Synthesis and Antimicrobial Activity of Some Annelated Quinazoline Derivatives

A. A. Aly

Chemistry Department, Faculty of Science, Benha University, Benha, Egypt

Reprint requests to Dr. A. A. Aly. E-mail: alymaboud@hotmail.com

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A highly efficient and versatile synthetic approach to the synthesis of annelated quinazoline derivatives *viz.* 3,4,9,10a-tetraazaphenanthrenes **5** – **7**, thiazolidinylquinazoline **9**, 2,4,9,10a-tetraazaphenanthrene **11**, 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 heterocyclization reactions of 4-methyl-*N*-[4-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl]benzenesulfonamide (**2**) with different reagents. The new compounds were synthesized with the objective of study their antimicrobial activity.

Key words: Tetraazaphenanthrene, Quinazolinoquinazoline, Pyrazolylquinazoline, Antimicrobial Activity

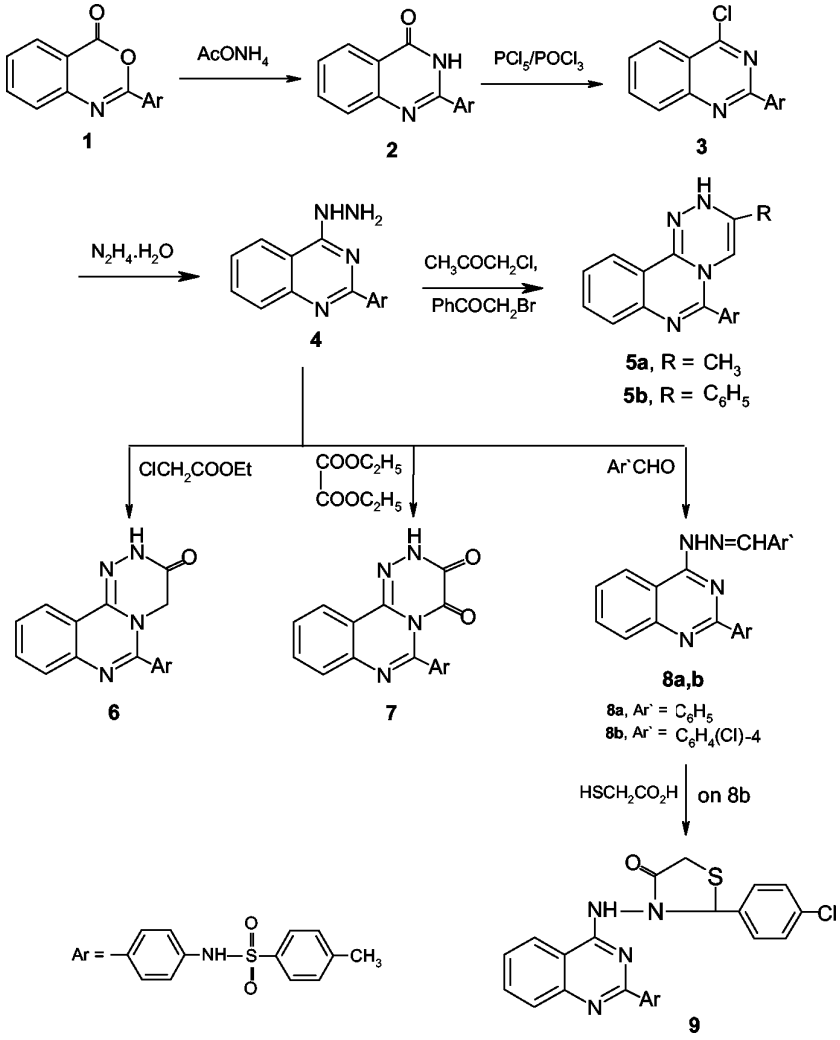
Introduction

Quinazoline derivatives and heterocyclic annelated quinazolines are reported to be physiologically and pharmacologically active [1], which exhibit a wide rang of activities as anticonvulsant, anti-inflammatory, antifungal, antimalarial and sedative [2 – 6]. Some of these compounds are identifies as drugs [7], such as quinethazone and metolazone are used in medicine as diuretics while prazosin is a vasodilator which is also used as antihypertensive drug. Moreover, sulfonamide derivatives have been widely used as bacteriostatic agents [8, 9]. Prompted us by above mentioned 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 synthesis a series of novel annelated quinazoline derivatives having sulfonamide moiety with potential 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 cyclization 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 ^{1}H NMR spectrum ($CDCl_3$) showed signal (3H) at $\delta = 2.36$ ppm assigned for methyl protons, a multiplet signals (12H) at (6.96 – 8.11 ppm) assigned for the aromatic protons and signal at 10.11 ppm assigned for NH which disappeared upon addition of D_2O to NMR sample and 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 yielded 4-chloroquinazoline derivative **3** in fairly good yield, which upon subsequent reaction with hydrazine hydrate in refluxing *n*-butanol furnished the target compound, 4-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 cyclocondensation of compound **4** with α-haloketones (*viz.* chloroacetone and phenacyl bromide) in dry xylene gave tetraaza-

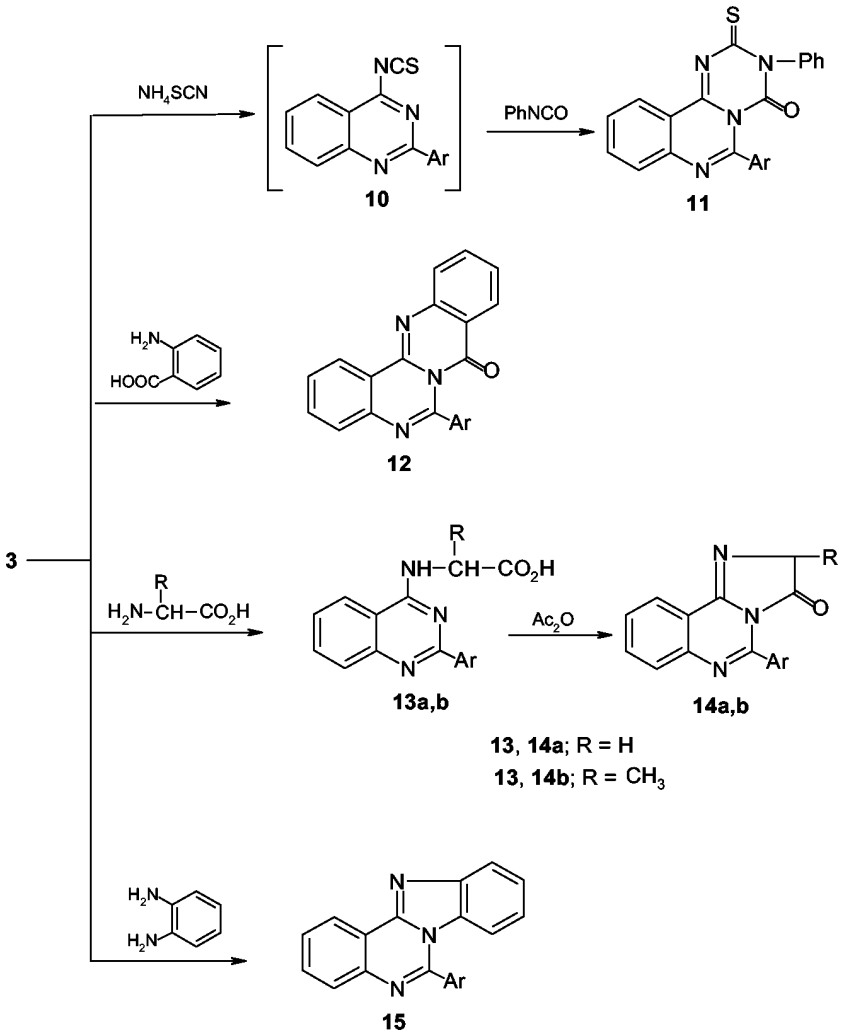


Scheme 1.

phenanthrene derivatives **5a,b**. Also, the reaction of compound **4** with ethyl chloroacetate yielded 4-methyl-*N*-[4-(2-oxo-2,3-dihydro-1*H*-3,4,9,10a-tetraazaphenanthren-10-yl)phenyl]benzenesulfonamide (**6**). Moreover, tetraazaphenanthrene-1,2-dione **7** 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 presence of catalytic amount of piperidine yielded thiazolidinone derivative **9** *via* nucleophilic addition of sulfur atom to activated C=N bond followed by cyclization 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 non-isolable 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 band at *m/z* (%) = 551 (M^+) for molecular formula $C_{29}H_{21}N_5O_3S_2$, in addition to IR spectrum which showed absorption band 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



Scheme 2.

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]benzenesulfonamide (**12**).

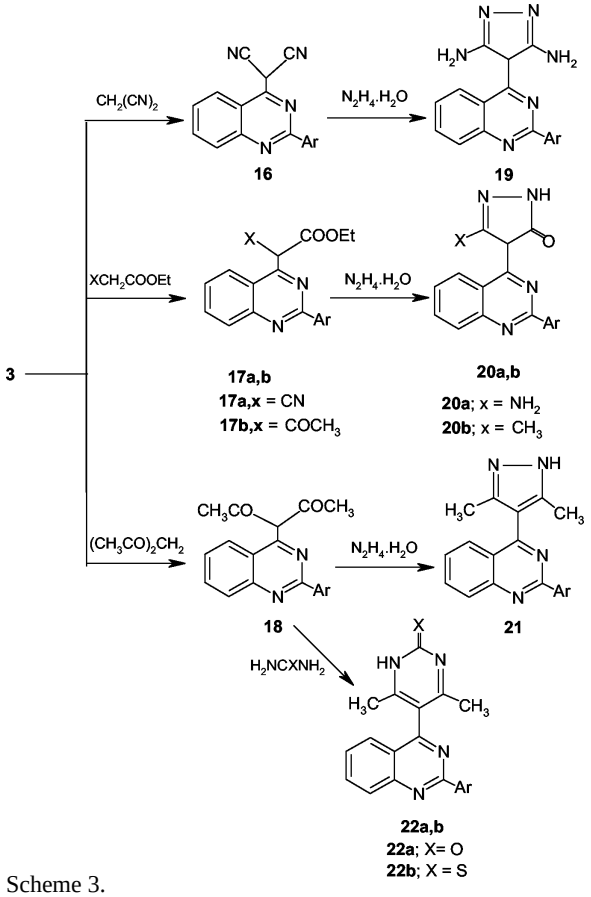
Treatment the chloroquinazoline **3** with the sodium salt of various amino acids (*viz.* glycine and alanine) under reflux, the corresponding quinazolinylamino acids **13a,b** were obtained. The amino acid derivatives **13a,b** were easily cyclized [18] by boiling in acetic anhydride in presence of 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-ylphenyl)-4-methylbenzenesulfonamide (**15**) (Scheme 2).

The behavior 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 infrared spectrum of compound **16** showed the presence of absorption peaks at 3310 due to (ν_{NH}) and 2225 – 2215 cm^{-1} due to (2C≡N).

The condensation of compounds **16-18** with hydrazine hydrate in refluxing absolute ethanol yielded the pyrazolylquinazoline derivatives **19** – **21**, respec-

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
Sulphadiazine	20	23	23	20	22	14	12

Table 1. The antimicrobial activity of the tested compounds. Diameters of inhibition zones are measured in mm.



Scheme 3.

tively. The infrared 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 synthesized compounds were assigned on the basis of elemental analysis and spectral data (*cf.* Experimental Section).

Antimicrobial activity

The antimicrobial activities of some synthesized compounds were determined *in vitro* using hole plate and filter paper disc methods [21]. A variety 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 synthesized compounds and sulphadiazine 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 summarized in Table 1.

It is apparent from the data listed in Table 1, the antimicrobial activity of the most synthesized 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 un-

der rather mild conditions providing an efficient synthetic methods for the preparation of various quinazoline derivatives of enhanced biological activity.

Experimental Section

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on an Varian Gemini 200 MHz and 50 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 El mode). All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F254 (Merck) plates.

^{13}C NMR values of 4-(toluene-4-sulfonylamino)phenyl–moiety for the synthesized compounds are the same as in compound **1** with $\delta \pm 1 - 0.5$ ppm.

4-Methyl-N-[4-(4-oxo-4H-benzo[d][1,3]oxazin-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 recrystallized from benzene to give **1**. Yield, 67%; m. p. 150 – 2 °C; IR: $\nu = 3260$ (NH), 1745 (CO), 1440, 1370 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$): $\delta = 2.36$ (s, 3H, CH_3), 6.96 – 8.11 (m, 12H, ArH), 10.11 (s, 1H, NH, exchangeable); MS: m/z: 392 (M^+); ^{13}C NMR: $\delta = 28.2$ (CH_3), 126.2 (C-8), 128.3 (C-4a), 129.5 (C-6), 134.4 (C-5), 138.3 (C-7), 148.2 (C-8a), 158.3 (C-2), 176.3 (CO), 113.4, 118.3, 120.3, 124.2, 125.3, 130.3, 133.5, 142.6 (C-aromatics); Analysis for $C_{21}H_{16}N_2O_4S$ (392.43): calcd. 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 (1.4g, 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 recrystallized from ethanol to give **2**. Yield, 69%; m. p. 187 – 9 °C; IR: $\nu = 3430 - 3250$ (OH, NH), 1680 (CO), 1610 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$): $\delta = 2.31$ (s, 3H, CH_3), 6.97 – 8.12 (m, 13H, ArH and NH of quinazolinone), 10.00 (s, 1H, NH, exchangeable); ^{13}C NMR: $\delta = 127.1$ (C-8), 128.3 (C-4a), 129.1 (C-6), 130.1 (C-5), 131.3 (C-7), 147.3 (C-8a), 158.2 (C-2), 173.4 (CO); Analysis for $C_{21}H_{17}N_3O_3S$ (391.44): calcd. 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 crystallized from benzene to give **3**. Yield, 73%; m. p. 163 – 5 °C; IR: $\nu = 3290$ (NH), 1620 cm^{-1} (CN); MS: m/z: 409 (M^+); ^{13}C NMR: $\delta = 118.3$ (C-4a), 119.5 (C-5), 124.3 (C-6), 125.3 (C-8), 130.3 (C-7), 135.6 (C-8a), 145.3 (C-2), 146.4 (C-4); Analysis for $C_{21}H_{16}ClN_3O_2S$ (409.89): calcd. 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 1-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 crystallized from 1-butanol to give **4**. Yield, 58%; m. p. 220 – 2 °C; IR: $\nu = 3400 - 3200$ (multiple bands, NH_2, NH), 1610 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$): $\delta = 2.34$ (s, 3H, CH_3), 5.3 (br s, 2H, NH_2), 7.11 – 8.23 (m, 12H, ArH), 9.51, 9.95 (2s, 2H, 2NH, exchangeable); MS: m/z: 405 (M^+); Analysis for $C_{21}H_{19}N_5O_2S$ (405.47): calcd. C 62.20, H 4.72, N 17.27; found C 62.58, H 4.94, N 17.10.

4-Methyl-N-[4-(2-methyl-/phenyl-3H-3,4,9,10a-tetra-azaphenanthren-10-yl)phenyl]benzenesulfonamide (**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 recrystallized from proper solvent to give **5a,b**.

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

5b; Yield, 57%, m. p. (201 – 3 °C (dioxane); IR: $\nu = 3280 - 3200$ (NH), 1612 – 1605 (CN), 1451, 1365 cm^{-1} (SO_2); MS: m/z: 505 (M^+); ^{13}C NMR: $\delta = 106.3$ (C-1), 125.3 (C-8), 125.5 (C-5a), 128.3 (C-6), 129.1 (C-5), 130.3 (C-7), 132.3 (C-2), 153.1 (C-8a), 155.4 (C-4a), 160.1 (C-10), 122.1, 122.4, 123.3, 123.6, 128.6, 130.1 (C-phenyl group); Analysis for $C_{29}H_{23}N_5O_2S$ (505.59): calcd. C 68.89, H 4.59, N 13.85; found C 68.45, H 4.21, N 13.61.

4-Methyl-N-[4-(2-oxo-2,3-dihydro-1H-3,4,9,10a-tetraazaphenanthren-10-yl)phenyl]-benzenesulfonamide (**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 recrystallization from dioxane gave **6**. Yield, 53%; m. p. 241 – 3 °C; IR: $\nu = 3310$ (NH), 1675 (CO), 1618 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$): $\delta = 2.33$ (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); Analysis for $C_{23}H_{19}N_5O_3S$ (445.49): calcd. C 62.01, H 4.30, N 15.72; found C 62.36, H 4.61, N 15.36.

N-[4-(1,2-Dioxo-2,3-dihydro-1H-3,4,9,10a-tetraazaphenanthren-10-yl)phenyl]-4-methylbenzenesulfonamide (**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 recrystallized from ethanol to give **7**. Yield, 65%; m. p. 252 – 4 °C; IR: $\nu = 3275$ (NH), 1690 – 1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 7.12 – 8.10 (m, 13H, ArH and NH of triazine), 10.20 (s, 1H, NH, exchangeable); Analysis for $C_{23}H_{17}N_5O_4S$ (459.48): calcd. 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 crystallized from suitable solvent to give **8a,b**.

8a; Yield, 61% (ethanol); m. p. 236 – 8 °C; IR: $\nu = 3360$ – 3200 (NH), 1620 – 1610 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$): $\delta =$ 2.33 (s, 3H, CH_3), 7.11 – 8.21 (m, 18H, ArH and benzylidene proton), 9.63, 10.00 (2s, 2H, 2NH, exchangeable); Analysis for $C_{28}H_{23}N_5O_2S$ (493.58): calcd. 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 – 3 °C; IR: $\nu = 3340$ – 3250 (NH), 1615 – 1605 cm^{-1} (CN); ^{13}C NMR: $\delta = 117.1$ (C-5), 118.3 (C-4a), 121.1 (C-6), 124.5 (C-8), 127.3 (C-7), 146.4 (CH=), 150.1 (C-2), 158.2 (C-7), 126.1, 129.2, 132.3, 134.3 (C-phenyl group); Analysis for $C_{28}H_{22}ClN_5O_2S$ (528.03): calcd. 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-oxothiazolidin-3-yl-amino]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 recyrstallized from benzene to give **9**. Yield, 71% (benzene), m. p. 216 – 8 °C; IR: $\nu = 3320$ – 3190 (NH), 1685 (CO), 1610 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$): $\delta = 2.31$ (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 (2s, 2H, 2NH, exchangeable); MS: m/z: 602 (M^+); ^{13}C NMR: $\delta = 41.1$ (CH_2 of thiazolidine), 61.3 (CH of thiazolidine), 112.2 (C-4a), 114.3 (C-5), 119.2 (C-6), 121.5 (C-8), 124.3 (C-7), 143.5 (C-8a), 153.6 (C-2), 156.1 (CO), 158.2 (C-2), 125.3, 127.7, 129.9, 131.2 (C- of phenyl group); Analysis for $C_{30}H_{24}ClN_5O_3S_2$ (602.13): calcd. C 59.84, H 4.02, N 11.63; found C 59.53, H 4.31, N 11.32.

4-Methyl-N-[4-(1-oxo-2-phenyl-3-thioxo-2,3-dihydro-1H-2,4,9,10a-tetraazaphenanthren-10-yl)phenyl]benzenesulfonamide (**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 r. t. Ammonium chloride was precipitated during the progress of the reaction. After filteration the ammonium chloride, phenyl isocyanate (0.6 g, 5 mmol) was added to the filterate. The reaction mixture was heated under reflux for 30 min. The solid product which separated after cooling, crystallized from ethanol to give **11**. Yield, 53%; m. p. 241 – 3 °C; IR: $\nu = 3320$ (NH), 1675 (CO), 1618 (CN), 1265 cm^{-1} (CS); ^{1}H NMR ($CDCl_3$): $\delta = 2.33$ (s, 3H, CH_3), 7.15 – 8.12 (m, 17H, ArH), 9.95 (s, 1H, NH, exchangeable); Analysis for $C_{29}H_{21}N_5O_3S_2$ (551.64): calcd. 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]benzenesulfonamide (***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 recrystallized from benzene to give **12**. Yield, 65%; m. p. 193 – 5 °C; IR: $\nu = 3290$ (NH), 1675 (CO), 1605 (CN), 1435, 1360 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$): $\delta = 2.33$ (s, 3H, CH_3), 6.97 – 7.89 (m, 16H, ArH), 9.98 (s, 1H, NH, exchangeable); Analysis for $C_{28}H_{20}N_4O_3S$ (492.55): calcd. 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 (10 mmol) (*viz.* glycine and alanine) 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 r. t., then treated with cold hydrochloric acid. The solid product obtained was filtered off, washed with water, and crystallized from proper solvent to give **13a,b**.

{2-[4-(Toluene-4-sulfonylamino)phenyl]quinazolin-4-ylamino}acetic acid (**13a**)

Yield, 71% (dioxane); m. p. 246 – 8 °C; IR: $\nu = 3420 - 3160$ (OH, NH), 1700 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): $\delta = 2.36$ (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); Analysis for $C_{23}H_{20}N_4O_4S$ (448.50): calcd. 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, 3 : 1); m. p. 236 – 8 °C; IR: $\nu = 3410 - 3220$ (OH, NH), 1695 (CO), 1605 cm^{-1} (CN); Analysis for $C_{24}H_{22}N_4O_4S$ (462.52): calcd. 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 crystallized from proper solvent to give **14a,b**.

4-Methyl-N-[4-(3-oxo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)phenyl]benzenesulfonamide (**14a**)

Yield, 56% (DMF); m. p. 181 – 3 °C; IR: $\nu = 3260$ (NH), 1680 (CO), 1610 cm^{-1} (CN); MS: m/z: 430 (M^+); ^{13}C NMR: $\delta = 63.5$ (CH_2), 119.2 (C-8), 121.2 (C-6), 123.1 (C-5), 124.9 (C-4a), 128.9 (C-7), 156.3 (C-4), 146.2 (C-8a), 158.3 (C-2), 176.3 (CO); Analysis for $C_{23}H_{18}N_4O_3S$ (430.48): calcd. 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 – 7 °C; IR: $\nu = 3280$ (NH), 1675 (CO), 1605 cm^{-1} (CN); ^1H NMR ($CDCl_3$): $\delta = 2.11$, 2.35 (2s, 6H, $2CH_3$), 4.10 (s, 1H, methine proton), 7.12 – 8.13 (m, 12H, ArH), 9.95 (s, 1H, NH, exchangeable); Analysis for $C_{24}H_{20}N_4O_3S$ (444.51): calcd. 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-ylphenyl]-4-methylbenzenesulfonamide (**15**)

An equimolar amounts 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 crystallized from n-butanol to give **15**. Yield, 64%; m. p. 206 – 8 °C; IR: $\nu = 3230$ (NH), 1610 (CN), 1450, 1360 cm^{-1} (SO_2); ^1H NMR (DMSO-d_6): $\delta = 2.34$ (s, 3H, CH_3), 7.11 – 8.14 (m, 16H, ArH), 9.88 (s, 1H, NH, exchangeable). Analysis for $C_{27}H_{20}N_4O_2S$ (464.54): calcd. 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**)

An active methylene compounds (10 mmol) (*viz.* malononitrile, ethyl cyanoacetate, ethyl acetoacetate and acetylacetone) 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 sulphate and removed under reduced pressure to give the compounds **16** – **18**, respectively.

N-[4-(4-Dicyanomethylquinazolin-2-yl)phenyl]-4-methylbenzenesulfonamide (**16**)

Yield, 64% (ethanol); m. p. 173 – 5 °C; IR: $\nu = 3330$ (NH), 2225 – 2215 (2 C≡N), 1620 cm^{-1} (CN); ^1H NMR ($CDCl_3$): $\delta = 2.31$ (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^+); ^{13}C NMR: $\delta = 43.1$ (CH), 113.2 (C-5), 115.1 (C-6), 117.2 (C-4a), 118.3 (C-8), 124.3 (C-7), 130.3 (CN), 143.5 (C-8a), 151.2 (C-2), 154.3 (C-4); Analysis for $C_{24}H_{17}N_5O_2S$ (439.49): calcd. C 65.59, H 3.90, N 15.94; found C 65.23, H 3.61, N 15.72.

Cyano-{2-[4-(toluene-4-sulfonylamino)phenyl]quinazolin-4-yl}acetic acid ethyl ester (**17a**)

Yield, 61% (1-butanol); m. p. 213 – 15 °C; IR: $\nu = 3290$ (NH), 2230 (CN), 1735 (CO), 1615 cm^{-1} (CN); ^1H NMR ($CDCl_3$): $\delta = 1.25$ (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). Analysis for $C_{26}H_{22}N_4O_4S$

(486.54): calcd. C 64.18, H 4.56, N 11.52; found: C 64.43, H 4.76, N 11.21.

3-Oxo-2-{2-[4-(toluene-4-sulfonylamino)phenyl]quinazolin-4-yl}butyric acid ethyl ester (**17b**)

Yield, 65% (benzene); m. p. 183 – 5 °C; IR: $\nu = 3310$ (NH), 1735, 1710 (2CO), 1605 cm^{-1} (CN); ^{13}C NMR: $\delta =$ 21.3 (CH_3CH_2), 29.8 (CH_3), 62.3 (CH_2), 118.2 (C-5), 120.1 (C-4a), 123.1 (C-6), 124.2 (C-8), 127.3 (C-7), 143.2 (C-8a), 151.2 (C-2), 153.2 (C-4), 161.3 ($COCH_3$), 195.1 (COO); Analysis for $C_{27}H_{25}N_3O_5S$ (503.57): calcd. 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 – 3 °C; IR: $\nu = 3370$ (NH), 1710 (CO), 1612 cm^{-1} (CN); ^1H NMR ($CDCl_3$): $\delta = 2.35$ (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). Analysis for $C_{26}H_{23}N_3O_4S$ (473.54): calcd. 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 recrystallized from proper solvent 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 – 13 °C; IR: $\nu = 3390$ – 3200 (multiple bands, NH_2, NH), 1615 – 1605 (CN), 1460, 1370 cm^{-1} (SO_2); MS: m/z: 471 (M^+); ^{13}C NMR: $\delta =$ 90.1 (C-4 of pyrazole), 118.2 (C-5), 119.3 (C-4a), 121.3 (C-6), 123.1 (C-8), 129.3 (C-7), 139.5 (C-8a), 150.1 (C-2), 157.3 (C-4), 160.2 (C- 3,5 of pyrazole); Analysis for $C_{24}H_{21}N_7O_2S$ (471.54): calcd. 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 – 3 °C; IR: $\nu = 3420$ – 3210 (multiple bands, NH_2, NH), 1675 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): $\delta = 2.45$ (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; Analysis for $C_{24}H_{20}N_6O_3S$ (472.52): calcd. 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% (1-butanol); m. p. 251 – 3 °C; IR: $\nu = 3300$ – 3120 (NH), 1675 (CO), 1610 cm^{-1} (CN); MS: m/z: 471 (M^+); ^{13}C NMR: $\delta = 26.1$ (CH_3), 96.2 (C-4 of pyrazole), 131.5 (C-5), 134.3 (C-4a), 139.6 (C-6), 140.2 (C-8), 143.5 (C-7), 154.3 (C-8a), 162.1 (C-3 of pyrazole), 164.2 (C-2), 169.4 (C-4), 178.9 (CO); Analysis for $C_{25}H_{21}N_5O_3S$ (471.53): calcd. 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 – 3 °C; IR: $\nu = 3320$ – 3210 (NH), 1610 (CN); ^1H NMR ($CDCl_3$): $\delta = 2.31$ (s, 3H, CH_3), 2.53, 2.64 (2s, 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^+); Analysis for $C_{26}H_{23}N_5O_2S$ (469.56): calcd. 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 recrystallized from proper solvent to give **22a,b**.

22a; Yield, 59% (ethanol); m. p. 191 – 3 °C; IR: $\nu =$ 3300 – 3200 (NH), 1670 (CO), 1610 cm^{-1} (CN); ^1H NMR ($CDCl_3$): $\delta = 2.32$ (s, 3H, CH_3), 2.51, 2.63 (2s, 6H, $2CH_3$ of pyrimidine), 7.13 – 8.21 (m, 12H, ArH), 9.95, 10.12 (2s, 2H, 2NH, exchangeable; Analysis for $C_{27}H_{23}N_5O_3S$ (497.57): calcd. 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 – 8 °C; IR: $\nu =$ 3340 – 3210 (NH), 1605 (CN), 1250 cm^{-1} (CS); MS: m/z: 513 (M^+); ^{13}C NMR: $\delta = 22.3$, 25.4 ($2CH_3$), 110.2 (C-5 of pyrimidine), 126.3 (C-4a), 129.2 (C-5), 131.2 (C-6), 134.2 (C-8), 141.3 (C-7), 151.1 (C-6 of pyrimidine), 153.4 (C-8a), 163.1 (C-2), 165.2 (C-4), 169.2 (C-4 of pyrimidine), 189.2 (CS); Analysis for $C_{27}H_{23}N_5O_2S_2$ (513.64): calcd. C 63.14, H 4.51, N 13.63; found C 63.51, H 4.92, N 13.31%.

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