale, M., Sangshetti, J., Pawar, R., Synthesis, antioxidant, antifungal, molecular docking and ADMET studies of some thiazolyl hydrazones, *Bioorg. Med. Chem. Lett.*, **2017**, *27*, 3891-3896. DOI: 10.1016/j.bmcl.2017.06.043

[15]Abdelrahman, M. A., Salama, I., Gomaa, M. S., Elaasser, M. M., Abdel-Aziz, M. M., Soliman, D. H., Design, synthesis and 2D QSAR study of novel pyridine and quinolone hydrazone derivatives as potential antimicrobial and antitubercular agents *Eur. J. Med. Chem.*, **2017**, *138*, 698-714. DOI: 10.1016/j.ejmech.2017.07.004

[16]Ahmed, M. H., E1-Hashash, M. A., Marzouk, M. I., E1-Naggar, A. M., Design, synthesis and biological evaluation of novel pyrazole, oxazole and pyridine derivatives as potential anticancer agents using mixed chalcone, *J. Heterocycl. Chem.*, **2019**, *56*, 114-123. DOI: 10.1002/jhet.3380

[17]Helal, M. H., El-Awdan, S. A., Salem, M. A., Abd-elaziz, T. A., Moahamed, Y. A., El-Sherif, A. A., Mohamed, G. A. M., Synthesis, biological evaluation and molecular modeling of novel series of pyridine derivatives as anticancer, anti-inflammatory and analgesic agents, *Spectrochim. Acta A*, **2015**, *135*, 764-773.DOI: 10.1016/j.saa.2014.06.145

[18]Lawson, M., Rodrigo, J., Baratte, B., Robert, T., Delehouzé, C., Lozach, O., Ruchaud, S., Bach, S., Brion, J. D., Alami, M., Hamze, A., Synthesis, biological evaluation and molecular modelling studies of imidazo[1,2-*a*]pyridines derivatives as protein kinase inhibitors, *Eur. J. Med. Chem.*, **2016**, *123*, 105-114. DOI: 10.1016/j.ejmech.2016.07.040

[19]Desai, N. C., Trivedi, A., Somani, H., Jadeja, K. A., Vaja, D., Nawale, L., Khedkar, V. M., Sarkar, D., Synthesis, biological evaluation and molecular docking study of pyridine clubbed 1,3,4-oxadiazoles as potential antituberculars, *Synth. Commun.*, **2018**, *48*, 524-540. DOI: 10.1016/j.bmcl.2016.02.043

[20]Dhumal,S. T., Deshmukh, A. R., Bhosale, M. R., Khedkar, V. M., Nawale, L. U., Sarkar, D., Mane, R. A., Synthesis and antitubercular activity of new 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffolds, *Bioorg. Med. Chem. Lett.*, **2016**, *26*, 3646-3651. DOI: 10.1016/j.bmcl.2016.05.093

[21]Oniga, S. D., Araniciu, C., Stoica, C. I., Palage, M. D., Vlase, L., Pirnau, A., Marutescu, L., Chifiriuc, M. C., Oniga, O.. Synthesis and antimicrobial activity evaluation of some new 2-(3-pyridil)-thiazolyl-1,3,4-oxadiazolines, *FARMACIA*, **2017**, *65*, 501-507.

[22]Savini, L., Chiasserini, L., Travagli, V., Pellerano, C., Novellino, E., Cosentino, S., Pisano, M. B., New *α*-(*N*)-heterocyclichydrazones: evaluation of anticancer, anti-HIV and antimicrobial activity, *Eur. J. Med. Chem.*, **2004**, *39*, 113-122. DOI: 10.1016/j.ejmech.2003.09.012

[23]Eswaran, S., Adhikari, A. V., Chowdhury, I. H., Pal, N. K., Thomas, K. D., New quinoline derivatives: synthesis and investigation of antibacterial and antituberculosis properties, *Eur. J. Med. Chem.*, **2010**, *45*, 3374-3383. DOI: 10.1016/j.ejmech.2010.04.022

[24]Nastasa, C., Tiperciuc, B., Duma, M., Benedec, D., Oniga, O., New hydrazones bearing thiazole scaffold: synthesis, characterization, antimicrobial and antioxidant investigation, *Molecules*, **2015**, *20*, 17325-17338. DOI: 10.3390/molecules200917325

[25]Baldisserotto, A., Demurtas, M., Lampronti, L., Moi, D., Balboni, G., Vertuani, S., Manfredini, S., Onnis, V., Benzofuran hydrazones as potential scaffold in the development of multifunctional drugs: synthesis and evaluation of antioxidant, photoprotective and antiproliferative activity, *Eur. J. Med. Chem.*, **2018**, *156*, 118-125. DOI: 10.1016/j.ejmech.2018.07.001

[26]Maia, R. C., Silva, L. L., Mazzeu, E. F., Fumian, M. M., de Rezende, C. M., Doriguetto, A. C., Correa, R. S., Miranda, A. L. P., Barreiro, E. J., Fraga, C. A. M., Synthesis and analgesic profile of conformationally constrained *N*-acylhydrazone analogues: discovery of novel *N*-arylideaminoquinazolin-4(3*H*)-one compounds derived from natural safrole, *Bioorg. Med. Chem.*, **2009**, *17*, 6517-6525. DOI: 10.1016/j.bmc.2009.08.009

[27]Moldovan, C. M., Oniga, O., Parvu, A., Tiperciuc, B., Verite, P., Pirnau, A., Crisan, O., Bojita, M., Pop, R., Synthesis and anti-inflammatory evaluation of some new acyl-hydrazones bearing 2-aryl-thiazole, *Eur. J. Med. Chem.*, **2011**, *46*, 526-534. DOI: 10.1016/j.ejmech.2010.11.032

[28]Kamal, R., Kumar, R., Kumar, V., Kumar, V., Bansal, K. K., Sharma, P. C., Synthesis, anthelmintic and antimicrobial evaluation of new 2-arylidene-1-(4-methyl-6-phenylpyrimidin-2-yl)hydrazines, *Chemistry Select*, **2019**, *4*, 713-717.DOI: 10.1002/slct.201802822

[29]Bondock, S., Naser, T., Ammar, Y. A., Synthesis of some new 2-(3-pyridyl)-4,5-disubstituted thiazoles as potent antimicrobial agents, *Eur. J. Med. Chem.*, **2013**, *62*, 270-279. DOI: 10.1016/j.ejmech.2012.12.050

[30]Jin, Y., Tan, Z., He, M., Tian, B., Tang, S., Hewlett, I., Yang, M., SAR and molecular mechanism study of novel acylhydrazone compounds targeting HIV-1 CA, *Bioorg. Med. Chem.*, **2010**, *18*, 2135-2140. DOI: 10.1016/j.bmc.2010.02.003

[31]Vicini, P., Incerti, M., La Colla, P., Loddo, R., Anti-HIV evaluation of benzo[*d*]isothiazole hydrazones, *Eur. J Med. Chem.*, **2009**, *44*, 1801-1807. DOI: 10.1016/j.ejmech.2008.05.030

[32]Bedia, K. K., Elcin, O., Seda, U., Fatma, K., Nathaly, S., Sevim, R., Dimoglo, A., Synthesis and characterization of novel hydrazide-hydrazones and the study of their structure-antituberculosis activity, *Eur. J. Med. Chem.*, **2006**, *41*, 1253-1261. DOI: 10.1016/j.ejmech.2006.06.009

[33]Muluk, M. B., Phatak, P. S., Pawar, S. B., Dhumal, S. T., Rehman, N. N. M. A., Dixit, P. P., Choudhari, P. B., Haval, K. P., Synthesis, antimicrobial and antioxidant activities of new pyridyl and thiazolyl bearing carbohydrazides, *J. Chin. Chem. Soc.*, **2019**, *66*, 1507-1517. DOI:10.1002/jccs.201900198

[34]Muluk, M. B., Dhumal, S. T., Phatak, P. S., Rehman, N. N. M. A., Dixit, P. P., Choudhari, P. B., Mane, R. A., Haval, K. P., Synthesis, antimicrobial activity, and molecular docking study of formylnaphthalenyloxymethyltriazolyl-*N*-phenyl-acetamides, *J. Heterocycl. Chem.*, **2019**, *56*, 2411-2418. DOI: 10.1002/jhet.3628

[35]Muluk, M. B., Dhumal, S. T., Rehman, N. N. M. A., Dixit, P. P., Kharat, K. R., Haval, K. P., Synthesis, anticancer and antimicrobial evaluation of new (*E*)-*N*′-benzyl-idene-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carbohydrazides,*Chemistry Select*, **2019**, *4*, 8993-8997. DOI: 10.1002/slct.201902030

[36]Kulkarni, R. S., Haval, N. B., Kulkarni, J. A., Dixit, P. P., Haval, K. P., Synthesis, characterization and biological evaluation of substituted 2-phenoxynicotinaldehydes as *α*-amylase inhibitors, *Eur. Chem. Bull.*, **2019**, *8*, 26-30. DOI: 10.1039/c7md00080d

[37]Khillare, L. D., Bhosale, M. R., Deshmukh, A. R., Mane, R. A., One-pot rapid synthesis of thiazole-substituted pyrazolyl-4-thiazolidinones mediated by diisopropylethylammonium acetate, *Res. Chem. Intermed.*, **2015**, *41*, 8955-8964. DOI: 10.1007/s11164-015-1940-6

[38]Bhale, P. S., Chavan, H. V., Dongare, S. B., Shringare, S. N., Mule, Y. B., Nagane, S. S., Bandgar, B. P., Synthesis of extended conjugated indolyl chalcones as potent anti-breast cancer, anti-inflammatory and antioxidant agents, *Bioorg. Med. Chem. Lett.*, **2017**, *27*, 1502-1507. DOI: 10.1016/j.bmcl.2017.02.052

[39]Trouba, K. J., Hamadeh, H. K., Amin, R. P., Germolec, D. R., Oxidative stress and its role in skin disease, *Antioxid. Redox Signal*, **2002**, *4*, 665-673. DOI: 10.1089/15230860260220175

[40]Srivastava, B. K., Solanki, M., Mishra, B., Soni, R., Jayadev, S., Valani, D., Jain, M., Patel, P. R., Synthesis and antibacterial activity of 4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine quinolones, *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 1924-1929. DOI: 10.1016/j.bmcl.2007.01.038

[41]Patil, S. R., Sarkate, A. P., Karnik, K. S., Arsondkar, A., Patil, V., Sangshetti, J. N., Bobade, A. S., Shinde, D. B., A facile synthesis of substituted 2-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)pyrazine using microwave irradiation and conventional method with antioxidant and anticancer activities, *J. Heterocycl. Chem.*, **2019**, *56*, 859-866. DOI: 10.1002/jhet.3464

[42]Phatak, P. S., Sathe, B. P., Dhumal, S. T., Rehman, N. N. M. A., Dixit, P. P., Khedkar, V. M., Haval, K. P., Synthesis, antimicrobial evaluation and docking studies of substituted acetylphenoxymethyl-triazolyl-*N*-phenylacetamides, *J. Heterocycl. Chem.*, **2019**, *56*, 1928-1938. DOI: 10.1002/jhet.3568

[44]Kamat, S. R., Salunkhe, R. S., Choudhari, P. B., Dhavale, R. P., Mane, A. H., Lohar, T. R., Efficient synthesis of chromeno[2,3-*c*]pyrazolyl-pyrazolol(s) in hydrotropic solution and their anti-infective potential, *Res. Chem. Intermed.*, **2018**, *44*, 1351-1362. DOI:10.1007/s11164-017-3171-5

[45](a) Kondhare, D. D., Gyananath, G., Tamboli, Y., Kumbhar, S. S., Choudhari, P. B., Bhatia, M. S., Zubaidha, P. K., An efficient synthesis of flavanones and their docking studies with aldose reductase.*Med. Chem. Res*., **2017**, *26*, 987-998. DOI: 10.1007/s00044-017-1813-1(b)Thalji, R. K., Raha, K., Andreotti, D., Checchia, A., Cui, H., Meneghelli, G., Profeta, R., Tonelli, F., Tommasi, S., Bakshi, T., Donovan, B. T., Howells, A., Jain, S., Nixon, C., Quinque, G., McCloskey, L., Bax, B. D., Neu, M., Chan, P. F., Stavenger, R. A., Structure-guided design of antibacterials that allosterically inhibit DNA gyrase, *Bioorg. Med. Chem. Lett*., **2019**, *29*, 1407-1412. DOI: 10.1016/j.bmcl.2019.03.029

[46]Daina, A., Michielin, O., Zoete, V., iLOGP: A simple, robust and efficient description of *n*-octanol/water partition coefficient for drug design using the gb/sa approach, *J. Chem. Inf. Model*, **2014**, *54*, 3284-3301. DOI: 10.1021/ci500467k

[43]Bauer, A. W., Kirby, W. M., Sherris, J. C., Turck, M., Antibiotic susceptibility testing by a standardized single disk method, *Am. J. Clin. Pathol.*, **1966**, *45*, 493-496. DOI: 10.1093/ajcp/45.4_ts.493

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