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

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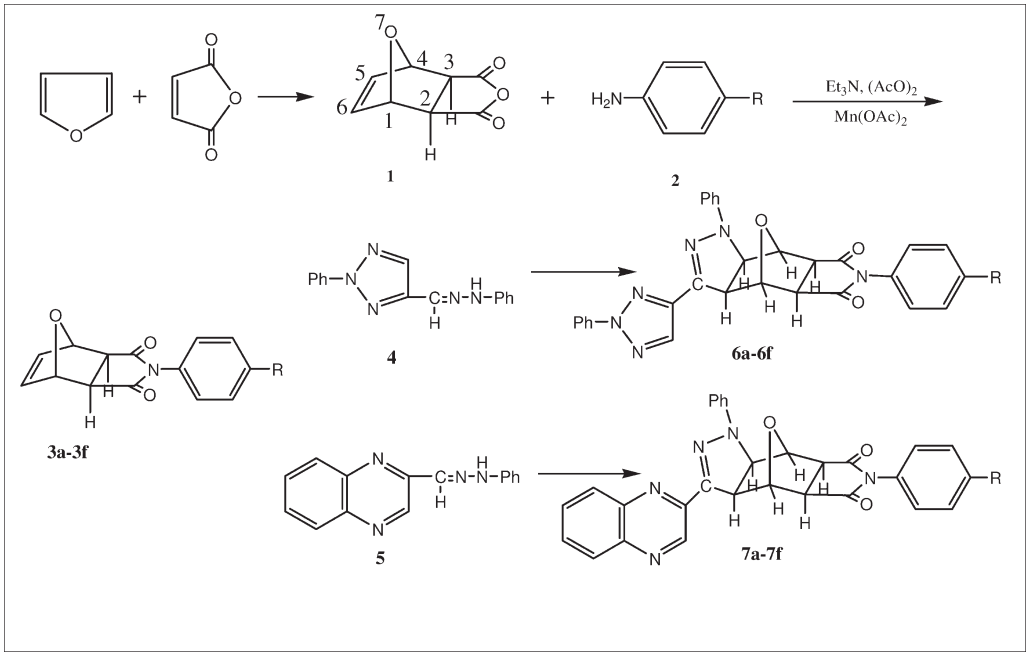

Highly efficient, practical and convenient synthesis of twelve compounds by the [3+2] 1, 3-dipolar cycloaddition reaction of norcantharidin derivatives of substituted aromatic amines with two hydrazines in the presence of chloramine-T.

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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]. Despite such qualities, the nephrotoxicity of cantharidin has prevented it from entering mainstream oncology. Norcantharidin (NCTD, Figure 1), the demethylated analogue of cantharidin, also possesses anticancer activity and stimulates the bone marrow, but without the urinary toxicity. Both agents are known 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, anti-inflammatory 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 synthesis of norcantharidin derivatives we have achieved a facile 1,3-dipolar cycloaddition method by the use of chloramines-T. Chloramine-T, 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

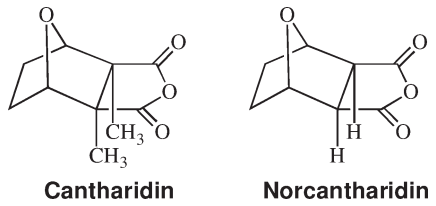


Figure 1. Chemical structures of cantharidin and norcantharidin.

may be of interest in chemistry, biochemistry and pharmacology [14].

RESULTS AND DISCUSSION

The precursor 5,6-dehydronorcantharidian derivatives **3a-3f** were synthesized by ''one pot'' method in good yield (Scheme 1) [12].

In this article, we have carried out the [4+2] cycloaddition of furan to maleic anhydride to obtain 5,6-dehydronorcantharidin **1**, then by "one pot" method, 5,6-dehydronorcantharidin reacted with substituted phenylamine **2a-2f** to give compounds **3a-3f**, after that, we carried out the [3+2] cycloaddition of **3a-3f** with **4**, **5** in the presence of chloramine-T respectively to obtain the target compounds **6a-6f**, **7a-7f** efficiently.

To identify the configuration of the pyrazoline with norcantharidin adducts (**6a-6f**, **7a-7f**), we have studied selective ^{1}H-^{1}HCOSY spectra, NOESY spectra of the compounds (take the example of **6a**). The exo-adduct (**6a-6f**, **7a-7f**) 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 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. This proves that the six protons are near in space and on the same side. The Diels-Alder adduct 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

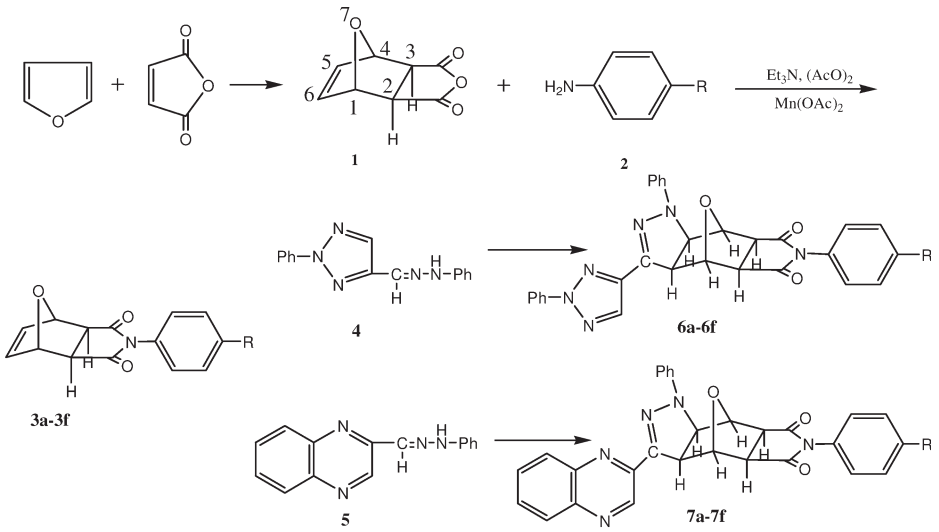
Melting points were obtained on a B-540 Bűchi melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Brucker AM-400 M Hz spectrometer with

Table 1

Physical data of the compounds.

Compound	R_1	Time (h)	Mp (°C)	Yield (%)	Molecular formula	Analysis % Calcd./Found		
						C	H	N
6a	H	7	278	88.3	$C_{29}H_{22}N_6O_3$	69.31	4.41	16.72
						69.30	4.44	16.71
6b	Cl	4	276	93.7	$C_{29}H_{21}ClN_6O_3$	64.87	3.94	15.65
						64.87	3.95	15.63
6c	CH_3	3	280	89.4	$C_{30}H_{24}N_6O_3$	69.76	4.68	16.27
						69.75	4.70	16.25
6d	OCH_3	5	256	89.7	$C_{30}H_{24}N_6O_4$	67.66	4.54	15.78
						67.65	4.56	15.76
6e	OH	8	260	72.4	$C_{29}H_{22}N_6O_4$	67.17	4.28	16.21
						67.18	4.29	16.20
6f	NO_2	4	239	85.2	$C_{29}H_{21}N_7O_5$	63.62	3.87	17.91
						63.61	3.89	17.92
7a	H	5	299	83.5	$C_{29}H_{21}N_5O_3$	71.45	4.34	14.37
						71.44	4.36	14.37
7b	Cl	4.5	293	85.4	$C_{29}H_{20}ClN_5O_3$	66.73	3.86	13.42
						66.74	3.85	13.41
7c	CH_3	4	266	79.3	$C_{30}H_{23}N_5O_3$	71.84	4.62	13.96
						71.85	3.64	13.95
7d	OCH_3	6	278	69.6	$C_{30}H_{23}N_5O_4$	69.62	4.48	13.53
						69.63	4.47	13.53
7e	OH	8	298	90.7	$C_{29}H_{21}N_5O_4$	69.18	4.20	13.91
						69.17	4.20	13.93
7f	NO_2	7	159	94.6	$C_{29}H_{20}N_6O_5$	65.41	3.79	15.78
						65.42	3.80	15.77

Scheme 1



2a, 3a, 4a, 5a R=H; **2b, 3b, 4b, 5b** R=Cl; **2c, 3c, 4c, 5c** R=CH_3;
2d, 3d, 4d, 5d R=OCH_3; **2e, 3e, 4e, 5e** R=OH; **2f, 3f, 4f, 5f** R=NO_2;

$SiMe_4$ 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-3f. All this work we have done before [12].

General procedure for the preparation of the pyrazole-linked norcantharidin derivatives of substituted aromatic amines (6a-6f, 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 2-phenyl-4-((2-phenylhydrazono) methyl)-2H-1, 2, 3-triazole **4** (1 mmole) in ethanol (20 mL), add chloramine T (1.2 mmole) and the reaction mixture was refluxed in ethanol for 3–8 h 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 menthol to give the compound **6a**. The synthesis of compounds **6b-6f, 7a-7f** was performed using the same method.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(phenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6a). This compound was obtained as yellow crystals, yield 88.3%, m.p. 278°C; ir (potassium bromide): 3473(N—C=O), 3064 (ArH), 1714 (C=O), 1597 (C=N), 1189 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.53(s, 1H, H—C=N), 8.20–6.93 (M, 15H, Ar—H), 5.51 (s, 1H, C_4—H) 5.34 (s, 1H, C_1—H) 4.65–4.62 (d, J = 9.60 Hz, 1H, C_5—H), 4.21–4.18 (d, J = 9.60 Hz, 1H, C_6—H), 3.41–3.39 (d, J = 7.20 Hz, 1H, C_3—H), 3.30–3.28 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 502 (M^+). *Anal*. Calcd. for $C_{29}H_{22}N_6O_3$: C, 69.31; H, 4.41; N, 16.72. Found: C, 69.30; H, 4.43; N, 16.71.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-chlorophenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6b). This compound was obtained as yellow crystals, yield 93.7%, m.p. 276°C; ir (potassium bromide): 3448(N—C=O), 3058 (ArH), 1700 (C=O), 1596 (C=N), 1199 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$)δ: 8.52(s, 1H, H—C=N), 8.21–6.93 (M, 14H, Ar—H), 5.50 (s, 1H, C_4—H) 5.34 (s, 1H, C_1—H) 4.66–4.64 (d, J = 9.20 Hz, 1H, C_5—H), 4.20–4.17 (d, J = 9.20 Hz, 1H, C_6—H), 3.41–3.39 (d, J = 7.20 Hz, 1H, C_3—H), 3.30–3.28 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 536 (M^+) 538 (M^++2). *Anal*. Calcd. for $C_{29}H_{21}ClN_6O_3$: C, 64.87; H, 3.94; N, 15.65. Found: C, 64.87; H, 3.95; N, 15.63.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(p-tolyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6c). This compound was obtained as yellow crystals, yield 89.4%, m.p. 280°C; ir (potassium bromide): 3482(N—C=O), 3057(ArH), 1717 (C=O), 1597 (C=N), 1202 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.51(s, 1H, H—C=N), 8.20–6.92 (M, 14H, Ar—H), 5.50 (s, 1H, C_4—H) 5.33 (s, 1H, C_1—H) 4.65–4.63 (d, J = 9.20 Hz, 1H, C_5—H), 4.21–4.19 (d, J = 9.20 Hz, 1H, C_6—H), 3.41–3.39 (d, J = 7.20 Hz, 1H, C_3—H), 3.30–3.28 (d, J = 7.20 Hz, 1H, C_2—H), 2.37 (s, 3H, CH_3). ms (70 ev): m/z 516 (M^+). *Anal*. Calcd. for $C_{30}H_{24}N_6O_3$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.75; H, 4.70; N, 16.25.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-methoxyphenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6d). This compound was obtained as yellow crystals, yield 89.7%, m.p. 256°C; ir (potassium bromide): 3448 (N—C=O), 3062 (ArH), 1711 (C=O), 1596 (C=N), 1190 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.54(s, 1H, H—C=N), 8.21–6.95 (M, 14H, Ar—H),

5.51 (s, 1H, C_4—H) 5.34 (s, 1H, C_1—H) 4.67–4.65 (d, J = 9.20 Hz, 1H, C_5—H), 4.21–4.19 (d, J = 9.20 Hz, 1H, C_6—H), 3.81 (s, 3H, OCH_3) 3.41–3.39 (d, J = 7.20 Hz, 1H, C_3—H), 3.31–3.29 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 532 (M^+). *Anal*. Calcd. for $C_{30}H_{24}N_6O_4$: C, 67.66; H, 4.54; N, 15.78 Found: C, 67.65; H, 4.56; N, 15.76.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-hydroxyphenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6e). This compound was obtained as yellow crystals, yield 72.4%, m.p. 260°C; ir (potassium bromide): 3448(N—C=O), 3022 (ArH), 1708 (C=O), 1596 (C=N), 1186 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.55(s, 1H, H—C=N), 8.21–6.95 (M, 14H, Ar—H), 5.50 (s, 1H, C_4—H) 5.33 (s, 1H, C_1—H) 4.67–4.64 (d, J = 9.20 Hz, 1H, C_5—H), 4.23–4.20 (d, J = 9.20 Hz, 1H, C_6—H), 3.42–3.40 (d, J = 7.20 Hz, 1H, C_3—H), 3.32–3.30 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 518 (M^+). *Anal*. Calcd. for $C_{29}H_{22}N_6O_4$: C, 67.17; H, 4.28; N, 16.21. Found: C, 67.18; H, 4.29; N, 16.20.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-nitrophenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6f). This compound was obtained as yellow crystals, yield 85.2%, m.p. 239°C; ir (potassium bromide): 3448(N—C=O), 3062 (Ar—H), 1710 (C=O), 1596 (C=N), 1174 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.54(s, 1H, H—C=N), 8.34–6.94 (M, 14H, Ar—H), 5.54 (s, 1H, C_4—H) 5.37 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.49–3.47 (d, J = 7.20 Hz, 1H, C_3—H), 3.38–3.36 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 547 (M^+). *Anal*. Calcd. for $C_{29}H_{21}N_7O_5$: C, 63.62; H, 3.87; N, 17.91 Found: C, 63.61; H, 3.89; N, 17.92.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(phenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (7a). This compound was obtained as yellow crystals, yield 83.5%, m.p. 299°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: 9.54 (s, 1H, H—C=N), 8.14–7.00 (M, 14H, Ar—H), 5.58 (s, 1H, C_4—H), 5.38 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.49–3.47 (d, J = 7.20 Hz, 1H, C_3—H), 3.38–3.36 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 487 (M^+). *Anal*. Calcd. for $C_{29}H_{21}N_5O_3$: C, 71.45; H, 4.34; N, 14.37. Found: C, 71.44; H, 4.36; N, 14.37.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-chlorophenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(1H,3aH)-dione (7b). This compound was obtained as yellow crystals, yield 85.4%, m.p. 293°C; ir (potassium bromide): 3448(N—C=O), 3065 (ArH), 1708 (C=O), 1560 (C=N), 1186 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.55 (s, 1H, H—C=N), 8.14–7.01 (M, 13H, Ar—H), 5.58 (s, 1H, C_4—H), 5.37 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.48–3.46 (d, J = 7.20 Hz, 1H, C_3—H), 3.36–3.34 (d, J = 7.20 Hz, 1H, C_2—H).ms (70ev): m/z 523 (M^++2), 522 (M^++1) 521 (M^+). *Anal*. Calcd. for $C_{29}H_{20}ClN_5O_3$: C, 66.73; H, 3.86; N, 13.42. Found: C, 66.74; H, 3.85; N, 13.41.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(p-tolyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f] indazole-5,7(1H,3aH)-dione (7c). This compound was obtained as yellow crystals, yield 79.3%, m.p. 266°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: 9.53 (s, 1H, H—C=N), 8.12–6.99 (M, 13H, Ar—H), 5.56 (s, 1H, C_4—H), 5.37 (s, 1H, C_1—H), 4.74–4.72 (d, J = 9.20 Hz, 1H, C_5—H), 4.38–4.36 (d, J = 9.20 Hz, 1H, C_6—H), 3.48–3.46 (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 (70 ev): m/z 501 (M^+). *Anal*. Calcd. for $C_{30}H_{23}N_5O_3$: C, 71.84; H, 4.62; N, 13.96. Found: C, 71.85; H, 3.64; N, 13.95.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-methoxyphenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(1H,3aH)-dione (7d). This compound was obtained as yellow crystals, yield 69.6%, m.p. 278°C; ir (potassium bromide): 3448(N—C=O), 3043 (ArH), 1701 (C=O), 1560 (C=N), 1201 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.56 (s, 1H, H—C=N), 7.40–6.56 (M, 13H, Ar—H), 5.57 (s, 1H, C_4—H), 5.39 (s, 1H, C_1—H), 4.74–4.72 (d, J = 9.20 Hz, 1H, C_5—H), 4.38–4.36 (d, J = 9.20 Hz, 1H, C_6—H), 3.81 (s, 3H, OCH_3), 3.48–3.46 (d, J = 7.20 Hz, 1H, C_3—H), 3.33–3.31 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 517(M^+). *Anal*. Calcd. for $C_{30}H_{23}N_5O_4$: C, 69.62; H, 4.48; N, 13.53. Found: C, 69.63; H, 4.47; N, 13.53.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-hydroxyphenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(1H,3aH)-dione (7e). This compound was obtained as yellow crystals, yield 90.7%, m.p. 298°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: 9.55 (s, 1H, H—C=N), 8.14–7.01 (M, 13H, Ar—H), 5.58 (s, 1H, C_4—H), 5.37 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.48–3.46 (d, J = 7.20 Hz, 1H, C_3—H), 3.36–3.34 (d, J = 7.20 Hz, 1H, C_2—H).ms (70 ev): m/z 503 (M^+). *Anal*. Calcd. for $C_{29}H_{21}N_5O_4$: C, 69.18; H, 4.20; N, 13.91. Found: C, 69.17; H, 4.20; N, 13.93.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-nitrophenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(1H,3aH)-dione (7f). This compound was obtained as yellow crystals, yield 94.6%, m.p. 159°C; ir (potassium bromide): 3442(N—C=O), 3045 (ArH), 1718 (C=O), 1598 (C=N), 1178 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.54 (s, 1H, H—C=N), 8.34–6.93 (M, 13H, Ar—H), 5.61 (s, 1H, C_4—H), 5.40 (s, 1H, C_1—H), 4.80–4.78 (d, J = 9.20 Hz, 1H, C_5—H), 4.43–4.41 (d, J = 9.20 Hz, 1H, C_6—H), 3.57–3.55 (d, J = 7.20 Hz, 1H, C_3—H), 3.42–3.40 (d, J = 7.20 Hz, 1H, C_2—H).ms (70 ev): m/z 532 (M^+). *Anal*. Calcd. for $C_{29}H_{20}N_6O_5$: C, 65.41; H, 3.79; N, 15.78. Found: C, 65.42; H, 3.80; N, 15.77.

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