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DESIGN, SYNTHESIS AND *IN VITRO* ANTIMICROBIAL ACTIVITY OF TRISUBSTITUTED s-TRIAZINE

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ABSTRACT

A variety of *N*-[4-chloro-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine, G were synthesized by using 2-methylquinolin-8-amine, quinolin-8-ol and cyanuric chloride. Structures of these compounds were confirmed by IR and ^{1}H NMR spectral analysis. The newly synthesized compounds were also evaluated for antimicrobial activity against variety of bacterial strains and some of these compounds have shown significant antibacterial and antifungal activities.

Key words: 2-Methylquinolin-8-amine, Quinolin-8-ol, s-Triazine, Antibacterial activity.

INTRODUCTION

The interest for chemist is to establish reliable and suitable drugs for most of disease. Any bacterial species acquired resistance to the most common classes of antibiotics. Bacterial resistance continues to develop and pose a significant threat both in hospitals and more recently, in the community. A relevant report on resistant antibacterial agents for human medicine is provided by World Health Organization. The panel agreed that the list of critically important antibacterial agents should be updated regularly as new information becomes available, including data on resistance patterns, new and emerging diseases and the development of new drugs. During the last few years, the potential of s-triazine derivatives in agrochemical and medicinal properties have been subjcted to investigation. Literature survey reveals that amino substituted s-triazine derivatives are associated with number of pronounced antibacterial activities against gram positive (*B. subtilis*, *B. sphaericus*, *S. aureus* etc) and gram negative organism (*E. coli*, *K. aerogenes*, *P. aeruginosa* etc). The biological activity is a function of physicochemical properties of the targeted molecule and this assessment is made of the sorts of chemicals that might fit into an active site. To randomly explore the novel compounds, our idea was to combine, 2-methylquinolin-8-amine, qunolin-8-ol, and s-triazine nucleus using cyanuric chloride and various amines. Substituted-s-triazines, derivatives remain attractive, with their significant biological activities and further incorporation of these derivatives with commercial drug could give access to a wide array of structures, which can be expected to show interesting antibacterial activities, thus, herein, we report the synthesis and antimicrobial activity of a variety of novel s-triazine derivatives.

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EXPERIMENTAL

Materials and methods

All the melting points were taken in open capillaries tube. The purity of compounds was checked routinely by TLC (0.5 mm thickness) using silica gel-G coated Al-plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra (cm^{-1}) were recorded on Shimadzu FTIR spectrophotometer using KBr or Nujol technique and ^1H NMR spectra on a Bruker's WM 400 FT MHz NMR instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference (chemical shifts in δ ppm). The elemental analysis (C, H, N) of compounds was performed on Carlo Erba-1108 elemental analyzer.

General experimentation

N-(4,6-dichloro-1,3,5-triazin-2-yl)-2-methylquinolin-8-amine (C)

To a stirred solution of cyanuric chloride (0.054 mole) in anhydrous THF (50 mL), 2-methylquinolin-8-amine (0.054 mole) was added drop wise at 0-5^oC. The resulting reaction mixture was stirred at this temperature for 3 hr. Then the reaction mass was neutralized by addition of 10% sodium bicarbonate ($NaHCO_3$) solution stirring for another 1 hr. The resulted reaction mixture was poured into crushed ice, and then filtered, dried and recrystalised from THF.

M.P. 108-110^oC; M.W: 158.2 g/mol; FT-IR (KBr): 3270 (N-H), 3060 (ArC-H), 2800-3000 (Alkane C-H), 1565, 1200, 850 (C-N, C3N3), 812 (s-triazine C-N str.).

N-[4-chloro-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (E)

To a stirred solution of *N*-(4,6-dichloro-1,3,5-triazin-2-yl)-2-methylquinolin-8-amine (C) (0.05 mole) in anhydrous THF (50 mL), quinolin-4-ol (0.05 mole) was added at 35-40^oC for 4 hr. Then reaction mass was neutralized by addition of 10% sodium bicarbonate ($NaHCO_3$) solution stirring for another 2 hrs. Then reaction mass poured into crushed ice, filtered and dried and recrystalised from THF.

M.P. 123-126^oC; M. W.: 414.84 g/mol; FT-IR (KBr): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1568, 1300, 847 (C-N, C_3N_3), 813 (s-triazine C-N str.); 1258 cm^{-1} (C-O-C).

General procedure for preparation of compounds (G)

To a solution of **(E)** (0.03 mole) in 1, 4-dioxane (50 mL), different substituted aniline derivatives were added and the reaction mixture was refluxed for 8 to 10 hr. 10% Sodium bicarbonate was used for the neutralization of the reaction mixture. After the completion of the reaction, it was treated with crushed ice, the precipitates obtained was filtered, dried and recrystalised from acetone to get final compound **(G)**.

Characterization of synthesized compounds (G)

(i) N-[4-aniline-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-1)

Yield: 70%; M.P.: 126-128^oC; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1255 (C-O-C), 1565, 1300, 845 (C-N, C_3N_3), 815 (s-triazine C-N str.); ^1H NMR (400 MHz, DMSO-*d6*) δ 0.9 (3 H, s, -CH_3); 7.1-7.3 (11H, s, -ArH), 7.3-7.6 (5H, m, -quinoline), 0.7-5 (H, s, -NH linkage); Anal. Calcd. for $C_{28}H_{21}N_7O$: C, 71.32; H, 4.49; N, 20.79; O, 3.39;

(ii) N-[4-(2-methylaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-2)

Yield: 68%; M.P.: 127-129^oC; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1250 (C-O-C), 1568, 1300, 844 (C-N, C_3N_3), 812 (s-triazine C-N str.); ^1H NMR (400 MHz, DMSO-

d6) δ 7.1-7.3 (4 H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2 H, s, -NH linkage), 0.9 (3 H, s, $-CH_3$); 1.0 (3H, s, $-CH_3$ of Aniline); Anal. Calcd. for $C_{29}H_{23}N_7O$: C, 71.74; H, 4.77; N, 20.19; O, 3.30.

(iii) N-[4-(3-methylaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-3)

Yield: 72%; M.P.: 124-126°C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1254 (C-O-C), 1567, 1302, 847 (C-N, C_3N_3), 816 (s-triazine C-N str.); ^1H NMR (400 MHz, DMSO-*d6*) δ 7.1-7.3 (4 H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2 H, s, -NH linkage), 0.9 (3 H, s, $-CH_3$); 1.0 (3H, s, $-CH_3$ of Aniline); Anal. Calcd. for $C_{29}H_{23}N_7O$: C, 71.74; H, 4.77; N, 20.19; O, 3.30.

(iv) N-[4-(4-methylaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-4)

Yield: 68%; M.P.: 125-127°C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1255 (C-O-C), 1568, 1299, 847 (C-N, C_3N_3), 813 (s-triazine C-N str.); ^1H NMR (400 MHz, DMSO-*d6*) δ 7.1-7.3 (4H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2H, s, -NH linkage), 0.9 (3H, s, -CH3); 1.0 (3H, s, $-CH_3$ of Aniline); Anal. Calcd. for $C_{29}H_{23}N_7O$: C, 71.74; H, 4.77; N, 20.19; O, 3.30;

(v) N-[4-(2-chloroaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-5)

Yield: 64%; M.P.: 128-130°C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1255 (C-O-C), 1568, 1300, 847 (C-N, C_3N_3), 813 (s-triazine C-N str.); 660-850 (C-Cl str.); ^1H NMR (400 MHz, DMSO- *d6*) δ 7.1-7.3 (4H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2H, s, -NH linkage), 0.9 (3H, s, $-CH_3$); Anal. Calcd. for $C_{28}H_20N_7OCl$: C, 66.47; H, 3.98; N, 19.38; O, 3.16; Cl, 7.01.

(vi) N-[4-(3-chloroaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-6)

Yield: 64%; M.P.: 126-128°C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1252 (C-O-C), 1566, 1300, 845 (C-N, C_3N_3), 815 (s-triazine C-N str.); 660-850 (C-Cl str.); ^1H NMR (400 MHz, DMSO- *d6*) δ 7.1-7.3 (4H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2H, s,-NH linkage), 0.9 (3H, s, $-CH_3$); Anal. Calcd. for $C_{28}H_{20}N_7OCl$: C, 66.47; H, 3.98; N, 19.38; O,3.16; Cl, 7.01.

(vii) N-[4-(4-chloroaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-7)

Yield: 65%; M.P.: 129-130°C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1254 (C-O-C), 1568, 1300, 847 (C-N, C_3N_3), 815 (s-triazine C-N str.); 660-850 (C-Cl str.); ^1H NMR (400 MHz, DMSO- *d6*) δ 7.1-7.3 (4H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2H, s,-NH linkage), 0.9 (3H, s, $-CH_3$); Anal. Calcd. for $C_{28}H_{20}N_7OCl$: C, 66.47; H, 3.98; N, 19.38; O, 3.16; Cl, 7.01.

(viii) N-[4-(2-nitroaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-8)

Yield: 71%; M.P : 127-129°C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1255 (C-O-C), 1570, 1303, 847 (C-N, C_3N_3), 814 (s-triazine C-N str.); 1550, 1350 (-N=O str.); ^1H NMR (400 MHz, DMSO-*d6*) δ 7.1-7.3 (4H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2H, s, -NH linkage), 0.9 (3H, s, $-CH_3$); Anal. Calcd. for $C_{28}H_{20}N_8O_3$: C, 65.11; H, 3.90; N, 21.69; O,9.29;

(ix) N-[4-(3-nitroaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]-2-methylquinolin-8-amine (G-9)

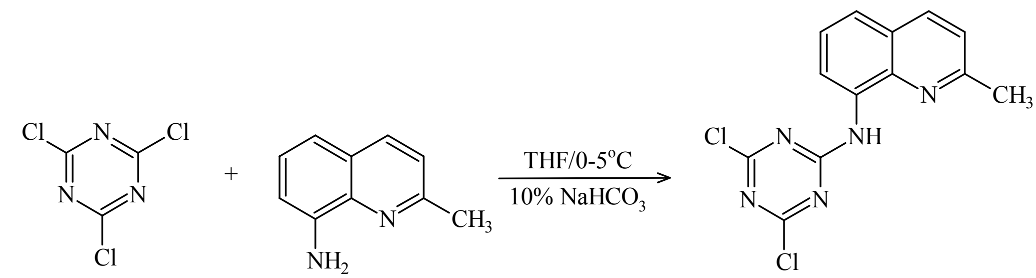
Yield: 68%; M.P.: 128-130°C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1255 (C-O-C), 1568, 1300, 847 (C-N, C_3N_3), 813 (s-triazine C-N str.); 1550, 1350 (-N=O str.); ^1H NMR (400 MHz, DMSO- *d6*) δ 7.1-7.3 (4H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2H, s,-NH linkage), 0.9 (3H, s, $-CH_3$); Anal. Calcd. for $C_{28}H_{20}N_8O_3$: C, 65.11; H, 3.90; N, 21.69; O,9.29.

(x) N-[4-(2-nitroaniline)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl-2-methylquinolin-8-amine (G-10)

Yield: 68%; M.P.: 126-128^{o}C; IR (KBr, cm^{-1}): 3150-3350 (N-H), 3070 (ArC-H), 2800-3000 (Alkane C-H), 1255 (C-O-C), 1568, 1300, 847 (C-N, C_3N_3), 813 (s-triazine C-N str.); 1550, 1350 (-N=O str.); ^{1}H NMR (400 MHz, DMSO- *d6*) δ 7.1-7.3 (4H, s, -ArH), 7.3-7.6 (11H, m, -quinoline), 0.7-5 (2H, s,-NH linkage), 0.9 (3H, s, -CH_3); Anal. Calcd. for $C_{28}H_{20}N_8O_3$: C, 65.11; H, 3.90; N, 21.69; O,9.29.

Reaction Scheme

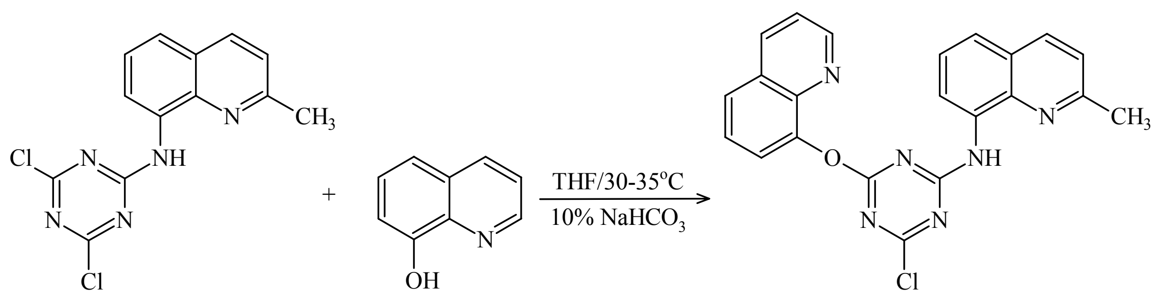
Step 1:



(a) **(b)** **(c)**

2,4,6-Trichloro-1, 3, 5-triazine | 2-Methylquinolin-8-amine | *N*-(4,6-dichloro-1,3,5-triazin-2-yl)-2-methylquinolin-8-amine

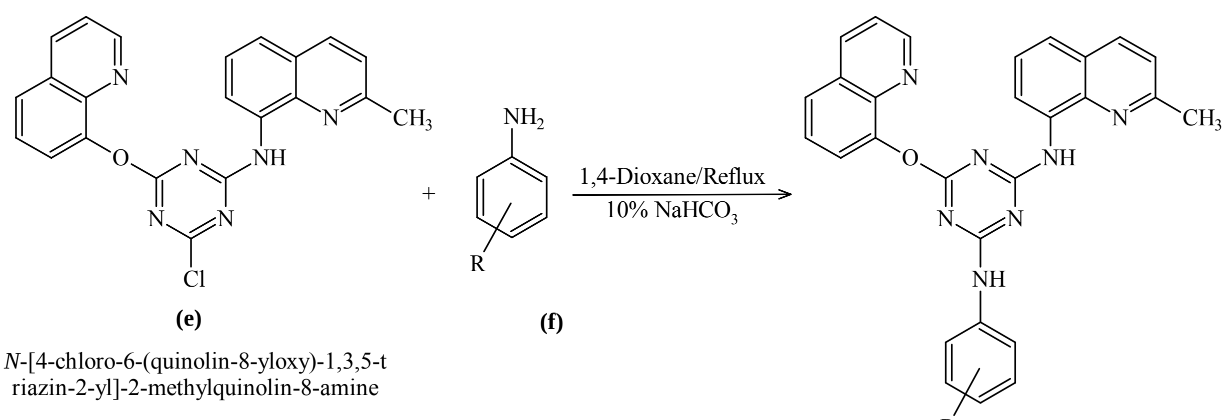
Step 2:



(c) **(d)** **(e)**

N-(4,6-dichloro-1,3,5-triazin-2-yl)-2-methylquinolin-8-amine | Quinolin-8-ol | *N*-[4-chloro-6-(quinolin-8-yloxy)-1,3,5-t riazin-2-yl]-2-methylquinolin-8-amine

Step 3:



(g)

N-[4-chloro-6-(quinolin-8-yloxy)-1,3,5-t riazin-2-yl]-2-methylquinolin-8-amine

Table 1

Compounds	R	Melting point (°C)	Yield (%)	Analytically calculated (Found)		
				% Carbon	% Hydrogen	% Nitrogen
G-1	H	126-128	70	71.32	4.49	20.79
G-2	2-CH_3	127-129	68	71.74	4.77	20.19
G-3	3-CH_3	124-126	72	71.74	4.77	20.19
G-4	4-CH_3	125-127	68	71.74	4.77	20.19
G-5	2-Cl	128-130	64	66.47	3.98	19.38
G-6	3-Cl	126-128	64	66.47	3.98	19.38
G-7	4-Cl	129-130	65	66.47	3.98	19.38
G-8	2-NO_2	127-129	71	65.11	3.90	21.69
G-9	3-NO_2	128-130	68	65.11	3.90	21.69
G-10	4-NO_2	126-128	68	65.11	3.90	21.69

Antibacterial activity

In vitro antibacterial screening of all the compounds were evaluated against selected (Table 1) Gram-positive organisms viz. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), *Staphylococcus aureus* (MTCC 96) and Gram-negative organisms viz. *Chromobacterium violaceum* (MTCC 2656), *Klebseilla aerogenes* (MTCC 39), *Pseudomonas aeruginosa* (MTCC 741), *Salomonella paratyphi* A (MTCC 735) and *Escherichia coli* (MTCC 443) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards. Standard antibacterial agent like benzyl penicillin and Streptomycin were also screened under identical conditions for comparison.

Antifungal activity

A. niger, *A. awamori* and *C. albicans* was employed for testing antifungal activity using the cup–plate method. The culture was maintained on Sabouraud's agar slants.

Fifteen milliliters of sterilized Sabouraud's agar medium was spread in a Petri dish (13 cm in diameter) and allowed to set for 30 min. Five milliliters of sterilized Sabouraud's agar medium was inoculated with 72 hr old 0.2 mL suspension of fungal spores in a test-tube and spread over the previously settled layer of Sabouraud's agar medium in the Petri dish. The cups (8 mm in diameter) were punched in the Petri dish and filled with 0.05 mL (40 µg) of a solution of the sample in DMF. The plates were incubated at 30°C for 48 hr. After the completion of the incubation period, the zones of inhibition of growth in millimeter were measured. Along with the test solutions in each Petri dish, one cup was filled up with solvent, which acts as the control. Standard antifungal agent like Griseofulvin was also screened under identical conditions for comparison. The zones of inhibition are recorded in Table 3.

Table 2: Antibacterial activity (Zone of inhibition in mm)

Compound	B.s	B.sph	S.a	K.a	C.v	P.a	E.c	S.p
G-1	15	16	17	14	15	17	16	17
G-2	14	15	15	16	21	16		18

Cont…

Compound	B.s	B. sph	S.a	K.a	C.v	P.a	E.c	S.p
G-3	18	17	17	15	15	16	21	17
G-4	17	16	16	18	17	17	22	20
G-5	23	21	19	18	18	17	19	15
G-6	15	14	15	16	16	14	18	16
G-7	18	16	16	17	18	18	16	15
G-8	20	23	18	17	18	15	15	17
G-9	19	22	18	18	17	15	16	20
G-10	19	18	22	17	20	17	18	16
Benzyl penicillin	27	29	30	30	28	29	31	29
Streptomycin	33	31	30	31	29	32	33	30

*Negative control: Acetone

Gram +ve Organisms	Gram –ve Organisms
B.s: : Bacillus subtilis (MTCC 121), B.sph.: Bacillus sphaericus (MTCC 11) S.a. : Staphylococcus aureus (MTCC 96)	K.a. : Klebseilla aerogenes (MTCC 39), C.v. : Chromobacterium violaceum (MTCC 2656), P.a. :Pseudomonas aeruginosa (MTCC 791), E.c. : Escherichia coli (MTCC 443) S.p. : Salomonella paratyphi A (MTCC 735)

Table 3: Antifungal activity (Zone of inhibition in mm)

Compound	*A. awamori*	*A. niger*	*C. albicans*
G-1	10	11	12
G-2	13	12	10
G-3	14	14	9
G-4	15	10	8
G-5	12	13	11
G-6	14	15	12
G-7	15	14	12
G-8	11	14	18
G-9	10	15	19
G-10	13	18	16
Griseofulvin	23	25	24

RESULTS AND DISCUSSION

In vitro antibacterial activity data of s-triazine derivatives (Table 1) against tested organisms displayed significant activity with a wide degree of variation. It was found that compound **G-6** displayed substantial activity against *B. subtilis* and remaining compounds are significantly active. Also **G-5**, and **G-9**

are equipotent against *B. sphaericus* compared to reference compound. Rest of the compounds have exhibited significant to substantial activity against the same strain. Substantial activity was achieved in case of compounds **G-7** against *S. aureus* and the remaining compounds are significantly active against the same species. All the s-triazine derivatives have exhibited significant to moderate activity against Gram-negative bacteria. Derivatives **G-1** and **G-7** have exhibited substantial activity against *C. violaceum*. Against *Salomonella paratyphi A*, compounds **G-4** and **G-9** have been found to possess significant activity. Comparatively weak activity has been reported by remaining compounds. E. coli was found to be more susceptible than rest of the other strains of bacteria, among them compounds **G-3** and **G-4** were showing significant activity for the same strain. All s-triazine derivatives are inactive towards *P.aeruginosa*, decreased activity was also observed in case of *K. aerogenes* with all the s-triazines. From *in vitro* antifungal activity (Table 2), data reveal that all the newly synthesized compounds displayed moderate to significant activity in comparison to standards. Thus, it is obvious from the structure-activity profile of substituted s-triazines; a small structural variation may induce an effect on antibacterial activity.

CONCLUSION

Trisubsituted s-triazine derivatives, Compounds **(G-1 to G-9)** was synthesized and characterized for their structures n. Antibacterial and antifungal studies of these compounds indicated that compounds were found to show comparable activity against some bacteria compared to standard antibiotic drugs. The produced compounds have good microbial toxicity due to presence of three pharmacologically active nucleus viz. s-triazine, 2-methylquinolin-8-amine and quinolin-8-ol. Such compounds may give good comparable anti-tuberculosis effect also which will be studied in details.

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