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One-pot access to pyridocoumarins via Povarov-hydrogen transfer cascade under auto-tandem catalysis of iodine in aqueous micelles

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ABSTRACT

A cascade of inverse electron demand Diels–Alder reaction of 6-aminocoumarin-derived aldimines with an excess of styrene and oxidative aromatization of the formal Povarov adducts under autotandem iodine catalysis in aqueous micellar conditions provides direct access to a small library of substituted pyridine annulated coumarins in good to acceptable yields (12 examples). The unusual formation of linearly annulated pyridocoumarins under essentially neutral conditions is a remarkable feature of the protocol.

Quinolines constitute core substructure of a broad spectrum of biologically relevant molecules including antimalarial,[1a] antiasthmatic,[1b] antihypertensive,[1c] antiinflammatory[1d] and several new generation antibacterial drugs.[2] Apart from their substantial presence in drug and pharmaceutical space, quinoline-based polymers find diverse utilities in electronics, optoelectronics and nonlinear optics.[3] Tetrahydroquinoline also features in naturally occurring alkaloids such as flindersine, oricine, vesprine with psychotropic antiallergic and oestrogenic activities.[4a–d] Aryl tetrahydroquinolines are potential neuroprotective agents[4e] and act as anti-HIV agents in vitro.[4f] Therefore, developing new multicomponent synthetic protocols for these functionalized heterocyclic scaffolds has evoked major contemporary response.[5] The three-component Lewis/Bronsted acid-catalysed version of the Povarov reaction involving aromatic amine, aldehyde and electron-rich dienophile is a popular approach for entry into this class of compounds.[6] It is an important tool for diversity oriented synthesis (DOS).[7] It allows for functional, skeletal and stereochemical diversity by installation of different functional elements in these components and appending other privileged heterocyclic motifs onto quinolines for construction of new chemotypes of biological relevance. 3-Aminocoumarin-derived aldimines have been recently employed as 'enamine-like' heterodiene components for inter-, intramolecular Povarov reactions.[8] Literature survey revealed that substrate scope of the amine for DOS library construction by Povarov reaction has received limited attention although a host of aldehydes and dienophiles have been exploited. In continuation of our interest to develop environmentally benign approaches[9] towards biologically important targets we became interested to evaluate the potential of 6-aminocoumarin (**1**) as an amine component for Povarov reaction with aromatic aldehyde and styrene as partners. It is easily accessible and the amino group is segregated from the electron withdrawing influence of the α-pyrone ring due to the absence of vinylogous resonance imparting it 'aniline-like' nature. This contention is supported by DFT calculation at B3LYP level which clearly shows the ambiphilic character of **1** with C-5 as the seat of highest electron density among ring carbons only to be followed by C-7 (C-5 and C-7 correspond to 6 and 4 positions of 6-aminocoumarin in DFT calculations, see Supporting information). The in situ 2-azadiene derived from it is anticipated to serve as a building block for tetrahydropyridocoumarins, either angularly or linearly fused with its benzenoid ring, via Povarov cycloaddition. It represents a different paradigm from 3-aminocoumarin-based annulation of the same motif onto 3, 4 position of α-pyrone. Iodine has emerged as an attractive mild Lewis acid catalyst for a plethora of organic transformations including C–C, C–O and C–N bond formation reactions.[10] It is non-toxic and may be used in water as well as organic solvents. Herein, we reveal one-pot three-component imino Diels–Alder reaction of 6-aminocoumarin (**1**), aromatic aldehyde and styrene with iodine catalyst under aqueous micellar conditions to deliver pyridine-annulated coumarins.

For initial exploratory studies, an assembly of 6-aminocoumarin (**1**, 1 equiv), benzaldehyde (**2a**, 1.1 equiv) and styrene (**3**, 1.2 equiv)

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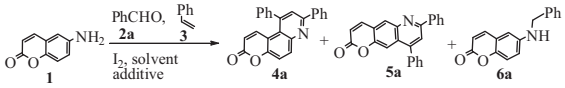
was submitted to reaction under aqueous micellar condition [H_2O (10 mL)-SDS (234 mg, 0.8 mmol)] without any additional catalyst at room temperature as well as 60–70 °C resulting in isolation of Schiff's base as the sole product (Table 1 entries 1 and 2). However, no Povarov adduct was formed in isolable amount. Attempted reaction with 2 mol % of iodine catalyst without surfactant under 'on water' condition[11] with a slurry of the reactants at 60–70 °C did not proceed to completion but, surprisingly, yielded Schiff's base reduction product **6a** together with minor amounts of two pyridocoumarins **4a** and **5a** in a sluggish reaction (entry 3). It was also revealed that the reaction was considerably accelerated upon addition of the sodium dodecyl sulfate (234 mg, 0.8 mmol) to the above reaction mixture under otherwise identical conditions and provided **4a** and **5a** in better yields (entry 4). Increment of catalyst loading to 5 mol % further improved the reaction rate and yield of products. But the major constraint was the substantial depletion of Schiff's base due to its concomitant reduction making it less available for generation of cycloadduct. To address the issue, we felt that an excess of styrene might be utilized in an additional role of external sacrificial oxidant to restrict the oxidative role of the imine particularly because its C=C is more prone to reduction than C=N bond of imines. It is a cost effective option than earlier approaches of using an excess of imine to attain higher yields of targeted quinolines.[12]

To our gratification, this diversionary strategy worked reasonably well and an impressive combined yield of **4a** and **5a** was accomplished with an excess of styrene using 5 mol % of iodine catalyst in H_2O-SDS at 60–70 °C (entry 7). Nevertheless, the oxidative capture of putative Povarov adduct by Schiff's base could not be eliminated altogether even under this condition. Attempt to circumvent this problem by using external oxidizers was not very much of a success either. In separate experiments, DDQ and CAN (2 millimolar each) were employed as additives and the reactions were performed in the presence of non-excess styrene (1.2 mmol) under otherwise similar conditions (entries 8 and 9). Comparable combined yields of **4a** and **5a** were scored under these conditions. However, variable amounts of reduced Schiff's base were also isolated implying that the internal hydrogen transfer process was not completely precluded under these conditions. Increasing catalyst loading to 10 mol % did not further improve the reaction efficiency. Cationic and neutral amphiphiles viz. CTAB and Triton-X 100 were also screened but they were less supportive to the reaction (entries 11 and 12). The superior catalytic activity of iodine was presumably linked to its activation by SDS.[13] It was also observed that iodine was a relatively poor catalyst in organic solvents such as CH_3CN and THF (entries 13 and 14). This optimized reaction condition[14] was applied successfully to a diverse range of aromatic aldehydes substituted with electron-releasing and electron withdrawing groups (12 cases). These results are summarized in Table 2.

The procedure proved successful for all aromatic aldehydes investigated (12 examples). The presence of electron-releasing *p*-allyloxy and -methoxy did not significantly influence either the combined yield of quinolines (73–66%) or the product distribution (entries 2 and 3). However, electronically similar 3, 4-methylenedioxybenzaldehyde delivered relatively poor overall yield of 54% (entry 4). On the other hand, those substituted with electron-withdrawing Br, F and CHO scored lower overall yields (30–48%), with the exception of *p*-chlorobenzaldehyde (76%). The angularly annulated products were always preferred to their linear counterparts. It was strikingly demonstrated for 4-fluorobenzaldehyde and benzene 1, 3-dialdehyde where isolable amount of the linear products was not formed (entries 8 and 9). The hydrophobic environment of the micellar cavity seems to favour the more compact angularly annulated product.[15] Another notable feature was the absence of formal tetrahydroquinoline precursors of all these products. 6-Amino-1-methyl quinoline-2-(1*H*)-one (**1a**) also participated in the reaction to provide two new skeletal structures, 8-(4-chlorophenyl)-4-methyl-10-phenylbenzo[*f*]quinolin-3(4*H*)-one (**4f**) and 7-(4-chlorophenyl)-1-methyl-9-phenylbenzo[*g*]quinolin-2(1*H*)-one (**5f**). Furyl-2-aldehyde (**2i**) was also tolerated and gave impressive yield of pyridocoumarins. Interestingly, the elusive tetrahydroquinoline intermediate was isolated as the major product (40%) with *p*-iodobenzaldehyde as the aldehyde

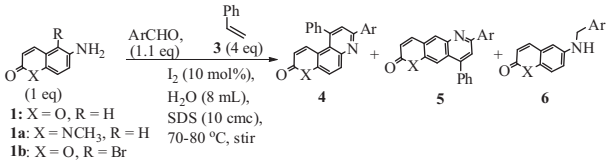
Table 1
Optimization of iodine-catalysed three-component reaction of 6-aminocoumarin, benzaldehyde and styrene



Entry	I_2 (mol %)	Solvent	Additives (mmol)	**3** (mmol)	Reaction time (h)[a]	Products[b] (%)		
						4a	**5a**	**6a**
1	—	H_2O	SDS	1.2	8[c]	—	—	—
2	—	H_2O	SDS	1.2	8[c]	—	—	—
3	2	H_2O	—	1.2	8	10	5	29
4	2	H_2O	SDS	1.2	5	16	7	44
5	5	H_2O	SDS	1.2	5	20	8	52
6	5	H_2O	SDS[d]	1.2	5	17	7	47
7	5	H_2O	SDS	4	2	55	20	10
8	5	H_2O	SDS, DDQ[e]	1.2	2	54	10	15
9	5	H_2O	SDS, CAN[e]	1.2	2	48	15	17
10	10	H_2O	SDS	4	2	53	20	14
11	5	H_2O	CTAB	4	2	35	18	20
12	5	H_2O	Triton-X 100	4	2	44	13	24
13	5	THF (5 mL)	—	4	4.5	40	12	22
14	5	CH_3CN (5 mL)	—	4	3	42	13	20

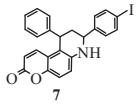
[a] Reactions were conducted on one milimolar scale of **1** with **2a** and **3** in 1.1 and 1.2/4 milimolar ratios respectively at 60–70 °C, solvent (10 mL), surfactant (0.8 mmol), unless otherwise stated. For entry 2, the reaction was performed at rt.
[b] Isolated yield upon column chromatography.
[c] Schiff's base was isolated in 42 and 58 %yields at rt and 60–70 °C respectively.
[d] SDS (0.4 mmol).
[e] 2 milimoles of DDQ and CAN were used.

Table 2
Cascade Povarov-hydrogen-transfer reaction catalysed by I_2



Entry	Amines	Ar	Time (h)	Products[a] (yield in %)		
1	**1**	**2a**, C_6H_5	2	**4a** (55)	**5a** (20)	**6a** (10)
2	**1**	**2b**, 4-OMe C_6H_4	2.5	**4b** (53)	**5b** (20)	**6b** (20)
3	**1**	**2c**, 4-*O*-allyl C_6H_4	2	**4c** (48)	**5c** (18)	**6c** (25)
4	**1**	**2d**,-OCH_2O-C_6H_4	3	**4d** (44)	**5d** (10)	**6d** (28)
5	**1**	**2e**, 4-Cl C_6H_4	2.5	**4e** (54)	**5e** (22)	**6e** (15)
6	**1a**	**2e**, 4-Cl C_6H_4	3.5	**4f** (40)	**5f** (15)	**6f** (30)
7	**1**	**2f**, 4-Br C_6H_4	3.5	**4g** (40)	**5g** (10)	**6g** (28)
8	**1**	**2g**, 4-F C_6H_4	3	**4h** (48)	—	**6h** (30)
9	**1**	**2h**, 3-CHO C_6H_4	3	**4i** (30)	—	**6i** (40)
10	**1**	**2i**, 	2.5	**4j** (50)	**5j** (30)	**6j** (10)
11	**1**	**2j**, 4-I C_6H_4	3	**4k** (25)	**7**[b] (40)	**6k** (7)
12	**1b**	**2a**, C_6H_5	5	**8**[b] (72)		

[a] Refers to isolated yield after chromatographic separation. All products were characterized by FTIR, ^1H, ^{13}C NMR, MS and elemental (C, H, N) analysis.
[b] Compounds **7** and **8** are tetrahydroquinolines.



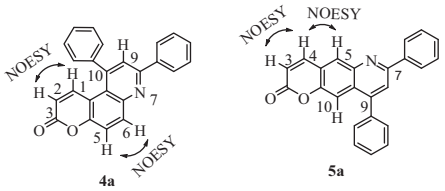


Figure 1. Single-crystal X-ray analysis of **7** confirmed its skeletal structure (Fig. 2).

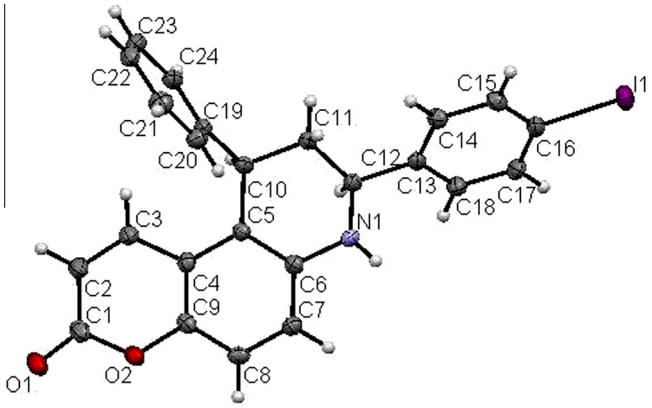


Figure 2. ORTEP diagram of **7**.

component (entry 11). It was reasoned that installation of bromine substituent at C-5 of 6-aminocoumarin would necessarily preclude angular annulation thereby directing the cycloaddition to otherwise less favourable C-7 position. Treating a mixture of 6-amino-5-bromocoumarin (**1b**), benzaldehyde (**2a**) and styrene under the optimized reaction conditions for 5 h led to exclusive formation of the corresponding linearly fused pyaranotetrahydroquinolone **8** in 72% yield (entry 12).

The ^1H NMR spectra **4a** and **5a** allowed complete assignment of their structures. The product **4a** exhibited, in addition to typical doublet signals of vinyl protons of the α-pyrone ring at 6.06 (1H, J = 10.2 Hz) and 7.33 (1H, J = 10.2 Hz), a diagnostic pair of one-proton doublets at δ 7.22 and 8.39 (each J = 9.2 Hz) corresponding to H-5 and H-6 respectively. This is consistent with angular annulations of the pyridine ring to the existing benzenoid ring of coumarin. A notable feature was the appearance of a sharp one-proton signal at δ 7.85 attributable to pyridine ring proton H-9 flanked by two phenyl groups. In contrast, ^1H NMR of **5a** significantly exhibited two sharp singlet resonance signals at 7.80 and 8.38 due to benzenoid *para* protons H-10 and H-5 respectively. The highly downfield nature of the signal was attributed to its *peri* nature with respect to pyridine nitrogen. The α-pyrone doublets also appeared relatively downfield at δ 6.53 and 7.93 (each J = 9.6 Hz) compared to those of **4a**. Their structures were further validated by NOESY studies. The cross peaks between H-2-H-1 and H-5-H-6 are compatible with angularly fused pyridocoumarin **4a**. Similarly, the presence of cross peaks between H-3-H-4 and H-4-H-5 confirms the formation of linear fusion in **5a** (Fig. 1). The exhibition of strong molecular ion base peaks at m/z = 350 $[M+1]^+$ for both **4a** and **5a** supports the assigned structures as 8,10-diphenyl-3*H*-pyrano[3,2-*f*]quinolin-3-one and 7,9-diphenyl-2*H*-pyrano[2,3-*g*]quinolin-2-one respectively.

It shows supramolecular dimeric nature through both intramolecular bifurcated hydrogen bonding between coumarin carbonyl and H-18 (Fig. 3, C=O···H, 2.56 Å) and π···π interactions. These dimeric units are further associated by C–H···π interactions (Fig. 3). Interestingly, noncovalent I···π interaction is also evident (Fig. 4) (supporting information).

This catalytic protocol basically relies upon orchestrated events of the formation of 6-aminocoumarin derived aldimine, its participation as a 2-azadiene in inverse electron demand Diels–Alder cycloaddition with styrene to give formal Povarov adducts and finally its aromatization by hydrogen transfer from either the N-coumarinyl aldimine or styrene delivering pyridocoumarins. A tentative catalytic cycle for the auto-tandem catalysis of iodine is depicted in Scheme 1.

To ascertain the influence of micellar environment and iodine in the initial event of Schiff's base formation, a vigorously stirred slurry of equimolar amounts of 6-aminocoumarin (**1**) and 4-bromobenzaldehyde (**2f**) was allowed to react in water at 60–70 °C for 6 h. The reaction did not proceed at all (TLC monitoring). In separate experiments, **1** and **2f** were reacted in H_2O-SDS, without and with iodine catalyst (5 mol %) under otherwise same conditions. Whereas the imine **9b** was obtained in 50% yield in water-SDS without iodine, marked improvement in yield and reaction rate was observed upon addition of iodine catalyst to the reaction mixture (Scheme 2). Nevertheless, the formation of Schiff's base, *albeit* slowly, in modest yield suggested the facilitatory role of aqueous micelles. The encapsulation of reactants in a compact hydrophobic interior of the micelle helps expulsion of polar water arising out of condensation from the reaction zone.[16] The control experiments also demonstrate the catalytic influence of iodine in this step presumably by way of electrophilic activation of aldehyde carbonyl. A similar facilitatory role of iodine catalyst has ample literature precedents.[9b,d,17] The major catalytic role of iodine in subsequent generation of **4a** and **5a** has been already underscored during optimization process (Table 1 entries 4–7). Significantly, the yield of the reduced Schiff's base **6a** was nearly twice the combined yield of **4a** and **5a** when non-excess amount of styrene was used (Table 1 entries 3–6). Inasmuch as elevation of tetrahydroquinoline to the oxidation level of the quinoline entails reduction of two C=N bonds, this observation confirms the aldimine as dehydrogenating

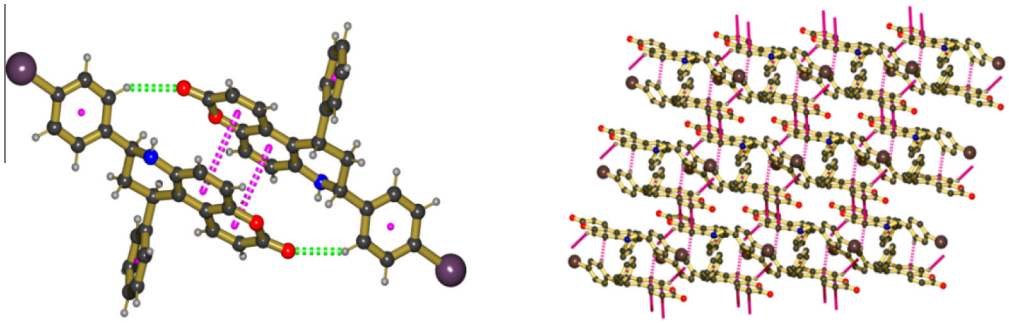


Figure 3. Non-covalent interactions in compound **7**.

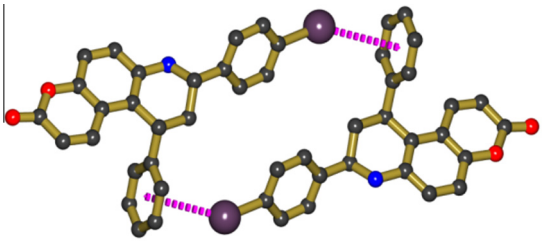
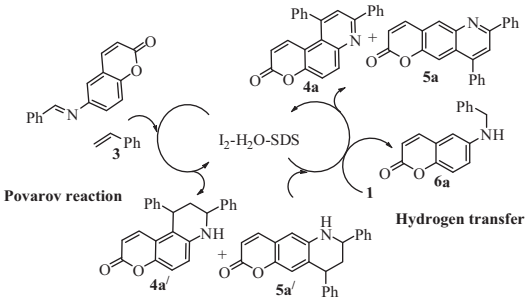
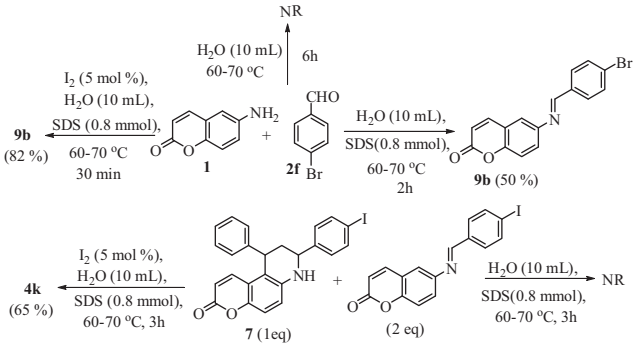


Figure 4. Iodine···π interaction.



Scheme 1.



Scheme 2.

agent. The absence of the anticipated tetrahydroquinolines in most cases is also mechanistically relevant. The major factor for facile aromatization seems to be the drive towards an extended Π-conjugated system encompassing the incipient pyridine moiety and the coumarin benzenoid ring further assisted by the two phenyl groups in the former. The predominant, if not exclusive, formation of quinolines was also reported under triflic imide catalysis with substituted styrenes as dienophiles.[12b,c] The implication of iodine catalyst in this step was also demonstrated by a control experiment. Attempted oxidation by exposing **7** to 2 mol equiv of the corresponding Schiff's base in H_2O-SDS without iodine at 60–70 °C for 3 h proved abortive. The desired oxidation was smoothly achieved upon addition of 5 mol % of iodine to the above reaction mixture (65%, 3 h). These experiments are presented in Scheme 2.

In conclusion, direct expeditious entry to pyrano[3.2-*f*]quinolin-3-ones and pyrano[2.3-*g*]quinolin-2-ones was accomplished by three-component coupling of 6-aminocoumarin, aromatic aldehyde and an excess of styrene by Povarov-hydrogen transfer auto-tandem catalytic route with iodine (5 mol %) in water in the presence of sodium dodecyl sulfate. The unusual linear fusion of the pyridine ring to the existing benzenoid ring of the coumarin and unprecedented autocatalytic role of iodine under essentially neutral micellar conditions are the key features of the protocol.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.078.

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14. *Representative procedure for synthesis of **4a** and **5a**:* To a vigorously stirring white emulsion of SDS (234 mg, ~0.8 mmol, 10 cmc) in water (10 mL) were sequentially added 6-aminocoumarin (160 mg, 1 mmol) and benzaldehyde (118 mg, 1.1 mmol), iodine (13 mg, ~5 mol %) and styrene (416 mg, 4 mmol) and the stirring was stirred for 2 h at 60–70 °C. The reaction was quenched by addition of 5 mol % of sodium thiosulfate solution (5 mL) and the cooled reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extract was washed with water (2 × 3 mL) and dried (Na_2SO_4). It was concentrated under reduced pressure to yield a yellow residue which was chromatographed over silica gel (60–120 mesh). Elution with EtOAc–light petrol (1:12) yielded a mixture of **4a** and **5a** and the amine **6a** in later fractions as a pure yellow solid (25 mg, ~10%). The mixture of **4a** and **5a** were separated by flash chromatography over silica gel (230–400 mesh) with EtOAc–light petrol (1:20) as eluent to give **4a** (192 mg, 55%) and **5a** (70 mg, 20%).
*Compound **4a**:* White solid; mp: 210–212 °C; IR (KBr): 1744, 1592, 1549, 1484, 1360, 1215, 1177, 1115, 982, 904, 825, 796, 716 cm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, J = 9.3 Hz, 1H), 8.21 (m, 2H), 7.85 (s, 1H), 7.72 (d, J = 9.3 Hz, 1H), 7.58–7.43 (m, 8H), 7.33 (d, J = 10.2 Hz, 1H), 6.06 (d, J = 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 156.0, 154.9, 148.0, 146.8, 141.7, 141.0, 138.3, 135.3, 129.8, 129.5, 129.0, 128.4, 127.4, 122.8, 122.3, 121.2, 113.8, 113.4, 105.2; MS (ESI): m/z = 350 [M+H]; Anal. Calcd for $C_{24}H_{15}NO_2$: C, 82.50; H, 4.33; N, 4.01. Found: C, 82.34; H, 4.09; N, 4.15.
*Compound **5a**:* White solid; mp: 216–218 °C; IR (KBr): 1733, 1634, 1592, 1538, 1450, 1354, 1234, 1182, 1121, 1089, 926, 825, 745 cm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.20–8.18 (m, 2H), 7.93 (d, J = 9.6 Hz, 1H), 7.90 (s, 1H), 7.80 (s, 1H), 7.58–7.49 (m, 8H), 6.53 (d, J = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 157.3, 150.5, 148.9, 145.2, 143.1, 138.9, 137.4, 129.8, 129.7, 129.4, 129.0, 128.9, 127.7, 127.5, 121.5, 120.8, 118.4, 111.4, 104.9; HRMS calcd for $C_{24}H_{15}NO_2$ [M+H]: 350.1176; found: 350.1179.
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