5,6-Dihydropyran-2-ones Possessing Various Sulfonyl Functionalities: Potent Nonpeptidic Inhibitors of HIV Protease

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On the basis of previous SAR findings and molecular modeling studies, a series of compounds were synthesized which possessed various sulfonyl moieties substituted at the 4-position of the C-3 phenyl ring substituent of the dihydropyran-2-one ring system. The sulfonyl substituents were added in an attempt to fill the additional S_3' pocket and thereby produce increasingly potent inhibitors of the target enzyme. Racemic and enantiomerically resolved varieties of selected compounds were synthesized. All analogues in the study displayed decent binding affinity to HIV protease, and several compounds were shown to possess very good antiviral efficacy and safety margins. X-ray crystallographic structures confirmed that the sulfonamide and sulfonate moieties were filling the S_3' pocket of the enzyme. However, the additional substituent did not provide improved enzymatic inhibitory or antiviral activity as compared to the resolved unsubstituted aniline. The addition of the sulfonyl moiety substitution does not appear to provide favorable pharamacokinectic parameters. Selected inhibitors were tested for antiviral activity in clinical isolates and exhibited similar antiviral activity against all of the HIV-1 strains tested as they did against the wild-type HIV-1. In addition, the inhibitors exhibited good antiviral efficacies against HIV-1 strains that displayed resistance to the currently marketed protease inhibitors.

Introduction

Since first identified as the etiological agent of acquired immune deficiency syndrome (AIDS),[1] the development of drugs to treat human immunodeficiency virus (HIV) infection has been an area of intense research efforts. One approach that has met with great success is the inhibition of HIV protease,[2,3] a virally encoded aspartyl protease essential for the production of mature, infectious virions. HIV protease is responsible for the posttranslational processing of the *Gag* and *Gag/Pol* polyproteins,[4] proteolytic activity that cannot be carried out by native enzymes of the infected host. The currently marketed HIV protease inhibitors which are peptidomimetics, though remarkably efficacious, have serious problems associated with high costs,[5] low bioavailability,[6] and significant drug interactions.[3,7] Additionally, the emergence of HIV-1 strains which are resistant to currently available therapies will mandate the need for new medications.[2,8,9]

Efforts in our laboratories to identify a potent nonpeptidic HIV protease inhibitor originated with the high-throughput screening lead **I.**[10] This achiral 4-hydroxypyran-2-one is a low-micromolar inhibitor of HIV protease lacking antiviral activity which is presumed to occupy two interior pockets (S_1 and S_1') of the target enzyme (Figure 1). Structure−activity relationship studies centered around the mass screening lead eventually resulted in the 5,6-dihydro-4-hydroxy-2-pyrone **II.**[11] Possessing one chiral center, **II** displayed a 300-fold increase in activity against the enzyme over the initial lead; however, it exhibited no antiviral activity. The lack of efficacy against the virus displayed by **II** may be due to the extensive hydrophobic nature of the compound. Recently, we have reported further efforts at structural modification and optimization, namely replacement of one of the phenyl rings with alkyl groups and adding polar substituents at both sides of the molecule, resulting in the identification of **III** (PD 178390, CI-1029) as a clinical candidate.[12] Inhibitor **III** exhibits subnanomolar activity against HIV protease, excellent antiviral efficacy and therapeutic index, favorable multispecies pharmacokinetic profiles, and little cross-resistance with currently marketed protease inhibitors.[13] X-ray crystal structure studies of **III** bound to HIV protease indicated that the inhibitor occupies the interior four pockets of the enzyme (S_1, S_2, S_1', and S_2') as shown in Figure 2. Active site interactions include hydrogen bond formation between the 4-hydroxyl group and the catalytic aspartic acids Asp25 and Asp125, as well as hydrogen bonds between the lactone moiety and NHs of the flap region Ile50 and Ile150 amino acid residues (Figure 2). H_2O-

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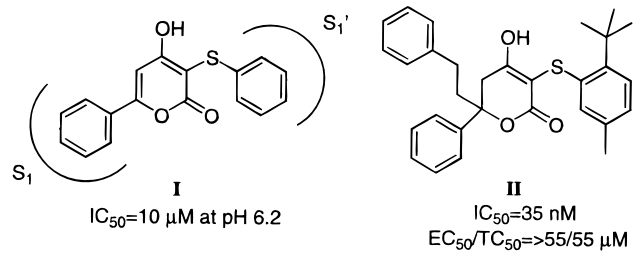


Figure 1.

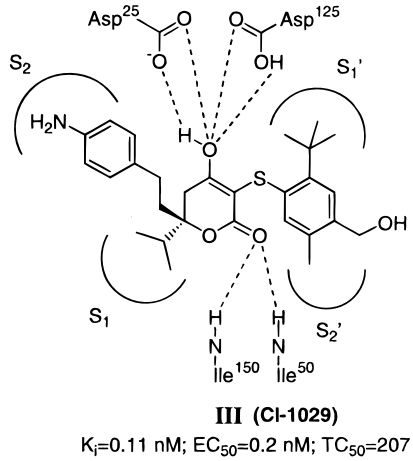


Figure 2. Lead compound CI-1029 occupying the interior four active site pockets with core interactions.

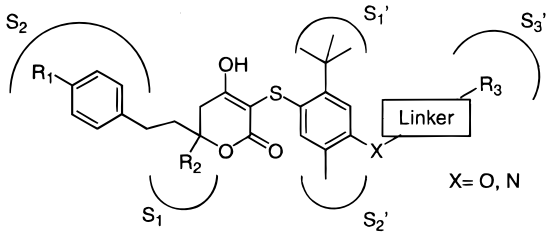


Figure 3. Target 5,6-dihydropyran-2-ones occupying the five enzymatic active site pockets.

301, commonly seen in X-ray crystallographic studies of HIV protease, is displaced by the carbonyl of the lactone moiety.[14,15]

Design

In an effort to identify more potent inhibitors of HIV protease, a series of compounds was synthesized in which an additional enzyme pocket could be filled in addition to the four inner pockets occupied by **III**. Molecular modeling studies indicated substitution at the 4′-position of the 3-*S*-(2-*tert*-butyl-5-methylphenyl) moiety could provide access to the S_3' pocket of the HIV protease enzyme (Figure 3). In addition, since the S_3' pocket of the enzyme is located toward the exposed solvent region one can use various substitutions, which might not only enhance the binding affinities of the inhibitors but also modify the physical properties of the inhibitors. An amino or hydroxyl group located at the 4′-position of the 3-*S*-(2-*tert*-butyl-5-methylphenyl) moiety could easily be functionalized to extend into the S_3' pocket. Recently, researchers at Pharmacia and Upjohn have reported employing a similar strategy in a related series of compounds.[16] This series of HIV protease inhibitors is also based on the 5,6-dihydropyran-2-one ring system and possesses sulfonamide functionalities which are seen to occupy the S_3' pocket. Recently, we reported preliminary results of HIV protease inhibitors possessing amide,[17] ether, carbamate, and sulfamate functionalities.[18] A variety of functional groups were investigated to better access the S_3' pocket of the enzyme. Herein, we report inhibitors possessing sulfonamide, sulfonate, and sulfonylurea functionalities with the proper orientation to fill the S_3' pocket.

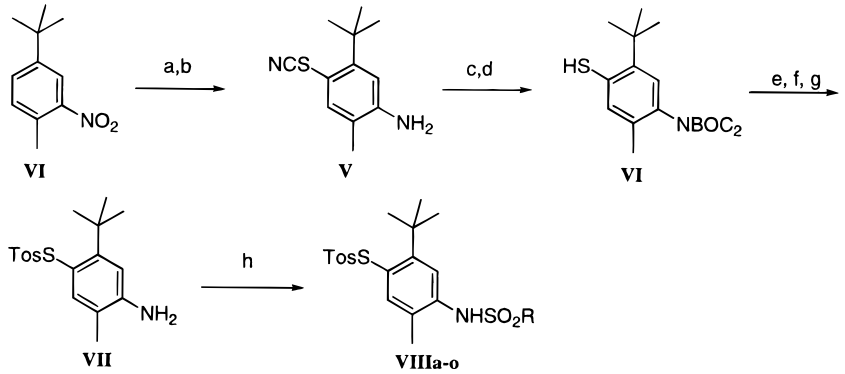
Chemistry

The target compounds (compounds **1**−**69S,** Table 3) were synthesized in a convergent manner involving the coupling of 5,6-dihydropyran-2-one with the appropriate thiotosylate (Table 1) in the presence of potassium carbonate in DMF. The synthetic pathway necessitated the synthesis of thiotosylates derived from an appropriately substituted aniline or phenol. In the case of the aniline-derived series (Scheme 1), 4-*tert*-butyl-1-methyl-2-nitrobenzene[19] (**VI**) was reduced to the aniline with Raney nickel and treated with bromine, sodium bromide, and sodium thiocyanide to yield the isothiocyanate derivative **V**. Protection of the amine was accomplished with di-*tert*-butyl dicarbonate followed by treatment with dithiothreitol to afford the thiol **VI**. The thiol was converted to the thiotosylate by reaction with tosyl bromide in the presence of triethylamine. The Boc protection was then removed with HCl gas in dichloromethane to yield the hydrochloride salt which was treated with phosphate buffer (pH 7.5) to give the free base **VII**. Finally, treatment with the appropriate sulfonyl chloride in pyridine and dichloromethane gave the desired thiotosylates **VIIIa**−**o**.

In the case of the phenol-derived thiotosylates (Scheme 2), 4-*tert*-butyl-1-methyl-2-nitrobenzene (**VI**) underwent reduction with Raney nickel followed by diazotization with sodium nitrite to give the phenol. Treatment of this compound with bromine, sodium bromide, and sodium thiocyanide afforded the isothiocyanate derivative **IX**. The isothiocyanate can then be subjected to dithiothreitol to produce the thiol, followed by tosylation with tosyl bromide in the presence of triethylamine to present **X.** Treatment with the appropriate sulfonyl chloride in the presence of triethylamine produces the desired thiotosylates **VIIIp**−**y**. Alternatively, **IX** can be converted to the sulfamate **XII** through reaction with the corresponding sulfamoyl chloride. Treatment with dithiothreitol followed by subsequent tosylation with tosyl bromide affords the desired thiotosylate **VIIIz**.

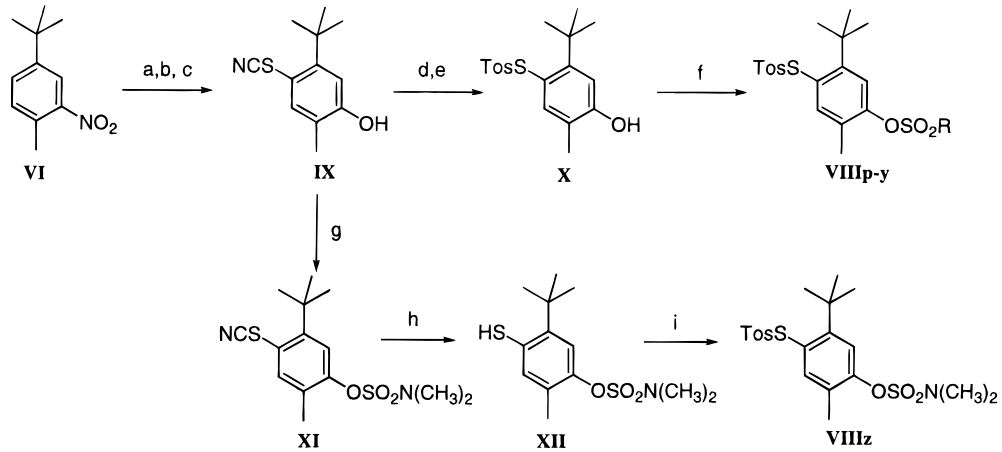
The racemic and enantiomerically resolved intermediate 5,6-dihydropyran-2-ones (Table 2) were synthesized as previously described[13] and are shown in Schemes 3 and 4, respectively. Enantiomerically pure 5,6-dihydropyran-2-ones (>95% enantiomeric purity) were synthesized with the key step being the resolution of the corresponding *β*-hydroxy acids (**(*S*)-XVII** and **(*R*)-XVII**; Scheme 4). Absolute stereochemistry was determined by small molecule X-ray of the intermediate *β*-hydroxy acid **(*S*)-XVIIb** as the salt of (*S*)-(−) α-(naphthyl)ethylamine which ultimately yielded the resolved 5,6-dihydopyran-2-one **(*S*)-XIVb**. Absolute stereochemistry was determined in a similar fashion in a closely related series.[20] The resolved *β*-hydroxy acids were elaborated to the corresponding *β*-keto esters which

Scheme 1. Synthesis of Thiotosylates Possessing a Sulfonamide Functionality[a]



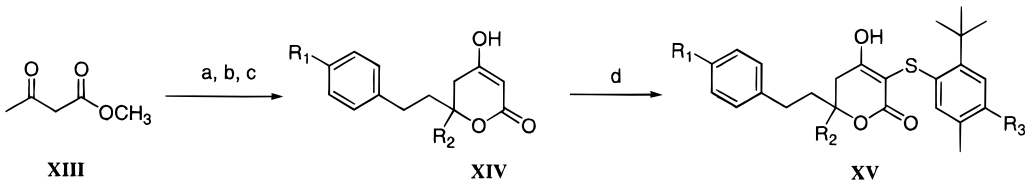
[a] Reaction conditions: (a) H_2, Raney nickel, MeOH; (b) NaSCN, Br_2, NaBr, MeOH; (c) Boc_2O, THF, 60 °C; (d) DTT, EtOH, phosphate buffer; (e) tosyl bromide, NEt_3, CCl_4; (f) HCl, CH_2Cl_2; (g) phosphate buffer, MeOH; (h) XSO_2R, pyridine, CH_2Cl_2.

Scheme 2. Synthesis of Thiotosylates Possessing a Sulfonate Functionality[a]



[a] Reaction conditions: (a) H_2, Raney nickel, MeOH; (b) $NaNO_3$, H_3O^+; (c) NaSCN, Br_2, NaBr, MeOH; (d) DTT, EtOH, phosphate buffer; (e) tosyl bromide, pyridine, CCl_4; (f) XSO_2R, NEt_3, CH_2Cl_2 or Et_2O; (g) *N*,*N*-dimethylsulfamoyl chloride, NEt_3, CH_2Cl_2; (h) DTT, EtOH, phosphate buffer; (i) tosyl bromide, NEt_3, CCl_4.

Scheme 3. Synthesis of Racemic Target 5,6-Dihydropyran-2-ones[a]



[a] Reaction conditions: (a) NaH, then *n*-BuLi, THF; (b) $R_2CO(CH_2)_2PhR_1$; (c) NaOH, then H^+; (d) thiotosylate, K_2CO_3, DMF.

upon treatment with sodium hydroxide cyclized to form the desired 5,6-dihydropyran-2-ones.

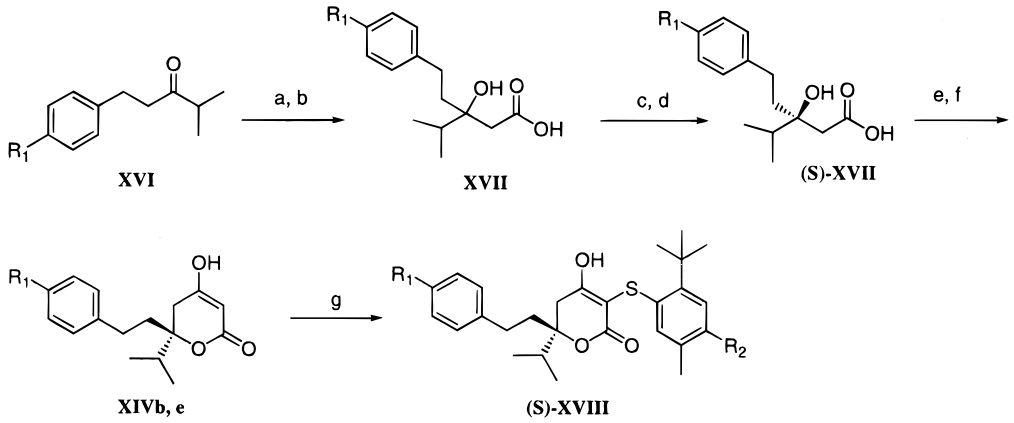
Biological Assays

Enzyme Inhibition Assay. For determination of IC_{50} values, affinity-purified HIV-1 protease (Bachem Bioscience; 1.1 nM) was added to a solution of the following: the inhibitor, 40 μM peptide substrate (His-Lys-Ala-Arg-Val-Leu-(*p*-NO_2-Phe)-Glu-Ala-Nle-Ser-NH_2; Bachem Bioscience), and 1.0% DMSO in assay buffer (1.0 mM dithiothreitol, 80 mM MES, 160 mM NaCl, 1.0 mM EDTA, 0.1% poly(ethylene glycol) (MW 8000), pH 6.2 at 25 °C.) The final volume was 100 μL; final concentration of HIV protease was 1.5 nM. The solution was mixed, incubated for 60 min at 37 °C, and then quenched with trifluoroacetic acid (2% final). In this assay, the Leu-(*p*-NO_2-Phe) bond of the substrate was cleaved by the enzyme, and the substrate and cleavage products were separated by reverse-phase HPLC. Absorbance was measured at 220 nm, peak areas were determined, and % conversion to product was used to calculate % control ([% conversion(+inhibitor)/% conversion(−inhibitor)] × 100).

Anti-HIV Activity Assay. Anti-HIV activity was determined in an in vitro cell culture assay employing HIV-IIIB-infected human lymphocyte-derived CEM cells using the XTT cytopathic protocol at Southern Research Institute.[21] Antiviral activity against clinical isolates was determined in a similar assay employing HIV-1-infected PBMC cells. EC_{50} refers to the effective concentration at which 50% of the cells are conferred protection against the cytopathic effects of HIV. TC_{50} refers to the toxic concentration of the drug that elicits cytotoxicity in 50% of CEM cells not infected with HIV.

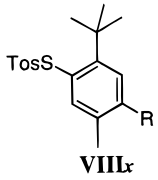
The probe substrates used to determine the inhibitory activities against CYP3A4, CYP2D, and CYP2C9 were

Scheme 4. Synthesis of Enantiomerically Pure Target 5,6-Dihydropyran-2-ones[a]



[a] Reaction conditions: (a) LDA, benzyl acetate, THF; (b) H_2, 5% Pd/C, MeOH; (c) (*S*)-α-methylbenzylamine, EtOAc; (d) 1 N HCl, ETOAc; (e) CDI, THF, then $Mg(O_2CCH_2CO_2Et)_2$; (f) 1 N NaOH, then 1 N HCl; (g) thiotosylate, K_2CO_3, DMF. Note: The resolved (*R*)-enantiomer of *β*-hydroxy acid (**XIV**) is obtained by utilizing (*R*)-α-methylbenzylamine in the resolution step (c) leading to the (*R*)-5,6-dihydro-4-hydroxy-2-pyranone (**XVI**).

Table 1. Method of Preparation of Thiotosylate Intermediates



VIIIx

entry	R	general method of preparation	method of purification	% yield
a	$NHSO_2Me$	A	triturated: EtOAc/hexanes	76
b	$NHSO_2Ph$	A	triturated: hexanes	58
c	$NHSO_2Ph(4\text{-}F)$	A	chromatographed ($CHCl_3$)	92
d	$NHSO_2Ph(4\text{-}Cl)$	A	chromatographed ($CHCl_3$:EtOAc 9:1)	85
e	$NHSO_2Ph(4\text{-}CF_3)$	A	chromatographed ($CHCl_3$:EtOAc 9:1)	67
f	$NHSO_2Ph(4\text{-}CN)$	A	chromatographed ($CHCl_3$:EtOAc 19:1)	66
g	$NHSO_2Ph(3\text{-}CN)$	A	triturated: EtO_2/hexanes	57
h	$NHSO_2Ph(4\text{-}NHCOMe)$	A	triturated: EtOAc/hexanes	79
i	$NHSO_2Ph(2\text{-}thiophene)$	A	triturated: EtOAc/hexanes	90
j	$NHSO_2$(*N*-methylimidazole)	A	triturated: hexanes	96
k	$NHSO_2(2\text{-}pyridyl)$	A	triturated: EtOAc/CH_2Cl_2/hexanes	78
l	$NHSO_2(3\text{-}pyridyl)$	A	triturated: EtOAc/hexanes	78
m	$NHSO_2[2\text{-}(5\text{-}CF_3)pyridyl]$	A	chromatographed ($CHCl_3$:EtOAc 9:1)	48
n	$NHSO_2NHCH_2CH_3$	A	chromatographed ($CHCl_3$:EtOAc 32:1)	76
o	$NHSO_2N(CH_3)_2$	A	chromatographed ($CHCl_3$/EtOAc 9:1)	77
p	OSO_2Me	B	chromatographed ($CHCl_3$)	65
q	OSO_2Ph	B	triturated: EtO_2	70
r	$OSO_2Ph(4\text{-}F)$	B	chromatographed ($CHCl_3$)	72
s	$OSO_2Ph(4\text{-}CN)$	B	chromatographed ($CHCl_3$)	78
t	$OSO_2(2\text{-}thiophene)$	B	triturated: EtO_2/hexanes	73
u	OSO_2(*N*-methylimidazole)	B	triturated: EtO_2	87
v	$OSO_2(2\text{-}pyridyl)$	B	triturated: EtO_2	68
w	$OSO_2(3\text{-}pyridyl)$	B	triturated: EtO_2/hexanes	66
x	$OSO_2NHCH_2CH_3$	B	none	98

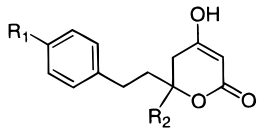
testosterone, bufurolol, and tolbutamide, respectively. The samples were analyzed by HPLC-UV or fluorescence.

Results and Discussion

In our previously reported SAR, which led to the identification of the lead compound CI-1029 (Figure 2), we found that to best fill the S_1 pocket of HIV protease, an alkyl substituent at the C-6 position of the 5,6-dihydropyran-2-one ring system was preferred. A *p*-(hydroxy or amino)phenethyl was found to be optimal for occupying the S_2 pocket.[12,13] In this study we initially held isopropyl and *p*-hydroxyphenethyl groups constant for occupying the S_1 and S_2 pockets, respectively, and varied the substituents that would fill the S_3' pocket. Though the steric bulk of the substituent occupying the S_3' pocket was varied, all the analogues in the study displayed decent binding affinity to HIV protease, with IC_{50} or K_i in the low-nanomolar to subnanomolar range. The presence or absence of a polar group on the C-6 phenethyl occupying the S_2 pocket did not have a great effect on enzymatic activity. The biological activities associated with the target inhibitors are shown in Tables 4−6.

I. Sulfonamides. A. C-6 Isopropyl Series. In this series of inhibitors (compounds **2**−**12**), increasing the steric bulk from a methyl (**2**) to a benzenesulfonamide (**3**) does not produce any significant increase in enzyme

Table 2. 5,6-Dihydropyran-2-one Intermediates Used for This Study[a]



XIV*x*

chirality	entry	R_1	R_2	chirality	entry	R_1	R_2
R/S	**a**	OH	isopropyl	*R/S*	**h**	OH	methyl
S	**b**	OH	isopropyl	*R/S*	**i**	OH	*n*-propyl
R	**c**	OH	isopropyl	*R/S*	**j**	OH	isobutyl
R/S	**d**	H	isopropyl	*R/S*	**k**	OH	cyclopropyl
S	**e**	H	isopropyl	*R/S*	**l**	OH	cyclopentyl
R	**f**	H	isopropyl	*R/S*	**m**	OH	cyclohexyl
R/S	**g**	NH_2	isopropyl				

[a] Syntheses of 5,6-dihydropyran-2-ones are shown in Schemes 3 and 4 and described in ref 13.

binding antiviral activity; however cytotoxicity is slightly higher. While *para*-substitution on the phenyl ring is allowed (**4**−**6**, **8**), it does not lead to any significant changes in cellular activity or cytotoxicity. Substitution in the *meta*-position with a nitrile group (**7**) leads to a decrease in antiviral activity by approximately 3-fold as compared to the *p*-cyano (**8**) derivative although they display similar K_i's. Replacement of the phenyl by a comparable isostere such as a thiophene (**9**) leads to a significant decrease in enzymatic binding; however, the antiviral activity is unaffected and the cytotoxicity is slightly lower. Increasing the size of the heterocycle to a 2-pyridyl (**10**) or 3-pyridyl (**11**) group results in a slight loss of cellular activity. *Para*-substitution on the 2-pyridyl (**12**) does not affect activity; however the associated toxicity is increased. The best compound in this series based on EC_{50} and TI was compound **6** possessing 4-trifluoromethylphenylsulfonamide. However, the unsubstituted aniline (**1**) displayed better activity than any of the sulfonamides with an EC_{50} of 1.0 μM and TC_{50} of 92 μM.

B. Other C-6 Alkyl Groups. The C-6 isopropyl group series did not provide any analogues with greatly enhanced biological activity as compared to the parent unsubstituted aniline (**1**). To fully investigate the effect of the alkyl substituent on biological activity, other groups possessing varied steric bulk were also placed at the C-6 position. In general, the methyl group at the C-6 position (compounds **14**−**22**) resulted in a consistent drop in antiviral activity when compared to the analogous isopropyl derivatives. This trend can be seen by comparing the activities associated with several of the inhibitors (**2** vs **14**, **3** vs **15**, **4** vs **16**, etc.). The best derivative in this series is the 4-fluorophenylsulfonamide (**16**) with an EC_{50} of 5.6 μM and a therapeutic index of 39.

To further analyze what effect the C-6 alkyl group has on activity, derivatives were synthesized where the sulfonyl moiety was held constant and the C-6 alkyl group was varied. In the sulfonamide series, the benzenesulfonamide was held constant while the C-6 alkyl group was varied from methyl (**15**), to isopropyl (**3**), to cyclopropyl (**23**), and to cyclopentyl (**24**). Reducing or increasing the size of the alkyl substituent from an isopropyl group does not enhance enzymatic inhibitory or antiviral activities. A C-6 isopropyl group is seen to be optimal for producing favorable biological activity.

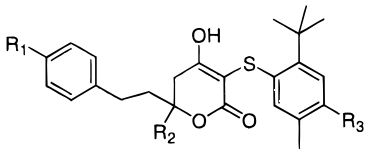
C. Polar Functionality on the Phenethyl Group. Since changing the C-6 alkyl group or varying the sulfonamido moiety did not result in substantial increases in desired activity, we decided to examine what effect polarity might have on activity. In our previous studies leading to CI-1029, the presence of a polar group on the 4-position of the phenethyl moiety was found to produce compounds with better overall therapeutic profiles though there was no influence on HIV protease binding affinity. This can be seen by examining the unsubstituted aniline derivatives with and without the phenolic moiety (compounds **1** and **25,** respectively). While both derivatives display similar inhibitory activity against the enzyme, the derivative possessing a *p*-hydroxy group on the phenethyl moiety exhibits better antiviral activity (1.0 μM vs 1.9 μM) and decreased cellular toxicity (92 μM vs 69 μM) as compared to the deshydroxy compound.

In this series (compounds **26**−**34**), a number of compounds were synthesized with various substitutions on the 4-position of the 3-*S*-(2-*tert*-butyl-5-methylphenyl) moiety while keeping the isopropyl group at the C-6 position constant and the phenethyl moiety with and without a polar substituent at the *para*-position. In this series of inhibitors, the presence of the *p*-hydroxy group on the phenethyl moiety had no significant effect on enzymatic activity. However, compounds that do not contain the *p*-hydroxyl on the phenethyl group generally displayed increased antiviral activity and similar toxicity as compared to inhibitors possessing the phenolic group. The increase in antiviral activity was seen to be from 3→7-fold. The compounds with a heterocyclic sulfonamide seemed to be affected most by the removal of the phenol. Compound **31** possessing a 2-pyridylsulfonamide exhibits an approximately 6-fold increase in activity against HIV and greater cytotoxicity as compared to the hydroxylated derivative **10** (66 μM vs >100 μM). The greatest increase in activity was found to be with the compound possessing the 2-(5-CF_3-pyridyl)-sulfonamide moiety (**34**) which exhibited an EC_{50} of 0.6 μM and a TI of 100, a greater than 7-fold potency improvement over the corresponding *p*-hydroxyphenethyl derivative (**12**).

Since analogous compounds that have a phenethyl or *p*-hydroxyphenethyl group as a C-6 substituent on the dihydropyran-2-one ring system display comparable enzymatic inhibitory activities, the differences in antiviral activities associated with equivalent derivatives may be related to changes in physical property. The sulfonamido moieties may confer additional hydrophilic properties to the molecule that necessitate the removal of a polar functionality for favorable antiviral activity. The overall polarity associated with the various inhibitors is important for antiviral activity.[12] It appears the amount of polarity required for favorable antiviral activity may be obtained through appropriate substitution on the C-6 or C-3 portion of the molecules.

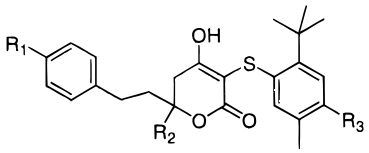
II. Sulfonates. A. C-6 Isopropyl Series. In this series (compounds **36**−**43**) the nitrogen group of the sulfonamide was replaced with an oxygen. The methanesulfonate (**36**) possesses an IC_{50} of 2.2 nM and EC_{50} of 0.6 μM with cellular toxicity of >100 μM for a TI of

Table 3. Dihydropyran-2-one Analogues and Their Physical Properties



entry	R_1	R_2	R_3	method of purification	% yield	mp (°C)	molecular formula[a]	anal.[b]
1	OH	isopropyl	NH_2	chromatographed; $CHCl_3$:MeOH (9:1)	56	125−127	$C_{27}H_{35}N_1O_4S_1\cdot 0.83H_2O$	CHN
1S	OH	isopropyl	NH_2	chromatographed; EtOAc	57	147−149 d	$C_{27}H_{35}N_1O_4S_1\cdot 0.31H_2O$	CHN
1R	OH	isopropyl	NH_2	chromatographed; CH_2Cl_2:EtOAc (3:1)	51	147−149 d	$C_{27}H_{35}N_1O_4S_1\cdot 0.45H_2O$	CHN
2	OH	isopropyl	$NHSO_2CH_3$	chromatographed; EtOAc:hexanes (9:1)	68	124 effer	$C_{28}H_{37}N_1O_6S_2$	CHN
3	OH	isopropyl	$NHSO_2Ph$	chromatographed; EtOAc:hexanes (7:3)	63	200−203 d	$C_{33}H_{39}N_1O_6S_2$	CHN
4	OH	isopropyl	$NHSO_2Ph$(4-F)	chromatographed; EtOAc:hexanes (7:3)	66	123−125	$C_{33}H_{38}F_1N_1O_6S_2\cdot 0.34H_2O$	CHN
5	OH	isopropyl	$NHSO_2Ph$(4-Cl)	chromatographed; EtOAc:hexanes (7:3)	70	214−218 d	$C_{33}H_{38}Cl_1N_1O_6S_2$	CHN
6	OH	isopropyl	$NHSO_2Ph$(4-CF_3)	chromatographed; EtOAc:hexanes (3:1)	61	227−229 d	$C_{34}H_{38}F_3N_1O_6S_2\cdot 0.47H_2O$	CHN
7	OH	isopropyl	$NHSO_2Ph$(3-CN)	chromatographed; EtOAc:hexanes (7:3)	51	>132 effer	$C_{34}H_{38}N_2O_6S_2$	CHN
8	OH	isopropyl	$NHSO_2Ph$(4-CN)	chromatographed; EtOAc:hexanes (7:3)	65	217−220 d	$C_{34}H_{38}N_2O_6S_2\cdot 0.37H_2O$	CHN
9	OH	isopropyl	$NHSO_2$(2-thiophene)	chromatographed; EtOAc:hexanes (7:3)	72	207−210 d	$C_{31}H_{37}N_1O_6S_3$	CHN
10	OH	isopropyl	$NHSO_2$(2-pyridyl)	chromatographed; EtOAc	68	>136 effer	$C_{32}H_{38}N_2O_6S_2$	CHN
11	OH	isopropyl	$NHSO_2$(3-pyridyl)	chromatographed; $CHCl_3$:MeOH (19:1)	33	>135 effer	$C_{32}H_{38}N_2O_6S_2\cdot 0.84H_2O$	CHN
12	OH	isopropyl	$NHSO_2$[2-(5-CF_3)-pyridyl]	chromatographed; CH_2Cl_2:MeOH (18:1)	72	>129 effer	$C_{33}H_{37}F_3N_2O_6S_2\cdot 0.29H_2O$	CHN
12S	OH	isopropyl	$NHSO_2$[2-(5-CF_3)-pyridyl]	chromatographed; CH_2Cl_2:MeOH (18:1)	38	>142 effer	$C_{33}H_{37}F_3N_20_6S_2\cdot 0.53H_2O$	CHN
12R	OH	isopropyl	$NHSO_2$[2-(5-CF_3)-pyridyl]	chromatographed; CH_2Cl_2:MeOH (18:1) then EtOAc:hexanes (7:3)	42	>134 effer	$C_{33}H_{37}F_3N_20_6S_2\cdot 0.49H_2O$	CHN
13	OH	methyl	NH_2	chromatographed; $CHCl_3$:MeOH (19:1)	70	158−168	$C_{25}H_{31}N_1O_4S_1\cdot 0.65H_2O\cdot 0.98HCl$	CHN,Cl^-
14	OH	methyl	$NHSO_2CH_3$	chromatographed; $CHCl_3$:MeOH (99:1)	57	133 effer	$C_{26}H_{33}N_1O_6S_2\cdot 0.51H_2O$	CHN
15	OH	methyl	$NHSO_2Ph$	chromatographed; $CHCl_3$:MeOH (9:1)	55	136 effer	$C_{31}H_{35}N_1O_6S_2\cdot 0.70H_2O$	CHN
16	OH	methyl	$NHSO_2Ph$(4-F)	chromatographed; EtOAc:hexanes (7:3)	50	122 effer	$C_{31}H_{34}F_1N_1O_6S_2\cdot 0.58H_2O$	CHN
17	OH	methyl	$NHSO_2Ph$(4-Cl)	chromatographed; EtOAc:hexanes (4:1)	52	>160 effer	$C_{31}H_{34}Cl_1N_1O_6S_2\cdot 0.33H_2O$	CHN
18	OH	methyl	$NHSO_2Ph$(4-CF_3)	chromatographed; EtOAc:hexanes (3:1)	55	128 effer	$C_{32}H_{34}F_3N_1O_6S_2$	CHN
19	OH	methyl	$NHSO_2Ph$(4-CN)	chromatographed; EtOAc:EtOH (49:1)	41	153 effer	$C_{32}H_{34}N_2O_6S_2\cdot 1.09H_2O$	CHN
20	OH	methyl	$NHSO_2Ph$(4-NHCOMe)	chromatographed; EtOAc:EtOH (49:1)	27	185 effer	$C_{33}H_{38}N_2O_7S_2\cdot 1.16H_2O$	CHN
21	OH	methyl	$NHSO_2Ph$(2-thiophene)	chromatographed; $CHCl_3$:MeOH (9:1)	66	>132 effer	$C_{29}H_{33}N_1O_6S_3\cdot 0.67H_2O$	CHN
22	OH	methyl	$NHSO_2$(*N*-methyl-imidazole)	triturated: Et_2O/hexanes	28	164 effer	$C_{29}H_{35}N_3O_6S_2\cdot 0.87H_2O$	CHN
23	OH	cyclopropyl	$NHSO_2Ph$	chromatographed; hexanes:EtOAc (3:1) then EtOAc	70	123−125	$C_{33}H_{37}N_1O_6S_2\cdot 1.0H_2O$	CHN
24	OH	cyclopentyl	$NHSO_2Ph$	chromatographed; hexanes:EtOAc (3:1) then EtOAc	62	125−127	$C_{35}H_{41}N_1O_6S_2\cdot 0.40H_2O$	CHN
25	H	isopropyl	NH_2	chromatographed; EtOAc:hexanes (starting at 1:4 gradient to 4:1)	52	104−105	$C_{27}H_{35}N_1O_3S_1$	CHN
26	H	isopropyl	$NHSO_2CH_3$	chromatographed; EtOAc:hexanes (4:1)	62	88	$C_{28}H_{37}N_1O_5S_2\cdot 0.72H_2O$	CHN
27	H	isopropyl	$NHSO_2Ph$(4-CF_3)	chromatographed; $CHCl_3$:MeOH (19:1)	51	188−192	$C_{34}H_{38}F_3N_1O_5S_2\cdot 0.60H_2O$	CHN
28	H	isopropyl	$NHSO_2Ph$(3-CN)	chromatographed; EtOAc:hexanes (7:3)	55	>175 effer	$C_{34}H_{38}N_2O_5S_2\cdot 0.40H_2O$	CHN
29	H	isopropyl	$NHSO_2Ph$(4-CN)	chromatographed; EtOAc:hexanes (7:3)	65	>125 effer	$C_{34}H_{38}N_2O_5S_2$	CHN
29S	H	isopropyl	$NHSO_2Ph$(4-CN)	chromatographed; CH_2Cl_2:MeOH (24:1)	89	>130 effer	$C_{34}H_{38}N_20_5S_2$	CHN
30	H	isopropyl	$NHSO_2$(2-thiophene)	chromatographed; EtOAc:hexanes (2:1)	50	96−116	$C_{31}H_{37}N_1O_5S_3$	CHN
31	H	isopropyl	$NHSO_2$(2-pyridyl)	chromatographed; EtOAc:hexanes (9:1)	64	>134 effer	$C_{32}H_{38}N_2O_5S_2\cdot 0.51H_2O$	CHN
32	H	isopropyl	$NHSO_2$(3-pyridyl)	chromatographed; $CHCl_3$:MeOH (18:1)	44	193−194 d	$C_{32}H_{38}N_2O_5S_2\cdot 0.40H_2O$	CHN
33	H	isopropyl	$NHSO_2$(*N*-methyl-imidazole)	chromatographed; $CHCl_3$:MeOH (18:1)	36	>146 effer	$C_{31}H_{39}N_3O_5S_2\cdot 1.04H_2O$	CHN
34	H	isopropyl	$NHSO_2$[2-(5-CF_3)-pyridyl]	chromatographed; CH_2Cl_2:MeOH (24:1)	46	>143 effer	$C_{33}H_{37}F_3N_2O_5S_2$	CHN
34S	H	isopropyl	$NHSO_2$[2-(5-CF_3)-pyridyl]	chromatographed; CH_2Cl_2:EtOAc (3:1)	75	>162 effer	$C_{33}H_{37}F_3N_2O_5S_2\cdot 0.33H_2O$	CHN
34R	H	isopropyl	$NHSO_2$[2-(5-CF_3)-pyridyl]	chromatographed; CH_2Cl_2:MeOH (48:1)	46	>145 effer	$C_{33}H_{37}F_3N_2O_5S_2$	CHN
35	OH	isopropyl	OH	chromatographed; hexanes:EtOAc (4:1) to EtOAc (100%) gradient	63	117−118	$C_{27}H_{34}O_5S_1$	CH
36	OH	isopropyl	OSO_2CH_3	chromatographed; EtOAc	81	>180 d	$C_{28}H_{36}O_7S_2$	CH
36S	OH	isopropyl	OSO_2 CH_3	chromatographed; EtOAc (100%) then EtOAc:hexanes (3:1)	45	>205 d	$C_{28}H_{36}O_7S_2$	CH

Table 3 (Continued)



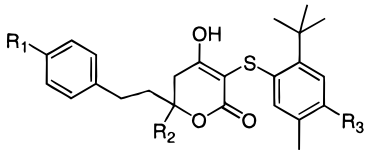
entry	R_1	R_2	R_3	method of purification	% yield	mp (°C)	molecular formula[a]	anal.[b]
37	OH	isopropyl	OSO_2Ph	chromatographed; EtOAc	77	>180 d	$C_{33}H_{38}O_7S_2$	CH
38	OH	isopropyl	OSO_2Ph(4-F)	chromatographed; EtOAc	75	>180 d	$C_{33}H_{37}F_1O_7S_2$	CH
39	OH	isopropyl	OSO_2Ph(4-CN)	chromatographed; EtOAc	80	200 d	$C_{34}H_{36}N_1O_7S_2 \cdot 0.40H_2O$	CHN
40	OH	isopropyl	OSO_2(2-thiophene)	chromatographed; EtOAc	75	>180 d	$C_{31}H_{36}O_7S_3$	CHN
41	OH	isopropyl	OSO_2(*N*-methyl-imidazole)	chromatographed; EtOAc	67	>170 effer	$C_{31}H_{38}N_2O_7S_2 \cdot 0.45H_2O$	CHN
42	OH	isopropyl	OSO_2(2-pyridyl)	chromatographed; EtOAc	86	>180 d	$C_{32}H_{37}N_1O_7S_2 \cdot 0.25H_2O$	CHN
43	OH	isopropyl	OSO_2(3-pyridyl)	chromatographed; EtOAc	64	>180 d	$C_{32}H_{37}N_1O_7S_2$	CHN
44	OH	methyl	OSO_2Ph	chromatographed; EtOAc	64	>180 d	$C_{31}H_{34}O_7S_2$	CH
45	OH	methyl	OSO_2Ph(4-F)	chromatographed; EtOAc:hexanes (7:3)	70	>170 d	$C_{31}H_{33}F_1O_7S_2$	CH
46	OH	methyl	OSO_2(*N*-methyl-imidazole)	triturated: $CHCl_3/Et_2O$	60	>160 effer	$C_{29}H_{34}N_2O_7S_2$	HPLC
47	OH	cyclohexyl	OSO_2Ph	chromatographed; EtOAc	58	>180 d	$C_{36}H_{42}O_7S_2 \cdot 0.50H_2O$	CH
48	OH	cyclohexyl	OSO_2Ph(4-CN)	chromatographed; EtOAc	74	>200 d	$C_{37}H_{41}N_1O_7S_2 \cdot 0.65H_2O$	CHN
49	OH	cyclohexyl	OSO_2Ph(4-F)	chromatographed; EtOAc	75	>180 d	$C_{36}H_{41}F_1O_7S_2 \cdot 0.65H_2O$	CH
50	OH	cyclohexyl	OSO_2(*N*-methyl-imidazole)	chromatographed; EtOAc	58	>153 effer	$C_{34}H_{42}N_2O_7S_2 \cdot 0.94H_2O$	CHN
51	OH	*n*-propyl	OSO_2(*N*-methyl-imidazole)	chromatographed; hexanes:EtOAc (3:1) to EtOAc (100%) gradient	72	169−171	$C_{31}H_{38}N_2O_7S_2 \cdot 2.8H_2O$	CHN
52	OH	isobutyl	OSO_2(*N*-methyl-imidazole)	chromatographed; hexanes:EtOAc (3:1) to EtOAc:hexanes (1:1) gradient then EtOAc:MeOH (19:1)	62		$C_{31}H_{38}N_2O_7S_2$	HPLC
53	H	isopropyl	OH	chromatographed; hexanes:EtOAc (4:1) to EtOAc (100%) gradient	70	87−89	$C_{27}H_{34}O_4S_1 \cdot 0.70H_2O$	CH
54	H	isopropyl	OSO_2(*N*-methyl-imidazole)	chromatographed; hexanes:EtOAc (3:1) to EtOAc:hexanes (4:1) gradient	63	120−122	$C_{31}H_{38}N_2O_6S_2 \cdot 0.50H_2O$	CHN
55	H	isopropyl	OSO_2(2-pyridyl)	chromatographed; EtOAc	82	>180 d	$C_{32}H_{37}N_1O_6S_2 \cdot 0.26H_2O$	CHN
56	H	isopropyl	OSO_2(3-pyridyl)	chromatographed; EtOAc	55	>180 d	$C_{32}H_{37}N_1O_6S_2 \cdot 0.40H_2O$	CHN
57	NH_2	isopropyl	OSO_2Ph(4-CN)	none	71	185 d	$C_{34}H_{38}N_2O_6S_2 \cdot 1.0HCl \cdot 0.46H_2O$	CHN,Cl^-
58	NH_2	isopropyl	OSO_2Ph(3-pyridyl)	none	65	>180 d	$C_{32}H_{38}N_2O_6S_2 \cdot 1.0HCl \cdot 0.32H_2O$	CHN,Cl^-
59	NH_2	isopropyl	OSO_2(*N*-methyl-imidazole)	none	57	>180 d	$C_{31}H_{39}N_3O_6S_2 \cdot 0.9HCl \cdot 0.50H_2O$	CHN,Cl^-
60	NH_2	isopropyl	OSO_2Ph(2-thiophene)	chromatographed; CH_2Cl_2:MeOH (9:1)	39	>150 d	$C_{31}H_{37}N_1O_6S_3$	CHN
61	OH	isopropyl	$NHSO_2N(CH_3)_2$	chromatographed; EtOAC:hexanes (3:1)	52	187−189 d	$C_{29}H_{40}N_2O_6S_2$	CHN
62	OH	isopropyl	$NHSO_2NHEt$	chromatographed; $CHCl_3$:MeOH (19:1)	52	>152 effer	$C_{29}H_{40}N_2O_6S_2$	CHN
63	H	isopropyl	$NHSO_2NHEt$	chromatographed; EtOAc:hexanes (9:1)	72	136 effer	$C_{29}H_{40}N_2O_5S_2 \cdot 0.20H_2O$	CHN
64	OH	isopropyl	$OSO_2N(CH_3)_2$	chromatographed; EtOAc	86	>180 d	$C_{29}H_{39}N_1O_7S_2$	CHN
65	OH	isopropyl	OSO_2NHEt	chromatographed; hexanes:EtOAc (4:1) to EtOAc (100%) gradient	59	97−99	$C_{29}H_{39}N_1O_7S_2$	CHN
66	NH_2	isopropyl	$OSO_2N(CH_3)_2$	triturated: Et_2O	52	>205 d	$C_{29}H_{40}N_1O_6S_2 \cdot 0.60H_2O$	CHN,Cl^-
67	NH_2	isopropyl	OSO_2NHEt	triturated: Et_2O	78	185−188	$C_{29}H_{40}N_1O_6S_2 \cdot 1.0HCl \cdot 1.0H_2O$	CHN,Cl^-
68	H	isopropyl	OSO_2NHEt	chromatographed; hexanes:EtOAc (4:1) to EtOAc (100%) gradient	68	78−79	$C_{29}H_{39}N_1O_6S_2$	CHN
69S	H	isopropyl	OSO_2Ph(4-CN)	chromatographed; CH_2Cl_2:MeOH (48:1)	59	>85 effer	$C_{34}H_{37}N_1O_6S_2$	CHN

[a] Water content was not experimentally determined. [b] All compounds were with in ±0.4% of the theoretical values.

>175. Contrary to what is observed with the sulfonamides, increasing the steric bulk of the sulfonate group from a methyl to a phenyl group (**37**) results in a greater than 4-fold drop in activity against the enzyme. Additionally, there is a modest decrease in antiviral activity, with an increase in toxicity as well, resulting in a TI of approximately 41. Substitution on the *para*-position of the phenyl ring (compounds **38** and **39**) has no significant effect on cellular activity. Replacement of the phenyl ring by a heterocyclic ring (inhibitors **40**−**43**) provided no substantial change in antiviral activity. In this series of inhibitors, compound **36** possessing a methanesulfonate moiety displays the best overall therapeutic profile. Compound **36** exhibits modestly better antiviral activity and is less cytotoxic than the unsubstituted phenol **35**.

B. Other C-6 Alkyl Groups. As in the sulfonamide series, to fully investigate the effect of the alkyl substituent on biological activity, other groups possessing varied steric bulk were also placed at the C-6 position. In general, a C-6 methyl group results in inhibitors (compounds **44**−**46**) that have similar enzymatic inhibitory activities as compared to the C-6 isopropyl analogues. The methyl analogues display approximately 3−4-fold less antiviral activity than the analogous isopropyl derivatives.

Table 4. Dihydropyran-2-one Analogues and Associated Biological Activities

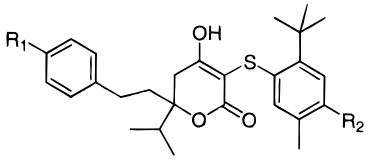


entry	R_1	R_2	R_3	IC_{50} (K_i)[a] (nM)	EC_{50}[b] (μM)	TC_{50}[c] (μM)	TI[d]
1	4-OH	isopropyl	NH_2	2.7 (0.67)	1.0	92	92
2	4-OH	isopropyl	$NHSO_2Me$	4.0	5.3	>100	>19
3	4-OH	isopropyl	$NHSO_2Ph$	1.8 (0.53)	1.4	74	53
4	4-OH	isopropyl	$NHSO_2Ph$(4-F)	4.1	1.8	66	37
5	4-OH	isopropyl	$NHSO_2Ph$(4-Cl)	5.3	1.6	66	41
6	4-OH	isopropyl	$NHSO_2Ph$(4-CF_3)	18.3	1.1	66	60
7	4-OH	isopropyl	$NHSO_2Ph$(3-CN)	(0.21)	5.3	>100	>19
8	4-OH	isopropyl	$NHSO_2Ph$(4-CN)	2.2 (0.41)	1.6	85	53
9	4-OH	isopropyl	$NHSO_2$(2-thiophene)	8.7	1.8	>100	>56
10	4-OH	isopropyl	$NHSO_2$(2-pyridyl)	2.6	4.1	>100	>24
11	4-OH	isopropyl	$NHSO_2$(3-pyridyl)	2.6	5.8	>100	>17
12	4-OH	isopropyl	$NHSO_2$[2-(5-CF_3)pyridyl]		4.3	68	16
13	4-OH	methyl	NH_2	13.0	3.7	>100	>27
14	4-OH	methyl	$NHSO_2Me$	9.7	19	>100	>5
15	4-OH	methyl	$NHSO_2Ph$	1.5	5.2	>100	>19
16	4-OH	methyl	$NHSO_2Ph$(4-F)	3.7	2.4	93	39
17	4-OH	methyl	$NHSO_2Ph$(4-Cl)	3.5	3.9	71	18
18	4-OH	methyl	$NHSO_2Ph$(4-CF_3)	12.3	3.5	79	23
19	4-OH	methyl	$NHSO_2Ph$(4-CN)	2.1	5.0	>100	>20
20	4-OH	methyl	$NHSO_2Ph$(4-NHCOMe)		55	>100	>2
21	4-OH	methyl	$NHSO_2Ph$(2-thiophene)	6.3	5.6	>100	>18
22	4-OH	methyl	$NHSO_2$(*N*-methylimidazole)	1.9	58	>100	>2
23	4-OH	cyclopropyl	$NHSO_2Ph$	3.6	2.4	76	32
24	4-OH	cyclopentyl	$NHSO_2Ph$	8.6	2.5	67	27
25	H	isopropyl	NH_2	3.6	1.9	69	36
26	H	isopropyl	$NHSO_2Me$	(0.83)	1.6	>100	>63
27	H	isopropyl	$NHSO_2Ph$(4-CF_3)	(27.0)	0.7	24	34
28	H	isopropyl	$NHSO_2Ph$(3-CN)	(1.4)	1.5	66	44
29	H	isopropyl	$NHSO_2Ph$(4-CN)	9.1	0.5	66	132
30	H	isopropyl	$NHSO_2$(2-thiophene)	3.6	2.1	61	29
31	H	isopropyl	$NHSO_2$(2-pyridyl)	3.0	0.7	67	96
32	H	isopropyl	$NHSO_2$(3-pyridyl)	3.5	1.6	76	48
33	H	isopropyl	$NHSO_2$(*N*-methylimidazole)	1.9	4.2	>100	>23
34	H	isopropyl	$NHSO_2$[2-(5-CF_3)pyridyl]	(1.04)	0.6	66	100
35	4-OH	isopropyl	OH	(0.03)	1.6	66	41
36	4-OH	isopropyl	OSO_2Me	2.2	0.6	>100	>175
37	4-OH	isopropyl	OSO_2Ph	10.4	1.6	66	41
38	4-OH	isopropyl	OSO_2Ph(4-F)	9.6	0.8	66	83
39	4-OH	isopropyl	OSO_2Ph(4-CN)	4.5	0.6	67	122
40	4-OH	isopropyl	OSO_2(2-thiophene)	21.8	2.4	72	30
41	4-OH	isopropyl	OSO_2(*N*-methylimidazole)	2.4	4.3	>100	>23
42	4-OH	isopropyl	OSO_2(2-pyridyl)	5.0	0.7	84	120
43	4-OH	isopropyl	OSO_2(3-pyridyl)	3.5	1.6	76	48
44	4-OH	methyl	OSO_2Ph	9.8	12	82	7
45	4-OH	methyl	OSO_2Ph(4-F)	16.9	6.3	100	16
46	4-OH	methyl	OSO_2(*N*-methylimidazole)	2.0	16	>100	>6
47	4-OH	cyclohexyl	OSO_2Ph	131	>59	59	<1
48	4-OH	cyclohexyl	OSO_2Ph(4-CN)	21.0	2.6	29	11
49	4-OH	cyclohexyl	OSO_2Ph(4-F)	29.0	9.5	66	7
50	4-OH	cyclohexyl	OSO_2(*N*-methylimidazole)	8.0	1.6	>100	63
51	4-OH	*n*-propyl	OSO_2(*N*-methylimidazole)	2.2	1.9	>100	54
52	4-OH	isobutyl	OSO_2(*N*-methylimidazole)	3.6	4.4	>100	23
53	4-H	isopropyl	OH	(1.1)	1.8	66	37
54	4-H	isopropyl	OSO_2(*N*-methylimidazole)	3.0	1.1	66	60
55	4-H	isopropyl	OSO_2(2-pyridyl)	6.7	1.4	65	46
56	4-H	isopropyl	OSO_2(3-pyridyl)	14.0	4.6	65	14
57	4-NH_2	isopropyl	OSO_2Ph(4-CN)	1.3	0.4	53	151
58	4-NH_2	isopropyl	OSO_2Ph(3-pyridyl)	4.1	2.2	66	30
59	4-NH_2	isopropyl	OSO_2(*N*-methylimidazole)	2.2	1.8	>100	>56
60	4-NH_2	isopropyl	OSO_2Ph(2-thiophene)	18.5	6.0	66	11

[a] Enzyme inhibition was determined at pH 6.2 as previously described.[12] [b] EC_{50} is the effective concentration at which 50% of the cells are protected from HIV infection and is the average of at least two runs. [c] TC_{50} is the concentration which elicits cytotoxicity in 50% of uninfected CEM cells. [d] TI, therapeutic index = TC_{50}/EC_{50}.

Several analogues were synthesized with a C-6 cyclohexyl group to examine its utility in providing desirable activity against HIV protease (**47**−**50**). Increasing the size of the C-6 substituent from an isopropyl to a cyclohexyl leads to a significant loss in enzymatic and antiviral activities. Compound **47**, which possesses a

Table 5. Dihydropyran-2-one Analogues Possessing a Sulfonylurea or Sulfamate Functionality and Their Chemical Data and Biological Activities



entry	R_1	R_2	IC_{50} (K_i) (nM)	EC_{50} (μM)	TC_{50} (μM)	TI
61	4-OH	$NHSO_2N(Me)_2$	3.6	1.7	>100	>59
62	4-OH	$NHSO_2NHEt$	1.7	3.3	>100	>30
63	4-H	$NHSO_2NHEt$	3.3	1.2	77	64
64	4-OH	$OSO_2N(Me)_2$	3.4	0.7	70	100
65	4-OH	OSO_2NHEt	4.9	1.0	>100	>100
66	4-NH_2	$OSO_2N(Me)_2$	3.9	0.8	64	80
67	4-NH_2	OSO_2NHEt	4.3	0.7	83	128
68	4-H	OSO_2NHEt	8.9	0.8	67	84

phenylsulfonate, displays approximately 13-fold less inhibitory activity against HIV protease than the analogous isopropyl derivative **37** and exhibits very little cellular activity. While *para*-substitution on the phenylsulfonate (compounds **48** and **49**) restores some of the desirable activity to the cyclohexyl analogues, they still show much less activity than the comparable isopropyl derivatives (**38** and **39**).

As in the sulfonamide series, to further investigate the effect of the C-6 alkyl substituent on biological activity, derivatives were synthesized where the sulfonyl moiety was held constant and the C-6 alkyl group was varied. In the sulfonate series, a *N*-methylimidazolesulfonate moiety was held constant while the C-6 alkyl group was varied (i.e., methyl (**46**), *n*-propyl (**51**), isopropyl (**41**), isobutyl (**52**), cyclohexyl (**50**)). Except for the cyclohexyl analogue, which was approximately 3−4-fold less active, all analogues displayed similar activity against the enzyme. Except for the methyl analogue which displayed less antiviral activity, the other analogues displayed a similar level of activity against the virus as the isopropyl derivative. This finding indicated that in this series of compounds, though a C-6 alkyl substituent is important for activity, the steric bulk of this alkyl substituent can vary greatly and still provide favorable activity.

C. *p*-Phenethyl Polar Group. In the sulfonate series, the presence of the *p*-hydroxyl on the C-6 phenethyl group was generally found to enhance antiviral activity. Only in the case of the *N*-methylimidazolesulfonate derivative (**54**) was the antiviral activity seen to be better for the comparable analogue that did not possess the *p*-hydroxyl on the phenethyl moiety. The presence or absence of the polar group on the phenethyl moiety did not have any significant effect on enzymatic inhibitory activity in these compounds.

Previous SAR studies indicated that the optimal *p*-phenethyl polar substituent for the C-6 phenethyl was found to be a primary amine. To examine if this was the case in this series, several compounds were synthesized in which the phenolic group was replaced with an anilino group (**57**−**60**). The replacement of the hydroxyl group with an amino group has no significant effect on enzymatic inhibition or antiviral activity.

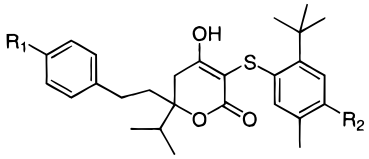
III. Sulfonylureas and Sulfamates. A logical extension of our SAR is the replacement of the alkyl or arylsulfonyl groups with sulfamoyl moieties to produce sulfonylurea and sulfamate derivatives (Table 5). While a number of various sulfonylureas and sulfamates were synthesized,[17,18] the most promising were derivatives with small alkyl groups on the sulfamoyl nitrogen. The dimethylsulfonylurea analogue (**61**) exhibits an EC_{50} of 1.7 μM and TC_{50} of >100 μM for a TI of >59. The monoethyl derivative (**62**) is less potent against the virus displaying an EC_{50} of 3.3 μM. Removal of the *p*-hydroxyl group from the C-6 phenethyl substituent slightly increases antiviral activity and cytotoxicity. The monoethylsulfamate **65** displays antiviral activity in the same range as dimethylsulfamate compound **64** (1.0 and 0.7 μM, respectively) and is less toxic in the cellular assay (>100 μM vs 70 μM). Replacement of the *p*-hydroxy group on the C-6 phenethyl substituent with a primary amine does not affect antiviral activity but modestly increases cytotoxicity in both the dimethyl- (**66**) and monoethylsulfamates (**67**). Removal of the polar substituent entirely on the phenethyl moiety (compound **68**) has similar effects on antiviral activity and cytotoxicity.

Enantiomerically Resolved 5,6-Dihydropyran-2-ones. As a result of the promising biological activities and therapeutic indices of a number of the racemic compounds, several enantiomerically pure dihydropyran-2-ones were synthesized (Scheme 4). The associated biological activities of these optically pure compounds are displayed in Table 6. The (*S*)-enantiomers **1S**, **12S,** and **34S** possess substantially increased binding affinity to HIV protease relative to the (*R*)-enantiomers **1R**, **12R,** and **34R** (19-, 24-, and 21-fold increased binding affinity, respectively). The (*S*)-enantiomers display greater antiviral activity as compared to the corresponding (*R*)-enantiomers, the greatest difference being in the case of the unsubstituted aniline compound **1S,** which displayed 0.49 μM antiviral activity while the (*R*)-enantiomer **1R** was essentially inactive against HIV. The (*S*)-enantiomers generally exhibited approximately 2-fold increases in activity against HIV relative to the racemic analogues. Only the (*S*)-enantiomer of the sulfonate compound **69S** was synthesized and was seen to possess similar activity against HIV as the comparable sulfonamide analogue **29S**.

X-ray Crystal Structures of Analogues 3 and 50 Bound to Wild-Type HIV Protease. The X-ray crystal structures of **3** and **50** bound to HIV protease both show a binding mode similar to that previously observed with this series of inhibitors. That is, the 5,6-dihydropyran-2-one ring spans the active site with the 4-hydroxyl group binding at the catalytic dyad, Asp25/125, and the carbonyl group interacting with Ile50 and/or Ile150 in the flap region. In addition, the substituents at the C-3 and C-6 positions of the dihydropyranone ring occupy the four pockets surrounding the catalytic site of the enzyme.

An overlay of the X-ray crystal structures of **3, 50,** and CI-1029 bound to HIV protease is shown in Figure 4. This figure highlights the similarity in the binding of the closely related substituted dihydropyranone core for **3** and CI-1029. A variation in binding is observed at the P_2 site, where the phenol group in **3** binds through a water molecule to Asp30, while the aniline group in CI-1029 has a direct contact with the Asp30 side chain.

Table 6. Enantiomerically Resolved Dihydropyran-2-ones[a] and Associated Biological Activities



entry	R_1	R_2	IC_{50} (K_i) (nM)	EC_{50} (μM)	TC_{50} (μM)	TI
1	OH	NH_2	2.7 (0.67)	1.0	92	92
1S	OH	NH_2	(0.07)	0.49	215	439
1R	OH	NH_2	(13.0)	91	211	2
12	OH	$NHSO_2$[2-(5-CF_3)pyridyl]		4.3	68	16
12S	OH	$NHSO_2$[2-(5-CF_3)pyridyl]	(0.39)	1.8	66	37
12R	OH	$NHSO_2$[2-(5-CF_3)pyridyl]	(9.54)	18.0	66	4
29	H	$NHSO_2$Ph(4-CN)	9.1	0.5	66	132
29S	H	$NHSO_2$Ph(4-CN)	(0.20)	0.22	31	141
34	H	$NHSO_2$[2-(5-CF_3)pyridyl]	(1.04)	0.6	66	100
34S	H	$NHSO_2$[2-(5-CF_3)pyridyl]	(0.31)	0.45	65	144
34R	H	$NHSO_2$[2-(5-CF_3)pyridyl]	(6.40)	5.9	66	11
36	OH	OSO_2CH_3	2.2	0.6	>100	>175
36S	OH	OSO_2CH_3	(0.03)	0.53	80	151
69S	H	OSO_2Ph(4-CN)	(0.70)	1.1	25	23

[a] The ratio of enantiomers is ≥95:5.

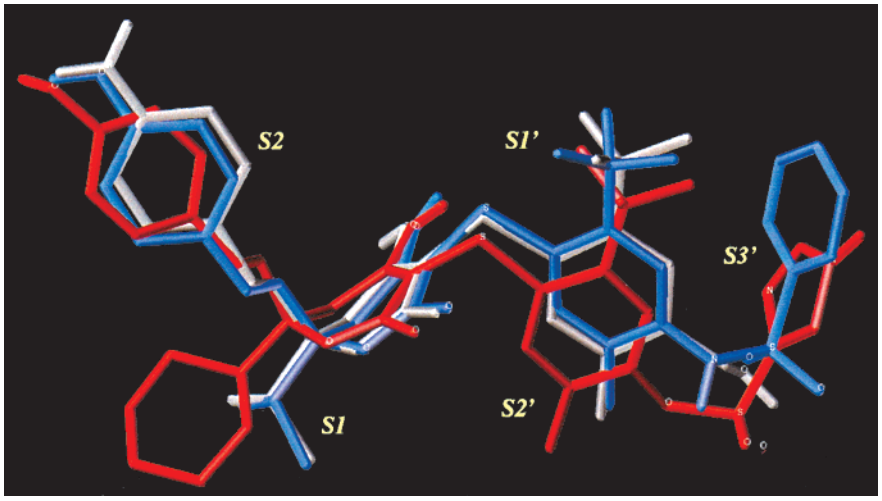


Figure 4. Overlay of the X-ray crystal structures of **3** (blue), **50** (red), and CI-1029 (white) bound to HIV protease. The enzyme sites are labeled in yellow.

In **3**, one oxygen of the sulfonamide group forms a hydrogen bond with Asp129(NH). This interaction is analogous to the hydrogen bond between the methylenehydroxy group in CI-1029 and Asp129(NH).

The benzenesulfonamido group in **3** occupies an additional site of the enzyme, the S_3' pocket, with the phenyl ring stacking against the Arg8/Asp129 ionic pair. However, this site of interaction does not increase the binding affinity of **3** relative to that of CI-1029. Any gain in enthalpy of binding is at least partially counterbalanced by the unfavorable entropic effect due to the addition of flexibility to the molecule.

Compound **50** has a cyclohexyl group at the P_1 site in place of the isopropyl moiety found in both **3** and CI-1029. Although the overall binding mode of the substituted core remains the same, a shift in orientation is observed (Figure 4). The bulky size of the cyclohexyl group may prevent the inhibitor from probing as deeply into the S_1 pocket, coming much closer to the flap region of the enzyme than the analogues with the isopropyl substituent at P_1. This results in the methyl-substituted *S*-phenyl ring at C-3 being drawn further into the binding cavity. Interestingly, the proximal Ile184 side chain then rotates from a −gauche orientation as observed in both the **3** and CI-1029 structures to +gauche in accommodating the binding of the methyl substituent (Figure 5).

At the P_2 site, the phenol group in **50** interacts directly with Asp30 as is observed with the CI-1029 aniline. In the prime side, **50** contains a *N*-methylimidazolesulfonate at the 4-position of the C-3 *S*-phenyl ring. The imidazole sits lower in the S_3' pocket than does the phenyl group of the benzenesulfonamido moiety in **3.** The orientation of the imidazole ring in the pocket eliminates any possibility of π system interactions with the side chain residues as is seen with compound **3**. The position of the imidazole ring does however allow one of the ring nitrogen atoms to form a hydrogen bond with Asp129(NH). The observed shift in binding also results in the P_1' *tert*-butyl group orienting lower in the S_1' region. The overall alteration in binding appears to result in nonoptimal occupancy of subsites and could contribute to the 4-fold drop in potency for **50** relative to **3**. It also illustrates, however, that while optimal binding may not be realized, inhibitors can still retain potent activity versus the enzyme. This characteristic

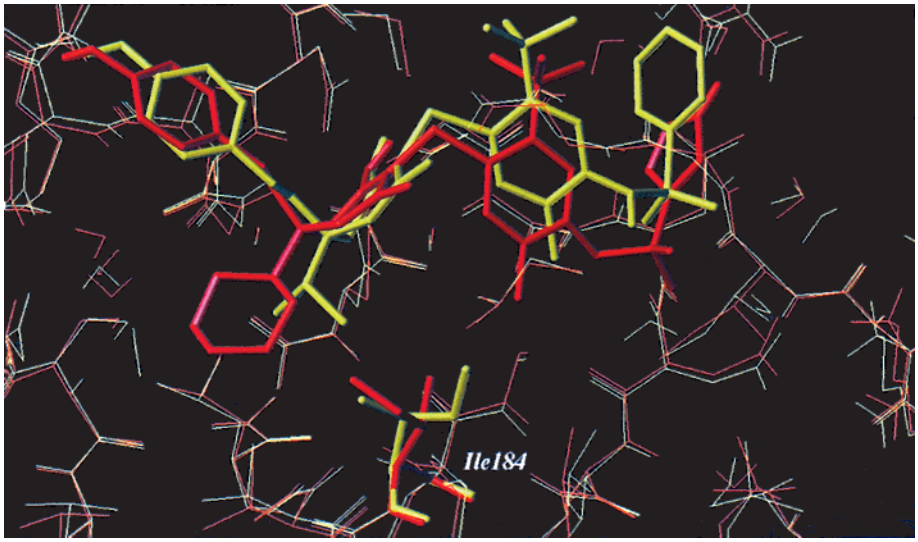


Figure 5. Overlay of the X-ray crystal structures of **3** (yellow) and **50** (red) bound to HIV protease. The inhibitors and Ile184 are shown with capped sticks representation.

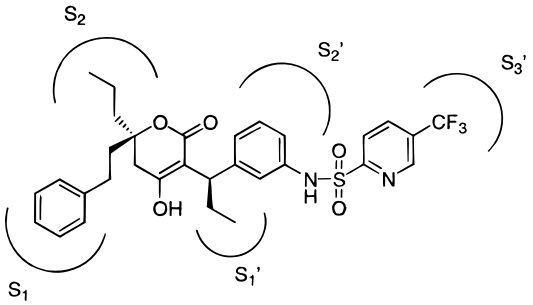


Figure 6. PNU-140690 illustrating the five enzymatic pockets binding mode.

Table 7. Pharmacokinetic Parameters of Selected Dihydropyran-2-one Analogues in Mice[a]

entry	vehicle[b]	C_{max} (μM)	AUC (μg·h/mL)	entry	vehicle[b]	C_{max} (μM)	AUC (μg·h/mL)
1	B	21.0	44.82	**36S**	B	6.54	5.4
1S	B	21.7	46.31	**43**	B	0.63	ND
12	B	1.27	0.98	**60**	B	0.22	ND
29	B	2.00	ND	**68**	A	0.62	ND
29S	B	10.3	ND	**69**	B	1.60	ND
31	B	1.14	ND	**70**	A	0.50	ND
34	B	0.54	0.56	**71**	B	0.93	1.58
34S	B	9.2	22.0				

[a] Dose: 25 mg/kg. [b] A: 20% 0.1 N NaOH/80% PEG 400. B: 20% 0.1 N NaOH/80% 0.5% methylcellulose. ND, not determined.

of this series of inhibitors may prove extremely advantageous in combating mutant proteases.

Comparison of Inhibitors 3 and 50 to PNU-140690. The structurally similar 5,6-dihydropyran-2-one HIV protease inhibitor PNU-140690 was recently identified by Pharmacia and Upjohn as a clinical candidate.[16,22] PNU-140690 in X-ray crystallographic studies has been shown to occupy five pockets of HIV protease (Figure 6). PNU-140690 and the current series of inhibitors share the 5,6-dihydropyran-2-one core template and display similar core binding interactions. PNU-140690 and inhibitors **3** and **50** interact through hydrogen bonds between the 4-hydroxyl group and the catalytic amino acids Asp25 and Asp125. Also similar to inhibitors **3** and **50**, PNU-140690 forms hydrogen bond interactions with NH groups of the flap region Ile50 and Ile150 amino acid residues. However, differences arise as to the method by which PNU-140690 and the inhibitors in this study fill the interior four enzymatic pockets that surround the catalytic site. Whereas the C-6 phenethyl substituent of the 5,6-dihydropyran-2-one ring system of PNU-140690 occupies the S_1 pocket of the enzyme, the 4-hydroxyphenethyl substituents of inhibitors **3** and **50** are seen to fill the S_2 pocket of the enzyme. The C-6 *n*-propyl substituent of PNU-140690 occupies the S_2 pocket of the target enzyme, in contrast to inhibitors **3** and **50** in which the C-6 alkyl moieties fill the S_1 pocket in the X-ray crystal structures. These results clearly illustrate that different enantiomers are the more active enantiomer in the two series of inhibitors, a finding that would not have been apparent without X-ray crystallography studies.[23] In both PNU-140690 and the current series of inhibitors, the sulfonyl moiety on the C-3 phenyl ring substituent of the 5,6-dihydropyran-2-one system is seen to occupy the S_3' pocket of the enzyme as anticipated.

Pharmacokinetic Studies. Several of the 5,6-dihydropyran-2-ones were dosed in mice to determine the effects of the various substitutions on bioavailability (Table 7). The mice were given a 25 mg/kg dose orally by gavage. The vehicle used for dosing was in most cases 20% 0.1 N NaOH/80% 0.5% methylcellulose. In two cases the vehicle used was 20% 0.1 N NaOH/80% PEG 400. The results of the mouse pharmacokinetic studies illustrate that substitution on the 3-*S*-(2-*tert*-butyl-5-methylphenyl) moiety with a sulfonyl-containing group greatly reduces plasma levels. The most favorable pharmacokinetic profile belongs to the unsubstituted aniline, compound **1**. Substitution on the aniline only served to produce low C_{max} levels and AUC values. In many cases the plasma C_{max} values were so low that adequate AUC values could not be determined. Interestingly, in the two cases where the racemic compounds (**29** and **34**) and the resolved (*S*)-enantiomers (**29S** and **34S**) of the sulfonyl compound were dosed, the (*S*)-enantiomer displayed significantly higher C_{max} levels (5- and 17-fold increases in C_{max} values, respectively). The increase in the level of C_{max} for the (*S*)-enantiomer compared to racemic analogue is not a constant phe-

Table 8. Pharmacokinetic Parameters of Selected Dihydropyran-2-ones in Rats[a]

entry	C_{max} (μM)	$T_{1/2}$ (h)	AUC (μg·h/mL)
29S	3.96	5.7	10.0
34S	3.50	2.3	6.7
36S	6.54	0.94	5.39

[a] Dose: 10 mg/kg, NaOH solution buffered to pH 7.4.

nomenon as this trend is not observed in the unsubstituted aniline (compounds **1** and **1S**).

The pharmacokinetic profiles of several compounds were also examined in rats (Table 8). Rats were given a 10 mg/kg dose orally with a NaOH solution buffered to pH 7.4 as the vehicle. The results of this study were similar to what was observed in mice: very low C_{max} and AUC values. Except for compound **36S**, the $T_{1/2}$ values were longer in the rat than in the mouse. The reason the substituted derivatives possess lesser pharmacokinetic parameters relative to the unsubstituted aniline (compounds **1** and **1S**) is unclear. The lower C_{max} and AUC values may be due to the higher molecular weight or lower solubilities of these compounds. The pharmacokinetics in rodents reported for PNU-140690 are similar to those for the compounds described here.

Antiviral Activity in Clinical Isolates. A major obstacle in the effective treatment of AIDS is the emergence of drug-resistance strains of HIV-1.[24,25] To assess their effectiveness against various strains, the anti-HIV activities of selected inhibitors were determined against a series of HIV-1 strains obtained from clinical isolates. The antiviral activity was measured in an in vitro assay employing HIV-1-infected PBMC cells. The antiviral activities of the inhibitors in this assay are shown in Table 9. Generally, each of the inhibitors displayed very good antiviral activity in the series of clinical isolates tested. Except for one instance (compound **40** against strain 1026-60), the antiviral activities of compounds **1S**, **29S**, **34,** and **40** against the selected HIV-1 strains were in the submicromolar range. Anti-HIV activities against the clinical isolates were within 2-fold of the associated antiviral activities of the inhibitors in the CEM cell assay (Table 2). Except against the protease inhibitor-resistant strain 144-44, inhibitor **29S** was the most antivirally potent against the clinically isolated strains that were tested. Of the five inhibitors tested in this assay, only compound **36** exhibited a significant decrease in antiviral activity against the clinical isolates as compared to CEM cells (approximately 2−3-fold less antiviral activity). All inhibitors possess very good activity against HIV-1 strains 1002-60, 1026-60, and 144-44 which exhibit resistance to the marketed protease inhibitors Indinavir and Saquinavir.

Cytochrome P450 Inhibition. One of the primary problems encountered with the currently marketed protease inhibitors is the occurrence of significant side effects and numerous drug interactions.[3,5b,7] These impediments to effective therapy are in many instances due to the inhibitory effects of the protease inhibitors on the cytochrome P450 system, particularly the CYP3A4 isozyme.[26,27] To assess their potential for metabolic liabilities, compounds **1S** and **39** were tested against several cytochrome P450 isozymes, and the results are shown in Table 10. The unsubstituted aniline analogue (**1S**) does not inhibit any of the three isozymes tested up to a concentration of 10 μM. Inhibition is observed at 100 μM drug concentration, particularly against CYP2C9. Compound **39**, which possesses a *p*-cyanophenylsulfonate moiety, displays notable inhibition at a concentration as low as 1 μM. Essentially complete inhibition of CYP3A4 and CYP2C9 occurs at 100 μM inhibitor concentration. The inhibition potential of compound **39** against CYP2D6 was not determined. These results suggest that the free aniline may possess less of a potential for drug interactions as a result of metabolic enzyme inhibition. On the other hand, compounds such as inhibitor **39,** which possesses the larger sulfonyl moiety, may have the potential for drug−drug interactions, similar to marketed protease inhibitors. Indinavir displays substantial inhibition of CYP3A4 at drug concentration of 1 μM and almost complete inhibition at 10 μM concentration. Indinavir has an inhibition profile similar to that of inhibitor **1S** against CYP2C9 and CYP2D6 with some differences at 100 μM drug concentrations.

Conclusions

On the basis of previous SAR and insights from X-ray crystallographic structures, a series of compounds was synthesized that possessed various sulfonyl moieties at the 4-position of the C-3 phenyl ring substituent of the dihydropyran-2-one ring system. The sulfonyl substituents were added in an attempt to fill the additional S_3' pocket and thereby produce more potent inhibitors of the target enzyme. The various sulfonyl moieties synthesized included sulfonamides, sulfonates, sulfonylureas, and sulfamates. Racemic and enantiomerically resolved varieties of selected compounds were synthesized with the (*S*)-enantiomer being the more potent enantiomer. All analogues in the study displayed decent binding affinity to HIV protease, with IC_{50} or K_i in the double-digit nanomolar to subnanomolar range. Several compounds from each series were shown to possess very good antiviral activities, with EC_{50}'s of 1 μM and TI's of >100. Generally, in the sulfonamide and sulfonylurea series, compounds that did not possess a polar group on the C-6 phenethyl moiety provided better anti-HIV activities. In the sulfonate and sulfamate series, the presence of the *p*-hydroxyl on the C-6 phenethyl group was generally seen to enhance antiviral activity. X-ray crystallographic structures of two inhibitors confirmed that the sulfonamide and sulfonate moieties were filling the S_3' pocket of the enzyme as anticipated. However, the added sulfonyl substitution did not provide improved enzymatic inhibitory or antiviral activity as compared to the resolved unsubstituted aniline **1S**. Inhibitor **1S**, which occupies only the four interior pockets of the enzyme, displays an EC_{50} of 0.49 μM antiviral activity and a TI of greater than 400. The addition of the sulfonyl moiety substitution does not appear favorable when examining pharamacokinetic parameters. Compounds that possessed the sulfonyl substitution exhibited lower plasma C_{max} levels and half-lives in all species tested as compared to the unsubstituted aniline derivative. Selected inhibitors exhibited similar antiviral activity against all of the HIV-1 clinical isolates tested, including highly resistant strains, as they did against the wild-type HIV-1. To assess their potential for inhibition of the cytochrome P450 system, selected compounds were tested against several cytochrome P450 isozymes. The unsubstituted aniline analogue (**1S**) does

Table 9. Selected Dihydropyran-2-ones and Their Associated Antiviral Activity[a] against Clinically Isolated HIV-1 Strains

entry	HIV-1 strain	EC_{50} (μM)	TC_{50} (μM)	TI	entry	HIV-1 strain	EC_{50} (μM)	TC_{50} (μM)	TI
1S	WeJo	0.25	>100	>400.0	**36**	WeJo	2.05	>100	>48.8
	RoJo	0.20	>100	>500.0		RoJo	1.24	>100	>80.6
	SLKA	0.22	>100	>454.5		SLKA	1.79	>100	>55.9
	TEKI	0.59	>100	>169.5		TEKI	1.93	>100	>51.8
	1002-60	0.74	>100	>135.1		1002-60	1.84	>100	>54.3
	1026-60	0.31	>100	>322.6		1026-60	1.12	>100	>89.3
	144-44	0.24	>100	>416.7		144-44	0.73	>100	>137.0
29S	WeJo	0.11	55.6	506	**40**	WeJo	0.39	>100	>259.1
	RoJo	0.12	55.6	464		RoJo	0.70	>100	>143.3
	SLKA	0.12	55.6	464		SLKA	0.50	>100	>200.0
	TEKI	0.10	55.6	556		TEKI	0.78	>100	>128.7
	1002-60	ND	ND			1002-60	ND	ND	
	1026-60	ND	ND			1026-60	1.42	>100	>70.32
	144-44	0.58	55.6	96		144-44	0.54	>100	>185.5
34	WeJo	0.69	>100	>144.9	Indinavir	1002-60	>100	>100	1
	RoJo	0.68	>100	>147.1		1026-60	16.55	>100	>6.0
	SLKA	0.71	>100	>140.8		144-44	3.0	>100	>33.3
	TEKI	0.81	>100	>123.5	Saquinavir	1002-60	14.54	>50	>3.4
	1002-60	0.61	>100	>163.9		1026-60	19.45	>50	>2.6
	1026-60	0.27	>100	>370.4		144-44	11.06	>50	>4.5
	144-44	0.26	>100	>384.6					

[a] Antiviral activity measured in HIV-1-infected PBMC cells. ND, not determined.

Table 10. Inhibition of Cytochrome P450 Activity by Selected Dihydropran-2-ones[a]

	3A4			2C9			2D6		
entry	1 μM	10 μM	100 μM	1 μM	10 μM	100 μM	1 μM	10 μM	100 μM
1S	103.0	96.8	41.1	93.2	75.5	21.6	105.0	95.0	56.7
39	79.0	34.6	6.86	83.5	18.1	BLD (0)	ND	ND	ND
Indinavir	27.0	5.0	BLQ (0)	93.0	89.0	68.0	100.0	82.0	31.0

[a] Percent cytochrome P450 activity remaining in the presence of HIV protease inhibitors. BLD, below levels of detection; ND, not determined.

not inhibit any of the three isozymes tested up to a concentration of 10 μM. In particular, inhibitor **1S** does not display substantial inhibition of the CYP3A4 isozyme activity up to concentrations of 100 μM.

Experimental Section

Enzyme Inhibition Assay. For determination of IC_{50} values, affinity-purified HIV-1 protease (Bachem Bioscience; 1.1 nM) was added to a solution of the following: the inhibitor, 40 μM peptide substrate (His-Lys-Ala-Arg-Val-Leu-(*p*-NO_2-Phe)-Glu-Ala-Nle-Ser-NH_2; Bachem Bioscience), and 1.0% DMSO in assay buffer (1.0 mM dithiothreitol, 80 mM MES, 160 mM NaCl, 1.0 mM EDTA, 0.1% poly(ethylene glycol) (MW 8000), pH 6.2 at 25 °C). The final volume was 100 μL; final concentration of HIV protease was 1.5 nM. The solution was mixed, incubated for 60 min at 37 °C, and then quenched with trifluoroacetic acid (2% final.) In this assay, the Leu-(*p*-NO_2-Phe) bond of the substrate was cleaved by the enzyme, and the substrate and cleavage products were separated by reverse-phase HPLC. Absorbance was measured at 220 nm, peak areas were determined, and % conversion to product was used to calculate % control ([% conversion(+inhibitor)/% conversion-(−inhibitor)] × 100).

Anti-HIV Activity Assay. Anti-HIV activity was determined in an in vitro cell culture assay employing HIV-IIIB-infected human lymphocyte-derived CEM cells using the XTT cytopathic protocol at Southern Research Institute.[20] EC_{50} refers to the effective concentration at which 50% of the cells are conferred protection against the cytopathic effects of HIV. TC_{50} refers to the toxic concentration of the drug that elicits cytotoxicity in 50% of CEM cells not infected with HIV. Antiviral activity against clinical isolates was determined in a similar assay employing HIV-1-infected PBMC cells.

Chemical Synthesis. Melting points were determined in open capillary tubes on a Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were determined in KBr pellets on a Nicolet FT IR SX-20 spectrophotometer. Proton magnetic resonance (NMR) spectra were recorded on Varian 300 and 400 spectrometers and chemical shifts are reported in δ units relative to internal standard, trimethylsilane. All mass spectra were obtained on a Finnigan 4500GCMS or VG analytical 7070E/F spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. or Quantitative Technologies, Inc. and all compounds gave analytical results of ±0.4% of theorectical values. All starting materials were obtained from commercial sources unless otherwise specified in the experimental. Flash chromatography was performed using silica gel 60, 230−400 mesh, purchased from Mallinckrodt.

5-Trifluoromethyl-2-pyridinesulfonyl Chloride. 2-Mercapto-5-(trifluoromethyl)pyridine (5.0 g, 27.91 mmol), CCl_4 (100 mL) and H_2O (20 mL) were cooled to 0 °C and Cl_2 gas bubbled through via pipet with stirring for 1 h. CH_2Cl_2 was added and the organic phase separated and washed with brine, dried over Na_2SO_4, filtered and concentrated to produce the title compound as a clear oil which solidified to a white solid upon storage in a freezer. The isolated product was used without further purification. Isolated yield: 5.9 g (86%). ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H), 8.33 (m, 1H), 9.08 (m, 1H).

2-Pyridinesulfonyl Chloride. 2-Mercaptopyridine (5.0 g, 27.91 mmol), CCl_4 (100 mL) and H_2O (20 mL) were cooled to 0 °C and Cl_2 gas bubbled through via pipet with stirring for 1 h. CH_2Cl_2 was added and the organic phase separated and washed with brine, dried over Na_2SO_4, filtered and concentrated to produce the title compound as a tinted oil which solidified upon storage in a freezer. The isolated product was used without further purification. Isolated yield: 5.0 g (63%). ^{1}H NMR ($CDCl_3$): δ 7.70 (m, 1H), 8.03−8.11 (m, 2H), 8.84 (m, 1H).

5-*tert*-Butyl-2-methylphenylamine. A solution of 4-*tert*-butyl-1-methyl-2-nitrobenzene[17] (**VI**) in MeOH (1.0 L) was treated with Raney nickel (25 g) in a Parr shaker. The apparatus was sealed under hydrogen pressure to 52 psi, heated at 35 °C for 15 h. The apparatus was then cooled to room temperature, vented and the contents filtered. The filtrate was concentrated in vacuo and distilled, collecting the major fraction (75−85 °C, 1.0 Torr) to afford the title com-

pound. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 9 H), 2.11 (s, 3 H), 3.54 (br s, 3 H), 6.69 (d, 1 H), 6.72 (dd, 1 H), 6.96 (d, 1 H).

5-*tert*-Butyl-2-methyl-4-thiocyanatophenylamine (V). A solution of 5-*tert*-butyl-2-methylphenylamine (1.0 g, 6.1 mmol), sodium thiocyanide (1.62 g, 20.0 mmol) and MeOH (4.0 mL) was cooled to 0 °C and treated via addition funnel with a solution of bromine (0.35 mL, 6.7 mmol), sodium bromide (0.63 g, 6.13 mmol), and MeOH (5.0 mL). The mixture was stirred for 30 min and then carefully diluted with saturated $NaHCO_3$ solution. The mixture was extracted twice with CH_2Cl_2, the organic phases combined, dried (Na_2SO_4) and the solvent evaporated. The resulting residue was subjected to flash silica gel chromatography, eluting with 4:1 CH_2Cl_2:hexanes to 19:1 CH_2Cl_2:hexanes + 1% MeOH to provide the title compound. ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9 H), 2.09 (s, 3 H), 3.80 (bs, 2 H), 6.69 (s, 1 H), 6.89,7.35 (s, 1 H).

[4-(Cyanothio)-5-(1,1-dimethylethyl)-2-methylphenyl]-imidodicarbonic Acid Bis(1,1-dimethylethyl) Ester. A solution of 5-*tert*-butyl-2-methyl-4-thiocyanatophenylamine (8.0 g, 36.36 mmol) and di-*tert*-butyl dicarbonate (31.7 g, 145.3 mmol) in THF (80 mL) was stirred at 60 °C under N_2 for 72 h. Solvent was then removed in vacuo and Et_2O added; the solution was washed with saturated $NaHCO_3$ solution, followed by brine, dried (Na_2SO_4), filtered and concentrated. The material was purified by flash chromatography on silica gel, eluting with 4:1 hexanes:EtOAc to 1:1 hexanes:EtOAc to afford the title compound. Isolated yield: 14.0 g (91%). ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 9 H), 1.43 (s, 3 H), 1.52 (s, 18 H), 7.14 (s, 1 H), 7.58 (s, 1 H).

[5-(1,1-Dimethylethyl)-4-mercapto-2-methylphenyl]imidodicarbonic Acid Bis(1,1-dimethylethyl) Ester (VI). To a solution of [4-(cyanothio)-5-(1,1-dimethylethyl)-2-methylphenyl]imidodicarbonic acid bis(1,1-dimethylethyl) ester (11.65 g, 27.7 mmol) in denatured EtOH (160 mL) were added dithiothreitol (16.8 g, 109.1 mmol) and 0.2 M KH_2PO_4 solution (40 mL) and the mixture was stirred overnight at 50 °C. The solvent was evaporated, H_2O was added and extracted with $CHCl_3$, the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash silica gel chromatography, eluting with 1:1 $CHCl_3$:hexanes switching to 19:1 $CHCl_3$:EtOAc, to afford the title compound. Isolated yield: 10.95 g (quantitative yield). ^{1}H NMR ($CDCl_3$): δ 1.40−1.46 (m, 27 H), 2.07 (s, 3 H), 7.00 (s, 1 H), 7.05 (s, 1 H).

[5-(1,1-Dimethylethyl)-2-methyl-4-[[(4-methylphenyl)-sulfonyl]thio]phenyl]imidodicarbonic Acid Bis(1,1-dimethylethyl) Ester. To a solution of tosyl bromide (17.1 g, 72.73 mmol) and NEt_3 (7.36 g, 72.73 mmol) in CCl_4 (250 mL) at 0 °C was added a solution of [5-(1,1-dimethylethyl)-4-mercapto-2-methylphenyl]imidodicarbonic acid bis(1,1-dimethylethyl) ester (10.7 g, 27.05 mmol) in CCl_4 (250 mL) dropwise over an 8 h period. The mixture was then allowed to warm to room temperature overnight. Chloroform was added, and the solution was washed with H_2O, followed by brine, dried over Na_2SO_4, filtered and concentrated. The resulting material was submitted to flash silica gel chromatography, eluting with 4:1 $CHCl_3$:hexanes to afford the title compound. Isolated yield: 11.5 g (77%). ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 9 H), 1.40 (s, 18 H), 2.10 (s, 3 H), 2.40 (s, 3 H), 7.07 (s, 1 H), 7.19 (d, 2 H), 7.40 (s, 1 H), 7.44 (d, 2 H).

Toluene-4-thiosulfonic Acid *S*-(4-Amino-2-*tert*-butyl-5-methylphenyl) Ester (VII). [5-(1,1-Dimethylethyl)-2-methyl-4-[[(4-methylphenyl)sulfonyl]thio]phenyl]imidodicarbonic acid bis(1,1-dimethylethyl) ester (10.95 g, 19.92 mmol) was dissolved in CH_2Cl_2 (200 mL) and HCl gas bubbled in while stirring at room temperature for 40 min. The solvent was evaporated, and the isolated residue was triturated with Et_2O to afford the title compound as the hydrochloride salt. Isolated yield: 7.0 g (91%). The free base was liberated by dissolving the isolated solid in MeOH, and pH 7.5 K_2HPO_4/KH_2PO_4 buffer was added until a precipitate formed. The resulting precipitate was filtered off and washed with H_2O and then hexanes. ^{1}H NMR (DMSO-d_6): δ 1.16 (s, 9 H), 1.96 (s, 3 H), 2.38 (s, 3 H), 5.88 (br s, 3 H), 6.83 (s, 1 H), 6.95 (s, 1 H), 7.39 (d, 2 H), 7.45 (d, 2 H).

5-*tert*-Butyl-2-methylphenol. 5-*tert*-Butyl-2-methylphenylamine (3.0 g, 18.4 mmol) was taken in 15% aqueous H_2SO_4 (110 mL) and heated to 70 °C. Sodium nitrite (1.41 g, 20.4 mmol) in H_2O (20 mL) was added dropwise the reaction mixture and mixture stirred an additional 30 min following complete addition. The reaction mixture was allowed to cool and extracted with EtOAc. The organic phase was washed with H_2O, followed by brine, dried over $MgSO_4$, filtered and the solvent removed in vacuo to afforded the title compound which was utilized without further purification. Isolated yield: 2.85 g (94%). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 2.22 (s, 3H), 5.30 (br s, 1H), 7.05 (s, 1H), 7.11 (d, 1H), 7.28 (d, 1H).

5-*tert*-Butyl-2-methyl-4-thiocyanatophenol (IX). A solution of 5-*tert*-butyl-2-methylphenol (350 g, 2.13 mol) and sodium thiocyanate (555 g, 6.85 mol) in MeOH (1400 mL) was cooled to 5 °C. A solution of sodium bromide (214 g, 2.08 mol), bromine (126 mL, 2.38 mol), and MeOH (1800 mL) was added slowly and the temperature raised to 40 °C over a period of 30 min. The precipitate was filtered and the filtrate concentrated by half. Saturated sodium carbonate (3.5 L) and H_2O (4.5 L) were added. The mixture was extracted several times with EtOAc (total 3 L), and the organic layers were combined and concentrated. To the resulting residue were added *tert*-butylmethyl ether (500 mL) and hexanes (500 mL) and the mixture was allowed to stand for 17 h at −5 °C. The resulting precipitate was filtered to give the title compound. Mp: 99−102 °C. ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.22 (s, 3H), 5.01 (s, 1H), 6.89 (s, 1H), 7.49 (s, 1H).

5-*tert*-Butyl-4-mercapto-2-methylphenol. To a round-bottom flask (500 mL) equipped with magnetic stir and condenser were added 5-*tert*-butyl-2-methyl-4-thiocyanatophenol (7.35 g, 158 mmol), dithiothreitol (25.61 g, 166 mmol), EtOH (250 mL), and 0.02 M KH_2PO_4 buffer solution (25 mL) and the reaction was heated to reflux. In 2 h the reaction was not complete by TLC, additional dithiothreitol (5.0 g 32.4 mmol) and 0.02 M KH_2PO_4 buffer solution (25 mL) was added and the reaction mixture refluxed an additional 2 h. The EtOH was removed under reduced pressure and the reaction quenched with brine and extracted with Et_2O:hexanes (1:1). The organic layer was washed with brine (3×), dried over $MgSO_4$ and the solvent removed in vacuo. The resulting residue submitted to flash silica gel column chromatography, eluting with $CHCl_3$ to afford the title compound. Isolated yield: 24.3 g (79%). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 2.15 (s, 3H), 3.43 (s, 1H), 4.56 (br s, 1H), 6.82 (s, 1H), 7.05 (s, 1H).

Toluene-4-thiosulfonic Acid *S*-(2-*tert*-Butyl-4-hydroxy-5-methylphenyl) Ester (X). To a solution of tosyl bromide (30.55 g, 130 mmol) and pyridine (10.51 mL, 130 mmol) in CCl_4 (50 mL) cooled to 0 °C was added a solution of 5-*tert*-butyl-4-mercapto-2-methylphenol (24.3 g, 123.8 mmol) in CCl_4 (150 mL) dropwise over a 30 min period. Chloroform was then added, and the solution was washed with H_2O, followed by brine, dried over $MgSO_4$, filtered and concentrated. The resulting solid was washed with hexanes:Et_2O (4:1) and filtered to present the title compound. Isolated yield: 40.0 g (91%). ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9H), 2.11 (s, 3H), 2.42 (s, 3H), 6.87 (s, 1H), 7.16 (s, 1H), 7.26 (d, 2H), 7.49 (d, 2H).

Synthesis of the Thiotosylates. General Method A: To a solution of toluene-4-thiosulfonic acid *S*-(4-amino-2-*tert*-butyl-5-methylphenyl) ester in neat pyridine or a pyridine/CH_2Cl_2 mixture was added the corresponding chloro derivative (1.2−1.5 equiv) and the mixture stirred under nitrogen at room temperature overnight. Generally, 1 N HCl was then added and the mixture extracted with EtOAc. The organic phase was again washed with 1 N HCl, then washed with brine:H_2O (1:1), followed by twice with brine, dried over $MgSO_4$ or Na_2SO_4, filtered and concentrated. The isolated material was generally purified by flash silica gel chromatography unless otherwise specified.

Toluene-4-thiosulfonic Acid *S*-(2-*tert*-Butyl-4-methanesulfonylamino-5-methylphenyl) Ester (VIIIa). The

title compound was prepared according to general method A using toluene-4-thiosulfonic acid *S*-(4-amino-2-*tert*-butyl-5-methylphenyl) ester (0.30 g, 0.86 mmol) and methanesulfonyl chloride (0.15 g, 1.29 mmol) in pyridine (8 mL) and CH_2Cl_2 (1 mL). The isolated material was triturated with EtOAc and hexanes to afford the title compound. Isolated yield: 0.28 g (76%). ^{1}H NMR (DMSO-d_6): δ 1.18 (s, 9H), 2.14 (s, 3H), 2.38 (s, 3H), 3.02 (s, 3H), 7.09 (s, 1H), 7.39 (m, 3H), 7.47 (d, 2H), 9.29 (br s, 1H).

General method A was also used to synthesis intermediates **VIIIb**−**o** (see Table 1).

General Method B: To a solution of toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxy-5-methyl-phenyl) ester in CH_2Cl_2 or Et_2O was added triethylamine (1.0−3.0 equiv) followed by the corresponding chloro derivative (1.0−2.0 equiv) neat or dissolved in CH_2Cl_2 or Et_2O and the mixture stirred under nitrogen at room temperature from 10 min to overnight, monitoring the reaction by thin-layer chromatography. Generally, 1 N HCl was then added and the mixture extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ or Na_2SO_4, filtered and concentrated. The isolated material was generally purified by flash silica gel chromatography unless otherwise specified.

Methanesulfonic Acid 5-*tert*-Butyl-2-methyl-4-(toluene-4-sulfonylsulfanyl)phenyl Ester (VIIIp). The title compound was prepared according to general method B using toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxy-5-methylphenyl) ester (1.50 g, 4.30 mmol), methanesulfonyl chloride (0.49 g, 4.30 mmol) and triethylamine (0.43 g, 4.30 mmol) in CH_2Cl_2 (30 mL). The isolated material was submitted to flash silica gel chromatography, eluting with $CHCl_3$ to afford the title compound. Isolated yield: 1.2 g (65%). ^{1}H NMR (DMSO-d_6): δ 1.18 (s, 9H), 2.14 (s, 3H), 2.38 (s, 3H), 3.02 (s, 3H), 7.09 (s, 1H), 7.39 (m, 3H), 7.47 (d, 2H), 9.29 (br s, 1H).

General method B was also used to synthesis intermediates **VIIIq**−**x** (see Table 1).

Dimethylsulfamic Acid 5-*tert*-Butyl-2-methyl-4-thiocyanatophenyl Ester (XI). To a round-bottom flask (250 mL) equipped with condenser, magnetic stir, and nitrogen purge were charged 5-*tert*-butyl-2-methyl-4-thiocyanatophenol (1.5 g, 6.80 mmol), cesium carbonate (2.44 g, 7.49 mmol), and acetonitrile (30 mL) and the slurry was brought to reflux for 15 min. Dimethylsulfamoyl chloride (0.80 mL, 7.49 mmol) was then added via syringe. A precipitate formed immediately and the reaction was monitored by TLC until complete. The reaction was quenched with brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting residue was submitted to flash silica gel column chromatography, eluting with hexanes:EtOAc (7:3) to afford the title compound. Isolated yield: 1.1 g (49%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.22 (s, 3H), 3.03 (s, 6H), 7.30 (s, 1H), 7.47 (s, 1H).

Dimethylsulfamic Acid 5-*tert*-Butyl-4-mercapto-2-methylphenyl Ester (XII). Dimethylsulfamic acid 5-*tert*-butyl-2-methyl-4-thiocyanatophenyl ester (1.1 g, 3.3 mmol) dissolved in EtOH (40 mL) and 0.02 M KH_2PO_4 buffer solution (5 mL) was treated with dithiothreitol (1.29 g, 8.35 mmol). The reaction was heated to reflux and allowed to stir overnight. The reaction was then quenched with H_2O (250 mL) and extracted with a 1:1 mixture of hexanes:Et_2O. The organic layer was again washed with H_2O (250 mL), followed by brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was dried under high vacuum to present the title compound. Isolated yield: 1.07 g (quantitative). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 2.25 (s, 3H), 3.02 (s, 6H), 3.57 (s, 1H), 7.01 (s, 1H), 7.28 (s, 1H).

Toluene-4-thiosulfonic Acid *S*-(2-*tert*-Butyl-4-dimethylsulfamoyloxy-5-methylphenyl) Ester (VIIIz). To a solution of tosyl bromide (1.64 g, 7.0 mmol) and triethylamine (0.98 mL, 7.0 mmol) in CCl_4 (25 mL) cooled to 0 °C in an ice water bath was added a solution of dimethylsulfamic acid 5-*tert*-butyl-4-mercapto-2-methylphenyl ester (1.07 g. 3.5 mmol) in CCl_4 (25 mL) dropwise over a 1 h period. After addition was complete, the ice bath was removed and the reaction was allowed to stir at room temperature overnight. CH_2Cl_2 was then added, and the solution was washed with H_2O, followed by brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue taken up in a small amount of EtOAc and hexanes added to present a solid which was filtered and dried under high vacuum to afford the title compound. Isolated yield: 1.09 g (68%). ^{1}H NMR ($CDCl_3$): δ 1.15 (s, 9H), 2.23 (s, 3H), 2.37 (s, 3H), 3.02 (s, 6H), 7.19 (d, 2H), 7.22 (s, 1H) 7.33 (s, 1H), 7.40 (d, 2H).

Synthesis of Target 4-Hydroxy-5,6-dihydropyran-2-ones. General Method C: The appropriate dihydropyrone (1 equiv) in DMF (1−12 mL per mmol of dihydropyrone) was treated with K_2CO_3 (2.2−8 equiv) followed by the appropriate thiotosylate reagent (1.0−1.2 equiv). The reaction was stirred at room temperature (2.5 h to overnight). The reaction was then taken in EtOAc and treated with either 1 N HCl or saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine:H_2O (1:1), then with brine, dried over $MgSO_4$, filtered and concentrated.

3-(4-Amino-2-*tert*-butyl-5-methylphenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isopropyl-5,6-dihydropyran-2-one (1). The title compound was prepared according to general method C using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isopropyl-5,6-dihydropyran-2-one (0.60 g, 2.17 mmol), toluene-4-thiosulfonic acid *S*-(4-amino-2-*tert*-butyl-5-methylphenyl) ester (0.84 g, 2.40 mmol), K_2CO_3 (0.90 g, 6.51 mmol) and DMF (12 mL). The isolated material was subjected to silica gel flash chromatography, eluting with $CHCl_3$:MeOH (9:1) to afford the pure product. Isolated yield: 0.57 g (56%). ^{1}H NMR (DMSO-d_6): δ 0.89 (d, 3H), 0.93 (d, 3H), 1.42 (s, 9H), 1.71 (s, 3H), 1.88−1.92 (m, 2H), 2.15 (m, 1H), 2.46−2.51 (m, partially obscured by DMSO, 2H), 2.67 (d of ABX q, 1H), 2.90 (d of ABX q, 1H), 6.55 (s, 1H), 6.61 (s, 1H), 6.64 (d, 2H), 6.93 (d, 2H), 9.13 (br s, 1H). IR (KBr): 3382, 2963, 2933, 2877, 1669, 1613, 1515, 1481, 1452, 1388, 1375, 1268, 1239, 1050, 911, 833, 763, 698 cm^{-1}. MS-APCI (*m*/*z*+): 470.2. Anal. ($C_{27}H_{35}N_10_4S_2$·0.83H_2O) C, H, N.

General method C was also used to synthesize final compounds **1S,R**−**69S**. Further experimental details are given in Table 2.

(*S*)-*N*-(5-*tert*-Butyl-4-{4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isopropyl-2-oxo-5,6-dihydro-2*H*-pyran-3-ylsulfanyl}-2-methylphenyl)-2-(5-trifluoromethyl)pyridinesulfonamide (12S). To (*S*)-3-(4-amino-2-*tert*-butyl-5-methylphenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isopropyl-5,6-dihydropyran-2-one (**1S**) (0.22 g, 0.47 mmol) in pyridine (5 mL) and CH_2Cl_2 (2 mL) was added 5-trifluoromethyl-2-pyridinesulfonyl chloride (0.17 g, 0.70 mmol) and the reaction mixture stirred at room temperature overnight. 1 N HCl was then added and the mixture extracted with EtOAc, the organic phase was again washed with 1 N HCl, then washed with brine:H_2O (1:1), followed by twice with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was subjected to silica gel flash chromatography, eluting with CH_2Cl_2:MeOH (18:1) to afford the title compound. Isolated yield: 0.13 g (38%). ^{1}H NMR (DMSO-d_6): δ 0.92 (d, 3H), 0.95 (d, 3H), 1.23 (s, 9H), 1.89−1.97 (m, 5H), 2.19 (m, 1H), 2.48−2.52 (m, partially obscured by DMSO, 2H), 2.73 (d of ABX q, 1H), 2.95 (d of ABX q, 1H), 6.50 (s, 1H), 6.65−6.69 (m, 3H), 6.96 (d, 2H), 7.99 (d, 1H), 8.49 (d, 1H), 9.17 (s, 1H), 9.28 (s, 1H), 9.97 (s, 1H). IR (KBr): 3430, 3411, 2966, 2929, 1679, 1611, 1597, 1515, 1387, 1368, 1328, 1262, 1235, 1177, 1147, 1110, 1074, 911, 720, 697, 622, 547 cm^{-1}. MS-APCI (*m*/*z*+): 679.2, 373.0. Anal. ($C_{33}H_{37}F_3N_20_6S_2$·0.53H_2O) C, H, N.

Supporting Information Available: Additional experimental details and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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