

Highly Efficient Synthesis of Novel Fluorine Bearing Quinoline-4-carboxylic Acid and the Related Compounds as Amylolytic Agents

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ABSTRACT

Highly efficient syntheses of novel fluorine bearing quinoline-4-carboxylic acids and the related compounds had been achieved from cyclocondensation of 2-amino-5-fluorophenyl glyoxylic acid **1** with benzoyl asetanilides **2** in boiling DMF, to give the target **3**. Decarboxylation of **3** produced 6-fluoro-2-phenyl-3-(substituted amino)-keto-quinolines **4**, while that reaction underwent refluxing, afforded 7-fluoro-1-(aryl)-3-phenyl-pyrrolo[3,4-c] quinoline-2,9-diones **5**. Structure of the products has been established from their elemental and spectral analysis. All targets exhibited a high to moderate activity against some *Aspergillus fungi* as amylyolytic agents.

Keywords: Amylolytic Activity; Amylolytic Agents; *Aspergillus fungi*; Efficient Synthesis; Fluoroquinoline; Quinoline-4-carboxylic Acids

1. Introduction

Quinoline derivatives are clinically used antimicrobial drugs [1], various heterocyclic systems bearing quinoline moieties distinguish moderate toxicity and CNS (Central Nervous System) stimulants [2,3]. An interesting quinoline derivatives which inhibited HIV-1 replication through interference with the transcription process have been reported, for example; fluoroquinolones (**K-12**) [8-difluoromethoxy-1-ethyl-6-fluoro-1,4-dihydro-7-[4-(2-methoxyphenyl)-1-piperazinyl]-4-oxo-quinoline-3-carboxylic acid] and **K-37** [7-(3,4-dihydro-4-phenyl-1-piperidinyl)-1,4-dihydro-6-fluoro-1-methyl-8-trifluoromethyl-4-oxo-quinoline-3-carboxylic acid] [4-8], (**Figure 1**).

Quinoline nucleus is significant in designing a number of pharmacologically active compounds [9-16]. In continues to our investigation towards quinolines synthesis [17-19] we successfully synthesized a number of fluorine bearing quinoline-4-carboxylic acids in high yield. These compounds are efficiently investigated on various fungi as amylyolytic agents.

2. Results and Discussion

The cyclocondensation of 2-amino-5-fluorophenyl glyoxylic acid **1** [obtained from basic treatments of 5-fluoroisatin] with benzoyl asetanilide derivatives **2** [obtained from preheated ethyl benzoyl acetate with halogenated

aromatic amines and or sulfa drugs] in DMF [20-25], yielded the target compounds 6-fluoro-2-phenyl-3-(arylamino)-oxo-quinoline-4-carboxylic acids **3a-d** (**Scheme 1**).

The decarboxylations of compounds **3a-d** by gentle warming with aqueous K_2CO_3 at $40^\circ C - 60^\circ C$ for 10 min produced the quinoline derivatives **4a-d**, while refluxing the potassium salt of compound **3** with K_2CO_3 solution for 2 h gave 7-fluoro-1-(arylamino)-3-phenylpyrrolo[3,4-c]quinoline-2,9-dione (**5a-d**). Thus, Compounds **3** were undergoing intramolecular heterocyclization via ring closure reaction by loss of one mole of KOH to give a more stabilized fused Reterobicyclic systems **5** (**Scheme 2**).

Structures of novel compounds have been deduced from their elemental analysis and spectral measurements. The IR spectra of compounds **3** showed broad bands at $3300 - 2800\text{ cm}^{-1}$ that attributed OH and NH functional groups in addition to sharp bands at 1700, 1630 and 1220 cm^{-1} due to presence of carboxylic acid, amide and C-F groups. 1H NMR spectra showed the COOH and NHCO protons at δ 14 and δ 11.5 respectively, while characteristic protons of aryl and phenyl appeared at δ 8.5 - 7.1 ppm. ^{13}C NMR spectra showed carbons of COOH, CONH, C=N, C-F and aryl at 168, 162, 151, 140 and 130-125 ppm respectively. Thus, compounds **4** showed the absence of COOH functional groups due to lack of OH and carbonyl peaks.

The structure of compound **5** was established from that

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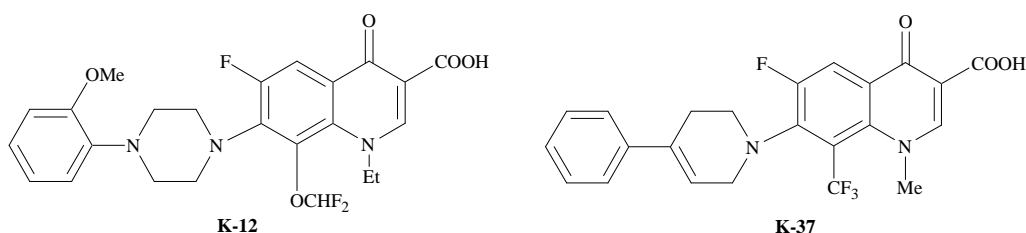
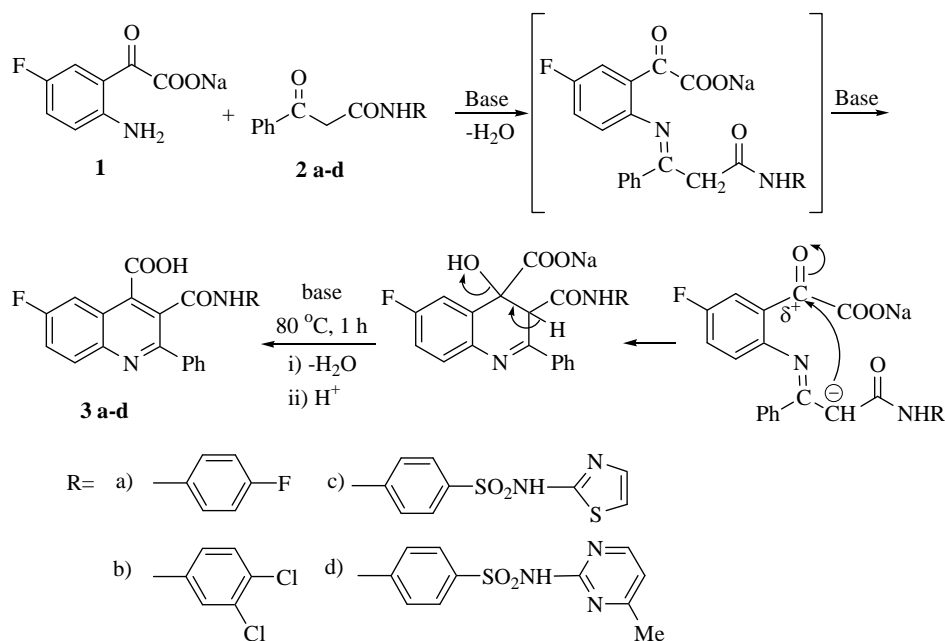
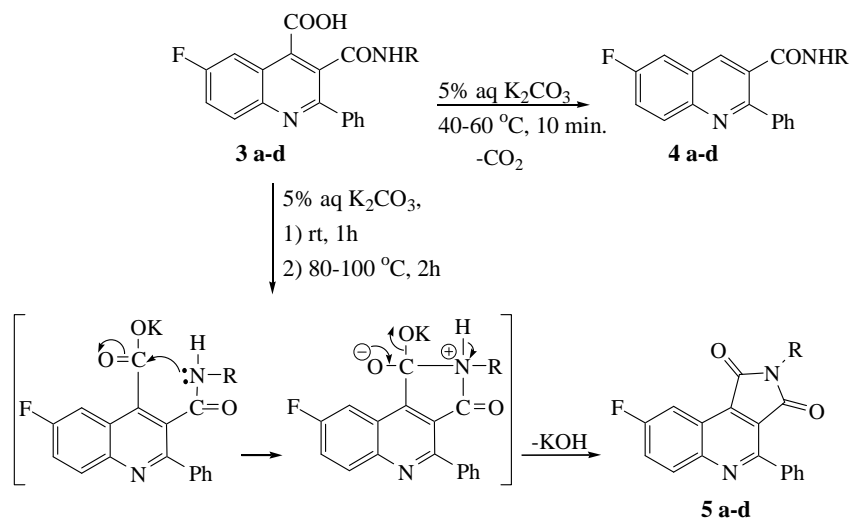


Figure 1. The chemical structure of fluoroquinolones K-12 and K-37.



Scheme 1. The synthesis of key compounds 3a-d.



Scheme 2. Synthetic strategy towards compounds 5a-d.

IR spectrum via lack of OH and NH peaks. While the carbonyl groups of pyrroloquinoline gave two sharp peaks at δ 1720 and 1680 cm^{-1} in addition to different ^1H NMR and ^{13}C NMR spectrum.

Study of IR spectra of the synthesized compounds in both solid and solution state (CHCl_3) showed 1) Lack of the absorption bands, of OH and NH, while the C=O and C-F bands moved to a higher wave length in a solution of

compounds **3** due to the interaction between the molecule and the solvent. 2) Compounds **5**, **4** solutions showed limited effect on IR wave length. The presence of carboxylic acid, amide and fluorine groups in compounds **3** should have an important activity towards tested organisms via hydrogen bonding or electrostatic interaction with the acceptor centre on the surface of microorganism.

The amylolytic activity of the synthesized fluoroquinolines was studied on Six types of *Aspergillus fungi*; *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus terreus* and *Aspergillus terricola*. The experimental: Culture medium used for amylase production was prepared according to the described method [26]. Amylase activity of compounds **3a-d**, **4a-d** and **5a-d** was assayed at the pH 4.6 and at 37°C [27,28]. The final pH and the mycelia dry weight for each fungus was also recorded, (Table 1). Under the investigation conditions employed, mycelia growth depends on the nature of organism of the tested *Aspergillus fungi* that showed moderate to lethal mycelia growth in the acidic range. Most organisms have been reported to produce acidic amylases [29,30].

The effect of the compounds prepared on the fungi amylolytic enzyme was studied by incubating these substances with the enzyme solution at 37°C for 30 min. Followed by addition of the amylase production (substrate) and estimating the activity in mg reducing sugar/wt of reaction mixture. It was taken into consideration that such substance may affect the enzyme or the substrate or both and enhance the reaction. On the other hand, the enzyme activity of *Aspergillus fungi*; was inhibited by action of compounds, **3a-d**, **5a** and **5c**, mostly due to fluorine and sulfathiazole moieties.

The pyrroloquinolines **5** showed more effect towards the tested fungi in comparison with **4**, which may be attributed to electrons asymmetrically distributed on different sites of compounds **5**. In addition, replacement of the carboxylic acid group at position 4 in compound **3** by hydrogen atom as in compound **4** led to lower effects of compounds **4** over **3**.

Finally, the high effect of the compound **3a** in comparison with **3b-d**, **4** and **5**, mainly attributed to full fluorine atoms and carboxylic group. Thus, the compound **3a** can be a good chemical probe on amylolytic activity on some *Aspergillus fungi*.

3. Conclusions

Fluoroquinolines of general structures **3**, **4** and **5** were efficiently synthesized. Most of these compounds showed significant activity against some *Aspergillus fungi* as amylolytic agents. The higher activity over other tested compounds was registered for compounds 4-F-C₆H₄ (**3a**, **4a**, **5a**) and sulfa thiazole moieties (**3-c**, **4-c**, **5-c**). These

novel molecules possibly will be a new promising anti fungal hit compounds. While, the presence of 3,4-Cl₂-C₆H₃ and absence of carboxylic group was an inhibited activity. This observation may indicate that biological target is different from that of halogen type. Furthermore, compound discussed herein showed no structural similarity to any other compounds active against some *Aspergillus fungi*, this may indicate that a novel fluorinated quinoline acts by a new mechanism of action.

In progress, a structural modification of compounds **3**, **4** and **5** in orders to enhance its efficacy against some *Aspergillus fungi*. This novel and simple method enjoys higher efficiency, environmental-friendly characteristics in addition to the importance of the organic C-F group in medicinal chemistry; due to it is metabolic transformations *in vivo* [31,32].

4. Experimental Section

General procedures. The melting points were determined with a Gallenkamp melting point apparatus and were uncorrected. NMR spectra were obtained on a Bruker Avance (400 MHz) spectrometer. Chemical shifts were expressed in δ (ppm) units using DMSO-d₆ as a solvent. Elemental Analysis was performed with a LECO CHNSFCI-932 instrument. IR spectra were recorded with a FT-IR Bomem MB 104 using nujol mulls and NaCl cells. Compounds **1** and **2** were prepared according to previously described procedures [22,23].

Synthesis of fluorinated quinoline-4 carboxylic acids (3a-d). An equimolar mixture of 2-amino-5-fluorophenyl-glyoxylic acid **1** and benzoyl asetanilide derivative **2a-d** in DMF was refluxed for 4 h then poured over ice. The resulting solid was filter, washed with water and crystallized from THF. The resulting solid was identified as fluorinated quinoline-4-carboxylic acids **3**.

6-Fluoro-2-phenyl-3-[(4'-fluorophenyl)amino]-oxoquinoline-4-carboxylic acid (3a). Yellow crystals, Yield 70%; m.p. 138°C - 140°C decomposition; (Found: C, 68.15; H, 3.42; N, 6.84; F, 9.49. C₂₃ H₁₄ N₂ F₂ O₃ requires C, 68.14; H, 3.45; N, 6.91; F, 9.62%); IR (Nujol mull), ν (cm⁻¹): 3300 - 2800 (br, OH, NH), 1710 (C=O) 1620 (CONH), 1580 (C=N) 1230 (C-F), 700, (C-Cl). ¹H NMR (DMSO-d₆), δ : 14.0 (s, 1H, COOH), 11.21 (s, 1H, CONH), 8.52, 8.20 (each d, 1H, 1H, *J* = 8.2 and 7.5 Hz), 8.12(m, 1H), 7.93 - 7.90 (each m, 2H, aryl), and 7.80, 7.40 (each m, 2H and 5H, aryl and phenyl protons). ¹³C NMR (DMSO-d₆), δ : 167.5 and 162.5 (2C=O), 151.76 and 151.0 (C-F), 140.6 (C-N), 136.2, 134.9, 130.2, 128.5, 128.2, 127.6, 126.8, 124.2 and 122.1 (aryl and phenyl carbons).

6-Fluoro-2-phenyl-3-[(2',4'-dichlorophenyl)amino]oxoquinoline-4-carboxylic acid (3b).

Yellow crystals, Yield 75%; m.p. 118°C - 120°C de-

Table 1. Amylolytic activity.

Tested Organisms	Final pH	Mycelial dry wt. (mg/50 ml culture med.)	Amylolytic Activity (mg reducing sugar/reaction mixture)												
			Control	3a	3b	3c	3d	4a	4b	4c	4d	5a	5b	5c	5d
<i>Aspergillus flavus</i>	3.8	115	3.89	2.11	3.15	2.50	3.55	3.5	3.80	3.60	3.78	3.40	3.55	3.18	3.70
<i>Aspergillus fumigain</i>	3.5	740	6.48	5.21	6.11	4.95	6.31	5.01	5.40	5.90	6.10	5.11	5.30	5.10	5.00
<i>Aspergillus nidulans</i>	4.0	720	5.18	4.55	4.90	4.81	5.00	5.00	5.15	5.10	5.18	4.90	4.99	4.80	5.00
<i>Aspergillus niger</i>	3.4	153	3.37	3.01	3.80	2.99	3.99	3.11	3.25	3.12	3.30	3.11	3.20	3.15	3.28
<i>Aspergillus terreus</i>	3.6	135	5.18	4.80	4.95	4.70	5.10	4.70	5.00	4.80	5.10	4.88	5.18	4.91	5.18
<i>Aspergillus terricola</i>	3.9	805	5.70	5.11	5.35	5.01	5.50	5.40	5.70	5.40	5.70	5.30	5.56	5.20	5.11

composition; (Found: C, 59.94; H, 2.81; N, 6.12; F, 4.11; Cl, 15.41. $C_{23}H_{13}N_2FCl_2O_3$ requires C, 55.90; H, 2.85; N, 6.15; F, 4.17; Cl, 15.60%); IR (Nujol mull), ν (cm^{-1}): 3300 - 2800 (br, OH and NH), 1710 (C=O), 1620 (CONH), 1580 (C=N), 1230 (C-F), 700 (C-Cl). 1H NMR (DMSO- d_6), δ : 14.12 (s, 1H, COOH), 11.50 (s, 1H, CONH), 8.41, 8.01 (each d, 1H, 1H, $J = 8.3$ and 7.8 Hz), 8.12 (m, 1H) 7.95 - 7.92 (each m, 2H, Aryl), 7.70, 7.30 (each m, 1H and 5H, aryl and phenyl protons). ^{13}C NMR (DMSO- d_6), δ : 168.0 (COOH), 163.1 (CONH), 151.0 (C-F) 148.5 (C-Cl), 140.8 (C-N), 136, 135, 130, 128.5, 126.9, 125.8, 124.1 and 123.9 ppm (Aryl and Phenyl carbons).

6-Fluoro-2-phenyl-3-[(4'-heteroaryl sulfonamidephenyl) amino] oxoquinoline-4-carboxylic acid (3c). Orange crystals, Yield 78%; m.p. 170°C - 172°C decomposition; (Found: C, 56.30; H, 3.05; N, 10.07; F, 3.42; S, 11.55. $C_{26}H_{17}N_4FS_2O_5$ requires: C, 56.93, H, 3.10; N, 10.21; F, 3.46, S, 11.67). IR (Nujol mull), ν (cm^{-1}): 3270 - 2750 (br, OH and NH), 1700 (C=O), 1610 (CONH), 1570 (C=N), 1540 (C=N), 1350 (SO₂NH), 1230 (C-F) cm^{-1} . 1H NMR (DMSO- d_6), δ : 14.50 (s, COOH), 13.10 (s, CONH), 11.50 (s, SO₂NH), 8.81, 8.72 (d, 2H, thiazole), 8.40, 8.31 (d, 1H, $J = 8.3$ Hz), 8.22 - 8.10 (m, 2H, *o*-fluorophenyl), 7.93 - 7.70, 7.60 - 7.41 (each m, 4H, 1,4-distributed phenyl). ^{13}C NMR (DMSO- d_6), δ : 170.0, 167.6 (COOH and CONH), 155.0 (N-C-S) 151.1, 150.2 (C-F, C=N), 148.7, 138.2, 136.3, 134.9, 130.1, 128.9, 128.17, 127.91, 126.84, 125.7, 124.31, 122.11 (hetero, aryl and phenyl carbons).

6-Fluoro-2-phenyl-3-[(4'-heteroaryl sulfonamidophenyl)amino]oxo-quinoline-4-carboxylic acid (3d). Yellow crystals, Yield 75%; m.p. 103°C - 105°C decomposition; (Found: C, 59.96; H, 3.55; N, 12.49; F, 3.36; S, 5.60. $C_{28}H_{20}N_5FSO_5$ requires C, 60.02; H, 3.59; N, 12.56; F, 3.31; S, 6.74). IR (Nujol mull), ν (cm^{-1}): 3300 - 2850 (br,

OH and NH), 1705 (COOH), 1610 (CONH), 1600, 1570, 1550 (3 C=N), 1480 (Me), 1360 (SO₂NH), 1230 (C-F). 1H NMR (DMSO- d_6), δ : 14.14 (s, COOH), 13.0 (s, CONH), 11.80 (s, SO₂NH), 8.90, 8.70 (each s, 2H, pyrimidine), 8.55 (d, 1H, $J = 7.7$ Hz.), 8.2 - 8.1 (m, 2H, *o*-fluorophenyl), 7.85 - 7.78 and 7.55 - 7.41 (each m, 4H, 1,4 disubstituted phenyl), 2.10 (s, 3H, CH₃). ^{13}C NMR (DMSO- d_6), δ : 170.1 (COOH), 167.3 (NHC=O), 151.0 (C-F), 150.0 (C=N), 148.1, 138.0, 136.1, 134.3, 130.0, 128.4, 128.1, 127.6, 126.4, 125.3, 124.9, 122.9 (hetero, aryl and phenyl carbons).

6-Fluoro-2-phenyl-3-(arylamino) oxo-quinolines (4a-d). A mixture of compound 3a-d (100 mg) and K₂CO₃ solution (5%, 100 ml) was heated at 40°C - 60°C for 10 mins, the cooled reaction mixture was neutralized by acetic acids. The yellow solid was collected, washed with cold water, dried and crystallized from dioxan to give 4a-d.

6-Fluoro-2-phenyl-3-[(4'-fluorophenyl)amino]-oxo-quinoline (4a). Yellow crystals, Yield 70%; m.p. 260°C - 262 °C; (Found = C, 72.59; H, 3.83, N, 7.66; F, 10.68, $C_{22}H_{14}N_2F_2O$ requires C, 73.13; H, 3.87, N, 7.75; F, 10.80); IR (Nujol mull), ν (cm^{-1}): 3100 - 3010 (br, NH and OH aryl), 1590 (CONH), 1550 (C=N), 1230 (C-F), 880,780 (aryl CH). 1H NMR (DMSO- d_6), δ : 11.70 (s, 1H, NHCO) 8.90 (s, 1H, of quinoline-4-yl), 8.5 (d, 1H, $J = 8.1$ Hz), 8.2 (t, 1H, $J = 7.1$ Hz). 7.90 - 7.83 (m, 4H) 7.53 - 7.40 (m, 3H) and 7.35 - 6.99 (m, 5H, aryl and phenyl protons). ^{13}C NMR (DMSO- d_6), δ : 159.8 (CONH), 145, 141(C-F), 139.0 (C-N), 136.0, 134.3, 132.5, 130.5, 129.11, 128.3, 127.7, 126.9, 125.1, 124.9, 123.9 (hetero, aryl and phenyl carbons).

6-Fluoro-2-phenyl-3-[(8',4'-dichlorophenyl)amino]-oxo-quinoline (4b). Faint Yellow crystals, Yield 68%; m.p. 195°C - 196°C; (Found= C, 63.75; H, 3.12; N, 6.74; F, 4.56; Cl, 17.08, $C_{22}H_{13}N_2FCl_2O$ requires C, 64.23; H, 3.16 N, 6.81; F, 4.62 Cl, 17.27). IR (Nujol mull), ν (cm^{-1}):

3090 - 3010 (br, NH, C-H_{arom}), 1620 (CONH), 1580 (C=N), 1220 (C-F), 890, 780 (aromatic CH), 700 (C-Cl) cm⁻¹; δ_H: 11.2 (s, 1H, NHCO), 8.9 (s, 1H of quinoline-4-yl), 8.66 (d, 1H, *J* = 8.1 Hz), 8.4 (t, 1H, *J* = 7.8 Hz), 8.2 (d, 1H, *J* = 7.5 Hz), 7.90 - 7.92 (m, 2H), 7.53 - 7.43 (m, 5H), ¹³C NMR (DMSO-d₆), δ: 160.1 (CONH), 142.0 (C-F), 140.8, 140.3 (2 C-Cl), 139.5 (C-N), 133.4, 132.5, 130.1, 129.7, 128.5, 127.3, 126.9 (hetero, aryl and phenyl carbons).

6-Fluoro-2-phenyl-3-[(4'-heteroaryl-sulfonamidophenyl)amino]-oxo-quinoline (4c). Yellow crystals, Yield 69%; m.p. 154°C - 156°C; (Found: C, 59.25; H, 3.33; N, 10.97; F, 3.71; S, 12.52, C₂₅H₁₇N₄FS₂O₃ requires: 59.52; H, 3.37; N, 11.11; F, 3.76; S, 12.69); IR (Nujol mull), ν (cm⁻¹): 3100 - 3000 (br, NH, CH_{arom}), 1620 (CONH), 1550 (C=N), 1520, 1350 (NCS and SO₂NH), 1250 (C-F), 870, 770 (CH_{arom}), 710 (C-F). ¹H NMR (DMSO-d₆), δ: 11.81 (s, 1H, CONH), 8.91, 8.73 (d, 2H, thiazole), 8.40 - 8.34 (d, 1H, *J* = 8.3 Hz), 8.20 - 8.10 (m, 2H, *o*-fluorophenyl), 7.81 - 7.71 and 7.55 - 7.35 (each m, 4H, 1,4-disubstituted phenyl). ¹³C NMR (DMSO-d₆), δ: 162.1 (CONH), 151.9 (N-C-S), 150.9, 150.1 (C-F and C-N), 147.9, 138.3, 137.0, 136.5, 135.0, 134.1, 132.3, 129.8, 128.7, 127.4, 126.1, 125.8 (hetero, aryl and phenyl carbons).

6-Fluoro-2-phenyl-3-[(4'-heteroaryl-sulfonamidophenyl)amino]-oxo-quinoline (4d). Orange crystals, Yield 75%; m.p. 158°C - 160°C; (Found: C, 62.66; H, 3.84; N, 13.48; F, 3.61; S, 6.16, C₂₇H₂₀N₅FSO₃ requires: C, 63.15; H, 3.89; N, 13.64; F, 3.70; S, 6.23). IR (Nujol mull), ν (cm⁻¹): 3090 - 3000 (br, NH, CH_{arom}), 1590 (CONH), 1580 (C=N), 1448 (deformation CH₃), 1330 (SO₂NH), 1250 (C-F), 850, 780 (aromatic CH) and 700 (C-F). ¹H NMR (DMSO-d₆), δ: 12.10 (s, 1H, CONH), 8.91 (s, 1H of quinolin-4-yl), 8.53 (d, 1H, *J* = 8.2 Hz), 8.20 (t, 1H, *J* = 7.11 Hz), 7.89 - 7.85 (m, 2H), 7.46 - 7.43 (m, 3H, aryl and aromatic protons). ¹³C NMR (DMSO-d₆), δ: 162.5 (CONH), 150.2, 150.6, 150.00 (C-F, C-N, N-C-S), 148.5 (C-4, quinoline) 138.1, 136.3, 135.4, 134.0, 132.8, 130.7, 128.8, 128.1, 127.0, 126.3, 125.3, 124.9, 123.0 (hetero aryl and phenyl carbons).

7-Fluoro-1-aryl-3-phenyl-pyrrolo-[3,4-*c*]-quinoline-2,9-diones (5a-d). A mixture of compounds **3a-d** (100 mg) and K₂CO₃ solution (5%, 100 ml) was first stirred at room temperature for 1h, the reaction was continue at 80°C - 100°C for further 2h, after cooling, the reaction mixture was neutralized by acetic acid (30% v/v), The produced solid was filtered, washed with cold water, dried and crystallized from dioxan to give **5a-d**.

7-Fluoro-1-(4'-fluorophenyl)-3-phenyl-pyrrolo [3,4-*c*] quinoline-2,9-dione (5a). Faint yellow crystals, Yield 65%; m.p. 230°C - 232°C; (Found = C, 70.89; H, 3.06; N, 7.05; F, 9.89, C₂₃H₁₂N₂F₂O₂ requires C, 71.31; H, 3.10;

N, 7.23, F, 10.07; IR (Nujol mull), ν (cm⁻¹): 3000 (aromatic CH), 1710, 1680 (2 C=O), 1580 (C=N) 1350 (SO₂NH) 1250 (C-F), 870, 820 (*p*-substituted phenyl). ¹H NMR (DMSO-d₆), δ: 8.21 (d, 1H, *J* = 7.5 Hz) 7.90 - 7.88 (m, 2H, hetero protons), 7.70 - 7.38 and 7.14 - 6.94 (each, m, 4H and SH aryl and phenyl protons). ¹³C NMR (DMSO-d₆), δ: 170.1, 168.1 (2 C=O), 151.6 and 151.1 (C-F), 141.0 (C-N), 136.5, 135.1, 134.8, 132.7, 130.8, 128.7, 127.9, 126.3, 125.1, 124.0, 122.0 (hetero, aryl and phenyl carbons).

7-Fluoro-1-(2',4'-dichlorophenyl)-3-phenyl pyrrolo [3,4-*c*] quinoline-2,9-dione (5b). Yellow crystals, Yield 68%; m.p. 218°C - 220°C; (Found: C, 62.75; H, 2.47; N, 6.30; F, 4.29; Cl 16.07, C₂₃H₁₁N₂FCl₂O₂ requires: C, 63.15; H, 2.15; N, 6.40; F, 4.34; Cl, 16.24). IR (Nujol mull), ν (cm⁻¹): 3010 (CH_{arom}), 1700, 1680 (2 C=O), 1580 (C=N), 1250 (C-F), 850, 820 (substituted phenyl), 710 (C-Cl). ¹H NMR (DMSO-d₆), δ: 8.11 (d, 1H, *J* = 7.8 Hz), 7.83 - 7.74 (m, 2H), 7.64 - 7.52 (m, 2H), 7.21 - 7.18 (aromatic protons). ¹³C NMR (DMSO-d₆), δ: 172.2, 169.5 (2 C=O), 150.3 (C-F), 146, 146.1 (2 C-Cl), 140.4 (C-N), 135.8, 134.1, 132.8, 130.1, 128.9, 127.6, 126.1, 125.9, 124.8, 123.0 (hetero aryl and phenyl protons).

7-Fluoro-1-(4'-heteroaryl sulfanamidophenyl)-3-phenyl pyrrolo (3,4-*c*) quinoline-2,9-dione (5c). Deep yellow crystals, 66%. M.p. 165°C - 166°C. (Found: C, 60.39; H, 2.85; N, 10.77; F, 3.64; S, 12.31, C₂₆H₁₅N₄FS₂O₃ requires: C, 60.70; H, 2.91; N, 10.89; F, 3.69, S, 12.45); IR (Nujol mull), ν (cm⁻¹): 3000 - 2990 (CH_{arom}), 1690, 1680 (2 C=O), 1605 (C=N), 1380 (SO₂NH), 1230 (C-F), 870, 790 (substituted phenyl). ¹H NMR (DMSO-d₆), δ: 8.9 (NHSO₂), 8.55 (d, 2H, thiazole), 8.40, 8.28 (d, 1H, *J* = 7.9 Hz), 8.20 - 8.12 (m, 2H of *o*-fluorophenyl), 7.70 - 7.51 (m, 9H, aryl and phenyl protons). ¹³C NMR (DMSO-d₆), δ: 174, 172 (2 C=O), 158.0 (N-C-S), 150.9, (C-F), 150.1 (C=N), 148.1 (C-N), 138.1, 137.5, 136.5, 134.9, 132.0, 128.7, 127.9, 126.6, 125.4, 124.1, 122.2 (hetero, aryl and phenyl carbons).

7-Fluoro-1-(4'-heteroaryl sulfanamidophenyl)-3-phenyl pyrrolo [3,4-*c*] quinoline-2,9-dione (5d). Yellow crystals, Yield 65%, m.p. 132°C - 135°C; (Found: C, 63.69; H, 3.37; N, 13.23; F, 3.59; S, 6.04, C₂₈H₁₈N₃FSO₃ requires C, 64.24; H, 3.44; N, 13.38; F, 3.63; S, 6.11), IR (Nujol mull), ν (cm⁻¹): 3010, 2985 (CH_{arom}), 1705, 1690 (2 C=O), 1590 (C=N), 1480 (deformation CH₃), 1340 (SO₂NH). 1250 (C-F), 850, 820 (substituted phenyl). ¹H NMR (DMSO-d₆), δ: 8.80 (s, 1H, SO₂NH), 8.33 and 8.21 (each t, 1H, *J* = 7.9 and 7.6 Hz) 7.91 - 7.85 (d, 2H, pyrimidine) 7.41 - 7.38 (m, 4H), 7.22 - 7.10 (m, 5H, Aryl and phenyl protons). ¹³C NMR (DMSO-d₆), δ: 171, 168.9 (2 C=O), 151.1 (C-F), 150.3 (C=N), 149.1 (C=N), 138, 137.7 (2 C-N), 132.6, 130.1, 128.7, 128.1, 126.9, 125.7, 124.5 and 123.0 (hetero aryl and phenyl carbons).

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