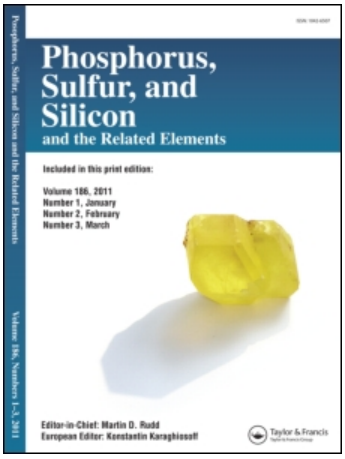

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The Utility of *p*-N-Succinimidobenzoyl Isothiocyanate in Synthesis of Benzoxazole, Quinazoline, Pyrimidine, 1,2,4-Triazoline, 1,3-Thiazolidine, and Thiourea Derivatives

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THE UTILITY OF *p*-N-SUCCINIMIDOBENZOYL ISOTHIOCYANATE IN SYNTHESIS OF BENZOXAZOLE, QUINAZOLINE, PYRIMIDINE, 1,2,4-TRIAZOLINE, 1,3-THIAZOLIDINE, AND THIOUREA DERIVATIVES

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Reactions of p-N-succinimidobenzoyl isothiocyanate (1) with different nucleophilic reagents afforded adducts. Simultaneous or subsequent cyclization of these adducts gave access to a variety of different heterocycles, including benzoxazole, quinazoline, pyrimidine, 1,2,4-triazoline, 1,3-thiazolidine and others. The structures of the new products were confirmed by their micro-analytical and spectral data.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Benzoxazole; pyrimidine; quinazoline; *p*-N-succinimidobenzoyl isothiocyanate; thiourea derivatives; 1,2,4-triazoline

INTRODUCTION

Isothiocyanates may serve as versatile building blocks to prepare a wide variety of nitrogen, sulfur, and oxygen heterocycles[1–13] besides thiourea derivatives, which are reported to exhibit antiviral[14] and antibacterial[15] activities. In the present investigation a synthetic procedure has been developed to describe a further application of the title compound **1** in heterocyclic synthesis. Of the heterocyclic systems, benzoxazole, quinazoline, 1,2,4-triazoline, 1,3-thiazolidine, and pyrimidine derivatives were synthesized. Furthermore, they were substituted with *N*-phenyl pyrrolidine dione moiety in an aim to increase their biological activities.

RESULTS AND DISCUSSION

The new derivatives were prepared according to the reaction sequences depicted in Schemes 1 and 2. As shown in Scheme 1, treatment of *p*-N-succinimidobenzoyl isothiocyanate (**1**) with 2-aminophenol in dry acetone produced thiourea derivative **2**. Heating of

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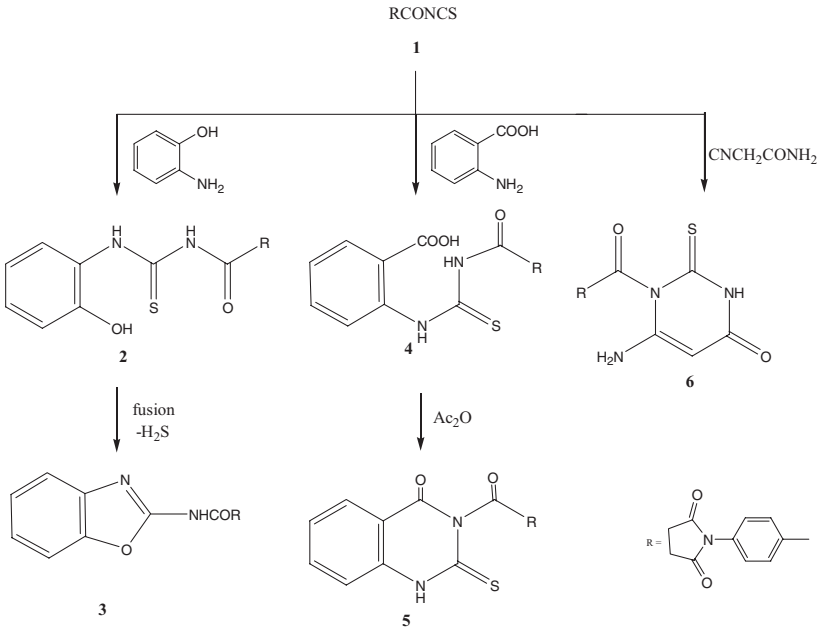
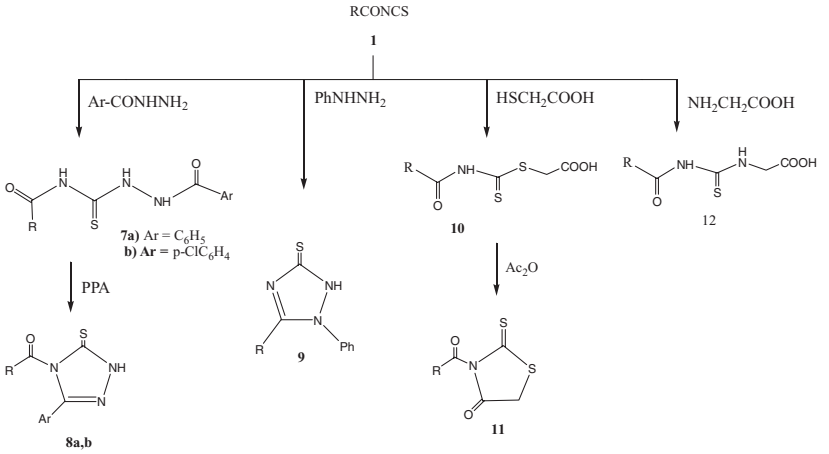


Scheme 1



Scheme 2

compound **2** just above its melting point led to evolution of H_2S gas and left a product formulated as benzoxazole derivative **3**. Similar treatment of isothiocyanate **1** with anthranilic acid yielded thiourea derivative **4**, which was cyclized to quinazoline derivative **5** upon heating with acetic anhydride. A further aspect of the reactivity of **1** was exemplified by its reaction with 2-cyanoacetamide to give pyrimidine derivative **6** in a one-pot reaction. Formation of compound **6** can be visualized on the basis of addition of an amino group of cyanoacetamide to the isothiocyanate carbon atom, followed by intramolecular cyclization, as illustrated in Scheme S1 (available online in the Supplemental Materials).

The structures of compounds **2–6** were proven by their microanalytical and spectral data. Their IR spectra showed the presence of υ (NH), υ (C=O), and υ (C=S). Their ^{1}H NMR spectra displayed signals due to $-CH_2CH_2-$ moiety and aromatic protons signals, as well as acidic protons signals in the downfield region that were exchangeable with D_2O.

Treatment of isothiocyanate **1** with aroyl hydrazine afforded thiourea derivatives **7a**,**b**. Heating of compounds **7a**,**b** with poly phosphoric acid furnished 1,2,4-triazole derivatives **8a**,**b**. Alternatively, the reaction of **1** with phenyl hydrazine produced 1,2,4-triazole derivative **9** in a one-pot reaction. Reaction of isothiocyanate **1** with thioglycolic acid yielded an adduct **10**, which upon heating with acetic anhydride easily converted into 1,3-thiazolidine derivatives **11**. Furthermore, reaction of **1** with glycine in the presence of a catalytic amount of pyridine gave the thiourea derivative **12** in a good yield as shown in Scheme 2.

The structures of compounds **7–12** were elucidated by their microanalytical and spectral data. Their IR spectra showed the presence of υ (NH) except compound **11**, υ (C=O), υ (C=S), as well as a broad OH band for compound **12**. In addition, their ^{1}H NMR spectra shed further light on the assigned structures as they displayed signals due to $-CH_2CH_2-$ and aromatic as well as acidic protons in downfield region. Further proof for the assigned structures of the synthesized compounds was gained from their MS, which revealed their molecular ion peaks.

CONCLUSION

Aroyl isothiocyanate is a bifunctional reagent that is capable of participating in a wide range of addition–cyclization reactions. The strong electron-attracting power of the aroyl group enhances the reactivity of the adjacent isothiocyanato function and promotes nucleophilic addition at this center. Simultaneous or subsequent cyclization of adducts gives access to a variety of five- or six-membered heterocyclic structures.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Gallenkemp melting point apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer 2000 FTIR and Maston 1000-FTIR spectrometers. The ^{1}H NMR spectra were measured on a Jeol (EX-400) spectrometer with chemical shift (δ) expressed in ppm downfield from TMS as internal standard in DMSO-d_6. All acidic protons disappeared by deuterium exchange (addition of D_2O). Mass spectra were determined with a JEOL-JMS, DX 303. Elemental analysis was determined by CHN Carder-MT-3 Yanaco and Perkin-Elemer 2400 CHN elemental analyzers. TLC was carried out the monitoring of the progress of all reactions and homogeneity of the synthesized compounds. TLC was determined using TLC aluminum sheets silica gel F_{254} (Merck).

p-N-Succinimidobenzoyl Isothiocyanate (1)

To *p*-N-succinimido-benzoyl chloride[16] (3 mmol) in dry acetone (30 mL), solid ammonium thiocyanate[17] (3 mmol) was added. The reaction mixture was stirred for half an hour at room temperature. The precipitated ammonium chloride was filtered off to give a clear yellow solution of *p*-N-succinimidobenzoyl isothiocyanate (**1**) in acetone.

Reactions of Isothiocyanate 1 with the Different Nucleophiles

To a solution of isothiocyanate **1** (3 mmole), each of *o*-aminophenol, anthranilic acid, 2-cyanoacetamide, benzoyl hydrazine, phenyl hydrazine, thioglycollic acid, or glycine in a dry acetone (50 mL) was added. A few drops of pyridine were added in the case of glycine. The mixture was refluxed for 2–3 h (as confirmed by TLC) and cooled to room temperature. The precipitated solid was filtered off, washed with ethanol, and recrystallized from the suitable solvent to give the corresponding compounds.

1-(2-Hydroxyphenyl)-3-(*p*-N-succinimidobenzoyl)thiourea (2). Yellow crystals (DMF), 80% yield; mp 220–221°C; IR (KBr) ν: 3480–2865 (br. OH), 3377, 3277, 1760, 1711, 1657, 1265 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.82 (s, 4, $-CH_2CH_2-$), 6.85 (t, 1, $J = 7.8$ Hz,), 6.95 (d, 1, $J = 8.3$ Hz,), 7.09 (t, 1, $J = 7.8$ Hz,), 7.45 (d, 2, $J = 8.30$ Hz), 8.07 (d, 2, $J = 8.79$ Hz), 8.55 (d, 1, $J = 7.32$ Hz,), 10.25 (s, 1, NH exchangeable), 11.59 (s, 1, NH exchangeable), 12.90 (s, 1, OH exchangeable); MS (70 eV) *m/z* (%): 369 ($M^{+\cdot}$, 1), 352 (1), 335 (10), 218 (8), 202 (100), 174 (10), 146 (10), 132 (20), 118 (2); *Anal. Calcd*. for $C_{18}H_{15}N_3O_4S$ (369.39): C, 58.53; H, 4.09; N, 11.38; Found: C, 58.23; H, 3.85; N, 11.12.

1-(2-Carboxyphenyl)-3-(p-N-succinimidobenzoyl)thiourea (4). Yellow crystals (acetic acid), 82% yield; mp 196°C dec.; IR (KBr) ν: br. 3430–3100, 3260, 1750, 1720, 1710, 1660, 1280 cm^{-1};^1H NMR: (DMSO-d_6) δ: 2.81 (s, 4, $-CH_2CH_2-$), 4.94 (br. s, 1, NH exchangeable), 7.29–8.56 (m, 8, ArH), 11.17 (br. s, 1, NH exchangeable), 11.40 (br. s, 1, OH exchangeable); MS (70 eV) *m/z* (%): 353 ($M^{+\cdot}$-CO_2, 1), 319 (1), 202 (50), 218 (25), 174 (5), 162 (50), 137 (30), 132 (10), 119 (100), 92 (70); *Anal.* Calcd. for $C_{19}H_{15}N_3O_5S$ (397.40): C, 57.42; H, 3.80; N, 10.57; Found: C, 57.62; H, 4.00; N, 10.82.

4-Amino-3-(p-N-succinimidobenzoyl)pyrimidin-6-one-2-thione (6). Colorless crystals (ethanol), 78% yield; mp 230–232°C; IR (KBr) ν: 3368, 3358, 3315, 1776, 1711, 1650, 1287;^1H NMR: (DMSO-d_6) δ: 2.82 (s, 4, $-CH_2CH_2-$), 7.42 (d, 2, $J = 8.00$ Hz), 7.50 (s, 1, C_5-H,), 7.85 (d, 2 $J = 8.2$ Hz), 8.92 (br. s, 2, NH exchangeable), 11.29 (br, s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 344 ($M^{+\cdot}$, 3), 311 (17), 285 (24), 202 (66), 174 (100), 146 (58); *Anal.* Calcd. for $C_{15}H_{12}N_4O_4S$ (344.34): C, 52.32 H, 3.51; N, 16.27 Found; C, 52.40; H, 3.33; N, 15.99.

1-Benzoyl-4-(*p*-N-succinimidobenzoyl)thiosemicarbazide (7a). Colorless crystals (DMF), 86% yield; mp 220–222°C; IR (KBr) ν: 3350, 3180, 1750, 1719, 1670, 1278 cm^{-1}, ^1H NMR: (DMSO-d_6) δ: 2.80 (s, 4, $-CH_2CH_2-$), 7.42 (d, 2, $J = 8.7$ Hz, ArH), 7.56–8.09 (m, 7, Ar—H), 9.11 (br.s, 1, NH exchangeable), 10.87 (br, s, 1, NH exchangeable), 11.11 (br.s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 396 ($M^{+\cdot}$, 1), 378 ($M^{+\cdot}$-H_2O, 2), 362 (2), 218 (1), 202 (100), 178 (1), 174 (10), 105 (70), 77 (50); *Anal.* Calcd. for $C_{19}H_{16}N_4O_4S$ (396.42): C, 57.57; H, 4.07; N, 14.13; Found: C, 57.33; H, 4.09; N, 13.97.

1-(*p*-Chlorobenzoyl)-4-(*p*-N-succinimidobenzoyl)thiosemicarbazide (7b). Colorless crystals (acetic acid), 80% yield; mp 310–312°C; IR (KBr) ν: 3320, 3200, 1755, 1705, 1665, 1280 cm^{-1}; ^1H NMR: (DMSO-d_6) δ: 2.80 (s, 4, $-CH_2CH_2-$), 7.47 (d, 1, $J = 8.8$ Hz), 7.50 (d, 1, $J = 8.8$Hz), 7.62 (d, 2, $J = 8.28$ Hz), 7.93 (d, 1, $J = 8.28$ Hz), 8.02 (d, 1, $J = 8.28$), 8.08 (d, 1, $J = 8.28$ Hz), 8.23 (d, 1, $J = 8.32$ Hz), 11.24 (br. s, 1, NH exchangeable), 11.87 (br. s, 1, NH exchangeable), 12.32 (br. s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 432 ($M^{+\cdot}$+2, 4), 430 ($M^{+\cdot}$, 13), 414 (11), 412 (23), 398 (1), 396 (8), 202 (100), 174 (10), 146 (10); *Anal.* Calcd. for $C_{19}H_{15}ClN_4O_4S$ (430.86): C, 52.96; H, 3.51; N, 13.00; Found: C, 52.74 H, 3.35; N, 12.81.

2-Phenyl-3-(*p*-N-succinimidophenyl)-2,5-dihydro-1*H*-1,2,4-triazole-5-thi one (9). Yellow crystals (DMF), 70% yield; mp 202–203°C; IR (KBr) ν: 3184, 1780, 1703, 1603, 1295 cm^{-1};^{1}H NMR (DMSO-d_6) δ: 2.81 (s, 4, $-CH_2CH_2-$), 7.43–7.49 (m, 3, ArH), 7.56 (t, 2, $J = 7.83$ Hz), 8.03 (d, 2, $J = 7.32$ Hz), 8.10 (d, 2, $J = 8.28$), 14.38 (br. s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 350 ($M^{+\cdot}$, 90), 318 (10), 291 (10), 202 (10), 176 (5), 174 (1), 91 (100); *Anal.* Calcd. for $C_{18}H_{14}N_4O_2S$ (350.39): C, 61.70; H, 4.03; N, 15.99; Found: C, 61.72; H, 4.15; N, 15.95.

Carboxymethyl N-(*p*-N-Succinimidobenzoyl)dithiocarbamate (10). Yellow crystals (ethanol), 76% yield; mp 213–215°C; IR (KBr) ν: br. 3700–2700, 1750, 1711, 1685, 1270 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ: 2.80 (s, 4, $-CH_2CH_2-$), 3.3 (s, 2, $S-CH_2$), 7.60 (d, 2, $J = 8.32$ Hz), 8.10 (d, 2, $J = 8.80$ Hz), 9.58 (br.s, 1, NH exchangeable), 11.34 (br. s, 1, OH exchangeable); MS (70 eV) *m/z* (%): 352 ($M^{+\cdot}$, 3), 307 (2), 302 (5), 218 (20), 202 (100), 174 (19), 90 (15); *Anal.* Calcd. for $C_{14}H_{12}N_2O_5S_2$ (352.39): C, 47.72; H, 3.43; N, 7.95; Found: C, 47.66; H, 3.50; N, 8.02.

1-Carboxymethyl-3-(*p*-N-succinimidobenzoyl)thiourea (12). Colorless crystals (ethanol), 88% yield; mp 208–210°C; IR (KBr) ν: br. 3416–2700, 1765, 1730, 1720, 1660, 1260 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.80 (s, 4, $-CH_2CH_2-$), 4.35 (d, 2, $J =$ 5Hz, $-\underline{CH_2}$) 7.43 (d, 2, $J = 8.00$ Hz), 8.03 (d, 2, $J = 8.79$ Hz), 9.83 (br. s, 1, NH or SH exchangeable), 11.10 (br. s, 1, NH exchangeable), 11.59 (br. s, 1, OH exchangeable); MS (70 eV) *m/z* (%): 335 ($M^{+\cdot}$, 1), 317 (1), 290 (1), 277 (4), 244 (2), 218 (20), 202 (100), 174 (15), 146 (15), 133 (30);.*Anal.* Calcd. for $C_{14}H_{13}N_3O_5S$ (335.34): C, 50.14; H, 3.91; N, 12.53; Found: C, 50.43; H, 4.12; N, 12.23.

General Procedure for the Synthesis of Compounds 5 and 11

Compounds **4** and **10** (2 mmol) were heated with acetic anhydride (20 mL) at 90°C for 1 h. Solid product obtained after cooling was filtered and recrystallized from acetic acid to give yellow crystals of compound **5** or **11**, respectively.

3-(*p*-N-Succinimidobenzoyl)quinazoline-4-one-2-thione (5). 86% yield; mp 265–266°C; IR (KBr) ν: 3370, 1760, 1718, 1650, 1285; ^{1}H NMR: (DMSO-d_6) δ: 2.80 (s, 4, $-CH_2CH_2-$), 7.46 (d, 1, $J = 8.75$ Hz), 7.55 (t, 1, $J = 7.33$ Hz), 7.70 (d, 1, $J = 7.8$ Hz), 7.90 (t, 1, $J = 7.32$ Hz), 8.08 (d, 2, $J = 7.33$ Hz), 8.15 (d, 2, $J = 8.50$ Hz), 12.41 (br. s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 379 ($M^{+\cdot}$, 10), 351 (5), 202 (100), 177 (2), 174 (10), 146 (16), (132 (20); *Anal.* Calcd. for $C_{19}H_{13}N_3O_4S$ (379.39): C, 60.15; H, 3.45; N, 11.08; Found: C, 59.82; H, 3.66; N, 10.82.

3-(*p*-N-Succinimidobenzoyl)-1,3-thiazolidine-4-one-2-thione (11). 73% yield; mp 213–215°C (ethanol); IR (KBr) ν: 1730, 1719, 1680, 1279 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.81 (s, 4, $-CH_2CH_2-$), 4.60 (s, 2, $-S\underline{CH_2}$) 7.55 (d, 2, $J = 8.32$ Hz), 8.21 (d, 2, $J = 8.76$ Hz); MS (70 eV) *m/z* (%): 334 ($M^{+\cdot}$, 10), 202 (100), 174 (10), 146 (5), 132 (15), 120 (20), 104 (2); *Anal.* Calcd. for $C_{14}H_{10}N_2O_4S_2$ (334.37): C, 50.29; H, 3.01; N, 8.38; Found: C, 50.40; H, 2.99; N, 8.65.

General Procedure for the Synthesis of Compounds 8a and 8b

A solution of compounds **7a** or **7b** (2 mmol) in glacial acetic acid (30 mL) was added to polyphosphoric acid (20 mL). The reaction mixture was heated at 150–180°C for 1 h, then left to cool at room temperature. The precipitated solid obtained after addition of ice-cold water was filtered off and recrystallized from a suitable solvent.

3-Phenyl-4-(*p*-N-succinimidobenzoyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (8a). Colorless crystals (acetic acid), 72% yield; mp 330–333°C; IR (KBr) ν: 3230, 1750, 1720, 1665, 1603, 1280 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.80 (s, 4, $-CH_2CH_2-$), 7.49 (d, 2, $J = 8.32$ Hz), 7.54–8.13 (m, 5, ArH), 8.23 (d, 2, $J = 8.23$ Hz), 13.25 (br. s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 378 ($M^{+\cdot}$, 20), 350 (15), 202 (100), 174 (10), 146 (10), 132 (20); *Anal.* Calcd. for $C_{19}H_{14}N_4O_3S$ (378.40): C, 60.31; H, 3.73; N, 14.81; Found: C, 59.96; H, 3.90; N, 14.71.

3-(*p*-Chlorophenyl)-4y-(*p*-N-succinimidobenzoyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (8b). Colorless crystals (DMF), 83% yield; mp 363–365°C; IR (KBr) ν: 3261, 1755, 1718, 1660, 1270 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.81 (s, 4, $-CH_2CH_2-$), 7.49 (d, 2, $J = 8.76$, Hz), 7.61(d, 2, $J = 8.70$ Hz), 8.01 (d, 2, $J = 8.32$ Hz), 8.23 (d, 2, $J = 8.80$), 13.29 (br. s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 414 ($M^{+\cdot}+2$, 3), 412 ($M^{+\cdot}$, 10), 386 (1), 384 (2), 202 (100), 174 (10), 146 (10), 132 (20); *Anal.* Calcd. for $C_{19}H_{13}ClN_4O_3S$ (412.85): C, 55.28; H, 3.17; N, 13.57; Found: C, 55.21; H, 2.95; N, 13.37.

2-(p-N-Succinimidobenzamido)-1,3-benzoxazole (3)

Compound **2** (2 mmol) was heated at 220–230°C. H_2S gas was evolved during the fusion process. After 1 h, H_2S evolution was ceased, the reaction mixture was left to cool, and the solid mass was triturated with ethanol. The solid that separated was collected and crystallized from ethanol to give pale yellow crystals. 81% yield; IR (KBr) ν: 3232, 1770, 1720, 1650, cm^{-1};^1H NMR (DMSO-d_6) δ: 2.81 (s, 4, $-CH_2CH_2-$), 6.85 (t, 1, $J = 7.90$ Hz), 6.70 (d, 1, $J = 8.30$ Hz), 7.13 (t, 1, $J = 7.60$ Hz), 7.47 (d, 2, $J = 8.10$ Hz), 8.07 (d, 2, $J = 8.79$), 8.55 (d, 1, $J = 7.32$ Hz), 11.33 (br. s, 1, NH exchangeable); MS (70 eV) *m/z* (%): 335 ($M^{+\cdot}$, 13), 218 (8), 202 (100), 174 (10), 146 (16), 132 (34), 118 (9), 109 (20); *Anal. Calcd*. for $C_{18}H_{13}N_3O_4$ (335.31): C, 64.47; H, 3.91; N, 12.53; Found: C, 64.72; H, 4.02; N, 12.77.

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