Synthesis of *s*-Triazine-Based Thiazolidinones as Antimicrobial Agents

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A novel series of thiazolidinone derivatives, namely 4-{4-dimethylamino-6-[4-oxo-2-phenyl-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1*H*-quinolin-2-ones, have been synthesized from the key intermediate 4-(4-amino-6-dimethylamino-[1,3,5]-triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one (**5**). Compound **5** was condensed with various aldehydes to give Schiff base derivatives, which after cyclization gave thiazolidinones that were linked with 1-pyridin-2-yl-piperazine to obtain the target compounds. The newly synthesized compounds were evaluated for their antimicrobial activity against eight bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Proteus vulgaris, Shigella flexneri*) and four fungi (*Aspergillus niger*, *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus clavatus*).

Key words: 4-Hydroxy-1-methyl-1*H*-quinolin-2-one, Thiazolidinone, 1-Pyridin-2-yl-piperazine, Antimicrobial Activity

Introduction

The increasing incidence of infections caused by the rapid development of microbial resistance to most of the known antibiotics is a serious health problem. A number of factors is responsible for mutations in the microbial genomes. As multidrug-resistant microbial strains proliferate, the necessity for effective therapy has stimulated research on the synthesis of novel antimicrobial compounds (Saleh *et al.*, 2010).

1,3,5-Triazine derivatives have been known for a long period of time. Based on a literature survey we found that 1,3,5-triazines showed biological activities such as antimicrobial (Chande *et al.*, 1998), antitumour (Brzozowski *et al.*, 2000), anticancer (Saczewski *et al.*, 2006), antimalarial (Gravestock *et al.*, 2011), and antiviral (Chen *et al.*, 2009). So we started our work by choosing 2,4,6-trichloro-[1,3,5]-triazine as starting material. The broad and potent activity of 4-thiazolidinones has established their structure as one of the biologically most important scaffolds (Verma and Saraf, 2008). In the development of an efficient procedure for the synthesis of some new thiazolidinone derivatives, we report herein the synthesis of the key intermediate 4-(4-amino-6-dimethylamino-[1,3,5]-triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one (**5**) which contains a quinolone moiety. The quinolones, such as ciprofloxacin, ofloxacin, lomefloxacin, and enoxacin, are established synthetic antibacterial agents (Boehm *et al.*, 2000). They are widely prescribed for the treatment of infections in humans. They disrupt the activities of prokaryotic type II topoisomerases, DNA gyrase, and topoisomerase IV, and thus cells are killed by the high levels of the generated double-stranded DNA breaks. Type II topoisomerases modulate the topological state of the genetic material by passing an intact DNA helix through a transient double-stranded break that they generate in a separate DNA segment (Zhang *et al.*, 1991). Like bacterial cells, eukaryotic species require a type II topoisomerase, known as topoisomerase II, for viability (Wang, 1996). Thus, in addition to the antibacterial quinolones, specific members of this drug family display high activity against eukaryotic type II topoisomerases, in cultured mammalian cells as well as in *in vivo* tumour models (Clement *et al.*, 1995). Quinolone derivatives are used as anticancer (Sissi and Palumbo, 2003), anti-HIV (Enrica *et al.*, 2001), antitumour (Sun *et al.*, 2006), antioxidant, anti-inflammatory (Detsi *et al.*, 2007), and antithyroid (Ukrainets *et al.*, 1997)

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compounds, respectively, and also as components of organic laser-active media, luminophores, and fluorescent labels (Vasil'eva *et al.*, 2002).

So compound **5** seems to be a good candidate to fulfill our objective via its condensation with different aldehydes to afford Schiff bases and further cyclization to get thiazolidinones. The piperazine ring is found in a number of biologically active compounds, including several marketed drugs (Dorsey *et al.*, 1994), and is considered to be a privileged structure in drug discovery (Horton *et al.*, 2003). In the light of these considerations, we report the synthesis of thiazolidinone derivatives combined with 1-pyridin-2-yl-piperazine. All novel derivatives were screened for their antimicrobial activity and the results are discussed.

Experimental

Analytical methods and instruments

Chemicals and solvents were obtained from commercial sources and used as received. Melting points were measured in an open capillary on a Veego (model VMP-D; Mumbai, India) electronic apparatus and are uncorrected. The IR spectra (4000–400 cm^{-1}) of synthesized compounds were recorded on a Shimadzu 8400-S FT-IR spectrophotometer (Shimadzu India PVT. LTD., Mumbai, India) using KBr. Thin layer chromatography (TLC) was performed on microscopic glass slides (2 x 7.5 cm) coated with silica gel-G, using an appropriate mobile phase system; spots were visualized under UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz model spectrometer (Varian India PVT. LTD., Mumbai, India), using dimethyl sulfoxide (DMSO) as a solvent and TMS (Me_4Si) as internal standard, with ^{1}H resonance frequency of 400 MHz and ^{13}C resonance frequency of 100 MHz. The ^{1}H NMR and ^{13}C NMR chemical shifts are reported as parts per million (ppm) downfield from TMS and were recorded at the Center for Excellence, Vapi, India. The splitting patterns are designated as follows; s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All new compounds were subjected to elemental analysis using a Heraeus Carlo Erba 1180 CHN analyzer (Hanau, Germany). All novel compounds gave C, H, and N analyses within 0.20 percent points from the theoretical values.

The thiazolidinone derivatives **8a–r** were examined for their antimicrobial activity against several bacteria (*Staphylococcus aureus* MTCC 96, *Bacillus cereus* MTCC 619, *Escherichia coli* MTCC 739, *Pseudomonas aeruginosa* MTCC 741, *Klebsiella pneumoniae* MTCC 109, *Salmonella typhi* MTCC 733, *Proteus vulgaris* MTCC 1771, *Shigella flexneri* MTCC 1457) and fungi (*Aspergillus niger* MTCC 282, *Aspergillus fumigatus* MTCC 343, *Aspergillus clavatus* MTCC 1323, *Candida albicans* MTCC 183) using the paper disc diffusion technique (Gillespie, 1994). The sterilized (autoclaved at 120 °C for 30 min) medium (40–50 °C) was inoculated (1 mL/100 mL of medium) with the suspension (10^5 cfu/mL) of the microorganism (matched to McFarland barium sulfate standard) and poured into a Petri dish to give a depth of 3–4 mm. The paper impregnated with the test compounds in DMSO was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37 °C for 24 and 48 h for assessment of their antibacterial and antifungal activities, respectively. Ciprofloxacin (100 μg/disc) and ketoconazole (100 μg/disc) were used as antibacterial and antifungal standard, respectively. Minimum inhibitory concentrations (MIC) of the compounds were determined by the agar streak dilution method (Hawkey and Lewis, 1994). A stock solution of each synthesized compound (100 μg/mL) in DMSO was prepared, and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for antibacterial activity and Sabouraud dextrose agar medium for antifungal activity). A specified quantity of the medium (40–50 °C) containing the compound was poured into a Petri dish to give a depth of 3–4 mm and allowed to solidify. A suspension of the respective microorganism was prepared to contain approximately 10^5 cfu/mL, applied to plates with serially diluted compounds with concentrations in the range of 3.12–100 μg/mL in DMSO, and incubated at 37 °C for 24 and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate.

*Synthesis of 4,6-dichloro-N,N-dimethyl-[1,3,5]-triazine-2-amine (**1**)*

To a stirred solution of 2,4,6-trichloro-[1,3,5]-triazine (20 g, 108 mmol) in anhydrous THF (150 mL), dimethylamine (4.89 g, 100 mmol) was

added drop-wise at 0–5 °C. The resulting reaction mixture was stirred at this temperature for 2 h, then triethylamine (10.97 g, 100 mmol) was added and stirring was continued for another 4 h. The resulting mixture was treated with crushed ice, followed by neutralization by dilute HCl, and then filtered and dried. In the above process, a very minor disubstituted compound was also formed, thus compound **1** was purified by column chromatography over silica gel using *n*-hexane/ethyl acetate (97:3 v/v) as eluent system.

White solid. – Yield: 14.86 g (77%). – M.p. 126–128 °C. – IR (KBr): $\bar{\nu}$ = 806 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 3.10 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 166.9, 163.4 (2C, Ar-C), 37.4 (H$_3$C-N-CH$_3$). – $C_5H_6Cl_2N_4$ (193.03): calcd. C 31.11, H 3.13, N 29.02; found C 31.17, H 3.06, N 29.06.

*Synthesis of 4-(4-chloro-6-dimethylamino-[1,3,5]-triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**3**)*

To a stirred solution of 4-hydroxy-1-methyl-1*H*-quinolin-2-one (13 g, 74 mmol) and 60% NaH (1.78 g, 74 mmol) in anhydrous THF (150 mL), compound **1** (14.28 g, 74 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature followed by stirring for another 14 h at 45–50 °C. After completion of the reaction, the solution was treated with crushed ice, filtered, dried, and recrystallized from acetone to afford **3**.

Light reddish solid. – Yield: 20.59 g (84%). – M.p. 210 – 215 °C. – IR (KBr): $\bar{\nu}$ = 1666 (C=O of quinolone), 1256 (C-O-C linkage), 806 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.31 (dd, *J* = 7.8, 1.6 Hz, 1H at quinolone), 8.05–7.61 (m, 3H, Ar-H of quinolone), 6.05 (s, 1H, H of quinolone), 3.55 (s, 3H, -CH$_3$ of quinolone), 3.10 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 170.9 (C-Cl), 170.1 (C-O-C), 165.5 [C-N-(CH$_3$)$_2$], 161.1 (quinolone-C2), 151.6 (quinolone-C4), 141.2, 131.9, 123.1, 122.5, 116.7, 115.8, 96.1 (7C, Ar-C), 37.1 (H$_3$C-N-CH$_3$), 32.6 (quinolone-C11). – $C_{15}H_{14}ClN_5O_2$ (331.76): calcd. C 54.30, H 4.25, N 21.11; found C 54.22, H 4.29, N 21.05.

*Synthesis of 4-(4-amino-6-dimethylamino-[1,3,5]-triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**5**)*

To a solution of **3** (15 g, 45 mmol) in 1,4-dioxane (150 mL), 15% ammonia (5.109 mL, 45 mmol) was added, and the reaction mixture was refluxed for 10–15 h as per TLC monitoring. Potassium carbonate was used for neutralization of the reaction mixture. After completion of the reaction, the mixture was treated with crushed ice and neutralized by dilute HCl. The precipitate thus obtained was filtered, dried, and recrystallized from THF to give **5**.

Grey solid. – Yield: – 11.52 g (82%). – M.p. 191–194 °C. – IR (KBr): $\bar{\nu}$ = 3473 (-NH$_2$), 1666 (C=O of quinolone), 806 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 11.27 (s, 2H, -NH$_2$), 8.34 (dd, 1H, *J* = 7.5, 1.4 Hz, H at C-5 of quinolone), 8.10–7.47 (m, 3H, 3H of quinolone), 6.02 (s, 1H, H at C-3 of quinolone), 3.47 (s, 3H, -CH$_3$ of quinolone), 3.13 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 177.1 (C-NH$_2$), 167.2 (C-O-C), 164.2 [C-N-(CH$_3$)$_2$], 161.3 (quinolone-C2), 152.8 (quinolone-C4), 140.1, 132.6, 123.7, 122.7, 116.6, 115.5, 97.2 (7C, Ar-C), 37.1 (H$_3$C-N-CH$_3$), 32.5 (quinolone-C11). – $C_{15}H_{16}N_6O_2$ (312.33): calcd. C 57.68, H 5.16, N 26.91; found C 57.61, H 5.19, N 26.86.

*General procedure for the synthesis of Schiff bases **6a–r***

To a solution of compound **5** (2 g, 6.4 mmol) in absolute ethanol (50 mL), containing a catalytic amount of piperidine, an equimolar amount of the appropriate aldehyde (for example benzaldehyde: 0.67 g, 6.4 mmol) was added. The reaction mixture was refluxed for 5–6 h. It was then cooled to room temperature, poured into crushed ice, filtered, washed, dried, and recrystallized from dimethylformamide (DMF) to yield the Schiff base. For example:

4-{4-(Benzylidene-amino)-6-dimethylamino-[1,3,5]-triazin-2-yloxy]-1-methyl-1H-quinolin-2-one (**6a**): Grey solid. – Yield: 1.81 g (71%). – M.p. 227–231 °C. – IR (KBr): $\bar{\nu}$ = 1666 (C=O of quinolone), 808 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.27 (dd, 1H, *J* = 7.5, 1.4 Hz, H at C-5 of quinolone), 8.14–7.53 (m, 3H, 3H of quinolone), 7.51 (s, 1H, N=CH-ph), 7.39–6.87 (m, 5H, Ar-H), 6.10 (s, 1H, H at C-3 of quinolone), 3.47 (s, 3H, -CH$_3$ of quinolone), 3.11 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 169.6 (C-N), 168.2 (C-O-C), 164.5 [C-N-(CH$_3$)$_2$], 161.5 (quinolone-C2), 152.7 (quinolone-C4), 141.3 (C=N of Schiff base), 139.1, 136.5, 132.7, 132.5, 128.8, 128.6, 128.2, 128.1, 123.7, 122.1,

115.8, 115.4, 96.7 (13C, Ar-C), 37.2 ($H_3\underline{C}$-N-$\underline{C}H_3$), 32.4 (quinolone-C11). – $C_{22}H_{20}N_6O_2$ (400.43): calcd. C 65.99, H 5.03, N 20.99; found C 65.92, H 5.14, N 20.90.

Schiff bases **6b–r** were synthesized following the procedure similar to that for **6a**.

*General procedure for the synthesis of thiazolidinones **7a–r***

A mixture of compound **6a** (1 g, 2.4 mmol) and thioglycolic acid (0.46 g, 4.9 mmol) in dry benzene (40 mL) was refluxed for 6 h. The water formed during the reaction was removed azeotropically by a Dean-Stark apparatus. Progress of the reaction was checked by TLC using benzene/diethyl ether (98:2 v/v) as eluent. After completion of the reaction, benzene was removed by distillation and the resulting solid dissolved in methanol (20 mL). This solution was warmed and treated with sodium bicarbonate solution to remove unreacted acid. The solid obtained was filtered, washed with diethyl ether, and purified by crystallization from methanol to give 4-[4-dimethylamino-6-(4-oxo-2-phenyl-thiazolidin-3-yl)-[1,3,5]-triazin-2-yloxy]-1-methyl-1*H*-quinolin-2-one (**7a**).

Brown solid. – Yield: 0.75 g (66%). – M.p. 267–269 °C. – IR (KBr): $\bar{\nu}$ = 1723 (C=O of thiazolidinone), 1667 (C=O of quinolone), 808 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35 (dd, 1H, J = 7.5, 1.4 Hz, H at C-5 of quinolone), 8.07–7.59 (m, 3H, 3H of quinolone), 7.42–6.94 (m, 5H, Ar-H), 6.14 (s, 1H, H at C-3 of quinolone), 5.09 (s, 1H, S-C$\underline{H}$-N), 3.66 (d, J = 12.5 Hz, 1H), 3.59 (d, J = 12.3 Hz, 1H), 3.39 (s, 3H, -CH_3 of quinolone), 3.07 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.8 (thiazolidinone-C4), 169.1 ($\underline{C}$-O-C), 165.8 ($\underline{C}$-N), 164.7 [$\underline{C}$-N-$(CH_3)_2$], 161.4 (quinolone-C2), 152.0 (quinolone-C4), 141.8, 140.2, 132.6, 132.6, 129.4, 128.8, 128.4, 127.1, 124.1, 122.3, 115.7, 115.2, 97.3 (13C, Ar-C), 68.2 (thiazolidinone-C2), 37.1 ($H_3\underline{C}$-N-$\underline{C}H_3$), 33.8 (-CH_2 of thiazolidinone), 32.4 (quinolone-C11). – $C_{24}H_{22}N_6O_3S$ (474.53): calcd. C 60.75, H 4.67, N 17.71; found C 60.79, H 4.72, N 17.66.

Compounds **7b–r** were synthesized following the procedure similar to that for **7a**.

*General procedure for the synthesis of target compounds **8a–r***

A mixture of paraformaldehyde (0.25 g, 2.5 mmol) and 1-pyridin-2-yl-piperazine (0.8 g, 5.0 mmol) in 30 mL of absolute ethanol was refluxed for 30 min until the paraformaldehyde was completely dissolved. A warmed solution of compound **7a** (4.80 g, 10 mmol) in 25 mL of ethanol was subsequently added to the reaction mixture. The entire reaction mixture was refluxed for 10–11 h and left at room temperature under stirring for 3 d. Thereafter the volatile material was evaporated. The dry residue was extracted with DMF to form 4-{4-dimethylamino-6-[4-oxo-2-phenyl-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1*H*-quinolin-2-one (**8a**). Compounds **8b–r** were synthesized following the similar procedure.

4-{4-Dimethylamino-6-[4-oxo-2-phenyl-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8a**): Yellow solid. – Yield: 63%. – M.p. 275–279 °C. – IR (KBr): $\bar{\nu}$ = 1719 (C=O of thiazolidinone), 1667 (C=O of quinolone), 808 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.38 (dd, 1H, J = 7.6, 1.2 Hz, H at C-5 of quinolone), 8.14–7.67 (m, 3H, 3H of quinolone), 7.61–7.47 (m, 2H, 2H of pyridine), 7.44–6.97 (m, 5H, Ar-H), 6.78 (dd, J = 7.3, 1.6 Hz, 1H of pyridine), 6.67 (td, J = 7.5, 1.3 Hz, 1H of pyridine), 6.22 (s, 1H, H at C-3 of quinolone), 5.14 (s, 1H, S-C$\underline{H}$-N), 3.62 (br s, 8H, piperazine), 3.44 (s, 3H, -$C\underline{H}_3$ of quinolone), 3.28 (t, J = 7.8 Hz, 1H, S-C$\underline{H}$-C=O), 3.22–3.10 (m, 2H, -$C\underline{H}_2$), 3.07 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.3 (thiazolidinone-C4), 167.5 ($\underline{C}$-O-C), 165.3 ($\underline{C}$-N), 164.1 [$\underline{C}$-N-$(CH_3)_2$], 162.1 (quinolone-C2), 161.4 (pyridine-C14), 152.5 (quinolone-C4), 148.2, 142.5, 139.2, 136.2, 132.5, 130.2, 130.1, 129.6, 123.1, 122.2, 117.8, 117.3, 116.1, 115.9, 113.5, 111.5, 96.2 (17C, Ar-C), 66.6 (thiazolidinone-C2), 64.1, 62.1 (4C, piperazine), 57.4 (thiazolidinone-C7), 55.4 (thiazolidinone-C5), 37.2 ($H_3\underline{C}$-N-$\underline{C}H_3$), 32.4 (quinolone-C11). – $C_{34}H_{35}N_9O_3S$ (649.77): calcd. C 62.85, H 5.43, N 19.40; found C 62.78, H 5.39, N 19.46.

4-{4-[2-(2,4-Dichloro-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8b**): White solid. – Yield: 68%. – M.p. 223–231 °C. – IR (KBr): $\bar{\nu}$ = 1723

(C=O of thiazolidinone), 1664 (C=O of quinolone), 806 (*s*-triazine, C-N str.), 779 cm^{-1} (-Cl). – ^1H NMR (400 MHz, DMSO-d_6): δ = 8.42 (dd, 1H, J = 7.8, 1.7 Hz, H at C-5 of quinolone), 8.16–7.73 (m, 3H, 3H of quinolone), 7.68–7.51 (m, 2H, 2H of pyridine), 7.43–7.05 (m, 3H, Ar-H), 6.84 (dd, J = 7.2, 1.4 Hz, 1H of pyridine), 6.69 (td, J = 7.1, 1.6 Hz, 1H of pyridine), 6.10 (s, 1H, H at C-3 of quinolone), 5.24 (s, 1H, S-C<u>H</u>-N), 3.67 (br s, 8H, piperazine), 3.45 (s, 3H, -C<u>H</u>$_3$ of quinolone), 3.37 (t, J = 7.8 Hz, 1H, S-C<u>H</u>-C=O), 3.31–3.20 (m, 2H, -C<u>H</u>$_2$), 3.09 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4 (thiazolidinone-C4), 168.7 (<u>C</u>-O-C), 165.5 (<u>C</u>-N), 164.1 [<u>C</u>-N-$(CH_3)_2$], 162.1 (quinolone-C2), 160.8 (pyridine-C14), 152.8 (quinolone-C4), 134.6, 133.7 (<u>C</u>-Cl), 149.4, 142.6, 138.4, 137.2, 131.9, 130.4, 123.8, 122.7, 117.2, 117.0, 116.4, 115.9, 113.5, 111.3, 96.4 (15C, Ar-C), 67.1 (thiazolidinone-C2), 62.5, 61.2 (4C, piperazine), 57.3 (thiazolidinone-C7), 54.8 (thiazolidinone-C5), 37.1 (H_3<u>C</u>-N-<u>C</u>H_3), 32.6 (quinolone-C11). – $C_{34}H_{33}Cl_2N_9O_3S$ (718.56): calcd. C 56.82, H 4.63, N 17.54; found C 56.89, H 4.67, N 17.47.

4-{4-[2-(3,4-Dichloro-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8c**): White solid. – Yield: 66%. – M.p. 255–258 °C. – IR (KBr): $\bar{\nu}$ = 1729 (C=O of thiazolidinone), 1670 (C=O of quinolone), 810 (*s*-triazine, C-N str.), 788 cm^{-1} (-Cl). – ^1H NMR (400 MHz, DMSO-d_6): δ = 8.25 (dd, 1H, J = 8.1, 1.6 Hz, H at C-5 of quinolone), 8.13–7.66 (m, 3H, 3H of quinolone), 7.58–7.41 (m, 2H, 2H of pyridine), 7.37–7.09 (m, 3H, Ar-H), 6.89 (dd, J = 7.5, 1.1 Hz, 1H of pyridine), 6.74 (td, J = 7.9, 1.3 Hz, 1H of pyridine), 6.26 (s, 1H, H at C-3 of quinolone), 5.28 (s, 1H, S-C<u>H</u>-N), 3.63 (br s, 8H, piperazine), 3.47 (s, 3H, -C<u>H</u>$_3$ of quinolone), 3.41 (t, J = 7.2 Hz, 1H, S-C<u>H</u>-C=O), 3.39–3.21 (m, 2H, -C<u>H</u>$_2$), 3.13 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.5 (thiazolidinone-C4), 168.6 (<u>C</u>-O-C), 165.3 (<u>C</u>-N), 163.9 [<u>C</u>-N-$(CH_3)_2$], 161.8 (quinolone-C2), 160.7 (pyridine-C14), 151.4 (quinolone-C4), 134.8, 133.6 (<u>C</u>-Cl), 148.9, 141.3, 139.1, 137.4, 132.2, 129.7, 123.7, 122.8, 117.2, 116.6, 116.1, 115.7, 112.6, 111.4, 94.7 (15C, Ar-C), 65.9 (thiazolidinone-C2), 64.9, 61.7 (4C, piperazine), 59.4 (thiazolidinone-C7), 55.8 (thiazolidinone-C5), 36.7 (H_3<u>C</u>-N-<u>C</u>H_3), 31.6 (quinolone-C11). – $C_{34}H_{33}Cl_2N_9O_3S$ (718.56): calcd. C 56.82, H 4.63, N 17.54; found C 56.91, H 4.66, N 17.45.

4-{4-Dimethylamino-6-[4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-2-p-tolyl-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8d**): Brown solid. – Yield: 72%. – M.p. 263–268 °C. – IR (KBr): $\bar{\nu}$ = 1719 (C=O of thiazolidinone), 1667 (C=O of quinolone), 1452 (-CH_3), 807 cm^{-1} (*s*-triazine, C-N str.). – ^1H NMR (400 MHz, DMSO-d_6): δ = 8.31 (dd, 1H, J = 7.9, 1.6 Hz, H at C-5 of quinolone), 8.17–7.71 (m, 3H, 3H of quinolone), 7.65–7.42 (m, 2H, 2H of pyridine), 7.38–6.91 (m, 4H, Ar-H), 6.84 (dd, J = 7.1, 1.3 Hz, 1H of pyridine), 6.69 (td, J = 7.6, 1.5 Hz, 1H of pyridine), 6.23 (s, 1H, H at C-3 of quinolone), 5.22 (s, 1H, S-C<u>H</u>-N), 3.66 (br s, 8H, piperazine), 3.52 (s, 3H, -C<u>H</u>$_3$ of quinolone), 3.45 (t, J = 7.4 Hz, 1H, S-C<u>H</u>-C=O), 3.34–3.23 (m, 2H, -C<u>H</u>$_2$), 3.09 (s, 6H, 2CH_3), 2.17 (s, 3H, ph-C<u>H</u>$_3$). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.7 (thiazolidinone-C4), 168.1 (<u>C</u>-O-C), 165.3 (<u>C</u>-N), 163.2 [<u>C</u>-N-$(CH_3)_2$], 161.4 (quinolone-C2), 160.8 (pyridine-C14), 152.6 (quinolone-C4), 137.3 (<u>C</u>-CH_3), 149.9, 141.3, 138.9, 136.1, 131.8, 130.4, 130.3, 124.1, 122.4, 117.6, 117.5, 116.8, 115.1, 114.8, 112.5, 97.6 (16C, Ar-C), 67.1 (thiazolidinone-C2), 63.8, 61.3 (4C, piperazine), 58.6 (thiazolidinone-C7), 55.4 (thiazolidinone-C5), 36.5 (H_3<u>C</u>-N-<u>C</u>H_3), 32.6 (quinolone-C11). – $C_{35}H_{37}N_9O_3S$ (663.79): calcd. C 63.33, H 5.62, N 18.99; found C 63.39, H 5.67, N 18.91.

4-{4-Dimethylamino-6-[2-(4-fluoro-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8e**): Yellow solid. – Yield: 65%. – M.p. 251–254 °C. – IR (KBr): $\bar{\nu}$ = 1721 (C=O of thiazolidinone), 1668 (C=O of quinolone), 1162 (C-F), 807 cm^{-1} (*s*-triazine, C-N str.). – ^1H NMR (400 MHz, DMSO-d_6): δ = 8.29 (dd, 1H, J = 7.9, 1.7 Hz, H at C-5 of quinolone), 8.13–7.75 (m, 3H, 3H of quinolone), 7.69–7.48 (m, 2H, 2H of pyridine), 7.42–6.95 (m, 4H, Ar-H), 6.81 (dd, J = 7.4, 1.5 Hz, 1H of pyridine), 6.63 (td, J = 7.2, 1.2 Hz, 1H of pyridine), 6.19 (s, 1H, H at C-3 of quinolone), 5.17 (s, 1H, S-C<u>H</u>-N), 3.61 (br s, 8H, piperazine), 3.47 (s, 3H, -C<u>H</u>$_3$ of quinolone), 3.25 (t, J = 7.9 Hz, 1H, S-C<u>H</u>-C=O), 3.21–3.10 (m, 2H, -C<u>H</u>$_2$), 3.04 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7 (thiazolidinone-C4), 167.9 (<u>C</u>-O-C), 167.2 (<u>C</u>-F), 165.5 (<u>C</u>-N), 163.4 [<u>C</u>-N-$(CH_3)_2$], 161.2 (quinolone-C2), 160.6 (pyridine-C14), 151.3 (quinolone-C4), 147.9, 142.2, 138.8, 135.8, 132.1, 131.19, 130.4,

124.3, 123.1, 117.6, 117.4, 116.5, 115.8, 113.7, 112.5, 96.8 (16C, Ar-C), 66.7 (thiazolidinone-C2), 65.3, 63.2 (4C, piperazine), 57.6 (thiazolidinone-C7), 55.3 (thiazolidinone-C5), 36.6 ($H_3\underline{C}$-N-$\underline{C}H_3$), 32.5 (quinolone-C11). – $C_{34}H_{34}FN_9O_3S$ (667.76): calcd. C 61.15, H 5.13, N 18.88; found C 61.11, H 5.18, N 18.79.

4-{4-Dimethylamino-6-[2-(3-fluoro-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8f**): Yellow solid. – Yield: 62%. – M.p. 265–268 °C. – IR (KBr): $\bar{\nu}$ = 1717 (C=O of thiazolidinone), 1666 (C=O of quinolone), 1160 (C-F), 807 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.47 (dd, 1H, *J* = 7.4, 1.3 Hz, H at C-5 of quinolone), 8.07–7.64 (m, 3H, 3H of quinolone), 7.59–7.44 (m, 2H, 2H of pyridine), 7.39–7.03 (m, 4H, Ar-H), 6.88 (dd, *J* = 7.2, 1.1 Hz, 1H of pyridine), 6.71 (td, *J* = 7.7, 1.8 Hz, 1H of pyridine), 6.28 (s, 1H, H at C-3 of quinolone), 5.20 (s, 1H, S-C$\underline{H}$-N), 3.55 (br s, 8H, piperazine), 3.51 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.42 (t, *J* = 7.5 Hz, 1H, S-C$\underline{H}$-C=O), 3.32–3.24 (m, 2H, -C$\underline{H}_2$), 3.10 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5 (thiazolidinone-C4), 168.1 ($\underline{C}$-O-C), 167.5 ($\underline{C}$-F), 165.4 ($\underline{C}$-N), 163.6 [$\underline{C}$-N-$(CH_3)_2$], 162.1 (quinolone-C2), 161.1 (pyridine-C14), 152.4 (quinolone-C4), 149.7, 141.3, 138.1, 136.3, 132.4, 131.23, 130.5, 123.9, 123.0, 117.8, 117.4, 116.3, 115.9, 114.7, 112.8, 96.6 (16C, Ar-C), 67.6 (thiazolidinone-C2), 63.7, 62.4 (4C, piperazine), 58.1 (thiazolidinone-C7), 55.3 (thiazolidinone-C5), 36.4 ($H_3\underline{C}$-N-$\underline{C}H_3$), 32.6 (quinolone-C11). – $C_{34}H_{34}FN_9O_3S$ (667.76): calcd. C 61.15, H 5.13, N 18.88; found C 61.10, H 5.21, N 18.82.

4-{4-[2-(4-Chloro-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8g**): Dark yellow solid. – Yield: 59%. – M.p. 240–245 °C. – IR (KBr): $\bar{\nu}$ = 1728 (C=O of thiazolidinone), 1666 (C=O of quinolone), 807 (*s*-triazine, C-N str.), 789 cm^{-1} (-Cl). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (dd, 1H, *J* = 7.6, 1.4 Hz, H at C-5 of quinolone), 8.15–7.69 (m, 3H, 3H of quinolone), 7.63–7.49 (m, 2H, 2H of pyridine), 7.43–6.89 (m, 4H, Ar-H), 6.76 (dd, *J* = 7.7, 1.4 Hz, 1H of pyridine), 6.67 (td, *J* = 7.2, 1.6 Hz, 1H of pyridine), 6.11 (s, 1H, H at C-3 of quinolone), 5.14 (s, 1H, S-C$\underline{H}$-N), 3.57 (br s, 8H, piperazine), 3.49 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.40 (t, *J* = 8.1 Hz, 1H, S-C$\underline{H}$-C=O), 3.23–3.10 (m, 2H, -C$\underline{H}_2$), 3.07 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5 (thiazolidinone-C4), 168.8 ($\underline{C}$-O-C), 165.4 ($\underline{C}$-N), 163.2 [$\underline{C}$-N-$(CH_3)_2$], 161.4 (quinolone-C2), 161.1 (pyridine-C14), 152.7 (quinolone-C4), 133.1 ($\underline{C}$-Cl), 149.2, 141.6, 138.6, 136.1, 132.6, 132.2, 130.4, 123.9, 122.7, 117.1, 116.8, 116.4, 115.6, 113.5, 111.6, 98.7 (16C, Ar-C), 66.8 (thiazolidinone-C2), 64.7, 61.6 (4C, piperazine), 58.2 (thiazolidinone-C7), 55.3 (thiazolidinone-C5), 36.7 ($H_3\underline{C}$-N-$\underline{C}H_3$), 32.6 (quinolone-C11). – $C_{34}H_{34}ClN_9O_3S$ (684.21): calcd. C 59.68, H 5.01, N 18.42; found C 59.75, H 5.06, N 18.36.

4-{4-Dimethylamino-6-[2-(4-nitro-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8h**): Yellow solid. – Yield: 55%. – M.p. 273–277 °C. – IR (KBr): $\bar{\nu}$ = 1722 (C=O of thiazolidinone), 1667 (C=O of quinolone), 1533 (N=O str.), 810 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (dd, 1H, *J* = 7.3, 1.7 Hz, H at C-5 of quinolone), 8.11–7.74 (m, 3H, 3H of quinolone), 7.67–7.54 (m, 2H, 2H of pyridine), 7.42–6.97 (m, 4H, Ar-H), 6.77 (dd, *J* = 7.5, 1.8 Hz, 1H of pyridine), 6.62 (td, *J* = 7.5, 1.4 Hz, 1H of pyridine), 6.16 (s, 1H, H at C-3 of quinolone), 5.19 (s, 1H, S-C$\underline{H}$-N), 3.63 (br s, 8H, piperazine), 3.57 (s, 3H, –C$\underline{H}_3$ of quinolone), 3.38 (t, *J* = 7.8 Hz, 1H, S-C$\underline{H}$-C=O), 3.34–3.21 (m, 2H, -C$\underline{H}_2$), 3.17 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.3 (thiazolidinone-C4), 167.9 ($\underline{C}$-O-C), 165.4 ($\underline{C}$-N), 163.3 [$\underline{C}$-N-$(CH_3)_2$], 161.3 (quinolone-C2), 161.0 (pyridine-C14), 151.8 (quinolone-C4), 148.6 ($\underline{C}$-NO_2), 148.2, 141.5, 138.5, 137.1, 132.7, 131.7, 130.5, 124.1, 122.6, 117.2, 116.9, 116.2, 115.6, 114.6, 112.3, 96.2 (16C, Ar-C), 66.4 (thiazolidinone-C2), 62.8, 59.4 (4C, piperazine), 57.2 (thiazolidinone-C7), 55.2 (thiazolidinone-C5), 36.8 ($H_3\underline{C}$-N-$\underline{C}H_3$), 32.5 (quinolone-C11). – $C_{34}H_{34}N_{10}O_5S$ (694.76): calcd. C 58.78, H 4.93, N 20.16; found C 58.72, H 4.97, N 20.21.

4-{4-Dimethylamino-6-[2-(2-nitro-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8i**): Yellow solid. – Yield: 49%. – M.p. 266–271 °C. – IR (KBr): $\bar{\nu}$ = 1713 (C=O of thiazolidinone), 1670 (C=O of quinolone), 1542 (N=O str.), 806 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50 (dd, 1H, *J* = 7.5, 1.9 Hz, H at C-5 of quinolone), 8.05–7.59 (m, 3H, 3H of quinolone), 7.55–7.36 (m, 2H, 2H of pyridine), 7.32–6.84 (m, 4H, Ar-H), 6.73 (dd,

J = 7.9, 1.6 Hz, 1H of pyridine), 6.58 (td, J = 7.6, 1.3 Hz, 1H of pyridine), 6.22 (s, 1H, H at C-3 of quinolone), 5.27 (s, 1H, S-C<u>H</u>-N), 3.62 (br s, 8H, piperazine), 3.51 (s, 3H,-C<u>H</u>$_3$ of quinolone), 3.41 (t, J = 7.5 Hz, 1H, S-C<u>H</u>-C=O), 3.36–3.29 (m, 2H, -C<u>H</u>$_2$), 3.16 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 172.4 (thiazolidinone-C4), 167.7 (<u>C</u>-O-C), 164.9 (<u>C</u>-N), 163.6 [<u>C</u>-N-(CH$_3$)$_2$], 161.4 (quinolone-C2), 160.8 (pyridine-C14), 152.8 (quinolone-C4), 148.5 (<u>C</u>-NO$_2$), 149.4, 141.6, 138.6, 136.6, 132.8, 131.2, 131.1, 123.4, 122.7, 117.3, 116.8, 116.1, 115.5, 113.8, 111.6, 94.4 (16C, Ar-C), 66.6 (thiazolidinone-C2), 65.5, 62.2 (4C, piperazine), 56.7 (thiazolidinone-C7), 55.6 (thiazolidinone-C5), 36.4 (H$_3$<u>C</u>-N-<u>C</u>H$_3$), 32.6 (quinolone-C11). – $C_{34}H_{34}N_{10}O_5S$ (694.76): calcd. C 58.78, H 4.93, N 20.16; found C 58.74, H 4.95, N 20.24.

4-{4-Dimethylamino-6-[2-(4-hydroxy-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8j**): White solid. – Yield: 75%. – M.p. 269–274 °C. – IR (KBr): $\bar{\nu}$ = 3224 (-OH), 1722 (C=O of thiazolidinone), 1666 (C=O of quinolone), 806 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.45 (dd, 1H, J = 7.2, 1.4 Hz, H at C-5 of quinolone), 8.11–7.72 (m, 3H, 3H of quinolone), 7.64–7.49 (m, 2H, 2H of pyridine), 7.37–6.89 (m, 4H, Ar-H), 6.77 (dd, J = 7.2, 1.3 Hz, 1H of pyridine), 6.70 (td, J = 7.6, 1.7 Hz, 1H of pyridine), 6.29 (s, 1H, H at C-3 of quinolone), 5.21 (s, 1H, S-C<u>H</u>-N), 4.57 (s, 1H, -O<u>H</u>), 3.64 (br s, 8H, piperazine), 3.54 (s, 3H, -C<u>H</u>$_3$ of quinolone), 3.49 (t, J = 7.5 Hz, 1H, S-C<u>H</u>-C=O), 3.36–3.17 (m, 2H, -C<u>H</u>$_2$), 3.05 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 172.5 (thiazolidinone-C4), 168.6 (<u>C</u>-O-C), 164.8 (<u>C</u>-N), 163.9 [<u>C</u>-N-(CH$_3$)$_2$], 161.8 (quinolone-C2), 161.1 (pyridine-C14), 158.6 (<u>C</u>-OH), 151.6 (quinolone-C4), 150.1, 141.1, 138.3, 136.1, 132.7, 130.4, 129.4, 124.1, 122.5, 117.3, 116.9, 116.3, 115.7, 114.4, 112.6, 97.4 (16C, Ar-C), 66.4 (thiazolidinone-C2), 65.5, 62.4 (4C, piperazine), 57.2 (thiazolidinone-C7), 55.6 (thiazolidinone-C5), 36.5 (H$_3$<u>C</u>-N-<u>C</u>H$_3$), 32.3 (quinolone-C11). – $C_{34}H_{35}N_9O_4S$ (665.76): calcd. C 61.34, H 5.30, N 18.93; found C 61.28, H 5.25, N 18.98.

4-{4-[2-(4-Bromo-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8k**): Grey solid. – Yield: 64%. – M.p. 279–283 °C. – IR (KBr): $\bar{\nu}$ = 1719 (C=O of thiazolidinone), 1667 (C=O of quinolone), 808 (*s*-triazine, C-N str.), 733 cm^{-1} (-Br). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.38 (dd, 1H, J = 7.5, 1.1 Hz, H at C-5 of quinolone), 8.15–7.63 (m, 3H, 3H of quinolone), 7.59–7.42 (m, 2H, 2H of pyridine), 7.33–6.91 (m, 4H, Ar-H), 6.82 (dd, J = 7.1, 1.6 Hz , 1H of pyridine), 6.59 (td, J = 7.4, 1.8 Hz, 1H of pyridine), 6.21 (s, 1H, H at C-3 of quinolone), 5.14 (s, 1H, S-C<u>H</u>-N), 3.61 (br s, 8H, piperazine), 3.45 (s, 3H, -C<u>H</u>$_3$ of quinolone), 3.34 (t, J = 8.2 Hz, 1H, S-C<u>H</u>-C=O), 3.28–3.12 (m, 2H, -C<u>H</u>$_2$), 3.10 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 172.2 (thiazolidinone-C4), 167.5 (<u>C</u>-O-C), 165.2 (<u>C</u>-N), 164.1 [<u>C</u>-N-(CH$_3$)$_2$], 162.2 (quinolone-C2), 161.4 (pyridine-C14), 152.6 (quinolone-C4), 121.6 (<u>C</u>-Br), 148.2, 142.6, 139.1, 136.2, 132.6, 130.1, 130.1, 123.1, 122.1, 117.8, 117.2, 116.2, 115.9, 113.5, 111.5, 96.2 (16C, Ar-C), 66.7 (thiazolidinone-C2), 64.8, 60.2 (4C, piperazine), 57.4 (thiazolidinone-C7), 55.4 (thiazolidinone-C5), 37.3 (H$_3$<u>C</u>-N-<u>C</u>H$_3$), 32.4 (quinolone-C11). – $C_{34}H_{34}BrN_9O_3S$ (728.66): calcd. C 56.04, H 4.70, N 17.30; found C 56.11, H 4.64, N 17.35.

4-{4-[2-(2-Bromo-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8l**): Grey solid. – Yield: 67%. – M.p. 292–296 °C. – IR (KBr): $\bar{\nu}$ = 1751 (C=O of thiazolidinone), 1673 (C=O of quinolone), 812 (*s*-triazine, C-N str.), 743 cm^{-1} (-Br). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.31 (dd, 1H, J = 7.7, 1.6 Hz, H at C-5 of quinolone), 8.10–7.75 (m, 3H, 3H of quinolone), 7.66–7.49 (m, 2H, 2H of pyridine), 7.45–7.11 (m, 4H, Ar-H), 6.91 (dd, J = 7.4, 1.9 Hz, 1H of pyridine), 6.79 (td, J = 7.9, 1.2 Hz, 1H of pyridine), 6.32 (s, 1H, H at C-3 of quinolone), 5.29 (s, 1H, S-C<u>H</u>-N), 3.72 (br s, 8H, piperazine), 3.52 (s, 3H, -C<u>H</u>$_3$ of quinolone), 3.43 (t, J = 7.6 Hz, 1H, S-C<u>H</u>-C=O), 3.38–3.19 (m, 2H, -C<u>H</u>$_2$), 3.15 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 173.8 (thiazolidinone-C4), 167.5 (<u>C</u>-O-C), 165.5 (<u>C</u>-N), 164.1 [<u>C</u>-N-(CH$_3$)$_2$], 162.4 (quinolone-C2), 161.1 (pyridine-C14), 151.8 (quinolone-C4), 122.2 (<u>C</u>-Br), 149.1, 142.6, 138.5, 137.7, 132.5, 131.3, 130.9, 123.3, 121.6, 117.9, 117.2, 115.9, 115.7, 114.4, 112.9, 91.9 (16C, Ar-C), 69.7 (thiazolidinone-C2), 63.5, 62.4 (4C, piperazine), 59.5 (thiazolidinone-C7), 53.2 (thiazolidinone-C5), 37.3 (H$_3$<u>C</u>-N-<u>C</u>H$_3$), 32.6 (quinolone-C11). – $C_{34}H_{34}BrN_9O_3S$ (728.66): calcd. C 56.04, H 4.70, N 17.30; found C 56.09, H 4.62, N 17.34.

2-{3-[4-Dimethylamino-6-(1-methyl-2-oxo-1,2-dihydro-quinolin-4-yloxy)-[1,3,5]-triazin-2-yl]-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-2-yl}-benzoic acid (**8m**): Brown solid. – Yield: 77%. – M.p. > 300 °C. – IR (KBr): $\bar{\nu}$ = 1724 (C=O of thiazolidinone), 1720 (-COOH), 1668 (C=O of quinolone), 806 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48 (dd, 1H, *J* = 7.3, 1.5 Hz, H at C-5 of quinolone), 8.06–7.57 (m, 3H, 3H of quinolone), 7.51–7.33 (m, 2H, 2H of pyridine), 7.26–6.81 (m, 4H, Ar-H), 6.72 (dd, *J* = 7.2, 1.6 Hz, 1H of pyridine), 6.56 (td, *J* = 8.1, 1.9 Hz, 1H of pyridine), 6.27 (s, 1H, H at C-3 of quinolone), 5.23 (s, 1H, S-C$\underline{H}$-N), 3.59 (br s, 8H, piperazine), 3.48 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.43 (t, *J* = 7.2 Hz, 1H, S-C$\underline{H}$-C=O), 3.28–3.05 (m, 2H, -C$\underline{H}_2$), 3.02 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.3 (thiazolidinone-C4), 170.4 ($\underline{C}$=O of COOH), 168.6 ($\underline{C}$-O-C), 165.3 ($\underline{C}$-N), 163.8 [$\underline{C}$-N-$(CH_3)_2$], 162.3 (quinolone-C2), 160.6 (pyridine-C14), 151.1 (quinolone-C4), 131.2 ($\underline{C}$-COOH), 149.2, 141.4, 138.5, 137.0, 131.5, 131.0, 130.0, 123.2, 121.8, 117.9, 116.4, 116.1, 115.7, 113.6, 112.8, 98.2 (16C, Ar-C), 67.20 (thiazolidinone-C2), 65.5, 61.2 (4C, piperazine), 56.6 (thiazolidinone-C7), 55.6 (thiazolidinone-C5), 36.1 ($H_3\underline{C}$-N-$\underline{C}H_3$), 31.6 (quinolone-C11). – $C_{35}H_{35}N_9O_5S$ (693.77): calcd. C 60.59, H 5.08, N 18.17; found C 60.63, H 5.13, N 18.11.

4-{3-[4-Dimethylamino-6-(1-methyl-2-oxo-1,2-dihydro-quinolin-4-yloxy)-[1,3,5]-triazin-2-yl]-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-2-yl}-benzoic acid (**8n**): Grey solid. – Yield: 68%. – M.p. 287–290 °C. – IR (KBr): $\bar{\nu}$ = 1733 (C=O of thiazolidinone), 1711 (-COOH), 1674 (C=O of quinolone), 810 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (dd, 1H, *J* = 7.9, 1.7 Hz, H at C-5 of quinolone), 8.18–7.79 (m, 3H, 3H of quinolone), 7.72–7.54 (m, 2H, 2H of pyridine), 7.44–6.96 (m, 4H, Ar-H), 6.85 (dd, *J* = 7.6, 1.5 Hz, 1H of pyridine), 6.67 (td, *J* = 7.7, 1.6 Hz, 1H of pyridine), 6.44 (s, 1H, H at C-3 of quinolone), 5.39 (s, 1H, S-C$\underline{H}$-N), 3.68 (br s, 8H, piperazine), 3.59 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.49 (t, *J* = 7.7 Hz, 1H, S-C$\underline{H}$-C=O), 3.35–3.23 (m, 2H, -C$\underline{H}_2$), 3.15 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.8 (thiazolidinone-C4), 170.1 ($\underline{C}$=O of COOH), 169.4 ($\underline{C}$-O-C), 165.3 ($\underline{C}$-N), 163.5 [$\underline{C}$-N-$(CH_3)_2$], 162.5 (quinolone-C2), 161.7 (pyridine-C14), 151.6 (quinolone-C4), 131.8 ($\underline{C}$-COOH), 149.3, 143.2, 138.9, 136.5, 132.2, 131.1, 130.1, 124.4, 122.5, 117.7, 116.6, 116.2, 115.7, 113.7, 111.7, 95.2 (16C, Ar-C), 70.4 (thiazolidinone-C2), 63.6, 60.5 (4C, piperazine), 59.6 (thiazolidinone-C7), 54.8 (thiazolidinone-C5), 37.2 ($H_3\underline{C}$-N-$\underline{C}H_3$), 31.7 (quinolone-C11). – $C_{35}H_{35}N_9O_5S$ (693.77): calcd. C 60.59, H 5.08, N 18.17; found C 60.66, H 5.15, N 18.10.

4-{4-Dimethylamino-6-[2-(4-methoxy-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8o**): Grey solid. – Yield: 60%. – M.p. 281–285 °C. – IR (KBr): $\bar{\nu}$ = 1718 (C=O of thiazolidinone), 1666 (C=O of quinolone), 1292 (-OCH_3), 807 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.43 (dd, 1H, *J* = 7.5, 1.3 Hz, H at C-5 of quinolone), 8.15–7.68 (m, 3H, 3H of quinolone), 7.60–7.46 (m, 2H, 2H of pyridine), 7.40–7.06 (m, 4H, Ar-H), 6.82 (dd, *J* = 7.7, 1.3 Hz, 1H of pyridine), 6.74 (td, *J* = 7.1, 1.2 Hz, 1H of pyridine), 6.23 (s, 1H, H at C-3 of quinolone), 5.16 (s, 1H, S-C$\underline{H}$-N), 3.90 (s, 3H, -OCH_3), 3.67 (br s, 8H, piperazine), 3.45 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.33 (t, *J* = 7.2 Hz, 1H, S-C$\underline{H}$-C=O), 3.29–3.14 (m, 2H, -C$\underline{H}_2$), 3.07 (s, 6H, 2CH_3). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.1 (thiazolidinone-C4), 168.2 ($\underline{C}$-O-C), 165.5 ($\underline{C}$-N), 164.7 [$\underline{C}$-N-$(CH_3)_2$], 161.8 (quinolone-C2), 160.5 (pyridine-C14), 160.0 ($\underline{C}$-OCH_3), 152.3 (quinolone-C4), 148.3, 141.5, 138.8, 137.1, 132.6, 131.5, 129.1, 123.1, 122.4, 117.8, 116.2, 116.1, 115.7, 114.9, 112.90, 96.3 (16C, Ar-C), 66.4 (thiazolidinone-C2), 62.4, 59.3 (4C, piperazine), 57.3 (thiazolidinone-C7), 56.1 ($\underline{C}$ of -O$\underline{C}H_3$), 55.5 (thiazolidinone-C5), 37.2 ($H_3\underline{C}$-N-$\underline{C}H_3$), 32.5 (quinolone-C11). – $C_{35}H_{37}N_9O_4S$ (679.79): calcd. C 61.84, H 5.49, N 18.54; found C 61.79, H 5.52, N 18.59.

4-{4-[2-(3,4-Dimethoxy-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8p**): White solid. – Yield: 73%. – M.p. >300 °C. – IR (KBr): $\bar{\nu}$ = 1720 (C=O of thiazolidinone), 1668 (C=O of quinolone), 1284 (-OCH_3), 807 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.47 (dd, 1H, *J* = 7.8, 1.6 Hz, H at C-5 of quinolone), 8.11–7.73 (m, 3H, 3H of quinolone), 7.69–7.51 (m, 2H, 2H of pyridine), 7.45–7.14 (m, 3H, Ar-H), 6.93 (dd, *J* = 7.5, 1.5 Hz, 1H of pyridine), 6.79 (td, *J* = 7.5, 1.5 Hz, 1H of pyridine), 6.17 (s, 1H, H at C-3 of quinolone), 5.24 (s, 1H, S-C$\underline{H}$-N), 3.86 (s, 3H, -OCH_3), 3.77 (s, 3H, -OCH_3), 3.58 (br s, 8H,

piperazine), 3.52 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.21 (t, J = 8.3 Hz, 1H, S-C$\underline{H}$-C=O), 3.17 – 3.08 (m, 2H, -C$\underline{H}_2$), 2.97 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 172.3 (thiazolidinone-C4), 168.4 ($\underline{C}$-O-C), 165.3 ($\underline{C}$-N), 163.9 [$\underline{C}$-N-(CH$_3$)$_2$], 161.4 (quinolone-C2), 160.8 (pyridine-C14), 160.1, 160.1 ($\underline{C}$-OCH$_3$), 152.7 (quinolone-C4), 148.9, 141.1, 139.7, 136.2, 132.6, 130.3, 130.1, 123.8, 122.6, 117.2, 116.9, 115.2, 113.9, 111.4, 101.4 (15C, Ar-C), 67.4 (thiazolidinone-C2), 64.8, 60.5 (4C, piperazine), 58.7 (thiazolidinone-C7), 56.1 ($\underline{C}$ of -O$\underline{C}$H$_3$), 55.4 (thiazolidinone-C5), 37.6 (H$_3\underline{C}$-N-$\underline{C}$H$_3$), 31.6 (quinolone-C11). – $C_{36}H_{39}N_9O_5S$ (709.82): calcd. C 60.92, H 5.54, N 17.76; found C 60.97, H 5.51, N 17.70.

4-{4-[2-(2,4-Dihydroxy-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8q**): Grey solid. – Yield: 83%. – M.p. > 300 °C. – IR (KBr): $\bar{\nu}$ = 3231 (-OH), 1719 (C=O of thiazolidinone), 1666 (C=O of quinolone), 806 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.66 (s, 1H, -O$\underline{H}$), 8.35 (dd, 1H, J = 7.6, 1.5 Hz, H at C-5 of quinolone), 8.16–7.75 (m, 3H, 3H of quinolone), 7.65–7.47 (m, 2H, 2H of pyridine), 7.41–7.11 (m, 3H, Ar-H), 6.87 (dd, J = 7.8, 1.2 Hz, 1H of pyridine), 6.60 (td, J = 7.4, 1.3 Hz, 1H of pyridine), 6.26 (s, 1H, H at C-3 of quinolone), 5.21 (s, 1H, S-C$\underline{H}$-N), 4.61 (s, 1H, -O$\underline{H}$), 3.63 (br s, 8H, piperazine), 3.49 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.36 (t, J = 7.8 Hz, 1H, S-C$\underline{H}$-C=O), 3.27–3.12 (m, 2H, -C$\underline{H}_2$), 3.03 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 171.4 (thiazolidinone-C4), 167.5 ($\underline{C}$-O-C), 165.3 ($\underline{C}$-N), 164.1 [$\underline{C}$-N-(CH$_3$)$_2$], 160.8 (quinolone-C2), 160.4 (pyridine-C14), 158.4 ($\underline{C}$-OH), 155.3 ($\underline{C}$-OH), 151.6 (quinolone-C4), 149.1, 142.2, 138.9, 137.1, 132.6, 131.2, 130.4, 124.0, 121.9, 116.8, 116.4, 115.3, 114.9, 112.5, 96.4 (15C, Ar-C), 66.2 (thiazolidinone-C2), 65.7, 62.5 (4C, piperazine), 57.7 (thiazolidinone-C7), 54.3 (thiazolidinone-C5), 36.5 (H$_3\underline{C}$-N-$\underline{C}$H$_3$), 32.2 (quinolone-C11). – $C_{34}H_{35}N_9O_5S$ (681.76): calcd. C 59.90, H 5.17, N 18.49; found C 59.82, H 5.13, N 18.55.

4-{4-[2-(2,3-Dihydroxy-phenyl)-4-oxo-5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-thiazolidin-3-yl]-6-dimethylamino-[1,3,5]-triazin-2-yloxy}-1-methyl-1H-quinolin-2-one (**8r**): Dark grey solid. – Yield: 88%. – M.p. >300 °C. – IR (KBr): $\bar{\nu}$ = 3244 (-OH), 1729 (C=O of thiazolidinone), 1661 (C=O of quinolone), 812 cm^{-1} (*s*-triazine, C-N str.). – ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.73 (s, 1H, -O$\underline{H}$), 8.29 (dd, 1H, J = 7.9, 1.5 Hz, H at C-5 of quinolone), 8.12–7.68 (m, 3H, 3H of quinolone), 7.61–7.44 (m, 2H, 2H of pyridine), 7.36–7.04 (m, 3H, Ar-H), 6.79 (dd, J = 7.5, 1.7 Hz, 1H of pyridine), 6.63 (td, J = 7.8, 1.7 Hz, 1H of pyridine), 6.20 (s, 1H, H at C-3 of quinolone), 5.34 (s, 1H, S-C$\underline{H}$-N), 4.65 (s, 1H, -O$\underline{H}$), 3.69 (br s, 8H, piperazine), 3.53 (s, 3H, -C$\underline{H}_3$ of quinolone), 3.42 (t, J = 7.4 Hz, 1H, S-C$\underline{H}$-C=O), 3.36–3.21 (m, 2H, -C$\underline{H}_2$), 3.14 (s, 6H, 2CH$_3$). – ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 174.6 (thiazolidinone-C4), 169.3 ($\underline{C}$-O-C), 165.2 ($\underline{C}$-N), 164.6 [$\underline{C}$-N-(CH$_3$)$_2$], 160.8 (quinolone-C2), 160.3 (pyridine-C14), 157.1 ($\underline{C}$-OH), 156.2 ($\underline{C}$-OH), 152.7 (quinolone-C4), 150.1, 143.1, 139.9, 138.7, 131.6, 131.0, 129.9, 123.8, 122.1, 116.7, 116.2, 115.2, 114.6, 113.4, 98.1 (15C, Ar-C), 68.2 (thiazolidinone-C2), 62.7, 60.2 (4C, piperazine), 59.1 (thiazolidinone-C7), 53.6 (thiazolidinone-C5), 37.9 (H$_3\underline{C}$-N-$\underline{C}$H$_3$), 32.4 (quinolone-C11). – $C_{34}H_{35}N_9O_5S$ (681.76): calcd. C 59.90, H 5.17, N 18.49; found C 59.85, H 5.11, N 18.53.

Results and Discussion

The strategy to synthesize the target compounds is shown in Fig. 1. 2,4,6-Trichloro-[1,3,5]-triazine reacting with dimethylamine at 0–5 °C yielded 4,6-dichloro-*N*,*N*-dimethyl-[1,3,5]-triazine-2-amine (**1**). Further reaction of **1** with 4-hydroxy-1-methyl-1*H*-quinolin-2-one yielded 4-(4-chloro-6-dimethylamino-[1,3,5]-triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one (**3**). The key intermediate 4-(4-amino-6-dimethylamino-[1,3,5]-triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one (**5**) was prepared in an excellent yield by the condensation of compound **3** with ammonia. Compound **5** was then treated with aromatic aldehydes (Fig. 2) to furnish the corresponding Schiff bases **6a**–**r**. Cyclization of these with thioglycolic acid led to the formation of the thiazolidinones **7a**–**r**. Finally, the target compounds **8a**–**r** were prepared by the reaction of **7a**–**r** with a mixture of paraformaldehyde and 1-pyridin-2-yl-piperazine in absolute ethanol.

The structures of the synthesized compounds were confirmed by spectral data and elemental analysis, which were in full agreement with those of the proposed structures. A C_3N_3 stretching in the *s*-triazine ring was observed at 806–812 cm^{-1} in the IR spectrum. The formation of compound **1** was confirmed by the appearance of a singlet

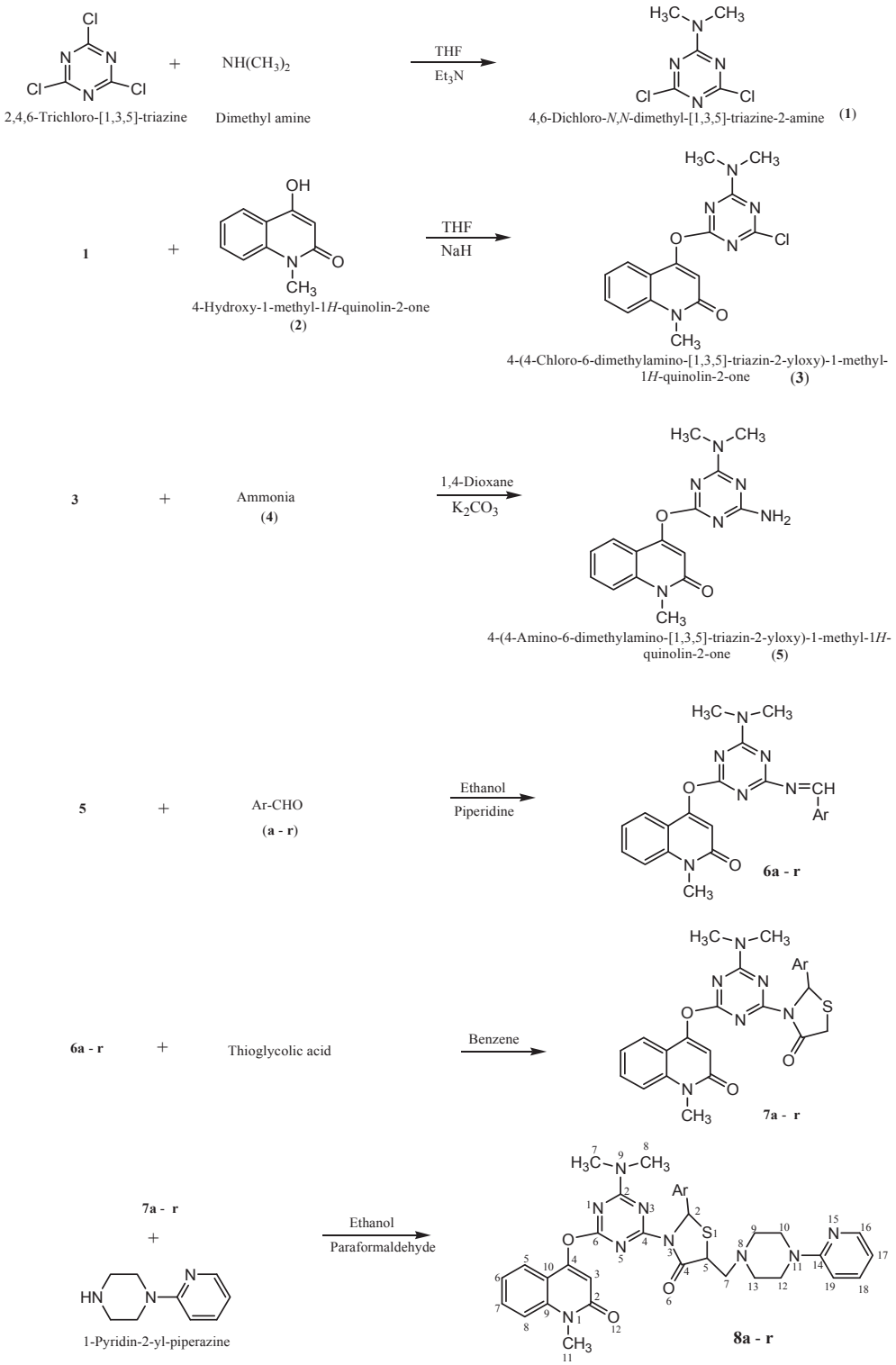

Fig. 1. Schematic diagram for the synthesis of the target compounds.

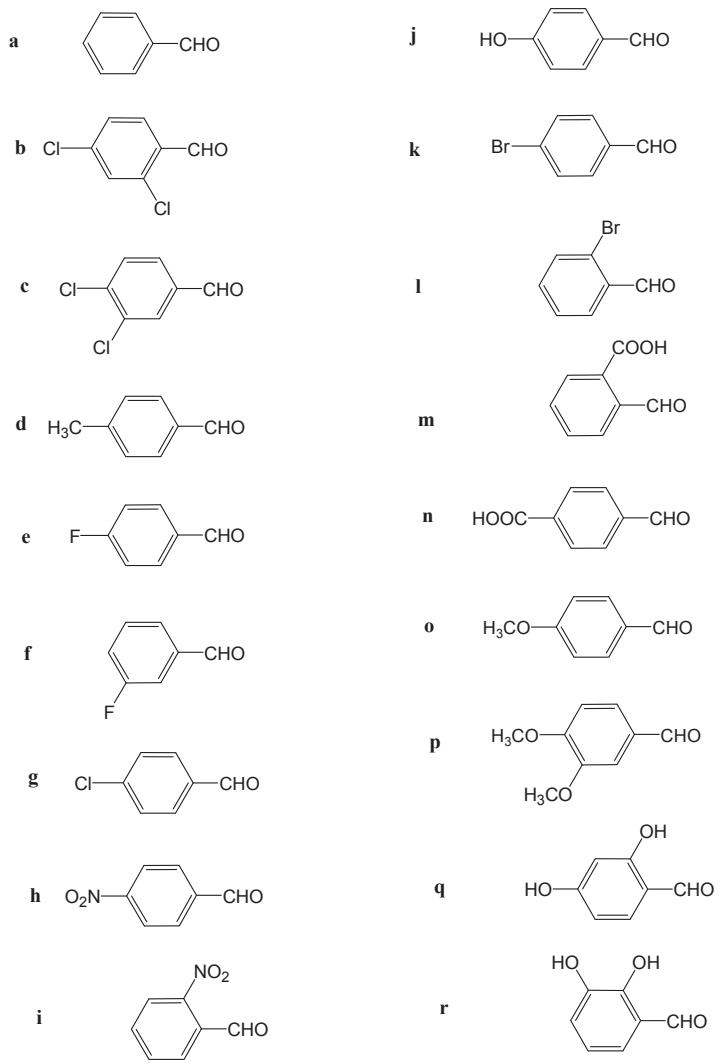

Fig. 2. Aromatic aldehydes (Ar) coupled to compound **5**.

signal in the ^{1}H NMR spectrum at δ_H 3.10 ppm due to -C$\underline{H}_3$. The formation of compound **3** bearing a quinolone moiety was confirmed by the ^{1}H NMR spectrum which indicated a signal at δ_H 3.55 ppm for -C$\underline{H}_3$ of quinolone. Protons corresponding to the quinolone moiety resonated a δ_H 6.05–8.51 ppm, whereas the ^{1}H NMR spectrum of the final derivative showed a doublet of doublet a δ_H 8.25–8.51 ppm due to a C-5 proton of the quinoline ring. Furthermore, in the IR spectrum, the band at 1666 cm^{-1} (C=O of quinolone) also confirmed the formation of compound **3**. Moreover, a characteristic band appeared at 1256 cm^{-1} corresponding to the C-O-C linkage, while disappearance of the -OH peak at 3600–3650 cm^{-1}, belonging to 4-hydroxy-*N*-methyl-quinolone, confirmed the formation of intermediate **3** as C-O-C linkage formed.

The formation of compound **5** was supported by the appearance of a singlet signal at δ_H 11.27 ppm for -N$\underline{H}_2$ in the ^{1}H NMR spectrum and a band at 3473 cm^{-1} for -NH$_2$ in the IR spectrum. Absence of a C-Cl stretching band at 700–760 cm^{-1} in the IR spectrum confirmed the formation of **5** by the condensation reaction with ammonia to an *s*-triazine ring. Compound **5** on treatment with aromatic aldehydes gave the corresponding hydrazones **6a–r** which did not show signals for

-NH_2 but showed the presence of a signal at δ_H 7.51 ppm for one proton of N=C<u>H</u>-ph. The ^{1}H NMR spectra of **7a–r** showed the presence of doublet signals at δ_H 3.59 and 3.66 ppm for two protons of S-C<u>H</u>$_2$ and a singlet at δ_H 5.09 ppm for S-C<u>H</u>-N, which confirmed the formation of the thiazolidinone ring. The compounds **7a–r** showed a characteristic absorption for the cyclic carbonyl group in the range 1713–1751 cm^{-1} in the IR spectra. The ^{1}H NMR spectra of compounds **8a–r** confirmed the absence of the -C<u>H</u>$_2$ absorption signal of the thiazolidinone ring and broad singlet signals of the methylene (4C<u>H</u>$_2$) protons of the 1-pyridin-2-yl-piperazine ring. The carbon atoms of the piperazine ring gave signals in the range δ_C 57–66 ppm in the ^{13}C NMR spectra.

The newly obtained derivatives were evaluated for their *in vitro* antimicrobial activity against several bacterial and fungal species, respectively, and the results are summarized in Tables I and II.

The antibacterial potency of the synthesized compounds was compared with that of the broad-spectrum antibiotic ciprofloxacin and their minimum inhibitory concentrations (MIC) are summarized in Table I. Most of the compounds exhibited a varied range (6.25–100 μg/mL) of antibacterial activity against the bacterial species tested. Compound **8a** without any substituent at the *ortho*-, *meta*-, and *para*-position of the phenyl group on the thiazolidinone ring showed a MIC value of 100 μg/mL against *S. aureus*, *E. coli*, *S. typhi*, and *P. vulgaris*. Compound **8a** exhibited good activity against *P. aeruginosa* with a MIC value of 25 μg/mL. Compounds **8b** and **8c**, which have an electron-withdrawing chloro substituent, respectively, at the *ortho*- (for **8b**) and *meta-para*-positions (for **8c**) of the phenyl ring attached to the thiazolidinone *para*-ring, were effective against all bacterial species. Compounds **8e**, **8f**, and **8o** exhibited similar MIC values of 6.25 μg/mL, just as **8c**, against *S. aureus.* Compounds **8b** and **8e** had the same MIC value of 6.25 μg/mL against *E. coli*, but the inhibition zones were slightly different. Compound **8c** showed the best activity against *K. pneumoniae* with a MIC value of 6.25 μg/mL. A Similar MIC value was found against *K. pneumoniae* for compound **8d** with a slightly reduced inhibition zone compared to **8c**. Compound **8d**, having an electron-donating methyl group in the *para*-position of the phenyl ring, showed good ability (MIC 6.25 μg/mL) to inhibit *B. cereus.* The best activity for compound **8d** was found with a MIC value of 6.25 μg/mL against *S. typhi* among all the synthesized compounds. Compounds **8e**, **8f**, and **8g**, having electron-withdrawing fluoro and chloro substituents on the phenyl ring attached to the thiazolidinone moiety exhibited good activities with MIC values in the range of 6.25–50 μg/mL against all tested bacterial species. Compound **8e** produced a very good MIC value of 6.25 μg/mL against *S. aureus* and *B. cereus*, respectively. Compound **8e** exhibited the highest activity against *E. coli*, *S. typhi*, and *S. flexneri* with MIC values of 6.25 μg/mL. Compound **8g** with mono-chloro substitution on the phenyl ring showed appreciable activity against all tested bacterial species. Thiazolidinones **8h** and **8i**, with a nitro substituent in the *para*- and *ortho*-position, respectively, of the phenyl ring, had similar MIC values of 100 μg/mL against *B. cereus*, *E. coli*, *P. vulgari*, and *S. flexneri*. Compound **8h**, having a *para*-nitro-substituted phenyl ring, showed good inhibition against the above mentioned bacterial species as compared to **8i**. Compound **8j** with an OH group on the phenyl ring in *para*-position displayed better activity against *B. cereus* than compounds **8q** and **8r**, which have a dihydroxy substitution at the phenyl ring. In addition, inhibition zones of compound **8q** against *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *S. typhi*, and *S. flexneri* were found to be higher than those for **8r**. The antibacterial activity of the bromo-substituted compounds **8k** and **8l** was poor as compared to the fluoro- and chloro-substituted compounds **8e**, **8f**, and **8g**. A strong inhibitory effect was shown by the derivatives **8n** and **8o** with MIC values of 6.25 μg/mL against *P. aeruginosa.* Compound **8p** was effective against all bacterial species with MIC values in the range of 6.25–50 μg/mL.

The *in vitro* antifungal activities of compounds **8a–r** were studied against the fungal species *A. niger*, *A. fumigatus*, *A. clavatus*, and *C. albicans* (Table II). Compound **8a** showed MIC values of 100 μg/mL against *A. niger*, *A. clavatus*, and *C. albicans*. Compound **8b** had a good activity against *A. fumigatus* with a MIC value of 6.25 μg/mL. Compounds **8c** and **8o** showed the highest activity against *A. clavatus* with MIC values of 6.25 μg/mL. Compound **8e** was active in the range of 6.25–25 μg/mL against all fungi. Compound **8e** exhibited the highest activity against *A. niger* with a MIC value of 6.25 μg/mL. Compounds **8f** and **8g** showed activity against all fungi with MIC values in the range 12.5–50 μg/mL. Compound **8o** showed good antifungal activity against all tested

Table I. *In vitro* antibacterial activity of compounds **8a**–**r**.

Compound	Zone of inhibition [mm] at 100 μg/disc ± SD[a] (MIC [μg/mL])							
	Gram (+)		Gram (–)					
	S. aureus	*B. cereus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*	*S. typhi*	*P. vulgaris*	*S. flexneri*
8a	12 ± 0.31 (100)	-	<10 (100)	18 ± 0.47 (25)	-	14 ± 0.25 (100)	13 ± 0.39 (100)	-
8b	21 ± 0.54 (12.5)	18 ± 0.11 (12.5)	27 ± 0.28 (6.25)	17 ± 0.27 (50)	22 ± 0.45 (12.5)	18 ± 0.13 (50)	21 ± 0.64 (25)	20 ± 0.51 (25)
8c	27 ± 0.30 (6.25)	23 ± 0.24 (12.5)	20 ± 0.19 (12.5)	19 ± 0.60 (12.5)	26 ± 0.35 (6.25)	22 ± 0.65 (12.5)	22 ± 0.31 (25)	18 ± 0.49 (50)
8d	18 ± 0.15 (25)	25 ± 0.10 (6.25)	22 ± 0.42 (50)	21 ± 0.56 (50)	25 ± 0.44 (6.25)	28 ± 0.33 (6.25)	24 ± 0.12 (12.5)	20 ± 0.53 (50)
8e	29 ± 0.28 (6.25)	27 ± 0.72 (6.25)	29 ± 0.37 (6.25)	22 ± 0.24 (25)	21 ± 0.40 (12.5)	25 ± 0.11 (6.25)	23 ± 0.20 (25)	25 ± 0.62 (6.25)
8f	23 ± 0.19 (6.25)	20 ± 0.11 (12.5)	24 ± 0.25 (12.5)	19 ± 0.21 (50)	17 ± 0.52 (12.5)	23 ± 0.45 (12.5)	21 ± 0.34 (25)	20 ± 0.39 (25)
8g	22 ± 0.65 (25)	17 ± 0.33 (50)	25 ± 0.27 (12.5)	16 ± 0.57 (50)	21 ± 0.72 (12.5)	19 ± 0.54 (12.5)	18 ± 0.21 (50)	20 ± 0.55 (25)
8h	-	12 ± 0.44 (100)	17 ± 0.38 (100)	16 ± 0.14 (100)	-	-	<10 (100)	18 ± 0.56 (100)
8i	11 ± 0.75 (100)	<10 (100)	<10 (100)	-	-	-	<10 (100)	11 ± 0.22 (100)
8j	-	11 ± 0.36 (100)	<10 (100)	17 ± 0.67 (50)	13 ± 0.50 (100)	-	12 ± 0.16 (100)	-
8k	-	<10 (100)	11 ± 0.63 (100)	<10 (100)	-	<10 (100)	12 ± 0.25 (100)	14 ± 0.49 (100)
8l	-	-	-	-	<10 (100)	<10 (100)	11 ± 0.32 (100)	12 ± 0.58 (100)
8m	16 ± 0.40 (100)	20 ± 0.23 (50)	15 ± 0.14 (100)	17 ± 0.55 (50)	12 ± 0.77 (100)	19 ± 0.73 (50)	15 ± 0.17 (100)	17 ± 0.25 (100)
8n	19 ± 0.31 (50)	22 ± 0.64 (25)	23 ± 0.61 (25)	27 ± 0.35 (6.25)	25 ± 0.59 (12.5)	22 ± 0.11 (25)	19 ± 0.15 (50)	24 ± 0.46 (12.5)
8o	27 ± 0.62 (6.25)	27 ± 0.58 (6.25)	25 ± 0.76 (12.5)	28 ± 0.43 (6.25)	20 ± 0.16 (50)	23 ± 0.70 (12.5)	26 ± 0.75 (6.25)	25 ± 0.63 (6.25)
8p	24 ± 0.53 (12.5)	26 ± 0.49 (6.25)	22 ± 0.67 (50)	25 ± 0.16 (25)	18 ± 0.71 (50)	25 ± 0.14 (12.5)	22 ± 0.60 (12.5)	20 ± 0.51 (25)
8q	14 ± 0.59 (100)	-	-	<10 (100)	17 ± 0.12 (100)	14 ± 0.28 (100)	-	<10 (100)
8r	<10 (100)	-	-	-	13 ± 0.37 (100)	11 ± 0.24 (100)	-	-
Ciprofloxacin	30 ± 0.25 (1.0)	31 ± 0.11 (1.0)	32 ± 0.39 (1.0)	33 ± 0.61 (1.0)	33 ± 0.45 (1.0)	30 ± 0.57 (1.0)	31 ± 0.19 (1.0)	32 ± 0.55 (≤3)
DMSO	-	-	-	-	-	-	-	

Each value is the mean of three independent experiments.
[a] SD, standard deviation.
- Not active at concentrations higher than 100 μg/mL.

Table II. *In vitro* antifungal activity of compounds **8a**–**r**.

Compound	Zone of inhibition [mm] at 100 μg/disc ± SD[a] (MIC [μg/mL])			
	A. niger	*A. fumigatus*	*A. clavatus*	*C. albicans*
8a	<10 (100)	-	13 ± 0.32 (100)	11 ± 0.17 (100)
8b	21 ± 0.29 (25)	26 ± 0.45 (6.25)	24 ± 0.41 (12.5)	22 ± 0.73 (25)
8c	23 ± 0.70 (12.5)	19 ± 0.37 (25)	27 ± 0.57 (6.25)	24 ± 0.64 (25)
8d	25 ± 0.41 (25)	21 ± 0.25 (25)	20 ± 0.59 (50)	18 ± 0.33 (50)
8e	28 ± 0.69 (6.25)	23 ± 0.13 (25)	21 ± 0.56 (25)	25 ± 0.52 (12.5)
8f	24 ± 0.48 (12.5)	20 ± 0.16 (25)	18 ± 0.25 (50)	21 ± 0.47 (50)
8g	20 ± 0.10 (50)	23 ± 0.34 (25)	25 ± 0.46 (12.5)	26 ± 0.76 (12.5)
8h	<10 (100)	18 ± 0.55 (100)	-	-
8i	-	<10 (100)	<10 (100)	-
8j	-	11 ± 0.63 (100)	-	-
8k	11 ± 0.23 (100)	-	13 ± 0.58 (100)	<10 (100)
8l	<10 (100)	-	11 ± 0.61 (100)	-
8m	11 ± 0.44 (100)	14 ± 0.49 (100)	16 ± 0.15 (100)	17 ± 0.22 (100)
8n	19 ± 0.56 (100)	21 ± 0.78 (50)	20 ± 0.71 (50)	18 ± 0.64 (100)
8o	26 ± 0.11 (6.25)	25 ± 0.36 (12.5)	27 ± 0.19 (6.25)	24 ± 0.71 (12.5)
8p	20 ± 0.57 (50)	18 ± 0.48 (50)	25 ± 0.13 (25)	22 ± 0.24 (50)
8q	<10 (100)	-	15 ± 0.21 (100)	-
8r	-	-	11 ± 0.36 (100)	<10 (100)
Ketoconazole	30 ± 0.18 (≤ 3)	29 ± 0.70 (1.0)	31 ± 0.26 (1.0)	33 ± 0.53 (1.0)
DMSO	-	-	-	-

Each value is the mean of three independent experiments.
[a] SD, standard deviation.
- Not active at concentrations higher than 100 μg/mL.

fungal species in the MIC range of 6.25–12.5 μg/mL. All remaining thiazolidinone derivatives showed satisfactory antifungal activity.

The results of the tests of the antimicrobial activities indicate that when an electron-withdrawing group, like mono-chloro, di-chloro, mono-fluoro, but also an electron-donating group, like methyl or methoxy, is attached to the phenyl ring at the thiazolidinone moiety, then these compounds showed very good activity against all bacterial and fungal species tested. The results indicate that compounds **8b**, **8c**, **8d**, **8e**, **8f**, **8g**, **8o**, and **8p** exhibited higher antimicrobial activities in comparison with other derivatives.

Boehm H. J., Boehringer M., Bur D., Gmuender H., Huber W., Klaus W., Kostrewa D., Kuehne H., Luebbers T., Meunier-Keller N., and Mueller F. (2000), Novel inhibitors of DNA gyrase: 3D structure based biased needle screening, hit validation by biophysical methods, and 3D guided optimization: A promising alternative to random screening. J. Med. Chem. **43**, 2664–2674.

Brzozowski Z., Saczewski F., and Gdaniec M. (2000), Synthesis, structural characterization and antitumour activity of novel 2,4-diamino-1,3,5-triazine derivatives. Eur. J. Med. Chem. **35**, 1053–1064.

Chande S. M., Dravid R. N., and Shetgiri N. P. (1988), Synthesis of new 1,3,5-thiadiazine and 1,3,5-triazine derivatives and their antimicrobial activity. J. Chem. Sci. **100**, 53–58.

Chen H., Huang S.-Q., and Xie J.-Y. (2009), Efficient synthesis of 2,4-dioxohexahydro-1,3,5-triazine *O*-acetyl-glycosyl glucosides and their antiviral activity. Chem. Heterocycl. Compd. **45**, 976–980.

Clement J. J., Burres N., Jarvis K., Chu D. T., Swiniarski J., and Alder J. (1995), Biological characterization of a novel antitumour quinolone. Cancer Res. **55**, 830–835.

Detsi A., Bouloumbasi D., Prousis K. C., Koufaki M., Athanasellis G., Melaqraki G., Afantitis A., Igglessi-Markopoulou O., Kontogiorgis C., and Hadjipavlou-Litina D. J. (2007), Design and synthesis of novel quinolinone-3-aminoamides and their α-lipoic acid adducts as antioxidant and anti-inflammatory agents. J. Med. Chem. **50**, 2450–2458.

Dorsey B. D., Levin R. B., McDaniel S. L., Vacca J. P., Guare J. P., Darke P. L., Zugay J. A., Emini E. A.,

Schleif W. A., and Quintero J. C. (1994), L-735, 524: The design of a potent and orally bioavailable HIV protease inhibitor. J. Med. Chem. **37**, 3443–3451.

Enrica F., Gabriele C., Oriana T., Violetta C., and Arnaldo F. (2001), QSAR study and VolSurf characterization of anti-HIV quinolone library. ACS Symp. Ser. **15**, 203–217.

Gillespie S. H. (1994), Medical Microbiology – Illustrated. Butterworth, Heinemann Ltd., London, UK, pp. 234–247.

Gravestock D., Rousseau A. L., Lourens A. C., Moleele S. S., Van Zyl R. L., and Steenkamp P. A. (2011), Expeditious synthesis and biological evaluation of novel 2,N^6-disubstituted 1,2-dihydro-1,3,5-triazine-4,6-diamines as potential antimalarials. Eur. J. Med. Chem. **46**, 2022–2030.

Hawkey P. M. and Lewis D. A. (1994), Medical Bacteriology – a Practical Approach. Oxford University Press, London, UK, pp. 181–194.

Horton D. A., Bourne G. T., and Smythe M. L. (2003), The combinatorial synthesis of bicyclic privileged structures or privileged substructures. Chem. Rev. **103**, 893–930.

Saczewski F., Bulakowska A., Bednarski P., and Grunert R. (2006), Synthesis, structure and anticancer activity of novel 2,4-diamino-1,3,5-triazine derivatives. Eur. J. Med. Chem. **41**, 219–225.

Saleh M., Abbott S., Lauzon V. C., Penney C., and Zacharie B. (2010), Synthesis and antimicrobial activity of 2-fluorophenyl-4,6-disubstituted [1,3,5]triazines. Bioorg. Med. Chem. Lett. **20**, 945–949.

Sissi C. and Palumbo M. (2003), The quinolone family: from antibacterial to anticancer agents. Curr. Med. Chem. Anticancer Agents **3**, 439–450.

Sun C., Keumnyeo J., and Jaesang R. (2006), Efficient synthesis of 2-substituted 2,3-dihydro-4-quinolones as potential intermediates for 2-substituted 1,2,3,4-tetrahydro-4-quinolone antitumour agents. Arch. Pharm. Res. **29**, 369–374.

Ukrainets I. V., Taran S. G., Kodolova O. L., Gorokhova O. V., and Kravchenko V. N. (1997), Synthesis and study of antithyroid properties of 1*H*-2-oxo-3-(coumarin-3-yl)-4-hydroxyquinolines. Chem. Heterocycl. Compd. **33**, 959–963.

Vasil'eva N. Y., Vusovich O. V., and Kozhevnikova N. M. (2002), Quantum-chemical study of proton transfer and photoreactions of quinolone derivatives. High Energy Chem. **36**, 265–271.

Verma A. and Saraf S. K. (2008), 4-Thiazolidinone – A biologically active scaffold. Eur. J. Med. Chem. **43**, 897–905.

Wang J. C. (1996), DNA topoisomerases. Annu. Rev. Biochem. **65**, 635–692.

Zhang M. Q., Haemers A., Vanden Berghe D., Pattyn S. R., Bollaert W., and Levshin I. (1991), Quinolone antibacterials. 2. 6-Substituted-7-(2-thiazolyl and thiazolidinyl)quinolones. J. Heterocycl. Chem. **28**, 685–695.