A Convenient Synthesis of 5- and 8-Nitroquinazoline-2,4-dione Derivatives

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3-Nitrophthalic acid **1** was converted selectively to the two regioisomeric monoesters **2** and **3**, which were subsequently transformed *via* Curtius rearrangement to the corresponding 5- and 8-nitroquinazoline-2,4-diones **4** and **5**, respectively. The reduction of the nitro group produced 5- and 8-aminoquinazoline-2,4-diones **6** and **7**, respectively, in good yields. The condensation of compounds **7b** and **7c** with carbon disulfide in pyridine afforded tricyclic derivatives **9,** which are analogues of the HIV-1 reverse transcriptase inhibitor 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO).

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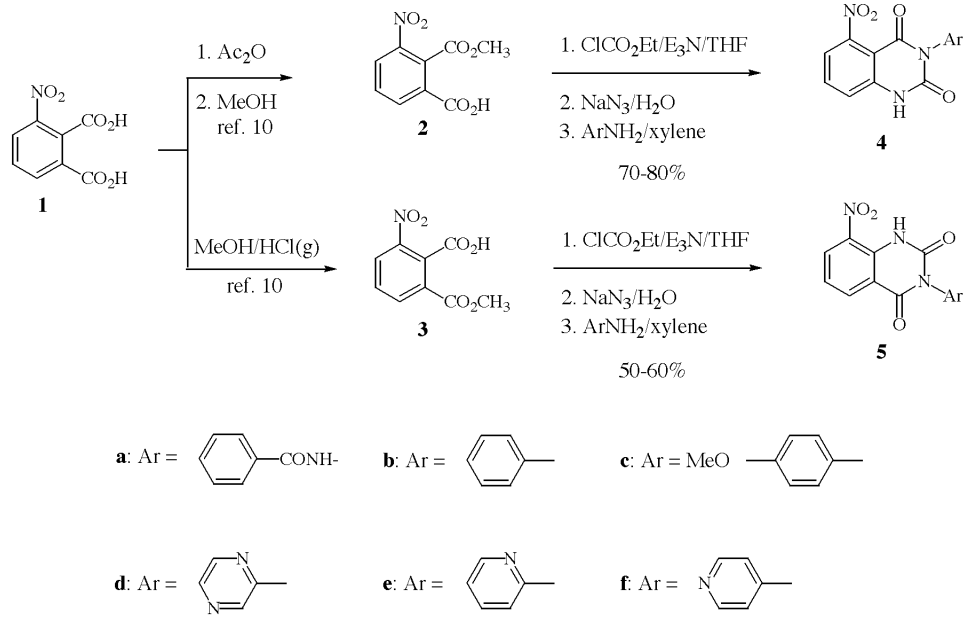
Quinazolines are important medicinal agents and pharmacological tools that have been applied to a variety of therapeutic areas [1]. In particular, quinazoline-2,4-diones form an interesting class of heterocycles with broad synthetic applications in medicinal chemistry as starting materials for biologically active compounds [2]. Additionally, some quinazoline-2,4-diones derivatives have been reported to exhibit anticonvulsant activity against electroshock [3], to possess sedative and hypotensive properties [4], and also to cause vasodilatation [5] in animals. They are also characterized as phosphodiesterase (PDE) inhibitors with antiinflammatory activity *in vivo* [6], and more recently as potent fibrinogen receptor antagonists [7]. Thus, several synthetic pathways for the preparation of these heterocyclic compounds have been described [8], most of them start from derivatives of anthranilic acid.

We have also shown [9] previously that the phthalic anhydride can be a versatile starting material for the synthesis of quinazoline-2,4-diones. In the present work, we describe a convenient and regioselective synthesis of the two regioisomeric 5- and 8-nitroquinazoline-2,4-diones **4** and **5** starting from commercially available 3-nitrophthalic acid **1**. In fact, the key intermediates,

Scheme 1

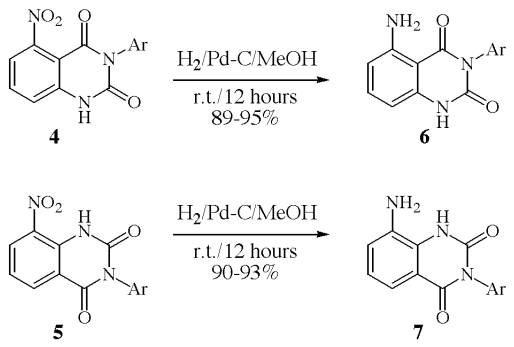


monoesters **2** and **3**, can be prepared on a large scale from **1** according to the literature methods [10]. First, the addition of acetic anhydride to **1** in methanol afforded the monoester **2** in good yield; on the other hand, treatment of **1** with a saturated solution of hydrogen chloride in methanol gave the monoester **3** in excellent yield.

Activation of the monoesters **2** and **3** with ethyl chloroformate in the presence of triethylamine and subsequent reaction with sodium azide afforded acyl azides. The unpurified acyl azides were then heated in refluxing xylene in the presence of various amines. Under these conditions, rearrangement of the acyl azides to isocyanates, trapping with the amines and cyclization to the corresponding nitroquinazoline-2,4-diones **4a-f** and **5a-f** occurred in one pot (Scheme 1).

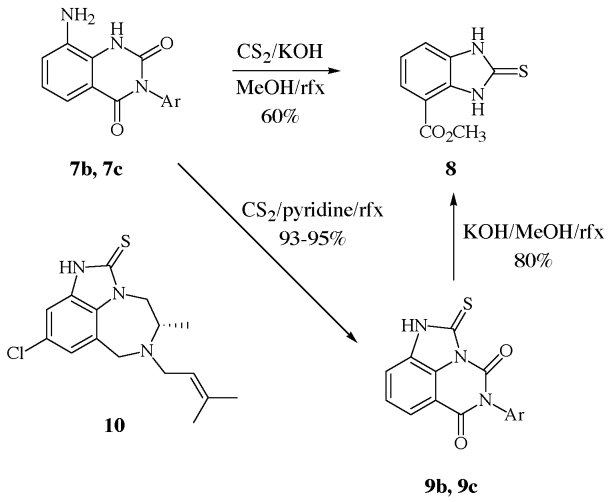
The reduction of aromatic nitro compounds by catalytic hydrogenation is probably the best known method to synthesize aromatic amines. Thus, reduction of the nitroquinazoline-2,4-diones **4a-f** and **5a-f**, was achieved in methanol in the presence of palladium on carbon to yield the 5- and 8-aminoquinazoline-2,4-diones **6a-f** and **7a-f,** respectively (Scheme 2).

Scheme 2



We then turned our attention to obtain tricyclic six-membered ring, analogues of the 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) [11] class of HIV-1 reverse transcriptase inhibitors exemplified by **10** (Scheme 3). When 8-amino-3-phenylquinazoline-2,4-dione **7b** or 8-amino-3-(*p*-methoxyphenyl)quinazoline-2,4-dione **7c** were reacted with carbon disulfide and potassium hydroxide in refluxing methanol to obtain the tricyclic derivatives **9b** or **9c**, the 4-carbomethoxybenzimidazol-2-thione **8** was the only product isolated. Obviously, **9b** or **9c** are formed in this reaction but they are easily converted, under these conditions, to **8** by a facile ring opening. This assumption is based on the fact that the compounds **9b** or **9c** treated with 1.1 equivalent of potassium hydroxide in methanol at reflux during 24 hours lead to the desired derivative **8** in 80% yield, while the same treatment applied to **7a** or **7c** leaves the starting material unchanged. However, when **7b** or **7c** were condensed with carbon disulfide in pyridine, the desired tricyclic derivatives **9b** or **9c** were isolated in good yield (Scheme 3).

Scheme 3



Compounds **4-9** were fully characterized by NMR spectroscopy, mass spectrometry and elemental analysis. The HMQC and HMBC data for **4-9** are in agreement with the proposed structures.

Anti-HIV activities of the synthetized compounds were evaluated in HeLa/CD_4/cells. No significant activities were observed against HIV. The toxicities of these quinazolinediones were also assessed, and these compounds did not exhibit any significant toxicities at concentration up to 100 μ*M* in HeLa cells.

In summary, we have described a versatile, simple, reliable, and an efficient method for the preparation of the two regioisomeric 5- and 8-nitroquinazoline-2,4-diones **4a-f** and **5a-f** and their amino derivatives **6a-f** and **7a-f**. The reaction of aminoquinazoline-2,4-diones **7b,c** with carbon disulfide in pyridine gave the tricycles **9b,c** in good yields.

EXPERIMENTAL

The ^{1}H nmr and ^{13}C nmr spectra were obtained with a Bruker Avance DPX250, 250 MHz instrument, in dimethyl-d_6 sulfoxide with TMS as internal standard, chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. The ir spectra were recorded as a KBr pellet on a Perkin-Elmer spectrometer FT PARAGON 1000PC, and ms spectra were recorded on a Perkin-Elmer mass spectrometer SCIEX API 300 (ionspray or heat nebuliser). Melting points were measured using a Kofler hot stage apparatus and are uncorrected. The solvents used were HPLC grade.

General Procedure for the Preparation of Nitroquinazolinediones **4a-f** and **5a-f**.

To a cold solution (-10 °C) of monoester **2** or **3** (1.2 g, 5.3 mmol) and triethylamine (1.60 ml, 11.5 mmol) in tetrahydrofuran (25 ml) was added dropwise ethyl chloroformate (0.80 ml, 8.4 mmol), and

the resulting solution was stirred with ice cooling for 1 hour. A solution of NaN_3 (Warning: explodes when heated) (0.93 g, 14.3 mmol) in water (7 ml) was then added dropwise with continued stirring for 1 hour. The salts were filtered off, the filtrate was diluted with water (20 ml), and the tetrahydrofuran was evaporated. The aqueous solution was extracted with ether (3x15 ml). The combined organic phases were dried (magnesium sulfate), filtered and concentrated to give the corresponding acyl azide. To a solution of acyl azide (1.34 g, 5.36 mmol) in xylene (20 ml) were added 1.2 equivalents of aromatic amine. The solution was heated in an oil bath for 8 hours to 140 °C. The solvent was then evaporated to dryness, and the crude products were recrystallized from ethanol.

N-[5-Nitro-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]benzamide (**4a**).

This compound was obtained as a white amorphous solid (73%), mp 271-273 °C, ir: ν 1680 (C=O), 1710 (C=O), 1740 (C=O), 3240 (NH), 3330 (NH) cm^{-1}; ^1H nmr: δ 7.46 (d, 1H, H-6, *J* = 8.0 Hz), 7.56-7.63 (m, 4H, H-8 and H_{arom}), 7.68-7.96 (m, 3H, H-7 and H_{arom}), 11.26 (broad s, 1H, NH), 12.27 (broad s, 1H, NH); ^{13}C nmr: δ 104.2 (C), 116.7 (CH), 118.5 (CH), 127.7 (2CH), 128.7 (2CH), 131.3 (C), 132.6 (CH), 136.5 (CH), 140.5 (C), 148.3 (C=O), 149.2 (C), 157.1 (C=O), 165.2 (C=O); ms: *m/z* 327 (M+1).

Anal. Calcd. for $C_{15}H_{10}N_4O_5$: C, 55.22; H, 3.09; N, 17.17. Found: C, 54.94; H, 3.21; N, 17.34.

5-Nitro-3-phenylquinazoline-2,4-(1*H*,3*H*)-dione (**4b**).

This compound was obtained as white crystals (75%), mp 337-338 °C, ir: ν 1680 (C=O), 1725 (C=O), 3330 (NH) cm^{-1}; ^1H nmr: δ 7.25 (d, 1H, H-6, *J* = 8.0 Hz), 7.35 (d, 1H, H-8, *J* = 8.0 Hz), 7.38-7.54 (m, 5H, H_{arom}), 7.80 (t, 1H, H-7, *J* = 8.0 Hz) 11.95 (broad s, 1H, NH); ^{13}C nmr: δ 105.1 (C), 116.1 (CH), 117.9 (CH), 128.4 (CH), 128.9 (2CH), 129.0 (2CH), 135.0 (C), 135.7 (CH), 141.1 (C), 149.3 (C=O), 149.6 (C), 158.9 (C=O); ms: *m/z* 284 (M+1).

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found: C, 59.65; H, 3.07; N, 14.64.

3-(4-Methoxyphenyl)-5-nitroquinazoline-2,4-(1*H*,3*H*)-dione (**4c**).

This compound was obtained as a white amorphous solid (80%), mp 353-354 °C, ir: ν 1680 (C=O), 1725 (C=O), 3379 (NH) cm^{-1}; H nmr: δ 3.78 (s, 1H, OCH_3), 7.00 (d, 2H, H_{arom}, *J* = 8.5 Hz), 7.22 (d, 2H, H_{arom}, *J* = 8.5 Hz), 7.41 (d, 1H, H-6, *J* = 8.0 Hz), 7.45 (d, 1H, H-8, *J* = 8.0 Hz), 7.82 (t, 1H, H-7, *J* = 8.0 Hz), 11.97 (broad s, 1H, NH); ^{13}C nmr: δ 55.6 (CH_3), 105.3 (C), 114.3 (2CH), 116.3 (CH), 118.0 (CH), 127.7 (C), 130.1 (2CH), 135.9 (CH), 141.3 (C), 149.5 (C=O), 150.0 (C), 159.2 (C=O), 159.3 (C); ms: *m/z* 314 (M+1).

Anal. Calcd. for $C_{15}H_{11}N_3O_5$: C, 57.51; H, 3.54; N, 13.41. Found: C, 57.80; H, 3.44; N, 13.65.

5-Nitro-3-pyrazin-2-ylquinazoline-2,4-(1*H*,3*H*)-dione(**4d**).

This compound was obtained as a white amorphous solid (72%), mp 347-348 °C, ir: ν 1680 (C=O), 1725 (C=O), 3380 (NH) cm^{-1}; ^1H nmr: δ 7.46 (d, 1H, H-6, *J* = 8.0 Hz), 7.54 (d, 1H, H-8, *J* = 8.0 Hz), 7.88 (t, 1H, H-7, *J* = 8.0 Hz), 8.72-8.75 (m, 1H, H_{arom}), 8.78 (d, 1H, H_{arom}, *J* = 3.0 Hz), 8.82-8.87 (m, 1H, H_{arom}), 11.92 (broad s, 1H, NH); ^{13}C nmr: δ 104.9 (C), 116.5 (CH), 118.5 (CH), 127.2 (CH), 136.1 (CH), 138.1 (C), 144.7 (CH), 148.2 (CH), 148.9 (C), 149.1 (C=O), 149.4 (C), 159.2 (C=O). ms: *m/z* 286 (M+1).

Anal. Calcd. for $C_{12}H_7N_5O_4$: C, 50.53; H, 2.47; N, 24.55. Found: C, 50.69; H, 2.30; N, 24.75.

5-Nitro-3-pyridin-2-ylquinazoline-2,4-(1*H*,3*H*)-dione (**4e**).

This compound was obtained as a white amorphous solid (70%), mp 315-316 °C, ir: ν 1679 (C=O), 1728 (C=O), 3370 cm^{-1} (NH); ^1H nmr: δ 7.46 (d, 1H, H-6, *J* = 8.0 Hz), 7.50-7.55 (m, 3H, H-8 and H_{arom}), 7.88 (t, 1H, H-7, *J* = 8.0Hz), 7.97-8.07 (m, 1H, H_{arom}), 8.55-8.65 (m, 1H, H_{arom}), 12.10 (broad s, 1H, NH); ^{13}C nmr: δ 104.8 (C), 116.2 (CH), 118.1 (CH), 124.3 (CH), 125.0 (CH), 135.9 (CH), 138.7 (CH), 141.2 (C), 148.4 (C), 149.1 (CH), 149.2 (C=O), 149.3 (C), 158.6 (C=O); ms: *m/z* 285 (M+1).

Anal. Calcd. for $C_{13}H_8N_4O_4$: C, 54.94; H, 2.84; N, 19.71. Found: C, 54.66; H, 3.04; N, 19.42.

5-Nitro-3-pyridin-4-ylquinazoline-2,4-(1*H*,3*H*)-dione (**4f**).

This compound was obtained as a yellow amorphous solid (70%), mp 327-328 °C, ir: ν 1680 (C=O), 1726 (C=O), 3380 (NH) cm^{-1}; ^1H nmr: δ 7.41 (d, 1H, H-6, *J* = 8.0 Hz), 7.44 (d, 2H, H_{arom}, *J* = 6.0 Hz), 7.53 (d, 1H, H-8, *J* = 8.0 Hz), 7.84 (t, 1H, H-7, *J* = 8.0 Hz), 8.73 (d, 2H, H_{arom}, *J* = 6.0 Hz), 12.11 (broad s, 1H, NH); ^{13}C nmr: δ 105.0 (C), 116.2 (CH), 118.0 (CH), 124.4 (2CH), 135.9 (CH), 141.2 (C), 142.9 (C), 149.0 (C), 149.2 (C=O), 150.6 (2CH), 158.5 (C=O); ms: *m/z* 285 (M+1).

Anal. Calcd. for $C_{13}H_8N_4O_4$: C, 54.94; H, 2.84; N, 19.71. Found: C, 54.69; H, 3.05; N, 19.51.

N-[8-Nitro-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]benzamide (**5a**).

This compound was obtained as a white amorphous solid (50%), mp 245-246 °C, ir: ν 1680 (C=O), 1710 (C=O), 1742 (C=O), 3245 (NH), 3331 (NH) cm^{-1}; ^1H nmr: δ 7.49 (t, 1H, H-6, *J* = 8.0 Hz), 7.55-7.67 (m, 3H, H_{arom}), 7.98 (d, 2H, H_{arom}, *J* = 7.0 Hz), 8.43 (d, 1H, H-5, *J* = 8.0 Hz), 8.62 (d, 1H, H-7, *J* = 8.0 Hz), 10.95 (broad s, 1H, NH), 11.40 (br s, 1H, NH); ^{13}C nmr: δ 116.5 (C), 123.0 (CH), 127.8 (2CH), 128.7 (2CH), 131.2 (CH), 132.2 (C), 132.6 (C), 133.5 (CH), 135.0 (C), 135.1 (CH), 147.8 (C=O), 159.0 (C=O), 165.1 (C=O); ms: *m/z* 327 (M+1).

Anal. Calcd. for $C_{15}H_{10}N_4O_5$: C, 55.22; H, 3.09; N, 17.17. Found: C, 55.07; H, 2.88; N, 17.20.

8-Nitro-3-phenylquinazoline-2,4-(1*H*,3*H*)-dione (**5b**).

This compound was obtained as a yellow amorphous solid (55%), mp 228-229 °C, ir: ν 1680 (C=O), 1730 (C=O), 3367 (NH) cm^{-1}; ^1H nmr: δ 7.25-7.38 (m, 2H, H_{arom}), 7.48 (t, 1H, H-6, *J* = 8.0 Hz), 7.50-7.60 (m, 3H, H_{arom}), 8.56 (d, 1H, H-5, *J* = 8.0 Hz), 8.63 (d, 1H, H-7, *J* = 8.0 Hz), 10.60 (broad s, 1H, NH); ^{13}C nmr: δ 117.9 (C), 122.5 (CH), 128.3 (2CH), 129.5 (CH), 129.8 (2CH), 130.1 (CH), 132.2 (C), 133.9 (C), 135.0 (CH), 137.1 (C), 149.1 (C=O), 160.8 (C=O); ms: *m/z* 284 (M+1).

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found: C, 59.61; H, 3.11; N, 14.70.

3-(4-Methoxyphenyl)-8-nitroquinazoline-2,4-(1*H*,3*H*)-dione (**5c**).

This compound was obtained as a white amorphous solid (60%), mp 254-255 °C, ir: ν 1683 (C=O), 1725 (C=O), 3336 (NH) cm^{-1}; ^1H nmr: δ 3.86 (s, 3H, OCH_3), 7.01 (d, 2H, H_{arom}, *J* = 8.3 Hz), 7.21 (d, 2H, H_{arom}, *J* = 8.3 Hz), 7.42 (t, 1H, H-6, *J* = 8.0 Hz), 8.42 (d, 1H, H-5, *J* = 8.0 Hz), 8.55 (d, 1H, H-7, *J* = 8.0 Hz),

10.60 (broad s, 1H, NH); ^{13}C nmr: δ 55.7 (CH_3), 115.1 (2CH), 117.5 (C), 122.5 (CH), 124.6 (C), 126.3 (CH), 129.3 (2CH), 132.1 (C), 137.1 (CH), 137.9 (C), 149.5 (C=O), 159.2 (C=O), 161.0 (C); ms: *m/z* 314 (M+1).

Anal. Calcd. for $C_{15}H_{11}N_3O_5$: C, 57.51; H, 3.54; N, 13.41. Found: C, 57.39; H, 3.60; N, 13.70.

8-Nitro-3-pyrazin-2-ylquinazoline-2,4-(1*H*,3*H*)-dione (**5d**).

This compound was obtained as a yellow amorphous solid (55%), mp 194-196 °C, ir: ν 1680 (C=O), 1725 (C=O), 3300 cm^{-1} (NH); ^{1}H nmr: δ 7.47 (t, 1H, H-6, *J* = 8.0 Hz), 8.39 (d, 1H, H-5, *J* = 8.0 Hz), 8.56 (d, 1H, H-7, *J* = 8.0 Hz), 8.70-8.97 (m, 3H, H_{arom}), 11.00 (broad s, 1H, NH); ^{13}C nmr: δ 118.2 (C), 122.8 (CH), 124.0 (CH), 124.9 (CH), 132.4 (C), 134.0 (C), 135.1 (CH), 137.0 (CH), 139.1 (CH), 148.9 (C=O), 150.3 (C), 160.8 (C=O); ms: *m/z* 286 (M+1).

Anal. Calcd. for $C_{12}H_7N_5O_4$: C, 50.53; H, 2.47; N, 24.55. Found: C, 50.41; H, 2.71; N, 24.25.

8-Nitro-3-pyridin-2-ylquinazoline-2,4-(1*H*,3*H*)-dione (**5e**).

This compound was obtained as a yellow amorphous solid (57%), mp 203-204 °C, ir: ν 1680 (C=O), 1716 (C=O), 3329 cm^{-1} (NH); ^{1}H nmr: δ 7.25-7.48 (m, 3H, H-6 and H_{arom}), 7.93 (t, 1H, H_{arom}, *J* = 5.0 Hz, H_{arom}), 8.54 (d, 1H, H-5, *J* = 8.0 Hz), 8.62 (d, 1H, H-7, *J* = 8.0 Hz), 8.69 (d, 1H, H_{arom}, *J* = 5.0 Hz), 10.60 (broad s, 1H, NH); ^{13}C nmr: δ 118.1 (C), 122.6 (CH), 123.9 (CH), 124.8 (CH), 132.3 (CH), 133.7 (C), 135.3 (CH), 136.9 (C), 139.0 (CH), 147.9 (C), 148.8 (C=O), 150.3 (CH), 160.5 (C=O); ms: *m/z* 285 (M+1).

Anal. Calcd. for $C_{13}H_8N_4O_4$: C, 54.94; H, 2.84; N, 19.71. Found: C, 54.67; H, 2.97; N, 19.55.

8-Nitro-3-pyridin-4-ylquinazoline-2,4-(1*H*,3*H*)-dione (**5f**).

This compound was obtained as a yellow amorphous solid (50%) from ethanol, mp 277-278 °C, ir: ν 1685 (C=O), 1731 (C=O), 3330 (NH) cm^{-1}; ^{1}H nmr: δ 7.30-7.47 (m, 3H, H-6 and H_{arom}), 8.37 (d, 1H, H-5, *J* = 8.0 Hz), 8.52 (d, 1H, H-7, *J* = 8.0 Hz), 8.63-8.75 (m, 2H, H_{arom}), 10.96 (broad s, 1H, NH); ^{13}C nmr: δ 117.4 (C), 122.3 (CH), 124.2 (2CH), 131.5 (CH), 131.6 (C), 134.0 (C), 134.7 (CH), 142.9 (C), 148.6 (C=O), 150.7 (2CH), 160.2 (C=O); ms: *m/z* 285 (M+1).

Anal. Calcd. for $C_{13}H_8N_4O_4$: C, 54.94; H, 2.84; N, 19.71. Found: C, 55.18; H, 2.71; N, 19.59.

General Procedure for the Preparation of Aminoquinazolinediones **6a-f** and **7a-f**.

To solution of **4a-f** or **5a-f** (2.15 mmol) in methanol (25 ml) was added palladium on carbon (10%) (90 mg). The mixture was stirred in a Parr apparatus under hydrogen (1 atm) for 12 hours at room temperature and then filtered through Celite. The filtrate was evaporated under reduced pressure and the residue obtained was recrystallized from methanol.

N-[5-Amino-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]benzamide (**6a**).

This compound was obtained as a white amorphous solid (90%), mp 316-317 °C, ir: ν 1680 (C=O), 1700 (C=O), 1730 (C=O), 3299 (NH), 3389 (NH), 3496 (NH) cm^{-1}; ^{1}H nmr: δ 6.26 (d, 1H, H-6, *J* = 8.0 Hz), 6.42 (d, 1H, H-8, *J* = 8.0 Hz), 7.11 (broad s, 2H, NH_2), 7.27 (t, 1H, H-7, *J* = 8.0 Hz), 7.60-7.90 (m, 5H, H_{arom}), 10.99 (broad s, 2H, NH); ^{13}C nmr: δ 98.9 (C), 100.1 (CH), 108.3 (CH), 127.6 (2CH), 128.5 (2CH), 131.3 (C), 132.3 (CH), 135.5 (CH), 140.1 (C), 148.8 (C=O), 151.5 (C), 162.5 (C=O), 165.2 (C=O); ms: *m/z* 297 (M+1).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.57; H, 4.15; N, 19.13.

5-Amino-3-phenylquinazoline-2,4-(1*H*,3*H*)-dione (**6b**).

This compound was obtained as a white amorphous solid (90%), mp 304-305 °C, ir: ν 1660 (C=O), 1721 (C=O), 3337 (NH), 3492 (NH) cm^{-1}; ^{1}H nmr: δ 6.23 (d, 1H, H-6, *J* = 8.0 Hz), 6.35 (d, 1H, H-8, *J* = 8.0 Hz), 7.09 (broad s, 2H, NH_2), 7.23 (t, 1H, H-7, *J* = 8.0 Hz), 7.27-7.30 (m, 2H, H_{arom}), 7.35-7.50 (m, 3H, H_{arom}), 11.17 (broad s, 1H, NH); ^{13}C nmr: δ 97.6 (C), 99.8 (CH), 107.9 (CH), 127.8 (CH), 128.6 (2CH), 129.2 (2CH), 135.0 (CH), 135.6 (C), 140.8 (C), 149.8 (C=O), 151.4 (C), 164.4 (C=O); ms: *m/z* 254 (M+1).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.33; H, 4.20; N, 16.81.

5-Amino-3-(4-methoxyphenyl)quinazoline-2,4-(1*H*,3*H*)-dione (**6c**).

This compound was obtained as a white amorphous solid (94%), mp 332-333 °C, ir: ν 1665 (C=O), 1725 (C=O), 3339 (NH), 3474 (NH) cm^{-1}; ^{1}H nmr: δ 3.80 (s, 3H, OCH_3), 6.20 (d, 1H, H-6, *J* = 8.0 Hz), 6.35 (d, 1H, H-8, *J* = 8.0 Hz), 6.96 (d, 2H, H_{arom}, *J* = 7.5 Hz), 7.05 (broad s, 2H, NH_2), 7.18 (d, 2H, H_{arom}, *J* = 7.5 Hz), 7.22 (t, 1H, H-7, *J* = 8.0 Hz), 11.10 (broad s, 1H, NH); ^{13}C nmr: δ 55.3 (CH_3), 97.7 (C), 99.9 (CH), 108.0 (CH), 114.0 (2CH), 128.1 (C), 130.2 (2CH), 135.1 (CH), 140.8 (C), 149.2 (C=O), 151.5 (C), 158.7 (C), 164.8 (C=O); ms: *m/z* 284 (M+1).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.29; H, 4.60; N, 14.98.

5-Amino-3-pyrazin-2-ylquinazoline-2,4-(1*H*,3*H*)-dione (**6d**).

This compound was obtained as a yellow amorphous solid (89%), mp 244-245 °C, ir: ν 1678 (C=O), 1740 (C=O), 3384 (NH), 3480 (NH) cm^{-1}; ^{1}H nmr: δ 6.22 (d, 1H, H-6, *J* = 8.0 Hz), 6.40 (d, 1H, H-8, *J* = 8.0 Hz), 7.10 (broad s, 2H, NH_2), 7.20 (t, 1H, H-7, *J* = 8.0 Hz), 8.70-8.90 (m, 3H, H_{arom}), 11.15 (broad s, 1H, NH); ^{13}C nmr: δ 97.3 (C), 100.4 (CH), 108.6 (CH), 135.8 (CH), 140.9 (C), 144.2 (CH), 144.7 (CH), 146.1 (CH), 146.4 (C), 149.7 (C=O), 151.8 (C), 164.6 (C=O); ms: *m/z* 256 (M+1).

Anal. Calcd. for $C_{12}H_9N_5O_2$: C, 56.47; H, 3.55; N, 27.44. Found: C, 56.67; H, 3.42; N, 27.50.

5-Amino-3-pyridin-2-ylquinazoline-2,4-(1*H*,3*H*)-dione (**6e**).

This compound was obtained as a white amorphous solid (95%), mp 275-276 °C, ir: ν 1666 (C=O), 1710 (C=O), 3375 (NH), 3436 (NH) cm^{-1}; ^{1}H nmr: δ 6.26 (d, 1H, H-6, *J* = 8.0 Hz), 6.38 (d, 1H, H-8, *J* = 8.0 Hz), 7.11 (broad s, 2H, NH_2), 7.24 (t, 1H, H-7, *J* = 8.0 Hz), 7.40-7.55 (m, 2H, H_{arom}), 7.97 (t, 1H, H_{arom}, *J* = 7.5 Hz), 8.58 (d, 1H, H_{arom}, *J* = 4.1 Hz), 11.30 (broad s, 1H, NH); ^{13}C nmr: δ 97.47 (C), 100.12 (CH), 108.28 (CH), 124.00(CH), 124.73 (CH), 135.43 (CH), 138.62 (CH), 141.00 (C), 149.30 (CH), 149.36 (C), 149.74 (C), 151.63 (C=O), 164.56 (C=O); ms: *m/z* 255 (M+1).

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.22; H, 4.10; N, 22.11.

5-Amino-3-pyridin-4-ylquinazoline-2,4-(1*H*,3*H*)-dione (**6f**).

This compound was obtained as a yellow amorphous solid (93%), mp 364-365 °C, ir: ν 1653 (C=O), 1716 (C=O), 3353 (NH), 3469 (NH) cm^{-1}; ^1H nmr: δ 6.23 (d, 1H, H-6, *J* = 7.4 Hz), 6.37 (d, 1H, H-8, *J* = 7.4 Hz), 6.85-7.60 (m, 5H, H-7, NH_2 and H_{arom}), 8.69 (d, 2H, H_{arom}, *J* = 6.0 Hz), 11.29 (broad s, 1H, NH); ^{13}C nmr: δ 97.54 (C), 100.05 (CH), 108.28 (CH), 124.88 (2CH), 135.43 (CH), 140.85 (C), 143.69 (C), 149.35 (C), 150.45 (2CH), 151.62 (C=O), 164.01 (C=O); ms: *m/z* 255 (M+1).

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.30; H, 3.99; N, 22.01.

N-[8-Amino-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]-benzamide (**7a**).

This compound was obtained as a white amorphous solid (92%), mp 246-247°C, ir: ν 1680 (C=O), 1708 (C=O), 1730 (C=O), 3249 (NH), 3309 (NH), 3457 (NH) cm^{-1}; ^1H nmr: δ 5.62 (broad s, 2H, NH_2), 6.95-7.08 (m, 2H, H-5 and H_{arom}), 7.24 (t, 1H, H-6, *J* = 8.0 Hz), 7.53-7.68 (m, 4H, H-7 and H_{arom}), 7.95-7.99 (m, 1H, H_{arom}), 10.80 (broad s, 1H, NH), 11.13 (broad s, 1H, NH); ^{13}C nmr: δ 114.4 (C), 114.6 (CH), 119.1 (CH), 123.6 (CH), 125.5 (C), 127.7 (2CH), 128.6 (2CH), 131.6 (C), 132.4 (C), 135.6 (CH), 149.1 (C=O), 160.8 (C=O), 165.1 (C=O); ms: *m/z* 297 (M+1).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.90; H, 3.97; N, 19.20.

8-Amino-3-phenylquinazoline-2,4-(1*H*,3*H*)-dione (**7b**).

This compound was obtained as a white amorphous solid (91%), mp 324-325 °C, ir: ν 1680 (C=O), 1720 (C=O), 3300 (NH), 3441 (NH) cm^{-1}; ^1H nm: δ 5.57 (broad s, 2H, NH_2), 6.93-7.10 (m, 2H, H-5 and H_{arom}), 7.20 (t, 1H, H-6, *J* = 8.0 Hz, H-6), 7.27-7.36 (m, 2H, H_{arom}), 7.40-7.55 (m, 3H, H-7 and H_{arom}), 10.64 (broad s, 1H, NH); ^{13}C nmr: δ 114.5 (CH), 115.0 (C), 118.6 (CH), 123.0 (CH), 126.2 (C), 128.0 (CH), 128.8 (2CH), 129.1 (2CH), 135.4 (C), 135.9 (C), 150.3 (C=O), 162.5 (C=O); ms: *m/z* 254 (M+1).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.30; H, 4.61; N, 16.68.

8-Amino-3-(4-methoxyphenyl)quinazoline-2,4-(1*H*,3*H*)-dione (**7c**).

This compound was obtained as a white amorphous solid (93%), mp 284-285 °C, ir: ν 1680 (C=O), 1720 (C=O), 3335 (NH), 3479 (NH) cm^{-1}; ^1H nmr: δ 3.80 (s, 3H, OCH_3), 5.60 (broad s, 2H, NH_2), 6.95-7.03 (m, 3H, H-5 and H_{arom}), 7.10-7.25 (m, 4H, H-6, H-7 and H_{arom}), 10.60 (broad s, 1H, NH); ^{13}C nmr: δ 55.4 (CH_3), 114.0 (2CH), 114.6 (CH), 115.0 (C), 118.5 (CH), 122.9 (CH), 126.2 (C), 128.4 (C), 130.0 (2CH), 135.3 (C), 150.5 (C=O), 158.8 (C), 162.7 (C=O); ms: *m/z* 284 (M^++1).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.77; H, 4.52; N, 15.01.

8-Amino-3-pyrazin-2-ylquinazoline-2,4(1*H*,3*H*)-dione (**7d**).

This compound was obtained as a white amorphous solid (90%), mp 242-243 °C, ir: ν 1680 (C=O), 1720 (C=O), 3335 (NH), 3479 (NH) cm^{-1}; ^1H nmr: δ 5.62 (broad s, 2H, NH_2), 6.85-7.3 (m, 3H, H-5, H-6 and H-7), 8.60-9.10 (m, 3H, H_{arom}), 10.86 (broad s, 1H, NH); ^{13}C nmr: δ 114.2 (C), 114.5 (CH), 119.1 (CH), 123.2 (CH), 126.0 (C), 135.5 (C), 144.2 (CH), 144.4 (CH), 145.5 (CH), 146.3 (C), 149.7 (C=O), 162.4 (C=O); ms: *m/z* 256 (M+1).

Anal. Calcd. for $C_{12}H_9N_5O_2$: C, 56.47; H, 3.55; N, 27.44. Found: C, 56.60; H, 3.49; N, 27.61.

8-Amino-3-pyridin-2-ylquinazoline-2,4-(1*H*,3*H*)-dione (**7e**).

This compound was obtained as a white amorphous solid (92%), mp 257-258 °C, ir: ν 1680 (C=O), 1735 (C=O), 3360 (NH), 3467 (NH) cm^{-1}; ^1H nmr: δ 5.73 (broad s, 2H, NH_2), 6.93-7.06 (m, 2H, H-7 and H-6), 7.19 (t, 1H, H_{arom}, *J* = 8.0 Hz), 7.45-7.60 (m, 2H, H-5 and H_{arom}), 7.99 (t, 1H, H_{arom}, *J* = 7.7 Hz), 8.60 (d, 1H, H_{arom}, *J* = 4.4 Hz), 10.82 (broad s, 1H, NH); ^{13}C nmr: δ 114.28 (CH), 114.91 (CH), 118.90 (CH), 123.23 (CH), 124.13 (CH), 124.49 (CH), 126.29 (CH), 135.72 (C), 138.74 (C), 149.34 (C), 149.46 (C=O), 150.02 (CH), 162.54 (C=O); ms: *m/z* 255 (M+1).

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.30; H, 4.09; N, 21.87.

8-Amino-3-pyridin-4-ylquinazoline-2,4-(1*H*,3*H*)-dione (**7f**).

This compound was obtained as a yellow amorphous solid (93%), mp 286-287 °C, ir: ν 1671 (C=O), 1728 (C=O), 3344 (NH), 3471 (NH) cm^{-1}; ^1H nmr: δ 5.75 (broad s, 2H, NH_2), 6.90-7.07 (m, 2H, H-7 and H-6), 7.12-7.25 (m, 1H, H_{arom}), 7.38-7.52 (m, 2H, H-5 and H_{arom}), 8.64-8.80 (m, 2H, H_{arom}), 10.86 (broad s, 1H, NH); ^{13}C nmr: δ 114.33 (C), 114.87 (CH), 118.82 (CH), 123.18 (CH), 124.67 (2CH), 126.17 (C), 135.72 (C), 143.86 (C), 149.62 (C=O), 150.53 (2CH), 162.14 (C=O); ms: *m/z* 255 (M+1).

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.55; H, 4.02; N, 22.19.

Preparation of 4-Carbomethoxybenzimidazole-2-thione (**8**).

To a solution of **7b** or **7c** (2 mmol) in methanol (20 ml) were added potassium hydroxide (0.12 g, 2.2 mmol) and carbon disulfide (1.5 ml, 25 mmol). The reaction mixture was refluxed for 24 hours and then cooled to room temperature. After evaporation of solvent and excess carbon disulfide, the residual product was acidified by the addition of hydrochloric acid (3 *N*). The crude product, which precipitated, was filtered and washed with water and then purified by recrystallization in ethanol to afford 4-carbomethoxybenzimidazole-2-thione **8** as a white amorphous solid (60%), mp 254-255 °C; ir: ν 1360 (C=S), 1711 (C=O), 3251 (NH) cm^{-1}; ^1H nmr: δ 3.96 (s, 3H, OCH_3), 7.25 (t, 1H, H-6, *J* = 7.9 Hz), 7.40 (d, 1H, H-5, *J* = 7.9 Hz), 7.68 (d, 1H, H-7, *J* = 7.9 Hz), 12.33 (broad s, 1H, NH), 12.90 (broad s, 1H, NH); ^{13}C nmr: δ 54.76 (CH_3), 114.61 (C), 116.46 (CH), 124.84 (CH), 126.15 (CH), 134.29 (C), 136.10 (C), 167.61 (C=O), 172.52 (C=S); ms: *m/z* 209 (M+1).

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 52.11; H, 3.80; N, 13.50; S, 15.23.

Preparation of 5-Aryl-4*H*-imidazo[4,5,1-*ij*]quinazoline-2,4,6(1*H*,5*H*)-thiones **9b** and **9c**.

To a solution of **7b** or **7c** (2 mmol) in pyridine (15 ml) was added carbon disulfide (2 ml, 33 mmol). The mixture was refluxed for 24 hours and then cooled to room temperature. After evaporation of solvent and excess carbon disulfide, the crude product was recrystallized from ethanol to afford the tricyclic compound **9b** or **9c**.

5-Phenyl-4*H*-imidazo[4,5,1-*ij*]quinazoline-2,4,6(1*H*,5*H*)-thione (**9b**).

This compound was obtained as a white amorphous solid (93%) from ethanol, mp 302-303 °C, ir: ν 1360 (C=S), 1667 (C=O), 1740 (C=O), 3280 (NH) cm^{-1}; ^1H nmr: δ 7.30-7.63 (m, 7H, H_{arom}), 7.66-7.78 (m, 1H, H_{arom}), 13.59 (broad s, 1H, NH); ^{13}C nmr: δ 111.73 (C), 113.98 (C), 119.46 (C), 126.03 (CH), 128.45 (CH), 128.51 (CH), 129.04 (2CH), 129.10 (2CH), 129.64 (CH), 135.80 (C), 145.72 (C=O), 160.85 (C=O), 169.01 (C=S); ms: *m/z* 296 (M+1).

Anal. Calcd. for $C_{15}H_9N_3O_2S$: C, 61.01; H, 3.07; N, 14.23; S, 10.86. Found: C, 61.17; H, 3.21; N, 14.15; S, 10.91.

5-(4-Methoxyphenyl)-4*H*-imidazo[4,5,1-*ij*]quinazoline-2,4,6(1*H*,5*H*)-thione (**9c**).

This compound was obtained as a white amorphous solid (95%), mp 296-297 °C, ir: ν 1355 (C=S), 1697 (C=O), 1736 (C=O), 3330 (NH) cm^{-1}; ^1H nmr: δ 3.82 (s, 3H, OCH_3), 7.05 (d, 2H, H_{arom}, *J* = 7.2 Hz), 7.27 (d, 2H, H_{arom}, *J* = 7.2 Hz), 7.41-7.60 (m, 2H, H_{arom}), 7.64-7.78 (m, 1H, H_{arom}), 13.97 (broad s, 1H, NH); ^{13}C nmr: δ 55.33 (CH_3), 111.69 (C), 113.89 (CH), 114.21 (2CH), 119.43 (CH), 125.97 (CH), 128.16 (C), 129.57 (C), 130.05 (C), 131.20 (2CH), 145.86 (C=O), 159.06 (C), 160.96 (C=O), 169.00 (C=S); ms: *m/z* 326 (M+1).

Anal. Calcd. for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92; S, 9.86. Found: C, 59.21; H, 3.54; N, 12.78; S, 9.80.

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