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SYNTHESIS AND ANTITUMOR ACTIVITY OF 2-ARYL-7-FLUORO-6-(4-METHYL-1-PIPERAZINYL)-4(3*H*)-QUINAZOLINONES

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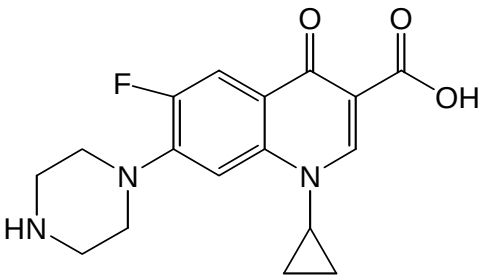
Abstract – A series of new 2-aryl-7-fluoro-6-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinones were prepared by the oxidative cyclization of the corresponding 2-arylidineamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamides**.** The new quinazolinones were evaluated for their antitumor activity.

INTRODUCTION

The synthesis of quinazolinone derivatives is an area of research that has attracted a great deal of attention in recent years as they possess a wide range of pharmacological activities,[1] such as fungicidal[2] anti-inflammatory,[3] antimalarial,[4] antitumor,[5] antihypertension,[6] cholecystokinin receptor antagonist[7] or anticonvulsant activities.[8] Recently, some of the quinazolinones are used as chemotherapeutic agents for various diseases, e.g., mecloqualone[9] or metolazone[10] are applied as sedative or diuretic drugs, respectively. To the best of our knowledge, quinazolinones incorporating both fluorine and *N*-piperazine substituents are undescribed in the literature. The presence of both substituents has enhanced considerably the antimicrobial potency of the quinolone drugs,[11] such as Ciprofloxacin® (**1**). Based on these findings, quinazolinone derivatives incorporating fluorine and piperazine as appendages might have potential biological activities. In this paper, we describe a multi-step synthesis and antitumor activity of new quinazolinones bearing fluorine and piperazine moieties (**2**).

RESULTS AND DISCUSSION

The starting material 2-nitro-4-fluoro-5-(4-methyl-1-piperazinyl)aniline (**3**) was prepared using a standard



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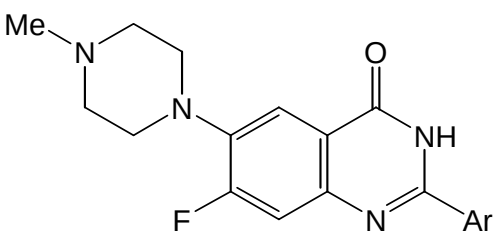

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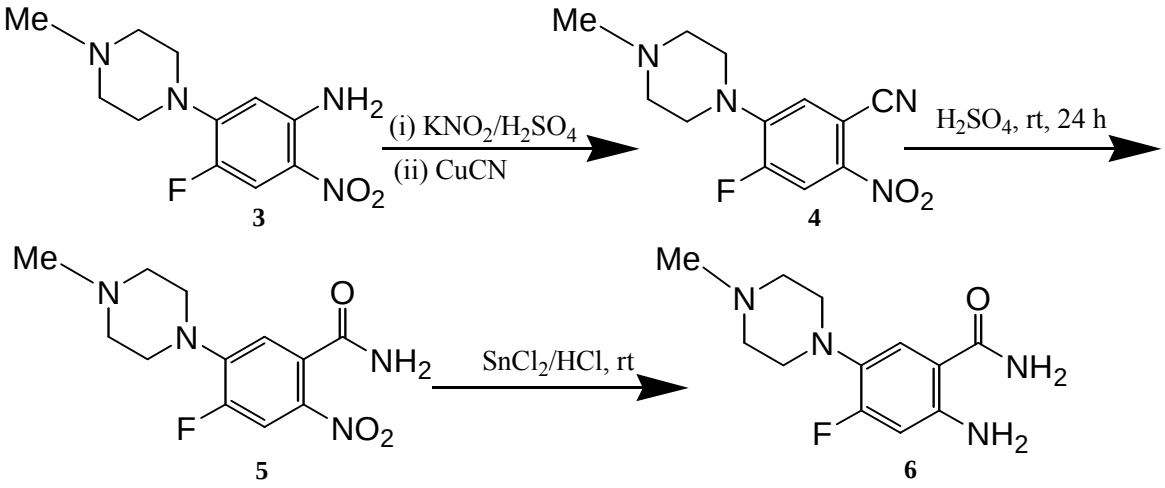
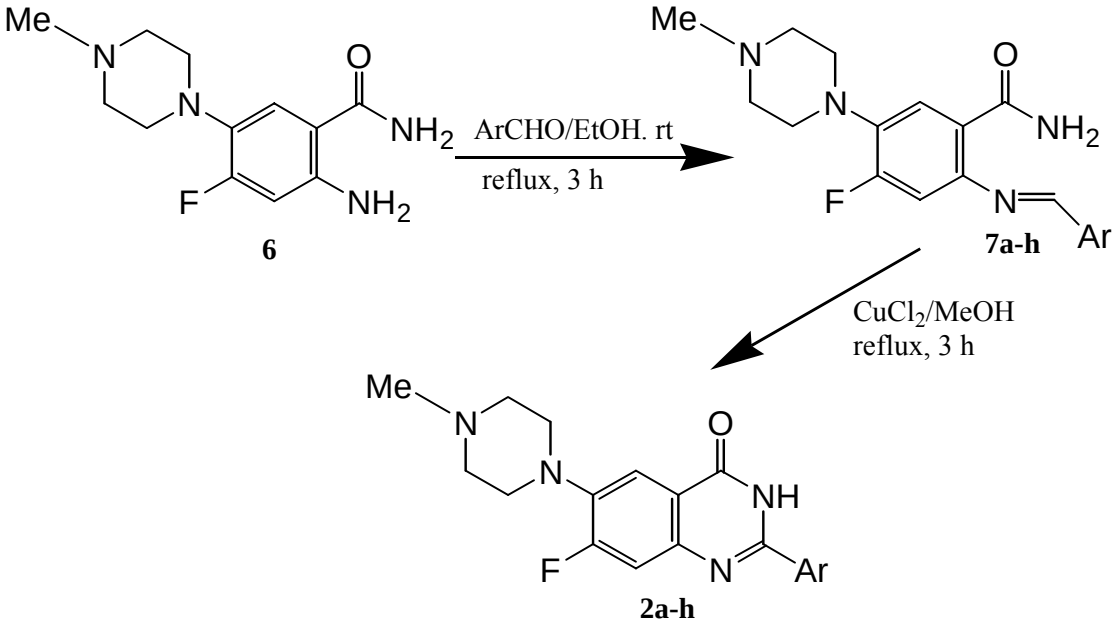
methodology[12] from commercially available 3-chloro-4-fluoroaniline by a sequence of steps involving acylation, nitration, deacylation and piperazinylation. The starting nitroaniline was diazotized using sulfuric acid and potassium nitrite and then coupled with copper(I) cyanide (generated *in situ* by reaction of copper(I) chloride with potassium cyanide) yielding the substituted benzonitrile (**4)**. Acidic hydrolysis at room temperature gave **5** in moderate yield. Subsequent reduction of **5** using tin(II) chloride in hydrochloric acid afforded the key intermediate 2-amino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamide (**6**) as shown in Scheme 1.



Scheme 1

The latter was then treated with the appropriate aldehyde to offer the Schiff's bases (**7a-h**) in high yields. Recently,[13] we have reported a new method for the synthesis of quinazolinones using $CuCl_2$ as a cyclizing agent. This cyclization reaction was conducted under various equivalents of $CuCl_2$, it was fastest (2 h), when the equivalents of $CuCl_2$ were threefold. With this standard reaction condition in hand, we turned our attention towards the simplification of the work up. In our first attempt to purify **2a**, the reaction mixture was evaporated under reduced pressure and the residue subjected to column chromatography using 30% methanol/dichloromethane. Thereafter, **2a** was still contaminated with traces of copper salts, and therefore

the column purification was repeated twice. To simplify the purification, hydrogen sulfide gas was bubbled through the hot reaction mixture for 5 min and the black copper sulfide was filtered off. Upon cooling and standing, the filtrate gave the quinazolinones in high purity which were further recrystallized from methanol yielding the desired products in 83-93 % yields.



No.	a	b	c	d	e	f	g	h
Ar	C_6H_5	*p*-F-C_6H_4	*p*-Cl-C_6H_4	*p*-MeO-C_6H_4	*p*-Me-C_6H_4	*p*-Br-C_6H_4	2-thienyl	2-furyl

Scheme 2

In the ^{1}H NMR spectra of **2a-h**, the aromatic proton signals (H-5 and H-8) appear as two doublets around δ 7.70-7.90 ppm and δ 7.58-7.70 ppm, respectively. The H-5 protons are more deshielded and show a smaller coupling with the adjacent fluorine atom (J_{H-F} = 8.00-9.60 Hz) than those of H-8 (J_{H-F} = 11.40-13.80 Hz). The N-CH_3 methyl protons appear as singlets around δ 2.90 ppm. The methylene proton signals of the piperazine moiety appear as two broad singlets at δ 3.40-3.70 ppm. The N-H protons give rise to broad singlets around δ 10.50-11.50 ppm. Moreover, the disappearance of the methine signals (around δ 8.31-8.5 ppm) and the appearance of the N-H signals at low field (around δ 10.50-11.50 ppm) in the ^{1}H NMR spectra of **2** and **7**, respectively, illustrate clearly the successful formation of the quinazolinone derivatives.

ANTITUMOR ACTIVITY

Compounds (**2a-h**), selected by the National Cancer Institute (NCI, USA), were tested using a one dose primary anticancer *in vitro* assay[14] against tumor in a three-cell line panel consisting of MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS), identifying **2b, d, g** as active compounds (Table 1). Based on the requirement for cell line screening set by NCI, the percent growth of tumor cells PG% (calculated on a

plate-by-plate basis for test wells relative to control wells and expressed as the ratio of fluorescence of test well (T) to average fluorescence of control wells (C) x 100 or T/C x 100) is 30% or less in at least one of the three cell lines. From the results obtained, compounds (**2b, g)** are active against NCI-H460 (lung) while compound (**2d)** is active against all three cell lines.

Table 1. Percent growth of tumor cells in a three-cell line panel.

Compound	Growth (%)		
	(Lung) H460	(Breast) MCF7	(CNS) SF-268
2b	18	56	52
2d	9	25	6
2g	1	52	58

CONCLUSION

We have successfully prepared a new series of substituted quinazolinones incorporating fluorine and piperazine substituents. The primary biological evaluation shown clearly a reasonable tumor activities. Further studies on the utilization of the new intermediates and the detailed antitumor activities are in progress and will be published in a due course.

EXPERIMENTAL

3-Chloro-4-fluoroaniline was purchased from Acros, *N*-methylpiperazine was acquired from Aldrich and all aldehydes used were obtained from Acros. Melting points were determined on SMP2 Stuart apparatus and are uncorrected. Elemental analyses were performed using a Perkin-Elmer elemental analyser, model 240. The El MS spectra were recorded on a Finnigan MAT 312 mass spectrometer.

^{1}H NMR spectra were measured with a Bruker WM 400-spectrometer (400 MHz) using TMS as internal standard. The chemical shifts are reported in parts per million (ppm).

BIOLOGICAL EVALUATION

Antitumor activity of all test compounds was tested primarily on a three-cell line panel, NCI-H460 (lung), MCF7 (breast) and SF-268 (CNS). In this prescreening procedure, cells were plated in a microtiter plate at a density of 1000 cells/well (NCI-H460), 5000 cells/well (MCF7) and 7500 cells/well (SF-268). Cells were suspended in 50µl RPMI-1640 culture media supplemented with 5% fetal bovine serum and 2mM

L-glutamine . Each plate contained all three cell lines in separate wells, total kill wells and untreated control wells. After 24 hours of incubation at 37°C, 5% CO_2, 95% air and 100% humidity, test compounds were separately added at a final concentration of 10^{-4}M. Cells were then incubated for an additional 48 hours at the indicated conditions. Alamar Blue was added at 10 µl/well, incubated for 4 hours and fluorescence was measured at an excitation wavelength of 530nm and an emission wavelength of 590nm. Percent growth was calculated on a plate-by-plate basis for test wells relative to control wells and expressed as the ratio of fluorescence of test well (T) to average fluorescence of control wells (C) x 100 or T/C x 100.

4-Fluoro-5-(4-methyl-1-piperazinyl)-2-nitrobenzonitrile (4)

Sulfuric acid (15 mL) was treated over 1 h at 5-10 °C with sodium nitrite (1.7 g, 24.6 mmol) and the mixture was slowly heated to 70 °C. The nitrosylsulfuric acid thus obtained was cooled to 10 °C and was treated under stirring for 30 min with a solution of 4-fluoro-5-(4-methyl-1-piperazinyl)- 2-nitroaniline (**3**, 5.0g, 19.7 mmol) in acetic acid (19.5 mL) at 15-20 °C. The mixture was stirred at the same temperature for 3 h and then added dropwise (30 min) with stirring to a solution of CuCN [prepared by treatment of a suspension of CuCl (3.3 g, 33.3 mmol) in water (17 mL) with a solution of KCN (6.8 g, 69.0 mmol) in water (24 mL)]. The solution was heated to 60 °C followed by the addition of a solution of Na_2CO_3 (40.5 g, 0.38 mol) in water (95 mL) at the same temperature, whereby CO_2 gas developed. The reaction mixture was heated to 85-90 °C for 30 min and cooled to rt. The precipitate obtained was filtered, washed with water, dried, dissolved in benzene (100 mL) at 70 °C and the undissolved material filtered off. The filtrate was dried and evaporated under vacuum to give a brown solid which was further crystallized from benzene / petroleum ether (40-60 °C) to give **4** (2.8 g, 54 %) as brown crystals, mp 153-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 13.1 Hz, 1H, H-3), 7.19 (d, J = 8.2 Hz, 1H, H-6), 3.37, 2.54 (each t, each J = 4.9, Hz, each 4H, piperazine), 2.31 (s, 3H, N-CH_3). IR (KBr): 2223 , 1591, 1330 cm^{-1}. *Anal*. Calcd for $C_{12}H_{13}N_4O_2F$: C, 54.54; H, 4.96; N, 21.20. Found: C, 54.43; H, 4.92; N, 21.13.

4-Fluoro-5-(4-methyl-1-piperazinyl)-2-nitrobenzamide (5)

A mixture of 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitrobenzonitrile (**4**) (5.0 g, 18.9 mmol) in conc. sulfuric acid (62 mL) was stirred at rt for three days. The reaction mixture was then poured slowly into ice water (100 mL) and was treated with a 50 % sodium hydroxide solution to a pH of 10. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined ethyl acetate extracts were dried (Na_2SO_4), evaporated under vacuum and crystallized (ethanol) to give **5** (3.9 g, 73 %), mp 194-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 13.1 Hz, 1H, H-3), 6.88 (d, J = 8.2 Hz, 1H, H-6), 3.32, 2.55 (each t, each J = 4.9, Hz, each 4H, piperazine), 2.33 (s, 3H, N-CH_3). IR (KBr): 3560, 3303, 2223, 1660 cm^{-1}. *Anal*. Calcd for $C_{12}H_{15}N_4O_3F$: C, 51.06; H, 5.36; N, 19.85. Found: C, 51.00; H, 5.33; N, 19.79.

2-Amino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamide (6)

To a solution of 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitrobenzamide (**5**) (5.0 g, 17.8 mmol) in conc. HCl (100 mL), stannous chloride (22.4 g, 0.12 mol) was slowly added (10 min) at rt. Stirring was continued for additional 30 min, then water (100 mL) was added and stirring was continued for 1 h. The reaction mixture was cooled (ice-water bath) and treated gradually with a solution of 40% NaOH until the solution is strongly alkaline (pH = 13), then the resulting precipitate was filtered, dried and crystallized (methanol) to give **6** (3.8 g, 85 %), mp 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, J = 9.0 Hz, 1H, H-6), 6.36 (d, J = 13.5 Hz, H-3), 2.96, 2.56 (each t, each J = 4.9, Hz, each 4H, piperazine), 2.31 (s, 3H, N-CH_3), 5.52, 5.80 (each br s, each 2H, NH_2, O=C-NH_2). IR (KBr): 3448, 3213, 1643 cm^{-1}. *Anal*. Calcd for $C_{12}H_{17}N_4O_3F$: C, 57.13; H, 6.79; N, 22.21. Found: C, 57.02; H, 6.72; N, 22.15.

2-Arylidinamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamides (7a-h)

General procedure: To a stirred solution of 2-amino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamide (**6**) (1.26 g, 5 mmol) in dry ethanol (20 mL) was added the appropriate aldehyde (15 mmol) and the reaction mixture was refluxed for 6 h. The resulting precipitate was collected and crystallized (ethanol) to give the corresponding Shiff's bases (**7a-h**).

2-Benzylidenamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamide (7a)

Yield (82 %), mp 178-180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H, CH=Ar), 7.50-7.82 (m, 5H, C_6H_5), 7.94 (d, J = 9.8 Hz, H-6), 6.88 (d, J = 13.2 Hz, 1H, H-3), 3.21, 2.63 (each t, each J = 4.9, Hz, each 4H, piperazine), 2.35 (s, 3H, N-CH_3), 9.10, 5.93 (each br s, each 1H, NH_2). IR (KBr): 3273 , 3116, 1670, 1592, 1603 cm^{-1}. *Anal*. Calcd for $C_{19}H_{21}N_4OF$: C, 67.04; H, 6.22; N, 16.46. Found: C, 66.92; H, 6.19; N, 16.39.

4-Fluoro-2-[4-fluorobenzylidinamino]-5-(4-methyl-1-piperazinyl)benzamide (7b)

Yield (81%); mp 222-224 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (s, 1H, CH=Ar), 7.29-7.95 (m, 4H, C_6H_4F), 8.05 (d, J = 9.5 Hz, H-6), 6.97 (d, J = 12.9 Hz, 1H, H-3), 3.32, 2.71 (each t, each J = 4.9, Hz, each 4H, piperazine), 2.71 (s, 3H, N-CH_3), 9.06, 6.04 (each br s, each 1H, NH_2). IR (KBr): 3283 , 3126, 1668, 1595, 1608 cm^{-1}. *Anal*. Calcd for $C_{19}H_{20}N_4OF_2$: C, 63.68; H, 5.62; N, 15.63. Found: C, 63.52; H, 5.59; N, 15.59.

4-Fluoro-2-[4-chlorobenzylidineamino]-5-(4-methyl-1-piperazinyl)benzamide (7c)

Yield (92 %), mp 228-230 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (s, 1H, CH=Ar), 7.46, 7.76 (each d, each J = 8.2, Hz, each 2H, C_6H_4Cl), 7.93 (d, J = 9.9 Hz, H-6), 6.86 (d, J = 13.1 Hz, 1H, H-3), 3.20, 2.34 (each t, each J = 4.9, Hz, each 4H, piperazine), 2.34 (s, 3H, N-CH_3), 8.91, 5.92 (each br s, each 1H, NH_2). IR (KBr):

3308 , 3196, 1654, 1587, 1606 cm^{-1}. *Anal*. Calcd for $C_{19}H_{21}N_4OClF$: C, 60.88; H, 5.38; N, 14.95. Found: C, 60.72; H, 5.36; N, 14.89.

4-Fluoro-2-[4-methoxybenzylidineamino]-5-(4-methyl-1-piperazinyl)benzamide (7d)

Yield (78 %), mp 250-251 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H, CH=Ar), 7.03, 7.48 (each d, each *J* = 8.9 Hz, each 2H, $C_6H_4OCH_3$), 7.36(d, *J* = 9.5 Hz, H-6), 6.60 (d, *J* = 13.1 Hz, 1H, H-3), 3.82 (s, 3H, $C_6H_4OCH_3$), 2.94, 2.58 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.29 (s, 3H, N-CH_3), 8.26, 5.76 (each br s, each 1H, NH_2). IR (KBr): 3288 , 3124, 1675, 1598, 1609 cm^{-1}. *Anal*. Calcd for $C_{20}H_{23}N_4O_2F$: C, 64.85; H, 6.26; N, 15.13. Found: C, 64.69; H, 6.22; N ,15.09.

4-Fluoro-2-[4-methoxybenzylidinamino]-5-(4-methyl-1-piperazinyl)benzamide (7e)

Yield (85 %), mp 248-249 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H, CH=Ar), 7.41, 7.84 (each d, each *J* = 8.0 Hz, each 2H, $C_6H_4CH_3$), 8.06 (d, *J* = 9.9 Hz, H-6), 6.98 (d, *J* = 13.3 Hz, 1H, H-3), 3.31, 2.71 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.54 (s, 3H, N-CH_3), 2.46 (s, 3H, $C_6H_4CH_3$), 9.23, 6.03 (each br s, each 1H, NH_2). IR (KBr): 3283 , 3119, 1670, 1588, 1609 cm^{-1}. *Anal*. Calcd for $C_{20}H_{23}N_4OF$: C, 67.78; H, 6.54; N, 15.81. Found: C, 67.68; H, 6.50; N ,15.79.

4-Fluoro-2-[4-bromobenzylidinamino]-5-(4-methyl-1-piperazinyl)benzamide (7f).

Yield (83 %), mp 230-232 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (s, 1H, CH=Ar), 7.43, 8.03 (each d, each *J* = 8.2 Hz, each 2H, C_6H_4Br), 7.99 (d, *J* = 9.9 Hz, H-6), 7.02 (d, *J* = 13.1 Hz, 1H, H-3), 3.22, 2.61 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.35 (s, 3H, N-CH_3), 8.95, 5.96 (each br s, each 1H, NH_2). IR (KBr): 3330 , 3107, 1667, 1559, 1628 cm^{-1}. *Anal*. Calcd for $C_{19}H_{20}N_4OBrF$: C, 54.43; H, 4.81; N, 13.36. Found: C, 54.29; H, 4.79; N , 13.29.

4-Fluoro-2-[2-thionylmethylenamino]-5-(4-methyl-1-piperazinyl)benzamide (7g).

Yield (78 %), mp 206-208 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H, CH=Ar), 7.92 (d, *J* = 9.7 Hz, H-6), 7.53 (m, 2H, thienyl), 7.14 (dd, J = 3.5, 4.8 Hz, 1H, thienyl), 6.87 (d, *J* = 13.1 Hz, 1H, H-3), 3.17, 2.57 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.35 (s, 3H, N-CH_3), 9.05, 6.00 (each br s, each 1H, NH_2). IR (KBr): 3360 , 3176, 1664, 1572, 1602 cm^{-1}. *Anal*. Calcd for $C_{17}H_{19}N_4OFS$: C, 58.94; H, 5.53; N, 16.17. Found: C, 58.80; H, 5.49; N , 16.11.

4-Fluoro-2-[2-furylmethylenamino]-5-(4-methyl-1-piperazinyl)benzamide (7h)

Yield (90 %), mp 208-209 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (s, 1H, CH=Ar), 8.06 (d, *J* = 9.7 Hz, H-6), 7.74 (dd, *J* = 0.9, 1.8 Hz, 1H, furyl), 7.10 (dd, *J* = 2.0, 4.1 Hz, 1H, furyl), 6.59 (dd, J = 0.7, 4.2 Hz,

1H, furyl), 7.00 (d, *J* = 13.1 Hz, 1H, H-3), 3.31, 2.69 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.45 (s, 3H, N-CH_3), 9.49, 6.16 (each br s, each 1H, NH_2). IR (KBr): 3312 , 3133, 1666, 1569, 1603 cm^{-1}. *Anal*. Calcd for $C_{17}H_{19}N_4O_2F$: C, 61.81; H, 5.80; N, 16.96. Found: C, 61.69; H, 5.77; N , 16.89.

2-Aryl-7-fluoro-6-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinones (2)

General procedure: A mixture of 2-arylidineamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamide (**7**) (3 mmol), $CuCl_2$ (1.2 g, 9 mmol) in methanol (100mL) was refluxed for 3 h. Hydrogen sulfide gas was then bubbled into the boiling mixture for 10 min. The black precipitate was filtered off and the filtrate allowed to cool to rt. The resulting precipitate was then collected, washed with cold methanol and further crystalized (methanol) to affored the desired quinazolinones (**2**) in good yields.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-phenyl-4(3*H*)quinazolinone (2a)

Yield (83 %), mp 288-290 °C. ^{1}H NMR (400 MHz, DMSO- d_6): δ 11.21 (s, 1H, N-H), 7.65-8.23 (m, 5H, C_6H_5), 7.76 (d, *J* = 9.5 Hz, H-5), 7.63 (d, *J* = 13.7 Hz, 1H, H-8), 3.64, 3.35 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.92 (s, 3H, N-CH_3). IR (KBr): 3380, 1709, 1630, 1649 cm^{-1}. *Anal*. Calcd for $C_{19}H_{19}N_4OF$: C, 67.04; H, 6.22; N, 16.46. Found: C, 66.92; H, 6.19; N, 16.39.

7-Fluoro-2-(4-fluorophenyl)-6-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (2b)

Yield (88 %), mp 300 °C (decomp). ^{1}H NMR (400 MHz, DMSO- d_6): δ 11.64 (s, 1H, N-H), 7.46-7.84 (m, 4H, C_6H_4F), 7.74 (d, *J* = 9.2 Hz, H-5), 7.69 (d, *J* = 11.5 Hz, 1H, H-8), 3.64, 3.36 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.89 (s, 3H, N-CH_3). IR (KBr): 3386, 1652, 1593, 1610 cm^{-1}. *Anal*. Calcd for $C_{19}H_{18}N_4OF_2$: C, 64.04; H, 5.09; N, 15.72. Found: C, 63.92; H, 5.11; N, 15.70.

7-Fluoro-6-2-(4-chlorophenyl)-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (2c)

Yield (88 %), mp 300 °C (decomp). ^{1}H NMR (400 MHz, DMSO- d_6): δ 11.44 (s, 1H, N-H), 7.70, 8.24 (each d, each *J* = 8.0 Hz, each 2H, C_6H_4Cl), 7.75 (d, *J* = 9.2 Hz, H-5), 7.66 (d, *J* = 13.0 Hz, 1H, H-8), 3.65, 3.36 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.90 (s, 3H, N-CH_3). IR (KBr): 3441, 1711, 1602, 1634 cm^{-1}. *Anal*. Calcd for $C_{19}H_{18}N_4OClF$: C, 61.21; H, 4.87; N, 15.03. Found: C, 61.08; H, 4.82; N, 14.95.

7-Fluoro-6-2-(4-methoxyphenyl)-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (2d)

Yield (83 %), mp 257-258 °C. ^{1}H NMR (400 MHz, DMSO- d_6): δ 11.34 (s, 1H, N-H), 7.24, 8.03 (each d, each *J* = 9.0 Hz, each 2H, $C_6H_4OCH_3$), 7.88 (d, *J* = 8.8 Hz, H-5), 7.60 (d, *J* = 12.5 Hz, 1H, H-8), 3.95 (s, 3H, $C_6H_4OCH_3$), 3.76, 3.35 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 3.01 (s, 3H, N-CH_3). IR (KBr): 3442, 1664, 1600, 1624 cm^{-1}. *Anal*. Calcd for $C_{20}H_{21}N_4O_2F$: C, 65.20; H, 5.75; N, 15.21. Found: C, 65.03; H,

5.70; N, 15.16.

7-Fluoro-6-2-(4-methylphenyl)-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (2e)

Yield (93 %), mp 220 °C (decomp). ^{1}H NMR (400 MHz, DMSO- d_6): δ 10.82 (s, 1H, N-H), 7.44, 8.12 (each d, each *J* = 8.0 Hz, each 2H, $C_6H_4CH_3$), 7.74 (d, *J* = 9.2 Hz, H-5), 7.65 (d, *J* = 12.9 Hz, 1H, H-8), 3.65, 3.31 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.93 (s, 3H, N-CH_3). IR (KBr): 3447, 1706, 1615, 1645 cm^{-1}. *Anal*. Calcd for $C_{20}H_{21}N_4OF$: C, 68.16; H, 6.01; N, 15.90. Found: C, 68.05; H, 5.99; N, 15.85.

7-Fluoro-6-2-(4-bromophenyl)-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (2f)

Yield (90 %), mp 304 °C (decomp). ^{1}H NMR (400 MHz, DMSO- d_6): δ 11.00 (s, 1H, N-H), 7.84, 8.18 (each d, each *J* = 8.0 Hz, each 2H, C_6H_4Cl), 7.76 (d, *J* = 9.6 Hz, H-5), 7.65 (d, *J* = 13.0 Hz, 1H, H-8), 3.66, 3.34 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.93 (s, 3H, N-CH_3). IR (KBr): 3390, 1659, 1580, 1607 cm^{-1}. *Anal*. Calcd for $C_{19}H_{18}N_4OBrF$: C, 54.69; H, 4.35; N, 13.43. Found: C, 54.58; H, 4.29; N, 13.39.

7-Fluoro-(4-methyl-1-piperazinyl)-6-(2-thienyl)-4(3*H*)-quinazolinone (2g)

Yield (88 %), mp 320 °C (decomp). ^{1}H NMR (400 MHz, DMSO- d_6): δ 10.98 (s, 1H, N-H), 8.29 (br s, 1H, thienyl), 7.94 (br d, *J* = 5.4 Hz, 1H, thienyl), 7.31 (br s, 1H, thienyl), 7.74 (d, *J* = 9.2 Hz, H-5), 7.57 (d, *J* = 13.0 Hz, 1H, H-8), 3.69, 3.32 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.92 (s, 3H, N-CH_3). IR (KBr): 3437, 1655, 1587, 1629 cm^{-1}. *Anal*. Calcd for $C_{17}H_{17}N_4OFS$: C, 59.28; H, 4.98; N, 16.27. Found: C, 59.11; H, 4.93; N, 16.19.

7-Fluoro-6-(2-furyl)-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (2h)

Yield (85 %), mp 205 °C (decomp). ^{1}H NMR (400 MHz, DMSO- d_6): δ 10.90 (s, 1H, N-H), 8.05 (br d, *J* = 5.9 Hz, 1H, furyl), 7.66 (br t, *J* = 4.7 Hz, 1H, furyl), 6.80 (m, 1H, furyl), 7.71 (d, *J* = 9.2 Hz, H-5), 7.58 (d, *J* = 12.7 Hz, 1H, H-8), 3.54, 3.32 (each t, each *J* = 4.9, Hz, each 4H, piperazine), 2.92 (s, 3H, N-CH_3). IR (KBr): 3345, 1662, 1587, 1605 cm^{-1}. *Anal*. Calcd for $C_{17}H_{17}N_4O_2F$: C, 62.19; H, 5.22; N, 17.06. Found: C, 62.05; H, 5.19; N, 16.99.

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