1,3-Dipolar Cycloaddition Reaction: Synthesis and Configuration of Norcantharidin Derivatives of Substituted Aromatic Amine

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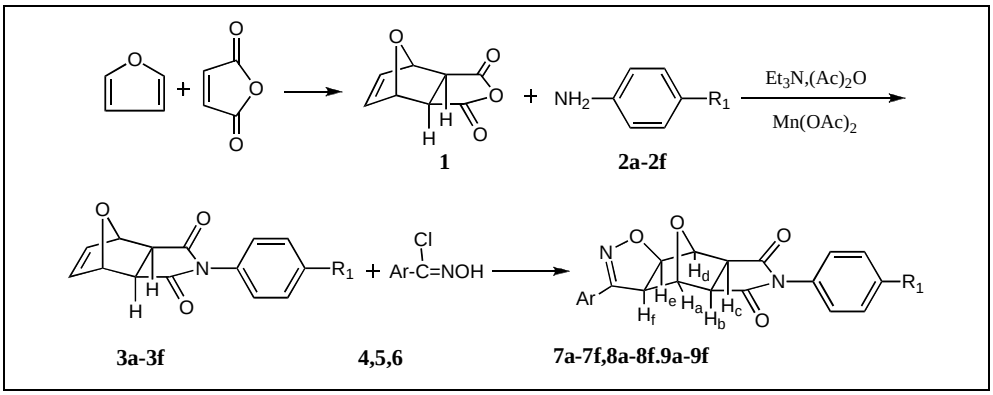

A series of eighteen novel compounds that have potential pharmacological properties has been synthesized by 1,3-dipolar cycloaddition reactions of 5,6-dehydronorcantharidin derivatives of substituted aromatic amine with nitrile oxide. The synthesis was carried out following straightforward three-step procedure described herein. IR, ^{1}H nmr and ms, H-H cosy and Noesy Cyclonoe, confirmed the structure of all products respectively. The biological evaluation of three series of norcantharidin analogues against HL60 cell has been screened.

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INTRODUCTION

Mylabris, the dried body of the Chinese blister beetle, has been used as Chinese medicine for over 2000 years. Its active constituent, Cantharidin (Figure 1), is the major effective ingredient for the malignant tumor treatment among the people in China [1]. Clinical trials indicated that cantharidin had effects on patients with primary hepatoma, but the application was limited by its severe toxicity for mucous membranes, mainly in the gastrointestinal tract, ureter and kidney. On the other hand, norcantharidin (Figure 1) show the same biological activity, less toxic and much easier to synthesize, which has been widely employed in clinical practice. It was also found that isoxazoline derivatives possess a wide range of pharmacological activities [2,3]. Thus, it seemed of interest to combine isoxazoline with 5,6-dehydronorcantharidin derivatives in one single molecule. In this context and with our sustained interest in the 1,3-dipolar cycloaddition of nitrile oxide, we successfully design and efficiently synthesize the norcantharidin isoxazoline adducts. Such types of compounds with potential versatile activities may be of interest in chemistry, biochemistry and pharmacology [4-6]. The synthesis routes of the compounds mentioned above are outlined in Scheme 1.

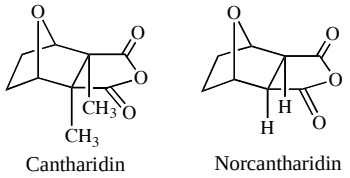


Figure 1

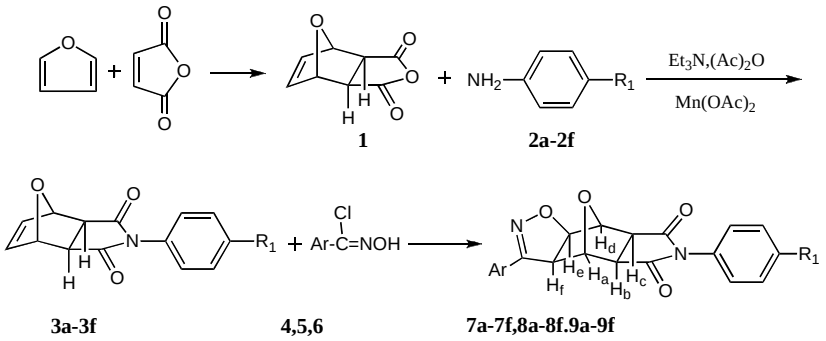
RESULTS AND DISCUSSION

The precursor 5,6-dehydronorcantharidian derivatives **3a-3f** was synthesized by "one pot" method in good yield [7].

Nitrile oxides are of great synthetic interest since the product isoxazolines are versatile intermediates for the synthesis of bifunctional compound. However, nitrile oxides are unstable and dimerize readily, hence we generate and react them *in situ* intermolecularly with 5,6-dehydronorcantharidian deratives of substituted aromatic amine to produce isoxazoline adducts in excellent yield.

We have studied the reactions of 5,6-dehydronorcantharidian derivatives **3a-3f** with three types of nitrile oxide which are benzoyl chloride oxime **4**, 4-methoxy-benzoyl chloride oxime **5**, 3-nitro-benzoyl chloride oxime **6**, which afforded eighteen novel cycloadducts respectively **(7a-7f, 8a-8f, 9a-9f)** in the end. Take the example of the synthesis of **7a**, which is done by the reaction of 3-acetyl-7-oxabicyclo-[2.2.1]hept-5-ene-2-carboxylic acid phenyl amide **3a** with benzoyl chloride oxime **4** in the presence of triethylamine at room temperature. Complete information of the synthesis procedure will be described in detail in experimental part.

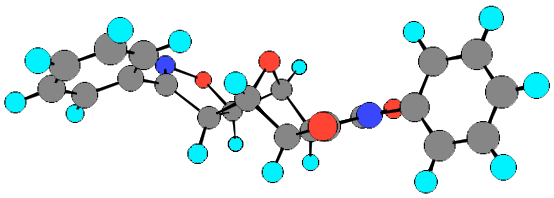
Scheme 1



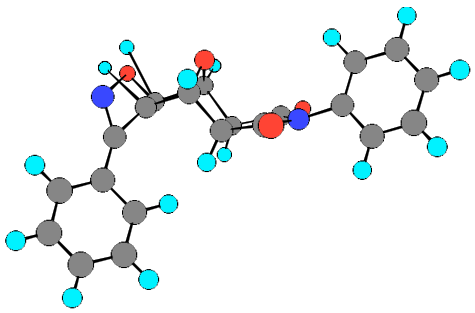
2a R_1=H; **2b** R_1= Cl; **2c** R_1=Br; **2d** R_1=CH_3; **2e** R_1=OCH_3; **2f** R_1= NO_2;
3a R_1=H; **3b** R_1= Cl; **3c** R_1=Br; **3d** R_1=CH_3; **3e** R_1=OCH_3; **3f** R_1= NO_2;
4 Ar=-ph ; **5** Ar=*p*-OCH_3 ph ; **6** Ar =m-NO_2 ph;
7a R_1=H; Ar=-ph ; **7b** R_1= Cl; Ar=-ph ; **7c** R_1=Br; Ar=-ph ;
7d R_1=CH_3; Ar=-ph; **7e** R_1=OCH_3; Ar=-ph; **7f** R_1= NO_2; Ar=-ph;
8a R_1=H; Ar=*p*-OCH_3 ph; **8b** R_1= Cl; Ar=*p*-OCH_3 ph ; **8c** R_1=Br; Ar=*p*-OCH_3 ph;
8d R_1=CH_3; Ar=*p*-OCH_3 ph; **8e** R_1=OCH_3; Ar=*p*-OCH_3 ph; **8f** R_1= NO_2; Ar=*p*-OCH_3 ph;
9a R_1=H; Ar =m-NO_2 ph; **9b** R_1= Cl; Ar =m-NO_2 ph; **9c** R_1=Br; Ar =m-NO_2 ph;
9d R_1=CH_3; Ar =m-NO_2 ph; **9e** R_1=OCH_3; Ar =m-NO_2 ph; **9f** R_1= NO_2; Ar =m-NO_2 ph ;

The structures of the new compounds **(7a-7f, 8a-8f, 9a-9f)** were established on the basis of their elemental microanalyses and spectral data. For example, the IR spectra of the compounds **(7a-7f, 8a-8f, 9a-9f)** contain the characteristic C=N stretching frequencies at 1520-1560cm^{-1} and the carbonyl group C=O stretching frequency at 1779-1714 cm^{-1}, the absorption of Ar-H at 3066cm^{-1} and 3045cm^{-1}, and the appearance of C-O-C at 1289cm^{-1}, 1256cm^{-1} respectively. The MS/EI spectra of **(7a-7f, 8a-8f, 9a-9f)** showed the characteristic molecular ion peaks. The *m/z* and relative abundances of molecular ions and fragment ions of the compounds are given in experimental part. Most interestedly we found that their mass spectrum was also characterized by retro-dipolar cycloaddition and retro Diels-Alder [4+2] cycloaddition fragments.

The ^{1}H nmr spectra of the new compounds measured in dimethyl sulfoxide-d_6 (DMSO-d_6) show the presence of the expected protons, in agreement with the proposed structures. The presence of multiple signal at δ 8.39-7.48 was assigned to the aromatic protons, H_e appeared as a doublet at δ 5.32-5.30, H_d appeared as a singlet at 5.15, H_a appeared as a singlet at 5.07, H_f appeared as a doublet at 4.52-4.50, H_c appeared as a doublet at 3.66-3.64, H_b appeared as a doublet at 3.47-3.45.



A Heat of Formation: -18.56338 kcal/mole



B Heat of Formation: -17.05506 kcal/mole

In order to identify the configuration of the isoxazoline with 5,6-dehydronorcantharidin adducts **(7a-7f, 8a-8f, 9a-9f)** is **A** or **B**, we have studied selective H-H COSY spectra, NOESY spectra, and CYCLONOE spectra of the compounds. The *exo*-adduct **(7a-7f, 8a-8f, 9a-9f)** showed characteristic coupling for the bridge-head proton in the 400 MHz NMR spectrum which indicate that the protons involved are attached to the vicinal protons, H–H COSY spectrum showed cross peaks between H_b and H_c; between H_e and H_f; NOESY spectrum showed cross peaks between H_b and H_f; between H_c and H_e. The adduct 5,6-dehydronorcantharidin of furan with maleic anhydride has been shown to have the *exo* configuration exclusively[8]; the endo isomer has never been reported. This information combined with that of the H-H COSY, NOESY and CYCLONOE spectral data gives us a definite configuration. Furthermore, to rationalize the configuration of adducts, we have also carried out some theoretical calculations using semi-empirical PM3 with the aid of TITAN software. The result shows that the heat

of formation of configuration **A** is –18.56 kcal/mole; and the heat of formation of configuration **B** is –17.06 kcal/mole. The result is in agreement with the configuration that we have referred and further confirmed the configuration **A** of the compound theoretically stable and reasonable in several respects.

The biological evaluation of three series of norcantharidin analogues has been screened. We note that most analogues were active against HL60 cell only in high concentration and inactive in low concentration. The lead compounds cantharidin and norcantharidin were somewhat more potent against cancer cells respectively. This study provides the basis for further development of this class of protein phosphatase inhibitors for the treatment of malignancy.

EXPERIMENTAL

Melting points were obtained on a B-540 Büchi melting point apparatus and are uncorrected. ^{1}H nmr spectra were recorded on a Brucker AM-400 MHz spectrometer with $SiMe_4$ as the internal standard in $CDCl_3$. When coupling pattern in ^{1}H nmr spectra is doublet, the chemical shift value reported corresponds to the center of two peaks. Mass Spectra were made with a HP5989B analyzer. Element analyses were performed on an EA-1110 instrument.

All solvents used were reagent grade except the dimethyl sulfoxide used for spectroscopic measurements (spectrophotometric grade). The preparation of 5, 6-dehydronorcantharidian **1** was done according to the literature [9]. "One-pot" Method for the Preparation of 3-Acetyl-7-oxa-bicyclo[2.2.1] hept-5-ene-2-carboxylic Acid Phenylamide **3a-3e**. All these work we have done before [7].

General procedure for the preparation of the 5,6-dehydronorcantharidin isoxazoline adducts 7a-7f,8a-8f,9a-9f. To a solution of 3-acetyl-7-oxa-bicyclo [2.2.1] hept-5-ene-2-carboxylic acid phenylamide **3a** (1 mmole) and benzoyl chloride oxime **4** (1 mmole) in dichloro-methane (20 ml), add dried triethylamine (6 drops) and vigorously stirred at room temperature. The reaction mixture was allowed to stir for 24 hours, then washed with water (30 ml) and extracted with dichloromethane (30 ml). The extracts were washed with water, dried over anhydrous sodium sulfate, concentrated in vacuum and the residue was recrystalized from acetone to gain the compound **7a**. The synthesis of compounds **7b-7f**, **8a-8f**, **9a-9f** were prepared by the same method.

***exo,exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-phenyl-3-phenyl-pyrrolo[3,4-*f*]-1,2-benzisoxazole (7a).** Yield 94.6%, m.p. 298-299°C; IR (KBr)$_v$: 3062 3027 (ArH), 1781, 1714(C=O), 1595(C=N), 1256 (C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d_6)δ:7.83-7.19 (m, 10H, Ar-H), 5.25-5.23 (d, *J*=7.92Hz, 1H, H_e), 4.98 (s, 1H, H_d), 4.75 (s, 1H, H_a), 4.53-4.51(d, *J*=7.92Hz, 1H, H_f), 3.60-3.58(d, *J*=7.92Hz, 1H, H_c), 3.39-3.37 (d, *J*=7.93Hz, 1H, H_b); MS (70ev) m/z (%) 360(M^+, 15.6), 228 (24.7), 159 (47), 156 (28), 144(36.4), 119 (100), 91 (48.2), 77 (65.0) 68 (63.6); Anal. Calcd for $C_{21}H_{16}N_2O_4$: C 69.99, H 4.48, N 7.77; found C 70.01, H 4.49, N 7.74.

***exo,exo*-6-(4-Chlorophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-phenyl-pyrrolo[3,4-*f*]-1,2-benzisoxazole (7b).** Yield 87.3%, m.p. >300°C; IR (KBr)$_v$: 3121 3040 (ArH), 1785, 1716(C=O), 1568 (C=N), 1243 (C-O-C), 782(C-Cl)cm^{-1}; ^{1}H NMR (DMSO-d_6)δ:7.83-7.25 (m, 9H, Ar-H), 5.24-5.22 (d, J=7.92 Hz, 1H, H_e), 4.98 (s, 1H, H_d), 4.76 (s, 1H, H_a), 4.52-4.50 (d, *J*=7.92Hz, 1H, H_f), 3.60-3.58 (d, *J*=7.92Hz, 1H, H_c), 3.39-3.37(d, *J*=7.92Hz, 1H, H_b); MS (70ev) m/z (%) 395.5(M^+, 13.7), 124(22.5), 103(14.3), 90 (22.8), 77(100), 68 (69.1) 43 (21.6), 39 (40.3); Anal. Calcd for $C_{21}H_{15}N_2O_4Cl$: C 63.89, H3.83, N 7.10; found C 63.89, H 3.80, N 7.13.

***exo,exo*-6-(4-Bromophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-phenyl-pyrrolo[3,4-*f*]-1,2-benzisoxazole (7c).** Yield 82.9%, m.p. >300°C; IR (KBr)$_v$: 3052 3027 (ArH), 1781, 1714(C=O), 1540 (C=N), 1256 (C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d_6)δ: 7.83-7.18 (m, 10H, Ar-H), 5.25-5.23 (d, *J*=7.92Hz, 1H, H_e), 4.98 (s, 1H, H_d), 4.76(s, 1H, H_a), 4.52-4.50 (d, *J*=7.92Hz, 1H, H_f), 3.61-3.59 (d, *J*=7.92Hz, 1H, H_c), 3.39-3.37 (d, *J*=7.93Hz, 1H, H_b); MS (70ev) m/z (%) 440(M^+, 13.2), 197 (35.6), 144(36.4), 119 (100), 90 (48.2), 77 (72.4), 68 (100); Anal. Calcd for $C_{21}H_{15}N_2O_4Br$: C 57.42, H 3.44, N 6.38; found C 57.40, H 3.47, N 6.41.

***exo,exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-3-phenyl-6-(p-tolyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (7d).** Yield 71.3%, m.p. 283～284°C; IR (KBr)$_v$: 3056 3043 (ArH), 1781 1714(C=O), 1567(C=N), 1254 (C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d_6)δ: 7.83-7.25 (m, 10H, Ar-H), 5.25-5.23 (d, *J*=7.92Hz, 1H, H_e), 4.98 (s, 1H, H_d), 4.75 (s, 1H, H_a), 4.52-4.50 (d, *J*=7.92Hz, 1H, H_f), 3.60-3.58 (d, *J*=7.92Hz, 1H, H_c), 3.39-3.37(d, *J*=7.93Hz, 1H, H_b); 2.89 (s, 3H, -CH_3) MS (70ev) m/z (%) 374(M^+, 11.2), 228 (22.6), 156(36.4), 133 (100), 91 (56.2), 77 (72.4), 68 (58.3); Anal. Calcd for $C_{22}H_{18}N_2O_4$: C 70.58, H 4.85, N 7.48; found C 70.54, H 4.87, N 7.46.

***exo,exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-(4-methoxyphenyl)-3-phenyl-pyrrolo[3,4-*f*]-1,2-benzisoxazole (7e).** Yield 70.5%, m.p. 257～258°C; IR (KBr)$_v$: 3072 3060 (ArH), 1754 1717(C=O), 1567 (C=N), 1254 (C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d_6)δ: 7.83-7.15(m, 10H, Ar-H), 5.24-5.22 (d, *J*=7.92Hz, 1H, H_e), 4.97 (s, 1H, H_d), 4.75 (s, 1H, H_a), 4.52-4.50 (d, *J*=7.92Hz, 1H, H_f), 3.60-3.58(d, *J*=7.92Hz, 1H, H_c), 3.36-3.34 (d, *J*=7.93Hz, 1H, H_b); 3.77 (s, 3H, -OCH_3); MS (70ev) m/z (%) 390(M^+, 11.7), 203 (22.5), 149(100), 134 (70.3), 106 (56.2), 103 (17.4), 77 (58.0); Anal. Calcd for $C_{22}H_{18}N_2O_5$: C 67.69, H4.65, N 7.18; found C 67.65, H 4.69, N 7.13.

***exo,exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-(4-nitrophenyl)-3-phenyl-pyrrolo[3,4-f]-1,2-benzisoxazole (7f).** Yield 56.8%, m.p. 245～246°C; IR (KBr)$_v$: 3051 3027 (ArH), 1738, 1716(C=O), 1563 (C=N), 1244(C-O-C), 1530 1383(-NO_2)cm^{-1}; ^{1}H NMR (DMSO-d_6)δ: 8.37-7.49(m, 9H, Ar- H), 5.26-5.24 (d, *J*=7.92Hz, 1H, H_e), 5.02(s, 1H, H_d), 4.80(s, 1H, H_a), 4.54-4.52 (d, *J*=7.92Hz, 1H, H_f), .67-3.65(d, 3*J*=7.92Hz, 1H, H_c), 3.45-3.43(d, *J*=7.92Hz, 1H, H_b); MS (70ev) m/z (%) 405(M^+, 9.8), 153(22.5), 119(14.3), 91 (22.8), 77(100), 68 (69.1) 43 (21.2), 39 (40.5); Anal. Calcd for $C_{21}H_{15}N_3O_6$: C 62.22, H3.73, N 10.37; found C 62.20, H 3.76, N 10.33.

***exo*,*exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-phenyl-3-(4-methoxyphenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (8a).** Yield 90.6%, m.p. 299～300°C; IR (KBr)$_v$: 3046 3008 (ArH), 1785 1717(C=O), 1517 (C=N), 1258(C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d$_6$)δ: 7.74-7.06 (m, 9H, Ar-H), 5.19-5.17 (d, *J*=7.92Hz, 1H, H$_e$), 4.95(s, 1H, H$_d$), 4.73(s, 1H, H$_a$), 4.49-4.47(d, *J*=7.92Hz, 1H, H$_f$), 3.60-3.58 (d, *J*=7.92Hz, 1H, H$_c$), 3.37-3.35 (d, *J*=7.93Hz, 1H, H$_b$); 3.82 (s, 3H, -OCH$_3$); MS (70ev) m/z (%) 390(M$^+$, 11.7), 149(10.8), 133 (32.5), 119 (70.3), 106 (37.2), 103 (17.4), 77 (58.0), 67(100); Anal. Calcd for $C_{22}H_{18}N_2O_5$: C 67.69, H4.65, N 7.18; found C 67.65, H 4.64, N 7.17.

***exo*,*exo*-6-(4-Chlorophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-methoxyphenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (8b).** Yield 81.7%, m.p. 278～279°C; IR (KBr)$_v$: 3055 3017 (ArH), 1779 1756(C=O), 1543 (C=N), 1252(C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d$_6$)δ: 7.75-7.06(m, 8H, Ar-H), 5.19-5.17 (d, *J*=7.92Hz, 1H, H$_e$), 4.95(s, 1H, H$_d$), 4.74(s, 1H, H$_a$), 4.48-4.46(d, *J*=7.92Hz, 1H, H$_f$), 3.60-3.58(d, *J*=7.92Hz, 1H, H$_c$), 3.38-3.36(d, *J*=7.93Hz, 1H, H$_b$); 3.83 (s, 3H, -OCH$_3$) MS (70ev) m/z (%) 427(M$^+$+2, 11.3), 425(M$^+$, 9.5) 155 (21.8), 153 (39.0), 127 (18.3), 125 (16.2), 106 (17.4), 104(15.6) 77 (58.0), 68(100); Anal. Calcd for $C_{22}H_{17}N_2O_5Cl$: C 62.20, H4.03, N 6.59; found C 62.22, H 4.05, N 6.55.

***exo*,*exo*-6-(4-Bromophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-methoxyphenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (8c).** Yield71.4%, m.p. 275～276°C; IR (KBr)$_v$: 3053 3027 (ArH), 1786 1740(C=O), 1550 (C=N), 1253(C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d$_6$)δ: 7.75-7.06(m, 8H, Ar-H), 5.19-5.17 (d, *J*=7.92Hz, 1H, H$_e$), 4.95(s, 1H, H$_d$), 4.74(s, 1H, H$_a$), 4.48-4.46 (d, *J*=7.92Hz, 1H, H$_f$), 3.60-3.58(d, *J*=7.92Hz, 1H, H$_c$), 3.38-3.36(d, *J*=7.93Hz, 1H, H$_b$); 3.83 (s, 3H, -OCH$_3$) MS (70ev) m/z (%) 470(M$^+$, 9.8) 262(41.8), 153 (39.0), 127 (18.3), 125 (16.2), 119(17.4), 91(15.6), 77(58.0), 68(100); Anal. Calcd for $C_{22}H_{17}N_2O_5Br$: C 56.31, H 3.65, N 5.97; found C 56.29, H 3.67, N 5.94.

***exo*,*exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-methoxyphenyl)-6-(*p*-tolyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (8d).** Yield 70.4%, m.p. 272～274°C IR (KBr)$_v$: 3053 3029 (ArH), 1776 1743(C=O), 1528 (C= N), 1233(C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d$_6$)δ 7.76-7.02(m, 8H, Ar-H), 5.18-5.16 (d, *J*=7.92Hz, 1H, H$_e$), 4.95(s, 1H, H$_d$), 4.74(s, 1H, H$_a$), 4.48-4.46(d, *J*=7.92Hz, 1H, H$_f$), 3.60-3.58(d, *J*=7.92Hz, 1H, H$_c$), 3.38-3.36(d, *J*=7.93Hz, 1H, H$_b$); 3.83 (s, 3H, -OCH$_3$), 2.87(d, 3H, -CH$_3$) MS (70ev) m/z (%) 404(M$^+$, 9.3) 176 (21.8), 133 (21.1), 119(17.4), 107(76.4), 91(15.6), 77(68.2), 68(100); Anal. Calcd for $C_{23}H_{20}N_2O_5$: C 68.31, H4.98, N 6.93; found C 68.32, H 4.96, N 6.94.

***exo*,*exo*-6-(4-Methoxyphenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-methoxyphenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (8e).** Yield 68.0%, m.p. 292～293°C IR (KBr)$_v$: 3058 3034(ArH), 1763 1725(C=O), 1541(C=N), 1233 (C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d$_6$)δ: 7.77-7.02(m, 8H, Ar-H), 5.18-5.16 (d, *J*=7.92Hz, 1H, H$_e$), 4.93(s, 1H, H$_d$), 4.72(s, 1H, H$_a$), 4.47-4.45 (d, *J*=7.92Hz, 1H, H$_f$), 3.60-3.58(d, *J*=7.92Hz, 1H, H$_c$), 3.38-3.36(d, *J*=7.93Hz, 1H, H$_b$); 3.83 (s, 3H, -OCH$_3$), 3.77(d, 3H, -OCH$_3$) MS (70ev) m/z (%) 421(M$^+$, 7.3) 188 (21.4)149 (21.6), 134(17.7), 107(76.4), 91(15.3), 77(68.5), 68(100); Anal. Calcd for $C_{23}H_{20}N_2O_6$: C 65.71, H4.79, N 6.66; found C 65.72, H 4.80, N 6.65.

***exo*,*exo*-6-(4-Nitrophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-methoxyphenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (8f).** Yield 58.3%, m.p. 224～225°C; IR (KBr)$_v$: 3057 3021 (ArH), 1753 1733(C=O), 1564 (C=N), 1227 (C-O-C)cm^{-1}; ^{1}H NMR (DMSO-d$_6$)δ: 7.86-7.22 (m, 8H, Ar-H), 5.20-5.18 (d, *J*=7.92Hz, 1H,, H$_d$), 4.72 (s, 1H, H$_a$), 4.47-4.45 (d, *J*=7.92Hz, 1H, H$_f$), 3.57-3.55(d, *J*=7.92Hz, 1H, H$_c$), 3.34-3.32(d, *J*=7.93Hz, 1H, H$_b$); 3.83 (s, 3H, -OCH$_3$) MS (70ev) m/z (%) 435(M$^+$, 10.3) 224(41.8), 143 (39.0), 127 (18.3), 119(17.4), 91(15.6), 77(58.0), 68(100); Anal. Calcd for $C_{22}H_{17}N_3O_7$: C 60.69, H3.94, N 9.65; found C 60.65, H 3.96, N 9.61.

***exo*,*exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-phenyl-3-(3-nitrophenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (9a).** Yield 70.4%, m.p. 296～297°C; IR (KBr)$_v$: 3088 3045(ArH), 1779, 1752 (C=O), (C-O-C) 1513, 1383(-NO$_2$) ; ^{1}H NMR (DMSO-d$_6$)δ: 8.56-7.18 (m, 9H, Ar-H), 5.34-5.32 (d, *J*=7.92Hz, 1H, H$_e$), 5.02(s, 1H, H$_d$), 4.86 (s, 1H, H$_a$), 4.63-4.61 (d, *J*=7.92Hz, 1H, H$_f$), 3.64-3.62(d, *J*=7.92Hz, 1H, H$_c$), 3.41-3.39(d, *J*=7.92 Hz, 1H, H$_b$); MS (70ev) m/z (%) 405(M$^+$, 13.7), 360(22.5), 143(14.3), 117(79), 91 (22.8), 77(65.2), 68 (69.1) 43 (21.6), 37 (100); Anal. Calcd for $C_{21}H_{15}N_3O_6$: C 62.22, H 3.73, N 10.37; found C 62.21, H 3.75, N 10.34.

***exo*,*exo*-6-(4-Chlorophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(3-nitrophenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (9b).** Yield 67.3%, m.p. 259～260°C; IR (KBr)$_v$: 3086 3051(ArH), 1774, 1753(C=O), 1253 (C-O-C)1513 1383(-NO$_2$) ; ^{1}H NMR (DMSO-d$_6$) δ: 8.56-7.23 (m, 8H, Ar-H), 5.34-5.32 (d, J=7.92Hz, 1H, H$_e$), 5.02 (s, 1H, H$_d$), 4.86 (s, 1H, H$_a$), 4.63-4.61 (d, *J*=7.92Hz, 1H, H$_f$), 3.64-3.62 (d, *J*=7.92Hz, 1H, H$_c$), 3.41-3.39 (d, *J*=7.92Hz, 1H, H$_b$); MS (70ev) m/z (%) 441 (M$^+$+2, 6.3), 439 (M$^+$, 9.7), 143(14.3), 113(71), 91 (22.8), 77(61.2), 68 (69.1), 59(0.83), 43 (21.0), 39(93), 37 (100); Anal. Calcd for $C_{21}H_{14}N_3O_6Cl$: C 57.35, H3.21, N 9.55; found C 57.32, H 3.21, N 9.51.

***exo*,*exo*-6-(4-Bromophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(3-nitrophenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (9c).** Yield 62.0%, m.p. 260～261°C; IR (KBr)$_v$: 3131 3089(ArH), 1781, 1753(C=O), 1575(C=N), 1224(C-O-C)1513 1383(-NO$_2$); ^{1}H NMR (DMSO-d$_6$)δ: 8.67-7.26(m, 8H, Ar-H), 5.35-5.33(d, *J*=7.92Hz, 1H, H$_e$), 5.02(s, 1H, H$_d$), 4.86(s, 1H, H$_a$), 4.63-4.61(d, *J*=7.92Hz, 1H, H$_f$), 3.64-3.62(d, *J*=7.92Hz, 1H, H$_c$), 3.41-3.39 (d, *J*=7.92Hz, 1H, H$_b$); MS (70ev) m/z (%) 485(M$^+$+2, 66.3), 483(M$^+$, 20.5), 343(3.0), 143(14.3), 113(79), 91 (22.4), 77(61.2), 68 (49.1), 56(0.83), 43 (21.0), 39(72), 37 (100); Anal. Calcd for $C_{21}H_{14}N_3O_6Br$: C 51.91, H2.97, N 8.62; found C 51.87, H 2.78, N 8.56.

***exo*,*exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(3-nitrophenyl)-6-(*p*-tolyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (9d).** Yield 59.6%, m.p. 298～299°C; IR (KBr)$_v$: 3127 3076(ArH), 1778, 1723(C=O), 1575(C=N), 1220(C-O-C)1513 1383(-NO$_2$) ; ^{1}H NMR (DMSO-d$_6$)δ: 8.56-7.06 (m, 8H, Ar- H), 5.35-5.33 (d, *J*=7.92Hz, 1H, H$_e$), 5.00 (s, 1H, H$_d$), 4.85 (s, 1H, H$_a$), 4.63-4.61 (d, *J*=7.92Hz, 1H, H$_f$), 3.62-3.60 (d, *J*=7.92Hz, 1H, H$_c$), 3.39-3.37 (d, *J*=7.92Hz, 1H, H$_b$), 2.87 (d, 3H, -CH$_3$); MS (70ev) m/z (%) 419(M$^+$, 9.7), 242(3.0), 206(14.3), 155(0.79), 102 (22.4), 91(61.2), 77 (49.1), 68(83), 63 (21.0), 39(61), 37 (100); Anal. Calcd for $C_{22}H_{17}N_3O_6$: C 63.01, H 4.09, N 10.02; found C 63.00, H 4.11, N 9.99.

***exo*,*exo*-6-(4-methoxyphenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(3-nitrophenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (9e).** Yield 56.6%, m.p. 297～298°C IR (KBr)$_v$: 3089 3062(ArH), 1776 1742 (C=O), 1563 (C=N), 1235 (C-O-C), 1513, 1383 (-NO$_2$) cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ: 8.56-7.02 (m, 8H, Ar-H), 5.33-5.31 (d, *J*=7.92Hz, 1H, H$_e$), 5.00 (s, 1H, H$_d$), 4.86 (s, 1H, H$_a$), 4.63-4.61 (d, *J*=7.92Hz, 1H, H$_f$), 3.62-3.60 (d, *J*=7.92Hz, 1H, H$_c$), 3.39-3.37 (d, *J*=7.92Hz, 1H, H$_b$), 3.83 (d, 3H, -OCH$_3$); MS (70ev) m/z (%) 419 (M$^+$, 9.7), 178(3.0), 147(14.3), 117(79), 113 (22.4), 91(61.2), 77 (49.1), 68(0.83), 63 (21.0), 39(71), 37 (100); Anal. Calcd for $C_{22}H_{17}N_3O_6$: C 63.01, H 4.09, N 10.02; found C 63.03, H 4.12, N 9.99.

***exo*,*exo*-6-(4-Nitrophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(3-nitrophenyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (9f).** Yield 67.3%, m.p. 259～260°C; IR $(KBr)_v$: 3125 3077(ArH), 1764, 1723(C=O), 1578(C=N), 1253 (C-O-C) 1583 1346(-NO_2); ^{1}H NMR (DMSO-d_6)δ: 8.57-7.24(m, 8H, Ar-H), 5.34-5.32(d, J=7.92 Hz, 1H, H_e), 5.01(s, 1H, H_d), 4.85(s, 1H, H_a), 4.62-4.60 (d, J=7.92 Hz, 1H, H_f), 3.60-3.58(d, J=7.92 Hz, 1H, H_c), 3.37-3.35(d, J=7.92 Hz, 1H, H_b); MS (70ev) m/z (%) 450(M^+, 9.2), 232(11.4), 189(14.3), 176(71), 149(22.8), 119(25.0), 77(61.2), 68 (69.1), 59(63), 43 (21.0), 39(93), 37 (100); Anal. Calcd for $C_{21}H_{14}N_4O_8$: C 56.01, H3.13, N 12.44; found C 56.01, H 3.15, N 12.42.

REFERENCES

[1] Wang, G.-S. *Acta Pharm. Sinica*. **1980**, *15*, 119; *Chem. Abstr*. **1981**, *94*, 120481v.

[2] Yi, S. N.; Wass, J.; Vincent, P.; Iland. H. *Leuk. Res*. **1991**, *15*, 883.

[3] Efferth, T.; Davey, M.; Olbrich, A.; Rucher, G.; Gebhart, E.; Davery, *R. Blood Cells Mol. Dis*. **2002**, *28*, 160.

[4] McCluskey, A.; Ackland, S. P.; Bowyer, M. C.; Baldwin, M. L.; Garner, J.; Walkom, C. C. *Bioorg. Chem*. **2003**, *31*, 68.

[5] Matsushita, T.; Ryu, E. K.; Hong, C. I. *Cancer Res*. **1981**, *41*, 2707.

[6] Szilagyi, G.; Kasztreiner, E.; Tardos, L.; Jaszlits, L.; Kosa, E.; Cseh, G.; Tolnay, P.; Kovacs-Szabo, I. *Eur. J. Med. Chem*. **1979**, *14*, 439.

[7] Deng, L.-P.; Liu F.-M.; Wang, H.-Y. *J. Heterocyclic Chem*. **2005**, *42*, 13.

[8] Ram, V. J.; Singha U. K.; Guru, P. Y. *Eur. J. Med. Chem*. **1990**, *25*, 533.

[9] Woodward, R. B.; Harold, B. J. *J. Am. Chem. Soc*. **1948**, *70*, 1161.