Construction of 3,4-Dihydro-1,2-diazete Ring through 4π Electron Cyclization of 4-Hydroxy-2-oxo-2*H* Chromene-3-carbaldehyde [(1*E*)-arylmethylene] Hydrazone

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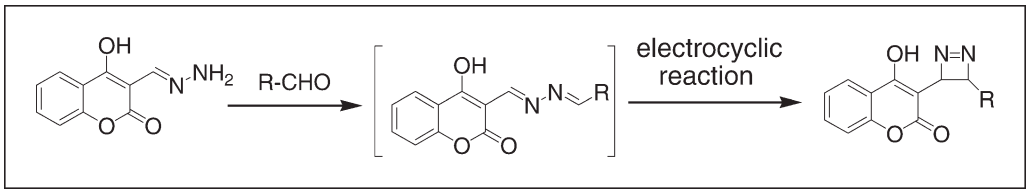

A new, short and efficient synthesis of 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one is described in which the 3,4-dihydro-1,2-diazete ring is constructed from arylmethylene hydrazone by 4π electron cyclization as per electrocyclic reaction.

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INTRODUCTION

Nitric oxide (NO) has been recognized as an important cellular mediator with diverse biological functions [1,2] including treatment for the respiratory, cardiovascular, infective, and other several diseases [3]. Derivatives of 3,4-dihydro-1,2-diazete-1,2-dioxide have recently been investigated as NO donors *in vitro* and *in vivo* and found to be highly effective vasodilators [4]. 1,2-Diazetine *N*,*N*-dioxides (diazetine dioxides) are a class of strained four-membered ring azo dioxide heterocycles. Although the first report of a diazetine dioxide was as early as 1971, only a handful of such compounds are currently known [5–9]. Diazetine dioxides have been used as highly effective low-energy triplet quenchers in photochemical reactions [10] and have been recently investigated for their biological activity as potent vasorelaxant and antiaggregant agents [7–9,11]. One of the more intriguing aspects of the reactivity of diazetine dioxides is their tendency to liberate 2 equiv of nitric oxide (NO) upon decomposition to yield the corresponding alkene [5,7]. It is the production of the biologically active molecule NO that has suggested the possibility of using diazetine dioxides as pharmaceutical agents [7,11]. The mechanism by which NO is liberated still remains a question [12,13]. Despite the marked pharmaceutical application of diazetidines [14], isosteric diazetenes [15], 1,2-dihydro-1,2-diazetenes [16], and 3,4-dihydro-1,2-dihydro-1,2-diazetenes [17] derivatives, their conjugation with heterocyclic compounds is less studied.

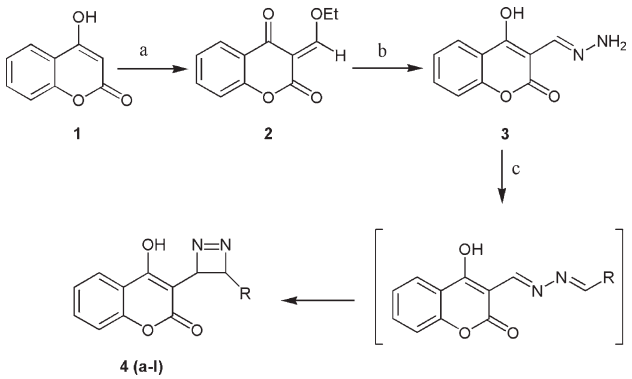
Coumarin and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity [18–26]. Many of these compounds have proved to be active as antitumor [18,19], antibacterial [20,21], antifungal [22–24], anticoagulant [25], and anti-inflammatory [26]. In addition, these compounds are used as additives to food and cosmetics [27], dispersed fluorescent and laser [28].

The potential pharmaceutical utility of 1,2-diazete derivatives and 4-hydroxy coumarin derivatives prompted us to synthesize new 3,4-dihydro-1,2-diazete derivatives incorporated with 4-hydroxy coumarin framework **4**(**a**–**l**).

RESULTS AND DISCUSSION

The synthesis of 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives **4**(**a**–**l**) is shown in Scheme 1. The precursor 4-hydroxy coumarin **1** was prepared by following the literature methods [29]. A mixture of **1** and triethyl orthoformate containing catalytic amount of *p*-toluene sulfonic acid (PTSA) was subjected to microwave irradiation at 240 W for 2 min to obtain 3-ethoxymethylene-3*H*-2,4-dione (**2**) in moderate yield (∼60%). The hydrolysis of **2** with K_2CO_3 resulted into 4-hydroxy coumarin-3-carbaldehyde [30]. Subsequent treatment of the **2** with hydrazine hydrate at ambient temperature afforded 4-hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde- hydrazone (**3**) in excellent yield (∼90%). It was found that the reaction did not require any solvent or external heating. When hydrazone **3** reacted with various aldehydes at 100°C in DMSO containing con. HCl as a catalyst, 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives

Scheme 1. Reagents and conditions: (a) Triethyl orthoformate. Microwave irradiation at 240 W, 2 min; (b) $NH_2NH_2 \cdot H_2O$, r.t., Stirr.; (c) R-CHO, DMSO, con. HCl, 100°C, 30 min.



4a–l were obtained in good yield (Table 1). One can envisage that the intermediates 4-hydroxy-2-oxo-2*H* chromene-3-carbaldehyde (arylmethylene) hydrazones underwent 4π electron cyclization to form a four membered 1,2-diazete ring system incorporates with 4-hydroxy coumarin nucleolus **4a–l** (Scheme 1). The formation of 1,2-diazete ring system was confirmed by IR, Mass, ^{1}H NMR, and ^{13}C NMR spectral study.

The IR spectrum of **4a** exhibited O—H stretching vibration peak in the range of 3200–3400 cm^{-1} and C=O Stretching vibration of coumarin at 1690 cm^{-1} indicating the presence of hydroxyl group. The ^{1}H NMR spectrum of compound **4a** displayed the hydroxyl proton at 14.04 δ ppm as a singlet. Two methine protons of diazete ring were observed at 8.8 and 8.6 δ ppm. The downfield chemical shift of these protons compared with simple 1,2-diazete ring system (4–5 δ ppm reported by G. W. Breton *et al*. [31] and 8.69 δ ppm reported by Yutaka Ishida *et al*. [32]) may be attributed to their conjugation with coumarin and phenyl ring system attached with the diazete structure. Moreover, the chemical shift of methine proton was also compared with that of compound **3** (7.19 δ ppm) also supporting the formation of diazete framework. The assignment of relative stereochemistry of both methine protons can be carried out based on coupling constant. The larger values of derived coupling constants place both protons in trans position. The mass spectrum of **4a** showed three signals M^++1, M^+, and M^+-N_2 at 294, 293, and 264, respectively. Extrusion of N_2 from compound in the mass spectra reveals the existence of the cyclic product, which is in accordance with the assigned structure of **4a**.

The mechanism involved in the formation of 1,2-diazete ring follows the electrocyclic reaction. Arylmethylene hydrazone is a conjugated chain containing 4π electron system which undergoes 4π electron cyclization as per pericyclic reaction (Scheme 2).

Table 1

Physical properties of the synthesized compounds **4(a–l)**.

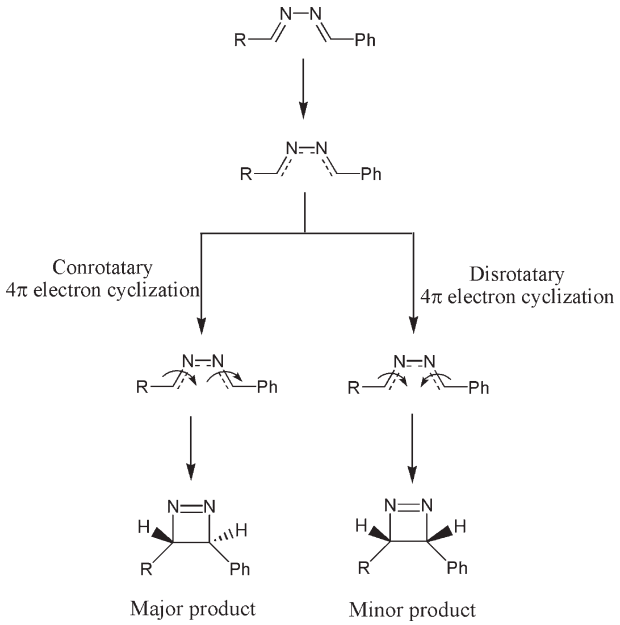
Entry	Product	R	Yield (%)[a]	Mp (°C)
1	**4a**	Ph	75	230–232
2	**4b**	4-CH_3-C_6H_4	71	214–216
3	**4c**	4-OCH_3-C_6H_4	76	206–208
4	**4d**	3,4-di-OCH_3-C_6H_4	85	218–220
5	**4e**	2,5-di-OCH_3-C_6H_4	79	210–212
6	**4f**	2-Cl-C_6H_4	65	212–214
7	**4g**	4-F-C_6H_4	65	206–208
8	**4h**	2-OH-C_6H_4	70	210–212
9	**4i**	4- NO_2-C_6H_4	80	214–216
10	**4j**	4-*N*,*N*-di-CH_3-C_6H_4	60	204–206
11	**4k**	3-Pyridyl	62	228–230
12	**4l**	2-Furyl	58	214–216

[a] Isolated yields after purification.

CONCLUSIONS

In summary, novel 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives (**4a–l**) were prepared from 4-hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde hydrazone and various aldehydes in DMSO *via* electrocyclic reaction through 4π electron cyclization. The pharmacological study of all compounds is currently under investigation.

Scheme 2. Plausible mechanism of 4π electron cyclization.



EXPERIMENTAL

Melting points were determined on electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Fluka, Sigma Aldrich, Merck, and Rankem and used without further purification.

3-Ethoxymethylene-3*H*-chromene-2,4-dione (2). A mixture of 6.2 mmol of 4-hydroxycoumarin (1.0 g, 6.2 mmol), triethyl orthoformate (7 mL), and *p*-toluenesulfonic acid monohydrate (0.02 g) was placed in a 50 mL beaker. The beaker was covered with a stem-less funnel and irradiated in the microwave oven for 2 min at 240 W. The resultant residue was cooled to room temperature, the solvent was decanted, and the residue was crystallized in chloroform to give pure yellow crystals. Yield: 0.81 g (60%); mp 140–141°C.

4-Hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde hydrazone (3). 3-(Ethoxymethylene)-3*H*-chromene-2,4-dione (**2**, 2.18 g, 10 mmol) was stirred at room temperature with excess 50% hydrazine hydrate for about 10–15 min. The solid separated out was filtered and crystallized from chloroform to give **3**, yield: 1.83 (90%); mp 138–140°C. IR (KBr): 3528, 3245, 1689, 1545; ^{1}H NMR (400 MHz, DMSO) δ 8.47 (s, 1H, OH), 7.98 (m, 1H, ArH), 7.55 (m, 1H, ArH), 7.23 (m, 2H, ArH), 7.19 (s, 1H, =CH), 5.88 (s, 2H, NH_2); MS(EI): 204 (M^+).

General procedure for the synthesis of 4-hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (4a). A mixture of equimolar amount of 4-hydroxy-2-oxo-2*H*-chromene-3-carbaldehyde hydrazone **3** and benzaldehyde was dissolved in DMSO containing catalytic amount of con. HCl and heated at 100°C for 30 min with stirring. The reaction mixture was allowed to attain room temperature. The separated solid was filtered off and washed with methanol. The crude product obtained was recrystallized from chloroform to give 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (**4a**) as a yellow solid. Yield 75%; mp 230–232°C; IR (KBr) 3200, 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.04 (s, 1H, OH), 8.80 (d, J = 12.36 Hz, 1H, CH), 8.67 (d, J = 15.52 Hz, 1H, CH), 7.96 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.57 (t, 1H, Ar), 7.45–7.39 (m, 3H, Ar), 7.26–7.17 (m, 2H, Ar); MS(EI) 292 $[M]^+$. Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.78; H, 4.25; N, 9.45.

Compounds **4b–l** were prepared by following the same procedure as described for **4a**.

4-Hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (4a). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3200, 1690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.04 (s, 1H, OH), 8.80 (d, J = 12.36 Hz, 1H, CH), 8.67 (d, J = 15.52 Hz, 1H, CH), 7.96 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.57 (t, 1H, Ar), 7.45–7.39 (m, 3H, Ar), 7.26–7.17 (m, 2H, Ar); MS(EI) 292 $[M]^+$. Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.78; H, 4.25; N, 9.45.

4-Hydroxy-3-[4-(4-methylphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4b). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3190, 1690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.14 (s, 1H, OH), 8.95 (d, J = 12.12 Hz, 1H, CH), 8.60 (d, J = 31.64 Hz, 1H, CH), 8.05 (t, 1H, Ar), 7.69 (d, 2H, Ar), 7.67 (t, 1H, Ar), 7.64–7.60 (m, 4H, Ar), 2.42 (s, 3H, CH_3); MS(EI) 306 $[M]^+$. Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.51; H, 4.54; N, 9.05.

4-Hydroxy-3-[4-(4-methoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4c). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3140, 1716 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.86 (d, J = 12.48 Hz, 1H, CH), 8.70 (d, J = 10.08 Hz, 1H, CH), 8.02 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.62 (t, 1H, Ar), 7.31–7.23 (m, 2H, Ar), 7.00–6.98 (m, 2H, Ar), 3.86 (s, 3H, OCH_3); MS(EI) 322 $[M]^+$. Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.11; H, 4.24; N, 8.58.

3-[4-(3,4-Dimethoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4d). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3210, 1699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.88 (d, J = 12.30 Hz, 1H, CH), 8.64 (d, J = 14.42 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.82 (d, 2H, Ar), 7.59 (t, 1H, Ar), 7.48–7.20 (m, 3H, Ar), 3.88 (s, 6H, OCH_3); MS(EI) 352 $[M]^+$. Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.61; H, 4.49; N, 7.81.

3-[4-(2,5-Dimethoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4e). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3235, 1687 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.96 (d, J = 2.64 Hz, 1H, CH), 8.90 (d, J = 12.4 Hz, 1H, CH), 8.03 (t, 1H, Ar), 7.91 (d, 2H, Ar), 7.62 (t, 1H, Ar), 7.44 (t, 1H, Ar), 7.30 (t, 1H, Ar); 7.26 (t, 1H, Ar), 3.88 (s, 6H, OCH_3); MS(EI) 352 $[M]^+$. Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.59; H, 4.71; N, 7.84.

3-[4-(2-Chlorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4f). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3221, 1702 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.80 (d, J = 12.28 Hz, 1H, CH), 8.68 (d, J = 18.06 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.61 (t, 1H, Ar), 7.43–7.49 (m, 3H, Ar), 7.22–7.27 (m, 1H, Ar); MS(EI) 326 $[M]^+$. Anal. Calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.37; H, 3.26; N, 8.47.

3-[4-(4-Fluorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4g). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3088, 1716 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.81 (d, J = 12.58 Hz, 1H, CH), 8.73 (d, J = 10.02 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.74 (d, 2H, Ar), 7.58 (t, 1H, Ar), 7.44–7.49 (m, 2H, Ar), 7.23–7.26 (m, 2H, Ar); MS(EI) 310 $[M]^+$. Anal. Calcd. for $C_{17}H_{11}FN_2O_3$: C, 65.81; H, 3.57; N, 9.03. Found: C, 65.73; H, 3.51; N, 9.12.

4-Hydroxy-3-[4-(2-hydroxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4h). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3400, 3259, 1696 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 14.09 (s, 1H, OH), 9.57 (s, 1H, OH), 8.79 (d, J = 12.30 Hz,

1H, CH), 8.66 (d, J = 11.38 Hz, 1H, CH), 7.96 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.57 (t, 1H, Ar), 7.46–7.39 (m, 2H, Ar), 7.25–7.17 (m, 2H, Ar); MS(EI) 308 $[M]^+$. Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.12; H, 4.06; N, 8.94.

4-Hydroxy-3-[4-(4-nitrophenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4i). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3490, 1697 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.81 (d, J = 12.18 Hz, 1H, CH), 8.68 (d, J = 15.55 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.56 (t, 1H, Ar), 7.48–7.57 (m, 3H, Ar), 7.23–7.21 (m, 1H, Ar); MS(EI) 337 $[M]^+$. Anal. Calcd. for $C_{17}H_{11}N_3O_5$: C, 60.54; H, 3.29; N, 12.46. Found: C, 60.47; H, 3.18; N, 12.55.

3-{4-[4-(Dimethylamino)phenyl]-3,4-dihydro-1,2-diazet-3-yl}-4-hydroxy-2*H*-chromen-2-one (4j). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3209, 1719 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 14.10 (s, 1H, OH), 8.87 (d, J = 12.28 Hz, 1H, CH), 8.71 (d, J = 14.68 Hz, 1H, CH), 8.02 (t, 1H, Ar), 7.75 (d, 2H, Ar), 7.60 (t, 1H, Ar), 7.40–7.32 (m, 2H, Ar), 7.27–7.23 (m, 2H, Ar), 2.97 (s, 6H, $N(CH)_2$); MS(EI) 335 $[M]^+$. Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.88; H, 5.03; N, 12.64.

4-Hydroxy-3-(4-pyridin-3-yl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (4k). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3235, 1699 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 14.10 (s, 1H, OH), 8.80 (d, J = 12.96 Hz, 1H, CH), 8.65 (d, J = 14.93 Hz, 1H, CH), 7.95 (t, 1H, Ar), 7.74 (d, 2H, Ar), 7.58 (t, 1H, Ar), 7.14–6.81 (m, 4H, Pyr.); MS(EI) 293 $[M]^+$. Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.37; H, 3.59; N, 14.15.

3-[4-(2-Furyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4l). This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3266, 1689 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 14.08 (s, 1H, OH), 8.78 (d, J = 11.08 Hz, 1H, CH), 8.64 (d, J = 15.34 Hz, 1H, CH), 7.90 (t, 1H, Ar), 7.70 (d, 2H, Ar), 7.54 (t, 1H, Ar), 6.98–6.69 (m, 3H, Fur.); MS(EI) 282 $[M]^+$. Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92. Found: C, 63.78; H, 3.41; N, 9.84.

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