Synthesis of 5- and 7-fluoroquinazolin-4(1*H*)-ones*

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5-Fluoroquinazoline-2,4-diones and their 2-thio analogs were obtained from 6-fluoroanthranilic acid. Two convenient routes to 5-fluoroquinazolin-4-ones involved cyclocondensation of 6-fluoroanthranilamide with acid chlorides (anhydrides) or with aromatic (heterocyclic) aldehydes. A method for the synthesis of 7-fluoroquinazolin-4-one from 2,4-difluorobenzoic acid was proposed.

Key words: fluoro-containing quinazolin-4-ones, quinazoline-2,4-dione, 2-amino-6-fluorobenzonitrile, 6-fluoroanthranilamide, 6-fluoroanthranilic acid, 2,4-difluorobenzonitrile, cyclocondensation, Schiff bases.

Quinazolin-4(1*H*)-ones constitute an important class of heterocyclic compounds. Some of them can inhibit various enzymes and show antiviral or other biological activity.[1—10] In turn, many fluoro-containing azaheterocycles are superior to nonfluorinated analogs in physiological effect.[11—15] For instance, some quinazolinone derivatives monofluorinated at the benzene ring are promising for use in medicinal chemistry: 6-fluoroquinazolinones are efficient for treatment of obesity and diabetes[16,17] and are neuroprotectors and inhibitors of the AMPA receptor,[18—22] 5- and 7-fluoroquinazolinones show antitumor activity,[23,24] and 8-fluoroquinazolinones are effective against human cytomegalovirus.[25]

Despite numerous publications concerned with the synthesis of quinazolin-4(1*H*)-ones,[26] a search for novel approaches to their design remains of current interest in heterocyclic chemistry. In particular, the synthesis of monofluorinated quinazolin-4(1*H*)-ones is illustrated with only few examples. For instance, monofluorinated 2-styrylquinazolin-4(3*H*)-ones have been obtained by reactions of fluoro-containing 2-aminobenzonitriles with 3-phenylacryloyl chloride followed by base-catalyzed oxidative cyclization of intermediate amides.[27,28] 4-Benzylamino-5-fluoroquinazoline has been synthesized from *N*′-(2-cyano-3-fluorophenyl)-*N*,*N*-dimethylformamidine and benzylamine under microwave radiation.[29] Another known route to 5-fluoroquinazolinones involves a transformation of 6-fluoroanthranilic acid under the action of acetic anhydride into 5-fluoro-2-methyl-3,1-benzoxazin-4-one; the reactions of the latter with 2-amino-1,3,4-thiadiazoles and DL-α-amino-ε-caprolactam lead to 3-substituted 5-fluoroquinazolin-4(3*H*)-ones.[30] In addition, treatment of 2-amino-3-fluorobenzonitrile with formic acid in the presence of sulfuric acid affords 8-fluoroquinazolin-4(1*H*)-one in 88% yield (see Ref. 31).

The goal of the present work was to search for simple synthetic routes to 5- and 7-fluoroquinazolin-4-ones containing various substituents in position 2, which is of interest for revealing correlations between the structures and biological activities of fluoro-containing quinazolinones.

Earlier, we have obtained 6-fluoro- and 6,7,8-trifluoroquinazolin-4(1*H*)-ones from 2-fluorobenzoyl chlorides and *S*-ethylisothiourea as a N,N′-dinucleophile.[32] This method was successfully employed for the synthesis of 2-ethylthio-7-fluoroquinazolinone (Scheme 1). For this purpose, we treated 2,4-difluorobenzoic acid (**1**) with thionyl chloride to give 2,4-difluorobenzoyl chloride **2**. A room-temperature reaction of chloride **2** with *S*-ethylisothiourea hydroiodide in CH_2Cl_2 in the presence of triethylamine afforded *N*-aroyl-*S*-ethylisothiourea **3** in 81% yield. Reflux of (2-fluorobenzoyl)thiourea **3** in dry DMF for 5 h gave 2-ethylthio-7-fluoroquinazolin-4(1*H*)-one (**4**). The ^{1}H NMR spectrum of compound **4** shows signals for aromatic protons, a broadened one-proton singlet for the NH group, and signals for the ethyl group. The mass spectrum of compound **4** contains a 100%-intensity peak with *m*/*z* 137 corresponding to the ion $[M - EtS - CN]^+$; the intensity of the molecular ion

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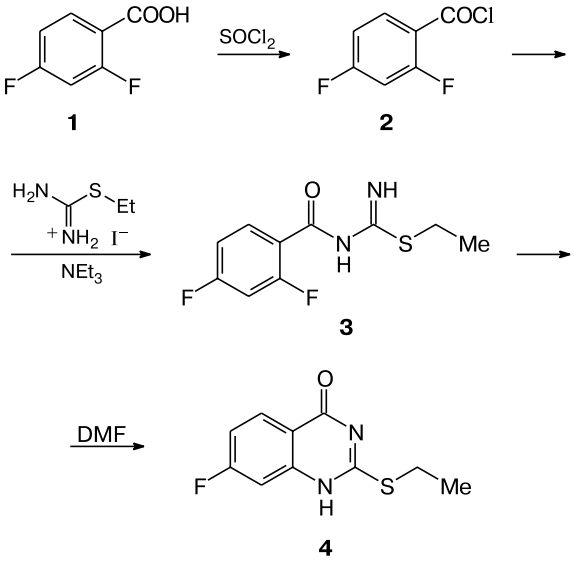
peak with *m/z* 224 was 82%. The structure of 2-(ethylthio)quinazolin-4-one was additionally confirmed by the peak of the ion $[M - EtS - CN - CO]^+$.

Scheme 1

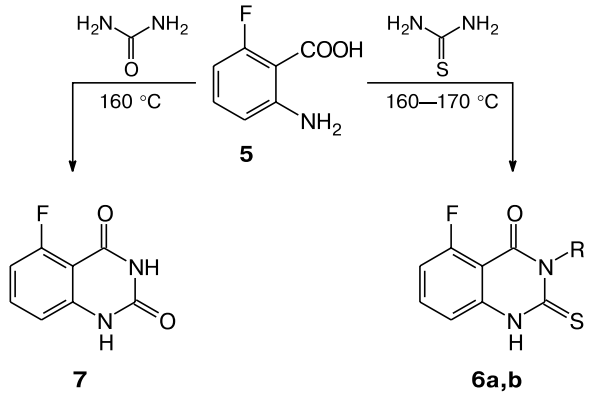


2-Amino-6-fluorobenzoic acid is another easily accessible synthon for construction of monofluorinated heterocycles. It is known that quinazoline-2,4-diones and their 2-thio analogs are most simply obtained by condensation of anthranilic acid with urea and thiourea derivatives.[26,33] This approach was successfully employed for the synthesis of 5-fluoroquinazolin-4-ones: fusion of 6-fluoroanthranilic acid (**5**) with thiourea, phenylthiourea, and urea at 160—170 °C gave quinazolin-4-ones **6a,b** and **7**, respectively (Scheme 2). Phenylthiourea reacted most readily; in the reactions of 6-fluoroanthranilic acid with unsubstituted urea and thiourea, prolonged heating was required and the yields of products were lower. The structures of compounds **6** and **7** were proved by ^{1}H NMR spectroscopy and mass spectrometry. Having the electron-withdrawing F atom, the starting anthranilic acid **5** is more reactive than nonfluorinated anthranilic acid and hence reacts under milder conditions (shorter reaction time and lower temperature).

We studied the possibility of obtaining monofluorinated quinazolin-4-ones from 2-amino-6-fluorobenzonitrile (**8**). In fact, treatment of compound **8** with formic acid in the presence of H_2SO_4 gave 5-fluoroquinazolin-4-one **9** (Scheme 3). However, this reaction is applicable only to the synthesis of 2-unsubstituted quinazolin-4(1*H*)-ones. Acid hydrolysis of nitrile **8** yielded 2-amino-6-fluorobenzamide (**10**), which allows wide variation of the substituent in position 2 of quinazolinones. For instance, 2-(quinolin-2-yl)quinazolin-4-one has been synthesized by acylation of 2-aminobenzamide with quinoline-2-carbonyl chloride followed by cyclization.[34]

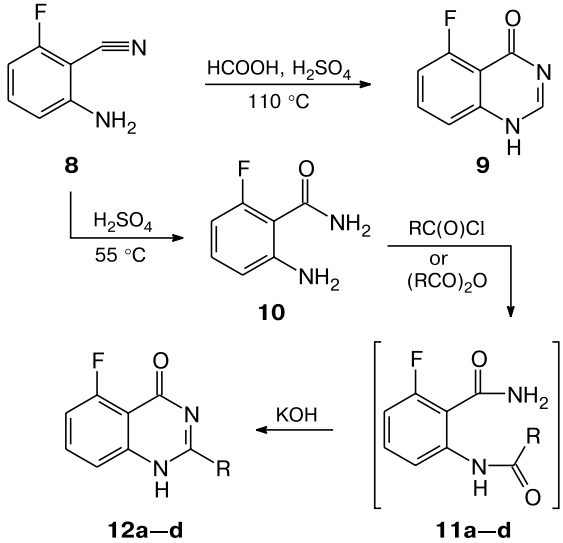
Analogously,[34] starting from 6-fluoroanthranilamide (**10**), we obtained fluoro-containing quinazolin-4(1*H*)-ones **12a—d** (Scheme 3). Compound **10** was refluxed with acetic anhydride for 3 h or kept with benzoyl, nicotinoyl, and isonicotinoyl chlorides at room temperature in the presence of triethylamine. Intermediates **11a—d** were not characterized; they underwent *in situ* cyclization on short-time reflux (5—10 min) in 5% KOH. The structures of compounds **9** and **12a—d** were confirmed by ^{1}H NMR and mass spectra. In the mass spectra of compounds **9** and **12a**, the intensity of the molecular ion peak was 100%. For compounds **12b—d**, the peak with *m/z* 137 corresponding to the ion $[M - RCN]^+$ (where R is the sub-

Scheme 2



R = H (**6a**), Ph (**6b**)

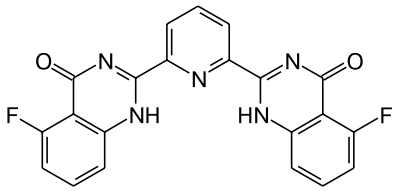
Scheme 3



11, 12: R = Me (**a**), Ph (**b**), 4-pyridyl (**c**), 3-pyridyl (**d**).

stituent in position 2 of the quinazolinone) has a 100% intensity.

2-Amino-6-fluorobenzamide (**10**) was also used for the synthesis of bis(4-oxoquinazolin-2-yl)pyridine **13**. For this purpose, pyridine-2,6-dicarbonyl dichloride was kept with 2-aminobenzamide **10** in the presence of NEt_3 and then the intermediate was heated in 5% KOH. The resulting 2,6-bis(5-fluoro-4-oxo-1,4-dihydroquinazolin-2-yl)pyridine **13** is a structural analog of 1,3-bis(4-oxo-1,4-dihydroquinazolin-2-yl)benzene, which exhibits a broad spectrum of antibacterial activity.[35] The structure of product **13** was confirmed by ^{1}H NMR spectroscopy and mass spectrometry.



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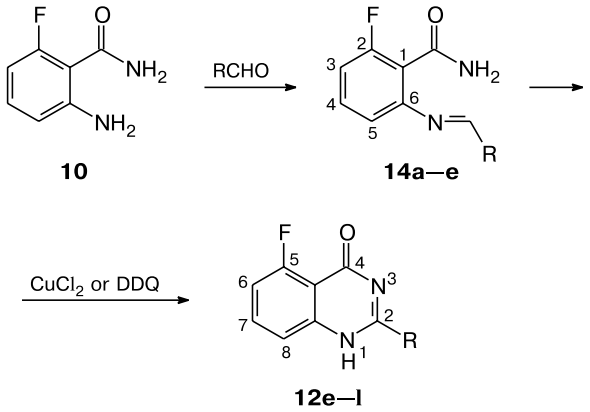
To extend the range of substituents in position 2 of 5-fluoroquinazolin-4-ones, we used aromatic and heterocyclic aldehydes in the reaction with 2-amino-6-fluorobenzamide. Note that the synthesis of 2-substituted quinazolinones from 2-aminobenzamide and aldehydes has been first proposed by Abdel-Jalil *et al.*[36]

A reaction of 2-amino-6-fluorobenzamide (**10**) with furfural in boiling ethanol easily gave the Schiff base **14a**; its structure was confirmed by ^{1}H NMR data (Scheme 4). When heated in methanol in the presence of $CuCl_2$ for 3 h, aldimine **14a** underwent oxidative cyclization into quinazolin-4-one **12e**. The ^{1}H NMR spectrum of compound **12e** shows no signals for the amide group and the N=CH group; instead, a broadened singlet for the NH group appears at δ 12.37. The "one pot" synthesis of quinazolin-4-one **12e** can be carried out by refluxing 2-amino-6-fluorobenzamide (**10**) and furfural in ethanol in the presence of $CuCl_2$. A reaction of 2-amino-6-fluorobenzamide (**10**) with pyridine-2-carboxaldehyde gave compound **14b** undergoing cyclization into 2-(pyridin-2-yl)quinazolin-4-one **12f** on heating in acetonitrile in the presence of DDQ.

To obtain monofluorinated quinazolin-4-ones containing various aryl substituents in position 2, we carried out reactions of 2-amino-6-fluorobenzamide (**10**) with salicylaldehyde, 5-nitrosalicylaldehyde, and anisaldehyde. The resulting Schiff bases **14c—e** easily underwent cyclization into the corresponding quinazolinones **12g—i** on heating with $CuCl_2$ for 40 min. 2-(2,4-Dihydroxyphenyl)-5-fluoro-1*H*-quinazolin-4-one (**12j**) was synthesized by heating 2-amino-6-fluorobenzamide (**10**) with benzene-1,3-dicarbaldehyde in the presence of $CuCl_2$ for 2 h. Reactions of benzamide **10** with 4-fluorobenzaldehyde and 4-trifluoromethylbenzaldehyde under the same conditions for 40 min gave quinazolin-4(1*H*)-ones **12k,l**.

Scheme 4



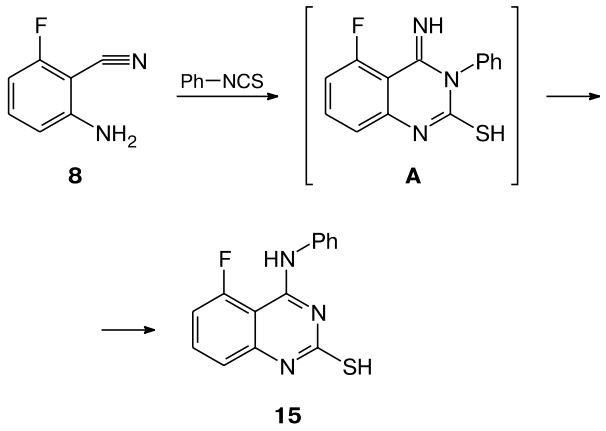
12,14: R — 2-furyl (**12e**, **14a**), 2-pyridyl (**12f**, **14b**), 2-hydroxyphenyl (**12g**, **14c**), 2-hydroxy-5-nitrophenyl (**12h**, **14d**), 4-methoxyphenyl (**12i**, **14e**), 2,4-dihydroxyphenyl (**12j**), 4-fluorophenyl (**12k**), 4-trifluoromethylphenyl (**12l**)

The ^{1}H NMR spectra of compounds **12e—l** are consistent with their structures. Their mass spectra contain a characteristic intense peak of the ion $[M - RCN - CO]^+$.

In an earlier[1,37] described reaction of 2-aminobenzonitrile with phenyl isothiocyanate, 4-phenylaminoquinazoline-2-thiol has been obtained *via* rearrangement of intermediate 4-imino-3-phenylquinazoline for 12 h.

We found that a reaction of 2-amino-6-fluorobenzonitrile (**8**) with phenyl isothiocyanate at 100 °C for 3 h gives 5-fluoro-4-phenylaminoquinazoline-2-thiol (**15**) (Scheme 5). The ^{1}H NMR spectrum of compound **15** shows signals for the aromatic protons, a broadened singlet at δ 12.74 for the SH group, and a doublet at δ 9.01

Scheme 5



($J_{H,F}$ = 15.3 Hz) for the NH proton. In the mass spectrum of compound **15**, the peak of the ion $[M - H]^+$ has the intensity I = 100%. As with quinazolinones **6**, **7**, and **12**, the main fragmentation pathway of quinazoline **15** involves detachment of the fragment [RCN] (R = S) from $[M]^+$. Introduction of a fluorine atom into 2-aminobenzonitrile, as well as into anthranilic acid, makes it possible to obtain the corresponding quinazolines under milder conditions (at lower temperature and shorter reaction time).

To sum up, the methods we proposed for the design of various 2-substituted fluoroquinazolin-4-ones extend the scope of the synthesis of fluoro-containing azaheterocycles.

Experimental

^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker DRX-400 spectrometers (250.14 and 400.13 MHz, respectively) with Me_4Si as the internal standard. Mass spectra were recorded on a Varian MAT 311A spectrometer (accelerating voltage 3 kV, cathode emission current 300 μA, ionizing energy 70 eV, direct inlet probe).

2,4-Difluorobenzoyl chloride (**2**) was prepared from 2,4-difluorobenzoic acid (**1**) and thionyl chloride in toluene as described earlier.[38]

1-(2,4-Difluorobenzoyl)-2-ethylisothiourea (3). Triethylamine (2.7 mL, 19.4 mmol) and a solution of 2,4-difluorobenzoyl chloride **2** (19.6 mL, 9.7 mmol) in toluene (6 mL) were added to a stirred suspension of S-ethylisothiourea hydroiodide (2.3 g, 9.7 mmol) in anhydrous CH_2Cl_2 (20 mL). The reaction mixture was kept at room temperature for 24 h and then concentrated. The residue was washed with water and recrystallized from ethanol. The yield of compound **3** was 1.92 g (81%), m.p. 144—146 °C. ^{1}H NMR (DMSO-d_6), δ: 1.32 (t, 3 H, CH_3, ^3J = 7.4 Hz); 3.11 (q, 2 H, SCH_2, ^3J = 7.4 Hz); 7.13, 8.07 (both m, 2 H and 1 H, $C_6H_3F_2$); 9.52 (br.s, 2 H, HN=C—NH—). Found (%): C, 48.89; H, 4.13; N, 11.39. $C_{10}H_{10}F_2N_2OS$. Calculated (%): C, 49.16; H, 4.13; N, 11.47.

2-Ethylthio-7-fluoroquinazolin-4(1*H*)-one (4). A solution of isothiourea **3** (0.7 g, 2.9 mmol) in anhydrous DMF (6 mL) was refluxed for 4 h and then concentrated. The residue was recrystallized from ethanol. The yield of quinazolinone **4** was 0.23 g (35%). ^{1}H NMR (DMSO-d_6), δ: 1.40 (t, 3 H, CH_3, ^3J = 7.5 Hz); 3.19 (q, 2 H, SCH_2, ^3J = 7.5 Hz); 7.13 (m, 2 H, H(5) and H(8)); 8.07 (m, 1 H, H(6)); 12.37 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 224 $[M]^+$ (82), 196 $[M - CO]^+$ (37), 137 $[M - EtS - CN]^+$ (100), 108 (96). Found (%): C, 53.25; H, 4.09; N, 12.93. $C_{10}H_9FN_2OS$. Calculated (%): C, 53.55; H, 4.05; N, 12.49.

5-Fluoro-4-oxo-1,2,3,4-tetrahydroquinazoline-2-thione (6a). A mixture of 2-amino-6-fluorobenzoic acid **5** (0.24 g, 3.2 mmol) and thiourea was heated at 160—170 °C for 2 h. On cooling, ethanol (3 mL) was added and the product was recrystallized. The yield of quinazolinone **6a** was 0.25 g (47%), m.p. 102—104 °C. ^{1}H NMR (DMSO-d_6), δ: 6.92, 7.18, 7.38 (all m, 1 H each, H(6), H(8), H(7)); 7.81 (br.s, 2 H, N(1)H, N(3)H). Found (%): C, 49.04; H, 2.59; N, 14.23. $C_8H_5FN_2OS$. Calculated (%): C, 48.97; H, 2.57; N, 14.28.

Compounds **6b** and **7** were obtained analogously from 2-amino-6-fluorobenzoic acid (**5**) and phenylthiourea or urea, respectively.

5-Fluoro-4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazoline-2-thione (6b). The reaction mixture was heated for 1 h. Yield 70%, m.p. 250—252 °C (from ethanol). ^{1}H NMR (DMSO-d_6), δ: 6.99 (t, H (7), ^3J = 8.4 Hz); 7.19 (d, 2 H, Ph, ^3J = 6.7 Hz); 7.28 (d, 1 H, H(8), ^3J = 8.2 Hz); 7.37—7.52 (m, 3 H, Ph); 7.69 (m, 1 H, H(6)); 12.99 (br.s, 1 H, N(1)H). MS, m/z (I_{rel} (%)): 272 $[M]^+$ (84), 271 $[M - H]^+$ (100), 137 $[M - Ph - NCS]^+$ (43), 110 $[(M + H) - PhNCS - CO]^+$ (56), 77 $[C_6H_5]^+$ (49). Found (%): C, 61.55; H, 3.39; N, 10.97. $C_{14}H_9FN_2OS$. Calculated (%): C, 61.75; H, 3.34; N, 10.29.

5-Fluoroquinazoline-2,4(1*H*,3*H*)-dione (7). The reaction mixture was heated for 3 h. Yield 50%, m.p. 320—322 °C (from ethanol). ^{1}H NMR (DMSO-d_6), δ: 6.80 (dd, 1 H, H(7), ^3J = 8.3 Hz, ^3J = 10.3 Hz); 6.98 (d, 1 H, H(8), ^3J = 8.3 Hz); 7.52 (ddd, 1 H, H(6), ^4J = 2.8 Hz, ^3J = 6.8 Hz, ^3J = 11.0 Hz); 11.11 (br.s, 2 H, N(1)H, N(3)H). MS, m/z (I_{rel} (%)): 180 $[M]^+$ (85), 137 $[M - CO - NH]^+$ (98), 110 $[M - OCN - CO]^+$ (100), 82 (30). Found (%): C, 53.15; H, 2.89; N, 15.53. $C_8H_5FN_2O_2$. Calculated (%): C, 53.33; H, 2.80; N, 15.55.

5-Fluoroquinazolin-4(1*H*)-one (9). A suspension of 2-amino-6-fluorobenzonitrile (**8**) (2 g, 14.6 mmol) in 85% HCOOH (15 mL) was added in portions to a mixture of conc. H_2SO_4 (0.8 mL) and 85% HCOOH (5 mL). The reaction mixture was heated at 105—115 °C for 50 min. On cooling, the mixture was poured onto ice and kept for 15 min. The precipitate that formed was filtered off, washed with water, and recrystallized from ethanol. The yield of quinazolinone **9** was 1.51 g (64%), m.p. 210—212 °C. ^{1}H NMR (DMSO-d_6), δ: 6.70 (br.s, 1 H, NH); 7.22 (t, 1 H, H(7), ^3J = 8.3 Hz); 7.51 (d, 1 H, H(8), ^3J = 8.3 Hz); 7.79 (m, 1 H, H(6)); 8.31 (s, 1 H, H(2)). MS, m/z (I_{rel} (%)): 164 $[M]^+$ (100), 163 $[M - H]^+$ (35), 137 $[M - CN]^+$ (22), 136 $[M - HCN]^+$ (36), 110 $[M - RCN - CO]^+$ (29), 108 (30). Found (%): C, 58.55; H, 3.09; N, 17.13. $C_8H_5FN_2O$. Calculated (%): C, 58.53; H, 3.08; N, 17.07.

2-Amino-6-fluorobenzamide (10). A solution of 2-amino-6-fluorobenzonitrile (**8**) (1.5 g, 11.0 mmol) in conc. H_2SO_4 (7.5 mL) was stirred with a magnetic stirring bar at 50—55 °C for 2 h. The reaction mixture was poured into water (300 mL) and neutralized with soda. The product was extracted with CH_2Cl_2 and the extract was dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from hexane. The yield of compound **10** was 0.9 g (54%), m.p. 87—89 °C. ^{1}H NMR (DMSO-d_6), δ: 5.77 (br.s, 1 H, NH); 6.11 (br.s, 2 H, NH_2); 6.35 (ddd, 1 H, H(4), ^4J = 1.0 Hz, ^3J = 7.8 Hz, ^3J = 13.2 Hz); 6.45 (d, 1 H, H(3), ^3J = 8.5 Hz); 6.65 (br.s, 1 H, NH); 7.12 (ddd, 1 H, H(5), ^4J = 2.0 Hz, ^3J = 7.5 Hz, ^3J = 14.5 Hz).

5-Fluoro-2-methylquinazolin-4(1*H*)-one (12a). A solution of 2-amino-6-fluorobenzamide (**10**) (0.7 g, 4.5 mmol) in acetic anhydride (3 mL) was refluxed for 3 h. The reaction mixture was cooled and neutralized with a solution of soda to pH 6—7. Intermediate **11a** was extracted with ethyl acetate. The extract was dried over Na_2SO_4. The solvent was removed and the residue was dissolved in ethanol (6 mL). The solution was refluxed with 5% KOH (13 mL) for 5 min. On cooling, the reaction mixture was neutralized with dilute acetic acid and the product was extracted with chloroform. The extract was dried over Na_2SO_4 and concentrated and the residue was recrystallized from ethanol. The yield of quinazoline **12a** was 0.65 g (92%),

m.p. 251—253 °C. ^{1}H NMR (DMSO-d_6), δ: 2.36 (s, 3 H, CH_3); 7.08 (dd, 1 H, H(7), ^3J = 8.0 Hz, ^3J = 10.8 Hz); 7.34 (d, 1 H, H(8), ^3J = 8.3 Hz); 7.67 (m, 1 H, H(6)); 12.16 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 178 $[M]^+$ (100), 163 $[M - NH]^+$ (25), 137 $[M - MeCN]^+$ (19), 110 $[M - MeCN - CO]^+$ (27), 108 (33). Found (%): C, 60.65; H, 3.99; N, 16.00. $C_9H_7FN_2O$. Calculated (%): C, 60.66; H, 3.97; N, 15.73.

5-Fluoro-2-phenylquinazolin-4(1*H*)-one (12b). Benzoyl chloride (0.63 mL, 4.5 mmol) and triethylamine (1.4 mL, 9 mmol) were added to a suspension of amide (**10**) (0.7 g, 4.5 mmol) in dry CH_2Cl_2 (8 mL). The reaction mixture was stirred with a magnetic stirring bar for 2 h. The precipitate of compound **11b** was filtered off and refluxed with 5% KOH (18 mL) in ethanol (6 mL) for 10 min. On cooling, the reaction mixture was neutralized with dilute acetic acid. The precipitate that formed was filtered off and recrystallized from DMSO. The yield of quinazoline **12b** was 0.65 g (90%), m.p. 308—310 °C. ^{1}H NMR (DMSO-d_6), δ: 7.13 (t, 1 H, H(7), ^3J = 8.6 Hz); 7.45—7.54 (m, 1 H, H(8) and 3 H, Ph); 7.73 (ddd, 1 H, H(6), ^4J = 2.1 Hz, ^3J = 6.9 Hz, ^3J = 9.9 Hz); 8.22 (m, 2 H, Ph); 12.42 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 240 $[M]^+$ (63), 137 $[M - PhCN]^+$ (100), 108 (20), 77 $[C_6H_5]^+$ (33). Found (%): C, 70.00; H, 3.80; N, 11.73. $C_{14}H_9FN_2O$. Calculated (%): C, 69.99; H, 3.78; N, 11.66.

Compounds **12c,d** and **13** were obtained analogously from 2-amino-6-fluorobenzamide (**10**) and isonicotinoyl, nicotinoyl, and pyridine-2,6-dicarbonyl chlorides, respectively.

5-Fluoro-2-(pyridin-4-yl)quinazolin-4(1*H*)-one (12c). Yield 86%, m.p. 310—312 °C (from DMSO). ^{1}H NMR (DMSO-d_6), δ: 7.19 (m, 1 H, H(7)); 7.53 (d, 1 H, H(8), ^3J = 7.8 Hz); 7.77 (m, 1 H, H(6)); 8.12 (dd, 2 H, H(3′), H(5′), ^4J = 1.4 Hz, ^3J = 4.6 Hz); 8.73 (d, 2 H, H(2′), H(6′), ^3J = 6.0 Hz); 12.66 (br.s, 1 H, N(1)H). MS, *m/z* (I_{rel} (%)): 241 $[M]^+$ (73), 137 $[M - RCN]^+$ (100), 110 $[(M + H) - RCN - CO]^+$ (25), 108 (26), 78 (21). Found (%): C, 64.65; H, 3.39; N, 17.33. $C_{13}H_8FN_3O$. Calculated (%): C, 64.72; H, 3.35; N, 17.42.

5-Fluoro-2-(pyridin-3-yl)quinazolin-4(1*H*)-one (12d). Yield 88%, m.p. 311—313 °C (from DMSO). ^{1}H NMR (DMSO-d_6), δ: 7.19 (ddd, 1 H, H(7), ^4J = 1.0 Hz, ^3J = 8.3 Hz, ^3J = 10.5 Hz); 7.53 (m, 2 H, H(8) and H(5′)); 7.76 (ddd, 1 H, H(6), ^4J = 2.3 Hz, ^3J = 6.7 Hz, ^3J = 10.2 Hz); 8.51, 8.72, 9.32 (all m, 1 H each, H(6′), H(4′), H(2′)); 12.62 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 241 $[M]^+$ (67), 137 $[M - RCN]^+$ (100), 110 $[(M + H) - RCN - CO]^+$ (25), 78 (22). Found (%): C, 64.65; H, 3.39; N, 17.53. $C_{13}H_8FN_3O$. Calculated (%): C, 64.72; H, 3.35; N, 17.42.

2,6-Bis(5-fluoro-4-oxo-1,4-dihydroquinazolin-2-yl)pyridine (13). Yield 76%, m.p. 352—354 °C (from DMSO). ^{1}H NMR (DMSO-d_6), δ: 7.29 (t, 2 H, H(7′), H(7″), ^3J = 9.8 Hz); 7.61 (d, 2 H, H(8′), H(8″) ^3J = 8.3 Hz); 7.82 (m, 2 H, H(6′), H(6″)); 8.30 (m, 1 H, H(4)); 8.72 (m, 2 H, H(3), H(5)); 13.22 (br.s, 2 H, N(1′)H and N(1″)H). MS, *m/z* ($I_{rel.}$ (%)): 403 $[M]^+$ (100), 404 $[M + H]^+$ (26), 375 $[M - CO]^+$ (29), 137 (61), 110 (49), 108 (43). Found (%): C, 61.95; H, 2.79; N, 17.33. $C_{21}H_{11}F_2N_5O_2$. Calculated (%): C, 62.53; H, 2.75; N, 17.37.

2-Fluoro-6-[(furan-2-ylmethylidene)amino]benzamide (14a). Furfural (0.72 mL, 8.7 mmol) was added to a suspension of 2-amino-6-fluorobenzamide (**10**) (0.9 g, 5.8 mmol) in ethanol (10 mL). The reaction mixture was refluxed for 3 h. On cooling, the precipitate was filtered off and recrystallized from ethanol. The yield of compound **14a** was 0.82 g (82%), m.p. 195—197 °C. ^{1}H NMR (DMSO-d_6), δ: 5.68 (s, 1 H, NH); 6.29—6.37 (m, 3 H, NH and 2 H, furyl); 6.58 (d, 1 H, H(3), ^3J = 8.3 Hz); 7.15, 7.38, 7.51 (all m, 1 H each, H(4), H(5) and H_{furyl}); 8.25 (s, 1 H, N=CH). Found (%): C, 62.10; H, 3.89; N, 12.13. $C_{12}H_9FN_2O_2$. Calculated (%): C, 62.06; H, 3.91; N, 12.07.

Compounds **14b—e** were obtained analogously from amide **10** and pyridine-2-carboxaldehyde, salicylaldehyde, 2-hydroxy-5-nitrobenzaldehyde, or 4-methoxybenzaldehyde, respectively.

2-Fluoro-6-[(pyridin-2-ylmethylidene)amino]benzamide (14b). Yield (85%), m.p. 202—204 °C (from ethanol). ^{1}H NMR (DMSO-d_6), δ: 5.65 (s, 1 H, NH); 6.28 (dd, 1 H, H(4), ^3J = 8.4 Hz); 6.57 (d, 1 H, H(3′), ^3J = 4.3 Hz); 7.11 (dd, 1 H, H(3), ^3J = 8.0 Hz); 7.30 (m, 1 H, H(5′)); 7.37 (s, 1 H, NH); 7.53 (d, 1 H, H(5), ^3J = 7.8 Hz); 7.78 (m, 1 H, H(4′)); 8.14 (s, 1 H, N=CH); 8.54 (d, 1 H, H(6′), ^3J = 4.4 Hz). Found (%): C, 64.15; H, 4.19; N, 17.23. $C_{13}H_{10}FN_3O$. Calculated (%): C, 64.18; H, 4.15; N, 17.28.

2-Fluoro-6-(2-hydroxybenzylideneamino)benzamide (14c). Yield 96%, m.p. 200—202 °C (from ethanol). ^{1}H NMR (DMSO-d_6), δ: 6.95 (m, 2 H, $C_6\underline{H}_4OH$); 7.09 (t, 1 H, H(4), ^3J = 8.5 Hz); 7.23 (d, 1 H, H(5), ^3J = 8.4 Hz); 7.36—7.45 (m, 1 H, H(3) and 1 H, $C_6\underline{H}_4OH$); 7.54 (s, 1 H, NH); 7.59—7.65 (m, 1 H, NH and 1 H, $C_6\underline{H}_4OH$); 7.79 (s, 1 H, N=CH); 8.87 (s, 1 H, OH). Found (%): C, 64.95; H, 4.39; N, 10.73. $C_{14}H_{11}FN_2O_2$. Calculated (%): C, 65.10; H, 4.30; N, 10.85.

2-Fluoro-6-(2-hydroxy-5-nitrobenzylideneamino)benzamide (14d). Yield 95%, m.p. 240—242 °C (from ethanol). ^{1}H NMR (DMSO-d_6), δ: 5.97 (s, 1 H, NH); 6.35 (m, 1 H, H(4)); 6.62 (d, 1 H, H(5), ^3J = 8.2 Hz); 7.00—7.12 (m, 1 H, NH and 1 H, $C_6\underline{H}_3OH(NO_2)$); 7.15 (m, H(6)); 7.90 (s, 1 H, N=CH); 8.05, 8.26 (both m, 1 H each, $C_6\underline{H}_3OH(NO_2)$). Found (%): C, 55.35; H, 3.39; N, 13.83. $C_{14}H_{10}FN_3O_4$. Calculated (%): C, 55.44; H, 3.33; N, 13.86.

2-Fluoro-6-(4-methoxybenzylideneamino)benzamide (14e). Yield 94%, m.p. 205—207 °C (from ethanol). ^{1}H NMR (DMSO-d_6), δ: 3.78 (s, 3 H, CH_3); 5.63 (s, 1 H, NH); 6.31 (td, 1 H, H(4), ^4J = 7.5 Hz, ^3J = 8.3 Hz); 6.54 (d, 1 H, H(5), ^3J = 8.3 Hz); 6.90 (d, 2 H, $C_6H_4(OCH_3)$, ^3J = 8.8 Hz); 7.09—7.18 (m, 2 H, H(3) and NH); 7.41 (d, 2 H, $C_6H_4(OCH_3)$, ^3J = 8.4 Hz); 7.93 (s, 1 H, N=CH). Found (%): C, 66.15; H, 4.89; N, 10.23. $C_{15}H_{13}FN_2O_2$. Calculated (%): C, 66.16; H, 4.82; N, 10.29.

5-Fluoro-2-(furan-2-yl)quinazolin-4(1*H*)-one (12e). ***A.*** Cupric chloride (0.35 g, 2.6 mmol) was added to a suspension of compound **14a** (0.4 g, 1.7 mmol) in methanol (6 mL). The mixture was refluxed for 3 h and then partially concentrated. The precipitate that formed was filtered off and recrystallized from CH_2Cl_2—hexane (1 : 1). The yield of quinazolin-4-one **12e** was 0.2 g (52%), m.p. 200—202 °C.

B. Furfural (0.4 mL, 5 mmol) and $CuCl_2$ (0.62 g, 4.5 mmol) were added to a suspension of 2-amino-6-fluorobenzamide **10** (0.7 g, 4.5 mmol) in ethanol (10 mL). The mixture was refluxed for 3 h and then partially concentrated. The precipitate that formed was filtered off and recrystallized from CH_2Cl_2—hexane (1 : 1). The yield of quinazolin-4-one **12e** was 0.4 g (63%), m.p. 200—202 °C. ^{1}H NMR (DMSO-d_6), δ: 6.66 (m, 1 H, furyl); 7.10 (m, 1 H, H(7)); 7.49 (m, 1 H, furyl); 7.62 (d, 1 H, H(8), ^3J = 8.3 Hz); 7.70 (m, 1 H, H(6)); 7.81 (m, 1 H, furyl); 12.37 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 230 $[M]^+$ (100), 231 $[M+H]^+$ (22), 138 $[(M + H) - RCN]^+$ (20), 110

$[(M + H) - RCN - CO]^+$ (21), 108 (26), 94 (37). Found (%): C, 62.15; H, 2.89; N, 12.23. $C_{12}H_7FN_2O_2$. Calculated (%): C, 62.60; H, 3.07; N, 12.17.

5-Fluoro-2-(pyridin-2-yl)quinazolin-4(1*H*)-one (12f). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (2.1 g, 9.3 mmol) was added to a suspension of compound **14b** (1.4 g, 5.8 mmol) in dry acetonitrile (86 mL). The mixture was refluxed for 2 h. On cooling, the precipitate was filtered off and recrystallized from ethanol. The yield of compound **12f** was 0.7 g (51%), m.p. 190—192 °C. ^{1}H NMR (DMSO-d_6), δ: 7.21 (td, 1 H, H(7), ^4J = 7.3 Hz, ^3J = 8.0 Hz); 7.58 (d, 1 H, H(8), ^3J = 7.9 Hz); 7.64 (m, 1 H, H(5′)); 7.80 (ddd, 1 H, H(6), ^4J = 2.9 Hz, ^3J = 7.0 Hz, ^3J = 11.1 Hz); 8.05 (m, 1 H, H(4′)); 8.50 (d, 1 H, H(3′), ^3J = 7.9 Hz); 8.74 (d, 1 H, H(6′), ^3J = 4.9 Hz); 11.31 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 241 $[M]^+$ (86), 242 $[M + H]^+$ (13), 213 $[M - CO]^+$ (25), 137 $[M - RCN]^+$ (100), 110 $[M - RCN - CO]^+$ (39), 108 (28), 78 (37). Found (%): C, 64.75; H, 3.39; N, 17.39. $C_{13}H_8FN_3O$. Calculated (%): C, 64.72; H, 3.35; N, 17.42.

5-Fluoro-2-(2-hydroxyphenyl)quinazolin-4(1*H*)-one (12g). Cupric chloride (0.36 mL, 2.7 mmol) was added to a suspension of compound **14c** (0.7 g, 2.7 mmol) in ethanol (8 mL). The mixture was refluxed for 40 min. On cooling, the precipitate was filtered off and recrystallized from DMSO. The yield of quinazolin-4-one **12g** was 0.60 g (83%), m.p. 322—324 °C. ^{1}H NMR (DMSO-d_6), δ: 6.89 (m, 2 H, $C_6\underline{H}_4OH$), 7.13 (dd, 1 H, H(7), ^4J = 7.4 Hz, ^3J = 8.2 Hz); 7.37 (m, 1 H, $C_6\underline{H}_4OH$); 7.46 (d, 1 H, H(8), ^3J = 8.2 Hz); 7.73 (ddd, 1 H, H(6), ^4J = 2.9 Hz, ^3J = 6.8 Hz, ^3J = 11.0 Hz); 8.18 (m, 1 H, $C_6\underline{H}_4OH$); 12.40 (br.s, 1 H, NH or OH); 13.43 (br.s, 1 H, NH or OH). MS, *m/z* (I_{rel} (%)): 256 $[M]^+$ (100), 137 $[M - RCN]^+$ (91), 110 $[M - RCN - CO]^+$ (41), 108 (11), 91 (13). Found (%): C, 65.75; H, 3.59; N, 10.93. $C_{14}H_9FN_2O_2$. Calculated (%): C, 65.62; H, 3.55; N, 10.93.

Products **12h** and **12i** were obtained analogously from compounds **14d** and **14c**, respectively.

5-Fluoro-2-(2-hydroxy-5-nitrophenyl)quinazolin-4(1*H*)-one (12h). Yield 80%, m.p. > 320 °C (from DMSO). ^{1}H NMR (DMSO-d_6), δ: 7.16 (d, 1 H, H(3′), ^3J = 9.2 Hz); 7.24 (m, 1 H, H(7)); 7.58 (d, 1 H, H(8), ^3J = 8.1 Hz); 7.82 (m, 1 H, H(6)); 8.28 (dd, 1 H, H(4′), ^3J = 9.0 Hz, ^4J = 2.3 Hz); 9.33 (d, H(6′), ^4J = 2.8 Hz); 12.38 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 301 $[M]^+$ (100), 271 (58), 137 $[M - RCN]^+$ (50), 110 $[M - RCN - CO]^+$ (54). Found (%): C, 55.75; H, 2.69; N, 13.93. $C_{14}H_8FN_3O_4$. Calculated (%): C, 55.81; H, 2.68; N, 13.95.

5-Fluoro-2-(4-methoxyphenyl)quinazolin-4(1*H*)-one (12i). Yield 91%, m.p. 288—290 °C (from DMSO). ^{1}H NMR (DMSO-d_6), δ: 3.90 (s, 3 H, CH_3); 6.96—7.10 (m, 1 H, H(7) and 2 H, $C_6\underline{H}_4(OCH_3)$); 7.45 (m, 1 H, H(8)); 7.67 (m, 1 H, H(6)); 8.22 (m, 2 H, $C_6\underline{H}_4(OCH_3)$); 12.25 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 270 $[M]^+$ (79), 137 $[M - RCN]^+$ (100), 110 $[M - RCN - CO]^+$ (16), 108 (15). Found (%): C, 67.00; H, 4.19; N, 10.23. $C_{15}H_{11}FN_2O_2$. Calculated (%): C, 66.65; H, 4.11; N, 10.37.

2-(2,4-Dihydroxyphenyl)-5-fluoroquinazolin-4(1*H*)-one (12j). Benzene-1,3-dicarbaldehyde (1.1 g, 7.8 mmol) and $CuCl_2$ (1.1 g, 7.8 mmol) were added to a suspension of 2-amino-6-fluorobenzamide **10** (1.2 g, 7.8 mmol) in ethanol (10 mL). The mixture was refluxed for 2 h. On cooling, the precipitate was filtered off and recrystallized from DMSO. The yield of quinazolin-4-one **12j** was 1.71 g (79%), m.p. 340—342 °C. ^{1}H NMR (DMSO-d_6), δ: 6.38 (m, 2 H, $C_6\underline{H}_3(OH)_2$); 7.14 (td, 1 H, H(7), ^4J = 7.3 Hz, ^3J = 8.0 Hz); 7.45 (d, 1 H, H(8), ^3J = 8.0 Hz); 7.66 (m, 1 H, H(6)); 8.08 (m, 1 H, $C_6\underline{H}_3(OH)_2$); 9.98 (br.s, 2 H, 2OH); 12.15 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 272 $[M]^+$ (67), 137 $[M - RCN]^+$ (100), 110 $[M - RCN - CO]^+$ (41), 108 (13). Found (%): C, 61.65; H, 3.39; N, 10.23. $C_{14}H_9FN_2O_3$. Calculated (%): C, 61.76; H, 3.34; N, 10.29.

Compounds **12k** and **12l** were obtained analogously from 2-amino-6-fluorobenzamide (**10**) and 4-fluorobenzaldehyde or 4-trifluoromethylbenzaldehyde, respectively.

5-Fluoro-2-(4-fluorophenyl)quinazolin-4(1*H*)-one (12k). The reaction mixture was refluxed for 40 min. The yield was 94%, m.p. 320—322 °C (from DMSO). ^{1}H NMR (DMSO-d_6), δ: 7.14 (td, 1 H, H(7), ^4J = 7.4 Hz, ^3J = 8.2 Hz); 7.25 (d, 2 H, C_6H_4F, ^3J = 5.6 Hz); 7.49 (d, 1 H, H(8), ^3J = 8.2 Hz); 7.74 (ddd, 1 H, H(6), ^3J = 15.2 Hz, ^3J = 7.0 Hz, ^4J = 2.7 Hz); 8.30 (dd, 2 H, C_6H_4F, ^3J = 5.5 Hz, ^3J = 2.0 Hz); 12.60 (br.s, 1 H, NH). Found (%): C, 64.99; H, 3.10; N, 11.00. $C_{14}H_9FN_2O_3$. Calculated (%): C, 65.12; H, 3.12; N, 10.85.

5-Fluoro-2-(4-trifluoromethylphenyl)quinazolin-4(1*H*)-one (12l). The reaction mixture was refluxed for 40 min. The yield was 96%, m.p. 290—292 °C (from DMSO). ^{1}H NMR (DMSO-d_6), δ: 7.17 (dd, 1 H, H(7), ^3J = 9.6 Hz, ^3J = 8.1 Hz); 7.53 (d, 1 H, H(8), ^3J = 8.2 Hz); 7.74 (m, 1 H, H(6)); 7.80 (d, 2 H, $C_6H_4CF_3$, ^3J = 8.5 Hz); 8.42 (d, 2 H, $C_6H_4CF_3$, ^3J = 8.3 Hz); 12.65 (br.s, 1 H, NH). Found (%): C, 58.41; H, 2.60; N, 9.00. $C_{14}H_9FN_2O_3$. Calculated (%): C, 58.45; H, 2.62; N, 9.09.

4-Anilino-5-fluoroquinazoline-2-thiol (15). A mixture of 2-amino-6-fluorobenzonitrile (**8**) (0.5 g, 3.6 mmol) and phenyl isothiocyanate (1 mL, 7.2 mmol) was heated at 100 °C for 3.5 h. On cooling, the precipitate was filtered off and recrystallized from DMSO. The yield of compound **15** was 0.93 g (95%), m.p. 260—262 °C. ^{1}H NMR (DMSO-d_6), δ: 7.02 (dd, 1 H, H(7), ^3J = 7.9 Hz, ^3J = 12.5 Hz); 7.17 (m, 1 H, Ph); 7.28 (d, 1 H, H(8), ^3J = 8.6 Hz); 7.39 (m, 2 H, Ph); 7.61 (ddd, 1 H, H(6), ^4J = 2.1 Hz, ^3J = 7.2 Hz, ^3J = 11.4 Hz); 7.82 (m, 2 H, Ph); 9.01 (d, 1 H, NH, $J_{H,F}$ = 15.3 Hz); 12.74 (br.s, 1 H, SH). MS, *m/z* (I_{rel} (%)): 271 $[M]^+$ (87), 270 $[M - H]^+$ (100), 213 $[M - SCN]^+$ (56), 93 $[C_6H_5NH_2]^+$ (34), 77 $[C_6H_5]^+$ (56), 272 $[M + H]^+$ (20). Found (%): C, 61.55; H, 3.39; N, 10.23. $C_{14}H_{10}FN_3S$. Calculated (%): C, 61.76; H, 3.34; N, 10.29.

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