


Sequentially Catalyzed Three-Component Masuda–Suzuki–Sonogashira Synthesis of Fluorescent 2-Alkynyl-4-(7-azaindol-3-yl)pyrimidines: Three Palladium-Catalyzed Processes in a One-Pot Fashion

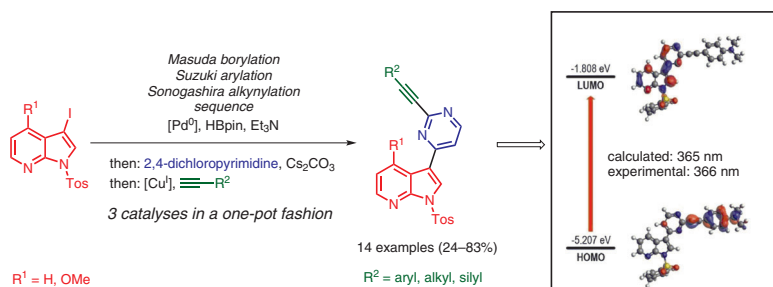
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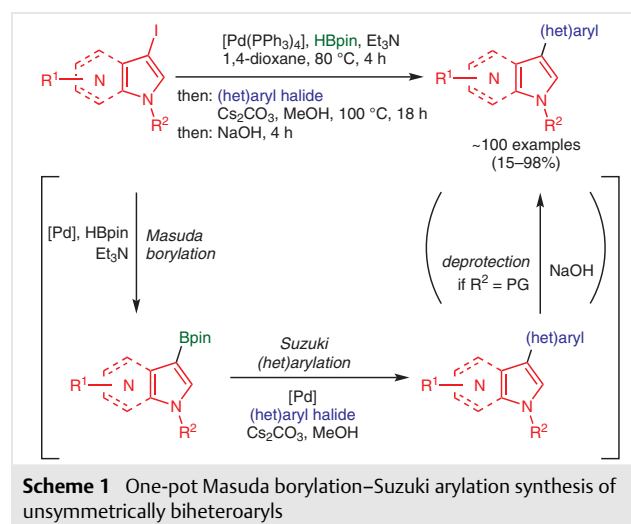
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Abstract The Masuda–Suzuki–Sonogashira sequence efficiently unites, in a one-pot fashion, a borylation, an arylation, and an alkyne reaction in the sense of a sequentially Pd-catalyzed three-component reaction to give fluorescent 2-alkynyl-4-(7-azaindol-3-yl) pyrimidines in yields of 24–83% (14 examples). Time-dependent density-functional theory calculations supported the electronic structure of the longest wavelength absorption bands, revealing that this novel consecutive three-component synthesis opens an efficient access to alkynyl meriolins, a novel class of potential inducers of apoptosis.

Key words arylation, alkyne, borylation, fluorescence, multi-component reaction, meriolins

Sequentially Pd-catalyzed processes¹ open the unique possibility of using an initially employed catalyst system for more than a single transformation in a one-pot fashion. Besides providing catalyst economy, the fine tuning of substrates additionally sets the stage for transition-metal-mediated syntheses of heterocyclic scaffolds, in the sense of multicomponent reactions² involving multiple catalytic steps. In recent years, we have established a sequential Pd-catalyzed process called the Masuda borylation–Suzuki coupling³ for concise one-pot syntheses of unsymmetrically substituted biheteroaryl compounds (Scheme 1). This sequence has been successfully applied to syntheses of natural products and biologically active compounds.^{3f–h,4} Particularly interesting are 7-azaindole derivatives, considered to be truncated hybrids of meridianins [2-amino-4-(indol-3-

yl)pyrimidines and variolins], which have shown considerable potential as inhibitors of protein kinases.⁵ We recently reported the application of the Masuda borylation–Suzuki coupling sequence for the synthesis of novel meriolin derivatives as potential inducers of rapid apoptosis in tumor cell lines.^{3h}



On the basis of our experience in applying the Pd–Cu catalyst systems in sequentially catalyzed one-pot processes⁶ and our general interest in transition-metal-mediated multicomponent synthesis of heterocycles,² we surmised that the Masuda–Suzuki sequence might be extended to a

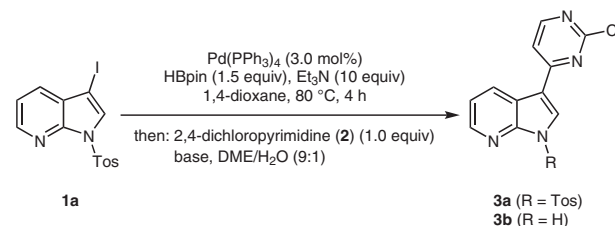
process involving three consecutive Pd-catalyzed steps. By employing 2,4-dichloropyrimidine as a suitable substrate for site-selective cross-coupling,⁷ we assumed that after Masuda borylation and Suzuki arylation at the 4-position, a selective final Sonogashira alkylation⁸ at the 2-position might lead to novel derivatives of meriolins. We reasoned that concatenation of three catalytic processes – borylation, heteroarylation, and alkylation – in a one-pot fashion without further Pd catalyst loading might provide a sequence that would be of practical use. Here, we report the development of a one-pot sequential Pd-catalyzed Masuda–Suzuki–Sonogashira sequence for the synthesis of meriolin derivatives, together with an experimental and computational study on the photophysical properties of selected derivatives.

Starting from the corresponding 7-azaindoles, by a one-pot two-step protocol involving iodination and tosylation, we prepared the two *N*-protected 3-iodo-7-azaindoles **1a** and **1b** in yields of 94 and 99%, respectively, as suitable substrates for our proposed sequence [for details, see the Supporting Information (SI)].^{3h} With *N*-tosyl-3-iodo-7-azaindole (**1a**), pinacolylborane, and 2,4-dichloropyrimidine (**2**) the Masuda–Suzuki coupling of dihalide **2** to give the 2-chloropyrimidyl meriolin derivative **3a** or **3b** (protected or unprotected, respectively) in a selective manner was optimized by changing the base, temperature, and reaction time (Table 1). Unlike our previous one-pot synthesis of apoptosis-inducing meriolins,^{3h} and due to the highly nucleophilic character of alcoholic carbonate solutions, the cosolvent for Suzuki coupling was changed to a mixture of 1,2-dimethoxyethane⁹ and water.

Even with water as cosolvent, cesium carbonate still represented the preferred base compared with sodium carbonate (Table 1, entries 1 and 2). Interestingly, with a reaction time of 42 hours for the Suzuki coupling step, cleavage of the tosyl group proceeded in situ to furnish the deprotected 2-chloropyrimidyl meriolin **3b**. Upon lowering the reaction temperature for the Suzuki coupling step to 80 °C, the tosyl group remained attached, permitting isolation of the *N*-tosylated product **3a** in high yield (entries 3–6). A slight increase in the amount of pinacolylborane in the Masuda step led to an excellent yield of the *N*-tosyl-2-chloropyrimidyl meriolin **3a** (entry 7). The selective formation of a single isomer was evident from the presence of a single set of signals in the NMR spectra, in agreement with the Pd-catalyzed 4-alkynylation of compound **2**.¹⁰ Furthermore, the connectivity of the 2-chloropyrimidyl-substituted derivative **3a** was unambiguously supported by 2D-ROESY-NMR spectroscopy (for details, see the SI).

The selective Masuda–Suzuki formation of the 2-chloropyrimidyl-substituted derivative **3a** set the stage for concatenation of a concluding alkylation. In a consecutive one-pot fashion, starting from *N*-tosyl 3-iodo-7-azaindoles **1**, pinacolylborane, and 2,4-dichloropyrimidine (**2**), and upon addition of an alkyne **4** and a catalytic amount of copper io-

Table 1 Optimization of the Masuda–Suzuki Synthesis of 2-Chloropyrimidyl Meriolin Derivatives **3**



Entry	Base (equiv)	Temp (°C)	Time (h)	Product	Yield (%)
1	Na ₂ CO ₃ (2.5)	100	42	3b	30
2	Cs ₂ CO ₃ (2.5)	100	42	3b	65
3	Cs ₂ CO ₃ (2.5)	80	42	3a	82
4	Cs ₂ CO ₃ (2.5)	80	16	3a	70
5	Cs ₂ CO ₃ (2.5)	60	20	3a	70
6	Cs ₂ CO ₃ (2.5)	80	20	3a	86
7 ^a	Cs ₂ CO ₃ (2.5)	80	18	3a	94

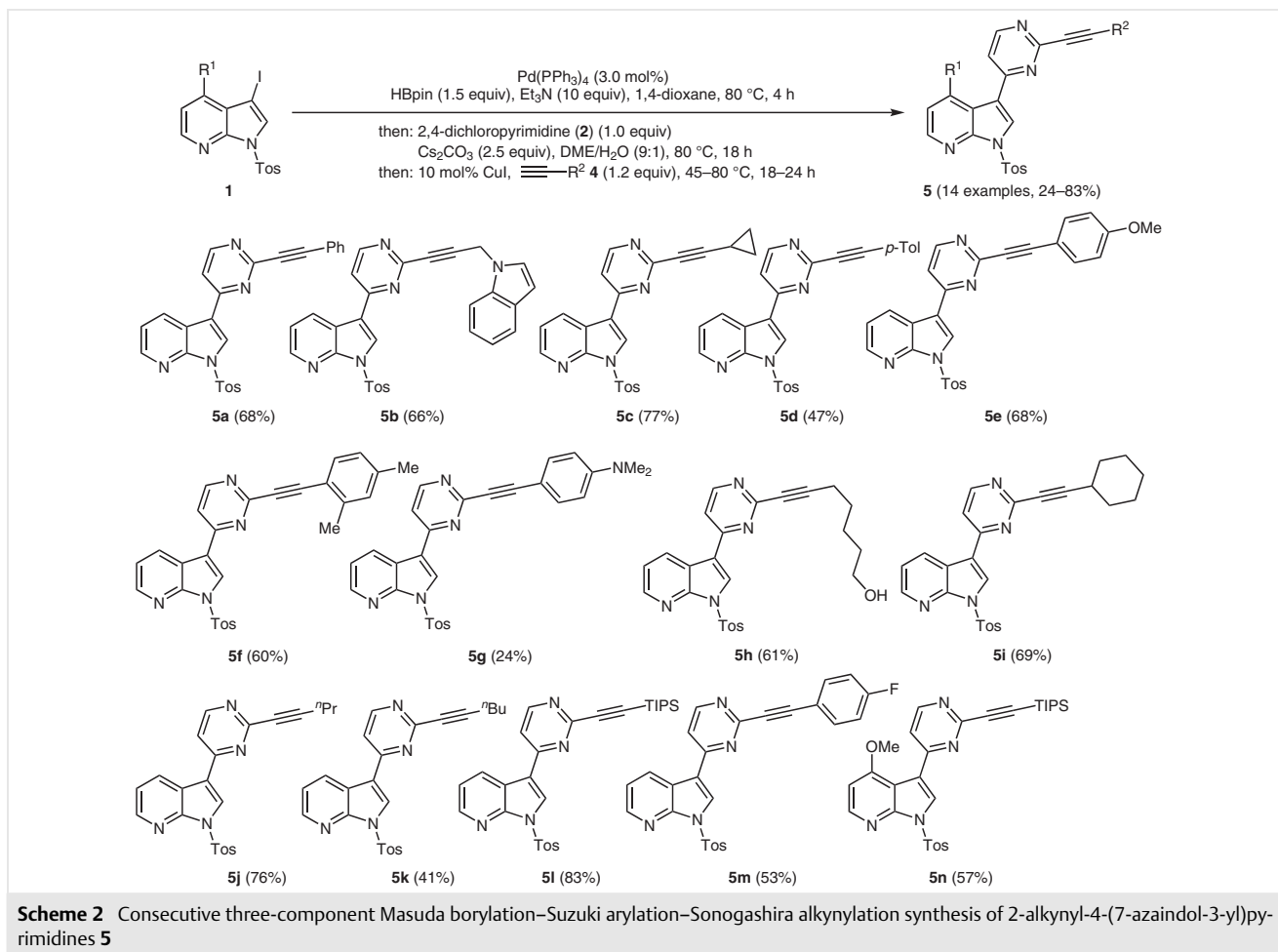
^a HBpin (1.7 equiv) was used in the Masuda borylation step.

dide, the corresponding 2-alkynyl-4-(7-azaindol-3-yl)pyrimidines **5** were isolated after single flash chromatography in moderate to good yields (Scheme 2).

Whereas copper iodide and the appropriate alkyne were added at this stage, no additional triethylamine or palladium catalyst needed to be added to the reaction mixture. Interestingly, a loading of 3.0 mol% of tetrakis(triphenylphosphine)palladium(0) proved to be sufficient to catalyze all three reaction steps in this novel Masuda–Suzuki–Sonogashira sequence. The structures of the products **5** were unambiguously supported by NMR spectroscopy, mass spectrometry, and the elemental composition as determined by combustion analysis.

The isolated yields of the title compounds **5** ranged from 24 to 83%, which equates to an average yield per bond-forming step in this consecutive three-component process of 62–94%. A variety of alkynes **4**, ranging from electron-deficient to electron-rich aromatic or aliphatic alkynes, as well as alkynes containing unprotected alcohol (**5h**) or TIPS groups (**5l** and **5n**), were well tolerated, highlighting the breadth of diversity of potential reactants. With 3-iodo-4-methoxy-7-azaindole (**1b**) as a substrate, targets substituted in the azaindole moiety were synthesized uneventfully (e.g., **5n**).

All the 2-alkynyl-4-(7-azaindol-3-yl) pyrimidines **5** produced intense blue-to-green emissions on excitation with UV light ($\lambda_{\text{exc}} = 365 \text{ nm}$). We therefore recorded the absorption and emission spectra of 12 compounds (Table 2). Almost all compounds **5** displayed similar absorption behaviors with intense maxima between 293 and 296 nm; the molar decadic absorption coefficients ϵ were in the range 23100–43900 L mol⁻¹ cm⁻¹ for aliphatic substituents and



48000–77000 L mol⁻¹ cm⁻¹ for aromatic substituents. Notably, the two strong donor-substituted derivatives **5e** and **5g** possessed red-shifted absorption maxima at 306 and 366 nm, respectively. Interestingly, the emission maxima were almost identical irrespective of the nature of the substituent R², with exception of *p*-(dimethylamino)phenyl- (**5g**), cyclohexyl- (**5i**), and propyl-substituted derivatives (**5j**). All other compounds fluoresced with emission maxima at about 447 nm. The Stokes shifts were remarkably high and amounted to 10300 to 11900 cm⁻¹, with exception of compound **5g** (8300 cm⁻¹).

The normalized absorption and emission spectra of the conjugated *p*-phenyl-substituted derivatives **5a**, **5d**, **5e**, and **5e** are almost superimposable (for details, see Figure S1, SI), indicating they have quite similar electronic structures. However, for the *p*-(dimethylamino)phenyl-substituted derivative **5g** in particular, in comparison to the phenyl- (**5a**), cyclohexyl- (**5i**), and propyl-substituted (**5j**) derivatives, the significant redshifts in the absorption (366 nm) and emission (525 nm) maximum can be ascribed to a change in the dominant underlying chromophore (Figure 1). Compound **5g** consists of a strongly polarizable donor–acceptor chro-

mophore with the *p*-(dimethylamino)phenyl moiety as an electron donor and the pyrimidyl unit as an acceptor. This chromophore axis is significantly different from the transition dipole orientation of the other derivatives, which are presumably oriented along the 7-azaindole–pyrimidine axis.

To achieve a qualitative understanding of the electronic structure of the absorption spectrum of compounds **5**, time-dependent density-functional theory (TDDFT) calculations for compounds **5a** (R² = Ph) and **5g** (R² = *p*-Me₂NC₆H₄) were performed with the PBE functional and the 6-31G** basis set as implemented in *Gaussian 09*.¹¹ The calculated longest wavelength absorption bands are best represented by vertical Franck–Condon transitions, as represented by the Kohn–Sham frontier molecular orbitals (FMOs) HOMO and LUMO (Figure 2), and these are in reasonably good agreement with the experimentally determined absorption bands (**5a**: calcd 287 nm; experimental 295 nm; **5g**: calcd 365 nm; experimental 366 nm).

However, the character of these transitions is substantially different. Whereas for compound **5a** (R² = Ph), coefficient densities of both the HOMO and LUMO are mainly lo-

Table 2 Summary of the UV/Vis-Absorption- and Emission-Specific Properties of the Alkyne-Substituted Meriolin Derivatives **6** in Dichloromethane at 293 K

Compound	R ²	Absorption $\lambda_{\text{max,abs}}$ (nm) (ϵ) (L·mol ⁻¹ ·cm ⁻¹) ^a	Emission $\lambda_{\text{max,em}}$ (nm) ^b	Stokes shift $\Delta\nu^c$ (cm ⁻¹) ^c
5a	Ph	295 (48900)	447	11600
5b	indol-1-ylmethyl	293 (27800)	447	11800
5c	cyclopropyl	293 (23100)	447	11700
5d	4-Tol	295 (48400)	447	11600
5e	4-MeOC ₆ H ₄	306 (49900)	447	10300
5f	2,4-Me ₂ C ₆ H ₃	294 (63200)	447	11600
5g	4-Me ₂ NC ₆ H ₄	366 (61700)	525	8300
5h	4-HO(CH ₂) ₄	296 (26000)	448	11500
5i	Cy	296 (32800)	430	10600
5j	Pr	296 (24800)	429	10500
5l	TIPS	298 (43900)	447	11200
5m	4-FC ₆ H ₄	293 (76700)	447	11900

^a [5] = 10⁻⁵ M.^b [5] = 10⁻⁷ M, $\lambda_{\text{exc}} = \lambda_{\text{max,abs}}$.^c $\Delta\nu^c = 1/\lambda_{\text{max,abs}} - 1/\lambda_{\text{max,em}}$ (cm⁻¹).

calized on the 2-(phenylethynyl)pyrimidin-4-yl part, the strong donor part of compound **5g** (R² = *p*-Me₂NC₆H₄) creates a dominant push-pull chromophore in which the HOMO and LUMO coefficient densities are spatially separated from each other and overlap only on the central pyrimidinyl core. Whereas the HOMO coefficient density is mostly localized on the [*p*-(dimethylamino)phenyl]ethynyl part, the LUMO coefficient density is localized in the 3-pyrimidin-4-yl-7-azaindole moiety. This spatial separation accounts for a significant charge-transfer character of the longest wavelength absorption band of structure **5g**. In the ex-

perimental spectrum, the strong bathochromic shift is accompanied by a strong absorption coefficient ϵ (62000 L mol⁻¹ cm⁻¹).

In conclusion, a novel sequentially Pd-catalyzed Masuda-Suzuki-Sonogashira synthesis of 2-alkynyl-4-(7-azaindol-3-yl)pyrimidines (i.e., alkynyl meriolin derivatives) was developed in the form of a consecutive three-component reaction.¹² This novel process not only concatenates three catalytic reactions – borylation, arylation, and alkynylation – efficiently and efficaciously in a single vessel without further addition of the initial palladium catalyst source, but also

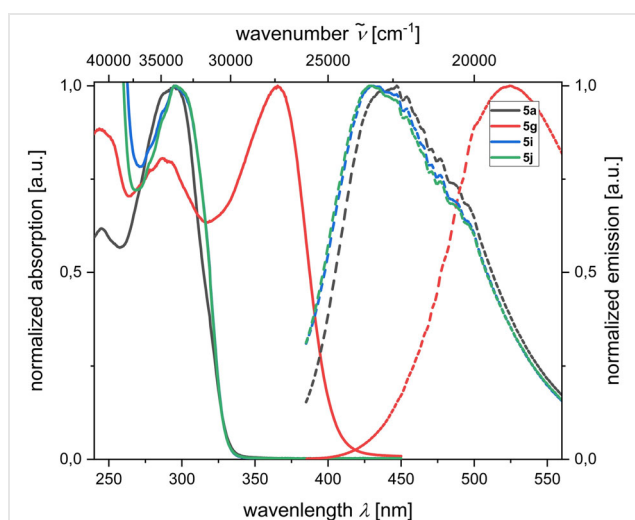


Figure 1 Normalized absorption (solid lines; [5] = 10⁻⁵ M) and emission (dashed lines; [5] = 10⁻⁷ M) spectra of selected derivatives **5** in dichloromethane at 293 K ($\lambda_{\text{exc}} = \lambda_{\text{max,abs}}$)

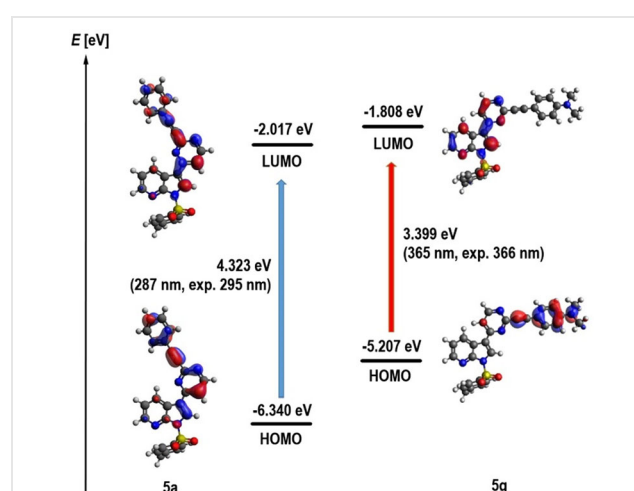


Figure 2 TDDFT-computed Kohn-Sham FMOs of dyes **5a** and **5g**, representing contributions of the TDDFT-computed longest wavelength Franck-Condon absorption band [PBEh1PBE/6-31G(d,p), PCM CH₂Cl₂, isosurface value at 0.04 a.u.]

provides easy access to interesting novel fluorophores. The broad variety of the alkynes used underlines the fact that variable functionalities can be introduced. Whereas strong donor substituents furnish significantly red-shifted fluorophores with excitations near the visible region, silyl alkynyl moieties permit tagging for further functionalization. The combination of the 7-azaindole substructure with functional alkynyl sidechains with substantial fluorescence suggests that this concise synthetic concept might be useful for protein-target-fishing strategies and for confocal microscopy in biophysical analytics. Expansion of the methodological scope of this novel one-pot process and its application to the development of new functional materials and probes is currently underway.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1707818>.

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- (12) **Products 5a–m; General Procedure**
7-azaindole **1a** (398 mg, 1.00 mmol) and (Ph₃P)₄Pd (35.0 mg, 0.03 mmol) were placed in a dry screw-cap vessel equipped with a magnetic stirrer bar. The vessel was evacuated and refilled with argon three times, then anhyd 1,4-dioxane (5.00

mL) was added and the resulting mixture was degassed with argon for 10 min. Dry Et₃N (1.40 mL, 10.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.25 mL, 1.70 mmol) were successively added and the mixture was stirred in a preheated oil bath at 80 °C for 4 h then cooled to r.t. (water bath). Dry 1,2-dimethoxyethane (9.00 mL) and H₂O (1.00 mL) were added, and the mixture was stirred at r.t. for 10 min. 2,4-Dichloropyrimidine (**2**; 149 mg, 1.00 mmol) and Cs₂CO₃ (823 mg, 2.50 mmol) were then added, and the mixture was stirred in a preheated oil bath at 80 °C for 18 h. When the Suzuki coupling was complete, the mixture was cooled to r.t. (water bath), and CuI (19.0 mg, 0.10 mmol) and the appropriate alkyne **4** (1.20 mmol) were added. The mixture was stirred at 45–80 °C for 18 h. When the Sonogashira coupling was complete (TLC), the mixture was cooled to r.t. (water bath), the solvents were removed in vacuo, and the residue was absorbed onto Celite. After purification by chromatography (silica gel, hexane–acetone), the product was sonicated in hexane–acetone (95:5) for further purification. The solvent was removed and the residue was dried in vacuo at 70 °C for 42 h.

1-[(4-Methylphenyl)sulfonyl]-3-[2-(phenylethynyl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine (5a)

The final Sonogashira step was carried out at 80 °C for 18 h to give a yellow solid; yield: 310 mg (0.68 mmol, 68%); mp 200.3–

202.7 °C; *R*_f = 0.48 (CH₂Cl₂–acetone, 6:4).

IR (neat): 3379 (w), 3107 (w), 3090 (w), 3026 (w), 2918 (w), 2218 (w), 1593 (m), 1570 (s), 1555 (w), 1533 (s), 1491 (m), 1479 (w), 1425 (w), 1398 (s), 1381 (m), 1368 (s), 1335 (w), 1302 (m), 1262 (m), 1244 (m), 1186 (s), 1171 (s), 1155 (s), 1123 (w), 1075 (w), 1036 (m), 1017 (m), 999 (w), 961 (s), 918 (w), 883 (m), 866 (w), 849 (w), 837 (m), 822 (m), 802 (m), 775 (s), 756 (s), 732 (s), 675 (s), 654 (s), 633 (w) cm⁻¹. ¹H NMR (600 MHz, DMSO-*d*₆): δ = 2.35 (s, 3 H, CH₃), 7.44–7.54 (m, 6 H, CHAr), 7.72 (d, ³*J*_{HH} = 6.7 Hz, 2 H, CHAr), 8.09 (d, ³*J*_{HH} = 8.5 Hz, 2 H, CHAr), 8.23 (d, ³*J*_{HH} = 5.4 Hz, 1 H, CHAr), 8.48 (dd, ³*J*_{HH} = 4.7 Hz, ⁴*J*_{HH} = 1.6 Hz, 1 H, CHAr), 8.85 (d, ³*J*_{HH} = 5.4 Hz, 1 H, CHAr), 8.88 (dd, ³*J*_{HH} = 8.0 Hz, ⁴*J*_{HH} = 1.6 Hz, 1 H, CHAr), 9.03 (s, 1 H, CHAr). ¹³C NMR (150 MHz, DMSO-*d*₆): δ = 21.1 (CH₃), 86.2 (C_{quat}), 88.6 (C_{quat}), 115.5 (C_{quat}), 116.4 (CH), 119.8 (CH), 120.4 (C_{quat}), 120.5 (C_{quat}), 128.0 (CH), 129.0 (CH), 129.2 (CH), 130.1 (CH), 130.2 (CH), 131.7 (CH), 132.2 (CH), 134.0 (C_{quat}), 145.7 (CH), 146.2 (C_{quat}), 146.9 (C_{quat}), 152.0 (C_{quat}), 157.8 (CH), 159.8 (C_{quat}). EI MS: *m/z* (%) = 450 (21) [M⁺], 386 (100) [C₂₁H₁₄N₄O₂S⁺], 385 (36), 296 (11), 268 (12), 267 (19), 155 (13) [C₇H₇O₂S⁺], 142 (14), 141 (12) [C₉H₅N₂⁺], 127 (11), 114 (14) [C₉H₆⁺], 91 (90) [C₇H₇⁺], 65 (14) [C₅H₅⁺]. Anal. Calcd for C₂₆H₁₈N₄O₂S (450.5): C, 69.32; H, 4.03; N, 12.44; S, 7.12. Found: C, 69.11; H, 3.75; N, 12.19; S, 7.31.