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A Facile Synthesis of the 4-Aza-analogs of 1-Arylnaphthalene Lignans Chinensin, Justicidin B, and Taiwanin C

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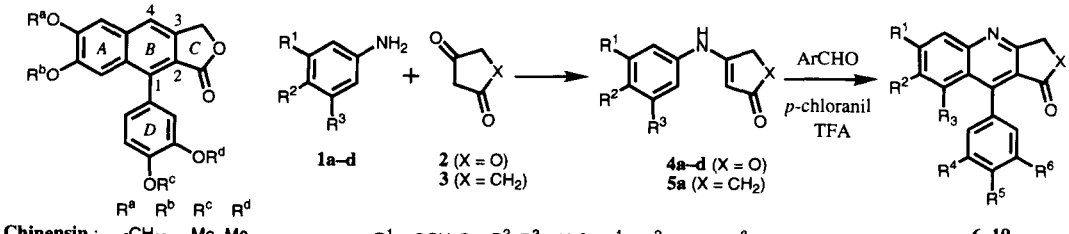
Abstract: Reaction of anilines **1a–d** with tetronic acid (**2**) or 1,3-cyclopentanedione (**3**) produced anilinolactones **4a–d** and anilinocyclopentenone **5a**, respectively, which were then condensed with benzaldehydes to yield 4-aza-1-arylnaphthalene lignan analogs **6–19**. © 1997 Elsevier Science Ltd.

1-Arylnaphthalene lignans are a class of compounds possessing various biological properties such as piscicidal,[1a] cytotoxic,[1b] antiviral,[1c] antiplatelet,[1d] leukotriene biosynthesis inhibitory[1e] and calcium absorption by bone inhibitory[1f] activities, which have attracted the attention of synthetic and medicinal chemists.[2]

Substitution of a particular carbon atom by a nitrogen atom often causes changes in the biological profile, and such modifications were successfully applied to other types of lignans, podophyllotoxin[3] and steganacin.[4] In spite of their various important biological activities which qualify them as lead compounds, little work has been done on the synthesis of their 4-aza-analogs since the previous method to prepare 4-aza-1-arylnaphthalene lignans requires polysubstituted 2-aminobenzophenones which are difficult to prepare.[5] We describe herein a highly convergent and very facile synthesis of such analogs.

Our approach is based on condensation of three components: anilines **1a–d**, tetronic acid (**2**) and benzaldehydes. When aniline **1a** was treated with an equimolar amount of tetronic acid (**2**) in dioxane at room temperature, anilinolactone **4a**[6] was obtained in 95% yield. Compound **4a** was then reacted with 3,4-dimethoxybenzaldehyde (1.1 equiv.) in the presence of *p*-chloranil (1 equiv.) in trifluoroacetic acid (TFA) at room temperature for 24 h to produce 4-azachinensin (**6**) in 82% yield. This method is very convergent and flexible. By changing the combination of the starting anilines **1a–d** and benzaldehydes, various analogs **7–18** shown in the Table, which include 4-azajusticidin B (**13**) and 4-azataiwanin C (**7**), were synthesized in the same manner. The combination of *meta*-alkoxyanilines and *para*-alkoxybenzaldehydes generally gave high yields. By using 1,3-cyclopentanedione (**3**) instead of **2**, the ring C carba-analog (*e.g.*, **19**) was also obtained.



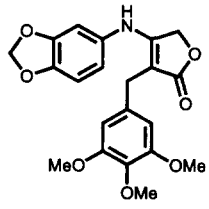
	R^a	R^b	R^c	R^d
Chinensin :	$-CH_2-$		Me	Me
Justicidin B :	Me	Me	$-CH_2-$	
Taiwanin C :	$-CH_2-$		$-CH_2-$	

a: $R^1 = OCH_2O = R^2$, $R^3 = H$; **b:** $R^1 = R^2 = OMe$, $R^3 = H$;
c: $R^1 = R^2 = R^3 = OMe$; **d:** $R^1 = R^2 = R^3 = H$

Table Reaction of **4a–d** and **5a** with Benzaldehydes

4/5	Benzaldehyde	Product	R^1	R^2	R^3	R^4	R^5	R^6	X	Yield (%)	Mp (°C)
4a	3,4-dimethoxy-	**6**	$-OCH_2O-$		H	OMe	OMe	H	O	82	255–257
4a	3,4-methylenedioxy-	**7**	$-OCH_2O-$		H	$-OCH_2O-$		H	O	80	>300
4a	3,4,5-trimethoxy-	**8**	$-OCH_2O-$		H	OMe	OMe	OMe	O	83	279–281
4a	3-methoxy-	**9**	$-OCH_2O-$		H	OMe	H	H	O	50	272
4a	4-methoxy-	**10**	$-OCH_2O-$		H	H	OMe	H	O	89	252–253
4a	benzaldehyde	**11**	$-OCH_2O-$		H	H	H	H	O	60	260–261
4b	3,4-dimethoxy-	**12**	OMe	OMe	H	OMe	OMe	H	O	79	249
4b	3,4-methylenedioxy-	**13**	OMe	OMe	H	$-OCH_2O-$		H	O	83	238–241
4b	3,4,5-trimethoxy-	**14**	OMe	OMe	H	OMe	OMe	OMe	O	90	279–282
4c	3,4-dimethoxy-	**15**	OMe	OMe	OMe	OMe	OMe	H	O	88	233–236
4c	3,4,5-trimethoxy-	**16**	OMe	OMe	OMe	OMe	OMe	OMe	O	96	211–213
4d	4-methoxy-	**17**	H	H	H	H	OMe	H	O	76	231–233
4d	benzaldehyde	**18**	H	H	H	H	H	H	O	35	203–207
5a	3,4,5-trimethoxy-	**19**	$-OCH_2O-$		H	OMe	OMe	OMe	CH_2	65	280–282

Interestingly, a stepwise procedure, condensation of **4** with aldehydes and successive dehydration, did not proceed well. When **4a** and 3,4,5-trimethoxybenzaldehyde were condensed in the absence of *p*-chloranil, compounds **8** and **20**[6] were obtained in yields of 47% and 36%, respectively, and the possible intermediate **21** was not obtained. Production of **8** and **20** would be accounted for by hydride transfer from **21** to the intermediary carbocation **22** initially generated from the reaction of **4a** with 3,4,5-trimethoxybenzaldehyde. *p*-Chloranil acts as an efficient hydride acceptor to prevent the formation of **20**.



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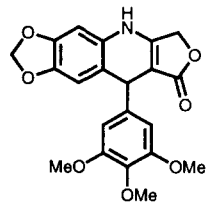

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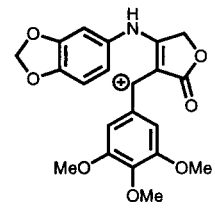

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6. **4a**: mp 245–246 °C; **4b**: Y. 92%, mp 210–211 °C; **4c**: Y. 93%, mp 175 °C; **4d**: 92%, mp 225–226 °C; **5a**: Y. 99%, mp 197–199 °C; **20**: mp 184–186 °C.

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