**Synthesis of novel pyridine-connected piperidineand 2*H*-thiopyranderivativesand their larvicidal,nematicidal,and antimicrobial activities**

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**Abstract**

A series of novelpyridine-connected piperidine derivatives (**2a-g)** and pyridine-connected2*H*-thiopyran derivatives (**4a-g)**were synthesized andscreened forlarvicidal,nematicidal, and antimicrobial activities. Compound**4e**exhibited larvicidal activity against second instar larvae with an LD50 value of0.8μg/mL.In addition,**4e**exhibited highnematicidal activity, with an LD50 value of 3.2μg/mL.Compounds**2e** (MIC: 4 μg/mL)and **2d** (MIC: 4 μg/mL) exhibitedhigh antibacterial activityagainst *Klebsiella pneumoniae*and *Escherichia coli*, respectively.Compounds**4b**(MIC: 0.25 μg/mL)and **4f**(MIC: 2 μg/mL) showed high antifungal activity against *Candida albicans*and *Microsporum audouinii,* respectively.Therefore, it can be suggested that compounds **2e, 2d, 4e, 4b,** and **4f**may be useful as lead molecules for the development of new classes ofdrugs withlarvicidal,nematicidal,and antimicrobial activities.

**Keywords** Larvicidal activity; Nematicidal activity; Antimicrobial activity; Piperidine; 2*H*-thiopyran derivatives

**Introduction**

Heterocyclic compounds,in particularpiperidines, are considered biologically important and are used as vitamins, hormones, and antibiotics[1].Piperidine nucleus is an important core of many drug molecules. Various pharmacological activities of piperidine and its analogs, including antihistamine, anticancer, and antibacterial properties, have been reported [2].Pyrrolidine and piperidine occupya unique place in the development of pharmacologically active substances by replacing the nucleus [3-4].Piperidine derivatives have been reported to possess significant pharmacological activities such as larvicidal [5],anti-inflammatory [6],local anesthetic [7], anticancer[8], and antimicrobial properties [9].

Thiopyran structures are consideredone of the most important classes of sulfur-containing heterocycles because of their usefulness in accessing certain natural and unnatural products. There has been an increased focuson sulfur-containing heterocyclic compounds because a broad range of biological activities related to the structure have been reported[10]. Thiopyran compounds shows antibacterial[11], anti-hyperplasia [12], anti-psychotic[13], analgesic, and anti-inflammatory [14] activities.

According to World Health Organization (WHO), one of the strategies to control Culex mosquitoes is to destroy their vectors or intermediate hosts. In addition, mosquito larvae can be controlled by insecticides [15-17], such as natural products and heterocyclic compounds. There is an urgent need to develop new insecticides that are environmentally-friendly and biodegradable and can target specific mosquitoes. Nematodes are the most numerous Metazoa on the earth and are essentially aquatic animals.Direct feeding by plant-parasitic nematodes can drastically decrease the uptake of water and nutrients by a plant.The best larvicides are natural products and heterocyclic compounds.For example, *N′*-*tert-*butyl-*N*,*N′*-dibenzoylhydrazine (RH-5849) was reported as the first nonsteroidal ecdysone agonist in the mid-1980s [18].In the present study,we synthesizeda series of pyridine-connectedpiperidinederivatives (**2a-g)** and 2*H*-thiopyran(**4a-g)**derivatives, and the compounds were screened forlarvicidal,nematicidal, and antimicrobial activities.

**Experimental**

**Materials**

All chemicals were purchased from Merck, Sigma-Aldrich and used without further purification. The solventswere dried and distilled prior to use. Merck pre-coated silica gel plates with a fluorescent indicator were used for analytical thin-layer chromatography (TLC). Flash column chromatography was performed using silica gel (Merck). Ethyl acetate (EtOAc)–hexane was used as the eluting solvent for TLC and column chromatography. Melting points were recorded in open capillary tubes and were uncorrected. The IR spectra (KBr) were recorded in KBr on a Shimadzu 8201pc (4000–400 cm-1). The ¹H NMR and 13C NMR spectra were recorded on a Bruker DRX-300 MHz. The elemental analysis (C, H, and N) wasconducted using an Elementer analyzer model (Varian EL III). The purity of the compounds was checked by TLC with silica gel plates.

***General procedure for synthesis of N-(2,6-Diphenyl-piperidin-4-ylidene)-N′-pyridin-2-yl methylene-hydrazine***(**2a-g**)

A mixture of compound **1a** (0.1mol) and 2-(hydrazonomethyl)pyridine (0.1 mol)in ethanol was heated and refluxed for 2h. After 2h, the product was confirmed by TLC (Hexane-EtOAc, 4:1, v/v). The final product was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc. The product was washed with distilled water to give the pure product of compound 2**a**.

Yellow color solid:mw 354; yield 81%; mp131ºC;IR(KBr,cm-1): 3045, 3010, 1671, 802, 712; 1H NMR (300MHz, DMSO-*d6*, *δ* (ppm): 11.15(1H, s, NH), 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1, *J*=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, *J*=7.4 Hz, Pyridine), 7.59–7.51(10H,m,Ph), 7.48(1H, s, -HC=N-),3.72 (2H, dd, *J*=13.7Hz,2C-H, 6C-H), 2.51 (2H,d, *J*=13.6Hz, 3C-Heq, 5C-Heq), 1.34(2H, d, 3C-Hax, 5C-Hax, *J*=13.4Hz); 13C NMR (75MHz, DMSO-*d6*, *δ* (ppm)): 168.3(1C, C=N), 164.2(1C, C=N), 153.2–134.2 (5C, Pyridine), 128.8–127.1(12C, ph), 46.8 (2C), 46.1(1C), 34.5 (1C); EI-Ms, m/z(Relative intensity %): 354.21 (M+, 26%); Elemental analysisC23H22N4, Calcd.:C, 77.94%; H, 6.26%; N, 15.81%; Found: C, 77.91%; H,6.21%; N, 15.80%.

***N-[2,6-Bis-(4-chloro-phenyl)-piperidin-4-ylidene]-N′-pyridin-2-ylmethylene-hydrazine*** (**2b**)

Yellow color solid, mw 423; yield 85%; mp 139ºC;IR(KBr, cm-1): 3082, 3020, 1681, 862, 831, 710; ¹H NMR (DMSO-d6), δ(ppm): 11.23(1H, s, NH), 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1, *J*=7.0Hz, Pyridine), 7.61(1H, dd, *J*=7.1Hz, *J*=7.4 Hz, Pyridine), 7.50(1H, s, -HC=N-) 7.47 (4H, d, *J*=7.2Hz, Ar), 7.38–7.22(4H,d, Ar), 3.79 (2H, dd,*J*=13.74Hz, *J*=13.74Hz, 2C-H, 6C-H), 3.57 (2H, d, *J*=11.34Hz 3C-Heq, 5C-Heq), 2.89 (2H, dd, *J*=11.46Hz, *J*=11.46Hz, 3C-Hax, 5C-Hax);13C NMR(DMSO-d6), δ(ppm): 166.1(C=N), 156.2 (C=N), 153.2–134.2(5C, Pyridine), 142.4–128.4 (10C, Ar), 131.8(2C, C-Cl), 61.8 (1C), 54.5(1C), 46.1(C5), 36.8(1C); EI-Ms, m/z (Relative intensity %): 423.44 (M+, 26%); Elemental analysis C23H20Cl2N4, Calcd.: C, 65.25%; H, 4.76%;N, 13.01%. Found: C, 65.46%; H, 4.72%; N, 13.10%.

***N-[2,6-Bis-(4-hydroxy-phenyl)-piperidin-4-ylidene]-N′-pyridin-2-ylmethylene-hydrazine***(**2c**)

Yellow color solid, mw 386; yield 80%;IR(KBr,cm-1): 3046, 1640, 1451, 828, 711; ¹H NMR (DMSO-d6), δ(ppm): ¹H NMR (DMSO-d6), δ(ppm): 11.71(1H, s, NH), 9.56(2H, s, OH), 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1 Hz J=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, *J*=7.4 Hz, Pyridine), 7.19(4H, d, *J*=7.82Hz, Ar), 6.70 (4H,d, *J*=7.80Hz, Ar), 7.56 (1H, s, -HC=N-), 3.74 (2H,dd, *J*=13.74Hz, *J*=13.10Hz, 2C-H, 6C-H), 3.32 (2H, d, *J*=11.67Hz, 3C-Heq, 5C-Heq), 2.24(2H, d, J=11.39Hz, 3C-Hax, 5C-Hax); 13C NMR (DMSO-d6), δ(ppm): 168.7 (C=N), 159.2 (2C, C-OH), 156.4 (1C, C=N), 153.2–134.2(5C, Pyridine), 133.8–117.4(10C, Ar), 62.6 (1C), 55.8(1C),46.1(1C), 36.8(1C); EI-Ms, m/z (Relative intensity %): 386.21 (M+, 21%); Elemental analysis C23H22N4O2, Calcd.: C, 71.48%; H, 5.74%; N, 14.50%;Found: C, 71.46%; H, 5.77%; N, 14.55%.

***N-[2,6-Bis-(4-nitro-phenyl)-piperidin-4-ylidene]-N′-pyridin-2-ylmethylene-hydrazine*** (**2d**)

Yellow color solid;mw 444;yield 74%; IR(KBr, cm-1):3079, 3021, 1684, 1531, 808, 721;¹H NMR (DMSO-d6), δ(ppm): 11.28(1H, s, NH), 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1Hz, J=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, *J* =7.4 Hz, Pyridine), 8.45(4H, d, *J*=7.2Hz, Ar), 7.29 (4H, d, *J*=7.2Hz, Ar), 3.79 (2H, d, *J*=13.7Hz, 2C-H, 6C-H), 3.35 (2H, d, *J*=11.6Hz, 3C-Heq, 5C-Heq), 7.72 (1H, s, -HC=N-), 2.11 (2H, d, *J*=11.39Hz 3C-Hax, 5C-Hax);13C NMR (DMSO-d6), δ(ppm):167.1 (1C, C=N), 157.7(1C, C=N), 153.2–149.1(5C, Pyridine), 146.0–124.0 (10C, Ar), 145.2 (2C, C-NO2), 61.8 (1C), 54.5(1C), 46.1(1C), 36.8(1C); EI-Ms, m/z(Relative intensity %): 444.14(M+, 26%);Elemental analysis C23H20N6O4, Calcd.: C, 62.16%; H, 4.54%; N, 18.91%;Found: C, 65.46%; H, 4.07%; N, 18.95%.

***N-[2,6-Bis-(4-methoxy-phenyl)-piperidin-4-ylidene]-N′-pyridin-2-ylmethylene-hydrazine*** (**2e**)

Yellow color solid; mw 414; yield 76%; IR (KBr,cm-1): 3085, 3023, 1671, 806, 729; ¹H NMR(DMSO-d6), δ(ppm): 11.23(1H, s,NH), 8.61(1H, d, *J*=7.4Hz, Pyridine), 7.90(1H,s, -HC=N-), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1, J=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, *J*=7.4 Hz, Pyridine), 7.22(4H, d, *J*=7.2Hz, Ar), 6.35(4H, d, *J*=7.2Hz, Ar), 3.85(6H, s, -OCH3), 3.72(2H, dd,*J*=13.7Hz, 2C-H, 6C-H), 3.49(2H, d, *J*=11.6Hz, 3C-Heq, 5C-Heq), 2.17 (2H, d, *J*=11.4Hz 3C-Hax, 5C-Hax); 13C-NMR (DMSO-d6), δ(ppm): 168.2(1C, C=N), 158.3(1C, C=N), 157.9 (2C, C-OCH3), 153.2–134.2(5C, Pyridine), 55.1(2C, OCH3), 132.2–114.4(10C, Ar), 61.8 (1C), 54.5(1C), 46.1(1C), 36.8(1C); EI-Ms, m/z(Relative intensity %): 414.12 (M+, 26%);Elemental analysis C25H26N4O2, Calcd.: C, 72.44%; H, 6.32%; N, 13.52%; Found: C, 72.46%; H, 6.07%; N, 13.95%.

***N-(2,6-Di-p-tolyl-piperidin-4-ylidene)-N′-pyridin-2-ylmethylene-hydrazine*** (**2f**)

Yellow color solid;mw 383; yield 81%; IR(KBr, cm-1):3094, 3013, 1651, 825, 710; ¹H NMR (DMSO-d6), δ(ppm): 11.26(1H,s, NH), 8.61(1H, d, *J*=7.4Hz, Pyridine), 7.93 (1H, s, HC=N-),7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1, *J*=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, *J*=7.4 Hz, Pyridine), 7.45(4H, d, *J*=7.2Hz, Ar), 7.29 (4H,d, *J*=7.2Hz, Ar), 3.72 (2H,dd, *J*=13.70Hz, 2C-H, 6C-H),3.36 (2H, d, *J*=11.6Hz, 3C-Heq, 5C-Heq), 2.28 (6H,s, CH3), 2.08 (2H, d, *J*=11.36Hz,3C-Hax, 5C-Hax); 13C-NMR(DMSO-d6), δ(ppm): 167.1(1C, C=N), 157.6 (1C, C=N), 179.1–146.5 (10C, Ar), 134.2–120.3(5C, Pyridine), 135.7(2C, C-CH3), 55.2 (2C, CH3), 61.8 (1C), 54.5 (1C), 46.1(1C), 36.8(1C)); EI-Ms, m/z(Relative intensity %): 382.04 (M+, 31%);Elemental analysis C25H26N4, Calcd.: C, 78.50%; H, 6.85%; N, 14.65%.Found: C, 78.46%; H, 6.07%; N, 14.95%.

***N-[2,6-Bis-(4-dimethylaminophenyl)-piperidin-4-ylidene]-N′-pyridin-2-ylmethylene-hydrazine*** (**2g**)

Yellow color solid,mw 441; yield 86%;IR (KBr, cm-1): 3046, 3010, 1625, 811, 726; ¹H NMR (DMSO-d6), δ(ppm): 11.28(1H, s, NH), 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.96 (1H, s, -HC=N-), 7.82 (1H, d, J=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1, *J*=7.0Hz, Pyridine), 7.61(1H, dd, *J*=7.1Hz, *J*=7.4 Hz, Pyridine), 7.19(4H, d, *J*=7.3Hz, Ar), 6.40(4H, d, *J*=7.4Hz Ar), 3.69 (2H, dd, *J*=13.2Hz, 2C-H, 6C-H), 3.53 (2H, d, *J*=11.4Hz, 3C-Heq, 5C-Heq), 3.14 (12H, s, -N(CH3)2), 2.31 (2H, d, *J*=11.22Hz, 3C-Hax, 5C-Hax); 13C NMR (DMSO-d6), δ(ppm): 168.6(1C, C=O), 159.4 (1C, C=N), 153.2–134.2 (5C, Pyridine), 132.6–113.5 (10C, Ar), 40.5(4C, N(CH3)2), 60.1 (1C), 54.2(1C), 46.6 (1C), 40.8 (2C, Ph-N(CH3)2), 37.3 (1C); EI-Ms, m/z(Relative intensity %): 441.03 (M+, 26%);Elemental analysisC27H32N6, Calcd.: C, 73.60%; H, 7.32%; N, 19.07%.Found: C, 73.46%; H, 7.07%; N, 19.95%.

***General procedurefor synthesis of N*-(2,6-Diphenyl-tetrahydro-thiopyran-4-ylidene)-*N*′-pyridin-2-ylmethylene-hydrazine**(**4b-4g**)

A mixture of compound **3a** (0.1mol) and 2-(hydrazonomethyl)pyridine (0.1 mol) in ethanol solvent was heated and refluxed for 2h. After 2h, the product was confirmed by TLC (Hexane-EtOAc, 4:1, v/v). The final product was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc. The product was washed with distilled water to give the pure product of compound **4a**.

Yellow color solid,mw 371; yield 88%; IR(KBr,cm-1): 760, 851,3037, 1625, 1752, 3018; ¹H NMR(DMSO-d6), δ(ppm): 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d,*J*=7.2Hz, Pyridine), 7.78(1H, s, -HC=N-), 7.71(1H, dd, *J*=7.1Hz, *J*=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, *J*=7.4Hz, Pyridine), 7.45–7.29 (10H,m, Ar-H), 3.61(2H, dd, *J*=13.73Hz, 2C-H, 6C-H), 3.44 (2H, d, *J*=11.5Hz, 3C-Heq, 5C-Heq), 2.16 (2H, d, *J*=11.4Hz, 3C-Hax, 5C-Hax,); 13C NMR(DMSO-d6), δ(ppm): 167.9(1C, C=N), 157.6(1C, C=N), 153.2–149.1(5C, Pyridine), 142.7–127.0 (12C, Ar), 60.7 (1C), 53.6(1C), 45.9(1C), 35.7(1C)); EI-Ms, m/z(Relative intensity %): 371.22 (M+, 34%); Anal. C23H21N3S, Calcd.: C, 74.36%; H, 5.70%; N, 11.31%.Found: C, 74.46%; H, 5.07%; N, 11.95%.

***N-[2,6-Bis-(4-chloro-phenyl)-tetrahydro-thiopyran-4-ylidene]-N′-pyridin-2-ylmethylene-hydra zine*** (**4b**)

Yellow color solid,mw 440; yield 82%; IR(KBr, cm-1): 3082, 3020, 1742, 1681, 862, 831, 671; ¹H NMR (DMSO-d6), δ(ppm): 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1, J=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, J=7.4 Hz, Pyridine), 7.56 (1H,s, -HC=N-),7.47(4H, d, J=7.3Hz, Ar),7.38 (4H, d, *J*=7.3Hz, Ar), 3.79 (2H, dd, *J*=13.74Hz, 2C-H,6C-H),3.57 (2H, d, *J*=11.34 Hz, 3C-Heq, 5C-Heq), 2.89 (2H, d, *J*=11.46Hz, 3C-Hax, 5C-Hax); 13C NMR(DMSO-d6), δ(ppm): 166.1(1C, C=N), 156.2 (1C, C=N), 153.2–149.1(5C, Pyridine), 142.4–128.4 (10C, Ar), 131.8(2C, C-Cl), 61.8 (1C), 54.5(1C), 46.1(1C), 36.8(1C); EI-Ms, m/z(Relative intensity %): 440.43 (M+, 26%); Elemental analysisC23H19Cl2N3S, Calcd.: C, 62.73%; H, 4.35%; N, 9.54%. Found: C, 62.46%; H, 4.07%; N, 9.95%.

***N-(2,6-Bis-(4-hydroxy-phenyl)-tetrahydro-thiopyran-4-ylidene)-N′-pyridin-2-ylmethylene-hydrazine*** (**4c**)

Yellow color solid,mw 403; yield 76 %; IR(KBr,cm-1): 3046, 1772, 1640, 1451, 828, 614; ¹H NMR (DMSO-d6), δ(ppm): ¹H NMR(DMSO-d6), δ(ppm): 9.56(s, 2H, OH), 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1Hz, *J*=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, J=7.4Hz, Pyridine), 7.46(1H –HC=N-), 7.19 (4H,d, *J*=7.3Hz, Ar), 6.70 (4H, d, *J*=7.3Hz, Ar), 3.74(2H, dd, *J*=13.7Hz, 2C-H,6C-H), 3.32(2H, d, *J*=11.6 Hz, 3C-Heq, 5C-Heq), 2.24 (2H, d, *J*=11.3Hz, 3C-Hax, 5C-Hax, 1H); 13C NMR(DMSO-d6), δ(ppm): 168.3 (1C, C=N), 159.2 (2C, C-OH), 156.4 (1C, C=N), 153.2–149.1(5C, Pyridine),133.8–127.1(10C, Ar), 62.6 (1C), 55.8(1C), 46.1(1C), 36.8(1C);EI-Ms, m/z (Relative intensity %): 403.13 (M+, 47%); Elemental analysisC23H21N3O2S, Calcd.: C, 68.46%; H, 5.25%; N, 10.41%. Found: C, 68.46%; H, 5.07%; N, 10.95%.

***N-[2,6-Bis-(4-nitro-phenyl)-tetrahydro-thiopyran-4-ylidene]-N′-pyridin-2-ylmethylene-hydra zine*** (**4d**)

Yellow color solid,mw 461; yield 86%; IR(KBr, cm-1): 3079, 3021, 1711, 1684, 1531, 808, 651; ¹H NMR (DMSO-d6), δ(ppm):8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1, J=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, J=7.4 Hz, Pyridine), 8.45(4H, d, *J*=7.8Hz, Ar), 7.40(1H, s, -HC=N-), 7.29 (4H, d, *J*=7.8Hz,Ar), 3.79 (2H, dd, *J*=13.70Hz, 2C-H,6C-H), 3.35 (2H, d, *J*=11.67Hz, 3C-Heq, 5C-Heq), 2.11 (2H, d, *J*=11.39Hz, 3C-Hax, 5C-Hax);13C NMR (DMSO-d6),δ(ppm): 167.1 (1C, C=N), 157.7(1C, C=N), 153.2–149.1(5C, Pyridine), 146.0–24.0 (10C, Ar), 145.2 (2C-NO2), 61.8 (1C), 54.5(1C), 46.1(1C), 36.8(1C); EI-Ms, m/z(Relative intensity %): 461.36 (M+, 51%);Elemental analysis C23H19N5O4S, Calcd.: C, 59.86%; H, 4.15%; N, 15.18%; S, 6.98%. Found: C, 59.46%; H, 5.07%; N, 15.95%; S,6.90%.

***N-[2,6-Bis-(4-methoxy-phenyl)-tetrahydro-thiopyran-4-ylidene]-N′-pyridin-2-ylmethylene-hy drazine*(4e)**

Yellow color solid,mw 432; yield 89%; IR (KBr,cm-1): 3085, 1732, 1671, 806, 661; ¹H NMR (DMSO-d6), δ(ppm):8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71 (1H, dd, *J*=7.1, *J*=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, J=7.4 Hz, Pyridine), 7.22(4H, d, *J*=7.1Hz,Ar), 6.35 (4H, d, *J*=7.1Hz, Ar), 7.43(1H, s,-HC=N-), 3.85 (6H, s, -OCH3), 3.72 (2H, dd, *J*= 13.7Hz, 2C-H, 6C-H), 3.49(2H, d, *J*=11.6Hz, 3C-Heq, 5C-Heq), 2.17 (2H, d,*J*=11.4Hz, 3C-Hax, 5C-Hax); 13C NMR(DMSO-d6), δ(ppm): 168.2(1C, C=N), 158.3(1C, C=N), 157.9 (2C-OCH3), 153.2–149.1(5C, Pyridine), 132.2–114.4(10C, Ar), 61.8(1C), 55.8 (1C-OCH3), 54.5(1C), 46.1(1C), 36.8(1C); EI-Ms, m/z(Relative intensity %): 432.11 (M+, 49%); Elemental analysisC25H25N3O2S,Calcd.: C, 69.58%; H, 5.84%; N, 9.74%; O, 7.41%; S, 7.43%. Found: C, 65.46%; H, 5.07%; N, 5.95%; S, 4.58%.

***N-(2,6-Di-p-tolyl-tetrahydro-thiopyran-4-ylidene)-N′-pyridin-2-ylmethylene-hydrazine (4f)***

Yellow color solid,mw 400; yield 84%; IR(KBr, cm-1): 3094, 1762, 1651, 825, 671; ¹H NMR (DMSO-d6), δ(ppm): 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1Hz, *J*=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, *J*=7.4 Hz, Pyridine), 7.45(4H, d, *J*=7.4Hz,Ar), 7.29 (4H, d, *J*=7.4Hz, Ar), 7.45 (1H, s, -HC=N-), 3.72 (2H, dd, *J*=13.7Hz, 2C-H, 6C-H), 3.36 (2H, d, *J*=11.6Hz, 3C-Heq, 5C-Heq), 2.28 (6H, s, CH3), 2.08 (2H, d, *J*=11.3Hz, 3C-Hax, 5C-Hax); 13C NMR(DMSO-d6), δ(ppm): 167.1(1C, C=N), 157.6 (1C, C=N), 179.1–153.2 (10C, Ar), 149.1–124.0(5C, Pyridine), 135.7(2C, -CH3), 61.8 (1C), 54.5 (1C), 46.1(1C), 36.8(1C) (2C-CH3); EI-Ms, m/z(Relative intensity %):400.12 (M+, 32%);Elemental analysisC25H25N3S, Calcd.: C, 75.15%; H, 6.31%; N, 10.52%; S,8.03%. Found: C, 75.18%; H, 6.37%; N, 10.55%; S, 8.10%.

***N*-(2,6-Bis-4-dimethylaminophenyl-tetrahydro-thiopyran-4-ylidene)-*N*′-pyridin-2-ylmeth ylene-hydrazine** (**4g**)

Yellow color solid,mw 458; yield 88%; IR (KBr, cm-1): 3046, 1782, 1625, 811, 664; ¹H NMR (DMSO-d6), δ(ppm): 8.61 (1H, d, *J*=7.4Hz, Pyridine), 7.82 (1H, d, *J*=7.2Hz, Pyridine), 7.71(1H, dd, *J*=7.1Hz, *J*=7.0Hz, Pyridine), 7.61 (1H, dd, *J*=7.1Hz, J=7.4Hz, Pyridine), 7.46 (1H, s, -HC=N-), 7.19(4H, d, *J*=7.1Hz, Ar), 6.40 (4H, d, *J*=7.2Hz, Ar), 3.69 (2H, dd, *J*=13.2Hz, 2C-H,6C-H), 3.53 (2H, d, *J*=11.4Hz, 3C-Heq, 5C-Heq), 3.14(12H, s, -N(CH3)2), 2.31(2H, d, *J*=11.2Hz, 3C-Hax, 5C-Hax); 13C NMR (DMSO-d6), δ(ppm): 168.6(1C, C=N), 159.4 (1C, C=N), 153.2–134.2(5C, Pyridine), 132.6–113.5(10C, Ar), 60.1(1C), 54.2(1C), 46.6 (1C), 40.8 (4C, Ph-N(CH3)2), 148.2(2C, C-N(CH3)2), 37.3 (1C);EI-Ms, m/z(Relative intensity %): 458.28 (M+, 16%); Elemental analysisC27H31N5S, Calcd.: C, 70.86%; H, 6.83%; N, 15.30%.Found: C, 70.46%; H, 6.07%; N, 15.95%.

**Biological activity**

***Larvicidal activity***

Larvicidal screening was performed by the method described previously[19][20].The synthesized compounds were tested against urban mosquito larvae (*Culex quinquefasciatus*) by using the standard bio assay protocol. The eggs of *C. quinquefasciatus* were obtained from drainage system.The eggs were placed in clean water at room temperature for hatching. The larval development was monitored for seven days. The second stage larvae were collected at the tip of a pasture pipette, placed on a cotton bud to remove excess water, and then transferred to the test vial. Larval mortality was observed using various concentrations of the synthesized compounds (10, 20, 30, and 40 μg/mL). The susceptibility or resistance of the mosquito larvae (*C.quinquefasciatus*) to the selected concentration of synthesized compounds (**2a-g**and**4a-g**)was determined by the standard bioassay protocol (WHO, 1981).

***Nematicidal activity***

Nematicidal activity was evaluated using juvenile nematodes of *Meloidogyne javanica*[19][20].The assay system was prepared with 2 mL Milli Q water containing different concentrations of seaweed extracts (10, 20, 30, and 40 mg/mL) in glass tubes. Different concentrations of solutions were prepared. The treated and control nematodes were held under the same conditions as used for colony maintenance.Ten juveniles of *M.javanica* were transferred to test, positive control (with 2% methanol), and negative (without vehicle) control tubes. Mortality was observed under a zoom stereomicroscope after 24 h of exposure.

***In vitroantimicrobial screening***

Antibacterial activity: The compounds **2a-g**, **3a-g,** and **4a-g** were evaluated against*Staphylococcus aureus* (ATCC-25923), *Klebsiella pneumoniae*(recultured), *Escherichia coli*(ATCC-25922), and *Pseudomonas aeruginosa* (ATCC-27853) bacterial strains according to the method described previously[20-21] [22-23].

***In vitro*antifungal screening:**The compounds **2a-g, 3a-g,** and **4a-g** were evaluated against*Aspergillus niger,Candida albicans, Microsporum audouinii,* and *Cryptococcus neoformans* (recultured) fungal strains according to the method described previously[22-23][24-25].The minimum inhibitory concentration (MIC) of all the synthesized compounds was determined.

**Statistical analysis**

IC50 (effective concentration required for 50% inhibition of mycelial growth) of each compound was calculated by Probit analysis. The data were analyzed using statistical analysis system software.

**Results and Discussion**

Chemistry: Compounds **1a-g**were synthesized according to the method described previously [19][24].Compounds **3a-g**were prepared by the method described previously [21] [25].Compounds **2a-g** and **4a-g** were synthesized by condensation method. The physicochemical data of compounds **2a-g** and **4a-g** are shown in experimental section. The formation of all the compounds was confirmed by recording the IR, ¹H NMR, 13C NMR spectra, and elemental analyses. The IR spectra of compounds**2a-g** showed absorption bands at 3045–3094, and 1625–1684cm-1 corresponding to the NH and C=N groups, respectively. The ¹H NMR spectra of compounds **2a-g** showed a sharp singlet at δ11.15–11.71 forNH proton and a singlet at δ 7.48–7.96 for HC=N- proton. The 13C NMR spectra of compounds**2a-g** showed characteristic peaks at δ 156.2–164.2 and δ166.1–168.7 ppm corresponding to C=N and -HC=N- carbons, respectively. The IR spectra of compounds**4a-g** showed absorption bands at 1711–1782, 1625–1684, and 614–760 cm-1 corresponding toC=N, HC=N, and C-S-C groups,respectively. The ¹H NMR spectra of compounds **4a-g** showed signalsat δ 7.40–7.78, which confirmed the presence of HC=N- proton. The 13C NMR spectra of compounds**4a-g** showed characteristic peaks at δ 166.1–168.6and δ 156.2–159.4ppm corresponding to C=N and -HC=N- carbons, respectively. In addition, mass spectra showed that the molecular ion signals matched the expected molecular weights of all the synthesized compounds**.**

**Larvicidal activity:** Compounds **2a-g** and **4a-g** were screened for larvicidal activity. Compounds **2a-g**exhibited lowerlarvicidal activity than compounds **4a-g.** Compound**4e** showed higher larvicidal activitythan other compounds and produced 100% mortality (20 µg/mL), with an LD**50** value of 0.8µg/mL. Compounds **4c, 4d, 4f,** and **4g**showed moderateactivity withLD50 valuesof 5.7, 1.2, 8.6, and 6.0 μg/mL, respectively. The values are summarized in table 1.

**Nematicidal activity:** Compounds **2a-g** and **4a-g** were screened for nematicidal activity, and compounds **2a-g**exhibited lowernematicidal activity than compounds **4a-g**. The screening was carried out atroom temperature and the toxicity of the compounds was measured. Compound **4e**showed higher nematicidal activity than other compounds and produced 100% mortality at 20 µg/mL, with an LD50 value of 3.2μg/mL. Compounds **4c**, **4d,4f,**and **4g**showed moderateactivity withLD50 valuesof 7.8, 5.5, 4.1, and 4.7 μg/mL, respectively. The values are summarized in table 2.

**Antibacterial activity:** The synthesized compounds **2a-g** and **4a-g** were screened for antibacterial activity against various bacterial species. Compound **2d** (MIC: 4 μg/mL)showed high antibacterialactivity against *E. coli*. Compound **2e** (MIC: 4 μg/mL) showed higherantibacterial activity against *K. pneumoniae*than ciprofloxacin (MIC: 16 μg/mL). The MIC values are summarized in table 3.

**Antifungal activity:** Compounds **2a-g** and **4a-g** were screened for antifungal activity against various fungal spices. Compound **4b (**MIC: 0.25 μg/mL)exhibited high antifungalactivity against *C.albicans.*Compound **4e** (MIC: 0.5 μg/mL) showed equipotent activity against *C. albicans.* Compound **4f**(MIC: 2 μg/mL) showed higher antifungal activity against *M. audouinii*than clotrimazole (MIC: 4 μg/mL). The antifungalactivity values are given in table [4](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VKY-4NDDKV6-2&_user=10&_coverDate=01%2F31%2F2008&_rdoc=6&_orig=browse&_srch=doc-info(%23toc%236135%232008%23999569998%23678674%23FLA%23display%23Volume)&_cdi=6135&_sort=d&_docanchor=&_ct=28&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&_fmt=full&md5=ddd65ee7d2f13515ed6330c542d3e75b#tbl4#tbl4).

**Structure-activity relationship**

The structure-activity relationship of target compound and the standard is shown in Fig. 1.Compound **4e**exhibited high larvicidal and nematicidal activitiesowing to the presence of pyridine with thiopyranmoiety as well as CH3O group. The low larvicidal and nematicidal activitiesof compounds 2**a-g**are due to the presence of pipridine with pyridine rings.

The high antibacterial activity of compound **2e** against *K.pneumoniae*is due to presence of pyridine with thiopyran moiety and CH3O group (MIC: 4 μg/mL). Thepresence of pyridine with thiopyran moiety and NO2 group is responsible for the high antibacterial activity ofcompound**2d** against *E.coli* (MIC: 4 μg/mL).The 4-substituted phenyl ring acts as a lipophilic domain, and the NH group presentin piperidine act as a hydrogen bonding domain. It can be suggested that piperidine ring isan essentialpharmacophore for antibacterial activity.

The presence of thiopyranmoiety with Cl-substituted benzene groups was responsible for the high antifungal activity of compound **4b** against *C.albicans* (MIC: 0.25 μg/mL). Compound **4f**showed highactivity against *M.audouinii*owing to the presence of thiopyranmoiety with –N(CH3)2 substituted benzene groups (MIC: 2 μg/mL).Notably,the thiopyran moiety showed significant antifungal activities.

**Conclusion**

Compounds **2a-g**and**4a-g** were synthesized and screened for larvicidal, nematicidal, and antimicrobial activities.Among the synthesized compounds,**4e** showed highlarvicidal and nematicidal activities. Compounds**2e** and **2d**showed high antibacterial activityagainst *K.pneumoniae* and *E.coli*, respectively. Compound **4b** exhibited high antifungalactivity against *C.albicans*. Thus, compounds**2e, 2d, 4e, 4b,** and **4f** can be used as leadmolecules for the developmentof larvicidal, nematicidal, and antimicrobial agents in future.

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**Conflict of interest**

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**Scheme 1.** Synthesis of 2-thio-imidazolidin-4-one derivatives **2a-g,** and **4a-g**

|  |
| --- |
| 1a, 2a, 3a, 4a:R= -H |
| 1b, 2b, 3b, 4b: R= -Cl |
| 1c, 2c, 3c, 4c:R =-HO |
| 1d, 2d, 3d, 4d: R = -NO2 |
| 1e,2e, 3e, 4e: R =-OCH3 |
| 1f, 2f, 3f, 4f: R = -CH3 |
| 1g, 2g, 3g, 4g: R = -N(CH3)2 |







**Fig.1**Structure-antimicrobial activity relationship

**Table 1**Larvicidal profile of compounds **(2a-g** and **4a-g)** on second instar larvae of Culex sp.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Comp.No | Mortality (%)Room temp | | | | LD50  (μg /mL) |
| Concentration(μg /mL)a | | | |
| 10 | 20 | 30 | 40 |
| ***2a*** | 30.4 ± 1.2 | 64.5 ± 1.5 | 72.3 ± 0.4 | 100 ± 0.0 | 17.4 |
| **2b** | 50.3 ± 1.7 | 66.3 ± 1.4 | 82.5 ± 1.0 | 100 ± 0.0 | 10.2 |
| **2c** | 39.2 ± 1.3 | 63.9 ± 1.0 | 78.0 ± 0.7 | 100 ± 0.0 | 16.8 |
| **2d** | 40.9 ± 1.8 | 61.3 ± 1.2 | 84.7 ± 1.0 | 100 ± 0.0 | 15.7 |
| **2e** | 32.2 ± 1.3 | 42.5 ± 1.1 | 69.4 ± 1.2 | 85.6 ± 2.1 | 24.3 |
| **2f** | 41.1 ± 0.7 | 51.4 ± 1.0 | 60.5 ± 1.0 | 82.4 ± 1.1 | 19.5 |
| **2g** | 32.0 ± 0.6 | 47.4 ± 1.6 | 81.6 ± 0.5 | 100 ± 0.0 | 21.3 |
| **4a** | 31.5 ± 0.8 | 62.0 ± 0.5 | 100 ± 0.0 | - | 16.6 |
| **4b** | 20.4 ± 0.3 | 40.4 ± 1.0 | 56.8 ± 0.0 | 75.7 ± 0.3 | 26.5 |
| **4c** | 62.4 ± 1.3 | 81.5 ± 1.4 | 100± 0.0 | - | 5.7 |
| **4d** | 80.3 ± 1.4 | 100± 0.0 | - | - | 1.2 |
| **4e** | 88.1 ± 1.9 | 100± 0.0 | - | - | 0.8 |
| **4f** | 57.4 ± 0.5 | 84.7 ± 1.0 | 100 ± 0.0 | - | 8.6 |
| **4g** | 61.3 ± 1.1 | 78.0 ± 1.1 | 100 ± 0.0 | - | 6.0 |
| **Positive control** | 43.1 ± 0.3 | 56.7 ± 0.1 | 61.8 ± 1.1 | 100 ± 0.0 | 15.2 |
| **Negative control** | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 |  |

a Valuesare the means of three replicates ± SD.

Positive control: *N*-*tert-*butyl-*N*,*N′*- dibenzoylhydrazine; Negative control: Dimethyl sulfoxide (DMSO)

**Table 2**Nematicidal activity of synthesized compounds **(2a-g** and **4a-g**)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Comp.No. | Mortality (%)Room temp | | | | LD50 |
| Concentration(μg /mL)a | | | |
| 10 | 20 | 30 | 40 |
| **2a** | 48.3 ± 3.5 | 62.0 ± 2.9 | 74.4 ± 2.4 | 88.0 ± 0.6 | 11.8 |
| **2b** | 40.2 ± 1.6 | 57.6 ± 2.0 | 72.2 ± 1.7 | 85.0 ± 0.0 | 15.5 |
| **2c** | 36.1 ± 2.0 | 59.5 ± 3.1 | 64.7 ± 2.0 | 100 ± 0.0 | 17.6 |
| **2d** | 48.8 ± 4.4 | 63.0 ± 3.0 | 81.0 ± 3.6 | 100 ± 0.0 | 11.2 |
| **2e** | 41.0 ± 3.1 | 59.2 ± 1.6 | 80± 1.0 | 100 ± 0.0 | 17.7 |
| **2f** | 48.6 ± 2.0 | 60 .2 ± 3.1 | 100 ± 0.0 | - | 12.5 |
| **2g** | 44.5 ± 4.2 | 69.1 ± 1.9 | 81.9 ± 2.9 | 100 ± 0.0 | 20.0 |
| **4ª** | 54.1 ± 2.1 | 66.7 ± 2.1 | 81.3 ± 1.5 | 100 ± 0.0 | 8.4 |
| **4b** | 51.0± 1.9 | 72.6 ± 2.5 | 84.5 ± 1.0 | 100 ± 0.0 | 9.5 |
| **4c** | 56.7± 0.3 | 62.0 ± 1.2 | 100± 0.0 | - | 7.8 |
| **4d** | 61.3 ± 2.5 | 87.6 ± 1.0 | 100 ± 0.0 | - | 5.5 |
| **4e** | 87.8 ± 2.5 | 100 ± 0.0 | - | - | 3.2 |
| **4f** | 72.4 ± 2.5 | 83.8 ± 2.5 | 100 ± 0.0 | - | 4.1 |
| **4g** | 69.2 ± 2.5 | 86.5 ± 2.5 | 100 ± 0.0 | - | 4.7 |
| **Positive control** | 40.9 ± 1.1 | 57.8 ± 1.2 | 80.2 ± 1.1 | 100± 0.0 | 14.2 |
| **Negative control** | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 |  |

a Valuesare the means of three replicates ± SD.

Positive control: (-)-Pinidinol; Negative control: Dimethyl sulfoxide (DMSO)

**Table3A**ntibacterial screening: MIC in μg/mL

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Compound | gram-positive |  | gram-negative | | |
| *S.aureus* | *E.coli* | *P. aeruginosa* | *K.pneumoniae* |
| ***2a*** | 32 | >100 | >100 | 64 |
| **2b** | 32 | 32 | 32 | 32 |
| **2c** | 32 | 32 | 32 | 32 |
| **2d** | 4 | 4 | 8 | 64 |
| **2e** | 8 | 64 | >100 | 4 |
| **2f** | 32 | 32 | 32 | 32 |
| **2g** | 4 | 16 | 16 | 32 |
| **4a** | 64 | >100 | >100 | >100 |
| **4b** | 64 | >100 | >100 | >100 |
| **4c** | 64 | >100 | >100 | >100 |
| **4d** | 64 | >100 | >100 | 64 |
| **4e** | 64 | 64 | 64 | 64 |
| **4f** | 64 | 64 | 64 | 64 |
| **4g** | 64 | 64 | 64 | 64 |
| **Ciprofloxacin** | 4 | 8 | 8 | 16 |

MIC (μg/mL):minimum inhibitory concentration

**Table 4** Antifungal screening: MIC in μg/mL

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Compound | *A.niger* | *C. albicans* | *M.audouinii* | *Cr. neoformans* |
| ***2a*** | >100 | >100 | >100 | >100 |
| **2b** | 32 | 4 | 32 | >100 |
| **2c** | >100 | >100 | >100 | >100 |
| **2d** | 64 | >100 | >100 | >100 |
| **2e** | 64 | >100 | >100 | >100 |
| **2f** | 64 | 64 | >100 | >100 |
| **2g** | >100 | 64 | >100 | >100 |
| **4a** | >100 | 32 | >100 | >100 |
| **4b** | >100 | 0.25 | 32 | 32 |
| **4c** | 16 | 32 | >100 | 16 |
| **4d** | 16 | 8 | 64 | 16 |
| **4e** | 16 | 0.5 | >100 | >100 |
| **4f** | 32 | 32 | 2 | 64 |
| **4g** | 16 | 32 | 16 | 8 |
| **Clotrimazole** | 1 | 0.5 | 4 | 2 |

MIC (μg/mL): Minimum inhibitory concentration

**Graphical abstract**

**Synthesis of novel pyridine-connected piperidine and 2*H*-thiopyran derivatives and their larvicidal, nematicidal, and antimicrobialactivities**

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