Synthesis and antimicrobial activity of some annelated quinazoline derivatives

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A highly efficient and versatile synthetic approach to the synthesis of annelated quinazoline derivatives *viz* [1,2,4]triazino[4,3-*c*]quinazoline **5–7**, [1,3,5]triazino[1,2-*c*]quinazoline **11**, thiazolidinylquinazoline **9**, quinazolino[4,3-*b*]quinazolin-8-one **12** and imidazoquinazolines **14a,b**,**15**. Also, a variety of pyrazolylquinazolines **19–21**, pyrimidinylquinazolines **22a,b** were obtained *via* a sequence of heterocyclisation reactions of 4-methyl-*N*-[4-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl]benzenesulfonamide (**2**) with different reagents. The new compounds were synthesised with the objective of studying their antimicrobial activity.

Keywords: triazinoquinazoline, quinazolinoquinazoline, pyrazolylquinazoline, antimicrobial activity

Quinazoline derivatives and heterocyclic annelated quinazolines are reported to be physiologically and pharmacologically active,[1] and exhibit a wide range of activities such as anticonvulsant, anti-inflammatory, antifungal, antimalarial and sedative.[2-6] Some of these compounds are identified as drugs[7] that are used as diuretics, vasodilator and antihypertensive agents. Moreover, sulfonamide derivatives have been widely used as bacteriostatic agents.[8,9] Prompted by these facts, and in conjunction with our ongoing program on the utility of readily obtainable starting material for the synthesis of heterocyclic systems of biological interest,[10-13] we have decided to synthesise a series of novel annelated quinazoline derivatives having sulfonamide moiety with a potentially wide spectrum of biological responses.

Results and discussion

The target compound, 4-methyl-*N*-[4-(4-oxo-4*H*-3,1-benzoxazin-2-yl)-phenyl]benzenesulfonamide (**1**) was readily obtained from cyclisation of 2-[4-(toluene-4-sulfonylamino) benzoylamino]benzoic acid by boiling in acetic anhydride.[14] The structure of the reaction product **1** was supported by elemental analyses and compatible spectroscopic data. Thus, its IR spectrum showed absorption bands at 3260 (ν_{NH}), 1745 (ν_{CO}) and 1440, 1370 cm^{-1} (ν_{SO2}). The ^1H NMR spectrum ($CDCl_3$) showed a signal (3H) at δ 2.36 ppm assigned for methyl protons, a multiplet signals (12H) at (6.96–8.11 ppm) assigned for the aromatic protons and a signal at 10.11 ppm assigned for NH which disappeared upon addition of D_2O to NMR sample. Its mass spectrum revealed a molecular ion peak at *m/z* = 392 (M^+) corresponding to the molecular formula $C_{21}H_{16}N_2O_4S$. Fusion of benzoxazinone derivative **1** with ammonium acetate in an oil bath at 160–170°C afforded 4-methyl-*N*-[4-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl]-benzenesulfonamide (**2**) which is a promising intermediate for the synthesis of a diverse annelated quinazoline derivatives. Reaction of compound **2** with a mixture of phosphorus pentachloride/phosphorus oxychloride on a water bath gave 4-chloroquinazoline derivative **3** in fairly good yield which, upon subsequent reaction with hydrazine hydrate in refluxing *n*-butanol, furnished the target compound, 04-hydrazinoquinazoline derivative **4** (Scheme 1).

As the preparation of novel tricyclic and tetracyclic systems is the main goal of this synthetic program, hydrazinoquinazoline was used as a precursor for the synthesis of triazinoquinazoline derivatives of biological applications.[15-17] Thus, the cyclo-condensation of compound **4** with α-haloketones (*viz* chloroacetone and phenacyl bromide) in dry xylene gave [1,2,4]triazino[4,3-*c*]quinazoline derivatives **5a,b**. Also, the reaction of compound **4** with ethyl chloroacetate yielded 3-oxo-*2H*-6-(toluene-4-sulfonylamino) phenyl][1,2,4]triazino[4,3-*c*]quinazoline (**6**). Moreover, [1,2,4]triazino-[4,3-*c*]quinazoline was also obtained from the reaction of compound **4** with diethyl oxalate in absolute ethanol. Reaction of compound **4** with aromatic aldehydes (*viz* benzaldehyde and *p*-chlorobenzaldehyde) gave quinazoline derivatives **8a,b**. Cyclocondensation reaction of **8b** with 2-mercaptoacetic acid in the presence of catalytic amount of piperidine yielded thiazolidinone derivative **9** *via* nucleophilic addition of sulfur atom to activated C=N bond followed by cyclisation to give **9** (Scheme 1).

Furthermore, chloroquinazoline **3** was also used for construction of novel triazinoquinazoline derivative **11** *via* the reaction of compound **3** with ammonium thiocyanate in dry acetone to afford the nonisolable intermediate **10**, which reacted *in situ* with phenyl isocyanate to yield triazinoquinazoline derivative **11** (Scheme 2).

The structure of compound **11** was confirmed by its mass spectrum which showed a molecular ion peak at *m/z* = 551 (M^+) for molecular formula $C_{29}H_{21}N_5O_3S_2$, in addition to IR spectrum which showed absorption bands at 3320 (ν_{NH}), 1680 (ν_{CO}) and at 1265 cm^{-1} (ν_{CS}). This contribution was extended to study some nucleophilic substitution reactions with chloroquinazoline **3** for construction a novel heteroaromatic systems. Thus, fusion of compound **3** with anthranilic acid in an oil bath at 165–175°C afforded 4-methyl-*N*-[4-(8-oxo-8*H*-quinazolino[4,3-b]quinazolin-6-yl)phenyl]benzene-sulfonamide (**12**).

Treatment of the chloroquinazoline **3** with the sodium salt of various amino acids (*viz* glycine and alanine) under reflux produced the corresponding quinazolinylamino acids **13a,b**. The amino acid derivatives **13a,b** were easily cyclised[18] by boiling in acetic anhydride in the presence of anhydrous sodium acetate to yield imidazoquinazoline derivatives **14a,b**. Incorporation of imidazolyl moiety in the quinazoline ring was also achieved by fusion of compound **3** with *o*-phenylenediamine to afford *N*-[4-([1,3]benzimidazo[1,2-*c*] quinazolin-6-yl)phenyl]-4-methylbenzenesulfonamide (**15**) (Scheme 2).

The behaviour of chloroquinazoline towards active methylene compounds was also studied with respect to the synthesis of highly substituted pyrazoles and pyrimidines.[19,20] Thus, the treatment of compound **3** with active methylene compounds (*viz* malononitrile, ethyl cyanoacetate, ethyl acetoacetate and acetylacetone) afforded the corresponding quinazoline derivatives **16–18**, respectively (Scheme 3). The IR spectrum of compound **16** showed the presence of absorption bands at 3310 due to (ν_{NH}) and 2225–2220 cm^{-1} due to (2C…N).

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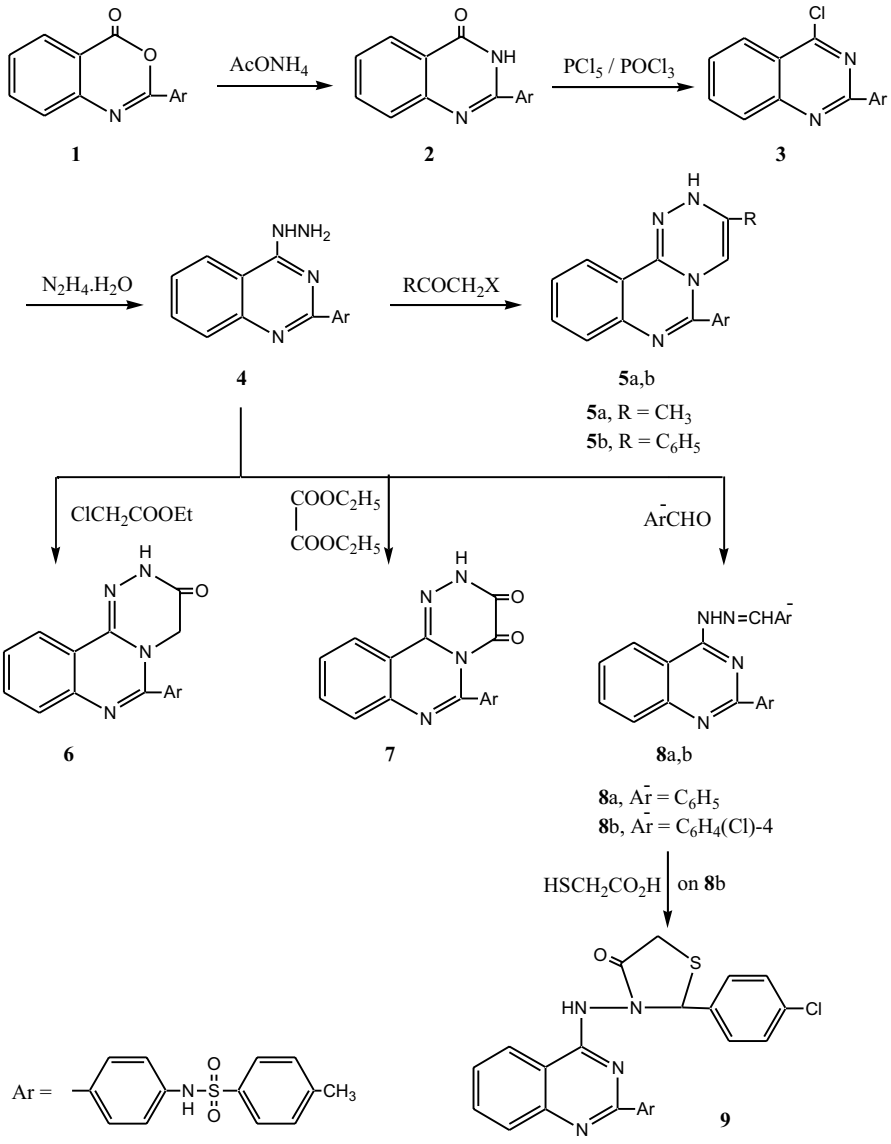


Scheme 1

The condensation of compounds **16–18** with hydrazine hydrate in refluxing absolute ethanol yielded the pyrazolylquinazoline derivatives **19–21**, respectively. The IR spectrum of compound **19** showed the absence of nitrile functional group and the presence of only NH/NH_2 groups. Moreover, the reaction of compound **18** with equimolar amounts of urea or thiourea, in refluxing ethanolic sodium ethoxide solution, provided the corresponding pyrimidinylquinazoline derivatives **22a,b** (Scheme 3). The structures of the synthesised compounds were assigned on the basis of elemental analysis and spectral data (*cf.* experimental).

Antimicrobial activity

The antimicrobial activity of some synthesised compounds were determined *in vitro* using hole plate and filter paper disc methods.[21] A variety of species of gram positive and gram negative bacteria, in addition to some fungal plant pathogens, were used. Also, a comparison between the activity of our synthesised compounds and sulfadiazine as standard drug was discussed. The tested compounds were dissolved in 10% acetone (V/V), and different concentrations have been chosen (125, 250, 500 μg/ml). A qualitative screen was performed on all compounds while quantitative assays were done on active compounds only. The results are summarised in Table 1.

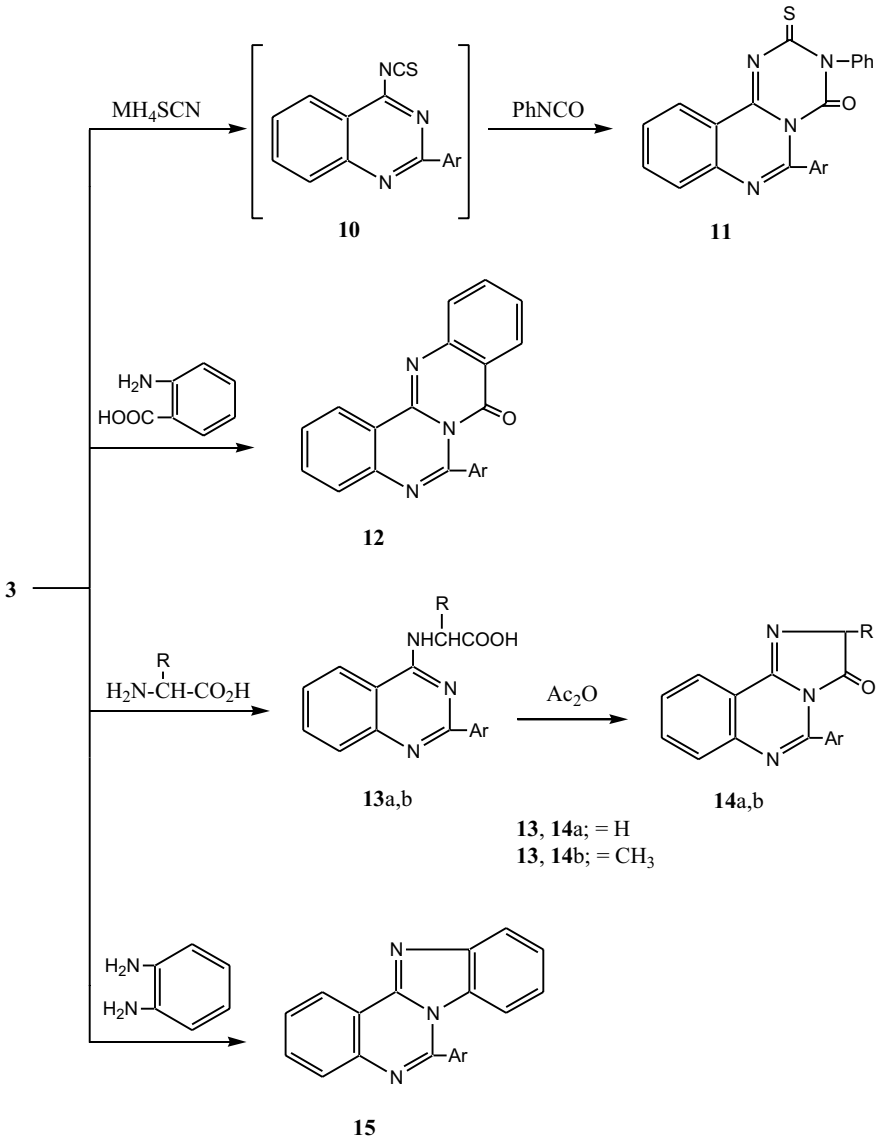
It is apparent from the data listed in Table 1 that the antimicrobial activity of the most synthesised compounds, **5a**, **6**, **7**, **9**, **11**, **19**, **21**, **22b** were highly active against gram +ve and gram –ve bacteria but showed moderate activity against the selected fungi as compared by reference drug used. The high activity of the tested compounds due to the incorporation of triazine, thiazole, pyrazole and pyrimidine moieties to quinazoline ring in addition to sulfonamide moiety.

On the other hand, the compounds **12**, **13a**, **14a**, **16** are moderately active towards bacteria and fungi, as compared with standard drug due to the introduction of polynuclear nonmixed heterocyclic systems to the quinazoline ring.

In summary, the ability of quinazoline derivative **2** was demonstrated to undergo annelation reactions under rather mild conditions providing an efficient synthetic methods for the preparation of various quinazoline derivatives of enhanced biological activity.

Experimental

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra were obtained on an Varian Gemini 200 MHz instrument using TMS as internal reference with chemical shifts expressed as δ ppm. Mass spectra were recorded on a Schimadzu GCMS-QP 1000 EX instrument (70 eV



Scheme 2

El mode). All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F254 (Merck) plates.

4-Methyl-N-[4-(4-oxo-4H-3,1-benzoxazin-2-yl)phenyl]benzenesulfonamide (**1**): To a solution of 2-[4-(toluene-4-sulfonylamino) benzoylamino]benzoic acid (8.2 g, 20 mmol) in acetic anhydride[14] (25 ml) was heated under reflux for 3 h on a water bath, then allowed to cool. The solid product was filtered off and recrystallised from benzene to give **1**. Yield, 67%; m.p. 150–152°C; IR: ν = 3260 (NH), 1745 (CO), 1440, 1370 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$): δ = 2.36 (s, 3H, CH_3), 6.96–8.11 (m, 12H, ArH), 10.11 (s, 1H, NH, exchangeable); MS: *m/z*: 392 (M^+); Anal. Calcd for $C_{21}H_{16}N_2O_4S$ (392.43): C, 64.27; H, 4.11; N, 7.14%. Found: C, 64.65; H, 4.53; N, 7.59%.

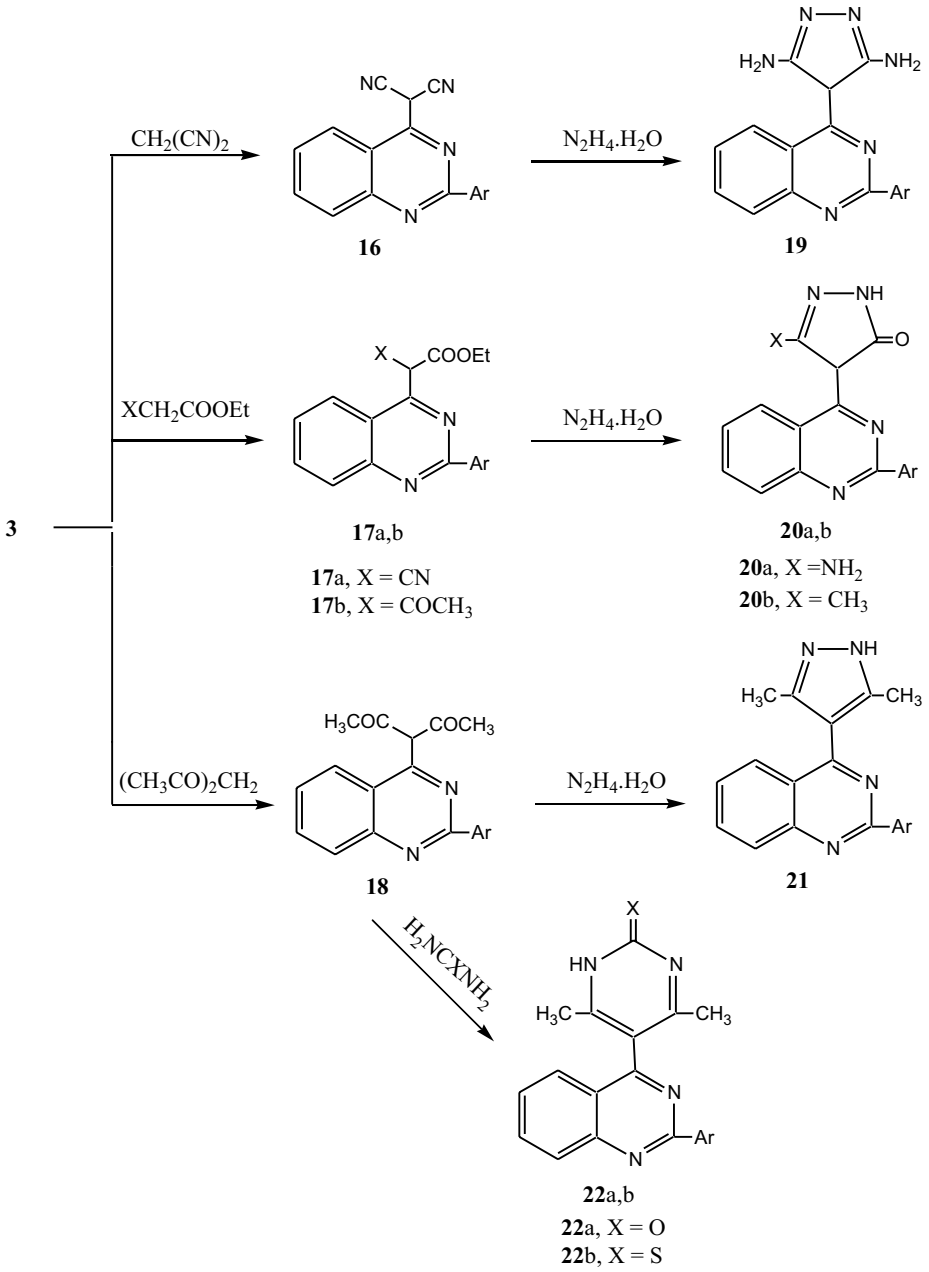
4-Methyl-N-[4-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl] benzenesulfonamide (**2**): A mixture of **1** (5.9 g, 15 mmol) and ammonium acetate (1.4 g, 18 mmol) was fused for 1 h in a fusion tube provided with an air condenser in an oil bath at 160–170°C, then cooled and added to cold water (50 ml). The solid obtained was filtered off and recrystallised from ethanol to give **2**. Yield, 69%; m.p. 187–189°C; IR: ν = 3430–3250(OH, NH), 1680 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.31 (s, 3H, CH_3), 6.97–8.12 (m, 13H, ArH and NH of quinazolinone), 10.00 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{21}H_{17}N_3O_3S$ (391.44): C, 64.43; H, 4.38; N, 10.73%. Found: C, 64.81; H, 43.62; N, 10.41%.

N-[4-(4-Chloroquinazolin-2-yl)phenyl]-4-methylbenzenesulfonamide (**3**): A suspension of compound **2** (3.9 g, 10 mmol) and PCl_5 (0.5 g) in $POCl_3$ (8 ml) was heated under reflux for 2 h on a water bath. The reaction mixture after cooling was poured slowly on crushed ice (30 g) and the solid formed was filtered off, washed with cold water, dried and crystallised from benzene to give **3**. Yield, 73%; m.p. 163–165°C; IR: ν = 3290 (NH), 1620 cm^{-1} (CN); MS: *m/z*: 409 (M^+); Anal. Calcd for $C_{21}H_{16}ClN_3O_2S$ (409.89): C, 61.53; H, 3.93; N, 10.25%. Found: C, 61.82; H, 4.11; N, 10.56%.

N-[4-(4-Hydrazinoquinazolin-2-yl)phenyl]-4-methylbenzenesulfonamide (**4**): A mixture of **3** (4.1 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) in *n*-butanol (30 ml) was heated under reflux for 3 h. The reaction mixture was cooled, then poured on cold water (30 ml) and the solid formed was collected and crystallised from *n*-butanol to give **4**. Yield, 58%; m.p. 220–222°C; IR: ν = 3400–3200 (multiple bands, NH_2, NH), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.34 (s, 3H, CH_3), 5.3 (br s, 2H, NH_2), 7.11–8.23 (m, 12H, ArH), 9.51, 9.95 (2 s, 2H, 2NH, exchangeable); MS: *m/z*: 405 (M^+); Anal. Calcd for $C_{21}H_{19}N_5O_2S$ (405.47): C, 62.20; H, 4.72; N, 17.27%. Found: C, 62.58; H, 4.94; N, 17.10%.

3-Methyl-/phenyl-2H-6-[4-(toluene-4-sulfonylamino)phenyl] [1,2,4]triazino[4,3-c]-quinazolines (**5a,b**): A mixture of **4** (2.03 g, 5 mmol) and α-haloketones (5 mmol) (*viz* chloroacetone and phenacyl bromide) in dry xylene (20 ml) was heated under reflux for 8 h. The solid which separated upon cooling was filtered off and recrystallised to give **5a,b**.

5a; Yield, 61%; m.p. 193–195°C (benzene); IR: ν = 3295–3190 (NH), 1615–1605 (CN), 1440, 1360 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$): δ = 2.33, 2.41 (2 s, 6H, $2CH_3$), 7.10–8.21 (m, 14H, ArH and NH of triazine), 10.12 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{24}H_{21}N_5O_2S$ (443.52): C, 64.99; H, 4.77; N, 15.79%. Found: C, 64.63; H, 4.32; N, 15.9%.



Scheme 3

Table 1 The antimicrobial activity of the tested compounds

Comp. no.	*Staphylococcus aureus*	*Bacillus subtilis*	*Bacillus cereus*	*Pseudomonas aurignosa*	*Escherichia coli*	*Aspergillus niger*	*Penicillium italicum*
2	8	10	12	11	10	7	6
5a	19	21	18	20	23	10	12
6	18	19	16	23	20	11	12
7	20	23	21	18	18	13	10
9	23	21	19	20	24	15	12
11	21	22	19	21	19	18	12
12	16	17	21	18	14	15	13
13a	18	19	18	15	10	11	12
14a	16	18	19	18	12	13	14
16	18	17	18	19	19	12	10
19	21	22	23	21	21	10	12
21	20	21	18	20	22	10	12
22b	23	22	24	20	24	17	12
Sulfadiazine	20	23	23	20	22	14	12

Diameter of inhibition zones is measured is mm.

5b; Yield, 57%, m.p. (201–203°C (dioxane); IR: ν = 3280–3200 (NH), 1612–1605 (CN), 1451, 1365 cm^{-1} (SO_2); MS: *m/z*: 505 (M^+); Anal. Calcd for $C_{29}H_{23}N_5O_2S$ (505.59): C, 68.89; H, 4.59; N, 13.85%. Found: C, 68.45; H, 4.21; N, 13.61%.

3-Oxo-2H-6-(toluene-4-sulfonylamino)phenyl][1,2,4]triazino [4,3-c]quinazoline (**6**): A mixture of **4** (2.03 g, 5 mmol) and ethyl chloroacetate (0.61 g, 5 mmol) in absolute ethanol (25 ml) was heated under reflux for 10 h. The solid separated after cooling and recrystallisation from dioxane gave **6**. Yield, 53%; m.p. 241–243°C; IR: ν = 3310 (NH), 1675 (CO), 1618 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.33 (s, 3H, CH_3), 3.67 (s, 2H, CH_2), 7.13–8.31 (m, 13H, ArH and NH of triazine), 9.96 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{23}H_{19}N_5O_3S$ (445.49): C, 62.01; H, 4.30; N, 15.72%. Found: C, 62.36; H, 4.61; N, 15.36%.

3,4-Dioxo-2H-6-[4-(toluene-4-sulfonylamino)phenyl][1,2,4] triazino[4,3-c]quinazoline (**7**): A mixture of **4** (2.03 g, 5 mmol) and diethyl oxalate (0.73 g, 5 mmol) in absolute ethanol (20 ml) was heated under reflux for 10 h. After cooling the separated solid produced was collected and recrystallised from ethanol to give **7**. Yield, 65%; m.p. 252–254°C; IR: ν = 3275 (NH), 1690–1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.35 (s, 3H, CH_3), 7.12–8.10 (m, 13H, ArH and NH of triazine), 10.20 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{23}H_{17}N_5O_4S$ (459.48): C, 60.12; H, 3.73; N, 15.24%. Found: C, 60.40; H, 3.98; N, 15.01%.

N-{4-[4-(N'-benzylidene-/4-chlorobenzylidenehydrazino) quinazolin-2-yl]phenyl}-4-methylbenzenesulfonamide (**8a,b**): A mixture of **4** (4.05 g, 10 mmol) and appropriate aldehydes (10 mmol) namely benzaldehyde and/or *p*-chlorobenzaldehyde in absolute ethanol (30 ml) was heated under reflux for 4 h in presence of catalytic amount of piperidine. The excess alcohol was distilled off and the reaction solution was left to cool to obtain the solid product which crystallised to give **8a,b**.

8a; Yield, 61% (ethanol); m.p. 236–238°C; IR: ν = 3360–3200 (NH), 1620–1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.33 (s, 3H, CH_3), 7.11–8.21 (m, 18H, ArH and benzylidene proton), 9.63, 10.00 (2 s, 2H, 2NH, exchangeable); Anal. Calcd for $C_{28}H_{23}N_5O_2S$ (493.58): C, 68.13; H, 4.70; N, 14.19%. Found: C, 68.45; H, 4.93; N, 14.01%.

8b; Yield, 67% (ethanol); m.p. 241–243°C; IR: ν = 3340–3250 (NH), 1615–1605 cm^{-1} (CN); Anal. Calcd for $C_{28}H_{22}ClN_5O_2S$ (528.03): C, 63.69; H, 4.20; N, 13.26%. Found: C, 63.40; H, 4.01; N, 13.62%.

N-(4-{4-[2-(4-Chlorophenyl)-4-oxo-1,3-thiazolidin-3-ylamino] quinazolin-2-yl}phenyl)-4-methylbenzenesulfonamide (**9**)*:* A mixture of **8b** (2.6 g, 5 mmol) and 2-mercaptoacetic acid (0.46 g, 5 mmol) was stirred in dry benzene (25 ml) for 15 min, then refluxed for 3 h. The yellow solution was distilled and the residue was recrystallised from benzene to give **9**. Yield, 71% (benzene), m.p. 216–218°C; IR: ν = 3320–3190 (NH), 1685 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.31 (s, 3H, CH_3), 3.72 (s, 1H, methine proton), 4.80 (s, 2H, CH_2), 7.01–8.12 (m, 16H, ArH), 9.21, 9.98 (2 s, 2H, 2NH, exchangeable); MS: *m/z*: 602 (M^+); Anal. Calcd for $C_{30}H_{24}ClN_5O_3S_2$ (602.13): C, 59.84; H, 4.02; N, 11.63%. Found: C, 59.53; H, 4.31; N, 11.32%.

4-Oxo-3-phenyl-2-thioxo-6-[4-(toluene-4-sulfonylamino)phenyl] [1,3,5]triazino[1,2-c]-quinazoline (**11**): To a stirred solution of chloroquinazoline **3** (2.0 g, 5 mmol) in dry acetone, ammonium thiocyanate (0.38 g, 5 mmol) in dry acetone was added. The reaction mixture was stirred for 1 h at room temperature. Ammonium chloride was precipitated during the progress of the reaction. After filtration the ammonium chloride, phenyl isocyanate (0.6 g, 5 mmol) was added to the filtrate. The reaction mixture was heated under reflux for 30 min. The solid product which separated after cooling, crystallised from ethanol to give **11**. Yield, 53%; m.p. 241–243°C; IR: ν = 3320 (NH), 1675 (CO), 1618 (CN), 1265 cm^{-1} (CS); ^1H NMR ($CDCl_3$): δ = 2.33 (s, 3H, CH_3), 7.15–8.12 (m, 17H, ArH), 9.95 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{29}H_{21}N_5O_3S_2$ (551.64): C, 63.14; H, 3.84; N, 12.70%. Found: C, 63.36; H, 3.97; N, 12.48%.

4-Methyl-N-[4-(8-oxo-8H-quinazolino[4,3-b]quinazolin-6-yl) phenyl]benzene-sulfonamide (**12**): A mixture of **3** (2.0 g, 5 mmol) and anthranilic acid (0.69 g, 5 mmol) was fused for 2 h in a fusion tube provided with an air condenser in an oil bath at 165–175°C, then cooled and added to cold water (40 ml). The solid product obtained was collected and recrystallised from benzene to give **12**. Yield, 65%; m.p. 193–195°C; IR: ν = 3290 (NH), 1675 (CO), 1605 (CN), 1435, 1360 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$): δ = 2.33 (s, 3H, CH_3), 6.97–7.89 (m, 16H, ArH), 9.98 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{28}H_{20}N_4O_3S$ (492.55): C, 68.28; H, 4.09; N, 11.37%. Found: C, 68.56; H, 4.48; N, 11.01%.

General procedure for the synthesis of quinazolinylamino acids (**13a,b**): Amino acids (*viz* glycine and alanine, 10 mmol) and sodium carbonate (0.53 g, 5 mmol) were dissolved in water (15 ml), then adjusted to pH 9–9.5. Compound **3** (2.0 g, 5 mmol) was added and the reaction mixture was stirred at 100°C for 8 h at controlled pH. The reaction mixture was left overnight at room temperature, then treated with cold hydrochloric acid. The solid product obtained was filtered off, washed with water, and recrystallised to give **13a,b**.

{2-[4-(Toluene-4-sulfonylamino)phenyl]quinazolin-4-ylamino} acetic acid (**13a**): Yield, 71%(dioxane); m.p. 246–248°C; IR: ν = 3420–3160 (OH, NH), 1700 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.36 (s, 3H, CH_3), 3.51 (s, 2H, CH_2), 7.11–8.12 (m, 13H, ArH and NH), 9.78 (s, 1H, $NHSO_2$, exchangeable); 10.61 (brs, 1H, OH, exchangeable); Anal. Calcd for $C_{23}H_{20}N_4O_4S$ (448.50): C, 61.59; H, 4.49; N, 12.49%. Found: C, 61.21; H, 4.13; N, 12.73%.

2-{2-[4-(Toluene-4-sulfonylamino)phenyl]quinazolin-4-ylamino} propionic acid (**13b**): Yield, 66% (DMF-H_2O); m.p. 236–238°C; IR: ν = 3410–3220 (OH, NH), 1695 (CO), 1605 cm^{-1} (CN); Anal. Calcd for $C_{24}H_{22}N_4O_4S$ (462.52): C, 62.32; H, 4.79; N, 12.11%. Found: C, 62.71; H, 4.97; N, 11.91%.

General procedure for the synthesis of imidazoquinazolines (**14a,b**): A mixture of **13a** or **13b** (5 mmol), acetic anhydride (10 ml), and anhydrous sodium acetate (0.41 g, 5 mmol) was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue washed with water, filtered, dried, and recrystallised to give **14a,b**.

4-Methyl-N-[4-(3-oxo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl) phenyl]benzene-sulfonamide (**14a**): Yield, 56% (DMF); m.p. 181–183°C; IR: ν = 3260 (NH), 1680 (CO), 1610 cm^{-1} (CN); MS: *m/z*: 430 (M^+); Anal. Calcd for $C_{23}H_{18}N_4O_3S$ (430.48): C, 64.17; H, 4.21; N, 13.01%. Found: C, 64.51; H, 4.62; N, 13.43%.

4-Methyl-N-[4-(2-methyl-3-oxo-2,3-dihydroimidazo[1,2-c] quinazolin-5-yl)phenyl]-benzenesulfonamide (**14b**): Yield, 61% (benzene); m.p. 175–177°C; IR: ν = 3280 (NH), 1675 (CO), 1605 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.11, 2.35 (2 s, 6H, $2CH_3$), 4.10 (s, 1H, methine proton), 7.12–8.13 (m, 12H, ArH), 9.95 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{24}H_{20}N_4O_3S$ (444.51): C, 64.85; H, 4.54; N, 12.60%. Found: C, 64.27; H, 4.24; N, 12.93%.

N-[4-([1,3]benzimidazo[1,2-c]quinazolin-6-yl)phenyl]-4-methyl-benzenesulfonamide (**15**): A mixture of compound **3** (2.0 g, 5 mmol) and *o*-phenylenediamine (0.54 g, 5 mmol) was fused for 2 h in an fusion tube provided with an air condenser in an oil bath at 170–180°C. After cooling, the reaction mixture was poured on cold water (40 ml) and the solid product which formed was crystallised from *n*-butanol to give **15**. Yield, 64%; m.p. 206–208°C; IR = ν = 3230 (NH), 1610 (CN), 1450, 1360 cm^{-1} (SO_2); ^1H NMR (DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 7.11–8.14 (m, 16H, ArH), 9.88 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{27}H_{20}N_4O_2S$ (464.54): C, 69.81; H, 4.34; N, 12.06%. Found: C, 69.36; H, 4.02; N, 12.49%.

General procedure for the synthesis of compounds (**16–18**): Active methylene compounds (*viz* malononitrile, ethyl cyanoacetate, ethyl acetoacetate and acetylacetone, 10 mmol) were added to an ethanolic sodium ethoxide solution (0.56 g of sodium in 50 ml ethanol)and stirred for 2 h. Compound **3** (4.1 g, 10 mmol) was added to an ethanolic sodium ethoxide solution (0.56 g of sodium in 50 ml ethanol) and stirred for 2 h. The reaction mixture was heated under reflux for 5 h. The ethanol was removed under reduced pressure and the residue was poured into cold water (100 ml) and extracted with ether. The extracted solvent was dried over anhydrous sodium sulfate and removed under reduced pressure to give the compounds **16–18**, respectively.

N-{4-[4-(Dicyanomethyl)quinazolin-2-yl]phenyl}-4-methyl-benzenesulfonamide (**16**): Yield, 64% (ethanol); m.p. 173–175°C; IR: ν = 3330 (NH), 2225–2220 (2C…N), 1620 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.31 (s, 3H, CH_3), 4.57 (s, 1H, CH), 7.11–8.12 (m, 12H, ArH), 10.01 (s, 1H, NH, exchangeable); MS: *m/z*: 439 (M^+); Anal. Calcd for $C_{24}H_{17}N_5O_2S$ (439.49): C, 65.59; H, 3.90; N, 15.94%. Found: C, 65.23; H, 3.61; N, 15.72%.

Ethyl cyano{2-[4-(toluene-4-sulfonylamino)phenyl]quinazolin-4-yl}acetate (**17a**): Yield, 61% (1-butanol); m.p. 213–215°C; IR: ν = 3290 (NH), 2230 (CN), 1735 (CO), 1615 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 1.25 (t, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.10 (s, 1H, CH), 4.31 (q, 2H, CH_2), 6.91–7.98 (m, 12H, ArH), 9.89 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{26}H_{22}N_4O_4S$ (486.54): C, 64.18; H, 4.56; N, 11.52%. Found: C, 64.43; H, 4.76; N, 11.21%.

Ethyl 3-oxo-2-{2-[4-(toluene-4-sulfonylamino)phenyl]quinazolin-4-yl}butyrate (**17b**): Yield, 65% (benzene); m.p. 183–185°C; IR: ν = 3310 (NH), 1735, 1710 (2CO), 1605 cm^{-1} (CN); Anal. Calcd for $C_{27}H_{25}N_3O_5S$ (503.57): C, 64.40; H, 5.00; N, 8.34%. Found: C, 64.75; H, 5.27; N, 8.11%.

N-{4-[4-(1-Acetyl-2-oxopropyl)quinazolin-2-yl]phenyl}-4-methylbenzenesulfonamide (**18**): Yield, 64% (dioxane); m.p. 161–163°C; IR: ν = 3370 (NH), 1710 (CO), 1612 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.35 (s, 3H, CH_3), 2.51 (br s, 6H, $2COCH_3$), 4.25 (s, 1H, CH), 6.99–8.11 (m, 12H, ArH), 10.11 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{26}H_{23}N_3O_4S$ (473.54): C, 65.94; H, 4.90; N, 8.87%. Found: C, 65.63; H, 4.71; N, 8.99%

General procedure for the synthesis of pyrazolylquinazolines **19–21**: A mixture of **16**, **17a**, **17b**, **18** (5 mmol) and hydrazine hydrate (0.25 g, 5 mmol) in absolute ethanol (20 ml) was heated under reflux for 6 h, then allowed to cool. The solid product was collected and recrystallised to give the compounds **19–21**, respectively.

N-{4-[4-(3,5-Diamino-4H-pyrazol-4-yl)quinazolin-2-yl]phenyl}-4-methylbenzenesulfonamide (**19**): Yield, 62% (benzene); m.p. 211–213°C; IR: ν = 3390–3200 (multiple bands, NH_2, NH), 1615–1605 (CN), 1460, 1370 cm^{-1} (SO_2); MS: *m/z*: 471 (M^+); Anal. Calcd for $C_{24}H_{21}N_7O_2S$ (471.54): C, 61.13; H, 4.49; N, 20.79%. Found: C, 61.48; H, 4.83; N, 20.34%

N-{4-[4-(3-Amino-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)quinazolin-2-yl]phenyl}-4-methylbenzenesulfonamide (**20a**): Yield, 63% (AcOH); m.p. 241–243°C; IR: ν = 3420–3210 (multiple bands, NH_2, NH), 1675 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.45 (s, 3H, CH_3), 4.21 (s, 1H, CH), 4.40 (br s, 2H, NH_2), 6.81–7.83 (m, 13H, ArH + NH of pyrazole), 9.96 (s, 1H, NH, exchangeable; Anal. Calcd for $C_{24}H_{20}N_6O_3S$ (472.52): C, 61.00; H, 4.27; N, 17.79%. Found: C, 61.48; H, 4.63; N, 17.31%.

4-Methyl-N-{4-[4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl) quinazolin-2-yl]-phenyl}benzenesulfonamide (**20b**): Yield, 65% (*n*-butanol); m.p. 251–253°C; IR: ν = 3300–3120 (NH), 1675 (CO), 1610 cm^{-1} (CN); MS: *m/z*: 471 (M^+); Anal. Calcd for $C_{25}H_{21}N_5O_3S$ (471.53): C, 63.68; H, 4.49; N, 14.85%. Found: C, 63.25; H, 4.12; N, 14.99%.

N-{4-[4-(3,5-Dimethyl-1H-pyrazol-4-yl)quinazolin-2-yl]phenyl}-4-methylbenzenesulfonamide (**21**): Yield, 60% (benzene); m.p. 201–203°C; IR: ν = 3320–3210 (NH), 1610 (CN); ^1H NMR ($CDCl_3$): δ = 2.31 (s, 3H, CH_3), 2.53, 2.64 (2 s, 6H, $2CH_3$ of pyrazole), 7.12–8.31 (m, 13H, ArH and NH of pyrazole), 10.01 (s, 1H, NH, exchangeable); MS: *m/z*: 469 (M^+); Anal. Calcd for $C_{26}H_{23}N_5O_2S$ (469.56): C, 66.50; H, 4.94; N, 14.91%. Found: C, 66.86; H, 4.51; N, 14.61%.

N-{4-[4-(4,6-Dimethyl-2-oxo-/thioxo-1,2-dihydropyrimidin-5-yl) quinazolin-2-yl]-phenyl}-4-methylbenzenesulfonamide (**22a,b**): To a solution of **18** (2.49 g, 5 mmol), in ethanolic sodium ethoxide solution (0.12 g, 5 mmol) [prepared by dissolving sodium metal (0.12 g, 5 mmol) in absolute ethanol (50 ml)] urea or thiourea was added. The reaction mixture was heated under reflux for 8 h. The solvent was evaporated *in vacuo*, and the residue was triturated with cold water whereupon the solid that formed was collected and recrystallised to give **22a,b**.

22a; Yield, 59% (ethanol); m.p. 191–193°C; IR: ν = 3300–3200 (NH), 1670 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ = 2.32 (s, 3H, CH_3), 2.51, 2.63 (2 s, 6H, $2CH_3$ of pyrimidine), 7.13–8.21 (m, 13H, ArH and NH of pyrimidine), 10.12 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{27}H_{23}N_5O_3S$ (497.57): C, 65.17; H, 4.66; N, 14.08%. Found: C, 65.43; H, 4.98; N, 14.49%.

22b; Yield, 61% (ethanol); m.p. 206–208°C; IR: ν = 3340–3210 (NH), 1605 (CN), 1250 cm^{-1} (CS); MS: *m/z*: 513 (M^+); Anal. Calcd for $C_{27}H_{23}N_5O_2S_2$ (513.64): C, 63.14; H, 4.51; N, 13.63%. Found: C, 63.51; H, 4.92; N, 13.31%.

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