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SYNTHETIC PTEROCARPANS WITH ANTI-HIV ACTIVITY

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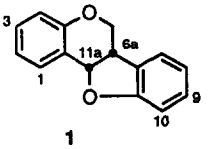
Abstract: Several pterocarpans were synthesized and tested *in vitro* for activity against HIV. 9-Alkoxy-8-hydroxy-3-methoxypterocarpans exhibited activities in the μM range.

Introduction. The worldwide spread of AIDS and the lack of generally effective methods for treatment and/or prevention of have generated intense efforts to discover new molecules for the treatment of HIV-1 infection, the causative agent of AIDS. Several different types of compounds[1] exhibit anti-HIV-1 activity by inhibiting HIV-reverse transcriptase, -protease or -integrase, by blocking or altering the interaction of HIV with CD4, by interaction with the viral RNA-DNA hybrid or one of several sites on HIV or by some other mechanism.[2] Problems with the potential therapeutic utility of many of these agents have emerged including the appearance of resistant strains of the virus, inactivity towards HIV-2, toxicity and questions of bioavailability. Thus, interest in the discovery of new classes of anti-HIV agents remains high. Herein, we report for the first time, to our knowledge, *in vitro* anti-HIV activity in analogs of naturally occurring pterocarpans.

Pterocarpans are isoflavonoids possessing the benzofurano-benzopyran ring system **1**. Many pterocarpans display potent and varied biological activity and some related isoflavonoids exhibit antiviral activity[3a] including the inhibition of the cytopathic activity of HIV.[3b] As part of a study to explore new synthetic methodology, we developed a new regio- and enantioselective route to pterocarpans.[4] In tests conducted by the National Cancer Institute (NCI),[5] one of our synthetic pterocarpans, **2**[4], exhibited significant activity *in vitro* against HIV-1 (vide infra). To obtain preliminary information on potential structure-activity relationships, we focused on the role of the three substituents at C-3, C-8 and C-9 in **2**[4c] and prepared a number of pterocarpans to submit to the NCI for biological evaluation.



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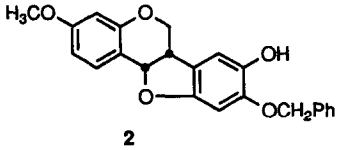

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Synthesis. Titanium(IV)-promoted reactions of 2H-chromenes **3** with 1,4-benzoquinones **4** produce pterocarpans **5** and/or cyclobutanes **6** (Scheme I and Table I).[7] The ratio of **5** to **6** found depends upon the reaction conditions and rearrangement of the cyclobutanes to the pterocarpans is observed upon treatment with protic acid (Table II); cation **7** is a likely intermediate. The cis stereochemistry at C-6a and C-11a in **5** is supported by ^{1}H-^{1}H NOE experiments and a $J_{H\text{-}6a/H\text{-}11a}$ = 6-7 Hz for each compound. Compounds **5e/f** are prepared by reactions of chromenes **3a/b**, respectively, with 2-carbomethoxy-1,4-benzoquinone, **4e**, which was prepared by MnO_2 oxidation of methyl 2,5-dihydroxybenzoate.[8] The position of the -CO_2Me moiety in **5e/f** is established by

Scheme I

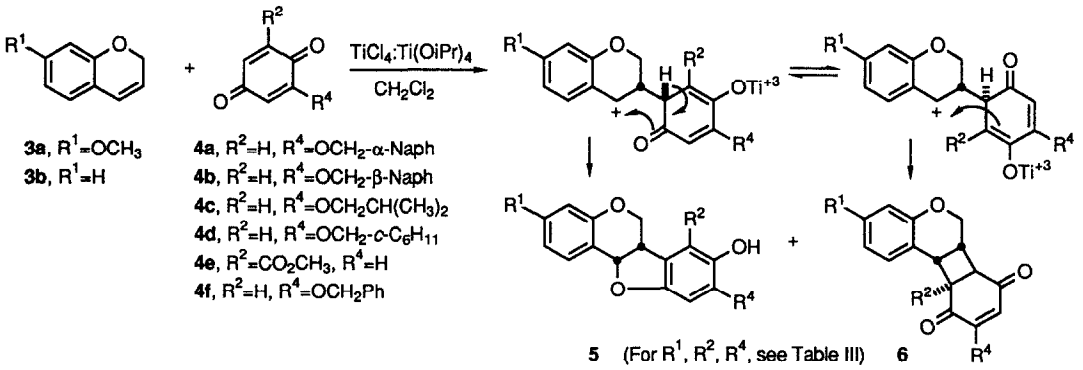


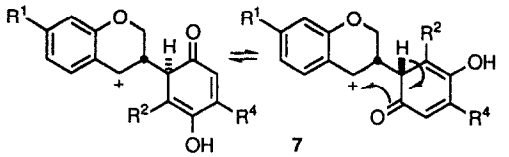
Table I. Titanium(IV)-Promoted Reactions of 2H-Chromenes **3** with 1,4-Benzoquinones **4**.[a]

Chromene	Quinone	$TiCl_4$:Ti(OiPr)$_4$ (equiv Ti^{+4})[b]	Temp (°C)	Time (h)	Products	(% Yields)
3a	**4a**	2:1(1)	-78	7.5	**5a** (26)	**6a** (51)
3a	**4a**	1:1(3)	-78 → -40	4	**5a** (57)	--[c]
3a	**4b**	1:1(2)	-78	2	**5b** (78)	--
3a	**4c**	1:1(1)	-78	2	**5c** (81)	--
3a	**4d**	1:1(1)	-78	0.3	--	**6d** (65)
3a	**4d**	2:1(1)	-78	1.0	**5d** (54)	--
3a	**4e**	1:1(2)	-78	1.5	**5e** (60)	--
3b	**4e**	1:1(2)	-78	1.5	**5f** (57)	--
3b	**4f**	2:1(1)	-78 → -40	7	**5g** (11)	**6g** (61)

[a] All reactions were conducted in CH_2Cl_2 under an N_2 or Ar atmosphere. [b] Equivalents with respect to quinone. [c] None of this product was isolated.

Table II. Protic Acid-Catalyzed Rearrangement of **6** to **5**.

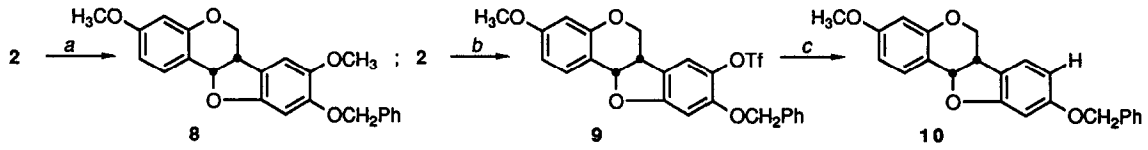
Cyclobutane	Conditions	Product	Yield (%)
6a	*p*-TsOH, CH_2Cl_2, rt	**5a**	99
6d	*p*-TsOH, CH_2Cl_2, rt	**5d**	40
6g	H_2SO_4, CH_2Cl_2, rt	**5g**	79



a $J_{H\text{-}9/H\text{-}10}$ = 9 Hz. Structure **6** is assigned by spectral comparison to molecules previously prepared in our laboratory and by mechanistic reasoning.[4] Methylation of **2** gives **8** and compound **10** is prepared by Pd(0)-catalyzed triethylammonium formate reduction of triflate **9** (Scheme II).

Biological Evaluation. Compounds **2**, **5a-g**, **8**, and **10-16** were tested *in vitro* for their ability to inhibit the cytopathic activity of HIV-1 on T4 lymphocytes (CEM cells, Table III). Several demonstrated significant anti-HIV activity; however, the IC_{50}/EC_{50} ratios were not high. All compounds were tested as racemic mixtures and it is possible that the activity of one of the constituent enantiomers may be higher. These preliminary data show that pterocarpans with a methoxy group at C-3, an OH moiety at C-8 and a substituted methoxy group at C-9

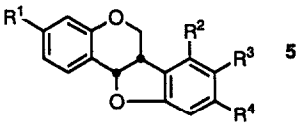
Scheme II



Reagents and Conditions: a) NaH, CH_3I, THF, 40 °C, 68%. b) $(F_3CSO_2)_2O$, pyridine, CH_2Cl_2, -78 °C to rt, 92%.
c) $[Pd(OAc)_2]_3$ (0.21 equiv), 1,1'-bis(diphenylphosphino)ferrocene (0.52 equiv), $(Et_3NH)^+ {}^-O_2CH$, DMF, 75 °C, 75%.

exhibit higher activity than those lacking any one of these groups. The α-naphthylmethyl substituted compound **5a** is the most active, although the activities of **5b-d** are within an order of magnitude. The good activities found in **2**, **5a-b** and **5c-d** and the lack of activity in **11** suggest that the steric bulk of the C-9 alkoxy group may be more significant than whether or not it contains π bonds.

Table III. Preliminary Evaluation of Anti-HIV-1 Activity of Various Pterocarpans **5** in the Primary Screening Assay.[a]



Compound	R^1	R^2	R^3	R^4	IC_{50} (M)	EC_{50} (M)	# of Experiments
2[4]	OCH_3	H	OH	OCH_2Ph	4.05×10^{-5} [b]	1.21×10^{-6} [c]	8
5a	OCH_3	H	OH	OCH_2-α-Naph	3.85×10^{-5}	4.30×10^{-7}	4
5b	OCH_3	H	OH	OCH_2-β-Naph	3.42×10^{-5}	3.35×10^{-6}	6
5c	OCH_3	H	OH	$OCH_2CH(CH_3)_2$	2.45×10^{-5}	2.28×10^{-6}	4
5d	OCH_3	H	OH	OCH_2-c-C_6H_{11}	2.22×10^{-5}	1.46×10^{-6}	4
8	OCH_3	H	OCH_3	OCH_2Ph	6.94×10^{-5}	5.70×10^{-6}	4
10	OCH_3	H	H	OCH_2Ph	2.00×10^{-4}	3.12×10^{-5}	4
11[4]	OCH_3	H	OH	OCH_3	Inactive		
12[4]	OCH_3	H	H	OCH_3	Inactive		
13[4]	OCH_3	H	$CH_2CH=C(CH_3)_2$	OCH_2Ph	Inactive		
5e	OCH_3	CO_2CH_3	OH	H	Inactive		
14[4]	OCH_3	H	-- (OCH_2O) --		Inactive		
5f	H	CO_2CH_3	OH	H	Inactive		
5g	H	H	OH	OCH_2Ph	Inactive		
15[4]	H	H	OH	OCH_3	Inactive		
16[4]	H	CH_3	OH	OCH_3	Inactive		

a) Tests were performed by the National Cancer Institute, see reference 5. b) Average for two experiments; in all other experiments, $IC_{50} > 2.4 \times 10^{-5}$ M. c) Average value.

Compound **2** was tested further against AZT-sensitive and AZT-resistant HIV-1, HIV-2, SIV and the Merck-resistant variant of HIV-1 (A17). It showed significant activity against the first two ($EC_{50} = 3 \times 10^{-6}$ M and 1.3×10^{-6} M, respectively) but was inactive against HIV-2, SIV and the A17 strain of HIV-1. The

mechanism of action of the pterocarpans is not known. The inactivity of **2** against HIV-2 and A17 is consistent with nonnucleoside reverse transcriptase inhibitors although this does not rule out alternative mechanisms.

In summary, the substituted pterocarpans **2** and **5** are a new class of anti-HIV agents and are noteworthy in the unusual nature of the C-9 alkoxy group. They are not likely to be found in nature, however, there is some structural similarity between them and known HIV-active phenolic isoflavonoids,[3b] flavonoids,[9] coumarins,[10] biaryls (tannins) and diaryl ethers,[11] benzophenones,[12] and triphenylcarbinols.[1bb] We are continuing studies in this area.

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