Clean Synthesis of Spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles and Spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles by One-Pot, Three-Component Reactions

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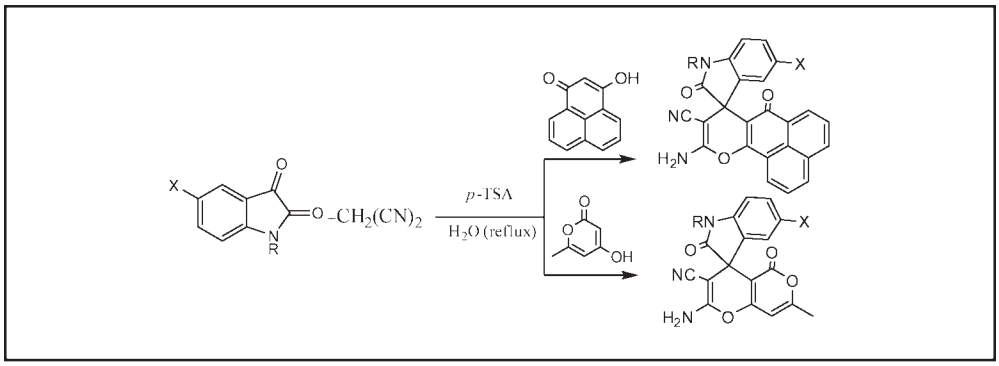

An environmentally benign three-component reaction in aqueous media has been reported for the synthesis of spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles and spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles.

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INTRODUCTION

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity [1]. One of the best methods to fulfill these goals is the development and use of multicomponent reactions (MCRs), which consist of several simultaneous bond-forming reactions and allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner [2]. MCRs are economically and environmentally very advantageous because multistep syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step.

Indole and indoline fragments are important moieties of a large number of a variety of natural products and medicinal agents [3], and some of indolines, spiro-annulated with heterocycles in the third position, have shown high biological activity [4–6]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [7–9]. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles [10].

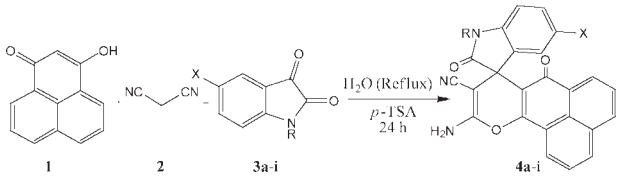
Chromene derivatives are an important group of compounds, widely exist in plants, including edible vegetables and fruits [11]. Synthetic analogues were developed over the years, some of them displaying remarkable effects as pharmaceuticals [12–14], including antifungal [15] and antimicrobial activity [16]. Similarly, substituted 2-amino-pyrans take a significant place among the six-membered oxygen-containing heterocycles. Some of them possess anticancer and antimicrobial activity [17]. Serotonin receptor modulators (pteropodine and its stereoisomers), natural alkaloids, containing both spiroindole and pyran cycles, were isolated from stem bark of *Uncaria tomentosa* [7]. Several spiroheterocycles, containing both indole and pyran heterocycles possess anticonvulsant and analgetic [18], herbicidal [19], and antibacterial activities [20].

As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds [21], we performed the preparation of some new spirooxindole containing chromene or pyran ring fragments via a three-component condensation reaction using water as the reaction medium. Organic transformations in water without using toxic organic solvents are one of the current focuses today, especially in our environmentally conscious society [22].

RESULTS AND DISCUSSION

The one-pot, three-component condensation reaction of 3-hydroxy-1*H*-phenalen-1-one 1, malononitrile 2, and

Scheme 1



isatins 3a–i in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst proceeded rapidly in refluxing water and were complete after 24 h to afford 10′-amino-1,2-dihydro-2,7′-dioxospiro[3*H*-indole-3,8′(7*H*,8*H*)-phenaleno[1,2-*b*]pyran]-9′-carbonitrile derivatives 4a–i in good yields (Scheme 1). ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of fused indoline phenalenopyran 4.

The optimized results are summarized in Table 1. The results were excellent in terms of yields and product purity using isatin derivatives in the presence of *p*-TSA, whereas without it the yields of products were low (<30%) even after 48 h. To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles **4**. However, when this reaction was carried out with ethyl cyanoacetate, the TLC and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; the expected product was obtained in only trace amount.

A possible mechanism for the formation of **4** is proposed in Scheme 2. It is reasonable to assume that **4** results from initial formation of intermediate isatylidene malononitriles **5** by standard Knoevenagel condensation of the malonitrile **2** and isatin **3**. Then, the subsequent Michael-type addition of the 3-hydroxy-1*H*-phenalen-1-one (**1**) to the intermediate **5**, followed by cyclization and tautomerization affords the corresponding products **4** (Scheme 2).

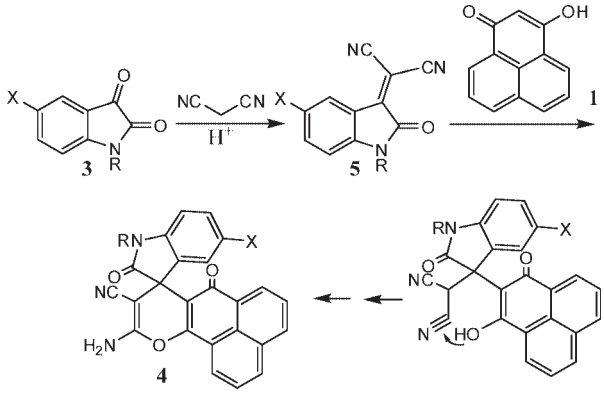
The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4** are stable solids whose structures are fully supported by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

Table 1

Synthesis of Spiro[indole-3,8′-phenalenopyran]-9′-carbonitriles **4**.

Products **4**	R	X	Yield (%)
a	H	H	93
b	Me	H	75
c	Et	H	83
d	H	NO_2	90
e	Me	NO_2	73
f	Et	NO_2	88
g	H	Br	94
h	Me	Br	91
i	Et	Br	89

Scheme 2



As expected, when the 3-hydroxy-1*H*-phenalen-1-one **1** was replaced by 4-hydroxy-6-methyl-2*H*-pyran-2-one **6**, another series of spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles **7** were obtained under the same reaction conditions (Scheme 3).

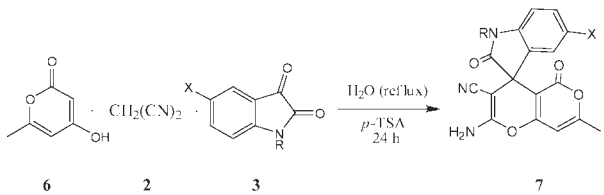
Finally, when we extended this reaction to 1*H*-inden-1,2,3-trion (**8**), product of 2′-amino-1,3-dihydro-7′-methyl-1,3,5′-trioxospiro[2*H*-indene-2,4′(4*H*,5*H*)-pyrano[4,3-*b*]pyran]-3′-carbonitrile **9** was generated in 65% yield after 24 h (Scheme 4).

In conclusion, we have developed an efficient, clean, one-pot and three-component synthesis of new spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles, spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles and spiro[2*H*-indene-2,4′(4*H*,5*H*)-pyrano[4,3-*b*]pyran]-3′-carbonitrile in aqueous media. Prominent among the advantages of this new method are operational simplicity, good yields, and easy work-up procedures used.

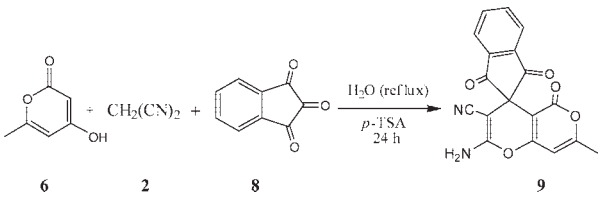
EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 MHz and 75.47 MHz, respectively. IR spectra were

Scheme 3



Scheme 4



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recorded using an FTIR apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of spirooxindoles 4a–i, 7a–c, and 9. A mixture of malononitrile (1 mmol), isatins (1 mmol), 3-hydroxy-1*H*-phenalen-1-one or 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), *p*-TSA (0.1 g) was refluxed in water (5 mL) for 24 h (TLC). After completion of reaction, the reaction mixture was filtered and the precipitate washed with ethanol to afford the pure product.

10′-Amino-1,2-dihydro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4a). Yellow powder (93%); mp >300°C dec. IR (potassium bromide): 3403, 3015, 2200, 1730, 1669 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 6.87–8.41 (m, 12H, H—Ar and NH_2), 10.63 (s, 1H, NH). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 48.2, 57.7, 109.8, 113.4, 117.8, 121.0, 122.2, 123.9, 125.4, 127.3, 127.7, 127.9, 128.8, 130.4, 131.9, 134.1, 134.9, 136.1, 142.7, 155.3, 156.2, 178.5, 181.0. MS (70 eV, electron impact) *m/z*: 391 (M^+). Anal. Calcd for $C_{24}H_{13}N_3O_3$: C, 73.65; H, 3.35; N, 10.74%. Found: C, 73.60; H, 3.39; N, 10.80%.

10′-Amino-1,2-dihydro-1-methyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4b). Yellow powder (75%); mp >300°C dec. IR (potassium bromide): 3347, 3111, 2200, 1724, 1663 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 3.25 (s, 3H, NCH_3), 6.95–8.48 (m, 12H, H—Ar and NH_2). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 31.7, 52.7, 62.2, 113.5, 118.1, 122.4, 125.8, 127.8, 128.4, 130.2, 132.1, 132.7, 133.8, 135.3, 136.7, 138.8, 139.0, 141.1, 149.0, 160.2, 164.1, 181.8, 185.8. MS (70 eV, electron impact) *m/z*: 405 (M^+). Anal. Calcd for $C_{25}H_{15}N_3O_3$: C, 74.07; H, 3.73; N, 10.36%. Found: C, 74.01; H, 3.67; N, 10.28%.

10′-Amino-1,2-dihydro-1-ethyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4c). Yellow powder (83%); mp >300°C dec. IR (potassium bromide): 3312, 2993, 2192, 17.9, 1664 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 1.24 (bs, 3H, CH_3), 4.05 (bs, 2H, NCH_2), 6.93–8.42 (m, 12H, H—Ar and NH_2). MS (70 eV, electron impact) *m/z*: 419 (M^+). Anal. Calcd for $C_{26}H_{17}N_3O_3$: C, 74.45; H, 4.09; N, 10.02%. Found: C, 74.40; H, 4.05; N, 10.09%.

Due to very low solubility of the product **4c**, we cannot report the ^{13}C NMR data for this product.

10′-Amino-1,2-dihydro-5-nitro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4d). Yellow powder (90%); mp >300°C dec. IR (potassium bromide): 3328, 3018, 2197, 1714, 1666 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 7.11–8.46 (m, 11H, H—Ar and NH_2), 11.41 (s, 1H, NH). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 48.4, 56.2, 109.9, 112.2, 117.6, 120.0, 121.1, 125.5, 126.3, 127.2, 127.3, 127.9, 128.1, 130.6, 131.9, 134.3, 135.9, 136.4, 143.0, 149.3, 156.1, 159.6, 179.2, 181.2. MS (70 eV, electron impact) *m/z*: 436 (M^+). Anal. Calcd for $C_{24}H_{12}N_4O_5$: C, 66.06; H, 2.77; N, 12.84%. Found: C, 66.12; H, 2.82; N, 12.75%.

10′-Amino-1,2-dihydro-1-methyl-5-nitro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4e). Yellow powder (97%); mp >300°C dec. IR (potassium bromide): 3311, 3198, 2197, 1730, 1666 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 3.36 (s, 3H, NCH_3), 7.36–8.48 (m, 11H, H—Ar and NH_2). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 27.4, 47.9, 55.8, 109.0, 112.1, 117.5, 119.7, 121.1, 125.5, 126.4, 127.1, 127.3, 127.9, 128.2, 130.7, 131.9, 134.5, 135.1, 136.5, 153.5, 150.1, 156.2, 159.7, 177.9, 181.2. MS (70 eV, electron impact) *m/z*: 450 (M^+). Anal. Calcd for $C_{25}H_{14}N_4O_5$: C, 66.67; H, 3.13; N, 12.44%. Found: C, 66.61; H, 3.17; N, 12.49%.

10′-Amino-1,2-dihydro-1-ethyl-5-nitro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4f). Yellow powder (88%); mp >300°C dec. IR (potassium bromide): 3435, 3322, 2207, 1719, 1667 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 1.30 (t, 3H, $^3J_{HH}$ = 6.9 Hz, CH_3), 3.87–4.01 (m, 2H, NCH_2), 7.39–8.45 (m, 11H, H—Ar and NH_2). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 12.7, 47.8, 56.0, 109.0, 112.0, 117.4, 119.8, 121.0, 125.5, 126.4, 127.0, 127.1, 127.2, 127.8, 128.1, 130.6, 131.9, 134.4, 135.3, 136.4, 143.3, 149.2, 156.2, 159.6, 177.4, 181.2. MS (70 eV, electron impact) *m/z*: 464 (M^+). Anal. Calcd for $C_{26}H_{16}N_4O_5$: C, 67.24; H, 3.47; N, 12.06%. Found: C, 67.30; H, 3.42; N, 12.13%.

10′-Amino-5-bromo-1,2-dihydro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4g). Yellow powder (94%); mp 310°C dec. IR (potassium bromide): 3322, 3198, 2199, 1724, 1665 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 6.86–8.40 (m, 11H, H—Ar and NH_2), 10.77 (s, 1H, NH). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 48.5, 57.0, 111.6, 112.7, 113.9, 117.8, 121.1, 125.4, 126.9, 127.2, 127.8, 130.4, 131.5, 131.8, 134.1, 136.1, 137.3, 142.1, 155.7, 159.3, 178.2, 181.1. MS (70 eV, electron impact) *m/z*: 471 (M^+ +2), 469 (M^+). Anal. Calcd for $C_{24}H_{12}BrN_3O_3$: C, 61.30; H, 2.57; N, 8.94%. Found: C, 61.25; H, 2.52; N, 8.87%.

10′-Amino-5-bromo-1,2-dihydro-1-methyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4h). Yellow powder (91%); mp >300°C dec. IR (potassium bromide): 3378, 3306, 3142, 2207, 1716, 1676 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 3.35 (s, 3H, NCH_3), 7.11–8.46 (m, 11H, H—Ar and NH_2). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 27.1, 48.0, 56.6, 110.7, 112.6, 114.8, 117.7, 121.1, 125.5, 126.7, 127.2, 127.3, 127.9, 128.0, 130.6, 131.7, 131.9, 134.3, 136.3, 136.4, 143.6, 155.8, 159.4, 176.8, 181.1. MS (70 eV, electron impact) *m/z*: 485 (M^+ +2), 483 (M^+). Anal. Calcd for $C_{25}H_{14}BrN_3O_3$: C, 62.00; H, 2.91; N, 8.68%. Found: C, 61.96; H, 2.96; N, 8.60%.

10′-Amino-5-bromo-1,2-dihydro-1-ethyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4i). Yellow powder (89%); mp >300°C dec. IR (potassium bromide): 3265, 2962, 2192, 1698, 1665 cm^{-1}.1H NMR (dimethyl sulfoxide-d_6): δ_H 1.25 (t, 3H, $^3J_{HH}$ = 6.9 Hz, CH_3), 3.74–3.90 (m, 2H, NCH_2), 7.10–8.47 (m, 11H, H—Ar and NH_2). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 110.0, 111.6, 112.0, 120.1, 120.8. 121.1, 121.8, 122.4, 126.0, 127.1, 127.6, 127.8, 129.5, 131.5, 133.1, 134.6, 138.7, 139.8, 140.7, 146.8, 149.7, 153.4. MS (70 eV, electron impact) *m/z*: 499 (M^+ +2), 497 (M^+). Anal. Calcd for $C_{26}H_{16}BrN_3O_3$: C, 62.67; H, 3.24; N, 8.43%. Found: C, 62.61; H, 3.20; N, 8.50%.

2′-Amino-1,2-dihydro-7′-methyl-2,5′-dioxospiro[3H-indoline-3,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (7a). Brown powder (54%); mp 265°C dec. IR (potassium bromide): 3337,

3187, 2192, 1735, 1691 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 2.24 (s, 3H, CH_3), 6.36 (s, 1H, CH), 6.80–7.21 (m, 4H, H—Ar), 7.46 (s, 2H, NH_2), 10.59 (s, 1H, NH). MS (70 eV, electron impact) *m/z*: 321 (M^+). Anal. Calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.49; H, 3.40; N, 13.01.

Due to very low solubility of the product **7a**, we cannot report the ^{13}C NMR data for this product.

2′-Amino-1,2-dihydro-7′-methyl-5-nitro-2,5′-dioxospiro[3H-indoline-3,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (7b). Brown powder (62%); mp >300°C dec. IR (potassium bromide): 3358, 3167, 2192, 1726, 1698 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 2.25 (s, 3H, CH_3), 6.40 (s, 1H, CH), 7.04–8.21 (m, 5H, H—Ar and NH_2), 11.36 (s, 1H, NH). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 19.7, 47.6, 55.8, 97.7, 98.7, 110.1, 117.4, 120.6, 126.7, 134.5, 143.1, 149.1, 159.4, 160.7, 160.8, 164.6, 178.5. MS (70 eV, electron impact) *m/z*: 366 (M^+). Anal. Calcd for $C_{17}H_{10}N_4O_6$: C, 55.74; H, 2.75; N, 15.30. Found: C, 55.79; H, 2.79; N, 15.36.

2′-Amino-1,2-dihydro-1,7′-dimethyl-5-nitro-2,5′-dioxospiro[3H-indoline-3,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (7c). Brown powder (57%); mp 269°C dec. IR (potassium bromide): 3414, 3168, 2187, 1714, 1690 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 2.25 (s, 3H, CH_3), 3.26 (s, 3H, NCH_3), 6.41 (s, 1H, CH), 7.30–8.31 (m, 5H, H—Ar and NH_2). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 19.8, 27.4, 47.1, 55.4, 97.6, 98.7, 109.2, 117.3, 120.2, 126.8, 133.7, 143.7, 150.0, 159.6, 160.7, 164.7, 177.1. MS (70 eV, electron impact) *m/z*: 380 (M^+). Anal. Calcd for $C_{18}H_{12}N_4O_6$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.79; H, 3.24; N, 14.79.

2′-Amino-1,3-dihydro-7′-methyl-1,3,5′-trioxospiro[2H-indene-2,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (9). Green powder (65%); mp 275°C. IR (potassium bromide): 3281, 2926, 2197, 1732, 1675, 1642 cm^{-1}. ^1H NMR (dimethyl sulfoxide-d_6): δ_H 2.27 (s, 1H, CH_3), 6.46 (s, 1H, CH), 7.90–8.08 (m, 6H, H—Ar and NH_2). ^{13}C NMR (dimethyl sulfoxide-d_6): δ_C 19.9, 52.1, 53.1, 97.1, 98.5, 117.0, 123.9, 137.7, 140.9, 160.2, 161.6, 161.8, 165.6, 199.7. MS (70 eV, electron impact) *m/z*: 334 (M^+). Anal. Calcd for $C_{18}H_{10}N_2O_5$: C, 64.67; H, 3.02; N, 8.38. Found: C, 64.61; H, 3.07; N, 8.44.

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