Green and Efficient Synthesis of 4-Heteryl-Quinolines and Their Antibacterial Evaluations

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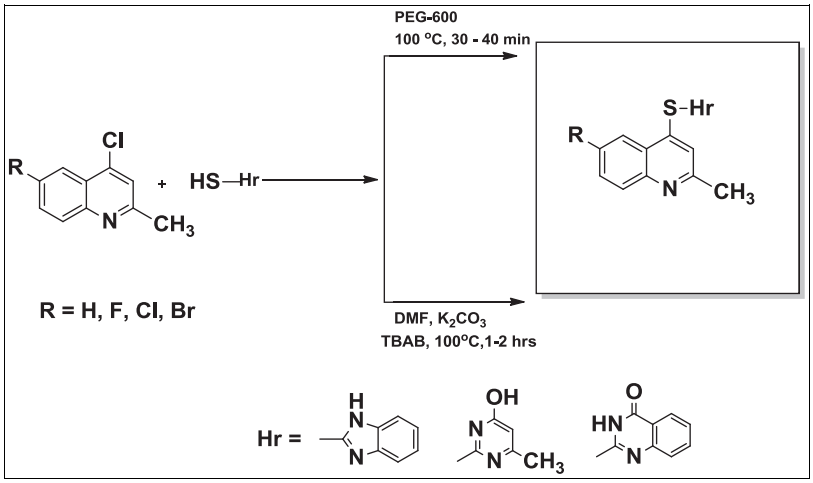


A green and efficient synthesis of 4-heteryl-quinolines **(9a–9d)**, **(10a–10d)** and **(11a–11d)** has been described using PEG-600 as a green solvent. Initially, 4-chloro-2-methylquinolines **(5a–5d)** on reaction with aromatic heterocyclic thiols **(6), (7),** and **(8)** using PEG-600 at 100°C for 30–40 min resulted in **(9)**, **(10)**, and **(11)** in good yields. Alternatively, **(9), (10),** and **(11)** could also be prepared in dimethylformamide using K2CO3 as base and tetrabutylammonium bromide as phase transfer catalyst at 100°C for 1–2 h. All the compounds were synthesized and characterized by IR, NMR, mass spectroscopy, and 13C NMR analysis. All synthesized compounds were screened for their antibacterial activity against clinical strains that include Gram-positive (Bacillus subtilis MTCC 121, staphylococcus aureus MLS-16 MTCC 2940, Micrococcus lutes MTCC 2470, and Staphylococcus aureus MTCC 96) and Gram-negative bacteria (Candida albicans MTCC 3017, Klebsiella planticola MTCC 530, Escherichia coli MTCC 739, and Pseudomonas aeruginosa MTCC 2453). The results revealed that compounds **(9a, 9d, 10a, 10c, 11b,** and **11d)** exhibited significant antibacterial activity almost equal to the standard drug, that is, Ciprofloxacin.

INTRODUCTION

Quinolines and its related compounds are used as very good antibiotics in developing countries, because synthesis and isolation of quinolone drugs are economically cheap and have easy synthetic procedures. Especially quinolines are used in treating malarial and urinary tract infections. Malaria is one of the most devastating infectious diseases in the world, affecting 200 to 500 million people and killing one to two million annually [1]. Since the discovery of cinchona alkaloids and synthesis of anti-malarial agents such as chloroquine, this has created a demand for the development of new anti-malarial agents. The heterocyclic systems containing a quinoline nucleus have long been used for the treatment of malaria, beginning with quinine (Fig. 1). Systematic modifications of quinine lead to the potent and inexpensive 4-aminoquinoline drug chloroquine. After the worldwide development of drug resistance to chloroquine, focused chemistry and screening efforts produced mefloquine, another quinoline-containing compound that was highly active against the chloroquine-resistant strains of *Plasmodium falciparum* [2]. Since the development of mefloquine, there have been several reports of new potent quinoline compounds [3,4]. The quinoline moiety has found broad application in drug development for the treatment of melanin-concentrating hormone receptor-related disorders [5]; cell proliferative diseases [6]; transmissible spongiform encephalopathies [7]; malignant tumors (such as stomach cancer, brain tumor, and large intestine cancer) [8]; and bacterial infections in mammals [9].

Reducing or eliminating the use of volatile organic solvents can minimize the generation of waste, which is essential in one of the principles of green chemistry [10].

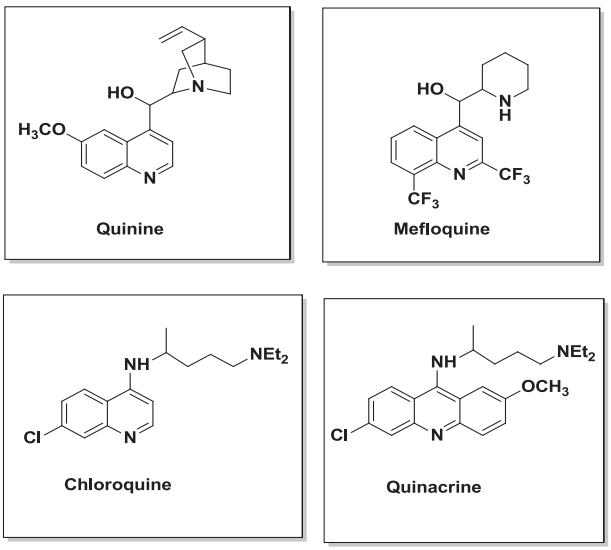


Figure 1. Quinoline anti-malarial drugs with diverse substitutions around the quinoline ring.

Liquid polymers have been used as green reaction media with unique properties such as thermal stability, commercial availability, non-volatility, immiscibility with organic solvents, and recyclability. Polyethylene glycol (PEG) stands as one of the best in comparison with other currently favored systems such as ionic liquids, supercritical carbon dioxide, and micellar systems [11]. PEGs systems were selected instead of other polymers because they are inexpensive, biodegradable, non-halogenated, and low toxicity.

Table 1

Synthesis of compounds **(9a–9d)** from **(5a–5d)** and 6 **at 100°C.**

Synthesis number	Product (R)	Solvent	Time (min)	Yield (%)[a]
1	$-OCH_3$	PEG-600	30	92
2	$-CH_3$	PEG-600	30	85
3	-F	PEG-600	40	90
4	- Cl	PEG-600	40	88
5	$-OCH_3$	DMF	60	78
6	$-CH_3$	DMF	60	75
7	-F	DMF	90	80
8	-Cl	DMF	90	75

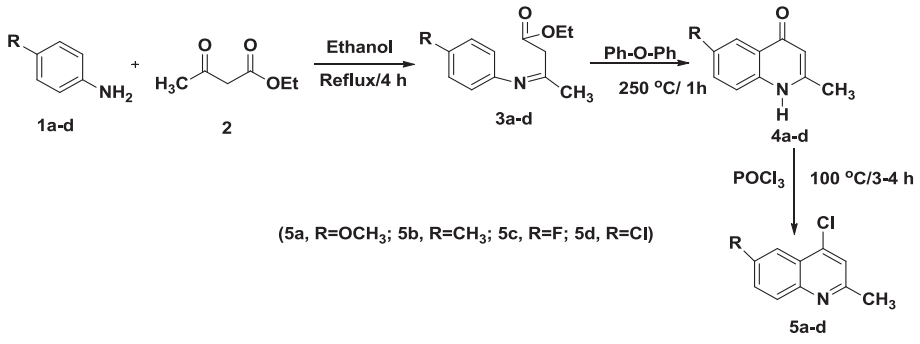
DMF, dimethylformamide.
[a]Reference to yields of crude products only.

Hence, we explored the possibilities of exploiting the versatile features of this green solvent PEG-600 [12]. In this connection, here, we report a simple, efficient, and green protocol for the synthesis of 4-thioquinolines as antimicrobial agents from substituted 4-chloro-2-methylquinolines and various heterocyclic thiols.

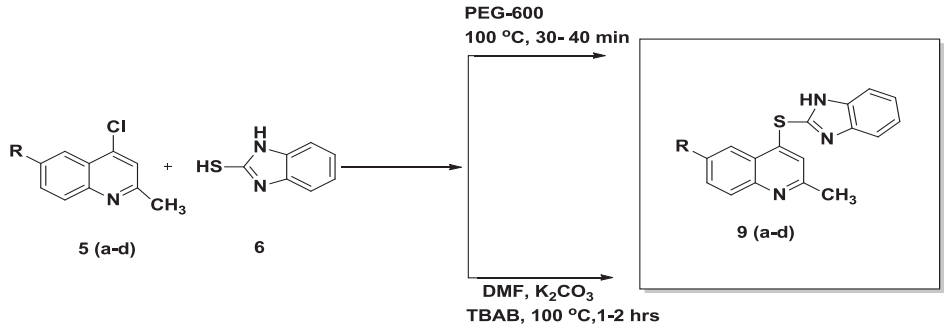
RESULTS AND DISCUSSION

The starting materials were prepared according to the literature method (Scheme 1) [13,14]. Anilines **(1a–1d)**

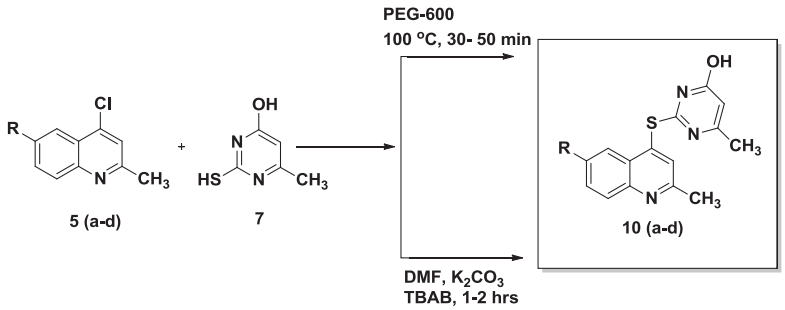
Scheme 1



Scheme 2



Scheme 3



were condensed with ethyl acetoacetate **2** in ethanol to obtain **(3a–3d),** which were subsequently cyclized to 2-methyl-4-quinolones **(4a–4d)** in diphenyl ether. The latter on treatment with $POCl_3$ at 100°C for 3–4 h resulted in 4-chloro-2-methylquinolines **(5a–5d),** which were used for substitution (SNAr) with heterocyclic thiols under green conditions.

Compounds **(5a–5d)** on reaction with different heterocyclic thiols such as 2-mercapto-benzimidazole using PEG-600 as a solvent at 100°C for 30–40 min without additional usage of any base resulted in the formation of 4-(1*H*-benzo[*d*]imidazol-2-ylthio)-6-methoxy-2-methylquinolines **(9a–9d)**. PEG-600 is a very effective solvent that dissolves both the substrate and the reagent, bringing them together and thereby providing an effective means for chemical reaction to occur. Further, PEG-600 is able to extract the proton from the -SH of 2-mercaptobenzimidazole and is able to retain it by chelation through several lone pairs of electrons in its oxygen-containing chain. This role of PEG-600 is very similar to that of proton sponge (i.e., 1, 8 dimethylaminonaphthalene), which is a very strong base because of its ability to extract proton from an acidic substrate and then retain it in its claws by chelation through lone pair of electrons on the two nitrogen atoms of proton sponge. In an alternative approach, compounds **(9a–9d)** were also prepared by refluxing **(9a–9d)** with 2-mercaptobenzimidazole **6** in dimethylformamide (DMF) using K_2CO_3 as a base and tetrabutylammonium bromide (TBAB) for 1–2 h (Scheme 2), and the results were summarized in **Table** 1.

Table 2

Synthesis of compounds **(10a–10d)** from **(5a–5d)** and **7 at 100 °C.**

Synthesis number	Product (R)	Solvent	Time (min)	Yield (%)[a]
1	-OCH_3	PEG-600	30	90
2	-CH_3	PEG-600	30	88
3	-F	PEG-600	45	90
4	-Cl	PEG-600	45	85
5	-OCH_3	DMF	60	80
6	-CH_3	DMF	60	75
7	-F	DMF	100	74
8	-Cl	DMF	100	76

DMF, dimethylformamide.
[a]Reference to yields of crude products only.

Compound **(5a–5d)** on reaction with 2-methyl-6-thio-4-pyrimidinones **7** heating with PEG-600 as a solvent at 100°C for 30–50 min resulted in the formation of 6-(6-methoxy-2-methylquinolin-4-ylthio)-2-methylpyrimidin-4-ol **(10a–10d)**. In an alternative approach, compounds **(10a–10d)** were also prepared by refluxing 2-methyl-6-thiolo-4-pyrimidinones **7** with **(5a–5d)** in DMF using K_2CO_3 as a base and TBAB for 1–2 h (Scheme 3). But the yields of **(10a–10d)** were reasonably more in PEG-600 when

Scheme 4

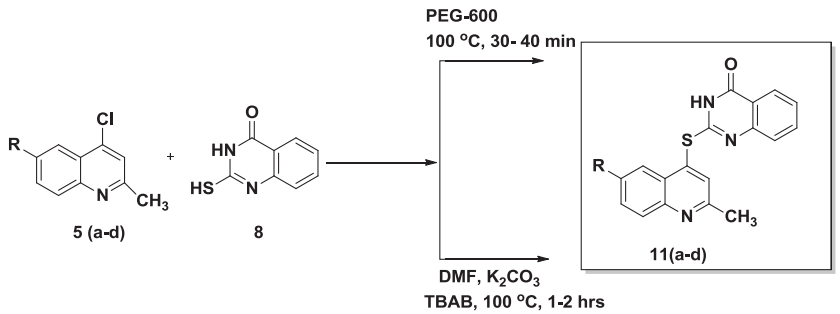


Table 3

Synthesis of compounds **(11a–11d)** from **(5a–5d)** and **8 at 100°C.**

Synthesis number	Product (R)	Solvent	Time (min)	Yield (%)[a]
1	-OCH_3	PEG-600	30	91
2	-CH_3	PEG-600	30	88
3	-F	PEG-600	40	90
4	-Cl	PEG-600	40	88
5	-OCH_3	DMF	60	78
6.	-CH_3	DMF	60	74
7	-F	DMF	90	76
8	-Cl	DMF	90	72

DMF, dimethylformamide.
[a]Reference to yields of crude products only.

compared with DMF, and the results were summarized in **Table** 2.

Similarly, compounds **(5a–5d)** on reaction with 2-thioquinazolinones **8** heating with PEG-600 at 100°C for 30–40 min resulted in the formation 2-(6-methoxy-2-methylquinolin-4-ylthio) quinazolin-4(3*H*)-one **(11a–11d)**. In an alternative approach, compounds **(9a–9d)** were also prepared by refluxing 2-thioquinazolinones **8** with **(5a–5d)** in DMF using K_2CO_3 as a base and TBAB for 1–2 h (Scheme 4), and the reaction was smoothly carried out in PEG-600 and gave high yields of products when compared with DMF, and all the results were summarized in **Table** 3.

Antibacterial assay. The antibacterial activity of all the synthesized quinolone compounds **(9a–9d), (10a–10d)** and **(11a–11d)** was determined using the well diffusion method (Amsterdam *et al.*, 1996) against different Gram-positive and Gram-negative microbial strains, which were produced from the Microbial Culture Collection CSIR–Indian Institute of Chemical Technology, Hyderabad, India. The clinical strains were seeded on the surface of the media Petri plates, containing Muller–Hinton agar with 0.1 mL of prepared microbial suspensions, which individually contains 1.5×10^8 cfu mL^{-1}. 6.0 mm wells were prepared in media plates by using a cork borer. And the synthesized compounds dissolved in 10 % DMSO at a dose range of 250−0.97 µg were added to each well, under sterile conditions in a laminar air flow chamber, Standard antibiotic solutions of ciprofloxacin (bacterial strains) and miconazole (*Candida albicans*) at a dose range of 250−0.97 µg. The plates were incubated for 28 h at 32°C, and the well containing the least concentration showing the inhibition zone is considered as the minimum inhibitory concentration. All experiments were carried out in duplicates, and mean values are represented. All the results were summarized in **Table** 4. It is clear that all the compounds possess good activity against both Gram-positive and Gram-negative bacteria, especially compounds **9a, 9d, 10a, 10c, 11b, and 11d that** showed promising antibacterial activity without any cytotoxicity against the tested cell lines.

Table 4

Antibacterial Activity of synthesized compounds **(9a–11d)**.

Synthesis number	Test compounds	*Micrococcus luteus* MTCC 2470	*Staphylococcus aureus* MTCC 96	*Staphylococcus aureus* MLS-16 MTCC 2940	*Bacillus subtilis* MTCC 121	*Escherichia coli* MTCC 739	*Pseudomonas aeruginosa* MTCC 2453	*Klebsiella planticola* MTCC 530	*Candida albicans* MTCC 3017
1	**9a**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	—
2	9b	31.2	7.9	3.9	3.9	31.2	31.2	15.8	—
3	9c	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	—
4	**9d**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	—
5	**10a**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	—
6	10b	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	—
7	**10c**	**32.2**	**32.2**	**3.7**	**32.2**	**63.4**	**>125.0**	**63.4**	—
8	10d	63.4	63.4	3.7	7.9	32.2	32.2	63.4	—
9	11a	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	—
10	**11b**	**8.1**	**1.9**	**0.8**	**0.8**	**8.1**	**8.1**	**8.1**	—
11	11c	8.1	1.9	0.8	0.8	8.1	8.1	8.1	—
12	**11d**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	**>125.0**	—
13	Ciprofloxacin (standard)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	—

CONCLUSION

In summary, we have synthesized a new series of substituted 4-heteryl-thioquinolines **(9, 10,** and **11)** by using PEG-600 as solvent without adding any base. Compounds **9,10,** and **11** could also be prepared by another method by using DMF and K_2CO_3/TBAB. But when compared in both methods, PEG-600 gave reasonably high yield and reaction time was also very less. This method shows simplicity, avoiding usage of base and phase transfer catalyst. All the synthesized compounds were evaluated for their biological activity; compounds **9a, 9d, 10a, 10c, 11b, and 11d** showed good activity against Gram-positive and Gram-negative bacteria.

EXPERIMENTAL

General information. All the reagents used in this work were obtained from commercial suppliers. Solvents were freshly distilled before being used. Melting points were determined using a Buchi melting point apparatus (Sigma-Aldrich, India) and are uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC) performed on silica gel G (Merck), and spots were exposed to iodine vapor and UV light (Medical Equipment India, Delhi, India). IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer (Perkin-Elmer, UK). ^{1}H NMR spectra were recorded on Brucker DPX-400 (Bruker, USA) at 400 MHz (chemical shifts in δ, ppm) and mass spectra on an Agilent LC-MS instrument (Agilent, Santa Clara, CA) giving only M+ values in Q + 1 mode.

Chemistry

General procedure for the synthesis of 4-thioquinolines (9, 10, 11) *Using PEG-600.* A mixture of **(5a–5d)** (1 mmol), heterocyclic thiols **6, 7,** and **8** (1 mmol) were added to PEG-600 (10 mL) in a round bottom flask and is allowed to heat at 100°C on a water bath for 30–40 min. The reaction was monitored by checking TLC for the disappearance of the starting material. At the end of this period, the reaction mixture is poured into ice-cold water (25 mL); the precipitated solid was filtered and washed with excess water to obtain the crude **9, 10,** and **11.** The latter was recrystallized from ethanol to obtain pure products.

Using DMF and K_2CO_3. A mixture of **(5a–5d)** (1 mmol), heterocyclic thiols **6, 7,** and **8** (1 mmol) were added to DMF (10 mL) followed by the addition of K_2CO_3 (3 mmol) and catalytic amount of TBAB in a round bottom flask and is allowed to heat at 100°C in an oil bath for 1–2 h. The reaction is monitored by checking TLC for the disappearance of the starting material. At the end, the reaction mixture was poured on ice-cold water (25 mL), adjusted pH aq.HCl solution, and the precipitated solid was filtered and washed with water and dried to obtain pure **9, 10,** and **11.**

4-((1H-benzo[d]imidazol-2-yl)thio)-6-methoxy-2-methylquinoline (9a). IR (KBr): 3461–3250 cm^{-1} (broad, medium, -NH); ^{1}H-NMR: δ 2.3 (s, 3H, -C**H$_3$**), 3.7 (s, 3H, -OC**H$_3$**), δ 6.3–8.4 (m, 8H, Ar-H), 10.2 **(s, 1H, -NH, D$_2$O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 26.3, 40.4, 121.1, 122.4, 123.1, 123.3, 124.5, 132.1, 132.5, 132.8, 132.9, 141.1, 145.4, 147.5, 147.8, 148.2, 149.5, 160.3. ms: m/z = **337 (M$^{+\cdot}$ + 1).** *Anal.* Calcd for $C_{19}H_{18}N_3OS$ (336.43): C, 67.83; H, 5.39; N, 12.49; Found: C, 67.80; H, 5.32; N, 12.46.

4-((1H-benzo[d]imidazol-2-yl)thio)-2,6-dimethylquinoline (9b). IR (KBr): 3462–3253 cm^{-1} (broad, medium, -NH); ^{1}H-NMR: δ 2.3 (s, 3H, -C**H$_3$**), 2.5 (s, 3H, -C**H$_3$**), δ 6.3–8.4 (m, 8H, Ar-H), 10.2 **(s, 1H, -NH, D$_2$O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 26.3, 26.9, 121.3, 122.2, 123.2, 123.5, 125.7, 132.2, 132.4, 132.6, 132.9, 141.3, 145.6, 147.8, 147.9, 148.3, 149.7, 160.2. ms: m/z = **321 (M$^{+\cdot}$ + 1).** *Anal.* Calcd for $C_{19}H_{18}N_3S$ (320.43): C, 71.22; H, 5.66; N, 13.11; Found: C, 71.24; H, 5.69; N, 13.10.

4-((1H-benzo[d]imidazol-2-yl)thio)-6-fluoro-2-methylquinoline (9c). IR (KBr): 3461–3255 cm^{-1} (broad, medium, -NH); ^{1}H-NMR: δ 2.4 (s, 3H, -C**H$_3$**), δ 6.3–8.4 (m, 8H, Ar-H), 10.2 **(s, 1H, -NH, D$_2$O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 26.5, 121.2, 122.4, 123.1, 123.6, 125.8, 132.3, 132.5, 132.7, 132.9, 141.2, 145.4, 147.6, 147.7, 148.4, 149.9, 160.1. ms: m/z = **325 (M$^{+\cdot}$ + 1).** *Anal.* Calcd for $C_{18}H_{15}FN_3S$ (324.40): C, 66.64; H, 4.66; N, 12.95; Found: C, 66.62; H, 4.64; N, 12.93.

4-((1H-benzo[d]imidazol-2-yl)thio)-6-chloro-2-methylquinoline (9d). IR (KBr): 3463–3252 cm^{-1} (broad, medium, -NH); ^{1}H-NMR: δ 2.2 (s, 3H, -C**H$_3$**), δ 6.1–8.3 (m, 8H, Ar-H), 10.3 **(s, 1H, -NH, D$_2$O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 26.2, 121.3, 122.4, 123.2, 123.4, 125.6, 132.2, 132.4, 132.8, 132.9, 141.1, 145.3, 147.5, 147.8, 148.7, 149.6, 160.2. ms: m/z = **342 (M$^{+\cdot}$ + 1).** *Anal.* Calcd for $C_{18}H_{15}ClN_3S$ (341.07): C, 63.43; H, 4.44; N, 12.33; Found: C, 63.41; H, 4.42; N, 12.30.

2-((6-methoxy-2-methylquinolin-4-yl)thio)-6-methylpyrimidin-4-ol (10a). IR (KBr): 3570–3325 cm^{-1} (broad, medium, -OH); ^{1}H-NMR: δ 2.2 (s, 3H, -C**H$_3$**), 2.4 (s, 3H, -C**H$_3$**) 3.8 (s, 3H, -OC**H$_3$**), δ 6.4–8.4 (m, 5H, Ar-H and 1H, -OH). ^{13}C NMR (DMSO-d_6, 100 MHz): 25.1, 26.2, 45.6, 122.1, 122.8, 123.3, 123.7, 132.4, 132.6, 132.8, 132.9, 136.4, 141.3, 145.8, 150.2, 155.0. ms: m/z = **314 (M$^{+\cdot}$ + 1).** *Anal.* Calcd for $C_{16}H_{15}N_3O_2S$ (313.37): C, 61.32; H, 4.82; N, 13.41; Found: C, 61.33; H, 4.80; N, 13.43.

2-((2,6-dimethylquinolin-4-yl)thio)-6-methylpyrimidin-4-ol (10b). IR (KBr): 3572–3324 cm^{-1} (broad, medium, -OH); ^{1}H-NMR: δ 2.3 (s, 3H, -C**H$_3$**), 2.4 (s, 3H, -C**H$_3$**) 2.6 (s, 3H, -C**H$_3$**), δ 6.6–8.5 (m, 5H, Ar-H and 1H, -OH). ^{13}C NMR (DMSO-d_6, 100 MHz): 25.4, 26.7, 27.5, 122.3, 122.9, 123.6, 123.8, 132.5, 132.7, 132.9, 132.9, 136.7, 141.4,

145.9, 150.7, 155.3. ms: m/z = **298 ($M^{+\cdot}$ + 1).** *Anal*. Calcd for $C_{16}H_{15}N_3OS$ (297.09): C, 64.62; H, 5.08; N, 14.13; Found: C, 64.64; H, 5.04; N, 14.11.

2-((6-fluoro-2-methylquinolin-4-yl)thio)-6-methylpyrimidin-4-ol (10c). IR (KBr): 3574–3325 cm^{-1} (broad, medium, -OH); ^{1}H-NMR: δ 2.3 (s, 3H, -C**H$_3$**), 2.4 (s, 3H, -C**H$_3$**), δ 6.6–8.5 (m, 5H, Ar-H and 1H, -OH)**.** ^{13}C NMR (DMSO-d_6, 100 MHz): 25.2, 26.5, 122.2, 122.6, 123.6, 123.9, 132.6, 132.6, 132.8, 132.9, 136.4, 141.3, 145.9, 150.4, 155.1. ms: m/z = **302 ($M^{+\cdot}$ + 1).** *Anal*. Calcd for $C_{15}H_{12}FN_3OS$ (297.09): C, 59.79; H, 4.01; N, 13.94; Found: C, 59.77; H, 4.03; N, 13.92.

2-((6-chloro-2-methylquinolin-4-yl)thio)-6-methylpyrimidin-4-ol (10d). IR (KBr): 3573–3326 cm^{-1} (broad, medium, -OH); ^{1}H-NMR: δ 2.1 (s, 3H, -C**H$_3$**), 2.2 (s, 3H, -C**H$_3$**), δ 6.4–8.3 (m, 5H, Ar-H and 1H, -OH)**.** ^{13}C NMR (DMSO-d_6, 100 MHz): 25.1, 26.3, 122.2, 122.5, 123.6, 123.7, 132.5, 132.6, 132.7, 132.8, 136.2, 141.4, 145.8, 150.3, 155.3. ms: m/z = **318 ($M^{+\cdot}$ + 1).** *Anal*. Calcd for $C_{15}H_{12}FN_3OS$ (297.09): C, 56.69; H, 3.81; N, 13.22; Found: C, 56.67; H, 3.83; N, 13.20.

2-((6-methoxy-2-methylquinolin-4-yl)thio)quinazolin-4(3H)-one (11a). IR (KBr): 3462–3252 cm^{-1} (broad, medium, -NH), 1693 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H-NMR: δ 2.2 (s, 3H, -C**H$_3$**), 3.8 (s, 3H, -OC**H$_3$**), δ 6.4–8.2 (m, 8H, Ar-H), 10.1 **(s, 1H, -NH, D_2O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 26.5, 40.3, 121.2, 122.4, 123.5, 123.1, 132.2, 132.6, 132.9, 132.9, 141.0, 145.2, 147.5, 160.3. ms: m/z = **350 ($M^{+\cdot}$ + 1).** *Anal*. Calcd for $C_{19}H_{15}N_3O_2S$ (349.41): C, 65.31; H, 4.33; N, 12.03; Found: C, 65.33; H, 4.30; N, 12.01.

2-((2,6-dimethylquinolin-4-yl)thio)quinazolin-4(3H)-one (11b). IR (KBr): 3463–3272 cm^{-1} (broad, medium, -NH), 1696 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H-NMR: δ 2.3 (s, 3H, -C**H$_3$**), 2.5 (s, 3H, -C**H$_3$**), δ 6.2–8.6 (m, 8H, Ar-H), 10.1 **(s, 1H, -NH, D_2O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 24.1, 26.5, 120.2, 123.1, 123.4, 124.0, 132.3, 132.4, 132.4, 132.6, 141.3, 145.1, 147.1, 160.2. ms: m/z = **334 ($M^{+\cdot}$ + 1).** *Anal*. Calcd for $C_{19}H_{15}N_3OS$ (333.41): C, 68.45; H, 4.53; N, 12.60; Found: C, 68.43; H, 4.51; N, 12.62.

2-((6-fluoro-2-methylquinolin-4-yl)thio)quinazolin-4(3H)-one (11c). IR (KBr): 3464–3273 cm^{-1} (broad, medium, -NH), 1690 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H-NMR: δ 2.3 (s, 3H, -C**H$_3$**), δ 6.3–8.2 (m, 8H, Ar-H), 10.3 **(s, 1H, -NH, D_2O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 25.2, 121.4, 122.4, 123.3, 125.1, 131.2, 131.3, 131.3, 132.4, 140.2, 146.1, 147.2, 160.3. ms: m/z = **338 ($M^{+\cdot}$ + 1).** *Anal*. Calcd for $C_{18}H_{12}N_3FOS$ (337.37): C, 64.08; H, 3.59; N, 12.46; Found: C, 64.06; H, 3.57; N, 12.44.

2-((6-chloro-2-methylquinolin-4-yl)thio)quinazolin-4(3H)-one (11d). IR (KBr): 3465–3263 cm^{-1} (broad, medium, -NH), 1693 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H-NMR: δ 2.4 (s, 3H, -C**H$_3$**), δ 6.4–8.1 (m, 8H, Ar-H), 10.2 **(s, 1H, -NH, D_2O exchangeable).** ^{13}C NMR (DMSO-d_6, 100 MHz): 25.1, 122.6, 122.9, 123.5, 125.2, 131.3, 131.5, 131.6, 132.2, 140.4, 146.5, 147.0, 160.4. ms: m/z = **354 ($M^{+\cdot}$ + 1).** *Anal*. Calcd for $C_{18}H_{12}N_3ClOS$ (353.83): C, 61.10; H, 3.42; N, 11.88; Found: C, 61.12; H, 3.40; N, 11.86.

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