Structural Transformation of Methoxy-Substituted Benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ones

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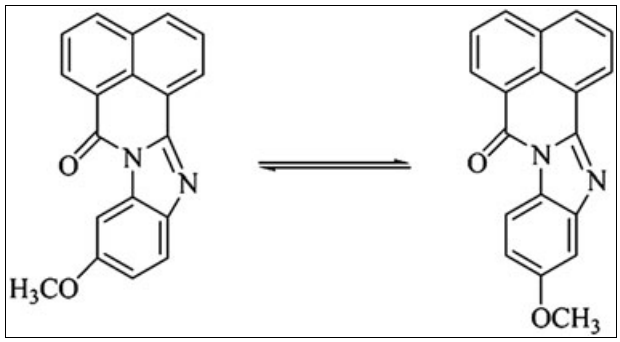

Structural transformation of two methoxy derivatives of benzo[*de*]benzo[4,5]imidazo[2,1-*a*]-isoquinolin-7-one were determined *via* spectroscopic analysis. The transformation mechanism was proposed as the breakage and reformation of the lactam bond.

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INTRODUCTION

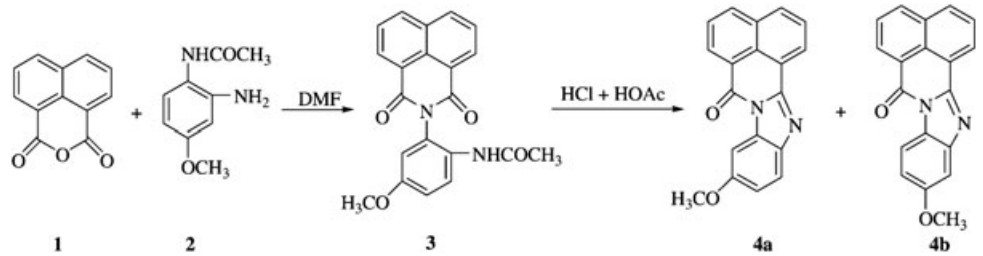
Naphthalimide derivatives constitute a family of important compounds because of their excellent photoconductive properties. Recently, they have found applications in various fields including organic solar cells [1], fluorescence switchers and sensors [2, 3], luminescent materials [4, 5], medicines [6, 7], and ion probes [8]. Among these derivatives, benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ones have been mostly paid more attention for their fluorescence properties [9, 10]. These heterocyclic compounds were usually synthesized by two methods: One in which 1,8-naphthalic anhydride was reacted with substituted 1,2-diaminobenzenes [11, 12] to obtain two isomeric mixtures. Alternatively, the condensation of the anhydride with substituted *o*-nitroanilines produced N-substituted naphthalimide intermediates, which were subsequently converted to the target products *via* reduction. In the latter method, only one compound was generally obtained. Through the former method, methoxy-substituted mixtures of benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ones were synthesized [13] and their luminescent properties were reported [14]. Interestingly, there is no report concerning the structural transformation of the two methoxy isomers of benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-one. Recently, studies in our laboratories revealed the formation of the two methoxy isomers from a common intermediate (**3**), as shown in Scheme 1.

RESULTS AND DISCUSSION

As depicted in Scheme 1, the condensation of 1,8-naphthalic anhydride (**1**) with 5-methoxy-2-acetaminoaniline (**2**) in N,N-dimethylformamide (DMF) gave intermediate 2-(2-acetamino-5-methoxyphenyl)-benzo[*de*]isoquinoline-1,3-dione (**3**). Then, compound **3** was heated with 30% hydrochloric acid (HCl) in acetic acid (HOAc) to form 10-methoxy-benzo[*de*]benzo[4,5]imidazo [2,1-*a*]isoquinolin-7-one (**4a**). Unexpectedly, its isomer 11-methoxy-benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-one (**4b**) was also obtained in 9.7% yield.

Characterization of the reaction products was undertaken following their separation by preparative thin layer chromatography (TLC). Results from high resolution mass spectrometry (HRMS) indicated that **4a** and **4b** had *m*/*z* 301.0984 and 301.0975, respectively. Further, Figure 1 results show ^{1}H NMR (1A) and ^{13}C NMR (1B) spectra for compound **4a** as well as the corresponding 2-D spectra, including correlation spectroscopy (COSY) (1C) and heteronuclear multiple-bond correlation (HMBC) (1D),

Scheme 1. Route used in the synthesis of **4a** and **4b**.



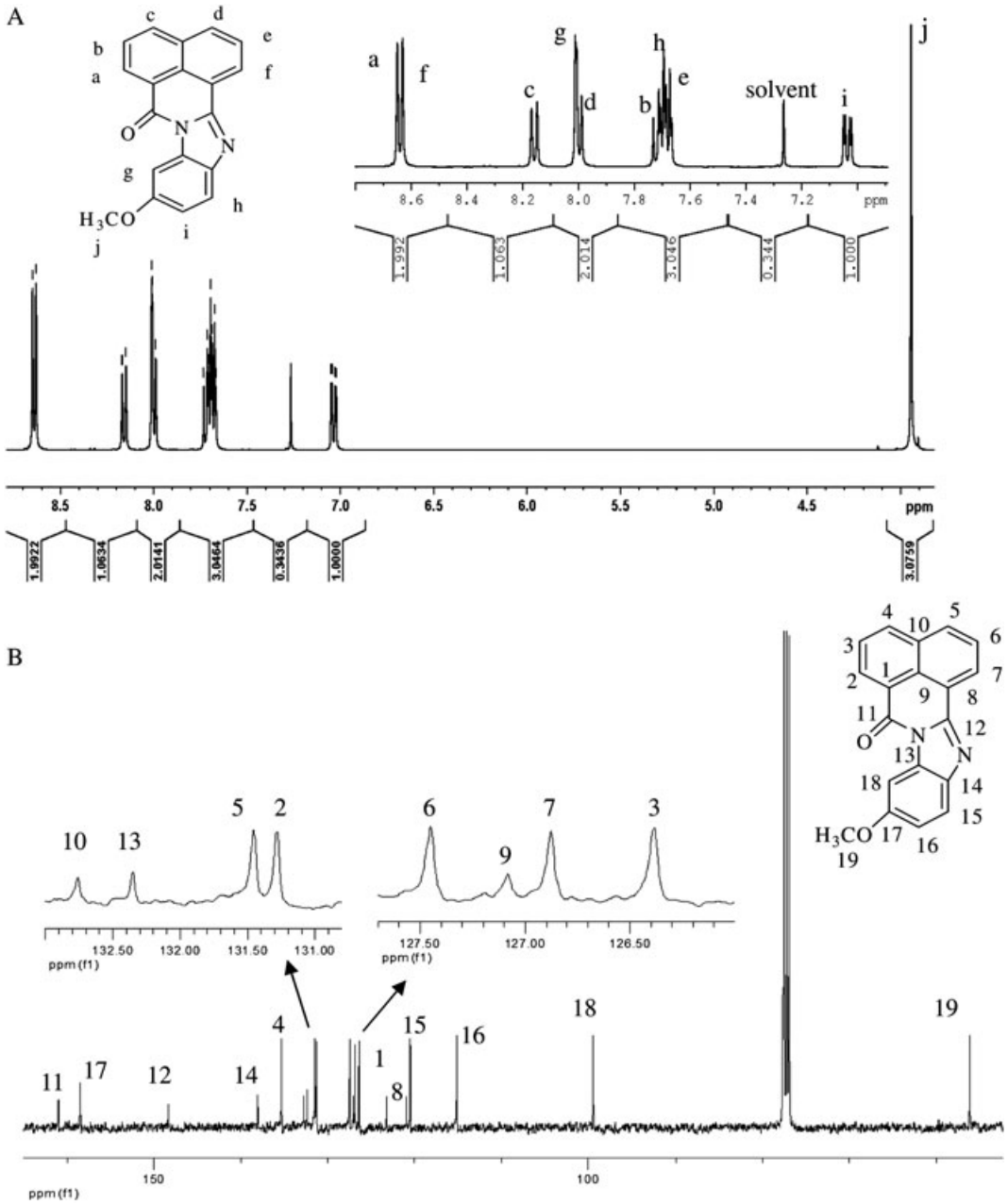


Figure 1. (A) ^{1}H NMR, (B) ^{13}C NMR, (C) COSY, and (D) HMBC spectra of **4a** in $CDCl_3$.

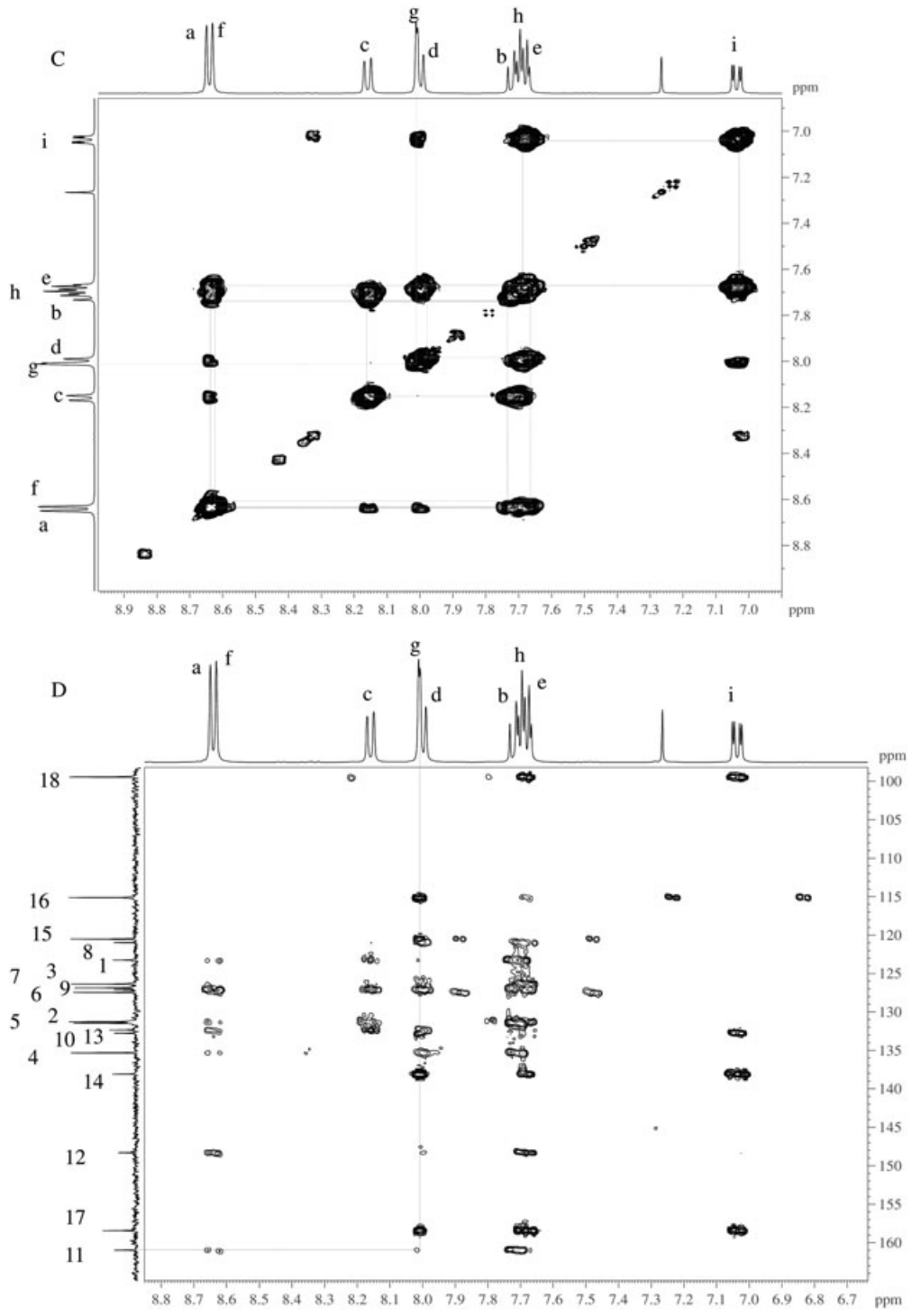


Figure 1. *(Continued)*

which were used to facilitate peak assignments for key protons and carbon atoms. The signals for protons H_j (methoxy group) appeared at 3.94 ppm in ^{1}H NMR spectrum [Fig. 1(A)], while the signals at 160.97, 158.43, and 56.11 ppm in ^{13}C NMR spectrum [Fig. 1(B)] were attributed to carbonyl carbon C_{11}, aromatic carbon C_{17}, and methoxy carbon C_{19}. The basic COSY experiment gave the 2-D ^{1}H–^{1}H spectra reported and assigned in Figure 1(C). On the basis of the ^{1}H–^{13}C correlation analysis shown in Figure 1(D), it was determined that carbonyl carbon C_{11} has a long range correlation with H_g through the ^4J, which permitted the peak assignment for H_g. Its

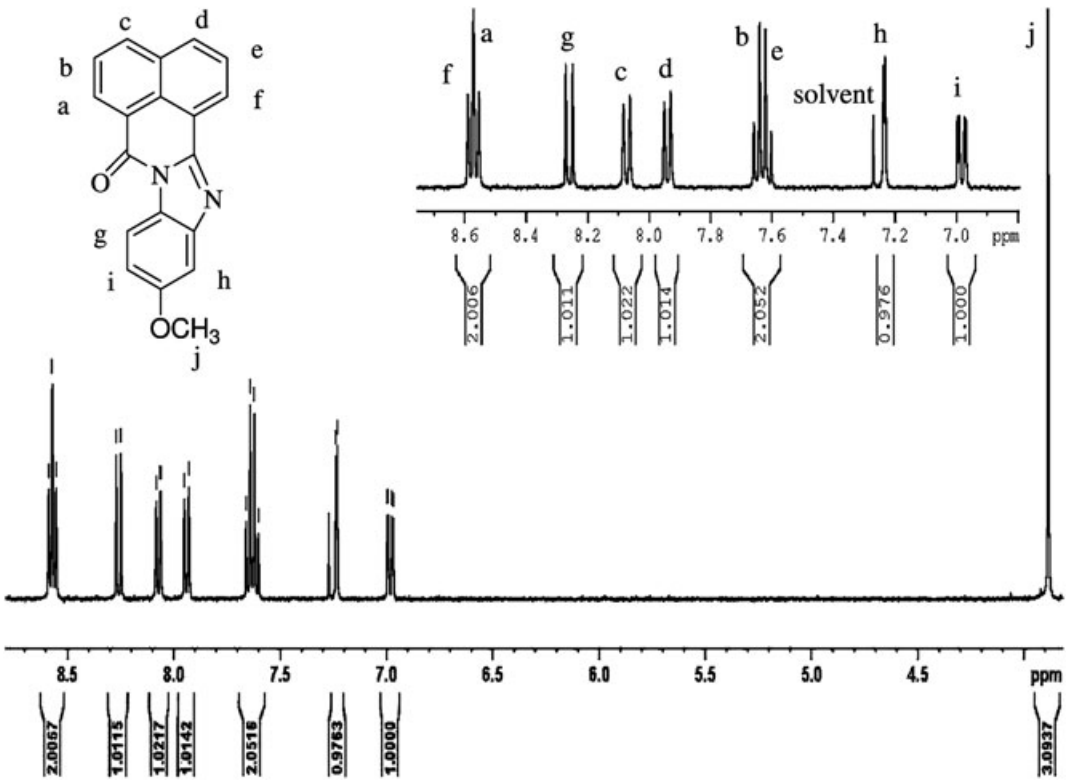


Figure 2. ^{1}H NMR spectrum of **4b** in $CDCl_3$.

appearance as a singlet at 8.01 ppm in the ^{1}H NMR spectrum [Fig. 1(A)] was key to establish the structure of isomer **4a**.

Similarly, the peak assignments in the proton and the carbon spectra for isomer **4b** were assisted by peak integrations in the proton spectra and analysis of 2-D COSY and HMBC spectra. The ^{1}H NMR spectrum of isomer **4b** is shown in Figure 2, where it can be seen that the chemical shift for H_g at 8.27–8.25 ppm shifted downfield compared with the corresponding signal for H_g in the spectrum for **4a**. Its appearance as a doublet having J = 8.8 helped confirm the structure of isomer **4b**.

The UV–vis spectra of the two products are shown in Figure 3, where it can be seen that **4b** gives an absorption maximum (λ_{max}) at 374 nm, whereas the λ_{max} of **4a** is 414 nm. Compound **4a** has a higher λ_{max}, because the lone pair electrons on the methoxy group can be delocalized to give a resonance structure of type **4a′** (Fig. 4). For **4b**, delocalization of the lone pair electrons into the naphthalene ring is not possible, which shortens the conjugated system and lowering λ_{max}.

To obtain more information about this reaction, purified **4a** was heated with HCl/HOAc, whereupon the high

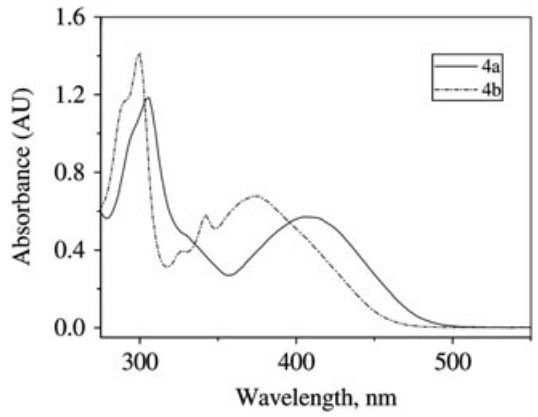


Figure 3. UV–vis spectra of **4a** and **4b** in $CHCl_3$.

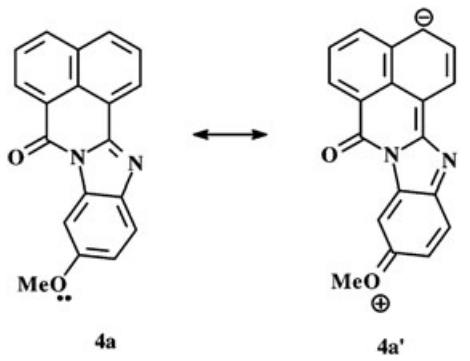
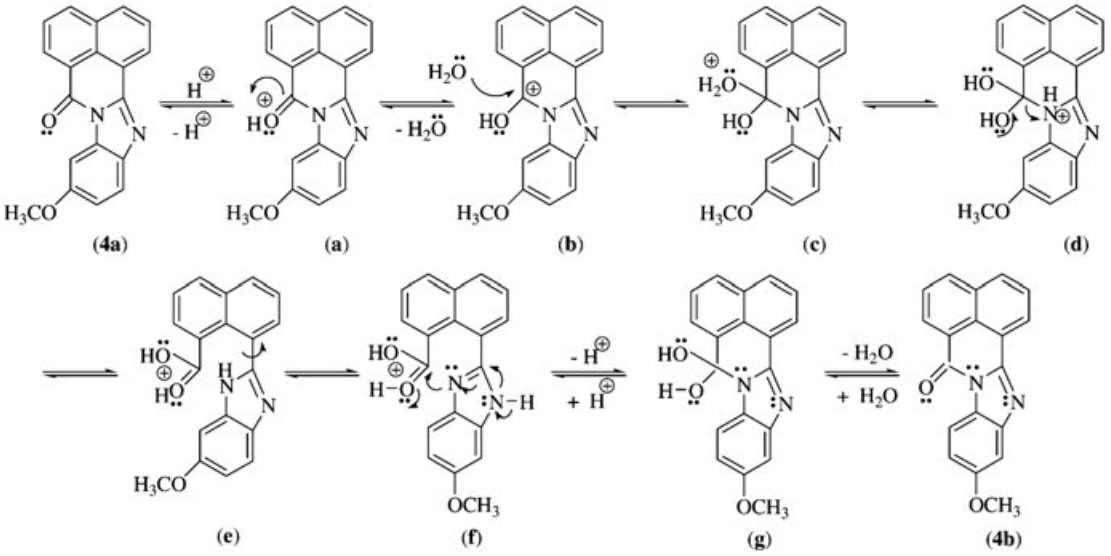


Figure 4. Resonance structure of **4a**.

Scheme 2. Proposed mechanism for the interconversion of **4a** and **4b**.



performance liquid chromatography (HPLC) analysis of the reaction mixture showed 14.5% conversion of **4a** to **4b** after 8 h. Similarly, after an 8-h acid treatment of purified **4b**, HPLC analysis indicated 10% conversion of **4b** to **4a**, thus confirming that the two compounds are readily interconverted.

On the basis of the aforementioned results, it is proposed that isomerization is characterized by the breakage and reformation of the lactam bond under acidic conditions, as outlined in the Scheme 2 mechanism for converting **4a** to **4b**. First, the carbonyl group is protonated and attacked by a water molecule to form intermediate "c." Protonation of the central N-atom followed by ring opening gives intermediate "e," followed by rotation of the benzimidazole group around the C C bond forms intermediate "f." The new lactam bond is formed by ring closure, giving a structure in which the methoxy group is *para* rather than *meta* to the central N-atom (*cf.* structure "g"). Elimination of a water molecule produces **4b**. In the same way, isomer **4b** also transformed to **4a**. In the proposed mechanism, the key steps are ring opening (d → e), rotation of the benzimidazole group (e → f), and ring closure (f → g).

CONCLUSIONS

Intermediate 2-(2-acetamino-5-methoxyphenyl)benzo [*de*]isoquinoline-1,3-dione is readily synthesized by the reaction of 1,8-naphthalic anhydride with 2-acetamino-5-methoxyaniline. Acid-induced ring-closure of this intermediate produces structural isomers of methoxy-substituted benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-one isomers. The structures of the two isomers have been assigned with the aid of HRMS, Fourier transform infrared spectroscopy (FTIR), and 1-D and 2-D ^{1}H NMR. A mechanism for the acid-induced interconversion of the two isomers was proposed.

EXPERIMENTAL

1,8-Naphthalic anhydride (>98%) and 2-acetamino-5-methoxyaniline (>98%) were provided by Quzhou Rainful Chemical (Quzhou, China) and Zhejiang Jihua Group (Hangzhou, China), respectively. Common reagent grade chemicals were commercially available and were used without further purification. Melting points were recorded on an X-6 digital melting point apparatus (Beijing Tech., Beijing, China). FTIR were recorded on a gas chromatography/FTIR spectrometer (NEXU EURO) using KBr pellets. NMR spectra were recorded on an AVANCE II 400 NMR spectrometer (Bruker, Fällanden, Switzerland). HRMS were recorded on a Q-T of Mass Spectrometer (Micromass, Manchester, UK). HPLC were recorded on an Agilent 1100 chromatographic instrument with the Elite C_{18} column (4.6 × 150 mm^2, 5 μm). The eluent was CH_3OH/H_2O (68/32, v/v) at a flow rate of 1.0 mL/min.

Synthesis of 2-(2-acetamino-5-methoxyphenyl)benzo[*de*] isoquinoline-1,3-dione (3). 5-Methoxy-2-acetaminoaniline (3.68 g, 20 mmol) and DMF (35 mL) were added to a three-necked round-bottomed flask equipped with a reflux condenser, and the solution was stirred, as 1,8-naphthalic anhydride (3.64 g, 18 mmol) was added slowly. The mixture was heated to 90°C, kept for 8 h, and then poured to 200 mL water. After filtration and washing with water, the product was air dried and crystallized from CH_2Cl_2 to obtain light pale needles in 92% yield. M.p.: 262°C; FTIR (KBr, cm^{-1}): 3316, 3053, 2942, 2837, 1708, 1667, 780; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.25 (s, 1H, NH), 8.52–8.50 (d, 4H, Ar), 8.10–8.08 (d, 1H, Ar), 7.93–7.89 (t, 2H, Ar), 7.02–7.00 (d, 2H, Ar), 3.73 (s, 3H, OCH_3), 1.88 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 168.2, 163.4, 155.3,

134.0, 131.4, 130.3, 129.7, 128.2, 127.4, 127.0, 123.5, 123.4, 114.9, 114.1, 55.4, 23.6; HRMS (ES Positive): *m/z* 383.0999 (M+Na, 100%), 743.2096 (2M+Na, 80%), Calc. 383.1008 (M+Na).

Synthesis of methoxy-benzo[*de*]benzo[4,5]imidazo[2,1-*a*] isoquinolin-7-ones (4). Acetic acid (18.7 g), 30% hydrochloric acid (9.80 g) and water (40 mL) were added to a three-necked round-bottomed flask equipped with a reflux condenser, and the solution was stirred. To this solution, compound **3** (7.21 g, 20 mmol) was added slowly and the mixture was heated to 90°C and kept for 4 h. The yellow product was collected by filtration and purified by preparative TLC (toluene/ethyl acetate = 5/1, v/v) to give **4a** and **4b** in 85 and 9.7% yield, respectively.

10-Methoxy-benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-one (4a). This compound was obtained as yellow needles (CH_2Cl_2). M.p.: 210°C; FTIR (KBr, cm^{-1}): 3078, 2973, 2841, 1693, 774; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.65 (s, 1H, Ar), 8.63 (s, 1H, Ar), 8.17–8.15 (d, 1H, Ar, J = 8.0), 8.01 (s, 1H, Ar), 7.99 (s, 1H, Ar), 7.73–7.67 (m, 3H, Ar), 7.05–7.02 (d–d, 1H, Ar, J = 8.8), 3.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.97, 158.43, 148.32, 138.07, 135.31, 132.74, 132.33, 131.44, 131.26, 127.43, 127.07, 126.86, 126.37, 123.23, 120.96, 120.50, 115.10, 99.45, 56.11; HRMS (ES Positive): *m/z* 301.0984 (M+H, 100%), Calc. 301.0977 (M+H).

11-Methoxy-benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-one (4b). This compound was obtained as yellow powder (CH_2Cl_2). M.p.: 194°C; FTIR (KBr, cm^{-1}): 3057, 2944, 2834, 1691, 772; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.59–8.55 (t, 2H, Ar), 8.27–8.25 (d, 1H, Ar, J = 8.8), 8.08–8.06 (d, 1H, Ar, J = 8.0), 7.95–7.93 (d, 1H, Ar, J = 8.0), 7.66–7.60 (q, 2H, Ar), 7.24–7.23 (s, 1H, Ar), 7.00–6.97 (d–d, 1H, Ar, J = 8.8), 3.89 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.20, 158.33, 149.64, 144.93, 135.13, 132.08, 131.70, 131.52, 127.27, 126.95, 126.80, 126.08, 123.00, 120.47, 116.24, 114.20, 102.65, 55.80; HRMS (ES Positive): *m/z* 301.0975 (M+H, 100%), Calc. 301.0977 (M+H).

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