4-Hydroxy-5,6-dihydropyrones. 2. Potent Non-Peptide Inhibitors of HIV Protease

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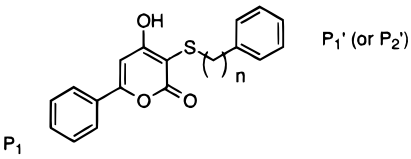
The 4-hydroxy-5,6-dihydropyrone template was utilized as a flexible scaffolding from which to build potent active site inhibitors of HIV protease. Dihydropyrone **1c** (5,6-dihydro-4-hydroxy-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one) was modeled in the active site of HIV protease utilizing a similar binding mode found for the previously reported 4-hydroxybenzopyran-2-ones. Our model led us to pursue the synthesis of 6,6-disubstituted dihydropyrones with the aim of filling S_1 and S_2 and thereby increasing the potency of the parent dihydropyrone **1c** which did not fill S_2. Toward this end we attached various hydrophobic and hydrophilic side chains at the 6-position of the dihydropyrone to mimic the natural and unnatural amino acids known to be effective substrates at P_2 and P_2'. Parent dihydropyrone **1c** (IC_{50} = 2100 nM) was elaborated into compounds with greater than a 100-fold increase in potency [**18c,** IC_{50} = 5 nM, 5-(3,6-dihydro-4-hydroxy-6-oxo-2-phenyl-5-[2-phenylethyl)thio]-2*H*-pyran-2-yl)pentanoic acid and **12c,** IC_{50} = 51 nM, 5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one]. Optimization of the 3-position fragment to fill S_1' and S_2' afforded potent HIV protease inhibitor **49** [IC_{50} = 10 nM, 3-[(2-*tert*-butyl-5-methylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one]. The resulting low molecular weight compounds (<475) have one or no chiral centers and are readily synthesized.

Introduction

Acquired immunodeficiency syndrome (AIDS) was first defined in 1982 as the clinical manifestations of immunodeficiency. The etiological agent of AIDS was later determined to be a retrovirus, human immunodeficiency virus (HIV), of the lentivirus subfamily.[1] Characterization of HIV has provided numerous potential antiviral approaches, one of which is inhibition of a viral encoded aspartyl protease.[2]

HIV protease is responsible for posttranslational processing of the precursor polyproteins *Gag* and *Gag/Pol*[3] and is essential for maturation of the virus. The proteolytic activity of HIV protease cannot be provided by host cellular enzymes. It has been shown that HIV which lacks this protease or contains a mutant defective protease is noninfectious.[4] The sum of these observations makes inhibition of HIV protease an attractive target for antiviral therapy.

The majority of the HIV protease inhibitors reported are peptidic or peptidomimetic in nature.[5] Peptidic compounds are known to possess pharmacological problems such as biliary excretion and low bioavailability. Additional issues with the four approved compounds include significant side effects and the requirement of substantial doses and, therefore, large quantities of drug.[6] Adequate supplies of these agents have been limited by the synthetic difficulties associated with large compounds containing multiple chiral centers.[7] The clinical emergence of resistant strains will necessitate an ever increasing armament of drugs.[8] Therefore, the need exists for small nonpeptide HIV protease inhibitors which are easy to synthesize, exhibit good bioavailability, and preferably have a unique pattern of resistance development.



PD 107067	n = 0	IC_{50} = 3,100nM
PD 150280	n = 1	IC_{50} = 1,700nM

Figure 1. 4-Hydroxypyrones: P_1−P_1'(or P_2').

Previous reports from our laboratory described modification of the pyrone template (Figure 1) into a number of ring systems including the tetronic acids and 5,6-dihydropyrones.[9] From our initial evaluation of these ring systems, we chose to focus our efforts on the 4-hydroxy-5,6-dihydropyrone template (Figure 2).[10] More recently Pharmacia Upjohn has also disclosed their efforts in this area.[11] This paper will focus on efforts to optimize the substitution on the dihydropyrone template with modifications designed to fill the internal four pockets (S_2, S_1, S_1', S_2') of HIV protease.

Molecular Modeling

Molecular modeling was carried out using the Sybyl software program[12] and a preliminary X-ray structure

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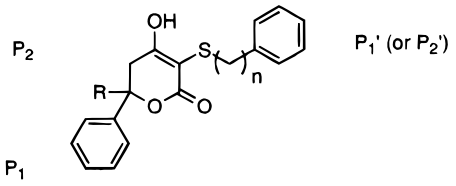
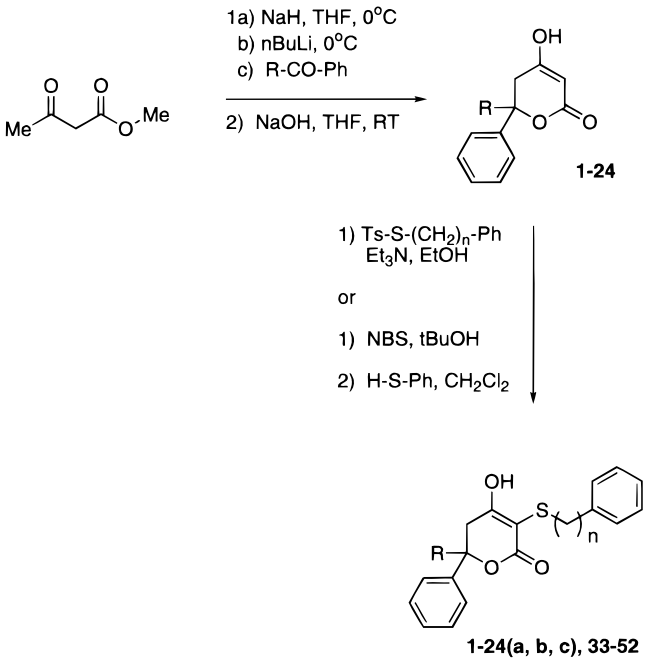


1b R = H n = 1 IC_{50} = 8,900nM

1c R = H n = 2 IC_{50} = 2,100nM

Figure 2. 4-Hydroxy-5,6-dihydropyrones: P_1-P_1'(or P_2').

Scheme 1. Synthesis of 4-Hydroxy-5,6-dihydropyrones



of HIV protease from a coumarin complex.[13] The dihydropyrone ring was docked in the protease active site according to the binding mode observed for the coumarin inhibitor. Specifically, the 4-hydroxyl group was positioned between the two carboxylates at the catalytic site, and the lactone was positioned to interact directly with Ile50/150 in the flap region. The lactone group would thus displace H_2O-301 normally observed with the peptidic inhibitors. Inhibitor **7b** was modeled with the S geometry and a ring puckering such that the phenyl ring was in the equatorial position and bound in S_1 and the isopentyl group was in the axial orientation and extended to S_2. The inhibitor was modeled in the cleft region, which included residues 8 Å from the bound coumarin inhibitor in the X-ray structure. The inner oxygen of the catalytic Asp 25 was protonated.

Chemistry

The synthetic pathway for the 4-hydroxy-5,6-dihydropyrone HIV protease inhibitors is shown in Scheme 1 and follows the method of Groutas et al.[14] Methyl acetoacetate was converted into its dianion by treatment with sodium hydride and then with *n*-butyllithium. To the dianion was added the appropriate aldehyde or ketone. The resulting aldol product could be isolated by quenching with ammonium chloride. The aldol product was cyclized by treatment with dilute NaOH (in the presence or absence of THF) to give the dihydropyrone ring system. Alternatively, the aldol product could be taken directly to the dihydropyrone without isolation by addition of water or dilute NaOH to the reaction mixture. The 3-position sulfur side chain (n = 0−3, Scheme 1) was attached to the 3-position by reaction with the appropriate thiotosylate reagent[15] and triethylamine to give the target compounds. The thiotosylates **(30)** were prepared as shown in Scheme 2 and Table 1, beginning with the derivatization of the corresponding phenol **27** with dimethylthiocarbamoyl chloride and subsequent thermal rearrangement to **28**.[16] Reduction to the thiol **29** was carried out with lithium aluminum hydride, and the resulting thiol converted to the desired thiotosylate **30** as described by Fuchs.[17] An alternative method for the synthesis of the dihydropyrone targets involved preparation of the 3-bromodihydropyrone derivative with NBS and then displacement of the bromide by the appropriately substituted thiophenol; this route was used to prepare **11a**, **11b**, **33**−**38**, **44**, **45**, **46**, and **47**.

Results and Discussion

The coumarin and pyrone ring systems (Figure 3) are rigid and planar which limit the flexibility of the substituents to adjust upon binding. Due to this rigidity, groups attached to the ring system are locked into position relative to each other and relative to the core binding interactions. We hypothesized that the dihydropyrones would offer a more flexible template which would allow the substituents to make modest conformational adjustments without interfering with the core binding.

Scheme 2. Preparation of Thiophenols and Tosyl Thiolates

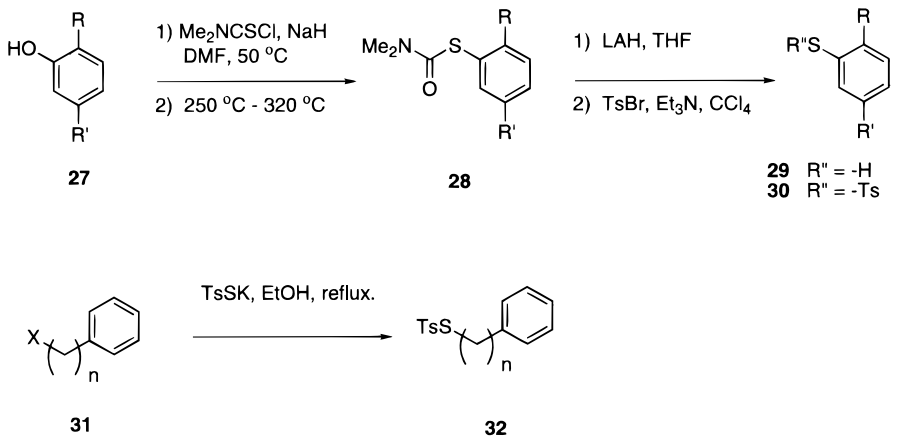
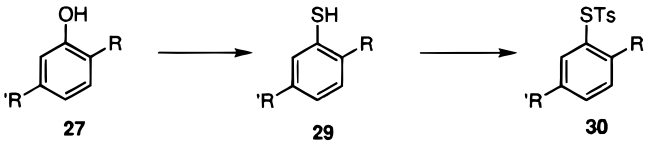


Table 1. Preparation of Aromatic Thiols and Thiotosylates



compd[a]	R	R′	source of **29**[b]	yield of **30**[c]
29a	Me	H	comm	
29b	$CHMe_2$	H	comm	
29c	CHMeEt	H	comm	
30d	cyclopentyl	H	expt	53
30e	cyclohexyl	H	expt	62
30f	CMe_3	H	comm	42
29g	$CHMe_2$	Me	ref 31	
29h	$CHMe_2$	$CHMe_2$	expt	
30i	CMe_3	Me	expt	72
30j	CMe_3	$CHMe_2$	prep	55

[a] **29** designates the benzenthiol which is used crude in general method 7; **30** designates the thiotosylate used in general method 5. [b] Comm: thiol is commercially available. Expt: corresponding phenol is commercially available and is elaborated into the desired thiol in the Experimental Section. Ref: thiol is prepared in the reference indicated. Prep: synthesis of the corresponding phenol is found in the Experimental Section. [c] Total yield from thiol.

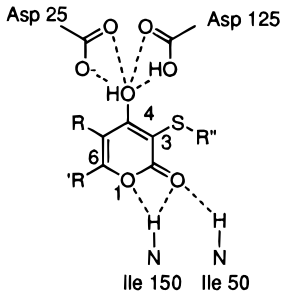


Figure 3. Potential coumarin and pyrone core interactions.

The X-ray cocrystal structure of HIV-1 protease with the 4-hydroxybenzopyran-2-one PD 099560 was informative in evaluating the potential binding modes of the dihydropyrones (Figure 3).[13] The key active site interactions of the pyrone template involve the 4-hydroxyl group which binds to the catalytic aspartic acids (Asp 25/125, Figure 3) and the lactone that is hydrogen bonded to NH's in the flap (Ile 50/150, Figure 3). The lactone carbonyl effectively displaces H_2O-301, which is normally found in X-ray structures of HIV protease bound with the peptide inhibitors. Due to the structural similarities among the 4-hydroxybenzopyran-2-one, the pyrone, and the dihydropyrone templates, we believed that a similar core binding mode would occur in all the templates. This was indeed substantiated by molecular modeling and later by X-ray cocrystal structures.

We believed that the thiobenzyl and thiophenethyl side chains at the three position (Figure 2) were flexible enough to have no substantial influence on the binding at the 6-position. Modeling indicated that the thiol chains could fill either S_1' or S_2'. Therefore, to ensure the 6-position SAR would be consistent with various 3-position side chains, both the thiobenzyl and thiophenethyl side chains at the 3-position were prepared. The better variations at the 6-position were then synthesized in combination with the thiophenyl side chain.

With the core binding and a flexible 3-position substituent set, we turned our attention to exploring ways of filling the S_2 and S_1 pockets. Our model of the 6-phenylpyrones such as PD 150280 and PD 107067 indicated that the 6-position substituent filled S_1 (Figure 1). It was apparent from analysis of a coumarin X-ray[13] and the subsequent dihydropyrone model that S_2 could be reached from the sp^3 carbon atom at the six position of the dihydropyrone by appending an appropriate substituent (R in Figure 2).

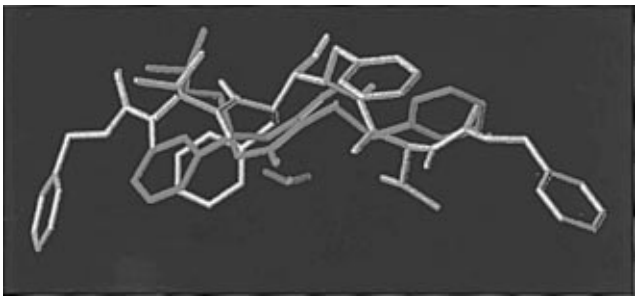


Figure 4. Overlay of a model of **7b** (red) docked in the HIV protease active site with the X-ray structure of A-74704 (white) bound to HIV protease. H_2O-301, from the A-74704 structure, is shown in green.

Figure 4 shows a model of **7b** overlaid with the Abbott HIV protease inhibitor (A-74704).[18] The Abbott structure assists in the visualization of the approximate position of P_1 and P_2 but does not define the surface area of the pockets. Our model indicated that from the 6-position we needed a two-atom spacer followed by the substituent to fill S_2. The model also predicted that a phenyl at the 6-position was a reasonable substituent to fill S_1. Therefore, we held the phenyl constant and varied the R group to reach for S_2.

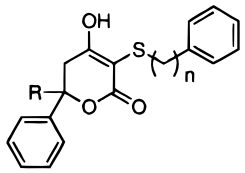
Our focus at S_2 was to fill the pocket with functional groups which would mimic the substrates amino acids known to fill both S_2 and S_2' due to the symmetry of the enzyme. Amino acids found at P_2 and P_2' in the native substrates include valine, isoleucine, leucine, asparagine, glutamine, and glutamic acid. Unnatural amino acids, such as phenylglycine, were also considered when they had been shown from literature precedent to be effective substituents at P_2.[17]

Our initial analysis consisted of preparing straight chain alkyl groups (**2b**,**c**−**5b**,**c** Table 2). Due to their flexibility, the straight chain alkyl groups could readily adjust to the surface of the enzyme to maximize hydrophobic interactions, albeit with an entropic price. In any event, the potency increased as the chain was lengthened from hydrogen (IC_{50} = 2100 nM, **1c**) to *n*-pentyl (IC_{50} = 84 nM, **4c**).

Branched alkyl groups designed to mimic the P_2 and P_2' hydrophobic amino acids, valine and leucine (**6b**,**c**−**8b**,**c** Table 2) were then investigated. Modeling predicted that isopentyl (**7a**,**b**,**c**) and isohexyl (**8b**,**c**) substituents would most closely mimic valine and leucine, respectively. Analogues with branched alkyl groups showed an increase in potency over the unsubstituted parent (IC_{50} = 2100 nM, **1c**) with the most potent compound being the isopentyl substituent (IC_{50} = 96 nM, **7c**), the valine mimic. The trends in activity were in excellent agreement with our modeling predictions.

Workers at Merck[19] have reported that phenylglycine is an effective P_2' replacement for valine in peptidic HIV protease inhibitors. In a logical extension of their work, we prepared the phenethyl derivatives (**12a**−**c**) as phenylglycine mimics. Compound **12c** showed excellent activity versus the enzyme with an IC_{50} of 51 nM. Indeed, phenethyl proved to be the most active of the hydrophobic P_2 substituents.

Table 2. Hydrophobic Groups Designed To Fill S_2: $P_2P_1-P_1'$(or P_2')



		IC$_{50}$ (nM)		
compd[a]	R	**a** ($n = 0$)	**b** ($n = 1$)	**c** ($n = 2$)
1b,c	H		8900	2100
2b,c	$(CH_2)_2Me$		290	5100
3b,c	$(CH_2)_3Me$		270	400
4b,c	$(CH_2)_4Me$		124	84
5b,c	$(CH_2)_5Me$		180	112
6b,c	CH_2CHMe_2		440	1200
7a,b,c	$(CH_2)_2CHMe_2$	1400	98	96
8b,c	$(CH_2)_3CHMe_2$		183	155
9b,c	CH_2-c-pentyl		88	510
10b	CH_2-c-hexyl		137	
11a,b,c	Ph	110	262	152
12a,b,c	$(CH_2)_2Ph$	130	60	51
13b[b]	$-(CH_2)_2-$		11800	
14b,c[b]	$-(CH_2)_3-$		2300	1300
15b[c]	$(CH_2)_4Me$		327	

[a] Where **a** is $n = 0$, **b** is $n = 1$, and **c** is $n = 2$. [b] Spirocyclic: The linker is connected to the ortho position of the 6-phenyl ring. [c] Symmetrical compound: 6,6-di-*n*-pentyl. All compounds are racemic or achiral. All IC$_{50}$'s are averages of at least two runs.

Our model indicated, and the activity confirmed, that the isobutyl group (**6b**,**c**) was not reaching far enough to fill S_2. To more effectively fill the S_2 pocket, the two methyls of the isobutyl group were expanded and cyclized into a 5-membered ring (**9b,c**) and a 6-membered ring (**10b**). In fact, compounds **9b** and **10b** were better than compound **6b** by more than 3-fold, thus suggesting enhanced interactions with the enzyme.

We were also interested in what effect restricting the rotation and therefore the orientation of the phenyl at P_1 might have on inhibitory activity. The spirocyclic derivatives **13b** and **14b**,**c** were found to be much less potent than the corresponding acyclic compounds. This is probably due to the inability of the three-carbon linker to fill a pocket effectively and/or the restriction of the phenyl ring into a conformation less compatible with the binding cleft.

An X-ray cocrystal structure of racemic **4c** bound into HIV-1 protease was obtained (Figure 5). The difference electron density map indicated that the general core interactions with Asp 25/125 and Ile 50/150 were consistent with those found in the coumarin X-ray and the dihydropyrone model. The presence of electron density in both S_1' and S_2' indicated a mixed population for the thiophenethyl group between the two pockets (Figure 5). It was hoped that only the more potent enantiomer would be bound in the active site, but the X-ray indicated that both enantiomers of **4c** were present. An accurate determination of the preference for the phenyl and *n*-pentyl groups to reside in S_1 or S_2 could not be obtained from the electron density. What was clear was that the substituents (phenyl and *n*-pentyl) fill both S_2 and S_1, thus increasing the potency of these compounds in the enzyme inhibition assay. The lack of apparent preference by the enzyme pockets for the phenyl or the *n*-pentyl group suggested the preparation of the achiral 6,6-diphenyl and 6,6-di-*n*-pentyl analogues. In fact, the symmetrical derivatives showed

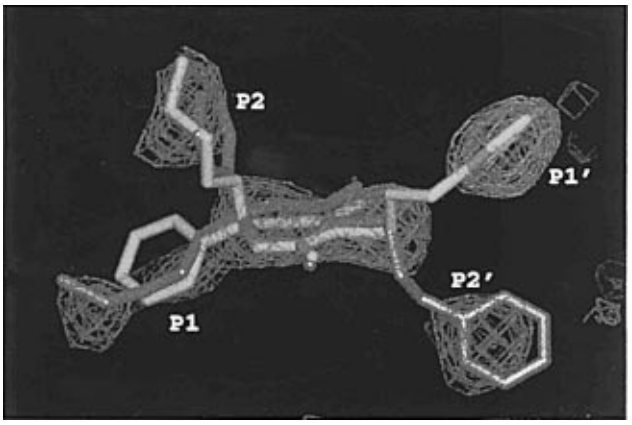
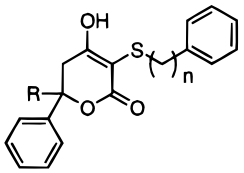


Figure 5. Superposition of the difference electron density with two binding modes of racemic **4c**. The *R* configuration is shown in magenta and the *S* configuration is shown in red.

Table 3. Polar Groups Designed To Fill S_2: $P_2P_1-P_1'$(or P_2')



compd[a]	*n*	R	IC$_{50}$(nM)
16c	2	$(CH_2)_2CO_2H$	1200
17c	2	$(CH_2)_3CO_2H$	270
18c	2	$(CH_2)_4CO_2H$	5
19c	2	$(CH_2)_3CONH_2$	1300
20c	2	$(CH_2)_4CONH_2$	338
21c	2	4-pyridyl	790
22c	2	$CH_2N(Me)Ph$	2280
23b	1	CH_2OPh	172
24b	1	$(CH_2)_4OH$	1260

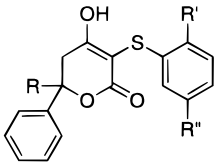
[a] Where **a** is $n = 0$, **b** is $n = 1$ and **c** is $n = 2$. All compounds are racemic. All IC$_{50}$'s are averages of at least two runs.

good potency with IC$_{50}$'s in the 110−327 nM range (**11a**−**c** and **15b**) although they were not as potent as the racemic 6-phenyl-6-*n*-pentyl parent (**4b**,**c**).

We next turned our attention to filling S_2 with side chains which mimic the more polar amino acids, asparagine, glutamine, and glutamic acid (Table 3). Asparagine has been used at S_2 in peptidic inhibitors such as Ro-31,8959 with excellent success. Analysis of the Ro-31,8959 interactions with HIV-1 protease indicated that the asparagine carbonyl is within hydrogen-bonding distance of Asp 29 (NH) and Asp 30 (NH) in the protein.[20] To mimic the polar amino acids such as asparagine, glutamine, and glutamic acid, modeling suggested that the optimal side chains should be -$(CH_2)_3CONH_2$, -$(CH_2)_4CONH_2$, and -$(CH_2)_4COOH$, respectively. The enzyme activity followed the modeling predictions relatively well with the maximal activity coming from carboxylic acid **18c** (IC$_{50}$ = 5 nM).[21] The potency decreased by almost 2 orders of magnitude when the carboxylic acid (**18c)** was replaced with a primary amide (**20c**). Replacing the acid in **17c** with a CH_2OH isostere **24b** reduced the in vitro activity by approximately 5-fold.

Additional derivatives with heteroatoms were prepared to evaluate the effect of polarity on the inhibitory activity (**21c**, **22c**, **23b**). The phenethyl linker in compound **12b** and **12c** was modified by replacing the distal methylene with the polar groups NMe (**22c**) and

Table 4. Optimization of $P_1'P_2'$ Substituent: $P_2P_1-P_1'P_2'$



compd[a]	R′	R″	IC_{50} (nM) R = Ph	IC_{50} (nM) R = $(CH_2)_2$Ph
11a, 12a	H	H	110	130
33, 34	Me	H	388	73
35, 36	$CHMe_2$	H	23	14
37, 38	CHMeEt	H	17	10
39	c-pentyl	H	14	
40, 41	c-hexyl	H	127	32
42, 43	CMe_3	H	49	3
44, 45	$CHMe_2$	Me	38	7
46, 47	$CHMe_2$	$CHMe_2$	119	14
48, 49	CMe_3	Me	12	10
50	CMe_3	$CHMe_2$		47
51 (*S*)	$CHMe_2$	Me		6
52 (*R*)	$CHMe_2$	Me		130

[a] All compounds are racemic or achiral except **51** (***S***) and **52** (***R***). All IC_{50}'s are averages of at least two runs.

oxygen (**23b**), respectively. These compounds were found to be less active than their respective carbon parents by at least 3-fold. Replacement of one phenyl in **11c** with a pyridyl (**21c**) also resulted in a reduction in activity.

The thiobenzyl ($n = 1$) and thiophenethyl side chains ($n = 2$) at C-3 showed relatively consistent SAR trends (Table 2). Selection of the 6-phenyl-6-phenethyl (**12a**−**c**) as a standard for optimizing the 3-position was based on this consistency of activity as well the potency. The 6,6-diphenyl (**11a**−**c**) variation was chosen as a standard mainly due to its lack of a chiral center.

A series of 3-(benzylthio)-5,6-dihydropyran-2-ones with a variety of ortho substituents on the benzylthio ring were prepared. In most cases, the potency decreased or remained constant when compared with the parent compounds.[22] Observed increases in efficacy were no more than 2-fold and were therefore judged insignificant. These results were dramatically different than those obtained in the pyrone series of inhibitors.[23]

Work in the pyrone series delineated the beneficial effect of substituting ortho to the sulfur linkage on the phenylthio with an isopropyl moiety.[24] Modeling of the *o*-isopropyl functional group with the 5,6-dihyropyrone template indicated that it probably filled the S_1' pocket. This observation led to modifications of the initial dihydropyrone lead, resulting in agents with improved enzyme potency (Table 4).

To address the question of steric requirements of S_1' (Table 4), a number of derivatives containing *o*-alkyl groups were prepared. Reducing the isopropyl group to a methyl decreased the activity by 5−10-fold (**33**, **34**); increasing the size to *sec*-butyl (**37**, **38**) or cyclopentyl (**39**) instead of isopropyl (**35**, **36**) provided equally potent compounds. Relative to isopropyl, an *o*-*tert*-butyl moiety engendered a 2-fold loss in activity when R′ = Ph (**42**) yet a 4−5-fold increase in activity when R′ = 2-phenethyl (IC_{50} of 3 nM, **43**). This observation suggested that slightly different orientations of the inhibitors in the active site of the enzyme arise from differences in substitution at the 6-position of the dihydropyrone ring system.

Assuming that the ortho substituent effectively satisfied S_1', attention turned to more optimally filling the S_2' pocket from the appropriate position of the phenyl ring (**44**−**50**). To determine that optimal substitution, a series of analogues were synthesized in which the ortho substituent was held constant as an isopropyl or *tert*-butyl group while varying the position para to the alkyl moiety. The methyl isomers display either the same activity (where R = Ph, **44**) or an enhancement in potency (where R = phenethyl, **45**). The size of the methyl group appeared to be nearly optimal, since the corresponding isopropyl compounds (**46**, **47**, **50**) all displayed a loss in activity versus the methyl derivatives (**44**, **45**, **49**).

In general, the inhibitory activity data indicated that a 2-*tert*-butyl/2-isopropyl group and 5-methyl moiety on the phenyl ring effectively fill the S_1' and S_2' pockets, respectively. To verify this model, an X-ray crystallographic study of racemic **45** with the protein was undertaken; unfortunately, from the electron density it was not possible to determine either the preferred enantiomer for binding or whether both enantiomers were bound. To overcome this problem, the *R*- and *S*-enantiomers were prepared[25] and tested (**51, 52**); the *S*-enantiomer (**51**) proved to be 20-fold more potent than the corresponding *R*-enantiomer (**52**).

X-ray crystallographic structures[26] of both the *S*-enantiomer **51** and the *R*-enantiomer **52** complexed with the protease enzyme were obtained (Figures 6 and 7). As expected, in each case, the dihydropyrone ring displaced H_2O-301 while the lactone interacted directly with the flap region (Ile-50). The 4-hydroxyl group binds at the catalytic dyad (Asp-25 and Asp-125). Also as predicted, the 3-position substituent occupies the S_1' site via the isopropyl group and the S_2' site via the 5-methyl substituent. The *S*-enantiomer binds the phenyl group in the S_1 site and orients the phenethyl chain in the S_2 pocket. Not surprisingly, the opposite binding at the 6-position is observed for the *R*-enantiomer: that is, the phenyl ring is bound in the S_2 pocket and the phenethyl group binds in S_1/S_3, extending out to solvent. The *S*-enantiomer, predicted to be the more potent inhibitor, displays a binding affinity of 6 nM, whereas the *R*-enantiomer has an $IC_{50} = 130$ nM. This is in contrast to recent reports by Upjohn where the 6-phenethyl occupies S_1/S_3 and a 6-*n*-propyl occupies S_2.[11] Although the Pharmacia Upjohn and Parke-Davis groups are both working on the dihydropyrone template, the preferred chirality of the substituents at the 6-position is apparently reversed.[27]

Unfortunately, the best compounds (**18c**, **43**, and **49**) did not show a significant therapeutic index (TD_{50}/EC_{50} >10-fold) in cellular assays and did not warrant claims of antiviral activity. This result is not surprising for compound **18c**, which would be subject to ionization of the carboxylic acid under the conditions of the cellular assay. The lack of cellular activity necessitated a close examination of possible explanations. One area of concern was the pK_a of the 4-hydroxyl group (pK_a = 4.5−6.5), which is more acidic than a normal alcohol. We believe the protonated form of the dihydropyrone is the bound form of the inhibitor in the active site. Thus we were interested to see what effect raising the pH of the assay would have on inhibitory activity. We therefore took the best compounds and ran the assay at pH 6.2.

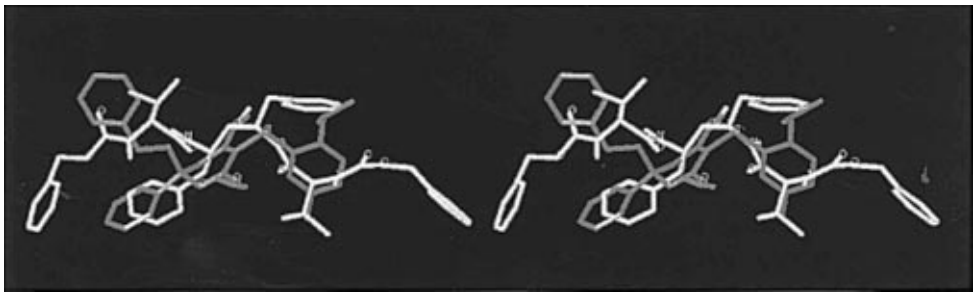


Figure 6. Overlay of the X-ray cocrystal structure of **51** (blue) and the X-ray cocrystal structure of A-74704 (yellow) bound to HIV protease. H_2O-301, from the A-74704 structure, is shown in red.

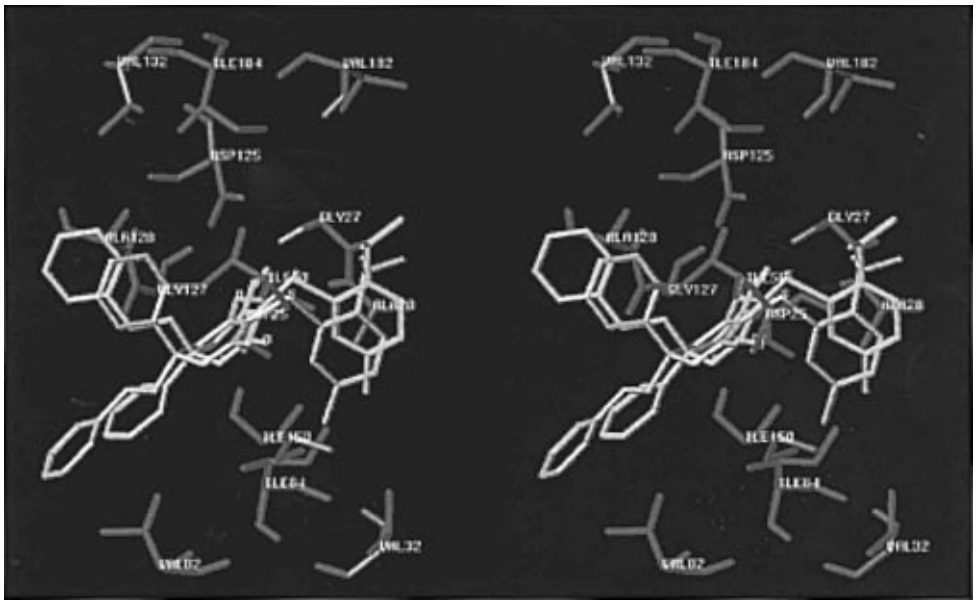
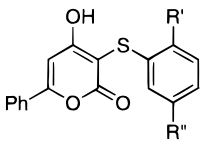
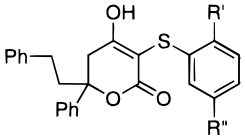


Figure 7. Overlay of the X-ray cocrystal structures of **51** (***S***) in yellow and **52** (***R***) in white shown with the HIV-1 protease active site.

Table 5. Effect of Assay pH on IC_{50}'s[a]



53-56



36, 43, 45, 49

R′	R″	compd[b]	pH = 4.7	pH = 6.2	compd	pH = 4.7	pH = 6.2
$CHMe_2$	H	**53**	37	700	**36**	14	97
$CHMe_2$	Me	**54**	17		**45**	7	79
CMe_3	H	**55**	17		**43**	3	104
CMe_3	Me	**56**	28	282	**49**	10	35

[a] All compounds are racemic or achiral. All IC_{50}'s (nM) are averages of at least two runs. [b] Reference 24.

Not unexpectedly, the dihydropyrones did lose potency at the higher pH (Table 5). Although all the compounds decreased in activity, the 2-*tert*-butyl-5-methyl compound (**49**) retained more of its inhibitory efficacy than did the other dihyropyrone derivatives. In addition, the dihydropyrones as a class were less affected by the increase in pH than the pyrones (Table 5).

Conclusions

As predicted, the 4-hydroxy-5,6-dihydropyrone heterocycle binds to the active site of HIV-1 protease in a manner similar to the coumarins and pyrones: the 4-hydroxyl group is hydrogen bonded to one or both of the catalytic aspartic acids Asp25/125 and the lactone carbonyl acts as a hydrogen bond acceptor with the flap isoleucine 50/150 NH's. The lactone carbonyl effectively displaces the H_2O-301 found in the X-ray cocrystal structures of peptide inhibitors with HIV protease. Substitution at the 6-position of the dihydropyrone ring system to mimic substituents reported at S_2 increased the inhibitory activity by almost 400-fold from an IC_{50} of 2100 nM (**1c**) to an IC_{50} of 51 nM (**12c**) and IC_{50} of 5 nM (**18c**). Filling the four internal pockets of HIV protease afforded compounds which were potent inhibitors of HIV protease (**43**, IC_{50} = 3 nM). Compound **49** (IC_{50} of 10 nM) was used as a base structure from which further modifications afforded cellularly active compounds.[28]

Experimental Section

The compounds were assayed against HIV-1 protease using the method described by Tummino et al.[29] The reported IC_{50}'s are an averaged value from two runs.

All melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR data were obtained on a Varian Unity 400 MHz NMR using TMS as an internal standard. CHN data were obtained from Parke-Davis analytical department and the sulfur analysis from Robertson Microlabs. Mass spectral data were obtained on a VG Analytical 7070 E/HF mass spectrometer. Infrared spectra were collected on a Mattison Cygnus 100 FTIR. Flash column chromatography was performed on silica gel 60, 230−400 mesh, purchased from Mallinckrodt. All starting materials were obtained from commercial sources unless otherwise specified in the experimental.

General Method 1. Preparation of 4-Hydroxy-5,6-dihydropyrones (1−24). Methyl acetoacetate (1 equiv) was added dropwise to a slurry of hexane-washed sodium hydride (1−1.2 equiv) in anhydrous THF at 0 °C and the reaction stirred at 0 °C for 15 min to 1 h. *n*-Butyllithium (1.1 equiv) was then added at 0 °C and the reaction stirred at 0 °C for 15 min to 1 h. The aldehyde or ketone (0.9−1.1 equiv), in THF, was added to the dianion, and the reaction was stirred at 0 °C (15 min to 24 h) and then allowed to warm to room temperature (15 min to 24 h). To the reaction mixture was added water or 0.1 N NaOH and the mixture allowed to stir for 15 min to overnight. After extracting with Et_2O, the aqueous layer was cooled to 0 °C and acidified with acid (2−6 N HCl) to pH 1−2. The aqueous layer was extracted with EtOAc or CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, and concentrated. Compounds **1**−**18**, and **21**−**23** were prepared according to this method.

5,6-Dihydro-4-hydroxy-6-phenyl-2*H*-pyran-2-one (1). Concentration produced a solid which was filtered off to give **1** in 62% yield: mp 145−146 °C; ^{1}H NMR ($CDCl_3$) δ 2.86−3.00 (m, 2*H*), 3.49 (d, J = 19.0 Hz, 1H), 3.67 (d, J = 19.0 Hz, 1H), 5.71 (dd, J = 10.0 Hz, J = 3.7 Hz, 1H), 7.26−7.52 (m, 5H); MS (EI^+) 190 (M + 1). Anal. ($C_{11}H_{10}O_3$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-2*H*-pyran-2-one (2). The product was triturated from Et_2O to afford **2** in 60% yield: mp 131.5−132 °C; MS (EI^+) 233 (M + 1). Anal. ($C_{14}H_{16}O_3$) C, H, N.

6-Butyl-5,6-dihydro-4-hydroxy-6-phenyl-2*H*-pyran-2-one (3). The product was triturated from Et_2O to afford **3** as a solid in 58% yield: mp 124−126 °C; MS (EI^+) 247 (M + 1). Anal. ($C_{15}H_{18}O_3$) C, H, N.

5,6-Dihydro-4-hydroxy-6-pentyl-6-phenyl-2*H*-pyran-2-one (4). Upon concentration of the reaction, a solid precipitated out which was triturated, washed with Et_2O, and filtered to give **4** as a solid in 41% yield: mp 123−124 °C; MS (CI + 1% NH_3 in CH_4) 261 (M + 1). Anal. ($C_{16}H_{20}O_3$) C, H, N.

5,6-Dihydro-6-hexyl-4-hydroxy-6-phenyl-2*H*-pyran-2-one (5). Upon concentration of the mixture, a solid precipitated out which was triturated with Et_2O and filtered to afford **5** as a solid in 27% yield: mp 119−120.5 °C; MS (CI + 1% NH_3 in CH_4) 275 (M + 1). Anal. ($C_{17}H_{22}O_3$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-phenyl-2*H*-pyran-2-one (6). The crude reaction was flash chromatographed using hexane/EtOAc 60/40 to 40/60 as eluent. The solid was triturated from Et_2O to afford **6** as a solid in 21% yield: mp 123.5−125 °C; MS (CI + 1% NH_3 in CH_4) 247 (M + 1). Anal. ($C_{15}H_{18}O_3 \cdot 0.09H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(3-methylbutyl)-6-phenyl-2*H*-pyran-2-one (7). Upon concentration of the reaction mixture, a solid precipitated out which was triturated with Et_2O and filtered to give **4** in 44% yield: mp 134−136 °C; MS (CI + 1% NH_3 in CH_4) 261 (M + 1). Anal. ($C_{16}H_{20}O_3$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(4-methylpentyl)-6-phenyl-2*H*-pyran-2-one (8). Isoheptanophenone was prepared by reacting the appropriate acid chloride with $AlCl_3$ in benzene as described by Vogel in *Practical Organic Chemistry* (1978, pp 770−775). Upon concentration of the reaction mixture, a solid precipitated out which was recrystallized from EtOAc to give 23% of **8**: mp 124−125 °C; MS (CI + 1% NH_3 in CH_4) 275 (M + 1). Anal. ($C_{17}H_{22}O_3$) C, H, N.

6-(Cyclopentylmethyl)-5,6-dihydro-4-hydroxy-6-phenyl-2*H*-pyran-2-one (9). 2-Cyclopentyl-1-phenylethanone was prepared by reacting the appropriate acid chloride with $AlCl_3$ in benzene as described by Vogel. Upon concentration of the reaction mixture, a solid precipitated out which was recrystallized from EtOAc to afford **9** in 41% yield: mp 158−160 °C; MS (CI + 1% NH_3 in CH_4) 273 (M + 1). Anal. ($C_{17}H_{20}O_3$) C, H, N.

6-(Cyclohexylmethyl)-5,6-dihydro-4-hydroxy-6-phenyl-2*H*-pyran-2-one (10). 2-Cyclohexyl-1-phenylethanone was prepared by reacting the appropriate acid chloride with $AlCl_3$ in benzene as described by Vogel. Upon concentration of the reaction, a solid precipitated out which was triturated from Et_2O to afford **10** in 6.5% yield: mp 128−130 °C; MS (CI + 1% NH_3 in CH_4) 287 (M + 1). Anal. ($C_{18}H_{22}O_3 \cdot 0.26H_20$) C, H, N.

5,6-Dihydro-6,6-diphenyl-4-hydroxy-2*H*-pyran-2-one (11). Upon concentrating the reaction a solid precipitated out which was triturated with Et_2O and filtered to give 79% of **11**: mp 170.5−173 °C; ^{1}H NMR ($CDCl_3$) δ 3.18 (s, 2H), 3.39 (s, 2H), 7.26−7.39 (m, 10H); MS (EI^+) 266. Anal. ($C_{17}H_{14}O_3$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (12). Upon concentrating, a solid precipitated out which was triturated with Et_2O and filtered to give 63% of **12**: mp 130−130.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.24−2.32 (m, 2H), 2.46−2.53 (m, 1H), 2.69−2.77 (m, 1H), 2.95 (d, J = 17.4 Hz, 1H), 2.97 (d, J = 20.4 Hz, 1H), 3.29 (d, J = 20.4 Hz, 1H), 3.38 (d, J = 17.3 Hz, 1H), 7.07−7.45 (m, 10H); MS (CI + 1% NH_3 in CH_4) 295 (M + 1). Anal. ($C_{19}H_{18}O_3$) C, H, N.

2,3-Dihydro-4′-hydroxyspiro[1*H*-indene-1,2′-[2*H*]pyran]-6′(3*H*′)-one (13). The product was recrystallized from EtOAc/Et_2O to afford a 22% yield of **13**: mp 119−120 °C; MS (CI + 1% NH_3 in CH_4) 217 (M + 1). Anal. ($C_{13}H_{12}O_3 \cdot 0.07H_2O$) C, H, N.

3,4-Dihydro-4′-hydroxyspiro[naphthalene-1(2*H*),2′-[2*H*]-pyran]-6′(3′*H*)-one (14). The product was recrystallized from EtOAc/Et_2O to afford a 47% yield of **14**: mp 117−119 °C; MS (CI + 1% NH_3 in CH_4) 231 (M + 1). Anal. ($C_{14}H_{14}O_3$) C, H, N.

4-Hydroxy-6,6-dipentyl-5,6-dihydropyran-2-one (15). The product was obtained as an oil in 82% yield which was carried on without further purification: ^{1}H NMR (DMSO-d_6) δ 0.87 (t, J = 6.5 Hz, 6H), 1.17−1.31 (m, 12H), 1.57−1.62 (m, 4H), 2.49 (q, J = 2 Hz, 2H), 4.93 (s, 1H); MS (CI + 1% NH_3 in CH_4) 255 (M + 1).

3-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-2*H*-pyran-2-yl)propanoic Acid (16). The title compound was prepared as described in general method 1 using 25 mmol of methyl acetoacetate, 27.5 mmol of NaH 60% dispersion in oil, 26.25 mmol of 1.6 M *n*-butyllithium in hexane in 50 mL of THF, and 25 mmol of 3-benzoylpropionic acid sodium salt in 60 mL of THF. 3-Benzoylpropionic acid sodium salt was prepared by reacting the acid (25 mmol) with hexane-washed NaH (26.25 mmol) in THF at 0 °C for 30 min. The crude product was flash chromatographed using CH_2Cl_2/MeOH/CH_3CO_2H (90/10/0.2) as eluent to give a 23% yield of **16** as a viscous gum: ^{1}H NMR ($CDCl_3$) δ 2.18−2.57 (m, 4 H), 2.93 (d, J = 17.2 Hz, 1 H), 2.97 (d, J = 20.5 Hz, 1 H), 3.30 (d, J = 20.5 Hz, 1 H), 3.36 (d, J = 17.2 Hz, 1 H), 7.27−7.45 (m, 5 H).

4-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-2*H*-pyran-2-yl)butyric acid (17). The title compound was prepared as described for compound **16**. The crude product was flash chromatographed using CH_2Cl_2/MeOH/CH_3CO_2H (99/1/0.1 to 97.5/2.5/0.1) to give a solid which was recrystallized from EtOAc to give 19% of **17**: mp 134−137 °C; MS (CI + 1% NH_3 in CH_4) 277 (M + 1). Anal. ($C_{15}H_{16}O_5$) C,H.

5-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-2*H*-pyran-2-yl)pentanoic Acid (18). The title compound was prepared as described for compound **16**. The crude solid was recrystallized from EtOAc to give a 28% yield of **18**: mp 136−140 °C; MS (CI + 1% NH_3 in CH_4) 291 (M + 1). Anal. ($C_{16}H_{18}O_5$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-6-pyridin-4-yl-2*H*-pyran-2-one (21). The reaction mixture was acidified with CH_3CO_2H and the crude solid was filtered off and then washed with ice water to give **21**: mp 148−150 °C. Anal. ($C_{16}H_{13}N_1O_3 \cdot 0.09H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-[(methylphenylamino)methyl]-6-phenyl-2*H*-pyran-2-one (22). The appropriate ketone, 2-(methylphenylamino)-1-phenylethanone, was prepared by reacting *N*-methylaniline (50 mmol), α-bromoacetophenone (50 mmol), and Et_3N (55 mmol) in Et_2O at room temperature overnight. The Et_2O was evaporated and replaced with *p*-dioxane, and the mixture refluxed for 15 h. The solid Et_3N−HCl was filtered. The filtrate was concentrated, and the solids were recrystallized from EtOAc to afford 17.5% of 2-(methylphenylamino)-1-phenylethanone as a solid: mp 118−120 °C; MS (CI + 1% NH_3 in CH_4) 226 (M + 1). Anal. ($C_{15}H_{15}N_1O_1 \cdot 0.09H_2O$) C, H, N.

Compound **22** was prepared as described in general method 1. The product was flash chromatographed using CH_2Cl_2/MeOH (99/1) to give a solid: mp 152−153 °C; MS (CI + 1% NH_3 in CH_4) 310 (M + 1). Anal. ($C_{19}H_{19}N_1O_3 \cdot 0.28H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(phenoxymethyl)-6-phenyl-2*H*-pyran-2-one (23). The crude product was triturated from Et_2O to afford **23** as a solid: mp 133−135 °C; MS (CI + 1% NH_3 in CH_4) 296. Anal. ($C_{18}H_{16}O_4$) C, H.

4-Hydroxy-6-phenyl-6-[4-(tetrahydropyran-2-yloxy)-butyl]-5,6-dihydropyran-2-one (24). The appropriate keto alcohol was prepared and then protected as a THP ether to afford 1-phenyl-5-(tetrahydropyran-2-yloxy)pentan-1-one.[30] The THP-protected alcohol was then reacted as described in general method 1. The produce was flash chromatographed using CH_2Cl_2/MeOH (99/1) to afford a 46% yield of **24** as an unknown mixture of diastereomers: mp 72.5−80.0 °C; MS (CI + 1% NH_3 in CH_4) 263 (M + 1). Anal. ($C_{16}H_{22}O_3$) C, H.

General Method 2. Preparation of Alkyl Thiotosylates. The thiotosylate reagents were prepared by reacting equal molar quantities of alkyl halide and potassium thiotosylate in absolute EtOH, refluxing for 24 h in DMF, and stirring at room temperature for 12−72 h. The solvent was stripped off, and the residue was taken up in EtOAc and washed with H_2O. Alternatively, H_2O was added, and the aqueous layer was extracted with Et_2O or EtOAc. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Compounds **25** and **26** were prepared according to this method.

Benzyl *p*-toluenethiosulfonate (25). The residue was recrystallized from hexane to yield 10.8 g (77%) of **25**: mp 52−56.5 °C.

Phenethyl *p*-Toluenethiosulfonate (26). The clear liquid obtained was used without purification: ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 2.92 (t, 2H), 3.24 (t, 2H), 7.1−7.4 (m, 7H), 7.84 (d, 2H).

General Method 3. Preparation of Benzenethiols (29). The appropriate phenol (1 equiv) was dissolved in DMF and added dropwise to a suspension of NaH (1.2 equiv) in DMF. After 1 h, the mixture was treated with *N*,*N*-dimethylthiocarbamoyl chloride all at once. The suspension was stirred at 60 °C for 18 h, poured into H_2O, and extracted with EtOAc. The organic layer was washed with 1 N NaOH, 1 N HCl, and brine and was dried over $MgSO_4$. The residue was chromatographed using hexane/EtOAc (6/1) to give an oily solid.

The intermediate prepared above was heated neat to 290−310 °C for 2−3 h and then cooled to room temperature. The rearranged product could be purified via chromatography or via crystallization from ether/hexane. This material (1 equiv) was dissolved in dry ether and added dropwise to a suspension of LAH (1.8 equiv) in ether at 0 °C. The cold bath was removed and the mixture was stirred at room temperature for 2−24 h. The suspension was treated cautiously with EtOAc, H_2O, and 1 N HCl/5% citric acid; the organic layer was separated, washed with brine, and dried over $MgSO_4$. Concentration gave an oil which was used without purification in the next step. Compounds **29d**, **29e**, **29h**, and **29i** were prepared in the same manner from the commercially available phenol. Compound **29j** was prepared from 2-*tert*-butyl-5-isopropylphenol, whose synthesis is included below.

2-*tert*-Butyl-5-isopropylphenol. A solution of 13.6 g (100 mmol) of 3-isopropylphenol, 15.0 g (200 mmol) of dry *t*-BuOH, and 3.0 mL of concentrated H_2SO_4 was heated at 70 °C for 4 h. The solution was cooled to room temperature, diluted with H_2O, and extracted with EtOAc. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated. The product was chromatographed, eluting with hexanes/EtOAc (5/1), to give 11.2 g (58% yield) of the title compound. Another 2.3 g of 2,4-di-*tert*-butyl-5-isopropylphenol was also obtained: ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.8 Hz, 6H), 1.36 (s, 9H), 2.78 (m, 1H), 4.64 (s, 1H), 6.50 (d, J = 1.8 Hz, 1H), 6.71 (dd, J = 1.8 Hz, 7.9 Hz, 1H), 7.15 (d, J = 8 Hz, 1H).

General Method 4. Preparation of Aryl Thiotosylates. A solution of tosyl bromide (1.05 equiv), NEt_3 (1.05 equiv), and CCl_4 was treated with a solution of the benzenethiol (1.0 equiv) in CCl_4 in a slow, dropwise fashion. When addition was complete, the solution was washed with 3 N HCl, saturated $NaHCO_3$, and brine and was dried over $MgSO_4$. Concentration gave an oil which was purified by chromatography, as noted in Table 1. Compounds **30d**, **30e**, **30f**, **30i**, and **30j** were prepared in this manner.

2-Cyclopentylphenyl *p*-Toluenesulfonate (30d). The product was obtained as a solid in 53% yield from the corresponding benzenethiol: ^{1}H NMR ($CDCl_3$) δ 1.6−2.0 (m, 8H), 2.52 (s, 3H), 2.95 (m, 1H), 7.22 (m, 2H), 7.48 (m, 4H), 7.90 (m, 2H).

2-Cyclohexylphenyl *p*-Toluenesulfonate (30e). The product was obtained as a solid in 62% yield from the corresponding benzenethiol: ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 7H), 1.69 (m, 3H), 2.49 (s, 3H), 2.60 (m, 1H), 7.18 (m, 2H), 7.45 (m, 4H), 7.88 (m, 2H).

2-*tert*-Butylphenyl *p*-Toluenesulfonate (30f). The product was obtained as a solid in a 42% yield from the corresponding benzenethiol: ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 9H), 2.40 (s, 3H), 7.22 (m, 3H), 7.43 (m, 4H), 7.44 (d, 1H).

2-*tert*-Butyl-5-methylphenyl *p*-Toluenesulfonate (30i). The product was obtained as a solid: ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H), 2.21 (s, 3H), 2.38 (s, 3H), 7.18 (m, 2H), 7.26 (m, 2H), 7.44 (d, 2H).

2-*tert*-Butyl-5-isopropylphenyl *p*-Toluenesulfonate (30j). The product was obtained as a solid in 55% yield: ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 6.8 Hz, 6H), 1.20 (s, 9H), 2.37 (s, 3H), 2.77 (m, 1H), 7.17 (m, 2H), 7.35 (m, 4H), 7.44 (d, 2H).

General Method 5. Preparation of Target Dihydropyrones. The desired compounds were prepared by adding the 5,6-dihydro-2*H*-pyrone-2-one, absolute EtOH, the *p*-toluenethiosulfonate reagent, and Et_3N to a reaction vessel. The solution was stirred at room temperature to reflux for 4 h to one week. The solvent was stripped off and the residue partitioned between 1 N HCl and CH_2Cl_2 or EtOAc. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 or EtOAc. The organic layers were combined and dried over $MgSO_4$. Compounds **1b**,**c**; **2b**,**c**; **3b**,**c**; **4b**,**c**; **5b**,**c**; **6b**,**c**; **7b**,**c**; **8b**,**c**; **9b**,**c**; **10b**; **11b**,**c**; **12b**,**c**; **13b**; **14b**,**c**; **15b**; **16c**; **17c**; **18c**; **19c**; **20c**; **21c**; **22c**; **23b**; **24b**; **39**; **40**; **41**;**42**; **43**; **48**; **49**; and **50** were prepared according to this method.

General Method 6. Preparation of 3-Bromodihydropyrones. The 3-bromo-5,6-dihydro-4-hydroxy-2*H*-pyran-2-one intermediates were prepared by reacting equimolar amounts of the appropriate dihydropyrone (**7**, **10**, **11)** with *N*-bromosuccinimide (NBS) in dry *t*-BuOH in the dark. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. This method was used to prepare compound **27** (3-bromo-5,6-dihydro-4-hydroxy-6,6-diphenyl-2*H*-pyran-2-one), **28** (3-bromo-5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one), and **29** (3-bromo-5,6-dihydro-4-hydroxy-(3-methylbutyl)-6-phenyl-2*H*-pyran-2-one) which were all used without further purification.

General Method 7. Alternate Preparation of Target Dihydropyrones. The desired compounds were prepared by adding piperidine (1.05 equiv) to a cold (ice bath) solution of the 3-bromo-5,6-dihydro-4-hydroxy-2*H*-pyran-2-ones (1.0 equiv, prepared in General Method 6), the requisite thiol (**29,** 1.05 equiv), and CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 8−48 h. Water was added, and the organic

phase was separated, dried over $MgSO_4$, and concentrated. This method was used to prepare **7a**, **11a**, **12a**, **33**, **34**, **35**, **36**, **37**, **38**, **44**, **45**, **46**, and **47**.

5,6-Dihydro-4-hydroxy-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (1b). Concentration in vacuo gave a solid which was broken up and made into a slurry in Et_2O and EtOAc. The solid was filtered off, and the mother liquors were concentrated and flash chromatographed on silica gel using CH_2Cl_2/MeOH (99/1 to 97/3) as eluants. The combined crops gave 55% of **1b** as a solid: mp 150−151.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.65 (dd, J = 17.6 Hz, J = 4.0 Hz, 1H), 2.78 (dd, J = 17.6 Hz, J = 11.8 Hz, 1H), 3.85 (d, J = 12.6 Hz, 1H), 3.94 (d, J = 12.6 Hz, 1H), 5.28 (dd, J = 11.8 Hz, J = 4.0 Hz, 1H), 7.19−7.43 (m, 11H); MS (FAB + thioglycerol) 313 (M + 1). Anal. ($C_{18}H_{16}O_3S$) C, H, N, S.

5,6-Dihydro-4-hydroxy-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (1c). The product was purified by flash chromatography using CH_2Cl_2/MeOH (99/1 to 97/3) as eluants. The viscous paste was triturated from Et_2O to yield **1c** as a solid in 64% yield: mp 98−99 °C; MS (CI + 1% NH_3 in CH_4) 327 (M + 1). Anal. ($C_{19}H_{18}O_3S$), C, H, N, S.

5,6-Dihydro-4-hydroxy-6-phenyl-3-[(phenylmethyl)thio]-6-propyl-2*H*-pyran-2-one (2b). The product was flash chromatographed (hexane/EtOAc, 75/25) to afford a 69% yield of **2b** as a viscous gum. MS (CI + 1% NH_3 in CH_4) 355 (M + 1). Anal. ($C_{21}H_{22}O_3S\cdot0.28H_2O$), C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-3-[(2-phenylethyl)thio]-6-propyl-2*H*-pyran-2-one (2c). The product was flash chromatographed (hexane/EtOAc, 60/40) to afford a 66% yield of **2c** as a viscous gum. MS (CI + 1% NH_3 in CH_4) 369 (M + 1). Anal. ($C_{22}H_{24}O_3S$), C, H, S.

6-Butyl-5,6-dihydro-4-hydroxy-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (3b). The product was purified by flash chromatography using CH_2Cl_2/MeOH (100/0 to 95/5) as eluent gave a 35% yield of **3b** as a viscous oil: MS (EI^+) 368. Anal. ($C_{22}H_{24}O_3S$) C, H, N.

6-Butyl-5,6-dihydro-4-hydroxy-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (3c). The product was purified by flash chromatography using CH_2Cl_2/MeOH (99/1) as eluent gave a 77% yield of **3c** as a viscous oil: MS (CI + 1% NH_3 in CH_4) 383 (M + 1). Anal. ($C_{23}H_{26}O_3S\cdot0.32H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-pentyl-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (4b). The product was flash chromatographed (hexane/EtOAc, 75/25) to afford a 58% yield of **4b** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 383 (M + 1). Anal. ($C_{23}H_{26}O_3S\cdot0.46H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-pentyl-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (4c). The product was flash chromatographed (hexane/EtOAc, 70/30) to afford a 58% yield of **4c** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 397 (M + 1). Anal. ($C_{24}H_{28}O_3S$) C, H, N.

5,6-Dihydro-6-hexyl-4-hydroxy-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (5b). The product was flash chromatographed using CH_2Cl_2/MeOH (99.5/0.5) to afford a 63% yield of **5b** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 397 (M + 1). Anal. ($C_{24}H_{28}O_3S\cdot0.29H_2O$) C, H, N.

5,6-Dihydro-6-hexyl-4-hydroxy-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (5c). The product was flash chromatographed using CH_2Cl_2/MeOH (99.75/0.25 to 99/1) to afford a 63% yield of **5c** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 411 (M + 1). Anal. ($C_{25}H_{30}O_3S\cdot0.21H_2O$) C, H, N, S.

5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (6b). The product was flash chromatographed (CH_2Cl_2/MeOH, 99.5/0.5) to afford a 60% yield of **6b** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 369 (M + 1). Anal. ($C_{22}H_{24}O_3S\cdot0.24H_2O$) C, H, N, S.

5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (6c). The product was flash chromatographed (CH_2Cl_2/MeOH, 99.5/0.5) to afford a 55% yield of **6c** as a viscous gum: MS (EI^+) 382. Anal. ($C_{23}H_{26}O_3S\cdot0.30H_2O$) C, H, N, S.

5,6-Dihydro-4-hydroxy-6-(3-methylbutyl)-6-phenyl-3-(phenylthio)-2*H*-pyran-2-one (7a). The crude product was chromatographed on silica gel, eluting first with $CHCl_3$ and then with 5% MeOH in $CHCl_3$, to give **7a** in 22% yield: (mp 154−155 °C): MS (CI + 1% NH_3 in CH_4) 369 (M + 1). Anal. ($C_{22}H_{24}O_3S\cdot0.60H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(3-methylbutyl)-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (7b). The product was flash chromatographed (hexane/EtOAc, 80/20) to afford a 44% yield of **7b** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 383 (M + 1). Anal. ($C_{23}H_{26}O_3S\cdot0.17H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(3-methylbutyl)-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (7c). The product was flash chromatographed (hexane/EtOAc, 80/20) to afford a 74% yield of **7c** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 397 (M + 1). Anal. ($C_{24}H_{28}O_3S\cdot0.17H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(4-methylpentyl)-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (8b). The product was flash chromatographed using CH_2Cl_2/MeOH (100/0 to 99/1) to afford a 28% yield of **8b** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 397 (M + 1). Anal. ($C_{24}H_{28}O_3S$) C, H, N.

5,6-Dihydro-4-hydroxy-6-(4-methylpentyl)-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (8c). The product was flash chromatographed using hexane/EtOAc (80/20) to afford a 67% yield of **8c** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 411 (M + 1). Anal. ($C_{25}H_{30}O_3S\cdot0.05H_2O$) C, H, N, H_2O.

6-(Cyclopentylmethyl)-5,6-dihydro-4-hydroxy-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (9b). The product was flash chromatographed using hexane/EtOAc (75/25) and then CH_2Cl_2/MeOH (99.5/0.5) to afford a 66% yield of **9b** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 395 (M + 1). Anal. ($C_{24}H_{26}O_3S$) C, H, N.

6-(Cyclopentylmethyl)-5,6-dihydro-4-hydroxy-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (9c). The product was flash chromatographed using hexane/EtOAc (75/25 to 60/40) to afford a 89% yield of **9c** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 409 (M + 1). Anal. ($C_{25}H_{28}O_3S\cdot0.23H_2O$) C, H, N.

6-(Cyclohexylmethyl)-5,6-dihydro-4-hydroxy-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (10b). The product was flash chromatographed using CH_2Cl_2/MeOH (100/0 to 99/1) to afford a 49% yield of **10b** as a viscous gum: MS (CI + 1% NH_3 in CH_4) 395 (M + 1). Anal. ($C_{25}H_{28}O_3S\cdot0.70H_20$) C, H, N.

5,6-Dihydro-4-hydroxy-6,6-diphenyl-3-(phenylthio)-2*H*-pyran-2-one (11a). The product was triturated with hexane/Et_2O (1/1) to afford **11a** in 78% yield as a solid: mp 78−80 °C; ^{1}H NMR (DMSO-d_6) δ 3.37 (bs, 2 H), 6.35 (m, 2 H), 6.93 (m, 3 H), 7.29−7.49 (m, 10 H); MS (CI + 1% NH_3 in CH_4) 375 (M + 1). Anal. ($C_{23}H_{18}O_3S\cdot0.60\ H_2O$) C, H, N, S.

5,6-Dihydro-4-hydroxy-6,6-diphenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (11b). The product was flash chromatographed (CH_2Cl_2/MeOH 100/0 to 98/2) to afford **11b** in 53% yield as a solid: mp 44−47.5 °C; MS (CI + 1% NH_3 in CH_4) 389 (M + 1). Anal. ($C_{24}H_{20}O_3S\cdot0.36H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6,6-diphenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (11c). The solid product was triturated from Et_2O to afford a 70% yield of **11c** as a solid: mp 153−154.5 °C; MS (CI + 1% NH_3 in CH_4) 403 (M + 1). Anal. ($C_{25}H_{22}O_3S$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-3-(phenylthio)-2*H*-pyran-2-one (12a). The product was triturated with hexane/Et_2O (1/1) to afford a solid. The crude product was chromatographed on silica gel, eluting first with $CHCl_3$ and then with 5% MeOH in $CHCl_3$, to give **12a** in 57% yield as a solid: mp 58−60 °C; MS (CI + 1% NH_3 in CH_4) 402 (M + 1). Anal. ($C_{25}H_{22}O_3S\cdot0.60H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (12b). The product was flash chromatographed (hexane/EtOAc, 80/20) to afford a 59% yield of **12b** as a viscous gum: ^{1}H NMR ($CDCl_3$) δ 2.13−2.39 (m, 3H), 2.72−2.79 (m, 1H), 2.97 (d, J = 17.5 Hz, 1H), 3.03 (d, J = 17.5 Hz, 1H), 3.53 (d, J = 13.0 Hz, 1H), 3.76 (d, J = 13.0 Hz, 1H), 6.85 (d, J = 6.7 Hz, 2H), 7.06−7.45 (m, 14H); MS (CI + 1% NH_3 in CH_4) 417 (M + 1). Anal. ($C_{26}H_{24}O_3S\cdot0.24H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (12c). The solid product was triturated from Et_2O to afford a 16% yield of **12c**

as a solid: mp 56−58 °C; MS (EI$^+$) 430. Anal. ($C_{27}H_{26}O_3S\cdot 0.26H_2O$) C, H, N, S.

2,3-Dihydro-4′-hydroxy-5′-[(phenylmethyl)thio]-spiro-[1*H*-indene-1,2′-[2*H*]pyran]-6′(3*H*′)-one (13b). The product was flash chromatographed using CH_2Cl_2/MeOH (99/1) to afford a 86% yield of **13b** as a solid: mp 42−46 °C; MS (CI + 1% NH_3 in CH_4) 339 (M + 1). Anal. ($C_{20}H_{18}O_3S\cdot 0.24H_2O$) C, H, N.

3,4-Dihydro-4′-hydroxy-5′-[(phenylmethyl)thio]spiro-[naphthalene-1(2*H*),2′-[2*H*]pyran]-6′(3′*H*)-one (14b). The product was flash chromatographed using hexane/EtOAc (90/10 to 60/40) and then triturated from Et_2O to afford a 37% yield of **14b** as a solid: mp 143−145 °C; MS (CI + 1% NH_3 in CH_4) 353 (M + 1). Anal. ($C_{21}H_{20}O_3S\cdot 0.12H_2O$) C, H, N.

3,4-Dihydro-4′-hydroxy-5′-[(2-phenylethyl)thio]-spiro-[naphthalene-1(2*H*),2′-[2*H*]pyran]-6′(3′*H*)-one (14c). The product was flash chromatographed using CH_2Cl_2/MeOH (100/0 to 98/2) to afford a solid which was recrystallized from CH_2Cl_2/Et_2O to afford **14c** in 48% yield as a solid: mp 125−126.5 °C; MS (CI + 1% NH_3 in CH_4) 367 (M + 1). Anal. ($C_{22}H_{22}O_3S$) C, H, N.

3-(Benzylsulfanyl)-4-hydroxy-6,6-dipentyl-5,6-dihydropyran-2-one (15b). The resulting oil was flash chromatographed twice using hexanes/EtOAc as elutant (5:1/1:1) affording the product as a syrup: ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 7 Hz, 6H), 1.11−1.27 (m, 12H), 1.37−1.50 (m, 4H), 2.50 (q, J = 2 Hz, 2H), 3.84 (s, 2H), 7.19−7.26 (m, 5H), 11.26 (bs, 1H); MS (CI + 1%NH_3 in CH_4) 377 (M + 1). Anal. $C_{22}H_{32}O_3S\cdot 0.50H_2O$.

3-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-5-[(2-phenylethyl)thio]-2*H*-pyran-2-yl)propanoic Acid (16c). The product was flash chromatographed using CH_2Cl_2/MeOH/$MeCO_2H$ (95/5/0.05) and then recrystallized from EtOAc to afford 23% yield of **16c** as a solid: mp 150.5−152 °C; MS (CI + 1% NH_3 in CH_4) 399 (M + 1). Anal. ($C_{22}H_{22}O_5S$) C, H, N.

4-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-5-[(2-phenylethyl)thio]-2*H*-pyran-2-yl)butyric Acid (17c). The product was flash chromatographed using CH_2Cl_2/MeOH/$MeCO_2H$ (95/5/0.05) to afford **17c** in 28% yield as an amorphous solid: MS (APCI + MeOH/CH_3CN (20/80) + 0.1% NH_4OH) 412. Anal. ($C_{23}H_{24}O_5S\cdot 0.60H_2O$) C, H, N.

5-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-5-[(2-phenylethyl)thio]-2*H*-pyran-2-yl)pentanoic Acid (18c). The product was flash chromatographed using CH_2Cl_2/MeOH/$MeCO_2H$ (99/1/0.05) to afford **18c** in 31% yield as a solid: mp 113−119.5 °C; MS (CI + 1% NH_3 in CH_4) 427 (M + 1). Anal. ($C_{24}H_{26}O_5S\cdot 0.35H_2O$) C, H, N.

4-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-5-[(phenylethyl)thio]-2*H*-pyran-2-yl)butyramide (19c). To a 50 mL reaction flask were added 0.75 mmol of **17**, 1.5 mmol of 4-methylmorpholine, and 7.5 mL of CH_2Cl_2. The reaction mixture was cooled to 0 °C, and 1.5 mmol of methyl chloroformate in 3.5 mL of CH_2Cl_2 was added. The reaction mixture was stirred at 0 °C for 2 h. Ammonia was bubbled into the vessel for 10−15 min and the reaction mixture allowed to stir for 30 min at 0 °C and then for 1.5 h at room temperature. The reaction was poured into EtOAc and 1 N HCl, and the aqueous layer was extracted with 2 × EtOAc, dried over $MgSO_4$, and concentrated. The crude reaction mixture was flash chromatographed using CH_2Cl_2/MeOH/$MeCO_2H$ (98/2/0.05) to afford 4-(3,6-dihydro-4-hydroxy-6-oxo-2-phenyl-2*H*-pyran-2-yl)butyramide as a solid (mp 51−54 °C).

The title compound was prepared as described in general method 3. The product was flash chromatographed using CH_2Cl_2/MeOH (90/10) and then triturated from Et_2O to afford **19b** as a solid: mp 119−124 °C; MS (APCI + MeOH/CH_3CN (20/80) + 0.1% NH_4OH) 412 (M + 1). Anal. ($C_{23}H_{25}N_1O_4S\cdot 0.29H_2O$) C, H, N.

5-(3,6-Dihydro-4-hydroxy-6-oxo-2-phenyl-5-[(2-phenylethyl)thio]-2*H*-pyran-2-yl)pentanoic Acid Amide (20c). The desired amide was prepared as described in **19c** using **18c** as the acid starting material. The crude solid was triturated from CH_2Cl_2 to afford 5-(3,6-dihydro-4-hydroxy-6-oxo-2-phenyl-2*H*-pyran-2-yl)pentanoic acid amide as a solid (mp 173−174 °C).

The title compound was prepared as described in general method 3. The product was flash chromatographed using CH_2Cl_2/MeOH (90/10) and then triturated from Et_2O to afford a 47% yield of **20c** as a solid (softened 100−105 °C, melted completely at 120 °C). MS (CI + 1% NH_3 in CH_4) 408 (M − 16). Anal. ($C_{24}H_{27}N_1O_4S\cdot 0.27H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenyl-3-[(2-phenylethyl)thio]-6-pyridin-4-yl-2*H*-pyran-2-one (21c). The solid product was triturated from EtOAc: mp 203−205 °C; MS (CI + 1% NH_3 in CH_4) 404 (M + 1). Anal. ($C_{24}H_{21}N_1O_3S\cdot 0.43H_2O$) C, H, N.

5,6-Dihydro-4-hydroxy-6-[(methylphenylamino)methyl]-6-phenyl-3-[(2-phenylethyl)thio]-2*H*-pyran-2-one (22c). The solid product was flash chromatographed using CH_2Cl_2/MeOH (99/1) to afford **22c** as a solid: mp 48−57 °C; MS (CI + 1% NH_3 in CH_4) 446 (M + 1). Anal. ($C_{27}H_{27}N_1O_3S$) C, H, N.

5,6-Dihydro-4-hydroxy-6-phenoxymethyl-6-phenyl-3-[(phenylmethyl)thio]-2*H*-pyran-2-one (23b). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 95/5) as eluent gave a solid: mp 161−163 °C; MS (CI + 1% NH_3 in CH_4) 461 (M + 1). Anal. ($C_{28}H_{28}O_4S$) C, H.

3-(Benzylsulfanyl)-5,6-dihydro-4-hydroxy-6-(4-hydroxybutyl)-6-phenyl-2*H*-pyran-2-one (24b). Purification by flash chromatography using CH_2Cl_2/MeOH (99/1 to 98/2) as eluent gave a solid: mp 43−49 °C; MS (CI + 1% NH_3 in CH_4) 385 (M + 1). Anal. ($C_{22}H_{24}O_4S\cdot 0.39H_2O$) C, H.

5,6-Dihydro-4-hydroxy-3-[(2-methylphenyl)sulfanyl]-6,6-diphenyl-2*H*-pyran-2-one (33). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 149−151 °C; MS (CI + 1% NH_3 in CH_4) 389 (M + 1). Anal. ($C_{24}H_{20}O_3S\cdot 0.9H_2O$) C, H.

5,6-Dihydro-4-hydroxy-3-[(2-methylphenyl)sulfanyl]-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (34). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 80−82 °C; MS (CI + 1% NH_3 in CH_4) 417 (M + 1). Anal. ($C_{26}H_{24}O_3S\cdot 0.3H_2O$) C, H.

5,6-Dihydro-4-hydroxy-3-[(2-isopropylphenyl)sulfanyl]-6,6-diphenyl-2*H*-pyran-2-one (35). Purification by trituration from ether gave a solid: mp 216−217 °C; MS (CI + 1% NH_3 in CH_4) 417 (M + 1). Anal. ($C_{26}H_{24}O_3S\cdot 0.6H_2O$) C, H.

5,6-Dihydro-4-hydroxy-3-[(2-isopropylphenyl)sulfanyl]-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (36). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 98/2) as eluent gave a solid: mp 109−111 °C; MS (CI + 1% NH_3 in CH_4) 445 (M + 1). Anal. ($C_{27}H_{26}O_3S\cdot 0.4H_2O$) C, H.

3-[(2-*sec*-Butylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6,6-diphenyl-2*H*-pyran-2-one (37). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 98/2) as eluent gave a solid: mp 161−162 °C; MS (CI + 1% NH_3 in CH_4) 431 (M + 1). Anal. ($C_{27}H_{26}O_3S$) C, H.

3-[(2-*sec*-Butylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (38). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 98/2) as eluent gave a solid: mp 67−68 °C; MS (CI + 1% NH_3 in CH_4) 459 (M + 1). Anal. ($C_{29}H_{30}O_3S\cdot 0.3H_2O$) C, H.

3-[(2-Cyclopentylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6,6-diphenyl-2*H*-pyran-2-one (39). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 168−170 °C; MS (CI + 1% NH_3 in CH_4) 443 (M + 1). Anal. ($C_{28}H_{26}O_3S\cdot 0.2H_2O$) C, H.

3-[(2-Cyclohexylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6,6-diphenyl-2*H*-pyran-2-one (40). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 185−186 °C; MS (CI + 1% NH_3 in CH_4) 457 (M + 1). Anal. ($C_{29}H_{28}O_3S\cdot 0.4H_2O$) C, H.

3-[(2-Cyclohexylphenyl)sulfanyl)-5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (41). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 198−200 °C; MS (CI + 1% NH_3 in CH_4) 485 (M + 1). Anal. ($C_{31}H_{32}O_3S\cdot 0.4H_2O$) C, H.

3-[(2-*tert*-Butylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6,6-diphenyl-2*H*-pyran-2-one (42). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 98/2) as eluent gave a solid: mp 191−192 °C; MS (CI + 1% NH_3 in CH_4) 431 (M + 1). Anal. ($C_{27}H_{26}O_3S\cdot 0.5H_2O$) C, H.

3-[(2-*tert*-Butylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (43). Purifica-

tion by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 81−83 °C; MS (CI + 1% NH_3 in CH_4) 459 (M + 1). Anal. ($C_{29}H_{30}O_3S·0.2H_2O$) C, H.

5,6-Dihydro-4-hydroxy-6,6-diphenyl-3-[(2-isopropyl-5-methylphenyl)sulfanyl]-2*H*-pyran-2-one (44). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 98/2) as eluent gave a solid: mp 183−184 °C; MS (CI + 1% NH_3 in CH_4) 431 (M + 1). Anal. ($C_{27}H_{26}O_3S·0.3H_2O$) C, H.

5,6-Dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-3-[(2-isopropyl-5-methylphenyl)sulfanyl]-2*H*-pyran-2-one (45). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 98/2) as eluent gave a solid: mp 66−67 °C; MS (CI + 1% NH_3 in CH_4) 459 (M + 1). Anal. ($C_{29}H_{30}O_3S·0.2H_2O$) C, H.

5,6-Dihydro-4-hydroxy-6,6-diphenyl-3-[(2,5-diisopropylphenyl)sulfanyl]-2*H*-pyran-2-one (46). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 66−67 °C; MS (CI + 1% NH_3 in CH_4) 459 (M + 1). Anal. ($C_{29}H_{30}O_3S$) C, H.

5,6-Dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-3-[(2,5-diisopropylphenyl)sulfanyl]-2*H*-pyran-2-one (47). Purification by flash chromatography using CH_2Cl_2/MeOH (100/0 to 98/2) as eluent gave a solid: mp 95−96 °C; MS (CI + 1% NH_3 in CH_4) 487 (M + 1). Anal. ($C_{31}H_{34}O_3S·0.4H_2O$) C, H.

3-[(2-*tert*-Butyl-5-methylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6,6-diphenyl-2*H*-pyran-2-one (48). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 125−127 °C; MS (CI + 1% NH_3 in CH_4) 445 (M + 1). Anal. ($C_{28}H_{28}O_3S·0.6H_2O$) C, H.

3-[(2-*tert*-Butyl-5-methylphenyl)sulfanyl]-5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (49). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 71−72 °C; MS (CI + 1% NH_3 in CH_4) 473 (M + 1). Anal. ($C_{30}H_{32}O_3S·0.15H_2O$) C, H.

3-[(2-*tert*-Butyl-5-isopropylphenyl)sulfanyl)-5,6-dihydro-4-hydroxy-6-phenyl-6-(2-phenylethyl)-2*H*-pyran-2-one (50). Purification by flash chromatography using hexane/EtOAc (4/1 to 3/2) as eluent gave a solid: mp 62−64 °C; MS (CI + 1% NH_3 in CH_4) 501 (M + 1). Anal. ($C_{32}H_{36}O_3S·0.4H_2O$) C, H.

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