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FACILE SYNTHESIS OF 2-PHENYLQUINOLINE-4-CARBOXAMIDE DERIVATIVES WITH VARIANT STRUCTURAL FEATURES

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Abstract – The quinoline scaffold is an important class of heterocyclic compounds that possesses diverse chemotherapeutic activities. Thus, the 2-phenylquinoline-4-carboxamide derivatives containing a variety of moieties, such as 2-(2-furanyl)-1,3,4-oxadiazole, *N*-(2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, 4,4'-bithiazole, purine, adamantine and resorcinol, have been designed and synthesized via Suzuki coupling, acid-base coupling and other typical reactions.

INTRODUCTION

Signal transducer and activator of transcription 3 (STAT3), a member of the STAT protein family, is a latent cytosolic transcription factor, that is widely recognized as a master regulator of crucial steps in cellular proliferation and survival, metastasis and angiogenesis, and immune evasion.[1-7] STAT3 is frequently over activated in various human cancers including prostate, breast, head and neck cancers, but not in normal epithelial cells.[1-7] Thus, STAT3 signaling pathway has been validated as a promising target for development of anticancer therapeutics.[1-8] Since most of the currently available chemotherapy options aim to initiate apoptosis, cancer cells have an intrinsic resistance to current treatment strategies. Therefore, the design and synthesis of organic compounds with the ability to disrupt STAT3-mediated anti-apoptotic gene expression is an important approach to search potential and selective anticancer drugs.

In the field of medicinal chemistry, synthesis of biologically active heterocyclic scaffolds is one of the continuing interests, since most of the therapeutic drugs are derived from heterocyclic structures. The quinoline nucleus is a significant class of heterocyclic compounds found in many synthetic and natural products with promising biological activities.[9-16] Development of new synthetic drugs based on quinoline

scaffold remains as an active research area, since the structural modification of a privileged moiety with therapeutic ability greatly alters its potency. Recently in a communication, we have reported the identification of *N*-[2-(1,3,4-oxadiazolyl)]quinoline-4-carboxamide (STX-0119)[17] as STAT3 inhibitor by virtual screening strategy combining molecular docking studies and cell-line assays.

Our ongoing interest in the synthesis of heterocyclic compounds with therapeutic ability has prompted us to further investigate the more functionalized quinoline derivatives. Hence in this paper, we report the synthesis of a range of novel 2-phenylquinoline-4-carboxamide derivatives (**I–V**) containing few other biologically important scaffolds (**Figure 1**).

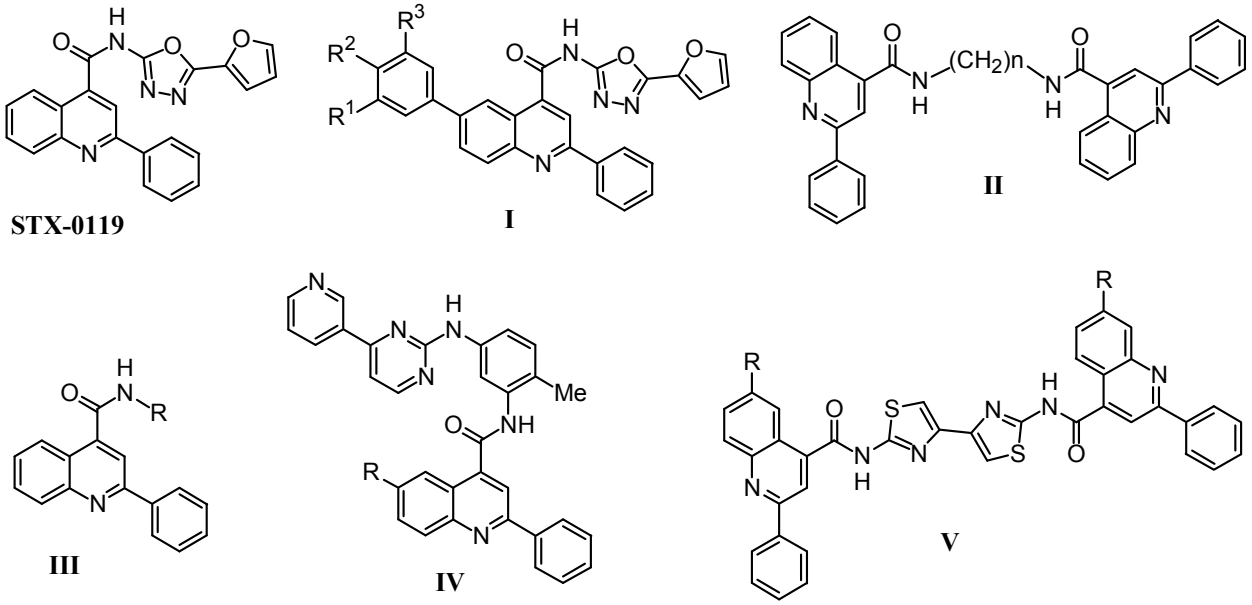
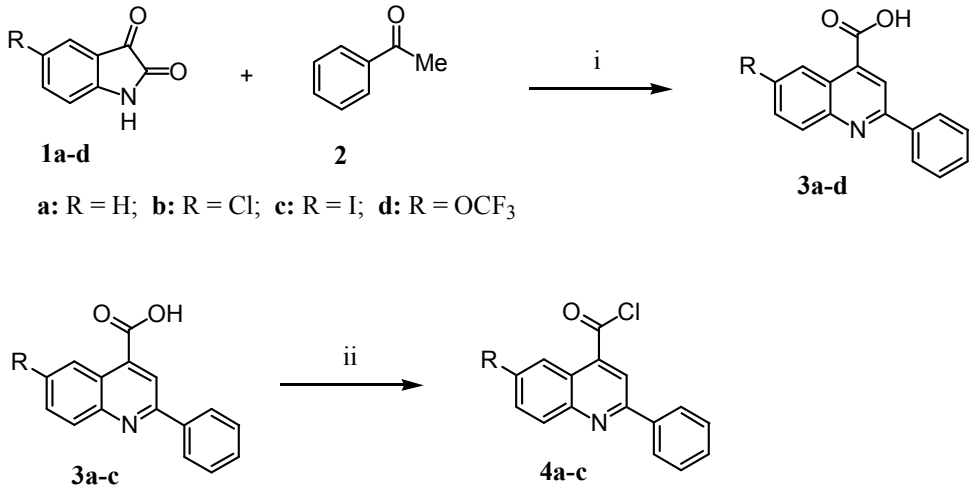


Figure 1

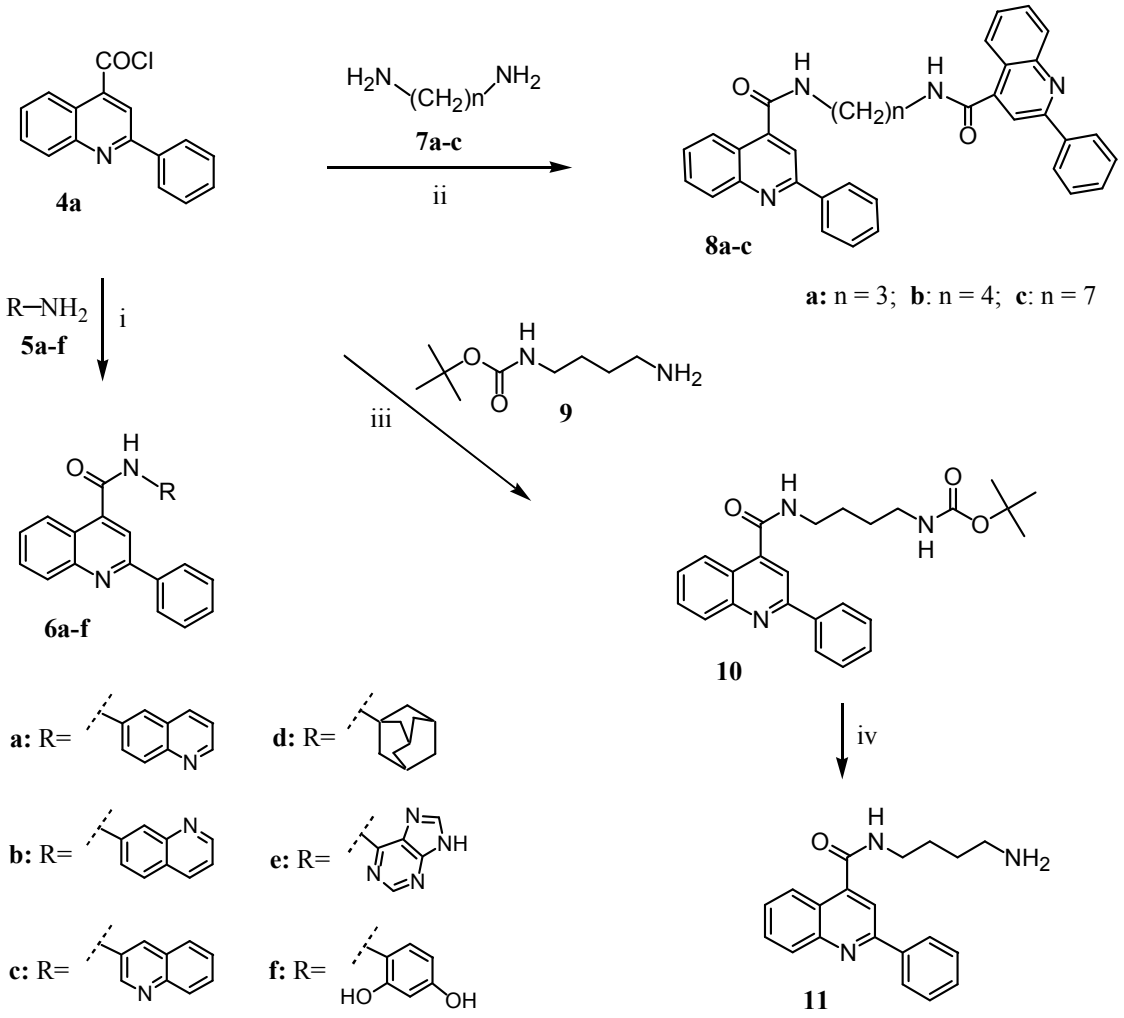
RESULTS AND DISCUSSION

Synthesis of requisite intermediates **3a-d** was accomplished as illustrated in **Scheme 1**. The Pfitzinger condensation[18,19] of an appropriate isatin (**1a-d**) and acetophenone (**2**) in the presence of potassium hydroxide in aqueous ethanol under reflux followed by neutralization afforded the corresponding 2-phenylquinoline-4-carboxylic acids (**3a-d**). Conversion of carboxylic acids (**3a-c)** to the corresponding acid chlorides (**4a-c**) was carried out by treating with excess oxalyl chloride in the presence of a catalytic amount of *N*,*N*-dimethylformamide (DMF) in dichloromethane at room temperature.

The acid chloride **4a** was treated with various commercially available amines (**5a-f**), such as the 3-, 6- and 7-aminoquinoline, 1-aminoadamantane, 6-aminopurine (adenine), and 4-aminoresorcinol, in the presence of triethylamine (Et_3N) in dehydrated THF/DMF at elevated temperature to produce the corresponding target compounds **6a-f** in good yields as outlined in **Scheme 2**. Preparation of **6a-f** took place smoothly in

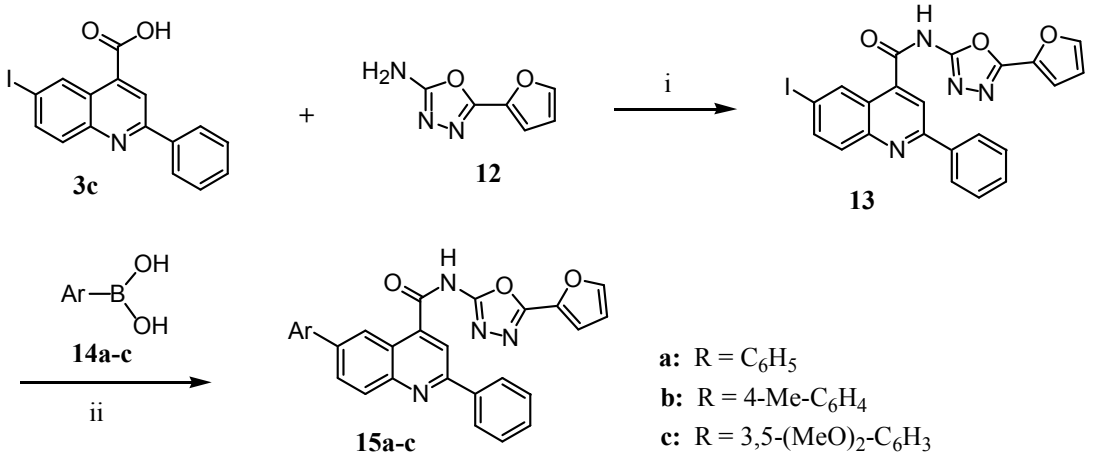


Scheme 1. *Reagents and conditions:* i, KOH, EtOH, water, 80-90 ^{o}C 18-36 h; ii, oxalyl chloride, DMF, CH_2Cl_2, rt, overnight.



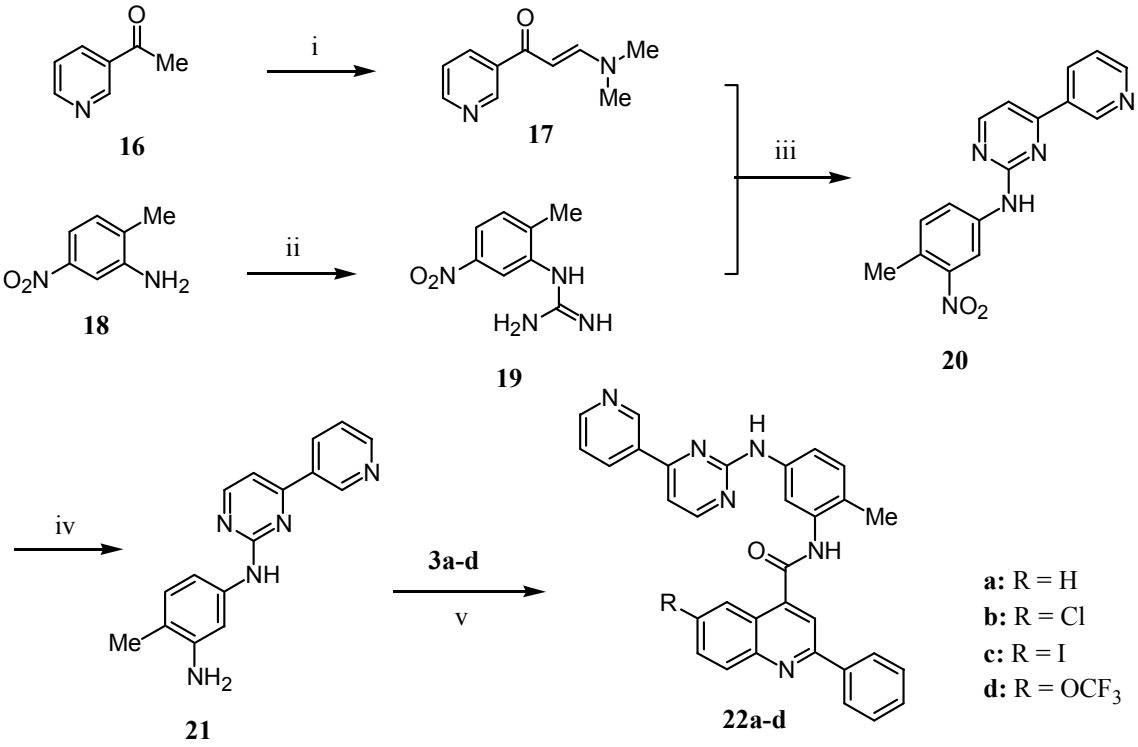
Scheme 2. *Reagents and conditions:* i, Et_3N, THF/DMF, reflux/(80-90 ^{o}C), 1.5-16 h; ii, Et_3N, THF, reflux, 1.5 h; iii, Et_3N, THF, 40-50 ^{o}C, 2 h; iv, F_3CCO_2H, CH_2Cl_2, rt, 8 h.

THF except **6e** due to its less reactivity and solubility in the reaction condition. Thus, preparation of **6e** was carried out at higher temperature (80-90 °C) in DMF. In order to increase the quinoline-4-carboxamide functionality in a single molecule, bis quinoline-4-carboxamides (**8a-c**) were prepared in excellent yields by treating **4a** with an appropriate diamine (**7a-c**) in the presence of Et_3N in THF under reflux. Under similar reaction condition, intermediate **4a** was also reacted with *N*-(4-aminobutyl)carbamic acid *tert*-butyl ester (**9**) to give compound **10** in 66% yield. Removal of *tert*-butyl carbamate (Boc) group from compound **10** was accomplished with trifluoroacetic acid in CH_2Cl_2 at room temperature to give compound **11** in 73% yield.



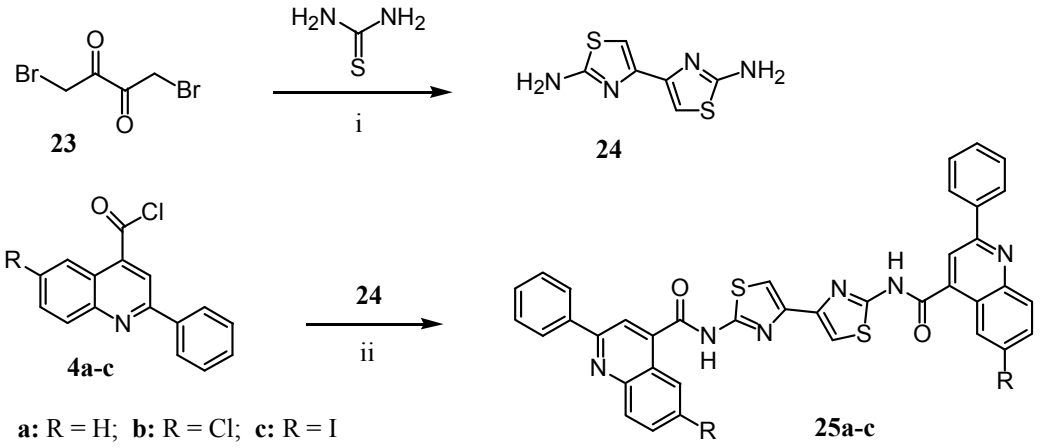
Scheme 3. *Reagents and conditions:* i, DIPEA, HBTU, HOBt, DMF, rt, 3 d; ii, $Pd(OAc)_2$, Xphos, K_3PO_4, BuOH, 100 ^oC, 2 d.

A lot of efforts have been directed toward the modification of quinoline scaffold to improve biological activities, though most of them have been accomplished either at the 2- or 4-position. Only a very little structural modification especially aryl group alteration at the 6-position along with the 4-position has been attained. Besides, hydrophobicity of drug is highly crucial for cell permeability. To raise the hydrophobic character in few of our target compounds, we incorporated aryl functionality at the 6-position of *N*-[5-(2-furanyl)-1,3,4-oxadiazol-2-yl]-2-phenylquinoline-4-carboxamide (STX-0119) by Suzuki-coupling reaction as delineated in **Scheme 3**. The acid-base coupling reaction of 6-iodoquinoline-4-carboxylic acid (**3c**) with 2-amino-5-(2-furyl)-1,3,4-oxadiazole (**12**) using coupling reagents *O*-(benzotriazolyl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and 1-hydroxybenzotriazole (HOBt), and base *N*,*N*-diisopropylethylamine (DIPEA) in DMF at room temperature furnished 6-iodo derivative **13** of STX-0119 in 62% yield. Subsequent Suzuki-coupling reaction of **13** with appropriate arylboronic acid **14a-c** using K_3PO_4, $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl (Xphos) in butanol at 100 °C gave the corresponding 6-aryl derivatives **15a-c** in 41-57% yields.



Scheme 4. *Reagents and conditions:* i, *N*,*N*-dimethylformamide dimethyl acetal, reflux, overnight; ii, cyanamide, HNO_3, EtOH, water, reflux, 2 d; iii, BuOH, reflux, 18 h, aq. NaOH; iv, H_2, Pd-C, THF-MeOH, rt, overnight; v, DIPEA, HBTU, HOBt, DMF, rt, 2 d.

The *N*-(2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine is an important fragment of recognized cell specific anticancer drugs such as Imatinib[20] and Nilotinib.[21] Hence, we have tried to prepare few compounds consisting of 2-phenylquinolines and above mentioned moiety as outlined in **Scheme 4**. The necessary amine **21** was prepared starting from 3-acetylpyridine (**16**) and 6-methyl-3-nitroaniline (**18**) according the reported method[22] with modification. **16** was converted to **17** by treating with excess *N*,*N*-dimethylformamide dimethyl acetal under reflux. On the other hand, aniline (**18**) was reacted with cyanamide and nitric acid in aqueous ethanol to produce the corresponding guanidinium nitrate salt, which on neutralization gave the free guanidine, **19**. The majority of literature procedures use guanidinium nitrate salt directly in next step followed *in situ* neutralization with alkali solution. The condensation of **17** and free guanidine **19** in butanol under reflux afforded *N*-(2-methyl-5-nitrophenyl)-4-(3-pyridinyl)-2-pyrimidinamine (**20**) in 87% yield, which on reduction with hydrogen using Pd-C as catalyst in a mixture of methanol and THF at room temperature gave the desired amine **21** (88%). Finally, the target compounds **22a-d** were synthesized in 64-72% yields by coupling **21** with an appropriate acid **3a-d** using HBTU, HOBt in the presence of DIPEA in DMF at room temperature.



Scheme 5. *Reagents and conditions:* i, MeOH, reflux, overnight, DMF-NH_4OH; ii, Et_3N, THF-DMF, reflux, overnight.

Synthesis of the *N*,*N*'-[4,4'-bithiazole]-2,2'-diylbis-2-phenylquinoline-4-carboxamides (**25a-c**) was carried out as outlined in **Scheme 5**. Treatment of the 1,4-dibromo-2,3-butanedione (**23**) with thiourea in methanol followed by neutralization with ammonia solution afforded the 4,4'-bithiazole]-2,2'-diamine (**24**) intermediate. Subsequent reaction of **24** with an appropriate quinoline-4-carbonyl chloride (**4a-c**) in the presence of Et_3N in a mixture of dehydrated THF and DMF under reflux produced the target compounds **25a-c** in 61-68% yields.

All new compounds have been characterized by elemental combustion analyses, and ^{1}H-NMR and mass spectral data. In the case of compounds **6e**, peak for one NH proton was not visible in the ^{1}H-NMR spectrum due to high acidity.

In conclusion, we have synthesized series of novel 2-phenylquinoline-4-carboxamides containing other significant moieties in the hope of searching STAT3 inhibitor. For this purpose, typical reactions including Suzuki coupling and acid-base coupling have been employed, and efficient procedures have been developed. Further synthesis of more derivatives and biological evaluation are currently ongoing, and will be reported in due course.

EXPERIMENTAL

Melting points were obtained on a digital melting point apparatus (Round Science, RFS-10, Japan) and were uncorrected. ^{1}H-NMR spectra were recorded on a 300 MHz spectrometer (JNM-AL 300, JEOL). The chemical shifts were reported in ppm (δ) relative to TMS. Coupling constants (*J*) were given in hertz (Hz), and multiplicities were expressed as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (doublet of doublet) and m (multiplet). Mass spectra were recorded on a Microflex Maldi-TOF mass spectrometer (Bruker Daltonics). Elemental analyses were performed on a J-Science LAB JM10 apparatus. Column chromatography was performed on Silica Gel G60 F254

(Merck).

General procedure for the preparation of 2-phenylquinoline-4-carboxylic acids (3a-d)

An appropriate isatin (**1a-d**) (14 mmol) and acetophenone (**2**) (16.5 mmol) were added to a solution of KOH (35 mmol) in 20% aqueous EtOH (50 mL). The reaction mixture was stirred at 80-90 °C for 18-36 h. Evaporation of solvent afforded a residue, which was dissolved in minimum water. The resulting solution was washed with Et_2O (2 × 20 mL). The ice-cold aqueous layer was acidified with HCl/AcOH. The resulting precipitate was collected by filtration followed by washing with water to give **3a-d** in 49-84% yields.

2-Phenylquinoline-4-carboxylic acid (3a)

Yield: 74%; off-white solid; mp 212–213 ºC (DMF-H_2O) (Lit.,[23] 209–210 ºC); ^{1}H-NMR (DMSO-d_6): δ 7.55 (br s, 3H), 7.69 (t, J = 8.4 Hz, 1H), 7.84 (t, J = 8.4 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 8.8 Hz, 2H), 8.46 (s, 1H), 8.65 (d, J = 8.6 Hz, 1H), 14.03 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 250.18.

6-Chloro-2-phenylquinoline-4-carboxylic acid (3b)

Yield: 54%; off-white solid; mp 244–245 ºC (EtOAc) (Lit.,[24] 241–243 ºC); ^{1}H-NMR (DMSO-d_6): δ 7.51-7.59 (m, 3H), 7.82 (dd, J = 8.8, 2.2 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 8.2 Hz, 2H), 8.52 (s, 1H), 8.76 (d, J = 2.2 Hz, 1H), 14.13 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 284.12.

6-Iodo-2-phenylquinoline-4-carboxylic acid (3c)

Yield: 49%; pale yellow solid; mp 249-250 ºC (EtOAc) (Lit.,[25] 249–250 ºC); ^{1}H-NMR (DMSO-d_6): δ 7.54 (br s, 3H), 7.89 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 8.25 (br s, 2H), 8.48 (s, 1H), 9.11 (s, 1H), 14.08 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 376.04.

2-Phenyl-6-trifluoromethoxyquinoline-4-carboxylic acid (3d)

Yield: 84%; pale yellow solid; mp 197–198 ºC (*n*-hexane-EtOAc); ^{1}H-NMR (DMSO-d_6): δ 7.56 (br s, 3H), 7.82 (d, J = 9.1 Hz, 1H), 8.27 (br s, 3H), 8.57 (s, 1H), 8.71 (s, 1H), 14.18 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 334.14.

General procedure for the preparation of 2-phenyl-4-quinolinecarbonyl chlorides (4a-c)

An appropriate 2-phenylquinoline-4-carboxylic acid (**3a-c**) (5 mmol) was suspended in dehydrated CH_2Cl_2 (50 mL), and the mixture was cooled to -5 to 0 °C. Oxalyl chloride (1 mL) was added dropwise with stirring over 15 min to the cold reaction mixture. To it was added DMF (2 drops), and stirring was

continued at -5 to 0 °C for 1 h. Ice-bath was removed, and the mixture was stirred at rt for overnight. Evaporation of solvent under reduced pressure afforded the crude acid chlorides (**4a-c**), which were used directly in the next step.

General procedure for the preparation of 2-phenylquinoline-4-carboxamides (6a-d)

To an ice-cold solution of an appropriate amine (**5a-d**) (1.05 mmol) and Et_3N (0.3 mL) in dehydrated THF (30 mL) was added the acid chloride (**4a**) (1 mmol). The reaction mixture was then heated under reflux for 2 h. Solvent was removed under reduced pressure. Water (20 mL) was added to the residue followed by addition of 10% aqueous Na_2CO_3 (2 mL). The mixture was stirred for 30 min. The resulting precipitate was filtered, washed with water, dried and recrystallized from an appropriate solvent to afford **6a-d** (81-89%).

***N*-(6-Quinolinyl)-2-phenylquinoline-4-carboxamide (6a)**

Yield: 85%; off-white solid; mp 241–242 ºC (EtOH-H_2O); ^{1}H-NMR (DMSO-d_6): δ 7.51-7.62 (m, 4H), 7.68 (t, J = 7.6 Hz, 1H), 7.87 (t, J = 7.4 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.21 (t, J = 8.8 Hz, 2H), 8.37-8.4 (m, 4H), 8.67 (s, 1H), 8.85 (s, 1H), 11.16 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 376.26; Anal. Calcd for $C_{25}H_{17}N_3O$: C, 79.98; H, 4.56; N, 11.19. Found: C, 80.17; H, 4.56; N, 11.05.

***N*-(7-Quinolinyl)-2-phenylquinoline-4-carboxamide (6b)**

Yield: 81%; off-white solid; mp 246–247 ºC (EtOH-H_2O); ^{1}H-NMR (DMSO-d_6): δ 7.55-7.64 (m, 4H), 7.70 (t, J = 7.6 Hz, 1H), 7.84-7.89 (m, 2H), 7.99 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 6.9 Hz, 2H), 8.56 (s, 1H), 8.62 (d, J = 8.6 Hz, 1H), 8.95 (s, 1H), 11.01 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 376.24; Anal. Calcd for $C_{25}H_{17}N_3O \cdot 1/8H_2O$: C, 79.50; H, 4.60; N, 11.13. Found: C, 79.45; H, 4.79; N, 11.02.

***N*-(3-Quinolinyl)-2-phenylquinoline-4-carboxamide (6c)**

Yield: 88%; off-white solid; mp 210–211 ºC (EtOH-H_2O); ^{1}H-NMR (DMSO-d_6): δ 7.54-7.73 (m, 6H), 7.87 (t, J = 7.7 Hz, 1H), 8.03 (t, J = 7.3 Hz, 2H), 8.19 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 7.7 Hz, 2H), 8.48 (s, 1H), 8.98 (s, 1H), 9.11 (s, 1H), 11.30 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 376.16; Anal. Calcd for $C_{25}H_{17}N_3O$: C, 79.98; H, 4.56; N, 11.19. Found: C, 80.15; H, 4.67; N, 11.21.

***N*-(1-Adamantanyl)-2-phenylquinoline-4-carboxamide (6d)**

Yield: 89%; white solid; mp 257–258 ºC (*n*-hexane-EtOAc); ^{1}H-NMR (DMSO-d_6): δ 1.69 (br s, 6H), 2.09 (br s, 3H), 2.16 (br s, 6H), 7.47-7.53 (m, 3H), 7.63 (t, J = 8.2 Hz, 1H), 7.78 (t, J = 8.2 Hz, 1H), 7.99

(s, 1H), 8.05-8.12 (m, 2H), 8.27-8.31 (m, 3H); TOF mass $(M+H)^+$ (*m/z*): 383.28; Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.78; H, 6.89; N, 7.21.

***N*-(9*H*-Purin-6-yl)-2-phenylquinoline-4-carboxamide (6e)**

To a suspension of adenine (**5e**) (149 mg, 1.1 mmol) and Et_3N (0.3 mL) in a dehydrated DMF (10 mL) was added the acid chloride (**4a**) (268 mg, 1 mmol) at room temperature. The reaction mixture was then heated at 80-90 °C for 16 h. Acetic acid (1 mL) was added to the cooled reaction mixture, and it was poured into water (80 mL). The resulting precipitate was filtered, washed with water and dried. The crude solid mass was purified by flash column chromatography on silica gel using EtOAc as eluent to give **6e** (231 mg, 63%) as pale yellow solid; mp 164–165 ºC (DMF-H_2O); ^{1}H-NMR (DMSO-d_6): δ 7.52-7.57 (m, 3H), 7.69 (t, *J* = 8.1 Hz, 1H), 7.87 (t, *J* = 7.3 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.34-8.37 (m, 3H), 8.49 (s, 1H), 8.58 (s, 1H), 8.75 (s, 1H), 12.22 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 367.17; Anal. Calcd for $C_{21}H_{14}N_6O \cdot 4/3H_2O$: C, 64.61; H, 4.30; N, 21.53. Found: C, 64.43; H, 4.29; N, 21.18.

***N*-(2,4-Dihydroxyphenyl)-2-phenylquinoline-4-carboxamide (6f)**

To an ice-cold solution of 2,4-dihydroxyanilinium chloride (**5f**) (170 mg, 1.05 mmol) and Et_3N (0.4 mL) in dehydrated THF (30 mL) was added the acid chloride (**4a**) (268 mg, 1 mmol). The mixture was heated under reflux for 1.5 h. Solvent was removed under reduced pressure, and water (20 mL) was added to the residue. The precipitated solid was filtered, washed with water and dried. The crude solid mass was purified by flash column chromatography on silica gel using EtOAc:CH_2Cl_2 (1:6) as eluent to give **6f** (175 mg, 49%) as tan solid; mp 264–265 ºC; ^{1}H-NMR (DMSO-d_6): δ 6.28 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.51-7.67 (m, 4H), 7.83 (t, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.24-8.38 (m, 4H), 9.28 (s, 1H), 9.55 (s, 1H), 9.86 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 357.13; Anal. Calcd for $C_{22}H_{16}N_2O_3 \cdot 5/6H_2O$: C, 71.15; H, 4.79; N, 7.54. Found: C, 71.17; H, 4.95; N, 7.46.

General procedure for the preparation of bis(2-phenylquinoline-4-carboxamides) (8a-c)

Compounds **8a-c** were prepared in 79-86% yields by reacting the acid chloride **4a** (1 mmol) with the appropriate diamine (**7a-c**) (0.5 mmol) in the presence of Et_3N (0.3 mL) following the general procedure described for the preparation of **6a-d.**

1,3-Bis(2-phenylquinoline-4-carbonylamino)propane (8a)

Yield: 81%; off-white solid; mp 244–245 ºC (DMF-H_2O); ^{1}H-NMR (DMSO-d_6): δ 1.8 (quin, *J* = 5.9 Hz, 2H), 3.54 (br s, 4H), 7.51-7.56 (m, 6H), 7.63 (t, *J* = 8.0 Hz, 2H), 7.82 (t, *J* = 8.0 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.19 (s, 2H), 8.24 (d, *J* = 8.4 Hz, 2H), 8.31 (d, *J* = 8.1 Hz, 4H), 8.94 (br s, 2H); TOF mass

$(M+H)^+$ (*m/z*): 537.32; Anal. Calcd for $C_{35}H_{28}N_4O_2$: C, 78.34; H, 5.26; N, 10.44. Found: C, 78.50; H, 5.22; N, 10.29.

1,4-Bis(2-phenylquinoline-4-carbonylamino)butane (8b)

Yield: 79%; white solid; mp 285–286 ºC (DMF-H_2O); ^{1}H-NMR (DMSO-d_6): δ 1.76 (br s, 4H), 3.46 (br s, 4H), 7.50-7.54 (m, 6H), 7.60 (t, *J* = 8.1 Hz, 2H), 7.80 (t, *J* = 8.1 Hz, 2H), 8.09-8.13 (m, 4H), 8.19 (t, *J* = 8.6 Hz, 2H), 8.27-8.3 (m, 4H), 8.92 (br s, 2H); TOF mass $(M+H)^+$ (*m/z*): 551.29; Anal. Calcd for $C_{36}H_{30}N_4O_2$: C, 78.52; H, 5.49; N, 10.17. Found: C, 78.44; H, 5.53; N, 10.01.

1,7-Bis(2-phenylquinoline-4-carbonylamino)heptane (8c)

Yield: 86%; white solid; mp 183–184 ºC (*n*-hexane-EtOAc); ^{1}H-NMR (DMSO-d_6): δ 1.43 (br s, 6H), 1.63 (br s, 4H), 3.38 (br s, 4H), 7.50-7.64 (m, 8H), 7.79 (t, *J* = 8.0 Hz, 2H), 8.09-8.17 (m, 6H), 8.29 (d, *J* = 8.6 Hz, 4H), 8.83 (br s, 2H); TOF mass $(M+H)^+$ (*m/z*): 593.40; Anal. Calcd for $C_{39}H_{36}N_4O_2$: C, 79.03; H, 6.12; N, 9.45. Found: C, 79.13; H, 6.10; N, 9.32.

{4-[(2-Phenylquinoline-4-carbonyl)amino]butyl}carbamic acid *tert*-butyl ester (10)

To an ice-cold suspension of the acid chloride **4a** (535 mg, 2 mmol) in dehydrated THF (40 mL) were added Et_3N (0.6 mL) and a solution of *N*-(4-aminobutyl)carbamic acid *tert*-butyl ester (**9**) (377 mg, 2 mmol) in THF (10 mL) dropwise, successively. The reaction mixture was heated at 40-50 °C for 2 h. Solvent was evaporated under reduced pressure. The residue was taken up in water (30 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with 5% aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The crude amide was recrystallized from a mixture of EtOAc and *n*-heptane to give **10** (554 mg, 66%) as pale yellow solid; mp 108–109 ºC; ^{1}H-NMR (DMSO-d_6): δ 1.36 (s, 9H), 1.47-1.56 (m, 4H), 2.78 (br s, 2H), 3.37 (br s, 2H), 6.84 (br s, 1H), 7.51-7.55 (m, 4H), 7.81 (t, *J* = 7.4 Hz, 1H), 8.09 (s, 1H), 8.15 (d, *J* = 9.1 Hz, 2H), 8.31 (d, *J* = 9.1 Hz, 2H), 8.84 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 420.37; Anal. Calcd for $C_{25}H_{29}N_3O_3 \cdot 5/16H_2O$: C, 70.63; H, 7.02; N, 9.88. Found: C, 70.87; H, 7.05; N, 9.49.

***N*-(4-Aminobutyl)-2-phenylquinoline-4-carboxamide (11)**

To a solution of **10** (420 mg, 1 mmol) in dry CH_2Cl_2 (20 mL) was added 30% TFA in CH_2Cl_2 (10 mL). The reaction mixture was then stirred at rt for 8 h, and the volatiles were removed under reduced pressure. To the residue were added dehydrated THF (30 mL) and anhydrous K_2CO_3 (1 g). The mixture was stirred for 1 h at rt and filtered. Solvent was removed under reduced pressure, and the residue was recrystallized from a mixture of *n*-heptane and THF to give **11** (233 mg, 73 %) as white solid; mp 178–179 ºC

(*n*-hexane-THF); ^{1}H-NMR (DMSO-d_6): δ 1.64 (br s, 4H), 2.86 (br s, 2H), 3.50 (br s, 4H), 7.52-7.65 (m, 4H), 7.83 (t, *J* = 8.1 Hz, 1H), 8.09-8.18 (m, 3H), 8.28 (d, *J* = 7.9 Hz, 2H), 8.93 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 320.26; Anal. Calcd for $C_{20}H_{21}N_3O\cdot(CF_3COOH + 3H_2O)/4$: C, 68.13; H, 6.34; N, 11.63. Found: C, 68.28; H, 6.54; N, 11.63.

***N*-[5-(2-Furanyl)-1,3,4-oxadiazol-2-yl]-6-iodo-2-phenylquinoline-4-carboxamide (13)**

To a solution of 6-iodo-2-phenylquinoline-4-carboxylic acid (**3c**) (375 mg, 1 mmol) in dehydrated DMF (15 ml) were added HBTU (759 mg, 2 mmol) and anhydrous HOBt (270 mg, 2 mmol) at rt under nitrogen. The resulting solution was stirred at rt for 30 min. DIPEA (258 mg, 2 mmol) was added, and the solution was stirred for another 30 min. Finally, 2-amino-5-(2-furyl)-1,3,4-oxadiazole (**12**) (265 mg, 1.75 mmol) was added, and the solution was stirred at rt for 3 d. The solution was poured into cold water (100 mL), and the resulting precipitate was filtered, washed well with water and dried. Recrystallization of crude mass from a mixture of DMF-water gave **13** (315 mg, 62%) as pale yellow solid; mp 241–242 ºC; ^{1}H-NMR (DMSO-d_6): δ 6.81 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.31 (d, *J* = 3.4 Hz, 1H), 7.54-7.63 (m, 3H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.05 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.34 (d, *J* = 7.2 Hz, 2H), 8.52 (s, 1H), 8.69 (s, 1H), 12.88 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 509.06; Anal. Calcd for $C_{22}H_{13}IN_4O_3$: C, 51.99; H, 2.58; N, 11.02. Found: C, 52.00; H, 2.78; N, 10.83.

General procedure for the Suzuki coupling reactions to prepare *N*-[5-(2-furanyl)-1,3,4-oxadiazol-2-yl]-6-aryl-2-phenylquinoline-4-carboxamides (15a-c)

A mixture of the 6-iodo compound **13** (203 mg, 0.4 mmol), an appropriate phenylboronic acid (**14a-c**) (0.8 mmol), anhydrous K_3PO_4 (212 mg, 1 mmol), Xphos (4.8 mg, 10 μmol) and BuOH (20 mL) was degassed. To the mixture was added $Pd(OAc)_2$ (1.1 mg, 5 μmol), and it was heated at 100 °C under nitrogen for 2 d. The mixture was filtered and washed with EtOAc (15 mL× 2). The combined filtrate was concentrated to dryness under reduced pressure. Then the crude material was dissolved in EtOAc (75 mL), and the solution was washed with 5% aqueous $NaHCO_3$, water, and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated to give crude solid mass, which was purified by column chromatography on silica gel using a mixture of CH_2Cl_2 and methanol (35:1) as eluent to give **15a-c** in 41-57% yield.

***N*-[5-(2-Furanyl)-1,3,4-oxadiazol-2-yl]-2,6-diphenylquinoline-4-carboxamide (15a)**

Yield: 49%; yellow solid; mp 226–227 ºC (*n*-hexane-EtOAc); ^{1}H-NMR (DMSO-d_6): δ 6.77 (s, 1H), 7.23 (br s, 2H), 7.51-7.58 (m, 6H), 7.76-7.82 (m, 2H), 8.01 (s, 1H), 8.14-8.22 (m, 2H), 8.35 (d, *J* = 7.8 Hz, 2H), 8.49 (s, 1H), 12.77 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 459.24; Anal. Calcd for $C_{28}H_{18}N_4O_3\cdot H_2O$: C,

70.58; H, 4.23; N, 11.76. Found: C, 70.62; H, 4.27; N, 11.51.

***N*-[5-(2-Furanyl)-1,3,4-oxadiazol-2-yl]-2-phenyl-6-(*p*-tolyl)-quinoline-4-carboxamide (15b)**

Yield: 41%; pale yellow solid; mp 154–155 ºC (*n*-hexane-EtOAc); ^{1}H-NMR (DMSO-d_6): δ 2.36 (s, 3H), 6.80 (dd, J = 3.4, 1.8 Hz, 1H), 7.28-7.33 (m, 3H), 7.57-7.71 (m, 5H), 8.05 (s, 1H), 8.22-8.27 (m, 2H), 8.35 (d, J = 7.4 Hz, 2H), 8.51 (s, 2H), 12.83 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 473.28; Anal. Calcd for $C_{29}H_{20}N_4O_3 \cdot H_2O$: C, 71.01; H, 4.52; N, 11.42. Found: C, 70.87; H, 4.38; N, 11.49.

***N*-[5-(2-Furanyl)-1,3,4-oxadiazol-2-yl]-6-(3,5-dimethoxyphenyl)-2-phenylquinoline-4-carboxamide (15c)**

Yield: 57%; yellow solid; mp 213–214 ºC (*n*-hexane-EtOAc); ^{1}H-NMR (DMSO-d_6): 3.75 (s, 6H), 6.51 (s, 1H), 6.71-6.83 (m, 3H), 7.21 (s, 1H), 7.52 (br s, 3H), 8.04 (s, 1H), 8.13 (br s, 2H), 8.29 (d, J = 7.6 Hz, 2H), 8.45 (s, 2H), 12.78 (br s, 1H); TOF mass $(M+H)^+$ (*m/z*): 519.28; Anal. Calcd for $C_{30}H_{22}N_4O_5 \cdot 6/7H_2O$: C, 67.48; H, 4.48; N, 10.49. Found: C, 67.83; H, 4.39; N, 10.10.

***N*-(2-Methyl-5-nitrophenyl)-4-(3-pyridinyl)-2-pyrimidinamine (20)**

Firstly, **17** was prepared in 82% yield by refluxing **16** (3.63 g, 30 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (10 mL) for overnight followed by evaporation of volatiles and recrystallization from *n*-hexane-EtOAc. Secondly, nitrate salt of **19** was prepared by treating a mixture of **18** (10 g, 65.7 mmol), 68% nitric acid (4.8 mL) and EtOH (30 mL) with a solution of cyanamide (4.3 g, 102 mmol) in water (4.3 mL) under reflux for 2 d followed by filtering and washing with EtOAc. The crude salt was suspended portion-wise into 2% aqueous NaOH solution (300 mL) and stirred at rt for overnight. The resulting precipitate was filtered and washed with water to afford free guanidine **19** (9.7 g, 76%). Finally a mixture of **17** (2.5 g, 14.2 mmol) and crude **19** (2.5 g, 12.9 mmol) in BuOH (20 mL) was heated under reflux for 18 h and cooled to rt. Separated precipitate was filtered, washed with water and dried to give **20**, which was used directly in the next step without further purification. Yield: 3.44 g (87%); yellow solid; mp 196–197 ºC (DMF-H_2O) (Lit.,[26] 196–197 ºC); ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 3H), 7.48-7.58 (m, 3H), 7.88 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 8.1 Hz, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.70 (d, J = 5.1 Hz, 1H), 8.80 (s, 1H), 9.22 (s, 1H), 9.31 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 308.14.

***N*-(5-Amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine (21)**

To a suspension of **20** (2.0 g, 6.5 mmol) in a mixture of MeOH (30 mL) and THF (70 mL) was added 10% Pd/C (600 mg) under nitrogen. After two vacuum/H_2 cycles to replace nitrogen inside the reaction flask with hydrogen, the reaction mixture was stirred at rt under hydrogen atmosphere for overnight. The

mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from a mixture of *n*-hexane and EtOAc to give **21** (1.59 g, 88% yield) as bright yellow solid; mp 140–141 ºC (Lit.,[26] 142–144 ºC); ^{1}H-NMR (DMSO-d_6): δ 2.04 (s, 3H), 4.86 (br s, 2H), 6.33 (d, *J* = 7.7 Hz, 1H), 6.77 (s, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 5.1 Hz, 1H), 7.48-7.54 (m, 1H), 8.39 (d, *J* = 7.8 Hz, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.69 (br s, 2H), 9.23 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 278.18.

General procedure for the preparation of *N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]-2-phenylquinoline-4-carboxamides (22a-d)

To a solution of an appropriate quinoline-4-carboxylic acid (**3a-d**) (0.6 mmol) in dehydrated DMF (10 mL) were added HBTU (455 mg, 1.2 mmol) and anhydrous HOBt (162 mg, 1.2 mmol) at rt, and the resulting solution was stirred for 30 min. To the solution was added DIPEA (194 mg, 1.5 mmol), and it was stirred for another 30 min. Finally, **21** (250 mg, 0.9 mmol) was added and stirring at rt was continued for 2 d. Reaction mixture was poured into cold water (100 mL), and resulting precipitate was filtered, washed well with water and dried. Recrystallization of crude solid mass from a mixture of DMF and water afforded **22a-d** in 64-72% yields.

***N*-[4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-2-phenylquinoline-4-carboxamide (22a)**

Yield: 72%; yellow solid; mp 241–242 ºC; ^{1}H-NMR (DMSO-d_6): δ 2.26 (s, 3H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.49-7.59 (m, 5H), 7.67 (t, *J* = 8.1 Hz, 1H), 7.85 (t, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.22 (s, 1H), 8.34-8.38 (m, 3H), 8.47-8.53 (m, 2H), 8.68 (d, *J* = 8.1 Hz, 1H), 9.03 (s, 1H), 9.31 (s, 1H), 10.79 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 509.25; Anal. Calcd for $C_{32}H_{24}N_6O$: C, 75.57; H, 4.76; N, 16.52. Found: C, 75.52; H, 4.81; N, 16.30.

***N*-[4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-6-chloro-2-phenylquinoline-4-carboxamide (22b)**

Yield: 69%; pale yellow solid; mp 259–260 ºC; ^{1}H-NMR (DMSO-d_6): δ 2.26 (s, 3H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.50-7.59 (m, 5H), 7.86 (d, *J* = 9.1 Hz, 1H), 8.16-8.25 (m, 3H), 8.36 (d, *J* = 7.7 Hz, 2H), 8.43 (s, 1H), 8.48-8.53 (m, 2H), 8.68 (s, 1H), 9.03 (s, 1H), 9.31 (s, 1H), 10.83 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 543.31; Anal. Calcd for $C_{32}H_{23}ClN_6O \cdot 1/2H_2O$: C, 69.62; H, 4.38; N, 15.22. Found: C, 69.59; H, 4.62; N, 15.04.

***N*-[4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-6-iodo-2-phenylquinoline-4-carboxamide (22c)**

Yield: 64%; yellow solid; mp 299–300 ºC; ^{1}H-NMR (DMSO-d_6): δ 2.26 (s, 3H), 7.26 (d, J = 8.2 Hz, 1H), 7.43-7.56 (m, 6H), 7.93 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.18 (s, 1H), 8.33-8.39 (m, 3H), 8.51 (br s, 2H), 8.59 (s, 1H), 8.68 (s, 1H), 9.04 (s, 1H), 9.301 (s, 1H), 10.82 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 635.12; Anal. Calcd for $C_{32}H_{23}IN_6O$: C, 60.58; H, 3.65; N, 13.25. Found: C, 60.69; H, 3.74; N, 13.02.

_N_-[4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-6-trifluoromethoxy-2-phenylquinoline-4-carboxamide (22d)

Yield: 66%; pale yellow solid; mp 249–250 ºC; ^{1}H-NMR (DMSO-d_6): δ 2.26 (s, 3H), 7.27 (d, J = 8.4 Hz, 1H), 7.45-7.59 (m, 6H), 7.86 (d, J = 8.7 Hz, 1H), 8.19 (br s, 2H), 8.32 (d, J = 8.1 Hz, 1H), 8.39 (d, J = 7.8 Hz, 2H), 8.49 (br s, 3H), 8.67 (s, 1H), 9.03 (s, 1H), 9.30 (s, 1H), 10.84 (s, 1H); TOF mass $(M+H)^+$ (*m/z*): 593.28; Anal. Calcd for $C_{33}H_{23}F_3N_6O_2$: C, 66.89; H, 3.91; N, 14.18. Found: C, 66.91; H, 4.13; N, 14.07.

4,4'-Bithiazole]-2,2'-diamine (24)

A mixture of 1,4-dibromo-2,3-butanedione (**23**) (4.51 g, 18.5 mmol) and thiourea (2.82 g, 37 mmol) in dehydrated MeOH (80 mL) was heated under reflux for overnight. The reaction mixture was cooled, filtered and washed with EtOH to give hydrobromide salt of **24**. The salt was dissolved in DMF by heating and the hot solution was made basic with aqueous NH_3. Water was added to the hot mixture and cooled. The precipitated solid mass was collected by filtration followed by washing with water to give **24** (2.82 g, 77%) as off-white solid; mp 264–266 ºC (DMF-H_2O) (Lit.,[27] 263–265ºC); ^{1}H-NMR (DMSO-d_6): δ 6.59 (s, 2H), 6.98 (br s, 4H); TOF mass $(M+H)^+$ (*m/z*): 199.07.

General procedure for the preparation of _N,N'_-[4,4'-bithiazole]-2,2'-diylbis-2-phenylquinoline-4-carboxamide (25a-c)

To a solution of **24** (99 mg, 0.5 mmol) and Et_3N (0.4 mL) in a mixture of dehydrated THF (30 mL) and DMF (7 mL) was added an appropriate acid chloride **4a-c** (1.2 mmol). The reaction mixture was then heated under reflux for overnight. The reaction mixture was concentrated to about 6/7 mL under reduced pressure, and was poured into water (30 mL). The resulting precipitate was filtered, washed with water and dried. The crude solid mass was purified by column chromatography on silica gel using a mixture of CH_2Cl_2 and MeOH (40:1) as eluent to give **25a-c** in 61-68% yield.

_N,N'_-[4,4'-Bithiazole]-2,2'-diylbis-2-phenylquinoline-4-carboxamide (25a)

Yield: 66%; pale yellow solid; mp >300 ºC (DMF-H_2O); ^{1}H-NMR (DMSO-d_6): δ 7.51-7.56 (m, 8H), 7.61 (t, J = 8.1 Hz, 2H), 7.87 (t, J = 7.8 Hz, 2H), 8.18 (d, J = 8.4 Hz, 2H), 8.29 (d, J = 8.1 Hz, 2H), 8.39 (d, J =

7.3 Hz, 4H), 8.52 (s, 2H), 13.33 (br s, 2H); TOF mass $(M+H)^+$ (*m/z*): 661.23; Anal. Calcd for $C_{38}H_{24}N_6O_2S_2 \cdot 1/3H_2O$: C, 68.45; H, 3.73; N, 12.60. Found: C, 68.77; H, 3.93; N, 12.26.

***N*,*N*'-[4,4'-Bithiazole]-2,2'-diylbis-6-chloro-2-phenylquinoline-4-carboxamide (25b)**

Yield: 68%; pale yellow solid; mp >300 ºC (DMF-H_2O); ^{1}H-NMR (DMSO-d_6): δ 7.52-7.58 (m, 8H), 7.86 (d, *J* = 8.6 Hz, 2H), 8.13 (d, *J* = 8.6 Hz, 2H), 8.37 (br s, 6H), 8.57 (s, 2H), 13.38 (br s, 2H); TOF mass $(M+H)^+$ (*m/z*): 729.05; Anal. Calcd for $C_{38}H_{22}Cl_2N_6O_2S_2 \cdot 1/3H_2O$: C, 62.04; H, 3.11; N, 11.42. Found: C, 61.86; H, 3.09; N, 11.24.

***N*,*N*'-[4,4'-Bithiazole]-2,2'-diylbis-6-iodo-2-phenylquinoline-4-carboxamide (25c)**

Yield: 61%; yellow solid; mp >300 ºC (DMF-H_2O); ^{1}H-NMR (DMSO-d_6): δ 7.53-7.58 (m, 8H), 7.93 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 7.1 Hz, 4H), 8.55 (s, 2H), 8.71 (s, 2H), 13.38 (br s, 2H); TOF mass $(M+H)^+$ (*m/z*): 912.94; Anal. Calcd for $C_{38}H_{22}I_2N_6O_2S_2 \cdot 1/4H_2O$: C, 49.77; H, 2.47; N, 9.16. Found: C, 49.89; H, 2.59; N, 9.11.

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REFERENCES

1. J. E. Darnell, Jr., *Nat. Rev. Cancer*, 2002, **2**, 740.
2. J. Bromberg and J. E. Darnell, Jr., *Oncogene*, 2000, **19**, 2468.
3. H. Yu and R. Jove, *Nat. Rev. Cancer*, 2004, **4**, 97.
4. J. Turkson and R. Jove, *Oncogene*, 2000, **19**, 6613.
5. R. Buettner, L. B. Mora, and R. Jove, *Clin. Cancer Res.*, 2002, **8**, 945.
6. J. E. Darnell, Jr., I. M. Kerr, and G. R. Stark, *Science*, 1994, **264**, 1415.
7. T. Bowman, R. Garcia, J. Turkson, and R. Jove, *Oncogene*, 2000, **19**, 2474.
8. S. Becker, B. Groner, and C. W. Muller, *Nature*, 1998, **394**, 145.
9. D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck, and D. Jasserand, *J. Med. Chem.*, 1995, **38**, 669.
10. A. A. Alhaider, M. A. Abdelkader, and E. J. Lien, *J. Med. Chem.*, 1985, **28**, 1394.
11. R. Musiol, J. Jampilek, K. Kralova, D. S. Richardson, D. Kalinowski, B. Podeszwa, J. Finster, H. Niedbala, A. Palka, and J. Polanski, *Bioorg. Med. Chem.*, 2007, **15**, 1280.

12. M. Robert, J. Josef, B. Vladimir, S. Luis, N. Halina, P. Barbara, P. Anna, M.-M. Katarzyna, O. Barbara, and P. Jaroslaw, *Bioorg. Med. Chem.*, 2006, **14**, 3592.
13. C. R. Gardner, R. Deacon, V. James, F. Parker, and P. Budhram, *Eur. J. Pharm.*, 1987, **142**, 285.
14. S. Juan, Z. Hui, Y. Zhong-Ming, and Z. Hai-Liang, *Eur. J. Med. Chem.*, 2013, **60**, 23.
15. S. K. Srivastava, A. Jha, S. K. Agarwal, R. Mukherjee, and A. C. Burman, *Anti-Cancer Agents Med. Chem.*, 2007, **7**, 685.
16. C. M. Hall, H. G. Johnson, and J. B. Wright, *J. Med. Chem.*, 1974, **17**, 685.
17. K. Matsuno, Y. Masuda, Y. Uehara, H. Sato, A. Muroya, O. Takahashi, T. Yokotagawa, T. Furuya, T. Okawara, M. Otsuka, N. Ogo, T. Ashizawa, C. Oshita, S. Tai, H. Ishii, Y. Akiyama, and A. Asai, *ACS Med. Chem. Lett.*, 2010, **1**, 371.
18. J. Li, J. Chen, C. Gui, L. Zhang, Y. Qin, Q. Xu, J. Zhang, H. Liu, X. Shen, and H. Jiang, *Bioorg. Med. Chem.*, 2006, **14**, 2209.
19. C.-C. Peng, J. L. Cape, T. Rushmore, G. J. Crouch, and J. P. Jones, *J. Med. Chem.*, 2008, **51***,* 8000.
20. R. Roskoski, Jr., *Biochem. Biophys. Res. Commun.*, 2003, **309**, 709.
21. U. Rix, O. Hantschel, G. Dürnberger, L. L. R. Rix, M. Planyavsky, N. V. Fernbach, I. Kaupe, K. L. Bennett, P. Valent, J. Colinge, T. Köcher, and G. Superti-Furgal, *Blood*, 2007, **110**, 4055.
22. Z. Szakacs, S. Beni, Z. Varga, L. Orfi, G. Keri, and B. Noszal, *J. Med. Chem.*, 2005, **48***,* 249.
23. A. E. M. Saeed and S. A. Elhadi, *Synth. Commun.*, 2011, **41**, 1435.
24. L.-M. Wang, L. Hu, H.-J. Chen, Y.-Y. Sui, and W. Shen, *J. Fluorine Chem.*, 2009, **130**, 406.
25. W. Borsche, H. Weussmann, and A. Fritzsche, *Ber. Dtsch. Chem. Ges.*, 1924, **57B**, 1770.
26. S. Chang, S.-L. Yin, J. Wang, Y.-K. Jing, and J.-H. Dong, *Molecules*, 2009, **14**, 4166.
27. B. W. Lee and S. D. Lee, *Tetrahedron Lett.*, 2000, **41**, 3883.