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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF SULFONE SUBSTITUTED HIV PROTEASE INHIBITORS

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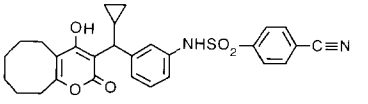
Abstract: The sulfonamide substituted pyranones (**1**) have recently been shown to be potent HIV protease inhibitors. We prepared a series of sulfone substituted analogs and compared their biological activities to those of the corresponding sulfonamide analogs. It was determined that although these compounds maintained activity as enzyme inhibitors, they showed somewhat diminished antiviral activity even though they may possess increased membrane permeability.

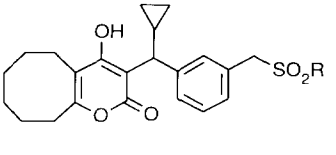
Recently, there has been much interest in the development of potent, nonpeptidic HIV protease inhibitors.[1] In particular, **1e** has been shown to be a potent inhibitor of HIV protease (K_i = 0.8 nM) and to possess good antiviral activity (IC_{50} = 1.5 μM). It also possesses favorable pharmacokinetics and is relatively easy to prepare.[2]



1e

Earlier studies of crystal structures of related analogs bound to HIV protease suggested that the sulfonamide group formed hydrogen bonds to Gly-48 and Asp-29 of the protease enzyme. These two bonds were thought to be key to the improved activity of this class of compounds. However, a crystal structure of the more active cyano compound (**1e**) bound to HIV protease showed that the presence of the *p*-cyano group caused the benzenesulfonamide moiety to shift its position, resulting in a weakening of the NH bond to Gly-48.

Since the presence of the NH bond to Gly-48 did not appear to be crucial to the HIV protease inhibiting activity of **1e** and since sulfonamides have been shown to significantly reduce intestinal absorption[3] we felt that replacement of the NH of the sulfonamide with a methylene group might afford compounds with improved membrane permeability and hence improved antiviral activity. To test this hypothesis, we prepared a series of sulfones based on the two templates shown below, both of which showed good activity in the sulfonamide series.[4,5]



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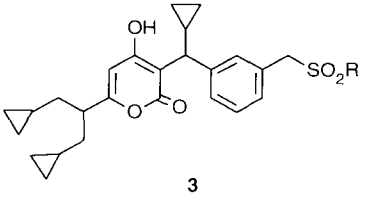

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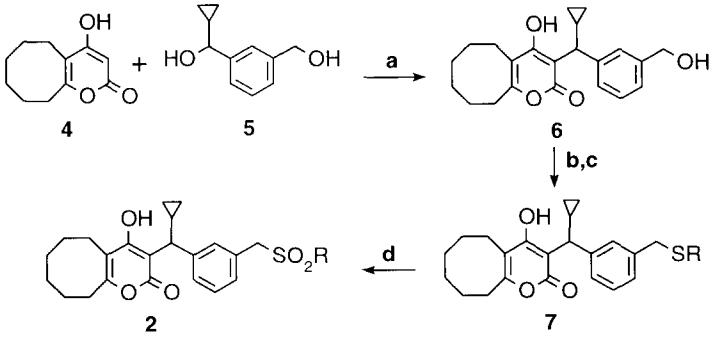
The cyclooctylpyranones were prepared in a straightforward manner involving the known acid mediated coupling of **4** with **5**, followed by conversion to the bromide upon treatment with triphenylphosphine and carbon tetrabromide (Scheme 1).[6,7] Treatment of the bromide with various thiols followed by oxidation afforded the desired sulfones. The dicyclopropyl sulfones were made in an analogous fashion (Scheme 2).

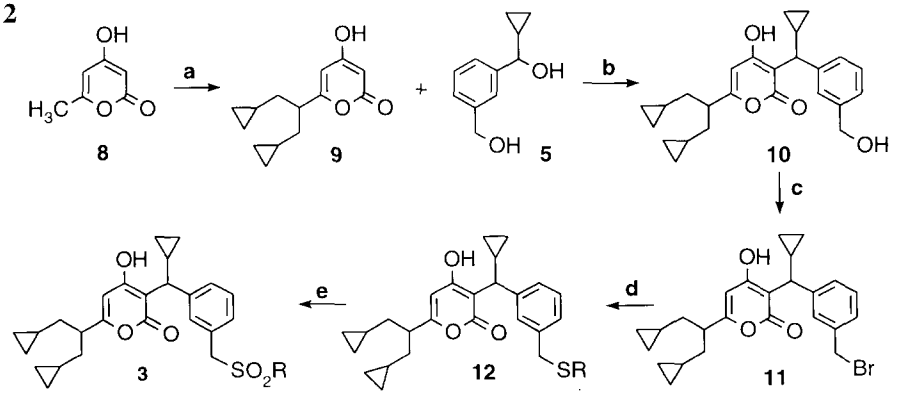
As is shown in Tables 1 and 2, in comparison to the sulfonamide analogs the sulfones maintained activity as enzyme inhibitors but had generally diminished antiviral activity.

Scheme 1



Reagents: (a) *p*-TsOH, CH_2Cl_2, 49%; (b) CBr_4, Ph_3P, CH_2Cl_2, (57%) (c) RSH, diisopropylethylamine, CH_2Cl_2, 73-92%; (d) oxone, THF, MeOH, H_20, 40-83%.

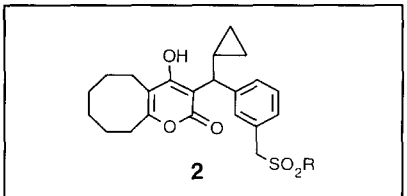
Scheme 2



Reagents: (a) LDA, HMPA, bromomethyl cyclopropane; (b) *p*-TsOH, CH_2Cl_2, 62%; (c) CBr_4, Ph_3P, CH_2Cl_2; (d) RSH, diisopropylethylamine, CH_2Cl_2, 47%-54%; (e) oxone, THF, H_20, 75-83%.

Interestingly, transcellular permeability of **2a** was approximately seven fold faster than analogs containing the sulfonamide, such as **1e** and **1c**, which are membrane-limited. Diffusion of these compounds through a continuous monolayer of Madin-Darby canine kidney epithelial cells in culture was measured according to

Table 1. Comparison of HIV-1 Protease Inhibitory and Antiviral Activity of Cyclooctylpyranone Sulfones and Sulfonamides. [8,9]



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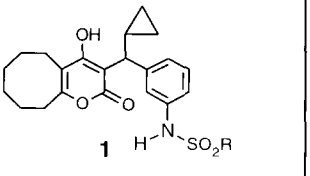
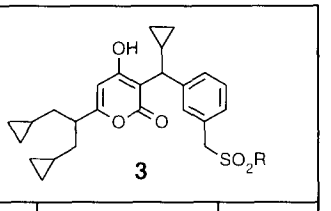


1

R	Compd #	Inhibition of HIV protease K_i (nM)	Antiviral Activity[a]	Compd #	Inhibition of HIV protease K_i (nM)	Antiviral Activity[a]
phenyl	**2a**	6	>30	**1a**	3	5
4-methylphenyl	**2b**	4.1	>30	**1b**	3	3.6
4-fluorophenyl	**2c**	2.1	14.5	**1c**	3.1	2.1
4-carboxyphenyl	**2d**	7	>30	**1d**	11	>10
4-cyanophenyl	**2e**	1.9	20.5	**1e**	0.8	1.5
2-pyridinyl	**2f**	1.9	10	**1f**	0.86	<1
2-(1-methyl-imidazoyl)	**2g**	3	20.4	**1g**	1.1	>3

[a](HIV_{111b} in H9 cells) IC^{50} μM)

Table 2. Comparison of HIV-1 Protease Inhibitory and Antiviral Activity of Dicyclopropylpyranone Sulfones and Sulfonamides.



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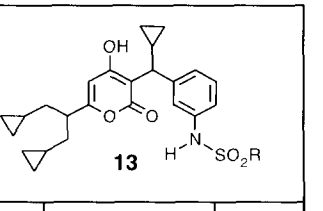

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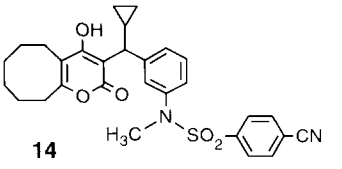
R	Compd #	Inhibition of HIV protease K_i (nM)	Antiviral Activity[a]	Compd #	Inhibition of HIV protease K_i (nM)	Antiviral Activity[a]
4-fluorophenyl	**3a**	19	19.8	**13a**	16	2.2
2-pyridinyl	**3b**	2.3	7.7	**13b**	0.66	>1, <3
2-(1-methyl-imidazoyl)	**3c**	3.1	12.0	**13c**	0.73	>1, <3

[a](HIV_{111b} in H9 cells) IC_{50} (μM)

Sawada et al.[10] Mass balance was obtained under sink conditions, metabolism was negligible, and permeability coefficients were corrected for the aqueous boundary layer. Modifications at the 4-phenyl position of the R group of the cyclooctyl sulfonamides, e.g., R = 4-cyanophenyl (**1e**), 4-fluorophenyl (**1c**), 4-chlorophenyl (not shown), and substitution of the phenyl with a methyl (R = methyl, not shown) had no impact upon permeability.[5] This result suggests that the sulfonamide introduces an energy barrier against partitioning of the molecule into lipid membranes. A similar finding with amides has been attributed to reduced permeability to hydration of the hydrogen donating group.[11] Moreover, the N-methylated analog **14** showed increased permeability approximately five fold relative to **1e**, supporting this interpretation.[12,13]



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7. The alcohol (**5**) was prepared by treatment of 3-bromobenzyl alcohol with methyllithium, n-butyllithium and cyclopropanecarboxaldehyde in sequence at -78 oC.
8. In vitro inhibition of HIV-1 protease was measured as described in the following: Thaisrivongs, S.; Tomich, P. K.; Watenpaugh, K. D.; Chong, K.-T.; Howe, W. J.; Yang, C.-P.; Strohbach, J. W.; Turner, S. R.; Spinelli, P. A.; Hinshaw, R. R.; Pagano, P. J.; Moon, J. B.; Ruwart, M. J.; Wilkinson, K. F.; Rush, B. D.; Zipp, G. L.; Dalga, R. J.; Schwende, F. J.; Howard, G. M.; Padbury, G. E.; Toth, L. N.; Zhao, Z.; Koeplinger, K. A.; Kakuk, T. J.; Cole, S. L.; Zaya, R. M.; Piper, R. C.; Jeffrey, P. *J. Med. Chem.* **1994**, *37*, 3200.
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13. The preparation of compounds of the general type **14** may be found in ref. 5.

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