Double Anion Capture Reactions of Anthranilic Esters with Oxaldiimidoyl Dichlorides − Efficient Synthesis of 2,2′-Biquinazoline-4,4′(3*H*,3′*H*)-diones

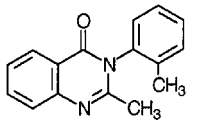
Peter Langer,*[a] Jörg Wuckelt,[b] Manfred Döring,*[b] and Helmar Görls[b]

Keywords: Alkaloids / Cyclization reactions / *N*-Heterocycles / Oxalic acid / Regioselectivity

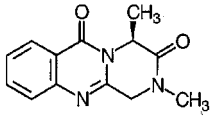
The reaction of anthranilic acids with oxaldiimidoyl dichlorides offers a new and convenient synthesis of quinazolin-4-ones. Condensation of anthranilic esters with diimidoyl dichlorides affords 2,2′-biquinazoline-4,4′(3*H*,3′*H*)-diones, which constitute a new class of dimeric heterocyclic compounds. In contrast, condensation of the dianion of *N*-methyl *ortho*-tolylamide with di(imidoyl) dichlorides affords seven- rather than six-membered ring products. Starting with 2-aminopyridine, 2,3-diimino-2,3-dihydroimidazo[1,2-*a*]pyridines could be efficiently prepared.

Introduction

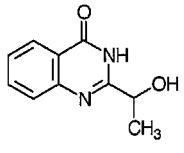
A variety of structurally relatively simple quinazolin-4-ones, such as the synthetic revonale or the alkaloid febrifugine, are of biological relevance due to their analgesic, narcotic, antimalarial, sedative, or hypoglycemic properties. The quinazolin-4-one system is also a fragment of a variety of natural products. The biologically relevant mold metabolite chrysogine was isolated from strains of *Penicillium chrysogenum* and *Alternaria citri*.[1] The highly toxic, tremor-inducing metabolite tryptoquivalone and other quinazolin-4-ones have been isolated from the fungus *Aspergillus clavatus* collected from mold-damaged rice.[2a,2b,3] Other quinazolin-4-one-derived natural products include the fungal metabolite *N*-acetyl ardeemin,[4] a potent reversal agent of multiple drug resistance in tumor cell lines, as well as the related glyantrypine,[5a] fumiquinazolines F and G,[5b,5c] fiscalin B,[5d] and auranthine.[5b] Quinazolin-4-ones have previously been prepared by means of multistep procedures, either by reaction of benzoxazin-4-one carboxylic esters with amines[6a] or by other methods.[6b−6d]



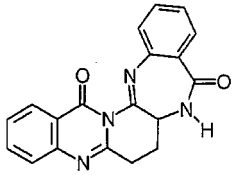
revonale



N-acetylardeemin analogue



chrysogine



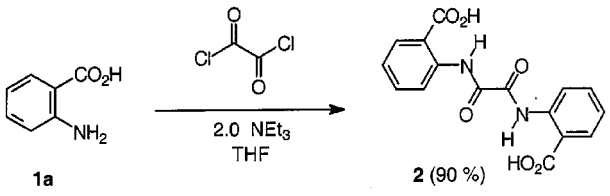
auranthine

[a] Institut für Organische Chemie der Georg-August-Universität Göttingen,
Tammannstraße 2, 37077 Göttingen, Germany
[b] Institut für Anorganische und Analytische Chemie der Universität Jena,
August-Bebel-Straße 2, 07743 Jena, Germany

In the course of our program directed towards the development of new cyclization reactions[7] of oxalic acid dielectrophiles, we have recently reported[8] a new and convenient one-pot synthesis of functionalized quinazolin-4-ones by regioselective cyclization of anthranilic acid derivatives **1** with oxaldiimidoyl dichlorides.[9] Herein, we wish to report full details of our new synthesis of quinazolin-4-ones and 2,2′-biquinazoline-4,4′(3*H*,3′*H*)-diones. Cyclization reactions of oxaldiimidoyl dichlorides with the dianion of *N*-methyl *ortho*-tolylamide and 2-aminopyridine are also reported. To assess the ambidentate character of the prepared quinazolin-4-ones, their deprotonation and coordination to transition metals has been studied.

Results and Discussion

Reaction of anthranilic acid **1a** with oxalyl dichloride afforded the open-chain product **2** by simple aminolysis (Scheme 1).[10] Our initial attempts to induce a cyclization in the reaction of anthranilic acids **1a−c** with oxaldiimidoyl dichlorides **3a−d** were unsuccessful. However, after some experimentation, it was found that extension of the reaction times (stirring for ca. 3 d at 60 °C) and the use of toluene rather than THF as the solvent were mandatory to obtain clean products. To our surprise, the colourless quinazolin-4-ones **4** rather than the isomeric seven-membered ring products were isolated in moderate to good yields (Scheme 2, Table 1). The constitution of **4b** was independently confirmed by X-ray structure analysis (Figure 1). This



Scheme 1

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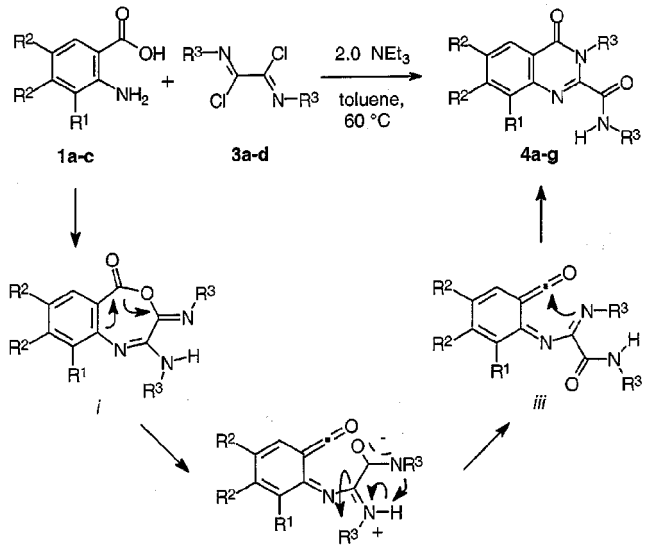
showed the quinazolin-4-one moiety to be planar. The tolyl group at N1 is twisted out-of-plane by almost 90° as a result of steric factors. The N3−C16 bond length is similar to the C−N distance in substituted ureas.[11] The hydrogen atom is located at the amide nitrogen N3. An intramolecular hydrogen bond N−HN is present (N−H distance 2.645 Å). This hydrogen bond is also present in solution, as indicated by the low-field shift of the relevant signal in the ^{1}H NMR spectrum in CD_2Cl_2 (δ = 9.37).



Scheme 2. Synthesis of quinazolin-4-ones **4a**−**g**

Table 1. Synthesis of 4-quinazolin-4-ones **4**

4	R^1	R^2	R^3	m.p. (°C)	%[a]
a	H	H	C_6H_5	240−242	62
b	H	H	4-$(CH_3)C_6H_4$	210−212	55
c	CH_3	H	4-$(CH_3)C_6H_4$	234−236	41
d	H	OCH_3	4-$(CH_3)C_6H_4$	266−268	46
e	CH_3	H	4-$(CH_3O)C_6H_4$	196−198	56
f	H	OCH_3	4-$(CH_3O)C_6H_4$	191−193	65
g	H	H	4-(tBu)C_6H_4	147−149	37

[a] Isolated yields.

We suggest the following mechanism for the formation of quinazolin-4-ones **4a**−**g**. Cyclization of the anthranilic acid with the oxaldiimidoyl dichloride first affords the seven-membered ring intermediate *i*. Cleavage of the lactone bond then gives the open-chain intermediate *ii*. A subsequent intramolecular prototropic shift results in the formation of intermediate *iii*. Nucleophilic attack of the amidine nitrogen atom on the ketene and aromatization finally affords the quinazolin-4-ones **4a**−**g**. The cyclization proceeds regioselectively via the more nucleophilic amidine rather than the amide nitrogen atom to give the thermodynamically favoured six-membered ring rather than the isomeric seven-membered ring. From a mechanistic viewpoint, the transformation of intermediate *i* into the quinazolin-4-ones **4** can be regarded as a Dimroth rearrangement including a ring contraction. A more simplistic mechanism for the condensation of the anthranilic acid with the diimidoyl dichloride would seem unlikely, considering the poor leaving ability of the hydroxy group of the acid under the basic reaction conditions. In principle, a conversion of the anthranilic acid into an acid chloride by reaction with the bis(imidoyl) chloride is possible, although this has not yet been reported in the literature.

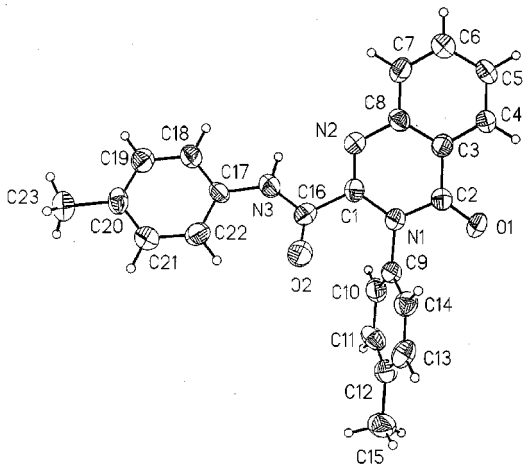
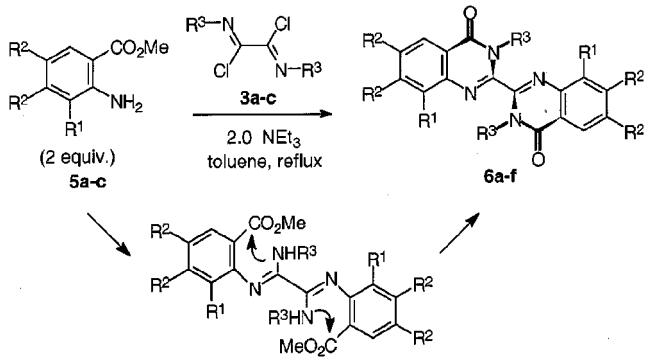


Figure 1. ORTEP plot of **4b**; thermal ellipsoids for the non-hydrogen atoms are drawn at a 50% probability level; selected bond lengths [Å] and angles [°]: C1−N1 1.378(6), N1−C9 1.467(7), N2−C8 1.383(7), N3−C17 1.417(7), C1−C16 1.524(9), C2−O1 1.208(6), C3−C4 1.383(8), C5−C6 1.398(8), N1−C2 1.395(7), N2−C1 1.295(7), N3−C16 1.349(8), C2−C3 1.469(8), C3−C8 1.385(7), C16−O2 1.211(7), C4−C5 1.384(8), C6−C7 1.372(8), C7−C8 1.389(8); N1−C1−C16 119.0(6), N1−C1−N2 124.3(6), N1−C2−C3 114.1(5), C1−N2−C8 117.9(5), C1−C16−N3 111.4(6)

We reasoned that the formation of quinazolin-4-ones **4** could be improved by replacing the acid with an ester group. However, a complex mixture was obtained from the stoichiometric reaction of anthranilic ester **5a** with oxaldiphenylimidoyl dichloride (**3a**). Interestingly, reaction of *two* equivalents of anthranilic esters **5a**−**c** with one equivalent of the diimidoyl dichlorides **3a**−**c** resulted in formation of the novel 2,2′-biquinazoline-4,4′(3*H*,3′*H*)-diones **6a**−**f** (Scheme 3, Table 2). As found for the formation of quinazolin-4-ones **4**, extended reactions times (toluene, reflux) were necessary to generate the dimers **6** in acceptable yields. To the best of our knowledge, the dimeric 2,2′-biquinazoline-4,4′(3*H*,3′*H*)-diones prepared here represent a new type of dimeric *N*-heterocyclic system. The synthesis and isolation of dimeric alkaloids is of current interest[12a] since the biological activity of many such dimers, for example the antimalarial activity of the axially chiral naphthylisoquinoline dioncophylline C,[12b] is enhanced relative to the corresponding monomers.

The formation of 2,2′-biquinazoline-4,4′(3*H*,3′*H*)-diones **6a**−**f** can be rationalized in terms of the condensation of two molecules of the anthranilic ester with the diimidoyl dichloride and subsequent twofold cyclization by attack of the amidine nitrogen atoms on the ester groups. The striking difference between the reactions of diimidoyl dichlorides **3** with anthranilic acids **1** and esters **5** can be accounted for by the higher electrophilicity of the ester relative to the acid. The constitution of **6c** was independently confirmed



Scheme 3. Synthesis of 2,2′-biquinazolin-4,4′-diones **6a**−**f**

Table 2. Synthesis of 2,2′-biquinazolin-4,4′-diones **6**

6	R^1	R^2	R^3	m.p. (°C)	%[a]
a	H	H	C_6H_5	226−227	21
b	H	OCH_3	C_6H_5	346−348	29
c	H	H	4-$(CH_3)C_6H_4$	310−312	26
d	H	H	4-$(CH_3O)C_6H_4$	280−282	29
e	CH_3	H	4-$(CH_3O)C_6H_4$	316−318	41
f	H	OCH_3	4-$(CH_3O)C_6H_4$	328−330	46

[a] Isolated yields.

by X-ray structure analysis (Figure 2). Due to the steric interaction between the aryl groups (R^3) and the quinazolin-4-one moieties, the rotation of the central carbon−carbon bond is severely restricted. In the crystal, the two planar quinazolin-4-one moieties are twisted out-of-plane by 65.4°. The tolyl groups at N1 and N3 are twisted out-of-plane by almost 90° as a result of steric factors. The hydrogen atom resides on the amide nitrogen N3. An intramolecular N−HN hydrogen bond is present (N−H distance 2.645 Å). This hydrogen bond is also present in solution, as indicated by the low-field shift of the relevant signal in the ^{1}H NMR spectrum in CD_2Cl_2 (δ = 9.37).

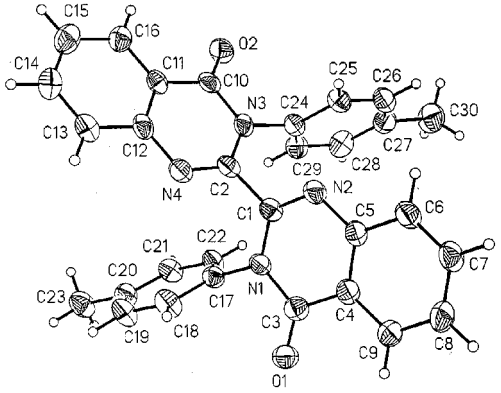
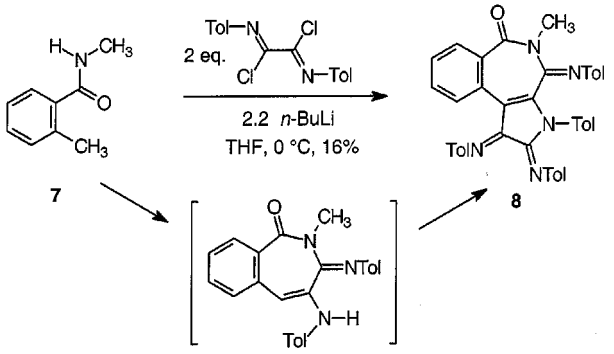


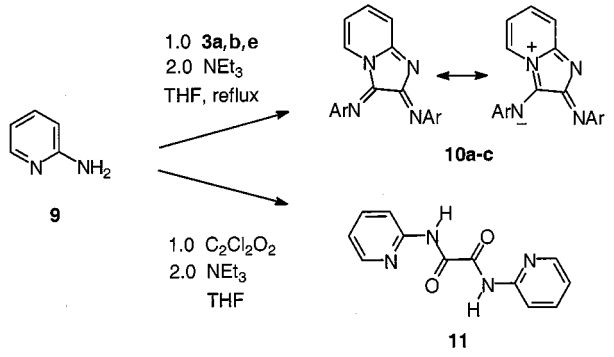
Figure 2. ORTEP plot of **6c**; thermal ellipsoids for the non-hydrogen atoms are drawn at a 50% probability level; selected bond lengths [A] and angles [°]: C1−N1 1.382(6), N3−C2 1.379(7), N2−C5 1.399(7), N4−C12 1.381(7), C1−N2 1.282(6), C2−N4 1.287(7), C3−N1 1.415(7), N3−C10 1.404(6), C3−C4 1.452(7), C10−C11 1.476(7), C4−C5 1.408(7), C11−C12 1.397(8), C1−C2 1.505(7); N1−C1−N2 126.6(4), N3−C2−N4 125.8(5), C1−N2−C5 117.3(4), N2−C1−C2 115.2(4), N4−C2−C1 116.2(4), C1−N1−C3 120.0(4), C2−N3−C10 121.3(4), C1−C2−N4 65.4

The condensation of oxaldiimidoyl dichloride **3b** with the dianion[13] of *N*-methyl *ortho*-tolylamide (**7**), which represents a carbaanalogue of anthranilic acid, afforded the pyrrolo[2,3-*d*]-[2]benzazepin-6(1*H*)-one (**8**) (Scheme 4). Interestingly, the product contained four rather than just two imino groups. This can be rationalized in terms of condensation of the enamine function of the 1:1 condensation product with a second molecule of the bis(imidoyl) chloride.



Scheme 4. Cyclization of the dianion of *N*-methyl *ortho*-tolylamide with oxaldi(*p*-tolyl)imidoyl dichloride

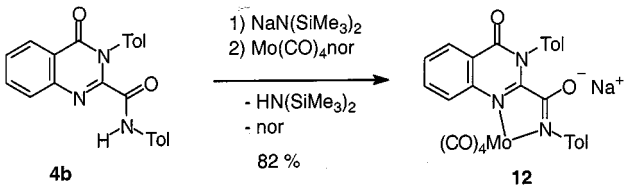
Reactions of 2-aminopyridine (**9**) with **3a**−**c** gave the 2,3-diimino-2,3-dihydroimidazo[1,2-*a*]pyridines **10a**−**c** (Scheme 5). The heterocyclic substructure of these compounds is of biological relevance.[14] The deep-purple colour of **10a**−**c** indicates the zwitterionic character of these novel heterocyclic merocyanines. For example, strong UV/Vis absorptions at around λ = 502, 573, and 580 nm are observed for **10a**. In analogy to the reaction with anthranilic acid, reaction of 2-aminopyridine with oxalyl chloride resulted in formation of an open-chain product (the amide **11**) rather than a cyclization product. This result supports our initial observation that cyclization of heterocyclic dinucleophiles with oxalic acid dielectrophiles can only be induced using oxaldiimidoyl dichlorides and not with oxalyl chloride.



Scheme 5. Synthesis of 2,3-diimino-2,3-dihydroimidazo[1,2-*a*]pyridines **10a**−**c**; **10a**: Ar = C_6H_5, 42%; **10b**: Ar = 4-$CH_3C_6H_4$, 38%; **10c**: Ar = 4-$NO_2C_6H_4$, 68%

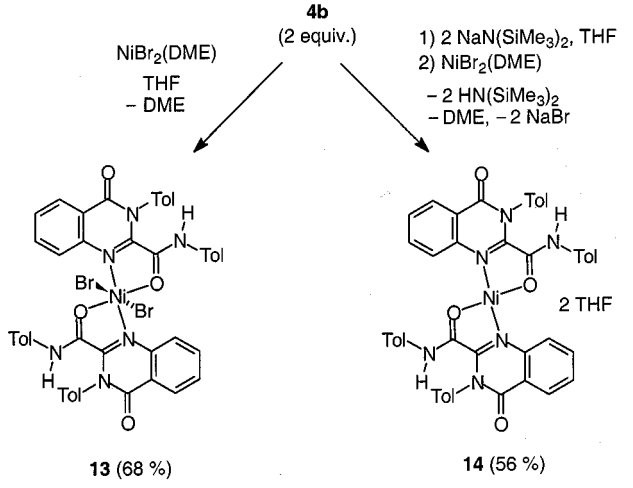
Quinazolin-4-ones **4** represent potentially ambidentate nucleophiles and heterodienes. The ambidentate character of the amidino-amide functionality of these compounds was studied by coordination of the quinazolin-4-one **4b** to transition metals. Deprotonation of **4b** with $NaN(SiMe_3)_2$ and subsequent reaction with $Mo(CO)_4$nor (nor = norbor-

nene) afforded the deep-red 1,4-diazadiene complex **12** (Scheme 6), in which the molybdenum atom is coordinated by two nitrogen atoms. The structural assignment was based on IR and ^{13}C NMR studies.



Scheme 6

Reaction of **4b** with $NiBr_2$(DME) afforded the nickel complex **13**. In this case, the metal atom is coordinated by the oxygen rather than the nitrogen atom of the amide moiety. Reaction of the carbanion of **4b** with $NiBr_2$(DME) also resulted in *N,O* rather than *N,N* complexation to give complex **14** (Scheme 7). The structural assignment of **13** was supported by the shift to lower wavenumber of the amide I vibration band (**4b**: 1690 cm^{-1}, **13**: 1616 cm^{-1}), which can be rationalized in terms of a weakening of the C=O bond upon complexation. In contrast, the amide II absorption is shifted to higher wavenumber (**4b**: 1523 cm^{-1}, **13**: 1546 cm^{-1}), which can be attributed to an enhancement of the double bond character of the C−N bond of the amide upon complexation. Furthermore, the structures of **13** and **14** have been independently confirmed through their analogy to related metal complexes of picolinic acid amides.[15]



Scheme 7

In summary, we have developed a new synthesis of the biologically significant quinazolin-4-one ring system. Additionally, the first 2,2′-biquinazoline-4,4′(3*H*,3′*H*)-diones have been efficiently prepared. In the light of the reported results, we are currently studying the development of transition metal mediated, regioselective ring transformations of quinazolin-4-ones and their application to the synthesis of natural products.

Experimental Section

General Procedure for the Preparation of Quinoxalin-4-ones (4a−g): Oxaldiimidoyl dichloride $C_2Cl_2(NPh)_2$ **3a** (10.0 mmol), anthranilic acid **1a** (10.0 mmol), and NEt_3 (2.80 mL, 20.0 mmol) were dissolved in toluene (100 mL) and the solution was stirred for 72−96 h at 50−60 °C until the starting material **3a** could no longer be detected by TLC. The precipitated $HNEt_3Cl$ was then removed by filtration and the solid was washed with hot toluene. The combined filtrate and washings were concentrated in vacuo. Addition of methanol to the residue led to the deposition of a solid, which was recrystallized from toluene to give **4a** (2.11 g, 62%) as colourless crystals.

3,4-Dihydro-4-oxo-*N*,3-diphenylquinazoline-2-carboxamide (4a): M.p. 240−241 °C. − ^1H NMR (200 MHz, CD_2Cl_2): δ = 7.15 (t, 1 H, *J* = 7.6 Hz, Ar), 7.33 (m, 3 H, Ar), 7.47−7.70 (m, 7 H, Ar, quinazoline-H), 7.88 (m, 2 H, quinazoline-H), 8.31 (d, *J* = 7.6 Hz, 1 H, quinazoline-H). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 120.3, 122.7, 125.4, 127.7, 128.2, 128.3, 129.0, 129.3, 129.4, 135.4, 137.6, 146.0, 147.1, 158.0, 162.2. − IR (Nujol): $\tilde{\nu}$ = 3345 cm^{-1} (m, ν_{NH}), 1708 (s, $\nu_{C=O}$), 1688 (s, amide I), 1591 (m), 1582 (m), 1558 (m), 1517 (s, amide II). − MS (CI, H_2O): *m/z* (%) = 342 [M^+ + 1] (100), 239 (8), 222 (16), 93 (46). − $C_{21}H_{15}N_3O_2$ (341.4): calcd. C 73.89, H 4.43, N 12.31; found C 74.16, H 4.65, N 12.07.

3,4-Dihydro-4-oxo-*N*,3-di(*p*-tolyl)quinazoline-2-carboxamide (4b): Yield 2.59 g of a colourless solid (55%); m.p. 210−212 °C. − ^1H NMR (200 MHz, $CDCl_3$): δ = 2.32, 2.44 (2 s, 2 × 3 H, tolyl-CH_3), 7.11−7.89 (m, 11 H, Ar, quinazoline-H), 8.26 (d, *J* = 6.9 Hz, 1 H, quinazoline-H), 9.37 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 20.9, 21.3 (tolyl-CH_3), 120.2, 122.6, 127.6, 127.8, 128.2, 129.1, 129.9, 130.0, 135.0, 135.2, 135.4, 139.2, 146.1, 147.6, 158.0, 162.3. − IR (Nujol): $\tilde{\nu}$ = 3357 cm^{-1} (m, ν_{NH}), 1698 (s, $\nu_{C=O}$), 1691 (s, amide I), 1604 (m), 1586 (m), 1561 (m), 1523 (s, amide II). − MS (CI, H_2O): *m/z* (%) = 370 [M^+ + 1] (100), 236 (18), 134 (4), 119 (5), 107 (9), 93 (42). − $C_{23}H_{19}N_3O_2$ (369.42): calcd. C 74.78, H 5.18, N 11.37; found C 75.15, H 5.17, N 11.00.

3,4-Dihydro-8-methyl-4-oxo-*N*,3-di(*p*-tolyl)quinazoline-2-carboxamide (4c): Yield 1.57 g of a colourless solid (41%); m.p. 234−236 °C. − ^1H NMR (200 MHz, CD_2Cl_2): δ = 2.32, 2.44 (2 s, 2 × 3 H, tolyl-CH_3), 2.70 (s, 3 H, quinazoline-CH_3), 7.11−7.71 (m, 10 H, Ar, quinazoline-H), 8.10 (d, *J* = 6.9 Hz, 1 H, quinazoline-H), 9.39 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 17.4 (quinazoline-CH_3), 21.0, 21.4 (tolyl-CH_3), 120.2, 122.7, 123.2, 125.3, 126.7, 127.8, 128.7, 129.9, 130.0, 135.2, 135.9, 137.0, 139.1, 144.5, 146.4, 158.2, 162.6. − IR (Nujol): $\tilde{\nu}$ = 3320 cm^{-1} (w, ν_{NH}), 1702 (s, $\nu_{C=O}$), 1691 (s, amide I), 1592 (m), 1567 (m), 1534 (s, amide II), 1510 (m). − MS (EI): *m/z* (%) = 383 [M^+] (51), 266 (45), 250 (100), 235 (20), 222 (10), 160 (30), 133 (21), 105 (25), 91 (15), 77 (8). − $C_{24}H_{21}N_3O_2$ (383.45): calcd. C 75.18, H 5.52, N 10.96; found C 75.17, H 5.74, N 10.72.

3,4-Dihydro-6,7-dimethoxy-4-oxo-*N*,3-di(*p*-tolyl)quinazoline-2-carboxamide (4d): Yield 1.98 g of a colourless solid (46%); m.p. 266−268 °C. − ^1H NMR (200 MHz, CD_2Cl_2): δ = 2.31, 2.37 (2 s, 2 × 3 H, tolyl-CH_3), 3.87, 3.96 (2 s, 2 × 3 H, quinazoline-OCH_3), 7.04−7.34 (m, 10 H, Ar, quinazoline-H), 9.36 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 21.0, 21.3 (tolyl-CH_3), 56.5, 56.6 (quinazoline-OCH_3), 106.3, 108.6, 115.9, 120.1, 128.0, 129.8, 129.9, 134.9, 135.1, 135.5, 139.1, 142.1, 146.6, 151.0, 155.7, 158.1, 161.5. − IR (Nujol): $\tilde{\nu}$ = 3325 cm^{-1} (w, ν_{NH}), 1695 (s, $\nu_{C=O}$), 1657 (s, amide I), 1609 (m), 1536 (m), 1500 (amide II). − MS (CI, H_2O): *m/z* (%) = 430 [M^+ + 1] (100), 296 (8), 215 (5), 179 (5), 93 (24). − $C_{25}H_{23}N_3O_4$ (429.48): calcd. C 69.92, H 5.40, N 9.78; found C 70.08, H 5.55, N 9.78.

3,4-Dihydro-*N*,3-bis(*p*-methoxyphenyl)-8-methyl-4-oxoquinazoline-2-carboxamide (4e): Yield 2.33 g of light-yellow crystals (56%); m.p.

196−198 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.68 (s, 3 H, quinazoline-CH_3), 3.78, 3.85 (2 s, 2 × 3 H, OCH_3), 6.84 (d, *J* = 8.8 Hz, 1 H, Ar), 6.98 (d, *J* = 8.8 Hz, 1 H, quinazoline-H), 7.19 (m, 3 H, Ar, quinazoline-H), 7.39 (d, *J* = 8.8 Hz, 2 H, Ar), 7.66 (d, *J* = 7.2 Hz, 2 H, quinazoline-H), 8.09 (d, *J* = 7.9 Hz, 2 H, quinazoline-H), 9.30 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 16.6 (quinazoline-CH_3), 55.8 (OCH_3), 114.5, 114.8, 121.9, 123.3, 126.7, 128.6, 129.2, 130.0, 130.7, 135.8, 139.1,144.6, 146.8, 151.6, 157.4, 160.1, 162.2. − IR (Nujol): $\tilde{\nu}$ = 3339 cm^{-1} (m, ν_{NH}), 1719 (m), 1702 (s, $\nu_{C=O}$), 1686 (m), 1665 (s), 1613 (m), 1593 (m), 1568 (w), 1529 (s), 1512 (s). − MS (CI, H_2O): *m*/*z* (%) = 416 [M$^+$ + 1] (100). − $C_{24}H_{21}N_3O_4$ (415.45): calcd. C 69.39, H 5.09, N 10.11; found C 68.98, H 5.35, N 9.89.

3,4-Dihydro-6,7-dimethoxy-*N*,3-bis(*p*-methoxyphenyl)-4-oxoquinazoline-2-carboxamide (4f): Yield 2.98 g of colourless crystals (65%); m.p. 191−193 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 3.76, 3.77 (2 s, 2 × 3 H, quinazoline-OCH_3), 3.84, 3.95 (2 s, 2 × 3 H, $ArOCH_3$), 6.88 (m, 4 H, Ar, quinazoline-H), 7.28 (m, 6 H, Ar, quinazoline-H), 9.31 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 55.7, 55.8 (quinazoline-OCH_3), 56.4, 56.6 ($ArOCH_3$), 106.1, 108.2, 114.4, 115.7, 121.8, 129.4, 130.8, 142.1, 147.1, 150.8, 155.7, 157.2, 158.6, 160.1, 161.6. − IR (Nujol): $\tilde{\nu}$ = 3346 cm^{-1} (s, ν_{NH}), 1678 (s, $\nu_{C=O}$), 1611 (s), 1595 (s), 1529 (s), 1510 (s), 1498 (s). − MS (CI, H_2O): *m*/*z* (%) = 462 [M$^+$ + 1] (63), 312 (7), 301 (100), 257 (8), 150 (5), 124 (8), 102 (9), 93 (58). − $C_{25}H_{23}N_3O_6$ (461.47): calcd. C 65.07, H 5.02, N 9.11; found C 64.78, H 5.25, N 9.56.

3,4-Dihydro-4-oxo-*N*,3-bis(4-*tert*-butylphenyl)quinazoline-2-carboxamide (4g): Yield 1.68 g of a colourless powder (37%); m.p. 147−149 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 1.32, 1.40 [2 s, 2 × 9 H, $C(CH_3)_3$], 7.21−7.83 (m, 11 H, Ar, quinazoline-H), 8.25 (d, *J* = 7.3 Hz, 1 H, quinazoline-H), 9.33 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 31.4, 31.6 [$C(CH_3)_3$], 34.8, 35.1 [$C(CH_3)_3$], 120.1, 122.6, 126.2, 127.5, 127.6, 128.6, 129.0, 134.9, 135.2, 135.3, 146.1, 147.9, 148.6, 152.2, 158.3, 162.2. − IR (Nujol): $\tilde{\nu}$ = 3262 cm^{-1} (m, ν_{NH}), 3197 (w), 3127 (w), 3072 (w), 1695 (s, $\nu_{C=O}$), 1665 (s, amide I), 1607 (s), 1592 (m), 1543 (amide II), 1515 (m). − MS (CI, H_2O): *m*/*z* (%) = 454 [M$^+$ + 1] (100), 398 (8), 278 (10), 263 (9), 212 (5). − $C_{29}H_{31}N_3O_2$ (453.58): calcd. C 76.79, H 6.89, N 9.26; found C 77.48, H 7.16, N 8.66.

General Procedure for the Preparation of 2,2′-Biquinazoline-4,4′(3*H*,3′*H*)-diones 6a−f: The oxaldiimidoyl dichloride derivative $C_2Cl_2[N(p\text{-}MeOC_6H_4)]_2$ (**3c**) (10.0 mmol), anthranilic methyl ester **5b** (20.0 mmol), and NEt_3 (2.8 mL, 20.0 mmol) were dissolved in toluene (100 mL). The solution was refluxed for 5−6 d until the starting material **3c** could no longer be detected by TLC. The precipitated $HNEt_3Cl$ was then removed by filtration and the solid was washed with hot toluene. The combined filtrate and washings were concentrated in vacuo. Addition of methanol to the residue led to the deposition of a solid, which was recrystallized from toluene to give **6f** (3.72 g, 60%) as colourless crystals.

3,3′-Diphenyl-2,2′-biquinazoline-4,4′(3*H*,3′*H*)-dione (6a): Yield 0.93 g of colourless crystals (21%); m.p. 226−227 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 7.28−7.47 (m, 10 H, Ar), 7.56 (t, 2 H, *J* = 7.5 Hz, 2 H, quinazoline-H), 7.76 (d, *J* = 8.0 Hz, 2 H, quinazoline-H), 7.84 (t, *J* = 7.5 Hz, 2 H, quinazoline-H), 8.22 (d, *J* = 7.5 Hz, 2 H, quinazoline-H). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 122.1, 127.3, 128.1, 128.6, 129.0, 129.8, 130.2, 135.2, 135.6, 146.7, 147.7, 161.4. − IR (Nujol): $\tilde{\nu}$ = 1689 cm^{-1} (s, $\nu_{C=O}$), 1608 (s), 1584 (s), 1564 (s), 1488 (m). − MS (CI, H_2O): *m*/*z* (%) = 443 [M$^+$ + 1] (67), 221 [M$^+$/2] (7), 152 (100), 120 (56), 93 (6). − $C_{28}H_{18}N_4O_2$ (442.5): calcd. C 76.01, H 4.10, N 12.66; found C 75.47, H 4.16, N 12.22.

6,6′,7,7′-Tetramethoxy-3,3′-diphenyl-2,2′-biquinazoline-4,4′(3*H*,3′*H*)-dione (6b): Yield 1.63 g of colourless crystals (29%); m.p. 346−348 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 3.93, 3.99 (2 s, 12 H, OCH_3), 7.13−7.50 (m, 14 H, Ar, quinazoline-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.3 (OCH_3), 106.1, 108.3, 115.0, 128.5, 129.3, 129.6, 134.7, 142.5, 150.1, 155.3, 160.3. − IR (Nujol): $\tilde{\nu}$ = 1677 cm^{-1} (s, $\nu_{C=O}$), 1606 (s), 1587 (s), 1559 (s), 1500 (s). − MS (CI, H_2O): *m*/*z* (%) = 563 [M$^+$ + 1] (100), 520 (6), 430 (27), 355 (15), 281 (10), 212 (26), 180 (10), 151 (10), 93 (98). − $C_{32}H_{26}N_4O_6$ (562.6): calcd. C 68.32, H 4.66, N 9.96; found C 68.04, H 4.88, N 9.95.

3,3′-Di(*p*-tolyl)-2,2′-biquinazoline-4,4′(3*H*,3′*H*)-dione (6c): Yield 2.40 g of colourless crystals (26%); m.p. 310−312 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.26 (s, 6 H, tolyl-CH_3), 7.15 (m, 8 H, Ar), 7.48 (t, *J* = 7.9 Hz, 2 H, quinazoline-H), 7.73 (d, *J* = 7.9 Hz, 4 H, quinazoline-H), 8.14 (d, *J* = 7.9 Hz, 2 H, quinazoline-H). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 21.2 (tolyl-CH_3), 122.1, 127.1, 128.0, 128.3, 129.5, 129.8, 132.6, 134.9, 140.0, 146.7, 148.0, 161.4. − IR (Nujol): $\tilde{\nu}$ = 1684 cm^{-1} (s, $\nu_{C=O}$), 1606 (m), 1587 (m), 1563 (m), 1508 (m). − MS (EI): *m*/*z* (%) = 470 [M$^+$] (41), 364 (28), 336 (14), 235 [M$^+$/2] (34), 209 (42), 180 (12), 116 (10), 107 (17), 91 (100), 77 (11), 65 (32), 39 (11), 32 (46). − $C_{30}H_{22}N_4O_2$ (470.5): calcd. C 76.58, H 4.71, N 11.91; found C 76.77, H 5.00, N 12.02.

3,3′-Bis(*p*-methoxyphenyl)-2,2′-biquinazoline-4,4′(3*H*,3′*H*)-dione (6d): Yield 1.46 g of colourless crystals (29%); m.p. 280−282 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 3.76 (s, 6 H, OCH_3), 6.88, 7.19 (2 d, *J* = 8.9 Hz, 2 × 4 H, Ar), 7.52 (t, *J* = 8.1 Hz, 2 H, quinazoline-H), 7.80 (d, *J* = 8.1 Hz, 4 H, quinazoline-H), 8.22 (d, *J* = 8.1 Hz, 2 H, quinazoline-H). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 57.3 (OCH_3), 115.7, 123.7, 128.8, 129.3, 129.6, 130.0, 132.9, 136.1, 148.4, 149.9, 162.0, 163.2. − IR (Nujol): $\tilde{\nu}$ = 1700 cm^{-1} (s, $\nu_{C=O}$), 1681 (s), 1609 (s), 1583 (m), 1562 (m), 1511 (s). − MS (CI, H_2O): *m*/*z* (%) = 503 [M$^+$ + 1] (88), 380 (3), 301 (2), 251 [M$^+$/2] (12), 225 (5), 182 (2), 93 (100). − $C_{30}H_{22}N_4O_4$ (502.5): calcd. C 71.70, H 4.41, N 11.15; found C 71.24, H 4.49, N 11.12.

3,3′-Bis(*p*-methoxyphenyl)-8,8′-dimethyl-2,2′-biquinazoline-4,4′(3*H*,3′*H*)-dione (6e): Yield 2.19 g of a colourless solid (41%); m.p. 316−318 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.60 (s, 6 H, CH_3), 3.77 (s, 6 H, OCH_3), 6.92 (d, *J* = 9.2 Hz, 6 H, Ar, quinazoline-H), 7.41 (t, *J* = 7.7 Hz, 2 H, quinazoline-H), 7.64 (d, *J* = 7.8 Hz, 4 H, Ar), 8.05 (d, *J* = 7.8 Hz, 2 H, quinazoline-H). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 17.5 (CH_3), 55.8 (OCH_3), 114.2, 122.2, 124.9, 128.0, 128.8, 135.7, 136.9, 145.3, 146.9, 160.5, 162.4. − IR (Nujol): $\tilde{\nu}$ = 1685 cm^{-1} (s, $\nu_{C=O}$), 1609 (s), 1590 (s), 1565 (s), 1507 (s). − MS (CI, H_2O): *m*/*z* (%) = 531 [M$^+$ + 1] (78), 408 (8), 301 (56), 123 (7), 93 (100). − $C_{32}H_{26}N_4O_4$ (530.6): calcd. C 72.44, H 4.94, N 10.56; found C 72.19, H 5.28, N 10.57.

6,6′,7,7′-Tetramethoxy-3,3′-bis(*p*-methoxyphenyl)-2,2′-biquinazoline-4,4′(3*H*,3′*H*)-dione (6f): Yield 2.85 g of colourless crystals (46%); m.p. 328−330 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 3.77 (s, 6 H, 4-methoxyphenyl-CH_3), 3.93, 3.99 (2 s, 2 × 6 H, quinazoline-OCH_3), 6.84, 7.12 (2 d, 2 × 4 H, *J* = 9.0 Hz, Ar), 7.16, 7.51 (2 s, 2 × 2 H, quinazoline-H). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 56.6 (4-methoxyphenyl-CH_3), 58.4 (quinazoline-OCH_3), 106.4, 108.6, 114.0, 115.4, 128.0, 131.4, 143.0, 147.3, 150.7, 155.9, 160.3, 161.0. − IR (Nujol): $\tilde{\nu}$ = 1680 cm^{-1} (m, $\nu_{C=O}$), 1663 (s), 1609 (s), 1587 (m), 1561 (m), 1498 (s). − MS (CI, H_2O): *m*/*z* (%) = 623 [M$^+$ + 1] (100), 609 (9), 311 [M$^+$/2] (25), 301 (63), 212 (36), 180 (15), 129 (7), 102 (18). − $C_{34}H_{30}N_4O_8$ (622.6): calcd. C 65.59, H 4.86, N 9.00; found C 65.89, H 4.71, N 9.21.

Synthesis of 2,3,4,5-Tetrahydro-5-methyl-3-(4-methylphenyl)-1,2,4-tris[(4-methylphenyl)imino]pyrrolo[2,3-*d*][2]benzazepin-6(1*H*)-one

(8): To a solution of *N*-methyl *o*-tolylamide (448 mg, 3.0 mmol) in THF (8 mL) at 0 °C was added *n*BuLi (4.15 mL, 1.6 M solution in hexane, 2.2 equiv.). After stirring for 30 min at 20 °C, this solution was added to a solution of *N*,*N*′-bis(*p*-tolyl)oxaldiimidoyl dichloride (1.8 g, 6.0 mmol) in THF (80 mL). The deep-red solution was stirred for 15 min at 0 °C and for 2 h at 20 °C. The solvent was removed in vacuo and the crude product was purified by chromatography (silica gel, diethyl ether/petroleum ether, 1:1) to give **8** as a red solid (294 mg, 16%); m.p. 166 °C. − ^{1}H NMR ([D$_8$]THF, 200 MHz): δ = 2.08, 2.20, 2.49 (2 s, 2 × 3 H, CH$_3$), 2.71 (s, 3 H, NCH$_3$), 5.78 (br, 1 H, Ar), 5.99 (br, 1 H, Ar), 6.25 (d, *J* = 8.5 Hz, 2 H, Ar), 6.62 (m, 4 H, Ar), 6.96 (br, 3 H, Ar), 7.10−7.55 (m, 8 H, Ar), 8.33 (d, 8.5 Hz, 1 H, Ar). − ^{13}C NMR ([D$_8$]THF, 50 MHz): δ = 20.44, 20.60, 20.84, 21.61 (tolyl-CH$_3$), 25.85 (NCH$_3$), 115.12, 115.28, 116.20, 120.55, 121.15, 122.55, 124.34, 126.33, 129.09, 129.32, 129.64, 132.41 (CH, Ar), 118.30, 130.63, 131.42, 132.92, 133.00, 133.82, 134.10, 144.77, 144.78, 144.79, 146.06, 146.14, 157.80, 157.90, 166.97 (C). − IR (KBr): $\tilde{\nu}$ = 3330 cm^{-1} (w), 3030 (w), 2922 (w), 1718 (s), 1662 (s), 1619 (m), 1520 (m), 1508 (m), 1478 (m), 1405 (m), 1375 (m), 1300 (m), 1238 (m), 1040 (m). − MS (CI, H$_2$O): *m*/*z* (%) = 614 [M$^+$ + 1] (100). − C$_{41}$H$_{35}$N$_5$O (613.7): calcd. C 80.24, H 5.75, N 11.41; found C 80.57, H 5.77, N 11.34.

General Procedure for the Preparation of 2,3-Bis(arylimino)-2,3-dihydroimidazo[1,2-*a*]pyridines 10a−c: A solution of 2-aminopyridine (0.52 g, 5.5 mmol) in THF (50 mL) was slowly added to a solution of the oxaldiimidoyl dichloride (5.0 mmol) in THF (50 mL) containing NEt$_3$ (1.45 mL, 10.0 mmol) and the mixture was refluxed for 8 h. After cooling to 20 °C, the precipitated HNEt$_3$Cl was filtered off and the filtrate was concentrated in vacuo. In the case of **10a**,**b**, the black residue was purified by chromatography (toluene/acetone, 10:1). In the case of **10c**, the product was isolated from the reaction mixture by filtration and subsequent recrystallization from DMF.

2,3-Bis(phenylimino)-2,3-dihydroimidazo[1,2-*a*]pyridine (10a): Yield 0.626 g (42%) of deep-purple crystals were isolated; m.p. 137−139 °C. − IR (Nujol): $\tilde{\nu}$ = 1640 cm^{-1} (m, $\nu_{C=N}$). − MS (EI): *m*/*z* (%) = 298 [M$^+$] (30), 194 (48), 103, 93, 77, 51. − C$_{19}$H$_{14}$N$_4$ (298.3): calcd. C 76.50, H 4.73; found C 76.39, H 4.92. Due to the low solubility of **10a**, no NMR spectroscopic data could be obtained.

2,3-Bis(4-tolylimino)-2,3-dihydroimidazo[1,2-*a*]pyridine (10b): Yield 0.62 g (38%) of deep-purple crystals were isolated; m.p. 140−141 °C. − ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 2.26, 2.33 (2 s, 2 × 3 H, tolyl-CH$_3$), 6.57 (t, *J* = 7.0 Hz, 1 H, quinazoline-H), 6.88 (d, *J* = 7.0 Hz, 1 H, quinazoline-H), 7.06, 7.15, 7.34, 7.45 (4 d, *J* = 8.1 Hz, 4 × 2 H, Ar), 7.60 (t, *J* = 7.0 Hz, 1 H, quinazoline-H), 8.04 (d, *J* = 7.0 Hz, 1 H, quinazoline-H). − ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 21.0, 21.1 (tolyl-CH$_3$), 110.8, 117.7, 121.0, 122.9, 123.1, 127.4, 128.8, 129.3, 129.5, 135.4, 135.5, 142.9, 143.0, 146.8, 146.9. − IR (Nujol): $\tilde{\nu}$ = 1646 cm^{-1} (m, $\nu_{C=N}$), 1608 (m), 1567 (m), 1505 (s). − MS (EI): *m*/*z* (%) = 326 [M$^+$] (36), 311 (100), 238, 209, 116, 91, 78, 65. − UV/Vis [λ (log ε), acetone]: λ_{max} = 502 nm (3.81), 573 (3.88), 580 (3.71). − C$_{21}$H$_{18}$N$_4$ (326.4): calcd. C 77.28, H 5.56, N 17.17; found C 77.35, H 6.02, N 16.60.

2,3-Bis(4-nitrophenylimino)-2,3-dihydroimidazo[1,2-*a*]pyridine (10c): Yield: 1.33 g (68%) of deep-purple crystals were isolated; m.p. 248−250 °C. − IR (Nujol): $\tilde{\nu}$ = 1670, 1652 cm^{-1} (m, $\nu_{C=N}$), 1584 (s), 1566 (s), 1506 (s). − MS (EI): *m*/*z* (%) = 388 [M$^+$] (15), 330 (16), 241 (51), 195 (31), 165 (37), 138 (38), 212 (18), 108 (21), 94 (26), 78 (69), 71 (100). − C$_{19}$H$_{12}$N$_6$O$_4$ (388.3): calcd. C 58.76, H 3.11, N 21.64; found C 58.28, H 2.94, N 21.34. Due to the low solubility of **10c**, no NMR spectroscopic data could be obtained.

Molybdenum Complex 12: To a solution of **4b** (0.37 g, 1.0 mmol) in THF (30 mL) was added a 1 M solution of NaN(SiMe$_3$)$_2$ in the same solvent (1 mL). After stirring for 30 min, a solution of Mo(CO)$_4$nor (0.30 g, 1.0 mmol) in THF (30 mL) was added. After stirring for a further 2 h, the precipitated product was collected by filtration and washed with THF to give complex **12** as red crystals (0.55 g, 82%). − ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.21, 2.31 (2 s, 2 × 3 H, tolyl-CH$_3$), 6.96−7.34 (m, 9 H, Ar, quinazoline-H), 7.63−8.68 (m, 3 H, quinazoline-H). − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 20.3, 20.6 (tolyl-CH$_3$), 119.6, 125.2, 126.4, 126.9, 127.4, 128.3, 129.3, 130.1, 133.4, 135.0, 136.3, 138.5, 146.4, 149.6, 154.8, 158.9, 160.8, 161.9, 167.3, 205.0, 221.5, 222.8. − IR (Nujol): $\tilde{\nu}$ = 2008 cm^{-1}, 1887, 1865, 1805 (s, $\nu_{C\equiv O}$), 1694 (s, $\nu_{C=O}$), 1619 (s), 1603 (s), 1579 (s), 1540 (s), 1508 (s). − C$_{31}$H$_{26}$N$_3$O$_7$NaMo (671.5): calcd. C 55.45, H 3.90, N 6.26; found C 55.36, H 4.33, N 6.13.

Nickel(II) Complex 13: A solution of NiBr$_2$(DME) (0.15 g, 0.5 mmol) and **4b** (0.37 g, 1.0 mmol) in THF (30 mL) was stirred for 24 h at 20 °C. The precipitated product was collected by filtration and washed with THF (1 mL) to give **13** as green crystals (0.65 g, 68%). − IR (Nujol): $\tilde{\nu}$ = 3353 cm^{-1} (s, ν_{NH}), 1709 (s, $\nu_{C=O}$), 1645 (s), 1602 (m), 1588 (m), 1546 (m), 1507 (m). − μ_{eff} = 3.4 BM. − C$_{46}$H$_{38}$N$_6$O$_4$Br$_2$Ni (957.3): calcd. C 57.71, H 4.00, N 8.78, Br 16.69, Ni 6.13; found C 57.21, H 3.81, N 8.75, Br 17.03, Ni 6.23.

Nickel(II) Complex 14: To a solution of **4b** (0.37 g, 1 mmol) in THF (25 mL) was added a 1 M solution of NaN(SiMe$_3$)$_2$ in the same solvent (1 mL). After stirring for 30 min, a solution of NiBr$_2$(DME) (0.15 g, 0.5 mmol) in THF (25 mL) was added. After stirring for a further 2 h, the precipitate was filtered off and the filtrate was concentrated to a volume of 10 mL. A layer of diethyl ether was placed on the top of the THF phase and the resulting precipitate was collected by filtration and washed with diethyl ether to give complex **14** as light-green crystals (0.53 g, 56%). − IR (Nujol): $\tilde{\nu}$ = 1697 cm^{-1} (s, $\nu_{C=O}$), 1616 (m), 1609 (m), 1581 (m), 1539 (m), 1504 (s). − $\mu_{eff.}$ = 3.1 BM. − C$_{54}$H$_{52}$N$_6$O$_6$Ni (939.7): calcd. C 69.02, H 5.58, N 8.94, Ni 6.25; found C 68.54, H 5.63, N 8.64, Ni 6.41.

Crystal Structure Determination: The intensity data for the compounds were collected on a Nonius CAD4 diffractometer using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[16] The structures were solved by direct methods (SHELXS)[17] and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97).[18] Only the amino hydrogen atoms of **4b** were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included in calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[18]

Crystal Data for 6c:[19] C$_{30}$H$_{22}$N$_4$O$_2$, M_r = 470.52 gmol^{-1}, colourless prism, size 0.40 × 0.38 × 0.30 mm^3, monoclinic, space group $P2_1$, *a* = 9.340(3), *b* = 25.952(11), *c* = 10.2342(6) Å, β = 106.144(8)°, *V* = 2383(1) Å^3, *T* = −90 °C, *Z* = 4, $\rho_{calcd.}$ = 1.312 gcm^{-3}, μ(Mo-K_α) = 0.84 cm^{-1}, *F*(000) = 984, 4053 reflections in *h*(−10/10), *k*(0/29), *l*(0/11), measured in the range 1.57° ≤ Θ ≤ 23.96°, completeness Θ_{max} = 99.7%, 3814 independent reflections, R_{int} = 0.056, 3328 reflections with $F_o > 4\sigma(F_o)$, 650 parameters, 1 restraint, $R1_{obs}$ = 0.057, $wR2_{obs}$ = 0.151, $R1_{all}$ = 0.073, $wR2_{all}$ = 0.171, GooF = 1.113, Flack parameter 1(2), largest difference peak and hole 0.300/−0.302 e·Å^{-3}.

Crystal Data for 4b:[19] C$_{23}$H$_{19}$N$_3$O$_2$, M_r = 369.41 gmol^{-1}, colourless prism, size 0.40 × 0.38 × 0.36 mm^3, orthorhombic, space

group $P2_12_12_1$, a = 5.404(1), b = 15.406(5), c = 22.138(5) Å, V = 1843.1(8) Å^3, T = −90 °C, Z = 4, $\rho_{calcd.}$ = 1.331 gcm^{-3}, μ(Mo-K_α) = 0.87 cm^{-1}, F(000) = 776, 2188 reflections in h(0/6), k(−19/0), l(0/27), measured in the range 2.64° ≤ Θ ≤ 26.29°, completeness Θ_{max} = 99.8%, 2188 independent reflections, 1015 reflections with $F_o > 4\sigma(F_o)$, 257 parameters, 0 restraints, $R1_{obs}$ = 0.059, wR^2_{obs} = 0.126, $R1_{all}$ = 0.188, wR^2_{all} = 0.149, GooF = 0.877, Flack parameter −1(4), largest difference peak and hole 0.208/−0.227 e·Å^{-3}.

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