# A simple and facile synthesis of amidoalkyl naphthols catalyzed by $Yb(OTf)_3$ in ionic liquids

**Anil Kumar, M. Sudershan Rao, Israr Ahmad, and Bharti Khungar**



**Abstract:** An improved, simple, and facile synthesis of amidoalkyl naphthols by employing three-component one-pot condensation reaction of β-naphthol, aromatic aldehydes, and amides in ionic liquids using ytterbium triflate as a mild Lewis acid catalyst is described. Advantageously, amidoalkyl naphthols were obtained in high yield under eco-friendly, economical, and non-corrosive conditions, and the catalyst was recycled.

*Key words:* amidoalkyl naphthols, ytterbium triflate, ionic liquid, β-naphthol, three-component condensation.

**Résumé :** On a mis au point une méthode simple, facile et améliorée de synthèse d'amidoalkylnaphtols impliquant une réaction de condensation monotope à trois composants, dont le β-naphtol, des aldéhydes et des amides aromatiques dans des liquides ioniques et faisant appel au triflate d'ytterbium comme catalyseur acide de Lewis doux. L'avantage de la méthode est que les amidoalkylnaphtols sont obtenus avec des rendements élevés, dans de bonnes conditions écologiques, économiques et non corrosives et que le catalyseur peut être recyclé.

*Mots-clés :* amidoalkylnaphtols, triflate d'ytterbium, liquide ionique, condensation à trois composants.

[Traduit par la Rédaction]

## Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry and have emerged as a powerful strategy in the preparation of structurally diverse libraries of drug-like molecules.[1] MCRs constitute an especially attractive synthetic strategy, since they provide easy and rapid access to large libraries of drug-like organic compounds with diverse substitution patterns.[2] As MCRs are one-pot reactions, they are easier to carry out and offer significant advantages over conventional linear-type syntheses.

The amidoalkyl naphthols are important precursors for the synthesis of 1,3-amino oxygenated compounds. The 1,3-amino oxygenated functionality is present in various biologically important natural products and drug molecules.[3] The amidoalkyl naphthols have been prepared by multi-component condensation of aldehydes, 2-naphthol, and acetonitrile or amide in the presence of Lewis[4–6] or Brønsted acid[7] catalysts. However, some of these catalysts require prolonged reaction times and suffer from low yields, toxicity, and recovery and reusability of the catalyst. Therefore, there is great need of an eco-friendly and green catalysts, which can be recycled at the end of reactions and give high yields of amidoalkyl naphthols under mild reaction conditions.

Recently, rare-earth metal triflates have enjoyed extensive applications in a variety of Lewis acid catalyzed organic reactions.[8] The growing interest in use of these salts is due to their ease of handling, non-corrosiveness, reusability, and unique reactivity and selectivity. Among all rare-earth metal triflates, ytterbium triflate has high acidity due to its small ionic radii.[8b] It was first used by Forsberg et al.,[9] and since then, it has found a wide utility in deprotection,[10] cycloaddition reactions,[11] aldol-Grob reaction,[12] imino-ene reaction,[13] electrophilic substitutionn, cyclization,[14] and synthesis of heterocyclic[15] and natural products.[16]

The ionic liquids, especially those based on 1,3-dialkylimidazolium cations, have gained considerable interest as green alternative to volatile organic solvents.[17] Various reactions have been reported with the immobilization of metal triflates in ionic liquids with increased catalytic activity along with their easy reuse.[18] During the course of our recent studies directed towards the development of eco-friendly procedures for various organic transformations,[19] we wish to report three-component, one-pot condensation of β-naphthol, aromatic aldehydes, and amides to amidoalkyl naphthols using $Yb(OTf)_3$ as a catalyst in ionic liquids (Scheme 1). To the best of our knowledge, there is no report on the use of lanthanide triflates and ionic liquids for the synthesis of amidoalkyl naphthols.

## Results and discussion

First, we studied the three-component condensation reaction of 4-chlorobenzaldehyde, 2-naphthol, and acetamide in the presence of catalytic amount of several Lewis acids in [bmim][$BF_4$] ionic liquid (Table 1). In the absence of the catalyst, no product formation was observed even after 48 h at 80 °C (Table 1, entry 1). Ytterbium triflate was found to be the most useful catalyst among all the used catalysts under these conditions, giving highest yield of product (92%) (Table 1, entry 7). The high activity of $Yb(OTf)_3$ compared with the metal triflates used may be attributed to its high acidity.

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**Scheme 1.** Synthesis of amidoalkyl naphthols in ionic liquid.

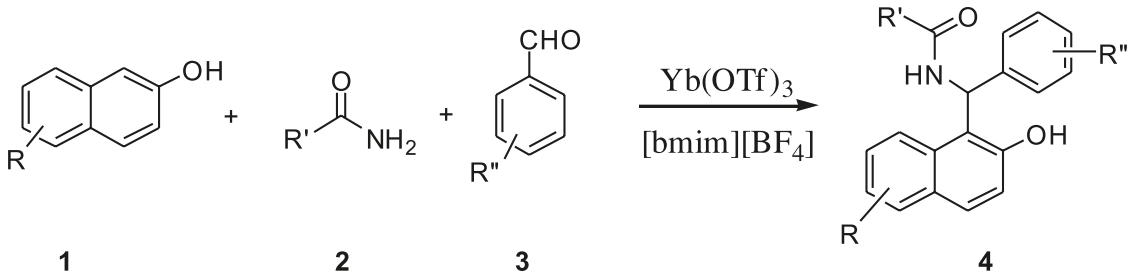



**Table 1.** Effect of different Lewis acid catalyst on the synthesis of **4a** in ionic liquid at 80 °C.

| Entry | Catalyst | Time (h) | Yield (%)[a] |
|---|---|---|---|
| 1 | — | 48 | —[b] |
| 2 | $CoCl_2$ | 12 | 20 |
| 3 | $BF_3{\cdot}Et_2O$ | 12 | 30 |
| 4 | $ZrOCl_2{\cdot}8H_2O$ | 12 | 50 |
| 5 | $In(OTf)_3$ | 8 | 55 |
| 6 | $Y(OTf)_3$ | 8 | 50 |
| 7 | $Yb(OTf)_3$ | 4 | 92 |
| 8 | $La(OTf)_3$ | 8 | 60 |
| 9 | $Sc(OTf)_3$ | 12 | 35 |
| 10 | $Zn(OTf)_2$ | 12 | Trace |
| 11 | $Ba(OTf)_3$ | 12 | Trace |

**Note:** In each case, 20 mol% catalyst was used.

[a]Isolated yield.

[b]No product formation observed.

The condensation of 4-chlorobenzaldehyde (**1**), 2-naphthol (**2**), and acetamide (**3**) at 80 °C in ionic liquid, [bmim][$BF_4$], containing 20 mol% $Yb(OTf)_3$, gave 92% of **4a** (Table 2, entry 1). After extraction from ionic liquid, the product was purified by recrystallization with ethanol and characterized by IR, MS, $^1$H NMR, and $^{13}$C NMR spectroscopy. Presence of a doublet at δ 8.53 ppm in $^1$H NMR spectrum for –CH–NH group along with other aromatic protons, peak at δ 169.45 ppm for C=O group in $^{13}$C NMR, and a strong peak at 1663 cm$^{-1}$ for –$NHCOCH_3$ group in IR confirms the structure of **4a**.

Next, we examined the effect of different solvents, such as [bmim][$BF_4$], toluene, DMSO, DMF, Ethanol, $H_2O$, PEG-400, 1,2-dichloroethane, $CHCl_3$, and DCM, as model reaction using $Yb(OTf)_3$ as catalyst. All the reactions were run using 20 mol% of the catalyst. As shown in Table 3, **4a** was obtained in excellent yield (92%) in the ionic liquid [bmim][$BF_4$]. Therefore, we chose [bmim][$BF_4$] as the solvent of choice for further reactions. These results point towards the need of the proper catalyst and solvent system, which play the key role for the success of the reaction. As shown in Table 3, no product formation was observed in polar organic solvents, such as DMSO, DMF, and ethanol, as well as aqueous solvent. It may be due to the interaction of these solvents with the catalyst.

Encouraged by our results for the one-pot condensation of 2-naphthol and acetamide with 4-chlorobenzaldehyde in ionic liquid, we next examined the generality of this methodology for the synthesis of various amidoalkyl naphthols by condensation of substituted β-naphthols, aldehydes, and amides. The results are shown in Table 2. Several functionalities present in the aldehydes and 2-naphthols, such as halogen, methoxy, and nitro groups, were tolerated. In all cases, the corresponding amidoalkyl naphthols were obtained in good to excellent yields (Table 2). When benzamide was used instead of acetamide in the one-pot condensation of 2-naphthol with benzaldehyde in ionic liquid, it resulted only in 35% yield of **4p** (Table 2, entry p). Similarly, when we used *N*-methylacetamide, we found that the reaction is slower compared with acetamide, and the yield of the corresponding product was only 61% after 12 h.

A plausible mechanism for the formation of amidoalkyl naphthols by the reaction of 2-naphthol with aldehydes in presence of ytterbium triflate is shown in Scheme 2. As reported in the literature, in situ generation of *ortho*-quinone methides (*o*-QMs) is expected to take place.[7a,7b] These *o*-QMs, generated in situ, react with amides via conjugate addition to form the amidoalkyl naphthols. The aromatic aldehydes with electron-withdrawing groups reacted faster than the aromatic aldehydes with electron-donating groups, which is in agreement with the reaction mechanism. The rate of conjugate addition is higher to *o*-QMs as the lowest unoccupied molecular orbital (LUMO) of alkene in *o*-QMs is at lower energy in the presence of electron-withdrawing groups compared with electron-donating groups.[20] The role of the ionic liquid is not yet clear, but it is expected that the noncoordinating nature and high dielectric constant of the ionic liquid may help in the generation of *o*-QMs and enhance the rate of nucleophilic conjugate addition. Such effect of ionic liquid on the rate of nucleophilic substitution reaction is reported in literature.[21] The lower reactivity of

**Table 2.** Synthesis of different amidoalkyl naphthols catalyzed by $Yb(OTf)_3$ in ionic liquid.

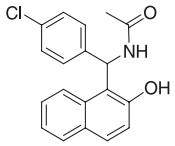
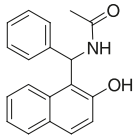
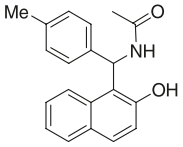
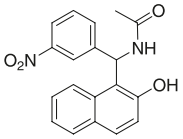
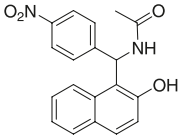
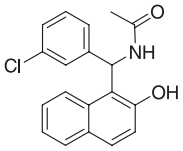
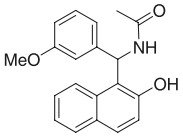
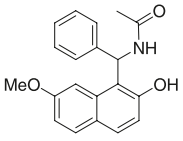
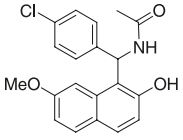
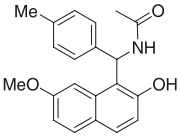
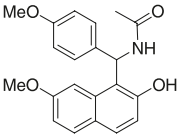
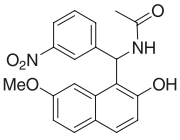
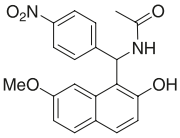
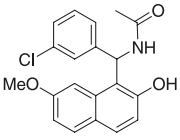
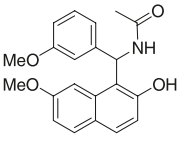
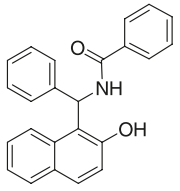
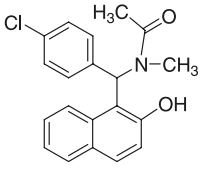
| Entry | Product | Time (h) | Mp (°C) | Yield[a, b] (%) |
|---|---|---|---|---|
| **a** |  | 4 | 218 | 92[c] |
| **b** |  | 6 | 234 | 90 |
| **c** |  | 6 | 220 | 87 |
| **d** |  | 4 | 245 | 88 |
| **e** |  | 4 | 237 | 89 |
| **f** |  | 4 | 235 | 91 |
| **g** |  | 8 | 228 | 88 |
| **h** |  | 6 | 168 | 89 |
| **i** |  | 4 | 120 | 90 |

**Table 2.** *Concluded.*

| Entry | Product | Time (h) | Mp (°C) | Yield[a, b] (%) |
|---|---|---|---|---|
| **j** |  | 6 | 180 | 85 |
| **k** |  | 6 | 192 | 88 |
| **l** |  | 5 | 205 | 85 |
| **m** |  | 4 | 217 | 89 |
| **n** |  | 4 | 186 | 89 |
| **o** |  | 8 | 177 | 88 |
| **p** |  | 10 | 181 | 35 |
| **q** |  | 12 | — | 61 |

[a] Isolated yield by column chromatography on silica gel.

[b] All products were characterized by IR, MS, $^1$H NMR, and $^{13}$C NMR.

[c] Yields for recycling of catalyst were 92, 91, 87, 85, and 86, respectively for five cycles.

benzamide compared with acetamide may be attributed to the difference in acidity constants of these weakly basic substrates in acidic media. The reported p$K_a$ values of acetamide and benzamide are –0.73 and –1.54, respectively.[22]

From an environmental point of view, it is desirable to minimize the amount of waste for each organic transformation. In this context, we recycled the catalyst solution for subsequent runs. To study the reusability, $Yb(OTf)_3$ immobi-

**Table 3.** Effect of different solvents on the synthesis of **4a** catalyzed by $Yb(OTf)_3$.

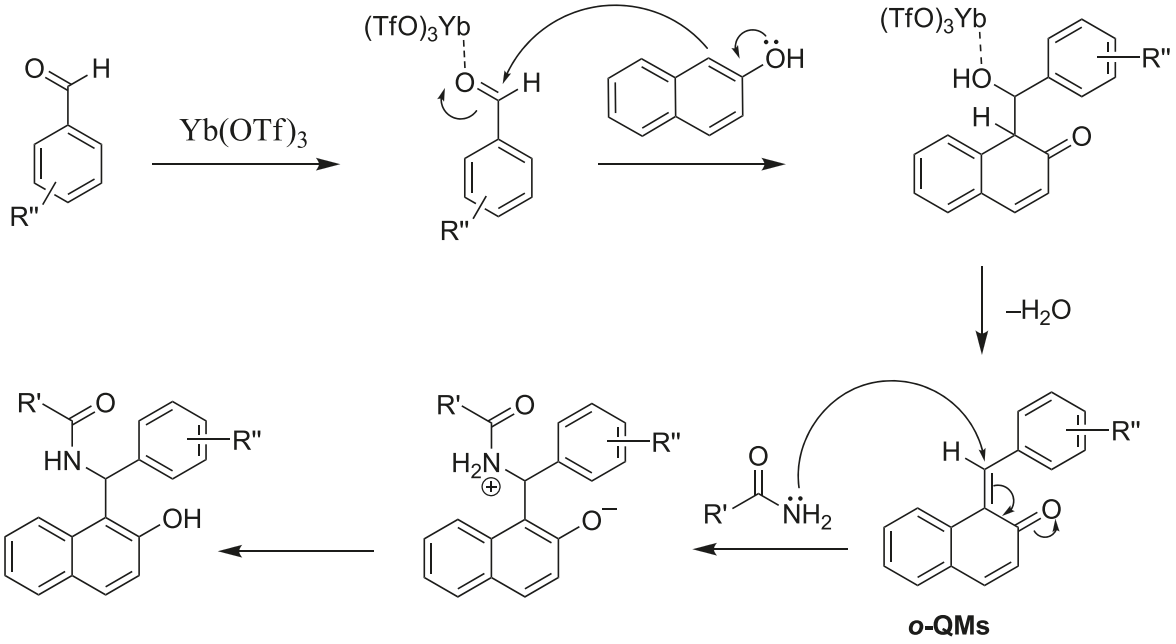
| Entry | Solvent | Temperature (°C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | [bmim][$BF_4$] | 80 | 4 | 92 |
| 2 | Toluene | 100 | 12 | Trace |
| 3 | DMSO | 100 | 12 | —[b] |
| 4 | DMF | 100 | 12 | —[b] |
| 5 | Ethanol | Reflux | 12 | —[b] |
| 6 | $H_2O$ | 100 | 12 | —[b] |
| 7 | PEG-400 | 100 | 12 | <10 |
| 8 | $ClCH_2CH_2Cl$ | 80 | 12 | 35 |
| 9 | $CHCl_3$ | Reflux | 12 | 20 |
| 10 | DCM | Reflux | 12 | 20 |

**Note:** $Yb(OTf)_3$, 20 mol%.

[a]Isolated yield.

[b]No product formation observed.

**Scheme 2.** Probable mechanism for the synthesis of amidoalkyl naphthols catalyzed by $Yb(OTf)_3$.




lized in ionic liquid, [bmim][$BF_4$], was reused for the synthesis of amidoalkyl naphthol **4a**. After extraction of amidoalkyl naphthols from ionic liquid with ethyl acetate – hexane mixture, the ionic liquid containing $Yb(OTf)_3$ was concentrated on rotatory evaporator under reduced pressure to remove the organic solvent for 30 min. To this dried ionic liquid containing $Yb(OTf)_3$, β-naphthol, 4-chlorobenzaldehyde, and acetamide were added and stirred at room temperature for 4 h. The reaction mixture was extracted by ethyl acetate – hexane mixture, and the combined organic layer was evaporated to give amidoalkyl naphthols **4a**. This cycle was repeated for five times. The catalysts showed good reactivity and yield even after five cycles with little deterioration in catalytic activity (Table 2, entry a).

## Conclusion

In conclusion, an efficient, simple, and eco-friendly method has been described for the synthesis of amidoalkyl naphthols by employing three-component one-pot condensation reaction of β-naphthol, aromatic aldehydes, and amides in ionic liquids using ytterbium triflate as a mild Lewis acid catalyst. The catalyst was recovered and recycled in successive reaction cycles.

## Experimental section

All chemicals and reagents were of analytical grade. β-Naphthol, acetamide, aldehydes, and acetyl chloride were purchased form S. D. Fine and Spectrochem, India. Sodium tetrafluoroborate and 1-methylimidazole were purchased from Aldrich. Ionic liquid, [bmim][$BF_4$], was prepared according to earlier reported procedure.[19a,19b] The $^1H$ NMR spectra were recorded on a Brucker Heaven Avance 11 400 (400 MHz) spectrophotometer using TMS as internal standard and $CDCl_3$ as solvent, and the chemical shifts were expressed in ppm. The IR spectra were recorded using KBr pellets on Shimadzu Prestige-21 FTIR spectrophotometer and $\nu_{max}$ was expressed in $cm^{-1}$. Mass spectra were recorded on a KC455 Waters TOF MS spectrometer. TLC was run on the silica-gel-coated aluminium sheets (Silica gel 60 $F_{254}$, E. Merck, Germany) and visualized in UV light (254 nm).

### General procedure for the synthesis of amidoalkyl naphthols catalyzed by $Yb(OTf)_3$ in ionic liquid

4-Chlorobenzaldehyde (103 μL, 1.49 mmol), β-naphthol (110 μL, 1.49 mmol), acetamide (1.79 mmol), and $Yb(OTf)_3$ (20 mol%, 46.2 mg) were added to a 10 mL round-bottom flask containing the ionic liquid, $[bmim][BF_4]$ (3.0 mL). The reaction mixture was stirred at 80 °C for 4 h in oil bath. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and extracted with ethyl acetate – hexane (2 × 5 mL, 4:1, *v*/*v*). The ionic liquid, containing ytterbium triflate, was recovered and dried under vacuum. The combined organic layer was evaporated under reduced pressure. The product was recrystallized from ethanol to give pure **4a** (450 mg, 92%). The product was characterized by $^1H$ and $^{13}C$ NMR, IR, and mass spectroscopic data.

### Spectral data of selected amidoalkyl naphthols

#### N-*((4-Chlorophenyl)(2-hydroxynaphthalen-1-yl)-methyl)acetamide (4a)*

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) δ: 2.02 (s, 3H), 7.14–7.32 (m, 7H), 7.39 (brs, 1H), 7.77–7.82 (m, 3H), 8.53 (s, 1H), 10.02 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ: 22.61, 47.42, 117.67, 118.42, 122.42, 123.16, 124.62, 126.47, 127.03, 127.89, 128.45, 129.47, 130.64, 133.23, 141.78, 153.22, 169.45. HR-MS-EI: *m*/*z* calcd. for $C_{19}H_{16}ClNO_2$ 325.0870; found: 326.1458 $[M + H]^+$.

#### N-*((2-Hydroxynaphthalen-1-yl)(phenyl)methyl)-acetamide (4b)*

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) δ: 2.01 (s, 3H), 7.15–7.26 (m, 8H), 7.36 (t, $J$ = 7.56 Hz, 1H), 7.79 (dd, $J$ = 8.0 Hz, 2H), 7.87 (brs, 1H), 8.58 (s, 1H), 10.02 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ: 22.68, 47.97, 118.67, 118.77, 122.17, 123.09, 126.05, 126.08, 126.25, 127.94, 128.25, 128.51, 129.14, 132.38, 142.73, 153.75, 169.19. HR-MS (EI): *m*/*z* calcd. for $C_{19}H_{17}NO_2$ 291.1259; found: 292.1458 $[M + H]^+$.

#### N-*((2-Hydroxynaphthalen-1-yl)(p-tolyl)methyl)-acetamide (4c)*

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) δ: 2.04 (s, 3H), 2.24 (s, 3H), 7.08 (d, $J$ = 7.81 Hz, 2H), 7.14 (d, $J$ = 7.84 Hz, 2H), 7.21–7.39 (m, 3H), 7.39 (t, $J$ = 8.0 Hz, 1H), 7.70 (dd, $J$ = 8.0 Hz, 2H), 7.94 (brs, 1H), 8.52 (d, $J$ = 8.0 Hz, 1H), 10.08 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ: 20.54, 22.70, 47.74, 118.55, 119.05, 122.37, 123.34, 126.05, 126.27, 128.56, 129.16, 132.38, 135.07, 139.59, 153.17, 169.27. HR-MS (EI): *m*/*z* calcd. for $C_{20}H_{19}NO_2$ 305.1416; found: 306.2213 $[M + H]^+$.

#### N-*((2-Hydroxynaphthalen-1-yl)(3-nitrophenyl)-methyl)acetamide (4d)*

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) δ: 2.07 (s, 3H), 7.27–7.30 (m, 3H), 7.43–7.45 (m, 1H), 7.51–7.56 (m, 1H), 7.61–7.63 (m, 1H), 7.82–7.84 (m, 2H), 7.95 (brs, 1H), 8.06–8.10 (m, 2H), 8.71 (s, 1H), 10.22 (d, $J$ = 8.6 Hz, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ: 22.54, 47.67, 117.84, 118.47, 120.47, 121.21, 122.61, 122.78, 126.77, 128.41, 128.69, 129.50, 129.90, 132.18, 132.85, 145.41, 147.72, 153.38, 169.79. HR-MS (EI): *m*/*z* calcd. for $C_{19}H_{16}N_2O_4$ 336.1110; found: 337.1523 $[M + H]^+$.

#### N-*((2-Hydroxynaphthalen-1-yl)(4-nitrophenyl)-methyl)acetamide (4e)*

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) δ: 2.09 (s, 3H), 7.25–7.32 (m, 3H), 7.43 (t, $J$ = 8.0 Hz, 1H), 7.46–7.49 (m, 3H), 7.82 (d, $J$ = 8.0 Hz, 1H), 7.89 (brs, 1H), 8.16 (d, $J$ = 8.0 Hz, 2H), 8.67 (d, $J$ = 8.0 Hz, 1H), 10.22 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ: 22.53, 47.96, 117.91, 118.45, 122.58, 122.87, 123.19, 126.72, 127.13, 128.45, 128.67, 129.88, 132.23, 145.90, 151.22, 153.43, 169.84. HR-MS (EI): *m*/*z* calcd. for $C_{19}H_{16}N_2O_4$ 336.1110; found: 337.1476 $[M + H]^+$.

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