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Nonpeptidic HIV Protease Inhibitors Possessing Excellent Antiviral Activities and Therapeutic Indices. PD 178390: A Lead HIV Protease Inhibitor

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Abstract—With the insight generated by the availability of X-ray crystal structures of various 5,6-dihydropyran-2-ones bound to HIV PR, inhibitors possessing various alkyl groups at the 6-position of 5,6-dihydropyran-2-one ring were synthesized. The inhibitors possessing a 6-alkyl group exhibited superior antiviral activities when compared to 6-phenyl analogues. Antiviral efficacies were further improved upon introduction of a polar group (hydroxyl or amino) on the 4-position of the phenethyl moiety as well as the polar group (hydroxymethyl) on the 3-(*tert*-butyl-5-methyl-phenylthio) moiety. The polar substitution is also advantageous for decreasing toxicity, providing inhibitors with higher therapeutic indices. The best inhibitor among this series, (*S*)-6-[2-(4-amino-phenyl)-ethyl]-(3-(2-*tert*-butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one (34*S*), exhibited an EC_{50} of 200 nM with a therapeutic index of >1000. More importantly, these non-peptidic inhibitors, 16*S* and 34*S*, appear to offer little cross-resistance to the currently marketed peptidomimetic PR inhibitors. The selected inhibitors tested in vitro against mutant HIV PR showed a very small increase in binding affinities relative to wild-type HIV PR. C_{max} and absolute bioavailability of 34*S* were higher and half-life and time above EC_{95} were longer compared to 16*S*. Thus 34*S*, also known as PD 178390, which displays good antiviral efficacy, promising pharmacokinetic characteristics and favorable activity against mutant enzymes and CYP3A4, has been chosen for further preclinical evaluation.

Key words: HIV protease inhibitors; nonpeptidic HIV protease inhibitors; aspartic protease inhibitors; antivirals; anti-HIV agents.
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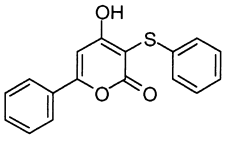
Introduction

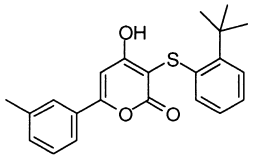
Reverse transcriptase (RT) and protease (PR) inhibitors are the current antiretroviral therapy choices for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.[1] These two targets play a crucial role in viral replication. The highly promising results of recent clinical trials with protease inhibitors in combination with RT inhibitors provide hope that antiretroviral therapy may succeed in significantly delaying the onset of progression to AIDS.[2] Each of the currently marketed protease inhibitors[3,4] can cause adverse effects and interact with other common medications.[5,6] Clinical data obtained with these drugs as monotherapy not only showed alarming resistance to HIV PR inhibitors but also clinical isolates exhibited phenotypical cross-resistance to the known marketed drugs.[7–9] Peptide derived HIV PR inhibitors often have low bioavailability, poor pharmacokinetics and several stereocenters.[10] However, nonpeptidic HIV-1 PR inhibitors that have been identified so far are still complex in structure and/or possess low antiviral activities[11,12] with the exception of DuPont–Merck's cyclic ureas and Pharmacia-Upjohn's pyran-2-ones.[13,14] Thus, research towards identifying simple, potent, low molecular weight HIV-1 PR inhibitors not cross-resistant with existing agents is still important.

Our efforts towards the discovery of potent nonpeptidic inhibitors began with **I**, originating from a mass screening of our chemical collection.[15] Further SAR led to inhibitor **II**, possessing no chiral center but occupying only three inner pockets of the enzyme.[16] Introduction of a chiral center by quaternizing the 6-position of 4-hydroxy-pyran-2-one ring led to structure **III**, whose substituents occupy the inner four pockets of the enzyme.[17] X-ray crystal structures[11,12,17] of pyran-2-ones and 5,6-dihydropyran-2-ones (e.g. **II** and **III**) bound to HIV PR show that the enolic hydroxyl group forms hydrogen-bonding interactions with Asp25 and/or Asp125 residues of the enzyme. More interestingly, all these inhibitors displace water-301 (unique to HIV PR[18]) with the lactone moiety. These inhibitors are primarily optimized for enzymatic binding and indeed showed excellent binding affinity to HIV PR. Preliminary results concerning 6-alkyl-5,6-dihydropyran-2-ones were described in recent communications.[19,20] This paper will discuss in more detail the design, synthesis, structure–activity relationships (SAR), experimental details and pharmacokinetics of 6-alkyl-5,6-dihydropyran-2-one



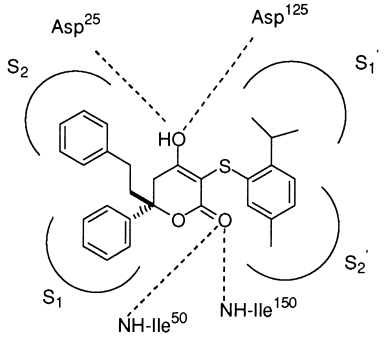
I

IC_{50}: 3.1 μM at pH 4.7



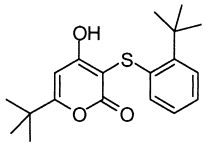
II

IC_{50}: 0.007 μM at pH 4.7



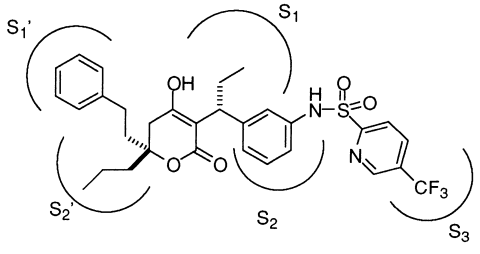
III

IC_{50}: 0.007 μM at pH 4.7



IV

IC_{50}: 0.043 μM at pH 4.7



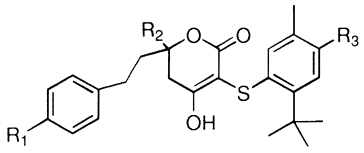
V (3αR, 6R) (PNU-140690)

series. The considerations used for the selection of PD 178390 as a lead compound for preclinical development will also be discussed.

Design

The X-ray crystal structure of **III** bound to HIV PR showed that 6-position substituents (the phenyl and phenethyl moieties) occupy the S_1 and S_2 pockets of the enzyme, respectively, complementing the key hydrogen bonding interactions from the core template as described above, while the 3-(2-isopropyl-5-methylphenythio) moiety occupies the S_2' and S_1' pockets of the enzyme. Even though analogues of **III** exhibited excellent inhibitory activities against HIV PR, they showed poor antiviral activities. We found that the 5,6-dihydropyran-2-one analogues with more lipophilic groups (for e.g. **III**) were binding to the human serum albumin in >98% (Table 1).[20] Moreover, some of these analogues

Table 1. Dihydropyran-2-one analogues[a] and their physical properties, HIV PR binding affinities and antiviral activities



Entry	R_1	R_2	R_3	Mp (°C)	Molecular formula[b]	Elements analyzed	IC_{50} (nM)[c]	EC_{50} (μM)	TC_{50} (μM)	Therapeutic index[e]
1	4-OH	Phenyl	H	199–201	$C_{30}H_{32}O_4S_1$•0.75 H_2O	CH	11	>69	69	1
2	4-OH	Methyl	H	130–131	$C_{25}H_{30}O_4S_1$•0.13 H_2O	CH	9.5	9.4	66	7
3	4-OH	*n*-Propyl	H	105–107	$C_{27}H_{34}O_4S_1$•0.3 H_2O	CH	19	7.8	66	9
4	4-OH	*n*-Butyl	H	59–61	$C_{28}H_{36}O_4S_1$	CH	30	>23	23	1
5	4-OH	*n*-Pentyl	H	73–75	$C_{29}H_{38}O_4S_1$	CH	18.4[d]	>27	27	1
6	4-OH	Isopropyl	H	88–90	$C_{27}H_{34}O_4S_1$•0.31 H_2O	CH	4.6	1.9	55	29
7	4-OH	Cyclopropyl	H	92–94	$C_{27}H_{32}O_4S_1$	CH	8.0	5.0	66	13
8	4-OH	Cyclopentyl	H	88–90	$C_{29}H_{36}O_4S_1$•0.1 H_2O	CH	7.2	5.9	54	9
9	4-OH	Cyclohexyl	H	82–87	$C_{30}H_{38}O_4S_1$	CH	33	4.1	45	11
10	4-OH	H	H	93–95	$C_{24}H_{28}O_4S_1$•0.36 H_2O	CH	338	ND[f]	ND	—
11	4-OH	Phenyl	CH_2OH	196–199(d)	$C_{31}H_{34}O_5S_1$•0.5 H_2O	CH	21.6	4.7	>100	>21
12	4-OH	Methyl	CH_2OH	143–145	$C_{26}H_{32}O_5S_1$•0.37 H_2O	CH	4.3	2.5	>100	>40
13	4-OH	*n*-Propyl	CH_2OH	127–129	$C_{28}H_{36}O_5S_1$•0.5 H_2O	CH	2.6	1.0	100	100
14	4-OH	*n*-Butyl	CH_2OH	128–130	$C_{29}H_{38}O_5S_1$	CH	4.1	0.9	63	70
15	4-OH	*n*-Pentyl	CH_2OH	100–102	$C_{30}H_{40}O_5S_1$	CH	5.9	0.6	32	53
16	4-OH	Isopropyl	CH_2OH	175–178	$C_{28}H_{36}O_5S_1$•0.5 H_2O	CH	3.6	0.6	>100	>182
17	4-OH	Isobutyl	CH_2OH	108–110	$C_{29}H_{38}O_5S_1$	CH	3.3	1.5	>100	>67
18	4-OH	Cyclopropyl	CH_2OH	152–154	$C_{28}H_{34}O_5S_1$	CH	1.0	1.6	>100	>63
19	4-OH	Cyclobutyl	CH_2OH	99–102	$C_{29}H_{36}O_5S_1$•0.57 H_2O	CH	2.2	0.8	>100	>125
20	4-OH	Cyclopentyl	CH_2OH	117–119	$C_{30}H_{38}O_5S_1$•0.2 H_2O	CH	3.1	0.6	>100	>167
21	4-OH	Cyclohexyl	CH_2OH	138–139	$C_{31}H_{40}O_5S_1$•0.84 H_2O	CH	2.5	0.5	75	156
22	4-OH	Methyl	OH	117–119	$C_{25}H_{30}O_5S_1$•014 H_2O	CH	6.5	>7	7	1
23	4-OH	Isopropyl	OH	117–118	$C_{27}H_{34}O_5S_1$	CH	0.03[d]	1.6	66	41
24	4-OH	Cyclohexyl	OH	100–103	$C_{30}H_{38}O_5S_1$•0.28 H_2O	CH	2.9	3.1	73	24
25	4-OH	Methyl	OCH_2CH_2OH	203–205	$C_{27}H_{34}O_6S_1$•0.75 H_2O	CH	6.8	3.4	>100	>29
26	4-OH	Methyl	OCH_2CH_2O CH_2O CH_3	88–90	$C_{29}H_{38}O_7S_1$	HPLC	20	4.6	68	15
27	4-OH	*n*-Propyl	OCH_2CH_2OH	92–94	$C_{29}H_{38}O_6S_1$•0.5 H_2O	CH	6	4.3	70	16
28	4-OH	*n*-Butyl	OCH_2CH_2OH	83–85	$C_{30}H_{40}O_6S_1$	HPLC	6.4	1.7	21	12
29	4-OH	*n*-Pentyl	OCH_2CH_2OH	99–100	$C_{31}H_{42}O_6S_1$•0.2 H_2O	CH	2.9	>9	9	1
30	4-OH	Isopropyl	OCH_2CH_2OH	90–92	$C_{29}H_{38}O_6S_1$•1.0 H_2O	CH	2.8	1.5	66	44
31	4-OH	Cyclopropyl	OCH_2CH_2OH	168–170	$C_{29}H_{36}O_6S_1$•0.8 H_2O	CH	3.8	1.6	>88.5	>55
32	4-OH	Cyclopentyl	OCH_2CH_2OH	113–115	$C_{31}H_{40}O_6S_1$	CH	2.8	1.2	78	65
33	4-NH_2	Phenyl	CH_2OH	218–221(d)	$C_{31}H_{35}O_4N_1S_1$•0.7 H_2O	CHN	3.1	3.7	94	25
34	4-NH_2	Isopropyl	CH_2OH	139–141	$C_{28}H_{37}O_4N_1S_1$•0.7 H_2O	CHN	2.7	0.5	>100	200
35	4-NH_2	Isobutyl	CH_2OH	168–170	$C_{29}H_{39}O_4N_1S_1$•0.6 H_2O	CHN	2.9	0.8	>100	>125
36	4-NH_2	Cyclohexyl	CH_2OH	214–216	$C_{31}H_{41}O_4N_1S_1$	CHN	3.2	1.4	80	57
37	H	Isopropyl	H	64–65	$C_{27}H_{34}O_3S_1$•0.17 H_2O	CH	1.1	15	59	4
38	H	Phenyl	CH_2OH	173–174	$C_{31}H_{34}O_4$•0.3 H_2O	CH	6.5	2.5	66	26
39	H	Isopropyl	CH_2OH	95–96	$C_{28}H_{36}O_4S_1$	CH	2.2	0.6	65	118
40	H	Isopropyl	OH	87–89	$C_{26}H_{34}O_4S_1$•0.7 H_2O	CH	1.1[d]	1.8	66	37
41	H	Phenyl	OCH_2CH_2OH	179–182	$C_{32}H_{36}O_5S_1$•0.2 H_2O	CH	6.8	>20	20	1
42	H	Isopropyl	OCH_2CH_2OH	86–88	$C_{29}H_{38}O_6S_1$•0.7 H_2O	CH	2.6	1.3	87	67

[a] All the compounds reported are racemic mixtures.
[b] Water content was not experimentally determined.
[c] Values are the average of at least two determinations measured at pH 6.2.
[d] K_i values measured at pH 6.2.
[e] Ratio of TC_{50} and EC_{50}.
[f] ND: not determined.

were also found to decrease their IC_{50} to HIV PR as well as their antiviral EC_{50} with the addition of human serum albumin. Therefore, it was reasoned that one probable explanation for the lack of antiviral activity with these compounds could be due to their affinity to bind to protein (antiviral assay uses 10% fetal calf serum). Hence, we focussed on the design and synthesis of compounds with reduced lipophilicity for enhancement in antiviral activity. Analysis of the X-ray structure of **III** bound to HIV PR suggested that aliphatic groups might be substituted in the place of the phenyl ring at the 6-position; we have already shown that aliphatic groups are also well tolerated in the 4-hydroxy pyran-2-one series (**IV**).[21] We speculated that our compounds of type **III** could maintain good selectivity against HIV PR due to the fact that significant binding is contributed by displacement of water-301.[16] Various polar functionalities were also introduced on the 3-(2-isopropyl-5-methylphenylthio) moiety to increase hydrophobicity and aqueous solubility compared to **III**.

Chemistry

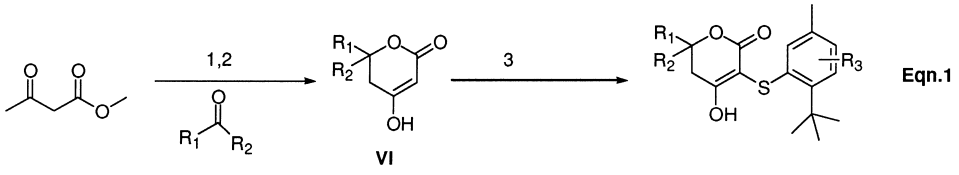
The compounds described in this paper were synthesized in a convergent fashion, by coupling the appropriately 6,6-disubstituted 5,6-dihydropyran-2-one (**VI**) with the corresponding thiotosylate in the presence of potassium carbonate in DMF (Scheme 1).[17] The 6,6-disubstituted 5,6-dihydropyran-2-ones were synthesized by the condensation of the dianion derived from methyl acetoacetate with the corresponding ketone, followed by cyclization in the presence of a base, usually sodium hydroxide (Scheme 1).

The ketones used above were synthesized either by the Claisen–Schmidt reaction (Scheme 2) or via Weinreb's methodology (Scheme 3). The Claisen–Schmidt reaction was performed by the condensation of the corresponding aldehydes with the appropriately substituted methyl ketones in the presence of alkali at room temperature.[22] The unsaturated ketones were converted to saturated ketones by hydrogenation of the double bond using Raney nickel or 5% $Pd/BaSO_4$ (Scheme 2). Alternatively, the ketones were synthesized by the reaction of the corresponding Weinreb amide with the appropriate Grignard reagent (Scheme 3).[23] Thiotosylates used in this study were synthesized as described previously.[19,20,24]

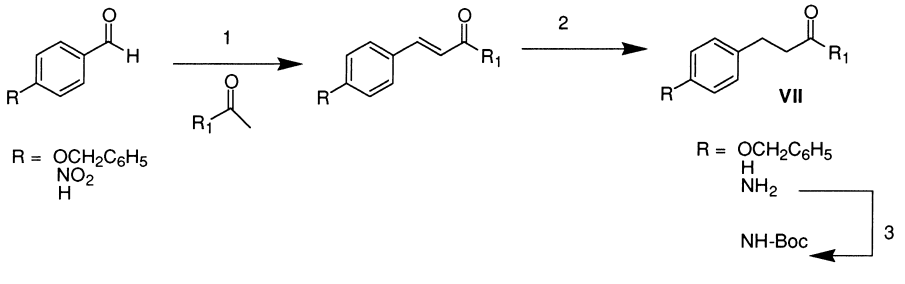
Enantiomerically pure 6,6-disubstituted-5,6-dihydropyran-2-ones were synthesized via resolution of the corresponding β-hydroxy acid (**VIII**) as shown in Scheme 4. The ketone, **VII**, was condensed with the anion derived from *tert*-butyl acetate (or benzyl acetate), and then saponified (or hydrogenolysis in the case of benzyl ester) to yield **VIII**. Compound **VIII** on treatment with 0.55 equivalent of (*S*)-α-methylbenzylamine gave the corresponding salt, which was crystallized from EtOAc/hexanes to furnish **VIII**-(*S*)-α-methylbenzylamine salt in >95% diastereomeric purity. Free acid **(*S*)-VIII** was liberated from the salt by treatment with 3 N hydrochloric acid. Compound **(*S*)-VIII** was elaborated to its β-keto ester, **(*S*)-IX**, via a two step protocol, viz., conversion of carboxylate with CDI to the corresponding imidazole followed by treatment with the magnesium salt of ethyl malonate. Compound **(*S*)-IX**, on treatment with sodium hydroxide, cyclized to 5,6-dihydropyran-2-one, **(*S*)-X**. Similarly **(*R*)-X** was prepared employing (*R*)-α-methylbenzylamine in the resolution procedure. **(*S*)-X** and **(*R*)-X**, on treatment with the corresponding thiotosylates as described in step 3, Scheme 1, afforded the 5,6-dihydropyran-2-one analogues (**16*S***, **16*R***, **34*S***, **34*R***, **39*S*** and **39*R***) of at least 95% optical purity.

Biological Assays

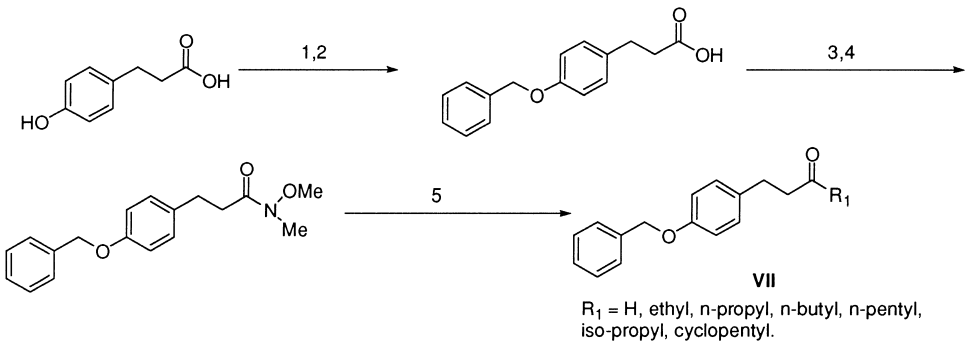
The compounds were tested for their inhibition of purified recombinant HIV PR using the peptide substrate



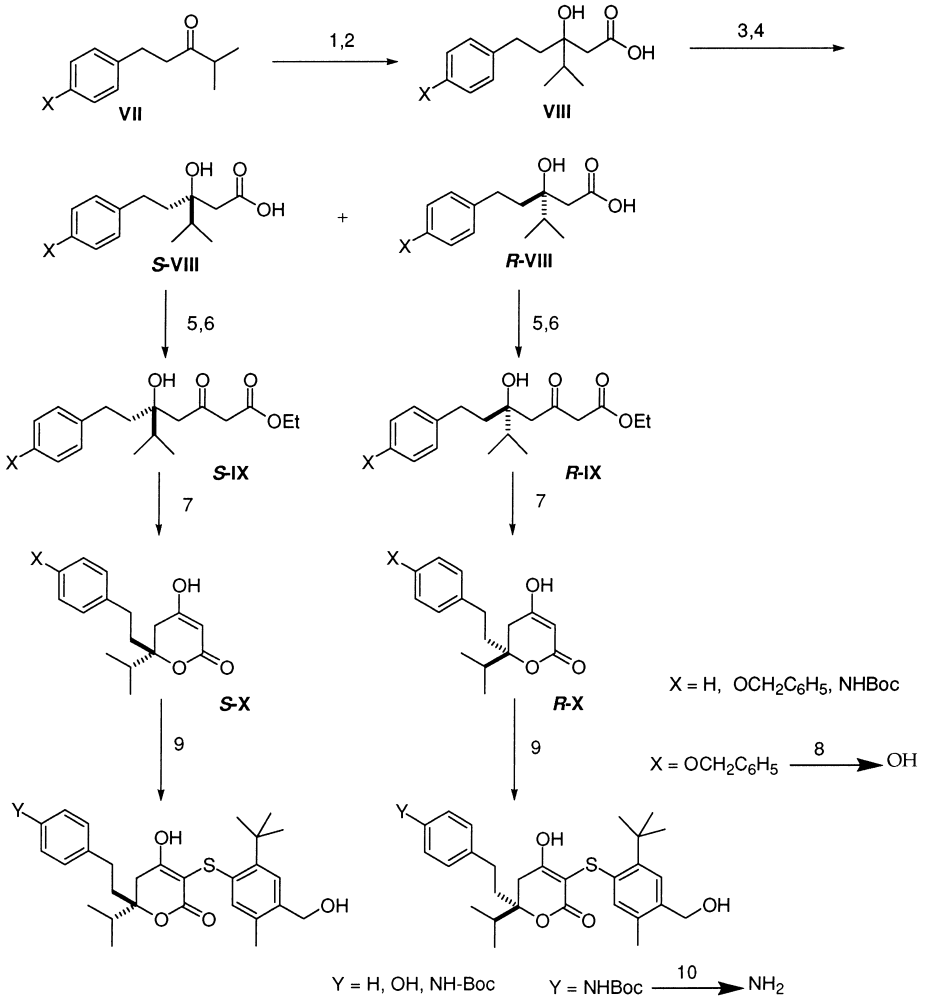
Scheme 1. Reaction conditions: 1. NaH, *n*-BuLi, THF, followed by ketone addition; 2. NaOH; 3. Corresponding thiotosylate, K_2CO_3, DMF.



Scheme 2. Reaction conditions: 1. $Ba(OH)_2$, EtOH; 2. Raney nickel or 5% $Pd/BaSO_4$ 20–50 psi, hydrogen; 3. di-*tert*-Butyl carbonate, CH_2Cl_2.



Scheme 3. Reaction conditions: 1. Benzyl bromide, K_2CO_3, acetone; 2. LiOH; 3. $SOCl_2$; 4. (OMe)NHMe·HCl, pyridine, CH_2Cl_2; 5. Corresponding Grignard reagent, THF.



Scheme 4. Reaction conditions: 1. LDA, *tert*-butyl acetate (or benzyl acetate), −78°C, addition of ketone; 2. LiOH (10% Pd/C, H_2 in the case of benzyl ester); 3. *S*-α-Methylbenzylamine, crystallizations; 4. 1 N HCl; 5. CDI; 6. Magnesium salt of ethyl malonate; 7. 0.1 N NaOH; 8. 20% Pd/C, H_2; 9. K_2CO_3, DMF, corresponding thiosulfonate; 10. NaOH, DMSO/H_2O.

His-Lys-Ala-Arg-Val-Leu-Phe(*p*-NO_2)-Glu-Ala-Nleu-Ser (Bachem Bioscience) at pH 6.2.[25] The enzyme cleaves the Leu-Phe(*p*-NO_2) bond of the substrate; the substrate and products were separated by reversed-phase HPLC, absorbance being measured at 220 nm.[26] All the compounds reported in this paper were also tested for anti-HIV activity at Southern Research Institute[27] in an in vitro cell culture assay with HIV-IIIB infected human lymphocyte derived CEM cells using the XTT cytopathic method. EC_{50} indicates the concentration of the drug which provides 50% protection against HIV. TC_{50} is the concentration of the drug which elicits cytotoxicity in 50% of uninfected cells. Therapeutic index is defined as TC_{50}/EC_{50}. The physical properties, enzyme binding affinity and antiviral activities of the compounds are shown in Tables 1 and 2.

Table 2. Chiral dihydropyran-2-one analogues[a] and their physical properties, HIV PR binding affinities and antiviral activities

Entry	Mp (°C)	Molecular formula[b]	Elements analyzed	Rotation in degrees (c, solvent)	K_i (nM)[c]	EC_{50} (μM)	EC_{90} (μM)	TC_{50} (μM)	Therapeutic index
16	176–178	$C_{28}H_{36}O_5S_1 \bullet 0.5\ H_2O$	CH	—	0.17	0.57	1	>100	>200
16*S*	205–207	$C_{28}H_{36}O_5S_1 \bullet 0.5\ H_2O$	CH	+35.6 (0.55, abs. EtOH)	0.09	0.46	1	>100	>200
16*R*	201–203	$C_{28}H_{36}O_5S_1 \bullet 0.5\ H_2O$	CH	−37.2 (0.66, abs. EtOH)	31	17	5.9	>100	>6
34	139–141	$C_{29}H_{37}N_1O_4S_1 \bullet 0.5\ H_2O$	CHN	—	0.43	0.5	1	>100	>200
34*S*	121	$C_{29}H_{37}N_1O_4S_1 \bullet 0.5\ H_2O$	CHN	+70.8 (1, MeOH)	0.11	0.2	1	210	1050
34*R*	128	$C_{28}H_{37}N_1O_4S_1$	CHN	ND	25	19.8	10.6	210	10.6
39	95–96	$C_{28}H_{36}O_4S_1$	CH	—	ND	0.6	1	65	118
39*S*	>108[d]	$C_{28}H_{36}O_4S_1$	CH	+61.58 (1, MeOH)	0.09	0.33	1	68	340
39*R*	>108[d]	$C_{28}H_{36}O_4S_1$	CH	−60.4 (1, MeOH)	160	4.37	ND[e]	69	16

[a] The ratio of enantiomers is at least >95:<5.
[b] Water content was not experimentally determined.
[c] K_i values measured at pH 6.2.
[d] Effervesces at that temperature.
[e] ND: not determined.

Results and Discussion

Dihydropyran-2-ones having various alkyl groups at the 6-position

Initial studies were focussed on probing the S_1 pocket of the enzyme by varying alkyl groups of different steric requirements at the 6-position of the dihydropyran-2-one ring. In all these dihydropyran-2-one analogues, the 4-hydroxyphenethyl group was kept constant at the 6-position of the dihydropyran-2-one template. This substituent had been shown to be optimal for occupying the S_2 pocket of the enzyme.[28] The 3-(2-isopropyl-5-methylphenylthio) group, which occupies the S_1' as well as S_2' pockets of the enzyme, was used at the C-3 position of the dihydropyran-2-one. Substitution of the 6-phenyl group (**1**) by a methyl group led to **2**. Surprisingly in vitro binding affinity to HIV PR is maintained. Furthermore, there is an increase in antiviral activity by >sevenfold (EC_{50}: 9.4 μM versus >69 μM for **2** and **1**, respectively).

Extending the methyl group to *n*-propyl, *n*-butyl and *n*-pentyl led to 5,6-dihydropyran-2-ones **3**–**5**. All these analogues except the *n*-propyl analogue **3** showed both lower enzymatic affinities and antiviral activities when compared to **2**. The isopropyl analogue **6** exhibited a twofold increase in binding affinity to HIV PR, whereas its antiviral activity was increased by fivefold compared to **2**. Cycloalkyl substituents at C-6 (**7**–**9**) were also active and comparable to **2**. When an alkyl group is removed from the above 5,6-dihydropyran-2-ones to give **10**, its binding affinity to HIV PR is reduced by 36-fold. In summary, relative to the phenyl analogue **1** these structure–activity studies showed that the isopropyl group conferred the greatest boost in anti-HIV activity (by 36-fold).

Dihydropyran-2-ones having polar functionality on the 3-(2-*tert*-butyl-5-methylphenylthio) moiety

Further analysis of the X-ray structure of **III** bound to HIV PR indicates that substituting at the 4-position of the thiophenyl group might afford binding to Asp129 and/or Asp130 either directly or through a water molecule. Specifically, a hydroxymethyl group substituted at the 4-position could form a hydrogen bond with Asp129 (NH). In addition, an $-OCH_2CH_2OH$ substituent at this site could interact with the side chain of Asp129 or Asp130, or with solvent. Thus, 5,6-dihydropyran-2-ones with a hydroxyl-containing group at the 4-position of the 3-(2-*tert*-butyl-5-methylphenylthio) moiety were synthesized and their biological activities were evaluated.

Hydroxymethyl analogues

In this series, the 3-(2-*tert*-butyl-4-hydroxylmethyl-5-methylphenylthio) group was kept constant at the 3-position of the 5,6-dihydropyran-2-one and the alkyl group at the 6-position was varied (Table 1). It is interesting to note that the 6-phenyl analogue containing a hydroxymethyl group on the 3-(*tert*-butyl-5-methylphenylthio) moiety **11** showed better antiviral activity (4.7 μM versus >69 μM) compared to des-hydroxymethyl analogue **1** even though their binding affinities were similar. However, the methyl analogue **12** exhibited a modest enhancement in binding affinity with the enzyme relative to **2** but a fourfold enhancement in antiviral activity was observed. Also noteworthy is that compound **12** exhibited less cytotoxicity when compared to **2** (TC_{50}: >100 μM versus 69 μM). Other hydroxymethyl analogues, **13**–**21**, showed either similar or slightly enhanced IC_{50}s when compared to the des-hydroxymethyl analogues in enzymatic assays. Most importantly, all these compounds showed much better antiviral activities compared to their des-hydroxymethyl analogues **3**–**9**.

Phenolic analogues

Replacement of the hydroxymethyl group by a phenol gave the derivatives **22**–**24**. Although these compounds showed good binding affinity to HV PR, their antiviral activities decreased when compared to the corresponding hydroxymethyl derivatives (**22** versus **12**, **23** versus **16** and **24** versus **21**) and are somewhat similar to compounds not substituted at this position (**22** versus **2**, **23** versus **6** and **24** versus **9**).

Dihydropyran-2-ones containing a 4-OCH_2CH_2OH moiety on the 3-(2-*tert*-butyl-5-methylphenylthio) moiety

In this series, the hydroxyl group was extended outward by two atoms relative to the hydroxymethyl series. The resulting derivatives containing hydroxyethyl ethers at the 4-position of (2-*tert*-butyl-5-methylphenylthio) moiety (**25, 27–32**) showed HIV PR binding affinity below 10 nM. Antiviral activities of these analogues were generally less than corresponding hydroxymethyl analogues (**25** versus **12**, **27** versus **13**, **28** versus **14**, **29** versus **15**, **30** versus **16**, **31** versus **18** and **32** versus **20**). When the terminal hydroxyl group was protected as the MOM ether **26**, a threefold loss of enzymatic binding affinity was observed, but the antiviral activity was comparable to the hydroxyl derivative **25**.

Dihydropyran-2-ones containing a 6-isopropyl-6-(4-aminophenethyl) moiety at the 6-position of the ring

In this series, the 4-hydroxyl group on the phenethyl moiety at C-6 was replaced with 4-amino. The resulting inhibitor **34** exhibited binding affinity to HIV PR, antiviral activity and therapeutic index all comparable to the 4-hydroxylphenethyl analogue **16**. As before, the inhibitor containing an isopropyl group at the 6-position (**34**) exhibited better binding affinity and greater antiviral activity when compared to its 6-phenyl analogue **33**. Increasing the size of the 6-position alkyl group from isopropyl to cyclohexyl (**36**) decreased the antiviral activity compared to **34**, though both showed similar binding affinity to HIV PR.

Dihydropyran-2-ones containing a 6-isopropyl-6-phenethyl moiety at the 6-position of the ring

In order to test the contribution of the polar group (4-hydroxyl or 4-amino) present on the 6-phenylethyl ring towards biological activity in the above series, the hydroxyl/amino group was removed and the isopropyl group was kept constant at P_1. As seen previously, the 5,6-dihydropyran-2-ones containing 6-position alkyl groups exhibited superior antiviral activities compared to 6-position phenyl analogues (**38** versus **39** and **41** versus **42**). These unsubstituted analogues displayed similar binding affinities to HIV PR compared to their 4-hydroxyl (**37** versus **6**, **39** versus **16**, **40** versus **23**, **42** versus **30**) or 4-amino counterparts (**34** versus **39**), a result which infers that the 4-hydroxyl or 4-amino group on the phenethyl moiety may not be contributing significantly to the binding of the enzyme. Interestingly, these des-hydroxy or des-amino derivatives exhibited similar antiviral activities, though their cytotoxicities are somewhat higher. Thus, the polar group at the 4-position of the phenethyl group confers a reduction of cytotoxicity, which in turn produces improved therapeutic indices.

The above SAR demonstrates that the addition of polar groups to the initial 5,6-dihydropyran-2-ones (for e.g. **III**) indeed increased the antiviral activities of these compounds. Even among 6-isopropyl series there is a decrease in antiviral activity when polar groups are removed from the molecule, for example inhibitor **37** (EC_{50}: 15 μM;) versus **6** (EC_{50}: 1.9 μM) or **16** (EC_{50}: 0.6 μM) or **39** (EC_{50}: 0.6 μM) or **40** (EC_{50}: 1.8 μM). However, we could not find any quantitative correlation between antiviral activity and calculated or measured log Ps, which shows that there could be several other factors for increased antiviral activities.

Chiral 5,6-dihydropyran-2-ones

Given the good therapeutic indices of several racemic 5,6-dihydropyran-2-ones (**16**, **34** and **39**), the optically pure 5,6-dihydropyran-2-ones were synthesized (Scheme 4). Their enzymatic binding affinities and antiviral activities are shown in Table 2. The (*S*)-enantiomers **16*S***, **34*S*** and **39*S*** showed a better binding affinity to HIV PR relative to their (*R*)-enantiomers. Chiral 5,6-dihydropyran-2-ones **34*S*** and **39*S*** exhibited a twofold increase in antiviral activity relative to **34** and **39**, respectively.

X-ray crystal structure of the 6-[(4-amino)phenethyl]-6-isopropyl analogue (34*S*) bound to WT HIV PR

The X-ray crystallographic structure of **34*S*** bound to HIV PR was determined at 2.0 Å resolution. In general, the inhibitor binds in the active site in a manner previously described for this series of compounds.[9,10,13] The 5,6-dihydropyran-2-one ring spans between the catalytic dyad and the flap region, and the substituents on the 5,6-dihydropyran-2-one ring occupy the S_1/S_1' and S_2/S_2' sites (Fig. 1).

Beyond the core binding, the aniline in the S_2 pocket can form a weak hydrogen bond with the Asp30 (CO) and also interacts through a water molecule with the Asp30 side chain (Fig. 2). In comparing the activity of the aniline inhibitor **34*S*** ($K_i = 0.11$ nM) with the compound having an unsubstituted phenethyl group at P_2 (**39*S*** $K_i = 0.09$ nM), no gain in enzyme binding is realized with the NH_2 substitution. Thus, the weak interaction of the amino group observed in the X-ray structure does not appear to contribute to overall improved binding, which is inconsistent with the experimental findings.

On the prime side, the hydroxymethyl group at the 4-position of the thiophenyl ring forms a hydrogen bond with Asp129 (NH), as expected. Surprisingly, however, in the corresponding series having a 4-hydroxyphenethyl group at P_2, the incorporation of the hydroxymethyl substituent does not result in a binding affinity gain (**6** versus **16**). In an X-ray structure of HIV protease bound with an inhibitor in which the 4-position of the thiophenyl ring is not substituted (data not shown), a water molecule is present, which binds to Asp129 (NH) and Asp130 (NH). The free energy in binding **6** with the hydroxymethyl group at the 4-position may be equalled by the free energy in binding the analogous derivative with no 4-position substituent and a water molecule. In general, polar groups attached *para* to the sulfur on the thiophenyl ring did provide improved enzyme binding.

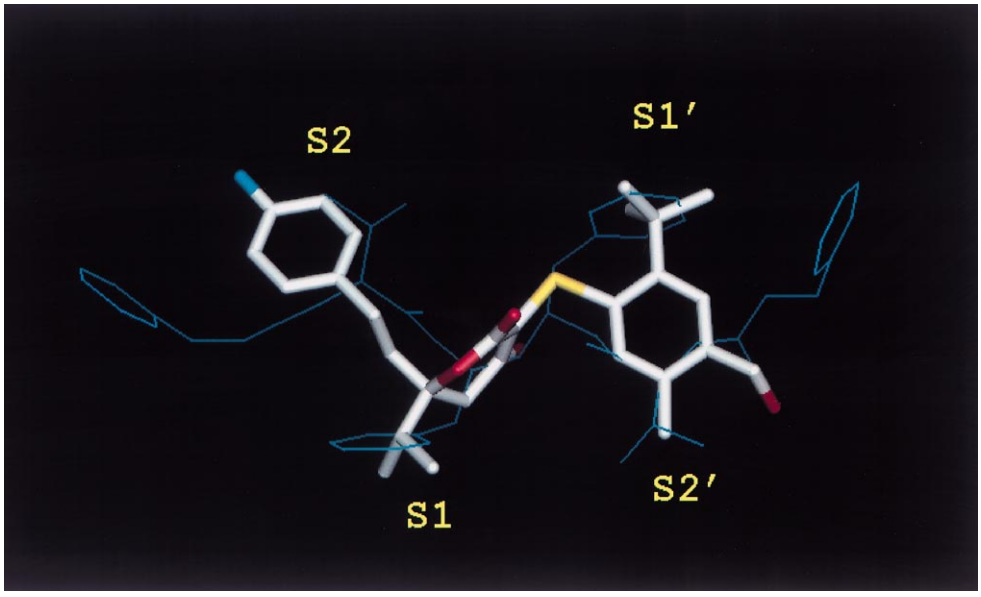


Figure 1. X-ray crystal structure of compound **37*S*** bound to HIV PR overlaid with the bound structure of A74704 (blue).

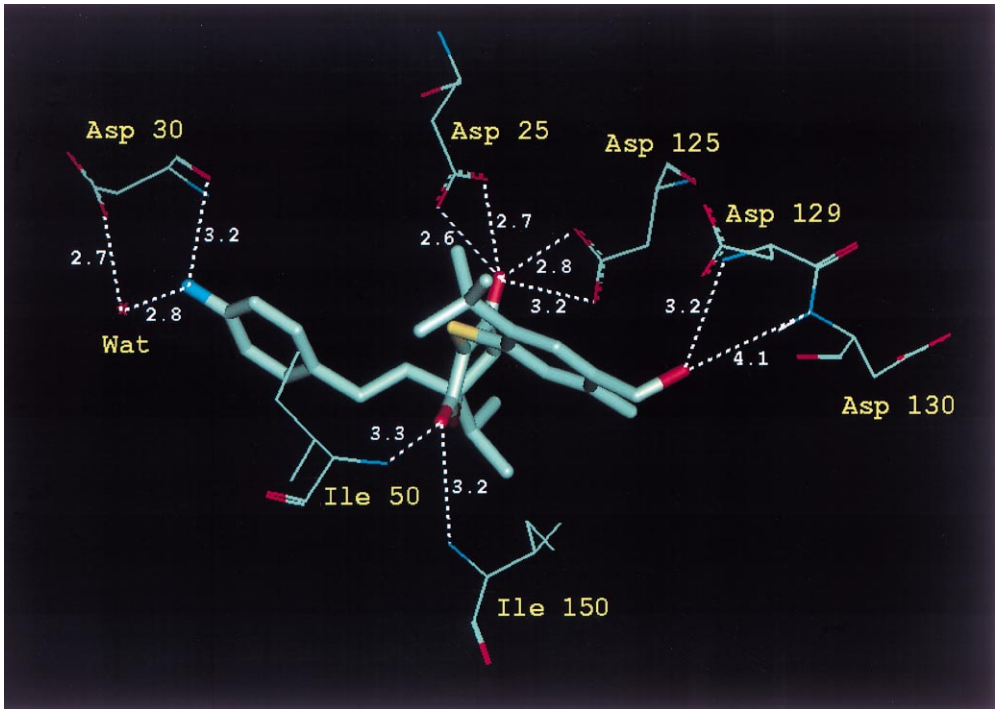


Figure 2. Interatomic distances of compound **37*S*** binding to HIV PR as derived from X-ray crystal structure. Distances are measured between heavy atoms.

Comparison of 16*S* and 34*S* to PNU-140690

Recently, Pharmacia-Upjohn has reported on a related series of 5,6-dihydropyran-2-ones (PNU-140690), which occupies five pockets of the enzyme.[29,30] It is interesting to note that PNU-140690 (**V**) contains *n*-propyl and phenethyl groups at the 6-position of the 5,6-dihydropyran-2-one ring, somewhat similar to **16*S*** and **34*S***. However, *n*-propyl and phenethyl groups in PNU-140690 occupy S_2 and S_1 pockets of the enzyme, respectively. This orientation contrasts with **16*S*** and **34*S***, wherein the small alkyl group (isopropyl) occupies the S_1 pocket of the enzyme and 4-substituted phenethyl group occupies S_2 pocket. This result clearly demonstrates that different enantiomers are most active in these two series of HIV PR inhibitor,[31,32] despite the common core.

Table 3. Dihydropyran-2-one analogues and their K_i values tested against subsite mutants of HIV PR in vitro

Enzyme	Pockets of the enzyme	Fold increase in K_i for inhibitors[a,b]				
		1	**16**	**21**	**16*S***	**34*S***
WT	—	1 (0.95)	1 (0.069)	1 (0.062)	1 (0.016)	1 (0.028)
V32I	S_2, S_2'	8.3	4.3	17	3.3	1.9
V82F	S_1, S_1', S_3, S_3'	12	2.2	26	1.1	2.5
I84V	S_1, S_1'	11	3.3	20	1.8	2.6
V32I/I84V	S_1, S_1', S_2, S_2'	52	13	40	6.9	14
V82F/I84V	S_1, S_1', S_2, S_2', S_3, S_3'	2.5	3.6	9.3	< 3.0	5.3
V82A	S_1, S_1', S_3, S_3'	—	—	—	4.3	1.3
D30N	S_2, S_2'	—	—	—	4.3	1.2
G48V/L90M		—	—	—	18.6	0.8

[a] The assays were done at pH 6.2 and K_i values are the average of at least four runs.
[b] Actual K_i values are given in parentheses.

Activity against HIV PR mutants

A major problem in the development of antiviral therapies for AIDS has been the emergence of drug resistance.[8,9,33] The various classes of PR inhibitors possessing different binding interactions could potentially lead to different resistance patterns. Selected 5,6-dihydropyran-2-ones with various substituents at the 6-position were evaluated for their inhibitory activity against various mutant enzymes in vitro.[34] Preliminary results are shown in Table 3.

Mutations at amino acids 82 and 84, which contribute to the formation of S_1, S_1' pockets of the enzyme, could affect binding affinities of the inhibitors with varying P_1 groups relative to the WT. When the size of P_1 group was increased from isopropyl (**16**) to phenyl (**1**) or cyclohexyl (**21**) there is a decrease in binding affinities with the V82F and I84V mutant enzymes. The same three 5,6-dihydropyran-2-ones were then assayed against HIV PR containing a mutation at amino acid 32, which contributes to the formation of the S_2 pocket. A similar trend was observed in that the larger alkyl groups at C-6 conferred a greater loss of potency. It was unclear why there is 17-fold increase in inhibitory activity with **21**, since all these inhibitors contains similar P_2 or P_2' groups. Obviously, compound **21** might bind with the wild type enzyme itself in a slightly different fashion compared to **16** and **1**.[31,32] Inhibitors **16*S*** and **34*S*** were also tested against all these panels of mutant enzymes. The decrease in inhibitory activities was within 14-fold including V32I and V32I/I84V mutants. It is important to note that V82I and I84V are clinically known mutants with the existing drugs.[35]

Selectivity

When 5,6-dihydropyran-2-ones **16*S*** and **34*S*** were tested against other human aspartic proteases (renin, human cathepsin D, recombinant cathepsin E, native gastricsin and recombinant human pepsin) these agents showed a selectivity index for HIV PR > 5000.

Pharmacokinetic studies of dihydropyran-2-ones varying 6-position alkyl groups

5,6-Dihydropyran-2-ones containing various 6-position alkyl groups were dosed in mice to determine which substitutions enhance bioavailability of this class of protease inhibitors.[36,37] Mice were dosed 25 mg/kg orally by gavage and in some cases subcutaneously. The compounds were dosed PO in a vehicle of either (A) 20% 0.1 N NaOH/80% PEG 400, (B) 40% 0.05 N NaOH/30% PEG 400/30% methylcellulose (MC), (C) 20% 0.1 N NaOH/80% of 0.5% MC (D), or 10% ethanol/15% PEG 400/75% water. For subcutaneous dosing the vehicle was 10% DMSO/PBS. The results are shown in Table 4. Among the vehicles used it appears that 20% 0.1 N NaOH/80% of 0.5% MC is preferred. The inhibitors containing 6-alkyl-6-hydroxyphenethyl derivatives showed C_{max} values of 3–9 μM and half-lives of 0.5–2 h. Among 6-position alkyl analogues, isopropyl and cyclopentyl analogues (**16, 34**) showed good drug concentrations, whereas cyclohexyl analogue (**21**) exhibited poor drug plasma concentrations. Encouraging to note is that the enantiomerically pure inhibitors **16*S*** and **34*S*** showed similar or slightly better drug concentrations in plasma relative to their racemic analogues **16** and **34**, respectively. Thus 5,6-dihydropyran-2-one inhibitors **16*S*** and **34*S***, which showed excellent therapeutic indices, also showed good pharmacokinetic

Table 4. Pharmacokinetic parameters of selected dihydropyran-2-one analogues in mice[a]

Entry	Vehicle[b]	C_{max} (μM)	t_{max} (h)	$t_{1/2}$ (h)	AUC (μg h/mL)
11	A	5.03	2	1.8	27.3
	B	5.7	1	3.7	34.9
12	A	3.63	0.5	ND	ND
14	A	4.37	0.5	3.4	28.6
16	A	2.8	2	2	24
	B	7.0	0.5	2.43	20.1
	C	17.3	0.5	2.0	37.3
	D	9.0	1	5.4	40
18	A	6.63	2	ND	ND
19	A	5.77	0.5	ND	ND
	B	6.04	0.5	3.1	12.1
21	A	0.4	0.5	0.9	0.8
	C	1.0	0.5	ND	ND
16*S*	C	19.61	0.5	2.9	27.8
16*R*	C	8.55	0.5	0.3	5.5
34*S*	C	26.49	0.5	2.2	81.8

[a] Dose: 25 mg/kg.
[b] A: 20% 0.1 N NaOH/80% PEG 400; B: 40% 0.05 N NaOH/30% PEG 400/30% methylcellulose; C: 20% 0.1 N NaOH/80% 0.5% methylcellulose; D: 10% ethanol/15% PEG 400/75% water.

properties with 42% (63% as sodium salt) bioavailability in mice.

Since **16*S*** and **34*S*** showed favorable pharmacokinetics, they were evaluated in rats and dog at 10 mg/kg dose. The results are shown in Table 5. Although both inhibitors exhibited favorable pharmacokinetic characteristics, the inhibitor containing the 4-amino group on the phenethyl moiety (**34*S***) gave a better C_{max}, half-life and bioavailability relative to **16*S***. Theoretically, the amino group could confer higher solubility in the low pH environment of the upper GI tract, thereby resulting in improved pharmacokinetics.

Cytochrome P-450 inhibition of selected HIV-protease inhibitors

One of the problems associated with the current marketed HIV PR drugs is their potential for drug–drug interactions. Several peptide-derived HIV PR inhibitors are known or suspected inhibitors of cytochrome P-450 isozyme CYP3A4.[38,39] Since CYP3A4 is the most abundant P-450 metabolic enzyme, the likelihood of interactions between these peptidic protease inhibitors and other drugs metabolized by the cytochrome P-450 pathway is high. Ritonavir also inhibits other cytochrome P-450 isozymes, most notably CYP2D6 and CYP2C9.[40] Thus it is useful to ascertain the possible inhibition profile of the present nonpeptidic inhibitors described here against cytochrome P-450 isozymes. Inhibitors **16*S*** and **34*S*** were tested against individual cytochrome P-450 isozymes, and the data are shown in Table 6. These two compounds do not inhibit CYP3A4 and CYP2D6 or CYP2C9 isozymes up to 10 μM concentration, but inhibition was observed at 100 μM concentration. These encouraging results suggest that these inhibitors might show fewer drug interactions with drugs known to be metabolized by these three cytochrome P-450 isozymes.

Table 5. Pharmacokinetic parameters of selected dihydropyran-2-ones in dog[a]

Entry	C_{max} (μM)	$t_{1/2}$ (h)	AUC (μg h/mL)	Hours above the EC_{95}	Bioavailability (%)
16*S*	32	1.9	10	4	16
34*S*	72	3.7	69	7	42

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

Table 6. P-450 inhibition of selected dihydropyrones (% of inhibition of individual isozymes[a])

Entry	3A4			2D6			2C9		
	1 μM	10 μM	100 μM	1 μM	10 μM	100 μM	1 μM	10 μM	100 μM
16*S*	9	14	36	5	9	33	0	14	50
34*S*	4	16	30	3	16	33	2	12	59

[a] Measures change of isozyme substrate/products in the presence/absence of inhibitor.

Conclusions

With the insight generated by the availability of X-ray crystal structures of various 5,6-dihydropyran-2-ones bound to HIV PR, inhibitors possessing various alkyl groups at the 6-position of 5,6-dihydropyran-2-one ring were synthesized. The inhibitors possessing a 6-alkyl group exhibited superior antiviral activities when compared to 6-position phenyl analogues. Antiviral efficacies were further improved upon introduction of a polar group (hydroxyl or amino) on the 4-position of the phenethyl moiety as well as the polar group (hydroxymethyl) on the 3-(*tert*-butyl-5-methyl-phenylthio) moiety. The polar substitution is also advantageous for decreasing toxicity, providing inhibitors with higher therapeutic indices. The best inhibitor among this series, **34*S***, exhibited an EC_{50} of 200 nM with a therapeutic index of >1000. The inhibitor **34*S*** was found to decrease its EC_{50} by only twofold when 40% of human serum albumin was added to in vitro antiviral test. Thus, the addition of hydrophilic groups to the initial 5,6-dihydropyran-2-ones (for e.g. **III**) indeed decreased protein binding. These results show that the decrease in protein binding may be at least one factor for increased antiviral activities. More importantly, these non-peptidic inhibitors, **16*S*** and **34*S***, appear to offer little cross-resistance to the currently marketed peptidomimetic PR inhibitors. The selected inhibitors tested in vitro against mutant HIV PR showed a very small increase in binding affinities relative to wild-type HIV PR. C_{max} and absolute bioavailability of **34*S*** were higher and half-life and time above EC_{95} were longer compared to **16*S***. Thus **34*S*** (PD 178390, CI-1029), which displays good antiviral efficacy, promising pharmacokinetic characteristics and favorable activity against mutant enzymes and CYP3A4, has been chosen for further preclinical evaluation.

Experimental

Biological assays. For the determination of IC_{50} values, the HPLC assay used was described previously. The final pH of the assay was set to 6.2.[16] Southern Research Institute as described earlier[23] performed antiviral and toxicity assays. The probe substrates used to determine the inhibitory activities against CYP3A4, CYP2D6 and CYP2C9 were testosterone, bufurolol and tolbutamide, respectively. The samples were analyzed using HPLC-UV or fluorescence.

Chemical synthesis. Melting points (mp) were determined in open capillary tubes on a Hoover mp apparatus and are uncorrected. Infrared (IR) spectra were determined in KBr pellets on a Nicolet FT IR SX-20 spectrophotometer. Proton magnetic resonance (NMR) spectra were recorded on Varian 300 and 400 spectrometers and chemical shifts are reported in δ units relative to internal standard, trimethylsilane. All mass spectra (MS) were obtained on a Finnigan 4500 GC–MS or VG analytical 7070E/F spectrometer. Robertson Microlit Laboratories, Inc. performed elemental analyses;

NJ and all compounds gave analytical results of ±0.4% of theoretical values. All alkyl lithiums and Grignard reagents used were from commercial sources and used as is. During work up, the organic layer was dried over anhyd $MgSO_4$. Flash column chromatography or medium pressure chromatography was performed using silica gel 32-63, 60A and concentrations were performed in vacuo at 10–30 mmHg.

Synthesis of aldehyde/ketones (VII): (a) via Claisen–Schmidt reaction

General procedure. To the corresponding benzaldehyde (1 equiv) taken in EtOH, the appropriate ketone (1–2 equiv) and $Ba(OH)_2$ (barium hydroxide octahydrate heated to 200°C under high vacuum for 4 h to remove water) or sodium hydroxide were added. The reaction was stirred at room temperature overnight. Initially all the reactants were soluble and as the reaction progressed, a precipitate was observed. The reaction mixture was diluted with EtOAc and dilute HCl was added until acidic. The organic layer was separated and the aqueous layer was extracted with EtOAc and dried. The crude product (purity >90%) was subjected to flash silica gel chromatography (10–15% EtOAc in hexanes) to afford analytically pure product. The pure unsaturated ketone thus obtained was subjected to hydrogenation conditions at room temperature at 20–50 psi of hydrogen using 5% palladium on barium sulfate or Raney nickel as a catalyst. The catalyst was filtered off and the resulting ketone recrystallized or purified by flash silica gel chromatography.

1-(4-Benzyloxy-phenyl)-4-methyl-pentan-3-one. The title compound was prepared according to the general procedure using 4-benzyloxybenzaldehyde (42.5 g, 200.0 mmol), 400 mL of EtOH, 3-methyl-2-butanone (34.4 g, 400.0 mmol) and $Ba(OH)_2$ (7.0 g). The crude product (purity >90%) was subjected to flash silica gel chromatography (10–15% EtOAc in hexanes) to afford analytically pure product. Isolated yield: 80%. The unsaturated ketone, 1-(4-benzyloxy-phenyl)-4-methyl-pent-1-ene-3-one, was subjected to hydrogenation conditions using Raney nickel in THF at 25 psi to afford the pure title compound. Isolated yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, 6H), 2.08 (m, 1H), 2.64 (t, 2H), 2.77 (t, 2H), 5.0 (s, 2H), 6.83 (d, 2H), 7.07 (d, 2H), 7.28 (t, 1H), 7.31–7.44 (m, 4H).

4-Benzyloxy-phenethyl cyclopropyl ketone. The title compound was prepared according to the general procedure using 4-benzyloxybenzaldehyde (50.0 g, 235.6 mmol), 250 mL of EtOH, cyclopropyl methyl ketone (83.26 g, 353.4 mmol) and $Ba(OH)_2$ (7.0 g). The crude product (purity ~90%; 50 g) was subjected to hydrogenation conditions using 5% $Pd/BaSO_4$ in THF (500 mL) at 48 psi to afford the title compound. The crude compound was subjected to flash chromatography (10–15% of EtOAc in hexanes as eluents). The compound thus obtained was stirred in EtOH solvent overnight, and the solid obtained was filtered and dried. Isolated yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (m, 2H), 1.0 (m, 2H), 1.86 (m, 1H), 2.81 (m, 4H), 5.01 (s, 2H), 6.89 (d, 2H), 7.08 (d, 2H), 7.31 (t, 1H), 7.32–7.42 (m, 4H).

3-(4-Benzyloxy-phenyl)-1-cyclobutyl-propan-1-one. The title compound was prepared as described in the general procedure using cyclobutyl methyl ketone (15.0 g, 153 mmol), 4-benzyloxybenzaldehyde (32.4 g, 153 mmol), $Ba(OH)_2$ (3.0 g) and 95% EtOH (400 mL). The reaction was kept under reflux for 16.5 h. The crude product was subjected to flash silica gel chromatography (CH_2Cl_2:MeOH = 99:1 eluent) and then rechromatographed (hexane:EtOAc:CH_2Cl_2 = 90:5:5 to 85:7.5:7.5 eluents) to afford 3.25 g of product, 3-(4-benzyloxy-phenyl)-1-cyclobutyl-prop-2-en-1-one. The unsaturated ketone (3.16g, 10.8 mmol) was subjected to hydrogenation conditions using 1.0 g of 5% $Pd/BaSO_4$ in 100 mL of THF at room temperature. The crude product was purified by flash silica gel chromatography (CH_2Cl_2:MeOH = 99:1 to 98:2) to afford 3.1 g of a gummy solid. Isolated yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.7–2.3 (m, 6H), 2.6–2.7 (t, 2H), 2.8–2.9 (t, 2H), 3.1–3.3 (m, 1H), 5.1 (s, 2H), 6.8–6.9 (d, 2H), 7.1–7.2 (d, 2H), 7.3–7.5 (m, 5H); MS-APCI (*m*/*z*): 293.

3-(4-Benzyloxy-phenyl)-1-cyclohexyl-propan-1-one. The title compound was prepared according to the general procedure using 4-benzyloxybenzaldehyde (29.3 g, 138 mmol), cylohexyl methyl ketone (17.4 g, 138 mmol), $Ba(OH)_2$ (3.2 g) and 95% EtOH (300 mL). The reaction was refluxed for 8 h. The crude product, 3-(4-benzyloxy-phenyl)-1-cyclohexyl-prop-2-en-1-one (25.9 g, 84 mmol), was subjected to hydrogenation using 5% $Pd/BaSO_4$ (1 g) in THF (60 mL). The crude product was subjected to flash silica gel chromatography (CH_2Cl_2:MeOH = 99:1 to 98:2 eluents) to afford 20.5 g of a gummy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 01.1–1.9 (m, 10H), 2.2–2.4 (m, 1H), 2.68–2.74 (m, 2H), 2.79–2.85 (m, 2H), 5.04 (s, 2H), 6.8–6.9 (d, 2H), 7.1–7.2 (d, 2H), 7.3–7.5 (m, 5H); MS-CI (*m*/*z*): 322.

1-(4-*tert*-Butyoxycarbonyl-amino-phenyl)-4-methyl-pentan-3-one. The title compound was prepared according to the general procedure using 4-nitrobenzaldehyde (22.5 g, 150 mmol), 3-methyl-2-butanone (30 mL), 1% NaOH (25 mL) and 100 mL of THF. The reaction was stirred at room temperature for 48 h and then kept under reflux for 6 h. The solution was cooled and concentrated; the residue was partitioned between water and Et_2O. The organic layer was washed with brine, dried and concentrated. The crude product was purified by flash silica gel chromatography (25% EtOAc in hexanes eluent) to afford 4-methyl-1-(4-nitro-phenyl)pent-1-ene-3-one. Isolated yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (d, 6H), 2.86 (m, 1H), 6.67 (d, 1H), 6.89 (d, 1H), 7.58 (d, 1H), 8.21 (d, 1H); MS-CI (*m*/*z*): 220. To 4-methyl-1-(4-nitro-phenyl)pent-1-ene-3-one (5.9 g, 26.9 mmol) taken in 100 mL of THF was added $Pd/BaSO_4$ (0.5 g) and shaken in a hydrogen atmosphere of 51 psi for 34 min. The crude material dissolved in 200 mL of THF was treated with di-*tert*-butyl carbonate (5.2 g, 26.9 mmol) and stirred at 55°C for 24 h, followed by 72 h at room temperature. The reaction mixture was concentrated and the residue was partitioned between

EtOAc and water. The organic layer was separated, dried and concentrated. The crude material was purified by flash silica gel chromatography (25% EtOAc in hexanes eluent). Isolated yield: 95%. ^{1}H NMR (400 MHz, DMSO): δ 0.91 (s, 6H), 1.40 (s, 9H), 2.53 (m, 1H), 2.68 (m, 2H), 2.62 (m, 2H), 7.00 (d, 2H), 7.26 (d, 2H), 9.16 (brs, 1H); MS-CI (*m*/*z*): 291.

1-(4-*tert*-Butoxycarbonyl-amino-phenyl)-5-methyl-hexan-3-one. The title compound was prepared according to the general procedure using 4-nitrobenzaldehyde (13.5 g, 90 mmol), 4-methyl-2-pentanone (16 mL, 130 mmol), 1% NaOH (20 mL) and 80 mL of THF. The reaction was stirred at the room temperature for 48 h. The reaction mixture was concentrated and the residue was partitioned between water and Et_2O. The organic layer was washed with brine, dried and concentrated. The crude product was crystallized from EtOH to afford 5-methyl-1-(4-nitro-phenyl)hex-1-ene-3-one. Isolated yield: 10%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, 6H), 2.16–2.26 (m, 1H), 2.52 (d, 2H), 6.80 (d, 1H), 7.52 (d, 1H), 7.66 (d, 2H), 8.22 (d, 2H); MS-CI (*m*/*z*): 234. 5-Methyl-1-(4-nitro-phenyl)hex-1-ene-3-one was subjected to hydrogenation conditions using 0.5 g of Pd/$BaSO_4$. The crude material (2.1 g, 10 mmol) taken in 100 mL of THF was added to di-*tert*-butyl carbonate (2.6 g, 12 mmol) and stirred at 50°C for 16 h. The reaction mixture was concentrated and the residue was partitioned between EtOAc and water. The organic layer was separated, dried and concentrated. The crude material was purified by flash silica gel chromatography (25% EtOAc in hexanes eluent). Isolated yield: 80%. ^{1}H NMR (400 MHz, DMSO): δ 0.76 (d, 6H), 1.41 (s, 9H), 1.94 (m, 1H), 2.22 (d, 2H), 2.62 (m, 4H), 7.00 (d, 2H), 7.27 (d, 2H), 9.16 (brs, 1H); MS-CI (*m*/*z*): 305.

1-(4-Boc-amino-phenyl)-4-cyclohexyl-pentan-3-one. The title compound was prepared according to the general procedure using 4-nitrobenzaldehyde (7.6 g, 50 mmol), acetyl cyclohexane (6.9 g, 55 mmol), $Ba(OH)_2$ (2.5 g) and 100 mL of 95% EtOH. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into dilute HCl and extracted with EtOAc (2×150 mL). The organic layer was separated, washed with brine, dried and concentrated. The crude product was crystallized from EtOH to give 4-cyclohexyl-1-(4-nitro-phenyl)but-1-ene-3-one. Isolated yield: 32%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.44 (m, 5H), 1.67 (m, 1H), 1.82 (m, 2H), 1.89 (m, 2H), 2.61 (m, 1H), 6.88 (d, 1H), 7.56 (d, 1H), 7.66 (dd, 2H), 8.21 (dd, 2H); MS-CI (*m*/*z*): 260. To 4-cyclohexyl-1-(4-nitro-phenyl)-but-1-ene-3-one (4.0 g, 15.4 mmol) taken in 50 mL of MeOH was added 0.4 g of 5% Pd/$BaSO_4$ and shaken in a hydrogen atmosphere of 52 psi for 14 h. The crude material (3.6 g, 15.4 mmol) taken in 200 mL of THF was added to di-*tert*-butyl carbonate (4.0 g, 18.3 mmol) and stirred at 55°C for 6 h, followed by 16 h at room temperature. The reaction mixture was concentrated and the residue was partitioned between EtOAc and water. The organic layer was separated, dried and concentrated. The crude material was purified by flash silica gel chromatography (33% EtOAc in hexanes eluent). Isolated yield: 65%. ^{1}H NMR (400 MHz, DMSO): δ 1.10–1.31 (m, 5H), 1.47 (s, 9H), 1.62 (m, 1H), 1.74 (m, 4H), 2.25 (m, 1H), 2.67 (m, 2H), 2.70 (m, 2H), 6.36 (brs, 1H), 7.05 (d, 2H), 7.21 (d, 2H); MS-CI (*m*/*z*): 331.

Synthesis of aldehyde/ketones (VII): (b) via Weinreb amide methodology

Benzyl ester of 3-(4-benzyloxyphenyl) propionic acid. 3-(4-Hydroxyphenyl)propionic acid (15.0 g, 90.3 mmol) was dissolved in 300 mL of acetone and treated with anhyd K_2CO_3 (25.0 g) and benzyl bromide (33.8 g, 198.6 mmol). The reaction was kept under reflux for 18 h, cooled to room temperature and concentrated. The residue was taken in water and extracted with EtOAc (3×200 mL). The organic layer was washed with brine and dried to furnish the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (t, 2H), 2.89 (t, 2H), 5.0 (s, 2H), 5.08 (s, 2H), 6.86 (d, 2H), 7.07 (d, 2H), 7.22–7.42 (m, 10H).

3-(4-Benzyloxyphenyl)propionic acid. To the crude benzyl ester of 3-(4-benzyloxyphenyl)propionic acid in THF (100 mL) was added 3 N lithium hydroxide (180.5 mmol) and MeOH (50 mL). The reaction was stirred at room temperature overnight. The solvents were evaporated and the residue was acidified with 3 N HCl. The product was extracted with 1:1 EtOAc and CH_2Cl_2 (3×300 mL), dried and concentrated to give a solid. Isolated yield: 65% (overall 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (t, 2H), 2.67 (t, 2H), 5.0 (s, 2H), 6.86 (d, 2H), 7.07 (d, 2H), 7.27 (t, 1H), 7.31–7.39 (m, 4H).

3-(4-Benzyloxy-phenyl)-*N*-methoxy-*N*-methyl propionamide. To the 3-(4-benzyloxyphenyl)propionic acid (15.0 g, 58.6 mmol) was added thionyl chloride (150 mL). The reaction mixture was kept under reflux for 5 h, and thionyl chloride was evaporated. The residue was taken in 10 mL of CH_2Cl_2 and cooled to 0°C. To it were added *N*,*O*-dimethylamine hydrochloride (7.1 g, 73.3 mmol) followed by 30 mL of pyridine. The reaction was stirred at room temperature for 18 h and quenched with 3 N HCl. The product was extracted into EtOAc (3×200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dilute HCl, brine and dried. The residue was purified by flash silica gel chromatography (10–20% EtOAc in hexanes as eluents). Isolated yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (t, 2H), 2.86 (t, 2H), 3.14 (s, 3H), 3.55 (s, 3H), 5.0 (s, 2H), 6.86 (d, 2H), 7.11 (d, 2H), 7.29 (t, 1H), 7.33–7.42 (m, 4H).

3-(4-Benzyloxyphenyl)propionaldehyde. To 3-(4-benzyloxy-phenyl)-*N*-methoxy-*N*-methyl propionamide (5.0 g, 16.8 mmol) taken in THF (150 mL) was added LAH (0.6 g, 16.8 mmol) in portions. The reaction was stirred at room temperature for 1 h. The reaction was quenched with water and diluted with dilute HCl and EtOAc. The organic layer was separated and dried to furnish the title compound. Isolated yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (t, 2H), 2.89 (t, 2H), 5.07 (s, 2H), 6.89 (d, 2H), 7.11 (d, 2H), 7.32 (t, 1H), 7.33–7.47 (m, 4H); 9.8 (s, 1H).

4-Benzyloxy-phenethyl propyl ketone. To 3-(4-benzyloxy-phenyl)-*N*-methoxy-*N*-methyl propionamide (10.0 g, 33.6 mmol) in THF (100 mL) was added 2 M *n*-propyl magnesium bromide (33.6 mL) in THF dropwise at room temperature. The reaction was stirred at room temperature for 16 h, and then quenched with 1 N HCl. The product was extracted into EtOAc (3×200 mL), dried and concentrated. The crude product was purified by flash silica gel chromatography (20% EtOAc in hexanes) to give the pure title compound. Isolated yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H), 1.53 (m, 2H), 2.33 (t, 2H), 2.66 (t, 2H), 2.81 (t, 2H), 5.0 (s, 2H), 6.86 (d, 2H), 7.06 (d, 2H), 7.25–7.42 (m, 5H).

4-Benzyloxy-phenethyl *n*-butyl ketone. The reaction was performed as described for 4-benzyloxy-phenethyl ethyl ketone, using 3-(4-benzyloxy-phenyl)-*N*-methoxy-*N*-methyl propionamide (8.5 g, 28.5 mmol), 2 M *n*-butyl magnesium chloride (21.4 mL, 42.8 mmol) and 100 mL of THF. The crude product was purified by flash silica gel chromatography (20% ethyl acetate in hexanes) to give the title compound. Isolated yield: 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H), 1.27 (m, 2H), 1.34 (m, 2H), 2.33 (d, 2H), 2.64 (d, 2H), 2.78 (t, 2H), 5.0 (s, 2H), 6.85 (d, 2H), 7.06 (d, 2H), 7.25 (t, 1H), 7.31–7.42 (m, 4H).

4-Benzyloxy-phenethyl isopropyl ketone. The reaction was performed as described for 4-benzyloxy-phenethyl ethyl ketone, using 3-(4-benzyloxy-phenyl)-*N*-methoxy-*N*-methyl propionamide (8.0 g, 26.9 mmol), 2 M isopropyl magnesium chloride (20.1 mL, 40.3 mmol) and 200 mL of THF. The crude product was purified by flash silica gel chromatography (20% EtOAc in hexanes) to give the title compound. Isolated yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, 6H), 2.08 (m, 1H), 2.64 (t, 2H), 2.77 (t, 2H), 5.0 (s, 2H), 6.83 (d, 2H), 7.07 (d, 2H), 7.28 (t, 1H), 7.31–7.44 (m, 4H).

4-Benzyloxy-phenethyl isobutyl ketone. The reaction was performed as described for 4-benzyloxy-phenethyl ethyl ketone, using 3-(4-benzyloxy-phenyl)-*N*-methoxy-*N*-methyl propionamide (5.0 g, 16.8 mmol), 2 M isobutyl magnesium chloride (12.6 mL, 25.2 mmol) and 100 mL of THF. The crude product was purified by flash silica gel chromatography (20% EtOAc in hexanes) to give the title compound. Isolated yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, 6H), 2.08 (m, 1H), 2.22 (d, 2H), 2.64 (t, 2H), 2.77 (t, 2H), 5.0 (s, 2H), 6.83 (d, 2H), 7.07 (d, 2H), 7.28 (t, 1H), 7.31–7.44 (m, 4H).

4-Benzyloxy-phenethyl cyclopentyl ketone. The reaction was performed as described for 4-benzyloxy-phenethyl ethyl ketone, using 3-(4-benzyloxy-phenyl)-*N*-methoxy-*N*-methyl propionamide (5.0 g, 16.8 mmol), 2 M cyclopentyl magnesium chloride (12.6 mL, 25.2 mmol) and 300 mL of THF. The crude product was purified by flash silica gel chromatography (20% EtOAc in hexanes) to give the title compound. Isolated yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44–1.77 (m, 8H), 2.69 (t, 2H), 2.77 (m, 3H), 5.0 (s, 2H), 6.86 (d, 2H), 7.07 (d, 2H), 7.28 (t, 1H), 7.33–7.42 (m, 4H).

Synthesis of 5,6-dihydropyran-2-ones

General procedure. Methyl acetoacetate was added dropwise to a slurry of hexane washed NaH in dry THF at 0°C and the reaction stirred at 0°C (15 min to 3 h). *n*-Butyl lithium was then added at 0°C and the reaction stirred at 0°C (15 min to 24 h). A solution of the requisite ketone (1 equiv) in THF was added, and the reaction mixture was stirred at 0°C to room temperature for 15 min to 24 h. To the reaction mixture was added AcOH (or dilute HCl or saturated NH_4Cl) with stirring, and the THF was removed on a rotary evaporator. The viscous reaction mixture was partitioned between H_2O and EtOAc. After separation of the layers, the aqueous layer was again extracted with EtOAc; the combined organic layers were dried and concentrated. The intermediates were either purified by flash silica gel chromatography or taken on crude. The aldol intermediate was dissolved in THF (1 vol) and treated with 9–10 volumes of NaOH (0.1–1.0 N). The reaction was stirred from 1 to 24 h at room temperature. The reaction mixture was acidified to pH 4–5 using HCl (0.1–6 N) or acetic acid. On occasions the product could be isolated by filtration. Alternatively the acidified extracts were extracted with EtOAc. The organic extracts were combined, dried and concentrated. Purification was accomplished by trituration from Et_2O or flash silica gel chromatography. The pure 5,6-dihydropyran-2-one thus obtained was subjected to hydrogenation conditions at room temperature at 20–50 psi of hydrogen using 20% Pd/C as a catalyst. The catalyst was filtered off and the resulting 5,6-dihydropyran-2-one was purified by flash silica gel chromatography or by crystallization.

4-Hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydropyran-2-one. The title compound was prepared according to the general procedure using 3-(4-benzyloxyphenyl)propionaldehyde (4.0 g, 16.8 mmol), methyl acetoacetate (5.9 g, 50.4 mmol), NaH (1.2 g, 50.4 mmol) and *n*-butyl lithium (1.64 M, 30.7 mL, 50.4 mmol). The intermediate aldol was cyclized using 0.2 N NaOH (378 mL) and THF (37.8 mL). Isolated yield: 50%. Debenzylation was carried out using 20% Pd/C in THF (65 mL) and MeOH (10 mL). The compound was purified by flash silica gel chromatography (20–70% EtOAc in hexanes as eluents) affording the title compound. Isolated yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (m, 2H), 2.27 (dd, 1H), 2.39 (dd, 1H), 2.47 (m, 1H), 2.58 (m, 1H), 4.2 (m, 1H), 4.89 (s, 1H), 6.61 (d, 2H), 6.94 (d, 2H), 9.11 (s, 1H); MS-APCI (*m*/*z*): 235.

4-Hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-methyl-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using 4-*t*-butyldimethylsilyloxy-phenethyl methyl ketone (16.9 g, 60.9 mmol), methyl acetoacetate (21.2 g, 182.7 mmol), NaH (4.39 g, 182.7 mmol) and *n*-butyl lithium (1.6 M, 114.2 mL, 182.7 mmol). The intermediate aldol was cyclized using 0.2 N NaOH (1370 mL) and THF (137 mL). The compound was purified by flash silica gel chromatography (20–70% EtOAc in hexanes as eluents) affording the title compound. Isolated yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (s, 3H), 1.8 (m,

2H), 2.31 (d of ABX q, 1H), 2.42–2.5 (m, 2H), 2.54 (d of ABX q, 1H), 4.92 (s, 1H), 6.61 (d, 2H), 6.92 (d, 2H), 9.14 (brs, 1H).

3-Hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-*n*-propyl-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using 4-benzyloxy-phenethyl *n*-propyl ketone (10.0 g, 35.5 mmol), methyl acetoacetate (10.3 g, 88.7 mmol), NaH (2.1 g, 88.7 mmol) and *n*-butyl lithium (1.64 M, 54.1 mL, 88.7 mmol). The intermediate aldol was cyclized using 0.2 N NaOH (799 mL) and THF (80 mL). After evaporation of solvents the residue was triturated from Et_2O/hexanes to afford 6-[2-(4-benzyloxy-phenyl)-ethyl]-6-*n*-propyl-4-hydroxy–5,6-dihydro-pyran-2-one. Isolated yield: 85%. Debenzylation was carried out using 20% Pd/C (0.5 g) in THF (150 mL), MeOH (100 mL) in the presence of hydrogen atmosphere. The crude product on trituration with Et_2O/hexanes gave the pure product. Isolated yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, 3H), 1.25 (m, 2H), 1.58 (m, 2H), 1.77 (q, 2H), 2.4 (m, 2H), 4.89 (s, 1H), 6.6 (d, 2H), 6.92 (d, 2H), 9.08 (s, 1H).

6-*n*-Butyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using 4-benzyloxy-phenethyl butyl ketone (4.0 g, 13.51 mmol), methyl acetoacetate (6.3 mL, 54.1 mmol), NaH (1.3 g, 54.1 mmol) and *n*-butyl lithium (1.64 M, 33 mL, 54.1 mmol). The intermediate aldol was cyclized using 0.2 N NaOH (304 mL) and THF (30 mL). The compound was purified by flash silica gel chromatography (20–80% EtOAc in hexanes as eluents) affording 6-[2-(4-benzyloxy-phenyl)-ethyl]-6-butyl-4-hydroxy-5,6-dihydro-pyran-2-one. Isolated yield: 35%. Debenzylation was carried out using 20% Pd/C (0.15 g) in THF (75 mL) in the presence of hydrogen atmosphere. The crude product was purified by flash silica gel chromatography (20–70% EtOAc in hexanes as eluents). Isolated yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8 (t, 3H), 1.2 (m, 4H), 1.61 (m, 2H), 1.81 (m, 2H), 2.42 (obscured by DMSO peak, 4H), 4.89 (s, 1H), 6.61 (d, 2H), 6.9 (d, 2H), 8.08 (s, 1H).

6-Isobutyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using 4-benzyloxy-phenethyl isobutyl ketone (15.0 g, 50.7 mmol), methyl acetoacetate (14.7 g, 126.8 mmol), NaH (3.0 g, 126.8 mmol) and *n*-butyl lithium (1.64 M, 77.3 mL, 126.8 mmol). The intermediate aldol was cyclized using 0.2 N NaOH (1141 mL) and THF (114 mL). The compound was purified by flash silica gel chromatography (20–80% EtOAc in hexanes as eluents) affording 6-[2-(4-benzyloxy-phenyl)-ethyl]-4-hydroxy-6-isobutyl-5,6-dihydro-pyran-2-one. Isolated yield: 35%. Debenzylation was carried out using 20% Pd/C (0.5 g) in THF (100 mL) in the presence of hydrogen atmosphere. The crude product was purified by flash silica gel chromatography (20–70% EtOAc in hexanes as eluents). Isolated yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (d, 3H), 0.86 (d, 3H), 1.61 (dd, 1H), 1.5 (dd, 1H), 1.69 (m, 2H), 1.83 (m, 1H), 2.42 (obscured by DMSO peak, 3H), 2.55 (d, 1H), 4.92 (s, 1H), 6.64 (d, 2H), 6.92 (d, 2H), 9.11 (s, 1H).

6-Cyclopropyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using 4-benzyloxy-phenethyl cyclopropyl ketone (4.5 g, 16.1 mmol), methyl acetoacetate (4.7 g, 40.2 mmol), NaH (1.0 g, 40.2 mmol) and *n*-butyl lithium (1.64 M, 24.5 mL, 40.2 mmol). The intermediate aldol was cyclized using 0.2 N NaOH (362 mL) and THF (36 mL). The compound was purified by flash silica gel chromatography (20–80% EtOAc in hexanes as eluents) affording 6-[2-(4-benzyloxy-phenyl)-ethyl]-4-hydroxy-6-cyclopropyl-5,6-dihydro-pyran-2-one. Isolated yield: 55%. Debenzylation was carried out using 20% Pd/C (0.5 g) in THF (100 mL) in the presence of hydrogen atmosphere. The crude product was purified by flash silica gel chromatography (20–70% EtOAc in hexanes as eluents). Isolated yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.32 (m, 1H), 0.42 (m, 3H), 2.14 (m, 1H), 1.89 (m, 2H), 2.36 (d, 1H), 2.55 (m, 3H), 4.89 (s, 1H), 6.61 (d, 2H), 6.94 (d, 2H), 9.11 (s, 1H).

6-Cyclobutyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one. The title compound was prepared as described in the general procedure using methyl acetoacetate (2.4 g, 20.4 mmol), NaH (60% dispersion in oil, 0.9 g, 21.4 mmol), 1.6 M *n*-butyl lithium in hexanes (13.0 mL, 20.9 mmol), 3-(4-benzyloxy-phenyl)-1-cyclobutyl-propan-1-one (3.0 g, 10.2 mmol) and THF (200 mL). After addition of the ketone, the reaction was stirred for 2 h at 0°C. The crude product was subjected to hydrogenolysis using 0.2 g of 20% Pd/C in THF (100 mL) at room temperature. To the crude product, 5-cyclobutyl-5-hydroxy-7-(4-hydroxy-phenyl)-3-oxo-heptanoic acid methyl ester, in THF (25 mL), was added 0.2 N NaOH (250 mL). The reaction was stirred for 2 h at room temperature. Purification was accomplished by flash silica gel chromatography (CH_2Cl_2:MeOH = 98:2 eluent) to give 2.4 g of the desired product as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.7–2.1 (m, 7 H), 2.2–2.3 (m, 1 H), 2.5–2.7 (t, 2 H), 2.6–2.7 (m, 3 H), 3.42 (s, 2 H), 4.61 (s, 1H), 6.75 (d, 2 H), 6.98 (d, 2 H); MS-APCI (*m*/*z*): 289.

6-Cyclopentyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using 4-benzyloxy-phenethyl cyclopentyl ketone (5.0 g, 16.24 mmol), methyl acetoacetate (4.7 g, 40.6 mmol), NaH (1.0 g, 40.48 mmol) and *n*-butyl lithium (1.64 M, 24.7 mL, 40.58 mmol). The intermediate aldol was cyclized using 0.2 N NaOH (365 mL) and THF (37 mL). The compound was purified by flash silica gel chromatography (20–80% EtOAc in hexanes as eluents) affording 6-[2-(4-benzyloxy-phenyl)-ethyl]-6-cyclopentyl-4-hydroxy-5,6-dihydro-pyran-2-one. Isolated yield: 75%. Debenzylation was carried out using 20% Pd/C (1.0 g) in THF (100 mL) in the presence of hydrogen atmosphere. The crude product was purified by flash silica gel chromatography (20–70% EtOAc in hexanes as eluents). Isolated yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14–1.77 (m, 8H), 1.8 (m, 2H), 2.25 (m, 1H), 2.36–2.53 (obscured by DMSO peak, 4H), 4.92 (s, 1H), 6.61 (d, 2H), 6.89 (d, 2H), 9.11 (s, 1H).

6-Cyclohexyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using methyl acetoacetate (11.6 g, 99.9 mmol), NaH (60% dispersion in mineral oil) (4.19 g, 105 mmol), 1.6 M *n*-butyl lithium in hexanes (64.0 mL, 102 mmol), 3-(4-benzyloxy-phenyl)-1-cyclohexyl-propan-1-one (16.1 g, 49.9 mmol) and 550 mL of THF. After addition of the ketone, the reaction was stirred for 2 h at 0°C, then 1 h at room temperature. The reaction was quenched with AcOH (12 mL) and worked up in the usual manner. The crude product was subjected to hydrogenolysis using 2.0 g of 20% Pd on carbon in 400 mL of THF at room temperature. The crude product was carried on without purification. To the 5-cyclohexyl-5-hydroxy-7-(4-hydroxy-phenyl)-3-oxo-heptanoic acid methyl ester taken in THF (100 mL) was added 0.2 N NaOH (900 mL). The reaction was stirred for 3 h at room temperature and then worked up as usual. Purification was accomplished by flash silica gel chromatography (CH_2Cl_2:MeOH = 99:1 to 98:2) to give 13.0 g of the desired product as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.0–1.9 (m, 12H), 1.9–2.1 (m, 1H), 2.5–2.7 (m, 3H), 2.8 (d, 1H), 3.4 (s, 2H), 6.75 (d, 2H), 7.05 (d, 2H).

6-[2-(4-(*tert*-Butoxycarbonylamino)-phenyl)-ethyl]-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one. The title compound was according to the general procedure using methyl acetoacetate (5.7 g, 49 mmol), NaH (60% dispersion in oil), (2.1 g, 52.5 mmol), 1.5 M *n*-butyl lithium in hexanes (36.0 mL, 54 mmol), 1-(4-*tert*-butoxycarbonyl-amino-phenyl)-4-methyl-pentan-3-one (5.7 g, 19.5 mmol) and 2000 mL of THF. After addition of the ketone, the reaction was stirred for 2 h at 0°C, then 1 h at room temperature. The reaction was quenched with AcOH (15 mL) and worked up in the usual manner. To the crude product taken in THF (130 mL) was added 1.0 N NaOH (1300 mL). The reaction was stirred for 3 h at room temperature and then worked up as usual. Purification was accomplished by flash chromatography ($CHCl_3$:MeOH = 99:1 to 98:2) to give 5.7 g of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.87 (m, 6H), 1.40 (s, 9H), 1.83 (m, 2H), 2.07 (m, 1H), 2.25 (d, 1H), 2.50 (d, 1H), 2.54 (m, partially obscured by DMSO, 2H), 4.91 (s, 1H), 6.98 (d, 2H), 7.28 (d, 2H), 9.17 (brs, 1H); MS-CI (*m*/*z*): 375.

6-[2-(4-(*tert*-Butoxycarbonylamino)-phenyl)-ethyl]-6-isobutyl-4-hydroxy-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using methyl acetoacetate (2.3 g, 19.4 mmol), NaH (60% dispersion in oil) (0.9 g, 21.4 mmol), 1.5 M *n*-BuLi in hexanes (14.0 mL, 21 mmol), 1-(4-*tert*-butoxycarbonyl-amino-phenyl)-5-methyl-hexan-3-one (2.7 g, 8.84 mmol) and THF (120 mL). After addition of the ketone, the reaction was stirred for 2 h at 0°C, then 1 h at room temperature. The reaction was quenched with AcOH (5 mL) and worked up in the usual manner. To the crude product taken in THF (50 mL) was added 1.0 N NaOH (500 mL). The reaction was stirred for 3 h at room temperature and then worked up as usual. Purification was accomplished by flash chromatography ($CHCl_3$:MeOH = 95:5) to give 1.5 g of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 6H), 1.40 (s, 9H), 1.48–1.53 (m, 1H), 1.59–1.64 (m, 1H), 1.71–1.75 (m, 1H), 1.82–1.88 (m, 2H), 2.36 (d, 1H), 2.54 (d, 1H), 4.92 (s, 1H), 7.01 (d, 2H), 7.29 (d, 2H), 9.18 (brs, 1H), 11.31 (brs, 1H); MS-CI (*m*/*z*): 389.

6-[2-(4-(*tert*-Butoxycarbonylamino)-phenyl)-ethyl]-6-cyclohexyl-4-hydroxy-5,6-dihydro-pyran-2-one. The title compound was prepared according to the general procedure using methyl acetoacetate (2.8 g, 23.7 mmol), NaH (60% dispersion in oil) (1.1 g, 27.5 mmol), 1.5 M *n*-butyl lithium in hexanes (19.0 mL, 28.5 mmol), 1-(4-*tert*-butoxycarbonyl-amino-phenyl)-3-cyclohexyl-hexan-3-one (3.1 g, 9.5 mmol) and THF (175 mL). After addition of the ketone, the reaction was stirred for 30 min at 5°C, then 1 h at room temperature. The reaction was quenched with AcOH (5 mL) and worked up in the usual manner. To the crude product taken in THF (60 mL) was added 1.0 N NaOH (600 mL). The reaction was stirred for 1.5 h at room temperature and then worked up as usual. Purification was accomplished by flash silica gel chromatography (EtOAc:hexanes = 1:1) to give 2.9 g of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02–1.25 (m, 5H), 1.46 (s, 9H), 1.64 (m, 1H), 1.73 (m, 5H), 1.87 (m, 2H), 2.31 (d, 1H), 2.55 (m, 2H), 2.61 (d, 1H), 4.96 (brs, 1H), 7.04 (d, 2H), 7.33 (d, 2H), 9.22 (s, 1H).

Synthesis of chiral 5,6-dihydropyran-2-ones

(*RS*)-3-Hydroxy-3-(2-phenethyl)-4-methyl-pentanoic acid (VIII, X = H). A 3-L 3-neck flask with mechanical stirrer was charged with diisopropylamine (86.1 g, 851.0 mmol) in 320 mL THF and cooled to −15°C. *n*-Butyl lithium (1.6 N, 531.9 mL, 851.0 mmol) was added dropwise over 30–40 min. After 30 additional min the reaction was cooled to −40°C and *t*-butylacetate (98.9 g, 851.0 mmol) in THF (240 mL) was added dropwise over 45 min. The reaction mixture was stirred an additional 30 min. Phenethyl isopropyl ketone (**III**) in 400 mL THF was added dropwise to the reaction mixture over 15 min followed by 30 min additional stirring. The cooling bath temperature was raised to −15 to −20°C and then the reaction quenched slowly with ~1500 mL of 3 N HCl. The reaction mixture was extracted with EtOAc; the organic phase was washed with brine, dried, filtered and concentrated to yield 130 g of oil. This material was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94–0.98 (dd, 6H), 1.48 (s, 9H), 1.74–1.85 (m, 2H), 1.87–1.96 (m, 1H), 2.40 (d, 1H), 2.52 (d, 1H), 2.64–2.73 (m, 2H), 3.92 (s, 1H), 7.16–7.21 (m, 3H), 7.26–7.34 (m, 2H). To the (*RS*)-3-hydroxy-3-(2-phenethyl)-4-methyl-pentanoic acid *tert*-butyl ester (124.4g, 425.5 mmol) in MeOH (1400 mL) LiOH (35.7 g, 851.0 mmol) in deionized water (140 mL) was added. The reaction was heated at reflux overnight. The reaction mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in water and extracted twice with EtOAc. The combined organic phases were washed with brine, dried, filtered and concentrated to give 79 g (78.6% isolated yield) of a white solid. The isolated material was used without further purification. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 0.96–1.00 (dd, 6H), 1.80–1.90 (m, 2H), 1.92–2.10 (m, 1H), 2.62–2.74 (m, 4H), 7.17–7.21 (m, 3H), 7.26–7.32 (m, 2H).

(*S*)-3-Hydroxy-3-(2-phenethyl)-4-methyl-pentanoic acid (*S*-VIII, X = H). To the β-hydroxyacid (**VIII**) (15.0 g, 63.5 mmol) in EtOAc (155 mL) was added 0.55 equiv of (*S*)-α-methylbenzylamine (4.2 g, 34.9 mmol). The reaction mixture was rapidly stirred until a solid precipitate began to form. The reaction flask was then placed on a steam bath and heated to reflux until homogeneous solution was obtained. The reaction mixture was allowed to cool slowly to room temperature and stand overnight. The resulting solids were cooled to 0°C in an ice bath for several hours. The material was diluted with cold EtOAc, and the solid was filtered off and washed with cold EtOAc and Et_2O to yield 7.7 g of white solid. The solid was dissolved in 500 mL 1 N HCl and then extracted twice with EtOAc. The combined organic phases were washed again with 1 N HCl and brine, dried, filtered and concentrated to yield 5.0 g of a clear oil which solidifies to a white solid on standing. Chiral HPLC analysis (Chiralcel OD 0.46 cm ϕ×25 cm chiral column, eluting with 97.5% hexanes / 2.5% isopropanol +0.1% formic acid at a rate of 1 mL/min) of the isolated material showed that it contained 96% (*S*)/4% (*R*) of the enantiomers.

(*S*)-5-Hydroxy-5-(2-phenethyl)-3-keto-6-methyl-heptanoic acid, ethyl ester (*S*-IX, X = H). To the β-hydroxyacid (***S*-VIII**) (10.1 g, 42.5 mmol) dissolved in THF (190 mL) was added carbonyldiimidazole (15.2, 93.6 mmol). After stirring at room temperature for 4 h magnesium ethyl malonate (12.3 g, 42.5 mmol) was added and the resulting gummy suspension was stirred at room temperature overnight. The reaction mixture was poured into 1 N HCl and extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$ followed by brine, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (15% EtOAc in hexanes as eluent) to yield 4.7 g oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93–0.97 (dd, 6H), 1.26 (t, 3H), 1.79–1.85 (m, 2H), 1.93–2.00 (m, 1H), 2.64–2.68 (m, 2H), 2.72 (d, 1H), 2.83 (d, 1H), 3.48 (s, 2H), 4.19 (q, 2H) 7.15–7.20 (m, 3H), 7.26–7.31 (m, 2H).

(*S*)-4-Hydroxy-6-isopropyl-6-(2-phenethyl)-5,6-dihydropyran-2-one (*S*-X, X = H). To the above β-ketoester (***S*-VII**) (4.7 g, 15.3 mmol) in THF (42 ml) 0.1 N NaOH (420 mL) was added and the resulting milky solution was stirred at room temperature overnight. The reaction flask was cooled to 0°C in an ice bath, acidified with 1 N HCl to ~pH 3 and extracted twice with EtOAc. The combined organic phases were washed with brine, dried, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (3% MeOH in CH_2Cl_2 as eluent) to afford 3.43 g (86% isolated yield) of the target compound as a clear oil which solidifies slowly to a solid on standing. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88–0.92 (dd, 6H), 1.83–1.94 (m, 2H), 2.07–2.16 (m, 1H), 2.31 (d of ABX q, 1H), 2.54–2.63 (m, 3H), 4.96 (s, 1H), 7.13–7.18 (m, 3H), 7.23–7.28 (m, 2H), 11.36 (br s, 1H).

(*R*)-3-Hydroxy-3-(2-phenethyl)-4-methyl-pentanoic acid (*R*-VIII, X = H). The mother liquor from the chiral resolution of the (*S*) enantiomer of the β-hydroxyacid (58.0 g, 245.4 mmol) was dissolved in 600 mL EtOAc and treated with (*R*)-α-methylbenzylamine (22.0 g, 181.6 mmol). The reaction mixture was stirred rapidly until a solid precipitate began to form, then heated to reflux until all solids dissolved. The reaction mixture was allowed to cool slowly to room temperature and stand overnight. The reaction mixture was cooled to 0°C in an ice bath for several hours. The material was diluted with cold EtOAc: the solids were filtered off and washed with cold EtOAc and Et_2O to yield 40.0 g of white solid. The solid was dissolved in 1 N HCl (~1000 mL) and extracted twice with EtOAc. The combined organic layers were washed again with 1 N HCl, followed by brine, dried, filtered and concentrated to yield 27.1 g of a clear oil which solidifies slowly to a white solid on standing. Chiral HPLC analysis (Chiralcel OD 0.46 cm ϕ×25 cm chiral column, eluting with 97.5% hexanes/2.5% isopropanol +0.1% formic acid at a rate of 1 mL/min) of the isolated material showed that it contained 96% (*R*)/4% (*S*) of enantiomers.

(*R*)-5-Hydroxy-5-(2-phenethyl)-3-keto-6-methyl-heptanoic acid, ethyl ester (*R*-IX, X = H). To the *R*-β-hydroxyacid (***R*-VIII**, 26.9 g, 113.83 mmol) in THF (500 mL), carbonyldiimidazole (40.6, 250.4 mmol) was added. After stirring the reaction mixture at room temperature for 4 h magnesium ethyl malonate (32.8 g, 113.8 mmol) was added and the resulting gummy suspension was stirred overnight. The reaction mixture was poured into 1 N HCl and extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$ followed by brine, dried, filtered and concentrated. The resulting residue after flash silica gel chromatography (20% EtOAc in hexanes as eluent) yielded 15.6 g of an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93–0.97 (dd, 6H), 1.26 (t, 3H), 1.79–1.85 (m, 2H), 1.93–2.00 (m, 1H), 2.64–2.68 (m, 2H), 2.72 (d, 1H), 2.83 (d, 1H), 3.48 (s, 2H), 4.19 (q, 2H), 7.15–7.20 (m, 3H), 7.26–7.31 (m, 2H).

(*R*)-4-Hydroxy-6-isopropyl-6-(2-phenethyl)-5,6-dihydropyran-2-one (*R*-X, X = H). To the β-ketoester (***R*-IX**) (15.6 g, 50.9 mmol) in THF (140 mL), 0.1 N NaOH (1400 mL) was added and the resulting milky solution was stirred at room temperature overnight. The reaction flask was cooled to 0°C and the reaction mixture was acidified with 1 N HCl to ~pH 3–4 and extracted twice with EtOAc. The combined organic phases were washed with brine, dried, filtered and concentrated. The resulting oil was dissolved in Et_2O and hexanes were added with cooling of the flask in an ice water bath to give a white solid. The solid was filtered off and washed with hexanes to afford 9.7 g (73% isolated yield) of the desired dihydropyrone as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88–0.92 (dd, 6H), 1.81–1.99 (m, 2H), 2.07–2.16 (m, 1H), 2.31 (d of ABX q, 1H), 2.52–2.63 (m, 3H), 4.967 (s, 1H), 7.13–7.17 (m, 3H), 7.23–7.28 (m, 2H), 11.36 (br s, 1H).

(*RS*)-3-Hydroxy-3-[2-(4-*tert*-butoxycarbonylamino-phenyl)ethyl]-4-methyl-pentanoic acid (VIII, X = NHBoc). A

solution of diisopropylamine (125 mL, 893 mmol) in dry THF (450 mL) was cooled to −20°C under nitrogen, treated dropwise with *n*-butyl lithium (338 mL, 811 mmol), and stirred at −30 to −10°C for 30 min. A solution of benzyl acetate (121.7 g, 810 mmol) in dry THF (300 mL) was added dropwise to the LDA solution; the anion was stirred at −20°C for 1 h and then cooled to −78°C. A solution of 1-(4-*tert*-butoxycarbonyl-amino-phenyl)-4-methyl-pentan-3-one in dry THF (300 mL) was added all at once. The reaction mixture was stirred at −78 to −40°C for 3 h. The reaction was quenched by adding AcOH (70 mL) and was allowed to warm to room temperature. The reaction mixture was diluted with water and EtOAc, the organic layer was separated, washed with brine, dried and concentrated. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H), 1.48 (s, 9H), 1.68–1.75 (m, 2H), 1.86–1.90 (m, 1H), 2.47–2.62 (m, 4H), 5.07 (s, 2H), 6.50 (brs, 1H), 7.02 (d, 2H), 7.20–7.33 (m, 2H). The crude product, 3-hydroxy-3-[2-(4-*tert*-butoxycarbonylamino-phenyl)ethyl]-4-methyl-pentanoic acid, benzyl ester thus obtained (208 g) taken in THF (1000 mL) was treated with 20% Pd/C (5 g) and shaken in a hydrogen atmosphere (51 psi) at room temperature for 7 h. The catalyst was filtered off and the filtrate was concentrated to about 200 mL. The solution was poured into 10% KOH (1200 mL), stirred vigorously for 30 min and partitioned with toluene (300 mL). The organic layer was acidified to pH 5.2 with acetic acid. The product was extracted with EtOAc (2×200 mL), and the organic layer was washed with brine, dried and concentrated to give 84 g of a solid. IR (KBr): 3389, 1703 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81–0.83 (m, 6H), 1.41 (s, 9H), 1.60–1.71 (m, 2H), 1.73–1.80 (m, 1H), 2.34 (q, 2H), 2.48 (m, 2H), 6.99 (d, 2H), 7.27 (d, 2H), 9.16 (brs, 1H); MS-APCI (*m*/*z*): 350.

(*S*)-3-Hydroxy-3-[2-(4-*tert*-butoxycarbonylamino-phenyl)-ethyl]-4-methyl-pentanoic acid (*S*-VIII, X = NH-Boc). To the β-hydroxyacid (**VIII**, X = NH-Boc) (85.0 g, 242 mmol) taken in 600 mL EtOAc was added 0.55 equiv of (*S*)-α-methylbenzylamine (18.7 mL, 145 mmol). The reaction mixture was heated to reflux under vigorous stirring until homogeneous solution was obtained. The reaction mixture was allowed to cool slowly to room temperature and stand overnight. The resulting solid (99:1 *S*/*R*, 20 g) was filtered and washed with EtOAc/Et_2O. The mother liquor was concentrated to obtain 7.3 g (97:3 *S*/*R*) of solid, which was filtered. The solid was dissolved in 500 mL 1 N HCl and then extracted thrice with EtOAc. The combined organic phases were washed again with 1 N HCl, followed by brine, dried, filtered and concentrated to yield a solid. Isolated (yield: 96%) material was >97:3 (*S*/*R*) based on chiral HPLC analysis (Chiralcel OD 0.46 cm ϕ×25 cm chiral column, eluting with 97.5% hexanes/2.5% *i*-PrOH +0.1% formic acid at a rate of 1 mL/min.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (d, 3H), 0.92 (d, 3H), 1.48 (s, 9H), 1.66–1.81 (m, 2H), 1.92 (m, 1H), 2.40 (d, 1H), 2.52 (d, 1H), 2.56–2.63 (m, 2H), 6.67 (s, 1H), 7.09 (d, 2H), 7.23 (d, 2H).

(*S*)-6-[2-(4-(*tert*-Butoxycarbonylamino)-phenyl)-ethyl]-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one (*S*-X, X = NH_2). To a solution of *S*-β-hydroxyacid (18.3 g, 52 mmol) in 500 mL dry THF was added carbonyldiimidazole (16.9 g, 104 mmol). After stirring the reaction mixture at room temperature for 2 h, magnesium ethyl malonate (37.2 g, 130 mmol) was added and the resulting gummy suspension was stirred overnight. The reaction mixture was poured into NH_4Cl solution and extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$ followed by brine, dried, filtered and concentrated. The resulting crude product was used further without any purification. Isolated yield: 100%. To the crude β-ketoester in THF (100 mL), 0.1 N NaOH (1000 mL) was added and the resulting solution was stirred at room temperature overnight. The reaction mixture was acidified with saturated ammonium phosphate solution to ∼pH 6 and extracted four times with EtOAc. The combined organic phases were washed with brine, dried, filtered and concentrated. The resulting solid (13.4 g, 82% isolated yield, and overall two steps) was pure and used further as such. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, 6H), 1.50 (s, 9H), 1.71–1.83 (m, 1H), 1.94–2.15 (m, 2H), 2.56–2.73 (m, 3H), 2.77 (d, 1H), 6.50 (s, 1H), 7.06 (d, 2H), 7.27 (d, 2H).

(*R*)- and (*S*)-3-Hydroxy-3-[2-(4-*tert*-butoxycarbonylamino-phenyl)ethyl]-4-methyl-pentanoic acid (VIII*R* and VIII*S*, X = NHBoc). Racemic 3-hydroxy-3-[2-(4-benzyloxy-carbonylamino-phenyl)ethyl]-4-methyl-pentanoic acid, benzyl ester (10 g) was subjected to HPLC using chiral AD column at a flow rate of 9–11 mL/min and 250 mg per injection. The *S* (peak 1) and *R* (peak 2) enantiomers obtained were concentrated separately and triturated with Et_2O/hexanes to obtain solid. The *S* enantiomer (4.2 g) was 96:4 (*S*/*R*), whereas *R* enantiomer (4.2 g) was >99:<1 (*S*/*R*) based on chiral HPLC. In the next step, (*R*)-3-hydroxy-3-[2-(4-benzyloxycarbonylamino-phenyl)-ethyl]-4-methyl-pentanoic acid, benzyl ester (4.2 g) was dissolved in THF (100 mL) and stirred in the presence of Pd/C (0.5 g) under hydrogen atmosphere. The (*R*)-3-hydroxy-3-[2-(amino-phenyl)ethyl]-4-methyl-pentanoic acid obtained was concentrated and used further without any purification. Isolated yield: quantitative. To the crude amino acid (2.2 g, 8.71 mmol) in THF (50 mL) was added di-*tert*-butyl carbonate (2.0 g, 9.2 mmol) in THF (20 mL). The reaction was stirred at 70°C for 24 h, followed by room temperature for three days. Solvents were removed and triturated with Et_2O/hexanes to a solid. Isolated yield: quantitative.

(*R*)-6-[2-(4-(*tert*-Butoxycarbonylamino)-phenyl)-ethyl]-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one (*R*-X, X = NH_2). To a solution of *R*-β-hydroxyacid (3.0 g, 8.6 mmol) in 50 mL dry THF was added carbonyldiimidazole (2.8 g, 17.1 mmol). After stirring the reaction mixture at room temperature for 3 h, magnesium ethyl malonate (5.0 g, 17.1 mmol) was added and the resulting gummy suspension was stirred overnight. The reaction mixture was poured into NH_4Cl solution and extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$ followed by brine, dried, filtered and concentrated. The resulting crude product was used further without any purification. Isolated yield: 88%. To the crude β-ketoester in THF (25 mL), 0.1 N NaOH (250 mL) was added and the resulting solution was

stirred at room temperature for 4 h. The reaction mixture was acidified with saturated ammonium chloride solution to ~pH 6.5 and extracted four times with EtOAc. The combined organic phases were washed with brine, dried, filtered and concentrated. The resulting solid (2.2 g, 77% isolated yield) was pure and used further as such.

Examples

General procedure. To the appropriate 5,6-dihydropyran-2-one (1 equiv) taken in DMF (1–12 mL per mmol of dihydropyrone), K_2CO_3 (4–8 equiv) was added followed by the appropriate thiotosylate reagent (1.1–1.5 equiv). The reaction was stirred at room temperature (2.5 h to overnight). The reaction was diluted in a mixture of EtOAc and either 1 N HCl or saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted again with EtOAc. The combined organic extracts were washed with brine, dried, concentrated and purified by flash silica gel chromatography. The final compounds, **2**–**12**, **29** and **40**, were purified using 20% EtOAc in hexanes to 60% EtOAc in hexanes as eluents. Compounds **13**–**28**, **30**–**35**, **41**–**45** were purified using 20% EtOAc in hexanes to 80% EtOAc in hexanes as eluents.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-phenyl-5,6-dihydro-pyran-2-one (1). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-phenyl-dihydropyran-2-one (0.2 g, 0.6 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.2 g, 0.7 mmol), K_2CO_3 (0.4 g, 2.5 mmol) and DMF (2 mL). The crude product was purified by flash silica gel chromatography (*i*-PrOH:CH_2Cl_2:hexanes = 1:40:10 eluent) to afford the pure material. Isolated yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 9H), 1.86 (s, 3H), 2.19–2.30 (m, 3H), 2.66 (m, 1H), 3.28 (d, 1H, J = 17.4 Hz), 3.35 (d, 1H, J = 17.4 Hz), 4.91 (s, 1H), 6.19 (s, 1H), 6.71 (d, 2H, J = 8.4 Hz), 6.82 (d, 1H, J = 7.96 Hz), 6.93 (d, 2H, J = 8.4 Hz), 7.20 (d, 1H, J = 7.96 Hz), 7.34–7.46 (m, 5H), 7.63 (s, 1H); MS-CI (*m*/*z*): 489.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-methyl-5,6-dihydro-pyran-2-one (2). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl)-6-methyl-dihydropyran-2-one (1 g, 4.1 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (1.4 g, 4.1 mmol), K_2CO_3 (2 g) and DMF (5 mL). Isolated yield: 83%. IR (KBr): 3293, 2954, 1683, 1589, 1516, 1220, 1047, 824 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.4 (s, 3H), 1.47 (s, 9H), 1.97 (dd, 2H, J = 6.75 Hz), 2.06 (s, 3H), 2.55 (dd, 2H, obscured by DMSO peak, J = 6.75 Hz), 2.81 (d of ABX, 1H, J = 17.36 Hz), 3.0 (d of ABX, 1H, J = 17.36 Hz), 6.66 (d, 2H, J = 8.68 Hz), 6.77 (s, 1H), 6.85 (d, 1H, J = 7.96 Hz), 7.0 (d, 2H, J = 8.68 Hz), 7.17 (d, 1H, J = 7.96 Hz), 9.19 (s, 1H); MS-APCI (*m*/*z*): 427.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-propyl-5,6-dihydro-pyran-2-one (3). The title compound was prepared according to the general procedure using 4-hydroxy-6-propyl-6-[2-(4-hydroxy-phenyl)-ethyl-5,6-dihydropyran-2-one (0.1 g, 0.2 mmol), 2-*tert*-butyl-4-5-methylphenyl-*p*-toluenethiosulfonate (0.1 g, 0.2 mmol), K_2CO_3 (0.1 g) and DMF (2 mL). Isolated yield: 63%. IR (KBr): 3420, 2960, 1683, 1600, 1515, 1385, 1250, 1046, 697 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93 (t, 3H, J = 6.99 Hz), 1.36 (m, 2H), 1.47 (s, 9H), 1.76 (m, 2H), 1.94 (m, 2H), 2.03 (s, 3H), 2.53 (m, 2H), 2.8 (d of ABX, 1H, J = 17.36 Hz), 2.92 (d of ABX, 1H, J = 17.36), 6.66 (d, 2H, J = 8.44 Hz), 6.77 (s, 1H), 6.83 (d, 1H, J = 7.96 Hz), 6.99 (d, 2H, J = 8.44 Hz), 7.17 (d, 1H, J = 7.96 Hz), 9.19 (s, 1H); MS-APCI (*m*/*z*): 455, 437.

6-Butyl-(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (4). The title compound was prepared according to the general procedure using 6-butyl-4-hydroxy-6-([2-4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.8 mmol), K_2CO_3 (0.3 g) and DMF (3 mL). Isolated yield: 70%. IR (KBr): 3384, 2956, 1598, 1515, 1249, 1046 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (t, 3H, J = 6.99 Hz), 1.31 (m, 4H) 1.47 (s, 9H), 1.77 (m, 2H), 2.03 (s, 3H), 2.55 (m, 2H, obscured by DMSO peak), 2.83 (d of ABX, 1H, J = 17.36 Hz), 2.94 (d of ABX, 1H, J = 17.36 Hz), 6.67 (d, 2H, J = 8.44 Hz), 6.75 (s, 1H), 6.83 (d, 1H, J = 7.96 Hz), 7.0 (d, 2H, J = 8.44 Hz), 7.17 (d, 1H, J = 7.96 Hz), 9.19 (s, 1H); MS-APCI (*m*/*z*): 469.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-6-[2-(4-hydroxy-phenyl)-ethyl]-6-pentyl-5,6-dihydro-pyran-2-one (5). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-pentyl-5,6-dihydropyran-2-one (0.3 g, 0.8 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 1.0 mmol), K_2CO_3 (0.3 g) and DMF (5 mL). Isolated yield: 63%. IR (KBr): 3325, 2954, 1677, 1597, 1515, 1384, 1046 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (t, 3H, J = 6.5 Hz), 1.31 (m, 6H) 1.34 (s, 9H), 1.77 (m, 2H), 1.97 (m, 2H), 2.03 (s, 3H), 2.53 (m, 2H, obscured by DMSO peak), 2.86 (d of ABX, 1H, J = 17.84 Hz), 2.97 (d of ABX, 1H, J = 17.84 Hz), 6.66 (d, 2H, J = 8.44 Hz), 6.77 (s, 1H), 6.84 (d, 1H, J = 7.96 Hz), 6.99 (d, 1H, J = 8.44 Hz), 7.17 (d, 1H, J = 7.96 Hz), 9.19 (s, 1H); MS-APCI (*m*/*z*): 483, 439.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (6). The title compound was prepared according to the general procedure using 4-hydroxy-6-(4-hydroxyphenyl)ethyl-6-isopropyl-dihydropyran-2-one (0.2 g, 0.4 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.2 g, 0.5 mmol), K_2CO_3 (0.5 g) and DMF (3 mL). Isolated yield: 50%. IR (KBr): 3426, 2963, 1612, 1515, 1387, 1046, 698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93 (d, 3H, J = 6.75 Hz), 0.97 (d, 3H, J = 6.75 Hz), 1.47 (s, 9H), 1.94 (s, 3H), 2.0 (m, 2H), 2.19 (m, 1H), 2.55 (m, 2H), 2.83 (d of ABX, 1H, J = 17.6 Hz), 2.97 (d of ABX, 1H, J = 17.84 Hz), 6.65 (d, 2H, J = 8.44 Hz), 6.72 (s, 1H), 6.81 (d, 1H, J = 7.96 Hz), 6.9 (d, 2H, J = 8.44 Hz), 7.19 (d, 1H, J = 7.96 Hz), 9.19 (s, 1H); MS-APCI (*m*/*z*): 455.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-6-cyclopropyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (7). The compound was prepared according to the general procedure using 6-cyclopropyl-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.4 g, 0.7 mmol), K_2CO_3 (0.2 g) and DMF (2 mL). Isolated yield: 60%. IR (KBr): 3422, 2955, 1681, 1599, 1515, 1263, 1046 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.37 (m, 1H), 0.55 (m, 3H), 1.25 (m, 1H), 1.47 (s, 9H), 1.99 (s, 3H), 2.03 (m, 2H), 2.64 (m, 2H), 2.77 (d of ABX, 1H, J = 17.06 Hz), 2.94 (d of ABX, 1H, J = 17.06 Hz), 6.66 (d, 2H, J = 8.44 Hz), 6.77 (s, 1H), 6.83 (d, 1H, J = 8.05 Hz), 6.99 (d, 2H, J = 8.44 Hz), 7.17 (d, 1H, J = 8.06 Hz), 9.17 (s, 1H); MS-APCI (m/z): 453, 409.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-cyclopentyl-5,6-dihydro-pyran-2-one (8). The title compound was prepared according to the general procedure using 6-cyclopentyl-4-hydroxyl-6-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.4 g, 1.4 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.5 g, 1.5 mmol), K_2CO_3 (0.5 g) and DMF (5 mL). Isolated yield: 56%. IR (KBr): 3347, 2955, 1677, 1599, 1515, 1264, 1046 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.33–1.75 (m, 8H), 1.47 (s, 9H), 1.92 (s, 3H), 1.97 (m, 2H), 2.55 (m, 2H), 2.83 (d of ABX, 1H, J = 17.84 Hz), 2.94 (d of ABX, 1H, J = 18.08 Hz), 6.66 (d, 2H, J = 8.44 Hz), 6.76 (s, 1H), 6.83 (d, 1H, J = 8.2 Hz), 6.98 (d, 2H, J = 8.68 Hz), 7.17 (d, 1H, J = 8.2 Hz), 9.19 (s, 1H); MS-APCI (m/z): 481, 463, 363.

3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-6-cyclohexyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (9). The title compound was prepared according to the general procedure using 6-cyclohexyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (0.6 g, 1.9 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.8 g, 2.3 mmol), K_2CO_3 (1.1 g, 7.6 mmol) and DMF (5 mL). Isolated yield: 80%. IR (KBr): 3390, 2930, 2856, 1683, 1600; ^1H NMR (400 MHz, $CDCl_3$): δ 1.0–1.4 (m, 6H), 1.56 (s, 9H), 2.05 (s, 3 H), 2.6–2.8 (d, m, 3H, J = 17.8 Hz), 3.0 (d, 1H, J = 17.8 Hz), 4.7 (bs, 1H), 6.6–6.7 (d, d, 3 H, J = 8.4 Hz, J = 7.96 Hz), 6.9 (d, 2H, J = 8.4 Hz), 7.3 (d, 1H, J = 7.96 Hz), 7.26 (s, 1H); MS-APCI: (m/z): 495.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (10). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.2 g, 0.6 mmol), 2-*tert*-butyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.8 mmol), K_2CO_3 (0.5 g) and DMF (2 mL). Isolated yield: 62%. IR (KBr): 3409, 2923, 1684, 1597, 1515, 1252, 1046, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.47 (s, 9H), 1.94 (m, 2H), 2.14 (s, 3H), 2.92–2.57 (m, 3H), 4.4 (m, 1H), 6.69 (d, 2H, J = 8.44 Hz), 6.77 (s, 1H), 6.83 (d, 1H, J = 7.96 Hz), 7.03 (d, 2H, J = 8.44 Hz), 7.17 (d, 1H, J = 8.19 Hz), 9.17 (s, 1H); MS-APCI (m/z): 413.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-phenyl-5,6-dihydro-pyran-2-one (11). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-phenyl-5,6-dihydropyran-2-one (0.2 g, 0.6 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.71 mmol), K_2CO_3 (0.4 g, 2.5 mmol) and DMF (3 mL). Isolated yield: 83%. ^1H NMR (400 MHz, DMSO-d_6): δ 1.44 (s, 9H), 1.76 (s, 3H), 2.08–2.21 (m, 3H), 2.42 (m, 1H), 3.36 (d, 1H, J = 17.4 Hz), 3.46 (d, 1H, J = 17.4 Hz), 4.32 (s, 2H), 4.91 (brs, 1H), 6.16 (s, 1H), 6.61 (d, 2H, J = 8.5 Hz), 6.86 (d, 1H, J = 8.5 Hz), 7.21 (s, 1H), 7.34–7.46 (m, 5H), 9.14 (s, 1H), 12.15 (brs, 1H); MS-APCI (m/z): 519.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-methyl-5,6-dihydro-pyran-2-one (12). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-methyl-dihydropyran-2-one (0.2 g, 0.6 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.7 mmol), K_2CO_3 (0.5 g) and DMF (3 mL). Isolated yield: 60%. IR (KBr): 3429, 2924, 1601, 1452, 759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.25 (s, 3H), 1.5 (s, 9H), 1.97 (m, 2H), 2.0 (s, 3H), 2.58 (t, 2H), 2.81 (d of ABX, 1H, J = 17.11 Hz), 2.97 (d of ABX, 1H, J = 17.11 Hz), 4.4 (d, 2H), 6.66 (d, 2H, J = 8.44 Hz), 6.72 (s, 1H), 7.2 (d, 2H, J = 8.44 Hz), 7.28 (s, 1H), 9.19 (s, 1H); MS-APCI (m/z): 457, 439.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-propyl-5,6-dihydro-pyran-2-one (13). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-propyl-5,6-dihydropyran-2-one (0.1 g, 0.2 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.9 g, 0.2 mmol), K_2CO_3 (0.2 g) and DMF (2 mL). Isolated yield: 55%. IR (KBr): 3390, 2959, 1682, 1599, 1515, 1246, 1050 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (t, 3H, J = 7.23 Hz), 1.36 (m, 2H) 1.47 (s, 9H), 1.76 (m, 2H), 1.93 (m, 2H), 1.98 (s, 3H), 2.53 (m, 2H, obscured by DMSO peak), 2.83 (d of ABX, 1H, J = 17.60 Hz), 2.94 (d of ABX, 1H, J = 17.60 Hz), 4.37 (s, 2H), 4.97 (s, 1H), 6.66 (d, 2H, J = 8.44 Hz), 6.72 (s, 1H), 6.98 (d, 2H, J = 8.44 Hz), 7.25 (s, 1H), 9.17 (s, 1H), 12.0 (brs, 1H); MS-APCI (m/z): 485, 467, 423.

6-Butyl-(3-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (14). The title compound was prepared according to the general procedure using 6-butyl-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.7 mmol), K_2CO_3 (0.3 g) and DMF (3 mL). Isolated yield: 67%. IR (KBr): 3423, 2955, 1680, 1599, 1515, 1233 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.89 (m, 3H), 1.31 (m, 4H) 1.5 (s, 9H), 1.64 (m, 2H), 1.97 (s, 3H), 1.89–2.03 (m, 2H, 2.44–2.56 (m, 2H, obscured by DMSO peak), 2.83 (d of ABX, 1H, J = 17.60 Hz), 2.94

(d of ABX, 1H, $J=17.60$ Hz), 4.24 (s, 2H), 4.97 (s, 1H), 6.67 (d, 2H, $J=8.44$ Hz), 6.72 (s, 1H), 6.98 (d, 1H, $J=8.85$ Hz), 7.28 (s, 2H), 9.17 (s, 1H), 12.0 (brs, 1H); MS-APCI (m/z): 499, 481, 437, 375.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-pentyl-5,6-dihydro-pyran-2-one (15). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-pentyl-5,6-dihydropyran-2-one (0.2 g, 0.6 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.2 g, 0.6 mmol), K_2CO_3 (0.2 g) and DMF (2 mL). Isolated yield: 65%. IR (KBr): 3409, 2929, 1676, 1515, 1253, 1044, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.89 (m, 3H), 1.31 (m, 8H) 1.5 (s, 9H), 1.77 (m, 2H), 1.97 (m, 2H), 2.0 (s, 3H), 2.58 (m, 2H, obscured by DMSO peak), 2.84 (d of ABX, 1H, $J=17.4$ Hz), 2.97 (d of ABX, 1H, $J=17.4$ Hz), 4.39 (s, 2H), 4.97 (brs, 1H), 6.66 (d, 2H, $J=8.44$ Hz), 6.72 (s, 1H), 7.0 (d, 2H, $J=8.44$ Hz), 7.28 (s, 1H), 9.17 (s, 1H); MS-APCI (m/z): 513, 495, 451, 259.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (16). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isopropyl-5,6-dihydropyran-2-one (0.2 g, 0.4 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.2 g, 0.5 mmol), K_2CO_3 (0.5 g) and DMF (3 mL). Isolated yield: 45%. IR (KBr): 3418, 2964, 1683, 1611, 1515, 1233, 1050 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (d, 3H, $J=6.99$ Hz), 0.96 (d, 3H, $J=6.75$ Hz), 1.49 (s, 9H), 1.89 (s, 3H), 1.92–2.0 (m, 2H), 2.2 (m, 1H), 2.35–2.6 (m, 2H), 2.75 (d of ABX, 1H, $J=17.60$ Hz), 2.97 (d of ABX, 1H, $J=17.60$ Hz), 4.36 (s, 2H), 4.94 (brs, 1H), 6.65 (d, 2H, $J=8.44$ Hz), 6.69 (s, 1H), 6.96 (d, 1H, $J=8.44$ Hz), 7.28 (s, 1H), 9.15 (s, 1H), 11.94 (brs, 1H); MS-APCI (m/z): 485, 423.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-isobutyl-5,6-dihydro-pyran-2-one (17). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isobutyl-5,6-dihydropyran-2-one (0.3 g, 1.0 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.4 g, 1.0 mmol), K_2CO_3 (0.4 g) and DMF (3 mL). Isolated yield: 44%. IR (KBr): 3375, 2957, 1682, 1598, 1515, 1250, 1042 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (d, 3H, $J=6.27$ Hz), 0.94 (d, 3H, $J=6.51$ Hz) 1.47 (s, 9H), 1.66 (m, 1H), 1.72 (m, 2H), 1.97 (m + s, 5H), 2.58 (m, 2H, obscured by DMSO peak), 2.77 (d of ABX, 1H, $J=17.60$ Hz), 3.0 (d of ABX, 1H, $J=17.60$ Hz), 4.39 (s, 2H), 4.97 (s, 1H), 6.66 (d, 2H, $J=8.44$ Hz), 6.75 (s, 1H), 6.99 (s, 1H), 7.28 (d, 2H, $J=8.44$ Hz), 9.17 (s, 1H), 12.0 (brs, 1H); MS-APCI (m/z): 499, 481, 437.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-6-cyclopropyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (18). The title compound was prepared according to the general procedure using 6-cyclopropyl-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.3 g, 1.1 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.4 g, 1.1 mmol), K_2CO_3 (0.4 g) and DMF (3 mL). Isolated yield: 50%. IR (KBr): 3408, 2954, 1681, 1614, 1515, 1263, 1048 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.36 (m, 1H), 0.53 (m, 3H), 1.25 (m, 1H) 1.47 (s, 9H), 1.92 (s, 3H), 2.03 (m, 2H), 2.64 (m, 2H), 2.77 (d of ABX, 1H, $J=17.4$ Hz), 2.92 (d of ABX, 1H, $J=17.4$ Hz), 4.36 (s, 2H), 4.94 (s, 1H), 6.66 (d, 2H, $J=8.44$ Hz), 6.75 (s, 1H), 6.97 (d, 2H, $J=8.44$ Hz), 7.28 (s, 2H), 9.17 (s, 1H), 12.0 (brs, 1H); MS-APCI (m/z): 483, 465, 421, 365.

3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-6-cyclobutyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (19). The title compound was prepared according to the general procedure using 6-cyclobutyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (0.1 g, 0.5 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.1 g, 0.4 mmol), K_2CO_3 (0.2 g, 1.4 mmol) and DMF (3 mL). Isolated yield: 45%. IR (KBr): 3339, 2946, 2866, 1679, 1599 in cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 9H), 1.7–2.1 (m, 7H), 2.02 (s, 3H), 2.2–2.4 (m, 1H), 2.5–2.65 (m, 2 H), 2.65 (d, 2H, $J=8.1$ Hz), 2.65–2.8 (m, 1 H), 2.83 (d, 1 H, $J=8.1$ Hz), 4.59 (s, 2H), 4.88 (bs, 1H), 6.71 (d, 2H, $J=6.5$ Hz), 6.76 (s, 1H), 6.96 (d, 2H, $J=6.5$ Hz), 7.34 (s, 1H), 7.71 (s, 1H); MS-APCI (m/z): 497.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-cyclopentyl-5,6-dihydro-pyran-2-one (20). The title compound was prepared according to the general procedure using 6-cyclopentyl-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.2 g, 0.7 mmol), K_2CO_3 (0.3 g) and DMF (2 mL). Isolated yield: 38%. IR (KBr): 3393, 2955, 1678, 1600, 1515, 1259, 1050 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.31–1.55 (m, 8H) 1.83 (s, 9H), 1.92 (m, 2H), 2.34 (m, 1H), 2.55 (m, 2H, obscured by DMSO peak), 2.77 (d of ABX, 1H, $J=17.82$ Hz), 2.89 (d of ABX, 1H, $J=17.82$ Hz), 4.31 (s, 2H), 4.89 (s, 1H), 6.61 (t, 2H), 6.64 (d, 1H, $J=7.31$ Hz), 6.92 (d, 1H, $J=7.31$ Hz), 7.2 (s, 1H), 9.17 (s, 1H), 11.9 (brs, 1H); MS-APCI (m/z): 511, 493, 449, 394.

3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-6-cyclohexyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (21). The title compound was prepared according to the general procedure using 6-cyclohexyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (0.2 g, 0.5 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.6 mmol), K_2CO_3 (0.3 mg, 2.2 mmol) and DMF (4 mL). Isolated yield: 55%. IR (KBr): 3339, 2931, 2857, 1674, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.0–1.30 (m, 6H), 1.48 (s, 9H), 1.60–2.00 (m, 9 H), 1.92 (s, 3H), 2.73 (d, 1H, $J=18$ Hz), 2.95 (d, 1H, $J=18$ Hz), 4.36 (s, 2H), 4.95 (brs, 1H), 6.65 (d, 2H, $J=8.4$ Hz), 6.69

(s, 1H), 6.96 (d, 2H, $J=8.5$ Hz), 7.27 (s, 1 H), 8.31 (s, 1H), 9.15 (s, 1H); MS-APCI (m/z): 525.

(3-(2-*tert*-Butyl-4-hydroxy-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-methyl-5,6-dihydro-pyran-2-one (22). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-methyl-dihydropyran-2-one (0.1 g, 0.3 mmol), 2-*tert*-butyl-4-hydroxy-5-methylphenyl-*p*-toluenethiosulfonate (0.1 g, 0.3 mmol), K_2CO_3 (0.5 g) and DMF (3 mL). Isolated yield: 67%. IR (KBr): 3389, 2954, 1679, 1598, 1385, 1245 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 3H), 1.47 (s, 9H), 1.92 (s, 3H), 1.86 (m, 2H), 2.53 (m, 2H), 2.75 (d of ABX, 1H, $J=17.36$ Hz), 2.94 (d of ABX, 1H, $J=17.36$ Hz), 6.64 (s, 1H), 6.69 (d, 2H, $J=8.44$ Hz), 6.77 (s, 1H), 6.97 (d, 2H, $J=8.44$ Hz), 9.06 (s, 1H), 9.19 (s, 1H), MS-APCI (m/z): 443.

(3-(2-*tert*-Butyl-4-hydroxy-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (23). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isopropyl-dihydropyran-2-one (0.4 g, 1.6 mmol), 2-*tert*-butyl-4-hydroxy-5-methylphenyl-*p*-toluenethiosulfonate (0.7 g, 1.9 mmol), K_2CO_3 (0.4 g) and DMF (5 mL). Isolated yield: 63%. IR (KBr): 3400, 2963, 1675, 1601, 1515, 1387, 1242, 1052 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (d, 3H, $J=6.99$ Hz), 0.97 (d, 3H, $J=6.75$ Hz), 1.44 (s, 9H), 1.77 (s, 3H), 1.94 (m, 2H), 2.19 (m, 1H), 2.53 (m, 2H, obscured by DMSO peak), 2.72 (d of ABX, 1H, $J=17.60$ Hz), 2.94 (d of ABX, 1H, $J=17.60$ Hz), 6.66 (m, 3H), 6.77 (s, 1H), 6.96 (d, 2H, $J=8.44$ Hz), 9.01 (s, 1H), 9.14 (s, 1H); MS-APCI (m/z): 471, 379, 307, 277, 107.

3-(2-*tert*-Butyl-4-hydroxy-5-methyl-phenylsulfanyl)-6-cyclohexyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (24). The title compound was prepared according to the general procedure using 6-cyclohexyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-4-hydroxy-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.7 mmol), K_2CO_3 (0.4 g, 2.7 mmol) and DMF (4 mL). Isolated yield: 80%. IR (KBr): 3339, 2931, 2857, 1674, 1601 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.0–1.4 (m, 6H), 1.45 (s, 9H), 1.80 (s, 3 H), 1.6–2.0 (m, 9H), 2.71 (d, 1H, $J=17.8$ Hz), 2.93 (d, 1H, $J=17.9$ Hz), 6.64 (d, 2H, $J=8.4$ Hz), 6.66 (s, 1H), 6.77 (s, 1 H), 6.94 (d, 2H, $J=8.4$ Hz), 8.31 (s, 1H), 9.02 (s, 1H), 9.13 (s, 1H), 11.75 (brs, 1H); MS-APCI (m/z): 512.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-methyl-5,6-dihydro-pyran-2-one (25). The compound **26** (0.1 g) was taken in 2 mL of THF and 2 mL of methanol. To it 2 mL of concentrated HCl was added and kept under stirring overnight. Solvents were evaporated and the residue was purified by flash silica gel chromatography. Isolated yield: 63%. IR (KBr): 3426, 2963, 1612, 1515, 1387, 1046, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 3H), 1.49 (s, 9H), 1.92 (s, 3H), 1.86–2.0 (m, 2H), 2.5 (m, 2H), 2.75 (d of ABX, 1H, $J=17.36$ Hz), 2.94 (d of ABX, 1H, $J=17.36$ Hz), 3.69 (brs, 2H), 3.92 (t, 2H), 4.81 (brs, 1H), 6.67 (d, 2H, $J=8.44$ Hz), 6.75 (s, 1H), 6.8 (s, 1H), 6.97 (d, 2H, $J=8.44$ Hz), 9.17 (s, 1H); MS-APCI (m/z): 487, 443.

(3-(2-*tert*-Butyl-4-(2-methoxymethoxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-methyl-5,6-dihydro-pyran-2-one (26). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-methyl-dihydropyran-2-one (0.5 g, 2.03 mmol), 2-*tert*-butyl-4-(2-methoxymethoxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.9 g, 2.0 mmol), K_2CO_3 (1 g) and DMF (5 mL). Isolated yield: 32%. IR (KBr): 3326, 2950, 1682, 1598, 1515, 1253, 1040 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.29 (s, 3H), 1.35 (s, 9H), 1.92 (s, 3H), 1.85–2.0 (m, 2H), 2.63 (s, 3H), 2.61–2.45 (t, 2H), 2.78 (d of ABX, 1H, $J=17.36$ Hz), 2.97 (d of ABX, 1H, $J=17.36$ Hz), 3.28 (s, 3H), 3.76 (m, 2H), 4.1 (m, 2H), 4.63 (s, 2H) 6.67 (d, 2H, $J=8.44$ Hz), 6.75 (s, 1H), 6.83 (s, 1H), 6.97 (d, 2H, $J=8.44$ Hz), 9.14 (s, 1H); MS-APCI (m/z): 531, 499, 487.

(3-(2-*tert*-Butyl-4-(2-methoxymethoxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-propyl-5,6-dihydro-pyran-2-one (27). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-propyl-5,6-dihydropyran-2-one (0.1 g, 0.5 mmol), 2-*tert*-butyl-4-(2-methoxymethoxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.6 mmol), K_2CO_3 (0.2 g) and DMF (2 mL). Isolated yield: 62%. IR (KBr): 3427, 2928, 1604, 1515, 1253, 1051 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (t, 3H, $J=7.23$ Hz), 1.34 (m, 2H), 1.5 (s, 9H), 1.75 (m, 2H), 1.92 (s, 3H), 1.94 (m, 2H), 2.5 (m, obscured by DMSO peak, 2H), 2.78 (d of ABX, 1H, $J=17.06$ Hz), 2.92 (d of ABX, 1H, $J=17.06$ Hz), 3.69 (q, 2H), 3.97 (t, 2H, $J=4.82$ Hz), 4.81 (brt, 1H), 6.66 (d, 2H, $J=8.44$ Hz), 6.75 (s, 1H), 6.83 (s, 1H), 6.99 (d, 2H, $J=8.44$ Hz), 9.14 (s, 1H); MS-APCI (m/z): 515, 471.

(3-(2-*tert*-Butyl-4-(2-hydroxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-butyl-5,6-dihydro-pyran-2-one (28). The title compound was prepared according to the general procedure using 4-hydroxy-6-(4-hydroxyphenyl)ethyl-6-butyl-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-4-(2-*tert*-butyldimethylsilyloxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.4 g, 0.8 mmol), K_2CO_3 (0.2 g) and DMF (3 mL). The crude compound obtained was taken in 2 mL of THF and 2 mL of MeOH. To it 2 mL of concentrated HCl was stirred overnight. Solvents were evaporated and the residue was purified by flash silica gel chromatography. Isolated yield: 48%. ^1H NMR (400 MHz, DMSO-d_6): δ 0.9 (t, 3H, $J=6.51$ Hz), 1.28 (m, 4H), 1.5 (s, 9H), 1.76 (m, 2H), 1.92 (s, 3H), 1.94 (m, 2H), 2.53 (m, 2H, obscured by DMSO peak), 2.81 (d of ABX, 1H, $J=17.6$ Hz), 2.92 (d of ABX, 1H, $J=17.6$ Hz), 3.69 (brs, 2H), 3.95 (t, 2H, $J=4.82$ Hz), 4.8 (brs, 1H), 6.66 (d, 2H, $J=8.44$ Hz), 6.75 (s, 1H), 6.83 (s, 1H), 6.98 (d, 2H, $J=8.44$ Hz), 9.17 (s, 1H); APCI (m/z): 529, 485.

(3-(2-*tert*-Butyl-4-(2-hydroxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-pentyl-5,6-dihydro-pyran-2-one (29). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-pentyl-5,6-dihydropyran-2-one (0.2 g, 0.6 mmol), 2-*tert*-butyl-4-(2-*tert*-butyldimethylsilyloxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.4 g, 0.7 mmol), K_2CO_3 (0.2 g) and DMF (3 mL). The crude compound obtained was taken in 2 mL of THF and 2 mL of MeOH. To it 2 mL of concentrated HCl was stirred overnight. Solvents were evaporated and the residue was purified by flash silica gel chromatography. Isolated yield: 52%. IR (KBr): 3429, 2928, 1679, 1603, 1515, 1252, 1048 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.89 (t, 3H, J = 6.75 Hz), 1.28 (m, 6H), 1.5 (s, 9H), 1.75 (s, 3H), 1.92 (m, 2H), 2.16 (m, 1H), 1.94 (m, 2H), 2.81 (d of ABX, 1H, J = 17.6 Hz), 2.92 (d of ABX, 1H, J = 17.6 Hz), 3.7 (brs, 2H), 3.97 (t, 2H), 4.8 (brs, 1H), 6.66 (d, 2H, J = 8.44 Hz), 6.73 (s, 1H), 6.83 (s, 1H), 6.98 (d, 2H, J = 8.44 Hz), 9.17 (s, 1H); MS-APCI (m/z): 543, 499, 335.

(3-(2-*tert*-Butyl-4-(2-hydroxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (30). The title compound was prepared according to the general procedure using 4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-6-isopropyl-dihydropyran-2-one (0.2 g, 0.4 mmol), 2-*tert*-butyl-4-(2-methoxymethoxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.6 mmol), K_2CO_3 (0.5 g) and DMF (2 mL). The crude compound obtained (0.1 g) was taken in 2 mL of THF and 2 mL of MeOH. To it 2 mL of concentrated HCl was stirred overnight. Solvents were evaporated and the residue was purified by flash silica gel chromatography. Isolated yield: 65%. IR (KBr): 3430, 2963, 1684, 1614, 1515, 1253, 1050 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (d, 3H, J = 6.99 Hz), 0.97 (d, 3H, J = 6.55 Hz), 1.47 (s, 9H), 1.81 (s, 3H), 1.93 (m, 2H), 2.16 (m, 1H), 2.43–2.56 (m, 2H), 2.72 (d of ABX, 1H, J = 17.36 Hz), 2.81 (d of ABX, 1H, J = 17.36 Hz), 3.67 (brs, 2H), 3.94 (t, 2H), 4.81 (brs, 1H), 6.64 (d, 2H, J = 8.44 Hz), 6.72 (s, 1H), 6.81 (s, 1H), 6.94 (d, 2H, J = 8.44 Hz), 9.14 (s, 1H); MS-APCI (m/z): 515, 497, 311.

(3-(2-*tert*-Butyl-4-(2-hydroxy-ethoxy)-5-methyl-phenylsulfanyl)-6-cyclopropyl-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-5,6-dihydro-pyran-2-one (31). The title compound was prepared according to the general procedure using 6-cyclopropyl-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl-5,6-dihydropyran-2-one (0.2 g, 0.6 mmol), 2-*tert*-butyl-4-(2-*tert*-butyldimethylsilyloxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.6 mmol), K_2CO_3 (0.2 g) and DMF (2 mL). The crude compound obtained was taken in 3 mL of THF. To it 1 mL of concentrated HCl was stirred at room temperature for 1 h. Solvents were evaporated and the residue was purified by flash chromatography. Isolated yield: 53%. IR (KBr): 3400, 2954, 1683, 1611, 1515, 1253, 1051 cm^{-1}; ^1H NMR (40 MHz, DMSO-d_6): δ 0.36 (m, 3H), 0.53 (m, 3H), 1.25 (m, 1H), 1.5 (s, 9H), 1.86 (s, 3H), 1.98 (t, 2H), 2.61 (m, 2H), 2.72 (d of ABX q, 1H, J = 17.60 Hz), 2.86 (d of ABX q, 1H, J = 17.60 Hz), 3.69 (brt, 2H), 3.94 (t, 2H, J = 5.06 Hz), 4.8 (brs, 1H), 6.66 (d, 2H, J = 8.44 Hz), 6.75 (s, 1H), 6.81 (s, 1H), 6.97 (d, 2H, J = 8.44 Hz), 9.14 (s, 1H); MS-APCI (m/z): 513, 416, 305.

(3-(2-*tert*-Butyl-4-(2-hydroxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-cyclopentyl-5,6-dihydro-pyran-2-one (32). The title compound was prepared according to the general procedure using 6-cyclopentyl-4-hydroxy-6-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-4-(2-*tert*-butyldimethylsilyloxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.7 g, 0.7 mmol), K_2CO_3 (0.2 g) and DMF (2 mL). The crude compound obtained was taken in 3 mL of THF. To it 1 mL of concentrated HCl was stirred at room temperature for 1 h. Solvents were evaporated and the residue was purified by flash silica gel chromatography. Isolated yield: 56%. IR (KBr): 3406, 2954, 1608, 1515, 1253, 1050 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.33–1.72 (m, 8H), 1.47 (s, 9H), 1.81 (s, 3H), 1.94 (m, 2H), 2.36 (m, 1H), 2.55 (m, 2H, obscured by DMSO peak), 2.81 (d of ABX, 1H, J = 17.60 Hz), 2.92 (d of ABX, 1H, J = 17.60 Hz), 3.69 (brd, 2H), 3.97 (t, 2H, J = 5.06 Hz), 4.81 (brs, 1H), 6.66 (d, 2H, J = 8.44 Hz), 6.75 (s, 1H), 6.81 (s, 1H), 6.97 (d, 2H, J = 8.44 Hz), 9.14 (s, 1H); MS-APCI (m/z): 541, 497, 423, 259.

6-[2-(4-Aminophenyl)-ethyl]-(3-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-phenyl-5,6-dihydro-pyran-2-one (33). The title compound was prepared according to the general procedure using 6-([2-4-actylaminophenyl)ethyl]-4-hydroxy-6-phenyl-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.9 mmol), K_2CO_3 (0.5 g) and DMF (5 mL). The suspension was cooled to 5°C and treated with 20 mL of water and 1 mL of glacial AcOH. The reaction mixture was extracted with EtOAc, washed with brine, dried, and concentrated. The residue on trituration with Et_2O afforded a solid, which was filtered and air-dried. Isolated yield: 64%. ^1H NMR (400 MHz, DMSO-d_6): δ 1.38 (m, 9H), 1.69 (s, 3H), 1.94 (s, 3H), 2.14 (m, 3H), 2.44 (m, 1H, obscured by DMSO peak), 4.26 (s, 2H), 4.90 (brs, 1H), 6.10 (s, 1H), 6.94 (d, 2H, J = 8.2 Hz), 7.16 (s, 1H), 7.29–7.47 (m, 7H), 9.78 (s, 1H). The solid obtained, the *N*-acetyl derivative (0.2 g, 0.34 mmol), was taken in 4 mL of 50% NaOH solution, treated with 30 mL of water and 5 mL of MeOH and was refluxed overnight. The reaction was cooled to room temperature, concentrated, and suspended in phosphate buffer (pH 7.5). The reaction mixture was acidified to pH 6.8 with phosphoric acid and extracted with CH_2Cl_2 (2× 50 mL); the combined extracts were washed with brine, dried and concentrated. Isolated yield: 56%. ^1H NMR (400 MHz, DMSO-d_6): δ 1.44 (s, 9H), 1.76 (s, 3H), 2.05–2.22 (m, 3H), 2.4 (m, 1H), 4.32 (s, 2H), 4.90 (brs, 1H), 6.17 (s, 1H), 6.47 (d, 2H, J = 8.2 Hz), 6.75 (d, 2H), 7.21 (s, 1H), 7.38–7.43 (m, 5H); MS-APCI (m/z): 518.

6-[2-(4-Aminophenyl)-ethyl]-(3-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one (34). The title compound was prepared according to the general procedure using

6-[2-(4-aminophenyl)ethyl]-4-hydroxy-6-isopropyl-5,6-dihydropyran-2-one (0.7 mmol prepared from 0.3 g (0.7 mmol) of the corresponding Boc-derivative and CH_2Cl_2 saturated with HCl gas), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.7 mmol), K_2CO_3 (1.0 g) and DMF (5 mL). Isolated yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (m, 6H), 1.42 (s, 9H), 1.87 (m, 5H), 2.14 (m, 1H), 2.4 (m, obscured by DMSO peak, 2H), 2.66 (d, 1H, J = 17.6 Hz), 2.88 (d, 1H, J = 17.8 Hz), 4.30 (s, 2H), 4.90 (brs, 1H), 6.43 (d, 2H, J = 8.3 Hz), 6.64 (s, 1H), 6.77 (d, 2H, J = 8.3 Hz), 7.20 (s, 1H); MS-APCI (m/z): 484.

6-[2-(4-Aminophenyl)-ethyl]-(3-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isobutyl-5,6-dihydro-pyran-2-one (35). The title compound was prepared according to the general procedure using 6-[2-(4-aminophenyl)ethyl]-4-hydroxy-6-isobutyl-5,6-dihydropyran-2-one (0.6 mmol prepared from 0.2 g (0.6 mmol) of the corresponding Boc-derivative and CH_2Cl_2 saturated with HCl gas), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.7 mmol), K_2CO_3 (1.0 g) and DMF (5 mL). Isolated yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93 (m, 6H), 1.48 (s, 9H), 1.62–1.84 (m, 3H), 1.91–1.99 (m, 2H), 2.45 (m, obscured by DMSO peak, 2H), 2.76 (d, 1H, J = 17.6 Hz), 2.94 (d, 1H, J = 17.3 Hz), 4.37 (s, 2H), 4.94 (brs, 1H), 6.49 (d, 2H, J = 8.2 Hz), 6.76 (s, 1H), 6.85 (d, 2H, J = 8.2 Hz), 7.26 (s, 1H); MS-APCI (m/z): 498.

6-[2-(4-Aminophenyl)-ethyl]-(3-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-6-cyclohexyl-4-hydroxy-5,6-dihydro-pyran-2-one (36). The title compound was prepared according to the general procedure using 6-[2-(4-aminophenyl)ethyl]-4-hydroxy-6-cyclohexyl-5,6-dihydropyran-2-one (0.8 mmol) (prepared from 0.3 g (0.6 mmol) of the corresponding Boc-derivative and CH_2Cl_2 saturated with HCl gas), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.3 g, 0.7 mmol), K_2CO_3 (1.0 g) and DMF (5 mL). Isolated yield: 74%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.0–1.35 (m, 5H), 1.48 (s, 9H), 1.63 (m, 1H), 1.78 (m, 5H), 1.95 (s + m, 7H), 2.45 (m, obscured by DMSO peak, 2H), 2.70 (d, 1H, J = 18.0 Hz), 2.85 (d, 1H, J = 17.8 Hz), 4.37 (s, 2H), 4.95 (brs, 1H), 6.49 (d, 2H, J = 8.2 Hz), 6.70 (s, 1H), 6.83 (d, 2H, J = 8.2 Hz), 7.27 (s, 1H); MS-APCI (m/z): 524.

(3-(2-*tert*-Butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydro-pyran-2-one (37). The title compound was prepared according to the general procedure using 4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydropyran-2-one (0.3 g, 1.2 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.5 g, 1.4 mmol), K_2CO_3 (0.3 g) and DMF (5 mL). Isolated yield: 70%. IR (KBr): 3482, 2964, 1657, 1602, 1384, 1046, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (d, 3H, J = 6.99 Hz), 0.97 (d, 3H, J = 6.75 Hz), 1.5 (s, 9H), 1.92 (s, 3H), 2.03 (m, 2H), 2.23 (m, 1H), 2.64 (m, 2H), 2.81 (d of ABX, 1H, J = 15.14 Hz), 3.0 (d of ABX, 1H, J = 15.14 Hz), 6.75 (d, 1H, J = 1.45 Hz), 6.82 (dd, 1H, J = 8.19 Hz, J = 1.45 Hz), 7.17 (m, 3H), 7.28 (m, 2H); MS-APCI (m/z): 439, 421, 395, 365.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-phenyl-6-phenethyl-5,6-dihydro-pyran-2-one (38). The title compound was prepared according to the general procedure using 4-hydroxy-6-phenyl-6-phenethyl-5,6-dihydropyran-2-one (0.5 g, 1.7 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.8 g, 2.1 mmol), K_2CO_3 (0.7 g) and DMF (5 mL). Isolated yield: 79%. IR (KBr): 3445, 1699, 1584 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (s, 9H), 1.70 (s, 3H), 2.19 (m, 3H), 2.47–2.53 (m, 1H), 3.35 (q, obscured by water peak, 2H), 4.26 (s, 2H), 4.85 (brs, 1H), 6.11 (s, 1H), 7.03–7.20 (m, 6H), 7.29–7.33 (m, 1H), 7.38 (m, 4H); MS-APCI (m/z): 501.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydro-pyran-2-one (39). The title compound was prepared according to the general procedure using 4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydropyran-2-one (0.2 g, 0.7 mmol), 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-*p*-toluenethiosulfonate (0.2 g, 0.7 mmol), K_2CO_3 (0.3 g) and DMF (2 mL). Isolated yield: 72%. IR (KBr): 3424, 2963, 1681, 1603, 1390, 1048, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (d, 3H, J = 6.99 Hz), 0.98 (d, 3H, J = 6.99 Hz), 1.5 (s, 9H), 1.89 (s, 3H), 2.03 (m, 2H), 2.25 (m, 1H), 2.64 (m, 2H), 2.77 (d of ABX, 1H, J = 17.84 Hz), 2.99 (d of ABX, 1H, J = 17.84 Hz), 4.36 (s, 2H), 4.97 (s, 1H), 6.69 (s, 1H), 7.19 (m, 3H), 7.28 (m, 3H); MS-APCI (m/z): 469, 451, 407.

(3-(2-*tert*-Butyl-4-hydroxy-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydro-pyran-2-one (40). The title compound was prepared according to the general procedure using 4-hydroxy-6-(4-hydroxyphenyl)ethyl-6-isopropyl-5,6-dihydropyran-2-one (0.4 g, 1.7 mmol), 2-*tert*-butyl-4-hydroxy-5-methylphenyl-*p*-toluenethiosulfonate (0.6 g, 1.8 mmol), K_2CO_3 (0.4 g) and DMF (5 mL). Isolated yield: 70%. IR (KBr): 3403, 2965, 1680, 1604, 1387, 1161, 1050, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (d, 3H, J = 6.99 Hz), 0.97 (d, 3H, J = 6.75 Hz), 1.45 (s, 9H), 1.75 (s, 3H), 2.0 (t, 2H), 2.2 (m, 1H), 2.61 (m, 2H), 2.75 (d of ABX, 1H, J = 17.84 Hz), 2.95 (d of ABX, 1H, J = 17.84 Hz), 6.64 (s, 1H), 6.76 (s, 1H), 7.17 (m, 3H), 7.26 (t, 2H, J = 6.99 Hz), 9.03 (s, 1H); MS-APCI (m/z): 455, 291, 247, 159.

(3-(2-*tert*-Butyl-4-(2-hydroxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydro-pyran-2-one (41). The title compound was prepared according to the general procedure using 4-hydroxy-6-(4-phenethyl)-6-phenyl-dihydropyran-2-one (0.3 g, 0.9 mmol), 2-*tert*-butyl-4-(2-*tert*-butyldimethylsilyloxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.5 g, 0.9 mmol), K_2CO_3 (0.6 g) and DMF (8 mL). The crude compound obtained (0.1 g) was dissolved in 2 mL of methanol and 1 mL of concd HCl was added. The reaction mixture was stirred at room temperature for 0.5 h. Solvents were evaporated and the residue was purified by flash silica gel chromatography. Isolated yield: 62%. IR (KBr): 3335, 2952, 1675, 1604, 1449, 1253, 1170, 1043, 767, 702 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53 (s, 9H), 1.75 (s, 3H), 1.92 (m, 1H), 2.19–2.42 (m,

3H), 2.75 (m, 1H), 3.31 (ABX q, 2H, $J = 17.36$ Hz), 3.94 (m, 2H), 4.03 (t, 2H), 6.19 (s, 1H), 6.83 (s, 1H), 7.08 (d, 2H, $J = 6.75$ Hz), 7.15 (t, 1H, $J = 7.5$ Hz), 7.23 (t, 2H, $J = 7.2$ Hz), 7.33–7.47 (m, 5H), 7.66 (brs, 1H); MS-APCI (m/z): 532, 325, 240, 208, 193.

(3-(2-*tert*-Butyl-4-(2-hydroxy-ethoxy)-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydropyran-2-one (42). The title compound was prepared according to the general procedure using 4-hydroxy-6-(4-hydroxyphenyl)ethyl-6-isopropyl-dihydropyran-2-one (0.2 g, 0.8 mmol), 2-*tert*-butyl-4-(2-*tert*-butyldimethylsilyloxy-ethoxy)-5-methylphenyl-*p*-toluenethiosulfonate (0.4 g, 0.8 mmol), K_2CO_3 (0.2 g) and DMF (3 mL). The crude compound obtained (0.1 g) was taken in 2 mL of THF and 2 mL of methanol. To it 2 mL of concd HCl was stirred overnight. Solvents were evaporated and the residue was purified by flash silica gel chromatography. Isolated yield: 48%. IR (KBr): 3419, 2962, 1604, 1486, 1384, 1253, 1047 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.94 (d, 3H, $J = 7.23$ Hz), 0.97 (d, 3H, $J = 6.99$ Hz), 1.5 (s, 9H), 1.81 (s, 3H), 2.0 (m, 2H), 2.2 (m, 1H), 2.64 (m, 2H), 2.75 (d of ABX, 1H, $J = 17.84$ Hz), 2.97 (d of ABX, 1H, $J = 17.84$ Hz), 3.66 (brs, 2H), 3.94 (t, 2H, $J = 5.06$ Hz), 4.8 (brs, 1H), 6.72 (s, 1H), 6.81 (s, 1H), 7.17 (t, 3H), 7.27 (t, 2H); MS-APCI (m/z): 499, 481, 291.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxypheny)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (16*S*). (*S*)-4-Hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (***S*-X**, **X = OH** 0.3 g, 1.1 mmol) in DMF (12 mL), K_2CO_3 (0.6 g, 4.34 mmol) was added followed by toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenyl) ester (0.4 g, 1.2 mmol). After stirring the reaction mixture overnight at room temperature, the product was partitioned between 1 N NaOH and Et_2O. The aqueous layer was acidified to pH 4–5 with 1 N HCl and extracted with EtOAc. The combined organic phases were washed dried and concentrated. The resulting residue on trituration with Et_2O furnished the title compound. ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (d, 3H, $J = 7.0$ Hz), 0.96 (d, 3H, $J = 6.75$ Hz), 1.49 (s, 9H), 1.89 (s, 3H), 1.92–2.0 (m, 2H), 2.2 (m, 1H), 2.35–2.6 (m, 2H), 2.75 (d of ABX q, 1H, $J = 18.3$ Hz), 2.97 (d of ABX, 1H, $J = 17.8$ Hz), 4.36 (s, 2H), 4.94 (brs, 1H), 6.65 (d, 2H, $J = 8.4$ Hz), 6.69 (s, 1H), 6.96 (d, 2H, $J = 8.4$ Hz), 7.28 (s, 1H), 9.15 (s, 1H), 11.97 (brs, 1H); MS-CI (m/z): 485.

(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-[2-(4-hydroxypheny)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (16*R*). To (*R*)-4-hydroxy-6-[2-(4-hydroxy-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (***R*-X**, **X = OH**, 0.12 g, 0.43 mmol) in DMF (5 mL), K_2CO_3 (0.2 g, 1.74 mmol) was added followed by toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenyl) ester (0.2 g, 0.5 mmol). After stirring the reaction mixture overnight at room temperature, the product was partitioned between 1 N NaOH and Et_2O. The aqueous layer was acidified to pH 4–5 with 1 N HCl and extracted with EtOAc. The combined organic phases were washed, dried and concentrated. The resulting residue on trituration with Et_2O furnished the title compound. ^1H NMR (400 MHz, DMSO-d_6): δ 0.92 (d, 3H, $J = 7.0$ Hz), 0.96 (d, 3H, $J = 6.75$ Hz), 1.49 (s, 9H), 1.89 (s, 3H), 1.92–2.0 (m, 2H), 2.2 (m, 1H), 2.35–2.6 (m, 2H), 2.75 (d of ABX q, 1H, $J = 18.1$ Hz), 2.97 (d of ABX, 1H, $J = 17.6$ Hz), 4.36 (s, 2H), 4.94 (brs, 1H), 6.65 (d, 2H, $J = 8.2$ Hz), 6.69 (s, 1H), 6.96 (d, 2H, $J = 8.4$ Hz), 7.28 (s, 1H), 9.15 (s, 1H), 11.97 (brs, 1H); MS-CI (m/z): 485.

(*S*)-6-[2-(4-Aminophenyl)-ethyl]-(3-(2-*tert*-butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one (34*S*). The title compound was prepared according to the general procedure using (*S*)-4-hydroxy-6-[2-(4-*tert*-butoxycarbonylamino-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (***S*-X**, **X = NH-Boc**, 15.0 g, 40 mmol), *p*-toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenyl) ester (16.0 g, 43.9 mmol), K_2CO_3 (24.3 g, 175.8 mmol) and DMF (50 mL). To the reaction mixture water was added and brought to pH 7.0 using ammonium phosphate solution. The product was extracted with EtOAc; the extracts were dried and concentrated to yield pure (*S*)-6-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethyl]-(3-(2-*tert*-butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one. Isolated yield: 86%. ^1H NMR (300 MHz, MeOH-d_4): δ 0.83–0.94 (m, 6H), 1.44 (s, 9H), 1.45 (s, 9H), 1.86 (s, 3H), 1.93–1.98 (m, 2H), 2.16–2.2 (m, 1H), 2.52–2.57 (m, 2H), 2.75 (d, 1H), 2.96 (d, 1H), 4,35 (s, 2H), 6.68 (s, 1H), 7.03 (d, 2H), 7.21 (s, 1H), 7.26 (d, 2H), 9.22 (s, 1H). The above compound (17.3 g, 29.6 mmol) taken in DMSO (50 mL) was added to sodium hydroxide (11.9 g, 296.3 mmol) in water (50 mL). The reaction mixture was degassed with nitrogen and heated to 120°C. After 2 h, the reaction mixture was cooled to room temperature and to it water (~400 mL) was added. The reaction mixture was neutralized with ammonium phosphate solution to pH 7.0. The product was extracted with EtOAc and the organic layer was filtered through a plug of Celite. Concentration of the organic layer afforded a solid, which was taken in Et_2O and filtered to obtain a solid. Isolated yield: 87%. IR (KBr): 8429, 2960, 2874, 1616, 1601, 1514, 1481, 1047, 1037 cm^{-1}; ^1H NMR (300 MHz, MeOH-d_4): δ 1.02 (d, 3H, $J = 6.84$ Hz), 1.04 (d, 3H, $J = 6.6$ Hz), 1.55 (s, 9H), 1.96 (s, 3H), 2.00–2.17 (m, 2H), 2.30 (m, 1H), 2.59–2.67 (m, 3H), 2.95 (d, 1H, $J = 16.60$), 4.49 (s, 2H), 6.81–6.85 (m, 3H), 7.01 (d, 2H, $J = 8.30$ Hz), 7.29 (s, 1H); MS-APCI (m/z): 484.

(*R*)-6-[2-(4-Aminophenyl)-ethyl]-(3-(2-*tert*-butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one (34*R*). The title compound was prepared according to the general procedure using (*R*)-4-hydroxy-6-[2-(4-*tert*-butoxycarbonylamino-phenyl)-ethyl]-6-isopropyl-5,6-dihydro-pyran-2-one (***R*-X**, **X = NH-Boc**, 1.9 g, 5.1 mmol), *p*-toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenyl) ester (2.0 g, 5.6 mmol), K_2CO_3 (2.1 g, 15.2 mmol) and DMF (5 mL). To the reaction mixture water was added and brought to pH 7.0 using ammonium phosphate solution. The product was extracted with EtOAc; the extracts were dried and concentrated to yield pure (*R*)-6-[2-(4-*tert*-

butoxycarbonylaminophenyl)-ethyl]-(3-(2-*tert*-butyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-5,6-dihydro-pyran-2-one. Isolated yield: 68%. Spectral data were the same as its *S* enantiomer. The Boc group from above product was deprotected using TFA (5 mL) and CH_2Cl_2 (5 mL). The crude product was purified by flash silica gel chromatography (5% EtOH in CH_2Cl_2). The spectral data of the final product is the same as its *S* enantiomer. Isolated yield: 45%.

(*S*)-3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydro-pyran-2-one (39*S*). To (*S*)-4-hydroxy-6-isopropyl-6-(2-phenthyl)-5,6-dihydropyran-2-one (***S*-X**, **X = H**, 0.5 g, 1.9 mmol) in DMF (12 mL), K_2CO_3 (0.8 g, 5.8 mmol) was added followed by toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenyl) ester (0.8 g, 2.1 mmol). The reaction mixture was stirred overnight at room temperature, poured into saturated NH_4Cl and extracted twice with EtOAc. The combined organic phases were washed twice with 1:1 H_2O:brine followed by brine, dried, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (4:1 Et_2O:hexanes) to give pure material, which on trituration with diethyl ether/hexanes furnished the desired product as a white solid. Isolated yield: 60%. IR (KBr): 3425, 2963, 2877, 1683, 1603, 1454, 1387, 1269, 1236, 1048, 761, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.92–0.98 (dd, 6H, $J = 6.95$ Hz), 1.47 (s, 9H), 1.85 (s, 3H), 1.98–2.06 (m, 2H), 2.16–2.27 (m, 1H), 2.61–2.68 (m, 2H), 2.77 (d of ABX q, 1H, $J = 17.76$ Hz), 2.98 (d of ABX q, 1H, $J = 17.94$ Hz), 4.34 (s, 2H), 6.68 (s, 1H), 7.16–7.27 (m, 6H); MS-APCI (*m*/*z*): 469.

(*R*)-(3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-phenethyl-5,6-dihydro-pyran-2-one (39*R*). To the (*R*)-4-hydroxy-6-isopropyl-6-(2-phenthyl)-5,6-dihydropyran-2-one (***R*-X**, **X = H**, 0.12 g, 0.46 mmol) taken in DMF (12 mL), K_2CO_3 (0.2 g, 1.4 mmol) was added followed by toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenyl) ester (0.2 g, 0.5 mmol). The reaction mixture was stirred overnight at room temperature, poured into saturated NH_4Cl and extracted twice with EtOAc. The combined organic phases were washed twice with 1:1 H_2O:brine followed by brine, dried, filtered and concentrated. The residue, after flash silica gel chromatography (1:1 EtOAc:hexanes eluents) followed by trituration with Et_2O/hexanes, afforded the desired product as a white solid. Isolated yield: 74%. IR (KBr): 3426, 3412, 2963, 2877, 1680, 1603, 1478, 1453, 1390, 1321, 1266, 1235, 1198, 1048, 760, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.92–0.97 (dd, 6H, $J = 6.95$ Hz), 1.47 (s, 9H), 1.85 (s, 3H), 1.98–2.07 (m, 2H), 2.17–2.26 (m, 1H), 2.61–2.68 (m, 2H), 2.77 (d of ABX q, 1H, $J = 18.1$ Hz), 2.98 (d of ABX q, 1H, $J = 17.8$ Hz), 4.34 (s, 2H), 6.68 (s, 1H), 7.16–7.27 (m, 6H); MS-APCI (*m*/*z*): 469.

Supporting information. All the CHN data of the final compounds **1**–**42** (2 pages).

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