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Enantiomers of an Indole Alkaloid Containing Unusual Dihydrothiopyran and 1,2,4-Thiadiazole Rings from the Root of *Isatis indigotica*

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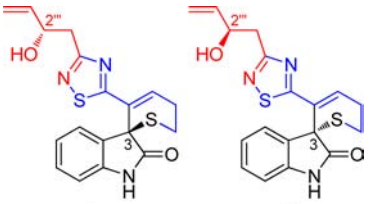
ABSTRACT



1a **1b**

A pair of enantiomers (1a and 1b) of an indole alkaloid containing dihydrothiopyran and 1,2,4-thiadiazole rings was isolated from an aqueous extract of the root of *Isatis indigotica*. The structures and absolute configurations of the enantiomers were determined by extensive spectroscopic analysis, especially 2D NMR, modified Mosher's method, and electronic CD (ECD). The proposed biosynthetic pathway and preliminary investigations of the biological activity of compounds 1a and 1b against influenza virus A/Hanfang/359/95 (H3N2) and HSV-1 are also discussed.

Isatis indigotica Fort. (Cruciferae) is a biennial herbaceous plant widely distributed and cultivated in China. Its dried roots and leaves (named "ban lan gen" and "da qing ye" in Chinese, respectively) are used in traditional Chinese medicine for the treatment of various diseases, especially influenza, cold, fever, and infections.[1] Diverse structures and significant biological activities from extracts of this plant have attracted considerable interest. Chemical and pharmacological studies have resulted in the characterization of constituents with different structural features and biological activities from ethanol extracts of the roots and leaves of *I. indigotica*, including alkaloids,[2] lignans,[3] ceramides,[4] flavonoids,[5] 2-hydroxy-3-butenyl thiocyanate,

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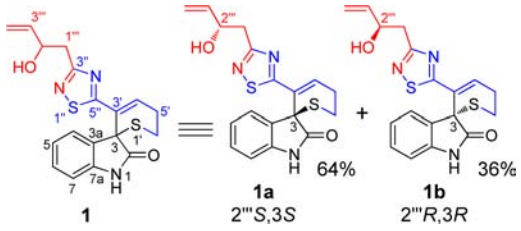

Figure 1. Structures of **1**, **1a**, and **1b**.

and sulfur-containing epigoitrin, goitrin, proepigoitrin, and progoitrin.[6] As part of a program to assess the chemical and biological diversity of traditional Chinese medicines, an aqueous extract of the roots of *I. indigotica* has been investigated. In our previous study, 31 indole alkaloids were isolated from the aqueous extract.[7] Some of them showed antiviral activity against influenza virus A/Hanfang/359/95 (H3N2) or Coxsackie virus B3, as well as protective activity against D,L-galactosamine (GalN)-induced hepatocyte (WB-F344 cell) damage. Subsequent investigation of the same extract led to the characterization of **1**, an indole alkaloid containing unusual dihydrothiopyran and 1,2,4-thiadiazole rings (Figure 1). Herein, we report details of the isolation and structure elucidation of a pair of enantiomers of **1**, **1a** and **1b**. The postulated biogenetic pathway and biological activity of the enantiomers are also discussed.[8]

Compound **1** was obtained as a colorless gum with $[\alpha]_D^{20}$ −14.1 (*c* 0.22, MeOH). The IR spectrum of **1** showed absorption bands for hydroxy and/or amino (3256 cm^{-1}), carbonyl (1715 cm^{-1}), and aromatic ring (1619 and 1474 cm^{-1}) functionalities. The positive mode ESIMS of **1** exhibited quasimolecular ion peaks at *m*/*z* 372 $[M + H]^+$, 394 $[M + Na]^+$, and 410 $[M + K]^+$. The molecular formula of $C_{18}H_{17}N_3O_2S_2$, with 12 degrees of unsaturation, was determined from HRESIMS at *m*/*z* 372.0844 $[M + H]^+$ (calcd for $C_{18}H_{17}N_3O_2S_2$, 372.0835) and 394.0659 $[M + Na]^+$ (calcd for $C_{18}H_{17}N_3O_2S_2Na$, 394.0654), combined with the NMR data (Table 1). The ^1H NMR spectrum of **1** in DMSO-d_6 displayed resonances attributable to (a) an *ortho*-disubstituted benzene ring [δ_H 7.02 (dd, J = 7.8 and 1.2 Hz, H-4), 6.88 (ddd, J = 1.2, 7.8, and 7.8 Hz, H-5), 7.24 (ddd, J = 1.2, 7.8, and 7.8 Hz, H-6), and 6.91 (dd, J = 7.8 and 1.2 Hz, H-7)]; (b) a trisubstituted double bond attached to an aliphatic methylene unit [δ_H 7.38 (dd, J = 5.4 and 3.0 Hz, H-4′)], of which the methylene protons resonated at δ_H 2.79 (m, H-5′a and H-5′b); (c) a terminal double bond connected to an oxymethine [δ_H 5.47 (ddd, J = 16.2, 10.8, and 5.4 Hz, H-3‴), 4.79 (ddd, J = 10.8, 1.8, and 1.8 Hz, H-4‴a), 4.77 (ddd, J = 16.2, 1.8, and 1.8 Hz, H-4‴b), and 4.17 (m, H-2‴)]; and (d) two other methylene units [δ_H 3.56 (ddd, J = 4.8, 10.8, and 15.6 Hz, H-6′a), 2.77 (m, H-6′b), 2.86 (dd, J = 13.8 and 6.6 Hz, H-1‴a), and 2.70 (dd, J = 13.8 and 7.2 Hz, H-1‴b)]. It also displayed exchangeable resonances assignable to an amide proton at δ_H 10.74 (brs, N*H*-1) and a secondary hydroxy proton at δ_H 4.93 (d, J = 5.4 Hz, O*H*-2‴). The ^{13}C NMR and DEPT spectra of **1** showed 18 carbon resonances, corresponding to the above units and four additional quaternary carbons including an sp^3-hybridized carbon [δ_C 48.4 (C-3)] and three sp^2-hybridized carbons [δ_C 176.8 (C-2), 172.9 (C-3″), and 185.7 (C-5″)] (Table 1). These spectroscopic data suggested that **1** was an aromatic alkaloid possessing unusual heterocycles.

Table 1. NMR Data for **1**[a]

	1 (DMSO-d_6)		**1** (acetone-d_6)	
no.	δ_H	δ_C	δ_H	δ_C
2		176.8		177.7
3		48.4		49.5
3a		129.1		130.3
4	7.02 dd (7.8, 1.2)	124.1	7.07 dd (7.8, 1.2)	125.2
5	6.88 ddd (1.2, 7.8, 7.8)	121.9	6.90 ddd (1.2, 7.2, 7.8)	122.9
6	7.24 ddd (1.2, 7.8, 7.8)	129.6	7.24 ddd (1.2, 7.2, 7.8)	130.5
7	6.91 dd (7.8, 1.2)	110.0	6.99 dd (7.8, 1.2)	110.9
7a		142.7		143.7
3′		126.7		128.6
4′	7.38 dd (5.4, 3.0)	141.6	7.40 dd (4.8, 4.2)	142.1
5′a	2.79 m	26.5	2.84 m	27.8
5′b	2.79 m		2.84 m	
6′a	3.56 ddd (4.8, 10.8, 15.6)	21.1	3.76 ddd (13.8, 8.4, 6.6)	22.2
6′b	2.77 m		2.74 ddd (13.8, 4.2, 3.6)	
3″		172.9		174.1
5″		185.7		187.3
1‴a	2.86 dd (13.8, 6.6)	40.7	2.88 dd (14.4, 6.6)	41.5
1‴b	2.70 dd (13.8, 7.2)		2.79 dd (14.4, 6.6)	
2‴	4.17 m	69.8	4.31 m	71.1
3‴	5.47 ddd (16.2, 10.8, 5.4)	140.8	5.63 ddd (16.8, 10.8, 5.4)	141.5
4‴a	4.79 ddd (10.8, 1.8, 1.8)	113.6	4.98 ddd (16.8, 1.8, 1.2)	114.0
4‴b	4.77 ddd (16.2, 1.8, 1.8)		4.86 ddd (10.8, 1.8, 1.2)	
NH-1	10.74 brs		9.68 brs	
OH-2‴	4.93 d (5.4)		3.95 d (4.2)	

[a] NMR data (δ) were measured at 600 MHz for ^1H and at 150 MHz for ^{13}C. Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on DEPT, $^1H-^1H$ gCOSY, gHSQC, and gHMBC experiments.

The structure of **1** was further elucidated by comprehensive 2D NMR data analysis in both DMSO-d_6 and acetone-d_6. The gHSQC spectrum furnished assignments of the proton-bearing carbon and corresponding proton resonances in the NMR spectra. In the $^1H-^1H$ gCOSY spectrum of **1**, the homonuclear coupling correlations of H-4/H-5/H-6/H-7, H-4′/H_2-5′/H_2-6′, and H_2-1‴/H-2‴/H-3‴/H_2-4‴ revealed the presence of structural units containing the vicinally coupled protons (Figure 2, thick lines). In the HMBC spectrum, two- and three-bond correlations of H-4/C-3, C-5, C-6, and C-7a; H-5/C-3a, C-4, and C-7; H-6/C-4 and C-7a; H-7/C-5 and C-3a; and

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(8) For plant material, experimental procedures, and physical−chemical properties for compounds **1a** and **1b**, see Supporting Information.

N*H*/C-2, C-3, C-3a, and C-7a were observed. These correlations, in combination with the shifts of these proton and carbon resonances and the quaternary nature of C-3, demonstrated the presence of a 3,3-disubstituted indolin-2-one moiety in **1**. HMBC correlations of H-4′/C-3, C-5′, C-6′, and C-5″; H_2-5′/C-3′, C-4′, and C-6′; and H_2-6′/C-4′ and C-5′, in combination with the shifts of these proton and carbon resonances, indicated that the C-3 of the indolin-2-one moiety and quaternary sp^2-hybridized C-5″ were linked to one end (C-3′) of the trisubstituted double bond with the two methylene units (CH_2-5′ and CH_2-6′) at the other end. Meanwhile, HMBC correlations from H_2-6′ to C-3, together with the shifts of these proton and carbon resonances including C-6′ and the coupling patterns of H-6′a and H-6′b, revealed that C-3 linked to C-6′ through a sulfur atom, forming an unusual 5′,6′-dihydrospiro-[indoline-3,2′-thiopyran]-2-one moiety in **1**. In addition, HMBC correlations of H_2-1‴/C-2‴, C-3″, and C-3‴; H-2‴/C-1‴, C-3‴, C-4‴, and C-3″; H-3‴/C-2‴; H-4‴/C-3‴ and C-2‴; and O*H*-2‴/C-1‴, C-2‴, and C-3‴ indicated the presence of a 2‴-hydroxybut-3‴-en-1‴-yl unit connected by the remaining quaternary sp^2 hybridized carbon, C-3″. The chemical shifts of C-3″ and C-5″ in the aforementioned moieties, along with the molecular composition and degree of unsaturation of **1**, indicated that the two quaternary carbons must be connected by the two remaining nitrogen atoms and the remaining sulfur atom to construct a 1″,2″,4″- or 1″,3″,4″-thiadiazole ring. The chemical shifts of C-3″ and C-5″ were consistent with those of the corresponding carbons in 1,2,4-thiadiazole derivatives[9] but significantly different from those in 1,3,4-thiadiazole analogues,[10] suggesting the presence of a 1″,2″,4″-thiadiazole ring in **1**. Therefore, the gross structure of **1** was determined to be 3′-[3″-(2‴-hydroxybut-3‴-en-1‴-yl)-1″,2″,4″-thiadiazol-5″-yl]-5′,6′-dihydrospiro[indoline-3,2′-thiopyran]-2-one.

Since the stereoisomers of the proposed biosynthetic precursors, epiprogoitrin and progoitrin, were presented in *I. indigotica* in a 2:1 ratio,[6b] it was suspected that **1** was a mixture of two enantiomers in unequal amounts, which resulted in the optical activity. This was supported by HPLC analysis of **1** on an analytical chiral column, showing two peaks with an integration of about 2:1 ratio. Subsequent separation of **1** yielded **1a** {$[\alpha]_D^{20}$ −29.1 (*c* 0.15, MeOH)} and **1b** {$[\alpha]_D^{20}$ +28.9 (*c* 0.07, MeOH)}, which had opposite specific rotations and ECD data, but NMR data

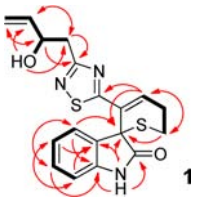

Figure 2. $^1H-^1H$ COSY (thick lines) and main HMBC (red arrows, from proton to carbon) correlations for **1**.

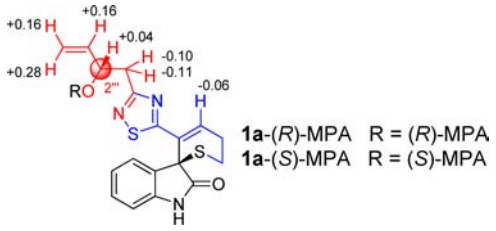

Figure 3. Δδ values ($\delta_R - \delta_S$, black data in ppm) for **1a**-(*R*)-MPA and **1a**-(*S*)-MPA.

were identical to those of **1** prior to HPLC separation. This confirmed that **1** was a mixture of enantiomers with a **1a**/**1b** ratio of ∼2:1. The absolute configuration at C-2‴ in **1a** was determined by Mosher's method.[11] Esterification of **1a** with (*R*)-(−)- and (*S*)-(+)-α-methoxyphenylacetic acid (MPA) gave the corresponding derivatives **1a**-(*R*)-MPA and **1a**-(*S*)-MPA. The ^1H NMR data of the diastereomers were assigned on the basis of $^1H-^1H$ COSY experiments. From the MPA determination rule based on the Δδ values[11] (Figure 3), the configuration of **1a** was determined to be 2‴*S* and that of the enantiomer (**1b**) was assigned as 2‴*R*. The absolute configurations at C-3 in **1a** and **1b** were determined by comparison of the experimental ECD spectra with those predicted from quantum mechanical time dependent density functional theory (TDDFT) calculations.[12] In the ECD calculation, the flexible 2‴-hydroxybut-3‴-enyl unit was replaced by a methyl group to simplify the computation since this unit may generate various conformations but has little effect on the ECD data.[13] A pair of enantiomers (**1A** and **1B**) was proposed as the model compounds. The theoretically calculated ECD spectra of **1A** and **1B** were in good agreement with the experimental ECD spectra of **1a** and **1b** (Figure 4), respectively. This indicated that **1a** and **1b** had the 3*S*- and 3*R*-configurations, respectively. Therefore, compounds **1a** and **1b** were determined as (−)-(2‴*S*,3*S*)- and (+)-(2‴*R*,3*R*)-3′-{3″-[2‴-hydroxybut-3‴-en-1‴-yl]-1″,2″,4″-thiadiazol-5″-yl}-5′,6′-dihydrospiro[indoline-3,2′- thiopyran]-2-one, respectively.[14]

Compounds **1a** and **1b** are characterized by the 5′,6′-dihydrospiro[indoline-3,2′-thiopyran]-2-one and 3″-(2‴-hydroxybut-3‴-en-1‴-yl)-1″,2″,4″-thiadiazole moieties,

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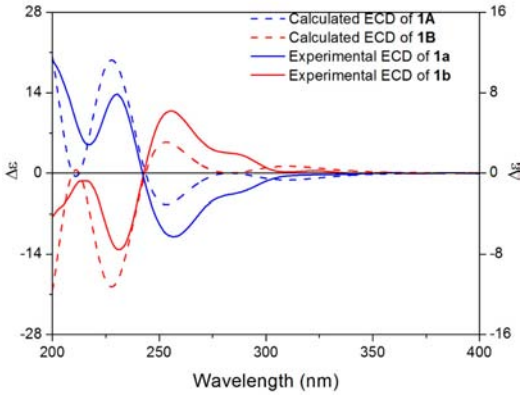
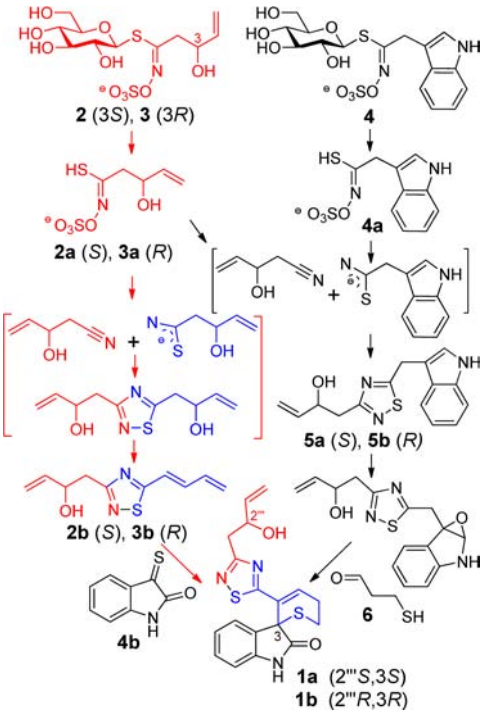


Figure 4. Measured ECD spectra of **1a** (blue) and **1b** (red) and the calculated ECD spectra of **1A** (blue dash) and **1B** (red dash).

which have never been presented in a natural product. However, dendrodoine, 5-[3-(*N*,*N*-dimethylamino-1,2,4-thiadiazolyl)-3-indolylmethanone which contains a similar thiadiazole ring, was reported from the marine tunicate *Dendrodoa grossularia*.[15] Two plausible biosynthetic pathways for **1a** and **1b** are proposed in Scheme 1 (shown as red and black arrows, respectively). The biosynthetic precursors are proposed to be glucosinolates, epiprogoitrin (**2**) for **1a** and progoitrin (**3**) for **1b**, as well as glucobrassicin (**4**) for both. These compounds are abundant in cruciferous plants[16] including *I. indigotica*.[6b] Myrosinase catalyzed hydrolysis of **2**–**4**[6b] liberates intermediates **2a**–**4a**, respectively. Condensation of two molecules of **2a** or **3a** (or one molecule each of **2a** and **3a**) followed by dehydration would generate **2b** or **3b**, which is possibly mediated by coupling between a nitrile and an imidothioate, the known breakdown products of **2a** and/or **3a**.[17] An enzyme-catalyzed Diels–Alder [4 + 2] cycloaddition[18] of **2b** and **3b** with 3-thioxoindolin-2-one (**4b**, a decomposition product of **4a**), followed by a simultaneous or sequential double bond rearrangement, would then give **1a** and **1b**.

Alternatively, the condensation of the nitrile from **2a** or **3a** with the imidothioate from **4a** would produce **5a** or **5b**,

Scheme 1. Plausible Biosynthetic Pathways of **1a** and **1b**



which would undergo oxidation and coupling with 3-mercaptopropanal (**6**, a possible plant metabolite[19]) to generate **1a** and **1b**.[20]

In preliminary in vitro assays,[21] compounds **1a** and **1b** showed antiviral activity against the herpes simplex virus 1 (HSV-1) with IC_{50} values of 33.33 and 25.87 μM and SI values of 2.0 and 3.9, respectively (the positive control acyclovir gave IC_{50} = 0.41 μM and SI = 241.9). Compound **1a** also inhibited the influenza virus A/Hanfang/359/95 (H3N2), with IC_{50} and SI values of 33.33 μM and 3.0, respectively, but **1b** was inactive (IC_{50} > 100) (the positive control, oseltamivir, gave IC_{50} = 1.62 μM and SI = 777.8).

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Supporting Information Available. Plant material, experimental procedures; physical–chemical properties; the measured and calculated ECD spectra; copies of IR, MS, HRMS, and 1D and 2D NMR spectra of **1**, **2**, **1a**-(*R*)-MPA, and **1a**-(*S*)-MPA. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(20) The similarity of the ratios between the precursors (**2**/**3**) and the final products (**1a**/**1b**) suggests that the alcohol is formed first and the spiro-center then follows. The spiro-center would be likely formed in a nonenantioselective manner, and this process would not be affected by the first because the chiral alcohol is away from the spiro-center. In addition, the presence of diastereoisomers of **1a** and **1b** in this material is speculated based on the isolation of a pair of enantiomers with a similar indoline moiety (see ref 7).

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