Copper-catalyzed cross-dehydrogenative coupling between quinazoline-3-oxides and indoles†

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A novel and simple protocol for the synthesis of 4-(indole-3-yl)quinazolines via cross-dehydrogenative coupling of quinazoline-3-oxides and indoles under an air atmosphere has been developed. A series of biheteroaryl products were obtained in moderate to good yields.

Introduction

The nitrogen-containing heterocycles occupy an important position in pharmaceuticals and natural products. Furthermore, they exhibit remarkable biological activities, such as anticancer, antileukemic, antiviral, and antifungal properties. The complexity and diversity of N-heterocycles have been employed broadly in the studies of advanced materials and ligands for transition metal catalysis. Among reported studies, quinazoline and indole derivatives are useful nitrogen-containing heterocyclic compounds, and are core structural motifs of many natural products and pharmaceuticals. Thus, heterocyclic compounds bearing these two skeletons most likely possess interesting biological and physicochemical properties. For example, indoloquinazoline derivatives have been reported to be protein kinase CK2 inhibitors and poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors. 4-(Indole-3-yl)quinazolines have been reported to be potent epidermal growth factor receptor tyrosine kinase inhibitors.

Over the past decade, substantial effort has been devoted to the development of reaction conditions for the coupling between quinazoline and indole compounds. One elegant methodology relies on the nucleophilic substitution of quinazoline chlorides or their analogous with indoles. However, this method cannot be widely employed due to the need for harsh reaction conditions and/or operationally complex protocols. For instance, the substitution reaction between 2,4-dichloroquinazolines and indoles relies on 1.2 equiv. of AlCl3 (Scheme 1a). Additionally, the reaction of quinazoline with indole required Brønsted acid mediator, followed by photocatalyzed aromatization to give the corresponding 4-(indol-3-yl)quinazoline product in 70% yield (Scheme 1b).

On the other hand, we have noticed that cross-dehydrogenative-coupling (CDC) reactions have emerged as an excellent alternative for the formation of C-C bonds. Furthermore, the N-oxide moiety in aza-heteroarenes has been recognized as a powerful and removable directing group for ortho C-H bond activation. In the past decade, pyridine N-oxides, pyrimidine N-oxides, quinoline N-oxides and isoquinoline N-oxides have been extensively employed as useful building block for the preparation of a diverse range of N-heterocycles. However, the C4–H functionalization of quinazoline N-oxides remains rare. Therefore, the development of a general and practical strategy for the synthesis of 4-(indole-3-yl)quinazolines via CDC reactions of quinazoline N-oxides and indoles under mild conditions, is highly desired. Recently, our group has directed its studies to that of the structural elaboration of quinazoline core, with the aim of constructing a quinazoline-based molecular library for bioactivity assays. Herein, we report a copper-catalyzed CDC reaction between the Csp2–H of quinazoline-3-oxide and the Csp2–H of various indoles for the synthesis of biheteroaryl structures using a mild and operationally simple procedure (Scheme 1c).

Scheme 1 Typical strategies for the synthesis of 4-(indole-3-yl)quinazolines.

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Results and discussion

We initiated our investigation on the model reaction of quinazoline-3-oxide (1a) with N-methyl-indole (2a) in order to optimize the reaction parameters (Table 1). First, the reaction was performed in the presence of 20 mol% CuCl₂ at 60 °C in toluene (Entry 1). To our delight, the desired product 3a was isolated in a moderate yield of 47%. Encouraged by this preliminary result, we then screened various solvents. The desired product was obtained in moderate or low yields when the reaction was carried out in THF, CH₃CN and DMF (Entries 2–4). Further studies showed that CH₃OH was the best solvent for this transformation, affording the desired product 3a in 77% yield (Entry 7). Incrementally reducing the catalyst loading from 20 to 5 mol%, showed that 10 mol% catalyst was the optimal amount (Entries 7–9). No transformation took place in the absence of metal catalyst in CH₃OH (Entry 10). Next, further screening of other metal salts was conducted, but no better conditions were discovered (Entries 11–15). Several copper salts were utilized to promote the reaction (Entries 16–20); however, it was found that copper(II) chloride was the most effective. No better result was obtained even at a higher or lower reaction temperature (Entries 21 and 22).

Under the optimized reaction conditions, the reaction scope was explored, and the results of which are shown in Table 2. The CDC reaction of quinazoline-3-oxides 1 and N-methylindole 2a occurred smoothly to generate the desired products 3 in good yields. When R² was an aryl group, both electron-donating and electron-withdrawing substituents on the aryl ring had a slight effect on the reaction (3aa–3ka), albeit strongly electron-withdrawing substituents, such as the nitro group, greatly retarded the reaction, forming 3ja in 61% yield. It was observed that an R² aliphatic substituent was also tolerated to give the corresponding product 3ma in 72% yield. When the parent quinazoline ring (R² = H) was used, the desired product 3ma was obtained in 68% yield. Subsequently, R² substituents on the phenyl ring moiety of the quinazoline 3-oxide were investigated. Methyl, methoxy, trifluoromethyl, chloro and bromo functionalities were all tolerated, providing the desired products 3na–3ra in 52–84% yields.

Subsequently, the indole scope was examined under the optimized reaction conditions. As shown in Table 3, quinazoline-3-oxide underwent smooth coupling with a variety

| Entry | Solvent | Catalyst | T°C | Yield/% |
|-------|---------|----------|-----|---------|
| 1     | Toluene | CuCl₂ (20 mol%) | 60  | 47      |
| 2     | THF     | CuCl₂ (20 mol%) | 60  | 57      |
| 3     | CH₃CN   | CuCl₂ (20 mol%) | 60  | 40      |
| 4     | DMF     | CuCl₂ (20 mol%) | 60  | 32      |
| 5     | PhCl    | CuCl₂ (20 mol%) | 60  | 70      |
| 6     | DCE     | CuCl₂ (20 mol%) | 60  | 75      |
| 7     | CH₃OH   | CuCl₂ (20 mol%) | 60  | 77      |
| 8     | CH₃OH   | CuCl₂ (10 mol%) | 60  | 78      |
| 9     | CH₃OH   | CuCl₂ (5 mol%) | 60  | 67      |
| 10    | CH₃OH   | —         | 60  | ND      |
| 11    | CH₃OH   | In(OTf)₃ (10 mol%) | 60  | Trace  |
| 12    | CH₃OH   | FeCl₂ (10 mol%) | 60  | 37      |
| 13    | CH₃OH   | FeCl₃ (10 mol%) | 60  | 40      |
| 14    | CH₃OH   | CoCl₂ (10 mol%) | 60  | 20      |
| 15    | CH₃OH   | Ni(OTf)₂ (10 mol%) | 60  | 17      |
| 16    | CH₃OH   | CuCl₂ (10 mol%) | 60  | 73      |
| 17    | CH₃OH   | Cu(acac)₂ (10 mol%) | 60  | Trace  |
| 18    | CH₃OH   | CuCl (10 mol%) | 60  | 62      |
| 19    | CH₃OH   | CuBr (10 mol%) | 60  | 73      |
| 20    | CH₃OH   | Cu(OAc)₂ (10 mol%) | 60  | 40      |
| 21    | CH₃OH   | CuCl₂ (10 mol%) | 80  | 53      |
| 22    | CH₃OH   | CuCl₂ (10 mol%) | 40  | 50      |

*a* Optimized conditions are denoted in bold. *b* Reaction conditions: 1a (0.2 mmol), 2a (0.3 mmol), catalyst, solvent (2.0 mL), 16 h, under air. *c* Isolated yield.
of substituted indoles. N-Methylindoles possessing alkyl, halide, and alkoxy substituents at the 5-position are amenable to the reaction conditions (3ab–3af), and the expected products were isolated in moderate to good yields. The coupled products were isolated in high yields for N-iPr and N-Bn substrates (3ag and 3ah). To our surprise, indole itself also proved to be a good coupling partner, providing the corresponding product (3ai) in 83% yield. Single-crystal X-ray analysis of 3ai confirmed its structure and demonstrated the high regioselectivity of the reaction (Fig. 1). In contrast, no desired coupling product was observed for 3-methylindole, which is consistent with selectivity for the C–H activation at the 3-position of the indole (this result is not shown in Table 3). When a CH₃ group is present at the 2-position of the indole, the steric hindrance arising from this substituent influences the reaction; the cross-coupling product 3aj was obtained in lower yield. However, indoles containing electron-withdrawing N-protecting groups, for example, N-tosylindole, were not amenable to this transformation, and none of the desired product (3ak) was isolated.

The coupled quinazoline-3-oxides products were easily deoxygenated to give the corresponding 4-(indole-3-yl) quinazolines. For example, when 3aa was treated with PCl₃ (rt, 30 min), clean reduction occurred and 4a was obtained in 86% yield (Scheme 2). The combination of the described C–H/C–H cross-dehydrogenative-coupling and subsequent reduction provides an attractive and simple procedure for the synthesis of indole-functionalized quinazoline derivatives.

In order to further understand the mechanism of this copper-catalyzed reaction of quinazoline-3-oxide 1 with indole 2, three control experiments were conducted (Scheme 3). The desired product was obtained in 84% yield when the reaction was conducted under oxygen atmosphere (Scheme 3a). However, only a trace amount of product 3aa was obtained when the reaction was carried out under argon, which indicates that oxygen plays a crucial role in this transformation (Scheme 3b). When 1a was replaced by 2-(p-tolyl)quinazoline, the desired product was not obtained (Scheme 3c).

On the basis of these observations and related reports, we have proposed a plausible mechanism for this reaction, as shown in Scheme 4. The CuCl₂ reacts with quinazoline-3-oxide 1a to form intermediate A via C–H activation of 1a. Next, A undergoes an insertion into the 3-position of the C–H bond of 2a to afford B. Oxidation of B to Cu(III) complex C occurs via disproportionation with a second equivalent of CuCl₂, liberating CuCl. C undergoes reductive elimination to give the product 3aa together with Cu(i), which is reoxidized to CuCl₂ by O₂ and HCl, to complete the cycle.

In conclusion, a novel, simple and efficient protocol for the synthesis of 4-(indole-3-yl)quinazolines via a cross-dehydrogenative coupling of quinazoline-3-oxides and indoles under an air atmosphere has been successfully developed. A series of biheteroaryl products were obtained in moderate to good yields. The unique reactivity and selectivity observed in the CDC reaction prompted us to initiate further studies on the reaction mechanism.

### Experimental section

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 mm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica.

| Table 3 | The reaction of quinazoline-3-oxide 1a with various indoles 2 afford a cross-dehydrogenative coupling of quinazoline-3-oxides and indoles under an air atmosphere has been successfully developed. A series of biheteroaryl products were obtained in moderate to good yields. The unique reactivity and selectivity observed in the CDC reaction prompted us to initiate further studies on the reaction mechanism. |

### Reaction conditions:
- 1a (0.2 mmol), 2a (0.3 mmol), CuCl₂ (10 mol%), CH₃OH (2.0 mL), 60 °C, under air.
- *Isolated yield.*

### Scheme 2 Deoxygenation reaction.
Control experiments.

Plausible mechanism.

General experimental procedure for synthesis of 3

The quinazoline-3-oxide (0.2 mmol), indole (0.3 mmol), CuCl2 (0.02 mmol) and 2.0 mL CH3OH were mixed in a dry reaction tube. The mixture was stirred at 60 °C under air for 12–16 hours. After completion of the reaction (monitored by TLC), the mixture was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether–ethyl acetate as eluent to give the desired product.

4-(1-Methyl-1H-indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3aa). Compound was obtained as a yellow solid: yield 78%; 1H NMR (400 MHz, CDCl3) δ 8.30 (s, 1H), 8.22 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.69 (td, J = 7.6, 1.2 Hz, 1H), 7.52–7.40 (m, 3H), 7.36–7.27 (m, 3H), 7.19 (t, J = 7.6 Hz, 1H), 3.94 (s, 3H), 2.43 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 155.7, 147.1, 141.2, 140.7, 136.7, 135.5, 130.6, 130.5, 130.3, 128.7, 128.6, 128.0, 127.6, 126.5, 123.1, 122.5, 121.7, 110.0, 102.6, 33.6, 21.6. HRMS (ESI): m/z [M + H]+ calcd for C24H25N3O: 366.1606, found 366.1609.

4-(1-Methyl-1H-indol-3-yl)-2-(m-tolyl)quinazoline 3-oxide (3ba). Compound was obtained as a yellow solid: yield 87%; 1H NMR (400 MHz, CDCl3) δ 8.32 (s, 1H), 8.12–7.85 (m, 3H), 7.95 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.54–7.36 (m, 4H), 7.35–7.28 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H), 3.95 (s, 3H), 2.43 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 156.0, 147.1, 141.2, 137.5, 136.7, 135.6, 133.4, 131.2, 130.65, 130.61, 128.8, 128.1, 127.9, 127.6, 127.4, 126.6, 123.2, 122.5, 121.6, 121.0, 110.0, 102.5, 33.6, 21.5. HRMS (ESI): m/z [M + H]+ calcd for C24H23N3O: 366.1606, found 366.1607.

4-(1-Methyl-1H-indol-3-yl)-2-(o-tolyl)quinazoline 3-oxide (3ca). Compound was obtained as a yellow solid: yield 71%; 1H NMR (400 MHz, CDCl3) δ 8.43 (s, 1H), 8.11–8.02 (m, 2H), 7.74 (td, J = 7.2, 1.2 Hz, 1H), 7.59–7.33 (m, 2H), 7.51–7.43 (m, 2H), 7.43–7.37 (m, 1H), 7.37–7.30 (m, 3H), 7.20 (t, J = 7.6 Hz, 1H), 3.92 (s, 3H), 2.35 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 157.8, 146.7, 146.9, 137.1, 136.8, 136.3, 134.1, 130.7, 130.2, 129.6, 128.8, 128.8, 128.3, 127.6, 126.7, 125.8, 123.2, 122.6, 121.7, 112.1, 110.1, 102.4, 33.6, 19.7. HRMS (ESI): m/z [M + H]+ calcd for C24H23N3O: 382.1555, found 382.1555.

2-(4-Methoxyphenyl)-4-(1-methyl-1H-indol-3-yl)quinazoline 3-oxide (3da). Compound was obtained as a yellow solid: yield 87%; 1H NMR (400 MHz, CDCl3) δ 8.49–8.37 (m, 2H), 8.28 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.70 (td, J = 7.4, 1.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.05–6.98 (m, 2H), 3.96 (s, 3H), 3.89 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 161.5, 155.1, 147.2, 141.3, 136.7, 135.3, 132.4, 130.6, 128.6, 127.8, 126.7, 125.7, 123.0, 122.5, 121.7, 120.9, 113.3, 110.0, 102.7, 55.4, 33.6. HRMS (ESI): m/z [M + H]+ calcd for C24H23N3O: 382.1555, found 382.1555.

2-(4-Fluorophenyl)-4-(1-methyl-1H-indol-3-yl)quinazoline 3-oxide (3ea). Compound was obtained as a yellow solid: yield 83%; 1H NMR (400 MHz, CDCl3) δ 8.45–8.35 (m, 2H), 8.30 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.49–7.41 (m, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.23–7.14 (m, 3H), 3.97 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 164.2 (d, J = 249.2 Hz), 154.5, 141.2, 136.8, 135.3, 132.8, 128.0, 129.4 (d, J = 3.3 Hz), 128.7, 128.2, 127.5, 126.6, 123.2, 122.6, 121.6, 112.1, 114.9 (d, J = 21.6 Hz), 110.1, 102.5, 33.6. HRMS (ESI): m/z [M + H]+ calcd for C25H17F2N3O: 370.1356, found 370.1381.

2-(4-Chlorophenyl)-4-(1-methyl-1H-indol-3-yl)quinazoline 3-oxide (3fa). Compound was obtained as a yellow solid: yield 82%; 1H NMR (400 MHz, CDCl3) δ 8.33 (d, J = 8.4 Hz, 2H), 8.28 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.55–7.41 (m, 5H), 7.34 (t, J = 7.4 Hz, 1H), 7.19 (t, J
(3) Compound was obtained as a yellow solid: yield 72%; `H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.51–7.41 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 3.94 (s, 3H), 3.34 (q, J = 7.2 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H). `C NMR (101 MHz, CDCl₃) δ 161.3, 145.8, 140.7, 136.7, 135.1, 130.4, 128.2, 127.5, 126.5, 122.8, 121.6, 120.1, 119.0, 107.1. HRMS (ESI): m/z [M + H⁺] calcd for C₂₅H₂₀N₂O: 352.1450, found 352.1437.

2-(4-Methyl-1H-indol-3-yl)-quinazoline 3-oxide (3b). Compound was obtained as a yellow solid: yield 78%; `H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 8.14–7.89 (m, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 3.94 (s, 3H). `C NMR (101 MHz, CDCl₃) δ 148.6, 141.5, 136.8, 135.4, 130.8, 128.7, 127.2, 126.8, 123.2, 122.7, 121.5, 121.1, 110.1, 101.7. HRMS (ESI): m/z [M + H⁺] calcd for C₁₉H₁₄N₂O: 276.1137, found 276.1132.

7-Methyl-4-(1-methyl-1H-indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3c). Compound was obtained as a yellow solid: yield 71%; `H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 8.22 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.45 (dd, J = 8.6, 1.8 Hz, 2H), 7.35–7.27 (m, 4H), 7.18 (t, J = 7.6 Hz, 1H), 3.95 (s, 3H), 2.56 (s, 3H), 2.43 (s, 3H). `C NMR (101 MHz, CDCl₃) δ 155.6, 146.7, 141.6, 141.5, 140.6, 136.7, 135.5, 130.6, 130.3, 130.1, 128.5, 127.9, 127.6, 123.3, 123.4, 123.1, 121.6, 121.1, 110.1, 102.3, 33.6. HRMS (ESI): m/z [M + H⁺] calcd for C₂₅H₂₁N₂O: 380.1763, found 380.1767.

6-Methoxy-4-(1-methyl-1H-indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3d). Compound was obtained as a yellow solid: yield 52%; `H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 8.18 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 9.2 Hz, 1H), 7.50–7.43 (m, 2H), 7.37–7.27 (m, 4H), 7.22–7.16 (m, 2H), 3.96 (s, 3H), 3.67 (s, 3H), 2.43 (s, 3H). `C NMR (101 MHz, CDCl₃) δ 158.9, 153.6, 146.0, 140.3, 137.3, 136.7, 135.5, 130.6, 130.1, 128.6, 127.2, 124.1, 122.4, 121.8, 120.6, 110.4, 106.2, 55.7, 33.6, 21.6. HRMS (ESI): m/z [M + H⁺] calcd for C₂₅H₂₄N₂O: 396.1712, found 396.1737.

2-(4-Methyl-1H-indol-3-yl)-2-(p-tolyl)-7-(trifluoromethyl)quinazoline 3-oxide (3a). Compound was obtained as a yellow solid: yield 76%; `H NMR (400 MHz, CDCl₃) δ 8.37–8.32 (m, 2H), 8.26 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 9.2 Hz, 1H), 7.50–7.43 (m, 2H), 7.37–7.27 (m, 4H), 7.22–7.16 (m, 2H), 3.96 (s, 3H), 3.67 (s, 3H), 2.43 (s, 3H). `C NMR (101 MHz, CDCl₃) δ 157.0, 147.0, 141.5, 140.2, 136.9, 136.0, 132.1 (q, J = 32.9 Hz), 130.5, 129.9, 128.8, 127.7, 127.4, 126.5 (q, J = 4.2 Hz), 124.6, 123.7 (q, J = 270.9 Hz), 123.6 (q, J = 3.0 Hz), 122.9, 121.45, 121.40, 110.3, 102.2, 33.7, 21.7. HRMS (ESI): m/z [M + H⁺] calcd for C₂₅H₁₉F₃N₂O: 434.1480, found 434.1478.
3H). 13C NMR (101 MHz, CDCl3) δ 155.9, 146.3, 141.1, 139.4, 136.8, 135.3, 134.0, 131.2, 130.3, 130.1, 130.3, 130.1, 128.6, 127.2, 125.0, 124.0, 122.7, 121.4, 121.3, 110.1, 102.3, 33.6, 21.6. HRMS (ESI†): m/z [M + H]+ cale for C30H24N3O: 400.1217, found 400.1219, and 402.1188.

4-(5-Bromo-1-methyl-1H-indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3af). Compound was obtained as a yellow solid: yield 87%; 1H NMR (400 MHz, CDCl3) δ 8.22 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0, 1H), 7.71 (t, J = 6.8 Hz, 1H), 7.57 (s, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 3H), 3.92 (s, 3H), 2.43 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 155.6, 146.5, 141.2, 140.9, 136.2, 130.8, 130.3, 128.9, 128.6, 128.5, 128.3, 127.0, 126.0, 123.1, 123.0, 111.0, 102.4, 33.7, 21.6. HRMS (ESI†): m/z [M + H]+ cale for C32H24BrN4O: 444.0711, found 444.0701, and 446.0691, found 446.0687.

4-(1-Isopropyl-1H-indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3ag). Compound was obtained as a yellow solid: yield 88%; 1H NMR (400 MHz, CDCl3) δ 8.46 (s, 1H), 8.19 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.56–7.44 (m, 3H), 7.36–7.28 (m, 3H), 7.18 (t, J = 7.4 Hz, 1H), 4.90–4.75 (m, 1H), 2.44 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 155.9, 147.5, 144.1, 144.0, 135.7, 131.0, 130.55, 130.2, 128.7, 127.9, 127.8, 126.7, 123.2, 122.1, 121.9, 120.9, 101.2, 34.2, 20.1, 18.6. HRMS (ESI†): m/z [M + H]+ cale for C23H23N3O4: 394.1919, found 394.1919.

4-(1-Benzyl-1H-indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3ah). Compound was obtained as a yellow solid: yield 82%; 1H NMR (400 MHz, CDCl3) δ 8.33 (s, 1H), 8.22 (d, J = 7.6 Hz, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 8.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.37–7.21 (m, 7H), 7.17 (t, J = 7.4 Hz, 1H), 5.45 (s, 2H), 2.42 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 155.8, 147.0, 141.1, 140.7, 136.3, 134.8, 130.53, 130.47, 130.3, 129.0, 128.8, 128.6, 128.1, 128.0, 127.2, 126.4, 123.2, 122.6, 121.9, 121.1, 110.6, 103.4, 51.0, 21.6. HRMS (ESI†): m/z [M + H]+ cale for C30H23N3O: 423.1693, found 424.1935.

4-(1H-Indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3ai). Compound was obtained as a yellow solid: yield 83%; 1H NMR (400 MHz, CDCl3) δ 10.24 (s, 1H), 8.28 (d, J = 7.2 Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.57–7.39 (m, 3H), 7.33 (d, J = 7.6 Hz, 2H), 7.08 (s, 3H), 2.44 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 155.5, 148.5, 141.5, 140.9, 136.1, 131.1, 131.0, 130.5, 130.4, 128.7, 128.6, 128.3, 126.6, 126.3, 123.5, 122.4, 121.4, 120.8, 112.3, 103.5, 21.6. HRMS (ESI†): m/z [M + H]+ cale for C26H14N4O: 352.1450, found 352.1447.

4-(2-Methyl-1H-indol-3-yl)-2-(p-tolyl)quinazoline 3-oxide (3aj). Compound was obtained as a yellow solid: yield 58%; 1H NMR (400 MHz, CDCl3) δ 9.55 (s, 1H), 8.31 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.7 Hz, 1H), 7.05 (s, 3H), 2.43 (s, 3H), 2.04 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 155.7, 149.4, 141.03, 140.99, 139.7,
Conflicts of interest
There are no conflicts to declare.

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