Liping Deng,[a,b]* Zhang Yong,[a] Weifeng Tao,[b] Jianfeng Shen,[c] and Wei Wang[b]

[a]Department of Pharmacology, Chemistry and Chemical Engineering Institute, Shaoxing University, Shaoxing 312000, Zhejiang, People's Republic of China
[b]Zhejiang Supor Pharmaceuticals, Shaoxing 312000, Zhejiang, People's Republic of China
[c]Zhejiang Zhenyuan Pharmaceuticals, Shaoxing 312000, Zhejiang, People's Republic of China
*E-mail: wwdlp@126.com

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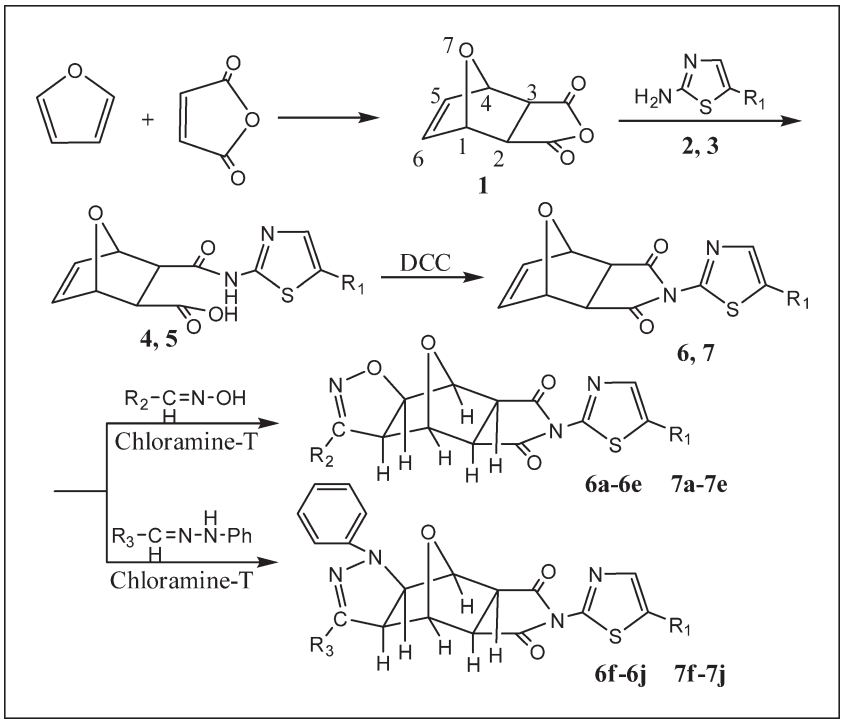

Twenty novel norcantharidin derivatives, which were substituted by thiazole ring, were synthesized in a single step by the [3+2] 1,3-dipolar cycloaddition reaction with oxime or hydrazone in the presence of chloramine-T when compared with the conventional method.

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INTRODUCTION

Cantharidin (CAN, *exo*, *exo*-2,3-dimethyl-7-oxabicyclo [2.2.1] heptane-2,3-dicarboxylic acid anhydride, Fig. 1) is an active ingredient of Chinese blister beetles Mylabris [1], which has been used in China as a medicinal agent for the treatment of cancer, in particular to hepatoma [2]. Recently, cantharidin has been found active in cervical, tongue, ginival, bone, leukaemia, ovarian, and colon cancer cells [3]. However, the renal toxicity of this drug has limited its application [4]. Norcantharidin (NCTD, the demethylated cantharidin derivative, Fig. 1) appeared to improve the awkward side of cantharidin making the drug safer in application. It was recently found to be capable of inducing apoptosis in human cervical, tongue, ginival, mucoepidermoid carcinoma, adenocystic carcinoma, neuroblastoma, bone, leukaemia, ovarian, and colon cancer cell lines [5].We have referred to all the known cantharidin SAR data, briefly: no modification of the bicycle [2.2.1] skeleton is permissible, the 7-oxa bridge is required to maintain the activity, the presence of a double bond (5,6-ene) has little effect on the activity. Replacement of the O-atom (anhydride) with N (as N-H and N-R, where R= thiazolyl or aryl) allows the development of a new series of anhydride modified cantharidin analogues; some are more potent than CAN or display potency similar to NCTD [6–10].

Isoxazoline and pyrazoline derivatives possess a wide range of pharmacological activities [11]. Thus, it seemed of interest to combine isoxazoline or pyrazoline with

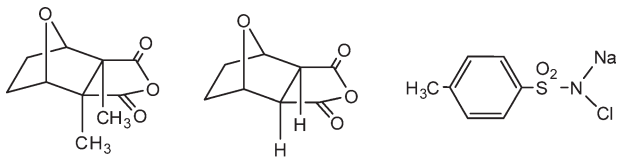

Figure 1. Chemical structures of CAN, NCTD, and chloramine-T.

norcantharidin derivatives in a single molecule. We have successfully synthesized some compounds before [12], but the method is somewhat complex because we have to synthesize nitrile oxide by the reaction of nitrile oximes with *tert*-butyl hypochloride. With our sustained interest in the synthesis of norcantharidin derivatives, we have achieved a facile 1,3-dipolar cycloaddition method by using chloramine-T (Fig. 1). Chloramine-T, which is a versatile reagent in organic synthesis [13], was used in this article for the *in situ* oxidation of oximes and hydrazones of aldehydes to generate the nitrile oxides; compared with the conventional method, the synthetic route is more facile and the reaction rate is enhanced tremendously.

In addition, thiazole derivatives are an important class of heterocyclic derivatives containing N and S elements; these compounds have a broad spectrum of biological activity, showing a good anti-bacterial, anti-virus, anti-tumor, weeding and regulation of plant growth, and other bioactivity. They play an important regulatory role in humans and other organisms' metabolic process. Therefore, the functional design of thiazole compounds takes people's attention [14]. So, we combine thiazole with norcantharidin derivatives. Cooperating with isoxazole or pyrazole, we look forward to the compounds obtained having a good biological activity.

RESULTS AND DISCUSSION

The synthetic route of the compounds mentioned is outlined in Scheme 1. Such type of compounds (Table 1) with versatile activities may be of interest in chemistry, biochemistry, and pharmacology [15].

EXPERIMENTAL

Melting points were obtained on a B-540 Buchi melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Brucker AM-400 M Hz spectrometer with $SiMe_4$ as the internal standard in $CDCl_3$. Element analyses were performed on an EA-1110 instrument.

Nitrile oxides are of great synthetic interest because the product, isoxazolines and pyrazolines, are versatile intermediates for the synthesis of bifunctional compounds. We have carried out the [4+2] cycloaddition of furan with maleic anhydride to obtain 5,6-dehydronorcantharin **1**, and then, reacted **1** with amino-substituted thiazole ring **2–3** to give compounds **4–5**. After that, we reacted compounds **4–5** with DCC to get compounds **6–7**.At last, we carried out the [3+2] cycloaddition of **6–7** with oxime or hydrazone in the presence of chloramine-T. Thus, we get compounds **6a–6j** and **7a–7j** [12,16].

General Procedure for the Preparation of the compounds 4–5. Compound **2** (10 mmol) was dissolved in acetone (10 mL). Then, this solution was added slowly to a solution of **1** (10 mmol) in acetone (20 mL). The reaction mixture reacted in acetone for 8 h, then leached. The residue was dried, giving the compound **4**. The synthesis of compound **5** was performed using the same method.

General Procedure for the Preparation of the compounds 6–7. Compound **4** (5 mmol) dissolved in DMF (10 mL), being ice-bath. When the solution was down to 0°C, DCC (5 mmol) was added. The reaction mixture was refluxed in DMF for 10 h, then leached. The extracts were poured into ice water (50 mL), separating out crystal, then leached. The residue was dried, then recrystallized from methanol to give the compound **6**. The synthesis of compound **7** was performed using the same method.

General Procedure for the Preparation of the 5,6-Dehydronorcantharidin-isoxazoline and 5,6-Dehydronorcantharidin-pyrazoline Adducts (6a–6j and 7a–7j)data. Chloramine-T (1.2 mmol) was added to a solution of **2** (1 mmol) and 4-fluorobenzaldehyde oxime (1 mmol) in ethanol (20 mL). The reaction mixture was refluxed in ethanol for 12 h, then leached. The residue was dried, then recrystallized from

Scheme 1

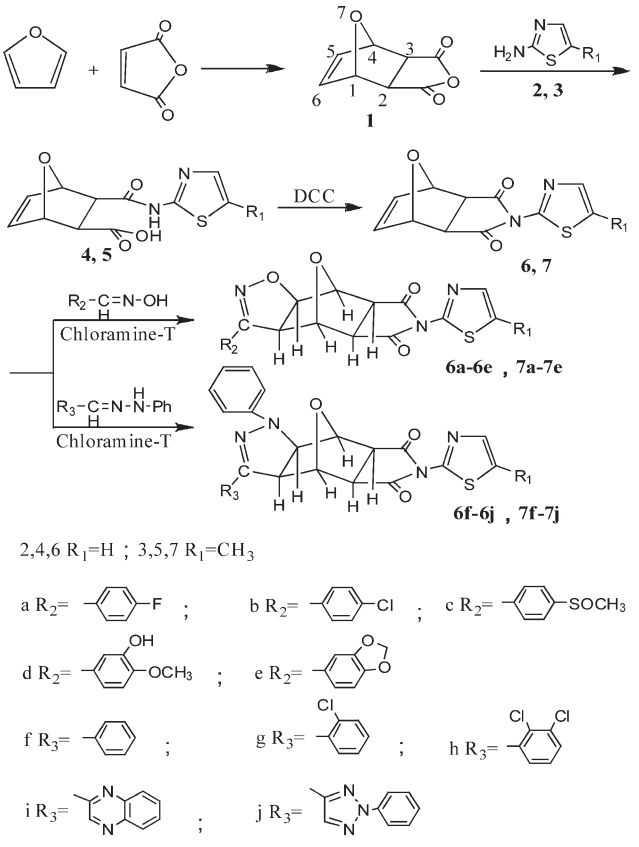

Table 1

Physical data of compounds.

Compound	R_1	R_2/R_3	Time (h)	M_p (°C)	Yield (%)	Molecular formula	Analysis % calcd./found C	H	N
4	H	/	8	163	75.1	$C_{11}H_{10}N_2O_4S$	49.62	3.79	10.52
							49.65	3.76	10.51
5	CH_3	/	8.5	158	59.7	$C_{12}H_{12}N_2O_4S$	51.42	4.32	9.99
							51.40	4.33	10.02
6	H	/	10	145	15.8	$C_{11}H_8N_2O_3S$	53.22	3.25	11.28
							53.23	3.24	11.30
7	CH_3	/	11	136	76.8	$C_{12}H_{10}N_2O_3S$	54.95	3.84	10.68
							54.97	3.85	10.65
6a	H	C_6H_4F	12	>300	27.8	$C_{18}H_{12}N_3O_4FS$	56.10	3.14	10.90
							56.08	3.15	10.87
6b	H	C_6H_4Cl	11	>300	22.5	$C_{18}H_{12}N_3O_4ClS$	53.80	3.01	10.46
							53.81	3.04	10.42
6c	H	$C_6H_4SOCH_3$	11.5	>300	24.3	$C_{19}H_{15}N_3O_5S_2$	53.14	3.52	9.78
							53.11	3.55	9.79
6d	H	$C_6H_3OCH_3OH$	12	>300	31.2	$C_{19}H_{15}N_3O_6S$	55.20	3.66	10.16
							55.18	3.64	10.15
6e	H	$C_7H_5O_2$	6	>300	40.6	$C_{19}H_{13}N_3O_6S$	55.47	3.19	10.21
							55.44	3.17	10.22
7a	CH_3	C_6H_4F	11.3	287	54.7	$C_{19}H_{14}N_3O_4FS$	57.14	3.53	10.52
							57.15	3.51	10.54
7b	CH_3	C_6H_4Cl	11	268	35.4	$C_{19}H_{14}N_3O_4ClS$	54.88	3.39	10.10
							54.86	3.41	10.13
7c	CH_3	$C_6H_4SOCH_3$	10.5	>300	27.4	$C_{20}H_{17}N_3O_5S_2$	54.12	3.86	9.47
							54.09	3.88	9.50
7d	CH_3	$C_6H_3OCH_3OH$	12	>300	33.4	$C_{20}H_{17}N_3O_6S$	56.20	4.01	9.83
							56.17	3.98	9.85
7e	CH_3	$C_7H_5O_2$	5	282	53.7	$C_{20}H_{15}N_3O_6S$	56.47	3.55	9.88
							56.50	3.53	10.01
6f	H	C_6H_5	10	>300	26.3	$C_{24}H_{18}N_4O_3S$	65.14	4.10	12.66
							65.12	4.11	12.64
6g	H	C_6H_4Cl	11	>300	22.9	$C_{24}H_{17}N_4O_3SCl$	60.44	3.59	11.75
							60.43	3.61	11.72
6h	H	$C_6H_3Cl_2$	10	>300	20.4	$C_{24}H_{16}N_4O_3Cl_2S$	56.37	3.15	10.96
							56.35	3.14	10.97
6i	H	$C_8H_5N_2$	7	>300	43.0	$C_{26}H_{18}N_6O_3S$	63.15	3.67	16.99
							63.17	3.66	16.96
6j	H	$C_8H_6N_3$	7	218	35.7	$C_{26}H_{19}N_7O_3S$	61.27	3.76	19.24
							61.26	3.74	19.22
7f	CH_3	C_6H_5	10.5	>300	32.8	$C_{25}H_{20}N_4O_3S$	65.77	4.42	12.27
							65.79	4.44	12.25
7g	CH_3	C_6H_4Cl	10	>300	41.1	$C_{25}H_{19}N_4O_3SCl$	61.16	3.90	11.41
							61.14	3.93	11.39
7h	CH_3	$C_6H_3Cl_2$	11	>300	29.7	$C_{25}H_{18}N_4O_3Cl_2S$	57.15	3.45	10.66
							57.17	3.43	10.63
7i	CH_3	$C_8H_5N_2$	7	>300	48.8	$C_{27}H_{20}N_6O_3S$	63.77	3.96	16.53
							63.78	3.99	16.50
7j	CH_3	$C_8H_6N_3$	6.5	>300	38.6	$C_{27}H_{21}N_7O_3S$	61.94	4.04	18.73
							61.92	4.01	18.75

methanol to give the compound **6a**. The synthesis of compounds **6b–6j** and **7a–7j** was performed using the same method.

Data. ***(1S,2R,4R)-3-(Thiazol-2-ylcarbamoyl)-7-oxabicyclo [2.2.1]hept-5-ene-2-carboxylic acid (4).*** This compound was obtained as beige crystals, yield 75.1%, m.p.163°C; ^{1}H NMR(DMSO-d_6) δ: 9.10 (s, 1H, —NH), 7.05–7.04 (d, J = 3.6 Hz, 1H, N—CH), 6.68–6.67 (d, J = 4.0 Hz, 1H, S-CH), 6.20 (s, 2H, C_5—H, C_6—H), 4.87 (s, 1H, C_1—H), 4.76 (s, 1H, C_4—H), 3.51 (s, 1H, C_3-H), 3.11 (s, 1H, C_2—H). Anal. Calcd. for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.79; N, 10.52. Found: C, 49.65; H, 3.76; N, 10.51.

(1S,2R,4R)-3-(5-Methylthiazol-2-ylcarbamoyl)-7-oxabicyclo [2.2.1]hept-5-ene-2-carboxylic acid (5). This compound was obtained as brown crystals, yield 59.7%, m.p.158°C; ^{1}H NMR(DMSO-d_6) δ: 9.15 (s, 1H, —NH), 7.25 (s, 1H, N—CH), 5.91 (s, 2H, C_5—H, C_6—H), 4.91 (s, 1H, C_1—H), 4.83 (s, 1H, C_4—H), 3.63 (s, 1H, C_3—H), 3.14 (s, 1H, C_2—H). 2.25 (s, 3H,

CH_3). Anal. Calcd. for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.32; N, 9.99. Found: C, 51.40; H, 4.33; N, 10.02.

2-(Thiazol-2-yl)-4,7-epoxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6). This compound was obtained as beige crystals, yield 15.8%, m.p.145°C; ^{1}H NMR($CDCl_3$) δ: 7.80–7.79 (d, J = 3.6 Hz, 1H, N—CH), 7.34–7.33 (d, J = 3.6, 1H, S-CH), 6.59–6.57 (d, J = 4.8, 2H, C_5—H, C_6—H), 5.44 (s, 2H, C_1—H, C_4—H), 3.09 (s, 2H, C_2—H, C_3—H). Anal. Calcd. for $C_{11}H_8N_2O_3S$: C, 53.22; H, 3.25; N, 11.28. Found: C, 53.23; H, 3.24; N, 11.30.

2-(5-Methylthiazol-2-yl)-4,7-epoxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (7). This compound was obtained as beige crystals, yield 76.8%, m.p.136°C; ^{1}H NMR ($CDCl_3$) δ: 7.43–7.42 (d, J = 1.2, 1H, N—CH), 6.57 (s, 2H, C_5—H, C_6—H), 5.42 (s, 2H, C_1—H, C_4—H), 3.05 (s, 2H, C_2—H, C_3—H), 2.48 (s, 3H, CH_3). Anal. Calcd. for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68. Found: C, 54.97; H, 3.85; N, 10.65.

exo,exo-6-(Thiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-fluorophenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (6a). This compound was obtained as beige crystals, yield 27.8%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.70–7.09 (m, 4H, Ar-H), 6.55–6.52 (d, J = 12.41 Hz, 1H, N—CH), 6.39–6.36 (d, J = 12.82 Hz, 1H, S-CH), 5.18 (d, J = 7.92 Hz, 1H, C_5—H), 4.95(s, 1H, C_4—H), 4.74(s, 1H, C_1—H), 4.47(d, J = 7.92 Hz, 1H, C_6—H), 3.59(d, J = 7.94 Hz, 1H, C_3—H), 3.37(d, J = 7.93 Hz, 1H, C_2—H). Anal. Calcd. for $C_{18}H_{12}N_3O_4FS$: C, 56.10; H, 3.14; N, 10.90. Found: C, 56.08; H, 3.15; N, 10.87.

exo,exo-6-(Thiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-chlorophenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (6b). This compound was obtained as beige crystals, yield 22.5%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.74–7.06 (m, 4H, Ar-H), 6.55–6.52 (d, J = 12.42 Hz, 1H, N—CH), 6.38–6.36 (d, J = 12.78 Hz, 1H, S-CH), 5.18 (d, J = 7.93 Hz, 1H, C_5—H), 4.95 (s, 1H, C_4—H), 4.73 (s, 1H, C_1—H), 4.48 (d, J = 7.92 Hz, 1H, C_6—H), 3.59 (d, J = 7.92 Hz, 1H, C_3—H), 3.36 (d, J = 7.93 Hz, 1H, C_2—H). Anal. Calcd. for $C_{18}H_{12}N_3O_4ClS$: C, 53.80; H, 3.01; N, 10.46. Found: C, 53.81; H, 3.04; N, 10.42.

exo,exo-6-(Thiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-(methylsulfinyl)phenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (6c). This compound was obtained as beige crystals, yield 24.3%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.81–6.96 (m, 4H, Ar-H), 6.55–6.52 (d, J = 12.40 Hz, 1H, N—CH), 6.38–6.35 (d, J = 12.80 Hz, 1H, S-CH), 5.24–5.22 (d, J = 7.92 Hz, 1H, C_5—H), 4.99 (s, 1H, C_4—H), 4.76 (s, 1H, C_1—H), 4.51–4.49 (d, J = 7.92 Hz, 1H, C_6—H), 3.60–3.58 (d, J = 7.92 Hz, 1H, C_3—H), 3.38–3.36 (d, J = 7.92 Hz, 1H, C_2—H), 2.64 (s, 3H, CH3). Anal. Calcd. for $C_{18}H_{12}N_3O_5S_2$: C, 53.14; H, 3.52; N, 9.78. Found: C, 53.11; H, 3.55; N, 9.79.

exo,exo-6-(Thiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(3-hydroxy-4-methoxyphenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (6d). This compound was obtained as beige crystals, yield 31.2%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.83–7.19 (m, 3H, Ar-H), 6.55–6.52 (d, J = 12.44 Hz, 1H, N—CH), 6.38–6.36 (d, J = 12.75 Hz, 1H, S-CH), 5.24 (d, J = 7.90 Hz, 1H, C_5—H), 4.98 (s, 1H, C_4—H), 4.75 (s, 1H, C_1—H), 4.52 (d, J = 7.93 Hz, 1H, C_6—H), 3.77 (s, 3H, OCH_3), 3.59 (d, J = 7.92 Hz, 1H, C_3—H), 3.38 (d, J = 7.92 Hz, 1H, C_2—H). Anal. Calcd. for $C_{19}H_{15}N_3O_6S$: C, 55.20; H, 3.66; N, 10.16. Found: C, 55.18; H, 3.64; N, 10.15.

exo,exo-6-(Thiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(benzo[d][1,3]dioxol-5-yl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (6e). This compound was obtained as beige crystals, yield 40.6%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.47–6.95 (m, 3H, Ar-H), 6.56–6.54 (d, J = 12.38 Hz, 1H, N—CH), 6.37–6.34 (d, J = 12.77 Hz, 1H, S-CH), 6.07 (s, 2H, OCH_2O), 5.27 (d, J = 7.93 Hz, 1H, C_5—H), 5.12 (s, 1H, C_4—H), 4.81 (s, 1H, C_1—H), 4.50 (d, J = 7.92 Hz, 1H, C_6—H), 3.56 (d, J = 7.92 Hz, 1H, C_3-H), 3.41 (d, J = 7.91 Hz, 1H, C_2-H). Anal. Calcd. for $C_{19}H_{13}N_3O_6S$: C, 55.47; H, 3.19; N, 10.21. Found: C, 55.44; H, 3.17; N, 10.22.

exo,exo-6-(5-Methylthiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-fluorophenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (7a). This compound was obtained as beige crystals, yield 54.7%, m.p. 287°C; ^{1}H NMR($CDCl_3$) δ: 7.70–7.22(m, 4H, Ar-H), 6.75 (s, 1H, N—CH), 5.18 (d, J = 7.91 Hz, 1H, C_5—H), 4.95(s, 1H, C_4—H), 4.74(s, 1H, C_1—H), 4.47(d, J = 7.92 Hz, 1H, C_6—H), 3.59(d, J = 7.94 Hz, 1H, C_3—H), 3.37(d, J = 7.93 Hz, 1H, C_2—H), 2.50 (s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{14}N_3O_4FS$: C, 57.14; H, 3.53; N, 10.52. Found: C, 57.15; H, 3.51; N, 10.54.

exo,exo-6-(5-Methylthiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-chlorophenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (7b). This compound was obtained as beige crystals, yield 35.4%, m.p. 268°C; ^{1}H NMR($CDCl_3$) δ: 7.84–7.46 (m, 4H, Ar-H), 6.74 (s, 1H, N—CH), 5.18 (d, J = 7.93 Hz, 1H, C_5—H), 4.95 (s, 1H, C_4—H), 4.73 (s, 1H, C_1—H), 4.51 (d, J = 7.92 Hz, 1H, C_6—H), 3.60 (d, J = 7.91 Hz, 1H, C_3—H), 3.36 (d, J = 7.93 Hz, 1H, C_2—H), 2.35 (s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{14}N_3O_4ClS$: C, 54.88; H, 3.39; N, 10.10. Found: C, 54.86; H, 3.41; N, 10.13.

exo,exo-6-(5-Methylthiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(4-(methylsulfinyl)phenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (7c). This compound was obtained as beige crystals, yield 27.4%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 8.05–7.74 (m, 4H, Ar-H), 6.74 (s, 1H, N—CH), 5.24–5.22 (d, J = 7.91 Hz, 1H, C_5—H), 4.99 (s, 1H, C_4—H), 4.76 (s, 1H, C_1—H), 4.51–4.49 (d, J = 7.92 Hz, 1H, C_6—H), 3.60–3.58 (d, J = 7.92 Hz, 1H, C_3—H), 3.38–3.36 (d, J = 7.90 Hz, 1H, C_2—H), 2.64 (s, 3H, CH3), 2.40 (s, 3H, CH_3). Anal. Calcd. for $C_{20}H_{17}N_3O_5S_2$: C, 54.12; H, 3.86; N, 9.47. Found: C, 54.09; H, 3.88; N, 9.50.

exo,exo-6-(5-Methylthiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(3-hydroxy-4-methoxyphenyl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (7d). This compound was obtained as beige crystals, yield 33.4%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.47–6.89 (m, 3H, Ar-H), 6.47 (s, 1H, N—CH), 5.24 (d, J = 7.90 Hz, 1H, C_5—H), 4.98 (s, 1H, C_4—H), 4.75 (s, 1H, C_1—H), 4.52 (d, J = 7.93 Hz, 1H, C_6—H), 3.83 (s, 3H, OCH_3), 3.59 (d, J = 7.92 Hz, 1H, C_3—H), 3.38 (d, J = 7.92 Hz, 1H, C_2—H), 2.30 (s, 3H, CH_3). Anal. Calcd. for $C_{20}H_{17}N_3O_6S$: C, 56.20; H, 4.01; N, 9.83. Found: C, 56.17; H, 3.98; N, 9.85.

exo,exo-6-(5-Methylthiazol-2-yl)-4,8-epoxy-3a,4,4a,7a,8,8a-hexahydro-3-(benzo[d][1,3]dioxol-5-yl)-pyrrolo[3,4-f]-1,2-benzisoxazole-5,7(1H,3aH)-dione (7e). This compound was obtained as beige crystals, yield 53.7%, m.p. 282°C; ^{1}H NMR($CDCl_3$) δ: 7.47–6.95 (m, 3H, Ar-H), 6.70 (d, 1H, N—CH), 6.12 (s, 2H, OCH_2O), 5.27 (d, J = 7.93 Hz, 1H, C_5—H), 5.12 (s, 1H, C_4—H), 4.81 (s, 1H, C_1—H), 4.50 (d, J = 7.90 Hz, 1H, C_6—H), 3.58 (d, J = 7.92 Hz, 1H, C_3—H), 3.41 (d, J = 7.92 Hz, 1H, C_2—H), 2.30 (s, 3H, CH_3). Anal. Calcd.

for $C_{20}H_{15}N_3O_6S$: C, 56.47; H, 3.55; N, 9.88. Found: C, 56.50; H, 3.53; N, 10.01.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(Thiazol-2-yl)-4,8-epoxy-1,3-diphenyl-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6f). This compound was obtained as beige crystals, yield 26.3%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.76–6.97 (m, 10H, Ar-H), 6.55–6.52 (d, J = 12.41 Hz, 1H, N—CH), 6.39–6.36 (d, J = 12.82 Hz, 1H, S-CH), 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). Anal. Calcd. for $C_{24}H_{18}N_4O_3S$: C, 65.14; H, 4.10; N, 12.66. Found: C, 65.12; H, 4.11; N, 12.64.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(Thiazol-2-yl)-4,8-epoxy-1-phenyl-3-(2-chlorophenyl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6g). This compound was obtained as beige crystals, yield 22.9%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.81–6.96 (m, 9H, Ar-H), 6.55–6.52 (d, J = 12.43 Hz, 1H, N—CH), 6.38–6.35 (d, J = 12.79 Hz, 1H, S-CH), 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). Anal. Calcd. for $C_{24}H_{17}N_4O_3SCl$: C, 60.44; H, 3.59; N, 11.75. Found: C,60.43; H, 3.61; N, 11.72.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(Thiazol-2-yl)-4,8-epoxy-1-phenyl-3-(2,3-dichlorophenyl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (6h). This compound was obtained as beige crystals, yield 20.4%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.65–6.94 (m, 8H, Ar-H), 6.54–6.51 (d, J = 12.40 Hz, 1H, N—CH), 6.38–6.35 (d, J = 12.81 Hz, 1H, S-CH), 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). Anal. Calcd. for $C_{24}H_{16}N_4O_3Cl_2S$: C, 56.37; H, 3.15; N, 10.96. Found: C, 56.35; H, 3.14; N, 10.97.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(Thiazol-2-yl)-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 (6i). This compound was obtained as beige crystals, yield 43.0%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 9.54 (s, 1H, HC=N), 8.14–7.00 (m, 9H, Ar-H), 6.55–6.52 (d, J = 12.40 Hz, 1H, N—CH), 6.38–6.35 (d, J = 12.80 Hz, 1H, S-CH), 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). Anal. Calcd. for $C_{26}H_{18}N_6O_3S$: C, 63.15; H, 3.67; N, 16.99. Found: C, 63.17; H, 3.66; N, 16.96.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(Thiazol-2-yl)-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 (6j). This compound was obtained as beige crystals, yield 35.7%, m.p. 218°C; ^{1}H NMR($CDCl_3$) δ: 8.53(s, 1H, H—C=N), 8.20–6.93 (m, 10H, Ar-H), 6.55–6.52 (d, J = 12.40 Hz, 1H, N—CH), 6.38–6.36 (d, J = 12.76 Hz, 1H, S-CH), 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). Anal. Calcd. for $C_{26}H_{19}N_7O_3S$: C, 61.27; H, 3.76; N, 19.24. Found: C, 61.26; H, 3.74; N, 19.22.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(5-Methylthiazol-2-yl)-4,8-epoxy-1,3-diphenyl-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (7f). This compound was obtained as beige crystals, yield 32.8%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.77–6.89 (m, 10H, Ar-H), 6.70 (s, 1H, N—CH), 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). Anal. Calcd. for $C_{25}H_{20}N_4O_3S$: C, 65.77; H, 4.42; N, 12.27. Found: C, 65.79; H, 4.44; N, 12.25.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(5-Methylthiazol-2-yl)-4,8-epoxy-1-phenyl-3-(2-chlorophenyl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (7g). This compound was obtained as beige crystals, yield 41.1%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.76–6.97 (m, 9H, Ar-H), 6.74 (s, 1H, N—CH), 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_2—H, C_3—H), 2.35 (s, 3H, CH_3). Anal. Calcd. for $C_{25}H_{19}N_4O_3SCl$: C, 61.16; H, 3.90; N, 11.41. Found: C,61.14; H, 3.93; N, 11.39.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(5-Methylthiazol-2-yl)-4,8-epoxy-1-phenyl-3-(2,3-dichlorophenyl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(1H,3aH)-dione (7h). This compound was obtained as beige crystals, yield 29.7%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 7.65–6.92 (m, 8H, Ar-H), 6.75 (s, 1H, N—CH), 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_2—H, C_3—H), 2.34 (s, 3H, CH_3). Anal. Calcd. for $C_{25}H_{18}N_4O_3Cl_2S$: C, 57.15; H, 3.45; N, 10.66. Found: C, 57.17; H, 3.43; N, 10.63.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(5-Methylthiazol-2-yl)-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 (7i). This compound was obtained as beige crystals, yield 48.8%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 9.53 (s, 1H, H—C=N), 8.12–6.99 (m, 9H, Ar-H), 6.76 (s, 1H, N—CH), 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). Anal. Calcd. for $C_{27}H_{20}N_6O_3S$: C, 63.77; H, 3.96; N, 16.53. Found: C, 63.78; H, 3.99; N, 16.50.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(5-Methylthiazol-2-yl)-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 (7j). This compound was obtained as beige crystals, yield 38.6%, m.p. >300°C; ^{1}H NMR($CDCl_3$) δ: 8.51(s, 1H, H—C=N), 8.20–6.92 (M, 10H, 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), 2.35 (s, 3H, CH_3). Anal. Calcd. for $C_{27}H_{21}N_7O_3S$: C, 61.94; H, 4.04; N, 18.73. Found: C, 61.92; H, 4.01; N, 18.75.

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