Intramolecular Azide–Alkyne [3+2] Cycloaddition: A Versatile Route for the Synthesis of 1,2,3-Triazole Fused Dibenzo[1,5]diazocine Derivatives

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Abstract: A facile synthesis of [1,2,3]triazolo dibenzo[1,5]diazocines by intramolecular Huisgen 1,3-dipolar cycloaddition of azide with alkynes has been achieved. The methodology offers clean reaction and easy isolation of products in excellent yields.

Key words: triazole, diazocine, intramolecular 1,3-dipolar cycloaddition, nitrogen heterocycle

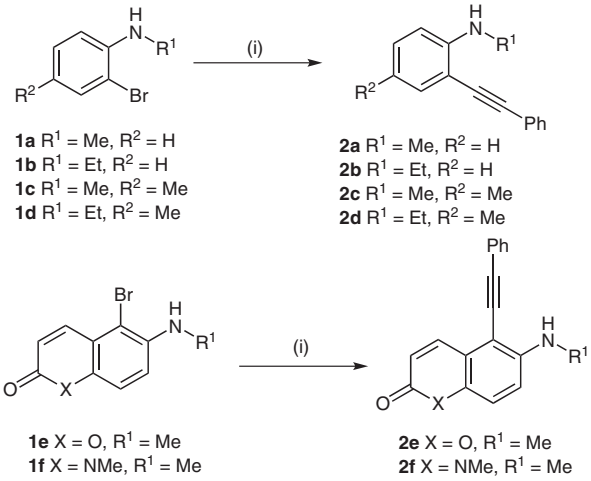
Huisgen 1,3-dipolar cycloaddition of an azide with an alkyne to afford the 1,2,3-triazole ring has been widely used in organic synthesis.[1]Several compounds containing the 1,2,3-triazole ring system possess a broad spectrum of biological activities including anti-HIV,[2] anti-allergic,[3] antifungal,[4] antiviral,[5] and antimicrobial activities.[6] 1,2,3-Triazole moieties are useful building blocks in chemistry and can be modified to exhibit important role in pharmacological applications due to their stability towards light, moisture, oxygen, and metabolism in the body.[7] Moreover these scaffolds find wide range of applications in industries as dyes, corrosion inhibitors, photostabilizers, photographic materials, and agrochemicals.[8] The dibenzo[*b*,*f*][1,5]diazocine nucleus is a privileged structure found in the Tröger's base[9] and its analogues,[10] that are mainly intended for the supramolecular chemistry. The derivatives of benzodiazocine are interesting because of their utility as amoebicidal agents.[11] Polycyclic benzodiazocines of natural origin are potent inhibitors of protein kinase C and cyclic nucleotide-dependent protein kinases, used in experimental pharmacology[12]and simple benzodiazocines have been used as homologues of benzodiazepine drugs.[12c]

Sharpless and Mendal independently discovered the copper-catalyzed version of the 1,3-dipolar cycloaddition, which produces 1,4-disubstituted triazoles in high regioselectivity[13,14] at a relatively shorter time and lower reaction temperature. Later on Fokin and co-workers[15] reported a ruthenium(II)-catalyzed azide-alkyne cycloaddition leading to exclusive formation of the corresponding 1,5-disubstituted regioisomeric 1,2,3-triazoles. However, these metal-catalyzed cycloaddition reactions are extensively used in an intermolecular fashion for the synthesis of various conjugates[16] and in an intramolecular fashion for the synthesis of triazole-containing small peptides.[17]

Ideally an intramolecular reaction is expected to provide a powerful method for the synthesis of structurally diversified analogues, which are usually difficult to obtain by an intermolecular fashion. This is particularly more so, to synthesize fused polycyclic triazole derivatives of interest to medicinal chemists. The potential of the intramolecular cycloaddition in the rapid synthesis of complex heterocyclic compounds offers further application of this reaction.

Though there are many synthetic routes toward the preparation of 1,2,3-triazoles[18–21] and benzodiazocines[22] individually, there is no report on the synthesis of triazole fused diazocinone derivatives. In continuation of our efforts to the synthesis of triazole containing nitrogen heterocycles[18c,23] of biological interest we have undertaken a study to synthesize fused triazolodibenzo diazocinone derivatives by intramolecular Huisgen 1,3-dipolar cycloaddition reaction and the results are reported here.

The precursors **3a–f** required for our present study were synthesized from amines **2a–f**. Compound **2a–f** were synthesized by Sonogoshira coupling of the corresponding bromo derivatives **1a–g** with phenylacetylene using $Pd(PPh_3)_2Cl_2$ as catalyst and CuI as co-catalyst in refluxing anhydrous DMF containing triethylamine (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) phenylacetylene, anhyd DMF, Et_3N, $Pd(PPh_3)_2Cl_2$, CuI, heat, 120 °C, 4–6 h.

The compounds **2a–f** were converted to the amide derivatives **3a–f** by treatment with 2-azidobenzoyl chloride (which is readily prepared by refluxing 2-azidobenzoic acid with thionyl chloride for 2 h) under phase-transfer ca-

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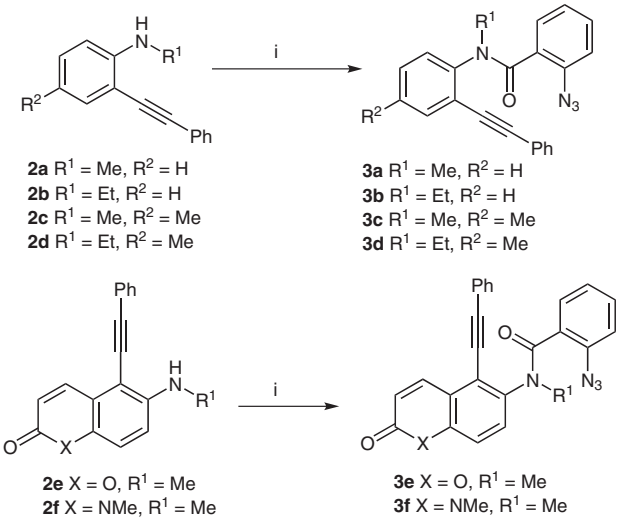
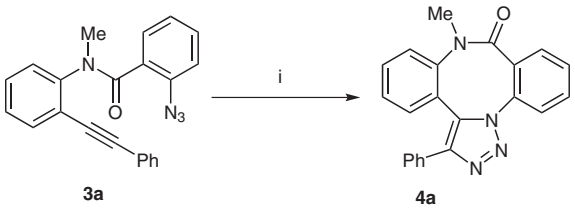


Scheme 2 *Reagents and conditions*: (i) 2-azidobenzoyl chloride, CH_2Cl_2/H_2O, TBAHS, K_2CO_3, r.t., 1 h.



Scheme 3 *Reaction conditions*: (i) heat, 120 °C, 5 h.

talysis conditions using TBAHS as catalyst and potassium carbonate as base (Scheme 2).

We have initiated our investigation with the compound **3a**. When **3a** was heated at 120 °C in DMF, it produces the final compound **4a** in 95% yield (Scheme 3).

We have also conducted the same reaction in other solvents like *N*,*N*-dimethylacetamide, dimethyl sulfoxide, 1,4-dioxane, and toluene. None of the solvents except *N*,*N*-dimethylacetamide and toluene afforded the desired product. The yield of the product was relatively lower (68% and 50%, respectively). DMF has been found to give the desired product in almost quantitative yield. Accordingly other substrates **3b–f** were treated and the desired cyclized products **4b–f** were obtained in 92–97% yields (Table 1).

Huisgen 1,3-dipolar cycloaddition has been widely used by many for the synthesis of several bicyclic, as well as polycyclic, triazole fused nitrogen-containing heterocycles[24] and also in the sysnthesis of oxygen-rich heterocycles.[25] Recently Chandrasekaran et al. have reported[26] the synthesis of 1,2,3-triazole-fused tetrahydropyrazine-6-ones in excellent yields from several primary amines and amino acids using intramolecular cycloaddition as the key step. Bolm and his co-workers have developed[27] the synthesis of sulfoximidoyl-substituted triazoles by Huisgen 1,3-dipolar cycloaddition. Here we have achieved a simple synthetic protocol for the synthesis of some triazole-fused dibenzodiazocinones in excellent yields using the same Huisgen 1,3-dipolar cycloaddition reaction.

In conclusion we have developed a simple approach for the synthesis of 1,2,3-triazole fused dibenzodiazocinone derivatives with potential biological activity using intramoleculer Huisgen 1,3-dipolar cycloaddition reaction. The protocol is very simple, high yielding, and offers easy isolation and purification of the products.

Melting points were determined in open capillaries and are uncorrected. IR spectra were run for KBr discs on a PerkinElmer 120-000A apparatus and ^{1}H NMR spectra were recorded for solutions in $CDCl_3$ with TMS as internal standard on a Bruker DPX-300, Bruker DPX-400 and Bruker DPX-500 MHz spectrometer. ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ on a Bruker DPX-400 spectrometer. HRMS were recorded on a Qtof Micro YA263 instrument. CHN analyses were determined on a 2400 series II CHN analyzer Perkin-Elmer at the Chemistry Department of Kalyani University. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel-G [E-Merck (India)] was used for TLC. Petroleum ether (PE) refers to the fraction with boiling range between 60 and 80 °C.

Amides 3a–f; 2-Azido-*N*-methyl-*N*-[2-(2-phenylethynyl)phenyl]benzamide (3a); Typical Procedure

To a stirred solution of 2-azidobenzoyl chloride (615 mg, 3.38 mmol) in CH_2Cl_2 (20 mL) was added a mixture of amine **2a** (500 mg, 2.82 mmol) and a catalytic amount of TBAHS in CH_2Cl_2 (20 mL). To this mixture, a solution of K_2CO_3 (584 mg, 4.23 mmol) in H_2O (10 mL) was added slowly. After stirring the mixture for 30 min, a TLC check indicated completion of the reaction. Then, the mixture was washed with 5% aq HCl (2 × 20 mL) and then with 5% aq NaOH (2 × 20 mL). Finally, the organic layer was washed with brine (20 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated and the crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc (4:1) as eluent to give **3a** as a solid; yield: 790 mg (79%); mp 150–152 °C.

IR (KBr): 1652, 2129, 2210 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.61 (m, 2 H), 7.42–7.46 (m, 1 H), 7.38–7.40 (m, 3 H), 7.28 (dd, *J* = 1.3, 6.1 Hz, 1 H), 7.13–7.22 (m, 4 H), 6.96 (d, *J* = 7.9 Hz, 1 H), 6.87 (t, *J* = 7.5 Hz, 1 H), 3.52 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.0, 85.7, 95.2, 118.1, 122.0, 122.3, 122.5, 124.2, 127.8, 128.3, 128.4, 128.6, 128.9, 131.7, 133.4, 136.5, 144.8, 149.3, 168.4.

HRMS: *m*/*z* calcd for $C_{22}H_{16}N_4O$: 353.1397 [M$^+$ + H]; found: 353.1406 [M$^+$ + H].

3b

Yield: 82%; solid; mp 180–182 °C.

IR (KBr): 1655, 2128, 2208 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.60 (m, 2 H), 7.36–7.42 (m, 4 H), 7.30–7.31 (m, 1 H), 7.19–7.22 (m, 1 H), 7.13–7.20 (m, 3 H), 6.93–6.98 (m, 1 H), 6.86–6.90 (m, 1 H), 4.25–4.33 (m, 1 H), 3.80–3.87 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

MS: *m*/*z* = 366 (M$^+$).

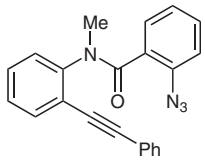
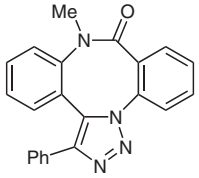
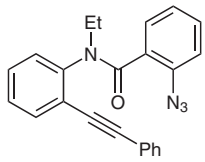
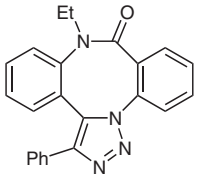
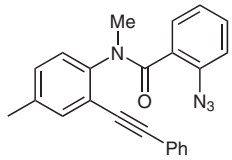
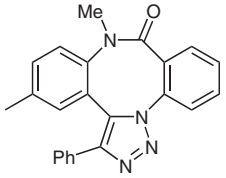
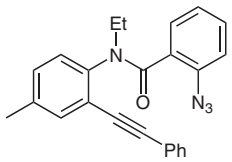
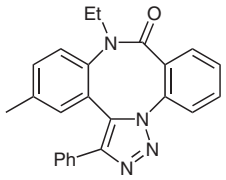
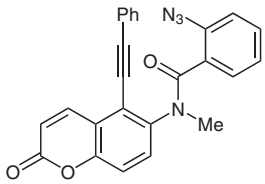
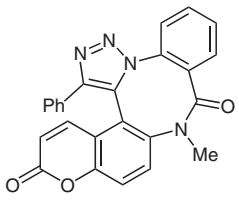
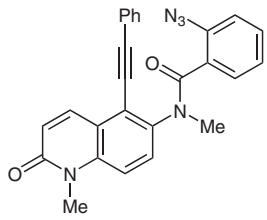
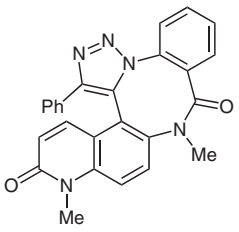
Anal. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.52; H, 4.98; N, 15.46.

3c

Yield: 79%; solid; mp 162–164 °C.

IR (KBr): 1652, 2129, 2210 cm^{-1}.

Table 1 Summarized Results of 1,3-Dipolar Cycloaddition

Substrate		Time (h)	Product		Yield (%)
3a		5	**4a**		95
3b		5	**4b**		97
3c		5	**4c**		95
3d		5.1	**4d**		93
3e		5.1	**4e**		92
3f		5.2	**4f**		94

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.71 (m, 2 H), 7.57–7.59 (m, 1 H), 7.44–7.51 (m, 3 H), 7.34–7.39 (m, 3 H), 7.28–7.33 (m, 2 H), 7.0 (s, 1 H), 3.34 (s, 3 H), 2.24 (s, 3 H).

MS: *m*/*z* = 366 (M^+).

Anal. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.61; H, 4.99; N, 15.50.

3d

Yield: 76%; solid; mp 236–238 °C.

IR (KBr): 1658, 2110, 2215 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.2 Hz, 2 H), 7.55–7.57 (m, 1 H), 7.41–7.48 (m, 3 H), 7.32–7.38 (m, 3 H), 7.28–7.30 (m, 2 H), 7.08 (s, 1 H), 4.35–4.44 (m, 1 H), 3.35–3.43 (m, 1 H), 2.24 (s, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

MS: *m*/*z* = 380 (M^+).

Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.96; H, 5.34; N, 14.94.

3e

Yield: 80%; solid; mp 140–142 °C.

IR (KBr): 1665, 1735, 2108, 2212 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.1 (d, *J* = 9.7 Hz, 1 H), 7.65–7.67 (m, 2 H), 7.43–7.47 (m, 4 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 7.20–7.23 (m, 1 H), 7.11 (d, *J* = 8.8 Hz, 1 H), 6.98 (d, *J* = 7.9 Hz, 1 H), 6.89–6.92 (m, 1 H), 6.48 (d, *J* = 9.7 Hz, 1 H), 3.52 (s, 3 H).

MS: *m*/*z* = 420 (M^+).

Anal. Calcd for $C_{25}H_{16}N_4O_3$: C, 71.42; H, 3.84; N, 13.33. Found: C, 71.64; H, 3.89; N, 13.53

3f

Yield: 78%; solid; mp 106–108 °C.

IR (KBr): 1650, 1658, 2127, 2207 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 9.6 Hz, 1 H), 7.67–7.69 (m, 2 H), 7.43–7.46 (m, 4 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.12–7.21 (m, 2 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 6.87 (t, *J* = 7.6 Hz, 1 H), 6.77 (d, *J* = 10.0 Hz, 1 H), 3.65 (s, 3 H), 3.53 (s, 3 H).

MS: *m*/*z* = 433 (M^+).

Anal. Calcd for $C_{26}H_{19}N_5O_2$: C, 72.04; H, 4.42; N, 16.16. Found: C, 72.25; H, 4.45; N, 16.39.

Compounds 4a–f; 8-Methyl-3-phenyldibenzo[*c*,*g*][1,2,3]triazolo[1,5-*a*][1,5]diazocin-9(8*H*)-one (4a); Typical Procedure

A solution of the amide **3a** (100 mg, 0.28 mmol) in DMF (5 mL) was heated at 120 °C for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled and H_2O (10 mL) was added. The mixture was then extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc (7:3) as eluent to obtain the pure product **4a** as a solid; yield: 95 mg (95%); mp 226–228 °C.

IR (KBr): 1652, 2928 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.68 (m, 2 H), 7.57–7.59 (m, 1 H), 7.43–7.52 (m, 5 H), 7.32–7.38 (m, 3 H), 7.28–7.30 (m, 1 H), 7.20 (dd, *J* = 1.6, 12 Hz, 1 H), 3.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.8, 126.0, 126.2, 126.8, 127.3, 128.3, 128.7, 128.8, 128.8, 130.0, 130.3, 131.0, 131.1, 131.6, 132.0, 133.0, 143.1, 143.9, 166.9.

HRMS: *m*/*z* calcd for $C_{22}H_{16}N_4O$: 353.1397 [M^+ + H]; found: 353.1406 [M^+ + H].

4b

Yield: 97%; solid; mp 198–200 °C.

IR (KBr): 1642, 2922 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.80 (m, 2 H), 7.55–7.58 (m, 1 H), 7.47–7.52 (m, 3 H), 7.41–7.45 (m, 2 H), 7.36–7.38 (m, 1 H), 7.32–7.34 (m, 2 H), 7.28–7.31 (m, 3 H), 4.39–4.48 (m, 1 H), 3.38–3.47 (m, 1 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 45.2, 126.0, 126.4, 127.3, 128.0, 128.3, 128.6, 128.6, 128.7, 129.9, 130.3, 130.9, 131.1, 131.6, 131.9, 133.4, 141.7, 143.2, 166.5.

MS: *m*/*z* = 366 (M^+).

Anal. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.25; H, 4.91; N, 15.43.

4c

Yield: 95%; solid; mp 248–250 °C.

IR (KBr): 1647, 2923 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 6.3 Hz, 2 H), 7.56–7.59 (m, 1 H), 7.47 (d, *J* = 5.4 Hz, 3 H), 7.29–7.37 (m, 5 H), 7.00 (s, 1 H), 3.34 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 37.8, 125.9, 126.0, 126.7, 127.0, 128.2, 128.8, 130.1, 130.2, 130.9, 131.1, 131.7, 132.1, 132.4, 133.2, 138.9, 140.6, 143.6, 167.1.

MS: *m*/*z* = 366 (M^+).

Anal. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.52; H, 4.98; N, 15.16.

4d

Yield: 93%; solid; mp 236–238 °C.

IR (KBr): 1651, 2925 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.82 (m, 2 H), 7.54–7.57 (m, 1 H), 7.44–7.49 (m, 2 H), 7.41–7.43 (m, 1 H), 7.36–7.39 (m, 1 H), 7.30–7.35 (m, 2 H), 7.28 (br s, 2 H), 7.08 (s, 1 H), 4.35–4.44 (m, 1 H), 3.35–3.44 (m, 1 H), 2.26 (s, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 20.9, 45.0, 126.0, 126.4, 127.0, 127.7, 128.2, 128.5, 128.7, 130.1, 130.2, 130.7, 131.1, 132.0, 132.0, 132.5, 133.6, 138.8, 139.1, 143.0, 166.5.

MS: *m*/*z* = 380 (M^+).

Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.90; H, 5.27; N, 14.98.

4e

Yield: 92%; solid; mp 272–274 °C.

IR (KBr): 1660, 1739, 2928 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.54 (m, 4 H), 7.50–7.52 (m, 2 H), 7.44–7.48 (m, 2 H), 7.32–7.36 (m, 3 H), 7.12 (d, *J* = 10.0 Hz, 1 H), 6.18 (d, *J* = 10.0 Hz, 1 H), 3.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.6, 117.5, 118.7, 120.6, 124.4, 125.9, 126.3, 127.1, 129.0, 129.0, 129.3, 130.3, 130.9, 131.5, 131.5, 132.8, 139.4, 139.9, 145.1, 153.5, 158.7, 166.7.

MS: *m*/*z* = 420 (M^+).

Anal. Calcd for $C_{25}H_{16}N_4O_3$: C, 71.42; H, 3.84; N, 13.33. Found: C, 71.58; H, 3.87; N, 13.49.

4f

Yield: 94%; solid; mp 196–198 °C.

IR (KBr): 1655, 1658, 2928 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.61 (m, 4 H), 7.43–7.52 (m, 4 H), 7.29–7.30 (m, 3 H), 7.15 (d, *J* = 10.0 Hz, 1 H), 6.47 (d, *J* = 9.6 Hz, 1 H), 3.68 (s, 3 H), 3.36 (s, 3 H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 14.1, 37.5, 117.8, 118.6, 124.1, 124.5, 125.9, 126.2, 127.9, 128.8, 128.8, 129.1, 129.3, 130.7, 131.3, 131.7, 133.1, 134.9, 137.8, 140.0, 145.0, 161.2, 167.0.

MS: *m*/*z* = 433 (M^+).

Anal. Calcd for $C_{26}H_{19}N_5O_2$: C, 72.04; H, 4.42; N, 16.16. Found: C, 72.19; H, 4.38; N, 16.35.

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