A Convenient Method of Facilitating Aryl–Aryl Bond-Formation Reactions in the Synthesis of Biquinoline- and Quinoline-Bearing Chromene Derivatives

Mathan Sankaran,[a] Kumarasamy Chandraprakash,[a] Chokkalingam Uvarani,[a] Kailasam Natesan Vennila,[b] Devadasan Velmurugan,[b] Palathurai Subramaniam Mohan*[a]

[a] School of Chemical Sciences, Bharathiar University, Coimbatore 641046, India
Fax +91(422)2459845; E-mail: psmohan59@gmail.com

[b] Centre for Advanced Study in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai 600025, India

Received: 25.08.2012; Accepted: 26.09.2012

Abstract: A method to derive functionalized biquinoline- and quinoline-bearing chromene bicyclic systems through aryl–aryl bond formation in a one-pot synthesis is described. The X-ray structure analysis provides insight into the mode of orientation of the molecules and opens the way to the synthesis of various hybrid molecules by making use of suitable substituents at R^1, R^2, and R^3.

Key words: one-pot synthesis, quinoline, chromene, sulfuric acid, *p*-toluenesulphonic acid

In recent years there has been an upsurge of interest from the chemical community in the design and construction of structurally versatile biquinoline scaffolds for use in polymer and organometallic chemistry.[1] These studies have included several polycyclic heterocyclic systems such as biquinolines or chromenes comprising bicyclic systems that were recognized as valuable entities in transition-metal coordination chemistry, crystal engineering for generating a wide variety of molecular architectures,[2–5] as building blocks for supramolecular complexes, and for the construction of (porous) metal frameworks.[6–10] The generation of such frameworks is a promising approach that can be used in the search for stable microporous metal-organic networks that exhibit reversible guest exchange and possibly selective catalytic activity.[11–14] They are also used as ligands for the preparation of metal complexes with biological activities such as antibacterial, antifungal, antimalarial, and antitumor agents, and as hydrogenation catalysts.[15,16] In addition to the aforementioned significance, polyquinolines possess n-type electrically conducting properties along with good thermal, mechanical, and oxidative attributes.[17,18] Although there are a few reports on the preparation of bicyclic quinolines,[19–25] most suffer drawbacks such as low yield, formation of by-products, the use of highly reactive coupling reagents, and competitive reductions in the presence of protonic sources.[26,27] To overcome these difficulties, we describe herein an efficient, one-pot synthesis of some new biquinoline/chromene-bearing quinoline systems linked through an aryl–aryl bond. To the best of our knowledge, no examples of such cyclization for the formation of biquinoline- and quinoline-bearing chromene systems accompanying aryl bond formation have been reported. In addition to the synthesis, the X-ray crystal structures of **5f** and **5g** have provided insight into structural orientation of these bicyclic systems. Some representative examples of biquinoline systems previously described are shown in Figure 1 and we have decided to use these analogues as model compounds for preparing **3a**–**j** and **5a**–**g** with the chloro and NH-substituents suitably placed as additional functional moieties. These results are interesting but suggest that there is still scope for structural functional modifications that will generate more valuable output in terms of efficacy in polymeric materials. In this class of quinoline-based bicycles, the presence of two donor atoms and the flexibility of the two quinolines or quinoline-chromene units linked together by a single aryl bond provide the possibility of coordination to metal ions in a variety of modes.

We initiated our experiment by using **1b** and **2a** (Table 1, entry 1) with concentrated H_2SO_4 (0.2 equiv) in methanol, and found that the product was obtained in 48% isolated yield (Table 1, entry 1). The yield of the product was improved to 59% when 0.5 equivalent of H_2SO_4 was added to the reaction media (Table 1, entry 2), however, little improvement was observed when the amount of catalyst H_2SO_4 was increased further (1 equiv, Table 1, entry 3). Identical results were obtained by increasing the amount of catalyst in *n*-BuOH (Table 1, entries 4 and 5). The reaction was then examined in different types of solvents, and the results show that solvents such as acetic acid afforded an excellent yield of the product (ca. 88%; Table 1, entries 6–10). During optimization studies, *p*-toluenesulfonic acid (PTSA) was tried under the same reaction conditions, which showed a significant reactivity for this reaction in acetic acid (Table 1, entry 10). A moderate to low yield of the corresponding product was obtained when MeCN or *n*-BuOH (Table 1, entries 11 and 12) were used as solvents with PTSA catalyst.

The starting precursor 4-substituted 3-acetylquinolin-2-ones **1a**–**d** and 3-acetylcoumarin-2-ones **4a** and **4b** were synthesized according to a previously described procedure.[28,29] In this context, Scheme 1[30] illustrates the synthetic approach to the biquinoline systems and their derivatives **3a**–**j**, starting from the appropriate 2-aminobenzophenone/2-aminoacetophenones **2a**–**d** with 3-acetylquinolin-2-ones **1a**–**d**, followed by cyclization to

SYNLETT 2012, 23, 2858–2864
Advanced online publication: 07.11.2012
DOI: 10.1055/s-0032-1317488; Art ID: ST-2012-D0711-L

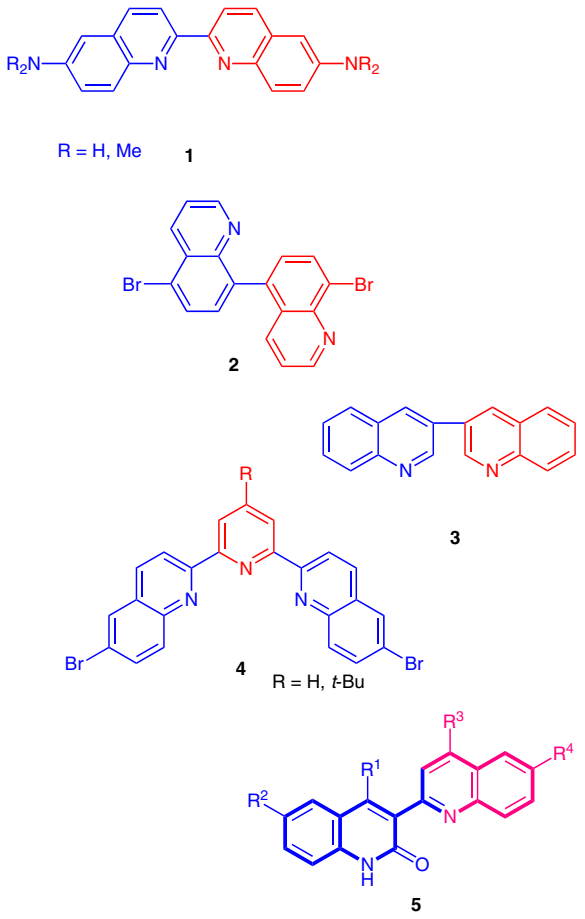


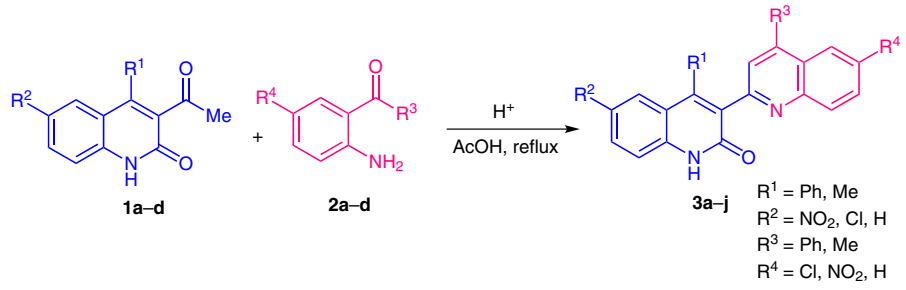
Figure 1 Representative examples of model compounds **1**–**4** and the derived analogue **5**

Table 1 Optimization of Reaction of 3-Acetyl-6-chloro-4-phenylquinolin-2(1*H*)-one (**1b**) and *o*-Aminobenzophenone (**2a**)[a] for the Formation of **3a**

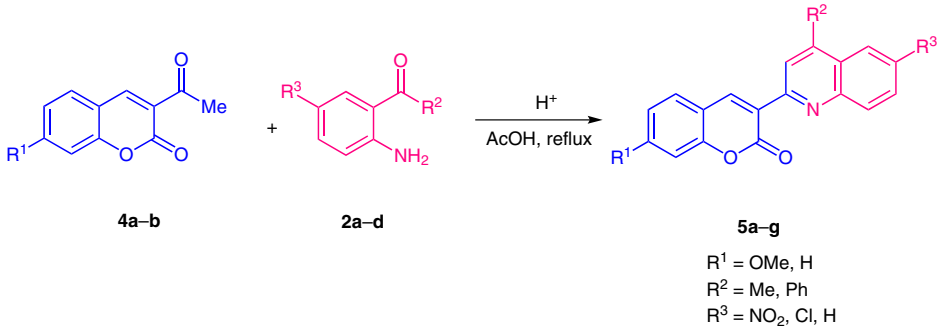
Entry	Catalyst (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	concd H_2SO_4 (0.2)	MeOH	80	16	48
2	concd H_2SO_4 (0.5)	MeOH	80	13	59
3	concd H_2SO_4 (1)	MeOH	80	12	64
4	concd H_2SO_4 (0.5)	*n*-BuOH	120	10	65
5	concd H_2SO_4 (1)	*n*-BuOH	120	9	68
6	concd H_2SO_4 (0.2)	AcOH	120	6	82
7	concd H_2SO_4 (0.5)	AcOH	120	5	88
8	concd H_2SO_4 (1)	AcOH	120	5	85
9	PTSA (0.2)	AcOH	120	9	77
10	PTSA (0.5)	AcOH	120	8	82
11	PTSA (0.5)	MeCN	80	8	56
12	PTSA (0.5)	*n*-BuOH	80	10	45

[a] Reaction conditions: **1b** (1 mmol), **2a** (1 mmol), catalyst.
[b] Isolated yield.

the corresponding biquinoline via the Friedländer condensation under the given conditions (Table 2, entries 1–10).[31] Most of the products were readily filtered off directly from the reaction medium, although a few required purification by column chromatography on silica gel (hexane–ethyl acetate).



Scheme 1 Synthesis of biquinoline analogues **3a**–**j**



Scheme 2 Synthesis of quinoline-bearing chromenes **5a**–**g**

Similarly, Scheme 2[32] illustrates the synthesis of quinoline-bearing chromene systems **5a**–**g** from the appropriate 2-aminoacetophenone/2-aminobenzophenone **2a**–**d** with 3-acetylchromen-2-ones **4a** and **4b**. The bicyclic chromene-quinoline systems **5a**–**g** were also generated by a similar straightforward approach to that depicted in Scheme 1. After completion of the reaction (TLC analysis of the reaction mixture), the residue was purified by column chromatography to afford the products **5a**–**g** (Scheme 2 and Table 2, entries 11–17). All the compounds were then recrystallized from tetrahydrofuran (THF)/methanol (5:1). The majority of compounds were soluble in common organic solvents (THF, $CHCl_3$, CH_2Cl_2) at concentrations of more than 10 mg/mL. The synthesized molecules were characterized by IR, ^1H and ^{13}C NMR, mass spectroscopy and elemental analysis; furthermore, in two cases, the characterization was unambiguously determined by single-crystal X-ray crystallographic analysis.

The ^1H NMR spectrum of analogue **3g** exhibited aromatic peaks, and signals associated with the acetyl group (δ = 2.6 ppm) and the 'NH_2' in *o*-aminoketone derivatives were no longer present. A singlet at δ = 8.63 ppm was attributed to the proton adjacent to the NO_2 group at C′-5, and a singlet at δ = 7.98 ppm was assigned to the proton adjacent to the ring carbon (C′-3). The signals resonating between δ = 7.34–8.64 ppm were assigned to entire aromatic region, and a signal around δ = 12.88 ppm was attributed to the amide function, which was further confirmed by ^{13}C NMR spectra in which the peak at δ = 161.36 ppm was attributed to the amide C=O function. The presence of this amide moiety was also evident in the IR spectrum, in which the stretching frequency due to acetyl group was absent. The ^{13}C NMR spectra of **3g** gave signals for 25 carbons, which is in accordance with the proposed structure. The structure was also confirmed by mass spectra (*m*/*z* 514 $[M]^+$) and elemental analyses data. The structures of compounds **5f** and **5g** were unambiguously determined by single-crystal XRD studies (Figure 2 and Figure 3).[33] The assignment of ^1H and ^{13}C NMR signals for **5g** was also achieved by using the same straightforward approach as described for **3g.**

Table 2 Synthesis of Biquinoline/Quinoline-Bearing Chromene Analogues **3a**–**j** and **5a**–**g**[a]

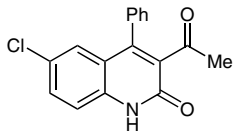
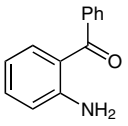
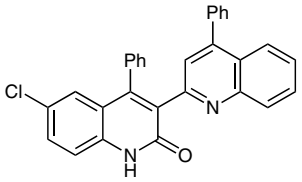
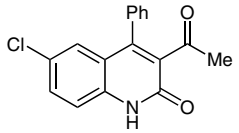
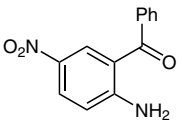
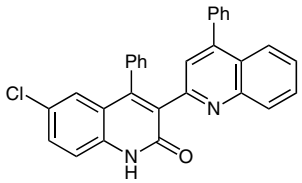
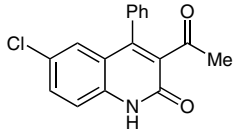
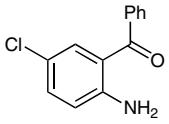
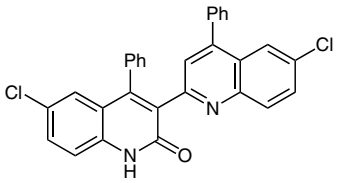
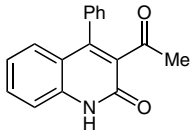
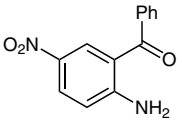
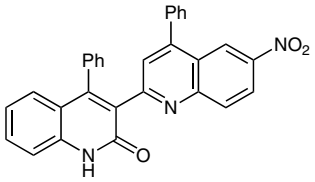
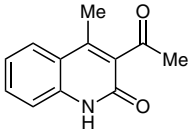
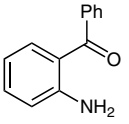
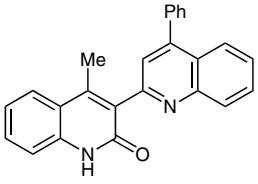
Entry	3-Acetylquinolines/ 3-acetylchromenes	*o*-Amino ketones	Product	Yield (%)[b]
1			**3a** 	85
2			**3b** 	88
3			**3c** 	84
4			**3d** 	68
5			**3e** 	82

Table 2 Synthesis of Biquinoline/Quinoline-Bearing Chromene Analogues **3a**–**j** and **5a**–**g**[a] (continued)

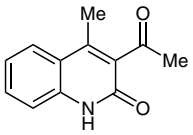
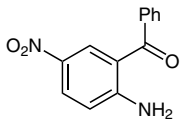
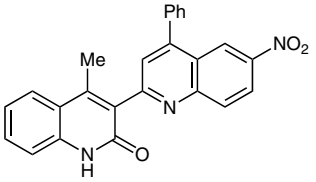
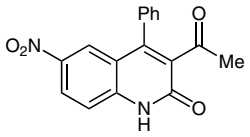
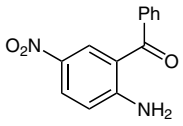
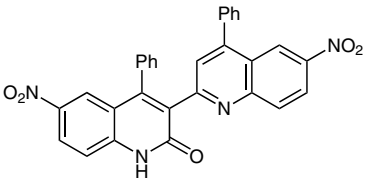
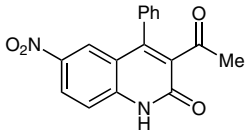
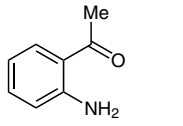
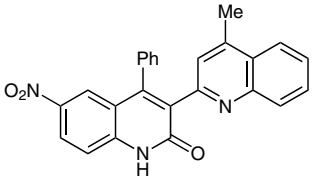
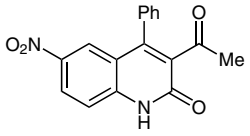
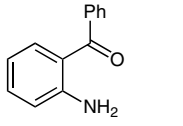
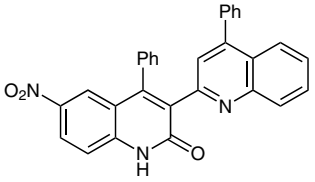
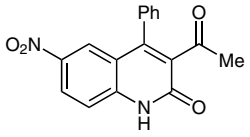
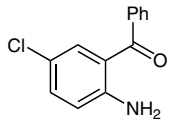
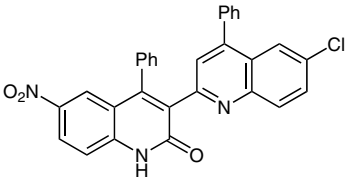
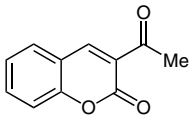
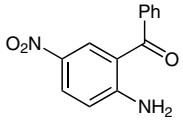
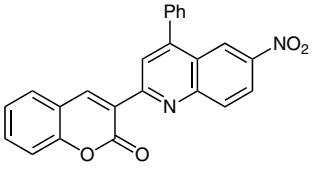
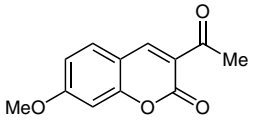
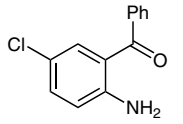
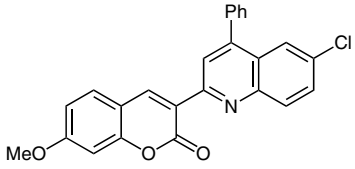
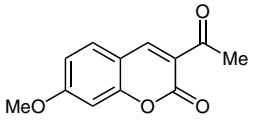
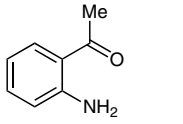
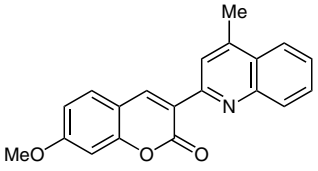
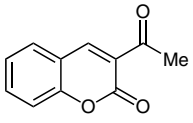
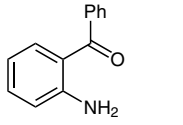
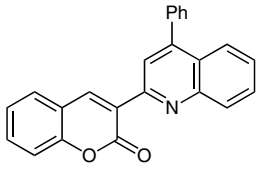
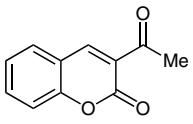
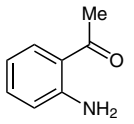
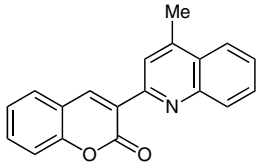
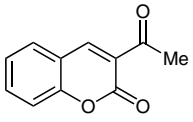
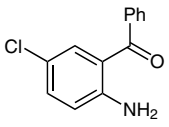
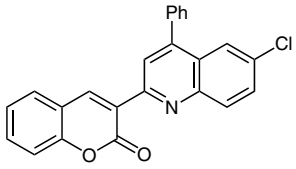
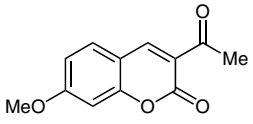
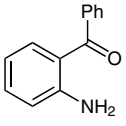
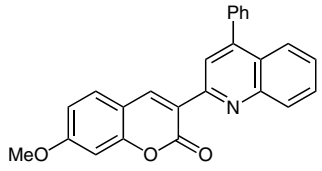
Entry	3-Acetylquinolines/ 3-acetylchromenes	*o*-Amino ketones	Product	Yield (%)[b]
6			**3f** 	77
7			**3g** 	72
8			**3h** 	76
9			**3i** 	75
10			**3j** 	66
11			**5a** 	81
12			**5b** 	86
13			**5c** 	82
14			**5d** 	82

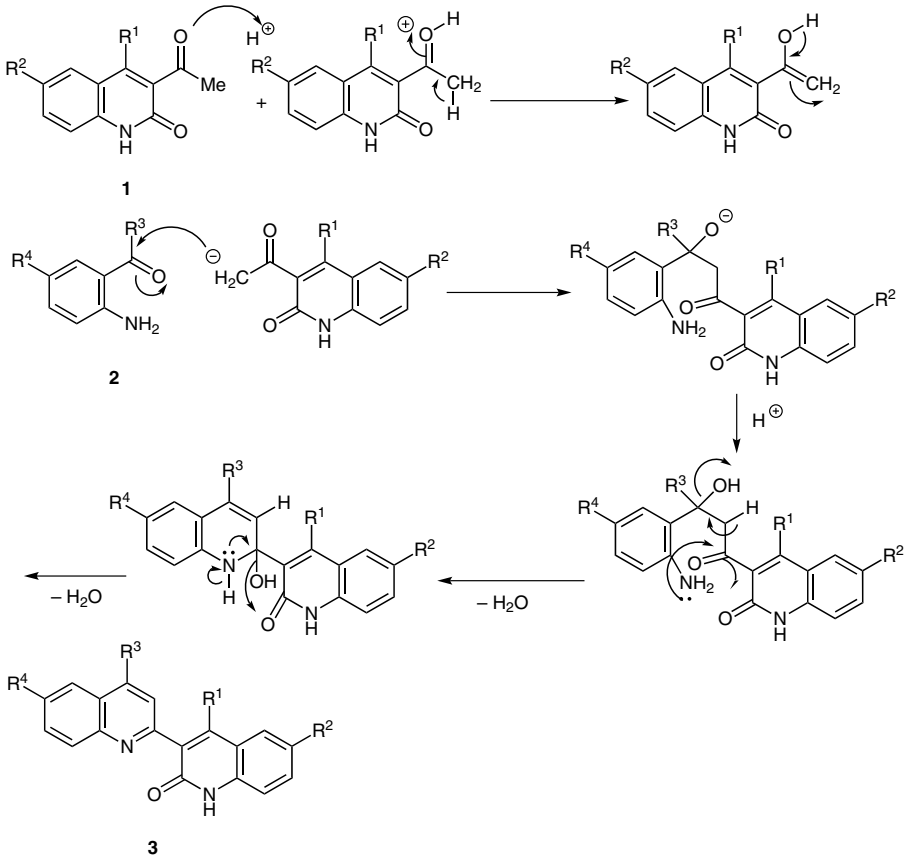
Table 2 Synthesis of Biquinoline/Quinoline-Bearing Chromene Analogues **3a**–**j** and **5a**–**g**[a] (continued)

Entry	3-Acetylquinolines/ 3-acetylchromenes	*o*-Amino ketones	Product	Yield (%)[b]
15			**5e** 	74
16			**5f** 	76
17			**5g** 	82

[a] Reaction conditions: *o*-aminobenzophenone (0.4 mmol), 3-acetylquinolin-2-one/3-acetylchromene-2-one (0.4 mmol), H_2SO_4, 120 °C.
[b] Isolated yield.

A plausible reaction mechanism is described in Scheme 3.

In conclusion, we have developed an efficient method for the construction of biquinoline- and quinoline-substituted chromene frameworks promoted by acid-catalyzed cyclization of 4-substituted quinoline-2-one and chromen-2-one. This strategy represents an efficient aryl bond forma-



Scheme 3 Plausible reaction mechanism for the formation of biquinoline

tion between quinoline-chromene systems, and opens up a new avenue for building conjugated organic materials. These functionalized biquinoline scaffolds can be readily attached to other conjugated moieties that can coordinate with metals to access new classes of organic-based materials.

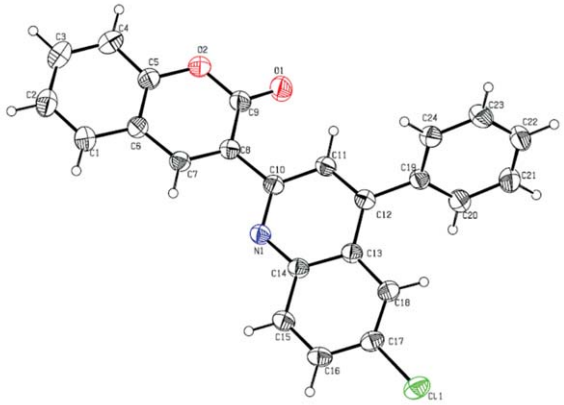


Figure 2 ORTEP diagram of compound **5f**

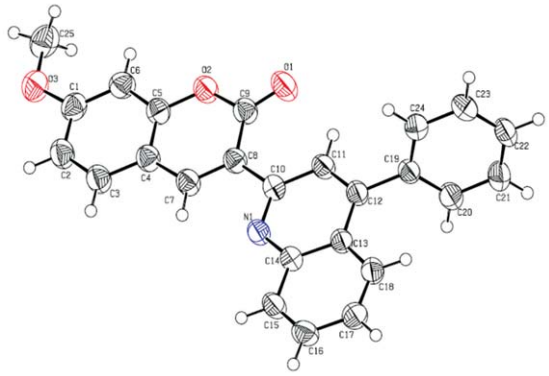


Figure 3 ORTEP diagram of compound **5g**

Acknowledgment

The Authors thank the Council of Scientific and Industrial Research CSIR-SRF (Ref No. 09/472(0415)/2K10–EMR-I) New Delhi, India, for financial assistance. We gratefully acknowledge Prof. Velmurugan (Crystallography and Biophysics Unit) University of Madras for single crystal X-ray analysis. We are grateful to SIF, IIT Madras and the University Universiti sains Malaysia, Penang, Malaysia for spectral studies.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Zhang, J. Y. P.; Zhang, K. Y. H.; Jiang, S.; Ye, L.; Yang, G.; Wang, Y. *J. Solid State Chem.* **2006**, *179*, 438. (b) Zhou, J.; Yan, S.; Zheng, X.; Lic, L.; Jin, L. *Cryst. Eng. Commun.* **2009**, *11*, 2640. (c) Pucci, D.; Crispini, A.; Ghedini, M.; Szerb, E. I.; Deda, M. L. *Dalton Trans.* **2011**, 4614.
(2) Depero, L. E.; Curri, M. L. *Curr. Opin. Solid State Mater. Sci.* **2004**, *8*, 103.
(3) Ruben, M.; Rojo, J.; Salguero, F. J. R.; Uppadine, L. H.; Lehn, J. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 3644.
(4) Maspoch, D.; Ruiz-Molinaa, D.; Veciana, J. *Chem. Soc. Rev.* **2007**, *36*, 770.
(5) Yan, Y.; Huang, J. *Coord. Chem. Rev.* **2010**, *254*, 1072.
(6) Batten, S. R.; Robson, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1460; *Angew. Chem.* **1998**, *110*, 1559.
(7) (a) Janiak, C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1431; *Angew. Chem.* **1997**, *109*, 1499. (b) Yaghi, O. M.; Li, H.; Davis, C.; Richardson, D.; Groy, T. L. *Acc. Chem. Res.* **1998**, *31*, 474.
(8) Lehn, J. M. *Supramolecular Chemistry*; Wiley-VCH: Weinheim, **1995**.
(9) MacGillivray, L. R.; Groeneman, R. H.; Atwood, J. L. *J. Am. Chem. Soc.* **1998**, *120*, 2676.
(10) Horcajada, P.; Chalati, T.; Serre, C.; Gillet, B.; Sebrie, C.; Baati, T.; Couvreur, P.; Gref, R. *Nature Materials* **2010**, *9*, 172.
(11) Batten, S. R.; Robson, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1460; *Angew. Chem.* **1998**, *110*, 1559.
(12) (a) Janiak, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1431; *Angew. Chem.* **1997**, *109*: 1499. (b) Yaghi, O. M.; Li, H.; Davis, C.; Richardson, D.; Groy, T. L. *Acc. Chem. Res.* **1998**, *31*, 474.
(13) Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1079; *Angew. Chem.* **1995**, *107*, 1181.
(14) Brunet, P.; Simard, M.; Wuest, J. D. *J. Am. Chem. Soc.* **1997**, *119*, 2737.
(15) Raynes, K.; Foley, M.; Tilley, L.; Deady, L. W. *Biochem. Pharmacol.* **1996**, *52*, 551.
(16) Ali, Basem. F.; Al-Souod, K.; Al-Ja'ar, N.; Nasser, A.; Zaghal, M. H.; Judeh, Z.; Al-Far, R.; Al-Refai, M.; Al-Obaidi, K. H. *J. Coord. Chem.* **2006**, *59*, 229.
(17) Wrasidlo, W.; Norris, S. O.; Wolfe, J. F.; Katto, T.; Stille, J. K. *Macromolecules* **1976**, *9*, 512.
(18) Wrasidlo, W.; Stille, J. K. *Macromolecules* **1976**, *9*, 505.
(19) Ichikawa, J.; Mori, T.; Miyazaki, H.; Wada, Y. *Synlett* **2004**, 1219.
(20) Saavedra, L. A.; Vallejos, C. G.; Kouznetsov, V. V.; Gutierrez, C. M.; Meléndez Gómez, C. M.; Leonor, Y.; Méndez, V.; Jaimes, J. H. B. *Synthesis* **2010**, 593.
(21) Viau, L.; Senechal, K.; Maury, O.; Guegan, J. P.; Dupau, P.; Toupet, L.; Bozec, H. L. *Synthesis* **2003**, 577.
(22) Janiak, C.; Deblon, S.; Uehlin, L. *Synthesis* **1999**, 959.
(23) Aksenov, A. V.; Goncharov, V. I. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2008**, *44*, 12.
(24) Hu, Y. Z.; Zhang, G.; Thummel, R. P. *Org. Lett.* **2003**, *5*, 2251.
(25) Pucci, D.; Crispini, A.; Ghedini, M.; Szerb, E. I.; Deda, M. L. *Dalton Trans.* **2011**, 4614.
(26) (a) Oparine, M. P. *Ber. Dtsch. Chem. Ges. B* **1931**, *64*, 569. (b) Bak, B. J. *J. Org. Chem.* **1956**, *21*, 797.
(27) Nakano, S. *J. Pharm. Soc. Jpn.* **1959**, *79*, 310.
(28) Lekhok, K. C.; Bhuyan, D.; Prajapati, D.; Boruah, R. C. *Mol. Diversity* **2010**, *14*, 841.
(29) Jian, F. Z.; Xiao, J. S.; Feng, W. L.; Meng, L.; Lu, L. *Z. Res. Chem. Intermed.* DOI: 10.1007/s11164-012-0696-5.
(30) **6,6′-Dinitro-4,4′-diphenyl-2,3′-biquinolin-2′(1′*H*)-one (3g):** To a stirred suspension of 2-amino-5-nitrobenzophenone (**2d**; 1 mmol) in acetic acid (20 mL), appropriate 3-acetyl-6-nitro-4-phenylquinolin-2(1*H*)-one (**1d**; 1 mmol) was added, followed by the addition of a catalytic amount of H_2SO_4 (0.5 equiv). The reaction mixture was heated to reflux for 3–5 h and the course of the reaction was monitored by TLC. After cooling to r.t., the mixture was poured into crushed ice (500 g) and the resulting residue was filtered to afford the desired product, which was purified by

silica gel column chromatography (hexane–EtOAc, 7:3 v/v) to afford the target compound (72%) as a pale-yellow solid. Mp 254–258 °C. IR (KBr): 3311.18, 2865.7, 1822.4, 1653.66, 1532.17, 1334.5, 1258.32, 1069.33, 897.70, 703.89 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.88 (s, 1 H, Q-NH), 8.63 (d, *J* = 2.5 Hz, 1 H, ArH), 8.42–8.45 (m, 2 H, ArH), 8.11 (d, *J* = 9.0 Hz, 1 H, ArH), 7.98 (d, *J* = 2.5 Hz, 1 H, ArH), 7.61–7.65 (m, 5 H, ArH), 7.46 (dd, *J* = 1.5, 8 Hz, 2 H, ArH), 7.33–7.36 (m, 5 H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.36, 158.77, 150.02, 149.08, 145.87, 143.61, 142.16, 136.31, 134.45, 132.98, 131.69, 129.88, 129.58, 129.04, 128.77, 125.86, 123.93, 113.33, 119.71, 117.21. MS: *m*/*z* = 514 [M + H]. Anal. Calcd for $C_{30}H_{18}N_4O_5$: C, 70.03; H, 3.53; N, 10.89. Found: C, 69.98; H, 3.55; N, 10.92%.

(31) Xuegang, C.; Dongfang, Q.; Liang, M.; Xanxiang, C.; Yanhou, G.; Zhiyuan, X.; Lixiang, W. *Transition Met. Chem.* **2006**, *31*, 639.

(32) **7-Methoxy-3-(4-phenylquinolin-2-yl)-2*H*-chromen-2-one (5g):** To a stirred suspension of 2-aminobenzophenone (**2a**; 1 mmol) in acetic acid (20 mL), appropriate 3-acetyl-7-methoxy-2*H*-chromen-2-one (**4b**; 1 mmol) was added, followed by the addition of a catalytic amount of H_2SO_4 (0.5 equiv). The reaction mixture was heated to reflux for 3–5 h, then the course of the reaction was monitored by TLC. After cooling to r.t., the mixture was poured into crushed ice (500 g); the resulting residue was filtered to afford the desired product, which was purified by silica gel column chromatography (hexane–EtOAc, 8:2 v/v) to afford the target compound (82%) as a pale-green solid. Mp 216–220 °C. IR (KBr): 3059.51, 1718.26, 617.02, 1583.27, 1502.28, 1358.6, 1237.11, 1187.94, 1021.12, 834.06, 703.89 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.99 (s, 1 H, C4-H), 8.40 (s, 1 H, C4–H), 8.22 (d, *J* = 8.50 Hz, 1 H, ArH), 7.97 (d, *J* = 8.50 Hz, 1 H, ArH), 7.76 (t, *J* = 8.00 Hz, 1 H, ArH), 7.51–7.60 (m, 6 H, ArH), 6.95 (d, *J* = 2.00 Hz, 1 H, ArH), 6.93 (dd, *J* = 2.50, 10.00 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.46, 160.80, 156.23, 152.16, 148.69, 148.52, 143.82, 138.22, 130.08, 129.76, 129.74, 129.48, 128.53, 128.38, 126.65, 126.26, 125.79, 122.57, 121.81, 113.41, 113.19, 100.31, 55.86; MS: *m*/*z* = 379 [M + H]. Anal. Calcd for $C_{25}H_{17}NO_3$: C, 79.14; H, 4.52; N, 3.69. Found: C, 7.19; H, 4.49; N, 3.71%.

(33) Cif files for **5f** and **5g** have been deposited with the Cambridge Crystallographic Data Centre as CCDC-895741 (**5f**) and 890933 (**5g**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. [Fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

