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Synthesis and Antimicrobial Study of Pyrimidinone Substituted 4(3H)-Quinazolinone Derivatives

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Abstract

A series of structurally diverse and newly designed pyrimidinone substituted 4(3*H*)-Quinazolinone derivatives **6a–6j** were synthesized in a simple and facile manner under both conventional and microwave heating conditions. Entitled compounds **6a–6j** were synthesized using *N*-acylanthranilic acid derivatives **1a**–**1j** and hydrazinylbenzenesulfonamide**2** as a key starting materials, which under goes hierarchy of the reactions *via* different intermediate stapes; quinazolinone derivatives **3a**–**3j** and hydrazonoquinazolinone derivatives **5a–5j**. All the synthesized compounds are 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 *in vitro* antibacterial activities. Some of the compounds displayed moderate to good *in vitro* antimicrobial activity by broth micro dilution method against pathogenic bacteria (*S. aureus*,*B. subtilis*, *B. megaterium*, *E. coli*, *P. vulgaris*, *P. aeruginosa*) species.

Keywords: Quinazolinone; Pyrimidinone; Antimicrobial activity; Microwave heating

Introduction

Heterocyclic scaffold has been under discovery due to their considerable therapeutic and medicinal importance. One of such heterocycles 2-pyrimidinone, while not naturally occurring, are receiving increased attention because of their wide-ranging biological activity like, an efficient inhibitor of DNA synthesis in *E. coli,* inhibitors of the enzyme *cytidinedeaminase*, and as metaphase inhibitors. Such pyrimidinone derivatives and the pharmaceutical acceptable salts thereof having remarkable antagonistic action against angiotensin II receptor, thereby, being useful in treating cardiovascular disease caused by binding angiotensin II to its receptor. Antitumor activity of pyrimidinones derivatives have shown statistically significant synergism with cyclophosphamide (CY) against antitumor / P388 leukemia etc. [1-7]. They have also shown anticancer [8,9], potent TF-FVIIa inhibitors [10] and inhibition of C5-cytosine DNA methyltransferases [11] activities.

In addition to that, quinazolinone and its derivatives comprise an important class of heterocyclic molecules due to their broad spectrum application in medicinal and pharmaceutical chemistry such as analgesic [12], antimicrobial and antitubercular [13,14], antitumor [15], anticancer [16], anti-inflammatory [17], anticonvulsant [18], antimalarial and antihistamine [19].

Moreover, there are many reports regarding synthesis of pyrimidinone derivatives [20,21] but no reports are available in which pyrimidinone is substituted at 3rd position of quinazolinone through hydrazono benzenesulfonamide linkage. Looking to the aforementioned literature and our ongoing research in the field of quinazolinone derivatization [22,23], we reports here synthesis of various pyrimidinone substituted quinazolinone derivatives linked through hydrazono benzenesulfonamide, of that some of the compounds showed good to moderate antimicrobial activity.

Experimental Section

Material and measurements

All the 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 [24]. 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_{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 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^{TM} Systems, Pune-India) with attachment of glass vessel prolonged by a reflux condenser with constant stirring, whereby microwaves were generated by magnetron at a frequency of 2450 MHz having an output energy range of 140 to 700 Watts, and the temperature was monitored with an external flexible probe.

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General procedure for the synthesis of 4-amino-*N*-(2-methyl/aryl-4-oxoquinazolin-3(4H)-yl)benzenesulfonamide derivatives(3a-3j)

Compounds 3a–3j were prepared according to the reported method [22,23]. The possible synthetic route is given in Scheme 1.

-3-yl)benzenesulfonamide (5b) m.p. 145–147°C, ESI MS (m/z): 520.1,

522.3 $[M]^+$.

4-[N'-(1-Acetyl-2-oxo-propylidene)hydrazino]-N-(6,8-dibromo-2-methyl-4-oxo-4H-quinazolin-3-yl)-benzenesulfonamide (5c) m.p. 172–174°C, ESI MS (m/z): 597.2, 599.1, 601.3 $[M]^+$.

4-[N'-(1-Acetyl-2-oxopropylidene)hydrazino]-N-(2-methyl-6-nitro-4-oxo-4H-quinazolin-3-yl)benzenesulfonamide (5d) m.p. 189–190°C, ESI MS (m/z): 549.4 $[M+H]^+$.

4-Amino-N-(2-methyl-4-oxoquinazolin-3(4H)-yl) benzenesulfonamide (3a)mp 217-218°C. ESI MS (m/z): 330.8 $[M+H]^+$.

4-Amino-*N*-(6-bromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl) benzenesulfonamide (3b)mp 187-189°C. ESI MS (m/z): 409.2, 411.3 $[M]^+$.

4-Amino-*N*-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl) benzenesulfonamide (3c) mp 212-214°C. ESI MS (m/z): 488.4, 490.4, 492.4 $[M]^+$.

4-Amino-*N*-(6-nitro-4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzenesulfonamide (3d)mp 206-209°C. ESI MS (m/z): 438.2 $[M+H]^+$.

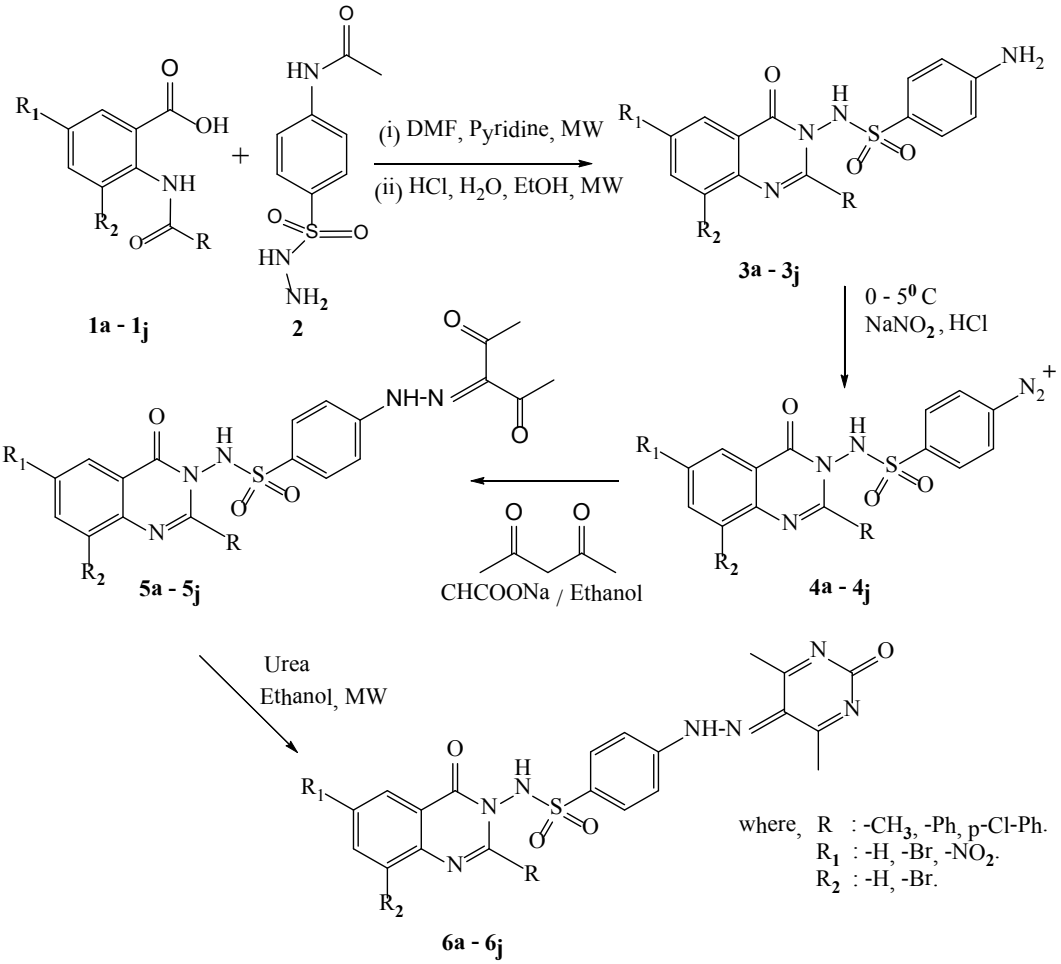
4-Amino-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzenesulfonamide (3e)mp 166-168°C. ESI MS (m/z): 393.4 $[M+H]^+$.

4-Amino-*N*-(6-bromo-4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzenesulfonamide (3f)mp 214-217°C. ESI MS (m/z): 471.3, 473.3 $[M]^+$.

4-Amino-*N*-(6,8-dibromo-4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzenesulfonamide (3g)mp 219-221°C. ESI MS (m/z): 548.3, 550.3, 552.3 $[M]^+$.

4-Amino-*N*-[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl] benzenesulfonamide (3h)mp 175-179°C. ESI MS (m/z): 426.9, 428.9 $[M]^+$.

4-Amino-*N*-[6-bromo-2-(4-chlorophenyl)-4-oxoquinazolin-



Scheme 1: Proposed synthetic route for the preparation of pyrimidinone substituted 4(3H)-quinazolinone derivatives compound (6a-6j).

3(4*H*)-yl]benzene-sulfonamide (3i)mp 186-187°C. ESI MS (m/z): 503.8, 505.8, 507.8 $[M]^+$.

4-Amino-*N*-[6,8-dibromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]benzene

sulfonamide (3j)mp 183-184°C. ESI MS (m/z): 582.5, 584.5, 586.5, 588.5 $[M]^+$.

General procedure for the diazotization of 4-amino-*N*-(2-methyl/aryl-4-oxoquinazolin-3(4H)-yl)benzenesulfonamide derivatives(4a-4j)

The diazotized derivatives **4a-4j** were prepared by following the reported method [23,25]. Schematic diagram to produce diazotized compounds **4a-4j** are shown in Scheme 1. The reaction mass was cooled at 0-5°C for 1 hours and was directly used for the next step.

General procedure for the synthesis of hydrazono derivatives of compounds 4a-4j using acetyl acetone as an active methylene compound (5a-5j)

Hydrazonoquinazolinone compounds **5a-5j** were prepared by following the reported method [23,26]. The synthetic route is shown in Scheme 1.

4-[N'-(1-Acetyl-2-oxo-propylidene)hydrazino]-N-(2-methyl-4-oxo-4H-quinazolin-3-yl)benzenesulfonamide (5a) m.p. 167–168°C, ESI MS (m/z): 442.2 $[M+H]^+$.

4-[N'-(1-Acetyl-2-oxo-propylidene)hydrazino]-N-(6-bromo-2-methyl-4-oxo-4H-quinazolin-[N'-(1-Acetyl-2-oxopropylidene)hydrazino]-N-(4-oxo-2-phenyl-4H-quinazolin-3-yl)benzenesulfonamide (5e) m.p. 164–166°C, ESI MS (m/z): 504.2 $[M+H]^+$.

4-[N'-(1-Acetyl-2-oxopropylidene)hydrazino]-N-(6-bromo-4-oxo-2-phenyl-4H-quinazolin-3-yl)benzenesulfonamide (5f) m.p. 183–184°C, ESI MS (m/z): 582.3, 584.4 $[M]^+$.

4-[N'-(1-Acetyl-2-oxo-propylidene)hydrazino]-N-(6,8-dibromo-4-oxo-2-phenyl-4H-quinazolin-3-yl)benzenesulfonamide (5g) m.p. 193–195°C, ESI MS (m/z): 660.0, 662.2, 663.9 $[M]^+$.

4-[N'-(1-Acetyl-2-oxopropylidene)hydrazino]-N-[6-bromo-2-(4-chloro-phenyl)-4-oxo-4H-quinazolin-3-yl]benzenesulfonamide (5h) m.p. 178–180°C, ESI MS (m/z): 538.0, 539.8 $[M]^+$.

4-[N'-(1-Acetyl-2-oxopropylidene)hydrazino]-N-[6-bromo-2-(4-chlorophenyl)-4-oxo-4H-quinazolin-3-yl]benzenesulfonamide (5i) m.p. 203–204°C, ESI MS (m/z): 616.2, 617.9, 620.0 $[M]^+$.

4-[N'-(1-Acetyl-2-oxopropylidene)hydrazino]-N-[6,8-dibromo-2-(4-chlorophenyl)-4-oxo-4H-quinazolin-3-yl]benzenesulfonamide (5j) m.p. 214–215°C, ESI MS (m/z): 693.8, 695.7, 697.7, 699.9 $[M]^+$.

Synthesis of pyrimidinone substituted quinazolinone derivatives 6a–6j

It was prepared using the appropriate hydazono compound 5a–5j(0.01 mol) and urea (0.015) in 40 ml absolute ethanol using anhydrous sodium acetate as a catalyst (0.001 mol). The reaction mixture was heated under reflux for 5 hours. Completion of reaction was checked by TLC using 9:1 $CHCl_3$:CH_3OH solvent system. After cooling to room temperature the reaction mixture was poured into crushed ice and the mixtures was stirred for 1 hours. Separated product was collected by filtration, washed with water, dried and recrystallized from aqueous ethanol. The colors of the compounds were yellowish to dark orange and are soluble in polar organic solvents like methanol, ethanol and pyridine. The synthetic route is shown in Scheme 1. Yield was in the range of 55-68%.

General microwave assisted procedure for the synthesis of pyrimidinone substituted quinazolinone derivatives 6a–6j

Appropriate hydazono compound 5a–5j (0.01 mol), urea (0.015 mol), anhydrous sodium acetate (0.001 mol) and 2 ml ethanol were taken in a two-neck round bottomed flask fitted with a device condenser. The mixture was then heated under microwave irradiation at 350 W for 3-5 minutes. After cooling to room temperature the reaction mixture was poured into crushed ice and the mixtures was stirred for 30 minutes. Separated product was collected by filtration, washed with water, dried and recrystallized from aqueous ethanol. The colors of the compounds were yellowish to dark orange and are soluble in polar organic solvents like methanol, ethanol and pyridine. Yield was in the range of 71-83%.

4-[N'-(4,6-Dimethyl-2-oxo-2H-pyrimidin-5-ylidene) hydrazino]-N-(2-methyl-4-oxo-4H-quinazolin-3-yl) benzenesulfonamide (6a)

Off white solid (Yield 76%).Mp: 145-147°C. IR (KBr): 3108 (C-H_{Ar}), 1694 (C=O), 1600 (C=N), 1339, 1156 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H, SO_2NH), 8.70 (s, 1H, -NH-), 7.79 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.71 (td, J = 13.16, 1.52 Hz, 1H, Ar-H), 7.49 (dd, J = 7.88, 1.41 Hz, 1H, Ar-H), 7.37 (td, J = 7.17, 1.40 Hz, 1H, Ar-H), 7.25 (dd, J = 8.64, 2.63 Hz, 2H, Ar-H), 6.44 (dd, J = 10.68, 2.14 Hz, 2H, Ar-H), 2.43 (s, 3H, CH_3), 2.18 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 172.36, 158.76, 158.10, 157.37, 155.10, 146.51, 142.63, 134.45, 130.25, 130.10, 127.17, 126.81, 123.70, 121.03, 113.06, 24.8, 23.12.MS *m/z*: 466.40 (M^+). Anal.Calcd for $C_{21}H_{19}N_7O_4S$: C-54.19, H-4.11, N-21.06, S-6.89. Found: C-54.35, H-4.22, N-20.98, S-5.70.

N-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene)hydrazinyl) benzenesulfonamide (6b)

Pale yellow (Yield 83%).Mp: 237-238 ˚C. IR (KBr): 3104 (C-H_{Ar}), 1697 (C=O), 1602 (C=N), 1336, 1154 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H, SO_2NH), 8.77 (s, 1H, -NH-), 7.79 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.71 (td, J = 13.16, 1.52 Hz, 1H, Ar-H), 7.49 (dd, J = 7.88, 1.41 Hz, 2H, Ar-H), 7.64 (td, J = 7.17, 1.40 Hz, 1H, Ar-H), 6.67 (dd, J = 10.68, 2.14 Hz, 2H, Ar-H), 2.20 (s, 3H, CH_3), 2.54 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 171.46, 159.15, 158.62, 158.11, 152.56, 148.82, 142.34, 137.18, 131.34, 127.56, 126.21, 125.78, 123.83, 122.29, 115.11, 24.7, 23.08. MS *m/z*: 545.1 (M^+). Anal.Calcd for $C_{21}H_{18}BrN_7O_4S$: C-46.33, H-3.33, N-18.01, S-5.89. Found: C-46.10, H-3.47, N-17.88, S-5.62.

N-(6,8-Dibromo-2-methyl-4-oxo-4H-quinazolin-3-yl)-4-[N'-(4,6-dimethyl-2-oxo-2H-pyrimidin-5-ylidene)hydrazino] benzenesulfonamide (6c)

Dark yellow (Yield 79%).Mp: 180-182°C. IR (KBr): 3102 (C-H_{Ar}), 1691 (C=O), 1598 (C=N), 1340, 1156 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H, SO_2NH), 8.83 (s, 1H, -NH-), 8.32 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 8.01 (td, J = 13.16, 1.52 Hz, 1H, Ar-H), 7.29 (dd, J = 7.88, 1.41 Hz, 1H, Ar-H), 7.37 (td, J = 7.17, 1.40 Hz, 1H, Ar-H), 6.78 (dd, J = 8.64, 2.63 Hz, 2H, Ar-H), 2.48 (s, 3H, CH_3), 2.19 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 172.55, 162.17, 159.45, 157.76, 152.57, 151.62, 143.67, 138.32, 133.67, 131.29, 127.42, 125.10,

119.21, 113.87, 112.13, 24.04, 22.88. MS *m/z*: 623 (M^+). Anal.Calcd for $C_{21}H_{17}Br_2N_7O_4S$: C-40.47, H-2.75, N-15.73, S-5.14. Found: C-40.29, H-2.54, N-15.88, S-5.25.

4-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene) hydrazinyl)-N-(2-methyl-6-nitro-4-oxoquinazolin-3(4H)-yl) benzenesulfonamide (6d)

Bright yellow (Yield 75%).Mp: 194-195°C. IR (KBr): 3110 (C-H_{Ar}), 1690 (C=O), 1594 (C=N), 1335, 1154 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H, SO_2NH), 8.78 (s, 1H, -NH-), 8.67 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.83 (td, J = 13.16, 1.52 Hz, 1H, Ar-H), 7.49 (dd, J = 7.88, 1.41 Hz, 1H, Ar-H), 7.37 (td, J = 7.17, 1.40 Hz, 1H, Ar-H), 7.42 (dd, J = 8.64, 2.63 Hz, 1H, Ar-H), 6.87 (dd, J = 10.68, 2.14 Hz, 2H, Ar-H), 2.48 (s, 3H, CH_3), 2.23 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 171.32, 159.11, 159.11, 158.93, 156.43, 154.88, 152.21, 144.67, 141.21, 132.65, 130.21, 127.43, 125.76, 123.47, 121.51, 113.11, 24.10, 22.83. MS *m/z*: 511 (M^+). Anal.Calcd for $C_{21}H_{18}N_8O_6S$: C-49.41, H-3.55, N-21.95, S-6.28. Found: C-49.22, H-3.31, N-22.09, S-6.47.

4-[N'-(4,6-Dimethyl-2-oxo-2H-pyrimidin-5-ylidene) hydrazino]-N-(4-oxo-2-phenyl-4H-quinazolin-3-yl) benzenesulfonamide (6e)

Cream solid (Yield 72%).Mp: 177-179°C. IR (KBr): 3103 (C-H_{Ar}), 1689 (C=O), 1601 (C=N), 1337, 1153 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H, SO_2NH), 8.34 (s, 1H, -NH-), 7.75 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.45 (m, 4H, Ar-H), 7.38 (dd, J = 7.88, 1.41 Hz, 1H, Ar-H), 7.37 (m, 5H, Ar-H), 7.17 (dd, J = 8.64, 2.63 Hz, 1H, Ar-H), 6.31 (dd, J = 10.68, 2.14 Hz, 1H, Ar-H), 2.09 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.12, 161.57, 157.87, 153.38, 152.39, 149.24, 139.22, 137.22, 132.45, 131.45, 130.27, 129.71, 127.21, 126.77, 126.02, 125.66, 123.42, 122.21, 115.18, 23.12. MS *m/z*: 528 (M^+). Anal.Calcd for $C_{26}H_{21}N_7O_4S$: C-59.19, H-4.01, N-18.59, S-6.08. Found: C-58.87, H-4.26, N-18.43, S-6.17.

N-(6-bromo-4-oxo-2-phenylquinazolin-3(4H)-yl)-4-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene)hydrazinyl) benzenesulfonamide (6f)

Light yellow (Yield 80%). Mp: 192-193°C. IR (KBr): 3112 (C-H_{Ar}), 1698 (C=O), 1605 (C=N), 1332, 1152 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H, SO_2NH), 8.37 (s, 1H, -NH-), 7.71 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.39 (m, 4H, Ar-H), 7.31 (dd, J = 7.88, 1.41 Hz, 1H, Ar-H), 7.15 (m, 4H, Ar-H), 6.69 (dd, J = 8.64, 2.63 Hz, 1H, Ar-H), 6.44 (dd, J = 10.68, 2.14 Hz, 1H, Ar-H), 2.11 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 171.45, 163.54, 157.76, 155.53, 153.83, 148.33, 143.71, 139.46, 135.17, 132.56, 131.65, 130.45, 129.67, 129.14, 125.76, 124.32, 123.88, 117.78, 113.95, 23.07. MS *m/z*: 607 (M^+). Anal.Calcd for $C_{26}H_{20}BrN_7O_4S$: C-51.49, H-3.32, N-16.17, S-5.29. Found: C-51.31, H-3.07, N-16.41, S-5.35.

N-(6,8-dibromo-4-oxo-2-phenylquinazolin-3(4H)-yl)-4-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene)hydrazinyl) benzenesulfonamide (6g)

Brownish yellow (Yield 77%).Mp: 209-211°C. IR (KBr): 3105 (C-H_{Ar}), 1694 (C=O), 1595 (C=N), 1334, 1151 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H, SO_2NH), 8.30 (s, 1H, -NH-), 7.63 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.57 (m, 3H, Ar-H), 7.34 (dd, J = 7.88, 1.41 Hz, 1H, Ar-H), 6.99 (m, 3H, Ar-H), 6.54 (dd, J = 8.64, 2.63 Hz, 1H, Ar-H), 6.36 (dd, J = 10.68, 2.14 Hz, 2H, Ar-H), 2.21 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 173.42, 162.74, 160.47, 158.87, 153.78, 152.32, 143.12, 137.32, 134.01, 132.65, 131.48, 130.37, 127.47, 129.54, 125.51, 124.91, 118.56, 115.11, 110.23, 23.05. MS *m/z*: 686 (M^+). Anal. Calcd for $C_{26}H_{19}Br_2N_7O_4S$: C-45.57, H-2.79, N-14.31, S-4.68. Found: C-45.35, H-2.96, N-14.18, S-4.77.

N-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-4-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene)hydrazinyl) benzenesulfonamide (6h)

Creamy white solid (Yield 71%).Mp: 215-217°C. IR (KBr): 3113 (C-H_{Ar}), 1688 (C=O), 1603 (C=N), 1329, 1158 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H, SO_2NH), 8.25 (s, 1H, -NH-), 7.81 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.45 (m, 3H, Ar-H), 7.37 (dd, J = 7.88, 1.41 Hz, 1H, Ar-H), 7.22 (d, J = 7.88 Hz, 2H, Ar-H), 6.82 (d, J = 7.88 Hz, 2H, Ar-H), 6.70 (dd, J = 8.64, 2.63 Hz, 1H, Ar-H), 6.38 (dd, J = 10.68, 2.14 Hz, 2H, Ar-H), 2.17 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 173.32, 164.58, 155.11, 153.65, 152.85, 149.75, 144.65, 137.83, 136.27, 132.17, 130.55, 129.41, 126.81, 126.61, 126.17, 126.02, 125.24, 122.66, 113.76, 23.19. MS *m/z*: 563 (M^+). Anal.Calcd for $C_{26}H_{20}ClN_7O_4S$: C-55.57, H-3.59, N-17.45, S-5.71. Found C-55.29, H-3.68, N-17.27, S-5.53.

N-(6-bromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-4-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene)hydrazinyl) benzenesulfonamide (6i)

Pale yellow (Yield 79%).Mp: 188-190°C. IR (KBr): 3104 (C-H_{Ar}), 1698 (C=O), 1606 (C=N), 1337, 1155 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H, SO_2NH), 8.31 (s, 1H, -NH-), 7.83 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.49 (m, 3H, Ar-H), 7.38 (d, J = 7.88 Hz, 1H, Ar-H), 7.26 (d, J = 7.88 Hz, 2H, Ar-H), 6.85 (d, J = 7.88 Hz, 1H, Ar-H), 6.72 (dd, J = 8.64, 2.63 Hz, 1H, Ar-H), 6.41 (dd, J = 10.68, 2.14 Hz, 2H, Ar-H), 2.18 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 172.67, 161.32, 159.11, 155.41, 152.35, 147.63, 142.14, 137.51, 136.71, 135.57, 134.17, 132.43, 130.64, 129.56, 126.33, 125.81, 123.09, 114.12, 113.59, 23.22. MS *m/z*: 641 (M^+). Anal.Calcd for $C_{26}H_{19}BrClN_7O_4S$: C-48.73, H-2.99, N-15.30, S-5.00. Found: C-48.56, H-2.73, N-15.42, S-5.17.

N-(6,8-dibromo-2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-4-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene)hydrazinyl) benzenesulfonamide (6j)

Yellowish orange (Yield 81%).Mp: 224-225°C. IR (KBr): 3110 (C-H_{Ar}), 1699 (C=O), 1603 (C=N), 1338, 1154 (S=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H, SO_2NH), 8.27 (s, 1H, -NH-), 7.82 (dd, J = 7.71, 1.56 Hz, 1H, Ar-H), 7.52 (m, 3H, Ar-H), 7.39 (d, J = 7.88 Hz, 1H, Ar-H), 7.24 (d, J = 7.88 Hz, 2H, Ar-H), 6.86 (d, J = 7.88 Hz, 1H, Ar-H), 6.36 (dd, J = 10.68, 2.14 Hz, 2H, Ar-H), 2.21 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ 171.78, 162.84, 160.78, 157.72, 154.35, 152.51, 143.56, 137.78, 136.32, 132.21, 133.17, 132.45, 131.42, 130.77, 128.21, 124.43, 117.69, 116.21, 110.18, 23.12. MS *m/z*: 720 (M^+). Anal. Calcd for $C_{26}H_{18}Br_2ClN_7O_4S$: C-43.38, H-2.52, N-13.62, S-4.45. Found: C-43.22, H-2.71, N-13.48, S-4.60.

In vitro antimicrobial studies

All the synthesized compounds were screened for their *in vitro* antimicrobial activities against selected pathogenic bacterial strains to determine minimum inhibitory concentrations (MIC) by broth micro dilution method [27] using Sulfanilamide as reference drugs of parent moieties, while Streptomycin 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

Compound	Minimum Inhibition Concentration in µg/mL					
	Gram positive bacteria			Gram negative bacteria		
	B. megaterium	*S. aureus*	*B. subtilis*	*E. coli*	*P. vulgaris*	*P. aeruginosa*
6a	300	200	300	225	200	250
6b	375	350	350	300	225	350
6c	400	395	400	250	300	420
6d	375	400	350	300	275	350
6e	225	200	225	175	200	225
6f	300	300	275	225	225	225
6g	250	200	225	225	250	200
6h	175	125	150	50	50	75
6i	200	175	200	75	50	150
6j	200	150	100	100	75	100
Sf*	425	375	400	375	400	425
Sm*	20	20	20	20	20	20

*Sf= Sulfanilamide, Sm = Streptomycin

Table 1: Antimicrobial activities of the synthesized compounds 6a-6j.

Negative), using the broth dilution method [27]. 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) was 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 tubes was kept as control. Each of the test tubes was inoculated with a suspension of standard microorganism to be tested and incubated at 35°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 1.

Results and Discussion

The intention of the present study was to synthesize and investigate the antimicrobial activities of pyrimidinone ring substituted at 3rd position of quinazolinone derivatives (6a-6j) through hydrazono benzenesulfonamide linkage in a single molecular frame work. Synthetic rout of the target molecules is outlined in the Scheme 1 under both conventional and microwave heating condition. When cyclization for the formation of pyrimidinone derivatives was performed under microwave irradiation, the reaction was taken place in 3 minutes in an improved yield.

All the synthesized compounds were characterized by their physical, analytical and spectral properties. The IR, ESI-MS and NMR (^{1}H and^{13}C) 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 6a-6j, while appearance of a characteristic two isotope peak ($[(M+H)^{+2}]^+$) 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. The IR spectrum of 6a-6j showed the presence of C═O group at ~1690 cm^{-1}due to ─CONH and ─COCH$_3$ groups. Two sharp bands at ~1340 and ~1160 cm^{-1} were due to asymmetric and symmetric stretching vibrations of SO_2 group respectively. The ^{1}H NMR of entitled compounds 6a-6j showed singlet around δ ~10.50 ppm due to highly deshielded proton of ─NHSO$_2$ group. One singlet was observed about δ ~8.77 ppm due to secondary amine group. The two more singlet appeared in the aliphatic region at δ 2.43 and 2.18 ppm due to ─CH$_3$(second position of the quinazolinone ring) and ─CH$_3$ (two methyl group of pyrimidinone ring) protons. All the eight aromatic protons resonated in the region of δ7.79 to 6.44 ppm. The ^{13}C NMR of final compounds 6a-6j showed two signals of carbonyls carbon around δ ~170 (CO of pyrimidinone ring), ~160 (CO of quinazolinone ring). The aromatic carbons appeared between δ 113-158 ppm. The signals due to aliphatic carbons appeared about ~24 and ~22.5 due to presence of two different methyl groups in quinazolinone ring and pyrimidinone ring.

In vitro antimicrobial activities

Inspection of the data of Table 1, on the preliminary *in vitro* antimicrobial evaluations of the entitled compounds 6a-6j revealed that all the screened compounds have a varied degree of antibacterial activity, evident 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 drug Sulfanilamide (Sf), while a very few of the screened compounds found to be equipotent to the standard drugs, Streptomycin (Sm). From the results of *in vitro* antibacterial activity data, it was observed that compounds 6e, 6h, 6i and 6j 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. 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(3*H*)-one nucleus led to increase their biological activities.

Conclusion

In summary, a series of new pyrimidinone substituted Quinazolin-4(3*H*)-one derivatives have been synthesized by adapting a simple and facile manner using both conventional and microwave heating condition in a good amount of yields. All the compounds were screened for their *in vitro* antimicrobial activity and results revealed

that compounds 6e, 6h, 6i and 6j demonstrated excellent activity against *E. coli* and *P. vulgaris*bacterial species.

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