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ARTICLE

Synthesis and Characterization of Novel 1,3,5-Thiadiazine Derivatives Integrated with Quinoline Moiety as Potent Antimicrobial Agents

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ABSTRACT

An expeditious synthesis of series of novel 1,3,5-thiadiazine (**5a-f**) and (**6a-f**) derivatives have been described. These compounds were synthesized by reaction of 1-(*N*-((6-methyl-2-(*p*-tolyloxy)quinoline-3-yl)methylene)carbamimidoyl)-3-arylthiourea (**3a-b**) derivatives with *N*-aryl isocyanodichloride (**4a-c**) in chloroform followed by basification with dilute NH_4OH to give the target compounds **5a-f**; which were acetylated further to afford six novel 1,3,5-thiadiazin-3-(6*H*)-yl)ethanone (**6a-f**) derivatives. Synthesis of intermediate compounds **3a-b** was obtained by reacting 6-methyl-2-(*p*-tolyloxy)quinoline-3-carbaldehyde (**2a**) and 1-carbamimidoyl-3-arylthiourea (**1a-b**) in chloroform. Structures of compounds **5a-f** and **6a-f** were established by FTIR, ^1H & ^{13}C NMR, mass spectra and further supported by elemental analysis. All synthesized compounds were investigated for their *in vitro* antimicrobial screening against a panel of pathogenic microorganism comprising *S. aureus* as Gram positive while *E. coli*, *P. vulgaris*, *S. typhi* as Gram-negative bacterial strains.

KEYWORDS

1,3,5-Thiadiazines, *p*-Tolyloxy quinoline-3-carbaldehyde, Aryl imino, Antimicrobial activity.

INTRODUCTION

Enormous importance has been focused on the heterocyclic compounds containing nitrogen and sulphur. Among many of such heterocycles 1,3,5-thiadiazine is a six membered compound containing two nitrogen atoms and one sulphur atom in alternate position has found to possess wide spectrum of biological and pharmacological actions. Consequently, in last few decades 1,3,5-thiadiazines related drugs have mesmerized the attention of the chemist leading to the synthetic utility of this ring as novel chemotherapeutic medicines. 1,3,5-Thiadiazines have been reported to exhibit a wide range of diverse bioactivities such as antimicrobial [1-5], antimycobacterial [6], anti-leishmanial activity [7], antioxidant activity [8], anti-protozoal [9-12], antituberculosis [13], anti-cancer [14], anti-epileptic prodrugs [15], lipophilic carriers [16], inhibitor of mercapto-proteinases [17], antifungal [18-22], antitumoral-activity relationships [23], new cell-cycle inhibitors [24], anti-proliferative activity [25], anti-malarial [26], anti-inflammatory agents [27], potential cardiovascular activity [28], alkaline

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phosphatase inhibitors [29], anticonvulsant activities [30]. Thus they are utilized as valuable synthetic templates for the synthesis of innovative compounds with specific biological, pharmaceutical and material properties [31].

Besides this, literature survey also indicated the significance of amalgamated heterocyclic compounds bearing 1,3,5-thiadiazines and *p*-tolyloxy quinoline carbaldehyde in the field of research. All of the above facts inspired us to synthesize some novel potential *N*-((6-methyl-2-(*p*-tolyloxy)quinolin-3-yl)-methylene)-2-(arylimino)-6-(arylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (**5a-f**) and its acetyl derivatives (**6a-f**) and screen them against some pathogenic bacterial strains with a thought that combination of 1,3,5-thiadiazine with quinoline moiety may boost their pharmacological activities.

EXPERIMENTAL

The melting points were logged in open capillary in paraffin bath and are uncorrected. The compounds are purified by using column chromatography on silica gel. The reactions were checked by E. Merck TLC aluminum sheet silica and imagining the spot in UV Cabinet and iodine chamber. Chemicals used for the synthesis were of AR grade of Merck, S.D. Fine and Aldrich. Positive-ion Electro Spray Ionization (ESI) mass spectra were obtained with a Waters Micromass Q-TOF Micro, Mass Spectrophotometer. IR spectra were recorded on a Shimadzu IR spectrophotometer (KBr, ν_{max}, cm^{-1}). ^1H NMR spectra were recorded on a Bruker AM 400 instrument using DMSO-d_6 as solvent and TMS as an internal reference. Elemental analysis was performed on Thermo Scientific (Flash-2000) CHNS analyzer.

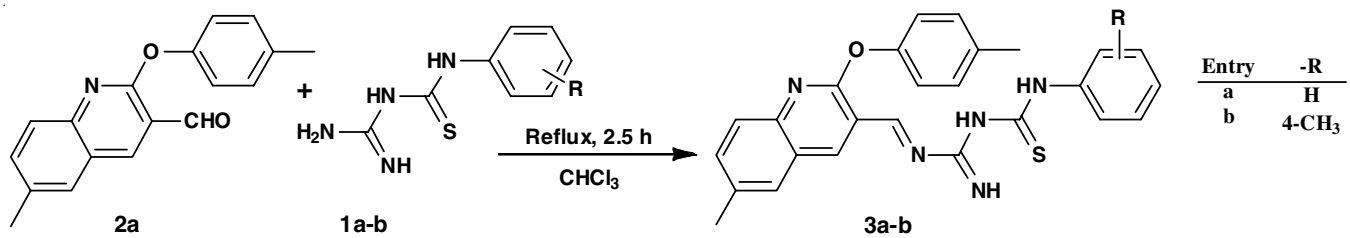
Synthesis of 1-(*N*-((6-methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)carbamimidoyl)-3-arylthiourea derivatives (3a-b): Equimolar quantity of 6-methyl-2-(*p*-tolyloxy)quinoline- 3-carbaldehyde (**2a**, 2.77 g, 0.01 mol) and 1-carbamimidoyl-3-phenyl thiourea (**1a**, 1.94 g, 0.01 mol) was taken in chloroform and refluxed for 2.5 h on water bath. Then chloroform from reaction mixture was allowed to evaporate to get 1-(*N*-((6-methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)carbamimidoyl)-3-arylthiourea (**3a**) as granular solid and recrystallized from ethanol (**Scheme-I**).

1-(*N*-((6-Methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)-carbamimidoyl)-3-phenylthiourea (3a) : Pale yellow crystalline solid; recrystallizing solvent, ethanol; m.p.: 204-205 ºC; yield 72%. IR (KBr, ν_{max}, cm^{-1}): 3100, 3885 (N-H *str.*), 3033 (C-H *str.*, arom.), 2976 (C-H_{asym} *str.*, aliph.), 2920 (C-H_{sym} *str.*, aliph.), 1434 (C-H_{asym} *def.*, aliph.), 1375 (C-H_{sym} *def.*, aliph.), 1018, 1059 (C-$H_{i.p.}$ *def.*, arom.), 824 (C-$H_{o.o.p.}$ *def.*, arom.), 1054 (C-O-C_{sym} *str.*, ether), 1249 (C-O-C_{asym} *str.*, pyrazole), 1343 (C-N *str.*, carbamimidoyl-3-*p*-tolylthiourea.), 1195 (C=S *str.*, carbamimidoyl-3-*p*-tolylthiourea), 1600, 1643, 1695 (C=N *str.*, quinoline). ^1H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, CH_3 attached to O-Ph ring), 2.44 (s, 3H, CH_3 group attached to quinoline ring), 3.65-3.76(broad, NH, -N<u>H</u>-CS-NH-Ph), 11.5 (broad, NH, -N<u>H</u>-CS-NH-Ph), 5.86 (broad, NH, -C=NH), 8.5 (s, 1H, proton at C_4 of quinoline), 6.58-8.28 (m, 12H, aromatic and hetero arom. ring protons). Elemental analysis for $C_{26}H_{23}N_5OS$ calcd. (found): N, 15.44 (15.35); S, 7.07 (7.11).

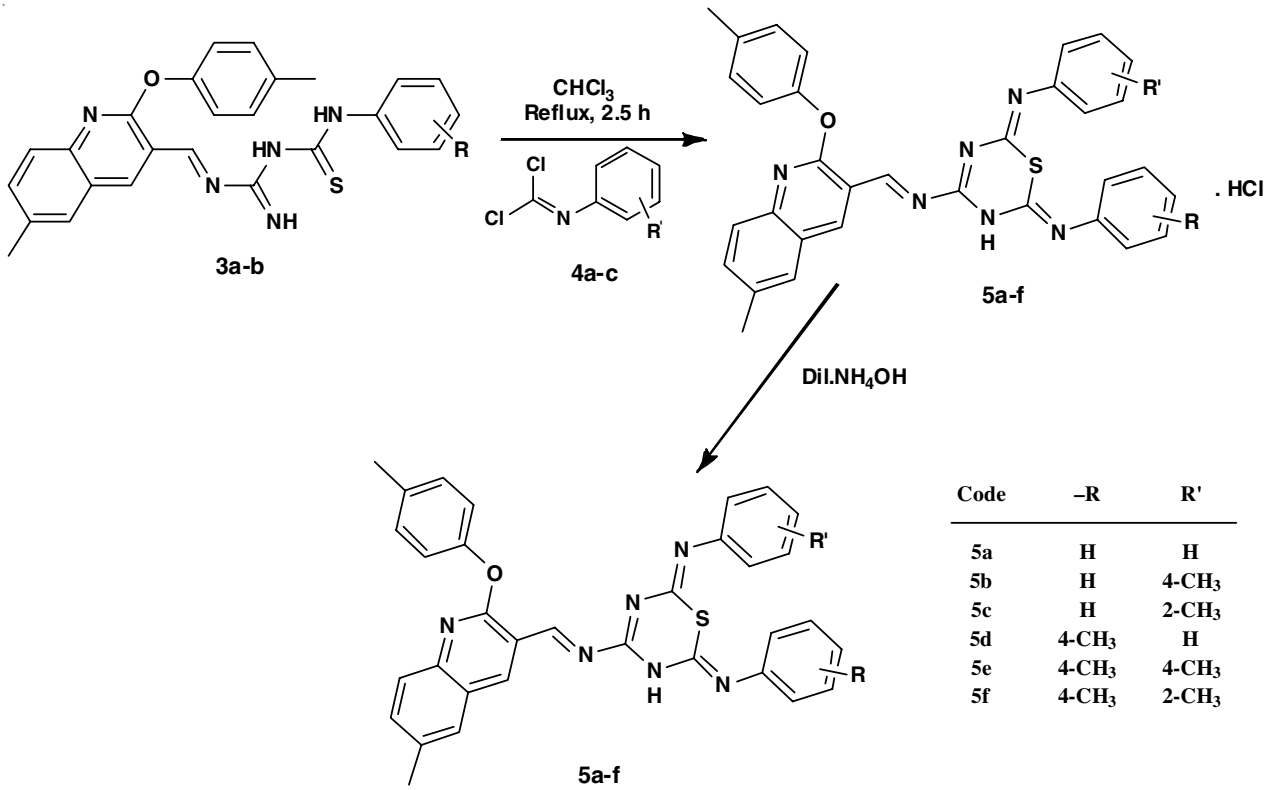
1-(*N*-((6-Methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)carbamimidoyl)-3-*p*-tolylthiourea (3b): Yellow crystalline solid; recrystallizing solvent: ethanol; m.p.: 220-221 ºC; yield: 74%. IR: (KBr, ν_{max}, cm^{-1}): 3105, 3889 (N-H *str.*), 3031 (C-H *str.*, arom.), 2975 (C-H_{asym} *str.*, aliph.), 2922 (C-H_{sym} *str.*, aliph.), 1436 (C-H_{asym} *def.*, aliph.), 1379 (C-H_{sym} *def.*, aliph.), 1019, 1056 (C-$H_{i.p.}$ *def.*, arom.), 820 (C-$H_{o.o.p.}$ *def.*, arom.), 1056 (C-O-C_{sym} *str.*, ether), 1251 (C-O-C_{asym} *str.*, pyrazole), 1348 (C-N *str.*, carbamimidoyl-3-*p*-tolylthiourea), 1199 (C=S *str.*, carbamimidoyl-3-*p*-tolylthiourea), 1602, 1642, 1692 (C=N *str.*, quinoline). ^1H NMR (DMSO-d_6) δ ppm: 2.30 (s, 3H, CH_3 attached to Ph ring), 2.38 (s, 3H, CH_3 attached to O-Ph ring), 2.45 (s, 3H, CH_3 group attached to quinoline ring), 3.69-3.71 (broad, NH, -N<u>H</u>-CS-NH-Ph), 11.3 (broad, NH, -N<u>H</u>-CS-NH-Ph), 5.85 (broad, NH, -C=NH), 8.7 (s, 1H, proton at C_4 of quinoline), 6.56-8.30 (m, 12H, aromatic and hetero aromatic ring protons). ^{13}C NMR (DMSO-d_6) δ ppm: 20 (CH_3 group attached to phenyl , phenoxy and quinoline ring), 121, 122, 124, 126, 128, 129, 132, 133, 134, 135, 138, 143, 148, 150, 157 (1C, -<u>C</u>=NH), 159 (one C,-<u>C</u>H=N-), 174 (1C, C_2 of quinoline ring to which tolyloxy group attached), 188 (1C,-NH<u>C</u>SNH- linkage). ESI-MS (*m/z*): 468 $[M+H]^+$, 469 $[M+2]^+$,490 $[M+Na]^+$. Elemental analysis for $C_{27}H_{25}N_5OS$ calcd. (found) %: C, 69.35 (69.44); H, 5.39 (5.38); N, 14.98 (14.94); S, 6.86 (6.90).

Synthesis of *N*-((6-methyl-2-(*p*-tolyloxy)quinolin-3-yl) methylene)-2-(arylimino)-6-(arylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine derivatives (5a-f): Mixture of **3a** (0.01mol) and *N*-*p*-tolyl isocyanodichloride (**4b**, 0.01mol) in chloroform (30 mL) was taken in a round bottom flask and the reaction mixture was refluxed for 2 h; HCl gas was evolved from resultant reaction content and chloroform was evaporated from reaction mixture and poured in china dish; sticky mass obtained was then washed with petroleum ether followed by addition of alcohol. On basification with dilute NH_4OH free base of compound **5b** was obtained. It was then purified using ethanol. Similarly, other products **(5a-f)** were obtained by adopting same procedure for synthesis of compound **5b** (**Scheme-II**).

***N*-((2-(*p*-Tolyloxy)-6-methylquinolin-3-yl)methylene)-3,6-dihydro-2,6-*bis*(phenylimino)-2*H*-1,3,5-thiadiazin-4-amine (5a):** Yellow crystalline solid; recrystallizing solvent, ethanol; m.p.: 192-193 ºC; yield 68%, R_f: 0.56. IR: (KBr, ν_{max},



Scheme-I



Code	–R	R'
5a	H	H
5b	H	4-CH_3
5c	H	2-CH_3
5d	4-CH_3	H
5e	4-CH_3	4-CH_3
5f	4-CH_3	2-CH_3

Scheme-II

cm^{-1}): 3640, 3135 (N-H *str*.), 3030 (C-H *str*., arom.), 2976 (C-H_{asym} *str*., aliph.), 2867(C-H_{sym} *str*., aliph.), 1601, 1689 (C=N *str*. quinoline ring), 1436 (C-H_{asym} *def*., aliph.), 1346 (C-H_{sym} *def*., aliph.), 1018, 1065 (C-$H_{i.p.}$ *def*., arom.), 822 (C-$H_{o.o.p.}$ *def*., arom.), 1500 (C=C *str*., arom.), 1250 (C-O-C_{asym} *str*., ether), 1126 (C-N-C *str*., quinoline), 696 (C-S *str*., 1,3,5-thiadiazine).

***N*-((6-Methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)-2-(phenylimino)-6-(*p*-tolylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (5b) :** Yellow crystalline solid; recrystallizing solvent: ethanol; m.p.: 188-189 ºC, yield: 78%; R_f: 0.48; IR: (KBr, ν_{max}, cm^{-1}): 3639, 3133 (N-H *str*.), 3032 (C-H *str*., arom.), 2979(C-H_{asym} *str*., aliph.), 2867 (C-H_{sym} *str*., aliph.), 1601, 1689 (C=N *str*. quinoline ring), 1438 (C-H_{asym} *def*., aliph.), 1346 (C-H_{sym} *def*., aliph.), 1018, 1065 (C-$H_{i.p.}$ *def*., arom.), 820 (C-$H_{o.o.p.}$ *def*., arom.), 1506 (C=C *str*., arom.), 1249 (C-O-C_{asym} *str*., ether), 1124 (C-N-C *str*., quinoline.), 694 (C-S *str*., 1,3,5-thiadiazine). ^{1}H NMR (DMSO-d_6) δ ppm: 2.29 (s, 3H, CH_3 group attached to imino phenyl ring), 2.40 (s, 3H, CH_3 group attached to phenoxy), 2.45 (s, 3H, CH_3 group attached to quinoline ring), 10.50 (broad, NH of thiadiazine ring), 8.91 (s, 1H, one proton at C_4 of quinoline ring), 8.72 (s, 1H, one proton of azomethine group, -C<u>H</u>=N-), 6.40-7.69 (m, 16H, aromatic and hetero aromatic ring protons). ^{13}C NMR δ ppm: 20 (CH_3 attached to phenyl, phenoxy and quinoline ring), 118, 120, 121, 123, 124, 125, 126, 127, 128, 129, 131, 133, 134, 135, 136, 142, 143, 144, 148, 150, 151, 153, 158, 159, 188 (one carbon, C_2 of quinoline ring to which tolyloxy group attached). ESI-MS(*m/z*): 568 $[M]^+$, 569 $[M+H]^+$, 570 $[M+2]^+$. Elemental analysis for $C_{34}H_{28}N_6OS$ calc. (found): C, 71.81 (71.88); H, 4.96 (4.92); N, 14.78 (14.82); S, 5.64 (5.59).

6-(*o*-Tolylimino)-*N*-((2-(*p*-tolyloxy)-6-methylquinolin-3-yl)methylene)-3,6-dihydro-2-(phenylimino)-2*H*-1,3,5-thiadiazin-4-amine (5c): Yellow crystalline solid; recrystallizing solvent: ethanol; m.p.: 197-198 ºC, yield: 66%, R_f: 0.35; IR: (KBr, ν_{max}, cm^{-1}): 3635, 3136 (N-H *str*.), 3030 (C-H *str*., arom.) 2982 (C-H_{asym} *str*., aliph.), 2865 (C-H_{sym} *str*., aliph.), 1600, 1690 (C=N *str*. quinoline ring), 1435 (C-H_{asym} *def*., aliph.), 1346 (C-H_{sym} *def*., aliph.), 1018, 1065 (C-$H_{i.p.}$ *def*., arom.), 820 (C-$H_{o.o.p.}$ *def*., arom.), 1506 (C=C *str*., arom.), 1249 (C-O-C_{asym} *str*., ether), 1124 (C-N-C *str*., quinoline), 694 (C-S *str*.,1,3,5-thiadiazine).

2-(*p*-Tolylimino)-*N*-((2-(*p*-tolyloxy)-6-methylquinolin-3-yl)methylene)-3,6-dihydro-6-(phenylimino)-2*H*-1,3,5-thiadiazin-4-amine (5d): Yellow crystalline solid; recrystallizing solvent: ethanol; m.p.: 228-229 ºC, yield: 59%, R_f: 0.33; IR: (KBr, ν_{max}, cm^{-1}): 3639, 3133 (N-H *str*.), 3032 (C-H *str*., arom.), 2979 (C-H_{asym} *str*., aliph.), 2867 (C-H_{sym} *str*., aliph.), 1601, 1689 (C=N *str*. quinoline ring), 1438 (C-H_{asym} *def*., aliph.), 1346 (C-H_{sym} *def*., aliph.), 1018, 1065 (C-$H_{i.p.}$ def., arom.), 820 (C-$H_{o.o.p.}$ *def*., arom.), 1506 (C=C *str*., arom.), 1249 (C-O-C_{asym} *str*., ether), 1124 (C-N-C *str*., quinoline), 694 (C-S *str*.,1,3,5-thiadiazine).

2,6-*bis*(*p*-Tolylimino)-*N*-((2-(*p*-tolyloxy)-6-methylquinolin-3-yl)methylene)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (5e): Yellow crystalline solid; recrystallizing solvent: ethanol; m.p.: 215-216 ºC, yield: 70%, R_f: 0.38; IR: (KBr, ν_{max}, cm^{-1}): 3639, 3133 (N-H *str*.), 3032 (C-H *str*., arom.), 2979 (C-H_{asym} *str*., aliph.), 2867 (C-H_{sym} *str*., aliph.), 1601, 1689 (C=N *str*. quinoline ring), 1438 (C-H_{asym} *def*., aliph.), 1346 (C-H_{sym} *def*., aliph.), 1018, 1065 (C-$H_{i.p.}$ *def*., arom.), 820 (C-$H_{o.o.p.}$ *def*., arom.), 1506 (C=C *str*., arom.), 1249 (C-O-C_{asym} *str*., ether), 1124 (C-N-C *str*., quinoline), 694 (C-S *str*., 1,3,5-thiadiazine).

6-(*o*-Tolylimino)-2-(*p*-tolylimino)-*N*-((2-(*p*-tolyloxy)-6-methylquinolin-3-yl)methylene)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (5f): Yellow crystalline solid; recrystal-

lizing solvent: ethanol; m.p.: 195-196 ºC, yield: 79%, R_f: 0.56; IR: (KBr, ν_{max}, cm^{-1}): 3639, 3133 (N-H *str.*), 3032 (C-H *str.*, arom.), 2979 (C-H_{asym} *str.*, aliph.), 2867 (C-H_{sym} *str.*, aliph.), 1601, 1689 (C=N *str.* quinoline ring), 1438 (C-H_{asym} *def.*, aliph.), 1346 (C-H_{sym} *def.*, aliph.), 1018, 1065 (C-$H_{i.p.}$ *def.*, arom.), 820 (C-$H_{o.o.p.}$ *def.*, arom.), 1506 (C=C *str.*, arom.), 1249 (C-O-C_{asym} *str.*, ether), 1124 (C-N-C *str.*, quinoline), 694 (C-S *str.*, 1,3,5-thiadiazine).

Synthesis of 1-(-4-(-(6-methyl-2-(*p*-tolyloxy)quinoline-3-yl)methyleneamino)-2-(arylimino)-6-(arylamino)-2*H*-1,3,5-thiadiazin-3(6*H*)-yl)ethanone (6a-f): Equimolar concentration of compound **5a** (0.001 mol) and acetic anhydride (0.001 mol) in acetic acid (10 mL) was kept for refluxing for about 2 h, the reaction content on cooling poured to crushed ice, the product obtained was washed, filtered and recrystallized from ethanol to get compound **6a**. Similarly, other products of the series **6b-f** were prepared by applying same procedure used for the synthesis of compound **6a** (**Scheme-III**).

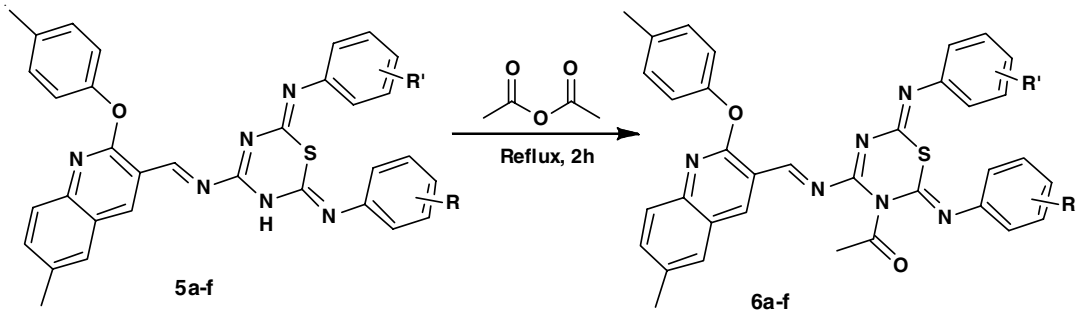
1-(-4-(-(6-Methyl-2-(*p*-tolyloxy)quinolin-3-yl)methyleneamino)-2,6-bis(phenylimino)-2*H*-1,3,5-thiadiazin-3-(6*H*)-yl)ethanone (6a) : Yellow crystalline solid; recrystallizing solvent: 1,4-dioxane; m.p.: 204-205 ºC, yield: 75%, R_f: 038. IR: (KBr, ν_{max}, cm^{-1}): 3039 (C-H *str.*, arom.), 2921 (C-H_{asym} *str.*, aliph.), 2866 (C-H_{sym} *str.*, aliph.), 1435 (C-H_{asym} *def.*, aliph.), 1391 (C-H_{sym} *def.*, aliph.), 1018, 1041, 1124 (C-$H_{i.p.}$ *def.*, arom.), 818 (C-$H_{o.o.p.}$ *def.*, arom.), 1597, 1690 (C=N *str.*, quinoline), 1506 (C=C *str.*, arom.), 1253, 1211 (C-O-C_{asym} *str.*, ether), 1041 (C-O-C_{sym} *str.*, ether), 1145 (C-N-C *str.*), 668, 713 (C-S *str.*, thioether linkage), 1347 (C-N *str.*). ^{1}H NMR (DMSO-d_6) δ ppm: 2.38 (s, 6H, CH_3 group attached to phenyl ring and other CH_3 group of -NCOC<u>H</u>$_3$), 2.48 (s, 3H, CH_3 group attached to quinoline ring), 8.70 (s, 1H, proton at C_4 of quinoline), 8.15 (s, 1H, proton of azomethine group, -CH=N-), 7.80 (s, 1H, proton at C_8 of quinoline), 7.16-7.58 (m, 16H, aromatic and hetero aromatic ring protons). ^{13}C NMR (DMSO-d_6) δ ppm: 20 (CH_3 attached to phenyl, phenoxy and quinoline ring), 99, 119, 121, 124, 126, 128, 129, 133, 134, 139, 146, 150, 159, 162, 172 (one carbonyl carbon of $COCH_3$), 188 (one carbon, C_2 of quinoline ring to which tolyloxy group attached). ESI-MS (*m/z*): 596 $[M]^+$, 597 $[M+H]^+$, 598 $[M+2]^+$. Elemental analysis for $C_{35}H_{28}N_6O_2S$ calcd. (found): C, 70.45 (70.48); H, 4.73 (4.80); N, 14.08 (14.04); S, 5.37 (5.42).

4-((2-(*p*-Tolyloxy)-6-methylquinolin-3-yl)methyleneamino)-6-(*p*-tolylimino)-2-(phenylimino)-2*H*-1,3,5-thiadiazin-3-(6*H*)-yl)ethanone (6b): Yellow crystalline solid; recrystallizing solvent: 1,4-dioxane; m.p.: 206-207 ºC, yield: 69%, R_f: 0.35. IR: (KBr, ν_{max}, cm^{-1}): 3037 (C-H *str.*, arom.), 2923 (C-H_{asym} *str.*, aliph.), 2868 (C-H_{sym} *str.*, aliph.), 1433 (C-H_{asym} *def.*, aliph.), 1393 (C-H_{sym} *def.*, aliph.), 1017, 1040, 1122 (C-$H_{i.p.}$ *def.*, arom.), 819 (C-$H_{o.o.p.}$ *def.*, arom.), 1593, 1690 (C=N *str.*, quinoline), 1505 (C=C *str.*, arom.), 1252, 1213 (C-O-C_{asym} *str.*, ether), 1044 (C-O-C_{sym} *str.*, ether), 1142 (C-N-C *str.*), 668, 714 (C-S *str.*, thioether linkage), 1345 (C-N *str.*). Elemental analysis for $C_{36}H_{30}N_6O_2S$ calcd. (found) %: C, 70.80 (70.70); H, 4.95 (4.93); N, 13.76 (13.64); S, 5.25 (5.22).

4-((2-(*p*-Tolyloxy)-6-methylquinolin-3-yl)methyleneamino)-6-(*o*-tolylimino)-2-(phenylimino)-2*H*-1,3,5-thiadiazin-3(6*H*)-yl)ethanone (6c): Yellow crystalline solid; recrystallizing solvent: 1,4-dioxane; m.p.: 180-181 ºC, yield: 74%, R_f: 0.42. IR: (KBr, ν_{max}, cm^{-1}): 3035 (C-H *str.*, arom.), 2923 (C-H_{asym} *str.*, aliph.), 2868 (C-H_{sym} *str.*, aliph.), 1436 (C-H_{asym} *def.*, aliph.), 1392 (C-H_{sym} *def.*, aliph.), 1016, 1045, 1121 (C-$H_{i.p.}$ def., arom.), 814 (C-$H_{o.o.p.}$ *def.*, arom.), 1597, 1691 (C=N *str.*, quinoline), 1502 (C=C *str.*, arom.), 1252, 1210 (C-O-C_{asym} *str.*, ether), 1041 (C-O-C_{sym} *str.*, ether), 1143 (C-N-C *str.*), 667, 715 (C-S *str.*, thioether linkage), 1344 (C-N *str.*). Elemental analysis for $C_{36}H_{30}N_6O_2S$ calc. (found) %: C, 70.80 (70.75); H, 4.95 (4.91); N, 13.76 (13.74); S, 5.25 (5.23).

4-((2-(*p*-Tolyloxy)-6-methylquinolin-3-yl)methyleneamino)-2-(*p*-tolylimino)-6-(phenylimino)-2*H*-1,3,5-thiadiazin-3(6*H*)-yl)ethanone (6d): Yellow crystalline solid; recrystallizing solvent: 1,4-dioxane; m.p.: 216-217 ºC, yield: 65%, R_f: 0.25; IR: (KBr, ν_{max}, cm^{-1}): 3040 (C-H *str.*, arom.), 2920 (C-H_{asym} *str.*, aliph.), 2862 (C-H_{sym} *str.*, aliph.), 1431 (C-H_{asym} *def.*, aliph.), 1394 (C-H_{sym} *def.*, aliph.), 1020, 1039, 1121 (C-$H_{i.p.}$ *def.*, arom.), 820 (C-$H_{o.o.p.}$ *def.*, arom.), 1599, 1695 (C=N *str.*, quinoline), 1502 (C=C *str.*, arom.), 1251, 1210 (C-O-C_{asym} *str.*, ether), 1044 (C-O-C_{sym} *str.*, ether), 1146 (C-N-C *str.*), 666, 711 (C-S *str.*, thioether linkage), 1349 (C-N *str.*) Elemental analysis for $C_{36}H_{30}N_6O_2S$ calcd. (found) %: C, 70.80 (70.77); H, 4.95 (4.90); N, 13.76 (13.74); S, 5.25 (5.20).

4-((2-(*p*-Tolyloxy)-6-methylquinolin-3-yl)methyleneamino)-2,6-bis(*p*-tolylimino)-2*H*-1,3,5-thiadiazin-3-(6*H*)-yl)ethanone (6e): Yellow crystalline solid; recrystallizing solvent: 1,4-dioxane; m.p.: 206-207 ºC, yield: 76%, R_f 0.49. IR (KBr, ν_{max}, cm^{-1}): 3042 (C-H *str.*, arom.), 2925 (C-H_{asym} *str.*, aliph.), 2869 (C-H_{sym} *str.*, aliph.), 1438 (C-H_{asym} *def.*, aliph.), 1395 (C-H_{sym} *def.*, aliph.), 1020, 1044, 1123 (C-$H_{i.p.}$ *def.*, arom.), 813 (C-$H_{o.o.p.}$ *def.*, arom.), 1599, 1695 (C=N *str.*, quinoline), 1500 (C=C *str.*, arom.), 1251, 1210 (C-O-C_{asym} *str.*, ether), 1042 (C-O-C_{sym} *str.*, ether), 1148 (C-N-C *str.*), 668, 711 (C-S *str.*, thioether linkage), 1349 (C-N *str.*). Elemental analysis for $C_{37}H_{32}N_6O_2S$ calcd. (found) %: C, 71.13 (71.10); H, 5.16 (5.10); N, 13.45 (13.41); S, 5.13 (5.12).



Code	–R	R'
6a	H	H
6b	H	4-CH_3
6c	H	2-CH_3
6d	4-CH_3	H
6e	4-CH_3	4-CH_3
6f	4-CH_3	2-CH_3

Scheme-III

4-((2-(*p*-Tolyloxy)-6-methylquinolin-3-yl)methyleneamino)-6-(*o*-tolylimino)-2-(*p*-tolylimino)-2*H*-1,3,5-thiadiazin-3(6*H*)-yl)ethanone (6f): Yellow crystalline solid; recrystallizing solvent: 1,4-dioxane; m.p.: 211-212 ºC, yield: 70%, R_f: 0.52. IR: (KBr, ν_{max}, cm^{-1}): 3042 (C-H *str*., arom.), 2924 (C-H_{asym} *str*., aliph.), 2867 (C-H_{sym} *str*., aliph.), 1433 (C-H_{asym} *def*., aliph.), 1394 (C-H_{sym} *def*., aliph.), 1020, 1043, 1120 (C-$H_{i.p.}$ *def*., arom.), 820 (C-$H_{o.o.p.}$ *def*., arom.), 1595, 1688 (C=N *str*., quinoline), 1502 (C=C *str*., arom.), 1251, 1210 (C-O-C_{asym} *str*., ether), 1043 (C-O-C_{sym} *str*., ether), 1147 (C-N-C *str*.), 664, 715 (C-S *str*., thioether linkage), 1349 (C-N *str*.). Elemental analysis for $C_{37}H_{32}N_6O_2S$ calcd. (found) %: C, 71.13 (71.10); H, 5.16 (5.14); N, 13.45 (13.44); S, 5.13 (5.10).

Determination of zone of inhibition: *in-vitro* antibacterial activity was determined by using Mueller Hinton Agar obtained from Hi Media Ltd., Mumbai, India. Petri plates were prepared by pouring 10 mL of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. Test solutions were prepared with known weight of compound in DMSO and half diluted suitably to give the resultant concentration of 31-1000 µg/mL. Whatmann no.1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. The discs were then applied and the plates were incubated at 37 ºC for 24 h (bacteria) and the inhibition zone was measured as diameter in four directions and expressed as mean.

RESULTS AND DISCUSSION

The synthesis of the title compounds **5a-f** described in **Schemes I-III**. At every stage reaction was monitored with TLC. The identities of synthesized compounds have been confirmed using elemental and different spectroscopic techniques such as IR, ^1H & ^{13}C NMR and were also evaluated for their antimicrobial activity. The synthesis of starting compound 1-carbamimidoyl-3-aryllthiourea (**1a-b**, **Scheme-I**) was afforded by refluxing substituted phenyl isothiocyanate with guanidine nitrate in presence of NaOH in ethanol. Compound **1a-b** was later on treated with **2a** to produce 1-(*N*-((6-methyl-2-(*p*-tolyloxy)-quinolin-3-yl)methylene)carbamimidoyl)-3-aryl thiourea (**3a-b**, **Scheme-I**). The IR spectrum of compound **3b** showed an absorption peak at 3105, 3889 cm^{-1} due to N-H stretch, characteristic peak at 1199 cm^{-1} was observed due to C=S stretch in carbamimidoyl-3-*p*-tolylthiourea. Absence of peak due to carbonyl group in compound **3b** indicated the formation of hydrazone. Rest of the infrared peaks due to C-N stretch in carbamimidoyl-3-*p*-tolylthiourea, C=N stretch in quinoline, symmetric and asymmetric stretch in aliphatic region, ether, and pyrazole, were present at the expected region for compound **3b**. ^1H NMR spectrum of compound **3b** showed three singlet′s; first at δ 2.30 ppm due to C$\underline{H}_3$ group attached to aromatic ring, second at δ 2.38 ppm due to C$\underline{H}_3$ group attached to -O-Ph ring, while the third at δ 2.45 ppm due to C$\underline{H}_3$ group attached to quinoline ring. One broad signal was observed in the range of at δ 3.69-3.71 due to -N$\underline{H}$-CS-NH-PH, while rest of two due to NH-CS-N$\underline{H}$-PH and -C=N$\underline{H}$ protons were obtained at δ 11.3 and 5.85 ppm, respectively which clearly supported the formation of compound **3b**. One deshielded proton of quinoline ring at C_4 showed a singlet at a higher δ 8.7 ppm. The remaining twelve aromatic and heterocyclic ring protons show multiplet in the range δ 6.56-8.30 ppm. Similarly, ^{13}C NMR spectrum for **3b** showed characteristic signals, one at δ 188 ppm due to carbon atom of C=S, and other at δ 159 ppm due to carbon atom of azomethine and imino group. Thus the number of carbon atoms present in the structure was confirmed by ^{13}C NMR. The mass spectra displayed molecular ion peaks of $[M+H]^+$ at 468, $[M+2]^+$ at 469 and $[M+Na]^+$ at 490. Thus IR, ^1H &^{13}C NMR, mass spectral data and elemental analysis confirmed the structure of **3b**. Reaction of *N*-aryl isocyano dichloride (**4a-c**) with **3a-b** in chloroform afforded hydrochloride derivatives of *N*-((6-methyl-2-(*p*-tolyloxy)quinolin-3-yl)-methylene)-2-(arylimino)-6-(arylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (**5a-f**) derivatives which on neutralization by adding NH_4OH afforded six different 1,3,5-thiadiazines (**5a-f**) (**Scheme-II**). The IR spectra supported the formation of **5b** as a characteristic absorption peak due to C-S stretch in 1,3,5-thiadiazine was observed at 694 cm^{-1}. The ^1H NMR spectra of compound **5b** also showed three singlet′s; one at δ 2.29 ppm due to C$\underline{H}_3$ group attached to NH-Ph ring, second at δ 2.40 ppm due to C$\underline{H}_3$ group attached to -O-Ph ring, and a third one at δ 2.45 ppm due to C$\underline{H}_3$ group attached to quinoline ring. Two prominent peaks were observed; one at δ 8.72 ppm that indicated proton of azomethine group -C$\underline{H}$=N- while a broad peak of NH occurred at δ 10.50 ppm confirmed the formation of thiadiazine ring. Compound **5b** indicated one more singlet at δ 8.91 ppm due to one proton at C_4 of quinoline ring as same observed in compound **3b**. The remaining sixteen proton of aromatic and hetero aromatic ring gave multiplet in the range of δ 6.40-7.69 ppm. ^{13}C NMR spectrum displayed a signal at δ 158 ppm was observed due to carbon atom at the sixth position of 1,3,5-thiadiazine, besides other signals were observed at 159 ppm due to C_2 and C_4 of the same ring. While rest of the signals of carbon atoms present in the structure were found to be at their specific positions. The mass spectra revealed *m/z* peaks at 568 $[M]^+$,569 $[M+H]^+$, 570 $[M+2]^+$ for compound **5b** also inveterate the structure having molecular formula $C_{34}H_{26}N_4O_2$. All these peaks and elemental analysis supported the formation of compound **5b** from compound **3b**. Reaction of 1,3,5-thiadiazines derivatives (**5a-f**) with acetic anhydride obtained six innovative derivatives of 1-(-4-(-(6-methyl-2-(*p*-tolyloxy)-quinolin-3-yl)methyleneamino)-2- (arylimino)-6-(arylimino) -2*H*-1,3,5-thiadiazin-3(6*H*)-yl)ethanone (**6a-f**) as shown in **Scheme-III**. The ^1H NMR spectra of compound **6a** showed singlet at δ 2.38 ppm for six protons due to three protons of one C$\underline{H}_3$ group attached to phenyl ring and other C$\underline{H}_3$ group attached to **–**NCOC$\underline{H}_3$. Another singlet at δ 2.48 ppm was also observed due to three protons attached to quinoline ring. One more singlet at δ 8.70 ppm was observed due to one proton at C_4 of quinoline ring. Similarly, one proton at C_8 of quinoline ring gave singlet at δ 7.80 ppm. Remaining sixteen protons of aromatic and heterocyclic ring of compound **6a** displayed multiplet in the range δ 7.16-7.58 ppm. Appearance of ^{1}HNMR signals corresponding to all the protons in compound **6a** supported the presence of twenty eight protons in the molecular formula $C_{35}H_{28}N_6O_2S$. Similarly, ^{13}C NMR spectra displayed a signal at δ 172 ppm due to one carbon atom of carbonyl in acetyl group attached to the nitrogen atom of 1,3,5-thiadiazine.

TABLE-1
ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS **5a-f** (ZONE OF INHIBITION IN mm)

Compd.	Concentration (µg/mL)											
	1000	500	250	125	63.5	31	1000	500	250	125	63.5	31
	Gram-positive: *S. aureus*						Gram-negative: *P. vulgaris*					
5a	26	24	20	18	16	18	27	24	25	20	19	15
5b	24	24	19	15	17	15	26	22	24	18	17	16
5c	25	21	19	16	15	14	25	23	19	20	15	14
5d	25	23	22	20	16	15	26	25	19	17	16	17
5e	22	24	21	19	18	13	27	23	22	20	18	16
5f	26	21	19	15	14	12	25	23	24	20	16	13
DMSO	–	–	–	–	–	–	–	–	–	–	–	–
Chloramphenicol	25	22	20	19	17	15	26	24	23	21	17	15
	Gram-negative: *E. coli*						Gram-negative: *S. typhi*					
5a	27	23	24	21	16	14	19	16	13	10	10	09
5b	25	22	24	21	18	12	18	17	12	13	09	08
5c	26	23	22	17	16	13	15	14	13	12	08	07
5d	24	25	23	22	17	11	18	13	11	12	10	08
5e	27	23	23	21	14	12	17	15	12	13	09	06
5f	23	21	18	16	15	13	16	13	11	09	07	05
DMSO	-	-	-	-	-	-	-	-	-	-	-	-
Chloramphenicol	26	24	23	21	17	14	17	15	12	11	09	08

Another signal at δ 162 ppm is obtained due to carbon atom of azomethine and carbon atom at C_2 and C_6 position, while a signal at δ 159 ppm was observed due to C_4 of 1,3,5-thiadiazine ring in compound **6a** confirmed its formation.The infrared spectra also supported the formation of compound **6a** as characteristic absorption peak due to C-S stretch was observed at 668 cm^{-1} while remaining IR absorption bands due to C=N stretch in quinoline, symmetric and asymmetric stretch in aliphatic region, ether and pyrazole were present at the expected region**.** The mass spectral data of compound **6a** is also in good agreement with molecular formula $C_{35}H_{28}N_6O_2S$ showing *m/z* peaks at 596 $[M]^+$, 597 $[M+H]^+$, 598 $[M+2]^+$.

Antibacterial activity: *in-vitro* Antibacterial screening of all the synthesized 1,3,5-thiadiazine derivatives (**5a-f**) was carried out against Gram-positive and Gram-negative bacterial strains. It is established that tested compounds showed variable toxicity against selected strains of bacteria (Table-1). This incongruity in toxicity may be due to combination of substituted *p*-tolyloxy quinoline to basic 1,3,5-thiadiazine nucleus, which enhances the biological activities. Antibacterial activity results revealed that most of the synthesized 1,3,5-thiadiazine derivatives (**5a-f**) showed substantial activities. Test compounds **5a**, **5c** and **5d** showed excellent activities than the standard drug chloramphenicol against Gram-positive bacteria *S. aureus* and Gram-negative bacteria *E. coli* while at other concentrations, it showed moderate activity.

Conclusion

In this work, the synthesis and antimicrobial activity of some novel 1,3,5-thiadiazine derivatives (**5a-f**) containing quinoline moieties in good yield and characterized.

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