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Fistulains A and B, New Bischromones from the Bark of *Cassia fistula*, and Their Activities

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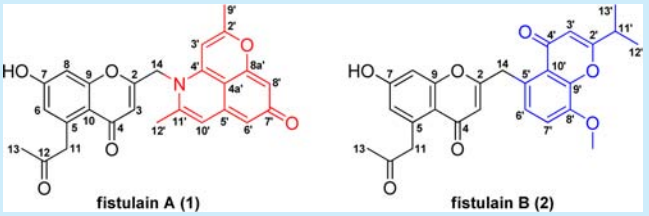
Supporting Information

ABSTRACT: Fistulains A and B (**1** and **2**), two novel bischromones with unique coupling patterns, alone with their biosynthetic related compound **3**, were isolated from the bark of *Cassia fistula*. Fistulain A represents a new type of dimeric chromone alkaloid biogenetically derived from a chromone and a tricyclic alkaloid through an unusual C-14−N linkage. Fistulain B has a new carbon skeleton with a C-14−C-5′ linkage formed between two different chromone units. Fistulain A displayed anti-TMV activity, and both **1** and **2** showed weak cytotoxicities.



Cassia Linn. is a major genus of the legume family (Fabaceae) comprising approximately 600 species, some of which possess broad-spectrum pharmacological properties and are used in ethnomedicine systems, such as the Ayurvedic medicine and the Chinese Dai tribal folk medicine.[1] The pharmacological properties of these medicinal plants are attributed to the occurrence of bioactive secondary metabolites such as alkaloids,[2] anthraquinones,[1d] and polyphenolics (flavanoids, catechines, and proanthocyanidins).[1b] For example, cassiarin A (Figure 1), a tricyclic alkaloid displaying promising antiplasmodial activity from the leaves of *C. siamea*,[2a] has attracted the widespread attention of synthetic chemists[3] and pharmacologists.[4]

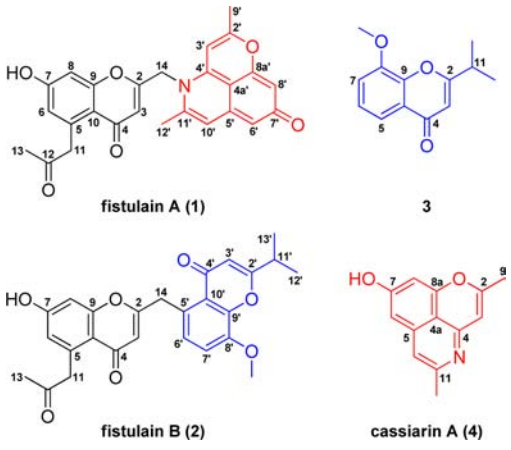


Figure 1. Structures of **1**−**3** and cassiarin A (**4**).

Several species of *Cassia* (e.g., *C. fistula*, *C. siamea*, *C. alata*, *C. tora*, and *C. occidentalis*) are used in the folk medicine of the tribe of Dai in China, notably for the treatment of skin infection, tumor, periodic fever, diabetes, and other ailments.[1,5] Among them, *C. fistula*, locally known as "Gou-Long-Liang", is frequently prescribed as a tonic, astringent, febrifuge, and purgative agent in the clinics and drug stores in the Xishuangbanna Prefecture of Yunnan Province of China.[1,5] It was reported that different parts of this plant displayed hepatoprotective, antidiabetic, antitumor, antioxidant, anti-inflammatory, antiparasitic, antiviral, antifungal, and antibacterial activities.[6]

In the present study, two new highly aromatized bischromones, fistulains A (**1**) and B (**2**), possessing unique cross-coupling patterns, together with a possible biogenetic precursor **3** (Figure 1), were isolated from the bark of *C. fistula*. Compound **1** displayed antitobacco mosaic virus activity, and all isolated compounds exhibited weak cytotoxicities in our test models. Herein, the isolation and structural elucidation of **1**−**3**, as well as their biological properties, are described in detail.

Compound **1** was obtained as yellow gum. Its molecular formula $C_{26}H_{21}NO_6$ was established from HRESIMS (*m*/*z* at 466.1261 $[M + Na]^+$), possessing an index of hydrogen deficiency of 17. The IR spectrum showed absorption bands

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Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR Spectroscopic Data of Compounds 1−3 in $CDCl_3$ (δ ppm)

	1			2			3		
no.	δ_C	δ_H	HMBC($^{1}H \rightarrow {}^{13}C$)	δ_C	δ_H	HMBC($^{1}H \rightarrow {}^{13}C$)	δ_C	δ_H	HMBC($^{1}H \rightarrow {}^{13}C$)
2	166.4 s			164.8 s			168.1 s		
3	113.1 d	6.21, s	2, 4, 10, 14	114.2 d	6.20, s	2, 4, 10, 14	105.8 d	6.38, s	2, 4, 10, 11
4	180.1 s			180.5 s			182.3 s		
5	138.5 s			138.3 s			123.6 d	7.36, d (7.8)	4, 6, 7, 9, 10
6	121.1 d	6.59, d (1.8)	5, 7, 8, 10, 11	120.5 d	6.58, d (1.3)	5, 7, 8, 10, 11	128.2 d	7.08, t (7.8)	5, 7, 8, 10
7	163.8 s			164.0 s			121.5 d	6.91, d (7.8)	5, 6, 8, 9
8	103.6 d	6.66, d (1.8)	6, 7, 9, 10	103.3 d	6.65, d (1.3)	6, 7, 9, 10	154.6 s		
9	161.4 s			161.4 s			148.2 s		
10	115.9 s			115.6 s			124.1 s		
11	50.5 t	4.24, s	5, 6, 10, 12, 13	50.8 t	4.20, s	5, 6, 10, 12, 13	34.4 d	2.68, q (6.8)	2, 3, 12, 13
12	207.9 s			208.4 s			19.2 q	1.29, d (6.8)	2, 11
13	30.8 q	2.26, s	11, 12	31.0 q	2.28, s	11, 12	19.2 q	1.29, d (6.8)	2, 11
14	58.2 t	3.45, s	2, 3, 9, 4′, 11′	36.5 t	3.29, s	2, 3, 5′, 6′, 10′			
2′	168.3 s			168.2 s					
3′	98.2 d	6.85, s	2′, 4′, 4a′, 9′	106.5 d	6.11, s	2′, 4′, 10′, 11′			
4′	146.3 s			181.5 s					
4a′	110.2 s								
5′	136.2 s			132.0 s					
6′	108.3 d	6.53, s	4a′, 5′, 7′, 8′, 10′	125.6 d	6.88, d (8.6)	C-14, 5′, 7′, 8′, 10′			
7′	175.1 s			122.5 d	7.00, d (8.6)	C-5′, 6′, 8′, 9′			
8′	105.3 d	6.78, s	4a′, 6′, 7′, 8a′	152.6 s					
8a′	155.9 s								
9′	22.1 q	2.38, s	2′, 3′, 8a′	148.8 s					
10′	116.8 d	6.93, s	4a′, 5′, 6′, 11′, 12′	123.1 s					
11′	141.6 s			33.1 d	2.66, q (6.8)	2′, 3′, 12′, 13′			
12′	21.6 q	2.51, s	14, 4′, 10′, 11′	18.7 q	1.12, d (6.8)	2′, 11′			
13′				18.7 q	1.12, d (6.8)	2′, 11′			
7-OH		10.21, br s	6, 7, 8		10.17, br s	6, 7, 8			
8-OMe							56.0 q	3.80, s	8
8′-OMe				55.9 q	3.81, s	8′			

due to hydroxyl (3446 cm^{-1}) and carbonyl (1730 cm^{-1}) groups. The ^{1}H NMR spectrum displayed signals of three methyl groups (δ_H 2.26, s, H_3-13; 2.38, s, H_3-9′; 2.51, s, H_3-12′), two methylene groups (δ_H 3.45, s, H_2-14; 4.24, s, H_2-11), five uncoupled aromatic protons (δ_H 6.21, s, H-3; 6.53, s, H-6′; 6.78, s, H-8′; 6.85, s, H-3′; 6.93, s, H-10′), and a 1,2,3,5-tetrasubstituted benzene ring (δ_H 6.59, d, J = 1.8 Hz, H-6; 6.66, d, J = 1.8 Hz, H-8). The 26 carbon resonances observed in the ^{13}C NMR and DEPT spectra (Table 1) were assignable to three methyls (including two aromatic methyl groups), two methylenes, seven aromatic methines, and 14 quaternary carbons (including three carbonyls and five oxygenated quaternary carbons). Among them, 3 carbonyls and 18 olefinic carbons account for 12 degrees of unsaturation, suggesting that **1** is a highly aromatized C_{26} nitrogen-containing structure with a pentacyclic ring system.

Taking reference to the NMR and MS data of previously reported compounds from the genus *Cassia*[2] prompted us to consider compound **1** as a heterodimer comprising two C_{13}-chromone moieties designated as subunits **1A** and **1B**. The gross structures of **1A** and **1B** were elucidated as follows.

In subunit **1A** (O-1 to C-14), the presence of a chromone nucleus (rings A and B) was deduced by their characteristic ^{13}C and/or ^{1}H signals (δ_C 166.4, 113.1, 180.1, 138.5, 121.1, 163.8, 103.6, 161.4, and 115.9; δ_H 6.21, 6.59, and 6.66), together with a set of HMBC correlations involving H-3 and C-2/C-4/C-10, H-6 and C-8/C-10, and H-8 and C-6/C-10 (Figure 2). In addition, an acetonyl group (C-11 to C-13) and a hydroxyl

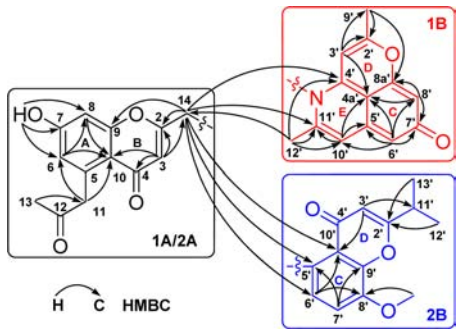

Figure 2. Selected HMBC correlations of **1** and **2**.

group (7-OH) were assigned to C-5 and C-7, respectively, which could be confirmed by the HMBC correlations observed between H_2-11 and C-6/C-10, and between 7-OH and C-6/C-7/C-8 (Figure 2). The above data were similar to those of 5-acetonyl-7-hydroxy-2-methylchromone previously obtained from *C. siamea*.[7] The only difference was that the C-14 methyl group in ring A was now attached to a heteroatom (N or O), as shown by the HMBC correlations between H-3 (δ_H 6.21, s) and C-14 (δ_C 58.2, t), as well as between H_2-14 (δ_H 3.45, s) and C-2 (δ_C 166.4, s), C-3 (δ_C 113.1, d), and C-9 (δ_C 161.4, s) ($^{4}J_{CH}$) (Figure 2). This led to the assignment of part **1A** being linked to unit **1B** through C-14.

The remaining 13 carbon resonances belonged to subunit **1B**, comprising two methyls, four methines, and seven quaternary

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carbons, attributable to a tricyclic C_{13}-chromone alkaloid (rings C−E). Five downfield quaternary carbons (δ_C 141.6, 146.3, 155.9, 168.3, and 175.1) were ascribed to carbons bonded to either a nitrogen or oxygen atom. The upfield shift of the carbonyl at δ_C 175.1 (C-7′) suggested conjugation with two double bonds, which was confirmed by the HMBC correlations between H-6′ and C-5′/C-7′/C-8′ and between H-8′ and C-6′/C-7′/C-8a′ (Figure 2). Taking into consideration the key HMBC correlations between H_3-9′ and C-2′/C-3′/C-8a′, between H-3′ and C-2′/C-4a′/C-9′, and between H-6′ and C-4a′/C-5′/C-7′/C-8′/C-10′ led to the assignment of a chromone skeleton (rings C and D) with a methyl at C-2′ and a conjugated carbonyl at C-7′.[2a]

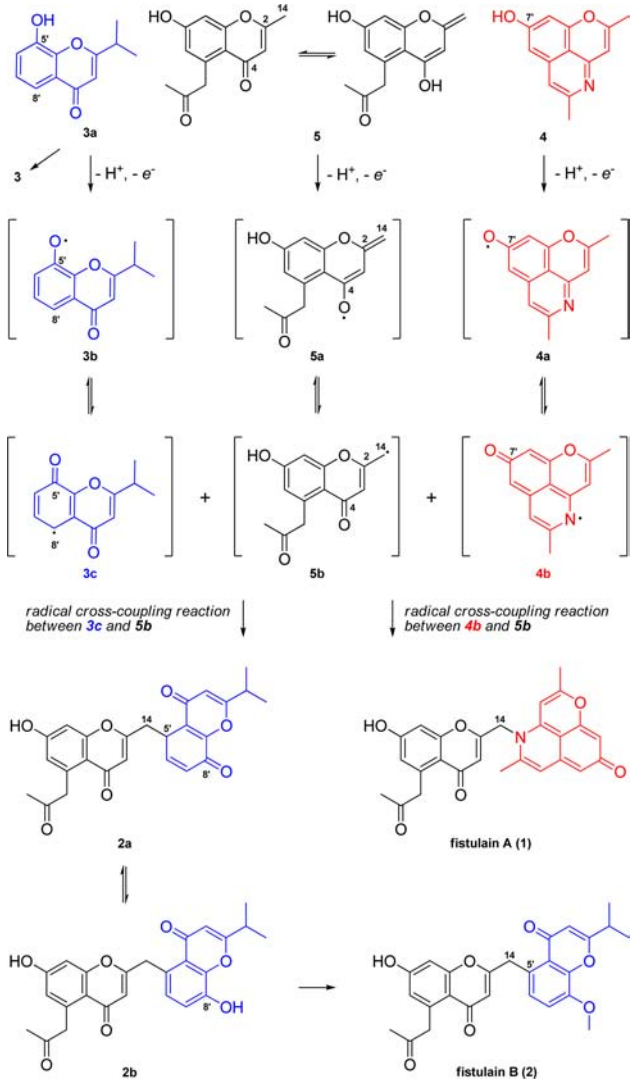
Meanwhile, the HMBC correlations between H-10′ and C-4a′/C-5′/C-6′/C-11′/C-12′ and between H-12′ and C-14/C-4′/C-10′/C-11′ revealed that C-4′, C-4a′, C-5′, C-10′, C-11′, C-12′, together with a nitrogen atom, have formed a 2-methylpyridine ring (ring E) which is coupled to the chromone (rings C and D) at C-4′, C-4a′, and C-5′. Finally, the direct linkage between **1A** and **1B** through the nitrogen atom and C-14 could be readily established by the key HMBC correlations observed between H_2-14 and C-4′/C-11′ and between H_3-12′ and C-14 (Figure 2). The above evidence led to the structural assignment of **1** as depicted in Figure 1, and it was given a trivial name of fistulain A.

The molecular formula of fistulain B (**2**) was deduced to be $C_{26}H_{24}O_7$ on the basis of positive HRESIMS at m/z 471.1427 $[M + Na]^+$. Analysis of the NMR spectra (Table 1), including HMBC (Figure 2) and ROESY, suggested that **2** was made up of two parts (subunits **2A** and **2B**). While subunit **2A** shares the same structure as **1A** (5-acetonyl-7-hydroxy-2-methylchromone), the NMR signals of subunit **2B** were almost identical to those of compound **3** (8-methoxy-2-isopropylchromone). Based on the HMBC spectral data, the singlet at δ_H 3.29 was assigned to H_2-14, and it was correlated to C-5′, C-6′, and C-10′, revealing the connection between **2A** and **2B** via C-14 and C-5′. All available data led to the structural assignment of **2** as depicted in Figure 1, and the compound was given a trivial name of fistulain B.

Compound **3** was obtained as yellow gum. The molecular formula $C_{13}H_{14}O_3$ was determined on the basis of HREIMS at m/z 241.0845 $[M + Na]^+$, corresponding to an index of hydrogen deficiency of 7. The ^1H and ^{13}C NMR spectra (Table 1) revealed signals for a chromone (δ_H 6.38, 7.36, 7.08, and 6.91; δ_C 168.1, 105.8, 182.3, 123.6, 128.2, 121.5, 154.6, 148.2, and 124.1), an isopropyl group (δ_H 2.68, 1.29, and 1.29; δ_C 34.4, 19.2, and 19.2), and a methoxyl group (δ_H 3.80; δ_C 56.0). The HMBC correlations between H-11 and C-3 and between H_3-12/13 and C-2 indicated that the isopropyl group was located at C-2. Similarly, the attachment of the methoxy group at C-8 was supported by the HMBC correlations between 8-OMe and C-8. Thus, the structure of **3** was established to be 8-methoxy-2-isopropylchromone (Figure 1).

Previous reports have disclosed the presence of bischromones from the *Cassia* genus.[8] Normally, these bischromones are derived from two monomeric units through a C-14−C-2′ linkage presumably via Michael addition.[8] In this respect, fistulains A and B represent two new types of heterodimers with unique coupling patterns (C-14−N and C-14−C-5′ bonds, respectively), presumably formed by unusual intermolecular oxidative phenol-coupling reactions between 5-acetonyl-7-hydroxy-2-methylchromone (**5**)[7] and a tricyclic C_{13}-chromone alkaloid (**4**)[2a] or 8-hydroxy-2-isopropyl-chromone (**3a**) (Scheme 1).

Scheme 1. Hypothetical Biogenetic Pathway of Compounds 1−3



Such coupling patterns are of particular significance from the biogenetic point of view.[8,9]

Generally speaking, intermolecular oxidative phenol coupling is considered a major process in nature for the formation of atropisomeric biaryl structures wherein the rotation of the aryl−aryl bond is restricted.[10] Recently, several examples for regio- and stereoselective biosynthesis of biaryl compounds in fungi, bacteria, and plants have been described.[11] However, unlike those axially chiral molecules, fistulains A and B do not display planar chirality, because the two subunits are connected by C−C or C−N bonds which can rotate freely. Further studies on the biogenesis of these two structurally unique dimers are warranted.

Considering the medicinal applications of the plant species and the biological activities of many chromones,[12] compounds **1−3** were tested for cytotoxicity, antitobacco mosaic virus, antimicrobial, and antidiabetic activities. In an *in vitro* model of insulin sensitivity in 3T3-L1 differentiated adipocytes,[13] no significant activity of these compounds was detected at concentrations up to 10 μM. Compounds **1−3** did not display antimicrobial activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *S. pneumonia*, *Escherichia coli* ATCC 25922, and *Enterococcus faecalis*, using the paper disc method.[14]

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The inhibitory activity against tobacco mosaic virus (TMV) replication was tested by the half-leaf method, using ningnamycin as the positive control.[12,15] Compound **1** exhibited significant activity with an IC_{50} value of 43.8 μM, comparable to the positive control (IC_{50} = 52.4 μM) (Table 2).

Table 2. Anti-TMV Activity on *Nicotiana tabacum* Leaf and Protective Effect of 1−3 on TMV Infection

compd	inhibition rate at 20 μM (%)[a]	IC_{50} (μM)[a]	inhibition rate at 20 μM (%)[b]
1	32.8 ± 3.0	43.8	33.4 ± 2.7
2	25.6 ± 2.6	62.9	22.9 ± 2.9
3	18.8 ± 2.3	147.5	16.9 ± 2.0
Ningnamycin	30.5 ± 2.8	52.4	28.6 ± 3.2

[a]Anti-TMV activity. [b]Protective effect on TMV infection.

Compounds **2** and **3** showed weak activities. In addition, the protective effect of **1**−**3** against TMV was evaluated by pretreating the tobacco leaves with the test compounds for 6 h before viral inoculation.[12,15] The protective effect on the host plant was observed in **1** with an inhibition rate of 33.4% at 20 μM, while **2** and **3** exhibited only weak activities (Table 2). The result suggests that pretreatment with **1** may increase the resistance of tobacco leaves against TMV infection.

Compounds **1**−**3** were also screened for cytotoxic activity in a panel of human cancer cell lines, including NB4 promyelocytic leukemia, A549 lung epithelial carcinoma, SHSY5Y neuroblastoma, PC3 prostate cancer, and MCF7 breast adenocarcinoma cells, using the MTT method with paclitaxel as the positive control.[15] Table 3 shows they exhibited weak cytotoxicity in several cell lines, with IC_{50} values ranging from 4.6 to 8.8 μM.

Table 3. Cytotoxic Activity of 1−3[a]

compd	NB4	A549	SHSY5Y	PC3	MCF7
1	5.5	4.6	>10	>10	8.8
2	8.2	5.6	>10	6.8	>10
3	>10	8.5	6.8	>10	>10
Taxol	0.02	0.02	0.1	0.1	0.05

[a]Results were expressed as IC_{50} values in μM.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01007.

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Notes

The authors declare no competing financial interest.

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