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Synthesis, Antimicrobial Activity, and Docking Studies of 2-Mercapto Substituted Quinazolin-4(3*H*)-one and Their Derivatives[1]

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Abstract—An efficient, eco-friendly synthesis of a series of 2-{[3-oxo-3-(alkyl/aryl-1-yl)alkyl]thio}-3-substituted quinazolin-4(3*H*)-ones employing quinazolin-4(3*H*)-one and corresponding halo-acyl/haloalkyl as electrophiles is presented. The products were assayed for anti-bacterial activity on four bacterial species (*Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, and *Staphylococcus aureus*). In-silico molecular docking studies were carried out.

Keywords: quinazolin-4(3*H*)-one derivatives, antibacterial activity, molecular docking

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INTRODUCTION

Among many types of therapeutic activities of quinazolinone derivatives, antibacterial [1–5], is one of the most pronounced. This encouraged us to focus on synthesis of 2-{[3-oxo-3-(alkyl/aryl-1-yl)alkyl]thio}-3-substituted quinazolin-4(3*H*)-ones **3a, 3b**, and **5a–5h** and screening their antibacterial activity.

Over the recent decade tetra *n*-butyl ammonium bromide (TBAB) has emerged as an inexpensive, mild and environmentally compatible phase transfer catalyst (PTC) in various organic transformations [6, 7]. Herein, we focused on phase transfer catalysis for the synthesis of the target compounds. The compounds **3b** and **5h** demonstrated the remarkable activity.

RESULTS AND DISCUSSION

The synthetic approach to 2-mercapto quinazolin-4(3*H*)-one substituted compounds **3a, 3b** and **5a–5h** is presented in Schemes 1 and 2.

The efficient synthesis of compounds **5a–5h** was carried out in water media. For optimizing the process TBAB and NaOH were added but the yield was not improved because of poor solubility of the reactants **1a** and **4** in water. For this reason various mixtures of solvents such as toluene, benzene, THF, and ethanol in presence of TBAB and NaOH in water were tested. Ethanol proved to be the most efficient leading to formation of compound **5a** in 80% yield (Tables 1, 2).

Structures of the products were confirmed by IR, ^{1}H and ^{13}C NMR, and Mass spectra.

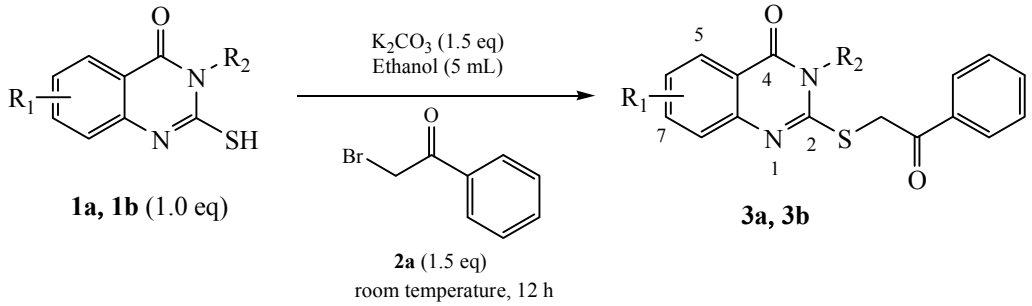
***In vitro* antibacterial studies.** Quinazolin-4(3*H*)-one derivatives were assessed for antibacterial activity against gram-positive and gram-negative human pathogenic bacterial strains by using the paper disc diffusion method. The bacterial strains, *Pseudomonas aeruginosa* (MTCC-424), *Escherichia coli* (MTCC-443), *Bacillus subtilis,* and *Staphylococcus aureus* (MTCC-96), were compared with the standard drugs Norfloxacin and Ofloxacin.

All products exhibited antibacterial activity against gram –ve and gram +ve bacteria (Table 3). Compounds **3a, 3b, 5d–5f, 5h** demonstrated the highest antibacterial activity with all species.

Molecular docking. The synthesized compounds **3a, 3b** and **5a–5h** were studied by the molecular docking method. Molecules were built using Maestro build panel and prepared by LigPrep 2.0 application. Crystal structures of *S. aureus* DNA gyrase (PDB id: 4PLB [8], was retrieved from protein data bank (www.rcsb.org). GLIDE 5.6 [9] was used for molecular docking. The protein was prepared using

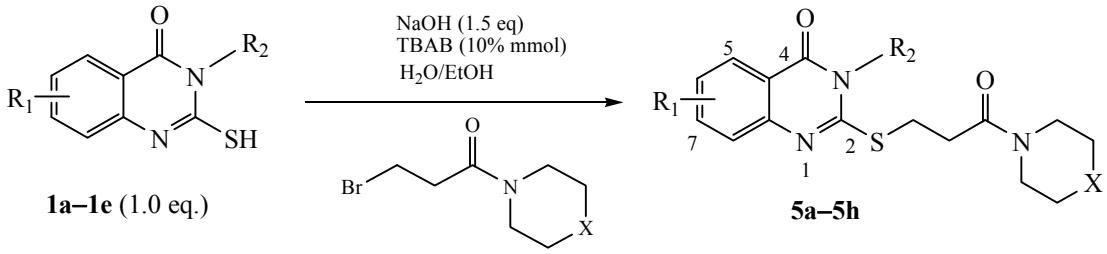
[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 2-[(2-oxo-2-phenylethyl)thio]-3-phenylquinazolin-4(3*H*)-one (**3a, 3b**).



R_1 = 6-Cl, R_2 = Ph (**1a, 3a**), R_1 = 5-I, R_2 = Ph (**1b**), R_1 = 6-I, R_2 = Ph (**3b**).

Scheme 2. Synthesis of 2-{[3-oxo-3-(alkyl/aryl-1-yl)alkyl]thio}-3-substitutedquinazolin-4(3*H*)-ones (**5a–5h**).



R_1 = H; R_2 = Ph^- (**1a**); R_1 = H; R_2 = 4-Cl-$C_6H_4^-$ (**1b**); R_1 = H; R_2 = Ph-CH_2^- (**1c**); R_1 = 6-Cl; R_2 = Ph^- (**1d**); R_1 = 5-I; R_2 = Ph^- (**1e**); R_1 = H, R_2 = Ph, X = CH_2 (**5a**); R_1 = H, R_2 = 4-Cl-$C_6H_4^-$, X = CH_2 (**5b**); R_1 = H, R_2 = 4-Cl-$C_6H_4^-$, X = O (**5c**); R_1 = H, R_2 = Ph-CH_2^-, X = CH_2 (**5d**); R_1 = H, R_2 = Ph-CH_2^-, X = O (**5e**); R_1 = 6-Cl, R_2 = Ph^-, X = CH_2 (**5f**); R_1 = 6-Cl, R_2 = Ph^-, X = O (**5g**); R_1 = 5-I, R_2 = Ph^-, X = O (**5h**).

protein preparation module applying the default parameters. Grid was generated around the active site of the receptor by selecting the co-crystallized ligand. Receptor Van-der-Waals scaling for the nonpolar atoms was fixed as 0.9 [10]. Low-energy conformation of the ligands was selected and docked into the grid using extra-precision (XP) docking mode. Dock pose of each ligand was analyzed for interactions with the receptor.

The binding mode of compound **5h** with DNA gyrase demonstrated one H-bond between O atom of **5h** and H atom of Met 1121 of the receptor, with bond length of 1.95 Å. The co-crystal ligand showed one H-bond interaction between H atom of the crystal

Table 1. Optimization of the synthesis of compound **5a**

Solvent	TBABr, mmol %	Time, h	Yield, %
H_2O	10	6	–
H_2O–Toluene	10	6	20
H_2O–Benzene	10	6	25
H_2O–THF	10	6	45
H_2O–Ethanol	10	6	80

Table 2. Synthetic data for compounds **5a–5h**[a]

Comp. no.	R^1	R^2	X	Yield[b], %	mp, °C
5a	H	Ph	CH_2	80	142–144
5b	H	*p*-Cl-Ph	CH_2	85	165–167
5c	H	CH_2-Ph	CH_2	85	150–152
5d	H	*p*-Cl-Ph	O	85	177–179
5e	H	CH_2-Ph	O	85	158–160
5f	6-Cl	Ph	O	80	198–200
5g	6-Cl	Ph	CH_2	85	178–180
5h	5-I	Ph	O	85	142–144

[a] Reaction conditions: 2-mercapto 3-substituted quinazolin-4(3*H*)-one (1.0 mmol), TBAB (1.5 mmol), K_2CO_3 (1.5 mmol), phenacyl bromide–amidoalkyl (1.5 mmol) in aqueous media.
[b] Isolated yield.

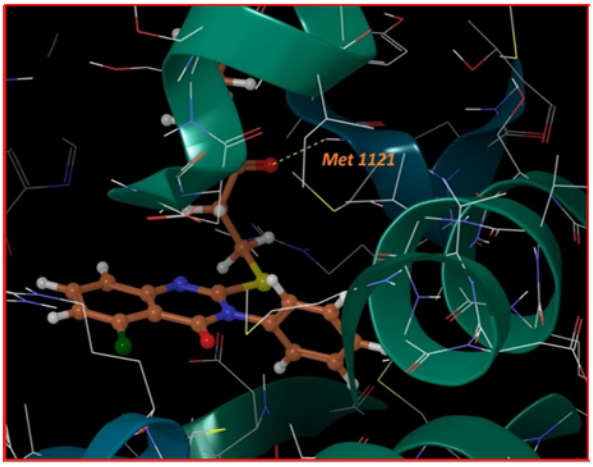


Fig. 1. Dock pose conformation of the most active compound **5h** in the active site of *S. aureus* DNA gyrase (H-bond with Met 1121 amino acid).

ligand and O atom of DNA gyrase, bond length 1.98 Å (Fig. 1). The ligand interaction diagram is presented in Fig. 2. The docking binding energies of all the compounds are tabulated in Table 4.

EXPERIMENTAL

TLC was carried out using pre-coated silica-gel plates (60 F_{254}, 0.2-mm layer, E. Merck). Column chromatography was carried out using silica gel (60–120 mesh). Melting points were determined on a Fischer-Johns apparatus. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrophotometer using KBr discs. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 400 and an Innova 75 MHz spectrometers in $CDCl_3$ media using Me_4Si as an internal standard. ESI-MS spectra were measured on a Finnigan MAT 1020 spectrometer.

Synthesis of 2-[(2-oxo-2-phenylethyl)thio]-3-phenylquinazolin-4(3*H*)-ones (3a, 3b) *(general procedure).* To the mixture of 2-mercapto-3-substituted quinazolin-4(3*H*)-one (**1a**) (1.0 mmol) with K_2CO_3 (1.5 mmol) in ethanol the respective phenacyl bromide **2** (1.5 mmol) was added upon stirring and the following stirred at room temperature lasted for 12 h. The solvent was removed under reduced pressure. The remaining mixture was extracted with ethyl acetate followed by evaporation of the solvent and purification by silica gel (60–120 mesh) using MeOH–$CHCl_3$ (1 : 9) as an eluent to give a corresponding derivative **3a, 3b**.

Synthesis of 2-{[3-oxo-3-(alkyl/aryl-1-yl)alkyl]thio}-3-substituted quinazolin-4(3*H*)-ones (5a–5h). 2-Mercapto-3-substituted quinazolin-4(3*H*)-one (**1a**) (1.0 mmol), NaOH (1.5 mmol) and TBAB (10 mmol %) were dissolved in water–ethanol (3 : 2) mixture. Upon following stirring, a respective amidoalkyl bromide **4**

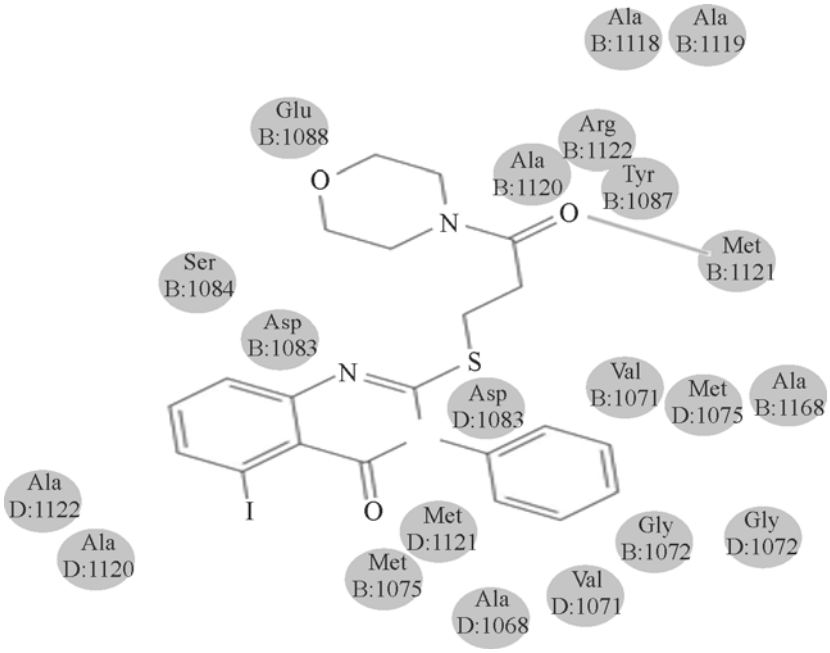


Fig. 2. Ligand interaction diagram for the most active compound **5h**.

(1.5 mmol) was added. The reaction mixture was stirred at room temperature for 12 h, then extracted with ethyl acetate followed by evaporation of the solvent and purification on silica gel (60–120 mesh) using MeOH–$CHCl_3$ (1 : 9) as an eluent to give the corresponding solid, mostly yellow, products **5a–5h** .

6-Chloro-2-[(2-oxo-2-phenylethyl)thio]-3-phenylquinazolin-4(3*H*)-one (3a). Colourless solid, yield 65%, mp 211–213°C. IR spectrum, ν, cm^{-1}: 2912, 1710, 1600, 1500. ^{1}H NMR spectrum, δ, ppm: 8.10 d (2H), 8.05 s (1H), 7.75 m (1H), 7.57–7.63 m (6H), 7.40–7.51 m (5H), 7.06 l (1H), 4.75 s (2H). ^{13}C NMR spectrum, δ, ppm: 193, 166, 162, 147, 137, 136, 134, 132, 130, 129, 128, 127, 124, 121, 120, 36. ESI-HRMS: *m/z:* 406.8805 $[M + H]^+$. $C_{22}H_{15}ClN_2S_2O$.

5-Iodo-2-[(2-oxo-2-phenylethyl)thio]-3-phenylquinazolin-4(3*H*)-one (3b). Pale yellow solid, yield 65%, mp 186–188°C. IR spectrum, ν, cm^{-1}: 3245, 1698, 1600, 1552. ^{1}H NMR spectrum, δ, ppm: 8.0 m (1H), 7.76–7.80 m (2H), 7.46–7.50 m (4H), 7.44–7.7.3 m (2H), 7.31 m (1H), 7.27–7.29 m (8H), 4.33 s (2H). ^{13}C NMR spectrum, δ, ppm: 194, 167, 165, 144, 140, 138, 135, 134, 132, 131, 129, 122, 98, 37. ESI-HRMS: *m/z:* 497.9987 $[M + H]^+$. $C_{22}H_{15}IN_2O_2S$.

2-{[3-Oxo-3-(piperidin-1-yl)propyl]thio}-3-phenylquinazolin-4(3*H*)-one (5a). IR spectrum, ν, cm^{-1}: 3377, 1710, 1594, 1499. ^{1}H NMR spectrum, δ, ppm:

Table 3. Range of minimum inhibitory concentration (MIC) value[a]

Compound	MIC, mg/mL			
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
	gram +ve		gram –ve	
3a	32	34	34	>50
3b	27	26	34	27
5a	>50	50	>50	>50
5b	27	45	34	45
5c	45	45	45	>50
5d	21	26	28	27
5e	35	40	34	35
5f	27	30	24	32
5g	35	45	34	45
5h	27	26	28	27
Norfloxacin	–	≤17	–	≤15
Ofloxacin	≤15	–	≤16	–

[a] The MIC values are interpreted as an average of triplets.

Table 4. Glide score, E model score, and ADME properties of the synthesized compounds

Comp. no.	Glide score (XP)	E model score	MWt	QPlog Po/w[a]	QPlog S[b]	QPP Caco[c]	QPlog BB[d]	QPPMD CK[e]	Human oral absorption[f], %
3a	–5.42	–56.87	393.5	3.51	–4.76	1115.94	–0.475	1142.39	100.00
3b	–5.06	–57.53	427.9	4.02	–5.52	1116.12	–0.316	2819.64	100.00
5a	–4.32	–58.76	429.9	2.89	–4.05	1101.24	–0.289	2788.44	100.00
5b	–4.62	–58.99	407.5	3.83	–4.80	1156.68	–0.589	1147.50	100.00
5c	–3.83	–48.99	409.5	2.70	-3.33	1141.12	–0.563	1134.68	100.00
5d	–5.72	–65.61	427.9	4.20	–5.76	1500.92	–0.203	3506.07	100.00
5e	–4.77	–55.69	429.9	2.89	–4.05	1101.41	–0.289	2788.06	100.00
5f	–4.28	–62.97	521.4	3.05	–4.10	1361.89	–0.183	3528.96	87.93
5g	–5.58	–62.39	406.9	4.22	–4.76	1613.57	–0.198	2966.99	100.00
5h	–6.03	–61.07	498.3	4.74	–5.96	1773.28	–0.302	2584.08	100.00

[a] Predicted octanol/water partition coefficient log *P* (acceptable range 2.0–6.5). [b] Predicted aqueous solubility in mol/L (acceptable range 6.5–0.5). [c] Predicted caco cell permeability in nm/s (acceptable range: <25 is poor and >500 is great). [d] Predicted blood brain barrier permeability (acceptable range 3–1.2). [e] Predicted apparent MDCK cell permeability in nm/s (acceptable range: <25 is poor and >500 is great). [f] Percentage of human oral absorption (acceptable range: <25 is poor and >80% is high).

7.95 s (2H), 7.76 s (1H), 7.44 t (2H), 7.52 m (2H) and 7.3 m (4H), 3.41 m (4H) 3.31 m (2H), 2.73 t (2H), 1.52 m (2H), 1.39 m (4H). ^{13}C NMR spectrum, δ, ppm: 175, 165, 163, 145, 135, 132, 130, 129, 127, 125, 123, 122, 121, 48, 30, 28, 24, 23. ESI-HRMS: *m/z:* 393.5896 $[M + H]^+$. $C_{22}H_{23}N_3O_2S$.

3-(4-Chlorophenyl)-2-{[3-oxo-3-(piperidin-1-yl)-propyl]thio}quinazolin-4(3*H*)-one (5b). IR spectrum, ν, cm^{-1}: 3430, 1726, 1601, 1511. ^{1}H NMR spectrum, δ, ppm: 7.98 d (1H), 7.50 d (3H), 7.48 s (1H), 7.28 d (1H), 7.21(s, 2H), 3.40 s (6H), 2.28 m (4H), 1.53 m (2H), 1.38 m (4H). ^{13}C NMR spectrum, δ, ppm: 174, 163, 160, 148, 134, 131, 129, 128, 127, 123, 122, 121, 50, 34, 27, 25. ESI-HRMS: *m/z:* 427.1134 $[M + H]^+$. $C_{22}H_{22}ClN_3O_2S$.

3-Benzyl-2-{[3-oxo-3-(piperidin-1-yl)propyl]-thio}quinazolin-4(3*H*)-one (5c). IR spectrum, ν, cm^{-1}: 3080, 1702, 1605, 1518, 1403. ^{1}H NMR spectrum, δ, ppm: 7.98 d (1H), 7.78 m (1H), 7.43 d (1H), 7.23–7.37 m (6H), 5.67 s (2H), 3.46 m (6H), 2.78 t (4H), 1.57 m (2H), 1.48 m (4H). ^{13}C NMR spectrum, δ, ppm: 176, 160, 155, 148, 141, 134, 130, 129, 128, 126, 124, 121, 47, 44, 33, 29, 27, 26. ESI-HRMS: *m/z:* 407.1734 $[M + H]^+$. $C_{22}H_{25}N_3O_2S$.

3-(4-Chlorophenyl)-2-[(3-morpholino-3-oxopropyl)-thio]quinazolin-4(3*H*)-one (5d). IR spectrum, ν, cm^{-1}: 2924, 1721, 1606, 1444. ^{1}H NMR spectrum, δ, ppm: 8.07 s (1H), 7.65 s (1H), 7.47 m (3H), 7.29 m (3H), 3.55 m (4H), 3.41 d (6H), 2.75 t (2H). ^{13}C NMR spectrum, δ, ppm: 170, 165, 160, 146, 136, 132, 130, 129, 128, 127, 123, 122, 120, 64, 56, 30, 27. ESI-HRMS: *m/z:* 429.0987 $[M + H]^+$. $C_{21}H_{20}ClN_3O_3S$.

3-Benzyl-2-[(3-morpholino-3-oxopropyl)thio]-quinazolin-4(3*H*)-one (5e). IR spectrum, ν, cm^{-1}: 2923, 1708, 1601, 1521, 1343. ^{1}H NMR spectrum, δ, ppm: 7.95 s (1H), 7.75 m (1H), 7.41 d (1H), 7.34–7.24 m (6H), 5.68 s (2H), 3.53 s (4H), 3.41 s (6H), 2.76 s (2H). ^{13}C NMR spectrum, δ, ppm: 172, 162, 153, 143, 140, 134, 129, 128, 127, 123, 122, 65, 47, 45, 33, 32, 25. ESI-HRMS: *m/z:* 409.1532 $[M + H]^+$. $C_{22}H_{23}N_3O_3S$.

6-Chloro-2-[(3-morpholino-3-oxopropyl)thio]-3-phenylquinazolin-4(3*H*)-one (5f). IR spectrum, ν, cm^{-1}: 2923, 1686, 1554, 1430. ^{1}H NMR spectrum, δ, ppm: 8.08 d (1H), 7.66 s (1H), 7.41–7.53 m (5H), 3.33–3.53 m (9H), 2.76 d (J = 6.8 Hz, 2H) 1.35–1.59 m (6H). ^{13}C NMR spectrum, δ, ppm: 173, 167, 165, 142, 135, 132, 131, 130, 129, 123, 122, 121, 48, 30, 28, 24, 23. ESI-HRMS: *m/z:* 429.0985 $[M + H]^+$. $C_{21}H_{20}ClN_3O_3S$.

6-Chloro-2-{[3-oxo-3-(piperidin-1-yl)propyl]thio}-3-phenylquinazolin-4(3*H*)-one (5g). IR spectrum, ν, cm^{-1}: 2924, 1708, 1606, 1541, 1408. ^{1}H NMR spectrum, δ, ppm: 8.09 d (1H), 7.64 s (1H), 7.41–7.56 m (6H), 3.31–3.48 m (9H), 2.75 t (2H), 1.55 s (2H), 1.39–1.46 m (4H). ^{13}C NMR spectrum, δ, ppm: 173, 167, 165, 142, 135, 132, 131, 129, 122, 121.5, 121, 48, 30, 28, 24, 23. ESI-HRMS: *m/z:* 427.1134 $[M + H]^+$. $C_{22}H_{22}ClN_3O_2S$.

5-Iodo-2-[(3-morpholino-3-oxopropyl)thio]-3-phenylquinazolin-4(3*H*)-one (5h). IR spectrum, ν, cm^{-1}: 3221, 1680, 1560, 1362. ^{1}H NMR spectrum, δ, ppm: 7.96 d (1H), 7.71 m (1H), 7.22–7.33 m (8H), 3.7 s (2H), 3.6 s (4H), 3.40 s (6H), 2.74 d (2H). ^{13}C NMR spectrum, δ, ppm: 172, 162, 153, 143, 141, 134, 129, 128, 127,124, 123, 121, 64, 47, 44, 33, 32, 25. HRMS: *m/z:* 521.0312 $[M + H]^+$. $C_{21}H_{20}IN_3O_3S$.

Antibacterial tests. Inoculation of all microbes obtained from Microbial Type Culture Collection (MTCC) in autoclaved LB broth media and incubated over night at 37°C for bacterial growth. From that 0.2 ml of the bacterial culture was taken and inoculated by using spreader on freshly prepared autoclaved agar plates, Petri dishes. After sterilizing of the 5 mm sample disc, the compounds **3a, 3b**, and **5a–5h** were dissolved in DMSO and kept on microbial plate along with positive controls Norfloxacin for *Staphylococcus, Pseudomonas* and Ofloxacin for *Bacillus* and *E. coli*. Incubation was carried out at 37°C overnight in a BOD incubator. Zones of inhibition were measured. The minimum inhibitory concentration (MIC) values were determined by the micro broth dilution method.

CONCLUSIONS

We have synthesized 2-[3-(alkyl/aryl-1-yl)thio]-3-substituted quinazolin-4(3*H*)-ones (**3a, 3b, 5a–5h**) according to the new protocol using TBAB as PTC in water–ethanol media with excellent yields. Antibacterial activity tests of the products indicated compounds **3b, 5h** as highly active. The binding mode of the synthesized compounds with protein active site was predicted using the molecular docking technique.

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