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Solvent free microwave synthesis and evaluation of antimicrobial activity of pyrimido[4,5-*b*]- and pyrazolo[3,4-*b*]quinolines

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Abstract—A series of 2-oxopyrimido[4,5-*b*]-, 2-thio[4,5-*b*]-, 1-(*p*-tosyl)pyrazolo[3,4-*b*]- and 1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]-quinolines have been synthesized in good to excellent yields by environmentally benign solvent free microwave-induced techniques involving the condensation of 2-chloro-3-formylquinolines with urea, thiourea, *p*-toluenesulfonylhydrazide and 2,4-dinitrophenylhydrazine, respectively, using PTSA as a catalyst. All the synthesized compounds were evaluated for their antibacterial and antifungal activities. Most of the compounds showed the best activity against *Escherichia coli* and *Pseudomonas aeruginosa*.

1. Introduction

Pyrimidones, pyrazoles, quinolines and their derivatives are important constituents of biologically active synthetic compounds,[1–6] as these systems have been associated with good biological activities such as antiviral,[7] antimalarial,[8,9] antibacterial[10,11] and anticancer activities.[12] Recently, microwave irradiation using commercial domestic oven has emerged as an important synthetic tool to accelerate organic reactions, because, the high heating efficiency gives remarkable rate enhancement and dramatic reduction in reaction time.[13,14] Solventless procedure[15] without the use of supporting reagents is particularly eco-friendly. Hence, the aim of this work was to demonstrate the advantage obtained by the use of microwave irradiation in the one-pot synthesis of pyrimido[4,5-*b*]- and N_1-substituted pyrazolo[3,4-*b*]-quinolines and to screen them for antimicrobial activities.

2. Chemistry

2-Oxopyrimido[4,5-*b*]quinoline (**2a**) was synthesized by the condensation reaction of 2-chloro-3-formylquinoline (**1a**) with urea in the presence of PTSA, using microwave irradiation for 5 min. IR spectrum of **2a** revealed the disappearance of the >C=O band at 1700 cm^{-1} thereby indicating the loss of carbonyl group. The ^1H NMR spectrum showed a triplet at δ 7.25 for C_7–H, doublet at δ 7.36 for C_9–H, triplet at δ 7.66 for C_8–H, doublet at δ 7.92 for C_6–H and singlets at δ 8.50, 10.25, and 12.21 for C_5–H, C_4–H and NH proton, respectively. The molecular ion peak at *m*/*z* 197 in its mass spectrum revealed the elimination of chlorine from **1a** and confirmed the formation of 2-oxopyrimido[4,5-*b*]quinoline (**2a**). The derivatives **2b**–**g** were synthesized using differently substituted quinolines and the thio analogues **3a**–**g** were similarly synthesized from **1a**–**g** and thiourea (Table 1; Scheme 1).

Recently, Paul et al. reported[16] PTSA was the best catalyst for the microwave synthesis of some pyrazolo[3,4-*b*]quinolines. Here, we have extended that technique for the synthesis of 1-(*p*-tosyl)pyrazolo[3,4-*b*]- (**4a**–**g**) and 1-(2′,4′-dinitrophenyl)-pyrazolo[3,4-*b*]quinolines (**5a**–**g**) from 2-chloro-3-formylquinolines (**1a**–**g**) using *p*-toluenesulfonylhydrazide and 2,4-dinitrophenylhydrazine, respectively (Table 1; Schemes 2 and 3). All the newly

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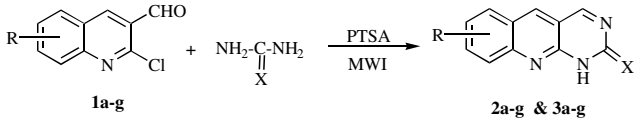
Table 1. Microwave synthesis of pyrimido[4,5-*b*]quinolines (**2a**–**g** and **3a**–**g**) and pyrazolo[3,4-*b*]quinolines (**4a**–**g** and **5a**–**g**) at 320 W

Compound	Time (min)	Yield (%)
2a	5	92
2b	5	96
2c	8	90
2d	9	92
2e	8	89
2f	10	77
2g	12	74
3a	8	95
3b	7	99
3c	7	97
3d	6	98
3e	9	90
3f	10	64
3g	11	68
4a	6	97
4b	5	94
4c	5	98
4d	4	97
4e	6	81
4f	8	78
4g	10	74
5a	8	93
5b	5	93
5c	5	96
5d	5	90
5e	7	84
5f	9	79
5g	13	78

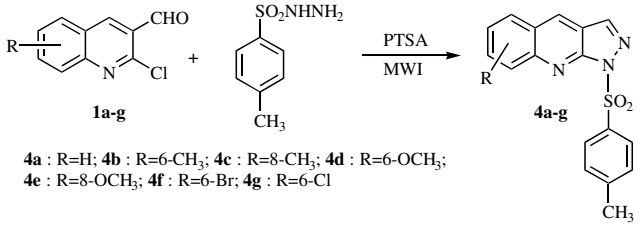


2 : X=O; **3** : X=S

2a : R=H; **2b** : R=7-CH_3; **2c** : R=9-CH_3; **2d** : R=7-OCH_3;
2e : R=9-OCH_3; **2f** : R=7-Br; **2g** : R=7-Cl

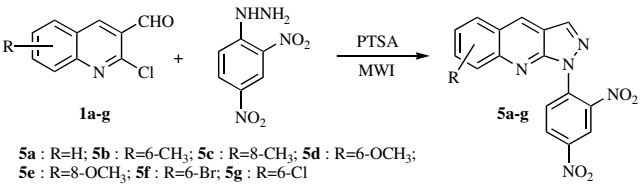
3a : R=H; **3b** : R=7-CH_3; **3c** : R=9-CH_3; **3d** : R=7-OCH_3;
3e : R=9-OCH_3; **3f** : R=7-Br; **3g** : R=7-Cl

Scheme 1.



4a : R=H; **4b** : R=6-CH_3; **4c** : R=8-CH_3; **4d** : R=6-OCH_3;
4e : R=8-OCH_3; **4f** : R=6-Br; **4g** : R=6-Cl

Scheme 2.



5a : R=H; **5b** : R=6-CH_3; **5c** : R=8-CH_3; **5d** : R=6-OCH_3;
5e : R=8-OCH_3; **5f** : R=6-Br; **5g** : R=6-Cl

Scheme 3.

synthesized compounds were characterized by IR, ^{1}H NMR, mass spectral data and elemental analysis.

3. Antimicrobial activity

All the synthesized compounds were screened for their antibacterial and antifungal activities. For preliminary screening, the antimicrobial tests were carried out by the disc-diffusion method.[17] One hundred microlitres of suspension containing 10^8 CFU/ml of bacteria, 10^6 CFU/ml of fungi were spread on Mueller–Hinton agar (MHA) medium and Sabouraud's dextrose agar (SDA) medium, respectively. The discs (6 mm in diameter), impregnated with 10 μl of the test compounds (500 and 1000 μg/disc) at the concentration of 50 and 100 mg/ml were placed on the inoculated agar. Negative controls were prepared using the same solvent (DMSO) employed to dissolve the test compounds. Ofloxacin (5 μg/disc) and Clotrimazole (10 μg/disc) were used as positive reference standards to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37 °C for 24 h and 27 °C for 72 h for bacterial and fungal strains, respectively. Antimicrobial activity was evaluated by measuring the diameter of zone of inhibition against test organisms.

Based on the results (Tables 2–5), it is inferred that pyrimido[4,5-*b*]quinolines **2a**–**g** and **3a**–**g** have significant inhibition effect on the growth of bacteria like *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Pseudomonas azotogensis* (Tables 2 and 3). The compounds **2a**–**g** exhibited good antifungal activity against *Candida albicans*, whereas the compounds **3a**–**g** were active against *Aspergillus flavus*. These compounds showed moderate activity against other bacteria and fungi (Tables 2 and 3).

Among pyrazolo[3,4-*b*]quinolines, 1-(*p*-tosyl)pyrazolo-[3,4-*b*]quinolines, (**4a**–**g**) registered good antibacterial activity against *E. coli* and *P. aeruginosa*, whereas 1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]quinolines (**5a**–**g**) were active against *Staphylococcus aureus*, *Staphylococcus albus*, *E. coli* and *P. aeruginosa* (Tables 4 and 5). The compounds, **4a**–**g** have a pronounced effect on the growth of fungi like *Rhodotorula rubra*, *C. albicans* and *Lipomyces lopofera* and **4d** indicated maximum activity of 17 and 22 mm at 500 and 1000 μg/disc, respectively, against *L. lopofera* (Table 4). The compounds **5a**–**g** have no activity against all the fungi (Table 5).

Minimum inhibitory concentration (MIC) of the compounds was also estimated by broth dilution assay[18] for the microorganisms which were determined as sensitive to the compounds in disc-diffusion assay. Nutrient broth (NB) and Sabouraud's dextrose broth (SDB) were used to estimate the MIC values of the test compounds against bacteria and fungi, respectively. A two fold serial dilution of test compounds were followed with 1 ml of sterile broth in test tubes to provide various concentration's range from 3.9 to 1000 μg/ml of the test compounds. Ten microlitres of the test organism was

Table 2. In vitro antimicrobial activity of pyrimido[4,5-*b*]quinolines (**2a–g**) (μg/disc) by disc-diffusion assay

Microorganisms	Diameter of zone of inhibition (mm)															
	2a (μg/disc)		**2b** (μg/disc)		**2c** (μg/disc)		**2d** (μg/disc)		**2e** (μg/disc)		**2f** (μg/disc)		**2g** (μg/disc)		**A** (μg/disc)	**B** (μg/disc)
	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Escherichia coli (NCIM 2065)[a]	9	13	8	14	10	14	9	13	8	10	9	12	9	13	23	—
Pseudomonas aeruginosa (NCIM 2200)[a]	8	10	8	10	10	12	10	13	8	11	9	11	10	14	22	—
Pseudomonas azotogensis (NCIM 2075)[a]	8	11	8	12	7	11	9	12	7	9	9	12	8	12	24	—
Klebsiella aerogenes (NCIM 2239)[a]	—	8	—	8	—	—	8	10	8	11	—	9	7	9	21	—
Bacillus subtilis (NCIM 2063)[a]	8	10	10	12	8	9	8	11	7	9	8	10	7	9	24	—
Bacillus cereus (NCIM 2155)[a]	—	—	—	—	—	—	—	—	—	8	—	—	—	8	19	—
Bacillus lentus (NCIM 2018)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	27	—
Staphylococcus aureus (NCIM 2079)[a]	—	8	—	9	—	8	7	9	—	—	—	9	—	8	25	—
Staphylococcus albus (NCIM 2178)[a]	—	7	—	8	—	9	8	10	—	—	7	9	—	9	21	—
Proteus vulgaris (NCIM 2027)[a]	—	9	—	—	8	9	8	10	8	12	8	10	8	10	19	—
Aspergillus niger (NCIM 1196)[b]	8	10	7	9	—	—	—	—	—	—	—	9	—	8	—	16
Aspergillus flavus (NCIM 535)[b]	9	10	10	11	—	—	—	—	8	10	—	—	—	—	—	16
Rhodotorula rubra (NCIM 3174)[b]	—	—	9	12	7	9	7	9	—	—	—	—	—	8	—	17
Candida albicans (NCIM 3471)[b]	11	12	9	12	8	12	9	11	11	12	9	12	9	11	—	18
Lipomyces lopofera (NCIM 3252)[b]	—	—	—	—	10	12	—	—	10	12	—	—	—	—	—	18

A, Ofloxacin; **B**, Clotrimazole; '—' no inhibition.
[a] Bacteria.
[b] Fungi.

added to each tube and incubated at 37 °C for 24 h and 27 °C for 72 h for bacterial and fungal strains, respectively. The highest dilution of the test compound completely inhibiting the test organism was considered as MIC value of the test compound, respectively. The results of the MIC values of the compounds are listed in Tables 6 and 7. The MIC values of the compounds range between 7.8 and 62.5 μg/ml, in most of the cases.

In conclusion, the salient feature of our approach is coupling microwaves with solvent free technique keeping modernization and simplification of classical procedure, avoiding volatile and toxic organic solvents, corrosive, mineral acids which make it a clean, efficient and cheap technology to synthesize pyrimido- and pyrazoloquinolines. These prepared quinolines have shown moderate to significant antibacterial and antifungal activities.

4. Experimental

Melting points (mp) were determined using a Boetius microheating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on a Shimadzu-8201 spectrophotometer. ^1H NMR spectra were recorded on an AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shifts in δ, ppm). Elemental analysis was performed on a Perkin Elmer CHN-analyzer. Mass spectra were recorded on a Shimadzu GCMS-QP5050A (70 eV) mass spectrometer. For microwave irradiation a Kenstar (OM-20ESP, 2450 MHz) domestic microwave oven was used.

4.1. General procedure for the preparation of the compounds 2-oxopyrimido[4,5-*b*]quinolines (2a–g), 2-thio[4,5-*b*]quinolines (3a–g), 1-(*p*-tosyl)pyrazolo[3,4-*b*]quinolines (4a–g) and 1-(2′,4′-dinitrophenyl)pyrazolo-[3,4-*b*]quinolines (5a–g)

2-Chloro-3-formylquinolines (1 mmol), urea or thiourea or *p*-toluenesulfonyl hydrazide or 2,4-dinitrophenylhydrazine (1.25 mmol) and PTSA (120 mg) were taken in a 100 ml beaker and mixed well. Then the reaction mixture was irradiated in a microwave oven for the respective time. (Table 1). After completion of the reaction, the mixture was poured into ice. The formed product was extracted with chloroform and purified using column chromatography.

Table 3. In vitro antimicrobial activity of pyrimido[4,5-*b*]quinolines (**3a–g**) (μg/disc) by disc-diffusion assay

Microorganisms	Diameter of zone of inhibition (mm)															
	3a (μg/disc)		**3b** (μg/disc)		**3c** (μg/disc)		**3d** (μg/disc)		**3e** (μg/disc)		**3f** (μg/disc)		**3g** (μg/disc)		**A** (μg/disc)	**B** (μg/disc)
	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Escherichia coli (NCIM 2065)[a]	8	13	9	14	8	12	9	12	13	17	9	14	8	12	23	—
Pseudomonas aeruginosa (NCIM 2200)[a]	8	9	8	9	10	13	9	12	10	14	10	14	10	16	22	—
Pseudomonas azotogensis (NCIM 2075)[a]	9	13	7	12	7	12	9	12	8	11	9	12	10	14	24	—
Klebsiella aerogenes (NCIM 2239)[a]	—	8	—	9	—	10	8	10	7	10	8	11	7	10	21	—
Bacillus subtilis (NCIM 2063)[a]	8	11	11	16	10	16	8	13	7	13	7	15	8	14	24	—
Bacillus cereus (NCIM 2155)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	19	—
Bacillus lentus (NCIM 2018)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	27	—
Staphylococcus aureus (NCIM 2079)[a]	—	—	—	8	—	8	8	11	8	10	—	9	—	8	25	—
Staphylococcus albus (NCIM 2178)[a]	—	—	—	8	—	9	—	—	7	8	—	10	—	8	21	—
Proteus vulgaris (NCIM 2027)[a]	—	9	—	—	—	—	—	8	—	9	—	7	—	7	19	—
Aspergillus niger (NCIM 1196)[b]	—	—	—	—	—	—	—	—	—	—	—	7	—	8	—	16
Aspergillus flavus (NCIM 535)[b]	8	10	10	11	8	10	8	9	10	12	9	12	8	10	—	16
Rhodotorula rubra (NCIM 3174)[b]	10	12	—	10	8	11	—	—	—	—	—	9	—	10	—	17
Candida albicans (NCIM 3471)[b]	10	13	10	12	—	—	8	9	10	12	—	9	8	9	—	18
Lipomyces lopofera (NCIM 3252)[b]	—	—	8	9	—	—	8	10	7	8	—	8	7	8	—	18

A, Ofloxacin; **B**, Clotrimazole; '—' no inhibition.
[a] Bacteria.
[b] Fungi.

4.1.1. 2-Oxopyrimido[4,5-*b*]quinoline (2a). Mp 214–215 °C; IR (KBr cm^{-1}): 3200–3000 (NH), 1685 (>C=O); ^1H NMR (DMSO-d_6): δ 7.25 (t, 1H, C_7–H), 7.36 (d, 1H, C_9–H), 7.66 (t, 1H, C_8–H), 7.92 (d, 1H, C_6–H), 8.50 (s, 1H, C_5–H), 10.25 (s, 1H, C_4–H), 12.21 (s, 1H, –NH); MS *m*/*z*: 197 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.32. Found: C, 67.05; H, 3.55; N, 21.30.

4.1.2. 7-Methyl-2-oxopyrimido[4,5-*b*]quinoline (2b). Mp 278–280 °C; IR (KBr cm^{-1}): 3250–3000 (NH), 1683 (>C=O); ^1H NMR (DMSO-d_6): δ 2.35 (s, 3H, C_7–CH_3) 7.29–8.41 (m, 4H, Ar-H) 10.24 (s, 1H, C_4–H), 12.14 (s, 1H, –NH); MS *m*/*z*: 211 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.90. Found: C, 68.23; H, 4.26; N, 19.87.

4.1.3. 9-Methyl-2-oxopyrimido[4,5-*b*]quinoline (2c). Mp 229.5–230 °C; IR (KBr cm^{-1}): 3250–3000 (NH), 1685 (>C=O); ^1H NMR (DMSO-d_6): δ 2.38 (s, 3H, C_9–CH_3) 7.30–8.45 (m, 4H, Ar-H) 10.25 (s, 1H, C_4-H), 12.15 (s, 1H, –NH); MS *m*/*z*: 211 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.90. Found: C, 68.22; H, 4.27; N, 19.89.

4.1.4. 7-Methoxy-2-oxopyrimido[4,5-*b*]quinoline (2d). Mp 214–216 °C; IR (KBr cm^{-1}): 3300–2900 (NH), 1684 (>C=O); ^1H NMR (DMSO-d_6): δ 3.90 (s, 3H, C_7–OCH_3) 7.28–8.43 (m, 4H, Ar-H) 10.24 (s, 1H, C_4–H), 12.13 (s, 1H, –NH); MS *m*/*z*: 227 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.50. Found: C, 63.42; H, 3.94; N, 18.48.

4.1.5. 9-Methoxy-2-oxopyrimido[4,5-*b*]quinoline (2e). Mp 246.5–248 °C; IR (KBr cm^{-1}): 3300–3000 (NH), 1685 (>C=O); ^1H NMR (DMSO-d_6): δ 3.91 (s, 3H, C_9–OCH_3) 7.30–8.44 (m, 4H, Ar-H) 10.25 (s, 1H, C_4–H), 12.11 (s, 1H, –NH); MS *m*/*z*: 227 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.50. Found: C, 63.40; H, 3.98; N, 18.47.

4.1.6. 7-Bromo-2-oxopyrimido[4,5-*b*]quinoline (2f). Mp 240–242 °C; IR (KBr cm^{-1}): 3300–2900 (NH), 1688 (>C=O); ^1H NMR (DMSO-d_6): δ 7.25–8.50 (m, 4H, Ar-H) 10.23 (s, 1H, C_4–H), 12.10 (s, 1H, –NH); MS *m*/*z*: 275 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_6BrN_3O$: C, 48.00; H, 2.19; N, 15.27. Found: C, 47.95; H, 2.14; N, 15.23.

Table 4. In vitro antimicrobial activity of pyrazolo[3,4-*b*]quinolines (**4a–g**) (μg/disc) by disc-diffusion assay

Microorganisms	Diameter of zone of inhibition (mm)															
	4a (μg/disc)		**4b** (μg/disc)		**4c** (μg/disc)		**4d** (μg/disc)		**4e** (μg/disc)		**4f** (μg/disc)		**4g** (μg/disc)		**A** (μg/disc)	**B** (μg/disc)
	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Escherichia coli (NCIM 2065)[a]	8	12	8	12	9	13	9	14	10	13	8	12	10	14	23	—
Pseudomonas aeruginosa (NCIM 2200)[a]	8	9	7	11	7	9	7	9	7	10	7	10	9	11	22	—
Pseudomonas azotogensis (NCIM 2075)[a]	—	—	—	—	—	—	—	—	—	9	—	—	—	8	24	—
Klebsiella aerogenes (NCIM 2239)[a]	—	—	—	—	—	—	—	—	—	8	—	—	—	8	21	—
Bacillus subtilis (NCIM 2063)[a]	9	12	8	13	—	9	—	11	—	10	—	7	8	10	24	—
Bacillus cereus (NCIM 2155)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	9	19	—
Bacillus lentus (NCIM 2018)[a]	—	—	—	—	—	9	—	10	—	9	—	—	—	10	27	—
Staphylococcus aureus (NCIM 2079)[a]	—	8	—	8	8	10	8	9	7	9	—	8	—	11	25	—
Staphylococcus albus (NCIM 2178)[a]	8	11	—	9	—	—	—	—	—	—	—	9	—	10	21	—
Proteus vulgaris (NCIM 2027)[a]	—	—	—	—	—	8	—	8	—	—	—	8	—	9	19	—
Aspergillus niger (NCIM 1196)[b]	8	9	—	—	—	—	—	—	—	—	—	—	—	—	—	16
Aspergillus flavus (NCIM 535)[b]	10	11	—	—	7	8	7	8	8	11	—	8	—	9	—	16
Rhodotorula rubra (NCIM 3174)[b]	11	13	9	12	9	13	10	12	9	13	7	9	8	10	—	17
Candida albicans (NCIM 3471)[b]	10	13	11	14	9	11	16	18	16	20	10	12	12	16	—	18
Lipomyces lopofera (NCIM 3252)[b]	16	18	11	15	12	16	17	22	15	18	8	12	10	13	—	18

A, Ofloxacin; **B**, Clotrimazole; '—' no inhibition.
[a] Bacteria.
[b] Fungi.

4.1.7. 7-Chloro-2-oxopyrimido[4,5-*b*]quinoline (2g). Mp 258–260 °C; IR (KBr cm^{-1}): 3200–2900 (NH), 1685 (>C=O); ^1H NMR (DMSO-d_6): δ 7.26–8.51 (m, 4H, Ar-H) 10.25 (s, 1H, C_4–H), 12.15 (s, 1H, –NH); MS *m*/*z*: 231 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_6ClN_3O$: C, 57.14; H, 2.80; N, 18.18. Found: C, 57.17; H, 2.82; N, 18.15.

4.1.8. 2-Thiopyrimido[4,5-*b*]quinoline (3a). Mp 201–202 °C; IR (KBr cm^{-1}): 3300–2900 (NH), 1340 (>C=S); ^1H NMR (DMSO-d_6): δ 7.20–8.41 (m, 5H, Ar-H) 10.21 (s, 1H, C_4–H), 11.90 (s, 1H, –NH); MS *m*/*z*: 213 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_7N_3S$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.95; H, 3.29; N, 19.70.

4.1.9. 7-Methyl-2-thiopyrimido[4,5-*b*]quinoline (3b). Mp 199–200 °C; IR (KBr cm^{-1}): 3200–2900 (NH), 1343 (>C=S); ^1H NMR (DMSO-d_6): δ 2.32 (s, 3H, C_7–CH_3) 7.21–8.40 (m, 4H, Ar-H) 10.25 (s, 1H, C_4–H), 11.84 (s, 1H, –NH); MS *m*/*z*: 227 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3S$: C, 63.43; H, 3.99; N, 18.50. Found: C, 63.37; H, 3.98; N, 18.47.

4.1.10. 9-Methyl-2-thiopyrimido[4,5-*b*]quinoline (3c). Mp 205–207 °C; IR (KBr cm^{-1}): 3250–2950 (NH), 1340 (>C=S); ^1H NMR (DMSO-d_6): δ 2.35 (s, 3H, C_9–CH_3) 7.20–8.40 (m, 4H, Ar-H) 10.23 (s, 1H, C_4–H), 11.84 (s, 1H, –NH); MS *m*/*z*: 227 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3S$: C, 63.43; H, 3.99; N, 18.50. Found: C, 63.40; H, 3.97; N, 18.48.

4.1.11. 7-Methoxy-2-thiopyrimido[4,5-*b*]quinoline (3d). Mp 215–218 °C; IR (KBr cm^{-1}): 3300–2950 (NH), 1345 (>C=S); ^1H NMR (DMSO-d_6): δ 3.90 (s, 3H, C_7–OCH_3) 7.23–8.50 (m, 4H, Ar-H) 10.21 (s, 1H, C_4–H), 11.82 (s, 1H, –NH); MS *m*/*z*: 243 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.25; H, 3.73; N, 17.28. Found: C, 59.24; H, 3.72; N, 17.26.

4.1.12. 9-Methoxy-2-thiopyrimido[4,5-*b*]quinoline (3e). Mp 225–230 °C; IR (KBr cm^{-1}): 3200–2900 (NH), 1344 (>C=S); ^1H NMR (DMSO-d_6): δ 3.92 (s, 3H, C_9–OCH_3) 7.25–8.41 (m, 4H, Ar-H) 10.21 (s, 1H, C_4–H), 11.89 (s, 1H, –NH); MS *m*/*z*: 243 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.25; H, 3.73; N, 17.28. Found: C, 59.22; H, 3.71; N, 17.25.

Table 5. In vitro antimicrobial activity of pyrazolo[3,4-*b*]quinolines (**5a–g**) (μg/disc) by disc-diffusion assay

Microorganisms	Diameter of zone of inhibition (mm)															
	5a (μg/disc)		**5b** (μg/disc)		**5c** (μg/disc)		**5d** (μg/disc)		**5e** (μg/disc)		**5f** (μg/disc)		**5g** (μg/disc)		**A** (μg/disc)	**B** (μg/disc)
	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Escherichia coli (NCIM 2065)[a]	8	17	8	16	10	14	9	16	10	16	9	12	10	14	23	—
Pseudomonas aeruginosa (NCIM 2200)[a]	7	9	7	8	7	9	9	10	7	9	9	10	7	10	22	—
Pseudomonas azotogensis (NCIM 2075)[a]	—	8	—	8	7	9	8	11	8	11	—	8	—	10	24	—
Klebsiella aerogenes (NCIM 2239)[a]	—	—	—	—	—	—	—	—	—	8	—	—	—	9	21	—
Bacillus subtilis (NCIM 2063)[a]	—	8	—	10	—	9	—	9	—	8	—	9	—	8	24	—
Bacillus cereus (NCIM 2155)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	19	—
Bacillus lentus (NCIM 2018)[a]	7	9	8	9	—	—	—	—	—	—	—	8	7	9	27	—
Staphylococcus aureus (NCIM 2079)[a]	9	12	8	10	7	9	8	9	9	11	8	9	9	11	25	—
Staphylococcus albus (NCIM 2178)[a]	7	8	8	11	7	11	7	11	8	12	7	9	10	13	21	—
Proteus vulgaris (NCIM 2027)[a]	—	7	—	8	—	8	—	9	—	10	7	8	7	11	19	—
Aspergillus niger (NCIM 1196)[b]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	16
Aspergillus flavus (NCIM 535)[b]	8	10	—	—	8	11	—	—	—	9	—	8	—	9	—	16
Rhodotorula rubra (NCIM 3174)[b]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17
Candida albicans (NCIM 3471)[b]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	18
Lipomyces lopofera (NCIM 3252)[b]	—	—	10	12	—	—	—	—	—	—	—	8	—	9	—	18

A, Ofloxacin; **B**, Clotrimazole, '—' no inhibition.
[a] Bacteria.
[b] Fungi.

Table 6. Minimum Inhibitory Concentration values of the pyrimido quinolines (μg/ml) against the microorganisms tested in broth dilution assay

Microorganisms	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
Escherichia coli (NCIM 2065)[a]	15.6	7.8	7.8	15.6	15.6	15.6	15.6	7.8	7.8	7.8	7.8	7.8	7.8	7.8
Pseudomonas aeruginosa (NCIM 2200)[a]	15.6	15.6	7.8	7.8	15.6	7.8	15.6	15.6	15.6	15.6	15.6	7.8	7.8	7.8
Pseudomonas azotogensis (NCIM 2075)[a]	15.6	15.6	15.6	15.6	31.2	31.2	31.2	7.8	7.8	7.8	7.8	7.8	7.8	7.8
Klebsiella aerogenes (NCIM 2239)[a]	—	—	—	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	15.6	31.2
Bacillus subtilis (NCIM 2063)[a]	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	15.6	15.6	31.2	31.2	31.2	31.2
Bacillus cereus (NCIM 2155)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Bacillus lentus (NCIM 2018)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Staphylococcus aureus (NCIM 2079)[a]	—	—	—	62.5	—	—	—	—	31.2	31.2	15.6	15.6	31.2	15.6
Staphylococcus albus (NCIM 2178)[a]	—	—	—	62.5	—	—	—	—	31.2	31.2	—	15.6	31.2	15.6
Proteus vulgaris (NCIM 2027)[a]	62.5	—	31.2	31.2	15.6	15.6	15.6	62.5	—	—	31.2	31.2	31.2	31.2
Aspergillus niger (NCIM 1196)[b]	31.2	—	—	31.2	—	—	—	—	—	—	—	—	—	—
Aspergillus flavus (NCIM 535)[b]	31.2	—	—	15.6	31.2	—	—	31.2	31.2	31.2	31.2	31.2	15.6	31.2
Rhodotorula rubra (NCIM 3174)[b]	—	31.2	31.2	31.2	—	—	—	31.2	62.5	62.5	—	—	—	31.2
Candida albicans (NCIM 3471)[b]	15.6	15.6	15.6	15.6	15.6	15.6	7.8	31.2	31.2	—	62.5	31.2	—	62.5
Lipomyces lopofera (NCIM 3252)[b]	—	—	15.6	—	15.6	—	—	—	62.5	—	31.2	62.5	—	62.5

'—' Not tested.
[a] Bacteria.
[b] Fungi.

4.1.13. 7-Bromo-2-thiopyrimido[4,5-*b*]quinoline (3f). Mp 222–223 °C; IR (KBr cm^{-1}): 3200–2900 (NH), 1345 (>C=S); ^1H NMR (DMSO-d_6): δ 7.25–8.45 (m, 4H, Ar-H) 10.21 (s, 1H, C_4–H), 11.80 (s, 1H, –NH); MS *m*/*z*: 291 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_6BrN_3S$: C, 45.36; H, 2.07; N, 14.43. Found: C, 45.35; H, 2.04; N, 14.41.

Table 7. Minimum inhibitory concentration values of the pyrazolo quinolines (μg/ml) against the microorganisms tested in broth dilution assay

Microorganisms	4a	4b	4c	4d	4e	4f	4g	5a	5b	5c	5d	5e	5f	5g
Escherichia coli (NCIM 2065)[a]	15.6	15.6	7.8	7.8	7.8	15.6	7.8	15.6	7.8	15.6	7.8	7.8	15.6	7.8
Pseudomonas aeruginosa (NCIM 2200)[a]	15.6	15.6	15.6	15.6	15.6	15.6	7.8	31.2	31.2	31.2	31.2	31.2	31.2	31.2
Pseudomonas azotogensis (NCIM 2075)[a]	—	—	—	—	31.2	—	31.2	—	—	62.5	62.5	31.2	—	62.5
Klebsiella aerogenes (NCIM 2239)[a]	—	—	—	—	31.2	—	31.2	—	—	—	—	—	—	—
Bacillus subtilis (NCIM 2063)[a]	31.2	31.2	62.5	31.2	31.2	—	31.2	—	62.5	—	—	—	—	—
Bacillus cereus (NCIM 2155)[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Bacillus lentus (NCIM 2018)[a]	—	—	—	31.2	—	—	31.2	62.5	62.5	—	—	—	—	—
Staphylococcus aureus (NCIM 2079)[a]	62.5	62.5	31.2	31.2	62.5	62.5	31.2	15.6	15.6	31.2	31.2	31.2	31.2	31.2
Staphylococcus albus (NCIM 2178)[a]	31.2	31.2	—	—	—	62.5	62.5	62.5	62.5	62.5	62.5	31.2	62.5	15.6
Proteus vulgaris (NCIM 2027)[a]	—	—	—	—	—	62.5	62.5	—	—	—	62.5	62.5	62.5	62.5
Aspergillus niger (NCIM 1196)[b]	62.5	—	—	—	—	—	—	—	—	—	—	—	—	—
Aspergillus flavus (NCIM 535) [b]	31.2	—	62.5	62.5	31.2	31.2	31.2	62.5	—	62.5	—	—	—	—
Rhodotorula rubra (NCIM 3174) [b]	15.6	31.2	31.2	31.2	15.6	31.2	31.2	—	—	—	—	—	—	—
Candida albicans (NCIM 3471) [b]	15.6	7.8	15.6	3.9	3.9	15.6	15.6	—	—	—	—	—	—	—
Lipomyces lopofera (NCIM 3252) [b]	7.8	7.8	7.8	3.9	3.9	31.2	31.2	—	62.5	—	—	—	—	—

'—' Not tested.
[a] Bacteria.
[b] Fungi.

4.1.14. 7-Chloro-2-thiopyrimido[4,5-*b*]quinoline (3g). Mp 219–220 °C; IR (KBr cm^{-1}): 3300–2950 (NH), 1340 (>C=S); ^1H NMR (DMSO-d_6): δ 7.20–8.41 (m, 4H, Ar-H) 10.23 (s, 1H, C_4–H), 11.85 (s, 1H, –NH); MS *m*/*z*: 247 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_6ClN_3S$: C, 53.44; H, 2.44; N, 17.00. Found: C, 53.42; H, 2.45; N, 16.95.

4.1.15. 1-(*p*-Tosyl)pyrazolo[3,4-*b*]quinoline (4a). Mp 171–174 °C; IR (KBr cm^{-1}): 1640 (>C=N), 1595 (>C=N), 1321 (>S=O), 1160 (>S=O); ^1H NMR (DMSO-d_6): δ 2.45 (s, 3H, C′$_4$–CH_3), 7.30–7.85 (m, 7H, Ar-H), 7.90 (d, 1H, C_5–H), 8.23 (s, 1H, C_4–H), 8.71 (s, 1H, C_3–H); MS *m*/*z*: 323 ($M^{+\cdot}$); Anal. Calcd for $C_{17}H_{13}N_3O_2S$: C, 63.15; H, 4.05; N, 13.00. Found: C, 63.07; H, 4.03; N, 12.92.

4.1.16. 6-Methyl-1-(*p*-tosyl)pyrazolo[3,4-*b*]quinoline (4b). Mp 175–176 °C; IR (KBr cm^{-1}): 1640 (>C=N), 1591 (>C=N), 1320 (>S=O), 1164 (>S=O); ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H, C′$_4$–CH_3), 2.54 (s, 3H, C_6–CH_3), 7.32–7.90 (m, 6H, Ar-H), 7.93 (s, 1H, C_5–H), 8.21 (s, 1H, C_4–H), 8.61 (s, 1H, C_3–H); MS *m*/*z*: 337 ($M^{+\cdot}$); Anal Calcd for $C_{18}H_{15}N_3O_2S$: C, 64.09; H, 4.48; N, 12.46. Found: C, 64.02; H, 4.40; N, 12.32.

4.1.17. 8-Methyl-1-(*p*-tosyl)pyrazolo[3,4-*b*]quinoline (4c). Mp 177–178 °C; IR (KBr cm^{-1}): 1641 (>C=N), 1590 (>C=N), 1310 (>S=O), 1164 (>S=O); ^1H NMR (DMSO-d_6): δ 2.41 (s, 3H, C′$_4$–CH_3), 2.50 (s, 3H, C_8–CH_3), 7.31–7.95 (m, 6H, Ar-H), 8.01 (d, 1H, C_5–H), 8.20 (s, 1H, C_4–H), 8.65 (s, 1H, C_3–H); MS *m*/*z*: 337 ($M^{+\cdot}$); Anal. Calcd for $C_{18}H_{15}N_3O_2S$: C, 64.09; H, 4.48; N, 12.46. Found: C, 64.01; H, 4.44; N, 12.41.

4.1.18. 6-Methoxy-1-(*p*-tosyl)pyrazolo[3,4-*b*]quinoline (4d). Mp 180–182 °C; IR (KBr cm^{-1}): 1641 (>C=N), 1591 (>C=N), 1321 (>S=O), 1165 (>S=O); ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H, C′$_4$–CH_3), 3.91 (s, 3H, C_6–OCH_3), 7.13–7.93 (m, 6H, Ar-H), 8.11 (s, 1H, C_5–H), 8.20 (s, 1H, C_4–H), 8.62 (s, 1H, C_3–H); MS *m*/*z*: 353 ($M^{+\cdot}$); Anal. Calcd for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89. Found: C, 61.15; H, 4.25; N, 11.80.

4.1.19. 8-Methoxy-1-(*p*-tosyl)pyrazolo[3,4-*b*]quinoline (4e). Mp 174.5–177 °C; IR (KBr cm^{-1}): 1640 (>C=N), 1590 (>C=N), 1320 (>S=O) 1165 (>S=O); ^1H NMR (DMSO-d_6): δ 2.40 (s, 3H, C′$_4$–CH_3), 3.90 (s, 3H, C_8–OCH_3), 7.91–8.01 (m, 6H, Ar-H), 8.15 (d, 1H, C_5–H), 8.21 (s, 1H, C_4–H), 8.65 (s, 1H, C_3–H); MS *m*/*z*: 353 ($M^{+\cdot}$); Anal. Calcd for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89. Found: C, 61.10; H, 4.27; N, 11.78.

4.1.20. 6-Bromo-1-(*p*-tosyl)pyrazolo[3,4-*b*]quinoline (4f). Mp 175–179 °C; IR (KBr cm^{-1}): 1641 (>C=N), 1593 (>C=N), 1323 (>S=O), 1160 (>S=O); ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H, C′$_4$–CH_3), 7.20–7.95 (m, 6H, Ar-H), 8.14 (s, 1H, C_5-H), 8.25 (s, 1H, C_4–H), 8.61 (s, 1H, C_3–H); MS *m*/*z*: 402 ($M^{+\cdot}$); Anal. Calcd for $C_{17}H_{12}N_3O_2SBr$: C, 50.74; H, 3.08; N, 10.44. Found: C, 50.70; H, 3.02; N, 10.40.

4.1.21. 6-Chloro-1-(*p*-tosyl)pyrazolo[3,4-*b*]quinoline (4g). Mp 170–171 °C; IR (KBr cm^{-1}): 1640 (>C=N), 1595 (>C=N), 1325 (>S=O), 1162 (>S=O); ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, C′$_4$–CH_3), 7.21–8.00 (m, 6H, Ar-H), 8.19 (s, 1H, C_5–H), 8.28 (s, 1H, C_4–H), 8.65 (s, 1H, C_3–H); MS *m*/*z*: 357 ($M^{+\cdot}$); Anal. Calcd for $C_{17}H_{12}N_3O_2SCl$: C, 57.14; H, 3.38; N, 11.76. Found: C, 57.08; H, 3.35; N, 11.67.

4.1.22. 1-(2′,4′-Dinitrophenyl)pyrazolo[3,4-*b*]quinoline (5a). Mp >300 °C; IR (KBr cm^{-1}): 1614 (>C=N), 1593 (>C=N), 1512 (–NO_2), 1335 (–NO_2); ^1H NMR (DMSO-d_6): δ 7.55–8.93 (m, 7H, Ar-H), 9.07 (s, 1H, C_4–H) 9.20 (s, 1H, C_3–H); MS *m*/*z*: 335 ($M^{+\cdot}$); Anal. Calcd for $C_{16}H_9N_5O_4$: C, 57.31; H, 2.70; N, 20.89. Found: C, 57.25; H, 2.65; N, 20.79.

4.1.23. 6-Methyl-1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]quinoline (5b). Mp 269–272 °C; IR (KBr cm^{-1}): 1620 (>C=N), 1595 (>C=N), 1513 (–NO_2), 1330 (–NO_2);

^{1}H NMR (DMSO-d_6): δ 2.51 (s, 3H, C_6–CH_3), 7.46–8.95 (m, 6H, Ar-H) 9.06 (s, 1H, C_4–H), 9.19 (s, 1H, C_3–H); MS *m*/*z*: 349 ($M^{+\cdot}$); Anal. Calcd for $C_{17}H_{11}N_5O_4$: C, 58.45; H, 3.17; N, 20.05. Found: C, 58.40; H, 3.15; N, 20.02.

4.1.24. 8-Methyl-1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]quinoline (5c). Mp >300 °C; IR (KBr cm^{-1}): 1621 (>C=N), 1591 (>C=N), 1515 (–NO_2), 1332 (–NO_2); ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 3H, C_8–CH_3), 7.45–9.00 (m, 6H, Ar-H), 9.02 (s, 1H, C_4–H), 9.10 (s, 1H, C_3–H); MS *m*/*z*: 349 ($M^{+\cdot}$); Anal. Calcd for $C_{17}H_{11}N_5O_4$: C, 58.45; H, 3.17; N, 20.05. Found: C, 58.43. H, 3.16; N, 20.00.

4.1.25. 6-Methoxy-1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]quinoline (5d). Mp >300 °C; IR (KBr cm^{-1}): 1620 (>C=N), 1593 (>C=N), 1514 (–NO_2), 1330 (–NO_2); ^{1}H NMR (DMSO-d_6): δ 3.94 (s, 3H, C_6–OCH_3), 7.54 – 8.91 (m, 6H, Ar-H) 9.07 (s, 1H, C_4–H), 9.21 (s, 1H, C_3–H); MS *m*/*z*: 365 ($M^{+\cdot}$); Anal. Calcd for $C_{17}H_{11}N_5O_5$: C, 55.89; H, 3.03; N, 19.17. Found: C, 55.88; H, 3.02; N, 19.12.

4.1.26. 8-Methoxy-1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]quinoline (5e). Mp >300 °C; IR (KBr cm^{-1}): 1614 (>C=N), 1587 (>C=N), 1512 (–NO_2), 1332 (–NO_2); ^{1}H NMR (DMSO-d_6): δ 3.95 (s, 3H, C_8–OCH_3), 7.59 – 8.95 (m, 6H, Ar-H), 9.10 (s, 1H, C_4–H), 9.25 (s, 1H, C_3–H); MS *m*/*z*: 365 ($M^{+\cdot}$); Anal. Calcd for $C_{17}H_{11}N_5O_5$: C, 55.89; H, 3.03; N, 19.17. Found: C, 55.85; H, 3.00; N, 19.15.

4.1.27. 6-Bromo-1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]quinoline (5f). Mp >300 °C; IR (KBr cm^{-1}): 1615 (>C=N), 1585 (>C=N), 1515 (–NO_2), 1335 (–NO_2); ^{1}H NMR (DMSO-d_6): δ 7.60–8.98 (m, 6H, Ar–H), 9.05 (s, 1H, C_4–H), 9.22 (s, 1H, C_3–H); MS *m*/*z*: 414 ($M^{+\cdot}$); Anal. Calcd for $C_{16}H_8N_5O_4Br$: C, 46.37; H, 1.94; N, 16.90. Found: C, 46.33; H, 1.89; N, 16.83.

4.1.28. 6-Chloro-1-(2′,4′-dinitrophenyl)pyrazolo[3,4-*b*]quinoline (5g). Mp >300 °C; IR (KBr cm^{-1}): 1614(>C=N), 1586 (>C=N), 1515 (–NO_2), 1333 (–NO_2); ^{1}H NMR (DMSO-d_6): δ 7.55–8.96 (m, 6H, Ar-H), 9.07 (s, 1H, C_4–H), 9.21 (s, 1H, C_3–H); MS *m*/*z*: 369 ($M^{+\cdot}$); Anal. Calcd for $C_{16}H_8N_5O_4Cl$: C, 52.03; H, 2.18; N, 18.97. Found: C, 52.00; H, 2.12; N, 18.95.

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