Synthesis of New 2-Naphthyl Ethers and Their Protective Activities against DNA Damage Induced by Bleomycin–Iron

Bakr F. Abdel-Wahab,*[,a] Abdel-Aziz S. El-Ahl,[b] and Farid A. Badria[c]

[a] *Applied Organic Chemistry Department, National Research Center; Dokki, Giza, Egypt:* [b] *Chemistry Department, Umm Al-Qura University, University College Makah; Kingdom of Saudi Arabia: and* [c] *Pharmacognosy Department, Faculty of Pharmacy, Mansoura University; Mansoura 35516, Egypt.*

Received May 13, 2009; accepted August 20, 2009; published online September 17, 2009

The reaction of 2-naphthaloxyacetic acid with thiosemicarbazide in the presence of phosphoryl chloride, followed by treatment with phenacylbromides, led to the formation of imidazo[2,1-*b*][1,3,4]thiadiazoles 3a—c. 2-(Naphthalen-3-yloxy)acetohydrazide 4 on treatment with ethyl 2-(2-arylhydrazono)-3-oxobutanoates (5a—c), 2-methoxymethylene)malononitrile, or ethyl 2-cyano-3,3-bis(methylthio)acrylate led to the formation of substituted pyrazoles 6—8. The reaction of the hydrazide 4 with hydrazonoyl chlorides 9a—c and 1,2,4,5-benzene tetracarboxylic-1,2:4,5-dianhydride produced bis-diazo compounds 10a—c and dimide 11 respectively. All new compounds were tested for their protective activity against DNA damage induced by bleomycin–iron complex. Compound 2 showed the greatest protection against DNA damage, thus diminishing chromogen formation between the damaged DNA and thiobarbituric acid.

Key words 2-naphthaloxyacetic acid; imidazo[2,1-*b*]-1,3,4-thiadiazole; pyrazole; hydrazonoyl chloride; 1,3,4-thiadiazole; DNA·bleomycin–iron complex

Aryloxyacetic acids and their derivatives often possess many important biological activities. Some of these compounds are used as herbicides and plant-growth regulators.[1—5] Substituted pyrazoles and 1,3,4-thiadiazoles have also attracted much attention due to their diverse biological activities, such as DNA protective,[6—8] antimicrobial,[9,10] antibacterial,[11] anesthetic,[12] and anticonvulsant[13] activities. On the other hand, imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives have been of interest to the medicinal chemists for many years because of their anticancer,[14] antitubercular,[15] antibacterial,[16] antifungal,[17] anticonvulsant, analgesic,[18] and antisecretory[19] activities. In continuation of our previous work on the synthesis of biologically active heterocycles,[20—23] we report here the preparation of a new series of compounds with a 2-naphthaloxyacetyl moiety in addition to 1,3,4-thiadiazoles, imidazo[2,1-*b*]-1,3,4-thiadiazoles, pyrazoles, or imide with the objective of obtaining new biologically active compounds.

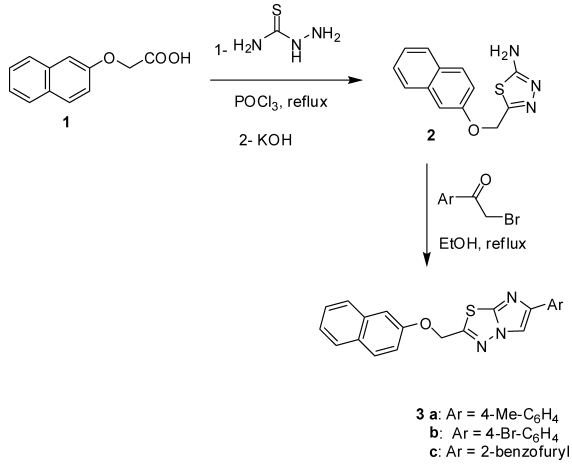
Results and Discussion

In the previous work, imidazo[2,1-*b*]-1,3,4-thiadiazoles were prepared by the reaction of 2-aminothiadiazoles with α-bromoketones.[24,25] Thus the 2-naphthaloxyacetic acid **1** required for the present study was synthesized by refluxing of 2-naphthol with chloroacetic acid in dry acetone containing anhydrous potassium carbonate,[26] which upon reaction with thiosemicarbazide in the presence of phosphorusoxychloride yielded 5-[(2-naphthaloxy)methyl]-1,3,4-thiadiazol-2-amine **2**. The imidazo[2,1-*b*]-1,3,4-thiadiazoles **3a**—**c** were obtained by the condensation of **2** with appropriate phenacyl bromides with refluxing in dry ethanol (Chart 1). The structures of compounds **2** and **3** were supported by spectral data such as IR, NMR, mass, and elemental analysis.

In the IR spectrum of 1,3,4-thiadiazol-2-amine **2**, broad absorption bands around 3107 and 3264 cm^{-1} indicates the presence of an NH_2 group in the compound, and its ^{1}H-NMR spectrum showed a singlet at δ 7.82 due to the NH_2 protons attached to the 1,3,4-thiadiazole ring. The proton of CH_2 resonated as a singlet at δ 5.28. The formation of the imidazothiadiazole **3** was indicated by the absence of the NH_2 band in the IR spectrum and the appearance of an imidazole proton (C_5-H) around δ 8.6 in the ^{1}H-NMR spectrum.

The hydrazide of 2-naphthaloxyacetic acid **4** has been used in the production of several compounds with potent biological activity.[27,28] Incorporation of the hydrazide portion of these compounds into a pyrazole ring led to a new class of pyrazole compounds.[29—32] We report here the synthesis of some new pyrazoles and discuss their protective activity against DNA damage induced by bleomycin–iron complex. Treatment of acid hydrazide **4** with equimolar quantities of ethyl 2-(2-arylhydrazono)-3-oxobutanoates **5a**—**c**, 2-(methoxymethylene)malononitrile, and/or ethyl 2-cyano-3,3-bis(methylthio)acrylate in absolute ethanol gave the pyrazoles **6**—**8** (Chart 2).

In the ^{1}H-NMR spectra of **6a**—**c**, a singlet proton at δ 10.22 to 10.33 ppm attributed to enolic OH was observed. The IR spectrum of compound **7** showed absorption bands in



3 a: Ar = 4-Me-C_6H_4
b: Ar = 4-Br-C_6H_4
c: Ar = 2-benzofuryl

Chart 1. Synthesis of 1,3,4-Thiadiazoles and Imidazo[2,1-*b*]-1,3,4-thiadiazoles

* To whom correspondence should be addressed. e-mail: Bakrfatehy@yahoo.com

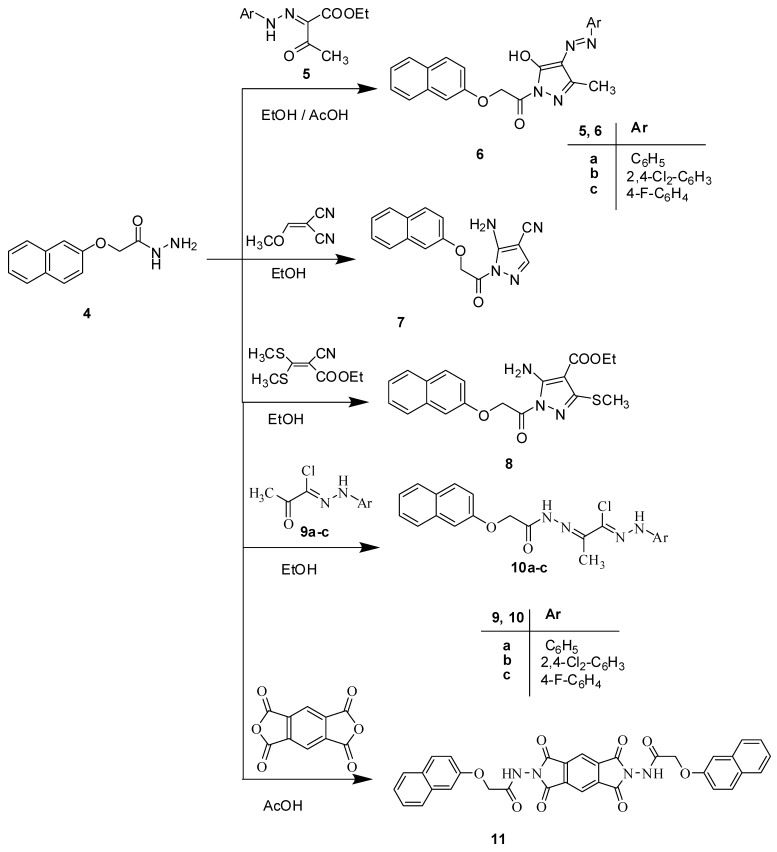


Chart 2. Synthesis of Compounds **6**—**11**

the region 2227, 3309 and 3235 cm^{-1} characteristic of carbonitrile and amino groups, while the IR spectrum of compound **8** showed absorption bands in the regions of 1749, 3324 and 3233 cm^{-1} attributed to ester C=O and NH_2 groups. In addition, bis-diazo compounds **10a**—**c** were formed by simple condensation of the hydrazide **4** with hydrazonoyl chlorides **9a**—**c** in ethanol (Chart 2). The formation of bis-diazo compounds **10a**—**c** was indicated by the absence of one carbonyl band in the IR spectra and the appearance of two singlet NH protons around δ 10.19 and 11.16 in their ^{1}H-NMR spectra.

The treatment of the acid hydrazide **4** with 1,2,4,5-benzene tetracarboxylic-1,2:4,5-dianhydride in refluxing glacial acetic acid for 5 h afforded the dimide **11** (Chart 2). The IR spectrum of compound **11** showed three absorption bands in the region of the 1786—1624 cm^{-1} characteristic of carbonyl groups, and in addition the mass spectrum of the dimide **11** showed a peak corresponding to its molecular ion peak at *m*/*z* 614.

Bleomycin-Dependent DNA Damage The bleomycins are a family of glycopeptide antibiotics that are used routinely as antitumor agents. The bleomycin assay has been adopted for assessing the prooxidant effects of food antioxidants. The antitumor antibiotic bleomycin binds iron ions and DNA. The bleomycin–iron complex degrades DNA that, upon heating with thiobarbituric acid (TBA), yields a pink chromogen. Upon the addition of suitable reducing agents antioxidants compete with DNA and diminish chromogen formation.[33)]

All the newly synthesized compounds were examined for its protective activity against DNA damage induced by the bleomycin–iron complex. The results in Table 1 show that compound **2** had the highest protection against DNA damage induced by the bleomycin–iron complex, thus diminishing chromogen formation between the damaged DNA and TBA. Compounds **3a**, **6c**, **10a**, **10b**, and **10c** showed weak to moderate activity, while compounds **3b**, **3c**, **6a**, **6b**, **7**, **8**, and **11** exhibited slight activities.

Table 1. Results of the Bleomycin-Dependent DNA Damage Assay of Synthesized Compounds

Sample (extract)	Absorbance (nm)
2	0.0064
3a	0.045
3b	0.18
3c	0.180
6a	0.180
6b	0.18
6c	0.052
7	0.180
8	0.180
10a	0.038
10b	0.050
10c	0.045
11	0.180

Structure–Activity Relationship From the shown results in Table 1 we conclude that the protective activity against DNA damage induced by the bleomycin–iron complex requires the 2-(naphthalen-2-yloxy) methyl moiety and 1,3,4-thiadiazole. An unsubstituted phenyl ring exhibits bet-

ter activity than the substituted derivatives as shown in **10a**, **10b**, and **10c**.

Conclusion

A series of new 2-naphthyl ethers was prepared using simple methods and their protective activities against DNA damage induced by bleomycin–iron were evaluated. The 1,3,4-thiadiazol-2-amine derivative **2** gave the greatest protection against DNA damage, while the others showed moderate to low activity.

Experimental

Chemistry All melting points were recorded on an Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data (in accord with the calculated values) were obtained from the microanalytical unit, Cairo University, Giza, Egypt. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H-NMR spectra were recorded at 270 MHz on a Varian EM-360 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shift (δ) values are given in parts per million. The mass spectra were recorded using a Varian MAT CH-5 spectrometer (70 eV). 2-(Naphthalen-7-yloxy)acetic acid **1**,[26] 2-(naphthalen-3-yloxy)acetohydrazide **4**,[34,35] hydrazonoyl chlorides **9a**—**c**[36,37] were prepared according to the procedures reported in literature.

5-[(Naphthalen-3-yloxy)methyl]-1,3,4-thiadiazol-2-amine (2) 2-(Naphthalen-7-yloxy)acetic acid (20.2 g, 0.1 mol) and thiosemicarbazide (9.1 g, 0.1 mol) in phosphorous oxychloride (30 ml) were refluxed gently for 30 min. The solution was cooled and water (90 ml) was added carefully. The separated solid was filtered, suspended in water, and basified with aqueous potassium hydroxide. The solid was filtered, washed with water, dried, and crystallized from a mixture of *N*,*N*-dimethylformamide (DMF) and ethanol (9 : 1) to obtain a colorless solid in 80% yield with a melting point of 192—193 °C.

IR (KBr) ν_{max}/cm^{-1} 3107, 3264 (NH_2); ^{1}H-NMR (DMSO-d_6) δ: 5.28 (s, 2H, OCH_2), 7.13—7.45 (m, 7H, Ar-H), 7.82 (s, 2H, NH_2, D_2O exchangeable), MS *m*/*z* (%): 257 (M^+, 36), 144 (100). *Anal.* Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.73; H, 4.51; N, 16.40; S, 12.59.

2-[(Naphthalen-2-yloxy)methyl]-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole (3a—c) A mixture of equimolar quantities of the 1,3,4-thiadiazol-2-amine **2** (2.57 g, 0.01 mol) and appropriately substituted bromoacetyl compound (0.01 mol) was refluxed in dry ethanol for 24 h. The excess of solvent distilled off, and the solid hydrobromide that separated was collected by filtration, suspended in water, and neutralized by aqueous sodium carbonate solution to yield the free bases (**3a**—**c**). They were filtered, washed with water, dried, and recrystallized from ethanol.

2-[(Naphthalen-2-yloxy)methyl]-6-*p*-tolylimidazo[2,1-*b*][1,3,4]thiadiazole (**3a**): Yield, 54%; mp 198—200 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 5.66 (s, 2H, OCH_2), 7.23—7.55 (m, 11H, Ar-H), 8.60 (s, 1H, C_5-H, imidazole), MS *m*/*z* (%): 371 (M^+, 83), 228 (100). *Anal.* Calcd for $C_{22}H_{17}N_3OS$: C, 71.14; H, 4.61; N, 11.31; S, 8.63. Found: C, 71.33; H, 4.88; N, 11.43; S, 8.75.

6-(4-Bromophenyl)-2-[(naphthalen-2-yloxy)methyl]imidazo[2,1-*b*]-[1,3,4]thiadiazole (**3b**) Yield, 61%; mp 196—197 °C; ^{1}H-NMR (DMSO-d_6) δ: 5.67 (s, 2H, OCH_2), 7.26—7.57 (m, 11H, Ar-H), 8.61 (s, 1H, C_5-H, imidazole), MS *m*/*z* (%): 437 (M^++1, 76), 436 (M^+, 78) 293 (100). *Anal.* Calcd for $C_{21}H_{14}BrN_3OS$: C, 57.81; H, 3.23; N, 9.63; S, 7.35. Found: C, 57.93; H, 3.43; N, 9.71; S, 7.55.

6-(Benzofuran-2-yl)-2-[(naphthalen-2-yloxy)methyl]imidazo[2,1-*b*]-[1,3,4]thiadiazole (**3c**) Yield, 38%; mp 219—220 °C; ^{1}H-NMR (DMSO-d_6) δ: 5.72 (s, 2H, OCH_2), 7.18 (s, 1H, benzofuran-H), 7.29—7.89 (m, 11H, Ar-H), 8.73 (s, 1H, C_5-H, imidazole), MS *m*/*z* (%): 397 (M^+, 0.5), 144 (100). *Anal.* Calcd for $C_{23}H_{15}N_3O_2S$: C, 69.50; H, 3.80; N, 10.57; S, 8.07. Found: C, 69.53; H, 3.97; N, 10.66; S, 8.18.

Synthesis of pyrazoles 6a—c To a solution of 2-(naphthalen-7-yloxy)-acetohydrazide **4** (0.43 g, 2 mmol) in ethanol (20 ml), ethyl 2-(2-(subs.phenyl)hydrazono)-3-oxobutanoates **5a**—**c** (2 mmol), and a few drops of glacial acetic acid were added. The reaction mixture was refluxed for 5 h, and then the reaction mixture was evaporated to half its volume and kept at room temperature overnight. The solid that separated was filtered off, washed with cold ethanol, dried, and recrystallized from ethanol to give a yellow powder of compounds **6a**—**c**.

1-[5-Hydroxy-3-methyl-4-(phenyldiazenyl)-1*H*-pyrazol-1-yl]-2-(naphthalen-2-yloxy)ethanone (**6a**): Yield, 42%; mp 180—181 °C; IR (KBr) ν_{max}/cm^{-1} 1652 (C=O), 3455 (enolic OH); ^{1}H-NMR (DMSO-d_6) δ: 2.41 (s, 3H, CH_3), 5.09 (s, 2H, OCH_2), 7.25—7.62 (m, 11H, Ar-H), 10.33 (s, 1H, OH, D_2O exchangeable), MS *m*/*z* (%): 386 (M^+, 12), 144 (100). *Anal.* Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.45; H, 4.81; N, 14.67.

1-{4-[(2,4-Dichlorophenyl)diazenyl]-5-hydroxy-3-methyl-1*H*-pyrazol-1-yl}-2-(naphthalen-2-yloxy)ethanone (**6b**): Yield, 53%; mp 195 °C; IR (KBr) ν_{max}/cm^{-1} 1662 (C=O), 3443 (enolic OH); ^{1}H-NMR (DMSO-d_6) δ: 2.34 (s, 3H, CH_3), 5.08 (s, 2H, OCH_2), 7.19—7.41 (m, 9H, Ar-H), 10.32 (s, 1H, OH, D_2O exchangeable), MS *m*/*z* (%): 423 (M^+, 12), 113 (100). *Anal.* Calcd for $C_{22}H_{16}Cl_2N_4O_3$: C, 58.04; H, 3.54; N, 12.31. Found: C, 58.23; H, 3.62; N, 12.43.

1-{4-[(4-Fluorophenyl)diazenyl]-5-hydroxy-3-methyl-1*H*-pyrazol-1-yl}-2-(naphthalen-2-yloxy)ethanone (**6c**): Yield, 53%; mp 196—197 °C; IR (KBr) ν_{max}/cm^{-1} 1635 (C=O), 3455 (enolic OH); ^{1}H-NMR (DMSO-d_6) δ: 2.46 (s, 3H, CH_3), 5.10 (s, 2H, OCH_2), 7.15—7.83 (m, 10H, Ar-H), 10.22 (s, 1H, OH, D_2O exchangeable), MS *m*/*z* (%): 402 (M^+−2, 1.86), 144 (100). *Anal.* Calcd for $C_{22}H_{17}FN_4O_3$: C, 65.34; H, 4.24; N, 13.85. Found: C, 65.45; H, 4.33; N, 13.92.

5-Amino-1-[2-(naphthalen-3-yloxy)acetyl]-1*H*-pyrazole-4-carbonitrile (7) To a solution of **4** (0.43 g, 2 mmol) in anhydrous ethanol (20 ml), 2-(methoxymethylene)malononitrile (0.22 g, 2 mmol) was added and the reaction mixture was refluxed for 4 h. The product which separated on cooling, were collected by filtration and recrystallized from ethanol to give the compound **7**. Yield 61%; mp 248—249 °C; IR (KBr) ν_{max}/cm^{-1} 1633 (C=O), 2227 (CN) 3309, 3235 (NH_2); ^{1}H-NMR (DMSO-d_6) δ: 4.89 (s, 2H, OCH_2), 7.35—7.77 (m, 7H, Ar-H), 7.82 (s, 1H, pyrazole-H), 10.32 (s, 2H, NH_2, D_2O exchangeable), MS *m*/*z* (%): 292 (M^+, 100). *Anal.* Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.84; H, 4.27; N, 19.26.

Ethyl 5-Amino-3-(methylthio)-1-[2-(naphthalen-3-yloxy)acetyl]-1*H*-pyrazole-4-carboxylate (8) A mixture of equimolar quantities of **4** (0.43 g, 2 mmol) ethyl 2-cyano-3,3-bis(methylthio)acrylate (0.43 g, 2 mmol) was refluxed in dry ethanol for 6 h. The product, that separated on cooling, was collected by filtration and recrystallized from ethanol to give the compound **8**. Yield, 58%; mp 170—172 °C; IR (KBr) ν_{max}/cm^{-1} 1622, 1749 (2C=O), 3324, 3233 (NH_2); ^{1}H-NMR (DMSO-d_6) δ: 1.5 (t, 3H, CH_3–ester), 2.43 (s, 3H, SCH_3), 4.20 (q, 2H, CH_2–ester), 5.23 (s, 2H, OCH_2), 7.36—7.79 (m, 7H, Ar-H), 10.20 (s, 2H, NH_2, D_2O exchangeable), MS *m*/*z* (%): 385 (M^+, 12), 144 (100). *Anal.* Calcd for $C_{19}H_{19}N_3O_4S$: C, 59.21; H, 4.97; N, 10.90; S, 8.32. Found: C, 59.35; H, 5.09; N, 10.98; S, 8.46.

Synthesis of Propanehydrazonoyl Chlorides (10a—c) A mixture of **4** (0.43 g, 2 mmol) and appropriate hydrazonoyl chloride **9a**—**c** (2 mmol) in 30 ml absolute ethanol was refluxed for 4 h. The solid formed was filtered off, dried, and crystallized from EtOH/DMF (2 : 1).

2-(2-(2-(Naphthalen-2-yloxy)acetyl)hydrazono)-*N*′-phenylpropanehydrazonoyl Chloride (**10a**): Yield, 77%; mp 220—221 °C; IR (KBr) ν_{max}/cm^{-1} 1663 (C=O), 3321—3183 (2NH); ^{1}H-NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 5.22 (s, 2H, OCH_2) 7.08—7.89 (m, 11H, Ar-H), 10.19, 11.16 (2s, 2H, 2NH, D_2O exchangeable), MS *m*/*z* (%): 394 (M^+, 1.1), 144 (100). *Anal.* Calcd for $C_{21}H_{19}ClN_4O_2$: C, 63.88; H, 4.85; N, 14.19. Found: C, 63.97; H, 4.96; N, 14.27.

N′-(2,4-Dichlorophenyl)-2-{2-[2-(naphthalen-2-yloxy)acetyl]hydrazono}-propanehydrazonoyl Chloride (**10b**): Yield, 75%; mp 239—241 °C; IR (KBr) ν_{max}/cm^{-1} 1673 (C=O), 3316—3192 (2NH); ^{1}H-NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 5.21 (s, 2H, OCH_2) 7.15—7.83 (m, 10H, Ar-H), 10.12, 11.14 (2s, 2H, 2NH, D_2O exchangeable), MS *m*/*z* (%): 462 (M^+, 0.9), 144 (100). *Anal.* Calcd for $C_{21}H_{17}C_{l3}N_4O_2$: C, 54.39; H, 3.69; N, 12.08. Found: C, 54.47; H, 3.76; N, 12.17.

N′-(4-Fluorophenyl)-2-{2-[2-(naphthalen-2-yloxy)acetyl]hydrazono}-propanehydrazonoyl Chloride (**10c**): Yield, 63%; mp 218—219 °C; IR (KBr) ν_{max}/cm^{-1} 1672 (C=O), 3311—3196 (2NH); ^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H, CH_3), 5.38 (s, 2H, OCH_2) 7.24—7.89 (m, 10H, Ar-H), 10.20, 11.32(2s, 2H, 2NH, D_2O exchangeable), MS *m*/*z* (%): 412 (M^+, 1.8), 144 (100). *Anal.* Calcd for $C_{21}H_{18}ClFN_4O_2$: C, 61.09; H, 4.39; N, 13.57. Found: C, 61.16; H, 4.56; N, 13.68.

***N*,*N*′-[1,3,5,7-Tetraoxopyrrolo[3,4-*f*]isoindole-2,6(1*H*,3*H*,5*H*,7*H*)-diyl]bis[2-(naphthalen-2-yloxy)acetamide] (11)** A mixture of **4** (0.43 g, 2 mmol) and 1,2,4,5-benzene tetracarboxylic-1,2:4,5-dianhydride (1.2 g, 2 mmol) in glacial acetic acid (25 ml) was refluxed for 5 h. The solid formed was filtered off, washed with 95% ethanol, and crystallized from AcOH : H_2O to give **11**. Yield, 77%; mp >300 °C; IR (KBr) ν_{max}/cm^{-1} 1786—1624 (6C=O); ^{1}H-NMR (DMSO-d_6) δ: 5.08 (s, 4H, 2OCH_2) 7.35—7.89 (m, 16H, Ar-H), 11.12 (2s, 2H, 2NH, D_2O exchangeable), MS *m*/*z* (%):

614 (M^+, 19), 144 (100). *Anal.* Calcd for $C_{34}H_{22}N_4O_8$: C, 66.45; H, 3.61; N, 9.12. Found: C, 66.56; H, 3.76; N, 9.28.

Bleomycin-Dependent DNA Damage Assay[33,38,39] To the reaction mixtures in a final volume of 1.0 ml, the following reagents at the final concentrations stated were added: DNA (0.2 mg/ml), bleomycin (0.05 mg/ml), $FeCl_3$ (0.025 mM), magnesium chloride (5 mM), KH_2PO_4–KOH buffer pH 7.0 (30 mM), and ascorbic acid (0.24 mM) or the test fractions diluted in MeOH to give a concentration of (0.1 mg/ml). The reaction mixtures were incubated in a water-bath at 37 °C for 1 h. At the end of the incubation period, 0.1 ml of ethylenediaminetetraacetic acid (EDTA) (0.1 M) was added to stop the reaction (the iron–EDTA complex is unreactive in the bleomycin assay). DNA damage was assessed by adding 1 ml 1% (w/v) thiobarbituric acid (TBA) and 1 ml of 25% (v/v) hydrochloric acid (HCl) followed by heating in a water-bath maintained at 80 °C for 15 min. The chromogen formed was extracted into butan-l-ol, and the absorbance was measured at 532 nm.

References

1) Shi Y. N., Lu Y. C., Fang J. X., Hua Y. L., *Chem. J. Univ.* (Chinese), **16**, 1710—1713 (1995).
2) Kitagawa M., Yamamoto K., Katakura S., Kanno H., Yamada K., *Chem. Pharm. Bull.*, **39**, 2681—2690 (1991).
3) Baker B. R., Hurlbut J. A., *J. Med. Chem.*, **12**, 677—680 (1969).
4) Jain P. K., Srirastara S. K., *J. Indian Chem. Soc.*, **69**, 402—409 (1992).
5) Li Y. J., Dai Y. J., Chen J. C., *Chem. J. Chin. Univ.* (Chinese), **9**, 584—591 (1988).
6) Vasquez H., Strobel H., *Int. J. Oncol.*, **18**, 553—557 (2001).
7) Nichols K. D., Kirby G. M., *Biochem. Pharm.*, **75**, 538—551 (2008).
8) Poorrajab F., Ardestani S. K., Foroumadi A., Emami S., Kariminia A., Behrouzi-Fardmoghadam M., Shafiee A., *Exp. Parasitol.*, **121**, 323—330 (2009).
9) Abdel-Wahab B. F., Abdel-Aziz H. A., Ahmed E. M., *Arch. Pharm.*, **341**, 734—739 (2008).
10) Abdel-Aziz H. A., Abdel-Wahab B. F., El-Sharief M. A. M. Sh., Abdulla M. M., *Monatsh. Chem.*, **140**, 431—437 (2009).
11) Mandour A. H., Fawzy N. M., El-Shihi T. H., El-Bazza Z. E., *Pak. J. Sci. Ind. Res.*, **38**, 402—405 (1995); *Chem. Abstr.*, **127**, 135773 (1997).
12) Mazzone G., Pignatello R., Mazzone S., Panico A., Pennisi G., *Farmaco*, **48**, 1207—1224 (1993).
13) Chufan E. E., Pedregosa J. C., Badini O. N., Bruno-Blanch L., *Farmaco*, **54**, 838—841 (1999).
14) Terzioglu N., Gürsoy A., *Eur. J. Med. Chem.*, **38**, 781—786 (2003).
15) Kolavi G., Hegde V., Khan I., Gadad P., *Bioorg. Med. Chem.*, **14**, 3069—3080 (2006).
16) Gadad A. K., Mahajanshetti C. S., Nimbalkar S., Raichurkar A., *Eur. J. Med. Chem.*, **35**, 853—857 (2000).
17) Andotra C. S., Langer T. C., Kotha A., *J. Indian Chem. Soc.*, **74**, 125—127 (1997).
18) Khazi I. A. M., Mahajanshetti C. S., Gadad A. K., Tarnalli A. D., Sultanpur C. M., *Arzneim.-Forsch./Drug. Res.*, **46**, 949—952 (1996).
19) Andreani A., Leonia A., Locatelli A., Morigi R., Rambaldi M., Simon W. A., Senn-Bilfinger J., *Arzneim.-Forsch./Drug. Res.*, **50**, 550—553 (2000).
20) Abdel-Wahab B. F., Mohamed S. F., Amr A. E., Abdalla M. M., *Monatsh Chem.*, **139**, 1083—1090 (2008).
21) Amer F. A., Hammouda M., El-Ahl A.-A. S., Abdel-Wahab B. F., *J. Heterocycl. Chem.*, **45**, 1549—1569 (2008).
22) Abdalla M. M., Abdel-Wahab B. F., Amr A. E., *Monatsh Chem.*, **140**, 129—137 (2009).
23) Amr A. E., Sabrry N. M., Abdalla M. M., Abdel-Wahab B. F., *Eur. J. Med. Chem.*, **44**, 725—735 (2009).
24) Jadhav V. B., Kulkarni M. V., Rasal V. P., Biradar S. S., Vinay M. D., *Eur. J. Med. Chem.*, **43**, 1721—1729 (2008).
25) Abdel-Wahab B. F., Farghaly M., Badria F. A., *Pharm. Chem. J.* (2009), accepted.
26) Yar M. S., Siddiqui A. A., Ali M. A., *J. Chinese Chem. Soc.*, **54**, 5—8 (2007).
27) Palaska E., Sahin G., Kelicen P., Durlu N. T., Altinok G., *Farmaco*, **57**, 101—107 (2002).
28) Sahin G., Palaska E., Ekizoglu M., Ozalp M., *Farmaco*, **57**, 539—542 (2002).
29) Yar M. S., Siddiqui A. A., Ali M. A., *Bioorg. Med. Chem. Lett.*, **16**, 4571—4574 (2006).
30) Holla B. S., Udupa K. V., *Indian J. Chem.*, **29B**, 887—889 (1990).
31) Holla B. S., Udupa K. V., Sridhar K. R., *Bull. Chem. Soc. Jpn.*, **62**, 3409—3411 (1989).
32) Hallur M. S., Sangapure S. S., *Asian J. Chem.*, **11**, 845—849 (1999).
33) Gutteridge J., Rowley D., Halliwell B., *Biochem. J.*, **199**, 263—265 (1981).
34) Mullican M. D., Wilson M. W., Connor D. T., Kostlan C. R., Schrier D. J., Dyer R. D., *J. Med. Chem.*, **36**, 1090—1099 (1993).
35) Husain M. I., Kumar A., Srivastava R. C., *Curr. Sci.*, **55**, 644—646 (1986).
36) Nedime E., Hamit O., Fak E., *J. Fac. Pharmacy Istanbul Univ.*, **17**, 1—24 (1981).
37) Dieckmann W., Platz O., *Chem. Ber.*, **38**, 2989—2992 (1905).
38) Badria F. A., Ameen M., Akl M., *Z. Naturforsch.*, **62c**, 656—660 (2007).
39) El-Gazzar A., Gaafar A. M., Youssef M. M., Abu-Hashem A., Badria, F. A., *Phosphorus, Sulfur, Silicon, Rel. Elem.*, **182**, 2009—2037 (2007).