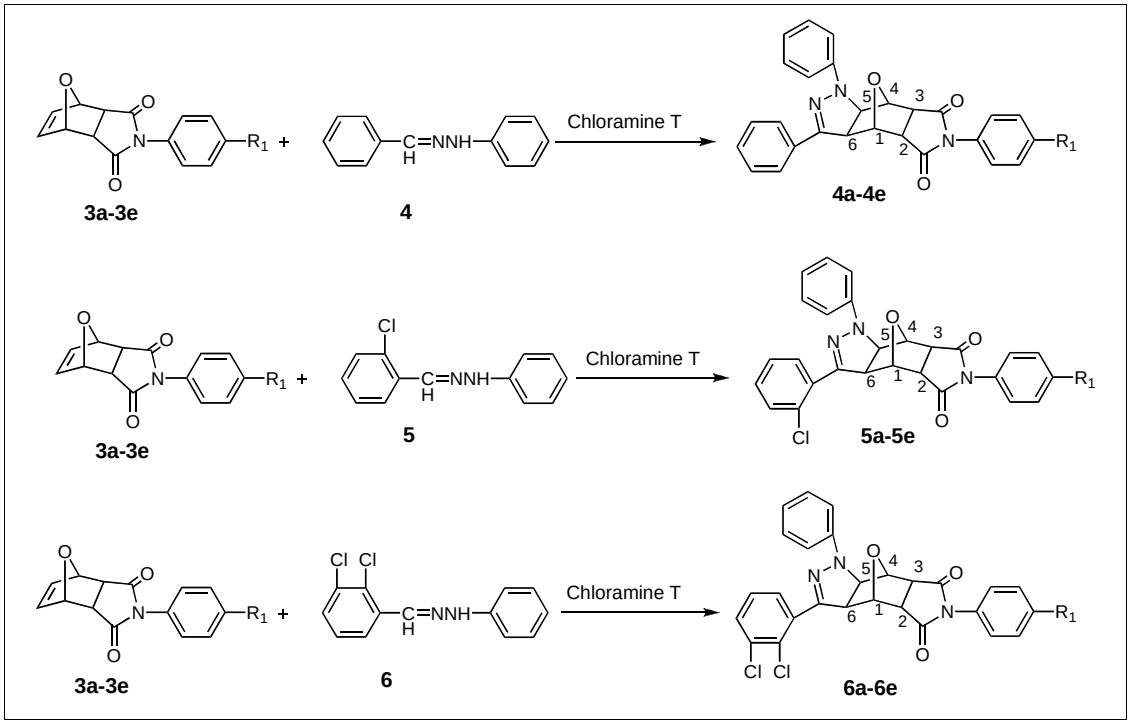
Synthesis of Novel Pyrazole-linked Norcantharidin Derivatives of Substituted Aromatic Amines with Efficient 1,3-Dipolar Cycloaddition

Liping Deng and Yongzhou Hu*

Zhejiang University, Department of Medicinal Chemistry, School of Pharmaceutical Science Hangzhou 310031, P.R.China

Received February 28, 2006

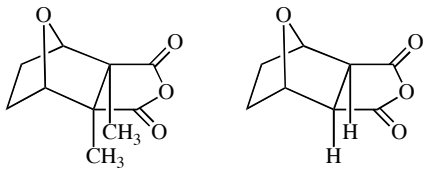


Highly efficient, practical and convient synthesis of fifteen compounds by the [3+2] 1,3-dipolar cycloaddition reaction of norcantharidin derivatives of substituted aromatic amines with three hydrazines in the presence of Chloramine-T.

J. Heterocyclic Chem., **43**, 1715 (2006).

Introduction.

Cantharidin (**Figure 1**), the principle active ingredient of Mylabris, a compound that has been used in China as a medicinal agent for 2000 years and for the treatment of cancer, particularly hepatoma [1]. Cantharidin is potentially attractive for the treatment of leukemia because it does not cause myelosuppression [2,3] and is effective against cells exerting the multidrug resistance phenotype [4]. Norcantharidin (NCTD **Figure 1**), the demethylated cantharidin derivative that also has clinical potential, is protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A) inhibitors [5]. Pyrazoles [6,7] have been the subject of chemical and biological studies due to their interesting pharmacology including antipyretic, analgesic, antiinflammatory potential herbicidal, fungicidal and leishmanicidal [8-11] properties. Stimulated by these findings, we combine pyrazoles with norcantharidin derivatives in one single molecule through 1,3-dipolar cycloaddition and we have successfully synthesized some compounds before[12]. With our sustained interest in the



Cantharidin **Norcantharidin**

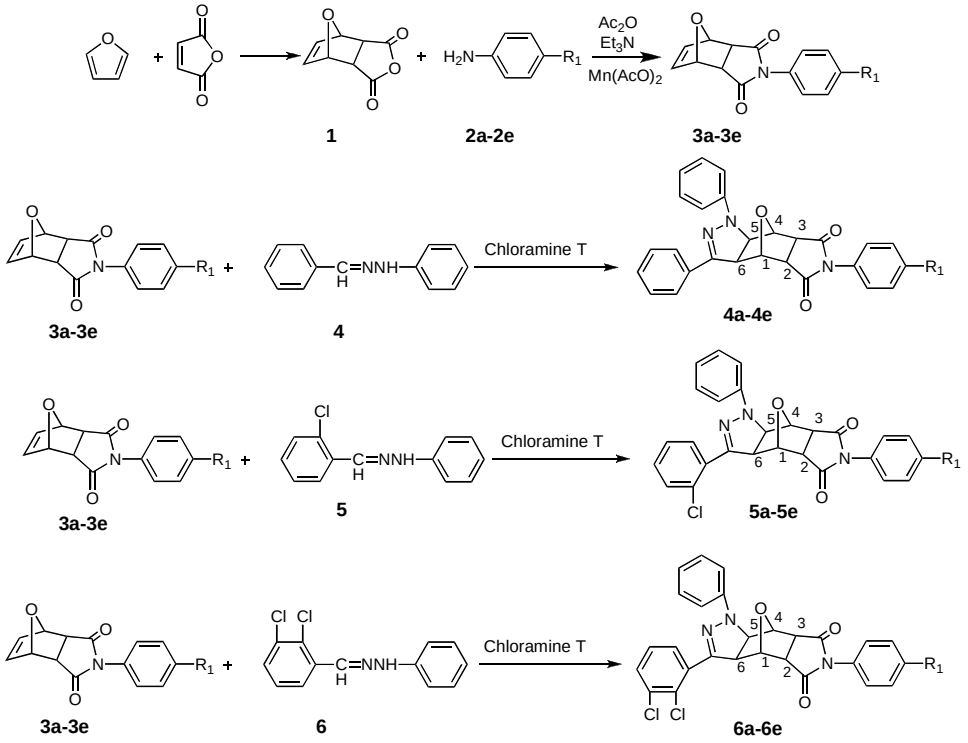
Figure 1

synthesis of norcantharidin derivatives we have achieved a facile 1,3-dipolar cycloaddition method by the use of chloramine-T. Chloramine-T,which is a versatile reagent in organic synthesis[13],was used in this article to generate nitrilimines *in situ* from hydrazines. Such type of compounds(**Table 1**) with versatile activities may be of interest in chemistry, biochemistry and pharmacology.

Table 1

Compound	R_1	Time hours	Mp (°C)	Yield %	Molecular Formula	Analysis % Calcd./Found C	H	N
4a	H	7	287	85.2	$C_{27}H_{21}N_3O_3$	74.47	4.86	9.65
						74.45	4.88	9.62
4b	F	4	279	93.2	$C_{27}H_{20}FN_3O_3$	71.51	4.45	9.27
						71.52	4.48	9.23
4c	Cl	3	294	95.1	$C_{27}H_{20}ClN_3O_3$	69.01	4.29	8.94
						69.00	4.29	8.93
4d	Br	5	272	89.7	$C_{27}H_{20}BrN_3O_3$	63.05	3.92	8.17
						63.04	3.92	8.15
4e	CH_3	8	283	72.4	$C_{28}H_{23}N_3O_3$	74.82	5.16	9.35
						74.80	5.17	9.34
5a	H	4	260	85.2	$C_{27}H_{20}ClN_3O_3$	69.01	4.29	8.94
						68.99	4.30	8.92
5b	F	5	238	83.6	$C_{27}H_{19}ClFN_3O_3$	66.46	3.93	8.61
						66.45	3.94	8.60
5c	Cl	4.5	267	85.4	$C_{27}H_{19}Cl_2N_3O_3$	64.30	3.80	8.33
						64.31	3.81	8.31
5d	Br	4	272	79.3	$C_{27}H_{19}BrClN_3O_3$	59.09	3.49	7.66
						59.08	3.50	7.65
5e	CH_3	6	243	62.6	$C_{28}H_{22}ClN_3O_3$	69.49	4.58	8.68
						69.48	4.57	8.66
6a	H	8	296	91.7	$C_{27}H_{19}Cl_2N_3O_3$	64.30	3.80	8.33
						64.29	3.82	8.31
6b	F	6	275	92.5	$C_{27}H_{18}C_{l2}FN_3O_3$	62.08	3.47	8.04
						62.08	3.48	8.02
6c	Cl	5	253	87.4	$C_{27}H_{18}Cl_3N_3O_3$	60.19	3.37	7.80
						60.18	3.39	7.77
6d	Br	3	250	95.3	$C_{27}H_{18}BrCl_2N_3O_3$	55.60	3.11	7.20
						55.61	3.11	7.19
6e	CH_3	7	249	76.5	$C_{28}H_{21}Cl_2N_3O_3$	64.87	4.08	8.11
						64.87	4.09	8.10

Scheme 1



a R_1=H;b R_1= F;c R_1=Cl;d R_1=Br; e R_1=CH_3;

Results and Discussion.

The precursor 5,6-dehydronorcantharidian derivatives **3a-3e** was synthesized by "one pot" method in good yield[12]

In this paper, 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 reacted with substituated phenylamine **2a-2e** to give compounds **3a-3e**, after that, we carried out the [3+2] cycloaddition of **3a-3e** with **4**, **5**, **6** in the presence of chloramine-T respectively to obtain the target compounds **4a-4e**, **5a-5e, 6a-6e** efficiently.

In order to identify the configuration of the pyrazoline with norcantharidin adducts (**4a-4e**, **5a-5e, 6a-6e**), we have studied selective ^{1}H-^{1}HCOSY spectra, NOESY spectra of the compounds(take the example of **4a**). The exo-adduct (**4a-4e**, **5a-5e, 6a-6e**) showed characteristic coupling for the bridge-head proton in the 400 M Hz nmr spectrum which indicate that the protons involved are attached to the vicinal proton, ^{1}H-^{1}HCOSY spectrum showed cross peaks between C_2-H and C_3-H; between C_5-H and C_6-H; NOESY spectrum showed cross peaks between C_1-H and C_2-H; C_1-H and C_4-H; C_2-H and C_3-H; C_3-H and C_4-H; C_2-H and C_6-H; between C_3-H and C_5-H which prove that the six protones are near in space and on the same side. The Diels-Alder adduct 5,6-dehydronorcantharidin of furan with maleic anhydride has been shown to have the exo configuration exclusively; the endo isomer has never been reported [11]. This information combined with ^{1}H-^{1}HCOSY spectra and NOESY spectra data give us a definite configuration as we have proved before [12].

EXPERIMENTAL

Melting points were obtained on a B-540 Bűchi melting point apparatus and were uncorrected. ^{1}Hnmr spectra were recorded on a Brucker AM-400 M Hz spectrometer with $SiMe_4$ as the internal standard in $CDCl_3$. Mass Spectra were made with a HP5989B analyzer. Element analyses were performed on a EA-1110 instrument.

"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. [12]

General Procedure for the Preparation of the 5,6-Dehydronorcantharidinisoxazoline Adducts (**4a-4e,5a-5e,6a-6e**).

To a solution of 3-acetyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid phenylamide **3a** (1 mmole) and **4** *N*-Benzylidene-*N*'-phenyl-hydrazine (1mmole) in ethanol (20 ml), add chloramine T (1.2mmole) and the reaction mixture was refluxed in ethanol for 3-8 hours which were monitored by thin-layer chromatography. Then washed with water (30 ml) and extracted with dichloromethane (30 ml). The extracts were dried over anhydrous sodium sulfate, concentrated *in vacuum* and the residue was recrystallized from methol to give the compound **4a**. The synthesis of compounds **4b-4e, 5a-5e, 6a-6e** was performed using the same method.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a,8,8a-hexahydro-1,6-diphenyl-3-(phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**4a**)

This compound was obtained as yellow crystals, yield 85.2%, m.p. 287° C; ir (potassium bromide): 3473(N-C=O), 3064 (ArH), 1714 (C=O), 1597 (C=N), 1189 (C-O-C) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.76-6.91 (M, 15H, Ar-H), 5.34 (s, 1H, C_4-H) 5.27 (s, 1H, C_1-H) 4.66-4.64 (d, J=9.60 Hz, 1H, C_5-H), 4.16-4.14 (d, J=9.60 Hz, 1H, C_6-H), 3.39-3.37 (d, J=7.20 Hz, 1H, C_3-H), 3.34-3.32 (d, J=7.20 Hz, 1H, C_2-H). ms (70ev): m/z 435 (M^+).

Anal. Calcd. for $C_{27}H_{21}N_3O_3$: C, 74.47; H, 4.86; N, 9.65. found: C, 74.45; H, 4.88; N, 9.62.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a,8,8a-hexahydro-1-(phenyl)-3-(phenyl)-6-(4-fluorophenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**4b**)

This compound was obtained as yellow crystals, yield 93.2%, m.p. 279° C; ir (potassium bromide): 3474(N-C=O), 3058 (ArH), 1717 (C=O), 1598 (C=N), 1203 (C-O-C) cm^{-1}; ^{1}H nmr ($CDCl_3$)δ:7.77-6.91 (M, 14H, Ar-H), 5.33 (s, 1H, C_4-H), 5.27 (s, 1H, C_1-H), 4.66-4.64 (d, J=9.60 Hz, 1H, C_5-H), 4.16-4.14 (d, J=9.60 Hz, 1H, C_6-H), 3.39-3.37 (d, J=7.20 Hz, 1H, C_3-H), 3.34-3.32 (d, J=7.20 Hz, 1H, C_2-H). ms(70ev): m/z 453 (M^+).

Anal. Calcd. for $C_{27}H_{20}FN_3O_3$: C, 71.51; H, 4.45; N, 9.27. found: C, 71.52; H, 4.48; N, 9.23.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a,8,8a-hexahydro-1-(phenyl)-3-(phenyl)-6-(4-Chlorophenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**4c**)

This compound was obtained as yellow crystals, yield 95.1%, m.p. 294° C; ir (potassium bromide): 3482(N-C=O), 3057(ArH), 1717 (C=O), 1597 (C=N), 1202 (C-O-C) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.76-6.90 (M, 14H, Ar-H), 5.33 (s, 1H, C_4-H), 5.26 (s, 1H, C_1-H), 4.66-4.64 (d, J=9.20 Hz, 1H, C_5-H), 4.16-4.14 (d, J=9.20 Hz, 1H, C_6-H), 3.39-3.37 (d, J=7.20 Hz, 1H, C_3-H), 3.35-3.33 (d, J=7.20 Hz, 1H, C_2-H). ms (70ev): m/z 471 (M^++2), 469 (M^+).

Anal. Calcd. for $C_{27}H_{20}ClN_3O_3$: C, 69.01; H, 4.29; N, 8.94. found: C, 69.00; H, 4.29; N, 8.93.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a,8,8a-hexahydro-1-(phenyl)-3-(phenyl)-6-(4-Bromophenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**4d**)

This compound was obtained as yellow crystals, yield 89.7%, m.p. 272° C; ir (potassium bromide): 3480 (N-C=O), 3062 (ArH), 1716 (C=O), 1597 (C=N), 1206 (C-O-C) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.77-6.92 (M, 14H, Ar-H), 5.34 (s, 1H, C_4-H), 5.26 (s, 1H, C_1-H), 4.66-4.64 (d, J=9.20 Hz,1H, C_5-H), 4.15-4.13 (d, J=9.20 Hz, 1H, C_6-H), 3.40-3.38 (d, J=7.20 Hz, 1H, C_3-H), 3.34-3.32 (d, J=7.20 Hz, 1H, C_2-H). ms (70ev): m/z 516 (M^++2), 514 (M^+).

Anal. Calcd. for $C_{27}H_{20}BrN_3O_3$: C, 63.05; H,3.92; N, 8.17; found: C, 63.04; H, 3.92; N, 8.15.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a,8,8a-hexahydro-1-(phenyl)-3-(phenyl)-6-(p-tolyl)-(3aa,4b,4aa,7aa,8b,8aa) (**4e**)

This compound was obtained as yellow crystals, yield 72.4%, m.p. 283° C; ir (potassium bromide): 3557(N-C=O), 3022 (ArH), 1712 (C=O), 1597 (C=N), 1208 (C-O-C) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ:

7.77-6.89 (M, 14H, Ar-H), 5.33 (s, 1H, C_4-H), 5.26 (s, 1H, C_1-H), 4.65-4.63(d, J=9.20 Hz,1H, C_5-H), 4.15-4.13 (d, J=9.20 Hz, 1H, C_6-H), 3.38-3.36 (d, J=7.20 Hz, 1H, C_3-H), 3.33-3.31 (d, J=7.20 Hz, 1H, C_2-H), 2.37 (s,3H, CH_3). ms (70ev): m/z 449 (M^+).

Anal. Calcd. for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. found: C, 74.80; H, 5.17; N, 9.34.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2-Chlorophenyl)-6-(phenyl)-(3aa, 4b,4aa,7aa,8b,8aa) (**5a**)

This compound was obtained as yellow crystals, yield 85.2%, m.p. 260° C; ir (potassium bromide): 3476(N-C=O), 3062 (ArH), 1710 (C=O), 1597 (C=N), 1229 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.81-6.96 (M, 14H, Ar-H), 5.31 (s, 1H, C_4-H), 5.01 (s, 1H, C_1-H) , 4.65 (s, 2H, C_5-H, C_6-H), 3.30 (s, 2H, C_3-H, C_2-H). ms (70ev): m/z 471 (M^++2), 469 (M^+).

Anal. Calcd. for $C_{27}H_{20}ClN_3O_3$: C, 69.01; H, 4.29; N, 8.94. found: C, 68.99; H, 4.30; N, 8.92.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2-Chlorophenyl)-6-(4-fluoro-phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**5b**)

This compound was obtained as yellow crystals, yield 83.6%, m.p. 238° C; ir (potassium bromide): 3474(N-C=O), 3045 (ArH), 1714 (C=O), 1598 (C=N), 1227 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.79-6.96 (M, 13H, Ar-H), 5.30 (s, 1H, C_4-H), 5.00 (s, 1H, C_1-H), 4.64 (s, 2H, C_5-H, C_6-H), 3.30 (s, 2H, C_3-H, C_2-H). ms (70ev): m/z 489 (M^++2), 487 (M^+).

Anal. Calcd. for $C_{27}H_{19}ClFN_3O_3$: C, 66.46; H,3.93; N, 8.61. found: C, 66.45; H, 3.94; N, 8.60.

4,8-Epoxypyrrolo[3,4-f]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2-Chlorophenyl)-6-(4-Chloro-phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**5c**)

This compound was obtained as yellow crystals, yield 85.4%, m.p. 267° C; ir (potassium bromide): 3507(N-C=O), 3065 (ArH), 1713 (C=O), 1597 (C=N), 1237 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.76-6.97 (M, 13H, Ar-H), 5.30 (s, 1H, C_4-H), 5.00 (s, 1H, C_1-H), 4.65 (s, 2H, C_5-H, C_6-H), 3.30 (s, 2H, C_3-H, C_2-H). ms (70ev): m/z 508 (M^++4), 506 (M^++2), 505 (M^++1) 504 (M^+).

Anal. Calcd. for $C_{27}H_{19}Cl_2N_3O_3$: C, 64.30; H, 3.80; N, 8.33. found: C, 64.31; H, 3.81; N, 8.31.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2-Chlorophenyl)-6-(4-Bromo-phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**5d**)

This compound was obtained as yellow crystals, yield 79.3%, m.p. 272° C; ir (potassium bromide): 3473(N-C=O), 3047 (ArH), 1715 (C=O), 1598 (C=N), 1226 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.76-6.92 (M, 13H, Ar-H), 5.30 (s, 1H, C_4-H), 5.01 (s, 1H, C_1-H), 4.65 (s, 2H, C_5-H, C_6-H), 3.29 (s, 2H, C_3-H, C_2-H). ms (70ev): m/z 552 (M^++4), 550 (M^++2), 548 (M^+).

Anal. Calcd. for $C_{27}H_{19}BrClN_3O_3$: C, 59.09; H, 3.49; N, 7.66. found: C, 59.08; H, 3.50; N, 7.65.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2-Chlorophenyl)-6-(p-tolyl)-(3aa, 4b,4aa,7aa,8b,8aa) (**5e**)

This compound was obtained as yellow crystals, yield 62.6%, m.p. 243° C; ir (potassium bromide): 3550(N-C=O), 3043 (ArH), 1711 (C=O), 1597 (C=N), 1207 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.76-6.97 (M, 13H, Ar-H), 5.29 (s, 1H, C_4-H), 5.00 (s, 1H, C_1-H), 4.64 (s, 2H, C_5-H, C_6-H), 3.28 (s, 2H, C_3-H, C_2-H), 2.37 (s, 3H, CH_3). ms (70ev): m/z 485 (M^++2), 483 (M^+).

Anal. Calcd. for $C_{28}H_{22}ClN_3O_3$: C, 69.49; H, 4.58; N, 8.68. found: C, 69.48; H, 4.57; N, 8.66.

4,8-Epoxypyrrolo[3,4-f]indazole-5,7-(1H,6H)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2,3-Dichlorophenyl)-6-(phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**6a**)

This compound was obtained as yellow crystals, yield 91.7%, m.p. 296° C; ir (potassium bromide): 3476(N-C=O), 3062 (ArH), 1710 (C=O), 1598 (C=N), 1210 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.65-6.94 (M, 13H, Ar-H), 5.31 (s, 1H, C_4-H), 5.00 (s, 1H, C_1-H), 4.67-4.65 (M, 2H, C_5-H, C_6-H), 3.31-3.29 (M, 2H, C_3-H, C_2-H). ms (70ev): m/z 508 (M^++4), 506 (M^++2), 504 (M^+).

Anal. Calcd. for $C_{27}H_{19}Cl_2N_3O_3$: C, 64.30; H, 3.80; N, 8.33. found: C, 64.29; H, 3.82; N, 8.31.

4,8-Epoxypyrrolo[3,4-f]indazole-5,7-(1H,6H)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2,3-Dichlorophenyl)-6-(4-fluoro-phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**6b**)

This compound was obtained as yellow crystals, yield 92.5%, m.p. 275° C; ir (potassium bromide): 3474(N-C=O), 3045 (ArH), 1709 (C=O), 1598 (C=N), 1206 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.66-6.94 (M, 12H, Ar-H), 5.31 (s, 1H, C_4-H), 4.95 (s, 1H, C_1-H),4.67- 4.65 (M, 2H, C_5-H, C_6-H), 3.30-3.29 (M, 2H, C_3-H, C_2-H). ms (70ev): m/z 526 (M^++4), 524 (M^++2), 522 (M^+).

Anal. Calcd. for $C_{27}H_{18}C_{l2}FN_3O_3$: C, 62.08; H,3.47; N, 8.04. found: C, 62.08; H, 3.48; N, 8.02.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2,3-Dichlorophenyl)-6-(4-Chloro-phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**6c**)

This compound was obtained as yellow crystals, yield 87.4%, m.p. 253° C; ir (potassium bromide): 3482(N-C=O), 3065 (ArH), 1703 (C=O), 1597 (C=N), 1201 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.66-6.93 (M, 12H, Ar-H), 5.30 (s, 1H, C_4-H), 4.94 (s, 1H, C_1-H),4.69-4.63 (M, 2H, C_5-H, C_6-H), 3.32-3.28 (M, 2H, C_3-H, C_2-H). ms (70ev): m/z 544 (M^++6), 542 (M^++4), 540 (M^++2), 538 (M^+).

Anal. Calcd. For $C_{27}H_{18}Cl_3N_3O_3$: C, 60.19; H, 3.37; N, 7.80. found: C, 60.18; H, 3.39; N, 7.77.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a,7a, 8,8a-hexahydro-1-(phenyl)-3-(2,3-Dichlorophenyl)-6-(4-Bromo-phenyl)-(3aa,4b,4aa,7aa,8b,8aa) (**6d**)

This compound was obtained as yellow crystals, yield 95.3%, m.p. 250° C; ir (potassium bromide): 3473(N-C=O), 3047 (ArH), 1704 (C=O), 1597 (C=N),1202 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.66-6.93 (M, 12H, Ar-H), 5.31 (s, 1H, C_4-H), 5.00 (s, 1H, C_1-H), 4.69-4.64 (M, 2H, C_5-H, C_6-H), 3.31-3.28 (M, 2H, C_3-H, C_2-H). ms (70ev): m/z 587 (M^++4), 586 (M^++3), 585 (M^++2), 583 (M^+).

Anal. Calcd. for $C_{27}H_{18}BrCl_2N_3O_3$: C, 55.60; H, 3.11; N, 7.20. found: C, 55.61; H, 3.11; N, 7.19.

4,8-Epoxypyrrolo[3,4-*f*]indazole-5,7-(1*H*,6*H*)-dione,3a,4,4a, 7a,8,8a-hexahydro-1-(phenyl)-3-(2,3-Dichlorophenyl)-6-(*p*-tolyl)-(3aa,4b,4aa,7aa,8b,8aa) (**6e**)

This compound was obtained as yellow crystals, yield 76.5%, m.p. 249° C; ir (potassium bromide): 3556(N-C=O), 3043 (ArH), 1702 (C=O),1597 (C=N),1205 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ:

7.65-6.92 (M, 12H, Ar-H), 5.30 (s, 1H, C_4-H), 4.94 (s, 1H, C_1-H), 4.68-4.62 (M, 2H, C_5-H, C_6-H),3.31-3.28 (M, 2H, C_3-H, C_2-H), 2.37 (s,3H, CH_3). ms (70ev): m/z 522 (M^++4), 520 (M^++2), 518 (M^+).

Anal. Calcd. for $C_{28}H_{21}Cl_2N_3O_3$: C, 64.87; H, 4.08; N, 8.11. found: C, 64.87; H, 4.09; N, 8.10.

REFERENCES AND NOTES

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

[2] X.-H Liu, I Blazsek, M. Comisso, S. Legras, S.Marion and P. Quittet, *Eur J Cancer*., **31A**, 953 (1995).

[3] S.N. Yi, J. Wass, P. Vincent and H. Iland, *Leuk Res*., **15**, 883, (1991).

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

[5] A. McCluskey, S.P. Ackland, M.C. Bowyer, M.L. Baldwin, J.Garner and C.C. Walkom. *Bioorg Chem*., **31**, 68 (2003).

[6] M. Nakanishi and R. Kobayashi, *Jpn. Kokai* 1972, 7231, 979. *Chem. Abstr*., **78**, 29769d(1972).

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

[8] T. W. Waldrep, J. R. Beck, M. P.Lynch and F. L.Wright, *J. Agric. Food Chem*., **38**, 541 (1990).

[9] J. Hupartz and L. Aust, *J. Chem.,* **38**, 221 (1985).

[10] J. Hupartz and L. Aust, *J. Chem*.,**36**, 135 (1983).

[11] V. J. Ram, U. K. Singha and P. Y. Guru, *Eur. J. Med. Chem*., **25**, 533 (1990).

[12] L.-P. Deng, F.-M. Liu and H.-Y. Wang, *J. Heterocyclic Chem*., **42**,13 (2005).

[13] V. Padmavathi, K. Venugopal Reddy, A. Padmaja and P.Venugopalan, *J. Org. Chem*., **68**, 1567 (2003).