Iodine-promoted facile synthesis of new (±)-N,2-diaryl-2,3-dihydroquinazolines

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Abstract

The reactivity of 2-amino-N′-arylbenzamidines 1a-e towards p-tolualdehyde 2a and 1-naphthaldehyde 2b under the catalytic influence of commercial iodine at ambient temperature has been examined. New chiral quinazolines 3a-e and 4a-d have been identified as reaction products. These products have subsequently been oxidised to N,2-diarylquinazolin-4-amines 12, 13a-d. The structures of the products were elucidated by their NMR, mass and IR spectra in addition to elemental analyses. The structure of 3e was further confirmed by X-ray structural analysis. The mechanism of formation of 3a-e and 4a-d is discussed.

Keywords: 2-Amino-N′-arylbenzamidines, aldehydes, quinazolines, iodine

Introduction

The pyrimidine nucleus is incorporated in a large number of alkaloids, drugs, antibiotics, agrochemicals, and antimicrobial agents. Thus, many fused pyrimidine derivatives are of importance in chemistry, biology, and medicine. Their synthesis is well recognized in the literature and there exist several review articles and monographs. Often the limiting factor for the above approaches is the difficulty encountered in obtaining key intermediates or their precursors in high enough yields.

This is also true for quinazolines which occupy a prominent position among these heterocycles. We have found that novel 2,4-disubstituted quinazolines could be produced in good yields under mild conditions from the reaction of 2-amino-N′-arylbenzamidines with tetracyanoethylene, 4-formyl[2.2]paracycophane, isatoic anhydride, and 2,3-dichloro-1,4-naphthoquinone.
Results and Discussion

The reaction of 2-amino-\(N'\)-arylbenzamidines 1a-e with p-tolualdehyde 2a and 1-naphthaldehyde 2b in the presence of molecular iodine at room temperature, leads to the formation of the N,2-diarylquinazolines 3a-e and 4a-d in moderate to good yields (59-71%) as shown in Scheme 1. Iodine is known as an inexpensive and non-toxic weak Lewis acid, is a readily available reagent for various organic transformations and often yields products with outstanding selectivity.\(^8\)

\[\text{Scheme 1. Reaction of 2-amino-}\(N'\)-arylbenzamidines 1a-e with p-tolualdehyde 2a and 1-naphthaldehyde 2b.}\]

It is noted that the products 3a-e and 4a-d possess a centre of chirality, so this route in principle could also provide optically active compounds. We found that the presence of iodine is crucial in obtaining high yields of the corresponding products, and thus set out first to investigate the effect of the concentration of the added iodine, hoping to identify optimal conditions for the cyclization to proceed. This study revealed that a tenth equivalent of molecular iodine is sufficient to convert one equivalent of substrate 1a-e into quinazoline derivatives 3a-e and 4a-d. Another important factor is the reaction temperature, and room temperature is sufficient to carry...
out the conversion. In comparison with reported methods using other condensing agents, our procedure can be carried out safely under milder conditions.

The products 3a-e and 4a-d as shown in Scheme 1 are produced as racemic mixtures of diasteromers. This is clearly seen in the TLC analysis (two poorly separated spots) and NMR spectra (line doubling in the $^{13}$C NMR spectra). Based on the signals of the $^1$H NMR spectrum we deduce that the diastereomers are formed in 4:1-ratio. The formation of the products 3a-e and 4a-d may be rationalized according to the pathway shown in Scheme 2.

![Scheme 2. Mechanism suggested for the formation of the products 3a-e and 4a-d.](image)

In the initial reaction the Lewis acid I$_2$ polarizes the carbonyl group as shown by structure 5a, b. With its reactivity enhanced the carbonyl group is attacked by the amino substituent of 1a-e and after (1,3-H$^+$ shift) water is lost from 8a-e and 9a-d to yield the Schiff base 10a-e and 11a-d which finally cyclizes to 3a-e and 4a-d.

The structures of the main diastereoisomeric products 3a-e were deduced from their elemental analyses and their IR, $^1$H NMR, $^{13}$C NMR and mass spectra as described in the experimental section.

As a typical example, the IR spectrum of the main diastereoisomeric product 3b displayed two strong absorption maxima at $\nu = 3415$ and 3257 cm$^{-1}$, indicating the presence of two different (NH-) groups, while the C=N group absorbs at $\nu = 1603$ cm$^{-1}$. Taking the $^1$H NMR
spectrum of the main product 3b as an example it exhibits two broad singlets at δ = 7.03 and 4.32 ppm indicating the presence of two -NH- groups. The hydrogen atom at the chiral carbon atom (C-2) is recorded at 5.56 ppm as a sharp singlet. However, the two methyl groups of the two aryl substituents resonated as two sharp singlets at δ = 2.35 and 2.26 ppm for the Z-isomer and we detected another two singlets at δ = 2.40 and 2.31 ppm for the corresponding groups of the E-isomer. The aromatic protons (H-9, -10 and H-13, -14) produce four doublets at δ = 7.40, 7.26, 7.19 and 7.07 ppm with coupling constants J = 7.99 and 7.82 Hz. In addition, two multiplets at δ = 7.31-7.28 and at 6.94-6.87 ppm assignable to ArH-5, -6, -7, and -8 are registered. The 13C NMR spectrum of the main product 3b showed twenty-one distinct resonance signals in agreement with the proposed structure. Two of these carbon atoms represent the methyl group carbon atoms and resonate at δ = 21.2 and 20.7 ppm. The quinazoline C-2 carbon atom of Z- and E-isomers resonated at δ = 68.4 and 68.0 ppm. Finally, the mass spectra show the molecular ion peaks in accordance with the proposed structures of 3a-e.

The structure of compound 3e was confirmed by X-ray structure analysis of the diethyl ether hemisolvate (Figure 1). The two independent molecules of 3e are closely similar, differing only in the orientation of the ring system C19-26 (by ca. 10°); a least-squares fit of all other non-H atoms gave a r.m.s. deviation of 0.085 Å. The molecular packing (Figure 2) consists of chains parallel to the x axis in which the two independent molecules alternate, connected by hydrogen bonds N1-H01λN18' and N1'-H01πN18; the ether molecule is connected to the second independent molecule by the hydrogen bond N3'-H03λO93.

**Figure 1.** The asymmetric unit of compound 3e in the crystal (including solvent). Ellipsoids represent 30% probability levels. Dashed lines indicate hydrogen bonds.

The packing of compound 3e in the crystal lattice is as shown in Figure 2. The 1H and 13C NMR spectra of 4a-d were similar to those of 3a-e except for the second aryl group, which exhibited characteristic signals with appropriate chemical shifts. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values (see experimental section).
Figure 2. Packing diagram of compound 3e in the crystal. Dashed lines indicate hydrogen bonds.

In the second part of this study the new products 3, 4a-d were oxidized, thus removing the chiral center. This was accomplished by treating 3, 4a-d with KMnO₄ in dry acetone (room temperature, 6-9 h; Scheme 3). The products 12, 13a-d were isolated in yields of 53-62% and characterized by their spectroscopic data as described in the experimental section.

Scheme 3. Oxidation of 2,3-dihydroquinazoline derivatives 3, 4a-d by KMnO₄ in dry acetone at room temperature.

<table>
<thead>
<tr>
<th>compound</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>R = R¹ = R² = R³ = H, R⁴ = CH₃</td>
<td>R = R³ = R⁴ = H, R¹ = R² = H,</td>
<td>R = R³ = R⁴ = H, R¹ = Cl,</td>
<td>R = R² = R³ = H, R¹ = Br,</td>
</tr>
<tr>
<td>4</td>
<td>R = R¹ = R⁴ = H, R² = R³ = -CH=CH₂</td>
<td>R² = R³ = -CH=CH₂</td>
<td>R² = R³ = -CH=CH₂</td>
<td>R² = R³ = -CH=CH₂</td>
</tr>
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X-Ray structure determination of (3e)

Crystal data: C₂₅H₂₈N₆O₀.₅, Mr = 378.50, monoclinic, P2₁/c, T = -173 °C, a = 11.5013(3), b = 32.8080(7), c = 11.4755(3) Å, β = 98.874(3)°, U = 4278.3 Å³, Z = 8, F(000) = 1624, λ(Mo Kα) = 0.71073 Å, μ = 0.07 mm⁻¹, Dₙ = 1.175 g cm⁻³. Data collection: A colourless tablet ca. 0.4 × 0.25
0.15 mm was mounted in inert oil on a glass fibre and transferred to the cold gas stream of an Oxford Diffraction Xcalibur E diffractometer. Data were recorded to $2\theta$ 59°. Structure refinement: The structure was refined using SHELXL-97. NH hydrogen atoms were refined freely, methyl groups as idealised rigid groups; other H were included using a riding model. The final $wR2$ (all reflections) was 0.130 for 11901 intensities and 538 parameters, with RI ($I > 2\sigma(I)$) 0.048; $S$ 1.01, max. $\Delta\rho$ 0.57 e Å$^{-3}$ (in solvent region).

X-ray crystallographic data (excluding structure factors) were deposited under the number CCDC-770795 and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conclusions

As part of our current research we have demonstrated one-pot synthesis of new (±)-N,2-diaryl-2,3-dihydroquinazolines through molecular iodine-catalyzed reactions from the reaction between 2-amino-N'-arylbenzamidines and p-tolualdehyde or 1-naphthaldehyde. In all cases the reaction of the two components proceeded rapidly to afford the corresponding desired products. The structure of the selected example 3e was further confirmed by single X-ray structural analysis. The mechanism of formation of the products 3a-e and 4a-d is discussed. This synthetic method has the advantage to deliver good yields, no need to use hazardous and expensive catalysts and an easy workup procedure giving rise to a process with minimum waste.

Experimental Section

General. All reagents were purchased from Alfa Aesar and Fluka and were used without further purification. 2-Amino-N'-arylbenzamidines 1a-e were prepared according to ref$^4$. Melting points were measured in capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. IR spectra were measured using a Bruker Tensor 27 instrument. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded, in CDCl$_3$ and DMSO-$d_6$, on a Bruker AM 400 MHz spectrometer with TMS as internal standard. The mass spectral measurements (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

General procedures for preparation of compounds (3a-e) and (4a-d)

In a round-bottomed flask fitted with a magnetic stirrer a solution of 1a-e (0.1 mmol) in dry EtOH (15 mL) was added at room temperature to a solution of aldehyde 2a, b (0.1 mmol) dissolved in dry EtOH (20 mL). A solution of iodine (0.01 mmol) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 1-3 h. After completion of the reaction (the reaction was followed by TLC), the main diastereoisomeric precipitate was
collected by filtration, washed and recrystallised from EtOH to afford products 3a-e and 4a-d in 59-71% yield.

(Z)-N-(2-p-Tolyl-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (3a). Yield: 48 mg, 71%; white microcrystals (from EtOH); mp 220-222 °C; IR: ν = 3412, 3273 (NH), 1608 (C=N) cm⁻¹; ¹H NMR δ 2.28 (s, 3H, CH₃), 4.48 (br s, 1H, NH), 5.72 (s, 1H), 6.64-6.75 (m, 2H), 7.07-7.11 (m, 1H), 7.27-7.30 (m, 1H), 7.14-7.20 (m, 2H), 7.37 (br s, 1H, NH), 7.44-7.49 (m, 2H), 7.83-7.86 (m, 1H), 7.91 (d, 2H, J = 8.0 Hz), 8.13 (d, 2H, J = 8.1 Hz); ¹³C NMR δ 20.7, 69.6, 114.3, 116.4, 119.5, 120.9, 121.6, 124.1, 126.8, 128.1, 128.3, 128.5, 129.0, 131.7, 136.4, 141.5, 151.7; MS: m/z = 313 (M⁺, 80), 298 (M⁺- CH₃, 32), 274 (18), 234 (6), 221 (48), 194 (16), 171 (12), 102 (8), 91 (16), 76 (8). Anal. Calcd. for C₂₁H₁₉N₃: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.28; H, 6.06; N, 13.28.

(Z)-4-Methyl-N-(2-p-tolyl-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (3b). Yield: 47 mg, 69%; white powder (from EtOH); mp 115-116 °C; IR: ν = 3415, 3257 (NH), 1603 (C=N) cm⁻¹; ¹H NMR δ 2.26 (s, 3H, CH₃), 2.35 (s, 3H, CH₃) (2 CH₃ of Z-isomer), 2.40 and 2.31 (s, 3H, 2CH₃) (2CH₃ of E-isomer), 4.32 (br s, 1H, NH), 5.56 (s, 1H), 6.68 (br s, 1H, NH), 6.87-6.92 (m, 2H), 7.07 (d, 2H, J = 7.9 Hz), 7.19 (d, 2H, J = 7.8 Hz), 7.26 (d, 2H, J = 7.8 Hz), 7.28-7.32 (m, 2H), 7.40 (d, 2H, J = 7.9 Hz); ¹³C NMR δ 20.8, 21.2, 68.4 (C-2, Z-isomer), 68.0 (C-2, E-isomer), 115.1, 116.8, 119.6, 121.4, 121.6, 123.1, 126.8, 127.4, 129.5, 130.0, 132.1, 132.2, 136.5, 139.6, 146.2, 150.5; MS: m/z = 327 (M⁺, 40), 313 (M⁺- CH₃, 100), 308 (10), 281 (4), 251 (4), 236 (56), 219 (20), 192 (16), 162 (10), 118 (12), 107 (16), 91 (28), 71 (14). Anal. Calcd. for C₂₂H₂₁N₃: C, 80.70; H, 6.46; N, 12.83. Found: C, 80.52; H, 6.45; N, 12.69.

(Z)-4-Chloro-N-(2-p-tolyl-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (3c). Yield: 46 mg, 65%; colorless powder (from EtOH); mp 126-127 °C; IR: ν = 3378, 3213 (NH), 1609 (C=N) cm⁻¹; ¹H NMR (DMSO- d₆) δ 2.38 (s, 3H, CH₃), 4.52 (br s, 1H, NH), 5.81 (s, 1H), 7.34 (d, 2H, J = 8.2 Hz), 7.44 (br s, 1H, NH), 7.51 (d, 2H, J = 8.9 Hz), 7.58-7.64 (m, 3H), 7.83-7.87 (m, 1H), 8.06 (d, 2H, J = 8.9 Hz), 8.37 (d, 2H, J = 8.2 Hz); ¹³C NMR (DMSO- d₆) δ 20.9, 66.9, 113.9, 116.0, 120.4, 121.1, 123.5, 126.6, 127.9, 128.3, 128.7, 129.1, 131.5, 133.1, 135.3, 138.4, 139.9, 145.1, 150.5; MS: m/z = 349 (M⁺ +2, 20), 347 (M⁺, 48), 311 (M⁺- HCl, 10), 252 (4), 219 (18), 192 (8), 172 (10), 153 (8), 128 (10), 102 (6), 91 (12), 65 (8). Anal. Calcd. for C₂₁H₁₈ClN₃: C, 72.51; H, 5.22; Cl, 10.19; N, 12.08. Found: C, 72.29; H, 5.18; Cl, 10.07; N, 11.87.

(Z)-4-Bromo-N-(2-p-tolyl-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (3d). Yield: 44 mg, 59%, colorless microcrystals (from EtOH); mp 113-114 °C; IR: ν = 3394, 3294 (NH), 1612 (C=N) cm⁻¹; ¹H NMR (DMSO- d₆) δ 2.23 (s, 3H, CH₃), 4.42 (br s, 1H, NH), 5.67 (s, 1H), 7.34-7.39 (d, 2H, J = 8.2 Hz), 7.44 (br s, 1H, NH), 7.51 (d, 2H, J = 8.7 Hz), 7.58-7.64 (m, 3H), 7.83-7.86 (m, 1H), 8.01 (d, 2H, J = 8.7 Hz), 8.25 (d, 2H, J = 8.2 Hz); ¹³C NMR (DMSO- d₆) δ 21.1, 68.2, 115.0, 115.3, 116.3, 119.1, 123.4, 123.7, 126.6, 127.2, 129.4, 131.5, 132.3, 132.4, 136.2, 139.6, 146.3, 147.0, 150.5; MS: m/z = 393 (M⁺ + 2, 78), 391 (M⁺, 80), 329 (10), 314 (28), 302 (32), 274 (18), 234 (6), 221 (48), 194 (16), 171 (12), 102 (8), 91 (16), 76 (8). Anal. Calcd. for C₂₁H₁₈BrN₃: C, 64.30; H, 4.62; N, 10.71. Found: C, 64.09; H, 4.59; N, 10.54.
(Z)-2,4-Dimethyl-N-(2-p-tolyl-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (3e). Yield: 41 mg, 59%, pale yellow powder (from EtOH); mp 120-121 °C; IR: ν = 3406, 3312 (NH), 1605 (C=NR) cm⁻¹; ¹H NMR δ 2.15 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 4.30 (s, 1H, NH), 5.52 (s, 1H), 6.63-6.67 (dd, 1H, J = 0.9, 8.1 Hz), 6.84-6.89 (m, 2H), 6.95 (d, 1H, J = 0.9 Hz), 7.17 (d, 2H, J = 7.8 Hz), 7.26-7.32 (m, 2H), 7.36 (d, 1H, J = 8.0 Hz), 7.77 (d, 2H, J = 7.8 Hz), 8.25 (s, 1H); ¹³C NMR δ 17.7, 20.7, 21.2, 68.2, 115.0, 119.6, 121.0, 127.3, 127.4, 128.4, 129.0, 129.2, 129.5, 129.7, 129.8, 131.4, 131.8, 131.9, 132.6, 139.7, 145.9, 149.2; MS: m/z = 341 (M⁺, 24), 339 (32), 308 (M⁺-2 CH₃, 8), 278 (9), 264 (10), 236 (8), 223 (100), 207 (28), 193 (6), 165 (8), 149 (16), 132 (44), 119 (22), 103 (10), 91 (26), 72 (16). Anal. Calcd. for C₂₅H₂₅N₃: C, 80.90; H, 6.79; N, 12.31. Found: C, 80.69; H, 6.73; N, 12.17.

(Z)-N-(2-(Naphthalen-1-yl)-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (4a). Yield: 40 mg, 67%, yellow powder (from EtOH); mp 212-214 °C; IR: ν = 3361, 3240 (NH), 1624 (C=N) cm⁻¹; ¹H NMR δ 4.50 (brs, 1H, NH), 6.13 (s, 1H), 7.29 (brs, 1H, NH), 7.35-7.42 (m, 4H), 7.47-7.55 (m, 3H), 7.74-7.81 (m, 4H), 7.94 (d, 2H, J = 6.6 Hz), 8.06 (d, 2H, J = 6.2 Hz), 8.75 (s, 1H); ¹³C NMR δ 68.0, 102.3, 113.3, 117.2, 120.4, 121.1, 123.8, 125.2, 125.6, 126.3, 126.6, 127.2, 128.9, 129.0, 129.1, 129.8, 131.3, 132.8, 134.1, 137.0, 138.6, 150.6; MS: m/z = 349 (M⁺, 44), 347 (80), 346 (100), 305 (8), 270 (24), 255 (16), 234 (10), 230 (28), 220 (8), 192 (4), 172 (18), 155 (12), 141 (4), 127 (24), 118 (16), 93 (12), 77 (24). Anal. Calcd. for C₂₄H₁₉N₃: C, 82.49; H, 5.48; N, 12.03. Found: C, 82.31; H, 5.47; N, 11.88.

(Z)-4-Methyl-N-(2-(naphthalen-1-yl)-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (4b). Yield: 37 mg, 60%, yellow microcrystals (from EtOH); mp 120-121 °C; IR: ν = 3380, 3239 (NH), 1626 (C=N) cm⁻¹; ¹H NMR δ 2.89 (s, 3H, CH₃), 4.77 (brs, 1H, NH), 6.29 (s, 1H), 6.66-6.73 (m, 1H), 6.97-7.01 (m, 1H), 7.07 (brs, 1H, NH), 7.32-7.36 (m, 1H), 7.45-7.52 (m, 2H), 7.57-7.62 (m, 2H), 7.77 (d, 2H, J = 7.7 Hz), 7.87 (s, 1H), 7.95 (d, 2H, J = 7.9 Hz), 8.12-8.19 (m, 3H); ¹³C NMR δ 20.8, 63.3, 101.7, 115.4, 119.5, 121.7, 125.4, 125.7, 125.8, 126.1, 126.2, 126.5, 127.1, 128.6, 129.0, 129.2, 129.5, 129.9, 130.0, 132.3, 135.4, 143.6, 152.0; MS: m/z = 363 (M⁺, 72), 360 (100), 344 (12), 319 (4), 270 (20), 236 (32), 209 (12), 192 (8), 172 (12), 141 (8), 127 (16), 107 (14), 77 (8). Anal. Calcd. for C₂₅H₂₀N₃: C, 82.61; H, 5.82; N, 11.56. Found: C, 82.48; H, 5.81; N, 11.43.

(Z)-4-Chloro-N-(2-(naphthalen-1-yl)-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (4c). Yield: 39 mg, 61%, pale yellow solid (from EtOH); mp 240-242 °C; IR: ν = 3307, 3247 (NH), 1608 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆) δ 4.25 (brs, 1H, NH), 6.21 (s, 1H), 7.27 (brs, 1H, NH), 7.60-7.69 (m, 4H), 7.77-7.87 (m, 4H), 7.89-7.95 (m, 3H), 8.19 (d, 2H, J = 8.2 Hz), 8.80 (d, 2H, J = 8.3 Hz); ¹³C NMR (DMSO- d₆) δ 65.71, 101.5, 115.0, 116.8, 119.3, 122.9, 123.4, 124.9, 125.7, 126.2, 126.5, 128.7, 129.8, 131.1, 131.8, 132.2, 134.3, 147.2, 151.4; MS: m/z = 385 (M⁺ + 2, 32), 383 (M⁺, 80), 380 (100), 344 (36), 317 (4), 270 (42), 255 (20), 228 (8), 190 (16), 172 (28), 153 (10), 127 (12), 111 (4), 75 (8). Anal. Calcd. for C₂₄H₁₈ClN₃: C, 75.09; H, 4.73; N, 10.95. Found: C, 74.87; H, 4.66; N, 10.77.

(Z)-4-Bromo-N-(2-(naphthalen-1-yl)-2,3-dihydroquinazolin-4(1H)-ylidene)aniline (4d). Yield: 36 mg, 54%, pale yellow solid (from EtOH); mp 160-161 °C; IR: ν = 3379, 3253 (NH),
1610 (C=N) cm$^{-1}$; $^1$H NMR $\delta$ 4.54 (br s, 1H, NH), 6.17 (s, 1H), 7.19-7.28 (m, 4H), 7.31 (br s, 1H, NH), 7.35-7.43 (m, 4H), 7.70-7.79 (m, 3H), 7.93 (d, 2H, $J = 8.3$ Hz), 8.31 (d, 2H, $J = 8.3$ Hz); $^{13}$C NMR $\delta$ 66.7, 103.2, 115.0, 116.8, 119.2, 121.6, 122.9, 123.5, 124.9, 125.8, 126.1, 126.3, 128.7, 129.8, 131.1, 131.9, 132.1, 132.4, 134.0, 146.7, 150.6, 152.2; MS: $m/z$ = 429 (M$^+$ + 2, 80), 427 (M$^+$, 76), 346 (12), 344 (20), 314 (8), 302 (60), 300 (100), 275 (40), 257 (60), 230 (8), 220 (20), 194 (14), 173 (58), 153 (12), 127 (24), 92 (18). Anal. Calcd. for C$_{24}$H$_{18}$BrN$_5$: C, 67.30; H, 4.24; N, 9.81. Found: C, 67.12; H, 4.19; N, 9.68.

General procedures for preparation of compounds (12, 13a-d)

To a solution of 3, 4a-d (0.1 mmol) dissolved in dry acetone (15 mL), a solution of KMnO$_4$ (0.11 mmol) was added drop by drop with constant stirring. The reaction mixture was stirred at room temperature for 6-9 h. After completion of the reaction, it was quenched with a saturated solution of sodium sulfite. After stirring for 1 h, the product was extracted three times with CH$_2$Cl$_2$ (20 mL), the collected organic layers were dried over anhydrous MgSO$_4$. The solvent was evaporated and the crude products 12, 13a-d was subjected to column chromatography over silica gel using CH$_2$Cl$_2$ as eluent to give the pure desired products in 53-62% yield.

$N$-Phenyl-$2$-$p$-tolylquinazolin-4-amine (12a).

Yield: 60 mg, 60%, pale yellow powder; mp 193-194 ºC; IR: $\nu$ = 3327 (NH), 1615, 1602 (C=N) cm$^{-1}$; $^1$H NMR $\delta$ 2.34 (s, 3H, CH$_3$), 7.05-7.11 (m, 2H), 7.21 (br s, 1H, NH), 7.19-7.24 (m, 2H), 7.36-7.43 (m, 3H), 7.67-7.74 (m, 2H), 7.84 (d, 2H, $J = 8.3$ Hz), 8.35 (d, 2H, $J = 8.2$ Hz); $^{13}$C NMR $\delta$ 24.7, 113.8, 116.0, 120.8, 121.4, 123.7, 125.6, 126.2, 127.2, 128.3, 128.7, 129.0, 129.2, 129.5, 132.6, 140.2, 150.9, 157.4, 160.2; MS: $m/z$ = 311 (M$^+$, 100), 281 (4), 265 (10), 249 (12), 234 (8), 219 (14), 192 (8), 179 (6), 155 (8), 125 (4), 119 (10), 97 (8), 91 (12). Anal. Calcd. for C$_{21}$H$_17$N$_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 80.77; H, 5.52; N, 13.35.

$N,2$-di-$p$-Tolylquinazolin-4-amine (12b).

Yield: 55 mg, 55%, pale yellow powder; mp 105-106 ºC; IR: $\nu$ = 3258 (NH), 1621, 1601 (C=N) cm$^{-1}$; $^1$H NMR $\delta$ 2.27 (s, 3H, CH$_3$), 2.36 (s, 3H, CH$_3$), 7.18 (d, 2H, $J = 8.2$ Hz), 7.34 (d, 2H, $J = 7.8$ Hz), 7.51 (br s, 1H, NH), 7.67-7.76 (m, 4H), 7.80 (d, 2H, $J = 7.9$ Hz), 8.40 (d, 2H, $J = 8.2$ Hz); $^{13}$C NMR $\delta$ 21.4, 22.1, 113.5, 120.1, 122.3, 125.8, 126.3, 128.3, 128.6, 128.7, 128.9, 129.1, 129.5, 132.7, 135.7, 137.2, 140.5, 151.8, 157.6, 160.4; MS: $m/z$ = 325 (M$^+$, 80), 324 (M$^+$-1, 100), 309 (M$^+$- CH$_3$, 4), 248 (10), 235 (14), 219 (12), 192 (10), 162 (12), 121 (16), 102 (6), 91 (8), 71 (4). Anal. Calcd. for C$_{22}$H$_{19}$N$_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.07; H, 5.87; N, 12.79.

$N$-(4-Chlorophenyl)-$2$-$p$-tolylquinazolin-4-amine (12c).

Yield: 57 mg, 57%, yellowish-white powder; mp 133-134 ºC; IR: $\nu$ = 3440 (NH), 1615, 1599 (C=N) cm$^{-1}$; $^1$H NMR $\delta$ 2.27 (s, 3H, CH$_3$), 7.17 (d, 2H, $J = 8.1$ Hz), 7.22 (d, 2H, $J = 8.8$ Hz), 7.63 (br s, 1H, NH), 7.69 (d, 2H, $J = 8.8$ Hz), 7.80-7.89 (m, 4H), 8.27 (d, 2H, $J = 8.2$ Hz); $^{13}$C NMR $\delta$ 21.4, 113.5, 120.1, 122.3, 125.8, 128.3, 128.6, 128.7, 128.9, 129.1, 129.4, 132.7, 135.7, 137.2, 140.5, 150.9, 156.9, 160.1; MS: $m/z$ = 347 (M$^+$ + 2, 24), 345 (M$^+$-1, 100), 308 (8), 268 (4), 228 (4), 219 (20), 192 (10), 153 (6), 119 (6), 102 (8), 91 (81), 65 (8). Anal. Calcd. for C$_{21}$H$_{16}$ClN$_3$: C, 72.93; H, 4.66; Cl, 10.25; N, 12.15. Found: C, 72.71; H, 4.65; Cl, 10.11; N, 11.99.
N-(4-Bromophenyl)-2-p-tolylquinazolin-4-amine (12d). Yield: 53 mg, 53%, colourless powder; mp 119-120 °C; IR: δ = 3372 (NH), 1612, 1600 (C=N) cm⁻¹; ¹H NMR δ 2.39 (s, 3H, CH₃), 7.31 (d, 2H, J = 8.1 Hz), 7.39 (br s, 1H, NH), 7.45-7.54 (m, 4H), 7.55 (d, 2H, J = 8.8 Hz), 7.80 (d, 2H, J = 8.8 Hz), 8.40 (d, 2H, J = 8.2 Hz); ¹³C NMR δ 24.8, 116.9, 120.1, 122.7, 126.0, 126.7, 127.3, 128.4, 129.2, 129.9, 131.9, 132.9, 135.6, 140.6, 149.7, 154.8, 160.0; MS: m/z = 391 (M⁺ + 2, 42), 389 (M⁺, 38), 281 (4), 265 (10), 249 (12), 234 (8), 219 (14), 192 (8), 179 (6), 155 (8), 125 (4), 119 (10), 97 (8), 91 (12). Anal. Calcd. for C₂₁H₁₆BrN₃: C, 64.63; H, 4.13; N, 10.77. Found: C, 64.39; H, 4.12; N, 10.65.

2-(Naphthalen-1-yl)-N-phenylquinazolin-4-amine (13a). Yield: 53 mg, 54%, yellowish-brown solid; mp 192-194 °C; IR: δ = 3294 (NH), 1617, 1603 (C=N) cm⁻¹; ¹H NMR δ 7.39 (br s, 1H, NH), 7.42 (m, 2H), 7.50-7.55 (m, 2H), 7.63-7.69 (m, 2H), 7.72-7.79 (m, 3H), 7.81-7.84 (m, 1H), 7.87-7.95 (m, 3H), 8.05-8.09 (m, 1H), 8.45-8.49 (m, 2H); ¹³C NMR δ 115.5, 119.6, 121.3, 125.4, 125.8, 126.1, 126.2, 126.5, 127.1, 128.6, 129.0, 129.2, 129.5, 129.9, 130.1, 131.2, 132.3, 135.4, 143.6, 152.0, 158.2, 160.5; MS: m/z = 347 (M⁺, 46), 270 (24), 255 (12), 234 (18), 230 (8), 220 (10), 192 (6), 172 (18), 155 (12), 141 (4), 127 (24), 118 (16), 93 (12), 77 (24). Anal. Calcd. for C₂₄H₁₇N₃: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.79; H, 4.90; N, 11.97.

2-(Naphthalen-1-yl)-N-p-tolylquinazolin-4-amine (13b). Yield: 56 mg, 57%, yellow microcrystals; mp 133-134 °C; IR: δ = 3277 (NH), 1612, 1600 (C=N) cm⁻¹; ¹H NMR δ 2.29 (s, 3H, CH₃), 7.39 (br s, 1H, NH), 7.42 (d, 2H, J = 8.0 Hz), 7.50-7.57 (m, 2H), 7.63-7.69 (m, 2H), 7.74-7.79 (m, 2H), 7.82 (d, 2H, J = 8.1 Hz), 7.87-7.91 (m, 1H), 8.05-8.11 (m, 2H), 8.45-8.53 (m, 2H); ¹³C NMR δ 20.9, 115.5, 119.5, 121.3, 125.4, 125.8, 126.1, 126.2, 126.5, 127.1, 128.6, 129.0, 129.2, 129.5, 129.9, 130.1, 132.3, 135.4, 143.6, 152.0, 158.2, 160.5; MS: m/z = 361 (M⁺, 88), 345 (32), 319 (10), 270 (12), 236 (22), 209 (12), 192 (8), 172 (12), 141 (8), 127 (16), 107 (14), 77 (8). Anal. Calcd. for C₂₅H₁₉N₃: C, 83.08; H, 5.30; N, 11.63. Found: C, 82.89; H, 5.28; N, 11.49.

N-(4-Chlorophenyl)-(2-naphthalen-1-yl)quinazolin-4-amine (13c). Yield: 54 mg, 55%, yellow powder; mp 185-186 °C; IR: δ = 3258 (NH), 1619, 1601 (C=N) cm⁻¹; ¹H NMR δ 7.30 (d, 2H, J = 8.9 Hz), 7.41-7.46 (m, 2H), 7.50 (br s, 1H, NH), 7.52-7.59 (m, 3H), 7.81 (d, 2H, J = 8.9 Hz), 7.84-7.92 (m, 3H), 8.05-8.08 (dd, 1H, J = 0.7, 8.4 Hz), 8.11-8.15 (dd, 1H, J = 1.3, 7.2 Hz), 8.73-8.77 (m, 1H); ¹³C NMR δ 113.3, 122.1, 122.0, 125.2, 125.7, 126.3, 126.5, 126.6, 128.4, 128.9, 129.0, 129.2, 129.5, 130.0, 131.3, 133.1, 134.2, 136.8, 137.2, 150.8, 156.9, 162.6; MS: m/z = 383 (M⁺ + 2, 52), 381 (M⁺, 100), 344 (M⁺- Cl, 24), 270 (32), 255 (10), 228 (6), 190 (12), 172 (20), 153 (8), 127 (12), 111 (4), 75 (8). Anal. Calcd. for C₂₅H₁₉ClN₃: C, 75.49; H, 4.22; Cl, 9.28; N, 11.00. Found: C, 75.22; H, 4.19; Cl, 9.13; N, 10.82.

N-(4-Bromophenyl)-(2-naphthalen-1-yl)quinazolin-4-amine (13d). Yield: 62 mg, 62%, yellow powder; mp = 169-171 °C; IR: δ = 3305 (NH), 1614, 1603 (C=N) cm⁻¹; ¹H NMR δ 7.30 (d, 2H, J = 8.9 Hz), 7.41-7.46 (m, 2H), 7.50 (br s, 1H, NH), 7.81 (d, 2H, J = 8.9 Hz), 7.52-7.56 (m, 3H), 7.84-7.89 (m, 3H), 8.04-8.07 (dd, 1H, J = 0.7, 8.4 Hz), 8.11-8.15 (dd, 1H, J = 1.3, 7.2 Hz), 8.73-8.78 (m, 1H); ¹³C NMR δ 113.3, 122.0, 122.1, 125.2, 125.5, 126.4, 126.5, 126.6, 128.4, 128.9, 129.1, 129.3, 129.5, 130.0, 131.3, 133.0, 134.1, 136.7, 136.9, 151.6, 155.8, 161.7;
MS: $m/z = 427$ (M$^+$ + 2, 64), 425 (M+, 60), 345 (M$^+$- Br, 18), 270 (12), 255 (18), 228 (16), 190 (4), 172 (6), 153 (8), 127 (12), 111 (4), 75 (8). Anal. Calcd. for C$_{24}$H$_{16}$BrN$_3$: C, 67.62; H, 3.78; N, 9.86. Found: C, 67.37; H, 3.77; N, 9.70.

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References