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**ABSTRACT**

A series of structurally diverse and newly designed N-(2-methylaryl-4-oxoquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl) benzenesulfonamide derivatives 7a-7j were synthesized under microwave irradiation. They were synthesized using 2-acetamidobenzoic acid derivatives 1a-1j via intermediate benzenesulfonamide substituted quinazolinone derivatives 5a-5j. 5a-5j was diazotized and coupled with rhodanine to obtain compounds 7a-7j in good amount of yield. The structure of entitle compounds have been evaluated on the basis of various spectroscopic techniques and analytical methods as well as all the synthesized compounds were subjected to \textit{in vitro} antibacterial and antifungal activities. All the compounds displayed moderate to good \textit{in vitro} antimicrobial activity by broth micro dilution method against pathogenic bacteria (S. aureus, B. subtilis, B. megaterium, E. coli, P. vulgaris, P. aeruginosa) and fungus (A. niger, A. clavatus, C. albicans) species.

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1. Introduction

Heterocyclic scaffold including nitrogen, sulfur and oxygen has been under exploration due to their significant therapeutic and medicinal properties. Among these types of molecules, 4-thiazolidinones have displayed various important biological activities. Especially rhodanine (2-thioxothiazolidine-4-ones) derivatives represent privileged scaffolds in drug discovery, due to the presence of >N–C–S linkage \cite{1} and have been found to be important both structurally as well as pharmacologically. Its derivatives have significant antitubercular activity \cite{2} and used in the treatment of diabetic complications \cite{3}. Some of them are under clinical trials as a potential thromimatic, antimicrobial, antiviral, anti-ischaemeric, cardiovascular, anticancer and thrombolytic drugs \cite{3}. They also displayed a wide range of activities like anti-HIV-1 \cite{4, 5}, anticancer and antiangiogenic \cite{6}.

Moreover, quinazolinone and its derivatives comprise an important class of heterocyclic molecules. In consideration of extensive range of bioactivities, this class of molecules reside an important role in medicinal and pharmaceutical chemistry. Quinazolinone having a broad spectrum of biological and pharmacological properties, as analgesic \cite{7}, antimicrobial and antitubercul\textsuperscript{a} \cite{8, 9}, antitumor \cite{10}, anticancer \cite{11}, anti-inflammatory \cite{12}, anticonvulsant \cite{13}, antimalarial and anthistamine \cite{14}.

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Furthermore, there are many reports regarding synthesis of 4-thiazolidinones derivatives \cite{15-20} but no reports are available in which rhodanine is substituted at 3\textsuperscript{rd} position of quinazolinone through hydrazino benzenesulfonamide linkage. Looking to the above mentioned literature and our ongoing research in the field of quinazolinone derivatization \cite{21, 22}, we are reporting here synthesis of various rhodanine substituted quinazolinone derivatives linked through hydrazino benzenesulfonamide, while some of these compounds showed excellent antimicrobial activity.

2. Experimental

2.1 Material and measurements

All chemicals were purchased from Spectro chem. Ltd. (Mumbai, India) and were used without further purification. Solvents employed were distilled, purified and dried by standard procedures prior to use \cite{23}. Melting points of the synthesized compounds were determined in open capillary tube method and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC on alluminium plates coated with silica gel 60 F\textsubscript{254}, 0.25 mm thickness purchased from E. Merck Ltd., Mumbai-India). The mobile phase was chloroform and methanol (9:1), and detection of the components was done under UV light or explore in Iodine chamber. Infrared (IR) spectra were recorded as potassium bromide pellets using a Shimadzu 8501 Fourier transform infrared (FTIR)
Spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCE II 400-MHz NMR spectrometer (Bruker Corporation, Billerica, MA, USA), with chemical shift in δ (ppm) downfield from TMS as an internal reference and DMSO-d$_6$ used as solvent. Carbon, hydrogen and nitrogen elemental analysis were estimated by PerkinElmer 2400-II CHN elemental analyzer, USA. The electro-spray ionization mass spectra in positive mode were recorded on a Shimadzu LC-MS 2010 eV mass spectrophotometer using acetonitrile.

All the microwave assisted reactions were carried out at atmospheric pressure using a multimode microwave reactor (Scientific Microwave Synthesis System, Model: Cata-R, Catalyst Systems, Pune-India) with attachment of glass vessel prolonged by a reflux condenser. The mixture was then heated under atmospheric pressure using a multimode microwave reactor (frequency of 2450 MHz having an output energy range of 140 to 700 Watts, and the temperature was monitored with an external flexible probe.

2.2 General procedure for the synthesis of 4-amino-N-(2-methylaryl-4-oxoquinazolin-3(4H)-yl)benzenesulfonamide derivatives (5a-5j)

It was synthesized by adapting a modified strategy of our earlier reported work [24], which was optimized (Table 1) for utilizing milder reaction conditions to give higher amount of yields.

Step–I: Synthesis of N-(4-(4-oxo-2-methylaryl substituted quinazolin-3(4H)-yl)sulfamoyl)phenylacetamides (4a-4j)

Appropriate N-acylanthranilic acid (1a-1j) (2 mmol) and 4-acetamidobenzenesulfonyl hydrazide (2) (2.6 mmol) were taken in a solution of DMF (0.5 mL) and pyridine (0.4 mmol) contained in a two-neck round bottomed flask fitted with a device condenser. The mixture was then heated under microwave irradiation at 35 W for an appropriate time (Table 2, Step – I). After cooling, the reaction mass was dissolved in ethyl acetate (40 mL) and washed with distilled water (20 mL), dil. HCl (2 × 20 mL), aq. NaHCO$_3$ (2 × 20 mL) and distilled water (20 mL) sequentially by liquid–liquid extraction. The organic layer was dried and the resulting crude product was by recrystallized from ethanol.

Step–II: Hydrolysis of 4a-4j

The product obtained in step – I (4a-4j) (1 mmol) was taken in a two-necked round bottomed flask containing 10 mL 50% HCl solution in 10 mL ethanol. The mixture was then irradiated under microwave for an appropriate time (Table 2, Step – II) with a power of 140 W. The clear solution thus obtained was cooled, diluted with 20 mL distilled water and pH was adjusted to 8 using saturated NaHCO$_3$ solution. The precipitated product was filtered, washed with distilled water and recrystallized from ethanol. The possible synthetic route is shown in Scheme 1.

Caution: All the reactions shown here were performed in an open reflux system. It is not recommended, to perform the reactions in a sealed vessel due to the possibility of generation of high pressure, as the reaction involves the use of HCl. It is recommended to use co-solvent such as ethanol in order to avoid bumping of reaction mass during microwave irradiation.

2.2.1.4-Amino-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)benzenesulfonamide (5a).

mp 217-218 °C. ESI MS (m/z): 330.8 [M+H]+.

2.2.2. 4-Amino-N-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)benzenesulfonamide (5b).

mp 187-189 °C. ESI MS (m/z): 409.2, 411.3 [M]+.

2.2.3. 4-Amino-N-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4H)-yl)benzenesulfonamide (5c).

mp 212-214 °C. ESI MS (m/z): 488.4, 490.4, 492.4 [M]+.

2.2.4. 4-Amino-N-(6-nitro-4-oxo-2-phenylquinazolin-3(4H)-yl)benzenesulfonamide (5d).

mp 206-209 °C. ESI MS (m/z): 438.2 [M+H]+.

2.2.5. 4-Amino-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzenesulfonamide (5e).

mp 166-168 °C. ESI MS (m/z): 393.4 [M+H]+.

2.2.6. 4-Amino-N-(6-bromo-4-oxo-2-phenylquinazolin-3(4H)-yl)benzenesulfonamide (5f).

mp 214-217 °C. ESI MS (m/z): 471.3, 473.3 [M]+.

2.2.7. 4-Amino-N-(6,8-dibromo-4-oxo-2-phenylquinazolin-3(4H)-yl)benzenesulfonamide (5g).

mp 219-221 °C. ESI MS (m/z): 548.3, 550.3, 552.3 [M]+.

2.2.8. 4-Amino-N-[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]benzenesulfonamide (5h).

mp 175-179 °C. ESI MS (m/z): 426.9, 428.9 [M]+.

2.2.9. 4-Amino-N-[6-bromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]benzenesulfonamide (5i).

mp 186-187 °C. ESI MS (m/z): 503.8, 505.8, 507.8 [M]+.

2.2.10. 4-Amino-N-[6,8-dibromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]benzenesulfonamide (5j).

mp 183-184 °C. ESI MS (m/z): 582.5, 584.5, 586.5, 588.5 [M]+.

Scheme 1 Proposed synthetic route for the preparation of compound 5a-5j
The solid yellow product obtained was filtered, washed with cold water and recrystallized from ethanol to give the corresponding hydrazono derivatives 7a-7j. The synthetic route is shown in Scheme 2.

2.4.1. N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzenesulfonamide (7a). Yield 71%, pale yellow, mp 245 °C. (KBr, v, cm⁻¹): 3174 (C-H, aromatic stretching), 1699 (-C=O stretching), 1601 (-C=C, aromatic stretching), 1551 (N-H aromatic band), 1470 (C-H of aliphatic), 1221 (-C=S stretching), 1154 (S=O asymmetric stretching double band). Anal. Calcd (%) for C₁₉H₁₄BrN₆O₄S₃: C, 34.97; H, 2.27; N, 17.11; S, 20.72. Found: C, 45.36; H, 2.18; N, 17.81; S, 20.30. ¹H-NMR (DMSO-d₆): δ 12.79 (1H, s), 10.80 (1H, s), 8.81 (1H, s), 8.82 (1H, dd, J = 8.0, 1.2 Hz), 8.06 (1H, td, J = 8.0, 1.2 Hz), 7.78 (1H, dd, J = 8.0, 1.2 Hz), 7.70 (1H, td, J = 7.6, 1.2 Hz), 7.59 (2H, dd, J = 8.8, 2.1 Hz), 6.81 (2H, dd, J = 10.4, 2.1 Hz), 2.51 (3H, s); ¹³C-NMR (DMSO-d₆): δ 191.10, 159.27, 158.23, 158.17, 157.73, 153.58, 147.11, 143.88, 134.45, 131.05, 126.17, 125.81, 123.70, 121.03, 113.06, 22.63; ESI MS m/z: 474.9 [M+H]⁺.

2.4.2. N-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzenesulfonamide (7b). Yield 78%, dark yellow, mp 234 °C. (KBr, v, cm⁻¹): 3204 (-C-H, aromatic stretching), 1692 (-C=O stretching), 1601 (-C=C, aromatic stretching), 1533 (N-H aromatic band), 1463 (C-H of aliphatic), 1201 (-C=S stretching), 1151 (S=O asymmetric stretching double band). Anal. Calcd (%) for C₁₉H₁₂Br₂N₆O₄S₃: C, 34.19; H, 1.91; N, 15.19; S, 17.38. Found (%): C, 39.10; H, 2.47; N, 15.09; S, 17.34. ¹H-NMR (DMSO-d₆): δ 12.86 (1H, s), 10.98 (1H, s), 8.86 (1H, s) 8.49 (1H, d, J = 2.1 Hz), 7.65 (1H, d, J = 10.4 Hz) 7.62 (1H, dd, J = 10.4, 2.1 Hz), 7.36 (2H, dd, J = 8.8, 2.1 Hz), 6.58 (2H, dd, J = 8.8, 2.1 Hz), 2.45 (3H, s); ¹³C-NMR (DMSO-d₆): δ 211.17, 165.27, 156.24, 154.78, 153.3, 148.38, 142.78, 134.19, 129.27, 127.33, 126.82, 125.25, 123.33, 121.17, 116.22, 24.23; ESI MS m/z: 553.9, 555.9 [M].

2.4.3. N-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzenesulfonamide (7c). Yield 67%, dark yellow, mp 239 °C. (KBr, v, cm⁻¹): 3307 (C-H, aromatic stretching), 1697 (-C=O stretching), 1601 (-C=C, aromatic stretching), 1542 (N-H aromatic band), 1456 (C-H of aliphatic), 1201 (-C=S stretching), 1155 (S=O asymmetric stretching double band). Anal. Calcd (%) for C₁₉H₁₀Br₂N₆O₄S₃: C, 34.19; H, 1.91; N, 13.29; S, 15.21. Found (%): C, 34.29; H, 1.88; N, 13.32; S, 15.30. ¹H-NMR (DMSO-d₆): δ 12.78 (1H, s), 10.87 (1H, s), 8.52 (1H, s) 8.43 (1H, d, J = 2.4 Hz), 8.13 (1H, d, J = 2.4 Hz), 7.46 (2H, dd, J = 8.8, 2.1 Hz), 6.57 (2H, dd, J = 10.8, 2.1 Hz), 2.47 (3H, s); ¹³C-NMR (DMSO-d₆): δ 187.37, 167.28, 163.93, 163.43, 154.68, 152.63, 138.38, 135.89, 133.48, 129.76, 128.22, 125.53, 121.13, 112.18, 23.99; ESI MS m/z: 631.8, 633.8, 635.8 [M].
2.4.4. N-(6-nitro-4-oxo-2-phenylquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzene sulfonamide (7d). Yield 78%, bright yellow, mp 169 °C. (KBr, ν, cm⁻¹): 3265 (C-H, aromatic stretching), 1691 (-C=O stretching), 1600 (-C=C, aromatic stretching), 1521 (N-H aromatic band), 1443 (C-H of aliphatic), 1181 (-C=S stretching), 1168, 1153 (S-O asymmetric stretching double band). Anal. Calcd (%) for C₂₃H₁₆N₆O₄S₃: C, 51.48; H, 3.01; N, 13.65; S, 15.63. Found (%): C, 44.64; H, 2.55; N, 13.77; S, 15.79. ¹H-NMR (DMSO-d₆): δ 12.84 (1H, s), 10.79 (1H, s), 8.83 (1H, s), 6.5-8.5 (12H, m); ¹³C-NMR (DMSO-d₆): δ 173.96, 125.96, 123.57, 121.76, 115.12; ESI MS m/z: 617.8 [M⁺].

2.4.5. N-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzene sulfonamide (7e). Yield 80%, yellow, mp 227 °C. (KBr, ν, cm⁻¹): 3243 (C-H, aromatic stretching), 1691 (-C=O stretching), 1602 (-C=C, aromatic stretching), 1528 (N-H aromatic band), 1456 (C-H of aliphatic), 1210 (-C=S stretching), 1155 (S-O asymmetric stretching double band). Anal. Calcd (%) for C₂₃H₁₅N₇O₆S₃: C, 47.50; H, 2.60; N, 14.72; S, 16.85. Found (%): C, 48.34; H, 2.58; N, 14.69; S, 16.90. ¹H-NMR (DMSO-d₆): δ 12.85 (1H, s), 10.83 (1H, s), 8.89 (1H s), 6.6-8.2 (12H, m); ¹³C-NMR (DMSO-d₆): δ 214.29, 161.83, 152.38, 150.53, 149.42, 146.43, 137.82, 137.58, 134.71, 132.67, 131.65, 129.67, 127.33, 126.77, 126.12, 125.36, 124.85, 123.47, 110.67; ESI MS m/z: 570.1, 572.1 [M⁺].

2.4.9. N-(6-bromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzenesulfonamide (7f). Yield 72%, light yellow, mp 187 °C. (KBr, ν, cm⁻¹): 3274 (C-H, aromatic stretching), 1693 (-C=O stretching), 1602 (-C=C, aromatic stretching), 1541 (N-H aromatic band), 1456 (C-H of aliphatic), 1176 (-C=S stretching), 1151 (S-O asymmetric stretching double band). Anal. Calcd (%) for C₂₃H₁₄BrClN₆O₄S₃: C, 42.53; H, 2.19; N, 12.88; S, 14.84. ¹H-NMR (DMSO-d₆): δ 12.89 (1H, s), 10.88 (1H, s), 8.94 (1H s), 6.6-8.4 (11H, m); ¹³C-NMR (DMSO-d₆): δ 210.46, 163.62, 158.62, 157.76, 153.83, 149.02, 144.78, 143.37, 125.94, 123.64, 123.14, 121.93, 128, 124.57, 123.53, 121.76, 115.12; ESI MS m/z: 650, 652, 654 [M⁺].

2.5.4. N-(6,8-dibromo-4-oxo-2-phenylquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzenesulfonamide (7g). Yield 77%, deep yellow, mp 211 °C. (KBr, ν, cm⁻¹): 3311 (C-H, aromatic stretching), 1698 (-C=O stretching), 1602 (-C=C, aromatic stretching), 1525 (N-H aromatic band), 1471 (C-H of aliphatic), 1187 (-C=S stretching), 1181, 1155 (S-O asymmetric stretching double band). Anal. Calcd (%) for C₂₃H₁₄Br₂ClN₆O₄S₃: C, 42.50; H, 2.17; N, 12.93; S, 14.80. Found (%): C, 42.53; H, 2.19; N, 12.88; S, 14.84. ¹H-NMR (DMSO-d₆): δ 12.89 (1H, s), 10.88 (1H, s), 8.94 (1H s), 6.5-8.4 (11H, m); ¹³C-NMR (DMSO-d₆): δ 210.46, 163.62, 158.62, 157.76, 153.83, 149.02, 144.78, 143.37, 125.94, 123.64, 123.14, 121.93, 128, 124.57, 123.53, 121.76, 115.12; ESI MS m/z: 650, 652, 654 [M⁺].

2.5.4. N-(6,8-dibromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-4-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)hydrazinyl)benzenesulfonamide (7h). Yield 72%, brownish yellow, mp 227 °C. (KBr, ν, cm⁻¹): 3237 (C-H, aromatic stretching), 1699 (-C=O stretching), 1600 (-C=C, aromatic stretching), 1534 (N-H aromatic band), 1443 (C-H of aliphatic), 1181 (-C=S stretching), 1179, 1157 (S-O asymmetric stretching double band). Anal. Calcd (%) for C₂₃H₁₄BrClN₆O₄S₃: C, 37.90; H, 1.80; N, 11.53; S, 13.20. Found (%): C, 37.73; H, 1.87; N, 11.28; S, 13.43. ¹H-NMR (DMSO-d₆): δ 12.82 (1H, s), 10.85 (1H, s), 8.91 (1H, s), 8.41 (1H, d, J = 2.4 Hz), 8.08 (1H, d, J = 4.6 Hz), 7.88 (2H, dd, J = 8.0, 2.8 Hz), 7.39 (2H, dd, J = 8.0, 2.8 Hz), 7.28 (2H, dd, J = 8.8, 2.8 Hz), 6.53 (2H, dd, J = 8.8, 2.8 Hz); ¹³C-NMR (DMSO-d₆): δ 216.46, 162.67, 159.63, 158.74, 153.45, 152.78, 147.24, 142.47, 138.34, 133.97, 133.56, 132.32, 131.78.
130.35, 126.78, 125.87, 124.45, 121.43, 117.12, 113.21; ESI MS m/z: 727.9, 729.9, 731.9, 733.9 [M]+.

2.4 In vitro antimicrobial studies
All the synthesized compounds were screened for their in vitro antimicrobial activities against selected pathogenic bacterial and fungal strains to determine minimum inhibitory concentrations (MIC) by broth micro dilution method [27] using Methaqualone and Sulfanilamide as reference drugs of parent moieties, while Streptomycin and Nystatin was employed as a standard antibacterial drug. The in vitro antimicrobial activities of all the synthesized compounds were screened for their antibacterial against Staphylococcus aureus, Bacillus subtilis, Bacillus megaterium (Gram Positive) and Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa (Gram Negative), where antifungal activity was assessed against Aspergillus niger, Aspergillus clavatus and Candida albicans using the broth dilution method [26]. All the ATCC culture was collected from institute of microbial technology, Bangalore. 2% Luria broth solution was prepared in distilled water while, pH of the solution was adjusted to 7.4±0.2 at room temperature and sterilized by autoclaving at 15 lb pressure for 25 min. The tested bacterial and fungal strains were prepared in the luria broth and incubated at 37 °C and 200 rpm in an orbital incubator for overnight. Sample solutions were prepared in DMSO for various concentration. The standard drug solution of Streptomycin (antibacterial drug) and Nystatin (antifungal drug) were prepared in DMSO. Serial broth micro dilution was adopted as a reference method. 10 µL solution of test compound was inoculated in 5 mL luria broth for each concentration respectively and additionally one test tube was kept as control. Each of the test tubes was inoculated with a suspension of standard microorganism to be tested and tubes was kept as control. Each of the test tubes was inoculated in 5 mL luria broth for each concentration respectively and additionally one test tube was kept as control. Each of the test tubes was inoculated with a suspension of standard microorganism to be tested and incubated at 37 °C for 24 h. At the end of the incubation period, the tubes were examined for the turbidity. Turbidity in the test tubes indicated that microorganism growth has not inhibited by the antibiotic contained in the medium at the test concentration. The antimicrobial activity tests were performed in triplicate and the deviation for any triplicate results was not more than ± 1% to 5% while average MIC values of the compounds are represented in Table 3.

3. Results and discussion
3.1 Chemistry
The key objective of the present study was to synthesize and investigate the antimicrobial activities of rhodanine substituted quinazolinone molecules. Synthesis of the intermediate and target molecules was performed according to the reactions outlined in Scheme 1 and 2. Majority of reported 4(3H)-quinazolinone derivatives were synthesized either from antranilic acid or its derivatives. There are number of reports on one pot synthesis of quinazoline-4(3H)-ones under solvent free conditions but, it involves the use of alkyl orthoesters which limits the variety of substitutions at 2nd position. Recently, Zhou and Gregor et al. developed an outstanding general method for the synthesis of 3-sulfonamide substituted quinazolinone derivatives by condensation of benzoaxazinones (3) and substituted sulfonyl hydrazides under solvent free conditions at 130 °C [28] (Scheme 1).

### Table 3 Antimicrobial activities of the synthesized compounds 7a-7j

<table>
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<th>Compound</th>
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<th>Gram negative bacteria</th>
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SA = S. aureus, BS = B. subtilis, BM = B. megaterium, EC = E. coli, PV = P. vulgaris, PA = P. aeruginosa, AN = A. niger, AC = A. clavatus, CA = C. albicans, Qm = Methaqualone, SF = Sulfanilamide, Sm = Streptomycin, Ny = Nystatin

However, this method was not recommended upon a scale up (> 0.2 mmol) because of the possible uncontrollable decomposition of the sulfonflylhydrazides. They have suggested that, a stepwise process using DMF as a solvent might have the potential for a safe scale-up. A pilot reaction was therefore attempted using equiv molar amount of benzoaxazine (3a, R2=methyl, R6=R8=H) and 4-acetamidobenzenesulfonyl hydrazide (2) in anhydrous DMF. In the beginning, mixture was shaken at room temperature [28] for 2 days, but tetramide...
formation as well as cyclized product 4a was not detected. Additionally, upon heating this mixture for 24 h at 80 °C [28], a mixture of tetramide (52%) and cyclized product 4a (28%) was isolated. Subsequently, we investigated the effect of microwave irradiation on the reaction rate as well as yield of the cyclized product.

Upon heating the equivalent amounts of 3a and 2 in DMF under the microwave irradiation (350 W), some improvement was observed in the yield (64%) of cyclized product (4a). Nevertheless, when pyridine was used as a solvent, formation of tetramide was significantly lower but the reaction required quite longer time to complete, as well as more decomposition of 2 was observed. Moreover, it was assumed that the yield of the desired quinazolinones (4) could be increased with the higher equivalents of 2, as it decomposes during the reaction. Therefore, it was thought worthwhile to optimize the reaction conditions by varying the reactant ratio and molecular equivalents of pyridine. The optimized reaction condition involving 1.3 equivalent of 2 and 0.2 equivalent of pyridine, resulted in 96% isolated yield of 4a (entry 3, Table 1). We envisioned that cyclization of tetramide leading to quinazolone 4a was presumably promoted by pyridine. However, the reaction proceeded gradually when pyridine alone was used as a solvent. This may be attributed to the less dielectric constant of pyridine. Furthermore, there are many instances which report the cyclization of diamides to quinazolinones under basic conditions [29, 30]. Therefore, it was decided to investigate effect of various bases e.g. triethyl amine (Et 3N), N-methyl morpholine (NMM), 4-(dimethylamino)pyridine (DMAP), N,N-diisopropylethylamine (DIPEA), on the efficiency of cyclization, hoping to identify an ideal combination that could optimize the reaction condition and contribute eventually to higher conversion of quinazolone. As shown in Table 1, a comparable yield of 4 was observed when Et 3N or NMM was used as a base. When DMAP or DIPEA was used as a base, a little decomposition of benzoxazinones to the corresponding N-acylanthranilic acids was observed, which led to the lower yield of 4. All other quinazolinone derivatives were synthesized using 1.3 equivalents of 2 in presence of 0.2 equivalent of pyridine under microwave irradiation at 350 W (Table 1). Once the quinazolinones were synthesized, then hydrolysis of N-(4-(N-(2-substituted-4-oxoquinazolin-3(4H)-yl)sulfamoyl)phenyl)acetamide (4a-4j) was carried out under acidic condition using microwave irradiation at 140W (Scheme 1). All of the synthesized compounds were characterized by their physical, analytical and spectral data given in experimental section. The ESI-MS and NMR (1H and 13C) spectral data of all the synthesized compounds were in good agreement with the structure assigned. Further, in the MS-ESI with positive mode spectra exhibited molecular ion peak ([M+H] +), appeared at different intensities, confirmed the exact mass or molecular weights of the examined compounds 7a-7j, while appearance of a characteristic two isotope peak ([M+H]+ 13C) along with molecular ion peak ([M+H] +) in an intense ratio almost 3:1 or 1:1 to the molecular ion peak confirmed the presence of halogen (Cl or Br) atoms of high abundance nature.

3.2 In vitro antimicrobial activities

The observation of the data (Table 3) on the preliminary in vitro antimicrobial evaluations of the compounds 7a-7j revealed that all the screened compounds found to possess varied degree of antibacterial and antifungal activities as apparent from their MIC values in μg/mL. Among the screened compounds, most of the compounds have shown more or equal antimicrobial activities compare to the reference drugs of parent moieties Methaqualone (Qm) and Sulfanilamide (Si), while a very few of the screened compounds found to be equivalent to the standard drugs, Streptomycin (Sm) and Nystatin (Ny). From the results of in vitro antibacterial activity data, it was found that compounds 7e, 7h and 7j demonstrated excellent activity against E. coli and P. vulgaris bacterial species. In general, compounds showed more selectivity against Gram negative over Gram positive species amongst all the bacterial strains. From the results of in vitro antifungal activity data, it was found that compounds 7b-7j demonstrated high to fair activity against both the fungal species. In general, compounds were enormously active against all the fungal strains and particularly effectiveness for A. niger is more than C. albicans. All the compounds were screened for their in vitro antimicrobial activities and results revealed that the group 4-chlorophenyl substitution at the 2nd position in quinazolin-4(3H)-one nucleus led to increase their biological activities.

4. Conclusion

In summary, a series of new rhodanine substituted 2,3-disubstituted quinazolin-4(3H)-one derivatives have been synthesized by adapting a modified strategy which has the improvement of employing non-dramatic reaction conditions to give good amount of yields. All the compounds were screened for their in vitro antimicrobial activities and results revealed that the group 4-chlorophenyl substitution at the 2nd position in quinazolin-4(3H)-one nucleus led to increase their biological activities. Nevertheless, further diversity in structural modifications are planned to enhance these activities.

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