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## PREPARATION OF NEW VINDOLINE DERIVATIVES BY PALLADIUM-CATALYZED CROSS-COUPPLING REACTION

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**Abstract** – A new series of aryl-substituted vindoline derivatives (**3**) was prepared by palladium-catalyzed cross-coupling reaction of 15-iodovindoline (**1c**) with arylboronic acids (**2**).

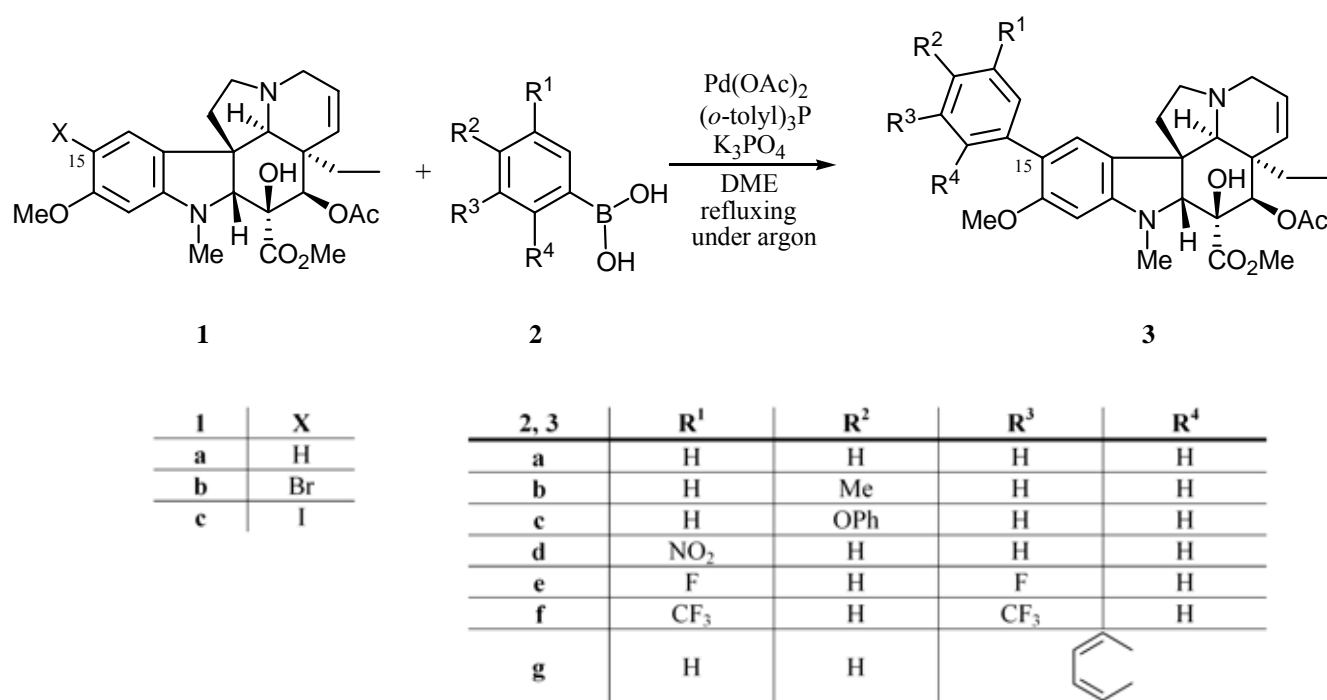
### INTRODUCTION

Vindoline (**1a**) was isolated from *Catharanthus roseus* (Madagascar) besides the bisindol alkaloids vincristine and vinblastine.<sup>1</sup> Lacks antitumor-activity alone but it formed the pentacyclic moiety in the above mentioned alkaloids used in the chemotherapy of cancer.<sup>2</sup> However, the antitumor activity of bisindol alkaloids was associated with toxic side effects. In the hope of preparation of pharmacologically efficient new compounds without serious side effects we had investigated the nucleophilic substitution of 15-halovindolines and synthesized a series of novel vindoline derivatives.

The palladium-catalyzed cross-coupling of aryl halides with arylboronic acids (Suzuki reaction) presents a powerful method for the synthesis of aromatic compounds.<sup>3, 4</sup> This strategy offers the advantage of easily available arylboronic acids, commercially available catalyst and functional group tolerance. Moreover, Suzuki-type cross-coupling reactions are insensitive to moisture and air. These prompted us to choose this method for the nucleophilic substitution reaction of 15-bromovindoline (**1b**).<sup>5</sup>

### RESULTS AND DISCUSSION

Cross-coupling reaction of **1b** with phenylboronic acid (**2a**)<sup>6</sup> gave pure conversion (Table 1). As it might be expected, this highly functionalized molecule showed low reactivity. Among the catalysts screened, the ligands of phosphorous seemed to play essential role in reactivity. According to previous findings by others, we got the higher conversion with tolylphosphine<sup>7</sup> ligands (Entries 2, 11 and 12). Among the solvents tested dimethoxyethane was the proper one (Entries 2 and 11).



Scheme 1

The failure with 15-bromovindoline prompted us to prepare the more reactive iodo compound (**1c**) and try to optimize the reaction conditions of its cross-coupling with phenylboronic acid. As seen from Table 2, the reaction was highly dependent upon the quality of both phosphino ligand and base. Namely, we have got the fastest reaction and the highest conversion with Pd(OAc)<sub>2</sub> and tolylphosphine catalysts system using K<sub>3</sub>PO<sub>4</sub> as base (Entry 4). With this standard reaction condition we could also efficiently synthesise a series of new 15-arylvindolines (**3b-g**, Table 3). We have observed acceptable rate of reactions even with hindered di-*meta*-substituted phenylboronic acids (**2e** and **f**) and bulky 2-naphthylboronic acid (**2g**).

**Table 1.-** Cross-coupling Reaction of 15-Bromovindoline (**1b**) with Phenylboronic Acid (**2a**)

Entry	Catalysts	Phosphino ligand	Base	Solvent	Conversion (%)			
					10 h	20 h	30 h	40 h
	Pd(OAc) <sub>2</sub>	PhP <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	DME				trace
2	Pd(OAc) <sub>2</sub>	( <i>o</i> -tolyl) <sub>3</sub> P	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	DME	14.5	15.8	16.0	15.4
3	Pd(OAc) <sub>2</sub>	dppp	(CsCl)	DME				-
4	Pd(OAc) <sub>2</sub>	( <i>t</i> -Bu) <sub>3</sub> P	Na <sub>2</sub> CO <sub>3</sub>	DME				-
5	Pd(Ph <sub>3</sub> ) <sub>4</sub>	-	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	DME				trace
6	Pd(OAc) <sub>2</sub>	dppp	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	DME				trace
7	PdCl <sub>2</sub>	dppf	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	DME				-
8	PdCl <sub>2</sub>	-	K <sub>2</sub> CO <sub>3</sub>	pyridine				-
9	Pd(OAc) <sub>2</sub>	-	K <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	acetone				-
10	PdCl <sub>2</sub>	PCy <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	acetone				-
11	Pd(OAc) <sub>2</sub>	( <i>o</i> -tolyl) <sub>3</sub> P	K <sub>3</sub> PO <sub>4</sub> /H <sub>2</sub> O	DME	23.1	23.2	25.2	24.6
12	Pd(OAc) <sub>2</sub>	( <i>o</i> -tolyl) <sub>3</sub> P	KOAc/H <sub>2</sub> O	DME	1.7	1.8		trace
13	Pd(OAc) <sub>2</sub>	( <i>o</i> -tolyl) <sub>3</sub> P	Na <sub>2</sub> CO <sub>3</sub>	DMF				-

**Table 2.-** Cross-coupling Reaction of 15-Iodovindoline (**1c**) with Phenylboronic Acid (**2a**)

Entry	Catalysts	Phosphino ligand	Base	Solvent	Conversion (%)			
					10 h	20 h	30 h	40 h
1	Pd(OAc) <sub>2</sub>	-	K <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	acetone	38.1	40.2	43.1	45.7
2	Pd(OAc) <sub>2</sub>	dppp	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	DME	10.4	14.8	23.5	27.7
3	Pd(OAc) <sub>2</sub>	( <i>o</i> -tolyl) <sub>3</sub> P	Na <sub>2</sub> CO <sub>3</sub> /H <sub>2</sub> O	DME	23.0	23.5	27.3	30.4
4	Pd(OAc) <sub>2</sub>	( <i>o</i> -tolyl) <sub>3</sub> P	K <sub>3</sub> PO <sub>4</sub> /H <sub>2</sub> O	DME	92.1	95.7	94.0	92.7

We can conclude that the above described method is suitable for the preparation of a new class of vindoline derivatives bearing substituent in position 15. This new compounds are of biological and medicinal interest. Spectral and analytical data for the compounds prepared are summarized in Table 4.

## EXPERIMENTAL

Melting points measured using a PHMK apparatus were uncorrected. IR spectra were recorded on Spekord 75IR spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained with a Bruker DRX-500 spectrometer; internal standard TMS. MS measurements were carried out on a Quattro Ultima Platinum instrument (electrospray ionization). Only selected peaks from the IR and MS spectra are quoted. Merck precoated silica gel 60 F<sub>254</sub> plates were used for TLC and Kieselgel 60 for column chromatography. All solvents were purified by means of standard methods.

**15-Iodovindoline (1c).** To a stirred solution of vindoline (**1a**; 3.0 g, 6.57 mmol) was added *N*-iodosuccinimide (0.54 g, 7.23 mmol), and the resulting mixture was stirred for 5 h at rt. The precipitate was filtered off and washed with cold DME. The filtrate was extracted with aqueous 5 % NaHCO<sub>3</sub> solution (20 mL), water (2 x 20 mL), and dried (MgSO<sub>4</sub>). Evaporation of the solvent yielded crystalline material, which was combined with the above solid to yield 3.75 g of crude **1c** (98 %) (which was used without further purification).

mp: 233 °C (decomp); TLC: 0.39; RP-18 F254 S aluminum sheets; eluent: MeOH : H<sub>2</sub>O : TFA 7 : 3 : 0.1; R<sub>f</sub> = 1.75; Purospher RP18e; eluent: acetonitrile-H<sub>2</sub>O-H<sub>3</sub>PO<sub>4</sub> 4:6:0.05; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ = 0.52 (t, *J* = 7.5 Hz, 3H, CH<sub>3</sub>); 1.12 (m, 1H, CH<sub>2</sub>); 1.66 (m, 1H, CH<sub>2</sub>); 2.08 (s, 3H, COCH<sub>3</sub>); 2.32 (m, 1H, C<sub>11</sub>-H); 2.42 (m, 1H, C<sub>11</sub>-H); 2.64 (m, 1H, C<sub>10</sub>-H); 2.7 (s, 3H, N-CH<sub>3</sub>); 2.75 (s, 1H, C<sub>12a</sub>-H); 2.93 (m, 1H, C<sub>8</sub>-H); 3.64 (m, 2H, C<sub>8</sub>-H and C<sub>10</sub>-H); 3.80 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>); 3.82 (s, 1H, C<sub>2</sub>-H); 3.87 (s, 3H, OCH<sub>3</sub>); 5.26 (d, *J* = 10 Hz, 1H, C<sub>6</sub>-H); 5.44 (s, 1H, C<sub>4</sub>-H); 5.87 (dd, *J* = 10 and 4 Hz); 6.06 (s, 1H, C<sub>17</sub>-H); 7.32 (s, 1H, C<sub>14</sub>-H); 9.64 (s, 1H, OH). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): 7.55 (CH<sub>3</sub>); 20.95 (COCH<sub>3</sub>); 30.91 (CH<sub>2</sub>); 38.07 (N-CH<sub>3</sub>); 42.72 (C-5); 43.52 (C-11); 50.84 (C-8); 51.88 (C-16); 52.22 (C-12); 52.27 (OCH<sub>3</sub>); 56.27 (OCH<sub>3</sub>); 67.29 (C-12a); 71.09 (C-15); 75.59 (C-4); 79.17 (C-3); 82.62 (C-2); 93.45 (C-17); 123.32 (C-7); 126.34 (C-13); 130.04 (C-6); 131.72 (C-14); 153.65 (C-18); 158.7 (C-16); 170.2 (O-C=O); 171.14

(O-C=O). MS: 583 [M+H]<sup>+</sup> (100), 523 [(M+H)<sup>+</sup>-CH<sub>3</sub>CO<sub>2</sub>H, 15], 477 (46), 314 (64). IR: 3432, 2958, 1736, 1600, 1248, 1048. Anal. Calcd for C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>O<sub>6</sub>I: C 51.55, H 5.36; Found: C 51.34, H 5.49.

**Preparation of phenylvindolines (3a-g); General Procedure.** A stirred mixture of **1c** (0.25 g, 0.43 mmol), the corresponding phenylboronic acid (0.56 mmol), Pd(OAc)<sub>2</sub> catalyst (4.8 mg, 0.0215 mmol), (*o*-tolyl)<sub>3</sub>P (13 mg, 0.043 mmol), and aqueous K<sub>3</sub>PO<sub>4</sub> (0.18 g, 0.86 mmol in 1 mL H<sub>2</sub>O) in DME (20 mL) was heated to reflux under argon. After cooling, the reaction mixture was dried, (MgSO<sub>4</sub>) and the solvent was evaporated in vacuo. The residue was purified by column chromatography (Kieselgel 60; CH<sub>2</sub>Cl<sub>2</sub>-EtOAc 10:1).

**Cross-coupling of 15-bromovindoline (1b) with phenylboronic acid (2a).** A stirred mixture of **1b** (0.2 g, 0.37 mmol), **2a** (60 mg, 0.48 mmol), catalyst, phosphino ligand, and base in a solvent was heated to reflux under argon. After every 10 h a small sample (1 mL) was taken, filtered through a short silica column, and then analysed by HPLC (Table 1.).

**Table 3.-** Cross-coupling of 15-Iodovindoline (**1c**) with Phenylboronic Acids (**2**).

Starting boronic acid	Product	Yield <sup>a</sup> (%)	TLC <sup>b</sup> (°C)	HPLC <sup>c</sup> (R <sub>f</sub> )
<b>2a</b>	<b>3a</b>	40	0.19	3.10
<b>2b</b>	<b>3b</b>	32	0.21	5.85
<b>2c</b>	<b>3c</b>	26	0.09	5.72
<b>2d</b>	<b>3d</b>	69	0.28	3.99
<b>2e</b>	<b>3e</b>	54	0.18	6.00
<b>2f</b>	<b>3f</b>	63	0.07	6.88
<b>2g</b>	<b>3g</b>	35	0.21	5.93

<sup>a</sup> Isolated yields were based on **1c** after separation by column chromatography

<sup>b</sup> RP-18 F<sub>254</sub>S aluminum sheets. Eluent: MeOH : H<sub>2</sub>O : TFA 7 : 3 : 0.1

<sup>c</sup> HPLC analysis was performed on a Perkin-Elmer 200 instrument, using Perkin-Elmer 235 C diode Array Detector and Purospher RP18e column system, with MeCN-H<sub>2</sub>O-H<sub>3</sub>PO<sub>4</sub> 4:6:0.05 eluent mixture.

**Table 4.-** Spectral and Analytical Data for Vindoline Derivatives Prepared

Pro-duct	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR (CDCl <sub>3</sub> ), δ, J (Hz)	<sup>13</sup> C NMR (CDCl <sub>3</sub> ), δ	MS ( <i>m/z</i> )	Analysis Calcd (Found) (%)
<b>3a</b>	3440, CDCl <sub>3</sub> ; 2880, CH <sub>3</sub> ; 1744, (m, 1H, CH <sub>2</sub> ); 1616, COCH <sub>3</sub> ; 1488, C <sub>11</sub> -H);	0.56 (t, <i>J</i> =7.5, 3H, CH <sub>2</sub> ); 1.68 (m, 1H, CH <sub>2</sub> ); 2.09 (s, 3H, CH <sub>3</sub> ); 2.35 (m, 2H, CH <sub>2</sub> ); 2.51 (m, 1H, C <sub>10</sub> -H);	7.76 (CH <sub>3</sub> ); 21.08 (COCH <sub>3</sub> ); 30.94 (CH <sub>2</sub> ); 42.93 (C-5); 51.10 (C-8); 52.27 (CO <sub>2</sub> OCH <sub>3</sub> );	533 [M+H] <sup>+</sup> ; 473 (57), 473 [M <sup>+</sup> -CH <sub>3</sub> CO <sub>2</sub> , 19], 385 (8), 372 (13), 264	C <sub>31</sub> H <sub>36</sub> N <sub>2</sub> O <sub>6</sub> C: 69.90 (69.67) H: 6.81 (7.04)

1228, 2.73 (s, 1H, C<sub>12a</sub>-H); 2.75 (s, (C-12); 55.71 (OCH<sub>3</sub>); 66.97 (100), 250 (42).  
 1040 3H, N-CH<sub>3</sub>); 2.82 (d, *J*=16, (C<sub>12a</sub>); 76.43 (C-4); 79.61  
 1H, C<sub>8</sub>-H); 3.42 (m, 1H, (C-3); 83.59 (C-2); 93.67  
 C<sub>10</sub>-H); 3.50 (dd, *J*=16, and (C-17); 121.96 (C-15); 124.24  
 4.5, 1H, C<sub>8</sub>-H); 3.79 (s, 1H, (C-7); 124.42 (C-14); 124.47  
 C<sub>2</sub>-H); 3.80 (s, 3H, OCH<sub>3</sub>); (C-13); 126.25 (C<sub>4</sub>); 127.94  
 3.81 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>); 5.27 (d, (C<sub>3'</sub> and C<sub>5'</sub>); 129.36 (C<sub>2'</sub> and  
*J*=10 1H, C<sub>6</sub>-H); 5.50 (s, 1H, C<sub>6'</sub>); 130.43 (C-6); 139.04  
 C<sub>4</sub>-H); 5.86 (dd, *J*=10, and 4, (C<sub>1'</sub>); 152.98 (C-18); 157.86  
 1H, C<sub>7</sub>-H); 6.18 (s, 1H, (C-16); 170.81 (O-C=O);  
 C<sub>17</sub>-H); 6.94 (s, 1H, C<sub>14</sub>-H); 171.91 (O-C=O).  
 7.26 (t, *J*=7.5, 1H, C<sub>4'</sub>-H);  
 7.36 (t, *J*=8, 2H, C<sub>3'</sub>-H and  
 C<sub>5'</sub>-H); 7.42 (d, *J*=7.5, 2H,  
 C<sub>2</sub>-H and C<sub>6</sub>-H); 9.61 (br s,  
 1H, OH).

**3b** 3456, 0.54 (t, *J*=7.5, 3H, CH<sub>3</sub>); 1.23 7.71 (CH<sub>3</sub>); 21.04 (COCH<sub>3</sub>); 547 [M+H<sup>+</sup>] C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>  
 2960, (m, 1H, CH<sub>2</sub>); 1.69 (m, 1H, 21.15 (CH<sub>3</sub>); 30.99 (CH<sub>2</sub>); (21), 487 C: 70.31  
 1740, CH<sub>2</sub>); 2.09 (s, 3H, COCH<sub>3</sub>); 38.59 (N-CH<sub>3</sub>); 42.92 (C-5); (M+H<sup>+</sup>- (70.05)  
 1616, 2.37 (m, 5H, C<sub>11</sub>-H, and 43.73 (C-11); 51.09 (C-8); CH<sub>3</sub>CO<sub>2</sub>H, 8), H: 7.01 (7.14)  
 1496, C<sub>4</sub>-H); 2.58 (m, 1H, C<sub>10</sub>-H); 52.17 (C-10); 52.34 (OCH<sub>3</sub>); 386 (7), 278  
 1240, 2.74 (s, 3H, N-CH<sub>3</sub>); 2.79 (br 52.86 (C-12); 55.71 (OCH<sub>3</sub>); (41), 153 (100)  
 1040 s, 1H, C<sub>12a</sub>-H); 2.87 (m, 1H, 67.33 (C-12a); 76.18 (C-4);  
 C<sub>8</sub>-H); 3.60 (m, 2H, C<sub>8</sub>-H and 79.56 (C-3); 83.13 (C-2); 97.78  
 C<sub>10</sub>-H); 3.78 (br s, 1H, C<sub>2</sub>-H); (C-17); 122.17 (C-15); 123.79  
 3.79 (s, 3H, OCH<sub>3</sub>); 3.81 (s, (C-7); 124.19 (C-13); 124.25  
 3H, CO<sub>2</sub>CH<sub>3</sub>); 5.27 (m, 1H, (C-14); 128.72 (C-3' and C-5');  
 C<sub>6</sub>-H); 5.50 (s, 1H, C<sub>4</sub>-H); 129.21 (C-2' and C-6'); 130.57  
 5.86 (dd, *J*=10 and 4, C<sub>7</sub>-H); (C-6); 135.96 (C-4'); 136.02  
 6.18 (s, 1H, C<sub>17</sub>-H); 6.93 (C-1'); 152.79 (C-18); 157.97  
 (s, 1H, C<sub>14</sub>-H); 7.18 (d, *J*=8, (C-16); 17.80 (O-C=O); 171.84  
 2H, C<sub>3</sub>-H and C<sub>5</sub>-H); 7.31 (O-C=O).  
 (d, *J*=8, 2H, C<sub>2</sub>-H and  
 C<sub>6</sub>-H); 9.64 (br s, 1H, OH).

**3c** 3440, 0.54 (t, *J*=7.5, 3 H, CH<sub>3</sub>); 7.71 (N-CH<sub>3</sub>); 21.03 (COCH<sub>3</sub>); 625 [M+H<sup>+</sup>] C<sub>37</sub>H<sub>40</sub>N<sub>2</sub>O<sub>7</sub>  
 2968, 1.23 (m, 1H, CH<sub>2</sub>); 1.69 (m, 31.00 (CH<sub>2</sub>); 38.55 (N-CH<sub>3</sub>); (34), 565 (14), C: 71.13  
 1744, 1H, CH<sub>2</sub>); 2.09 (s, 3H, 42.93 (C-5); 43.57 (C-11); 464 (19), 356 (71.02)  
 1616, COCH<sub>3</sub>); 2.40 (m, 2H, 51.08 (C-8); 52.20 (C-10); (56). H: 6.45 (6.19)  
 1492, C<sub>11</sub>-H); 2.61 (m, 1H, C<sub>10</sub>-H); 52.38 (CO<sub>2</sub>CH<sub>3</sub>); 52.82 (C-12);  
 1368, 2.74 (s, 3H, N-CH<sub>3</sub>); 2.82 (m, 55.74 (OCH<sub>3</sub>); 67.52 (C<sub>12a</sub>);  
 1232, 1H, C<sub>12a</sub>-H); 2.90 (m, 1H, 75.93 (C-4); 79.54 (C-3);  
 1040 C<sub>8</sub>-H); 3.60 (m, 2H, C<sub>8</sub>-H and 82.92 (C-2); 93.81 (C-17);  
 C<sub>10</sub>-H); 3.81 (m, 7H, 2 x 118.31 (C<sub>3'</sub> and C<sub>5'</sub>); 119.00  
 OCH<sub>3</sub> and C<sub>2</sub>-H); 5.28 (m, (C<sub>2''</sub> and C<sub>6''</sub>); 121.55 (C-15);  
 1H, C<sub>6</sub>-H); 5.49 (s, 1H, 123.22 (C<sub>4''</sub>); 123.6 (C-6);  
 C<sub>4</sub>-H); 5.87 (dd, *J*=10 and 4, 124.15 (C-13); 124.17 (C-14);  
 1H, C<sub>7</sub>-H); 6.18 (s, 1H, 129.72 (C<sub>3''</sub> and C<sub>5''</sub>); 130.59  
 C<sub>17</sub>-H); 6.95 (s, 1H, C<sub>17</sub>-H); (C<sub>2'</sub> and C<sub>2</sub>); 130.64 (C-6);  
 7.00 (d, *J*=8.5, 2H, C<sub>3</sub>-H and 133.89 (C<sub>1'</sub>); 152.88 (C-18);

- $C_{5'}\text{-H}$ ); 7.05 (d,  $J=8$ , 2H, 155.83 ( $C_{4'}$ ); 157.28 ( $C_{1''}$ );  
 $C_{2''}\text{-H}$  and  $C_{6''}\text{-H}$ ); 7.10 157.99 (C-16); 170.79  
 (t,  $J=7.5$ , 1H,  $C_{4''}\text{-H}$ ); 7.34 (O-C=O); 171.78 (O-C=O).  
 (t,  $J=8$ , 2H,  $C_{3''}\text{-H}$  and  
 $C_{5''}\text{-H}$ ); 7.38 (d,  $J=8$ , 2H,  
 $C_{2'}\text{-H}$  and  $C_{6'}\text{-H}$ ); 9.64 (br s,  
 1H, OH).
- 3d** 3440, 0.59 (t,  $J=7.5$ , 3H,  $\text{CH}_3$ ); 1.21 7.70 ( $\text{CH}_3$ ); 21.07 ( $\text{COCH}_3$ ); 578  $[\text{M}+\text{H}^+]$   $\text{C}_{31}\text{H}_{35}\text{N}_3\text{O}_8$   
 2880, (m, 1H,  $\text{CH}_2$ ); 1.69 (m, 1H, 30.93 ( $\text{CH}_2$ ); 38.13 (N- $\text{CH}_3$ ); (100), 518 C: 64.46  
 1616,  $\text{CH}_2$ ); 2.09 (s, 3H,  $\text{COCH}_3$ ); 42.89 (C-3); 44.00 (C-11);  $[\text{M}^+-\text{CH}_3\text{CO}$ , (64.24)  
 1528, 2.35 (m, 2H,  $C_{11}\text{-H}$ ); 2.58 (m, 50.99 (C-8); 51.65 (C-10); 25], 417 (30), H: 6.11 (6.36)  
 1372, 1H,  $C_{10}\text{-H}$ ); 2.78 (s, 4H, 52.31 ( $\text{CO}_2\text{CH}_3$ ); 52.96 (C-12); 329 (38), 307  
 1248, N- $\text{CH}_3$  and  $C_{12a}\text{-H}$ ); 2.86 55.72 ( $\text{OCH}_3$ ); 66.74 ( $C_{12a}$ ); (100).  
 1036 (d,  $J=16$ , 1H,  $C_8\text{-H}$ ); 3.45 76.27 (C-4); 79.59 (C-3); 83.39  
 (m, 1H,  $C_{10}\text{-H}$ ); 3.8 (s, 1H, (C-2); 93.27 (C-17); 118.87  
 $C_2\text{-H}$ ); 3.82 (s, 3H,  $\text{CO}_2\text{CH}_3$ ); (C-15); 120.88 (C-4'); 124.04  
 3.84 (s, 3H,  $\text{OCH}_3$ ); 5.27 (d, (C-2'); 124.08 (C-14); 124.32  
 $J=10$ , 1H,  $C_6\text{-H}$ ); 5.47 (s, 1H, (C-7); 124.83 (C-13); 128.66  
 $C_4\text{-H}$ ); 5.89 (dd,  $J=10$  and 4, (C-5'); 130.30 (C-6); 135.42  
 1H,  $C_7\text{-H}$ ); 6.18 (s, 1H, (C-6'); 140.63 (C-1'); 148.16  
 $C_{17}\text{-H}$ ); 6.96 (s, 1H,  $C_{14}\text{-H}$ ); (C-3'); 153.88 (C-18); 157.97  
 7.51 (t,  $J=8$ , 1H,  $C_{5'}\text{-H}$ ); 7.77 (C-16); 170.78 (O-C=O);  
 (d,  $J=7.5$ , 1H,  $C_{6'}\text{-H}$ ); 8.09 (d, 171.78 (O-C=O).  
 $J=8$ , 1H,  $C_{4'}\text{-H}$ ); 8.29 (br s,  
 1H,  $C_2\text{-H}$ ); 9.61 (s, 1H, OH).
- 3e** 3464, 0.56 (t,  $J=7.3$ , 3H,  $\text{CH}_3$ ); 1.18 7.69 ( $\text{CH}_3$ ); 21.05 ( $\text{COCH}_3$ ); 569  $[\text{M}+\text{H}]^+$   $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_6\text{F}_2$   
 2960, (m, 1H,  $\text{CH}_2$ ); 1.69 (m, 1H, 30.96 ( $\text{CH}_2$ ); 38.19 (N- $\text{CH}_3$ ); (100), 509 (22), C: 65.48  
 1744,  $\text{CH}_2$ ); 2.09 (s, 3H,  $\text{COCH}_3$ ); 42.90 (C-5); 43.87 (C-11); 407(19), 299 (65.59)  
 1616, 2.33 (m, 1H,  $C_{11}\text{-H}$ ); 2.36 51.02 (C-8); 51.87 (C-10); (92). H: 6.03 (6.32)  
 1232, (m, 1H,  $C_{11}\text{-H}$ ); 2.60 (m, 1H, 52.35 ( $\text{CO}_2\text{CH}_3$ ); 52.87 (C-12);  
 1040  $C_{10}\text{-H}$ ); 2.76 (s, 3H, N- $\text{CH}_3$ ); 55.72 ( $\text{OCH}_3$ ); 67.05 (C-12a);  
 2.79 (s, 1H,  $C_{12a}\text{-H}$ ); 2.89 76.16 (C-4); 79.54 (C-3); 83.21  
 (m, 1H,  $C_8\text{-H}$ ); 3.54 (m, 2H, (C-2); 93.41 (C-17); 101.36  
 $C_8\text{-H}$  and  $C_{10}\text{-H}$ ); 3.81 (s, 4H, (t,  $^2J_{\text{CF}}=2.5$ , C-4'); 111.98  
 $\text{OCH}_3$  and  $C_2\text{-H}$ ); 3.83 (s, 3H, (dd,  $^2J_{\text{CF}}=20$  and  $^4J_{\text{CF}}=5.5$ , C-2'  
 $\text{OCH}_3$ ); 5.27 (m, 1H,  $C_6\text{-H}$ ); and C-6'), 119.33 (C-15);  
 5.46 (s, 1H,  $C_4\text{-H}$ ); 5.88 124.01 (C-14); 124.03 (C-7);  
 (m, 1H,  $C_7\text{-H}$ ); 6.16 (s, 1H, 124.58 (C-13); 130.39 (C-6);  
 $C_{17}\text{-H}$ ); 6.69 (m, 1H,  $C_{4'}\text{-H}$ ); 142.12 (t,  $^3J_{\text{CF}}=9$ , C-1');  
 6.91 (s, 1H,  $C_{14}\text{-H}$ ); 6.96 153.72 (C-18); 157.98 (C-16);  
 (m, 2H,  $C_2\text{-H}$  and  $C_6\text{-H}$ ); 162.63 (dd,  $^1J_{\text{CF}}=246$  and  
 9.64 (s, 1H, OH).  $^3J_{\text{CF}}=13.5$  C-3' and C-5');  
 170.79 (O-C=O); 171.79  
 (O-C=O).
- 3f** 3448, 0.59 (t,  $J=7.2$ , 3H,  $\text{CH}_3$ ); 1.23 7.54 ( $\text{CH}_3$ ); 21.04 ( $\text{COCH}_3$ ); 670 (62), 669  $\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_6\text{F}_6$   
 2952, (m, 1H,  $\text{CH}_2$ ); 1.70 (m, 1H, 30.97 ( $\text{CH}_2$ ); 38.03 (N- $\text{CH}_3$ );  $[\text{M}+\text{H}^+]$  (100), C: 59.28  
 1740,  $\text{CH}_2$ ); 2.09 (s, 3H,  $\text{COCH}_3$ ); 42.89 (C-5); 43.72 (C-11); 667 (8) (59.01)  
 1620, 2.35 (m, 1H,  $C_{11}\text{-H}$ ); 2.44 50.91 (C-8); 51.68 (C-10); H: 5.13 (5.28)  
 1472, (m, 1H,  $C_{11}\text{-H}$ ); 2.69 (m, 1H, 52.42 ( $\text{CO}_2\text{CH}_3$ ); 52.84 (C-12);

1380, C<sub>10</sub>-H); 2.77 (C<sub>12a</sub>-H); 2.78 55.76 (OCH<sub>3</sub>); 66.99 (C-12a); 1280, (s, 3H, N-CH<sub>3</sub>); 2.98 (m, 1H, 75.95 (C-4); 79.59 (C-3); 82.81 1040 C<sub>8</sub>-H); 3.63 (m, 2H, C<sub>8</sub>-H and (C-2); 93.26 (C-17); 118.43 C<sub>10</sub>-H); 3.82 (s, 3H, (C-15); 119.69 (sept, <sup>3</sup>J<sub>CF</sub>=3.6, CO<sub>2</sub>CH<sub>3</sub>); 3.84 (s, 3H, C-4'); 123.6 (q, <sup>1</sup>J<sub>CF</sub>=272.6, OCH<sub>3</sub>); 3.90 (m, 1H, C<sub>2</sub>-H); CF<sub>3</sub>); 123.90 (C-7); 123.97 5.31 (d, J=10, 1H, C<sub>6</sub>-H); (C-14); 124.61 (C-13); 129.30 5.45 (s, 1H, C<sub>4</sub>-H); 5.90 (dd, (C-2' and C-6'); 130.43 (C-6); J=10 and 4, C<sub>7</sub>-H); 6.18 (s, 131.11 (q, <sup>2</sup>J<sub>CF</sub>=32.8, C-3' and 1H, C<sub>17</sub>-H); 6.94 (s, 1H, C-5'); 140.92 (C-1'); 154.12 C<sub>14</sub>-H); 7.74 (s, 1H, C<sub>4</sub>-H); (C-18); 158.12 (C-16); 170.78 7.86 (s, 2H, C<sub>2</sub>-H and (O-C=O); 171.65 (O-C=O). C<sub>2</sub>'-H); 9.68 (br s, 1H, OH).

**3g** 3424, 1:1 mixture of rotamers. Only 1:1 mixture of rotamers. Only 583 [M+H]<sup>+</sup> C<sub>35</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>  
2960, selected peaks are cited: 0.53 selected peaks are cited: 7.81 (100), 523 (22), C: 72.14  
1744, and 0.30 (CH<sub>3</sub>), 2.10 and 2.11 and 7.98 (CH<sub>3</sub>), 21.09 and 422 (30), 314 (72.03)  
1504, (s, COCH<sub>3</sub>), 2.78 and 2.80 21.11 (COCH<sub>3</sub>), 38.62 and (88). H: 6.57 (6.36)  
1616, (s, N-CH<sub>3</sub>), 5.54 and 5.59 38.65 (N-CH<sub>3</sub>), 76.51 and  
1240, (s, C<sub>4</sub>-H). 76.58 (C-4), 130.34 and 130.44  
1040 (C-6), 170.86 and 170.92  
(O-C=O), 171.97 and 172.00  
(O-C=O).

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