Tetrahedron Letters 50 (2009) 2057–2059

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chlorosulfonic acid-mediated cyclization of 4-phenyl-3-isocoumarincarboxylic acids and 4-phenyl-3-isoquinolinonecarboxylic acids: an efficient synthesis of 3-oxoindeno[2,1-*c*]isocoumarins and 3-oxoindeno[2,1-*c*]isoquinolinones

Prakash G. Jagtap *, Zhiyu Chen, Garry J. Southan

Inotek Pharmaceuticals Corporation, 33 Hayden Avenue, Lexington, MA 02421, United States

ARTICLE INFO

Article history:
Received 24 December 2008
Revised 10 February 2009
Accepted 11 February 2009
Available online 15 February 2009

ABSTRACT

A highly efficient and clean method has been developed for the synthesis of 3-oxoindeno[2,1-*c*]isocoumarins and 3-oxoindeno[2,1-*c*]isoquinolinones from 4-phenyl-3-isocoumarincarboxylic acids and 4-phenyl-3-isoquinolinonecarboxylic acids, respectively.

Isoquinolinones and compounds possessing an isoquinolinone-pharmacophore are well known for their important therapeutic potential.[1–7] Some isoquinolinone derivatives exhibit prominent biological effects such as antitumor,[1,6,7] cytotoxic antibiotic,[2] and cardiovascular activities.[3] The tetracyclic isoquinolinone, 11-oxo-indeno[1,2-*c*]isoquinoline (**1a**), has been known for several years.[8] Formation of its derivative was initially reported while synthesizing nitidine chloride[6a,b] which was later identified as a potential topoisomerase I (top1) inhibitor, NSC 314622.[6c] Recently, we have reported the results from structure–activity relationship (SAR) studies[9] of poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors,[10] which are based on the indeno[1,2-*c*]isoquinolinone scaffold (**1b**). The recent reports[11,12] on new syntheses of indenoisoquinolinone and benz[d]indeno[1,2-b]pyran-5,11-dione derivatives (**1a–d**) as the top1 and PARP-1 inhibitors justify the reevaluation of this class of tetracyclic scaffolds (Fig. 1).

We were interested in the synthesis[13] of indeno[2,1-*c*]isoquinolinones (**2** and **3**) due to their structural similarity with indeno[1,2-*c*]isoquinolinones analogues (**1**) that we investigated recently as PARP-1 inhibitors.[9] There are a limited number of literature methods[7,14] available for the synthesis of lactams **2** and **3**. Patented method[7] for the synthesis of **2a** from **7a** requires harsh reaction conditions (i.e., PPA at 100 °C). As a result of its tedious workup procedure, we were unable to isolate the product as reported. Additionally, the treatment of 2-*O*-benzoylindanone with 90% H_2SO_4 did not produce even a trace of the desired product **8** by following the literature methods (Fig. 2).[14] Due to the above mentioned reasons, it was imperative to investigate new synthetic methods that will give an easy access to these tetracyclic lactones and lactams. Herein, we present an efficient method for the rapid construction of 3-oxoindeno[2,1-*c*]isocoumarins (**6**) and 3-oxoindeno[2,1-*c*]isoquinolinones (**2**) from 4-phenyl-3-isocoumarincarboxylic acids (**5**) and 4-phenyl-3-isoquinolinonecarboxylic acids (**7**), respectively (Schemes 1 and 2).

The syntheses of 3-oxoindeno[2,1-*c*]isocoumarin (**6**) and 3-oxoindeno[2,1-*c*]isoquinoline (**2**) were performed as depicted in Scheme 1. Using the literature method,[15] the commercially available 2-benzoylbenzoic acids (**4a–d**) were converted to 4-phenyl-3-isocoumarincarboxylic acids (**5a–d**). Cyclization of **5a** using neat polyphosphoric acid (PPA)[7,16] resulted in poor yield. A similar cyclization reaction with PPA in xylene[17] produced **6a** but the workup procedure to isolate the product in pure form was complicated. However, our further attempts to cyclize **5a** using chlorosulfonic acid produced isocoumarin **6a** in excellent yield. Cyclization was completed in less than 30 min and as a result of its simple workup procedure, the product was readily isolated from the reaction mixture. Additionally, we have not seen any aromatic chlorosulfonylated byproducts under these conditions. The potential of this intramolecular cyclization was studied with isocoumarin derivatives **5b**, **5c,** and **5d**. Their reaction with chlorosulfonic acid was immediate and produced **6b**, **6c,** and **6d** in excellent yield.

As shown in Scheme 1, the 4-phenyl-3-isoquinolinonecarboxylic acids (**7a–d**) were prepared from isocoumarin derivatives (**5a–d**) using ammonia. Similarly, under the above mentioned reaction conditions, treatment of **7a** with chlorosulfonic acid at 0 °C produced exclusively indenoisoquinolinone **2a** in excellent yield (Table 1). Indenoisoquinolinone derivatives **2b**, **2c,** and **2d** were also obtained in excellent yield from the cyclization of **7b**, **7c,** and **7d**, respectively. However, the treatment of chlorosulfonic acid with nitro derivative **7e** (Scheme 2) did not produce the desired tetracyclic product. The 4-nitro-compound **7e** remained unreactive under the above mentioned reaction conditions.

* Corresponding author. Tel.: +1 781 676 2118; fax: +1 781 676 2155.
E-mail address: pjagtap@inotekcorp.com (P.G. Jagtap).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.089

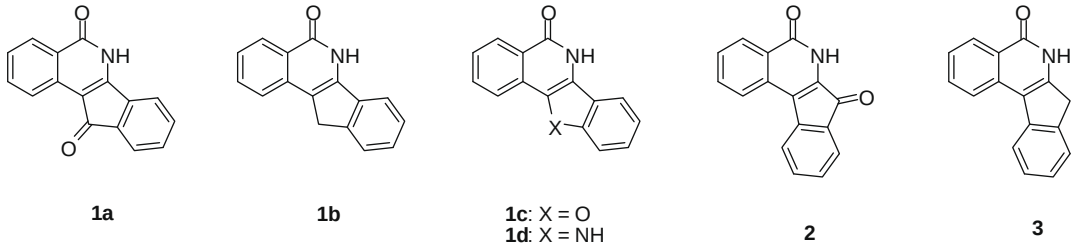


Figure 1. Structures of tetracyclic lactam scaffolds 5*H*-indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (**1a**), 6,11-dihydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (**1b**), benzofuro[3,2-*c*]isoquinolin-5(6*H*)-one (**1c**), 6,11-dihydro-5*H*-indolo[3,2-*c*]isoquinolin-5-one (**1d**), 5*H*-indeno[2,1-*c*]isoquinoline-5,7(6*H*)-dione (**2**), and 6,7-dihydro-5H-indeno[2,1-*c*]isoquinolin-5-one (**3**).

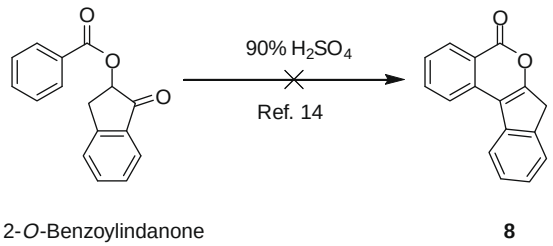
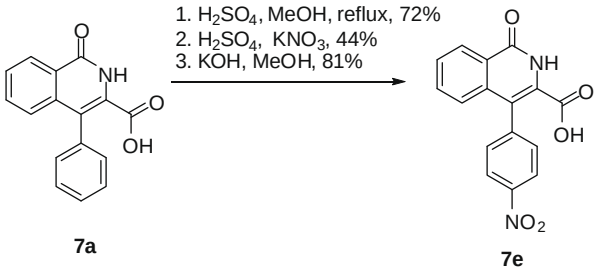


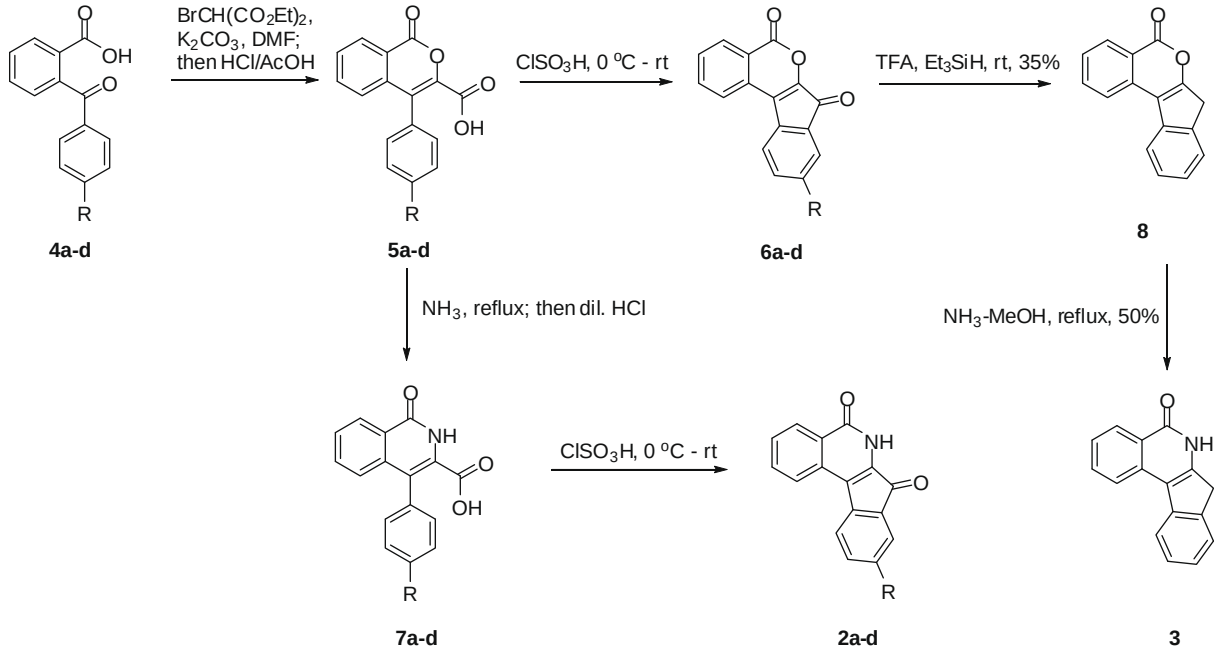
Figure 2. Attempts to make **8** using the literature method.[14]



Scheme 2. Synthesis of **7e**.

Since our attempts to make an intermediate **8** using literature methods[14] were fruitless, we selected compound **6a** as a starting material for the synthesis of **3**. It was reacted with TFA and triethylsilane at room temperature,[9] which provided a mixture of products. The desired product **8** was then separated from the mixture using silica gel column chromatography. However, the reaction of **2a** with TFA and triethylsilane produced a mixture of **3** along with several other non-separable byproducts. The product obtained from the reduction of **6a** was more easily purified by column chromatography than the product obtained from the reaction of insoluble lactam derivative **2a**. Indenoisoquinolinone **3** was ultimately obtained from the reaction of **8** with ammonia in MeOH.

In summary, an efficient method has been developed for the synthesis of 3-oxoindeno[2,1-*c*]isocoumarins and 3-oxoindeno[2,1-*c*]isoquinolinone using chlorosulfonic acid as cyclizing agent. These new routes allow practical and reproducible syntheses of tetracyclic compounds **2**, **3**, **6,** and **8**, and gave an easy access to them as compared to the literature methods.[7,14] The in vitro and in vivo experimental results of lead compounds from scaffolds **2** and **3** will be published elsewhere.



Scheme 1. Synthesis of 3-oxoindeno[2,1-*c*]isocoumarins (6a–d) and 3-oxoindeno[2,1-*c*]isoquinolinones (2a–d).

Table 1
Indenoisocoumarin and indenoisoquinolinone derivatives and intermediates produced via Scheme 1

Entry	Starting compound	Reagent	Product	Yield (%)
1	**4a** (R = H)	$BrCH(CO_2Et)_2$	**5a** (R = H)[15b]	89
2	**4b** (R = Me)	$BrCH(CO_2Et)_2$	**5b** (R = Me)[16]	92
3	**4c** (R = $(CH_2)_3COOH$)	$BrCH(CO_2Et)_2$	**5c** (R = $(CH_2)_3COOH$)[19]	80
4	**4d** (R = Cl)	$BrCH(CO_2Et)_2$	**5d** (R = Cl)[19]	66
5	**5a** (R = H)[15b]	$ClSO_3H$	**6a** (R = H)[18]	95
6	**5b** (R = Me)[16]	$ClSO_3H$	**6b** (R = Me)[16]	89
7	**5c** (R = $(CH_2)_3COOH$)	$ClSO_3H$	**6c** (R = $(CH_2)_3COOH$)[19]	88
8	**5d** (R = Cl)	$ClSO_3H$	**6d** (R = Cl)[19]	96
9	**7a** (R = H)[15a]	$ClSO_3H$	**2a** (R = H)[18]	96
10	**7b** (R = Me)[15c]	$ClSO_3H$	**2b** (R = Me)[19]	94
11	**7c** (R = $(CH_2)_3COOH$)	$ClSO_3H$	**2c** (R = $(CH_2)_3COOH$)[19]	95
12	**7d** (R = Cl)	$ClSO_3H$	**2d** (R = Cl)[19]	93
13	**7e** (R = NO_2)[15a]	$ClSO_3H$	**2e** (R = NO_2)	0
14	**6a**	TFA-Et_3SiH	**8**[19]	35
15	**8**	NH_3-MeOH	**3**[19]	50

See Refs. 18 and 19 for the general cyclization procedure of **6a** and **2a**, and spectral data of **6a**, **5c–d**, **2a–d**, **7c–d**, **8,** and **3**.

Acknowledgments

This work was supported by grants from the National Institutes of Health (R44DK054099 and R44GM058986).

References and notes

1. Cheon, S. H.; Park, J. S.; Lee, J. Y.; Yi, H.; Chung, B. H.; Choi, B. G.; Cho, W. J.; Choi, S. U.; Lee, C. O. *Arch. Pharm. Res.* **2001**, *24*, 276.
2. Fidalgo, M. L.; Arias, M. S.; Soliveri, J.; Arias, M. E. *J. Antibiot.* **1992**, *45*, 1759.
3. (a) Chiarugi, A.; Meli, E.; Calvani, M.; Picca, R.; Baronti, R.; Camaioni, E.; Costantino, G.; Marinozzi, M.; Pellegrini-Giampietro, D. E.; Pellicciari, R.; Moroni, F. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 943; (b) Hutchinson, J. H.; Cook, J. J.; Brashear, K. M.; Breslin, M. J.; Glass, J. D.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Hartman, G. D. *J. Med. Chem.* **1996**, *39*, 4583.
4. Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Takagi, M.; Kikkawa, K.; Omori, K. *J. Med. Chem.* **2001**, *44*, 2204.
5. Matsui, T.; Sugiura, T.; Nakai, H.; Iguchi, S.; Shigeoka, S.; Takada, H.; Odagaki, Y.; Nagao, Y.; Ushio, Y.; Ohmoto, K.; Iwamura, H.; Yamazaki, S.; Arai, Y.; Kawamura, M. *J. Med. Chem.* **1992**, *35*, 3307.
6. (a) Cushman, M.; Cheng, L. *J. Org. Chem.* **1978**, *43*, 286; (b) Cushman, M.; Cheng, L. *J. Org. Chem.* **1978**, *43*, 3781; (c) Kohlhagen, G.; Paull, K.; Cushman, M.; Nagafuji, P.; Pommier, Y. *Mol. Pharmacol.* **1998**, *54*, 50.
7. Okazaki, S.; Asao, T.; Wakida, M.; Ishida, K.; Washinosu, M.; Utsugi, T.; Yamada, Y. WO9532187.
8. (a) Chatterjea, J. N.; Mukherjee, H. *J. Indian Chem. Soc.* **1960**, *37*, 379; (b) Dusemund, J.; Kroeger, E. *Arch. Pharm.* **1984**, *317*, 381; (c) Ando, K.; Tokoroyama, T.; Kubota, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1008.
9. Jagtap, P. G.; Baloglu, E.; Southan, G. J.; Mabley, J. G.; Zhou, J.; Li, H.; van Duzer, J.; Salzman, A. L.; Szabó, C. *J. Med. Chem.* **2005**, *48*, 5100.
10. For the reviews of PARP Inhibitors see: (a) Jagtap, P.; Szabó, C. *Nat. Rev. Drug Disc.* **2005**, *4*, 421; (b) Peukert, S.; Schwahn, U. *Exp. Opin. Ther. Pat.* **2004**, *14*, 1531–1551; (c) Southan, G. J.; Szabó, C. *Curr. Med. Chem.* **2003**, *10*, 321; (d) Cosi, C. *Exp. Opin. Ther. Pat.* **2002**, *12*, 1047.
11. Jagtap, P. G.; Baloglu, E.; Southan, G.; Williams, W.; Roy, A.; Nivorozhkin, A.; Landrau, N.; Desisto, K.; Salzman, A.; Szabó, C. *Org. Lett.* **2005**, *7*, 1753.
12. Morrell, A.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *Bioorg. & Med. Chem. Lett.* **2006**, *16*, 1846.
13. Jagtap, P.; Szabó, C. U.S. patent 7,217,709 B2, 2007.
14. (a) Jha, G.; Srivastava, J. N. *Indian J. Chem., Sect B* **1985**, *24B*, 440; (b) Srivastava, S.; Kumar, P.; Thakur, S. N.; Sahay, L. K.; Jagdish, N. *J. Ind. Chem. Soc.* **1989**, *66*, 276; (c) Chatterjea, J. N.; Banerjee, B. K.; Jha, H. C. *J. Ind. Chem. Soc.* **1967**, *44*, 911.
15. (a) Duro, F.; Condorelli, P. *Boll. Sedute Accad. Gioenia Sci. Nat. Catania* **1960**, *6*, 606; Duro, F.; Condorelli, P. *Chem. Abstr.* **1963**, *58*, 9010; (b) Duro, F.; Santagati, N. A.; Vittori, F. *Farmaco* **1981**, *36*, 400; (c) Nunami, K.; Suzuki, M.; Yoneda, M. *J. Org. Chem.* **1979**, *44*, 1887.
16. Chatterjea, J. N.; Jha, H. C.; Chattopadhyaya, A. K. *J. Liebigs Ann. Chem.* **1974**, 1126.
17. Guy, A.; Guette, J.-P.; Lang, G. *Synthesis* **1980**, 222.
18. Typical procedure for the cyclization of 4-phenyl-3-isocoumarincarboxylic acids (**5**) and 4-phenyl-3-isoquinolinonecarboxylic acids (**7**) using chlorosulfonic acid: Acid **5a** (5 g, 18.79 mmol) was slowly added to chlorosulfonic acid (50 ml) over 5 min. at 0 °C and vigorously stirred for 5 min. Then, the ice bath was removed and the reaction mixture was stirred at rt for additional 10 min. The mixture was slowly poured on the ice. The orange colored solid precipitated out was filtered and washed thoroughly with water. It was then dried under vacuum to provide cyclized product **6a** (4.440 g, 95%). ^{1}H NMR (DMSO-d_6): δ 7.30–7.35 (dd, J = 8.1 and 7.2 Hz, 1H), 7.44–7.49 (dd, J = 8.1 and 7.5 Hz, 1H), 7.51–7.56 (t, J = 7.5 Hz, 1H), 7.80–7.85 (t, J = 7.5 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.99–8.04 (dd, J = 7.5 and 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H). ^{13}C NMR δ 123.08 (2 ArC), 124.26, 125.72, 129.01, 129.52, 131.02, 131.68, 132.14, 135.77, 136.10, 136.67 (2 ArC), 139.36, 166.39, 180.20.
19. ^{1}H and ^{13}C NMR data of **5c–d**, **7c–d**, **2a–d**, **8,** and **3** (300 MHz, DMSO-d_6): Compound **5c** ^{1}H NMR δ 1.80–1.90 (m, 2H), 2.23–2.28 (dd, J = 7.2 and 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 7.5 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.69–7.84 (m, 2H), 8.27 (d, J = 7.8 Hz, 1H), 12.20 (bs, 1H), 13.42 (bs, 1H). Compound **5d** ^{1}H NMR δ 6.99 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.7 HZ, 2H), 7.70–7.75 (dd, J = 7.2 and 7.5 Hz, 1H), 7.80–7.84 (dd, J = 7.2 and 6.9 Hz, 1H), 8.27 (d, J = 7.2 Hz, 1H), 13.58 (s, 1H). Compound **7c** ^{1}H NMR δ 1.93–2.03 (m, 2H), 2.31–2.36 (dd, J = 7.2 and 7.5 Hz, 2H), 2.71–2.76 (dd, J = 7.8 and 7.2 Hz, 2H), 7.12 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.61–7.74 (m, 2H), 8.33 (d, J = 7.5 Hz, 1H), 12.35 (s, 1H). Compound **7d** ^{1}H NMR δ 6.99 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 6.9 Hz, 1H), 7.56 (t, J = 6.9 Hz, 1H), 8.23 (d, J = 7.5 Hz, 1H), 10.23 (s, 1H, NH). Compound **2a** ^{1}H NMR δ 7.22–7.27 (dd, J = 7.2 and 7.5 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.71–7.76 (dd, J = 7.5 and 7.8 Hz, 1H), 7.89–7.95 (m, 2H), 8.36 (d, J = 9.0 Hz, 1H), 8.40 (d, J = 9.3 Hz, 1H), 12.18 (bs, 1H). ^{13}C NMR δ 122.17, 124.15, 124.41, 125.41, 128.13, 129.28 (2 ArC), 129.98, 130.88, 132.76, 134.20, 134.43, 135.89, 142.99, 161.88 (lactam CO), 188.68 (keto CO). Compound **2b** ^{1}H NMR δ 2.30 (s, 3H), 7.29 (s, 1H), 7.70–7.75 (dd, J = 7.2 and 7.8 Hz, 2H), 7.78–7.80 (dd, J = 8.1 and 6.9 Hz, 1H), 7.88–7.92 (dd, J = 7.5 and 6.9 Hz, 1H), 8.34 (d, J = 7.8 Hz, 2H), 12.13 (s, 1H). Compound **2c** ^{1}H NMR δ 2.07–2.11 (dd, J = 5.4 and 6.6 Hz, 2H), 2.61–2.65 (t, J = 6.3 Hz, 2H), 2.99–3.03 (dd, J = 5.4 and 5.7 Hz, 2H), 7.02 (d, J = 7.8 Hz, 1H), 7.44 (s, 1H), 7.57–7.69 (m, 4H), 8.28–8.31 (dd, J = 1.2 and 7.8 Hz, 1H), 11.10 (s, 1H); MS (ES$^+$): m/z 334.1616 (M+1). Compound **2d** ^{1}H NMR δ 7.45 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.70–7.75 (dd, J = 8.1 and 7.2 Hz, 1H), 7.88(d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 8.4 Hz, 2H), 12.25 (s, 1H). Compound **8**: δ 3.94 (s, 2H), 7.26–7.31 (dd, J = 7.2 and 7.5 Hz, 1H), 7.40–7.45 (dd, J = 7.2 and 7.8 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.63–7.68 (dd, J = 7.5 and 7.8 Hz, 1H), 7.95–8.00 (dd, J = 7.8 and 7.5 Hz, 1H), 8.08 (d, 7.5 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.33 (d, 8.4 Hz, 1H). ^{13}C NMR δ 36.29, 114.26, 120.02, 121.28, 123.50, 125.16, 125.66, 127.80, 128.64, 131.18, 134.59, 136.48 (2 ArC), 137.40, 139.30, 166.37. Compound **3**: δ 3.85 (s, 2H), 7.16–7.21 (dd, J = 7.2 and 7.5 Hz, 1H), 7.35–7.40 (dd, J = 7.5 and 7.8 Hz, 1H), 7.51–7.57 (m, 2H), 7.82–7.88 (dd, J = 7.5 and 7.8 Hz, 1H), 8.05 (d, J = 7.5 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 8.38 (d, J = 8.1 Hz, 1H), 12.16 (s, 1H). ^{13}C NMR δ 36.13 (CH_2), 113.84, 120.37, 123.35, 124.37, 125.06, 125.63, 126.32, 127.70, 128.83, 133.65, 134.87, 139.12, 141.52, 147.13, 162.50.