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Synthesis of Novel Pyridine-connected Piperidine and 2*H*-thiopyran Derivatives and their Larvicidal, Nematicidal, and Antimicrobial Activities

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Abstract. A series of novel pyridine-connected piperidine derivatives (**2a-g)** and pyridine-connected 2*H*-thiopyran derivatives (**4a-g)** were synthesized and evaluated for larvicidal, nematicidal, and antimicrobial activities. Compound **4e** exhibited larvicidal activity against second instar larvae with an LD_{50} value of 0.8 µg/mL. In addition, **4e** was most effective against root knot nematode *Meloidogyne javanica***,** with an LD_{50} value of 3.2 µg/mL. Compounds **2e** (MIC: 4 µg/mL) and **2d** (MIC: 4 µg/mL) exhibited high antibacterial activity against *Klebsiella pneumonia,* 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, overall activity profiles envisages that compounds **2e, 2d, 4e, 4b,** and **4f** could be employed for the development of new classes of drugs with larvicidal, nematicidal, and antimicrobial activities.
Keywords: Larvicidal activity; Nematicidal activity; Antimicrobial activity; Piperidine; 2*H*-Thiopyran derivatives.

Resumen. Se sintetizaron una serie de nuevos derivados de piperidina conectados con piridina (**2a-g**) y derivados de 2*H*-tiopirano conectados con piridina (**4a-g**) para evaluar las actividades larvicidas, nematicidas y antimicrobianas. El compuesto **4e** exhibió actividad larvicida contra larvas de segundo estadio con un valor de LD_{50} de 0.8 µg / mL. Además, **4e** fue más efectivo contra el nematodo de nudo de la raíz *Meloidogyne javanica*, con un valor de LD_{50} de 3.2 µg / mL. Los compuestos **2e** (MIC: 4 µg / ml) y 2d (MIC: 4 µg / ml) mostraron una alta actividad antibacteriana contra la neumonía de *Klebsiella* y *Escherichia coli*, respectivamente. Los compuestos **4b** (MIC: 0.25 µg / ml) y **4f** (MIC: 2 µg / ml) mostraron una alta actividad antifúngica contra *Candida albicans* y *Microsporum audouinii*, respectivamente. Por lo tanto, los perfiles de actividad general prevén que los compuestos **2e**, **2d**, **4e**, **4b** y **4f** podrían emplearse para el desarrollo de nuevas clases de fármacos con actividades larvicidas, nematicidas y antimicrobianas.
Palabras clave: Actividad larvicida; Actividad nematicida; Actividad antimicrobiana; Piperidina; Derivado 2H-Tiopirano.

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Introduction

Heterocyclic compounds, in particular piperidines, are considered biologically important and are used as vitamins, hormones, and antibiotics [1]. Piperidine nucleus is an important core of many drug molecules. Diverse pharmacological activities of piperidine and its analogs, including antihistamine, anticancer, and antibacterial properties, have been reported [2]. Pyrrolidine and piperidine occupy a 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 considered as one 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 focus on 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.

Mosquito larvae can be controlled by insecticides [15-17] and the best larvicides are natural products and heterocyclic compounds. For instance, *N'*-*tert*-butyl-*N*,*N'*-dibenzoylhydrazine (RH-5849) was reported as the first nonsteroidal ecdysone agonist in the mid-1980s [18]. The mosquito borne diseases not only cause high levels of morbidity and mortality but also cause great economic loss to health care. Recent estimates from the World Health Organization (WHO) evidenced that malaria accounts for at least 500 million infections and 3 million deaths annually. The prevalence of dengue fever has increased over the last 50 years, and over 2 billion people are under risk in more than 100 countries [19]. In the wake of this, there is an urgent need to develop new insecticides that are environmentally-friendly and biodegradable and can target specific mosquitoes.

Thousands of crops and trees are susceptible, and the disease caused by phytonematodes results in huge agricultural loss annually [20]. Levamisole is used to treat parasitic worm infections [21]. Plants infested by nematodes show retarded growth and development, as well as loss in the quality and quantity of the harvest. Due to environmental problems, nematicides, such as dibromochloropropane (DBCP) and ethylenedibromide (EDB) were withdrawn from the market. Howbeit, some simple coumarins, furocoumarins, and dicoumarolums, display excellent nematicidal activity, and their skeletons have drawn interest for the development of efficient nematicides [15].

Considering these observations, in the present study, we synthesized a series of pyridine-connected piperidine derivatives (**2a-g)** and 2*H*-thiopyran (**4a-g)** derivatives, and screened them for larvicidal, nematicidal, and antimicrobial activities.

Experimental

Materials

All chemicals were purchased from Merck, Sigma-Aldrich and used without further purification. The solvents were 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). 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 ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 MHz. The elemental analysis (C, H, and N) was conducted 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 2-(hydrazonomethyl)pyridine (HMP)

A mixture of pyridine 2-aldehyde (0.1 mol) and hydrazine hydrate (0.1 mol) in ethanol was heated at refluxed for 5 min. After completed reaction the solid material was filtered and washed with distilled water. The product was confirmed by TLC (hexane-EtOAc, 4:1, v/v). The product (HMP) was purified by flash column chromatography.

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General procedure for synthesis of (E)-2-(((2,6-diphenylpiperidin-4-ylidene)hydrazono) methyl)pyridine (2a-g)

A mixture of compound **1a** (0.1 mol) and 2-(hydrazonomethyl)pyridine (0.1 mol) in ethanol was heated at refluxed for 2 h. The product **2a** was purified by flash column chromatography on silica gel using hexane/EtOAc.

Yellow solid: yield 81%. mp 129-131 ºC; IR (KBr,cm^{-1}): 3045, 3010, 1671, 802, 712; ^{1}H NMR (300 MHz, DMSO-*d6*): δ 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, aryl), 7.48 (1H, s, -HC=N-), 3.72 (2H, dd, *J* = 13.7Hz, *J* = 13.10Hz, 2C-H, 6C-H), 2.51 (2H, dd, *J* = 13.6Hz, *J* = 13.04 Hz, 3C-Heq, 5C-Heq), 1.34 (2H, dd, *J* = 13.4Hz, *J* = 13.08Hz, 3C-Hax, 5C-Hax); ^{13}C NMR (75MHz, DMSO-*d*$_6$) δ: 168.3 (1C, C=N), 164.2 (1C, C=N), 153.9 (1C), 146.7 (1C), 136.9 (1C), 128.8–127.1 (12C, aryl), 126.1 (1C), 121.0 (1C), 46.8 (2C), 46.1 (1C), 34.5 (1C); EI MS *m/z* (rel.int): 354 [M]$^+$ (26), 277 (13), 264 (24), 244 (24), 237 (100), 161 (11), 85 (10), 73 (21), 44 (18); Anal C 77.91%, H 6.21%, N 15.80%, Calcd for $C_{23}H_{22}N_4$, C 77.94%, H 6.26%, N 15.81%.

(*E*)-2-(((2,6-Bis(4-chlorophenyl)piperidin-4-ylidene)hydrazono)methyl)pyridine (**2b**). Yellow solid: yield 85%; mp 137-139 ºC; IR(KBr, cm^{-1}): 3082, 3020, 1681, 862, 831, 710; ^{1}H NMR (DMSO-d$_6$): δ 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* = 7.0 Hz, 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, aryl), 7.43-7.39 (2H, d, *J* = 4.8 Hz, aryl), 7.48-7.44 (2H, d, *J* = 4.8Hz, aryl), 3.79 (2H, dd, *J* = 13.7Hz, *J* = 11.34 Hz, 2C-H, 6C-H), 3.57 (2H, dd, *J* = 13.4 Hz, *J* = 11.34 Hz, 3C-Heq, 5C-Heq), 2.89 (2H, dd, *J* = 11.46Hz, *J* = 11.46 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR(DMSO-d$_6$): δ 166.1 (1C, C=N), 156.2 (1C, C=N), 152.4 (1C), 146.4 (1C), 136.5 (1C), 126.3 (1C), 121.3 (1C), 128.9 (4C), 128.0 (4C), 140.5 (2C), 131.8 (2C, C-Cl), 61.8 (1C), 54.5 (1C), 46.1 (1C), 36.8 (1C); EIMS *m/z* (rel.int): 423 [M]$^+$ (26), 346 (14), 333 (18), 318 (23), 306 (32), 237 (100), 161 (16), 85 (28), 73 (19), 44 (10); Anal C 65.46%, H 4.72%, N 13.10%, Calcd for $C_{23}H_{20}Cl_2N_4$, C 65.25%, H 4.76%, N 13.01%.

(*E*)-4,4'-(4-((Pyridin-2-ylmethylene)hydrazono)piperidine-2,6-diyl)diphenol (**2c**). Yellow solid: yield 80%; mp 145-149 ºC; IR (KBr, cm^{-1}): 3046, 1640, 1451, 828, 711; ^{1}H NMR (DMSO-d$_6$): δ 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* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.19-7.10 (4H, d, *J* = 8.2 Hz, aryl), 6.70-6.67 (4H, d, *J* = 7.80 Hz, aryl), 7.56 (1H, s, -HC=N-), 3.74 (2H, dd, *J* = 13.74 Hz, *J* = 13.10 Hz, 2C-H, 6C-H), 3.32 (2H, dd, *J* = 13.62 Hz, *J* = 11.67 Hz, 3C-Heq, 5C-Heq), 2.24 (2H, dd, *J* = 13.68 Hz, *J* = 11.39 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR (DMSO-d$_6$): δ 168.7 (1C, C=N), 159.2 (2C, C-OH), 156.4 (1C, C=N), 153.2 (1C), 147.0 (1C), 136.1 (1C), 135.9 (2C), 128.3 (4C), 126.4 (1C), 121.3 (1C), 115.6 (4C), 62.6 (1C), 55.8 (1C), 46.1 (1C), 36.8 (1C); EIMS *m/z* (rel.int): 386 [M]$^+$ (21), 309 (18), 231 (27), 269 (17), 237 (100), 161 (21), 85 (17), 73 (20), 44 (11); Anal C 71.46%, H 5.77%, N 14.55%, Calcd for $C_{23}H_{22}N_4O_2$, C 71.48%, H 5.74%, N14.50%.

(*E*)-2-(((2,6-Bis(4-nitrophenyl)piperidin-4-ylidene)hydrazono)methyl)pyridine (**2d**). Yellow solid: yield 74%; mp 155-159 ºC; IR (KBr, cm^{-1}): 3079, 3021, 1684, 1531, 808, 721; ^{1}H NMR (DMSO-d$_6$): δ 11.28 (1H, s, NH), 8.61 (1H, d, *J* = 7.4Hz, pyridine), 8.45 (4H, d, *J* = 7.2 Hz, aryl), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.72 (1H, s, -HC=N-), 7.71 (1H, dd, *J* = 7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.29 (4H, d, *J* = 7.2 Hz, aryl), 3.79 (2H, dd, *J* = 13.7 Hz, *J* = 13.8 Hz, 2C-H, 6C-H), 3.35 (2H, dd, *J* = 13.8 Hz, *J* = 11.6 Hz, 3C-Heq, 5C-Heq), 2.11 (2H, d, *J* = 11.39 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR (DMSO-d$_6$): δ 167.1 (1C, C=N), 157.7 (1C, C=N), 153.7 (1C), 148.4 (2C), 146.4 (1C), 145.2 (2C, C-NO$_2$), 136.1 (1C), 126.7 (1C), 125.9 (4C), 124.8 (4C), 121.5 (1C), 61.8 (1C), 54.5 (1C), 46.1 (1C), 36.8 (1C); EIMS *m/z* (rel. int): 444 [M]$^+$ (26), 367 (16), 354 (10), 339 (28), 327 (32), 237 (100), 161 (27), 85 (19), 73 (15), 44 (5); Anal C 62.16%, H 4.57%, N 18.92%, Calcd for $C_{23}H_{20}N_6O_4$, C 62.16%, H, 4.54%, N 18.91%.

(*E*)-2-(((2,6-Bis(4-methoxyphenyl)piperidin-4-ylidene)hydrazono)methyl)pyridine (**2e**). Yellow solid: yield 76%; mp 154-158 ºC; IR (KBr, cm^{-1}): 3085, 3023, 1671, 806, 729; ^{1}H NMR(DMSO-d$_6$): δ 11.23 (1H, s, NH), 8.61 (1H, d, *J* = 7.4Hz, pyridine), 7.90 (1H, s, -HC=N-), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.71

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(1H, dd, *J* = 7.1 Hz, J = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.22-7.20 (4H, d, *J* = 7.2Hz, aryl), 6.35-6.31 (4H, d, *J* = 7.2 Hz, aryl), 3.85 (6H, s, -OCH_3), 3.72 (2H, dd, *J* = 13.7 Hz, *J* = 11.6 Hz, 2C-H, 6C-H), 3.49(2H, dd, *J* = 13.4 Hz, *J* = 11.6 Hz, 3C-Heq, 5C-Heq), 2.17 (2H, dd, *J* = 13.3 Hz, *J* = 11.4 Hz 3C-Hax, 5C-Hax); ^{13}C-NMR (DMSO-d_6): δ 168.2 (1C, C=N), 158.3 (1C, C=N), 157.9 (2C, C-OCH_3), 153.3 (1C), 147.2 (1C), 137.8 (1C), 126.2 (1C), 121.5 (1C), 114.8 (4C), 126.9 (4C), 134.7 (2C), 61.8 (1C), 55.1 (2C, OCH_3), 54.5 (1C), 46.1 (1C), 36.8 (1C); EIMS *m/z*(rel.int): 414 $[M]^+$ (26), 336 (21), 310 (19), 297 (34), 237 (100), 161 (10), 85 (10), 73 (18), 44 (6); Anal C 72.46%, H 6.07%, N 13.95%, Calcd for $C_{25}H_{26}N_4O_2$ C 72.44%, H 6.32%, N 13.52%.

(*E*)-2-(((2,6-Di-*p*-tolylpiperidin-4-ylidene)hydrazono)methyl)pyridine (**2f**). Yellow solid; yield 81%; mp 167-171 ºC; IR (KBr, cm^{-1}): 3094, 3013, 1651, 825, 710; ^{1}H NMR (DMSO-d_6): δ 11.26 (1H, s, NH), 8.61 (1H, d, *J* = 7.4 Hz, pyridine), 7.93 (1H, s, HC=N-), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.71(1H, dd, *J*= 7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.45-7.40 (4H, d, *J* = 7.2 Hz, aryl), 7.29-7.26 (4H, d, *J* = 7.2 Hz, aryl), 3.72 (2H, dd, *J* = 13.7 Hz, *J* = 11.6 Hz, 2C-H, 6C-H), 3.36 (2H, dd, *J* =13.5 Hz, *J* = 11.6 Hz, 3C-Heq, 5C-Heq), 2.28 (6H, s, CH_3), 2.08 (2H, dd, *J* =13.3 Hz, *J* = 11.36 Hz, 3C-Hax, 5C-Hax); ^{13}C-NMR(DMSO-d_6): δ 167.1 (1C, C=N), 157.6 (1C, C=N), 153.3 (1C), 146.1 (1C), 136.7 (1C), 126.4 (1C), 121.3 (1C), 128.1 (4C), 125.8 (4C), 138.7 (2C), 135.7 (2C, C-CH_3), 61.8 (1C), 55.2 (2C, CH_3), 54.5 (1C), 46.1(1C), 36.8 (1C)); EIMS *m/z* (rel.int): 383 $[M]^+$ (31), 305 (27), 278 (19), 265 (09), 237 (100), 161 (08), 85 (16), 73 (16), 44 (5); Anal C 78.46%, H 6.07%, N 14.95%, Calcd for $C_{25}H_{26}N_4$, C 78.50%, H 6.85%, N 14.65%.

(*E*)-4,4'-(4-((Pyridin-2-ylmethylene)hydrazono)piperidine-2,6-diyl)bis(*N*,*N*-dimethylaniline) (**2g**). Yellow solid: yield 86%; mp 173-175 ºC; IR (KBr, cm^{-1}): 3046, 3010, 1625, 811, 726; ^{1}H NMR (DMSO-d_6): δ 11.28 (1H, s, NH), 8.61 (1H, d, *J* = 7.4 Hz, pyridine), 7.96 (1H, s, -HC=N-), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.71(1H, dd, *J* = 7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61(1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.19-7.17 (4H, d, *J* = 7.3 Hz, aryl), 6.40-6.37 (4H, d, *J* = 7.4 Hz, aryl), 3.69 (2H, dd, *J* = 13.2 Hz, *J* = 11.4 Hz, 2C-H, 6C-H), 3.53 (2H, dd, *J* = 13.1 Hz, *J*= 11.4 Hz, 3C-Heq, 5C-Heq), 3.14 (12H, s, -$N(CH_3)_2$), 2.31 (2H, d, *J* = 11.22 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR (DMSO-d_6): δ 168.6 (1C, C=N), 159.4 (1C, C=N), 153.2 (1C), 146.3 (1C), 136.1 (1C), 126.3 (1C), 121.2 (1C), 149.2 (2C), 112.9 (4C), 131.9 (4C), 133.1 (2C), 60.1 (1C), 54.2 (1C), 46.6 (1C), 40.8 (4C, -$N(CH_3)_2$), 37.3 (1C); EIMS *m/z* (rel.int): 441 $[M]^+$ (32), 363 (28), 351 (20), 336 (19), 323 (7), 237 (100), 161(14); Anal C 73.46%, H 7.07%, N 19.95%, Calcd for $C_{27}H_{32}N_6$, C 73.60%, H 7.32%, N 19.07%.

General procedure for synthesis of (*E*)-2-(((2,6-Diphenyltetrahydro-4-thiopyran-4-ylidene)hydrazono)methyl)pyridine (**4a-4g**).

A mixture of compound **3a** (0.1 mol) and 2-(hydrazonomethyl)pyridine (0.1 mol) in ethanol was heated at refluxed for 2 h. The product **4a**, was purified by flash column chromatography on silica gel using hexane/EtOAc.

Yellow solid: yield 88%; mp 211-214 ºC; IR (KBr, cm^{-1}): 760, 851,3037, 1625, 1752, 3018; ^{1}H NMR (DMSO-d_6): δ 8.61 (1H, d, *J* = 7.4 Hz, pyridine), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.78 (1H, s, -HC=N-), 7.71 (1H, dd, *J* = 7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.45–7.29 (10H, m, aryl), 3.61 (2H, dd, *J* = 13.73 Hz, *J* = 11.5 Hz, 2C-H, 6C-H), 3.44 (2H, dd, *J* = 13.1 Hz, *J* = 11.5 Hz, 3C-Heq, 5C-Heq), 2.16 (2H, dd, *J* = 13.1 Hz, *J* = 11.4 Hz, 3C-Hax, 5C-Hax,); ^{13}C NMR (DMSO-d_6): δ 167.9 (1C, C=N), 157.6 (1C, C=N), 153.8 (1C), 146.1 (1C), 142.7–127.0 (12C, aryl), 136.0 (1C), 126.3 (1C), 121.2(1C), 60.7 (1C), 53.6 (1C), 45.9 (1C), 35.7 (1C)); EIMS *m/z* (rel.int): 371 $[M]^+$ (34), 294 (26), 282 (17), 267 (11), 254 (100), 102 (20), 90 (6), 61(10); Anal C 74.46%, H 5.07%, N 11.95%. Calcd for $C_{23}H_{21}N_3S$, C 74.36%, H 5.70%, N 11.31%.

(*E*)-2-(((2,6-Bis(4-chlorophenyl)tetrahydro-4*H*-thiopyran-4-lidene) hydrazono) methyl) pyridine (**4b**). Yellow solid: yield 82%; mp 245-249 ºC; IR (KBr, cm^{-1}): 3082, 3020, 1742, 1681, 862, 831, 671; ^{1}H NMR (DMSO-d_6): δ 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* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.56 (1H, s, -HC=N-), 7.47-7.44 (4H, d, *J* = 7.3 Hz, aryl), 7.38-7.34 (4H, d, *J* = 7.3 Hz, aryl), 3.79 (2H, dd, *J* = 13.74 Hz, *J* = 11.34 Hz, 2C-H, 6C-H), 3.57 (2H, dd, *J* = 13.30 Hz, *J* = 11.34 Hz, 3C-Heq, 5C-Heq), 2.89 (2H, dd, *J* = 13.34 Hz, *J*

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= 11.46 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR (DMSO-d_6): δ 166.1 (1C, C=N), 156.2 (1C, C=N), 152.3 (1C), 147.1 (1C), 135.3 (1C), 127.9 (4C), 126.4 (1C), 121.2 (1C), 128.9 (4C), 141.3 (2C), 131.8 (2C, C-Cl), 61.8 (1C), 54.5 (1C), 46.1 (1C), 36.8 (1C); EIMS *m/z* (rel.int): 440 $[M]^+$ (32), 363 (15), 350 (21), 335 (10), 323 (12), 254 (100), 102 (13), 90 09), 61 (03); Anal C 62.46%, H 4.07%, N 9.95%, Calcd for $C_{23}H_{19}Cl_2N_3S$, C 62.73%, H 4.35%; N 9.54%.

(*E*)-4,4'-(4-((Pyridin-2-ylmethylene)hydrazono)tetrahydro-2*H*-thiopyran-2,6-diyl)diphenol (4c). Yellow solid: yield 76 %; mp 265-268 ºC; IR (KBr,cm^{-1}): 3046, 1772, 1640, 1451, 828, 614; ^{1}H NMR (DMSO-d_6): δ 9.56 (2H, s, OH), 8.61 (1H, d, *J* = 7.4 Hz, pyridine), 7.82 (1H, d, *J* = 7.2Hz, pyridine), 7.71(1H, dd, *J* = 7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1Hz, *J* = 7.4 Hz, pyridine), 7.46 (1H – HC=N-), 7.19-7.17 (4H, d, *J* = 7.3Hz, aryl), 6.70-6.65 (4H, d, *J* = 7.3 Hz, aryl), 3.74 (2H, dd, *J* =13.7 Hz, *J* = 11.6 Hz, 2C-H, 6C-H), 3.32 (2H, dd, *J* = 13.8 Hz, *J* = 11.6 Hz, 3C-Heq, 5C-Heq), 2.24 (2H, dd, *J* =1 3.8 Hz, *J* = 11.3 Hz, 3C-Hax, 5C-Hax, 1H); ^{13}C NMR (DMSO-d_6): δ 168.3 (1C, C=N), 159.2 (2C, C-OH), 156.4 (1C, C=N), 153.0 (1C), 146.2 (1C), 136.7 (1C), 136.3 (2C), 127.9 (4C), 126.4 (1C), 121.1 (1C), 115.6 (4C), 62.6 (1C), 55.8 (1C), 46.1 (1C), 36.8 (1C); EI MS *m/z* (rel.int): 403 $[M]^+$ (47), 326 (16), 314 (23), 299 (11), 286 (23), 254 (100), 102 (16), 90 (7), 61 (2); Anal C 68.46%, H 5.07%, N 10.95%, Calcd for $C_{23}H_{21}N_3O_2S$, C 68.46%, H 5.25%, N 10.41%.

(*E*)-2-(((2,6-Bis(4-nitrophenyl)tetrahydro-4*H*-thiopyran-4-ylidene)hydrazono)methyl)pyridine (4d). Yellow solid: yield 86%; mp 255-258 ºC; IR (KBr, cm^{-1}): 3079, 3021, 1711, 1684, 1531, 808, 651; ^{1}H NMR (DMSO-d_6): δ 8.61 (1H, d, *J* = 7.4 Hz, pyridine), 8.45-8.40 (4H, d, *J* = 7.8 Hz, aryl), 7.82 (1H, d, *J* =7.2 Hz, pyridine), 7.71 (1H, dd, *J* = 7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.40 (1H, s, -HC=N-), 7.29-7.27 (4H, d, *J* = 7.8 Hz, aryl), 3.79 (2H, dd, *J* =13.70 Hz, *J* = 11.67 Hz, 2C-H, 6C-H), 3.35 (2H, dd, *J* = 13.68 Hz, *J* = 11.67 Hz, 3C-Heq, 5C-Heq), 2.11 (2H, dd, *J* = 13.67 Hz, *J* = 11.39 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR (DMSO-d_6): δ 167.1 (1C, C=N), 157.7 (1C, C=N), 153.2 (1C), 148.3 (2C), 147.2 (1C), 145.2 (2C-NO_2), 136.1 (1C), 127.0 (1C), 124.9 (4C), 124.6 (4C), 121.3 (1C), 61.8 (1C), 54.5 (1C), 46.1 (1C), 36.8 (1C); EI MS *m/z* (rel.int): 461 $[M]^+$ (51), 382 (35), 357 (18), 344 (28), 254 (100), 102 (28), 90 (14), 61 (7); Anal C 59.46%, H 5.07%, N 15.95%, S 6.90, Calcd for $C_{23}H_{19}N_5O_4S$, C 59.86%, H 4.15%, N 15.18%, S 6.98%.

(*E*)-2-(((2,6-Bis(4-methoxyphenyl)tetrahydro-4*H*-thiopyran-4-ylidene)hydrazono)methyl) pyridine (4e). Yellow solid: yield 89%; mp 272-277 ºC; IR (KBr, cm^{-1}): 3085, 1732, 1671, 806, 661; ^{1}H NMR (DMSO-d_6): δ 8.61 (1H, d, *J* = 7.4 Hz, pyridine), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.71 (1H, dd, *J* =7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.22-7.20 (4H, d, *J* = 7.1 Hz, aryl), 6.35-6.32 (4H, d, *J* = 7.1 Hz, aryl), 7.43 (1H, s, -HC=N-), 3.85 (6H, s, -OCH_3), 3.72 (2H, dd, *J* = 13.9 Hz, *J* = 11.6 Hz, 2C-H, 6C-H), 3.49 (2H, d, *J* = 11.6 Hz, 3C-Heq, 5C-Heq), 2.17 (2H, dd, *J* = 13.8 Hz, *J* = 11.4 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR(DMSO-d_6): δ 168.2 (1C, C=N), 158.3 (1C, C=N), 157.9 (2C, C-OCH_3), 154.2 (1C), 147.0 (1C), 135.8 (2C), 135.2 (1C), 127.1 (1C), 121.4 (1C), 114.3 (4C), 126.4 (4C), 61.8 (1C), 55.8 (2C, -OCH_3), 54.5 (1C), 46.1 (1C), 36.8 (1C); EIMS *m/z* (rel.int): 432 $[M]^+$ (49), 354 (26), 327 (54), 314 (24), 254 (100), 102 (28), 90 (17), 61 (8); Anal C 69.56%, H 5.87%, N 9.75%, S 7.48%, Calcd for $C_{25}H_{25}N_3O_2S$, C 69.58%; H, 5.84%; N, 9.74%; S, 7.43%.

(*E*)-2-(((2,6-Di-*p*-tolyltetrahydro-4*H*-thiopyran-4-ylidene)hydrazono)methyl)pyridine (4f). Yellow solid: yield 84%; mp 258-261 ºC; IR (KBr, cm^{-1}): 3094, 1762, 1651, 825, 671; ^{1}H NMR (DMSO-d_6): δ 8.61 (1H, d, *J* =7 .4 Hz, pyridine), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.71 (1H, dd, *J* = 7.1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.48 (1H, s, -HC=N-), 7.45-7.41 (4H, d, *J* = 7.4Hz, aryl), 7.29-7.25 (4H, d, *J* = 7.4 Hz, aryl), 3.72 (2H, dd, *J* = 13.7 Hz, *J* = 11.3 Hz, 2C-H, 6C-H), 3.36 (2H, dd, *J* = 13.5 Hz, *J* = 11.3 Hz, 3C-Heq, 5C-Heq), 2.28 (6H, s, CH_3), 2.08 (2H, dd, *J* = 13.6 Hz, *J* = 11.3 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR(DMSO-d_6): δ 167.1 (1C, C=N), 157.6 (1C, C=N), 153.1 (1C), 146.0 (1C), 138.7 (2C), 136.1 (1C), 135.7 (2C, Ph-CH_3), 128.1 (4C), 126.4 (1C), 125.8 (4C), 121.2 (1C), 61.8 (1C), 54.5 (1C), 46.1 (1C), 36.8 (1C), 21.7 (2C-CH_3); EI MS *m/z* (rel.int): 400 $[M]^+$ 32), 322 (37), 295 (21), 282 (19), 254 (100), 102 (36), 90 (18), 61 (11); Anal C 75.18%, H 6.37%, N 10.55%, S 8.10%, Calcd for $C_{25}H_{25}N_3S$, C 75.15%,; H 6.31%, N 10.52% S 8.03%.

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(*E*)-4,4'-(4-((Pyridin-2-ylmethylene)hydrazono)tetrahydro-2*H*-thiopyran-2,6-diyl)bis(*N*,*N*-dimethylaniline) (4g). Yellow solid: yield 88%; mp 268-270 ºC; IR (KBr, cm^{-1}): 3046, 1782, 1625, 811, 664; ^{1}H NMR (DMSO-d_6): δ 8.61 (1H, d, *J* = 7.4 Hz, pyridine), 7.82 (1H, d, *J* = 7.2 Hz, pyridine), 7.71 (1H, dd, *J* =7 .1 Hz, *J* = 7.0 Hz, pyridine), 7.61 (1H, dd, *J* = 7.1 Hz, *J* = 7.4 Hz, pyridine), 7.46 (1H, s, -HC=N-), 7.23-7.19 (4H, d, *J* = 7.1Hz, aryl), 6.48-6.42 (4H, d, *J* = 7.2 Hz, aryl), 3.69 (2H, dd, *J* = 13.2Hz, *J* = 11.4 Hz, 2C-H, 6C-H), 3.53 (2H, dd, *J* =13.1 Hz, *J* = 11.4 Hz, 3C-Heq, 5C-Heq), 3.14 (12H, s, -N(CH_3)$_2$), 2.31 (2H, d, *J* = 11.4 Hz, 3C-Hax, 5C-Hax); ^{13}C NMR (DMSO-d_6): δ 168.6 (1C, C=N), 159.4 (1C, C=N), 153.8 (1C), 148.2 (2C, C-N(CH_3)$_2$), 146.1 (1C), 136.3 (1C), 133.1 (2C), 131.9 (4C), 126.6 (1C), 121.2 (1C), 112.9 (4C), 60.1 (1C), 54.2 (1C), 46.6 (1C), 40.8 (4C, Ph-N(CH_3)$_2$), 37.3 (1C); EIMS *m/z* (rel.int): 458 $[M]^+$ (16), 381 (43), 354 (24), 341 (17), 254 (100), 102 (21), 90 (10), 61 (3); Anal C 70.46%, H 6.07%, N 15.95%, Calcd for $C_{27}H_{31}N_5S$, C 70.86%, H 6.83%, N 15.30%.

Larvicidal activity

Larvicidal screening was performed following the methodology described in our previous study [22]. Synthesized compounds were tested against the urban mosquito larvae, *Culex quinquefasciatus*. Eggs of *C. quinquefasciatus* were obtained from the city drainage system. Eggs were placed in clean water and kept at room temperature for hatching. Larval development was monitored for 7 days. Second stage larvae were collected using a pasture pipette, placed in cotton to remove excess water, and transferred to test vials. Larval mortality was observed using increasing concentrations of synthesized compounds (10, 20, 30, and 40 µg/mL). The susceptibility or resistance of the mosquito larvae to the selected concentration of the synthesized compounds was determined with a standard protocol (WHO, 1981).

Nematicidal activity

Nematicidal activity was evaluated using juvenile nematodes of *Meloidogyne javanica* [22]. The assay system was prepared with 2 mL Milli-Q® water, containing different concentrations of compound (10, 20, 30, and 40 µg/mL) in glass tubes. Treated and control nematodes were held under the same conditions used for colony maintenance. Ten nematode juveniles were transferred into each tube. Positive (levamisole) and negative (2% DMSO) control tubes were included. Mortality was observed under a zoom stereomicroscope after 24 h of exposure. The mortality percentage was converted into probit scale to determine the LD_{50} values.

In vitro antimicrobial screening

Antimicrobial activity: The compounds **2a-g**, **3a-g,** and **4a-g** were inspected for their *in vitro* antibacterial activity against a battery of human type culture pathogens such as *Staphylococcus aureus* (ATCC-25923), *Klebsiella pneumoniae, Escherichia coli* (ATCC-25922), and *Pseudomonas aeruginosa* (ATCC-27853) by disc diffusion method [23] using Mueller-Hinton broth (Hi-media). The same compounds were evaluated for *in vitro* antifungal activity against a panel of human fungal pathogens such as *Aspergillus niger*, *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans* and *Microsporum audouinii* using an broth dilution method [24] in Sabouraud's dextrose broth (Hi-Media).

In order to determine the minimum inhibitory concentration (MIC), tube dilution method was used with respective compounds aliquoted in phosphate-buffered saline (pH 7.2) as test solution. Briefly, the dosing range of compounds were calculated by the factor 2 (anti log 0.3) in order to obtain a dose range between 0.5 to 128 µg per mL in Mueller Hinton broth. Afterwards, respective tubes were inoculated with100 µL of fresh culture of appropriate bacterial and fungal pathogens (10^4 to 10^5 CFU/mL) and incubated at 37± 2°C for 24-72 h, respectively. MICs were recorded as the lowest concentrations inhibiting visible growth of the microorganisms as compared to the negative controls.

Statistical analysis

All the experiments were repeated three times to validate the findings statistically [25]. All the data are presented as mean ± standard deviation (S.D.). Mean values were compared among treatments and the control using one way analysis of variance (ANOVA) using SPSS at $P < 0.05$ levels.

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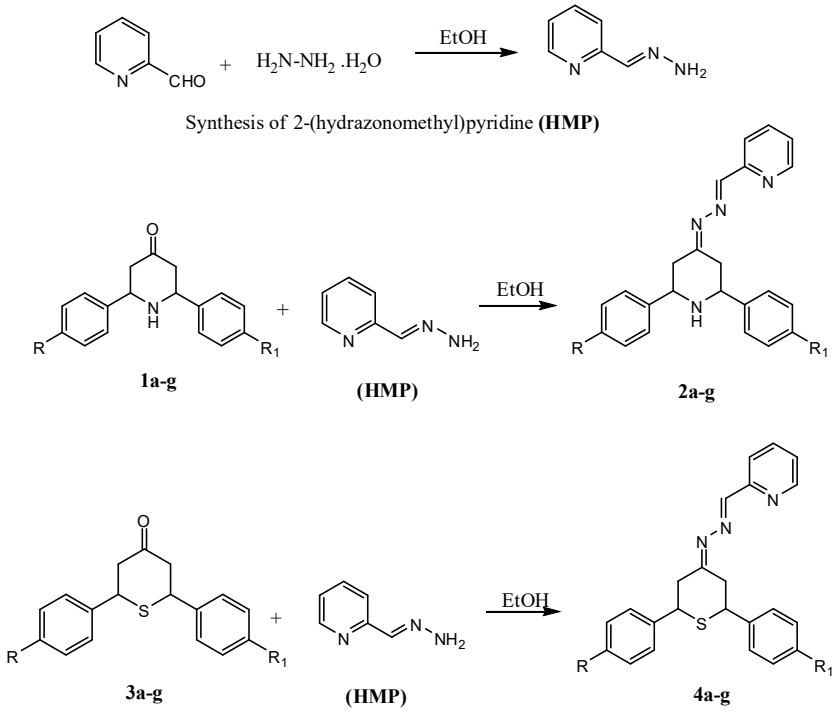
Results and discussion

Chemistry. Compounds **1a-g** were synthesized according to the method described previously [26]. Compounds **3a-g** were prepared by the method reported elsewhere [27-28]. Compounds **2a-g** and **4a-g** were synthesized by condensation method (Scheme 1). 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, ^{1}H NMR, ^{13}C NMR spectra, and elemental analyses. The IR spectra of compounds **2a-g** showed absorption bands at 3045–3094, and 1625–1684 cm^{-1} corresponding to the NH and C=N groups, respectively. The ^{1}H NMR spectra of compounds **2a-g** showed a sharp singlet at δ 11.15–11.71 for NH proton and a singlet at δ 7.48–7.96 for HC=N- proton. The ^{13}C NMR spectra of compounds **2a-g** showed characteristic peaks at δ 156.2–164.2 and δ 166.1–168.7 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 to C=N, HC=N, and C-S-C groups, respectively. The ^{1}H NMR spectra of compounds **4a-g** showed signals at δ 7.40–7.78, which confirmed the presence of HC=N- proton. The ^{13}C NMR spectra of compounds **4a-g** showed characteristic peaks at δ 166.1–168.6 and δ 156.2–159.4 ppm 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**.**



1a, 2a, 3a, 4a: R, R_1 = -H
1b, 2b, 3b,4b: R, R_1 = -Cl
1c, 2c, 3c,4c: R, R_1 = -HO
1d, 2d, 3d, 4d: R, R_1 = -NO_2
1e, 2e, 3e, 4e: R, R_1 = -OCH_3
1f, 2f, 3f, 4f: R, R_1 = -CH_3
1g, 2g, 3g, 4g: R, R_1 = -$N(CH_3)_2$

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

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Larvicidal activity. Compounds **2a-g** and **4a-g** were screened for larvicidal activity. Compounds **2a-g** exhibited lower rank of larvicidal activity than compounds **4a-g.** Compound **4e** showed higher rank of larvicidal activity than other compounds and produced 100% mortality (20 μg/mL), with corresponding LD_{50} value of 0.8 μg/mL. Compounds **4c, 4d, 4f,** and **4g** showed moderate activity with concomitant LD_{50} values of 5.7, 1.2, 8.6, and 6.0 μg/mL, respectively. The values are summarized in Table 1.

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

Comp.No	Mortality (%)Room temp				LD_{50} (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] Values are the means of three replicates ± SD.
Positive control: *N-tert*-butyl-*N*,*N'*- dibenzoylhydrazine;
Negative control: Dimethyl sulfoxide (DMSO)

Nematicidal activity. Compounds **2a-g** and **4a-g** were inspected for nematicidal activity, and compounds **2a-g** exhibited lower range of nematicidal activity than compounds **4a-g**. The screening was carried out at 37 °C and the toxicity of the compounds were measured. Compound **4e** showed higher degree of nematicidal activity than other compounds and produced 100% mortality at 20 μg/mL, with corresponding LD_{50} value of 3.2 μg/mL. Compounds **4c**, **4d, 4f,** and **4g** showed moderate range of activities with LD_{50} values of 7.8, 5.5, 4.1, and 4.7 μg/mL, respectively. The values are summarized in Table 2.

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

Comp.No.	Mortality (%)Room temp				LD_{50} (µg /mL)
	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] Values are the means of three replicates ± SD.
Positive control: (-)-Pinidinol;
Negative control: Dimethyl sulfoxide (DMSO)

Antibacterial activity. The synthesized compounds **2a-g,** and **4a-g** were evaluated for antibacterial activity against various human bacterial pathogens. Compound **2d** (MIC: 4 µg/mL) showed high antibacterial activity against *E. coli*. Compound **2e** (MIC: 4 µg/mL) showed higher antibacterial activity against *K. pneumoniae* than ciprofloxacin (MIC: 16 µg/mL). The MIC values are summarized in Table 3.

Table 3. Antibacterial screening: Minimum inhibitory concentration (MIC) in µg/mL

Compounds	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

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Antifungal activity. Compounds **2a-g** and **4a-g** were screened for antifungal activity against various fungal pathogens. Compound **4b (**MIC: 0.25 μg/mL) exhibited high antifungal activity against *C. albicans* whereas the compound **4e** (MIC: 0.5 μg/mL) showed slight equipotent activity against *C. albicans.* Compound **4f** (MIC: 2 μg/mL) showed higher activity against *M. audouinii* than clotrimazole (MIC: 4 μg/mL). The antifungal activity values are appended in Table 4.

Table 4. Antifungal screening: Minimum inhibitory concentration (MIC) in μg/mL

Compounds	*A. niger*	*C. albicans*	*M. audouinii*	*C. 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

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 activities owing to the presence of pyridine with thiopyran moiety besides CH_3O group. The lower degree of larvicidal and nematicidal activities showed by the compounds 2**a-g** could be due to the presence of piperidine with pyridine rings.

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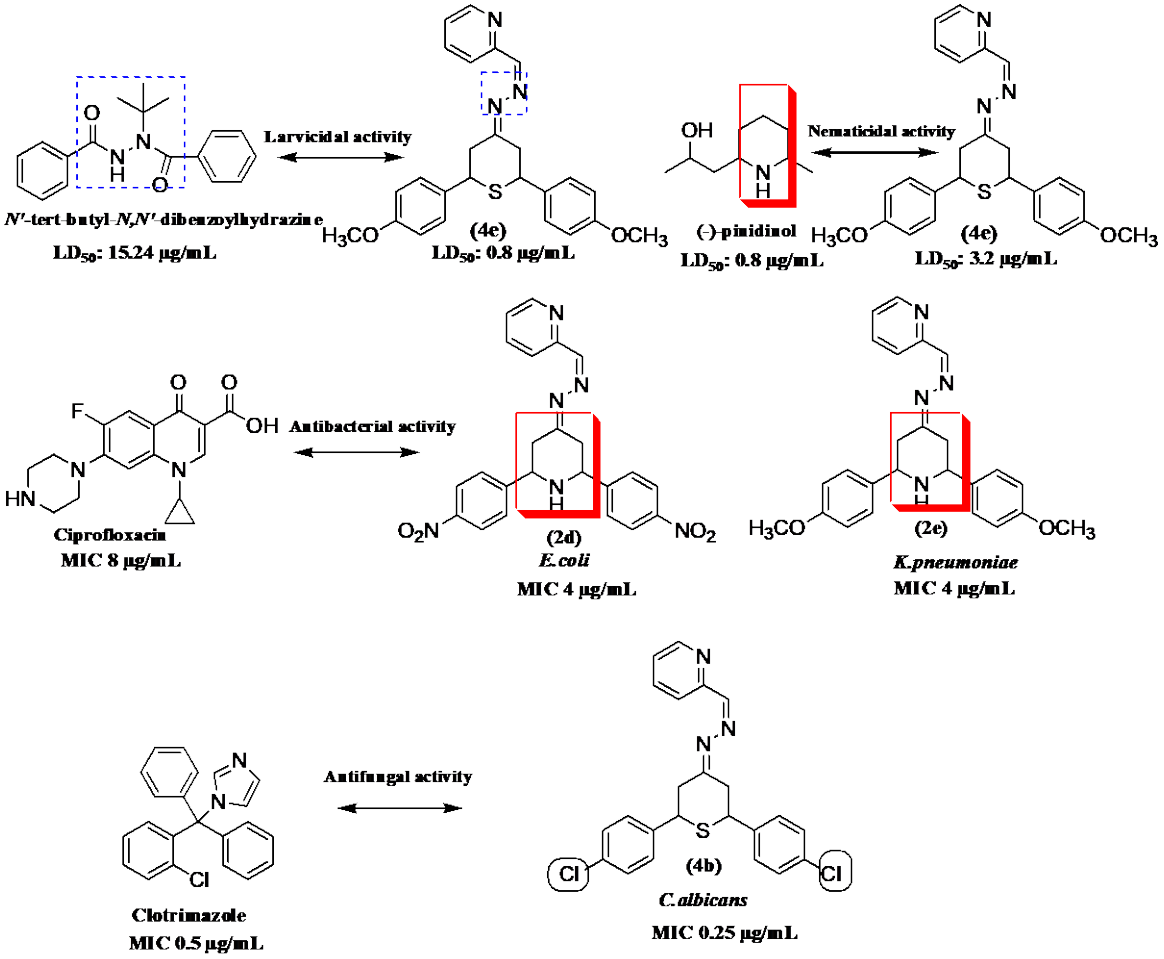

Fig. 1. Structure activity relationship.

The high antibacterial activity of compound **2e** against *K. pneumoniae* is due to presence of pyridine with piperidine moiety and CH_3O group (MIC: 4 µg/mL). The presence of pyridine with piperidine moiety and NO_2 group is responsible for the high antibacterial activity of compound **2d** against *E.coli* (MIC: 4 µg/mL). The 4-substituted phenyl ring acts as a lipophilic domain, and the NH group present in piperidine act as a hydrogen bonding domain. It can be suggested that piperidine ring is an essential pharmacophore for antibacterial activity.

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

In our previous study [22], the compounds (piperidin-connected 2-thioxoimidazolidin-4-one) were found to be lethal to the second instar larvae of mosquito, which produced a LD_{50} value of 1.37 µg/mL as compared to pinidinol and hyantocidin (LD_{50} values of 18.28 and 22.11 µg/mL respectively), however it was low active as compared to compound **4e** of present study. Nematicidal activity of previous study [22] showed that the compound (piperidin-connected 2-thioxoimidazolidin-4-one) with LD_{50} value of 1.57 µg/mL demonstrated high activity as compared to pinidinol and hyantocidin (LD_{50} values of 14.25, 26.30µg/mL respectively) but very low active in comparison to compound **4e**. Therefore, according to the previous study, the 2-thioxoimidazolidin-4-one with piperidin ring showed low potentiality as compared with compound **4e** against mosquito larvae and nematodes. At the same time results of the present study evidenced that piperidine series has very low activity as compared to thiopyran **4a-4g** series.

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Conclusions

Compounds **2a-g** and **4a-g** were synthesized and screened for larvicidal, nematicidal, and antimicrobial activities. Among the synthesized compounds, **4e** showed high larvicidal and nematicidal activities. Compounds **2e** and **2d** showed high antibacterial activity against *K. pneumoniae* and *E. coli*, respectively. Compound **4b** exhibited high antifungal activity against *C. albicans*. Therefore overall results of the present study envisaged that compounds **2e, 2d, 4e, 4b,** and **4f** can be used as lead molecules for the development of larvicidal, nematicidal, and antimicrobial agents in future.

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