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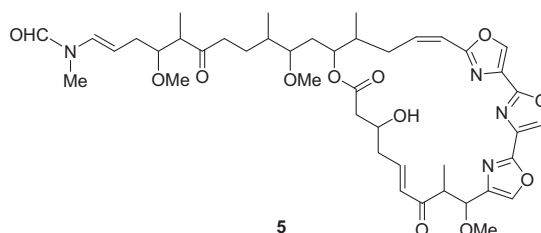
Contents

ARTICLES

Actin depolymerizing effect of trisoxazole-containing macrolides

pp 3198–3201

Soon-Chun Chung, So-Hyoung Lee, Kyoung Hwa Jang, Wanki Park, Ju-eun Jeon, Hana Oh, Jongheon Shin*, Ki-Bong Oh*

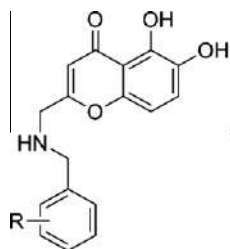


(19Z)-Halichondramide (5) with enhanced actin depolymerizing activity and potent antifungal activity.

2-Arylmethylaminomethyl-5,6-dihydroxychromone derivatives with selective anti-HCV activity

pp 3202–3205

Hye Ri Park, Kwang-Su Park, Youhoon Chong*

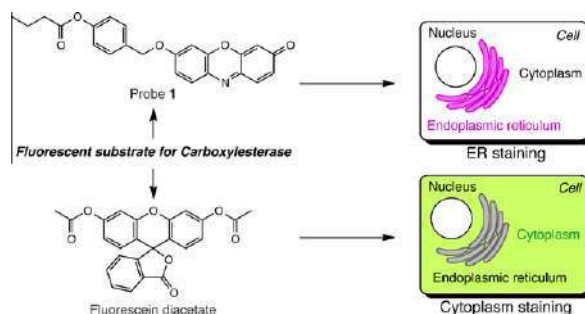


Compd	R	EC ₅₀ (μM)	CC ₅₀ (μM)
3i	3-Cl	14.0	>100
3j	3-Br	3.6	>100
3k	3-I	7.3	>100
3n	3-Me	2.0	>100

Design and synthesis of an ER-specific fluorescent probe based on carboxylesterase activity with quinone methide cleavage process

pp 3206–3209

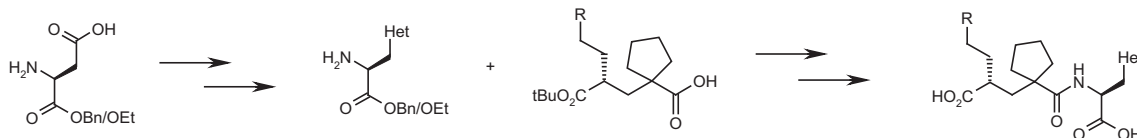
Wataru Hakamata*, Aki Machida, Tadatake Oku, Toshiyuki Nishio



Synthesis and evaluation of heteroarylalanine diacids as potent and selective neutral endopeptidase inhibitors

pp 3404–3406

Melanie S. Glossop*, Richard J. Bazin, Kevin N. Dack, David N. A. Fox, Graeme A. MacDonald, Mark Mills, Dafydd R. Owen, Chris Phillips, Keith A. Reeves, Tracy J. Ringer, Ross S. Strang, Christine A. L. Watson

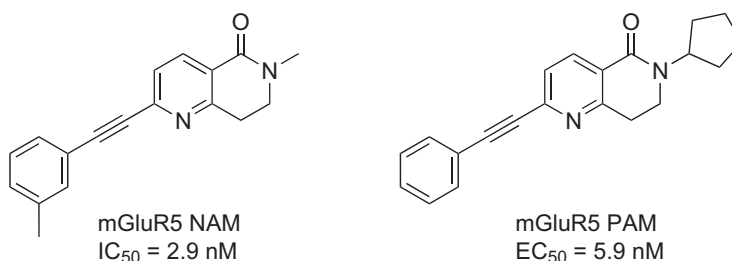


Novel heteroarylalanines derived from L-aspartic acid were designed and synthesised as potential inhibitors of Neutral Endopeptidase (NEP).

Efficacy switching SAR of mGluR5 allosteric modulators: Highly potent positive and negative modulators from one chemotype

pp 3407–3410

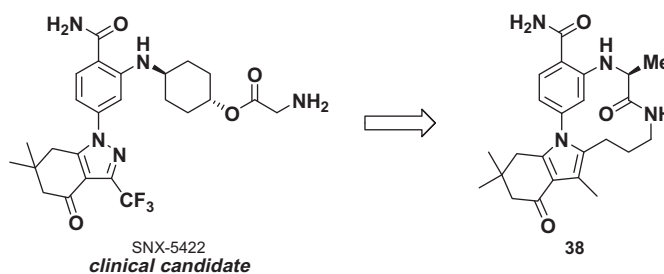
Anette Graven Sams, Gitte Kobberø Mikkelsen, Robbin M. Brodbeck, Xiaosui Pu, Andreas Ritzén*



Macrocyclic lactams as potent Hsp90 inhibitors with excellent tumor exposure and extended biomarker activity

pp 3411–3416

Christoph W. Zapf*, Jonathan D. Bloom, Jamie L. McBean, Russell G. Dushin, Thomas Nittoli, Mercy Otteng, Charles Ingalls, Jennifer M. Golas, Hao Liu, Judy Lucas, Frank Boschelli, Yongbo Hu, Erik Vogan, Jeremy I. Levin

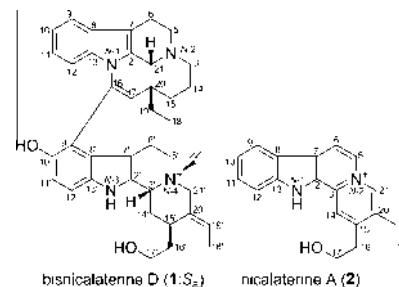


New antiplasmodial indole alkaloids from *Hunteria zeylanica*

pp 3417–3419

Alfarius E. Nugroho, Masatomo Sugai, Yusuke Hirasawa, Takahiro Hosoya, Khalijah Awang, A. Hamid A. Hadi, Wiwied Ekasari, Aty Widyawaruyanti, Hiroshi Morita*

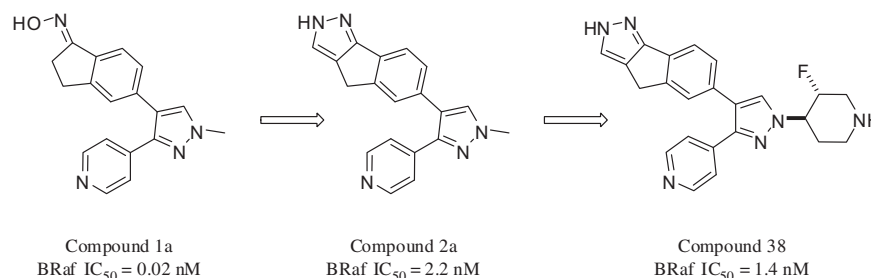
Two new indole alkaloids, bisnicalaterine D (1), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (2) were isolated from the bark of *Hunteria zeylanica*. Their structures were elucidated by various spectroscopic data such as NMR and CD spectra. A series of bisnicalaterines and nicalaterine A showed potent antiplasmodial activity against *Plasmodium falciparum* 3D7.



Non-oxime pyrazole based inhibitors of B-Raf kinase

pp 3488–3492

Bradley J. Newhouse*, Joshua D. Hansen, Jonas Grina, Mike Welch, George Topalov, Nicole Littman, Michele Callejo, Matthew Martinson, Sarah Galbraith, Ellen R. Laird, Barbara J. Brandhuber, Guy Vigers, Tony Morales, Rich Woessner, Nikole Randolph, Joseph Lyssikatos, Alan Olivero



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COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 206.]

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New antiplasmodial indole alkaloids from *Hunteria zeylanica*

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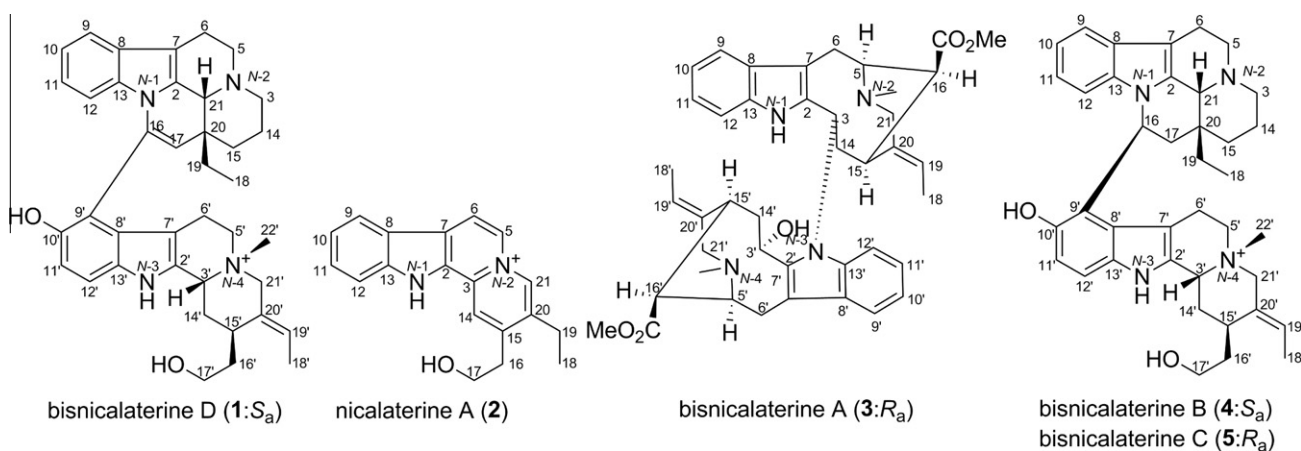
ABSTRACT

Two new indole alkaloids, bisnicalaterine D (**1**), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) were isolated from the bark of *Hunteria zeylanica*. Their structures were elucidated by various spectroscopic data such as NMR and CD spectra. A series of bisnicalaterines and nicalaterine A showed potent antiplasmodial activity against *Plasmodium falciparum* 3D7.

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In our search for new bioactive alkaloids from tropical plants in Malaysia and Indonesia, we have previously reported a series of cassiarins with potent antiplasmodial activity.^{1,2} *Hunteria zeylanica* (Retz.) Gardner ex Thwaites is a member of the Apocynaceae family in Malaysia, found mostly in Pahang and Selangor,³ and the bark and leaves have been known to produce various skeletal alkaloids depending on the area where the plants were distributed.^{4–9} In our

previous paper,^{10,11} we have reported the isolation of new bisindole alkaloids, bisnicalaterines A–C (**3–5**) from *H. zeylanica*. In this Letter, we report the isolation and structure elucidation of bisnicalaterine D (**1**), a new bisindole alkaloid consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) as well as the antimalarial activity of **1–5** against *Plasmodium falciparum* 3D7.



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The bark of *H. zeylanica*¹² was extracted with MeOH, and part (33 g) of the extract was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na₂CO₃ (aq) to pH 10 and extracted with CHCl₃ and *n*-BuOH subsequently. The *n*-BuOH fraction was subjected to an HP-20 column (H₂O/MeOH 0:1 to 1:0), and the 80% MeOH fraction (3.5 g) was further separated by using a Sephadex LH-20 column. Fractions containing **1** was then separated by a silica gel column (CHCl₃/MeOH, 9:1 to 0:1), followed by an ODS Sep-Pak (MeOH/H₂O 1:9 to 1:0) to give bisnicalaterine D (**1**, 8.1 mg, 0.003%), while purification of fractions containing **2** by an amino silica gel column (CHCl₃/MeOH, 9:1 to 0:1) and a silica gel column (CHCl₃/MeOH, 8:2) yielded nicalaterine A (**2**, 2.0 mg, 0.0008%).

Bisnicalaterine D (**1**),¹³ a yellowish amorphous solid, [α]_D²⁰ –72 (c 1.0, MeOH), showed a molecular formula, C₃₉H₄₇N₄O₂, which was determined by HRESIMS [*m/z* 603.3689 (M)⁺, Δ –0.5 mmu]. IR absorption band (3430 cm^{–1}) was characteristic of amino or

Table 1
¹H and ¹³C NMR data of bisnicalaterine D (**1**) and nicalaterine A (**2**) in CD₃OD at 300 K^a

Position	1		2	
	[δ_{H} (J, Hz)]	[δ_{C}]	[δ_{H} (J, Hz)]	[δ_{C}]
2		125.3		131.5
3a	3.37 (1H, m)	46.7		132.4
3b	3.37 (1H, m)			
5a	3.87 (1H, m)	53.1	8.69 (1H, br s)	127.3
5b	3.97 (1H, m)			
6a	3.13 (1H, m)	16.9	8.44 (1H, br s)	117.0
6b	3.30 (1H, m)			
7		108.2		123.0
8		128.7		122.3
9	7.48 (1H, d, 7.6)	119.7	8.21 (1H, d, 7.6)	122.6
10	6.97 (1H, m)	121.7	7.39 (1H, t, 7.6)	124.0
11	6.69 (1H, t, 8.3)	124.2	7.64 (1H, t, 7.6)	130.4
12	5.83 (1H, d, 8.3)	113.4	7.70 (1H, br s)	113.7
13		136.2		143.0
14a	1.83 (1H, m)	19.4	8.58 (1H, s)	121.2
14b	1.98 (1H, m)			
15a	1.68 (1H, m)	29.1		151.1
15b	1.86 (1H, m)			
16		131.9	3.22 (2H, br s)	36.2
17	5.26 (1H, s)	117.7	4.09 (2H, br s)	61.4
18	1.11 (3H, t, 7.6)	8.8	1.45 (3H, t, 7.2)	13.7
19a	1.85 (1H, m)	27.9	2.98 (2H, q, 7.2)	24.8
19b	2.00 (1H, m)			
20		39.2		139.5
21	5.22 (1H, s)	59.1	8.94 (1H, s)	135.1
2'		131.3		
3'	4.68 (1H, dd, 11.0, 3.5)	62.8		
5a'	2.93 (1H, m)	52.2		
5b'	3.76 (1H, m)			
6a'	1.53 (1H, m)	18.7		
6b'	2.93 (1H, m)			
7'		102.6		
8'		126.8		
9'		112.1		
10'		150.9		
11'	6.96 (1H, m)	114.3		
12'	7.39 (1H, d, 8.2)	114.8		
13'		133.0		
14a'	2.16 (1H, m)	36.1		
14b'	2.25 (1H, m)			
15'	3.16 (1H, m)	30.4		
16a'	1.86 (1H, m)	34.5		
16b'	1.96 (1H, m)			
17a'	3.51 (1H, m)	60.1		
17b'	3.62 (1H, m)			
18'	1.73 (3H, d, 6.9)	13.3		
19'	5.79 (1H, q, 6.9)	132.1		
20'		129.2		
21a'	3.66 (1H, m)	68.1		
21b'	4.18 (1H, br d, 13.8)			
22'	2.50 (3H, s)	48.6		

^a δ In ppm.

hydroxyl group. ¹H and ¹³C NMR data (Table 1) suggested the presence of one sp³ quaternary carbon, 12 sp³ methylenes, three sp³ methines, three methyls, eight sp² methines, and 12 sp² quaternary carbons. The ¹³C NMR spectrum of **1** is very similar to those of bisnicalaterines B (**4**).¹¹ Compared to spectroscopic data of **4**, **1** has two less sp³ carbons, two additional sp² carbons (δ_{C} 131.9 and δ_{C} 117.7) and also 2 amu smaller which suggests the existence of an additional double bond in **1**. The existence of a double bond between C-16 and C-17 was confirmed by the HMBC correlations of H-17 to C-16, C-19, C-20, C-21 and C-9', H₃-18 to C-20, and H-21 to C-15. Further analysis of the two-dimensional NMR data (¹H–¹H COSY, HMQC, and HMBC spectra) revealed the gross structure of **1** as shown in Figure 1.

The stereochemistry of each monoterpeneindole unit in **1** was assigned by NOESY correlations as shown in computer-generated 3D drawing (Fig. 2). In unit A, the NOESY correlations of H₂-19/H-21 suggested that H-21 and an ethyl group (C-18–C-19) were β -oriented. While in unit B, the NOESY correlations of H-3'/H₃-22', H-21'b, and H₂-16', H₃-22'/H-21'b and H-21'b/H-16'b suggested that H-3', C-16' and C-22' were β -oriented, while the correlations of H-19'/H-21'a and H-15'/H₃-18' established the *E*-configuration of the ethylidene side chain. Thus the relative stereochemistry of units A and B was assigned as shown in Figure 2.

In the case of bisnicalaterines B (**4**) and C (**5**), there were two possible conformations around C-16–C-9' bond, the twisted and extended conformations.¹¹ In bisnicalaterine D (**1**), the NOESY correlation of H-6'b/H-21 and the highly shifted chemical shift (δ_{H} 1.53 and 2.50, respectively) of H-6'a and H₃-22' at ammonium nitrogen atom suggested that **1** possessed the twisted conformation observed in bisnicalaterine B (**4**).¹¹

The absolute structure of **1** was deduced by comparing its CD spectrum to that of bisnicalaterine B (**4**). The CD spectrum¹³ of **1** showed a similar CD pattern to that of **4**,¹¹ thus the absolute structure of **1** was determined to be of 2*0R*, 21*R*, 4'*R*, 3'*R*, 15'*R*.

Nicalaterine A (**2**),¹⁴ a yellowish amorphous solid, showed a molecular formula, C₁₉H₁₉N₂O, which was determined by HRESIMS [*m/z* 291.1496 (M)⁺, Δ –0.1 mmu]. IR absorption band (3430 cm^{–1}) was characteristic of amino or hydroxyl group. The UV spectrum suggested the presence of a highly conjugated ring system [λ_{max} 386 (ϵ 8000), 346 (8300), 291 (6900), 240 (16,100), and 235 (sh, 15,000)] as in flavopereirine.¹⁵ ¹H and ¹³C NMR data (Table 1) suggested the presence of three sp³ methylenes, one methyl, eight sp²

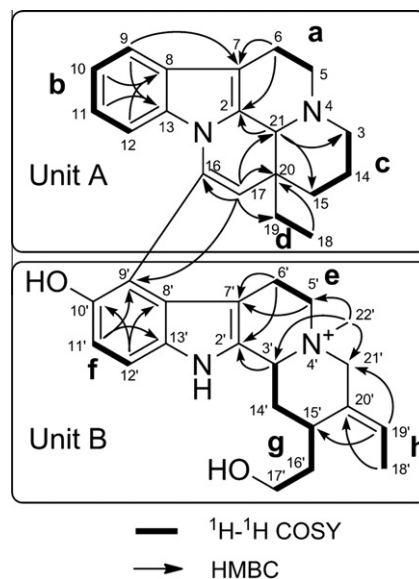


Figure 1. Selected 2D NMR correlations for bisnicalaterine D (**1**).

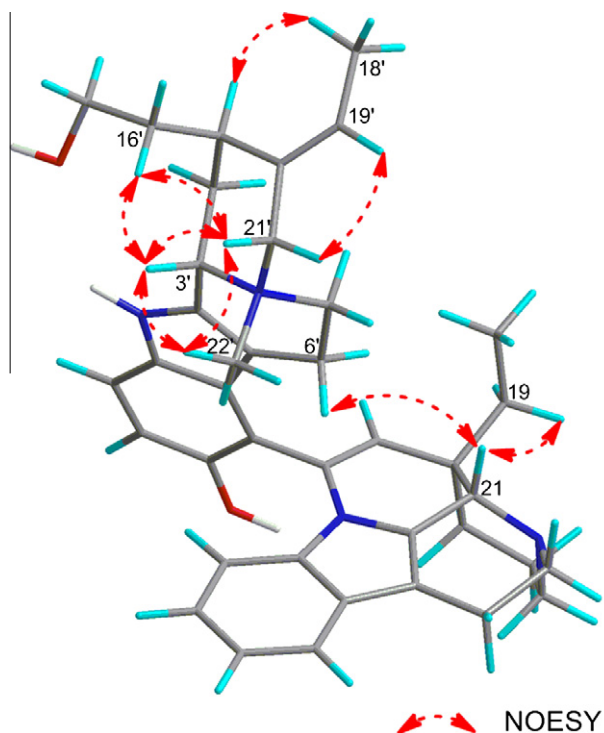


Figure 2. Selected NOESY correlations for bisnicalaterine D (1).

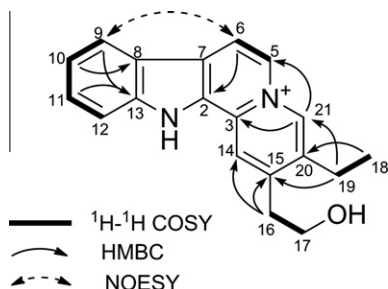


Figure 3. Selected 2D NMR correlations for nicalaterine A (2).

Table 2
Antiplasmodial activity of 1–5 against *P. falciparum* 3D7

	Antiplasmodial activity (IC ₅₀ , μM)	Cytotoxic activity ^a (IC ₅₀ , μM)	SI
1	>50	>50	–
2	0.11	>50	>450
3	4.36	16.2	3.7
4	1.13	>50	>44
5	0.05	>50	>1000

^a Against HL-60.

methines, and seven sp² quaternary carbons. The HMBC correlations of H₂-19 to C-15 and C-21, H₃-18 to C-20, and H₂-16 to C-15 and C-14 allowed the attachment of the ethyl side chain (C-18 and C-19) to C-20 and the 2-hydroxyethyl side chain to C-15. Further analysis of the two-dimensional NMR data (¹H-¹H COSY, HSQC, and HMBC spectra in CD₃OD) revealed the gross structure of **2** as shown in Figure 3.

Antimalarial activity^{16–18} for **1–5** against *P. falciparum* 3D7 was evaluated (Table 2). Nicalaterine A (**2**) and bisnicalaterine C (**5**)

showed potent antimalarial activity (IC₅₀ 0.11 and 0.05 μM, respectively) with a good selectivity (SI >450 and >1000, respectively). Bisnicalaterine C (**5**) with an extended conformation showed 20 times more effective than that of bisnicalaterine B (**4**) with a twisted conformation. On the other hand, bisnicalaterine D (**1**), which also possessed a twisted conformation, showed practically no antimalarial activity. It is interesting to note that the conformation around the C-16 - C-9' bond may play important roles to show antimalarial activity.

Acknowledgments

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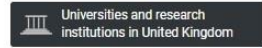
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- Bark of *H. zeylanica* were collected in Kampung Padang, Malaysia, in 1994. The botanical identification was made by Mr. Teo Leong Eng, Faculty of Science, University of Malaya. A voucher specimen (Herbarium No. KL 4345) is deposited at the Herbarium of the Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia.
- Bisnicalaterine D, yellowish amorphous solid, [α]_D²⁰ –72 (c 1.0, MeOH), UV (MeOH) λ_{max} 217 (ε 16800), 249 (6100), 277.5 (5300), 302 (4100); CD (MeOH) λ_{max} 205 (Δε 5.95), 218 (–6.09), 243 (6.54), 280 (–4.22), 365 (3.07); IR (KBr) ν_{max} 3430 cm^{–1}; ¹H and ¹³C NMR data see Table 1; EI-MS m/z 603 M⁺; HRESIMS [m/z 603.3689 (M)⁺, calcd for C₃₉H₄₇N₄O₂, 603.3694].
- Nicalaterine A (**2**), a yellowish amorphous solid, UV (MeOH) λ_{max}, 235 (sh, 15,000), 240 (16,100), 291 (6900), 346 (8300), and 386 (ε 8000); IR (KBr) ν_{max} 3430 cm^{–1}; ¹H and ¹³C NMR data see Table 1; EI-MS m/z 291 M⁺; HRESIMS [m/z 291.1496 (M)⁺, calcd for C₁₉H₁₉N₂O, 291.1497].
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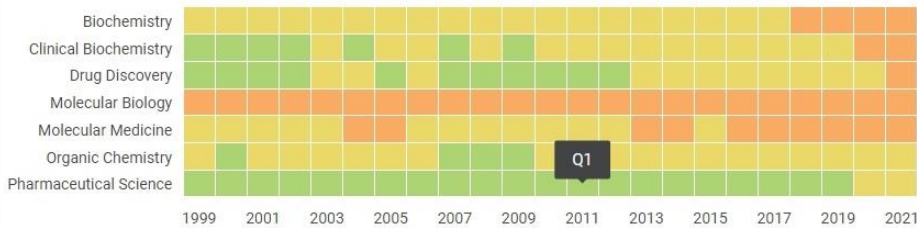
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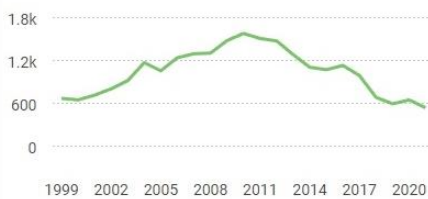
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