Tipranavir (PNU-140690): A Potent, Orally Bioavailable Nonpeptidic HIV Protease Inhibitor of the 5,6-Dihydro-4-hydroxy-2-pyrone Sulfonamide Class[▽]

Steve R. Turner,*[,†] Joseph W. Strohbach,[†] Ruben A. Tommasi,[‡] Paul A. Aristoff,[∥] Paul D. Johnson,[∥] Harvey I. Skulnick,[∥] Lester A. Dolak,[†] Eric P. Seest,[†] Paul K. Tomich,[§] Michael J. Bohanon,[§] Miao-Miao Horng,[§] Janet C. Lynn,[§] Kong-Teck Chong,[⊥] Roger R. Hinshaw,[⊥] Keith D. Watenpaugh,[†] Musiri N. Janakiraman,[†] and Suvit Thaisrivongs[†]

Departments of Structural, Analytical & Medicinal Chemistry, Medicinal Chemistry, Discovery Technologies, and Infectious Diseases Research, Pharmacia & Upjohn, Inc., 301 Henrietta Street, Kalamazoo, Michigan 49001

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A broad screening program previously identified phenprocoumon (**1**) as a small molecule template for inhibition of HIV protease. Subsequent modification of this lead through iterative cycles of structure-based design led to the activity enhancements of pyrone and dihydropyrone ring systems (**II** and **V**) and amide-based substitution (**III**). Incorporation of sulfonamide substitution within the dihydropyrone template provided a series of highly potent HIV protease inhibitors, with structure−activity relationships described in this paper. Crystallographic studies provided further information on important binding interactions responsible for high enzymatic binding. These studies culminated in compound **VI**, which inhibits HIV protease with a K_i value of 8 pM and shows an IC_{90} value of 100 nM in antiviral cell culture. Clinical trials of this compound (PNU-140690, Tipranavir) for treatment of HIV infection are currently underway.

The worldwide AIDS epidemic has stimulated a large research effort directed toward identifying therapeutic protocols effective for control of the disease and its causative agent, HIV. One approach of intense scrutiny over the past few years has been inhibition of the virally encoded protease, an enzyme essential for maturation of viral particles to their infectious stage.[1,2] A number of highly potent peptidemimetic HIV protease inhibitors have been described in the literature,[3−6] though the therapeutic utility of this structural type is often compromised by low oral bioavailability and rapid excretion.[7] Recent advances have led to protease inhibitors of reduced peptidic nature which generally exhibit improved pharmacokinetic properties. An increasing number of protease inhibitors[8−21] are undergoing clinical trials or have been approved for AIDS therapy.

We have previously described[20] the discovery of phenprocoumon (**I**, Figure 1) as a lead nonpeptide HIV protease inhibitor. This compound, which was identified via broad screening of the Pharmacia & Upjohn compound library, inhibited HIV protease with a K_i of 1 μM and showed weak antiviral activity (ED_{50} 100−300 μM). With this compound as a starting point, we embarked on a series of iterative cycles of structure-based design, leading to the enhancements shown in Figure 1.[20,21] Favorable effects on enzymatic binding were observed by replacing the 4-hydroxycoumarin ring system with the corresponding 4-hydroxypyrone system, as exemplified by compound **II** (K_i 38 nM),[20] and by

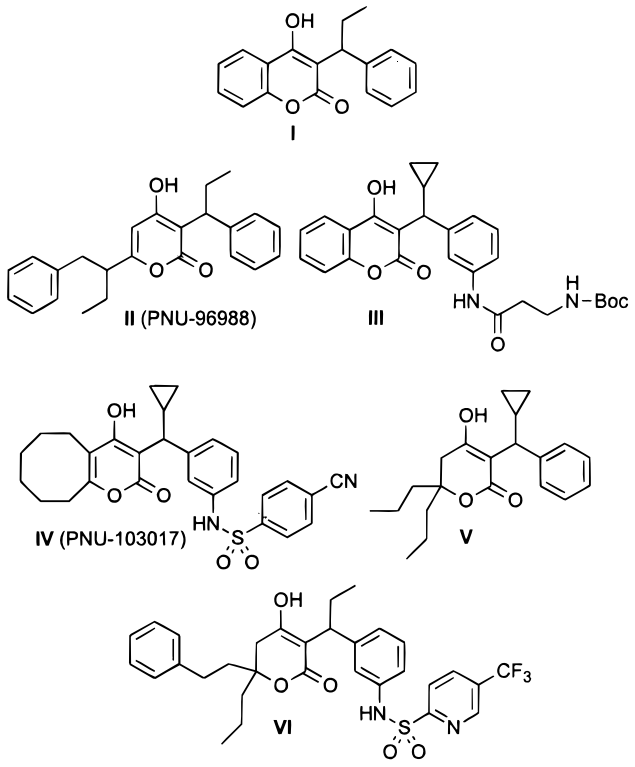

Figure 1.

introduction of carboxamide functionality at the *meta* position of the phenyl side chain, as exemplified by compound **III** (K_i 86 nM).[22] Further improvements in enzymatic and antiviral activity were realized via cycloalkane and sulfonamide modifications, exemplified by **IV**[21] (K_i < 1 nM, antiviral IC_{50} 1−2 μM), and in the dihydropyrone series, exemplified by **V**[23] (K_i 15 nM, IC_{50} 5 μM). Most recently, we reported preliminary results of dihydropyrone inhibitors containing appended sul-

[▽] Dedicated to Prof. Robert E. Ireland on the occasion of his 70th birthday.

[†] Structural, Analytical & Medicinal Chemistry.

[‡] Present address: Novartis Pharmaceuticals Corp., RES-322, 556 Morris Avenue, Summit, NJ 07901.

[∥] Medicinal Chemistry.

[§] Discovery Technologies.

[⊥] Infectious Diseases Research.

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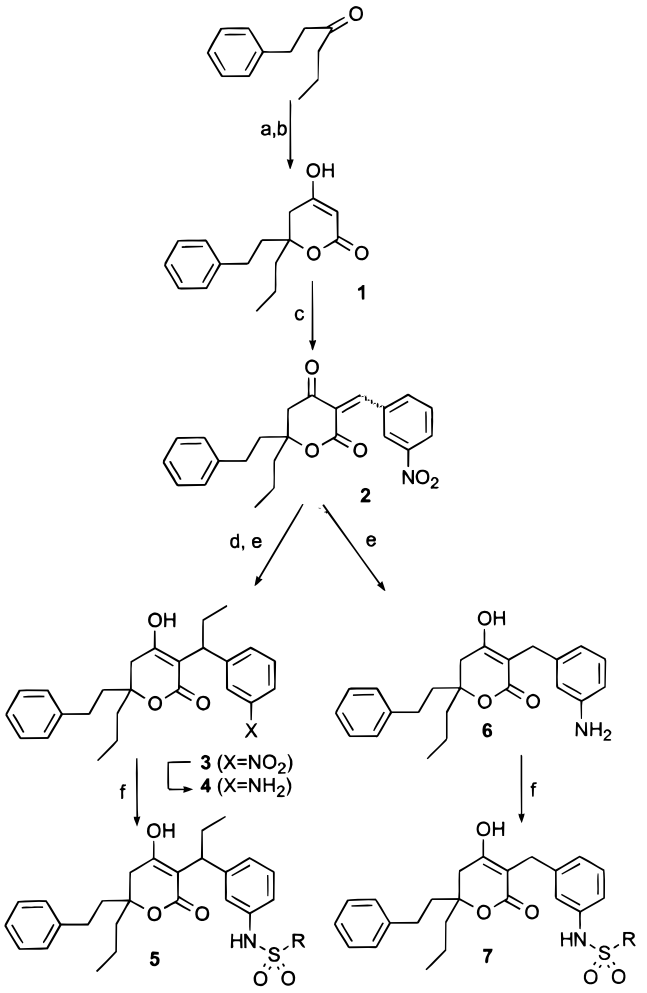
Scheme 1[a]



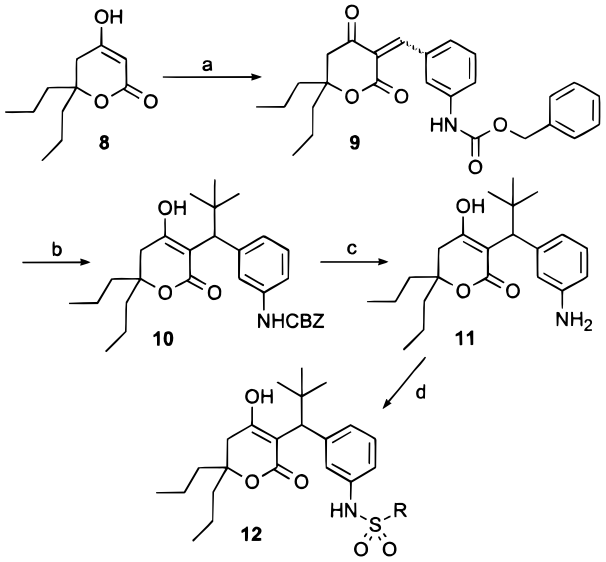
[a] (a) $CH_3COCH_2CO_2CH_3$, NaH, THF; (b) NaOH then H_3O^+; (c) *m*-$NO_2C_6H_4CHO$, $AlCl_3$, THF; (d) Et_3Al, CuBr−Me_2S, THF; (e) H_2, Pd/C, MeOH; (f) RSO_2Cl, pyr, CH_2Cl_2.

fonamide functionality, exemplified by **VI**.[24] Compounds **II**, **IV**, and **VI** represent Pharmacia & Upjohn's first, second, and third generation clinical candidates for potential treatment of AIDS. The purpose of this full report is to describe structure−activity relationships within this latest structural class.

Chemistry

Preparation of a representative series of sulfonamide-containing dihydropyrones is depicted in Scheme 1. Reaction of the dianion of methyl acetoacetate with 1-phenyl-3-hexanone, followed by hydrolysis of the intermediate β-ketoester and spontaneous ring closure upon acidification, provided the phenethyl propyl dihydropyrone ring system **1** in 72% yield. Aluminum chloride catalyzed condensation of the dihydropyrone with *m*-nitrobenzaldehyde afforded benzylidene intermediate **2**, which was generally not isolated but reacted directly with triethylaluminum in the presence of copper(I) bromide−dimethyl sulfide to give the fully functionalized dihydropyrone **3** in 80% yield. Reduction of the nitro group was accomplished using catalytic hydrogenation to provide amine **4**, which could be coupled with a wide variety of sulfonyl chlorides in the presence of pyridine to afford the final sulfonamides **5** in good yield. The selection of base used in the sulfonylation reaction was important, as use of stronger tertiary amine bases led exclusively to O-sulfonylation.

Scheme 2[a]



[a] (a) *m*-$CbzNHC_6H_4CHO$, $AlCl_3$, THF; (b) *t*-BuMgCl or "*t*-BuCu(CN)ZnI", CuBr−Me_2S, THF; (c) H_2, Pd/C, MeOH; (d) RSO_2Cl, pyr, CH_2Cl_2.

Preparation of C-3α unsubstituted analogues required addition of hydrogen to benzylidene intermediate **2**. Treatment of the benzylidene compound with sodium cyanoborohydride in methanol selectively reduced the benzylidene double bond, and subsequent hydrogenation of the nitro group afforded amine **6**. Alternately, both steps could be conducted simultaneously by simple catalytic hydrogenation of **2** using palladium on carbon. Sulfonylation of the amine using an appropriate sulfonyl chloride in the presence of pyridine provided C-3α methylene analogues **7**.

Although the above route proved quite general for conversion of a variety of ketones to the correspondingly 6-substituted dihydropyrones, it was less well suited for introduction of a wide array of substitution at C-3α, due to the limited selection of available trialkylaluminums. Attempted utilization of Grignard reagents for addition of functionality to benzylidene intermediate **2** was problematic, usually leading to numerous side reactions. Presumably the source of this interference was electron transfer between the Grignard reagent and the nitrated substrate. To circumvent this difficulty, we explored the organocopper−zinc reagents described by Knochel.[25] Reaction of activated zinc dust with *tert*-butyl iodide in dry THF at 45 °C using ultrasound provided the putative organozinc species, which was subsequently modified by treatment with copper(I) cyanide and lithium chloride. Reaction of this reagent with the freshly prepared benzylidene intermediate **2** at 0 °C resulted in relatively clean conjugate addition, giving products corresponding to **3** in ca. 60% yield.

Alternatively, as shown in Scheme 2, Grignard reagents could be utilized as a source of C-3α functionality if the reactive nitro group was absent from the conjugate addition substrate. Aluminum trichloride catalyzed condensation of dihydropyrone **8** with the benzyloxycarbonyl derivative of *m*-aminobenzaldehyde, in the same fashion as described above, provided the analogous

benzylidene intermediate **9**. Conjugate addition of, for example, *tert*-butylmagnesium chloride to **9** in the presence of 50 mol % copper bromide−dimethyl sulfide provided the product **10** in 57% yield. In practice, these additions were nearly titrations; Grignard reagent was added until a transient deep red coloration persisted, after which little or no starting material remained. Knochel organocopper−zinc reagents could also be utilized in this addition. Removal of the CBZ protecting group using catalytic transfer hydrogenolysis provided amine **11** in 58% yield, and sulfonylation of the amine with a variety of sulfonyl chlorides afforded the corresponding sulfonamides **12** in good yield.

We felt it imperative in this study to examine the effect on activity of the stereochemical configurations at C-3α and C-6. For this purpose, we initially resorted to preparative chiral HPLC separation of stereoisomeric mixtures obtained as described above. In most cases, these resolutions were found to be most efficient using substrates containing a side chain Cbz-amino group (e.g., compound **10**). Chiral HPLC was effective at separating both enantiomers and diastereomers; thus, compounds containing stereocenters at both C-3α and C-6 provided four components each, in roughly equivalent amounts. A single X-ray crystal structural determination of one diastereomeric intermediate was sufficient to correlate and assign all four stereoisomers, as relative stereochemical relationships among these, whether antipodal or diastereomeric, were unambiguously evident from examination of the associated NMR spectra. Efficient stereoselective syntheses of these compounds were also subsequently developed.[26]

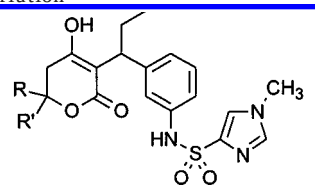
Results and Discussion

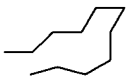
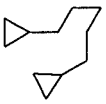
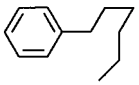
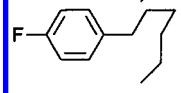
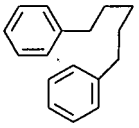
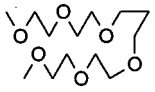
Table 1 lists a number of dihydropyrone protease inhibitors with varying functionality at C-6. For purposes of comparison, the C-3α side chain and sulfonamide moieties contained in the compounds shown have been held fixed as ethyl and 1-methylimidazole-4-yl, respectively, groups that have been proven effective in previous work with pyrone-based inhibitors.[27] Shown in the table are K_i values against HIV-1 protease and IC_{50} and IC_{90} values in a cell culture assay using HIV-1_{IIIB} infected H9 cells.

Within this series of compounds, K_i values were found to be relatively insensitive to the nature of the C-6 substituents. Inhibitory data obtained for analogues containing simple alkyl substituents (**13**−**16**) or phenyl-terminated alkyl substituents (**18**−**20**) are virtually indistinguishable. A limit to the tolerances of the S_1'−S_2' sites is illustrated by adamantyl derivative **17**, which shows a 10-fold decrease in activity relative to acyclic congeners. The oligoether derivative **21**, prepared with the goal of improving aqueous solubility, also displayed reduced affinity, in accordance with the known preference of the S_1' and S_2' subsites for lipophilic functionality. Antiviral IC_{90} values in cell culture for the more enzymatically potent members of this series were generally under 3 μM, with the most active compound (phenethyl propyl analogue **18**) having both IC_{50} and IC_{90} values in the submicromolar range.

Exploration of C-3α variation is shown in Table 2. Simple alkyl groups were uniformly effective at this position, with slight improvements in K_i values being seen with cyclopropyl. Effects on antiviral activity were marginal. Removing the C-3α side chain entirely led to decreased activity (**24**, **27**), indicating benefit derived from projection of this functionality into the protease S_1 subsite (vide infra).

Table 1. C-6 Variation

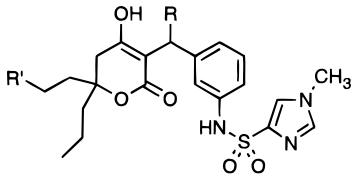


R,R'	Cpd	K_i (nM)	IC_{50} (μM)	IC_{90} (μM)
	**13**	1.8	0.8	2.0
	**14**	2.6	1	<3
	**15**	3.0	1.8	7.4
	**16**	1.7	1.8	2.9
	**17**	23	na	na
	**18**	1.2	0.5	0.9
	**19**	3.0	0.7	2.0
	**20**	1	0.64	2.0
	**21**	28	0% @ 3 μM	

Variation in the sulfonamide portion of the molecule is shown in Table 3. Data are shown for two templates, which differ at the C-3α substituent. Within the C-3α ethyl series, one aliphatic sulfonamide prepared (**28**) showed only weak activity, discouraging further exploration of this structural type. In contrast, the simple benzensulfonamide **29** showed a K_i value of 17 nM, with further improvements being realized by appendage of cyano, fluoro, or pyridyl moieties (**30**, **31**, **33**) or an additional pyridyl ring (**32**). Superior enzymatic and antiviral activities were observed with substituted pyridyl sulfonamides, with K_i values for compound **33** reaching into the low subnanomolar range.

Similar aromatic sulfonamides were also very effective within the C-3α *tert*-butyl template, as shown in the right half of Table 3. The inhibitor containing a cyanobenzenesulfonamide (**34**) showed a K_i value of 12 nM. Replacement of the benzene sulfonamide with a pyridyl sulfonamide in this molecule led to order of

Table 2. C-3α Variation



R	R'	Cpd	K_i (nM)	IC_{50} (μM)	IC_{90} (μM)
ethyl	Ph	**18**	1.2	0.5	0.9
*cyclo*propyl	Ph	**22**	0.71	<1	~1
tert-butyl	Ph	**23**	1.2	0.15	0.69
H	Ph	**24**	13	0% @ 1 μM	
ethyl	Me	**13**	1.8	0.8	2.0
*cyclo*propyl	Me	**25**	0.52	>1	3
tert-butyl	Me	**26**	0.87	0.6	1.0
H	Me	**27**	50%@1 μM	5% @ 3 μM	

magnitude increases in both enzymatic and antiviral activity, as exemplified by inhibitor **35**. The nitrile function in **35** could be replaced by nitro, trifluoromethyl, or amino (**36**, **37**, and **38**, respectively) without loss of enzymatic or antiviral activity, although potential toxic liabilities associated with the nitroaromatic and anilino moieties contained in **36** and **38** discouraged consideration of these compounds for further development.

To evaluate the effect of stereochemistry on activity, individual stereoisomers of some of the more active compounds were isolated via chiral HPLC. In general, the best chiral resolutions were obtained using the CBZ derivatives of the penultimate amines (corresponding to **4**, Scheme 1). Enzymatic and antiviral assay results for three sets of stereoisomers are shown in Table 4. In these cases, enzymatic K_i data were derived from inhibition assay using a tandem linked enzyme construct,[28] which prevents subunit dissociation at low enzyme concentrations and allows accurate K_i determination for very potent inhibitors. It was commonly observed that, within a stereochemical quartet, isomers having the *R* configuration at C-3α were significantly superior, enzymatically and antivirally, to those containing the *S* configuration at this center. The influence of the C-6 configuration was less dramatic, but in all cases a preference for the 6*R* isomer was observed. On the basis of these results, as well as pharmacokinetic and safety evaluations, compound **39b** (PNU-140690) was selected as a clinical development candidate.

An X-ray crystal structure of compound **18** complexed to an HIV-1 protease triple mutant (Q7K/L33I/L63I, utilized due to its greater stability in structural studies)[29] has previously been determined.[24] The complex showed nearly symmetrical hydrogen bonding between the inhibitor 4-hydroxy group and the catalytic aspartates and between the carbonyl oxygen and the flap region isoleucine 50/50′ NH groups. The C-6 phenethyl and propyl side chains projected into the S_1' and S_2' enzyme subsites, and the C-3α ethyl and aromatic groups occupied the S_1 and S_2 subsites, respectively, with the sulfonamide moiety extending into the S_3 subsite. Hydrogen-bonding interactions were also present between the sulfonamide linkage and active site residues.

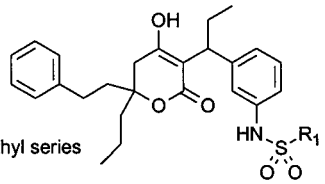
The X-ray crystal structure of **39b** complexed with the triple mutant protease construct was determined. Salient hydrogen-bonding interactions are illustrated in Figure 2, which shows the dihydropyrone ring to be centered in the enzyme active site. The lactone oxygen atom of the ring forms 3.1 Å hydrogen bonds with the NH groups of the flap region isoleucine residues (Ile50/50′), and the 4-hydroxy group is pseudosymmetrically bonded to the catalytic aspartate residues 25/25′, at distances of 2.8 and 2.5 Å. The contribution of the sulfonamide functionality to overall binding is clearly observed, with two hydrogen-bonding interactions formed with Asp30 and an additional interaction with an nearby bound water molecule.

Figure 3 more clearly illustrates the fit of the inhibitor upon the active site surface. In this view, the enzyme flaps have been peeled aside, with the observer peering down into the active site region. The C-6 phenethyl and propyl substituents of the inhibitor project into the S_2' and S_1' enzyme pockets, respectively. The C-3α ethyl and phenyl groups access the S_1 and S_2 subsites, respectively, with the trifluoromethylpyridyl sulfonamide moiety extending into the S_3 subsite.

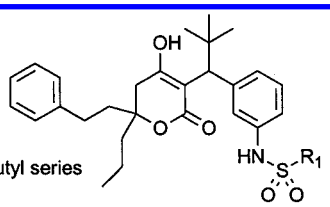
PNU-140690 also inhibited HIV-2 protease with high potency (K_i < 1 nM) and was also effective against V82A and V82F/I84V mutants (K_i 3.0 and 0.25 nM, respectively). Selectivity for HIV protease was demonstrated by high K_i values (2, 15, and 9 μM) against other representative aspartyl proteases (human pepsin and cathepsins D and E, respectively).[30] The effect of protein binding on antiviral activity was investigated in HIV-1_{IIIB} infected cells in the presence of 10% fetal bovine serum and 75% human plasma. In this medium, in which >99% of the inhibitor is protein bound, an IC_{90} value of 1.4 μM was observed. Studies with ritonavir resistant HIV-1 laboratory isolates[31] have shown them to be highly resistant to saquinavir, indivanir, and nelfinavir as well,[32] with 47- to >125-fold increases in IC_{90} values relative to the parent strains. These isolates, however, remained highly sensitive to PNU-140690, with only a 6-fold increase in IC_{90} values relative to the wild type.[32] In addition, a study of four ritonavir resistant clinical isolates (showing 32- to 67-fold increases in IC_{90} values) indicated only a 2−3-fold decrease in sensitivity to PNU-140690,[32] and evaluation of the inhibitor against a panel of 10 AZT resistant clinical isolates, representing a clinically relevant cross section of viral resistance, showed IC_{90} values ranging from 0.067 to 0.32 μM and averaging 0.16 μM.[33]

After 5 mg/kg IV dosing in rats, CL_{tot} was 0.17 ± 0.10 L/h/kg, V_{ss} was 0.51 ± 0.14 L/kg, and $t_{1/2}$ was 5.4 ± 0.3 h. Following 10 mg/kg oral dosing in rats, *F* was 30% (relative to 5 mg/kg IV dosing). Importantly, blood levels of PNU-140690 exceeded 1 μM, the in vitro IC_{90} value in the presence of 10% FBS and 75% human plasma, for 8−12 h. The single-dose safety, tolerance, and pharmacokinetics of PNU-140690 in a dosage range of 100 to 2000 mg were studied in normal healthy

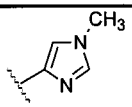
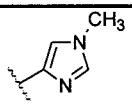
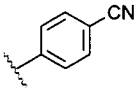
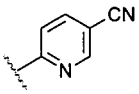
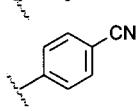
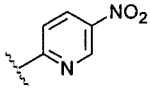
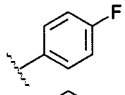
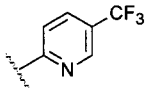
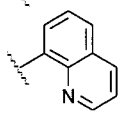
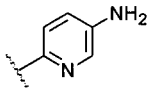
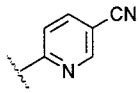
Table 3. Sulfonamide Variation



C-3α ethyl series

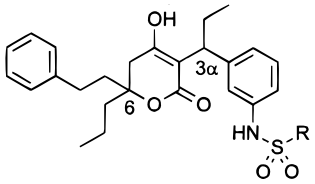


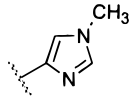
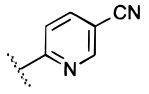
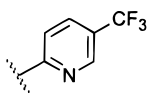
C-3α *t*-butyl series

R_1	Cpd	K_i (nM)	IC_{50} (μM)	IC_{90} (μM)	R_1	Cpd	K_i (nM)	IC_{50} (μM)	IC_{90} (μM)
	**18**	1.2	0.5	0.9		**23**	1.2	0.15	0.69
	**28**	>1 μM	na	na		**34**	12	1.2	3.0
	**29**	17	1.6	7.3		**35**	1.9	0.14	0.34
	**30**	8.2	1.1	4.2		**36**	2.3	2.3	>3
	**31**	6.1	1.2	4.3		**37**	4.3	0.53	0.99
	**32**	3.1	1.0	3.0		**38**	0.20[a]	0.23	0.74
	**33**	0.10[a]	0.13	0.47					

[a] K_i in tandem HIV assay.

Table 4. Stereochemical Variation



R	Cpd	(3α,6)	K_i (nM)[a]	IC_{50} (μM)	IC_{90} (μM)
	**18**				
	a	R,S	0.12	0.58	1
	b	R,R	0.06	0.13	0.56
	c	S,S	1.0	>>1	>>1
	d	S,R	0.3	>>1	>>1
	**33**				
	a	R,S	0.04	0.11	0.89
	b	R,R	0.007	0.04	0.26
	c	S,S	0.12	>>1	>>1
	d	S,R	0.10	0.49	1.0
	**39**				
	a	R,S	0.018	0.14	0.84
	b	R,R	0.008	0.03	0.10
	c	S,S	0.22	1.7	3.0
	d	S,R	0.032	0.41	1.8

[a] Tandem HIV assay.

volunteers.[34] Drug concentrations in excess of 1 μM, the predicted IC_{90} value based on in vitro virology and protein binding data, were observed for greater than 8 h after a single dose of 500 mg and above. Further clinical evaluation of PNU-140690 (Tipranavir) for treatment of HIV infection is continuing.

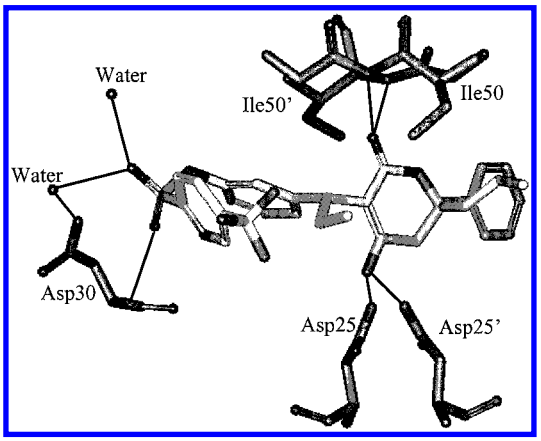


Figure 2. PNU-140690: Active site hydrogen-bonding interactions.

Conclusion

In summary, previous work identified the 5,6-dihydro-4-hydroxy-2-pyrone ring system as a promising template for small molecule HIV protease inhibitors. We undertook a systematic evaluation of the substitution patterns at three critical regions of the template with the goal of optimizing enzymatic binding, in vitro cell culture antiviral activity, and pharmacokinetic parameters essential for therapeutic efficacy. Structural variation was examined at the dihydropyrone 3α- and 6-positions

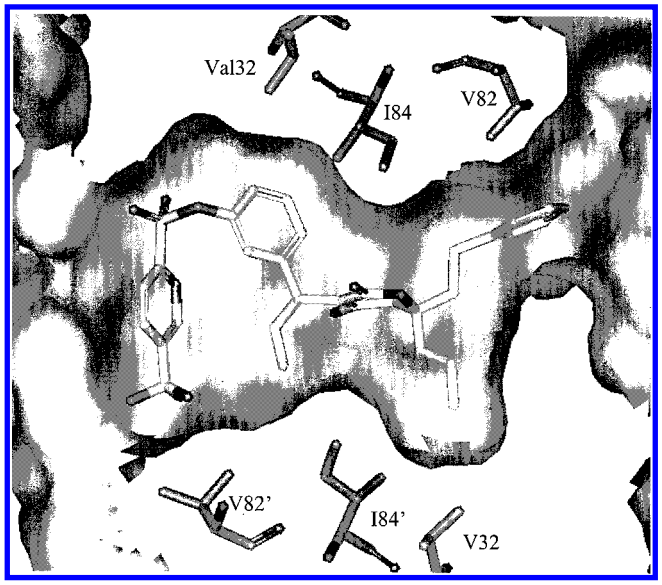


Figure 3. PNU-140690: Protease active site surface view.

as well as within the side chain sulfonamide moiety. The results of these studies led to the identification of PNU-140690 as a potent HIV protease inhibitor exhibiting low toxicity and acceptable drug delivery and distribution characteristics. PNU-140690 (Tipranavir) is currently undergoing clinical trials as a therapeutic agent for treatment of AIDS.

Experimental Section

Chemistry. Reagents were from commercial sources and used without further purification unless otherwise noted. Diethyl ether was Mallinckrodt anhydrous grade. Dichloromethane was stored over 4 Å molecular sieves. Tetrahydrofuran (THF) was distilled under argon from potassium benzophenone ketyl immediately prior to use. Solvents for chromatography were reagent grade. Flash chromatography was conducted using EM silica gel 60, 230−400 mesh. Thin layer chromatography (TLC) was conducted on precoated glass plates (EM silica gel 60 or Analtech silica gel GF, 0.25 mm).

^{1}H NMR spectra were obtained in the indicated solvent using a Bruker AM-300 spectrometer operating at 300 MHz and are reported as δ values relative to tetramethylsilane. Spectra of dihydropyrones were generally complex due to mixtures of tautomers, rotamers, and diastereomers. Infrared spectra were obtained on a Biorad FTS-25 FTIR spectrophotometer or by the Structural, Analytical, and Medicinal Chemistry department at Pharmacia & Upjohn. Mass spectra and combustion analyses were obtained by the Structural, Analytical, and Medicinal Chemistry department at PNU.

5,6-Dihydro-4-hydroxy-6-phenethyl-6-propyl-2*H*-pyran-2-one (1). To a cooled (0 °C), stirred slurry of 2.86 g (71 mmol) of sodium hydride dispersion (60% in oil) in 100 mL of THF under argon was added dropwise 7.3 mL (68 mmol) of methyl acetoacetate. The mixture was stirred for 10 min, and then 43 mL (69 mmol) of *n*-BuLi (1.6 M in hexanes) was added via cannula over about 20 min. After another 10 min, 10 g (57 mmol) of 1-phenyl-3-hexanone was added neat, and the mixture stirred at 0 °C for 1 h and then poured into saturated aqueous NH_4Cl. The aqueous phase was rendered acidic by addition of 6 N HCl and extracted with one portion of EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to an oil. This was stirred in 100 mL of MeOH, 250 mL of water, and 58 mL of 1 N NaOH for 1 h, after which the aqueous solution was extracted with ether to remove any remaining starting material. The aqueous phase was cooled in ice and acidified with 6 N HCl, and the precipitate extracted with 4 portions of CH_2Cl_2. The combined organic extract was dried ($MgSO_4$) and concentrated, and the residue crystallized from ether to afford 10.72 g (72%) of **1** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.48 (m, 2H), 1.72 (m, 2H), 1.98 (m, 2H), 2.73 (m, 4H), 3.43 (s, 2H), 7.15−7.32 (m, 5H); IR 1658, 1605, 1218 cm^{-1}. Anal. ($C_{16}H_{20}O_3$) C, H.

5,6-Dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-phenethyl-6-propyl-2*H*-pyran-2-one (3). A solution of anhydrous $AlCl_3$ was prepared by cautious addition of 35 mL of THF to 5.33 g (40 mmol) of $AlCl_3$ at −78 °C under argon followed by warming to room temperature, and this solution was added via cannula to a stirred, argon-covered solution of 5.21 g (20 mmol) of **1** and 3.02 g (20 mmol) of *m*-nitrobenzaldehyde in 70 mL of THF. The solution was stirred at room temperature under argon for 2 h, and then quenched by addition of 11.5 g of Na_2CO_3·10H_2O. Celite and $MgSO_4$ were added and the mixture was stirred vigorously for 5 min, then filtered through diatomaceous earth with ether rinses. Removal of solvent left 8.95 g of benzylidene intermediate **2** as a yellow oil. To this was added 1.23 g (6 mmol) of CuBr−Me_2S and 70 mL of THF, and the flask was filled with argon and surrounded by a cold water bath during the addition of 24 mL of Et_3Al (1.0 M in hexane). After 20 min the mixture was cooled to 0 °C and cautiously quenched with ice and then 6 N HCl. The mixture was extracted twice with ether and the organic extract dried ($MgSO_4$) and concentrated. Flash chromatography of the residue using 35−40% EtOAc in hexane provided 6.80 g (80%) of **3** as a foam: ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.88−0.97 (m, 6H), 1.3 (m, 2H), 1.7 (m, 2H), 1.8−2.2 (m, 3H), 2.22−2.28 (m, 1H), 2.55−2.64 (m, 4H), 4.2 (m, 1H), 7.05−7.28 (m, 5H), 7.37 (t, J = 7.9 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 8.0 (m, 1H), 8.28 (s, 1H); IR 2965, 1607, 1529, 1388, 1350 cm^{-1}; FAB-HRMS calcd for $C_{25}H_{29}NO_5$ + H_1 424.2124, found 424.2129. Anal. ($C_{25}H_{29}N_1O_5$) C, H, N.

5,6-Dihydro-4-hydroxy-3-[1-(3-aminophenyl)propyl]-6-phenethyl-6-propyl-2*H*-pyran-2-one (4). A mixture of 6.80 g (16 mmol) of **3** and 350 mg of 10% Pd/C in 80 mL of methanol was stirred vigorously under 1 atm H_2 for 2 h, then filtered through Celite. The filtrate was concentrated and the residue flash chromatographed using 10% EtOAc in CH_2Cl_2 to afford 5.83 g (92%) of amine **4** as a tan foam: ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.83−0.98 (m, 6H), 1.34 (m, 2H), 1.6−2.1 (m, 5H), 2.2 (m, 1H), 2.6 (m, 4H), 3.95 (m, 1H), 6.5 (m, 1H), 6.8 (m, 2H), 7.0−7.3 (m, 6H); IR 1606, 1385 cm^{-1}. Anal. ($C_{25}H_{31}N_1O_3$) C, H, N.

Chiral HPLC Resolution of CBZ Derivative of Amine 4. The CBZ derivative of amine **4** was resolved on a 5 × 50 cm Chiralcel OD column (Chiral Technologies, Inc.); the mobile phase was 15% ethanol in heptane with addition of 0.025% acetic acid v/v at 50 mL/min flow rate, monitored at 238 nm (retention times: 17.1, 18.4, 25.4, and 30.3 min for the four diastereomers), 2 g injection size.

3-(1-[3-Aminophenyl]methyl)-5,6-dihydro-4-hydroxy-6-phenethyl-6-propylpyran-2-one (6). To a flame-dried flask containing 800 mg (6.0 mmol) of $AlCl_3$ at −78 °C, under argon, was slowly added 7.0 mL of dry THF. The flask was warmed to room temperature with vigorous stirring, then cannulated into a solution of 450 mg (3.0 mmol) of *m*-nitrobenzaldehyde and 780 mg (3.0 mmol) of **1** in 7 mL of THF. After 2 h the reaction mixture was treated with 1.8 g of Na_2CO_3·10H_2O. After 5 min the suspension was diluted with 15 mL of dry diethyl ether and filtered through a pad of Celite with ether washes. The combined filtrates were concentrated under reduced pressure and the residue dissolved in 10 mL of dry methanol, and this solution cooled to 0 °C for the addition of 230 mg (3.7 mmol) of sodium cyanoborohydride. After 1 h the resulting mixture was carefully treated with water and partioned against diethyl ether. The aqueous phase was extracted with three additional portions of diethyl ether. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the residue using 60 to 80% ethyl acetate in hexane provided 650 mg (1.65 mmol) of the corresponding nitro compound as an off-white foam: TLC R_f 0.39 (75% ethyl acetate in hexane); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.85 (t, 3H, J = 7.2 Hz), 1.3 (m,

2H), 1.65 (m, 2H), 1.8−2.0 (m, 2H), 2.55 (m, 2H), 2.7 (m, 2H), 3.73 (s, 2H), 7.0 (m, 2H), 7.1−7.3 (m, 4H), 7.55 (m, 1H), 7.95 (m, 1H), 8.1 (s, 1H); EI-MS *m*/*z* (rel intensity) 395 (M^+, 6), 352 (17), 159 (30), 157 (24), 136 (18), 117 (23), 91 (100); EI-MS M^+ = 395 found for $C_{23}H_{25}NO_5$.

To a solution of 400 mg (1.0 mmol) of the above nitro compound in 5.0 mL of methanol was added 1.0 g (16 mmol) of ammonium formate followed by 100 mg of 10% palladium on carbon. The mixture was stirred for 2 h, then filtered through a pad of Celite with methanol washes. The filtrate was concentrated under reduced pressure and triturated with dichloromethane. The triturates were combined and concentrated to give 365 mg of crude **6** as a tan foam, which was used directly without further purification: TLC R_f 0.20 (25% ethyl acetate in dichloromethane).

5,6-Dihydro-4-hydroxy-6,6-dipropyl-2*H*-pyran-2-one (8). To a cooled (0 °C) stirred slurry of 2.86 g (71 mmol) of sodium hydride (60% in mineral oil) in 100 mL of dry THF under argon was added dropwise 7.3 mL (68 mmol) of methyl acetoacetate. The mixture was stirred for 15 min, and then 43 mL (69 mmol) of *n*-BuLi (1.6 M in hexanes) was added over about 20 min. The solution was stirred another 15 min, and then 7.9 mL (56 mmol) of 4-heptanone was added via cannula. After 1 h at 0 °C, the reaction mixture was partitioned between EtOAc and cold dil. HCl, and the aqueous phase extracted with one additional portion of EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude β-ketoester as a yellow oil. This was stirred in a mixture of 250 mL water, 100 mL of methanol, and 58 mL of 1 N NaOH for 1 h, then methanol was removed under reduced pressure, and the residue washed once with ether. The aqueous phase was cooled in ice and acidified with 6 N HCl, and the resulting precipitate was extracted into three portions of CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to an oil. Recrystallization from 80% ether−hexane provided 9.80 g (88%) of dihydropyrone **8** as a white crystalline solid: ^{1}H NMR (CD_3OD) δ 0.92 (t, 6H), 1.3 (m, 4H), 1.7 (m, 4H), 2.48 (s, 2H); FAB-HRMS calcd for $C_{11}H_{18}O_3 + H_1$ 199.1334, found 199.1350. Anal. ($C_{11}H_{18}O_3$) C, H.

3-[1-(3-Benzyloxycarbonylaminophenyl)-2,2-dimethylpropyl]-5,6-dihydro-4-hydroxy-6,6-dipropyl-2*H*-pyran-2-one (10). Into a stirred solution of 991 mg (5.0 mmol) of dihydropyrone **8** and 1.28 g (5.0 mmol) of 3-(benzyloxycarbonylamino)benzaldehyde in 20 mL of dry THF was cannulated a solution of 1.33 g (10 mmol) of anhydrous aluminum trichloride in 10 mL of dry THF. After 2 h, 2.9 g of sodium carbonate decahydrate was added, and the mixture was stirred vigorously for 5 min. Ether, Celite, and $MgSO_4$ were added, and the mixture was filtered through Celite with ether rinses. Removal of the solvent under reduced pressure provided the crude benzylidene intermediate. To this were added 514 mg (2.5 mmol) of CuBr−Me_2S and 20 mL of dry THF, and to this mixture under argon was added dropwise a 1 M solution of *tert*-butylmagnesium chloride in THF. An ice bath was used to moderate the temperature of the exothermic reaction. Each drop of Grignard reagent caused a transient deep red color to form; when the red color persisted (ca. 9 mL added), the reaction was cautiously quenched with dilute HCl. The mixture was extracted twice with EtOAc, and the combined organic phase washed with brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure, followed by flash chromatography of the residue using 35% EtOAc in hexane provided 1.41 g (57%) of **10** as a yellow foam: ^{1}H NMR ($CDCl_3$) δ 0.7−1.9 (m), 1.11 (s), 2.2−2.8 (m), 5.17 (s), 5.2 (m), 6.9−7.5 (m); EI-MS *m*/*z* 493.

3-[1-(3-Aminophenyl)-2,2-dimethylpropyl]-5,6-dihydro-4-hydroxy-6,6-dipropyl-2*H*-pyran-2-one (11). To a solution of 1.15 g (2.33 mmol) of CBZ compound **10** in 10 mL of methanol under argon was added 1.55 g (24.6 mmol) of ammonium formate and 150 mg of 10% palladium on carbon. The black slurry was stirred for 2 h, then filtered through a pad of Celite with methanol washings. The combined filtrates were concentrated, and the residue was partioned between water and CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), and finally concentrated under reduced pressure. The residue was flash chromatographed eluting with 10% EtOAc in CH_2Cl_2 to afford 820 mg (2.28 mmol) of amine **11** as an off-white foam: ^{1}H NMR ($CDCl_3$) δ 7.0−6.4 (m, 4H), 4.05 (s, 1H), 2.5−2.3 (m, 2H), 1.8−0.7 (m, 8H), 1.0 (s, 9H), 0.82 (t, 6H); EI-MS M^+ = 359 found for $C_{22}H_{33}N_1O_3$.

Representative Procedure for Sulfonylation: *N*-[3-{1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2*H*-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (26). To a cold (0 °C), stirred solution of 54 mg (0.15 mmol) of amine **11** and 24 μL (0.30 mmol) of pyridine in 1 mL of CH_2Cl_2 was added 27 mg (0.15 mmol) of 1-methylimidazole-4-sulfonyl chloride. The solution instantly turned bright orange-red. After 3−18 h, the reaction mixture was flash chromatographed using 3−5% MeOH in CH_2Cl_2 to afford 52.8 mg (69%) of sulfonamide **26** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.8−1.0 (m, 6H), 0.96 (s, 9H), 1.2−1.4 (m, 5H), 1.4−1.8 (m, 4H), 2.5 (m, 1H), 3.6−3.8 (m, 4H), 6.9−7.5 (m, 6H); EI-HRMS calcd for $C_{26}H_{37}N_3O_5S$ 503.2454, found 503.2422.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2*H*-pyran-3-yl)propyl]phenyl]-1-methyl-1*H*-imidazolesulfonamide (13):** ^{1}H NMR (CD_3OD) δ 0.88 (m, 9H), 1.32 (m, 4H), 1.64 (m, 4H), 1.93 (m, 1H), 2.16 (m, 1H), 2.56 (s, 2H), 3.68 (s, 3H), 3.91 (m, 1H), 6.87 (m, 1H), 7.03 (m, 2H), 7.14 (s, 1H), 7.53 (s, 1H), 7.64 (s, 1H); HRMS calcd for $C_{24}H_{33}N_3O_5S_1 + H_1$ 476.2219, found 476.2223. Anal. Calcd for $C_{24}H_{33}N_3O_5S_1$: C, 60.61; H, 6.99; N, 8.83. Anal. Found for $C_{24}H_{33}N_3O_5S_1 \cdot 0.4H_2O$: C, 59.64; H, 7.04; N, 8.48.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipentyl-2*H*-pyran-3-yl)propyl]phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (14):** ^{1}H NMR (CD_3OD) δ 0.87 (m, 9H), 1.25 (m, 12H), 1.55−1.68 (m, 4H), 1.92 (m, 1H), 2.13 (m, 1H), 2.57 (s, 2H), 3.66 (s, 3H), 3.93 (dd, 1H, J = 9.7, 6.6 Hz), 6.86 (m, 1H), 7.03 (m, 2H), 7.16 (s, 1H), 7.55 (s, 1H), 7.63 (s, 1H); HRMS calcd for $C_{28}H_{41}N_3O_5S_1 + H_1$ 532.2845, found 541.3951. Anal. Calcd for $C_{28}H_{41}N_3O_5S_1$: C, 63.25; H, 7.77; N, 7.90. Anal. found for $C_{28}H_{41}N_3O_5S_1 \cdot 0.3H_2O$: C, 62.58; H, 7.47; N, 7.84.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-6,6-diisobutyl-2-oxo-2*H*-pyran-3-yl)propyl]phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (15):** ^{1}H NMR (CD_3OD) δ 0.82−0.94 (m, 15H), 1.52−1.83 (m, 6H), 1.86−2.03 (m, 1H), 2.06−2.22 (m, 1H), 2.60 (s, 2H), 3.68 (s, 3H), 3.92 (m, 1H), 6.87 (m, 1H), 7.03 (m, 2H), 7.16 (s, 1H), 7.56 (s, 1H), 7.65 (s, 1H); HRMS calcd for $C_{26}H_{37}N_3O_5S_1 + H_1$ 504.2532, found 504.2531. Anal. ($C_{26}H_{37}N_3O_5S_1$) C, H, N.

***N*-(3-[1-(6,6-Di-(2-cyclopropylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2*H*-pyran-3-yl)propyl]phenyl)-1-methyl-1*H*-imidazole-4-sulfonamide (16):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.0 (m, 4H), 0.43 (m, 4H), 0.65 (m, 2H), 0.92 (t, 7.3 Hz, 3H), 1.1−1.4 (m, 6H), 1.7−2.1 (m, 5H), 2.1−2.2 (m, 1H), 3.71 (s, 3H), 3.95 (m, 1H), 6.8−7.0 (m, 1H), 7.1−7.2 (m, 3H), 7.3−7.4 (m, 1H), 7.4−7.6 (m, 1H); FAB-HRMS calcd for $C_{28}H_{38}N_3O_5S$ 528.2532, found 528.2537.

***N*-[3-[1-(3,6-Dihydro-4-hydroxy-6-oxospiro[2*H*-pyran-2,2′-tricyclo[3.3.1.1^{3,7}]decan]-5-yl)propyl]phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (17):** ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J = 6.7 Hz), 7.0−7.1 (m, 2H), 6.88 (t, 2H, J = 8.0 Hz), 3.77 (m, 1H), 3.64 (s, 3H), 2.80 (d, 2H, J = 6.0 Hz), 1.4−2.2 (m, 16H), 0.76 (t, 3H, J = 8.0 Hz); EI-HRMS calcd for $C_{27}H_{33}N_3O_5S$ 511.2141, found, 511.2126.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl]phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (18):** ^{1}H NMR ($CDCl_3$) δ 0.75−0.96 (m, 6H), 1.17−1.43 (m, 2H), 1.45−2.11 (m, 6H), 2.43−2.68 (m, 2H), 3.24 (s, 2H), 3.64 (s, 3H), 3.94 (m, 1H), 6.72−7.51 (m, 13H); HRMS calcd for $C_{29}H_{35}N_3O_5S_1 + H_1$ 538.2376, found 538.2383.

***N*-[3-{1(*R*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*S*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (18a):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.79−1.0 (m, 6H), 1.2−2.4 (m, 10H), 2.5−2.7 (m, 2H), 3.2−3.7 (m, 4H), 6.8−7.6 (m, 11H); EI-HRMS calcd for $C_{29}H_{35}N_3O_5S$ 537.2297, found 537.2317.

***N*-[3-{1(*R*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (18b):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.6−1.0 (m, 6H), 1.2−1.5 (m, 3H), 1.5−2.4 (m, 7H), 2.5−2.7 (m, 2H), 3.3−3.7 (m, 4H), 6.8−7.6 (m, 11H); EI-HRMS calcd for $C_{29}H_{35}N_3O_5S$ 537.2297, found 537.2275.

***N*-[3-{1(*S*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*S*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (18c):** ^{1}H NMR spectrum identical to compound **18b** and different from **18a**, particularly in the δ 2.6, 3.3−3.4, 6.8, and 7.5 regions; EI-HRMS calcd for $C_{29}H_{35}N_3O_5S$ 537.2297, found 537.2329.

***N*-[3-{1(*S*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (18d):** ^{1}H NMR spectrum identical to compound **18a**; EI-HRMS calcd for $C_{29}H_{35}N_3O_5S$ 537.2297, found 537.2312.

***N*-[3-{1-(5,6-Dihydro-4-hydroxy-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (19):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.8 (m, 6H), 1.3 (m, 2H), 1.6−2.2 (m, 5H), 2.5 (m, 3H), 3.56 (s, 2H), 3.61 (s, 3H), 3.9 (m, 1H), 6.8−7.4 (m, 10H); EI-HRMS calcd for $C_{29}H_{34}N_3O_5FS$ 555.2203, found 555.2192.

***N*-[3-{1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-diphenethyl-2*H*-pyran-3-yl)propyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (20):** ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.9−2.2 (m, 5H), 2.6−2.7 (m, 5H), 3.6 (s, 2H), 3.8 (s, 3H), 3.97 (dd, J = 9.3, J = 6.9 Hz, 1H), 6.9−7.5 (m, 16H); FAB-HRMS calcd for $C_{34}H_{38}N_3O_5S$ 600.2532, found 600.2521.

***N*-[3-{1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-bis((2-(2-methoxyethoxy)ethoxy)methyl)-2*H*-pyran-3-yl)propyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (21):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.88 (t, J = 7.3 Hz, 3H), 2.0 (m, 2H), 3.3−4.0 (m), 6.9 (m), 7.1 (m), 7.4 (m), 7.6 (m); FAB-HRMS calcd for $C_{30}H_{46}N_3O_{11}S_1$ 656.2853, found: 656.2845.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)cyclopropylmethyl]phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (22):** ^{1}H NMR (CD_3OD) δ 0.13 (m, 2H), 0.42 (m, 1H), 0.67 (m, 1H), 0.95 (m, 3H), 1.44 (m, 2H), 1.68−2.13 (m, 5H), 2.56 (m, 4H), 3.17 (m, 1H), 3.65 (2s, 3H), 6.91 (m, 1H), 7.01−7.33 (m, 8H), 7.52 (m, 1H), 7.63 (m, 1H); HRMS calcd for $C_{30}H_{35}N_3O_5S_1$ + H_1 550.2376, found 550.2370.

***N*-[3-{1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (23):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.9−1.0 (m, 3H), 0.97 (s, 9H), 1.2−1.4 (m, 2H), 1.6−2.1 (m, 4H), 2.4−2.7 (m, 4H), 3.6 (2s, 3H), 4.08 (s, 1H), 6.9−7.5 (m, 11H); FAB-HRMS calcd for $C_{31}H_{39}N_3O_5S$ + H_1 566.2689, found 566.2684. Anal. Calcd for $C_{31}H_{39}N_3O_5S_1$: C, 65.82; H, 6.95; N, 7.43; S, 5.67. Found: C, 63.94; H, 6.78; N, 7.80.

***N*-(3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)methyl]phenyl)-1-methyl-1*H*-imidazole-4-sulfonamide (24):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.93 (t, 3H), 1.35 (m, 2H), 1.75 (m, 2H), 1.9 (m, 1H), 2.0 (m, 1H), 2.6 (m, 4H), 3.57 (m, 2H), 3.63 (s, 3H), 6.9−7.5 (m, 11H); FAB-HRMS calcd for $C_{27}H_{32}N_3O_5S$ 510.2063, found 510.2052.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2*H*-pyran-3-yl)cyclopropylmethyl]phenyl]-1-methyl-1*H*-imidazolesulfonamide (25):** ^{1}H NMR (CD_3OD) δ 0.12 (m, 2H), 0.43 (m, 1H), 0.68 (m, 1H), 0.90−0.97 (m, 6H), 1.36 (m, 4H), 1.71 (m, 4H), 2.60 (m, 2H), 3.12 (d, 1H, J = 10.6 Hz), 3.67 (s, 3H), 6.88 (m, 1H), 7.06 (m, 2H), 7.24 (s, 1H), 7.51 (s, 1H), 7.65 (s, 1H); HRMS calcd for $C_{25}H_{33}N_3O_5S_1$ + H_1 488.2219, found 488.2225. Anal. ($C_{25}H_{33}N_3O_5S_1$) C, H, N.

***N*-(3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2*H*-pyran-3-yl)methyl]phenyl)-1-methyl-1*H*-imidazole-4-sulfonamide (27):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.89 (t, 6H, J = 7.2 Hz), 1.35 (m, 4H), 1.65 (m, 4H), 2.54 (s, 2H), 3.55 (s, 2H), 3.66 (s, 3H), 6.8−7.5 (m, 6H); EI-HRMS calcd for $C_{22}H_{29}N_3O_5S$ 447.1828, found 447.1839.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl]phenyl]benzenesulfonamide (29):** ^{1}H NMR ($CDCl_3$) δ 0.82−0.92 (m, 6H), 1.23−1.41 (m, 1H), 1.50−2.17 (m, 6H), 2.49−2.66 (m, 3H), 3.93 (m, 1H), 6.86−7.32 (m, 10H), 7.33−7.51 (m, 2H), 7.69−7.82 (m, 2H).

4-Cyano-*N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl]phenyl]benzenesulfonamide (30): ^{1}H NMR ($CDCl_3$) δ 0.6−1.1 (m, 6H), 1.2−2.2 (m, 9H), 2.4−2.7 (m, 3H), 3.86−4.01 (m, 1H), 6.89−7.45 (m, 9H), 7.66−7.92 (m, 4H); HRMS calcd for $C_{32}H_{34}N_2O_5S_1$ + H_1 559.2243, found 559.2267.

4-Fluoro-*N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl]phenyl]benzenesulfonamide (31): ^{1}H NMR (CD_3OD) δ 0.75−0.96 (m, 6H), 1.31−1.48 (m, 2H), 1.57−2.01 (m, 5H), 2.09−2.22 (m, 1H), 2.48−2.71 (m, 4H), 3.92 (m, 1H), 6.86−7.24 (m, 11H), 7.72 (m, 2H); HRMS calcd for $C_{31}H_{34}F_1N_1O_5S_1$ + H_1 552.2220, found 552.2230.

***N*-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl]phenyl]-8-quinolinesulfonamide (32):** ^{1}H NMR ($CDCl_3$) δ 0.66 (t, 3H, J = 6.9 Hz), 0.90 (t, 3H, J = 6.7 Hz), 1.17−1.44 (m, 3H), 1.58−2.03 (m, 6H), 2.38−2.64 (m, 3H), 3.77 (m, 1H), 6.68−7.27 (m, 9H), 7.35−7.69 (m, 2H), 8.02 (m, 1H), 8.26 (m, 2H), 9.14 (m, 1H); HRMS calcd for $C_{34}H_{36}N_2O_5S_1$ + H_1 585.2423, found 585.2402.

***N*-[3-{1(*R,S*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R,S*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (33):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.7−0.9, 1.2−2.7, 3.3−3.6 (m), 6.8−7.3 (m), 7.8−8.2 (m), 8.8 (m); FAB-HRMS calcd for $C_{31}H_{34}N_3O_5S$ 560.2219, found 560.2231.

***N*-[3-{1(*R*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*S*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (33a):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.7−1.0 (m, 6H), 1.2−1.4 (m, 3H), 1.4−2.3 (m, 7H), 2.4−2.7 (m, 2H), 3.3−3.6 (m, 1H), 6.8−7.3 (m, 10H), 7.8−8.2 (m, 2H), 8.8−9.0 (m, 1H); FAB-HRMS calcd for $C_{31}H_{34}N_3O_5S$ 560.2219, found 560.2210.

***N*-[3-{1(*R*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (33b):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.6−1.1 (m, 6H), 1.2−2.4 (m, 10H), 2.5−2.7 (m, 2H), 3.3−3.6 (m, 1H), 6.9−7.3 (m, 10H), 7.8−8.2 (m, 2H), 8.8−9.0 (m, 1H); IR (mull) 3087, 3063, 3026, 1641, 1606, 1591, 1497, 1340, 1290, 1255, 1175, 1108, 701, 644, 632 cm^{-1}; UV λ_{max} 224 (20600, 95% ethanol); FAB-HRMS calcd for $C_{31}H_{34}N_3O_5S$ 560.2219, found 560.2215. Anal. ($C_{31}H_{33}N_3O_5S_1$) C, H, N.

***N*-[3-{1(*S*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*S*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (33c):** ^{1}H NMR identical to compound **33b** and different from **33a**, particularly in the δ 2.5, 3.4, and 7.0 regions; FAB-HRMS calcd for $C_{31}H_{34}N_3O_5S$ 560.2219, found 560.2210.

***N*-[3-{1(*S*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (33d):** ^{1}H NMR identical to that of compound **33a**; FAB-HRMS calcd for $C_{31}H_{34}N_3O_5S$ 560.2219, found 560.2210.

***N*-(3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)-2,2-dimethylpropyl]phenyl)-4-cyanobenzenesulfonamide (34):** ^{1}H NMR δ 0.8−1.0 (m, 4H), 1.06 (s, 9H), 1.3−2.8 (m, 8H), 4.2 (m, 1H), 6.2 (bs, 1H), 7.0−7.3 (m, 10H), 7.68 (d, 2H, J = 7.0 Hz), 7.83 (d, 2H, J = 7.0 Hz); EI-HRMS calcd for $C_{34}H_{38}N_2O_5S$ 586.2501, found 586.2516.

***N*-(3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)-2,2-dimethylpropyl]phenyl)-5-cyano-2-pyridinesulfonamide (35):** ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.89 (s, 1H), 7.96 (m, 2H), 7.39 (s, 1H), 7.3−6.8 (m, 8H), 4.05 (s, 1H), 2.7−2.4 (m, 4H), 2.0−0.8 (m, 9H), 0.92 (s, 9H); FAB-HRMS calcd for $C_{33}H_{38}N_3O_5S$ 588.2532, found 588.2526.

***N*-(3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)-2,2-dimethylpropyl]phenyl)-5-nitro-2-pyridinesulfonamide (36):** ^{1}H NMR δ 9.41 (m, 1H), 8.49 (m, 1H), 8.0 (d, 1H), 7.40 (s, 1H), 7.3−6.8 (m, 8H), 4.04 (s, 1H), 2.6−2.4 (m, 4H), 1.9−0.8 (m, 9H), 0.91 (s, 9H); FAB-HRMS calcd for $C_{32}H_{38}N_3O_7S$ 608.2430, found 608.2412.

***N*-(3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)-2,2-dimethylpropyl]phenyl)-5-trifluoromethyl-2-pyridinesulfonamide (37):** ^{1}H NMR (CD_3OD) δ 0.73 (m, 12H), 1.28−1.08 (m, 4H), 1.68−1.40 (m, 2H), 2.5−2.25 (m, 4H), 3.88 (s, 1H), 7.09−6.70 (m, 8H), 7.19 (m, 1H), 7.87−7.7 (m, 1H), 8.07−7.95 (m, 1H), 8.78 (m, 1H); FAB-HRMS calcd for $C_{33}H_{37}N_2O_5F_3S$ 540.1906, found 540.1938.

***N*-(3-[1-(5,6-dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl)-2,2-dimethylpropyl]phenyl)-5-amino-2-pyridinesulfonamide (38):** ^{1}H NMR δ 7.87 (m, 1H), 7.44 (d, 1H), 7.27 (s, 1H), 7.2−6.7 (m, 8H), 3.99 (s, 1H), 2.6−2.4 (m, 4H), 1.9−0.8 (m, 9H), 0.88 (s, 9H); EI-MS M^+ = 577 found for $C_{32}H_{39}N_3O_5S$.

***N*-[3-{1(*R*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*S*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-trifluoromethylpyridine-2-sulfonamide (39a):** ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H), 1.37 (m, 4H), 1.69 (m, 4H), 1.91 (m, 2H), 2.13 (m, 1H), 2.51 (m, 1H), 2.50 (d, J = 17.2 Hz, 1H), 2.69 (d, J = 17.2 Hz, 1H), 3.95 (dd, 1H), 6.88 (d, J = 7.0 Hz, 1H), 6.97 (m, 1H), 7.25−7.04 (m, 5H), 8.00 (d, J = 8.2 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.91 (s, 1H); FAB-MS *m*/*z* (rel intensity) 603 (MH^+, 99), 735 (18), 625 (12), 605 (11), 604 (34), 603 (99), 585 (28), 201 (16), 134 (14), 133 (35), 91 (38); EI-HRMS calcd for $C_{31}H_{33}F_3N_2O_5S_1$ 602.2062, found 602.2053. Anal. ($C_{31}H_{33}F_3N_2O_5S_1$) C, H, N, S.

***N*-[3-{1(*R*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-trifluoromethylpyridine-2-sulfonamide (39b, PNU-140690):** ^{1}H NMR (CD_3OD) δ 0.93−1.03 (m, 6H), 1.36−1.47 (m, 2H), 1.79−2.13 (m, 6H), 2.18−2.30 (m, 1H), 2.63−2.81 (m, 4H), 4.04 (m, 1H), 7.09−7.36 (m, 9H), 8.16 (d, J = 8.1 Hz, 1H), 8.33 (m, 1H), 9.08 (m, 1H); $[\alpha]_D$ +20° (ethanol); HRMS calcd for $C_{31}H_{33}N_2O_5F_3S_1$ + H_1 603.2140, found 603.2153. Anal. ($C_{31}H_{33}N_2O_5F_3S_1$) C, H, N, S.

***N*-[3-{1(*S*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*S*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-trifluoromethylpyridine-2-sulfonamide (39c):** mp 93−95 °C; ^{1}H NMR (CD_3OD) δ 8.94 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.24−6.93 (m, 10H), 3.92 (dd, J = 7.0, 9.3 Hz, 1H), 2.68−2.51 (m, 4H), 2.22−2.05 (m, 1H), 1.98−1.64 (m, 5H), 1.36−1.28 (m, 2H), 0.90−0.80 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.5, 165.5, 160.1, 146.7, 146.2, 141.4, 136.3, 135.6, 128.8, 128.4, 128.1, 127.8, 125.6, 124.7, 122.7, 121.1, 118.8, 104.7, 80.4, 42.2, 39.4, 39.1, 36.0, 31.4, 29.5, 24.4, 16.5, 13.3, 11.9; $[\alpha]_D$ (MeOH, *c* 0.80) −21°; HRMS calcd for $C_{31}H_{33}N_2O_5F_3S_1$ + H_1 603.2140, found 603.2149. Anal. ($C_{31}H_{33}N_2O_5SF_3$) C, H, N.

***N*-[3-{1(*S*)-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R*)-phenethyl-6-propyl-2*H*-pyran-3-yl)propyl}phenyl]-5-trifluoromethylpyridine-2-sulfonamide (39d):** mp 156−159 °C; ^{1}H NMR (CD_3OD) δ 8.90 (s, 1H), 8.16 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.26 (s, 1H), 7.20−6.97 (m, 7H), 6.88 (d, J = 6.9 Hz, 2H), 3.95 (dd, J = 6.9, 9.2 Hz, 1H), 2.69−2.40 (m, 4H), 2.20−2.10 (m, 1H), 1.96−1.82 (m, 2H), 1.79−1.61 (m, 3H), 1.40−1.28 (m, 2H), 0.94−0.80 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.2, 165.5, 160.1, 146.6, 146.0, 141.4, 136.3, 135.6, 128.8, 128.4, 128.1, 127.8, 125.5, 124.8, 122.8, 121.0, 118.8, 104.8, 80.4, 41.8, 39.4, 39.0, 36.0, 31.4, 29.4, 24.2, 16.5, 13.3, 11.8; $[\alpha]_D$ (MeOH, *c* 1.5) −31°; HRMS calcd for $C_{31}H_{33}N_2O_5F_3S_1$ + H_1 603.2140, found 603.2154. Anal. ($C_{31}H_{33}N_2O_5SF_3$) C, H, N.

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