

Supporting Information

A Series of 2,4-Disubstituted Quinolines as a New Class of Allosteric Enhancers of the Adenosine A₃ Receptor

*Laura H. Heitman, Anikó Göblyös, Annelien J. M. Zweemer, Renée Bakker, Thea Mulder-Krieger, Jacobus P. D. van Veldhoven, Henk de Vries, Johannes Brussee, Adriaan P. IJzerman**

Table of Contents:

S1: Title page

S2-S7: Synthetic procedures and spectral data of compounds **2-33**

S8: Elemental analysis of compounds **16-33**

Division of Medicinal Chemistry, Leiden/Amsterdam Center for Drug Research,
Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

*To whom correspondence should be addressed. Phone: +31- (0)71 527 4651. Fax:
+31- (0)71 527 4565.

E-mail address: ijzerman@lacdr.leidenuniv.nl (A.P. IJzerman)

Synthetic procedures and spectral data

Quinoline-1-oxide (2). To a solution of quinoline (25.83 g, 0.2 mol) in acetic acid (70 mL) was added H₂O₂ (35% in water, 1.5 eq, 29 mL) and the reaction mixture was stirred at 70 °C for 21 hours. pH was adjusted to 8 with 2M NaOH and the reaction mixture was extracted with DCM (4 x 80 mL). The organic layer was dried over MgSO₄ and evaporated. The product was purified by column chromatography, with ethyl acetate as the eluent. The product was crystallized from ethyl acetate. Yield: 21.72 g, 72% of yellow solid. ¹H NMR (CDCl₃) δ 7.30 (t, 1H, *J* = 7.66, 6.96 Hz, Ar), 7.61-7.90 (m, 4H, Ar), 8.54 (d, 1H, *J* = 5.84 Hz, Ar), 8.75 (d, 1H, *J* = 8.78 Hz, Ar).

4-Nitroquinoline-1-oxide (3). Compound **2** (19.10 g, 0.13 mol) was dissolved in concentrated sulfuric acid and warmed to 65 °C. Nitric acid (65%, 1.1 eq, 15 mL) was added slowly, dropwise. The reaction mixture was stirred at 65 °C for 2 hours, after which it was cooled and poured on ice. The product precipitated as a yellow solid, which was filtered off, washed with 5% Na₂CO₃ (1 x 10 mL), water (2 x 10 mL), ethanol (1 x 10 mL) and dried. Yield: 21.90 g, 88% of yellow solid. ¹H NMR (CDCl₃) δ 7.85-7.94 (m, 2H, Ar), 8.21 (d, 1H, *J* = 6.58 Hz, Ar), 8.53 (d, 1H, *J* = 7.30 Hz, Ar), 8.73-8.86 (m, 1H, Ar).

2-Bromo-4-nitroquinoline (4). Compound **3** (1.86 g, 9.8 mmol) was dissolved in CHCl₃ and cooled in an ice-bath. POBr₃ (1.25 eq) was added and the reaction mixture was stirred in an ice-bath for 2 hours, after which it was poured on ice and extracted with DCM (3 x 80 mL) after the pH had been adjusted to 9 with 2M NaOH. The product was purified by column chromatography, eluent DCM. Yield: 1.30 g, 52 % of light yellow solid. ¹H NMR (CDCl₃) δ 7.63-7.94 (m, 2H, Ar), 8.06 (s, 1H, Ar), 8.17 (t, 1H, *J* = 7.16, 6.84Hz, Ar), 8.38 (d, 1H, *J* = 8.76 Hz, Ar).

4-Amino-2-bromoquinoline (5). Compound **4** (1.82 g, 7.2 mmol) was dissolved in acetic acid. Iron powder (5 eq) was added and the reaction mixture stirred at 65 °C for 2.5 hours. The iron powder was filtered off, washed with DCM. pH was adjusted to 9 with 2M NaOH. This was filtered again and the residue was washed with ammonia. The aqueous layer was extracted with DCM, dried on MgSO₄ and evaporated. The product was purified by column chromatography, eluent DCM. Yield: 0.69 g, 43% of off-white solid. ¹H NMR (CDCl₃) δ 4.81 (bs, 2H, NH₂), 6.76 (s, 1H, Ar), 7.48 (t, 1H, *J* = 7.31, 7.06 Hz, Ar), 7.62-7.73 (m, 2H, Ar), 7.94 (d, 1H, *J* = 8.76 Hz, Ar). ¹³C NMR (CDCl₃) δ 106.60, 117.82, 120.21, 125.37, 129.19, 130.40, 142.59, 148.78, 150.90.

2,4-Dichloroquinoline (8). Malonic acid (8.32 g, 0.08 mol) was dissolved in POCl₃ (60 mL) and cooled in an ice-bath. Aniline (1.25 eq) was added dropwise. The reaction mixture was refluxed for 2.5 hours, then it was cooled to room temperature and poured on ice. pH was adjusted to 9 with 2M NaOH. The precipitate was filtered off and the aqueous layer was extracted with DCM. The product was purified by column chromatography, eluent DCM. Yield: 5.51 g, 35% of yellow solid. ¹H NMR (CDCl₃) δ 1.25 (s, 1H, Ar), 7.64 (t, 1H, *J* = 7.84, 6.16 Hz, Ar), 7.79 (t, 1H, *J* = 6.89, 6.71 Hz, Ar), 8.03 (d, 1H, *J* = 8.16 Hz, Ar), 8.21 (d, 1H, *J* = 8.21 Hz, Ar).

4-Amino-2-chloroquinoline (9). Compound **8** (0.35 g, 1.8 mmol) was suspended in ammonia (28-30% in water, 3 mL). The reaction was carried out in the microwave at 160 °C for 2.5 hours. After the reaction was completed, ammonia was evaporated off.

The product was purified by column chromatography, eluent 3% MeOH in DCM. Yield: 0.14 g, 44% of light yellow solid. ^1H NMR (CDCl_3) δ 4.83 (bs, 2H, NH_2), 6.62 (s, 1H, Ar), 7.43-7.51 (m, 1H, Ar), 7.63-7.73 (m, 2H, Ar), 7.89-7.95 (m, 1H, Ar). ^{13}C NMR (600MHz, CDCl_3) δ 103.07, 117.60, 120.08, 125.27, 129.13, 130.46, 148.26, 151.40, 151.41.

***N*-(2-Bromoquinolin-4-yl)cyclopentanecarboxamide (10).** Compound **5** (0.32 g, 1.40 mmol) was dissolved in pyridine (5 mL) and cyclopentanecarbonyl chloride (1.3 eq) was added. The reaction mixture was stirred at 115 °C for 2 hours. After the reaction was completed, pyridine was evaporated. The product was purified by column chromatography, eluent for column chromatography 5% MeOH in DCM. The product was crystallized from MeOH to give white crystals. Yield: 0.35 g, 79%. MS (ESI) m/z : 319.9 $[\text{M}+\text{H}]^+$, $[\text{M}-\text{H}]^+$. ^1H NMR (CDCl_3) δ 1.64-2.07 (m, 8H, 4 CH_2), 2.53-3.00 (m, 1H, CH), 7.54-7.62 (m, 1H, Ar), 7.69-7.79 (m, 2H, Ar), 7.92 (bs, 1H, NH), 7.99-8.08 (m, 1H, Ar), 8.43 (s, 1H, Ar). ^{13}C NMR (CDCl_3) δ 25.96, 30.51, 47.2, 114.51, 118.85, 126.76, 129.89, 130.40, 141.56, 143.17, 148.63, 175.07

General procedure for the preparation of *N*-(2-chloroquinolin-4-yl)carboxamides (11-15)

Compound **9** was dissolved in pyridine (1 mmol/3 mL) and the appropriate acid chloride (1.3 eq) was added. The reaction mixture was stirred at 60 °C for 90 minutes. After the reaction was completed, pyridine was evaporated. The product was purified by column chromatography.

***N*-(2-Chloroquinolin-4-yl)cyclopentanecarboxamide (11).** Scale: 1.6 mmol. Eluent 5% MeOH in DCM. Yield: 0.34 g, 78%. ^1H NMR (CDCl_3) δ 1.58-2.18 (m, 8H, 4 CH_2), 2.81-2.98 (m, 1H, CH), 7.53-7.61 (m, 1H, Ar), 7.68-7.76 (m, 2H, Ar), 7.95-8.03 (m, 2H, Ar, NH), 8.42 (s, 1H, Ar). ^{13}C NMR (CDCl_3) δ 26.18, 30.72, 47.43, 91.47, 94.32, 111.33, 118.94, 126.86, 130.04, 130.65, 142.41, 148.26, 152.24, 175.28.

***N*-(2-Chloroquinolin-4-yl)cyclohexanecarboxamide (12).** Scale: 2.2 mmol. Eluent 2-5% MeOH in DCM. The product was crystallized from MeOH to give white crystals. Yield: 0.60 g, 95%. ^1H NMR (CDCl_3) δ 1.28-2.04 (m, 10H, 5 CH_2), 2.38-2.53 (m, 1H, CH), 7.56-7.63 (m, 1H, Ar), 7.71-7.79 (m, 2H, Ar), 7.96-7.63 (m, 2H, Ar, NH), 8.44 (s, 1H, Ar). ^{13}C NMR (CDCl_3) δ 25.51, 29.66, 46.83, 111.21, 118.52, 118.73, 126.67, 129.89, 130.46, 142.17, 148.05, 152.09, 174.71.

***N*-(2-Chloroquinolin-4-yl)benzamide (13).** Scale: 3.91 mmol. Eluent DCM. Yield: 0.47 g, 42%. ^1H NMR (CDCl_3) δ 7.52-7.65 (m, 4H, Ar), 7.72-7.84 (m, 2H, Ar), 7.94-8.06 (m, 3H, Ar), 8.51 (s, 1H, Ar), 8.64 (bs, 1H, NH). ^{13}C NMR (CDCl_3) δ 111.40, 118.83, 126.50, 126.89, 128.83, 129.38, 130.26, 132.56, 133.47, 141.93, 147.72, 151.48, 165.67.

***N*-(2-Chloroquinolin-4-yl)-2-furamide (14).** Scale: 3.36 mmol. Eluent DCM. Yield: 0.52 g, 57%. ^1H NMR (CDCl_3) δ 6.65-6.68 (m, 1H, Ar), 7.39 (d, 1H, $J = 3.65$ Hz, Ar), 7.60-7.90 (m, 4H, Ar), 8.05 (d, 1H, $J = 12.00$ Hz, Ar), 8.52 (s, 1H, Ar), 8.93 (bs, 1H, NH). ^{13}C NMR (CDCl_3) δ 110.49, 112.98, 116.77, 118.10, 118.59, 126.60, 129.42, 130.33, 141.36, 144.94, 146.58, 147.67, 151.49, 155.65.

***N*-(2-Chloroquinolin-4-yl)cyclobutanecarboxamide (15).** Scale: 3.92 mmol. Eluent 1% MeOH in DCM. Yield: 0.89 g, 87%. ^1H NMR ($\text{CDCl}_3 + 1$ drop of MeOD) δ 1.72-

2.58 (m, 6H, 3CH₂), 3.28-3.45 (m, 1H, CH), 7.52-7.60 (m, 1H, Ar), 7.69-7.83 (m, 3H, Ar, NH), 7.98-8.03 (m, 1H, Ar), 8.43 (s, 1H, Ar). ¹³C NMR (CDCl₃+1 drop of MeOD) δ 17.85, 25.04, 40.74, 111.13, 118.38, 118.89, 126.35, 129.29, 130.23, 142.09, 147.73, 151.58, 173.81.

General procedure for the preparation of 2,4-substituted quinolines (16-33).

Method A: Compounds **10-15** were dissolved/suspended in absolute ethanol (1.5 mmol/2.5 mL) and the appropriate amines (3 eq) were added. The mixture was heated in the microwave at 140 °C for 80 min. After the reaction was completed, ethanol was evaporated and the residue was dissolved in DCM (100 mL) and washed with 1 M NaOH (3 x 100 mL). The organic layer was dried on MgSO₄. The products were purified by column chromatography and recrystallized. *Method B:* Compounds **10-15** and the appropriate amines (10 eq) were heated in the microwave without any solvent at 180 °C for 90 min. After the reaction was completed, the reaction mixture was dissolved in DCM (100 mL) and washed with water (2 x 50 mL), brine (1 x 50 mL). The organic layer was dried on MgSO₄. The products were purified by column chromatography and recrystallized.

***N*-(2-Anilinoquinolin-4-yl)cyclopentanecarboxamide (16).** Method A. Scale: 0.36 mmol of compound **10**. Eluent 3-10% MeOH in DCM. The product was recrystallized from methanol to give yellow crystals. Mp 173-174 °C. Yield: 0.039 g, 33%. MS (ESI) m/z: 332.2 [M+H]⁺. ¹H NMR (CDCl₃) δ 1.72-2.04 (m, 8H, 4CH₂), 2.80-2.98 (m, 1H, CH), 6.93 (br s, 1H, NH), 7.07 (t, 1H, J = 5.74, 8.06 Hz, Ar), 7.25-7.41 (m, 3H, Ar), 7.57-7.67 (m, 5H, m; Ar), 7.78-7.83 (m, 1H, Ar), 8.01 (s, 1H, NH). ¹³C NMR (CDCl₃) δ 25.63, 30.18, 46.89, 100.90, 116.18, 118.36, 119.73, 122.50, 127.25, 129.46, 139.77, 140.96, 147.54, 154.51, 174.87.

***N*-(2-[(3,4-Dichlorophenyl)amino]quinolin-4-yl)cyclopentanecarboxamide (17).** Method B. Scale: 0.34 mmol of compound **10**. Eluent 2% MeOH in DCM. The product was recrystallized from methanol to give white crystals. Mp 216-217 °C. Yield: 0.024 g, 19%. MS (ESI) m/z: 400.3 [M+H]⁺. ¹H NMR (CDCl₃) δ 1.61-2.01(m, 8H, 4CH₂), 2.80-2.97 (m, 1H, CH), 6.79 (bs, 1H, NH), 7.32-7.51 (m, 3H, Ar), 7.57-7.67 (m, 2H, Ar), 7.81-7.94 (m, 3H, Ar, NH), 8.08 (s, 1H, Ar). ¹³C NMR δ (CDCl₃+1 drop of MeOD) δ 25.84, 30.45, 46.40, 102.78, 117.03, 118.30, 119.49, 120.40, 122.97, 124.13, 127.22, 129.68, 130.04, 132.10, 140.41, 141.32, 147.35, 154.21, 176.62.

***N*-(2-(Benzylamino)quinolin-4-yl)cyclopentanecarboxamide (18).** Method A. Scale: 0.35 mmol of compound **10** and 3 eq of benzylamine-HCl. Eluent 3-5% MeOH in DCM. The product was recrystallized from methanol to give yellow crystals. Mp 154-155 °C. Yield: 0.040 g, 33%. MS (ESI) m/z: 345.4 [M+H]⁺. ¹H NMR (CDCl₃) δ 1.65-2.09 (m, 8H, 4CH₂), 2.79-2.92 (m, 1H, CH), 4.73 (d, 2H, J = 8.0 Hz, CH₂), 5.06 (bs, 1H, NH), 7.20-7.41 (m, 7H, Ar), 7.51-7.59 (m, 2H, Ar), 7.70 (s, 1H, Ar), 7.74 (s, 1H, NH). ¹³C NMR (CDCl₃) δ 25.66, 30.24, 45.40, 46.92, 100.11, 115.82, 118.27, 121.52, 126.92, 127.10, 127.49, 128.28, 129.25, 139.11, 140.44, 148.42, 157.18, 174.98.

***N*-(2-[(4-Methylphenyl)amino]quinolin-4-yl)cyclopentanecarboxamide (19).** Method A. Scale: 0.36 mmol of compound **10**. Eluent 0-2% MeOH in DCM. The product was recrystallized from methanol to give light brown crystals. Mp 188-190 °C. Yield: 0.050 g, 40%. MS (ESI) m/z: 345.4 [M+H]⁺. ¹H NMR (CDCl₃) δ 1.56-

2.05 (m, 8H, 4CH₂), 2.31 (s, 3H, CH₃), 2.72-2.88 (m, 1H, CH), 6.87 (bs, 1H, NH), 7.10-7.28 (m, 3H, Ar), 7.43-7.57 (m, 4H, Ar), 7.73-7.89 (m, 3H, Ar, NH). ¹³C NMR (CDCl₃) δ 20.26, 25.42, 29.97, 46.61, 100.53, 116.03, 118.21, 120.03, 122.00, 127.16, 129.10, 131.98, 137.01, 140.56, 147.81, 154.78, 174.77.

***N*-[2-(2,3-Dihydro-1*H*-inden-5-ylamino)quinolin-4-yl]cyclopentanecarboxamide (20).** Method A. Scale: 0.35 mmol of compound **10**. Eluent 5% MeOH in DCM. The product was recrystallized from methanol to give brown crystals. Mp 115-117 °C. Yield: 0.054 g, 45%. MS (ESI) *m/z*: 371.5 [M+H]⁺. ¹H NMR (CDCl₃) δ 1.59-2.13 (m, 8H, 4CH₂), 2.74-2.90 (m, 6H, 3CH₂), 6.93 (bs, 1H, NH), 7.14-7.31 (m, 4H, Ar), 7.42-7.58 (m, 3H, Ar), 7.75 (d, 1H, *J* = 8.58 Hz, Ar), 7.88 (s, 1H, NH). ¹³C NMR (CDCl₃) δ 25.60, 25.90, 30.45, 32.27, 33.03, 47.07, 101.02, 116.42, 117.00, 118.64, 118.85, 122.43, 124.58, 127.58, 129.58, 138.05, 139.05, 140.93, 145.23, 148.29, 155.42, 175.22.

***N*-{2-[(4-Methoxyphenyl)amino]quinolin-4-yl}cyclopentanecarboxamide (21).** Method A. Scale: 0.84 mmol of compound **11**. Eluent 3% MeOH in DCM. The product was recrystallized from methanol to give brown crystals. Mp 191-192 °C. Yield: 0.12 g, 39%. MS (ESI) *m/z*: 361.4 [M+H]⁺. ¹H NMR (CDCl₃) δ 1.60-2.06 (m, 8H, 4CH₂), 2.77-2.95 (m, 1H, CH), 3.82 (s, 3H, CH₃), 6.69 (bs, 1H, NH), 6.88-6.97 (m, 2H, Ar), 7.23-7.31 (m, 1H, Ar), 7.44-7.60 (m, 4H, Ar), 7.73-7.90 (m, 3H, Ar, NH). ¹³C NMR (CDCl₃) δ 25.93, 30.48, 47.25, 55.50, 100.32, 114.48, 116.30, 118.42, 122.43, 122.91, 127.70, 129.68, 133.01, 140.96, 148.45, 155.79, 155.97, 175.10.

***N*-[2-(Cyclopentylamino)quinolin-4-yl]cyclopentanecarboxamide (22).** Method A. Scale: 0.93 mmol of compound **11**. Eluent 5% MeOH in DCM. The product was recrystallized from methanol to give off-white crystals. Mp 183-184 °C. Yield: 0.039 g, 14%. MS (ESI) *m/z*: 323.4 [M+H]⁺. ¹H NMR (CDCl₃) δ 1.40-2.16 (m, 16H, 8CH₂), 2.77-2.95 (m, 1H, CH), 4.15-4.32 (m, 1H, CH), 4.92 (bs, 1H, NH), 7.20 (t, 1H, *J* = 9.76 Hz, Ar), 7.48-7.84 (m, 6H, Ar, NH). ¹³C NMR (CDCl₃) δ 23.78, 25.96, 30.51, 33.64, 47.28, 53.20, 99.44, 115.54, 118.39, 121.49, 126.98, 129.58, 140.74, 148.72, 157.70, 175.28.

***N*-[2-(1*H*-Indazol-6-ylamino)quinolin-4-yl]cyclopentanecarboxamide (23).** Method A. Scale: 0.87 mmol of compound **11**. Eluent 5-10% MeOH in DCM. The product was recrystallized from methanol to give grey crystals. Mp 222-224 °C. Yield: 0.15 g, 47%. MS (ESI) *m/z*: 371.4 [M+H]⁺. ¹H NMR 300 MHz (CDCl₃+1 drop of MeOD) δ 1.62-2.03 (m, 8H, 4CH₂), 2.84-2.92 (m, 1H, CH), 7.26-7.32 (m, 2H, Ar), 7.43-7.50 (m, 2H, Ar), 7.58 (t, 1H, *J* = 5.33, 4.75 Hz, Ar), 7.67 (d, 1H, *J* = 5.33 Hz, Ar), 7.77 (d, 1H, *J* = 5.40 Hz, Ar), 7.85 (s, 1H, Ar), 8.02 (s, 1H, Ar), 8.08 (s, 1H, Ar). ¹³C NMR (CDCl₃+1 drop of MeOD) δ 25.84, 30.39, 46.46, 101.62, 110.57, 112.03, 116.85, 119.55, 122.37, 123.40, 126.52, 129.74, 133.25, 133.65, 137.41, 141.47, 147.87, 156.00, 176.31.

***N*-(2-Anilinoquinolin-4-yl)cyclobutanecarboxamide (24).** Method B. Scale: 0.77 mmol of compound **15**. Eluent 1-2% MeOH in DCM. The product was recrystallized from ethyl acetate to give white crystals. Mp 154-155 °C. Yield: 0.17 g, 71%. ¹H NMR (CDCl₃) δ 1.93-2.56 (m, 6H, 3CH₂), 3.24-3.41 (m, 1H, CH), 6.84 (bs, 1H, NH), 7.05 (t, 1H, *J* = 7.30 Hz, Ar), 7.26-7.40 (m, 3H, Ar), 7.53-7.82 (m, 6H, Ar, NH), 7.99

(s, 1H, NH). ^{13}C NMR (CDCl_3) δ 17.75, 25.11, 40.64, 101.94, 116.52, 118.74, 119.40, 122.10, 122.38, 127.41, 128.74, 129.35, 140.32, 140.50, 147.90, 154.63, 174.28.

***N*-{2-[(3,4-Dichlorophenyl)amino]quinolin-4-yl}cyclobutanecarboxamide (25).** Method B. Scale: 0.77 mmol of compound **15**. Eluent 0-0.5% MeOH in DCM. The product was recrystallized from methanol to give white crystals. Mp 193-194 °C. Yield: 0.13 g, 44%. ^1H NMR (CDCl_3) δ 1.95-2.53 (m, 6H, 3CH₂), 3.23-3.42 (m, 1H, CH), 6.79 (bs, 1H, NH), 7.31-7.39 (m, 2H, Ar), 7.47-7.70 (m, 5H, Ar, NH), 7.86 (d, 1H, J = 8.40 Hz, Ar), 7.95 (s, 1H, Ar), 8.09 (s, 1H, Ar). ^{13}C NMR ($\text{DMSO-}d_6$) δ 17.90, 24.78, 103.57, 117.49, 118.25, 119.06, 121.58, 121.94, 122.58, 127.10, 129.70, 130.28, 130.80, 141.89, 141.95, 147.47, 154.29, 174.45.

***N*-(2-Anilinoquinolin-4-yl)cyclohexanecarboxamide (26).** Method A. Scale: 1.04 mmol of compound **12**. Eluent 2-4% MeOH in DCM. The product was recrystallized from methanol to give white crystals. Mp 191-192 °C. Yield: 0.26 g, 73%. ^1H NMR (CDCl_3) δ 1.22-2.12 (m, 10H, 5CH₂), 2.31-2.49 (m, 1H, CH), 6.88 (bs, 1H, NH), 7.04 (t, 1H, J = 8.38, 7.62 Hz, Ar), 7.26-7.38 (m, 3H, Ar), 7.54-7.67 (m, 4H, Ar), 7.79 (d, 1H, J = 8.22 Hz, Ar), 7.87 (s, 1H, NH), 7.96 (s, 1H, Ar). ^{13}C NMR (CDCl_3) δ 25.57, 25.84, 29.33, 44.16, 46.25, 98.56, 115.33, 120.40, 121.06, 122.28, 123.52, 125.19, 129.52, 131.31, 137.68, 141.23, 144.66, 153.91, 175.92.

***N*-{2-[(3,4-Dichlorophenyl)amino]quinolin-4-yl}cyclohexanecarboxamide (27).** Method B. Scale: 0.17 mmol of compound **12**. Eluent 1% MeOH in DCM. The product was recrystallized from ethyl acetate to give white crystals. Mp 226-227 °C. Yield: 0.16 g, 43%. ^1H NMR (CDCl_3) δ 1.23-2.17 (m, 10H, 5CH₂), 2.35-2.50 (m, 1H, CH), 6.77 (bs, 1H, NH), 7.32-7.41 (m, 2H, Ar), 7.49 (dd, 1H, J = 6.22, 2.56 Hz, Ar), 7.58-7.67 (m, 2H, Ar), 7.84-7.88 (m, 2H, Ar, NH), 7.95 (s, 1H, Ar), 8.09 (d, 1H, J = 2.56 Hz, Ar). ^{13}C NMR ($\text{DMSO-}d_6$) δ 25.23, 25.48, 29.27, 38.30, 44.46, 103.69, 117.58, 118.24, 119.03, 121.55, 122.00, 122.55, 127.07, 129.67, 130.28, 130.80, 141.89, 141.98, 147.50, 154.26, 175.87.

***N*-{2-[(4-Methylphenyl)amino]quinolin-4-yl}cyclopentanecarboxamide (28).** Method A. Scale: 1.00 mmol of compound **12**. Eluent DCM:ethyl acetate:MeOH = 70:20:10. The product was recrystallized from MeOH:petroleum ether = 1:30. Mp 189-190 °C. Yield: 0.14 g, 39%. ^1H NMR (CDCl_3) δ 1.30-2.09 (m, 10H, 5CH₂), 2.34-2.46 (m, 1H, CH), 2.34 (s, 3H, CH₃), 6.71 (bs, 1H, NH), 7.15-7.35 (m, 4H, Ar), 7.47-7.62 (m, 3H, Ar), 7.79 (d, 1H, J = 7.30 Hz, Ar), 7.99 (s, 1H, Ar). ^{13}C NMR ($\text{DMSO-}d_6$) δ 20.58, 25.34, 29.46, 46.60, 100.64, 116.25, 118.20, 120.29, 122.32, 127.69, 129.42, 132.27, 137.27, 140.64, 148.25, 155.07, 174.60.

***N*-[2-(2,3-Dihydro-1*H*-inden-5-ylamino)quinolin-4-yl]cyclohexanecarboxamide (29).** Method A. Scale: 1.20 mmol of compound **12**. Eluent 10-17% ethyl acetate in DCM. The product was recrystallized from MeOH:petroleum ether = 1:30 to give white crystals. Mp 175-176 °C. Yield: 0.08 g, 16%. ^1H NMR (CDCl_3) δ 1.35-2.40 (m, 10H, 5CH₂), 2.86-2.98 (m, 1H, CH), 6.72 (s, 1H, NH), 7.19-7.34 (m, 4H, Ar), 7.48-7.62 (m, 2H, Ar), 7.79 (d, 1H, J = 8.00 Hz, Ar), 7.97 (s, 1H, Ar). ^{13}C NMR ($\text{DMSO-}d_6$) δ 14.16, 21.02, 25.58, 25.65, 29.70, 32.32, 33.08, 46.83, 60.37, 100.86, 116.43, 116.99, 118.42, 118.86, 122.48, 124.63, 127.83, 129.61, 138.11, 139.10, 140.81, 145.28, 148.45, 155.47, 174.78.

***N*-(2-Anilinoquinolin-4-yl)-2-furamide (30).** Method A. Scale: 0.58 mmol of compound **14**. Eluent 1-2% MeOH in DCM. The product was recrystallized from methanol to give white crystals. Mp 215-216 °C. Yield: 0.058 g, 32%. ¹H NMR (CDCl₃) δ 6.52-6.54 (m, 1H, Ar), 7.02 (t, 1H, *J* = 7.30 Hz, Ar), 7.24-7.35 (m, 6H, Ar), 7.51-7.62 (m, 5H, Ar, NH), 8.09 (s, 1H Ar), 8.74 (bs, 1H, NH). ¹³C NMR (CDCl₃) δ 101.06, 112.74, 116.19, 118.22, 119.47, 122.19, 122.62, 127.74, 128.77, 129.47, 139.93, 140.17, 144.57, 147.02, 148.05, 154.63, 156.12.

***N*-{2-[(3,4-Dichlorophenyl)amino]quinolin-4-yl}-2-furamide (31).** Method B. Scale: 0.77 mmol of compound **14**. Eluent 0-1% MeOH in DCM. The product was recrystallized from methanol to give white crystals. Mp 217-218 °C. Yield: 0.18 g, 59%. ¹H NMR (CDCl₃) δ 6.58-6.61 (m, 1H, Ar), 7.26-7.50 (m, 4H, Ar), 7.59-7.83 (m, 4H, Ar), 8.08 (s, 1H, Ar), 8.15 (s, 1H, Ar). ¹³C NMR (DMSO-*d*₆) δ 106.42, 112.36, 115.88, 118.37, 118.64, 119.19, 121.82, 122.61, 122.85, 126.95, 129.92, 130.34, 130.86, 141.50, 141.71, 146.44, 146.95, 147.56, 153.99, 156.96.

***N*-(2-Anilinoquinolin-4-yl)benzamide (32).** Method A. Scale: 0.71 mmol of compound **13**. Eluent 1-2% MeOH in DCM. The product was recrystallized from methanol to give white crystals. Mp 223-224 °C. Yield: 0.12 g, 49%. ¹H NMR (CDCl₃) δ 6.86 (bs, 1H, NH), 7.07 (t, 1H, *J* = 8.03, 6.57 Hz), 7.29-7.42 (m, 3H, Ar), 7.50-7.69 (m, 8H, Ar), 7.85 (d, 1H, *J* = 8.40 Hz, Ar), 7.93-7.98 (m, 1H, Ar), 8.11 (s, 1H, Ar), 8.50 (bs, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 107.03, 118.46, 118.88, 120.97, 122.19, 122.79, 126.79, 128.13, 128.55, 129.61, 132.04, 134.43, 141.65, 141.89, 148.02, 154.66, 166.66.

***N*-{2-[(3,4-Dichloro-phenyl)amino]quinolin-4-yl}benzamide (33).** Method B. Scale: 0.94 mmol of compound **13**. Eluent 0.25% MeOH in DCM. The product was recrystallized from methanol to give white crystals. Mp 224-225 °C. Yield: 0.16 g, 42%. ¹H NMR (CDCl₃) δ 6.85 (bs, 1H, NH), 7.39 (t, 2H, *J* = 8.40, 8.04 Hz, Ar), 7.49-7.71 (m, 6H, Ar), 7.87-7.99 (m, 3H, Ar), 8.09-8.13 (m, 2H, Ar), 8.54 (bs, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 106.45, 118.34, 118.85, 119.12, 121.76, 122.79, 126.95, 128.16, 128.52, 129.86, 130.37, 130.86, 132.10, 134.40, 141.77, 142.32, 147.59, 154.08, 166.75.

Elemental Analysis

Comp.	Mol. Formula	Theoretical (%)			Experimental (%)		
		C	H	N	C	H	N
16	$C_{21}H_{21}N_3O \cdot 0.3H_2O$	74.89	6.46	12.48	74.89	6.81	12.18
17	$C_{21}H_{19}N_3OCl_2 \cdot 0.55CH_2Cl_2$	59.38	4.53	9.40	59.00	4.43	9.72
18	$C_{22}H_{23}N_3O \cdot 0.4H_2O$	74.93	6.80	11.92	74.86	6.76	12.16
19	$C_{22}H_{23}N_3O \cdot 0.5H_2O$	74.55	6.82	11.86	74.38	6.81	11.94
20	$C_{24}H_{25}N_3O \cdot 1.5H_2O$	72.34	7.08	10.54	72.47	6.84	10.32
21	$C_{22}H_{23}N_3O_2 \cdot 0.5H_2O$	71.53	6.53	11.34	71.55	6.44	11.36
22	$C_{22}H_{21}N_5O$	67.13	6.95	10.97	66.87	7.23	11.34
23	$C_{22}H_{23}N_3O \cdot 0.3H_2O$	71.13	5.7	18.86	71.16	5.75	18.78
24	$C_{20}H_{19}N_3O \cdot 0.5H_2O$	73.60	6.18	12.87	73.94	6.15	12.95
25	$C_{20}H_{17}Cl_2N_3O$	62.19	4.44	10.88	61.85	4.65	10.82
26	$C_{22}H_{23}N_3O \cdot 0.3H_2O$	75.32	6.78	11.98	75.14	6.97	11.88
27	$C_{22}H_{21}Cl_2N_3O \cdot 0.5H_2O$	62.42	5.24	9.93	62.67	5.20	9.94
28	$C_{23}H_{25}N_3O \cdot 0.5H_2O$	74.97	7.11	11.40	74.97	6.96	11.39
29	$C_{24}H_{27}N_3O$	77.18	7.29	11.25	76.77	7.63	11.05
30	$C_{20}H_{15}N_3O_2$	77.86	5.05	12.38	77.56	5.20	12.46
31	$C_{20}H_{13}Cl_2N_3O_2$	64.72	3.70	10.29	64.42	3.85	10.34
32	$C_{22}H_{17}N_3O$	72.93	4.59	12.75	72.35	4.61	12.59
33	$C_{22}H_{15}Cl_2N_3O$	60.23	3.29	10.55	60.10	3.48	10.59