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A General Approach to the Synthesis of Substituted Isoxazolo[4,3-*c*]quinolines via Chalcones[‡]

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A general and practical approach to the synthesis of substituted isoxazolo[4,3-*c*]quinolines from the substituted isoxazolines obtained by 1,3-dipolar cycloadditions between 2-nitrobenzonitrile oxide and chalcones is described. $SnCl_2 \cdot 2H_2O$-mediated reduction of the nitro group, followed by intramolecular cyclization involving the amino and the keto groups in these substrates, furnished mixtures of isoxazolo[4,3-*c*]quinolines and 3,5-dihydroisoxazolo[4,3-*c*]-quinolines. In contrast, the reduction of these substrates with Fe/AcOH unexpectedly yielded 3-benzoylquinolin-4-ylamine derivatives.

Introduction

Annulated heterocyclic systems have a variety of pharmacological uses,[1,2] which provides incentive to synthetic organic chemists to devise novel yet simple strategies for the generation of these molecular frameworks. The development of isoxazole-annulated ring systems has been a topic of continuous research due to the synthetic and medicinal importance of such scaffolds.[3–12] In one of the activities of our research group, we have been involved in the development of novel protocols for the synthesis of such ring systems and have reported the synthesis of furo[3,4-*d*]isoxazol-4-one, 5*H*-isoxazolo[4,5-*d*]pyridazin-4-ones, 5,8-dihydroisoxazolo[4,5-*c*]azepin-4-ones, and isoxazolobenzazulenes.[13–15] During the program we became interested in the synthesis of isoxazolo[4,3-*c*]quinolines. A literature survey revealed that, although there exist a number of strategies for the synthesis of isoxazolo[4,5-*c*]quinolines,[16–19] only two reports[20–21] of the synthesis of isoxazolo[4,3-*c*]quinolines exist, despite their significance as structural components of MRP-1 inhibitors.[22,23] Initially we reasoned that such an architecture could be generated from 3-(2-nitrophenyl)isoxazole-4-carboxylate by reduction of the nitro group to an amino group and subsequent cyclization with the carboxylate or formyl function. However, as reported recently, this approach resulted exclusively in the formation of quinolin-4-ylamine derivatives.[24]

In our continuing efforts in this direction, we reasoned that the synthesis of such ring systems might be accomplished from a substituted isoxazoline derivative containing a 2-nitrophenyl group at the 3-position and a benzoyl moiety at the 4-position, obtainable through 1,3-dipolar cycloadditions between 2-nitrobenzonitrile oxide and chalcones. In principle, the reduction of the nitro group would result in a 2-aminophenyl derivative, in which the amino group should readily undergo intramolecular cyclization with the keto moiety of the benzoyl group to furnish isoxazolo[3,4-*c*]quinoline. The rationale for such a strategy was based on reports by Rossi et al.[16] on the synthesis of isoxazolo[4,5-*c*]quinolines from β-(2-aminophenyl)-α,β-ynones and Kaye et al.[25a] on the generation of quinolines by Baylis–Hillman chemistry. More recently, we have also reported that the keto group has a preference for cyclization with the amino moiety for the construction of the quinoline ring.[25b] In order to explore our strategy we carried out the synthesis of 2-isoxazoline derivatives from chalcones and subjected them to reduction. Interestingly, the reduction of the nitro group under catalytic hydrogenation conditions or in the presence of $SnCl_2 \cdot 2H_2O$ yielded mixtures of substituted 3,5-dihydroisoxazolo[4,3-*c*]quinolines and substituted isoxazolo[4,3-*c*]quinolines. In contrast, Fe/AcOH-mediated reduction afforded 3-benzoylquinolin-4-ylamine derivatives. These results prompted us to discuss the details of our study in this paper.

Results and Discussion

Initially, the substituted chalcones **1a**–**e** and **2a**–**b** were synthesized in excellent yields through the reactions be-

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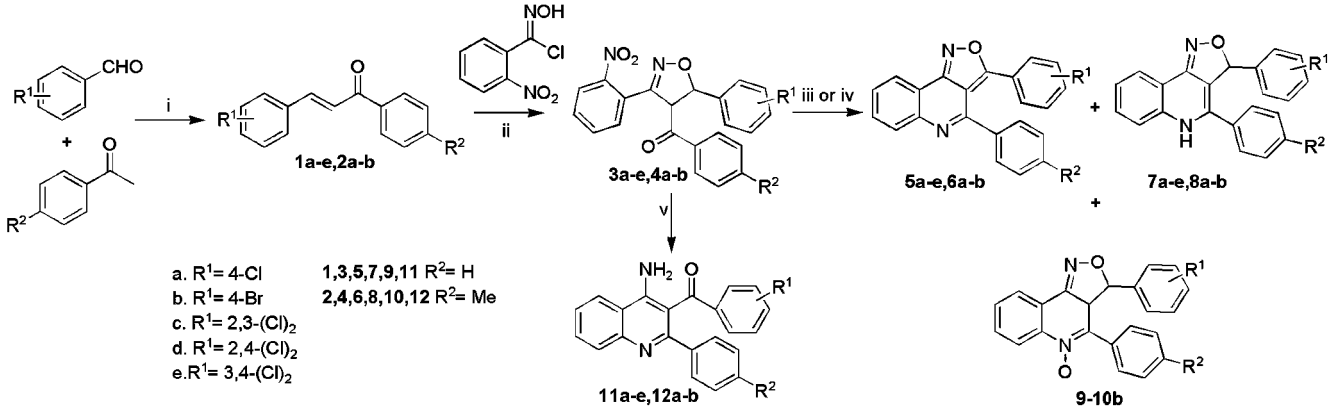
tween different aldehydes and acetophenones. The authenticity of these chalcones was confirmed by comparing their melting points with those reported in the literature.[26,27] Treatment of chalcones **1a**–**e** and **2a**–**b** with 2-nitrobenzonitrile oxide (generated from α-chloro-2-nitrobenzaldoxime) in the presence of triethylamine in diethyl ether at –78 °C furnished the isoxazolines **3a**–**e** and **4a**–**b**, respectively, in 3–4 h and in 54–64% yields (Scheme 1). Although the spectroscopic data supported the structural assignments for **3a**–**e** and **4a**–**b**, the structures were secured by X-ray crystallographic analysis of **3a** (Figure 1).[28] Interestingly, this reaction was diastereoselective for the *trans* isomer, as only faint spots, probably attributable to the *cis* stereomers, were observed by TLC.

In the next stage of the synthesis, chemoselective reduction of the nitro group was desired. Generally, this can be achieved either by catalytic hydrogenation or by use of metals including In, Fe, or Zn in the presence of additives or metal halides such as $SnCl_2$. Catalytic hydrogenation is known to cause cleavage of the 2-isoxazoline ring, but in the light of our recent results[24] in which we demonstrated that a 2-isoxazoline ring bearing a nitrophenyl group at the 3-position is stable under catalytic hydrogenation conditions we decided to employ it for our cause. Therefore, in the first instance we subjected **3a** to hydrogenation in the presence of 10% Pd/C at 2.76 bar of H_2 on a Parr assembly. Gratifyingly, the reaction was complete in 30 min, affording a mixture of products. Careful silica gel column chromatography resulted in the isolation of two products, and spectral analysis of the less polar product, which was obtained in 11% yield, led us to establish the structure of the compound as **5a**. On the contrary, the polar product, which was isolated in 39% yield, was assigned the structure of **7a**. The formation of **5a** may have resulted following the cyclization of the hydroxylamine intermediate with the keto group. This hydroxylamine intermediate would have resulted from partial reduction of the nitro group. On the other hand, product **7a** would have formed through the intramolecular cyclization taking place after the complete reduction of the nitro group to an amino group.

Subsequently, compound **3a** was also subjected to treatment with $SnCl_2 \cdot 2H_2O$ in methanol at reflux temperature. It was pleasing to note that here, too, the reaction was complete within 30 min and that the obtained product was a mixture of only two compounds that could be readily separated by column chromatography. The minor compound,



Scheme 1. Reagents and conditions: (i) aq. KOH, MeOH, 15–30 min. (ii) Et_3N, diethyl ether, –78 °C to room temp., 14–16 h. (iii) $SnCl_2 \cdot 2H_2O$, MeOH, reflux, 80 °C, 30 min. (iv) Pd/C (10%), 2.76 bar of H_2, room temp., 30 min. (v) Fe, AcOH, reflux, 110 °C, 30 min.

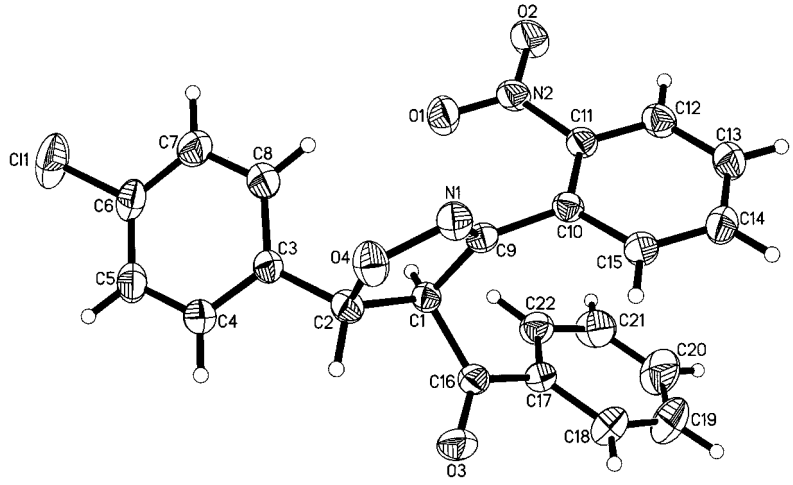


Figure 1. ORTEP diagram of compound **3a** (probabilities of 30%), showing the atomic numbering scheme.

isolated here in 21% yield, was **5a**, while the major product, obtained in 57% yield, was **7a**. In view of the better yields and easy separation observed with this procedure, the other substrates **3b**–**e** and **4a**–**b** were also subjected to the $SnCl_2{\cdot}2H_2O$-promoted reactions. Expectedly, these substrates yielded the corresponding products **5b**–**e**, **7b**–**e**, **6a**–**b**, and **8a**–**b**. The unambiguous assignment of the structures of these compounds was achieved by carrying out X-ray crystallographic analysis of representative compounds **5c** and **7d** (Figures 2 and 3).[29,30]

It is worth mentioning that the crystal of **7d** used for X-ray analysis was obtained from the recovered ^{13}C NMR sample, because of which we observed entrapped $(CH_3)_3Si–Si(CH_3)_3$.

Interestingly, during the reduction of **3**–**4b**, third products, which were isolated in major yields, were invariably formed. On the basis of spectral evidence the structures of these products were established as **9**–**10b**. Although the formation of quinoline *N*-oxide during the $SnCl_2{\cdot}2H_2O$-promoted reduction of the nitro group and subsequent intramolecular cyclization has literature precedence,[25a] the formation of these products only in the cases of **3**–**4b** is at present unexplainable. Nevertheless, the chemical evidence for the assigned structure was obtained by treatment of **9b** with PBr_3 in DMF to furnish **5a** as reported earlier.[25a]

In the next stage of the study, our objective being to avoid the formation of two products, we also investigated the reduction of the nitro group with other metals. While reduction with indium in the presence of HCl in water furnished a complex mixture that was not characterized, similar treatment with Fe/AcOH gave an interesting result. Treatment of **3a** with Fe/AcOH at reflux temperature resulted in complete disappearance of the starting substrate within 30 min. Subsequent purification led to isolation of a

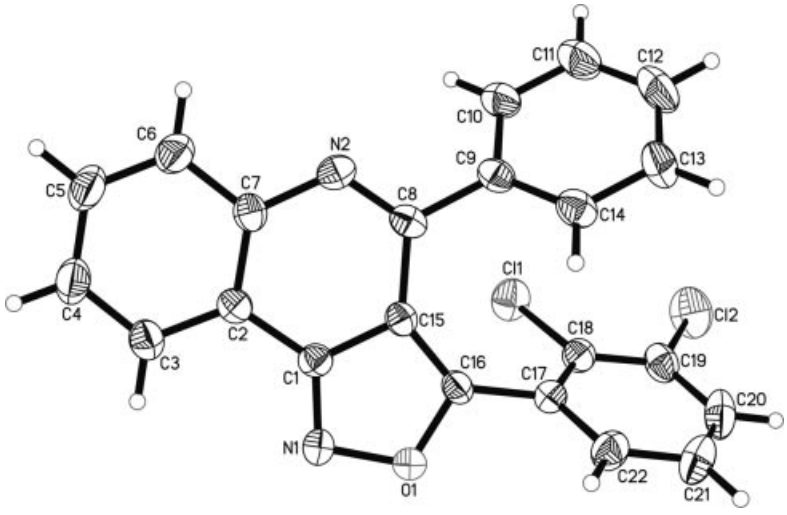


Figure 2. ORTEP diagram of compound **5c** (probability of 30%), showing the atomic numbering scheme.

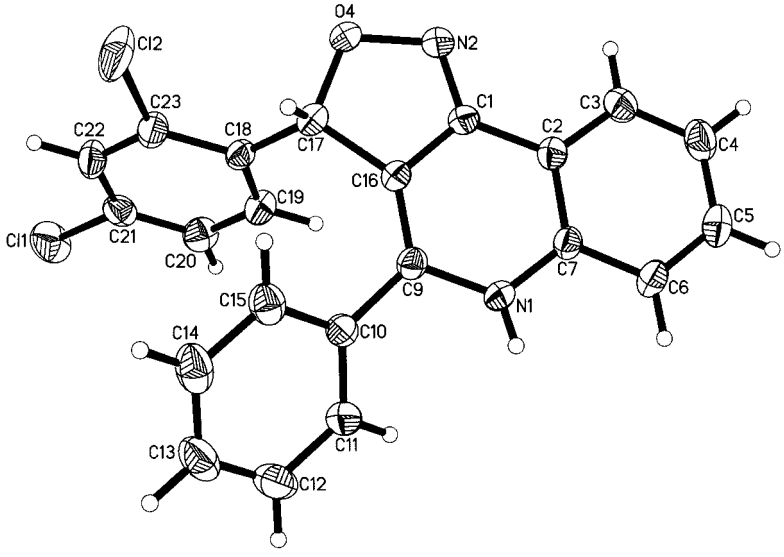


Figure 3. ORTEP diagram of compound **7d** (probability of 30%), showing the atomic numbering scheme. A solvent molecule $[(CH_3)_3Si–Si(CH_3)_3]$ has been omitted for clarity.

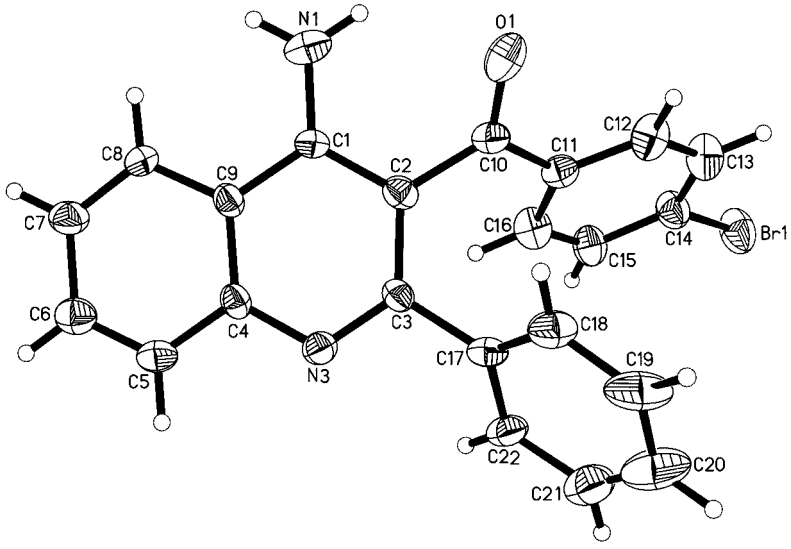


Figure 4. ORTEP diagram of compound **11b** (probability of 30%), showing the atomic numbering scheme.

single compound, identified as 3-(4-chlorobenzoyl)-2-phenylquinolin-4-ylamine (**11a**), in 65% yield. In order to examine the general application of this reaction, isoxazolines **3b**–**e** and **4a**–**b** were also treated with Fe in the presence of AcOH. In all cases the corresponding quinolin-4-ylamines **11b**–**e** and **12a**–**b**, respectively, were isolated in good yields. This is an unusual observation, since formation of quinolin-4-ylamines can be explained on the basis of a cascade reaction. It is believed that the reduction of the nitro group would have occurred first, followed by intramolecular cyclization of the amino group with the carbonyl functionality to afford an isoxazolo[4,3-*c*]quinoline derivative and simultaneous cleavage of the isoxazoline ring. X-ray crystallographic analysis of a representative compound **11b** (Figure 4)[31] unequivocally confirmed the assigned structure of the product. Additional chemical evidence for the formation of these products was obtained by subjecting **5a** to hydrogenation in the presence of Raney-Ni to furnish compound **11a** exclusively.

Conclusions

We have demonstrated a general and convenient synthesis of isoxazolo[4,3-*c*]quinoline derivatives through the reduction of the nitro groups of (2-nitrophenyl)isoxazolines, which in turn were afforded by chalcones. This synthetic strategy is impressive because of easy availability of the starting substrates, simple reaction conditions, and short reaction times. The formation of quinolin-4-ylamine derivatives bearing benzoyl moieties at the 3-position during reduction in the presence of Fe/AcOH provides an excellent alternative for the synthesis of this important scaffold.

Experimental Section

General: Melting points are uncorrected and were determined in capillary tubes with an apparatus containing silicon oil. Infrared spectra were recorded with a Perkin–Elmer RX I FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker DPX 200 MHz or Bruker Avance 300 MHz FT spectrometers, with TMS as an internal standard (chemical shifts in δ values, J in Hz). The FAB mass spectra were recorded with JEOL/SX-102 spectrometers, and the ES mass spectra were recorded with a MICROMASS LCMS system. Elemental analyses were performed with a Carlo Erba 1108 microanalyzer or an Elementar Vario EL III microanalyzer. Only representative data for the chalcones are provided. Hydrogenation was performed in the usual manner on a Parr assembly. Compound **8a** was insoluble in any solvent; therefore, no NMR spectroscopic data are included. ***CAUTION:*** Round-bottomed flasks containing α-chloro-2-nitrobenzaldoxime (around 5.0 g) exploded a few times during evaporation under vacuum with a rotary evaporator; it should therefore be handled carefully.

Preparation of Chalcones 1a–e, 2a–b. General Procedure: Aq. KOH (26 mmol, 1.43 g in 9.5 mL of water) was added dropwise at room temperature to a mixture of the appropriate benzaldehyde (17 mmol) and the appropriate acetophenone (17 mmol) in methanol (25 mL), and the reaction mixture was stirred for 15 min. After completion, the reaction mixture was neutralized with dilute HCl, filtered through a Büchner funnel, and washed freely with water. The resultant solids **1a**–**e** and **2a**–**b** were dried over P_2O_5 in a dessicator.

3-(4-Chlorophenyl)-1-*p*-tolylpropenone (2a): Yield: 82% (3.0 g from 3.66 g) as a white solid, m.p. 148–150 °C. R_f (10% EtOAc/hexanes) = 0.56. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 3 H, CH_3), 7.23–7.28 (m, 4 H, ArH), 7.32–7.46 (m, 2 H, ArH and =CH), 7.54–7.58 (m, 2 H, ArH, and =CH), 7.93 (d, J = 8.2 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.1, 122.8, 129.1, 129.6, 129.8, 130.0, 133.9, 135.8, 136.7, 143.3, 144.3, 190.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1659 (CO) cm^{-1}. ESI-MS: m/z = 257.2 [M + 1]$^+$.

Preparation of Isoxazolines 3a–e, 4a–b. General Procedure: The appropriate chalcone **1a**–**e** or **2a**–**b** (15 mmol) was added to a solution of α-chloro-2-nitrobenzaldoxime (10 mmol, 2.0 g) in dry diethyl ether (10 mL), and the mixture was cooled to –78 °C. Et_3N (20 mmol, 2.8 mL) was added dropwise at this temperature with stirring. After the addition was complete, the reaction was brought to room temperature and the stirring was continued for 3–4 h. Thereafter, the reaction mixture was extracted with ethyl acetate (3 × 50 mL) and water (100 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography on silica gel (60–120 mesh) with hexanes/EtOAc (95:5, v/v) as solvent system to yield the desired product **3a**–**e** or **4a**–**b**.

[5-(4-Chlorophenyl)-3-(2-nitrophenyl)-4,5-dihydroisoxazol-4-yl]-(phenyl)methanone (3a): This compound was isolated in 59% yield (2.36 g from 2.0 g) as a yellow solid, m.p. 146–148 °C. R_f (20% EtOAc/hexanes) = 0.5. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.65 (d, J = 8.2 Hz, 1 H, CH), 6.03 (d, J = 8.2 Hz, 1 H, CH), 7.31–7.36 (m, 2 H, ArH), 7.46 (s, 4 H, ArH), 7.49–7.57 (m, 2 H, ArH), 7.61–7.66 (m, 4 H, ArH), 8.09 (d, J = 8.3 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 66.1, 87.5, 125.2, 128.5, 129.0, 129.3, 129.7, 131.3, 133.8, 134.4, 134.7, 135.4, 135.6, 137.9, 147.5, 153.8, 194.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1687 (CO), 1525, 1345 (NO_2) cm^{-1}. ESI-MS: m/z = 407.0/409.0 $[M + 1]^+$. $C_{22}H_{15}ClN_2O_4$ (406.82): calcd. C 64.95, H 3.72, N 6.89; found C 65.08, H 4.01, N 6.65.

[5-(4-Bromophenyl)-3-(2-nitrophenyl)-4,5-dihydroisoxazol-4-yl]-(phenyl)methanone (3b): This compound was isolated in 62% yield (1.80 g from 1.30 g) as a brown solid, m.p. 155–157 °C. R_f (20% EtOAc/hexanes) = 0.66. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.65 (d, J = 8.1 Hz, 1 H, CH), 6.02 (d, J = 8.1 Hz, 1 H, CH), 7.31–7.41 (m, 4 H, ArH), 7.50–7.57 (m, 2 H, ArH), 7.60–7.66 (m, 6 H, ArH), 8.09 (d, J = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 66.1, 87.5, 123.6, 125.3, 128.8, 129.0, 129.3, 130.1, 130.3, 131.3, 132.6, 133.8, 134.4, 134.8, 135.6, 138.4, 147.5, 153.8, 194.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1698 (CO), 1533, 1346 (NO_2) cm^{-1}. ESI-MS: m/z = 451.1/453.0 $[M + 1]^+$. $C_{22}H_{15}BrN_2O_4$ (451.27): calcd. C 58.55, H 3.35, N 6.21; found C 58.22, H 3.57, N 6.22.

[5-(2,3-Dichlorophenyl)-3-(2-nitrophenyl)-4,5-dihydroisoxazol-4-yl]-(phenyl)methanone (3c): This compound was isolated in 64% yield (2.12 g from 1.50 g) as a yellow solid, m.p. 159–160 °C. R_f (20% EtOAc/hexanes) = 0.67. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.49 (d, J = 5.9 Hz, 1 H, CH), 6.58 (d, J = 5.9 Hz, 1 H, CH), 7.27–7.42 (m, 4 H, ArH), 7.46–7.54 (m, 4 H, ArH), 7.65–7.71 (m, 3 H, ArH), 8.05–8.08 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 65.5, 84.8, 124.7, 125.4, 126.2, 128.5, 128.8, 129.3, 129.7, 130.7, 131.4, 133.2, 133.7, 134.5, 134.6, 135.7, 140.3, 147.4, 153.4, 194.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1696 (CO), 1523, 1345 (NO_2) cm^{-1}. ESI-MS: m/z = 441.0/443.0 $[M + 1]^+$. $C_{22}H_{14}Cl_2N_2O_4$ (441.26): calcd. C 59.88, H 3.20, N 6.35; found C 60.03, H 3.45, N 6.65.

[5-(2,4-Dichlorophenyl)-3-(2-nitrophenyl)-4,5-dihydroisoxazol-4-yl]-(phenyl)methanone (3d): This compound was isolated in 63% yield (2.21 g from 1.60 g) as a white solid, m.p. 150–152 °C. R_f (20% EtOAc/hexanes) = 0.58. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.50 (d, J = 6.2 Hz, 1 H, CH), 6.52 (d, J = 6.2 Hz, 1 H, CH), 7.28–7.33 (m, 2 H, ArH), 7.35–7.38 (m, 1 H, ArH), 7.42–7.54 (m, 5 H, ArH), 7.64–7.73 (m, 3 H, ArH), 8.06–8.09 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 63.8, 82.5, 123.1, 123.7, 126.7, 127.1, 127.4, 127.6, 128.1, 129.7, 130.6, 131.6, 132.8, 132.9, 133.7, 134.1, 134.9, 145.7, 151.8, 192.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1688 (CO), 1526, 1345 (NO_2) cm^{-1}. FAB-MS: m/z = 441 $[M + 1]^+$. $C_{22}H_{14}Cl_2N_2O_4$ (441.26): calcd. C 59.88, H 3.20, N 6.35; found C 60.11, H 3.30, N 6.51.

[5-(3,4-Dichlorophenyl)-3-(2-nitrophenyl)-4,5-dihydroisoxazol-4-yl]-(phenyl)methanone (3e): This compound was isolated in 58% yield (1.92 g from 1.50 g) as a pale yellow solid, m.p. 141–142 °C. R_f (20% EtOAc/hexanes) = 0.59. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.62 (d, J = 7.9 Hz, 1 H, CH), 6.04 (d, J = 7.9 Hz, 1 H, CH), 7.32–7.47 (m, 3 H, ArH), 7.51–7.77 (m, 5 H, ArH), 8.09–8.17 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 64.4, 84.6, 124.6, 126.2, 127.3, 127.5, 128.2, 128.9, 129.5, 129.8, 130.2, 131.5, 131.9, 132.6, 132.9, 133.8, 135.0, 138.1, 146.7, 152.1, 192.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1688 (CO), 1521, 1350 (NO_2) cm^{-1}. ESI-MS: m/z = 441 $[M + 1]^+$. $C_{22}H_{14}Cl_2N_2O_4$ (441.26): calcd. C 59.88, H 3.20, N 6.35; found C 59.91, H 3.16, N 6.43.

[5-(4-Chlorophenyl)-3-(2-nitrophenyl)-4,5-dihydroisoxazol-4-yl](*p*-tolyl)methanone (4a): This compound was isolated in 57% yield (1.80 g from 1.50 g) as a white solid, m.p. 160–162 °C. R_f (20% EtOAc/hexanes) = 0.48. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.35 (s, 3 H, CH_3), 5.62 (d, J = 8.2 Hz, 1 H, CH), 5.99 (d, J = 8.2 Hz, 1 H, CH), 7.13 (d, J = 8.1 Hz, 2 H, ArH), 7.45 (s, 4 H, ArH), 7.53–7.57 (m, 3 H, ArH), 7.62–7.64 (m, 2 H, ArH), 8.10 (d, J = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.6, 65.5, 87.3, 124.8, 128.1, 128.7, 128.8, 129.2, 129.3, 129.6, 129.7, 130.8, 133.5, 134.0, 134.8, 135.6, 138.4, 147.5, 153.8, 194.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1694 (CO), 1525, 1350 (NO_2) cm^{-1}. FAB-MS: m/z = 421 $[M + 1]^+$. $C_{23}H_{17}ClN_2O_4 \cdot H_2O$ (438.86): calcd. C 62.95, H 4.36, N 6.38; found C 63.04, H 4.66, N 6.65.

[5-(4-Bromophenyl)-3-(2-nitrophenyl)-4,5-dihydroisoxazol-4-yl](*p*-tolyl)methanone (4b): This compound was isolated in 54% yield (1.50 g from 1.20 g) as a yellow solid, m.p. 154–155 °C. R_f (20% ethyl acetate/hexanes) = 0.53. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.34 (m, 3 H, ArH), 5.60 (d, J = 8.1 Hz, 1 H, CH), 5.96 (d, J = 8.1 Hz, 1 H, CH), 7.12 (d, J = 8.1 Hz, 2 H, ArH), 7.37 (d, J = 8.4 Hz, 2 H, ArH), 7.49–7.63 (m, 7 H, ArH), 8.09 (d, J = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.4, 64.2, 86.1, 121.8, 123.5, 127.1, 127.5, 128.4, 129.5, 130.9, 131.5, 132.2, 132.7, 136.8, 144.4, 145.9, 152.3, 192.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1682 (CO), 1530, 1347 (NO_2) cm^{-1}. ESI-MS: m/z = 465.2/467.2 $[M + 1]^+$. $C_{23}H_{17}BrN_2O_4$ (465.29): calcd. C 59.37, H 3.68, N 6.02; found C 59.59, H 3.94, N 5.99.

$SnCl_2 \cdot 2H_2O$-Mediated Reduction of 3a–e or 4a–b. General Procedure: $SnCl_2 \cdot 2H_2O$ (6.15 mmol, 1.17 g) was added to a solution of the appropriate isoxazoline **3a**–**e** or **4a**–**b** (1.23 mmol) in dry methanol (15 mL), and the mixture was maintained at reflux temperature for 30 min. Thereafter, the reaction mixture was concentrated to remove excess methanol and neutralized with saturated $NaHCO_3$ solution. It was then filtered through a Celite bed, and the residue was washed with ethyl acetate. The water layer was further extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, washed with brine solution, dried with Na_2SO_4, and concentrated under reduced pressure to provide a crude product. The crude product was purified by column chromatography on silica gel (60–120 mesh) with hexanes/EtOAc (98–97:2–3, v/v) to provide **5a**–**e** or **6a**–**b** and with further elution with hexanes/EtOAc (80–70:20–30, v/v) to provide **7a**–**e** or **8a**–**b**.

3-(4-Chlorophenyl)-4-phenylisoxazolo[4,3-*c*]quinoline (5a): This compound was isolated in 21% yield (0.11 g from 0.60 g) as a pale yellow solid, m.p. 211–213 °C. R_f (20% EtOAc/hexanes) = 0.8. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.20 (s, 4 H, ArH), 7.29–7.33 (m, 2 H, ArH), 7.38–7.49 (m, 3 H, ArH), 7.65 (dt, ^1J = 1.2, ^2J = 7.5 Hz, 1 H, ArH), 7.81 (dt, ^1J = 1.3, ^2J = 7.2 Hz, 1 H, ArH), 8.12 (d, J = 8.0 Hz, 1 H, ArH), 8.52 (dd, ^1J = 1.2, ^2J = 7.8 Hz, 1 H, ArH)

ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 108.7, 115.9, 123.8, 125.9, 128.5, 128.9, 129.0, 129.3, 130.2, 130.4, 131.2, 132.0, 137.5, 138.4, 145.7, 156.9, 157.8, 168.1 ppm. ESI-MS: *m/z* = 357.3/359.2 [M + 1]$^+$. HR-EIMS: calcd. for $C_{22}H_{13}ClN_2O$ 356.0716; found 356.0711.

3-(4-Bromophenyl)-4-phenylisoxazolo[4,3-*c*]quinoline (5b): This compound was isolated in 19% yield (0.072 g from 0.42 g) as a yellow solid, m.p. 132–133 °C. R_f (20% EtOAc/hexanes) = 0.82. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50–7.51 (m, 2 H, ArH), 7.52–7.53 (m, 3 H, ArH), 7.55–7.56 (m, 3 H, ArH), 7.58–7.62 (m, 2 H, ArH), 8.02–8.05 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 121.3, 123.5, 127.2, 127.4, 128.5, 130.9, 131.7, 132.5, 136.8, 142.1, 188.9 ppm. ESI-MS: *m/z* = 401.2/403.1 [M + 1]$^+$. $C_{22}H_{13}BrN_2O$ (401.25): calcd. C 65.85, H 3.27, N 6.98; found C 65.54, H 3.09, N 7.16.

3-(2,3-Dichlorophenyl)-4-phenylisoxazolo[4,3-*c*]quinoline (5c): This compound was isolated in 19% yield (0.081 g from 0.48 g) as a light brown solid, m.p. 200–201 °C. R_f (20% EtOAc/hexanes) = 0.82. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.08–7.18 (m, 4 H, ArH), 7.30–7.32 (m, 1 H, ArH), 7.39–7.41 (m, 2 H, ArH), 7.53–7.56 (m, 1 H, ArH), 7.69 (t, *J* = 7.5 Hz, 1 H, ArH), 7.84 (t, *J* = 7.4 Hz, 1 H, ArH), 8.17 (d, *J* = 8.1 Hz, 1 H, ArH), 8.56 (d, *J* = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 111.2, 116.0, 123.9, 124.6, 127.5, 128.2, 128.6, 128.7, 129.8, 130.0, 130.4, 130.5, 132.1, 132.9, 134.3, 137.7, 145.8, 156.8, 157.2, 166.0 ppm. ESI-MS: *m/z* = 391.2/393.2 [M + 1]$^+$. $C_{22}H_{12}Cl_2N_2O$ (391.24): calcd. C 67.54, H 3.09, N 7.16; found C 67.66, H 3.41, N 7.39.

3-(2,4-Dichlorophenyl)-4-phenylisoxazolo[4,3-*c*]quinoline (5d): This compound was isolated in 17% yield (0.075 g from 0.50 g) as a pale yellow solid, m.p. 128–129 °C. R_f (20% EtOAc/hexanes) = 0.81. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.09–7.21 (m, 4 H, ArH), 7.30–7.36 (m, 1 H, ArH), 7.38–7.43 (m, 3 H, ArH), 7.67 (dt, ^1J = 1.1, ^2J = 7.8 Hz, 1 H, ArH), 7.82 (dt, ^1J = 1.5, ^2J = 7.3 Hz, 1 H, ArH), 8.15 (d, *J* = 8.3 Hz, 1 H, ArH), 8.54 (dd, ^1J = 1.3, ^2J = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 109.6, 114.3, 122.2, 125.7, 126.6, 126.9, 127.2, 127.4, 128.4, 128.5, 128.8, 130.4, 131.3, 133.7, 136.1, 136.4, 144.1, 155.1, 155.6, 163.9 ppm. ESI-MS: *m/z* = 391.2/393.1 [M + 1]$^+$. $C_{22}H_{12}Cl_2N_2O$ (391.24): calcd. C 67.54, H 3.09, N 7.16; found C 67.88, H 3.20, N 7.08.

3-(3,4-Dichlorophenyl)-4-phenylisoxazolo[4,3-*c*]quinoline (5e): This compound was isolated in 19% yield (0.085 g from 0.50 g) as a yellow solid, m.p. 201–202 °C. R_f (20% EtOAc/hexanes) = 0.75. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.15–7.18 (m, 1 H, ArH), 7.25–7.28 (m, 1 H, ArH), 7.33–7.38 (m, 3 H, ArH), 7.46–7.50 (m, 3 H, ArH), 7.68 (t, *J* = 7.5 Hz, 1 H, ArH), 7.82 (t, *J* = 7.5 Hz, 1 H, ArH), 8.15 (d, *J* = 8.1 Hz, 1 H, ArH), 8.53 (d, *J* = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 109.1, 115.8, 123.8, 127.0, 128.6, 128.8, 129.1, 129.2, 130.4, 130.6, 131.9, 132.2, 133.1, 135.7, 138.3, 145.6, 156.6, 157.8, 166.4 ppm. ESI-MS: *m/z* = 391.2/393.2 [M + 1]$^+$. $C_{22}H_{12}Cl_2N_2O{\cdot}2H_2O$ (427.28): calcd. C 64.56, H 3.45, N 6.84; found C 64.80, H 3.41, N 6.79.

3-(4-Chlorophenyl)-4-(*p*-tolyl)isoxazolo[4,3-*c*]quinoline (6a): This compound was isolated in 14% yield (0.08 g from 0.65 g) as a yellow solid, m.p. 232–234 °C. R_f (20% EtOAc/hexanes) = 0.72. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.09 (d, *J* = 7.8 Hz, 2 H, ArH), 7.22 (s, 4 H, ArH), 7.36 (d, *J* = 7.8 Hz, 2 H, ArH), 7.63 (t, *J* = 7.2 Hz, 1 H, ArH), 7.78 (t, *J* = 7.2 Hz, 1 H, ArH), 8.11 (d, *J* = 8.0 Hz, 1 H, ArH), 8.50 (d, *J* = 7.5 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.8, 108.8, 115.9, 123.8, 126.0, 128.3, 129.3, 129.5, 130.3, 131.3, 131.9, 135.7, 137.5, 140.4, 145.8, 156.9, 157.8, 168.0 ppm. ESI-MS: *m/z* = 370.2/372.1 [M + 1]$^+$. $C_{23}H_{15}ClN_2O$ (370.83): calcd. C 74.49, H 4.08, N 7.55; found C 74.54, H 4.19, N 7.35.

3-(4-Bromophenyl)-4-(*p*-tolyl)isoxazolo[4,3-*c*]quinoline (6b): This compound was isolated in 18% yield (0.08 g from 0.50 g) as a yellow solid, m.p. 218–220 °C. R_f (20% EtOAc/hexanes) = 0.74. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.38 (s, 3 H, CH_3), 7.07–7.21 (m, 4 H, ArH), 7.33–7.39 (m, 4 H, ArH), 7.62 (t, *J* = 7.3 Hz, 1 H, ArH), 7.77 (t, *J* = 7.2 Hz, 1 H, ArH), 8.10 (d, *J* = 8.0 Hz, 1 H, ArH), 8.50 (d, *J* = 7.3 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.8, 108.8, 115.9, 123.8, 125.9, 126.4, 128.3, 129.3, 129.5, 130.3, 131.4, 131.8, 131.9, 135.6, 140.4, 145.8, 156.2, 157.87, 168.1 ppm. ESI-MS: *m/z* = 415.2/417.1 [M + 1]$^+$. $C_{23}H_{15}BrN_2O$ (415.28): calcd. C 66.52, H 3.64, N 6.75; found C 66.54, H 3.50, N 6.90.

3-(4-Chlorophenyl)-4-phenyl-3,5-dihydroisoxazolo[4,3-*c*]quinoline (7a): This compound was isolated in 57% yield (0.30 g from 0.60 g) as a yellow solid, m.p. 220–222 °C. R_f (20% EtOAc/hexanes) = 0.32. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.69 (s, 1 H, CH), 7.07 (dd, ^1J = 1.9, ^2J = 6.5 Hz, 2 H, ArH), 7.11–7.17 (m, 1 H, ArH), 7.19 (dd, ^1J = 1.8, ^2J = 6.7 Hz, 2 H, ArH), 7.34–7.39 (m, 4 H, ArH), 7.42–7.48 (m, 3 H, ArH), 7.70 (dd, ^1J = 1.1, ^2J = 7.8 Hz, 1 H, ArH), 10.20 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 80.7, 111.5, 115.6, 116.6, 122.0, 123.1, 1215.8, 126.3, 126.8, 127.3, 127.7, 127.9, 128.7, 130.2, 131.4, 132.1, 135.6, 138.7, 139.3, 150.5 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3300 (NH) cm^{-1}. ESI-MS: *m/z* = 359.2/361.2 [M + 1]$^+$. $C_{22}H_{15}ClN_2O$ (358.82): calcd. C 73.64, H 4.21, N 7.81; found C 73.53, H 4.40, N 7.65.

3-(4-Bromophenyl)-4-phenyl-3,5-dihydroisoxazolo[4,3-*c*]quinoline (7b): This compound was isolated in 17% yield (0.063 g from 0.42 g) as a yellow solid, m.p. 227–229 °C. R_f (20% EtOAc/hexanes) = 0.4. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.68 (s, 1 H, CH), 7.01 (d, *J* = 8.0 Hz, 2 H, ArH), 7.14 (t, *J* = 7.3 Hz, 1 H, ArH), 7.32–7.37 (m, 5 H, ArH), 7.43–7.46 (m, 3 H, ArH), 7.70 (d, *J* = 7.7 Hz, 1 H, ArH), 10.19 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 80.7, 111.5, 115.6, 116.6, 120.1, 122.0, 123.1, 126.8, 127.7, 128.2, 128.7, 130.2, 132.1, 135.6, 138.7, 139.7, 150.5 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3432 (NH) cm^{-1}. ESI-MS: *m/z* = 403.2/405.1 [M + 1]$^+$. $C_{22}H_{15}BrN_2O$ (403.27): calcd. C 65.52, H 3.75, N 6.95; found C 65.54, H 3.79, N 7.11.

3-(2,3-Dichlorophenyl)-4-phenyl-3,5-dihydroisoxazolo[4,3-*c*]quinoline (7c): This compound was isolated in 49% yield (0.21 g from 0.48 g) as a yellow solid, m.p. >250 °C. R_f (20% EtOAc/hexanes) = 0.36. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.04 (s, 1 H, CH), 7.16–7.19 (m, 3 H, ArH), 7.31–7.34 (m, 3 H, ArH), 7.40–7.47 (m, 5 H, ArH), 7.69 (d, *J* = 7.8 Hz, 1 H, ArH), 10.36 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 80.1, 112.5, 115.4, 117.9, 123.3, 124.3, 127.7, 128.6, 128.8, 129.9, 130.5, 131.5, 132.0, 133.3, 137.2, 139.9, 140.2, 152.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3434 (NH) cm^{-1}. ESI-MS: *m/z* = 393.1/395.1 [M + 1]$^+$. $C_{22}H_{14}Cl_2N_2O$ (393.26): calcd. C 67.19, H 3.59, N 7.12; found C 67.34, H 3.66, N 7.01.

3-(2,4-Dichlorophenyl)-4-phenyl-3,5-dihydroisoxazolo[4,3-*c*]quinoline (7d): This compound was isolated in 52% yield (0.23 g from 0.50 g) as a yellow solid, m.p. 230–231 °C. R_f (20% EtOAc/hexanes) = 0.28. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.96 (s, 1 H, CH), 7.10–7.21 (m, 3 H, ArH), 7.30–7.33 (m, 3 H, ArH), 7.37–7.46 (m, 5 H, ArH), 7.67 (d, *J* = 7.7 Hz, 1 H, ArH), 10.30 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 82.6, 116.0, 119.0, 121.5, 126.9, 127.9, 131.3, 131.5, 132.4, 133.5, 135.0, 135.3, 136.9, 137.1, 137.2, 140.4, 140.7, 143.5, 155.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3421 (NH) cm^{-1}. ESI-MS: *m/z* = 393.1/395.0 [M + 1]$^+$. $C_{22}H_{14}Cl_2N_2O$ (393.26): calcd. C 67.19, H 3.59, N 7.12; found C 66.98, H 3.42, N 7.23.

3-(3,4-Dichlorophenyl)-4-phenyl-3,5-dihydroisoxazolo[4,3-*c*]quinoline (7e): This compound was isolated in 47% yield (0.21 g from 0.50 g) as a yellow solid, m.p. 195–197 °C. R_f (20% EtOAc/hexanes)

= 0.33. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 6.69 (s, 1 H, CH), 7.06–7.09 (m, 2 H, ArH), 7.11–7.21 (m, 3 H, ArH), 7.34–7.39 (m, 4 H, ArH), 7.42–7.48 (m, 3 H, ArH), 7.70 (d, J = 7.8 Hz, 1 H, ArH), 10.20 (s, 1 H, NH) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3400 (NH) cm^{-1}. ESI-MS: m/z = 393.2/395.2 [M + 1]$^+$. $C_{22}H_{14}Cl_2N_2O$ (393.26): calcd. C 67.19, H 3.59, N 7.12; found C 73.64, H 4.21, N 7.81.

3-(4-Chlorophenyl)-4-(*p*-tolyl)-3,5-dihydroisoxazolo[4,3-*c*]quinoline (8a): This compound was isolated in 61% yield (0.35 g from 0.65 g) as a yellow solid, m.p. 260–262 °C. R_f (20% EtOAc/hexanes) = 0.26. IR (KBr): $\tilde{\nu}_{max}$ = 3352 (NH) cm^{-1}. ESI-MS: m/z = 373.2 [M + 1]$^+$. $C_{23}H_{17}ClN_2O$ (372.84): calcd. C 74.09, H 4.60, N 7.51; found C 74.24, H 4.31, N 7.81.

3-(4-Bromophenyl)-4-(*p*-tolyl)-3,5-dihydroisoxazolo[4,3-*c*]quinoline (8b): This compound was isolated in 16% yield (0.072 g from 0.50 g) as a yellow solid, m.p. 200–202 °C. R_f (20% EtOAc/hexanes) = 0.24. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 2.30 (s, 3 H, CH$_3$), 6.45 (s, 1 H, CH), 6.95 (d, J = 8.3 Hz, 2 H, ArH), 7.04 (t, J = 6.8 Hz, 1 H, ArH), 7.10 (d, J = 8.0 Hz, 2 H, ArH), 7.20–7.24 (m, 4 H, ArH), 7.29–7.34 (m, 2 H, ArH), 7.68 (d, J = 7.9 Hz, 1 H, ArH), 9.92 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 20.2, 80.8, 111.4, 114.9, 116.6, 120.1, 121.7, 123.0126.6, 128.0, 128.1, 129.3, 129.9, 130.1, 135.8, 138.3, 138.6, 139.7, 150.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3402 (NH) cm^{-1}. ESI-MS: m/z = 417.2/419.1 [M + 1]$^+$. $C_{23}H_{17}BrN_2O$ (417.29): calcd. C 66.20, H 4.11, N 6.71; found C 66.30, H 4.19, N 6.77.

3-(4-Bromophenyl)-4-phenylisoxazolo[4,3-*c*]quinoline 5-Oxide (9b): This compound was isolated in 48% yield (0.19 g from 0.42 g) as a yellow solid, m.p. 235–237 °C. R_f (20% EtOAc/hexanes) = 0.32. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 6.94 (dd, ^1J = 1.7, ^2J = 6.9 Hz, 2 H, ArH), 727–7.37 (m, 4 H, ArH), 7.41–7.49 (m, 3 H, ArH), 7.82 (dt, ^1J = 1.1, ^2J = 7.6 Hz, 1 H, ArH), 7.90 (dt, ^1J = 1.4, ^2J = 8.6 Hz, 1 H, ArH), 8.52 (dd, ^1J = 1.2, ^2J = 7.7 Hz, 1 H, ArH), 8.83 (d, J = 7.9 Hz, 1 H, ArH) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 107.8, 116.2, 120.6, 122.5, 123.9, 124.0, 127.3, 128.7, 128.9, 129.0, 130.1, 131.0, 135.9, 140.2, 150.6, 163.8 ppm. ESI-MS: m/z = 417.2/419.1 [M + 1]$^+$. $C_{22}H_{13}BrN_2O_2$ (417.25): calcd. C 63.33, H 3.14, N 6.71; found C 63.29, H 3.42, N 6.88.

3-(4-Bromophenyl)-4-(*p*-tolyl)isoxazolo[4,3-*c*]quinoline 5-Oxide (10b): This compound was isolated in 52% yield (0.24 g from 0.50 g) as a yellow solid, m.p. >250 °C. R_f (20% EtOAc/hexanes) = 0.32. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 2.38 (s, 3 H, CH$_3$), 6.94 (d, J = 8.5 Hz, 2 H, ArH), 7.13 (d, J = 8.1 Hz, 2 H, ArH), 7.29–7.36 (m, J = 7.3 Hz, 4 H, ArH), 7.80 (t, J = 7.6 Hz, 1 H, ArH), 7.88 (t, J = 8.5 Hz, 1 H, ArH), 8.51 (d, J = 7.8 Hz, 1 H, ArH), 8.81 (d, J = 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 21.2, 107.9, 116.2, 120.6, 122.5, 123.8, 124.1, 125.8, 126.2, 127.6, 127.9, 128.6, 128.8, 129.3, 129.9, 130.4, 130.7, 131.0, 136.3, 139.1, 140.2, 163.9 ppm. ESI-MS: m/z = 431.2/433.1 [M + 1]$^+$. $C_{23}H_{15}BrN_2O_2$ (431.28): calcd. C 64.05, H 3.51, N 6.50; found C 63.82, H 3.80, N 6.67.

Fe/AcOH-Mediated Reduction of 3a–e and 4a–b. General Procedure: Fe powder (7.39 mmol, 0.41 g) was added to a solution of appropriate isoxazoline **3a**–**e** or **4a**–**b** (1.23 mmol) in glacial acetic acid (10 mL), and the reaction mixture was heated at 110 °C for 30 min. Thereafter, the reaction mixture was concentrated to remove excess acetic acid, neutralized with saturated aqueous $NaHCO_3$ solution, and then filtered through a Celite bed. The residue was washed with ethyl acetate and the water layer was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined, washed with brine solution (50 mL), dried with Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was further purified by column chromatography on silica gel (60–120 mesh) with hexanes/EtOAc (90:10, v/v) as eluent to obtain the pure products.

(4-Amino-2-phenylquinolin-3-yl)(4-chlorophenyl)methanone (11a): This compound was isolated in 66% yield (0.29 g from 0.50 g) as a yellow solid, m.p. 249–250 °C. R_f (20% ethyl acetate/hexanes) = 0.57. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 6.45 (s, 2 H, NH$_2$), 7.07 (d, J = 8.5 Hz, 2 H, ArH), 7.16–7.21 (m, 3 H, ArH), 7.34 (d, J = 8.5 Hz, 2 H, ArH), 7.48–7.58 (m, 3 H, ArH), 7.80 (t, J = 7.3 Hz, 1 H, ArH), 7.90 (d, J = 8.3 Hz, 1 H, ArH), 8.13 (d, J = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 119.5, 124.3, 126.7, 126.9, 127.5, 128.3, 128.9, 129.2, 130.1, 136.8, 158.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1688 (C=O), 3424 (NH$_2$) cm^{-1}. ESI-MS: m/z = 359.3/361.3 [M + 1]$^+$. $C_{22}H_{15}ClN_2O$ (358.8): calcd. C 73.64, H 4.21, N 7.81; found C 73.47, H 4.10, N 7.77.

(4-Amino-2-phenylquinolin-3-yl)(4-bromophenyl)methanone (11b): This compound was isolated in 56% yield (0.20 g from 0.40 g) as a yellow solid, m.p. >250 °C. R_f (20% EtOAc/hexanes) = 0.57. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 6.46 (br. s, 2 H, NH$_2$), 7.16–7.20 (m, 3 H, ArH), 7.22–28 (m, 4 H, ArH), 7.48–7.51 (m, 2 H, ArH), 7.53–7.58 (m, 1 H, ArH), 7.77–7.83 (m, 1 H, ArH), 7.90 (d, J = 8.2 Hz, 1 H, ArH), 8.13 (d, J = 8.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 108.7, 116.3, 122.3, 124.1, 125.3, 127.0, 127.4, 128.4, 130.0, 130.1, 130.3, 137.5, 140.6, 146.9, 150.6, 157.4, 196.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1713 (CO), 3352 (NH$_2$) cm^{-1}. MS (ES+): m/z = 403.4/405.4 [M + 1]$^+$. $C_{22}H_{15}BrN_2O$ (403.27): calcd. C 65.52, H 3.75, N 6.95; found C 65.24, H 3.54, N 7.02.

(4-Amino-2-phenylquinolin-3-yl)(2,3-dichlorophenyl)methanone (11c): This compound was isolated in 65% yield (0.26 g from 0.45 g) as a pale yellow solid, m.p. 238–240 °C. R_f (20% EtOAc/hexanes) = 0.58. ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 6.81–6.89 (m, 2 H, ArH), 7.10–7.20 (m, 4 H, ArH), 7.34–7.37 (m, 2 H, ArH), 7.43 (brs, 2 H, NH$_2$), 7.53 (dt, ^1J = 1.0, ^2J = 8.1 Hz, 1 H, ArH), 7.79 (dt, ^1J = 1.0, ^2J = 8.1 Hz, 1 H, ArH), 7.93 (d, J = 8.3 Hz, 1 H, ArH), 8.07 (d, J = 8.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 108.6, 115.7, 119.7, 124.4, 125.1, 126.7, 127.1, 127.8, 128.9, 130.0, 130.7, 132.3, 140.6, 141.2, 146.5, 152.4, 160.5, 194.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1625 (CO), 3322 (NH$_2$) cm^{-1}. ESI-MS: m/z 393.3/395.2 [M + 1]$^+$. $C_{22}H_{14}Cl_2N_2O$ (393.26): calcd. C 67.19, H 3.59, N 7.12; found C 66.89, H 3.81, N 7.22.

(4-Amino-2-phenylquinolin-3-yl)(2,4-dichlorophenyl)methanone (11d): This compound was isolated in 59% yield (0.25 g from 0.48 g) as a yellow solid, m.p. 200–201 °C. R_f (20% EtOAc/hexanes) = 0.48. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 7.00 (d, J = 8.2 Hz, 1 H, ArH), 7.10 (d, J = 8.2 Hz, 1 H, ArH), 7.18–7.26 (m, 6 H, ArH), 7.55 (t, J = 7.2 Hz, 1 H, ArH), 7.76–7.88 (m, 2 H, ArH), 8.36 (s, 2 H, NH$_2$), 8.49 (d, J = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 108.1, 116.5, 122.5, 124.3, 125.7, 126.8, 127.2, 128.1, 128.4, 130.9, 131.0, 1345.1, 138.2, 141.3, 146.6, 153.1, 159.8, 193.8 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1628 (CO) cm^{-1}. ESI-MS: m/z = 393.2/395.1 [M + 1]$^+$. $C_{22}H_{14}Cl_2N_2O$ (393.26): calcd. C 67.19, H 3.59, N 7.12; found C 67.31, H 3.51, N 7.32.

(4-Amino-2-phenylquinolin-3-yl)(3,4-dichlorophenyl)methanone (11e): This compound was isolated in 62% yield (0.30 g from 0.54 g) as a pale yellow solid, m.p. 160–162 °C. R_f (20% EtOAc/hexanes) = 0.59. IR (KBr): $\tilde{\nu}_{max}$ = 1628 (CO), 3428 (NH$_2$) cm^{-1}. ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 6.63 (s, 1 H, NH), 7.11–7.19 (m, 5 H, ArH), 7.39–7.53 (m, 4 H, ArH), 7.71–7.93 (m, 2 H, ArH), 8.10 (d, J = 12.5 Hz, 1 H, ArH) ppm. ^{13}C NMR ([D$_6$]Py, 75 MHz): δ = 110.8, 119.3, 124.7, 126.5, 129.2, 129.7, 130.0, 130.4, 131.1, 131.3, 132.3, 132.5, 142.0, 143.8, 154.7, 160.8, 197.3 ppm. ESI-MS: m/z = 393.4/395.3 [M + 1]$^+$. $C_{22}H_{14}Cl_2N_2O$ (393.26): calcd. C 67.19, H 3.59, N 7.12; found C 67.44, H 3.81, N 7.29.

(4-Amino-2-*p*-tolylquinolin-3-yl)(4-chlorophenyl)methanone (12a): This compound was isolated in 61% yield (0.28 g from 0.52 g) as a yellow solid, m.p. 240–242 °C. R_f (20% EtOAc/hexanes) = 0.45. ^{1}H NMR (CD_3OD, 200 MHz): δ = 2.13 (s, 3 H, CH_3), 6.91 (d, J = 7.8 Hz, 2 H, ArH), 7.01–7.05 (m, 2 H, ArH), 7.16–7.26 (m, 4 H, ArH), 7.44–7.48 (m, 1 H, ArH), 7.68–7.71 (m, 1 H, ArH), 7.85 (d, J = 8.4 Hz, 1 H, ArH), 8.16 (d, J = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR ([D$_5$]Py, 75 MHz): δ = 21.8, 111.6, 119.2, 124.8, 126.2, 129.4, 129.9, 131.1, 131.2, 132.2, 136.7, 139.0, 139.5, 139.9, 153.9, 160.3, 198.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1685 (CO), 3424 (NH_2) cm^{-1}. ESI-MS: m/z = 373.3/375.3 [M + 1]$^+$. $C_{23}H_{17}ClN_2O$ (372.84): calcd. C 74.09, H 4.60, N 7.51; found C 73.93, H 4.76, N 7.65.

(4-Amino-2-*p*-tolylquinolin-3-yl)(4-bromophenyl)methanone (12b): This compound was isolated in 61% yield (0.30 g from 0.55 g) as a yellow solid, m.p. 210–212 °C. R_f (20% EtOAc/hexanes) = 0.52. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.23 (s, 3 H, CH_3), 6.44 (s, 2 H, NH_2), 6.97 (d, J = 7.9 Hz, 2 H, ArH), 7.22–7.29 (m, 5 H, ArH), 7.38 (d, J = 8.0 Hz, 2 H, ArH), 7.48–7.53 (m, 1 H, ArH), 7.74–7.79 (m, 1 H, ArH), 7.87 (d, J = 8.3 Hz, 1 H, ArH), 8.11 (d, J = 8.3 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.9, 98.7, 108.9, 115.6, 119.5, 124.1, 125.5, 127.6, 128.3, 128.9, 129.3, 129.7, 130.0, 137.4, 137.5, 146.9, 150.2, 158.5, 196.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1691 (CO), 3428 (NH_2) cm^{-1}. ESI-MS: m/z = 317.4/319.3 [M + 1]$^+$. $C_{23}H_{17}BrN_2O$ (417.29): calcd. C 66.20, H 4.11, N 6.71; found C 65.98, H 4.31, N 6.66.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H NMR, ^{13}C NMR and mass spectra of representative compounds; copies of HSQC and HMBC spectra for compounds **5a** and **7a**.

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[25] Quinoline synthesis by reduction of a 2-nitrophenyl group with $SnCl_2{\cdot}2H_2O$, followed by intramolecular cyclization with a keto group: a) O. B. Familoni, P. J. Klaas, K. A. Lobb, V. E. Pakade, P. T. Kaye, *Org. Biomol. Chem.* **2006**, *4*, 3960–3965; b) S. Madapa, V. Singh, S. Batra, *Tetrahedron* **2006**, *62*, 8740–8747 and references cited therein.
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[28] Crystal data for **3a** ($CHCl_3$/EtOH): $C_{22}H_{15}ClN_2O_4$, M = 406.81, triclinic, $P\bar{1}$, a = 8.421(1), b = 10.709(1), c = 12.077(2) Å, α = 103.33(1), β = 101.24(1), γ = 110.090(1)°, V = 949.5(2) Å^3, Z = 2 $D_{calcd.}$ = 1.423 g cm^{-3}, μ (Mo-K_α) = 0.23 mm^{-1}, F^2(000) = 420, colorless block, dimensions 0.25 × 0.20 × 0.15 mm, 4008 reflections measured (R_{int} = 0.0205), 3267 unique, wR_2 = 0.111, conventional R = 0.0418 on F^2 values of 2129 reflections with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max}$ = 000, S = 1.022 for all data and 263 parameters. Structure solutions by direct methods and refinements by full-matrix, least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument Inc., Madison, WI, USA, **1996**) for data collection and data processing; SHELXTL-NT (Bruker AXS Inc., Madison, Wisconsin, USA, **1997**) for structure determination, refinements and molecular graphics. CCDC-644536 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; for queries relating to X-ray data, please contact maulik_prakas@yahoo.com).
[29] Crystal data for compound **5c** (EtOAc/hexane): $C_{22}H_{12}Cl_2N_2O$, M = 391.24, monoclinic, $P2_1/c$, a = 16.207(2), b = 6.834(1), c = 17.281(2) Å, β = 107.57(1)°, V = 1824.7(4) Å^3, Z = 4, $D_{calcd.}$ = 1.424 g cm^{-3}, μ (Mo-K_α) = 0.37 mm^{-1}, F^2(000) = 800, colorless block, dimensions 0.3 × 0.25 × 0.2 mm, 4539 reflections measured (R_{int} = 0.0496), 3200 unique, wR_2 = 0.1542, conventional R = 0.0626 on F values of 1543 reflections with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max}$ = 000), S = 0.988 for all data and 244 parameters. CCDC-644537 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[30] Crystal data for compound **7d** ([D$_6$]DMSO containing TMS): $C_{22}H_{14}Cl_2N_2O{\cdot}[(CH_3)_3Si]_2$, M = 466.44, triclinic, $P\bar{1}$, a = 8.774(1), b = 11.963(1), c = 12.624(1) Å, α = 63.01, β = 76.76(1), γ = 72.69(1)°, V = 1120.36(2) Å^3, Z = 2 $D_{calcd.}$ = 1.383 g cm^{-3}, μ (Mo-K_α) = 0.36 mm^{-1}, F^2(000) = 486, colorless block, dimensions 0.275 × 0.25 × 0.15 mm, 4637 reflections measured (R_{int} = 0.018), 3814 unique, wR_2 = 0.1734, conven-

tional R = 0.0605 on F^2 values of 2995 reflections with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max}$ = 000, S = 1.022 for all data and 288 parameters. CCDC-644538 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[31] Crystal data for compound **11b** ($CHCl_3$/EtOH): $C_{22}H_{15}BrN_2O$, M = 403.27, orthorhombic, *Aba*2, a = 12.616(2), b = 24.779(3), c = 11.587(1) Å, V = 3622.2(8) Å^3, Z = 8 $D_{calcd.}$ = 1.479 g cm^{-3}, μ (Mo-K_α) = 2.28 mm^{-1}, $F^2(000)$ = 1640, colorless block, dimensions 0.3 × 0.25 × 0.2 mm, 2096 reflections measured (R_{int} = 0.0238), 1822 unique, wR_2 = 0.0807, conventional R = 0.0476 on F^2 values of 1269 reflections with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max}$ = 000, S = 1.002 for all data and 235 parameters. CCDC-644535 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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