On the Mechanism of Formation and the Synthesis of Pantoprazole Sodium Sesquihydrate-Related Compound E: A Phantom Chemical Entity

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Supporting Information

ABSTRACT: A mechanism for the formation of pantoprazole related compound E (RC E) is proposed involving the formation of a radical cation in the pH range of 5−8. pH dependence of RC E is demonstrated, and the contribution of the difluoromethoxy group in stabilizing the C-6 free radical, a prerequisite to the formation of the dimer byproduct, is discussed. Also, the synthesis of pantoprazole RC E is reported using the benzidine rearrangement.

INTRODUCTION

Active pharmaceutical ingredients (APIs) must meet the purity criteria set by internationally recognized pharmacopeia such as the United States Pharmacopeia (USP). Quantification of known impurities, referred to as related compound (RC) or related substances (RS), and unknown impurities is a regulatory requirement and must be reported on the Certificate of Analysis of APIs.1 Accordingly, the purity of APIs is of paramount importance to their manufacturers, who carry out extensive R&D to minimize the formation of byproducts in various synthetic steps. Also, purification of an API is usually the most difficult step in its production and can be facilitated by suppressing byproduct formation. This, in turn, requires a thorough understanding of the mechanism of formation of impurities, which, once established, provides opportunities to manipulate reaction conditions to minimize their formation, generation of waste, and to improve the reaction yield.

Primary reference standards (PRS), available from recognized pharmacopeias, are used in validated high-performance liquid chromatography (HPLC) protocols. They provide relative retention time and response factor of each impurity at the wavelength described by the pharmacopeia, allowing quantification of the RCs. PRS are very expensive, usually costing hundreds of dollars for 5−20 mg. Accordingly, API and Drug Product manufacturers use secondary reference standards (SRS, also known as working standards or house standards) for routine analysis of APIs. SRS are purchased from reputable suppliers or synthesized in-house. SRS must be characterized (IR, UV, 1H NMR, 13C NMR, and mass spectrometry (MS)), their purity and assay determined (HPLC), and must be established to be identical to their PRS. This is referred to as “specification” and involves the comparison of at least two spectroscopic characteristics of the SRS with its PRS. To this end, λmax and HPLC retention time are usually used, both of which can be determined in a single HPLC experiment and compared to the PRS values.2

Pantoprazole sodium sesquihydrate (PAN−Na+·1.5H2O) binds to cystein 822 of H+/K+ATPase as an irreversible inhibitor.3 The protein, also referred to as the proton pump, transfers H+ from the blood into parietal cells of the stomach with concomitant transfer of K+ from the cells into the blood.4 The USP identifies five known impurities, namely, RC A, B, D, and F (mixture) and RC E (mixture of isomers).5 There is very little information available on RC E in the chemical literature. It has not been assigned a Chemical Abstracts Service (CAS) number, and there is no report on its mechanism of formation or its synthesis. It is therefore a “phantom” chemical entity in the abovementioned terms. In this report, we propose a pH-dependent mechanism for the formation of RC E and report its synthesis using the benzidine rearrangement.

RESULTS AND DISCUSSION

Pantoprazole is synthesized by the condensation of 5-difluoromethoxy-2-mercaptopbenzimidazole (1) with 2-chlor-
omethyl-3,4-dimethoxy pyridine hydrochloride (2) to afford a thioether (3), which is subsequently oxidized to the product. Sodium hypochlorite is usually used as the oxidizing reagent because of its low cost and commercial availability. Other oxidizing reagents such as hydrogen peroxide with metal oxide catalysts, peracids, and N-bromosuccinimide have also been used to affect the conversion of thioethers to sulfoxides (Scheme 1).

The USP specifies five RCs for PAN Na\(^{+}\)·1.5H\(_2\)O. These are shown in Scheme 2.

RCs A, B, and C are anticipatory. RC A is a product of overoxidation of pantoprazole (sulfoxide) to the corresponding sulfone. RC B is the penultimate thioether intermediate, and RC C is one of the two starting materials used in the synthesis of PAN Na\(^{+}\)·1.5H\(_2\)O.

RC D and RC F are a mixture of N-2 and N-7 methylation of the benzimidazole moiety. No reasonable mechanism for their formation has been provided. In some methods, however, a mixture of dichloromethane and methanol is used with peracids or with sodium hypochlorite for the oxidation of the thioether wherein methanol may be converted to formaldehyde and formic acid, possibly resulting in the Eschweiler–Clarke reaction and affording trace amounts of the N-2 and N-7 methylated byproducts. Perhaps more importantly, commercial methanol may contain trace quantities of formaldehyde, which is subsequently converted to formic acid in the presence of sodium hydroxide. In fact, the formation of trace amounts of methylated drug substances during routine analytical experiments has been attributed to the presence of trace amounts of formaldehyde in HPLC-grade methanol. Finally, it should be noted that the N-2 and N-7...
methylation byproduct is limited to pantoprazole and omeprazole, both of which contain an electron-donating group on C-5 of the benzimidazole moiety (Table 1). The

| Table 1. Substituents of H+/K⁺ ATPase Inhibitors Approved for Clinical Use |
|-----------------------------------------------|
| **H⁺/K⁺ ATPase inhibitor** | **C-5 benzimidazole** | **C-5 pyridine** | **C-4 pyridine** | **C-5 pyridine** |
| Omeprazole | CH₃O | CH₃ | CH₂O | CH₃ |
| Rabeprazole | H | CH₃ | CH₂O(CH₂)₃O | H |
| Lansoprazole | H | CH₃ | CF₃CH₂O | H |
| Pantoprazole | CF₂HO | CH₂O | CH₂O | H |

methoxy group (omeprazole) and the difluoromethoxy group (pantoprazole) can expedite the Eschweiler–Clarke reaction by inductive effects. We used methyl iodide in refluxing dichloromethane for the methylation of pantoprazole to obtain RC D/RC E.

The formation of RC E requires close inspection for a number of reasons. First, although RC E is included as a known impurity in all major pharmacopeias, this dimer compound has not been assigned a CAS number. Second, we could not uncover any information on its mechanism of formation or its synthesis in the chemical literature. And third, and most interesting, although all proton pump inhibitors share a common molecular skeleton and differ only with regard to the substituents on both heterocyclic rings (Table 1), the dimer impurity (RC E) has been observed only in the case of pantoprazole. This is particularly noteworthy when comparing the C-5 substituent of pantoprazole with omeprazole.

The formation of biaryls has been studied extensively, and nearly all mechanistic routes involve oxidative coupling of the aromatic rings using free-radical-forming reagents such as (Tl(CF₃COO)₃/CF₃COOH)₁⁶ and AgNO₃/MeCN, followed by NaClO₄ and MeO, room temperature (rt);¹⁷ FeCl₃/CH₂Cl₂; rt; MeOH;¹⁸ FeCl₃/no solvent, 50 °C;¹⁹ MoCl₅/CH₂Cl₂, 0 °C;²⁰ CuCl₂, MeOH, and (CH₃)CNH₂, 50 °C;²¹ and H₂O₂.²² Other methods of biaryl formation involve activation of the carbon atom of the aromatic ring. This may be accomplished by (a) halogenation, followed by reaction with copper (Ulmann reaction),²³ zinc (Negishi reaction),²⁴ or magnesium (Grignard reaction);²⁵ (b) halogenation, followed by boric acid analogue formation;²⁶ and condensation in the presence of palladium catalysts such as Pd(PPh₃)₄ (Suzuki–Miyaura reaction)²⁶ and (c) nitration, followed by reduction and the formation of diazide salt (Gutterman or Gomberg–Bachmann–Hey reaction).²⁷ However, none of these reactions are employed in the synthesis of the benzimidazole moiety, and therefore it is unlikely that RC E is formed from a benzimidazole biaryl impurity. Accordingly, a different mechanism must be operative in the formation of RC E.

Considering the similarity of the C-5 substituents of pantoprazole (CHF₂–O–) and omeprazole (CH₃–O–), it is reasonable to assume that CHF₂–O– imparts a unique property to the benzimidazole moiety of pantoprazole, which promotes biaryl formation during the production of this drug substance. A review of the literature shows that nearly all reported methods for the production of pantoprazole employ highly basic pH reaction media, which results in the formation of pantoprazole sodium salt. Lower pH is avoided since proton pump inhibitors are known to undergo extensive degradation. In fact, their stability in aqueous solution is pH dependent; the rate of degradation increases with decreasing pH, resulting in intense discoloration.²⁸ However, in some of the reported procedures, the pH of the mixture is lowered to about 7.5–9²⁹ at the end of synthesis in order to convert the benzimidazole sodium salt to benzimidazole, thereby increasing its log P (partition coefficient) and allowing for its extraction into an organic solvent. Upon the separation of the aqueous phase, the organic phase containing pantoprazole free base is treated with the appropriate amount of sodium hydroxide to reform PAN⁺Na⁺, and an adequate quantity of water is added to form and isolate PAN⁺Na⁺·1.5H₂O as the pharmacopeia drug substance.²⁹

We have not observed the formation of RC E in numerous experiments carried out at high pH. It therefore occurred to us that the formation of RC E may be limited to those processes in which log P of pantoprazole is temporarily increased for its extraction into an organic phase (vide supra). This contention was tested by subjecting PAN⁺Na⁺·1.5H₂O to pH of 5–8 for 24 h and measuring the formation of RC E in each experiment by a validated HPLC method. The results are shown in Figure 1 and demonstrate that in fact the formation of RC E is a pH-

![Figure 1. Formation of RC E as a function of pH.](image-url)
The captodative effect has been proposed to facilitate and stabilize free-radical formation because of the contributions of electron-donating and electron-withdrawing substituents. The contribution of the captodative effect to the free energy of formation of radicals is small and on the order of a few kcal/mol. Therefore, the importance of captodative effect to radical formation has been a subject of debate. Nonetheless, there appears to be general agreements on two points. First, the captodative effect is expected when substituents are directly connected to the atom that will form the radical, and second, stabilized, short-lived radicals form dimers in high yields. Both of these criteria are applicable to the formation of RC E. Furthermore, Parsafar et al. have carried out comparative theoretical calculations on the stability of the CF₂ and CH₂ free radicals and have reported that CHF₂ is a highly reactive site for free-radical formation, affording a more stable free radical. Combined, the free-radical-cation mechanism of Previtera et al. and the synergistic effect of the two fluorine atoms (electron withdrawing) as well as the oxygen atom (electron donating) may be the determining factor for the formation of RC E biaryl in the case of pantoprazole. Application of Previtera’s free-radical-cation formation is shown in Scheme 3 for pantoprazole. Captodative effect of CHF₂O− group on imparting additional stability for C-6 aromatic free radical is demonstrated in Scheme 4.

Scheme 3. Cation-free-Radical Mechanism for the Formation of RC E

The captodative effect of difluoromethoxy group on stabilizing free radical 5 is shown in Scheme 4. It is reasonable to assume that the central difference between omeprazole, which does not form a dimer byproduct, and pantoprazole lies in the presence of two fluorine atoms of the 4-methoxy function. Whereas the methoxy group in omeprazole is only electron donating, the difluoromethoxy group of pantoprazole is endowed with the duality of being electron donating (oxygen atom) and concomitantly electron withdrawing (two fluorine atoms). Therefore, the difluoromethoxy group imparts a synergistic captodative effect on pantoprazole, allowing for the formation of the biaryl impurity at pH ≤ 8. Finally, inductive effects of the nitrogen atoms of the imidazole ring may prevent the formation of 3,3′- or the 6,6′-biaryl, leaving C-6 as the only candidate for free-radical formation (Scheme 5).

For direct comparison of the dimer byproduct with authentic RC E, we synthesized RC E using the benzidine rearrangement as shown in Scheme 5. The rearrangement was carried out on 3-(difluoromethoxy)nitrobenzene affording the corresponding benzidine hydrochloride. The latter was acetylated and nitrated and the nitro groups reduced to afford the penultimate intermediate for the formation of the biaryl of 2-mercaptopenimidazole. The resulting dimer is used as substrate for the synthesis of RC E, using the established method for the synthesis of pantoprazole. To this end, the biaryl of 2-mercaptopenimidazole is condensed with compound 2 affording the corresponding thioether, which is subjected to sodium hypochlorite oxidation to afford PAN RC E.

The mechanism of the benzidine rearrangement for the formation of compound 18 is shown in Scheme 6.

Conclusions

Our results demonstrate that the formation of pantoprazole dimer (RC E) is pH dependent, and this byproduct forms only at pH values ≤ 8. There is a direct relation between the pH value and the rate of formation of the biaryl impurity. A mechanism for the formation of pantoprazole dimer RC E is proposed based on free-radical-cation formation at pH 5–8. The contribution of the difluoromethoxy group in stabilizing the C-6 free radical is discussed in terms of the captodative effect, its dual character as an electron-donating and electron-withdrawing group, as well as the synergistic contribution that transpires from this duality. Combined, our experimental results and recent reports on the unique properties of difluoromethoxy group provide a reasonable explanation for the exclusivity of pantoprazole for dimer formation. Although not the main objective of this report, a brief explanation for the formation of RC D/RC F is provided.

Experimental Section

General Methods and Instrumentation: Chemical Synthesis. All reagents were purchased from Merck AG or Aldrich Chemicals. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated aluminum sheets; compound spots were visualized by ultraviolet light at 254/365 nm. Chromatography was performed using silica gel 60 (0.063–0.200 mm mesh). IR spectra were recorded on an Avatar 360 FT-IR spectrometer. 1H NMR and 13C NMR spectra were taken using a Bruker 300/500 MHz in CDCl3/DMSO-d6. Mass spectroscopy was carried out on Agilent Technologies, 5975C. HPLC analysis was carried out on Knauer 2550, and the method of analysis was adapted from USP 39 monograph for pantoprazole sodium.

pH-Dependent Formation of RC E in Aqueous Media. Pharmaceutical-grade PAN’Na1.5H2O (0.5 g, 1.15 mmol) was dissolved in a mixture of deionized water (2.5 mL) and dichloromethane (2.5 mL), and the pH of the mixture was
adjusted to 8, 7, 6, and 5 in separate 25 mL round-bottom flasks (RBF). The reaction mixtures were stirred under a nitrogen atmosphere for 24 h. The organic layer was separated and dried over sodium sulfate, and thereafter the solvent was removed under reduced pressure at 30 °C. The resulting solids were submitted to HPLC analysis using the validated HPLC method of USP 39. The chromatograms were analyzed for the level of RC E. Each run was spiked with synthetic RC E to ascertain the retention time and response factors. The results are shown in Figure 1.

Synthesis of Pantoprazole RC D/RC F with Methyl Iodide. In a 250 mL round-bottom flask equipped with a magnetic stirrer was added dichloromethane (50 mL) and PAN−Na+·1.5H2O (10 g, 23 mmol). About 10 mL of the solvent was distilled, and thereafter methyl iodide (3.7 g, 26 mmol) was added, the mixture was refluxed for 3 h, and reaction progress was monitored by TLC (CH2Cl2/MeOH/NH4OH 80:20:1). After reaction completion, the mixture was cooled to 25 °C, filtered, and washed with dichloromethane. The filtrate was concentrated under reduced pressure until turbidity was observed. The mixture was cooled to 10 °C and stirred for 3 h. The resulting precipitate was filtered, washed with cold dichloromethane, and dried under vacuum at 50 °C to a constant weight to yield 6 g (58%) of the titled compound.

Scheme 4. Captodative Effect of CHF2O Group on Imparting Additional Stability for C-6 Aromatic Free Radical

Scheme 5. Synthesis of RC E Using the Benzidine Rearrangement

Scheme 6. Benzidine Rearrangement
**Procedure for the Synthesis of Pantoprazole Related Compound E with Sodium Hypochlorite.**

2,2′-Bis(difluoromethoxy)benzidine Hydrochloride (18). In a 1 L RBF equipped with a mechanical stirrer, thermometer, and reflux condenser, compound 17 (50 g, 264 mmol) was dissolved in methanol (500 mL), and the resulting yellow solution was stirred at room temperature. Sodium hydroxide (53 g, 1.325 mol) was dissolved in water (100 mL) and added to the reaction flask. Thereafter, the mixture was charged with zinc dust (66.4 g, 1.01 mol, <63 μm), the mixture was heated to reflux, and reaction progress was monitored by TLC (CHCl₃/n-heptane 2:1). The reaction turns red (azobenzene formation) and then yellow (hydrazobenzene formation) and was completed in 16 h. The mixture was then evaporated under reduced pressure to remove about 400 mL of the solvent. Thereafter, water (100 mL) and diethyl ether (450 mL) were added dropwise over a 2 h period to 350 mL of 32% HCl (equal to 7 volumes to compound 17), which was previously cooled to 5–10 °C. The mixture was stirred for a further 1 h, the orange precipitate formed, which was then filtered and washed with water (20 mL) and dried at 70 °C to a constant weight of 81.1 g (74%) of the titled compound as a creamy powder. Mp: 248 °C for 6 h to yield 29 g (56%) of the titled compound as a creamy powder. Mp: 248 °C (dec).

H NMR (300 MHz, DMSO-d₆): δ (ppm) 6.86 (d, 3J = 8.1 Hz, 2H, Ar-H), 6.80 (t, 2H, 4J = 7.46 Hz, OCHF₂), 6.42 (d, 5J = 8.1 Hz, 2H, Ar-H), 5.38 (5H, −NH₂); 13C NMR (300 MHz, DMSO-d₆): δ (ppm) 149.53, 149.31 (C−F, 7J = 16.60 Hz), 149.65, 121.19, 120.18, 116.80 (C−F, 11J = 255.05 Hz), 115.95, 113.42, 110.52, 103.46; IR (KBr, cm⁻¹): 3440, 3219, 2360, 2342, 1616, 1559, 1399, 1186, 1110, 1026, 669; MS m/z: 316.3 (M⁺). Anal. calc for C₁₇H₁₇F₃N₃O₇: C, 53.17; H, 3.82; N, 8.86. Found: C, 52.99; H, 3.81; N, 8.83.

2,2′-Bis(difluoromethoxy)-4,4′-biphenylenediacetamide (19). In a 250 mL flask, compound 18 (10 g, 25.4 mmol) was suspended in water (40 mL). Potassium hydroxide (2.9 g, 51.4 mmol) was dissolved in water (10 mL), added to the above mixture, and stirred at room temperature. The reaction was then charged with 35 mL of acetic acid, affording a brown solution. Acetic anhydride (10.2 mL, 100 mmol) was then added all at once with vigorous stirring, resulting in the formation of a solid mass. Reaction progress was monitored by TLC (CHCl₃/MeOH 90:10). The mixture was stirred for 3 h at room temperature and 1 h at 10 °C, filtered and washed with water (20 mL), and dried at 60 °C to yield 9.76 g (95%) of the titled compound as a creamy powder, mp: 240 °C (dec).

H NMR (300 MHz, DMSO-d₆): δ (ppm) 10.22 (br s, 2H, −NH), 7.64 (s, 2H, Ar-H), 7.44 (d, 3J = 8.3 Hz, 2H, Ar-H), 7.23 (d, 5J = 8.3 Hz, 2H, Ar-H), 6.97 (t, 4J = 7.36 Hz, 2H, OCHF₂), 2.07 (s, 6H, −CH₃); 13C NMR (300 MHz, DMSO-d₆): δ (ppm) 168.69, 168.60 (C−F, 7J = 6.79 Hz), 148.50, 140.16, 140.05 (C−F, 11J = 8.30 Hz), 131.85, 122.78, 119.97, 116.56 (C−F, 15J = 257.31 Hz), 115.36, 113.15, 108.91, 24.05; IR (KBr, cm⁻¹): 3307, 2360, 1670, 1602, 1541, 1488, 1405, 1375, 1315, 1268, 1178, 1124, 1081, 1048, 827, 668; MS m/z: 404.0 (M⁺).

2,2′-Bis(difluoromethoxy)-5,5′-dinitro-4,4′-biphenylenediacetamide (20). In a 250 mL round-bottom flask, compound 19 (8.92 g, 22.3 mmol) was dissolved in a mixture of glacial acetic acid (89.2 mL equal to 10 volumes to compound 19) and acetic anhydride (71.3 mL, equal to 8 volumes to compound 19) and then cooled to 5–10 °C. Thereafter, a mixture of 65% nitric acid (12.64 mL, 185 mmol) and 8.92 mL of glacial acetic acid was added to the above-cooled solution within 40 min. The mixture was then allowed to reach room temperature and stirred for 6 h. The reaction was monitored by TLC (CHCl₃/MeOH 90:10). After reaction completion, the mixture was stirred at 5–10 °C for 1 h. A yellow precipitate formed, which was then filtered and washed with water (20 mL) and dried at 70 °C to a constant weight of 81.1 g (74%) of the titled compound, mp: 251 °C (dec).

H NMR (300 MHz, DMSO-d₆): δ (ppm) 10.51 (br s, 2H, −NH), 8.11 (s, 2H, Ar-H), 7.69 (s, 2H, Ar-H), 7.3 (t, 4J = 7.5 Hz, 2H, OCHF₂), 2.13 (s, 6H, −CH₃); 13C NMR (300 MHz, DMSO-d₆): δ (ppm) 168.89, 168.82 (C−F, 7J = 5.28 Hz), 151.79, 151.67, 137.47 (C−F, 11J = 15.09 Hz), 133.63, 133.54 (C−F, 15J = 6.79 Hz), 128.75, 121.50, 119.37, 115.92 (C−F, 15J = 255.82 Hz), 112.49, 112.04, 111.89 (C−F, 11J = 11.31 Hz), 23.72; IR (KBr, cm⁻¹): 3383, 2360, 1712, 1626, 1586, 1508, 1457, 1399, 1287, 1249, 1137, 1108, 1062, 648; MS m/z: 490.4 (M⁺).
hot MeOH (50 mL), and the yellow filtrate was used for the next step without further purification. (Note: The filtrate must be used immediately; otherwise, it decomposes to a dark brown solution.) A small quantity of the filtrate was sampled as standard for TLC comparison for the next step.

6,6′-Bis(difluoromethoxy)-2,2′-bis(mercapto-benzimidazole) (23). To the 1 L RBF equipped with a reflux condenser was added the yellow solution from a previous step and then charged with carbon disulfide (8.86 mL, 146 mmol) and aqueous potassium hydroxide (5.46 g, 97.66 mmol, and 30 mL of water), and the resulting yellow solution was heated to reflux temperature and stirred for 3 h. The reaction was monitored by TLC (CHCl₃/MeOH/NaOH 85:15:1). After reaction completion, the solvent was removed under reduced pressure to afford an oily orange residue, which was then dissolved in water (80 mL) and methanol (80 mL) and heated to 70 °C. Thereafter, acetic acid was added to adjust the pH to 7. The resulting creamy mixture was stirred at room temperature for 3 h and then filtered and washed with a 1:1 mixture of methanol/water (3 × 30 mL) and finally washed with n-heptane (50 mL) and dried at room temperature to yield 4.73 g (90%) of the titled compound as a creamy powder, mp: 249 °C (dec). ¹H NMR (500 MHz, DMSO-d₆): δ (ppm) 12.71 (brs, 2H, −SH), 12.68 (brs, 2H, −NH), 7.05 (s, 2H, Ar-H), 7.02 (s, 2H, Ar-H), 6.97 (d, ¹JH−F = 74.0 Hz, 2H, OCF₂), 13C NMR (500 MHz, DMSO-d₆): δ (ppm) 170.38, 158.58, 158.38, 145.93, 145.17, 144.68, 141.07, 138.56, 125.03, 120.54 (C−F, ¹J = 257.31 Hz), 118.95, 117.13, 113.76, 108.38, 105.94, 60.59, 57.39, 56.00; ¹⁹F NMR (282.4 MHz, DMSO-d₆): δ (ppm) −74.0; IR (KBr, cm⁻¹): 3419, 3135, 2360, 1698, 1618, 1558, 1541, 1508, 1473, 1397, 1330, 1162, 1126, 1031, 858, 645; MS m/z: 429.4 (M⁰).

6,6′-Bis(difluoromethoxy)-2,2′-bis([3,4-dimethoxypropyridin-2-yl)methyl]thio)-1H,1′H-5,5′-bib-enzimidazole (15). In a 250 mL flask, sodium hydroxide (2.28 g, 55.5 mmol) was dissolved in water (96 mL) and stirred at room temperature. Compound 23 (4.8 g, 11.1 mmol) was added to the sodium hydroxide solution, and the mixture was stirred to dissolution. Compound 2 (4.97 g, 22.2 mmol) was dissolved in water (49 mL), and the resulting solution was added dropwise to the reaction mixture over a period of 90 min. The reaction was monitored by TLC (CHCl₃/MeOH/NH₄OH 85:15:1). After reaction completion, the solvent was removed under reduced pressure to obtain a brown gummy precipitate, which was then suspended in diethyl ether (8 mL) and filtered, washed with diethyl ether, and dried under reduced pressure to room temperature to a constant weight to afford 0.32 g (20%) of the title compound as a brown light powder, mp: 126–128 °C. ¹H NMR (500 MHz, DMSO-d₆): δ (ppm) 13.87 (br s, 2H, −NH), 8.18 (d, 2H, ¹J = 5.2, Py-H), 7.64 (s, 2H, Ar-H), 7.51 (s, 2H, Ar-H), 7.12 (d, 2H, ¹J = 5.2, Py-H), 7.09 (d, ¹J = 13.1, 2H, −SOCH₂), 4.69 (d, ¹J = 13.1, 2H, −SOCH₂), 3.90 (s, 6H, −OCH₃), 3.78 (s, 6H, −OCH₃); ¹³C NMR (300 MHz, DMSO-d₆): δ (ppm) 155.88, 151.85, 149, 130, 133, 112, 112, 103, 858, 645; MS m/z: 762.9 (M⁺); assay (HPLC, 96.97%). Anal. calc. for C₃₁H₂₆F₄N₄O₄S₂: C, 50.24; H, 3.67; N, 11.04; S, 8.43. Found: C, 50.24; H, 3.67; N, 11.04; S, 8.43.

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