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O-Alkylation chemistry of neocupferron

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Abstract

O-Alkylation of *N*-hydroxy-*N*-nitroso-1-naphthalenamine ammonium salt (neocupferron) leads to two isomers, (1,4) naphthoquinone *O*-alkyl oxime oxime (**A**) and *N*-alkyloxy-*N*′-naphthyldiimide *N*′-oxide (**B**). Characterization was done by ^{1}H, ^{13}C NMR and X-ray analysis. These derivatives showed increased stability compared to their parent compound, neocupferron, in the ability to release nitric oxide (NO). Some of these *O*-alkyl derivatives can be novel photo-releasing NO compounds.

Nitric oxide plays key roles in a wide variety of biological processes including vasodilatory and antiplatelet effects, macrophage-induced cytotoxicity, and neurotransmission.[1–3] Currently, interest is in the development of novel nitric oxide donors for the controlled release of NO.[4] We have shown, as well as others, that *N*-nitroso-*N*-oxybenzenamine ammonium salt (cupferron) and its *ortho*- and *para*-substituted derivatives could be utilized as NO donors.[5,6]

Here we report that *O*-alkylation of *N*-hydroxy-*N*-nitroso-1-naphthalenamine ammonium salt leads to the formation of two isomers. As expected, these derivatives were found to be more stable than neocupferron. In addition, these derivatives can be designed and synthesized to photolytically release NO in a controlled manner.

O-Alkylation of neocupferron occurs readily between neocupferron and different alkyl halides (Table 1). A typical procedure for the *O*-alkylation of neocupferron is as follows: neocupferron was dissolved in DMF and cooled to 0°C, then a slight excess of alkyl halide (1.2 equiv.) was injected into the reaction flask, and stirred overnight. TLC was used to monitor the reaction progress. Once complete, the reaction mixture was diluted with water, extracted with methylene chloride, and dried over Na_2SO_4. After evaporating the solvent in vacuo, the product was isolated by flash chromatography using ethyl acetate–hexane as an eluent.

Two isomeric derivatives, (1,4) naphthoquinone *O*-alkyl oxime oxime[7] (**A**) and *N*-alkyloxy-*N*′-naphthyldiimide *N*′-oxide (**B**), were isolated from the *O*-alkylation of neocupferron (Scheme 1). Structure

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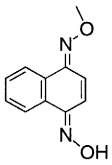
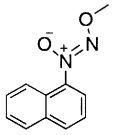
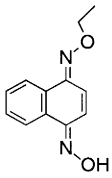
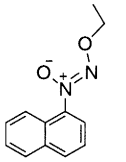
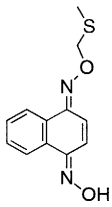
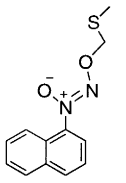
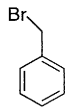
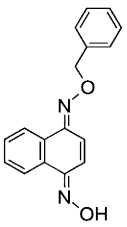
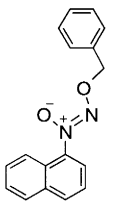
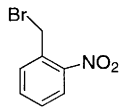
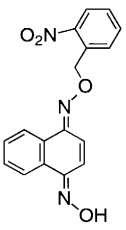
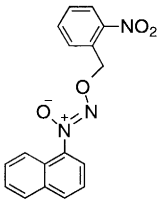
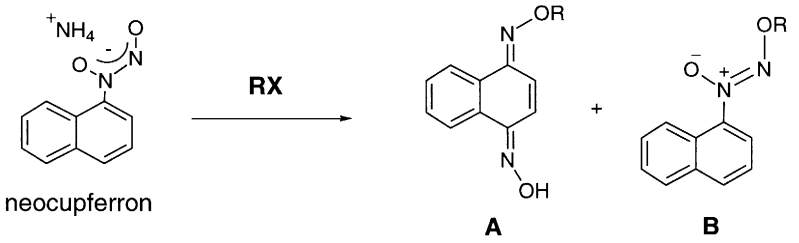
Table 1
O-Alkyl derivatives of neocupferron

Entry	RX	1,4 naphthoquinone *O*-alkyl oxime oxime, **A**	Yield%	*N*-alkyloxy-*N* ′-naphthyldiimide-*N* ′-oxide, **B**	Yield%	Ratio
1	CH_3I		11		53	1:4.8
2	C_2H_5I		12		52	1:4.3
3			12		52	1:4.3
4			11		46	1:4.2
5			11		56	1:5.1

*RX : neocupferron, 1:1.2; isolated yield %.

determination was done by ^1H, ^{13}C NMR,[8] and X-ray analysis. As shown by the X-ray analysis, two molecules of (1,4) naphthoquinone *O*-benzyl oxime oxime forms a dimmer via hydrogen bonding (Fig. 1). The other isomer, *N*-benzyloxy-*N*′-naphthyldiimide *N*′-oxide, is similar to the *O*-alkyl derivative of cupferron (Fig. 2).[9] The ratio of the two isomers is around 4 to 5 with the *N*-(alkyloxy)-*N*′-naphthyldiimide *N*′-oxide (**B**) as the favored product.

The *O*-alkylation mechanism of neocupferron is proposed in Scheme 2. *O*-Alkylation can occur via path A and path B. When the terminal oxygen attacks the electrophile R, the *O*-alkyl reaction occurs via path B and product **B** is obtained as the major product. In the case of path A, the interior oxygen



Scheme 1. Synthesis of *O*-alkyl derivatives of neocupferron. R: 1, -CH_3; 2, -Et; 3, CH_2SCH_3; 4, -Bn; 5, -Bn(*o*-NO_2)

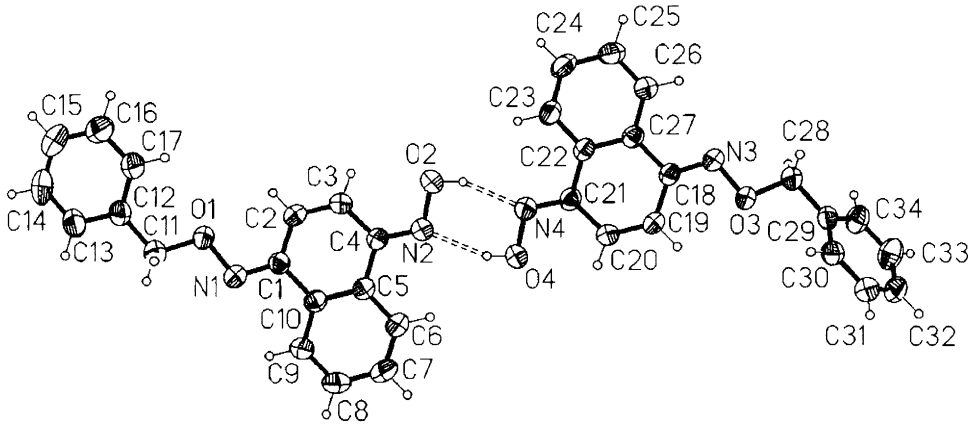


Fig. 1. X-Ray structure of (1,4) naphthoquinone *O*-benzyl oxime oxime (**4A**)

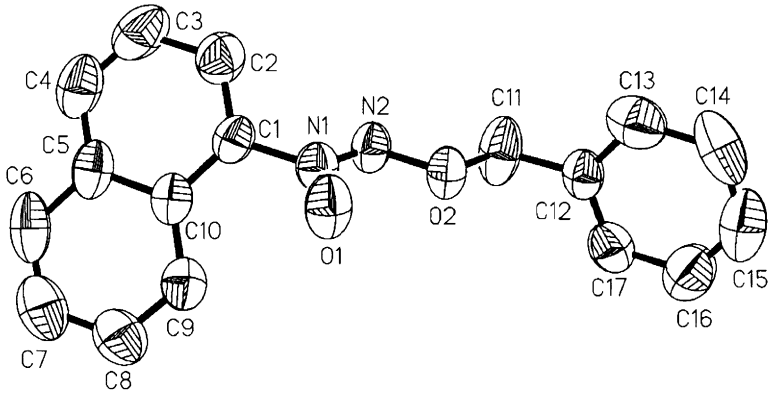
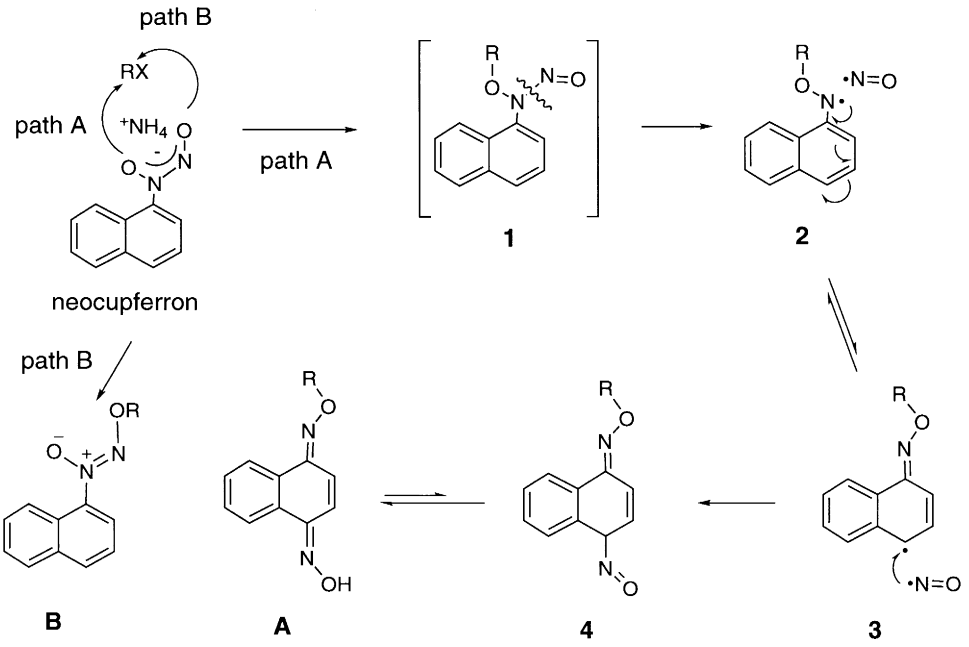


Fig. 2. X-Ray structure of *N*-benzyloxy-*N*′-naphthyldiimide *N*′-oxide (**4B**)

reacts with R which leads to the formation of an intermediate **1**. The N–N bond can then be cleaved homolytically to form an NO radical. Rearrangement of the aromatic ring followed by the addition of the NO radical affords another intermediate **4**. This intermediate in turn transforms to the more stable (1,4) naphthoquinone *O*-alkyl oxime oxime (**A**). The addition of NO occurs specifically at the *para* position due to stabilization of the allylic radical.

Both derivatives are found to be significantly more stable than neocupferron. However, comparing the two isomers, (1,4) naphthoquinone *O*-alkyl oxime oxime is less stable than *N*-alkyloxy-*N*′-naphthyldiimide *N*′-oxide.

N-Alkyloxy-*N*′-naphthyldiimide *N*′-oxide can release NO upon photochemical activation. With the purpose of developing stable NO donors, a type of photo releasing NO compound, *N*-(2-nitrobenzyloxy)-



Scheme 2. Proposed mechanisms for the *O*-alkylation of neocupferron

N′-naphthyldiimide *N*′-oxide **5B**, was synthesized. The photolytic release of NO from **5B** is shown in Fig. 3. The compound was placed in a stirred cuvette. Upon irradiation with UV light (λ=350 nm), NO was released in solution and measured with an NO electrode (ISO-NO Mark II NO-electrode equipped with a Duo-18 data acquisition system, World Precision Instruments, Sarasota, FL*)*. The compound was stable to the thermal release of NO as indicated by the line with a slope of zero prior to irradiation. Once the solution was illuminated (indicated by an arrow in Fig. 3) a linear release of NO was observed for the first 400 sec. The rate of NO release then diminished as **5B** was consumed.

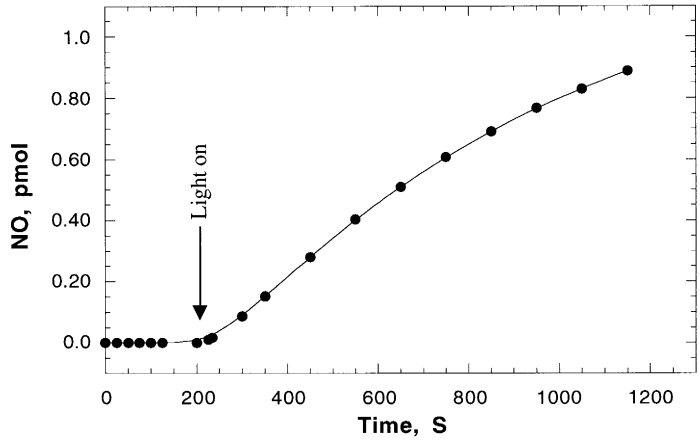


Fig. 3. Photolytic NO release from *N*-benzyloxy-*N*′-naphthyldiimide *N*′-oxide (**5B**). The compound was dissolved at *c*=16 mM in a mixture of 50% MeOH and phosphate buffer solution at 25°C. The sample was exposed to a 50 W quartz-halogen lamp (λ=350 nm). The NO released was measured by an NO electrode

In summary, we investigated the *O*-alkylation of neocupferron. We demonstrated that *O*-alkyl derivatives of neocupferron can be utilized as photo-releasing NO donors. These *O*-alkyl derivatives could

also be used to design other NO based pro-drugs. The potential application extends into the synthetic community as well as biomedical research.

Acknowledgements

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7. Compound (1,4) naphthoquinone *O*-methyl-oxime oxime has been reported by Chantot et al., however, it was not synthesized from *O*-alkylation of neocupferron. See: Chantot, J.-F.; Dargelos, A. *C. R. Hebd. Seances Acad. Sci. Ser. C*. **1972**, *274*, 2001.
8. NMR spectra data: (1,4) Naphthoquinone *O*-methyl oxime oxime (**1A**): Synthesized from the reaction of neocupferron with MeI. ^{1}H NMR (CD_2Cl_2) δ 4.16 (s, 3H, CH_3), 7.45–7.56 (m, 4H, aromatic), 8.13–8.15 (m, 1H, aromatic), 8.21–8.24 (m, 1H, aromatic). ^{13}C NMR δ 64.03 (CH_3), 120.04, 120.87, 123.80, 123.95, 129.89, 130.15, 130.22, 130.26, 147.24, 147.66. MS *m/z* (EI, relative intensity) 75 (5), 102 (14), 114 (7), 128 (15), 140 (35), 157 (13), 169 (13), 186 (8), 202 (M^+, 100). HRMS (EI) calcd for $C_{11}H_{10}N_2O_2$ (M^+): 202.0742; found: 202.0742 (M^+). *N*-Methoxy-*N*′-naphthyldiimide *N*′-oxide (**1B**): Synthesized from the reaction of neocupferron with MeI. ^{1}H NMR ($CDCl_3$) δ 4.29 (s, 3H, CH_3), 7.50–7.72 (m, 4H, aromatic), 7.92–7.94 (dd, 1H, aromatic, *J*=8.8, 1.2 Hz), 8.00–8.02 (d, 1H, aromatic, *J*=8.0 Hz), 8.12–8.14 (dd, 1H, aromatic, *J*=8.8, 1.2 Hz). ^{13}C NMR δ 62.99 (CH_3), 123.25, 123.57, 125.60, 127.57, 128.31, 129.29, 132.51, 135.24, 141.41. MS *m/z* (EI, relative intensity) 51 (4), 63 (4), 77 (10), 87 (2), 101 (7), 115 (5), 127 (100), 143 (6), 157 (78), 171 (2), 202 (M^+, 39). HRMS (EI) calcd for $C_{11}H_{10}N_2O_2$ (M^+): 202.0742; found: 202.0743. (1,4) Naphthoquinone *O*-ethyl oxime oxime (**2A**): Synthesized from the reaction of neocupferron with EtI. ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3H, CH_3, *J*=7.2 Hz), 4.41 (q, 2H, CH_2, *J*=7.2 Hz), 7.44–7.54 (m, 5H, aromatic), 8.10–8.15 (m, 1H, aromatic), 8.22–8.26 (m, 1H, aromatic). ^{13}C NMR δ 15.84 (CH_3), 72.11 (CH_2), 119.93, 121.32, 123.87, 124.10, 130.06, 130.25, 130.50. MS *m/z* (EI, relative intensity) 50 (10), 63 (12), 75 (15), 88 (8), 102 (32), 113 (20), 128 (59), 140 (64), 157 (11), 171 (28), 200 (24), 216 (M^+, 100). HRMS (EI) calcd for $C_{12}H_{12}N_2O_2$ (M^+): 216.0899; found: 216.0893 (M^+). *N*-Ethoxy-*N*′-naphthyldiimide *N*′-oxide (**2B**): Synthesized from the reaction of neocupferron with EtI. ^{1}H NMR ($CDCl_3$) δ 1.52 (t, 3H, CH_3, *J*=7.2 Hz), 4.55 (q, 2H, CH_2, *J*=7.2 Hz), 7.48–7.56 (m, 3H, aromatic), 7.68–7.70 (dd, 1H, aromatic, *J*=7.2, 1.2 Hz), 7.89–7.92 (dd, 1H, aromatic, *J*=8.8, 1.2 Hz), 7.98 (d, 1H, aromatic, *J*=8.4 Hz), 8.12 (dd, 1H, aromatic, *J*=8.4, 0.8 Hz). ^{13}C NMR δ 15.72 (CH_3), 71.86 (CH_2), 123.21, 123.59, 125.62, 127.61, 128.26, 129.23, 129.28, 132.40, 135.23, 141.62. MS *m/z* (EI, relative intensity) 43 (40), 51 (9), 63 (7), 77 (17), 87 (3), 101 (11), 115 (6), 127 (100), 141 (4), 157 (85), 187 (7), 216 (M^+, 22). HRMS (EI) calcd for $C_{12}H_{12}N_2O_2$ (M^+): 216.0899; found: 216.0903. (1,4) Naphthoquinone *O*-methylthiomethyl oxime oxime (**3A**): Synthesized from the reaction of neocupferron with chloromethyl methyl sulfide. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 7.44–7.57 (m, 4H, aromatic), 8.06–8.09 (m, 1H, aromatic), 8.18–8.22 (m, 1H, aromatic). ^{13}C NMR δ 16.25 (CH_3), 80.45 (CH_2), 120.46, 120.94, 123.43, 124.00, 129.44, 129.58, 130.04, 130.08, 148.50, 148.71. MS *m/z* (EI, relative intensity) 61 (100), 69 (5), 76 (3), 102 (3), 113 (3), 128 (4), 140 (6), 155 (4), 185 (11), 202 (4), 232 (6), 248 (M^+, 7). HRMS (EI) calcd for $C_{12}H_{12}N_2O_2S_1$ (M^+): 248.0619; found: 248.0620 (M^+). *N*-Methylthiomethoxy-*N*′-naphthyldiimide *N*′-oxide (**3B**): Synthesized from the reaction of neocupferron with chlorolmethyl methyl sulfide. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 7.46–7.62

(m, 3H, aromatic), 7.70–7.72 (d, 1H, aromatic, *J*=8.5), 7.87–7.89 (d, 1H, aromatic, *J*=8.5), 7.96–7.97 (d, 1H, aromatic, *J*=8.5 Hz), 8.12–8.13 (d, 1H, aromatic, *J*=8.5). ^{13}C NMR δ 16.24 (CH_3), 80.06 (CH_2), 122.91, 123.15, 125.22, 127.03, 127.91, 128.91, 128.95, 132.25, 134.82, 141.20. MS *m/z* (EI, relative intensity) 51 (3), 61 (100), 77 (5), 101 (3), 115 (7), 127 (11), 143 (11), 157 (6), 172 (2), 188 (3), 218 (M-30, 8). HRMS (EI) calcd for $C_{12}H_{12}N_2O_2S_1$ (M-30): 218.0640; found: 218.0641. (1,4) Naphthoquinone *O*-benzyl oxime oxime (**4A**): Synthesized from the reaction of neocupferron with benzyl bromide. ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 2H, CH_2), 7.35–7.54 (m, 10H, aromatic), 8.09–8.13 (m, 1H, aromatic), 8.22–8.26 (m, 1H, aromatic); ^{13}C NMR δ 78.52 (CH_2), 120.27, 121.44, 123.83, 124.27, 129.23, 129.52, 129.77, 130.26, 130.35, 138.38, 148.09, 149.31. MS *m/z* (EI, relative intensity) 51 (6), 65 (9), 77 (6), 91 (100), 102 (3), 140 (6), 262 (10), 278 (M^+, 11). HRMS (EI) calcd for $C_{17}H_{14}N_2O_2$ (M^+): 278.1055; found: 278.1056. *N*-Benzyloxy-*N′*-naphthyldiimide *N′*-oxide (**4B**): Synthesized from the reaction of neocupferron with benzyl bromide. ^{1}H NMR ($CDCl_3$) δ 5.51 (s, 2H, CH_2), 7.42–7.54 (m, 8H, aromatic), 7.92–8.02 (m, 4H, aromatic), ^{13}C NMR δ 77.62 (CH_2), 123.31, 123.63, 125.63, 127.52, 128.23, 129.20, 129.23, 129.82, 129.96, 130.02, 132.48, 135.20, 136.59. MS *m/z* (EI, relative intensity) 51 (8), 65 (8), 77 (12), 91 (100), 101 (3), 127 (27), 157 (7), 218 (2), 248 (M-30, 11). MS (CI, 279, M+ H^+). HRMS (EI) calcd for $C_{17}H_{14}N_2O_2$ (M-30): 248.1075; found: 248.1079 (M-30). (1,4) Naphthoquinone *O*-2-nitrobenzyl oxime oxime (**5A**): Synthesized from the reaction of neocupferron with 2-nitrobenzyl bromide. ^{1}H NMR (DMSO-d_6) δ 5.66 (s, 2H, CH_2), 7.34–7.53 (m, 4H, aromatic), 7.57–7.60 (t, 1H, aromatic, *J*=8.0, 7.0), 7.69–7.70 (d, 1H, aromatic, *J*=7.5), 7.74–7.77 (t, 1H, aromatic, *J*=7.5, 7.5), 7.96–7.97 (d, 1H, aromatic, *J*=8.0), 8.06–8.08 (q, 2H, aromatic, *J*=4.0, 4.0, 4.0), 12.47 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 73.61 (CH_2), 118.99, 121.04, 123.01, 123.38, 125.33, 128.19, 129.66, 129.87, 130.01, 130.30, 130.55, 133.56, 134.61, 146.61, 148.14, 148.43. MS *m/z* (EI, relative intensity) 51 (8), 65 (7), 78 (40), 89 (5), 136 (100), 157 (7), 172 (11), 188 (7), 323 (M^+, 9). HRMS (EI) calcd for $C_{17}H_{14}N_2O_2$ (M^+): 323.0906; found: 323.0899 (M^+). *N*-(2-Nitrobenzyloxy)-*N′*-naphthyldiimide *N′*-oxide (**5B**): Synthesized from the reaction of neocupferron with 2-nitrobenzyl bromide. ^{1}H NMR ($CDCl_3$) δ 5.94 (s, 2H, CH_2), 7.48–7.63 (m, 4H, aromatic), 7.66–7.67 (d, 1H, aromatic, *J*=7.0), 7.73–7.76 (t, 1H, aromatic, *J*=7.5, 7.0), 7.84–7.85 (d, 1H, aromatic, *J*=7.5), 7.90–7.92 (d, 1H, aromatic, *J*=8.0), 7.99–8.00 (d, 1H, aromatic, *J*=8.5), 8.06–8.08 (d, 1H, aromatic, *J*=8.5), 8.17–8.18 (d, 1H, aromatic, *J*=8.0). ^{13}C NMR δ 72.83 (CH_2), 122.47, 122.54, 124.72, 125.43, 126.56, 127.47, 128.48, 128.87, 129.19, 131.87, 132.84, 134.37, 134.43, 140.50, 147.28. MS *m/z* (EI, relative intensity) 51 (8), 65 (6), 78 (23), 127 (68), 136 (34), 157 (100), 187 (8), 276 (9), 323 (M^+, 38). HRMS (EI) calcd for $C_{17}H_{14}N_2O_2$ (M^+): 323.0906; found: 323.0906 (M^+). Anal. calcd for $C_{17}H_{14}N_3O_4$: C, 63.08; H, 4.01; N, 12.96; found: C, 63.15; H, 4.05; N, 13.00.

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