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Microwave assisted synthesis and *in vitro* antimicrobial assessment of quinolone based *s*-triazines

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Abstract

A series of 1,3,5-triazine derivatives that contain aniline, 4-hydroxy-*N*-methylquinolone and different piperazine and piperidine moieties as substituents on the carbon atoms of the triazine ring has been synthesized by a simple and efficient synthetic protocol. Comparative studies were performed on the compounds, which were synthesized with conventional and microwave heating methods. The microwave method was observed to be more beneficial as it provides an increase in yield and 90%–95% reduction time. The antimicrobial activity of the compounds was tested against seven bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Salmonella typhi*, *Proteus vulgaris*) and two fungi (*Aspergillus niger*, *Candida albicans*). The results indicate that some of the novel *s*-triazines have noteworthy activity in MIC and agar diffusion tests.

Keywords: antimicrobial activity; microwave irradiation; piperazine; piperidine; quinolone; *s*-triazine.

Introduction

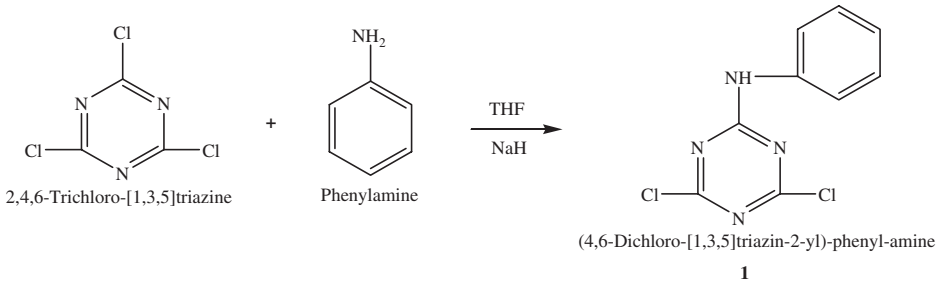
Controlling the deadliest infectious diseases in the world is seriously threatened by the sharpening increase in the multidrug resistance of human pathogenic strains to a wide range of currently available antimicrobial agents. Worryingly, in most of the developing countries, this problem is at an alarming level, where resistant infections lead to increased mortality. Furthermore, an increased number of immunocompromised patients attributable to the ongoing HIV epidemic can further increase the burden of antimicrobial resistance in human civilization by facilitating the spread of resistant pathogens (Nathan, 2004). Significant impact of the affliction of infectious disease in developing countries due to multidrug resistance posed by bacteria, has driven us to examine newly synthesized derivatives against the representative panel of bacterial and fungal strains in order to reduce drug resistance to the pathogenic strains and in order to maintain a pool of new bioactive candidates at all times.

Various 1,3,5-triazines show powerful antimicrobial (Srinivas et al., 2006; Zhou et al., 2008), antiprotozoal (Alessandro et al., 2005), anticancer (Rita et al., 2004), antimalarial (Sergio et al., 2008) and antiviral (Yuan-Zhen et al., 2008) activities. On the other hand, 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 corrupt the activities of prokaryotic type II topoisomerases, DNA gyrase and topoisomerase IV, and induce them to kill cells by generating high levels of 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; Drlica and Zhao, 1999). Like bacterial cells, eukaryotic species require a type II topoisomerase, known as topoisomerase II, for viability (Burden and Osheroff, 1998). Thus, in addition to the antibacterial quinolones, specific members of this drug family display high activity against eukaryotic type II topoisomerases, as well as cultured mammalian cells and *in vivo* tumor models (Clement et al., 1995). Quinolone derivatives are used as anticancer (Karl and Xilin, 1997), anti-HIV (Enrica et al., 2001), antitumor (Sun et al., 2006), antioxidant, anti-inflammatory (Anastasia et al., 2007) and antithyroid agents (Ukrainets et al., 1997). Quinolones are also used as components of organic-laser active media, luminophores, and fluorescent labels (Vasil'eva et al., 2002). Compounds synthesized as part of this work are structural combinations of 1,3,5-triazine and quinolone moieties.

Microwave technology has become a powerful tool in organic synthesis, since by employing this technique it is generally possible to prepare organic compounds very quickly, with high purity and better yields compared to other more conventional methods (Kayes, 2002; Kappe and Stadler, 2005). In particular, we carried out the reaction of 4-(4-chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one (**3**) with different amines under microwave irradiation. This method proved to be superior to the traditional heating.

Results and discussion

Compounds **5a-u** have been synthesized according to the Scheme 1. Two basic approaches, conventional heating and microwave irradiation, were applied for the final nucleophilic substitution reactions of the intermediate product **3**

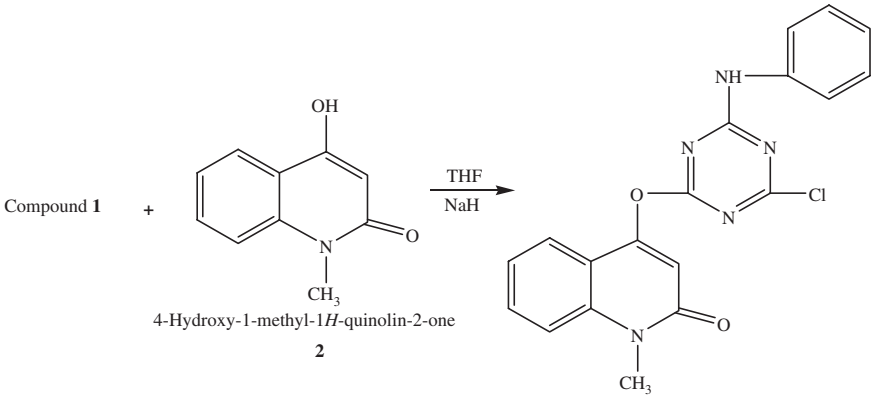


2,4,6-Trichloro-[1,3,5]triazine

Phenylamine

(4,6-Dichloro-[1,3,5]triazin-2-yl)-phenyl-amine

1

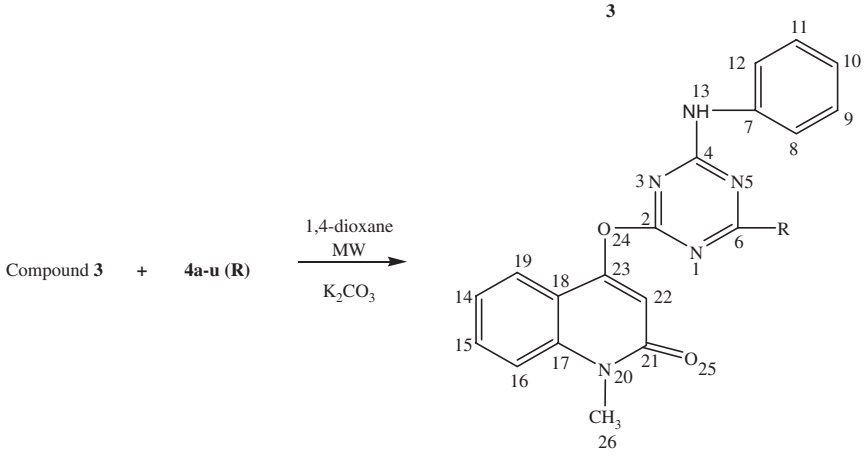


4-Hydroxy-1-methyl-1*H*-quinolin-2-one

2

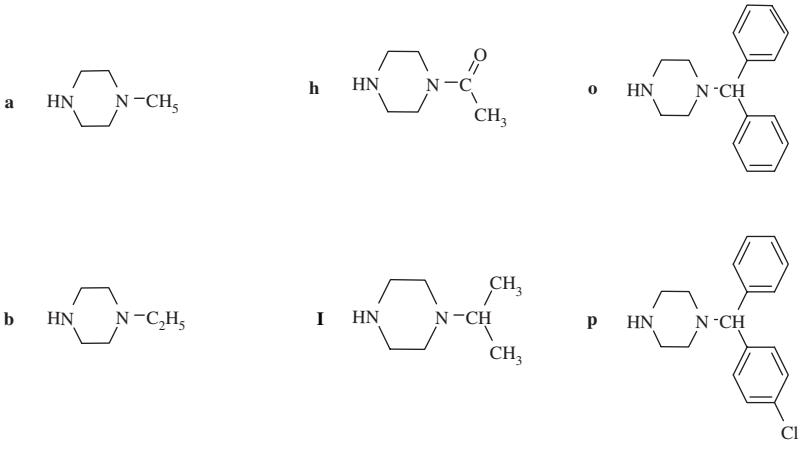
4-(4-Chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one

3

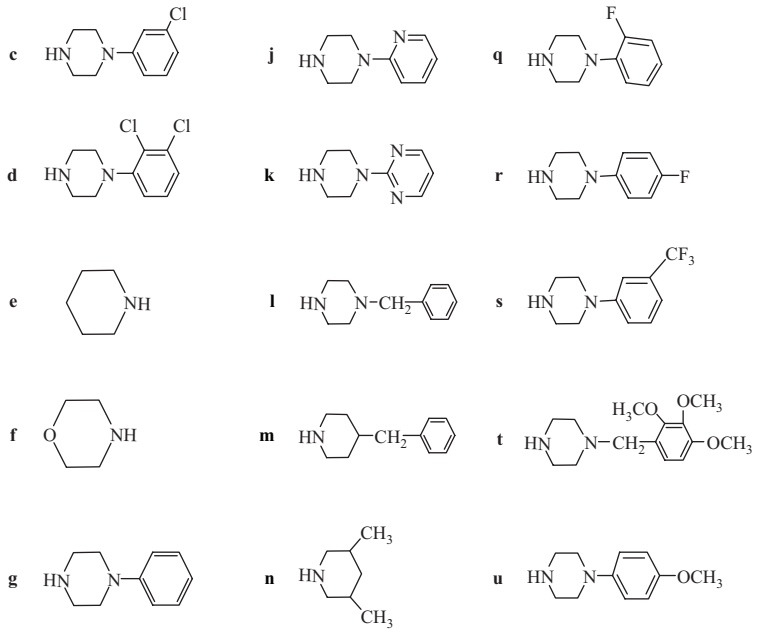


5a-u

Amines **4a-u** (R-H) coupled to compound **3**



Scheme 1 (Continued)



Scheme 1 Synthesis of target compounds.

with amines **4a-u** to furnish the desired products **5a-u**. A comparative study of the yields of products under microwave irradiation and conventional heating showed that the use of microwave irradiation substantially reduced the reaction times from h to min and appreciably increased the yields (Table 1). The disubstituted *s*-triazine intermediate **3**, in turn, was obtained by the reaction between *N*-(4,6-dichloro-[1,3,5]-triazin-2-yl)aniline (**1**) and 4-hydroxy-*N*-methyl-2 -quinolone **2** in the presence of 60% NaH at 45–50°C. As already mentioned, substitution reaction of **3** with appropriate piperazines and piperidines **4a–u** provided the target compounds **5a–u**.

All the synthesized compounds were tested against seven bacteria, namely *E. coli, P. aeruginosa, K. pneumoniae, S. typhi, P. vulgaris, S. aureus, B. cereus* and two fungi *C. albicans* and *A. niger*.

The results of antimicrobial data are shown in Table 2. Final *s*-triazinyl compounds **5d**, **5n**, and **5s** showed substantial activity (MIC, 6.25 µg/ml) against Gram-positive strain *S. aureus.* Compound **5u** exhibited a similar inhibitory concentration of 6.25 µg/ml against *S. aureus* with 1 mm of lesser zone of inhibition. Compounds **5p** and **5t** were found half as active (MIC, 12.5 µg/ml) against *S. aureus* as compared to most active analogues tested against the same strain. Final *s*-triazinyl analogues **5s** and **5t** displayed strong inhibitory profile at 6.25 µg/ml against Gram-positive *B. cereus*, while compounds **5h** and **5r** exhibited a similar inhibitory concentration of 6.25 µg/ml against *B. cereus* with 1 mm of lesser zone of inhibition along with 0.5-fold comparative activity of compounds **5p** and **5n** (MIC, 12.5 µg/ml) against the same bacterial strain. Compounds **5c** and **5q** (26 mm of zone of inhibition) were found to have good activity (MIC, 12.5 µg/ml) along with similar inhibitory concentration level of compound **5r** (25 mm of zone of inhibition) towards Gram-negative strain *E. coli*, while compounds **5d**, **5p**, **5s**, and **5t** demonstrated 25 µg/ml of inhibitory concentration level against *E. coli*. Compounds **5i** and **5s** (26 mm – zone of inhibition) as well as **5n** (25 mm – zone of inhibition) appeared with remarkable activity against Gram-negative *P. aeruginosa* at 6.25 µg/ml of MIC, where the 0.5-fold activity was observed (MIC, 12.5 µg/ml) for compounds **5d** and **5t** against the same bacteria. Inhibition of Gram-negative bacteria *K. pneumoniae* was also noted for *s*-triazine derivatives **5t** and **5u** at 12.5 µg/ml as well as **5s** with quite reduced zone diameter (23 mm). Another five derivatives **5c**, **5d**, **5n**, **5p** and **5s** exhibited 0.5-fold growth inhibition of the same bacteria (MIC, 25 µg/ml). Compound **5h**, **5i** and **5u** (26 mm – zone of inhibition), and compound **5t** (25 mm – zone of inhibition) possessed the highest activity (MIC, 12.5 µg/ml) against Gram-negative *S. typhi* along with 0.5-fold activity profile of compounds **5b** and **5n** (MIC, 25 µg/ml). Final *s*-triazine derivatives **5m**, **5p**, and **5s** (27 mm – zone of inhibition) and **5n** (26 mm – zone of inhibition) were superior in inhibiting the growth of Gram-negative *P. vulgaris* (MIC, 6.25 µg/ml), whereas 0.5-fold activity was observed in the case of compounds **5h** and **5t** at 12.5 µg/ml.

The antifungal bioassay results revealed that *s*-triazine derivative **5p**, **5r**, **5s**, and **5u** displayed excellent antigrowth activity (MIC, 12.5 µg/ml) against *A. niger,* which was found to be equivalent to the standard drug tested. Compounds **5c**, **5d** and **5t** appeared with 0.5-fold inhibitory action against the same fungi at MIC, 25 µg/ml. Compounds **5d**, **5h**, **5t** and **5u** appeared with excellent inhibition of *C. albicans* at 25 µg/ml. Compound **5s** displayed similar MIC µg/ml but the zone of inhibition was reduced to 1 mm. Compounds **5p**, **5q**, and **5r** indicated 0.5-fold activity (50 µg/ml) of the most active analogues towards *C. albicans*.

Table 1 Comparison of the synthesis of **5a-u** using microwave irradiation and conventional heating (see Scheme 1 for the structures of **5a-u**).

Entry	R	Microwave method		Conventional method	
		Reaction time (min)	Yield (%)	Reaction time (h)	Yield (%)
5a	*N*-methylpiperazino	2	79	9	60
5b	*N*-ethylpiperazino	2	81	9	72
5c	4-(3-chlorophenyl)piperazino	3	77	10	61
5d	4-(2,3-dichlorophenyl)piperazino	4	83	10	70
5e	Piperidino	5	87	8	64
5f	Morpholino	4	89	9	62
5g	4-phenylpiperazino	6	84	9	65
5h	4-acetylpiperazino	4	80	11	63
5i	4-isopropylpiperazino	7	75	10	60
5j	4-(2-pyridyl)piperazino	8	85	12	73
5k	4-(2-pyrimidyl)piperazino	8	82	12	71
5l	4-benzylpiperazino	3	87	11	79
5m	4-benzylpiperidino	2	86	13	77
5n	3,5-dimethylpiperidino	4	90	8	75
5o	4-benzhydrylpiperazino	2	72	9	66
5p	4-chlorobenzhydrylpiperazino	5	77	12	63
5q	4-(2-fluorophenyl)piperazino	6	92	12	78
5r	4-(4-fluorophenyl)piperazino	6	90	11	81
5s	4-(3-(trifluoromethyl)phenyl)piperazino	7	87	12	61
5t	4-(2,3,4-trimethoxybenzyl)piperazino	5	80	10	65
5u	4-(4-methoxyphenyl)piperazino	4	74	11	60

Table 2 *In vitro* antibacterial activity of compounds **5a-u**. For structures, see Table 1 and Scheme 1.

Compound (100 µg/disc)	Zone of inhibition [mm (MIC in µg/ml)]						
	Gram (+)		Gram (-)				
	S. aureus	*B. cereus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*	*S. typhi*	*P. vulgaris*
5a	19 (100)	21 (100)	18 (100)	19 (100)	20 (100)	21 (50)	19 (100)
5b	20 (100)	22 (25)	20 (100)	19 (100)	19 (100)	23 (25)	20 (100)
5c	23 (25)	25 (25)	26 (12.5)	24 (25)	23 (25)	23 (100)	22 (50)
5d	28 (6.25)	26 (6.25)	25 (25)	25 (12.5)	22 (25)	23 (50)	23 (12.5)
5e	22 (100)	20 (100)	16 (100)	16 (100)	17 (100)	17 (100)	16 (100)
5f	21 (100)	20 (100)	16 (100)	19 (100)	16 (100)	18 (100)	16 (100)
5g	19 (100)	17 (100)	15 (100)	16 (100)	19 (100)	16 (100)	16 (100)
5h	24 (25)	26 (6.25)	23 (50)	23 (25)	22 (50)	26 (12.5)	24 (12.5)
5i	23 (100)	22 (50)	22 (50)	26 (6.25)	21 (100)	26 (12.5)	22 (50)
5j	21 (100)	18 (100)	16 (100)	20 (100)	19 (100)	19 (100)	17 (100)
5k	20 (100)	21 (100)	18 (100)	20 (100)	17 (100)	19 (100)	21 (100)
5l	21 (100)	19 (100)	17 (100)	20 (100)	18 (100)	17 (100)	20 (100)
5m	23 (50)	19 (100)	17 (100)	17 (100)	18 (100)	20 (100)	27 (6.25)
5n	28 (6.25)	26 (12.5)	23 (50)	25 (6.25)	22 (25)	24 (25)	26 (6.25)
5o	22 (50)	20 (100)	19 (100)	18 (100)	19 (100)	18 (100)	21 (100)
5p	25 (12.5)	25 (12.5)	25 (25)	21 (50)	22 (25)	22 (100)	27 (6.25)
5q	24 (25)	23 (25)	26 (12.5)	21 (50)	23 (12.5)	24 (50)	23 (50)
5r	25 (25)	26 (6.25)	25 (12.5)	22 (25)	22 (50)	23 (50)	22 (25)
5s	28 (6.25)	27 (6.25)	25 (25)	26 (6.25)	23 (25)	24 (50)	27 (6.25)
5t	26 (12.5)	27 (6.25)	24 (25)	24 (12.5)	25 (12.5)	25 (12.5)	25 (12.5)
5u	27 (6.25)	24 (25)	22 (50)	21 (25)	25 (12.5)	26 (12.5)	23 (25)
Ciprofloxacin (100 µg/disc)	30 (1.0)	31 (1.0)	32 (1.0)	33 (1.0)	33 (1.0)	30 (1.0)	31 (1.0)
DMSO	–	–	–	–	–	–	–

The MIC values were evaluated at concentration range of 3.12–100 µg/ml.
Each value is the mean of three independent experiments.

Table 3 *In vitro* antifungal activity of compounds **5a-u**. For structures, see Table 1 and Scheme 1.

Compound (100 µg/disc)	Zone of inhibition in [mm (MIC in µg/ml)]	
	A. niger	*C. albicans*
5a	16 (100)	16 (100)
5b	20 (100)	17 (100)
5c	24 (25)	24 (100)
5d	24 (25)	28 (25)
5e	16 (100)	17 (100)
5f	19 (100)	15 (100)
5g	21 (100)	17 (100)
5h	23 (50)	28 (25)
5i	21 (100)	20 (100)
5j	18 (100)	17 (100)
5k	16 (100)	17 (100)
5l	17 (100)	16 (100)
5m	17 (100)	20 (100)
5n	24 (50)	24 (100)
5o	19 (100)	21 (100)
5p	25 (12.5)	26 (50)
5q	24 (50)	26 (50)
5r	25 (12.5)	27 (50)
5s	25 (12.5)	27 (25)
5t	25 (25)	28 (25)
5u	25 (12.5)	28 (25)
Ketoconazole (100 µg/disc)	30 (≤3)	33 (1.0)
DMSO	–	–

The MIC values were evaluated at concentration range of 3.12–100 µg/ml.
Each value is the mean of three independent experiments.

Conclusions

This study indicates that the developed procedure for synthesis of title compounds using microwave-assisted synthesis is much more simple, easier to work with, and safer compared to the conventional method. From the bioassay results, it is clear that substituents on the *s*-triazine ring strongly affect the antimicrobial activity. Some modifications to improve the potency of the series by changing the position and the type of substituents are currently under investigation and will be reported in future.

Experimental section

Microwave assisted reactions were carried out on a microwave reactor model-Roto Synth Terminal-640. The melting points were determined in open capillaries on a Veego VMP-D electronic apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 8400-S FT-IR spectrophotometer in KBr pellets. Thin layer chromatography was performed on microscopic glass slides (2×7.5 cm) coated with silica gel-G, using appropriate mobile phase system and spots were visualized under UV radiation. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer at 400 MHz and 100 MHz, respectively, in $CDCl_3$ using TMS as internal standard. The ^{19}F spectra were recorded on the same instrument in $CDCl_3$ using $CFCl_3$ as internal standard. All new compounds were subjected to elemental analysis using a Heraeus Carlo Erba 1180 CHN analyzer.

N-(4,6-Dichloro-[1,3,5,]triazin-2-yl)aniline (1)

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine (15 g, 0.081 mol) in anhydrous tetrahydrofuran (THF) (150 ml) aniline (7.97 g, 0.081 mol) was added dropwise at 0–5°C. The resulting mixture was stirred at this temperature for 2 h, then treated with triethylamine (8.28 g, 0.081 mol), and stirring was continued for another 4 h. The mixture was then treated with crushed ice, neutralized with dilute HCl and the precipitate was filtered, dried, and crystallized from acetone to afford 17.0 g (87%) of **1**; mp 191–194°C; IR: 3296.5 cm^{-1} (-NH); ^{1}H NMR: δ 9.15 (s, 1H, NH), 6.93–7.69 (m, 5H, Ar-H); ^{13}C NMR 117.9, 122.8, 128.8, 139.6, 165.4, 171.2. Analysis: calculated for $C_9H_6Cl_2N_4$: C, 44.84; H, 2.51; N, 23.24. Found: C, 44.76; H, 2.40; N, 23.29.

4-(4-Chloro-6-anilino-[1,3,5]triazin-2-yl)oxy)-1-methyl-1*H*-quinolin-2-one (3)

To a stirred mixture of 4-hydroxy-*N*-methylquinolone (**2**, 8.63 g, 0.05 mol) and 60% NaH (1.18 g, 0.05 mol) in anhydrous THF (150 ml), compound **1** (11.89 g, 0.05 mol) was added. The mixture was stirred for 1 h at room temperature and then for another 14 h at 45–50°C, after which time it was treated with crushed ice, and the solid precipitate was filtered, dried, and crystallized from THF to afford 7.53 g (86%) of **3**; mp 265–269°C; IR: 1243–1251 cm^{-1} (C-O-C), 1700.4 cm^{-1} (C=O); ^{1}H NMR: δ 9.17 (s, 1H, NH), 7.10–7.82 (m, 9H, Ar-H), 6.47 (s, 1H, H at C-22 of quinolone), 3.25 (s, 3H, CH_3 of quinolone); ^{13}C NMR 32.5, 97.2, 115.5, 118.7, 122.5, 123.1, 123.8, 126.6, 132.0, 140.1, 141.2, 151.7, 165.6, 172.4. Analysis: calculated for $C_{19}H_{14}ClN_5O_2$: C, 60.09; H, 3.72; N, 18.44. Found: C, 60.17; H, 3.59; N, 18.37.

General procedures for preparation of compounds 5a-u

Conventional method To a solution of **3** (3.79 g, 0.01 mol) in 1,4-dioxane (30 ml), piperazine or piperidine derivative was added. For example, 1-benzyl piperazine (**4i**, 1.57 g, 0.01 mol) was added and the mixture was heated under reflux for 10–15 h as per TLC monitoring. Potassium carbonate was used for the neutralization of the reaction mixture. After completion of the reaction, it was treated with crushed ice, neutralized by dilute HCl, and the precipitate thus obtained was filtered, dried and crystallized from THF (15 ml) to give 4.19 g (79%) of **5i** as light brown solid. The same procedure was applied for the synthesis of other final compounds.

Microwave method The microwave irradiation of the final nucleophilic substitution mixtures were carried out on the same scale, using the same solvent (1,4-dioxane) and under similar concentration conditions as indicated above. The reaction time was found to be dramatically reduced for each substitution from 10 to 15 h (conventional heating method) to 2–6 min under microwave irradiation. Microwave assisted reactions of **3** with various amines were conducted in septum-sealed reaction vessels in a microwave reactor. For example, compound **3** (3.79 g, 0.01 mol) in the presence of K_2CO_3 (1.41 g) was condensed with 4-benzylpiperidine (**4m**, 1.74 g, 0.01 mol) using 1,4-dioxane (30 ml) as a solvent under microwave irradiation at 180 W power for 2–6 min. The mixture was heated until completion as determined by silica gel TLC analysis (1:1 chloroform/methanol developing system). After completion of reaction the solvent was removed by using vacuum solvent recovery module. The residue was

treated with crushed ice, neutralized with diluted HCl, filtered, and the solid material was dried and crystallized from THF to give 4.46 g (86%) of compound **5m.** The **s**ame procedure was applied for synthesis of the other final compounds. The conventional method and the microwave assisted methods are compared in Table 1.

Characterization of compounds 5a-u

1-Methyl-[4-[4-(4-methylpiperazino)-6-anilino-[1,3,5]triazin-2-yl] oxy]-1*H*-quinolin-2-one **(5a)**: mp 258–261°C; IR: 3296.4 (N-H str.), 1712.2 cm^{-1} (C=O of quinolone), 1463.0 (CH_3), 1260.5 (C-O-C), 811.2 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.17 (s, 1H, -NH), 6.97–8.21 (m, 9H, Ar-H), 6.45 (s, 1H, H at C-22 of quinolone), 3.60 (s, 3H, CH_3 of quinolone), 3.19 (br-s, 8H, piperazine), 2.57 (s, 3H, CH_3 of piperazine); ^{13}C NMR: δ 171.9 (C-6, C-N at piperazine linkage), 171.3 (C-2, C-O-C at quinolone linkage), 165.4 (C-4, C-NH at aniline linkage), 159.2 (C-21, C=O of quinolone), 152.8 (C-23, C-O-C at quinolone), 142.6, 140.1, 132.7, 128.8, 128.8, 123.7, 123.6, 122.7, 118.8, 1188, 116.8, 115.9 (12 C, Ar-C), 110.1 (C-22, C-C=O of quinolone), 64.1, 45.0 (4C, piperazine), 32.7 (C-26, CH_3 of quinolone). Analysis: calculated for $C_{24}H_{25}N_7O_2$: C, 65.00; H, 5.68; N, 22.11. Found: C, 65.17; H, 5.61; N, 22.02.

[4-[4-(4-Ethylpiperazino)-6-anilino-[1,3,5]triazin-2-yl]oxy]-1-methyl-1*H*-quinolin-2-one **(5b)**: mp 253–258°C; IR: 3296.5 (N-H str.), 1694.4 (C=O of quinolone), 1490.3 (CH_2CH_3), 1256.3 (C-O-C), 806.2 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.12 (s, 1H, -NH), 6.85–8.19 (m, 9H, Ar-H), 6.47 (s, 1H, H at C-22 of quinolone), 3.31 (s, 3H, CH_3 of quinolone), 3.57 (br-s, 8H, piperazine), 2.60 (s, 3H, CH_2-CH_3 of piperazine), 1.90 (s, 2H, CH_2-CH_3 of piperazine); ^{13}C NMR 171.9 (C-6, C-N at piperazine linkage), 171.3 (C-2, C-O-C at quinolone linkage), 165.4 (C-4, C-NH at aniline linkage), 159.23 (C-21, C=O of quinolone), 152.8 (C-23, C-O-C at quinolone), 142.7, 140.2, 132.7, 128.8, 128.7, 123.7, 123.5, 122.7, 118.6, 118.9, 116.8, 115.9 (12 C, Ar-C), 110.1 (C-22, C-C=O of quinolone), 58.2, 46.9 (4C, piperazine), 51.7 (C-34, CH_2-CH_3 of piperazine), 32.6 (C-26, CH_3 of quinolone), 15.4 (C-33, CH_2-CH_3 of piperazine). Analysis: calculated for $C_{25}H_{27}N_7O_2$: C, 65.63; H, 5.95; N, 21.43. Found: C, 65.51; H, 5.88; N, 21.56.

4-[4-[4-(3-Chlorophenyl)piperazino]-6-anilino-[1,3,5]triazin-2-yl]-oxy]-1-methyl-1*H*-quinolin-2-one **(5c)**: mp 230–236°C; IR: 3293.1 (N-H str.), 1697.5 (C=O of quinolone), 1270.1 (C-O-C), 816.91 (Cl), 814.2 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.14 (s, 1H, -NH), 6.62–8.24 (m, 13H, Ar-H), 6.41 (s, 1H, H at C-22 of quinolone), 3.39 (s, 3H, CH_3 of quinolone), 3.31 (br-s, 8H, piperazine); ^{13}C NMR 172.1 (C-6, C-N at piperazine linkage), 171.8 (C-2, C-O-C at quinolone linkage), 165.3 (C-4, C-NH at aniline linkage), 159.3 (C-21, C=O of quinolone), 152.7 (C-23, C-O-C at quinolone), 152.8, 152.0, 132.6, 131.1, 128.8, 128.7, 123.9, 122.7, 119.1, 118.6, 118.8, 117.5, 115.8, 115.2 (14C, Ar-C), 110.2 (C-22, C-C=O of quinolone), 53.1, 47.51 (4C, piperazine), 31.8 (C-26, -CH_3 of quinolone). Analysis: calculated for $C_{29}H_{26}ClN_7O_2$: C, 64.50; H, 4.85; N, 18.16. Found: C, 64.56; H, 4.72; N, 18.27.

4-[4-[4-(2,3-Dichlorophenyl)piperazino]-6-anilino-[1,3,5]triazin-2-y]oxy]-1-methyl-1*H*-quinolin-2-one **(5d)**: mp 249–254°C; IR: 3298.4 (N-H str.), 1695.3 (C=O of quinolone), 1262.4 (C-O-C), 817.0 (s-triazine C-N str.), 804.2 cm^{-1} (-Cl); ^{1}H NMR: δ 9.19 (s, 1H, -NH), 6.80–8.14 (m, 12H, Ar-H), 6.47 (s, 1H, H at C-22 of quinolone), 3.35 (s, 3H, CH_3 of quinolone), 3.62 (br-s, 8H, piperazine); ^{13}C NMR 171.7 (C-6, C-N at piperazine linkage), 171.3 (C-2, C-O-C at quinolone linkage), 166.1 (C-4, C-NH at aniline linkage), 1601 (C-21, C=O of quinolone), 152.8 (C-23, C-O-C at quinolone), 148.6, 132.7, 130.5, 129.5, 128.8, 128.5, 123.7, 123.5, 122.7, 120.2, 119.7, 118.8, 118.6, 116.1 (14C, Ar-C), 110.4 (C-22, C-C=O of quinolone), 50.2, 46.8 (4C, piperazine), 32.4 (C-26, -CH_3 of quinolone). Analysis: calculated for $C_{29}H_{25}Cl_2N_7O_2$: C, 60.63; H, 4.39; N, 17.07. Found: C, 60.51; H, 4.47; N, 17.15.

[4-(4-Anilino-6-piperidino-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5e)**: mp 262–265°C; IR: 3297.1 (N-H str.), 1694.3 (C=O of quinolone), 1261.4 (C-O-C), 812.1 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.22 (s, 1H, -NH), 7.01–8.17 (m, 9H, Ar-H), 6.41 (s, 1H, H at C-22 of quinolone), 3.40 (s, 3H, CH_3 of quinolone), 2.57–3.16 (m, 10H, piperidine); ^{13}C NMR: δ 171.8 (C-6, C-N at piperazine linkage), 171.3 (C-2, C-O-C at quinolone linkage), 165.4 (C-4, C-NH at aniline linkage), 159.1 (C-21, C=O of quinolone), 152.6 (C-23, C-O-C at quinolone), 1422, 140.0, 132.6, 128.8, 128.4, 123.7, 123.4, 122.7, 117.8, 118.5, 116.7, 115.8 (12C, Ar-C), 109.3 (C-22, C-C=O of quinolone), 46.8, 31.3, 34.7 (5C, piperidine), 32.4 (C-26, CH_3 of quinolone). Analysis: calculated for $C_{24}H_{24}N_6O_2$: C, 67.27; H, 5.65; N, 19.61. Found: C, 67.21; H, 5.52; N, 19.50.

4-[(6-Anilino-4-morpholino-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5f)**: mp 216–266°C; IR: 3296.2 (N-H str.), 1705.1 (C=O of quinolone), 1260.2 (C-O-C), 814.2 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.05 (s, 1H, -NH), 6.97–8.17 (m, 9H, Ar-H), 6.53 (s, 1H, H at C-22 of quinolone), 3.80–3.82 (m, 8H, morpholine), 3.34 (s, 3H, -CH_3 of quinolone); ^{13}C NMR: δ 171.9 (C-6, C-N at piperazine linkage), 171.2 (C-2, C-O-C at quinolone linkage), 165.3 (C-4, C-NH at aniline linkage), 159.3 (C-21, C=O of quinolone), 152.8 (C-23, C-O-C at quinolone), 143.9, 132.5, 132.5, 129.9, 128.7, 123.5, 122.3, 120.2, 119.66, 116.5, 115.0, 112.4 (12C, Ar-C), 109.9 (C-22, C-C=O of quinolone), 64.4, 52.3 (4C, morpholine), 32.2 (C-26, CH_3 of quinolone). Analysis: calculated for $C_{23}H_{22}N_6O_3$: C, 64.17; H, 5.15; N, 19.52. Found: C, 64.10; H, 5.26; N, 19.39.

4-[(4-Anilino-6-(4-phenylpiperazino)-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5g)**: mp 273–276°C; IR: 3298.4 (N-H str.), 1697.2 (C=O of quinolone), 1260.3 (C-O-C), 817.14 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.11 (s, 1H, -NH), 6.82–8.21 (m, 14H, Ar-H), 6.57 (s, 1H, H at C-22 of quinolone), 3.56 (br-s, 8H, piperazine), 3.29 (s, 3H, CH_3 of quinolone); ^{13}C NMR: δ 172.21 (C-6, C-N at piperazine linkage), 171.45 (C-2, C-O-C at quinolone linkage), 165.26 (C-4, C-NH at aniline linkage), 159.30 (C-21, C=O of quinolone), 152.72 (C-23, C-O-C at quinolone), 150.9, 132.9, 130.1, 129.9, 128.8, 128.7, 123.9, 123.5, 122.8, 119.5, 118.8, 118.4, 116.9, 116.3, 116.3, 115.2 (16C, Ar-C), 110. (C-22, C-C=O of quinolone), 50.4, 46.1 (4C, piperazine), 32.1 (C-26, -CH_3 of quinolone). Analysis: calculated for $C_{29}H_{27}N_7O_2$: C, 68.89; H, 5.38; N, 19.39. Found: C, 68.81; H, 5.50; N, 19.32.

4-[(4-(4-Acetylpiperazino)-6-anilino-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5h)**: mp 266–271°C; IR: 3297.5 (N-H str.), 1696.3 (C=O of quinolone), 1258.2 (C-O-C), 1692.1 (C=O of $COCH_3$), 1491.4 (CH_3 of $COCH_3$), 810.2 (s-triazine C-N str.); ^{1}H NMR: δ 9.15 (s, 1H, NH), 6.96–8.17 (m, 9H, Ar-H), 6.52 (s, 1H, H at C-22 of quinolone), 3.62 (br-s, 8H, piperazine), 3.32 (s, 3H, CH_3 of quinolone), 2.36 (s, 3H, $COCH_3$); ^{13}C NMR: δ 172.2 (C-6, C-N at piperazine linkage), 171.8 (C-2, C-O-C at quinolone linkage), 169.77 (C-33, $COCH_3$), 166.1 (C-4, C-NH at aniline linkage), 160.3 (C-21, C=O of quinolone), 152. 6 (C-23, C-O-C at quinolone), 141.1, 140.2, 132.8, 128.9, 128.8, 123.8, 123.5, 122.7, 118.9, 118.6, 116.8, 115.3 (12C, Ar-C), 109.5 (C-22, C-C=O of quinolone), 49.6,

47.1 (4C, piperazine), 31.2 (C-26, -$\underline{C}H_3$ of quinolone), 24.2 (C-35, CO$\underline{C}H_3$). Analysis: calculated for $C_{25}H_{25}N_7O_3$: C, 63.68; H, 5.34; N, 20.79. Found: C, 63.60; H, 5.27; N, 20.85.

4-[(4-Anilino-6-isopropylpiperazino-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5i)**: mp 271–279°C; IR: 3297.9 (N-H str.), 1697.5 (C=O of quinolone), 1261.2 (C-O-C), 1490.4 (-CH_3), 809.9 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.10 (s, 1H, -NH), 7.01–8.12 (m, 9H, Ar-H), 6.49 (s, 1H, H at C-22 of quinolone), 3.54 (br-s, 8H, piperazine), 3.34 (s, 3H, CH_3 of quinolone), 2.57 (s, 1H, CH_3-C$\underline{H}$-CH_3), 1.75 (s, 6H, -CH_3)$_2$; ^{13}C NMR: δ 171.8 (C-6, $\underline{C}$-N at piperazine linkage), 171.2 (C-2, $\underline{C}$-O-C at quinolone linkage), 165.8 (C-4, $\underline{C}$-NH at aniline linkage), 159.4 (C-21, $\underline{C}$=O of quinolone), 152.4 (C-23, $\underline{C}$-O-C at quinolone), 141.2, 140.1, 132.8, 128.8, 128.1, 123.8, 123.4, 122.6, 118.9, 118.5, 116.7, 115.1 (12C, Ar-C), 110.3 (C-22, $\underline{C}$-C=O of quinolone), 57.2 (C-33, CH_3-$\underline{C}$H-CH_3), 49.9, 46.2 (4C, piperazine), 32.5 (C-26, -$\underline{C}H_3$ of quinolone), 26.7 (C-34, C-35, $\underline{C}H_3$-CH-$\underline{C}H_3$). Analysis: calculated for $C_{26}H_{29}N_7O_2$: C, 66.22; H, 6.20; N, 20.79. Found: C, 66.10; H, 6.27; N, 20.68.

4-[(4-Anilino-6-(4-pyridin-2-yl-piperazino)-[1,3,5]triazin-2-yl)-oxy]-1-methyl-1*H*-quinolin-2-one **(5j)**: mp 277–286°C; IR: 3297.3 (N-H str.), 1696.5 (C=O of quinolone), 1257.1 (C-O-C), 820.0 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.14 (s, 1H, -NH), 6.70–8.20 (m, 13H, Ar-H), 6.55 (s, 1H, H at C-22 of quinolone), 3.56 (br-s, 8H, piperazine), 3.41 (s, 3H, CH_3 of quinolone); ^{13}C NMR: δ 171. 9 (C-6, $\underline{C}$-N at piperazine linkage), 171.4 (C-2, $\underline{C}$-O-C at quinolone linkage), 165.1 (C-4, $\underline{C}$-NH at aniline linkage), 159.7 (C-21, $\underline{C}$=O of quinolone), 152.8 (C-23, $\underline{C}$-O-C at quinolone), 148.7, 140.1, 140.1, 132.69, 128.8, 128.64, 123.9, 123.4, 122.4, 118.9, 118.9, 116.8, 115.0, 114.7, 114.2 (15C, Ar-C), 109.65 (C-22, $\underline{C}$-C=O of quinolone), 50.7, 47.2 (4C, piperazine), 32.5 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{28}H_{26}N_8O_2$: C, 66.39; H, 5.17; N, 22.12. Found: C, 66.44; H, 5.30; N, 22.03.

4-[(4-Anilino-6-(4-pyrimidin-2-yl-piperazino)-[1,3,5]triazin-2-yl)-oxy]-1-methyl-1*H*-quinolin-2-one **(5k)**: mp >300°C; IR: 3298.5 (N-H str.), 1698.2 (C=O of quinolone), 1263.4 (C-O-C), 810.3 cm^{-1} (s-triazine C-N str.); ^{1}H NMR: δ 9.10 (s, 1H, -NH), 6.85–8.40 (m, 12H, Ar-H), 6.45 (s, 1H, H at C-22 of quinolone), 3.58 (br-s, 8H, piperazine), 3.39 (s, 3H, CH_3 of quinolone); ^{13}C NMR: δ 172.1 (C-6, $\underline{C}$-N at piperazine linkage), 171.4 (C-2, $\underline{C}$-O-C at quinolone linkage), 165.3 (C-4, $\underline{C}$-NH at aniline linkage), 159.6 (C-21, $\underline{C}$=O of quinolone), 153.1 (C-23, $\underline{C}$-O-C at quinolone), 157.4, 157.1, 152.4, 141.2, 140.1, 132.7, 128.8, 128.6, 123.8, 123.5, 122.7, 118.8, 118.5, 116.8, 115.8, 113.9 (16C, Ar-C), 109.5 (C-22, $\underline{C}$-C=O of quinolone), 50.2, 46.3 (4C, piperazine), 31.3 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{27}H_{25}N_9O_2$: C, 63.89; H, 4.96; N, 24.84. Found: C, 63.94; H, 5.10; N, 24.77.

4-[(4-Anilino-6-(4-benzylpiperazino)-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5l)**: mp 282–287°C; IR: 3296.4 (N-H str.), 1706.4 (C=O of quinolone), 1262.5 (C-O-C); ^{1}H NMR: δ 9.16 (s, 1H, -NH), 6.96–8.31 (m, 14H, Ar-H), 6.52 (s, 1H, H at C-22 of quinolone), 3.75 (s, 2H, CH_2 at piperazine linkage), 3.54 (br-s, 8H, piperazine), 3.36 (s, 3H, CH_3 of quinolone); ^{13}C NMR: δ 171.7 (C-6, $\underline{C}$-N at piperazine linkage), 171.3 (C-2, $\underline{C}$-O-C at quinolone linkage), 164.9 (C-4, $\underline{C}$-NH at aniline linkage), 159.5 (C-21, $\underline{C}$=O of quinolone), 152.6 (C-23, $\underline{C}$-O-C at quinolone), 141.2, 139.2, 132.7, 128.7, 128.7, 128.2, 128.3, 128.3, 127.2, 123.7, 123.4, 122.6, 118.7, 118.2, 116.7, 115.3 (16C, Ar-C), 109.7 (C-22, $\underline{C}$-C=O of quinolone), 65.2 (C-33, -$\underline{C}H_2$) 509, 47.1 (4C, piperazine), 31.4 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{30}H_{29}N_7O_2$: C, 69.35; H, 5.63; N, 18.87. Found: C, 69.21; H, 5.56; N, 18.97.

4-[(4-Anilino-6-(4-benzylpiperidino)-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5m)**: mp 278–284°C; IR: 3296.2 (N-H str.), 1694.3 (C=O of quinolone), 1262.2 cm^{-1} (C-O-C); ^{1}H NMR: δ 9.07 (s, 1H, NH), 7.03–8.11 (m, 14H, Ar-H), 6.49 (s, 1H, H at C-22 of quinolone), 3.83 (t, 4H, piperidine), 3.65 (t, 4H, piperidine), 3.39 (s, 3H, CH_3 of quinolone), 2.58 (d, 2H, CH_2 at piperidine linkage), 1.83 (t, 1H, CH, piperidine); ^{13}C NMR: δ 171.9 (C-6, $\underline{C}$-N at piperidine linkage), 171.4 (C-2, $\underline{C}$-O-C at quinolone linkage), 165.4 (C-4, $\underline{C}$-NH at aniline linkage), 159.3 (C-21, $\underline{C}$=O of quinolone), 152.8 ($\underline{C}$-O-C at quinolone), 140.8, 139.1, 132.8, 129.1, 129.1, 128.9, 128.8, 128.6, 128.4, 125.6, 123.9, 123.6, 122.5, 118.7, 118.4, 115.3 (16C, Ar-C), 109.6 (C-22, $\underline{C}$-C=O of quinolone), 63.7 (C-33, -$\underline{C}H_2$), 41.6, 39.8, 35.1 (5C, piperidine), 31.4 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{31}H_{30}N_6O_2$: C, 71.79; H, 5.83; N, 16.20. Found: C, 71.60; H, 5.71; N, 16.28.

4-[(4-Anilino-6-(3,5-dimethylpiperidino)-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5n)**: mp 271–274°C; IR: 3296.4 (N-H str.), 1705.1 (C=O of quinolone), 1455.2 (CH_3), 1260.3 cm^{-1} (C-O-C); ^{1}H NMR: δ 9.04 (s, 1H, -NH), 7.02–8.06 (m, 9H, Ar-H), 6.41 (s, 1H, H at C-22 of quinolone), 3.68–3.75 (m, 4H, piperidine), 2.41 (br-s, 2H, CH_2, piperidine), 1.93 (q, 2H, piperidine), 1.84 (6H, d, 2-CH_3); ^{13}C NMR: δ 172.1 (C-6, $\underline{C}$-N at piperidine linkage), 171.5 (C-2, $\underline{C}$-O-C at quinolone linkage), 165.2 (C-4, $\underline{C}$-NH at aniline linkage), 159.2 (C-21, $\underline{C}$=O of quinolone), 152.8 (C-23, $\underline{C}$-O-C at quinolone), 140.1, 139.1, 132.7, 128.8, 128.6, 123.9, 123.6, 122.6, 118.8, 118.3, 116.5, 114.2 (12C, Ar-C), 109.3 (C-22, $\underline{C}$-C=O of quinolone), 45.4, 42.3, 33.3 (5C, piperidine ring carbons), 32.5 (C-26, -$\underline{C}H_3$ of quinolone), 23.8 (C-33, C-34, -$\underline{C}H_3$). Analysis: calculated for $C_{26}H_{28}N_6O_2$: C, 68.40; H, 6.18; N, 18.41. Found: C, 68.29; H, 6.30; N, 18.46.

4-[(4-Anilino-6-(4-benzhydrylpiperazino)-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5o)**: mp >300°C; IR: 3298.2 (N-H str.), 1710.1 (C=O of quinolone), 1261.5 cm^{-1} (C-O-C); ^{1}H NMR: δ 9.13 (s, 1H, -NH), 6.91–8.30 (m, 19H, Ar-H), 6.39 (s, 1H, H at C-22 of quinolone), 5.26 (s, H, N-CH at piperazine linkage), 3.34 (s, 3H, CH_3 of quinolone), 3.60 (br-s, 8H, piperazine); ^{13}C NMR: δ 172.1 (C-6, $\underline{C}$-N at piperazine linkage), 171.5 (C-2, $\underline{C}$-O-C at quinolone linkage), 164.9 (C-4, $\underline{C}$-NH at aniline linkage), 160.3 (C-21, $\underline{C}$=O of quinolone), 152.9 (C-23, $\underline{C}$-O-C at quinolone), 141.7, 139.4, 139.1, 132.8, 128.9, 128.9, 128.9, 128.8, 128.8, 128.8, 128.5, 128.5, 128.4, 128.4, 126.6, 126.5, 123.7, 123.5, 122.7, 118.8, 118.6, 114.1 (22C, Ar-C), 110.3 (C-22, $\underline{C}$-C=O of quinolone), 72.9 (C-33, N-$\underline{C}$H at piperazine linkage), 51.2, 46.9 (4C, piperazine), 32.5 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{36}H_{33}N_7O_2$: C, 72.59; H, 5.58; N, 16.46. Found: C, 72.64; H, 5.70; N, 16.49.

4-[4-Anilino-6-((4-chlorophenyl)-phenyl-methylpiperazino)[1,3,5]-triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5p)**: mp >300°C; IR: 3292.4 (N-H str.), 1696.9 (C=O of quinolone), 1262.3 (C-O-C), 820.1 (-Cl); ^{1}H NMR: δ 9.17 (s, 1H, -NH), 6.87–8.22 (m, 18H, Ar-H), 6.45 (s, 1H, H at C-22 of quinolone), 5.31 (s, H, N-CH at piperazine linkage), 3.42 (s, 3H, CH_3 of quinolone), 3.60 (br-s, 8H, piperazine); ^{13}C NMR: δ 171.8 (C-6, $\underline{C}$-N at piperazine linkage), 171.2 (C-2, $\underline{C}$-O-C at quinolone linkage), 165.1 (C-4, $\underline{C}$-NH at aniline linkage), 160.1 (C-21, $\underline{C}$=O of quinolone), 151.6 (C-23, $\underline{C}$-O-C at quinolone), 141.3, 32.5, 130.2, 129.0, 128.93, 128.90, 128.87, 128.83, 128.0, 127.5, 127.4, 126.6, 123.6, 122.7, 122.5, 118.70, 118.3, 115.2 (18C, Ar-C), 109.32 (C-22, $\underline{C}$-C=O of quinolone), 74.6 (C-33, N-$\underline{C}$H at piperazine

linkage), 50.9, 47.4 (4C, piperazine), 31.4 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{36}H_{32}ClN_7O_2$: C, 68.62; H, 5.12; N, 15.56. Found: C, 68.57; H, 5.22; N, 15.67.

4-[(4-Anilino-6-(4-(2-fluorophenyl)piperazino)-[1,3,5]triazin-2-yl)-oxy]-1-methyl-1*H*-quinolin-2-one **(5q)**: mp 295–298°C; IR: 3298.2 (N-H str.), 1697.2 (C=O of quinolone), 1268.1 (C-O-C), 1157.32 (C-F); ^{1}H: δ 9.09 (s, 1H, -NH), 6.49–8.14 (m, 13H, Ar-H), 6.41 (s, 1H, H at C-22 of quinolone), 3.36 (s, 3H, -CH_3 of quinolone), 3.64 (br-s, 8H, piperazine); ^{19}F NMR: δ -122.14; ^{13}C NMR: δ 171.8 (C-6, $\underline{C}$-N at piperazine linkage), 171.4 (C-2, $\underline{C}$-O-C at quinolone linkage), 164.6 (C-4, $\underline{C}$-NH at aniline linkage), 159.3 (C-21, $\underline{C}$=O of quinolone), 151.7 (C-23, $\underline{C}$-O-C at quinolone), 156.1, 151.8, 140.1, 132.9, 128.9, 128.4, 125.7, 123.7, 123.5, 122.7, 118.7, 118.4, 116.9, 115.1 (14C, Ar-C), 110.1 (C-22, $\underline{C}$-C=O of quinolone), 50.9, 46.3 (4C, piperazine), 32.3 (C-26, -$\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{29}H_{26}FN_7O_2$: C, 66.53; H, 5.01; N, 18.73. Found: C, 66.42; H, 5.12; N, 18.78.

4-[(4-Anilino-6-(4-(4-fluorophenyl)piperazino)-[1,3,5]triazin-2-yl)-oxy]-1-methyl-1*H*-quinolin-2-one **(5r)**: mp >300°C; IR: 3298.2 (N-H str.), 1696.4 (C=O of quinolone), 1266.4 (C-O-C), 1161.26 (C-F); ^{1}H NMR: δ 9.12 (s, 1H, -NH), 6.49–8.17 (m, 13H, Ar-H), 6.37 (s, 1H, H at C-22 of quinolone), 3.30 (s, 3H, -CH_3 of quinolone), 3.57 (br-s, 8H, piperazine); ^{19}F NMR: δ -119.47; ^{13}C NMR: δ 171.9 (C-6, $\underline{C}$-N at piperazine linkage), 171.3 (C-2, $\underline{C}$-O-C at quinolone linkage), 164.5 (C-4, $\underline{C}$-NH at aniline linkage), 159.4 (C-21, $\underline{C}$=O of quinolone), 151.7 (C-23, $\underline{C}$-O-C at quinolone), 156.2, 151.6, 139.9, 132.8, 128.9, 128.3, 125.7, 123.7, 123.6, 122.7, 118.9, 118.5, 116.8, 115.2 (14C, Ar-C), 110.3 (C-22, $\underline{C}$-C=O of quinolone), 50.9, 46.4 (4C, piperazine), 32.4 (C-26, -$\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{29}H_{26}FN_7O_2$: C, 66.53; H, 5.01; N, 18.73. Found: C, 66.45; H, 5.08; N, 18.81.

4-[(4-Anilino-6-(4-(3-trifluoromethylphenyl)piperazino)-[1,3,5]-triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5s)**: mp >300°C; IR: 3298.1 (N-H str.), 1697.2 (C=O of quinolone), 1264.3 (C-O-C), 1161.2 (C-F); ^{1}H NMR: δ 9.19 (s, 1H, -NH), 7.02–8.10 (m, 13H, Ar-H), 6.41 (s, 1H, H at C-22 of quinolone), 3.46 (s, 3H, CH_3 of quinolone), 3.52 (br-s, 8H, piperazine); ^{19}F NMR: δ -65.10; ^{13}C NMR: δ 171.8 (C-6, $\underline{C}$-N at piperazine linkage), 171.2 (C-2, $\underline{C}$-O-C at quinolone linkage), 165.4 (C-4, $\underline{C}$-NH at aniline linkage), 160.3 (C-21, $\underline{C}$=O of quinolone), 152.2 (C-23, $\underline{C}$-O-C at quinolone), 151.1, 141.2, 140.1, 132.6, 128.8, 128.7, 123.9, 123.5, 122.7, 118.9, 118.8, 116.9, 116.6, 115.9 (14C, Ar-C), 109.5 (C-22, $\underline{C}$-C=O of quinolone), 50.2, 47.1 (4C, piperazine), 31.4 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{30}H_{26}F_3N_7O_2$: C, 62.82; H, 4.57; N, 17.09. Found: C, 62.88; H, 4.45; N, 17.20.

4-[(4-Anilino-6-(4-(2,3,4-trimethoxybenzyl)piperazino)-[1,3,5]-triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5t)**: mp 292–296°C; IR: 3297.5 (N-H str.), 1697.3 (C=O of quinolone), 1269.2 (-OCH_3), 1264.6 (C-O-C); ^{1}H NMR: δ 9.10 (s, 1H, -NH), 6.68–8.13 (m, 11H, Ar-H), 6.44 (s, 1H, H at C-22 of quinolone), 3.36 (s, 3H, -CH_3 of quinolone), 3.62–3.69 [m, 9H, $(OCH_3)_3$], 3.67 (br-s, 8H, piperazine), 2.60 (s, 2H, -CH_2); ^{13}C NMR: δ 172.0 (C-6, $\underline{C}$-N at piperazine linkage), 171.4 (C-2, $\underline{C}$-O-C at quinolone linkage), 164.2 (C-4, $\underline{C}$-NH at aniline linkage), 160.2 (C-21, $\underline{C}$=O of quinolone), 152.7 (C-23, $\underline{C}$-O-C at quinolone), 152.2, 141.1, 139.3, 132.5, 128.9, 128.7, 124.4, 123.9, 123.5, 123.4, 122.7, 118.9, 118.6, 116.4, 106.2 (15C, Ar-C), 109.3 (C-22, $\underline{C}$-C=O of quinolone), 58.7, 58.1, 60.3 (C-40, C-42, C-44, -O$\underline{C}H_3$), 50.2, 47.1 (4C, piperazine), 31.7 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{33}H_{35}N_7O_5$: C, 65.01; H, 5.79; N, 16.08. Found: C, 65.11; H, 5.60; N, 16.01.

4-[(4-Anilino-(6-(4-methoxyphenyl)piperazino)-[1,3,5]triazin-2-yl)oxy]-1-methyl-1*H*-quinolin-2-one **(5u)**: mp >300°C; IR: 3296.2 (N-H str.), 1697.4 (C=O of coumarin), 1270.3 (-OCH_3), 1265.4 cm^{-1} (C-O-C); ^{1}H NMR: δ 9.21 (s, 1H, -NH), 6.77–8.11 (m, 13H, Ar-H), 6.47 (s, 1H, H at C-22 of quinolone), 3.78 (s, 3H, -OCH_3), 3.39 (s, 3H, CH_3 of quinolone), 3.63 (br-s, 8H, piperazine); ^{13}C NMR: δ 171. 9 (C-6, $\underline{C}$-N at piperazine linkage), 171.1 (C-2, $\underline{C}$-O-C at quinolone linkage), 164.3 (C-4, $\underline{C}$-NH at aniline linkage), 161.3 (C-21, $\underline{C}$=O of quinolone), 152.8 (C-23, $\underline{C}$-O-C at quinolone), 152.4, 152.4, 140.2, 132.1, 128.8, 128.6, 123.9, 123.6, 122.7, 118.8, 118.6, 117.5, 117.4, 116.9, 116.0, 115.12 (16C, Ar-C), 110.1 (C-22, $\underline{C}$-C=O of quinolone), 62.4 (C-40, -O$\underline{C}H_3$), 49.3, 46.8 (4C, piperazine), 32 (C-26, $\underline{C}H_3$ of quinolone). Analysis: calculated for $C_{30}H_{29}N_7O_3$: C, 67.27; H, 5.46; N, 18.31. Found: C, 67.15; H, 5.56; N, 18.44.

Antimicrobial activity

The *s*-triazinyl piperazine and piperidine compounds **5a-u** were examined for antimicrobial activity against five Gram-negative bacteria (*E.coli* MTCC 739*, P. aeruginosa* MTCC 741, *K. pneumonia* MTCC 109, *S. typhi* MTCC 733, *P. vulgaris* MTCC 1771), two Gram-positive bacteria (*S. aureus* MTCC 96 and *B. cereus* MTCC 619), and two fungal species (*C. albicans* MTCC 183 and *A. niger* MTCC 282) using disc diffusion sensitivity test (Cruickshank et al., 1975). The Mueller-Hinton agar media were sterilized (autoclaved at 120°C for 30 min), poured at a uniform depth of 5 mm and allowed to solidify. The microbial suspension (10^5 CFU/ml) (0.5 McFarland Nephelometery Standards) was streaked over the surface of media using a sterile cotton swab (15 min at 180°C) to ensure even growth of the organisms. The tested compounds were dissolved in dimethyl sulfoxide to get a solution of 3–100 µg/ml concentration. Sterile filter paper discs measuring 6.25 mm in diameter (Whatman no. 1 filter paper), previously soaked in a known concentration of the test compounds in dimethyl sulfoxide were placed on the solidified nutrient agar medium that had been inoculated with the microbials, and the plates were incubated for 24 h at 37°C. A control disc impregnated with an equivalent amount of dimethyl sulfoxide without any sample was also used and did not reveal any inhibition. Ciprofloxacin and ketoconazole (100 µg/disc) were used as control drugs for antibacterial and antifungal activity, respectively.

To determine the minimum inhibitory concentration (MIC), a stock solution of the synthesized compound (100 µg/ml) in dimethyl sulfoxide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar, nutrient agar for antibacterial, and sabouraud dextrose agar for antifungal activity evaluation. The medium containing the test compound was poured into a Petri dish at a depth of 4–5 mm and allowed to solidify under aseptic conditions. Suspension of the micro-organism was prepared to contain approximately 10^5 CFU/ml and applied to plates with serially diluted compounds with required concentration of 3.12–100 µg/ml in dimethyl sulfoxide to be tested and incubated at (37±1)°C for 24 and 48 h for bacteria and fungi, respectively.

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