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Antimicrobial and Pharmacological Activities of Some 3-Substituted Thieno[3,2-d]-pyrimidin-4(3*H*)-one

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A series of new 3-substituted-7-(2-chloro-6-ethoxypyridin-4-yl)-9-(2,4-dichlorophenyl)-2-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one derivatives (**3-10**) were synthesized using 7-(2-chloro-6-ethoxypyridin-4-yl)-9-(aryl)-2-methyl-4*H*-pyrido-[3',2':4,5]thieno[3,2-*d*]-[1,3]oxazin-4-one (**2a,b**) as a starting material. All the newly synthesized compounds were evaluated for their antimicrobial activities. The antimicrobial screening showed that many of these obtained compounds have good antimicrobial activities comparable to streptomycin and fusidic acid as reference drugs. Also, the pharmacological screening showed that many compounds have good analgesic and antiparkinsonian activities comparable to Valdecoxib® and Benzotropine® as reference drugs. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS spectral data and elemental analysis.

Keywords: Oxazinone, Thienopyrimidine, Schiff base, Imide derivatives, Antimicrobial and pharmacological agents.

INTRODUCTION

In particular, pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3*H*)-ones were reported to be act as 5-HT1A receptor antagonists and serotonin reuptake inhibitors[1], antiinflammatory[2,3] and antimalarial agents[4]. Moreover, this triheterocyclic system showed highly potent dual 5-HT1A and 5-HT1B antagonists as potential antidepressant drugs[5]. Many of thieno-pyrimidines are found to exhibit a variety of biological activities, including antimicrobial[6] and analgesic[7] properties, inhibition of cancer cell proliferation[8] and antagonism of α1 adre-noceptors[9]. In addition, literature survey reveals that pyrimidines and their synthetic analogs possess a variety of pharmacological activities, such as antiinflammatory, antimicrobial[10], antimalarial[11], antituberculous[12], anti-HIV[13], antitumor[14], tyrosine kinase inhibitor[15], activities. Similarly thienopyrimi-dine[16,17] and pyridopyrimidine[18], the bioisosters of quinazolin-ones are known to possess good anticonvulsant activity. On the other hand, Schiff bases derived from aromatic amines and aromatic aldehydes have a wide variety of applications in many fields, *e.g.*, biological, inorganic and analytical chemistry[19,20]. Also, some of sulfur and nitrogen heterocyclic compounds has a broad spectrum of biological activities i.e. antidepressant[21], antifungal[22] activities. In view of these observations and in continuation of our previous works[23-32] in heterocyclic chemistry, we have herein synthesized some new heterocyclic fused ring systems containing thienopyrimidine moiety and tested their anti-microbial activities in comparison to streptomycin and fusidic acid as positive controls.

EXPERIMENTAL

Melting points were measured using electrothermal 9100 digital melting point apparatus (Büchi, Switzerland) and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FTIR (Perkin-Elmer) in KBr discs. ^{1}H- and ^{13}C NMR spectra were measured on a Jeol 5000 MHz spectrometer (Jeol, Japan) in DMSO-d_6 and chemical shifts were recorded in δ ppm relative to the internal standard TMS. The mass spectra were run at 70 eV with a Finnigan SSQ 7000 spectrometer (Madison, WI, USA) using EI and the values of *m/z* are indicated in Dalton. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer (Perkin-Elmer, USA) and were found within ± 0.4 % of the theoretical values. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F_{254}, Merck). Starting materials **2a-c** was prepared from the corresponding cinnamoyl derivatives **1a-c** according to reported procedures[23,24].

Synthesis of compounds (3a,b and 4a,b): A mixture of 7-(2-chloro-6-ethoxypyridin-4-yl)-9-(4-fluorophenyl)-2-

methyl-4*H*-pyrido-[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (**2a,b**) (1 mmol) and aniline or phenylhydrazine (1 mmol) in glacial acetic acid (25 mL) was heated under reflux for 6 h. The reaction mixture was concentrated under reduced pressure, pour in ice-cold water and the formed solid was filtered, washed with water, dried and crystallized from the proper solvent to afford the corresponding 3-substituted pyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine derivatives **3a,b** and **4a,b**, respectively.

7-(2-Chloro-6-ethoxypyridin-4-yl)-9-(4-fluorophenyl)-2-methyl-3-phenylpyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-4(3*H*)-one (3a): Yield 85 %, m.p. 218-220 °C; IR (KBr, ν_{max}, cm^{-1}): 1671 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.18 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.78 (q, 2H, CH_2), 7.12-7.76 (m, 11H, 9 Ph-H + 2 pyr-H), 8.54 (s, 1H, pyr-5'-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.01, 25.12, 64.18, 100.08, 101.28, 116.24, 120.36, 121.62, 124.35, 126.42, 128.88, 129.62, 132.75, 132.83, 136.44, 145.66, 146.24, 149.80, 151.76, 154.12, 154.72, 157.44, 159.65, 162.78, 164.27; MS, *m/z* (%): 543 [M^+, 14], 358 [100, base peak]; Elemental analysis for $C_{29}H_{20}N_4O_2SClF$ (543.01): Calcd.: C, 64.14; H, 3.71; Cl, 6.53; N, 10.32; S, 5.91; Found: C, 64.10; H, 3.66; Cl, 6.49; N, 10.28; S, 5.86.

7-(2-Chloro-6-ethoxypyridin-4-yl)-9-(4-chlorophenyl)-2-methyl-3-phenylpyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-4(3*H*)-one (3b): Yield 72 %, m.p. 214-216 °C; IR (KBr, ν_{max}, cm^{-1}): 1672 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.24 (t, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.82 (q, 2H, CH_2), 7.08-7.75 (m, 11H, 9 Ph-H + 2 pyr-H), 8.62 (s, 1H, pyr-5'-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.82, 26.33, 64.12, 100.01, 101.12, 120.50, 121.72, 124.32, 126.82, 128.01, 128.84, 129.15, 132.82, 133.40, 135.80, 136.43, 145.38, 146.97, 149.75, 150.82, 153.80, 154.62, 157.32, 160.00, 164.20; MS, *m/z* (%): 559 [M^+, 8], 132 [100, base peak]; Elemental analysis for $C_{29}H_{20}N_4O_2SCl_2$ (559.47): Calcd.: C, 62.26; H, 3.60; Cl, 12.67; N, 10.01; S, 5.73; Found: C, 62.20; H, 3.55; Cl, 12.60; N, 9.95; S, 5.65.

7-(2-Chloro-6-ethoxypyridin-4-yl)-9-(4-fluorophenyl)-3-benzyl-2-methylpyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidine-4(3*H*)-one (4a): Yield 65 %, m.p. 168-170 °C; IR (KBr, ν_{max}, cm^{-1}): 3348 (NH), 1675 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.30 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.84 (q, 2H, CH_2), 6.68-7.71 (m, 11H, 9 Ph-H + 2 pyr-H), 8.54 (s, 1H, pyr-5'-H), 9.15 (s, 1H, NH changeable with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.78, 24.96, 64.18, 101.00, 102.42, 113.24, 116.24, 119.34, 121.02, 126.42, 129.04, 129.86, 132.91, 136.54, 145.68, 146.32, 150.12, 151.05, 151.96, 154.11, 154.65, 157.22, 159.56, 162.78, 164.35; MS, *m/z* (%): 559 [M^+ + 1, 12], 234 [100, base peak]. Elemental analysis for $C_{29}H_{21}N_5O_2SClF$ (558.03): Calcd.: C, 62.42; H, 3.79; Cl, 6.35; N, 12.55; S, 5.75; Found: C, 62.38; H, 3.75; Cl, 6.30; N, 12.50; S, 5.70.

7-(2-Chloro-6-ethoxypyridin-4-yl)-9-(4-chlorophenyl)-3-benzyl-2-methylpyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidine-4(3H)-one (4b): Yield 56 %, m.p. 206-208 °C; IR (KBr, ν_{max}, cm^{-1}): 3354 (NH), 1671 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.40 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.92 (q, 2H, CH_2), 6.72-7.74 (m, 11H, 9 Ph-H + 2 pyr-H), 8.68 (s, 1H, pyr-5'-H), 9.08 (s, 1H, NH changeable with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.02, 27.05, 64.22, 99.88, 100.25, 113.25, 119.65, 121.15, 127.31, 128.01, 129.12, 129.55, 133.56, 136.18, 136.84, 145.37, 146.82, 149.66, 151.06, 151.14, 153.88, 155.00, 157.52, 159.86, 164.16; MS, *m/z* (%): 574 [M^+, 5], 412 [100, base peak]. Elemental analysis for $C_{29}H_{21}N_5O_2SCl_2$ (574.48): Calcd.: C, 60.63; H, 3.68; Cl, 12.34; N, 12.19; S, 5.58; Found: C, 60.55; H, 3.62; Cl, 12.30; N, 12.14; S, 5.54.

Synthesis of 3-amino-7-(2-chloro-6-ethoxypyridin-4-yl)-9-aryl-2-methylpyrido[3',2':4,5]-thieno[3,2-d]pyrimidin-4(3*H*)-one (5a,b): A mixture of **2a,b** (1 mmol) and hydrazine hydrate (8 mmol) in absolute ethanol (50 mL) was refluxed for 4 h. After cooling, the obtained solid was collected by filtration, dried and crystallized from the proper solvent to give the title compound derivatives **5a,b**, respectively.

3-Amino-7-(2-chloro-6-ethoxypyridin-4-yl)-9-(4-fluorophenyl)-2-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3*H*)-one (5a): Yield 68 %, m.p. 268-270 °C; IR (KBr, ν_{max}, cm^{-1}): 3365 (NH_2), 1672 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.24 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.86 (q, 2H, CH_2), 4.78 (s, 2H, NH_2 exchangeable with D_2O), 7.05-7.74 (m, 6H, 4 Ph-H + 2 pyr-H), 8.74 (s, 1H, pyr-5'-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.01, 24.99, 64.22, 100.16, 101.41, 116.19, 120.32, 126.44, 128.98, 132.91, 136.40, 145.77, 146.22, 149.80, 151.76, 154.10, 154.86, 157.30, 159.60, 162.70, 164.28; MS, *m/z* (%): 482 [M^+, 24], 136 [100, base peak]. Elemental analysis for $C_{23}H_{17}N_5O_2SClF$ (481.93): Calcd.: C, 57.32; H, 3.56; Cl, 7.36; N, 14.53; S, 6.65; Found: C, 57.28; H, 3.50; Cl, 7.30; N, 14.48; S, 6.60.

3-Amino-7-(2-chloro-6-ethoxypyridin-4-yl)-9-(4-chlorophenyl)-2-methylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (5b): Yield 75 %, m.p. 216-218 °C; IR (KBr, ν_{max}, cm^{-1}): 3358 (NH_2), 1673 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.30 (t, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.80 (q, 2H, CH_2), 4.84 (s, 2H, NH_2 exchangeable with D_2O), 7.18-7.78 (m, 6H, 4 Ph-H + 2 pyr-H), 8.77 (s, 1H, pyr-5'-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.98, 24.97, 64.22, 100.12, 101.48, 120.36, 126.45, 128.22, 128.98, 134.55, 135.76, 136.37, 145.76, 146.26, 149.75, 151.70, 154.09, 154.85, 157.32, 159.64, 164.32; MS, *m/z* (%): 498 [M^+, 24], 164 [100, base peak]. Elemental analysis for $C_{23}H_{17}N_5O_2SCl_2$ (498.38): Calcd.: C, 55.43; H, 3.44; Cl, 14.23; N, 14.05; S, 6.43; Found: C, 55.38; H, 3.40; Cl, 14.18; N, 14.00; S, 6.38.

Synthesis of 1-{(2-Chloro-6-ethoxypyridin-4-yl)-9-aryl-2-methyl-4-oxopyrido[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl}-3-phenylthiourea (6a,b): To a mixture of **5a,b** (1 mmol) and phenylisothiocyanate (1 mmol) in dry dioxane (25 mL), triethylamine (2 mL) was added with stirring. The reaction mixture was heated under reflux for 10 h. The solvent was evaporated under reduced pressure, the obtained residue was solidified with *n*-hexane. The solid formed was collected by filtration, washed with diethyl ether, dried and crystallized from the proper solvents to afford the corresponding thiourea derivatives **6a,b**, respectively.

1-{(2-Chloro-6-ethoxypyridin-4-yl)-9-(4-fluorophenyl)-2-methyl-4-oxopyrido[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl}-3-phenylthiourea (6a): Yield 72 %, m.p. 156-158 °C; IR (KBr, ν_{max}, cm^{-1}): 3338-3250 (NH), 1678 (C=O), 1236 (C=S); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): **δ** 1.16 (s, 3H, CH_3), 2.14 (t, 3H, CH_3), 3.86 (q, 2H, CH_2), 4.28, 4.36 (2s, 2H,

2NH exchangeable with D_2O), 6.95-7.78 (m, 11H, 9 Ph-H + 2 pyr-H), 8.47 (s, 1H, pyr-5′-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.88, 27.12, 64.20, 99.90, 100.28, 113.25, 119.60, 121.13, 127.30, 128.05, 129.17, 129.56, 133.58, 136.22, 136.90, 145.40, 146.86, 149.68, 151.00, 151.08, 153.90, 155.04, 157.55, 159.80, 164.20, 177.66; MS, *m/z* (%): 617 [M^+, 12], 150 [100, base peak]. Elemental analysis for $C_{30}H_{22}N_6O_2S_2ClF$ (617.12): Calcd.: C, 58.39; H, 3.59; Cl, 5.74; N, 13.62; S, 10.39; Found: C, 58.33; H, 3.54; Cl, 5.70; N, 13.58; S, 10.34.

1-{(2-Chloro-6-ethoxypyridin-4-yl)-9-(4-chlorophenyl)-2-methyl-4-oxopyrido[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl}-3-phenylthiourea (6b): Yield 78 %, m.p. 216-218 °C; IR (KBr, ν_{max}, cm^{-1}): 3348-3232 (NH), 1676 (C=O), 1242 (C=S); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.18 (s, 3H, CH_3), 2.18 (t, 3H, CH_3), 3.79 (q, 2H, CH_2), 4.32, 4.42 (2s, 2H, 2NH exchangeable with D_2O), 6.98-7.85 (m, 11H, 9 Ph-H + 2 pyr-H), 8.56 (s, 1H, pyr-5′-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.05, 27.15, 64.20, 99.92, 100.26, 113.28, 119.60, 121.22, 127.24, 128.11, 129.22, 129.56, 133.58, 136.22, 136.85, 145.40, 146.85, 149.68, 151.13, 151.10, 153.89, 155.02, 157.50, 159.80, 164.14, 177.60; MS, *m/z* (%): 634 [M^+, 32], 136 [100, base peak]. Elemental analysis for $C_{30}H_{22}N_6O_2S_2Cl_2$ (633.57): Calcd.: C, 56.87; H, 3.50; Cl, 11.19; N, 13.26; S, 10.12; Found: C, 56.82; H, 3.45; Cl, 11.13; N, 13.20; S, 10.08.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(phthalimido or 2,3,4,5-tetrachlorophthalimido)-9-aryl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-7-yl]pyridine 7a-d: A mixture of **5a,b** (1 mmol) and phthalic anhydride or 2,3,4,5-tetrachlorophthalic anhydride (1 mmol) in glacial acetic acid (30 mL) was heated under reflux for 6 h. The reaction mixture was evaporated under reduced pressure, the obtained residue was solidified with diethyl ether. The obtained solid was filtered off, washed with diethyl ether, dried and crystallized from the proper solvents to afford the corresponding N-phthalimido derivatives **7a-d**, respectively.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(phthalimido)-9-(4-fluorophenyl)-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidin-7-yl]pyridine (7a): Yield 70 %, m.p. 224-226 °C; IR (KBr, ν_{max}, cm^{-1}): 1722 (C=O), 1670 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.28 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.82 (q, 2H, CH_2), 6.70-7.56 (m, 6H, 4 Ph-H + 2 pyr-H), 7.86-8.04 (m, 4H, Ar-H), 8.48 (s, 1H, pyr-5′-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.95, 25.00, 64.24, 100.18, 101.42, 116.22, 120.36, 123.18, 126.45, 128.96, 131.78, 132.45, 132.90, 136.42, 145.75, 146.18, 149.84, 151.78, 154.12, 154.85, 157.32, 159.65, 162.760, 164.30, 165.15; MS, *m/z* (%): 612 [M^+, 12], 254 [100, base peak]. Elemental analysis for $C_{31}H_{19}N_5O_4SClF$ (612.03): Calcd.: C, 60.84; H, 3.13; Cl, 5.79; N, 11.44; S, 5.24; Found: C, 60.80; H, 3.08; Cl, 5.74; N, 11.40; S, 5.20.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(phthalimido)-9-(4-chlorophenyl)-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-7-yl]pyridine (7b): Yield 65 %, m.p. 178-180 °C; IR (KBr, ν_{max}, cm^{-1}): 1726 (C=O), 1668 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.32 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.78 (q, 2H, CH_2), 6.85-7.64 (m, 6H, 4 Ph-H + 2 pyr-H), 7.82-8.10 (m, 4H, Ar-H), 8.52 (s, 1H, pyr-5′-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.12, 24.95, 64.20, 100.24, 101.52, 120.38, 123.24, 126.40, 128.20, 128.93, 131.80, 132.52, 134.60, 135.72, 136.35, 145.70, 146.23, 149.70, 151.65, 154.00, 154.80, 157.30, 159.60, 164.30, 164.80; MS, *m/z* (%): 429 [M^+ + 1, 12], 318 [100, base peak]. Elemental analysis for $C_{31}H_{19}N_5O_4SCl_2$ (628.48): Calcd.: C, 59.24; H, 3.05; Cl, 11.28; N, 11.14; S, 5.10; Found: C, 59.20; H, 3.00; Cl, 11.23; N, 11.10; S, 5.04.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(2,3,4,5-tetrachlorophthalimido)-9-(4-fluorophenyl)-3,4-di-hydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-7-yl]pyridine (7c): Yield 65 %, m.p. 115-117 °C; IR (KBr, ν_{max}, cm^{-1}): 1732 (C=O), 1674 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.32 (t, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.86 (q, 2H, CH_2), 6.76-7.62 (m, 6H, 4 Ph-H + 2 pyr-H), 8.54 (s, 1H, pyr-5'-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.98, 25.02, 64.30, 100.16, 101.45, 116.25, 120.34, 126.48, 127.18, 128.98, 131.75, 132.92, 134.75, 136.46, 145.78, 146.25, 149.85, 151.75, 154.16, 154.87, 157.34, 159.60, 162.70, 164.32, 165.18; MS, *m/z* (%): 750 [M^+, 6], 280 [100, base peak]. Elemental analysis for $C_{31}H_{15}N_5O_4SCl_5F$ (749.81): Calcd.: C, 49.66; H, 2.02; Cl, 23.64; N, 9.34; S, 4.28; Found: C, 49.60; H, 1.95; Cl, 23.60; N, 9.29; S, 4.21.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(2,3,4,5-tetrachlorophthalimido)-9-(4-chlorophenyl)-3,4-di-hydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-7-yl]pyridine (7d): Yield 76 %, m.p. 235-237 °C; IR (KBr, ν_{max}, cm^{-1}): 1737 (C=O), 1672 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.24 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.83 (q, 2H, CH_2), 6.88-7.65 (m, 6H, 4 Ph-H + 2 pyr-H), 8.48 (s, 1H, pyr-5'-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.98, 24.90, 64.24, 100.28, 101.56, 120.42, 126.45, 127.16, 128.24, 128.90, 132.94, 134.66, 134.70, 135.70, 136.42, 145.74, 146.28, 149.77, 151.69, 154.05, 154.82, 157.34, 159.65, 164.35, 164.84; MS, *m/z* (%): 766 [M^+, 16], 450 [100, base peak]. Elemental analysis for $C_{31}H_{15}N_5O_4SCl_6$ (766.26): Calcd.: C, 48.59; H, 1.97; Cl, 27.76; N, 9.14; S, 4.18; Found: C, 48.54; H, 1.90; Cl, 27.70; N, 9.10; S, 4.12.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(4-fluorophenylmethylidene)amino)-9-aryl-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidin-7-yl]pyridines (8a,b): A mixture of **5a,b** (1 mmol) and 4-fluorobenzaldehyde (1 mmol) in absolute ethanol (20 mL) was refluxed for 5 h. After cooling, the obtained solid was filtered off, washed with ethanol, dried and and crystallized from the proper solvents to give the corresponding the title compounds **8a,b**, respectively.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(4-fluorophenylmethylidene)amino)-9-(4-fluorophenyl)-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-7-yl]pyridine (8a): Yield 66 %, m.p. 135-137 °C; IR (KBr, ν_{max}, cm^{-1}): 1675 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.18 (t, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.78 (q, 2H, CH_2), 6.25 (s, 1H, CH=N), 6.85-7.85 (m, 10H, 8 Ph-H + 2 pyr-H), 8.52 (s, 1H, pyr-5'-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.08, 25.10, 64.32, 100.22, 101.36, 115.45, 116.28, 120.45, 123.16, 126.52, 130.15, 130.70, 132.12, 136.48, 143.18, 145.82, 146.22, 149.86, 152.15, 154.10, 155.05, 157.28, 159.72, 162.74, 164.90, 166.75; MS, *m/z* (%): 588 [M^+, 5], 122 [100, base peak]. Elemental analysis for $C_{30}H_{20}N_5O_2SClF_2$ (588.03): Calcd.: C, 61.28; H, 3.43; Cl, 6.03; N, 11.91; S, 5.45; Found: C, 61.20; H, 3.38; Cl, 5; .96N, 11.85; S, 5.40.

2-Chloro-6-ethoxy-4-[2-methyl-4-oxo-3-(4-chlorophenylmethylidene)amino)-9-(4-fluorophenyl)-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-7-yl]pyridine (8b): Yield 78 %, m.p. 214-216 °C; IR (KBr, ν_{max}, cm^{-1}): 1678 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.22 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.75 (q, 2H, CH_2), 6.12 (s, 1H, CH=N), 6.92-7.95 (m, 10H, 8 Ph-H + 2 pyr-H), 8.54 (s, 1H, pyr-5′-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.45, 24.90, 64.28, 100.02, 101.50, 116.08, 120.44, 123.32, 126.42, 128.90, 130.80, 131.52, 134.56, 135.70, 136.38, 144.08, 145.72, 146.20, 149.66, 151.68, 154.08, 154.76, 157.34, 159.62, 165.04, 166.05; MS, *m/z* (%): 604 [M^+, 16], 287 [100, base peak]. Elemental analysis for $C_{30}H_{20}N_5O_2SCl_2F$ (604.48): Calcd.: C, 59.61; H, 3.33; Cl, 3.14; N, 11.59; S, 5.30; Found: C, 59.55; H, 3.28; Cl, 11.70; N, 11.54; S, 5.25.

Synthesis of compounds 9a,b and 10a,b

A mixture of **5a,b** (2 mmol) and tetracarboxylic acid dianhydride, namely, 1,2,4,5-benzene tetracarboxylic dianhydride or 1,8,4,5-naphthalenetetracarboxylic dianhydride (1 mmol) in glacial acetic acid (30 mL) was heated under reflux for 5 h. The obtained residue was filtered off, washed with acetic acid, dried and crystallized from the proper solvents to afford the corresponding *bis*-derivatives **9a,b** and **10a,b**, respectively.

2,6-*Bis*[7-(2-chloro-6-ethoxypyridin-4-yl)-9-(4-fluorophenyl)-3-hydroxy-2-methylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-on-3-yl)]pyrrolo[3,4-f]isoindole-1,3,5,7(2*H*,6*H*)-tetrone (9a): Yield 55 %, m.p. 278-280 °C; IR (KBr, ν_{max}, cm^{-1}): 1756 (C=O), 1672 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.32 (t, 6H, 2 CH_3), 2.42 (s, 6H, 2 CH_3), 3.86 (q, 4H, 2 CH_2), 6.80-7.92 (m, 12H, 8 Ph-H + 4 pyr-H), 8.56 (s, 2H, 2 pyr-5'-H), 9.15 (s, 2H, benzene-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 13.88, 25.01, 64.20, 101.04, 101.68, 116.32, 120.38, 123.08, 125.45, 128.90, 131.73, 135.16, 136.40, 145.70, 146.24, 149.82, 151.80, 154.16, 154.80, 157.30, 159.60, 162.76, 164.22, 165.34; MS, *m/z* (%): 1146 [M^+, 4], 465 [100, base peak]. Elemental analysis for $C_{56}H_{32}N_{10}O_8S_2Cl_2F_2$ (1145.95): Calcd.: C, 58.69; H, 2.81; Cl, 6.19; N, 12.22; S, 5.60; Found: C, 58.65; H, 2.77; Cl, 6.15; N, 12.17; S, 5.54.

2,6-*Bis*[7-(2-chloro-6-ethoxypyridin-4-yl)-9-(4-chlorophenyl)-3-hydroxy-2-methylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-on-3-yl)]pyrrolo[3,4-*f*]isoindole-1,3,5,7(2*H*,6*H*)-tetrone (9b): Yield 62 %, m.p. 302-304 °C; IR (KBr, ν_{max}, cm^{-1}): 1748 (C=O), 1668 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.26 (t, 6H, 2 CH_3), 2.48 (s, 6H, 2 CH_3), 3.92 (q, 4H, 2 CH_2), 6.76-7.90 (m, 12H, 8 Ph-H + 4 pyr-H), 8.45 (s, 2H, 2 pyr-5'-H), 9.18 (s, 2H, benzene-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.15, 25.08, 64.18, 101.15, 101.76, 116.42, 121.02, 122.88, 125.65, 128.78, 131.68, 135.24, 136.45, 145.65, 146.32, 150.05, 151.84, 154.12, 155.08, 157.26, 159.61, 162.74, 164.18, 165.46; MS, *m/z* (%): 1179 [M^+, 8], 156 [100, base peak]. Elemental analysis for $C_{56}H_{32}N_{10}O_8S_2Cl_4$ (1178.86): Calcd.: C, 57.06; H, 2.74; Cl, 12.03; N, 11.88; S, 5.44; Found: C, 57.00; H, 2.69; Cl, 11.98; N, 11.82; S, 5.40.

Compound 10a: Yield 55 %, m.p. 325-327 °C; IR (KBr, ν_{max}, cm^{-1}): 1752 (C=O), 1670 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.28 (t, 6H, 2 CH_3), 2.45 (s, 6H, 2 CH_3), 3.83 (q, 4H, 2 CH_2), 6.78-7.90 (m, 12H, 8 Ph-H + 4 pyr-H), 8.52 (s, 2H, 2 pyr-5'-H), 8.62 (d, 4H, naphthalen-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.08, 25.12, 64.26, 101.15, 101.72, 116.36, 120.42, 121.45, 123.10, 128.94, 131.65, 135.22, 136.38, 139.64, 145.65, 146.30, 149.80, 151.76, 154.22, 154.75, 157.18, 158.65, 159.64, 162.70, 165.44; MS, *m/z* (%): 1196 [M^+, 18], 634 [100, base peak]. Elemental analysis for $C_{60}H_{34}N_{10}O_8S_2Cl_2F_2$ (1196.01): C, 60.25; H, 2.87; Cl, 5.93; N, 11.71; S, 5.36; Found: C, 60.20; H, 2.80; Cl, 5.88; N, 11.66; S, 5.30.

Compound 10b: Yield 56 %, m.p. 336-338 °C; IR (KBr, ν_{max}, cm^{-1}): 1746 (C=O), 1674 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.30 (t, 6H, 2 CH_3), 2.52 (s, 6H, 2 CH_3), 3.90 (q, 4H, 2 CH_2), 6.84-7.96 (m, 12H, 8 Ph-H + 4 pyr-H), 8.42 (s, 2H, 2 pyr-5′-H), 8.65 (d, 4H, naphthalen-H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 14.38, 25.12, 64.24, 101.23, 101.66, 116.53, 121.10, 121.78, 122.80, 128.70, 131.65, 135.34, 136.48, 139.05, 145.72, 146.40, 150.12, 151.80, 154.16, 155.12, 157.34, 158.65, 159.78, 162.70, 165.40; MS, *m/z* (%): 1229 [M^+, 8], 165 [100, base peak]. Elemental analysis for $C_{60}H_{34}N_{10}O_8S_2Cl_4$ (1228.92): C, 58.64; H, 2.79; Cl, 11.54; N, 11.40; S, 5.22; Found: calcd.: C, 58.60; H, 2.73; Cl, 11.50; N, 11.34; S, 5.16.

Biological assay: The antimicrobial activities were determined by Agar diffusion method. The microorganism inoculums were uniformly spread using sterile cotton swab on a sterile Petri dish containing Malt extract agar (for fungi) and nutrient agar (for bacteria). Each sample (100 µL) was added to each well (6 mm diameter holes cut in the agar gel, 20 mm apart from one another). The systems were incubated for 24-48 h at 37 °C (for bacteria) and at 28 °C (for fungi). After incubation, microorganism growth was observed. Inhibition of the bacterial and fungal growth were measured in mm. Tests were performed in triplicate[33].

Pharmacology screening: All animals were obtained from Animal House Colony, Research Institute of Ophthalmology, Giza, Egypt.

Determination of acute toxicity (LD_{50}): The LD_{50} for compounds were determined by injected different gradual increased doses of the tested compounds to adult mail albino rats, then calculate the dose cause 50% animal death, according to Austen *et al.*[34] (Table-2).

Analgesic activity: Sixty Webster mice of both sexes weighting from 20-25 g were divided into 10 groups. One group was kept as control (received saline), the second group received vehicle (*Gum acacia*) and the third one received Valdecoxib® as a reference drug, whereas the other groups received tested compounds (SC administration). Mice were dropped gently in a dry glass beaker of one-liter capacity maintained at 55-55.5 °C. Normal reaction time in seconds for all animals was determined at time intervals of 10, 20, 30, 45, 60, 90 and 120 min. This is the interval extending from the instant the mouse reaches the hot beaker till the animals licks its feet or jump out of the beaker (dose 5 mg/kg)[35], relative potencies to valdecoxib® were determined (Table-3).

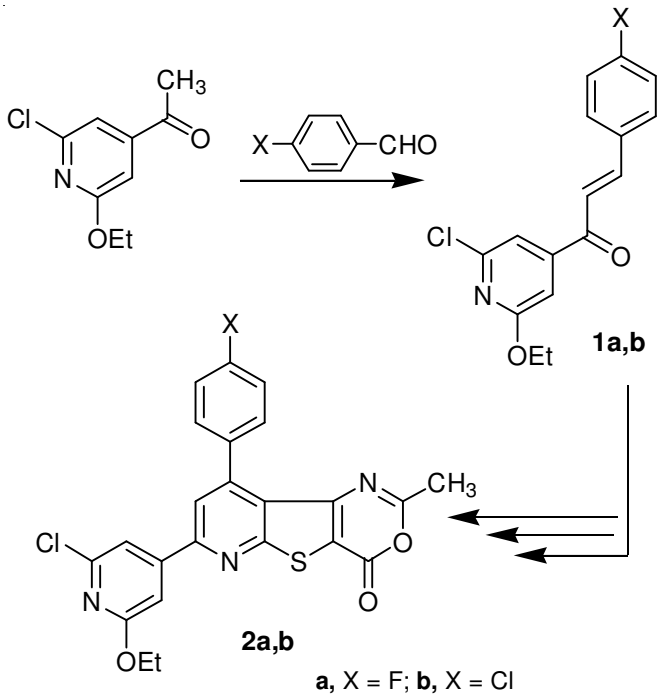
Antiparkinsonian activity: Groups of eight mail mice (18-20 g) were used. They were dosed orally with the tested compounds (5 mg/kg) or the standard (benzatropine®, 5 mg/kg)[36] 1 h prior to the administration of 0.5 mg/kg of oxotremorine® S.C. Rectal temperature was measured before

administration of the compounds and 1 h after oxotremorine® dosage. The score for the recorded signs are zero (absent), one (slight), two (mediums) and three (highs) (Table-4).

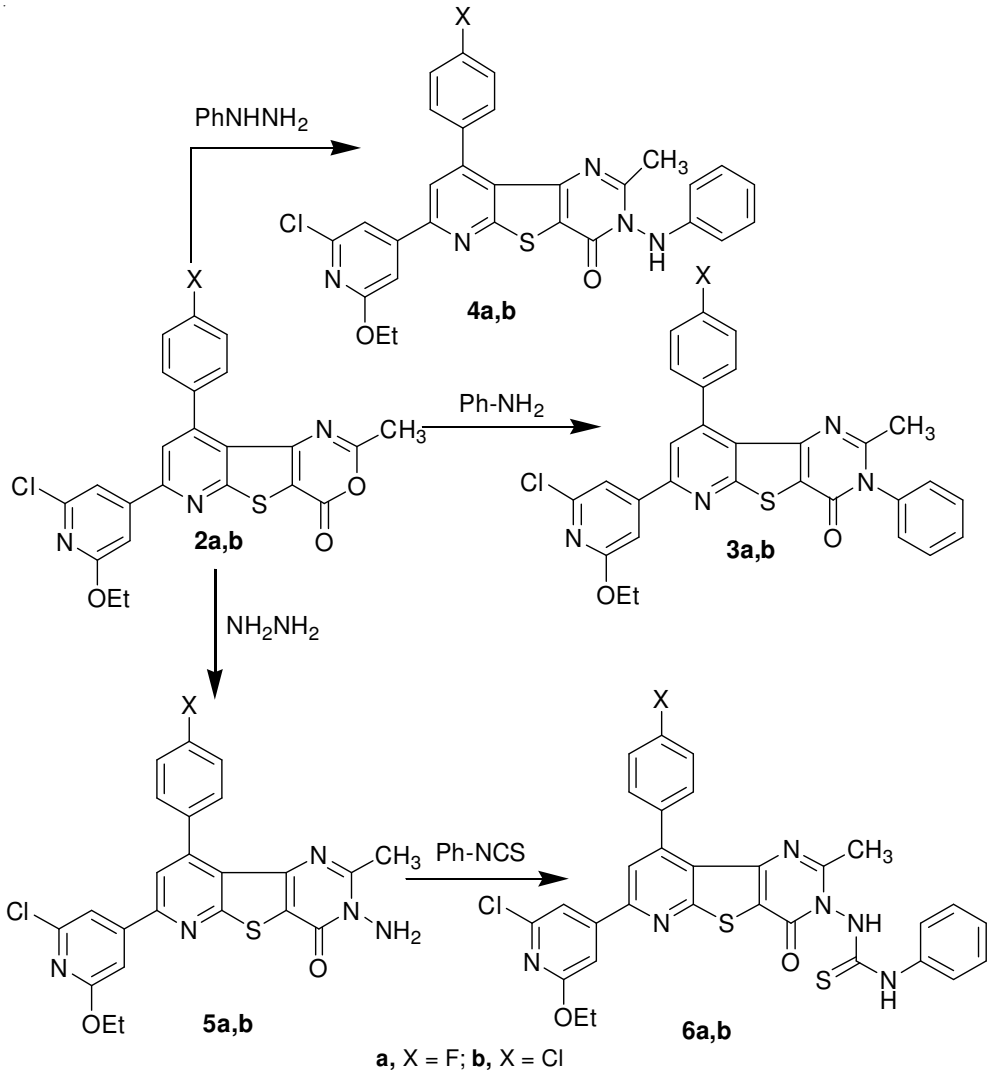
RESULTS AND DISCUSSION

In the present work, 2-chloro-6-ethoxy-4-[(2-methyl-4-oxo-9-(substituted phenyl)pyrido-[3′,2′:4,5]thieno[3,2-*d*]oxazin-7-yl]pyridines (**2a,b**) was used as starting material and it was prepared from the corresponding 1-(2-chloro-6-ethoxypyridin-4-yl)-3-(substituted phenyl)prop-2-en-1-one **1a,b** according to our reported methods[23,24] (**Scheme-I**).

Treatment of oxazinone derivatives **2a,b** with aniline or phenylhydrazine in glacial acetic acid under reflux condition afforded the corresponding 7-(2-chloro-6-ethoxypyridin-4-yl)-9-aryl-2-methyl-3-phenyl-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4(3*H*)-one (**3a,b**) and 7-(2-chloro-6-ethocypyridin-4-yl)-9-aryl-3-benzyl-2-methylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine-4(3*H*)-one (**4a**,**b**), respectively. In addition, reacting of **2a**,**b** with hydrazine hydrate in refluxing ethanol afforded the corresponding *N*-aminothienopyrimidine derivatives (**5a**,**b**), which was reacted with phenylisothiocyanate to give the corresponding thiosemicarbazide derivatives (**6a**,**b**), respectively (**Scheme-II**).

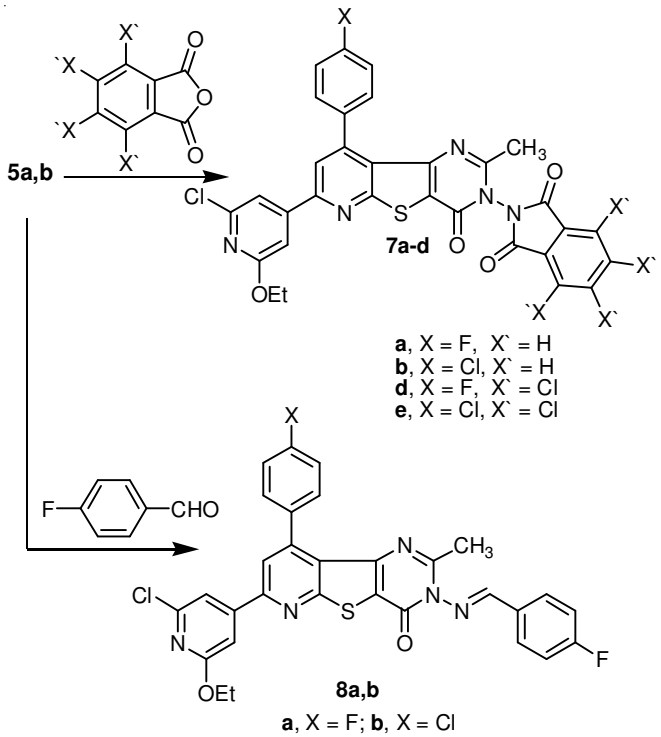


Scheme-I: Synthetic pathway for starting material **2**



Scheme-II: Synthetic pathway for compounds **3-6**

Additionally, condensation of **5a**,**b** with *p*-fluorobenzaldehyde in refluxing ethanol containing a few drops of piperidine yielded the corresponding Schiff's bases **8a,b**. Also, the reaction of **5a**,**b** with phthalic anhydride or 2,3,4,5-tetrachlorophthalic anhydride in refluxing acetic acid gave the corresponding 3-imido-pyrimidinone derivatives **7a-d** (**Scheme-III**).



Scheme-III: Synthetic pathway for compounds **7** and **8**

Finally, treatment of **5a**,**b** with 1,2,4,5-benzenetetracarboxylic acid dianhydride or 1,8,4,5-naphthaline-tetracarboxylic acid dianhydride in acetic acid gave the corresponding *bis*-compounds **9a**,**b** and **10a**,**b**, respectively (**Scheme-IV**).

Antimicrobial activity: *in vitro* Antimicrobial screening of compounds prepared in this study was carried out using cultures of four fungal strains, including *Aspergillus niger* and *Candida albicans* as well as four bacteria species, namely, Gram positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, Gram negative bacteria, *Escherichia coli*. Streptomycin and fusidic acid were used as positive reference drugs to evaluate the potency of the tested compounds under the same conditions. Most of the newly synthesized compounds showed highest with respect to control drugs. Ten of the synthesized compounds **3a**, **3b**, **4b**, **6a**, **6b**, **7c**, **7d**, **8a**, **9b** and **10b** exhibited potent antibacterial and antifungal bioactivity compared with the standard drug used. The other tested compounds were found to exhibit a moderate to low antibacterial activities (Table-1). The most active compound is **8a** which due to the increase in the fluorine number in the phenyl rings. The results of antimicrobial activities were shown in Table-1.

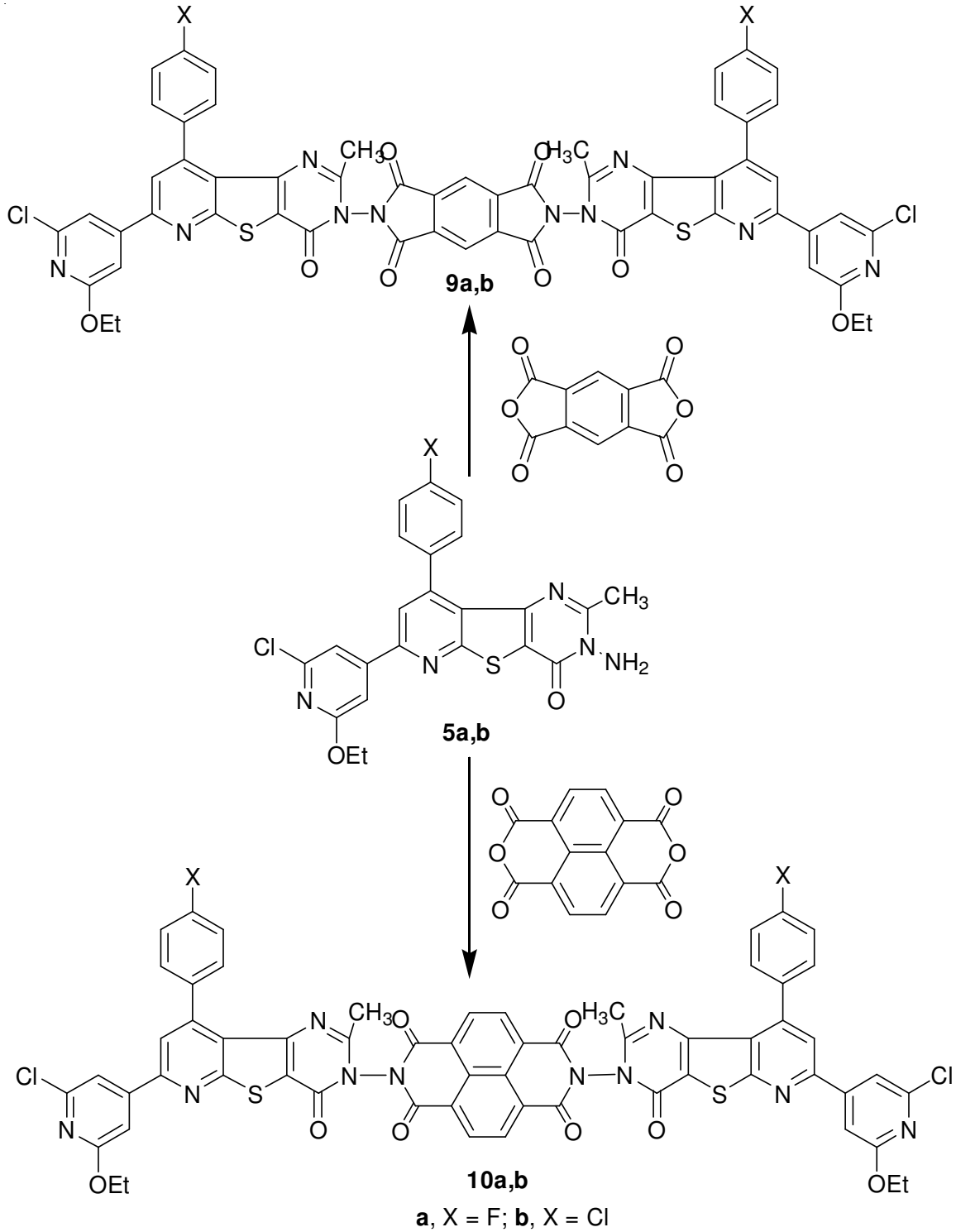
Pharmacological screening: Initially, the acute toxicity of the compounds was assayed *via* the determination of their LD_{50} (Table-2). The tested two pharmacological activities namely,

TABLE-2
ACUTE TOXICITY LD_{50} OF THE SYNTHESIZED AND STARTING COMPOUNDS

Compound No.	LD_{50} (mg kg^{-1})
Valdecoxib®	1.68
3b	1.75
3a	1.81
4a	2.35
6a	2.30
6b	1.96
7c	2.48
7d	2.82
8a	3.54
9b	1.72
10b	2.40

TABLE-1
ANTIMICROBIAL ACTIVITIES OF NEWLY SYNTHESIZED COMPOUNDS **3-10**

Compound no.	Fungi		Gram +ve bacteria		Gram -ve bacteria
	Aspergillus niger	*Candida albicans*	*Staphylococcus aureus*	*Bacillus subtilis*	*Escherichia coli*
3a	16.4	16.8	20.0	20.4	19.9
3b	15.6	16.7	18.5	19.8	20.4
4a	10.5	9.8	10.2	12.4	6.4
4b	16.3	16.9	19.3	20.2	18.2
5a	13.2	12.8	16.8	14.6	12.3
5b	12.8	112	14.4	15.3	9.6
6a	15.9	16.9	18.8	19.9	20.4
6b	16.3	17.2	19.2	19.8	19.2
7a	12.8	17.2	14.8	12.6	14.0
7b	11.6	12.2	13.3	16.7	15.9
7c	16.2	16.8	20.4	21.2	18.9
7d	16.4	17.0	18.1	20.9	18.2
8a	17.9	17.8	20.6	21.8	21.5
8b	12.8	11.4	12.4	15.6	9.5
9a	12.8	11.5	13.4	16.5	9.4
9b	16.7	15.4	18.9	20.3	19.7
10a	10.4	9.2	12.0	14.3	7.4
10b	16.3	15.7	19.2	19.4	20.2
Streptomycin	-	-	21.0	22.0	22.0
Fusidic acid	17.0	18.0	-	-	-



Scheme-IV: Synthetic pathway for compounds **9** and **10**

analgesic and antiparkinsonian activities of their different biological receptors yet all of a neurological. Ten representative compounds **3a**,**b**, **4a**, **6a**,**b**,**7c**,**d**, **8a**, **9b**, **10b** were studied with respect to analgesic and antiparkinsonian activities.

Analgesic activity: All compounds tested exhibited analgesic activities in a hot plate assay (Table-3). The most potent are compounds **7c** and **8a** showed higher activity than voldecoxib® by nearly 140-160 % (compound **8a** showed the most pronounced effect). Also, the analgesic activities of another compounds approached those of valdecoxib® and showed 62-84 % activity as compared to valdecoxib® (= 100 %) (Table-3).

Antiparkinsonian activity: The antiparkinsonian activity measured by the ability of compounds to protect animals against the parkinsonian like sings induced by agonists. Compounds **3a**, **4a**, **6a** and showed nearly no antiparkinsonian activities, while compounds **3b, 6b** and **7d** showed moderate antiparkinsonian activities. Compounds **7c**, **8a** and **10a** are the most potent antiparkinsonian agents (Table-4).

TABLE-3
ANALGESIC ACTIVITIES OF SELECTED COMPOUNDS IN A HOT PLATE ASSAY

Comp. No.	Analgesic activity related to Valdecoxib® after						
	10 min ± SE	20 min ± SE	30 min ± SE	45 min ± SE	60 min ± SE	90 min ± SE	120 min ± SE
Valdecoxib®	1.00 ± 0.010	1.00 ± 0.010	1.00 ± 0.010	1.00 ± 0.010	1.00 ± 0.010	1.00 ± 0.010	1.00 ± 0.010
3a	0.79 ± 0.010	0.85 ± 0.013	0.86 ± 0.013	0.88 ± 0.014	0.86 ± 0.015	0.86 ± 0.010	0.85 ± 0.017
3b	0.84 ± 0.015	0.94 ± 0.014	0.92 ± 0.017	0.97 ± 0.021	0.96 ± 0.030	0.94 ± 0.015	0.95 ± 0.024
4a	0.93 ± 0.010	0.94 ± 0.010	0.93 ± 0.015	0.90 ± 0.019	0.85 ± 0.021	0.82 ± 0.016	0.65 ± 0.012
6a	0.63 ± 0.014	0.75 ± 0.010	0.82 ± 0.001	0.84 ± 0.014	0.87 ± 0.015	0.86 ± 0.013	0.85 ± 0.035
6b	0.66 ± 0.010	0.66 ± 0.016	0.75 ± 0.014	0.74 ± 0.016	0.76 ± 0.016	0.76 ± 0.015	0.79 ± 0.014
7c	0.98 ± 0.013	0.99 ± 0.012	1.42 ± 0.135	1.58 ± 0.211	1.55 ± 0.351	1.58 ± 0.341	1.45 ± 0.451
7d	0.65 ± 0.011	0.64 ± 0.011	0.88 ± 0.011	0.89 ± 0.016	0.90 ± 0.021	0.90 ± 0.017	0.89 ± 0.018
8a	1.30 ± 0.176	1.44 ± 0.14	1.46 ± 0.131	1.45 ± 0.201	1.42 ± 0.321	1.40 ± 0.291	1.41 ± 0.278
9b	0.60 ± 0.011	0.67 ± 0.012	0.75 ± 0.013	0.76 ± 0.019	0.78 ± 0.014	0.79 ± 0.012	0.78 ± 0.012
10b	0.89 ± 0.011	0.88 ± 0.010	0.90 ± 0.010	0.92 ± 0.016	0.93 ± 0.015	0.92 ± 0.014	0.90 ± 0.016

TABLE-4
ANTIPARKINSONIAN ACTIVITIES OF SYNTHESIZED COMPOUNDS AS COMPARED WITH BENZOTROPENE®

Compound no.	Salivation and lacrimation score	Tremors score	% Decrease from Oxotremerine rectal temperature (%) ± SE	Relative potency compared to Benzotropene mesilate ± SE
Control	0	0	0	0
Benzotropene®	1	1	25.0 ± 0.400	1.00 ± 0.09
3a	3	3	4.0 ± 0.010	0.13 ± 0.014
3b	2	2	16.0 ± 0.288	0.59 ± 0.060
4a	3	3	5.0 ± 0.011	0.15 ± 0.015
6a	3	3	4.0 ± 0.016	0.13 ± 0.012
6b	1	1	17.0 ± 0.301	0.65 ± 0.07
7c	1	1	20.0 ± 0.142	0.82 ± 0.08
7d	2	2	11.0 ± 0.101	0.41 ± 0.030
8a	1	1	21.0 ± 0.368	0.80 ± 0.076
9a	3	3	5.0 ± 0.010	0.17 ± 0.010
10a	1	1	21.0 ± 0.481	0.80 ± 0.070

Conclusion

In conclusion, we reported herein antimicrobial activities of some new synthesized methyl-pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine derivatives (**3-10**) by using 2-chloro-6-ethoxy-4-[(2-methyl-4-oxo-9-(substituted phenyl)pyrido[3′,2′:4,5]-thieno[3,2-*d*]oxazin-7-yl]pyridines **2a**,**b** as starting materials. All the newly synthesized compounds were evaluated for antimicrobial activities. Ten of the synthesized compounds **3a**, **3b**, **4b**, **6a**, **6b**, **7c**, **7d**, **8a**, **9b** and **10b** exhibited potent antibacterial and antifungal bioactivity compared with the standard drug used. The other tested compounds were found to exhibit a moderate to low antibacterial activities (Table-1). The most active compound is **8a** which due to the increase in the fluorine number in the phenyl rings.

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