1,3-Dipolar Cycloaddition Reaction: Synthesis of Novel 5,6-Dehydronorcantharidin Derivatives of Substituted Aromatic Amines with potential antitumor activities

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Twelve novel compounds were synthesized by the [3+2] 1,3-dipolar cycloaddition reaction of 5,6-dehydronorcantharidin derivatives of substituted aromatic amines with nitrile oxides. The structure and the configuration of all compounds were confirmed by ^{1}H NMR, IR, MS, ^{1}H-^{1}HCOSY, and NOESY spectral data. Their anti-tumor activities are under way.

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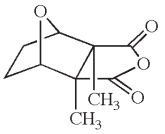
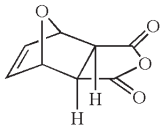
Cantharidin, is the major effective ingredient for the malignant tumor treatment among the people in China [1]. Recent study showes that cantharidin can treat liver cancer to some extent [2], and can also enhance white cell without inhibiting the immune system [3]. So, cantharidin is of great pharmacological interest and has gained great attention. However, cantharidin is somewhat toxic and difficult to synthesize. On the other hand, the derivatives of the 5,6-dehydronorcantharidin show the same biological activity, are less toxic and much easier to synthesize. Furthermore, many compounds containing the 1,2,3-trizolye ring have become a hot topic in heterocyclic chemistry because of their antitumor, anti-virus, analgesic, sedative and fungicidal activities [4-6]. It has been shown recently that the pharmacological activities of parent molecules will apparently be improved with the introduction of 1,2,3-triazole to some active molecules, such as penicillin, cephalesporins and so on. Tests with derivatives of quinoxaline show them having anticancer, anti-HIV, antifungal, antidepressant, anthelmintic and herbicidal properties [7-10]. Although 1,3-dipolar cycloaddition reactions of nitrile oxides is the general method to synthesize isoxazolines, there has been very little work on the 1,3-dipolar cycloaddition reaction of 5,6-dehydronorcantharidin derivatives. These observations prompted us to study the synthesis of 5,6-dehydronorcantharidin derivatives. We have successfully designed and efficiently synthesized the 5,6-dehydronorcantharidin isoxazoline adducts which possess a 1,2,3-triazole or quinoxaline ring linked to 5,6-dehydronorcantharidin, with a view of comparing their biological properties.



cantharidin



5,6-dehydronorcantharidin

Results and Discussion.

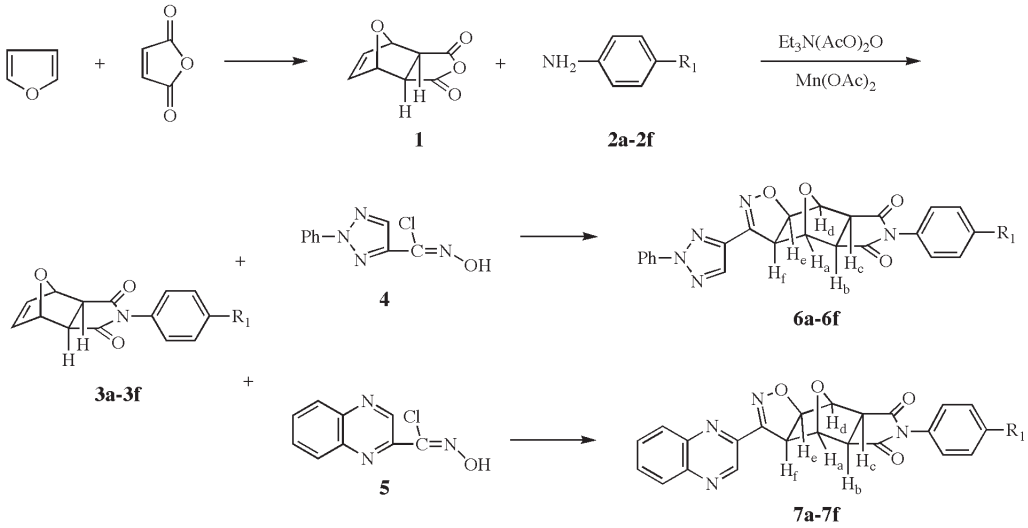
The synthetic routes of the compounds mentioned above are outlined in Scheme 1. The precursor 5,6-dehydronorcantharidin derivatives **3a-3f** were synthesized by novel method in good yield, which was reported for the first time.

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

We have carried out the [4+2] cycloaddition of furan with maleic anhydride to obtain 5,6-dehydronorcantharidin **1**, then by "one pot" method, 5,6-dehydronorcantharidin **1** reacted with substituated phenylamine **2a-2f** to give compounds **3a-3f**, after that, we carried out the [3+2] cycloaddition of **3a-3f** with two nitrile oxides, generated (*in situ*) in the presence of triethylamine from α-chloro-2-phenyl-2*H*-[1,2,3]triazole–4-formaldehyde oxime **4** and α-chloro-quinoxaline-2-formaldehyde oxime **5** to obtain the target compounds **6a-6f** and **7a-7f** respectively**.** The reactions were monitored by thin-layer chromatography. Complete information of the synthesis procedure will be described in detail in experimental part.

The structure and configuration of the new compounds **(6a-6f** and **7a-7f)** were established by their elemental microanalyses and spectral data. For example, the IR spectra of compounds **(6a-6f** and **7a-7f)** 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 3066 cm^{-1} and 3045 cm^{-1}, and the appearance of C-O-C at 1289 cm^{-1} and 1256 cm^{-1} respectively. The MS/EI spectra of **(6a-6f** and **7a-7f)** showed the characteristic molecular ion peaks. The *m/z* and relative abundances of molecular ions and fragment ions of the compounds are given in the experimental section. They are also characterized by retro-dipolar cycload-

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;
6a R_1=H; **6b** R_1= Cl; **6c** R_1=Br; **6d** R_1=CH_3; **6e** R_1=OCH_3; **6f** R_1= NO_2;
7a R_1=H; **7b** R_1= Cl; **7c** R_1=Br; **7d** R_1=CH_3; **7e** R_1=OCH_3; **7f** R_1= NO_2;

dition 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 Diels-Alder adduct 5,6-dehydronorcantharidin **1** of furan with maleic anhydride has been shown to have the *exo* configuration exclusively; the *endo* isomer has never been reported [11-12]. For target compounds **6a–6f** and **7a–7f**, the presence of multiple signal at δ 8.39-

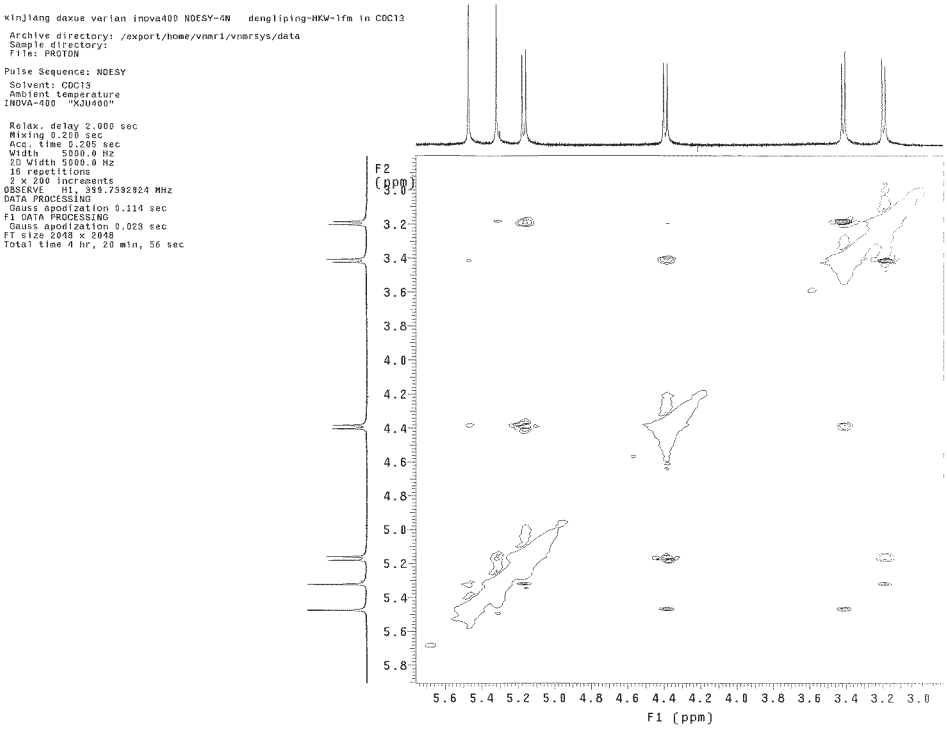


Figure 1. NOESY spectrum of **7a**.

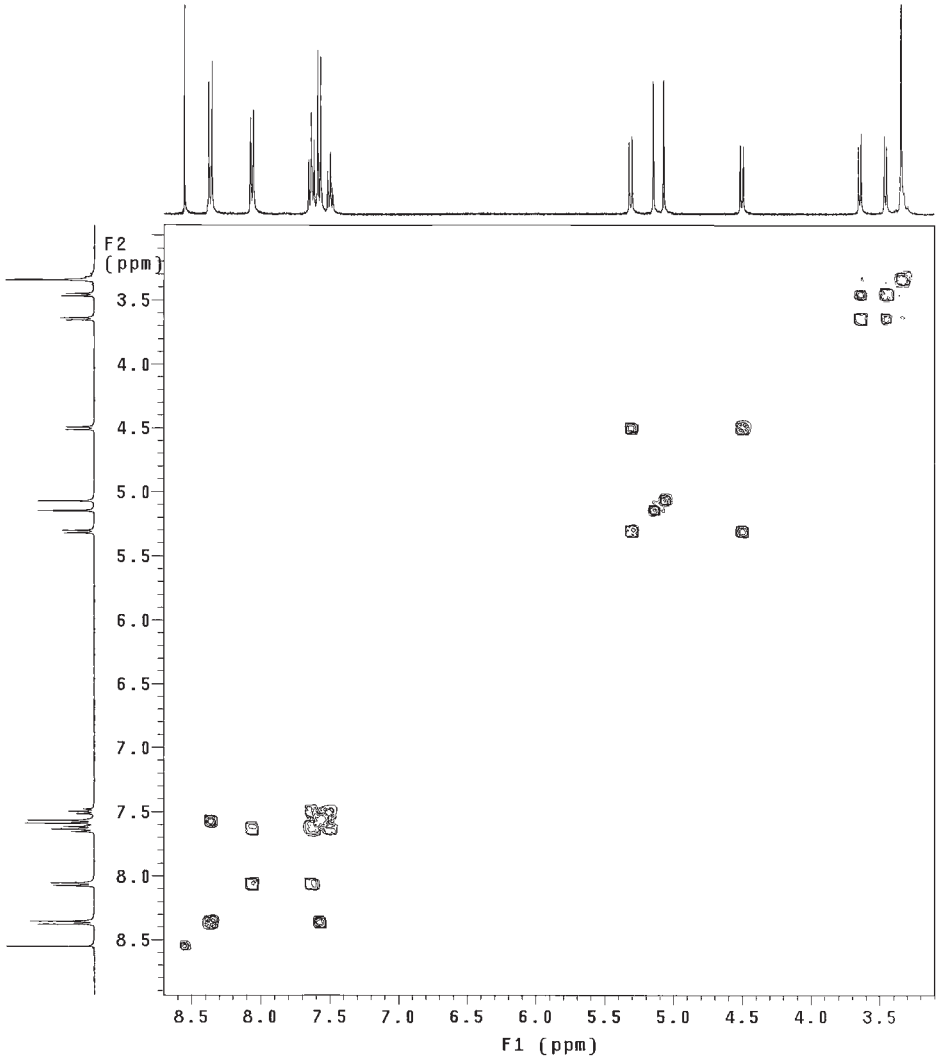


Figure 2. COSY spectrum of **6f**.

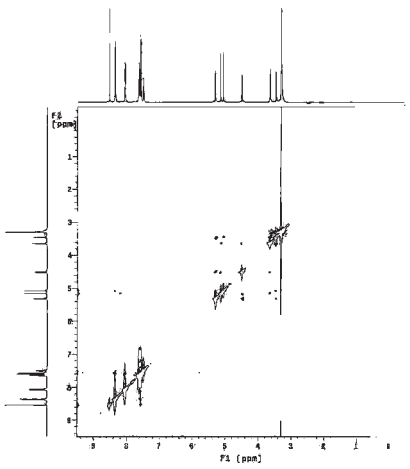
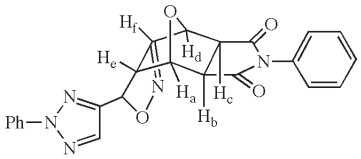


Figure 3. NOESY Spectrum of **6f**.

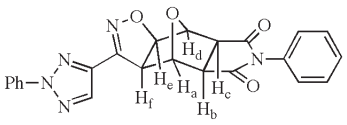
7.48 was assigned to the aromatic protons, H_d and H_a appeared as singlets, H_e, H_f, H_c, H_b appeared as doublets due to the coupling between H_e and H_f, H_c and H_b. Complete information of ^1H nmr chemical shift and coupling constants observed for compounds **6a-6f** and **7a-7f** are presented in experimental part.

In order to identify the configuration of the isoxazoline with 5,6-dehydronorcantharidin adducts **(6a-6f** and **7a-7f)**, we have studied selective ^1H-^1HCOSY spectra and NOESY spectra of the compounds. ^1H-^1HCOSY spectra show the cross peaks between resonances for H_b and H_c; H_e and H_f; NOESY spectra show that there are corresponding peaks between resonances for H_a and H_b; H_a and H_f; H_d and H_c; H_d and H_e; H_b and H_f; H_c and H_e which prove that the six protons are near in space and on the same side. In order to rationalize the configuration of adducts, we have also carried out theoretical calculation using

semi-empirical PM3 with the aid of TITAN software. The result shows that the heat of formation of structure **A** is 201.9861 kcal/mole; the heat formation of structure **B** is 200.6798 kcal/mole; so structure **B** is theoretically the more stable isomer. The calculation result combined with ^{1}H-^{1}HCOSY and NOESY spectral data gives us a definite configuration.



A heat of formation: 201.9861 kcal/mole



B heat of formation: 200.6798 kcal/mole

The compounds will be investigated for their antiviral and antibacterial as well as antitumor activity and the results will be reported when they become available.

EXPERIMENTAL

All melting points were determined on a mettler FP-5 capillary melting point apparatus and are uncorrected. The ^{1}H nmr, H-H COSY and NOESY spectra were recorded on a Warlan Inova-400 (400MHz) spectrometer. The IR spectra were measured on a Biorad FT-40 infrared spectrometer. The purity of all compounds was checked by thin-layer chromatography (tlc) on silica gel 60-F-254 precoated plates and the spots were located in using UV light or by iodine vapor. Elemental microanalyses were done using Perkin-Elmer 2400 CHNS Analyser, IR spectra were recorded with a Biorad FT-40 spectrophotometer (KBr pellets), Mass spectra were recorded on a VG ZAB-HS, spectrometer (EI, 70eV).

All solvents used were reagent grade except the dimethyl sulfoxide used for spectroscopic measurements (spectrophotometric grade). The preparation of 5,6-dehydronorcantharidin **1** was performed according to the literature [13].

"One-pot" Method for the Preparation of 3-Acetyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Phenylamide **3a-3f**.

A mixture containing 10 mmol 5,6-dehydronorcantharidin **1** and 10 mmol amine **2a** in 30 ml acetone was stirred at room temperature for about an hour. During which a large ammount of white precipitate was formed. Then 0.1g $Mn(Ac)_2$, 7ml Et_3N and 60ml $(AcO)_2O$ was added and the mixture was heated to 50-60 °C for about two hours, during which the solvent again became clear. The solution was then cooled, nonsoluble solids were filtered, and the filtrate was poured into 50 ml ice–water. The precipitated solid was collected by filtration and recrystalized from menthanol to give compound **3a**. Under similar experimental conditions the reaction of 5,6-dehydronorcantharidin **1** with 4-chloro- aniline **2b** gave 4-(4-chlorophenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione **3b**; the reaction of 5,6-dehydronorcantharidin **1** with 4-bromoaniline **2c** gave 4-(4'-bromophenyl)-10-oxa-4-aza-tricyclo [5.2.1.0^{2,6}]dec-8-ene-3,5-dione **3c**; the reaction of 5,6-dehydronorcantharidin **1** with *p*-tolylamine **2d** gave 4-*p*-tolyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione **3d**; the reaction of 5,6-dehydronorcantharidin **1** with 4-methoxy- aniline **2e** gave 4-(4'-methoxyphenyl)-10-oxa-4-aza-tricyclo [5.2.1.0^{2,6}]dec-8-ene-3,5-dione **3e**; the reaction of 5,6-dehydronorcantharidin **1** with 4-nitro- aniline **2f** gave 4-(4'-nitro-phenyl)-10- oxa-4-aza- tricyclo-[5.2.1.0^{2,6}]dec-8-ene-3,5-dione **3f**. **3a**: yield 68.8%, m. p. 162-163 °C; **3b**:yield 69.2%, m. p. 166-167 °C; **3c**:yield 70.8%, m. p. 178-179 °C **3d**:yield 59.7%, m. p. 168-169 °C; **3e**:yield 58.1%, m. p. 163-164 °C; **3f**:yield 46.9%, m. p. 177-178 °C.

General Procedure for the Preparation of the 5,6-Dehydronorcantharidinisoxazoline Adducts (**6a-6f** and **7a-7f**).

To a solution of 3-acetyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid phenylamide **3a** (1 mmole) and **4** (1 mmole) in dichloromethane (20 ml), add dried triethylamine (6 drops) and the reaction mixture was vigorously stirred at room temperature 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 recrystallized from acetone to give the compound **6a**. The synthesis of compounds **6b-6f** and **7a-7f** was performed using the same method.

exo,*exo*-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-phenyl-3-(2-phenyltriazolo-4-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**6a**).

Compound **6a** was obtained as a colorless solid, yield 95%, m.p. 277-278° C; MS (70eV) *m/z* (%) 427(M$^+$), 286(3.2), 144(3.7), 119(42.5), 91(48.0), 77(53.8), 67(100); ir (KBr): 3066, 3045 (ArH), 1779, 1714 (C=O), 1530 (C=N), 1289, 1256 (C-O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$, 400MHz): δ 8.55 (s, 1H, H-C=N), 8.07-7.19 (m, 10H, ArH), 5.30 (d, 1H, H$_e$), 5.11 (s, 1H, H$_d$), 5.04 (s, 1H, H$_a$), 4.49 (d, 1H, H$_f$), 3.59 (d, 1H, H$_c$), 3.40 (d, 1H, H$_b$).

Anal. Calcd. for $C_{23}H_{17}N_5O_4$: C, 64.64; H , 3.98; N, 16.39. Found: C, 64.42; H, 3.87; N, 16.22.

exo,*exo*-6-(4-Chlorophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(2-phenyltriazolo-4-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**6b**).

Compound **6b** was obtained as a colorless solid, yield 87%, m.p. 289-291 °C; MS (70eV) *m/z*(%) 462(M$^+$), 226(10.3), 166 (19), 131 (11.5), 127 (10.7), 118 (8.2), 91 (29.0), 77 (22.4), 66 (100) ; ir (KBr): 3103, 3040 (ArH), 1783, 1705 (C=O), 1594 (C=N), 782 (C-Cl), 1270, 1243 (C-O-C) cm^{-1}; ^{1}H nmr (DMSO-d$_6$, 400MHz): δ 8.55 (s, 1H, H-C=N), 8.07-7.25 (m, 9H, ArH), 5.30 (d, 1H, H$_e$), 5.11 (s, 1H, H$_d$), 5.03 (s, 1H, H$_a$), 4.49(d, 1H, H$_f$), 3.59 (d 1H, H$_c$), 3.40 (d, 1H, H$_b$).

Anal. Calcd. for $C_{23}H_{16}N_5O_4Cl$: C, 59.74; H, 3.46; N, 15.15. Found: C, 59.56; H, 3.39; N, 15.18.

exo,exo-6-(4-Bromophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(2-phenyltriazolo-4-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**6c**).

Compound **6c** was obtained as a colorless solid, yield 91%, m.p. 278-279 °C; MS (70eV) *m/z*(%) 506(M^+), 239(14.5), 136 (23.7) ,127 (7.2), 91 (43.8), 77 (45.4), 68 (100) cm^{-1} ; IR (KBr): 3078, 3056 (ArH), 1785, 1722 (C=O) 1595 (C=N), 1256 , 1249 (C-O) ; ^1H nmr (DMSO-d_6, 400MHz): δ 8.55 (s, 1H, H-C=N), 8.07-7.18 (m, 9H, ArH), 5.29 (d, *J*=8.40 Hz, 1H, H_e), 5.11 (s, 1H, H_d), 5.04 (s, 1H, H_a), 4.49 (d, *J*=8.40 Hz, 1H, H_f), 3.59 (d, *J*=7.20 Hz, 1H, H_c), 3.40 (d, *J*=7.20 Hz, 1H, H_b).

Anal. Calcd. for $C_{23}H_{16}N_5O_4Br$: C, 54.55; H, 3.16; N, 13.83. Found: C, 54.61; H ,3.21; N, 13.90.

exo,exo-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(2-phenyltriazolo-4-yl)-6-(*p*-tolyl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**6d**).

Compound **6d** was obtained as a colorless solid, yield 71%, m.p. 275-276 °C; MS (70eV) *m/z*(%) 441(M^+), 368 (10.4), 223 (13.6), 104 (59.7) ,102 (21.3), 91 (32.8), 77 (36.0), 68 (100); IR (KBr): 3082, 3056 (ArH), 1784, 1749 (C=O), 1596 (C=N), 1278, 1266 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6, 400MHz): δ 8.55 (s, 1H, H-C=N), 8.07-7.07 (m, 9H, ArH), 5.29 (d, 1H, H_e), 5.10 (s, 1H, H_d), 5.04 (s, 1H, H_a), 4.48 (d, 1H, H_f), 3.57(d,1H, H_c), 3.38 (d, 1H, H_b), 2.33 (-CH_3).

Anal. Calcd. for $C_{24}H_{19}N_5O_4$: C 65.31, H 4.31, N 15.87. Found: C 65.34, H 4.29, N 15.73.

exo,exo-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-(4-methoxyphenyl)-3-(2-phenyltriazolo-4-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**6e**).

Compound **6e** was obtained as a colorless solid, yield 68%, m.p. 268-269 °C; MS (70ev) *m/z*(%) 457(M^+), 359(11.7), 347 (18.3), 148 (49.4), 123 (46.8) ,103 (30.6), 91 (15.5), 77 (38.2), 68(100); IR (KBr): 3080, 3055 (Ar-H), 1784, 1746 (C=O), 1596 (C=N), 1252, 1266 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6, 400MHz): δ 8.55 (s, 1H, H-C=N), 8.07-7.06 (m, 9H, ArH), 5.29 (d, 1H, H_e), 5.10 (s, 1H, H_d), 5.02 (s, 1H, H_a), 4.48 (d,1H, H_f), 3.57 (d, 1H, H_c), 3.38 (d,1H, H_b), 3.77(-OCH_3).

Anal. Calcd. for $C_{24}H_{19}N_5O_5$: C, 63.02; H,4.16; N ,15.32. Found: C, 63.14; H, 4.08; N,15.17.

exo,exo-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro6-(4-nitrophenyl)-3-(2-phenyltriazolo-4-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**6f**).

Compound **6f** was obtained as a yellow solid, yield 62%, m.p. 266-268 °C; MS (70eV) *m/z*(%), 472(M^+), 221(34.4) 208(28.7), 138(20.5), 127(7.3), 110(47.5), 91(36.6), 77(21.3), 68(100); IR (KBr): 3089, 3055 (ArH), 1755, 1723(C=O), 1537(C=N), 1299, 1240(C-O) cm^{-1}; ^1H nmr (DMSO-d_6, 400MHz): δ 8.55 (s, 1H, H-C=N), 8.39-7.48 (m, 9H, ArH), 5.31 (d, 1H, H_e), 5.15 (s, 1H, H_d), 5.07 (s, 1H, H_a) 4.51(d, 1H, H_f), 3.65(d, 1H, H_c), 3.46 (d, 1H, H_b).

Anal. Calcd. for $C_{23}H_{16}N_6O_6$: C, 58.47; H, 3.39; N,17.80. Found: C, 54.39; H, 3.37; N, 17.64.

exo,exo-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-phenyl-3-(quinoxaline-2-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**7a**).

Compound **7a** was obtained as a colorless solid, yield 68%, m.p. 300 °C; MS (70eV) *m/z*(%) 413(M^+), 241 (11.3), 197 (18.8), 155 (49.7), 129 (46.8), 103 (30.6), 91 (15.7), 77 (38.2), 68 (100); IR (KBr): 3081, 3056 (ArH) 1783, 1747(C=O), 1598 (C=N), 1252, 1265 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6, 400MHz): δ 9.49 (s, 1H, H-C=N), 8.21-7.23 (m, 10H, ArH), 5.47 (s, 1H, H_d), 5.32 (s, 1H, H_a), 5.17 (d, 1H, H_e), 4.39 (d, 1H, H_f), 3.41 (d, 1H, H_c), 3. 19 (d, 1H, H_b).

Anal. Calcd. for $C_{23}H_{17}N_4O_4$: C, 66.83; H, 4.12; N, 13.56. Found: C, 66.67; H, 4.14; N, 13.48.

exo,exo-6-(4-Chlorophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(quinoxaline-2-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**7b**).

Compound **7b** was obtained as a colorless solid, yield 70%, m.p. 300 °C; MS (70eV) *m/z*(%) 448(M^+), 450(M^++2), 276 (23.1), 155 (49.4), 124 (11.6), 119 (43.2), 103 (33.8), 91 (18.2), 77 (35.5), 68 (100); IR (KBr) : 3080 3055 (ArH), 1782, 1743 (C=O), 1598 (C=N), 1257, 1264 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6, 400MHz): δ 9.49 (s, 1H, H-C=N), 8.21-7.23 (m, 10H, ArH), 5.48 (s, 1H, H_d), 5.32 (s, 1H, H_a), 5.17(d, 1H, H_e), 4.39(d, 1H, H_f), 3.41(d, 1H, H_c), 3.19 (d, 1H, H_b).

Anal. Calcd. for $C_{23}H_{16}N_4O_4Cl$: C, 61.61; H, 3.57; N, 14.29. Found: C, 61.48; H, 3.52; N, 14.35.

exo,exo-6-(4-Bromophenyl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(quinoxaline-2-yl)-pyrrolo[3,4-f]-1,2-benzisoxazole (**7c**).

Compound **7c** was obtained as a colorless solid, yield 78%, m.p. 300 °C; MS (70eV) *m/z*(%) 493(M^++2), 491(M^+), 320 (11.7), 241 (11.0), 155 (49.5), 119 (43.3), 103 (28.2), 91 (34.7), 77 (22.8), 68 (100); IR (KBr) :3086 3059 (ArH), 1783, 1743(C=O), 1597(C=N), 1256, 1263(C-O) cm^{-1}, ^1H nmr (DMSO-d_6, 400MHz): δ 9.49 (s, 1H, H-C=N), 8.21-7.23 (m, 10H, ArH), 5.47 (s, 1H, H_d), 5.32 (s, 1H, H_a), 5.17 (d,1H, H_e), 4. 39(d, 1H, H_f), 3.41(d, 1H, H_c), 3.19 (d, 1H, H_b).

Anal. Calcd. for $C_{23}H_{16}N_4O_4Br$: C, 56.21; H, 3.26; N, 13.03. Found: C, 56.23; H, 3.32; N, 13.04.

exo,exo-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-(4-*p*-tolyl)-3-(quinoxaline-2-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**7d**).

Compound **7d** was obtained as a colorless solid, yield 69%, m.p. 300 °C; MS (70eV) *m/z* (%) 427(M^+), 255 (13.4), 241 (13.6), 197 (18.8), 155 (44.7), 133 (23.1), 119 (46.7), 103 (35.4), 91 (14.1), 77 (38.5), 68 (100); IR $(KBr)_v$: 3081, 3056 (ArH), 1783, 1747 (C=O), 1598 (C=N), 1252, 1265 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6, 400MHz): δ 9.49 (s, 1H, H-C=N), 8.21-7.26 (m, 10H, ArH), 5.47 (s, 1H, H_d), 5.32 (s, 1H, H_a), 5.17 (d,1H, H_e), 4.39 (d, 1H, H_f), 3.41(d, 1H, H_c), 3.19 (d, 1H, H_b), 2.36 (-CH_3).

Anal. Calcd. for $C_{24}H_{19}N_4O_4$: C, 67.45; H, 4.45; N, 13.11. Found: C, 67.40; H, 4.29; N, 13.04.

exo,exo-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-(4-methoxyphenyl)-3-(quinoxaline-2-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**7e**).

Compound **7e** was obtained as a colorless solid, yield 66%, m.p. 300 °C; MS (70eV) *m/z*(%) 443(M^+), 270 (18.4), 241 (13.5), 197 (18.0), 155 (47.2), 149 (21.8), 119 (46.2), 103 (37.3), 91 (16.7), 77 (33.6), 68 (100) ;IR (KBr) : 3081, 3056 (ArH), 1783, 1747 (C=O), 1598 (C=N) , 1252, 1265 (C-O) cm^{-1}, ^1H nmr (DMSO-d_6, 400MHz): δ 9.50 (s, 1H, H-C=N), 8.21-7.23 (m, 10H, ArH), 5.48 (s, 1H, H_d), 5.32 (s, 1H, H_a), 5.17(d, 1H, H_e), 4.39(d, 1H, H_f), 3.41(d, 1H, H_c), 3.19(d, 1H, H_b), 3.77 (-OCH_3).

Anal. Calcd. for $C_{24}H_{19}N_4O_5$: C, 65.01; H, 4.30; N, 12.64. Found: C, 65.08; H, 4.29; N, 12.54.

exo,exo-4,8-Epoxy-3a,4,4a,7a,8,8a-hexahydro-6-(4-nitrophenyl)-3-(quinoxaline-2-yl)-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**7f**).

Compound **7f** was obtained as a yellow solid, yield 66%, m.p.

300 °C; MS (70eV) *m/z* (%) 443 (M^+), 270 (18.0), 241 (13.1), 197(18.2), 155 (47.7), 149 (21.3), 119 (46.2), 103 (37.5), 91 (16.4), 77 (33.2), 68 (100) IR (KBr): 3081, 3056 (ArH), 1783, 1747 (C=O), 1598 (C=N), 1252, 1265 (C-O) cm^{-1}, ^1H nmr (DMSO-d_6, 400MHz): δ 9.51 (s, 1H, H-C=N), 8.26-7.28 (m, 10H, ArH), 5.48 (s, 1H, H_d), 5.33 (s, 1H, H_a), 5.1 8(d,1H, H_e), 4.39 (d, 1H, H_f), 3.41(d,1H, H_c), 3.19 (d,1H, H_b).

Anal. Calcd. for $C_{23}H_{16}N_4O_6$: C, 60.39; H, 3.50; N, 15.32. Found: C, 60.26; H, 3.58; N, 15.30.

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