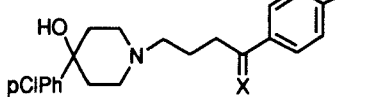
Synthesis of Haloperidol Ethanedithioketal HIV-1 Protease Inhibitors: Magnesium Chloride Facilitated Addition of Grignard Reagents

Zhihua Sui, James J. De Voss, Dianne L. DeCamp, Jia Li, Charles S. Craik, Paul R. Ortiz de Montellano*
Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143-0446, USA
Received 24 July 1992; revised 28 December 1992

Haloperidol ketals and ethanedithioketals of interest as HIV-1 protease inhibitors were synthesized by addition of organolithium and organomagnesium reagents to ketone precursors already containing the ketal or thioketal functionality. Addition of Grignard reagents to the thioketal containing ketone was enhanced remarkably, and to the ketal containing ketone moderately, by the addition of magnesium chloride. The effect of magnesium chloride is attributed to its ability to competitively prevent chelation of the Grignard reagent and proton abstraction from the 4-oxopiperidine ring. The biological activities of the ketals and thioketals indicate that the thioketal function conveys greater ability to inhibit the HIV-1 protease than the ketal function.

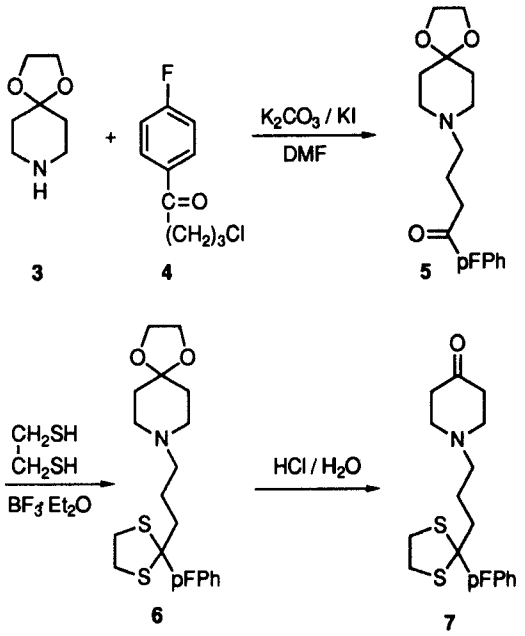
The HIV-1 protease has become an important chemotherapeutic target for anti-AIDS drug design.[1] Haloperidol **1** was recently identified as a lead compound for the rational design of non-peptide HIV-1 protease inhibitors by a computer-assisted, structure-based search.[2] Subsequent structure/activity investigations of the haloperidol structure have shown that haloperidol ethanedithiol ketal **2** is a better inhibitor than haloperidol against both the HIV-1 and HIV-2 proteases. The basis for this enhanced activity has been partially clarified by the X-ray structure of **2** complexed with the HIV-1 protease.[3] It was thus of interest to synthesize a range of haloperidol ethanedithiol ketal derivatives to further define the applicable structure/activity relationships. We were particularly interested in the synthesis of derivatives of the chlorophenyl ring containing a hydrogen-bond donor/acceptor moiety or which explored the spatial requirements of the pocket in which the chlorophenyl ring is bound.



1 X = O
2 X = SCH_2CH_2S

The synthesis of a series of such compounds by the methods usually employed for the preparation of haloperidol derivatives[4,5] was not attractive because several steps are required for the synthesis of each compound. We therefore explored an alternative route to the synthesis of haloperidol ethanedithioketals involving the addition of organometallic reagents to the carbonyl group of piperidone **7**. This piperidone was synthesized by alkylation of 1,4-dioxa-8-azaspiro[4.5]decane (**3**) with 4-chloro-4′-fluorobutyrophenone (**4**), boron trifluoride–diethyl ether complex catalyzed thioketalization of the resulting ketone **5**, and subsequent selective deketalization of **6** in moderate overall yield (42 % over three steps) (Scheme 1).

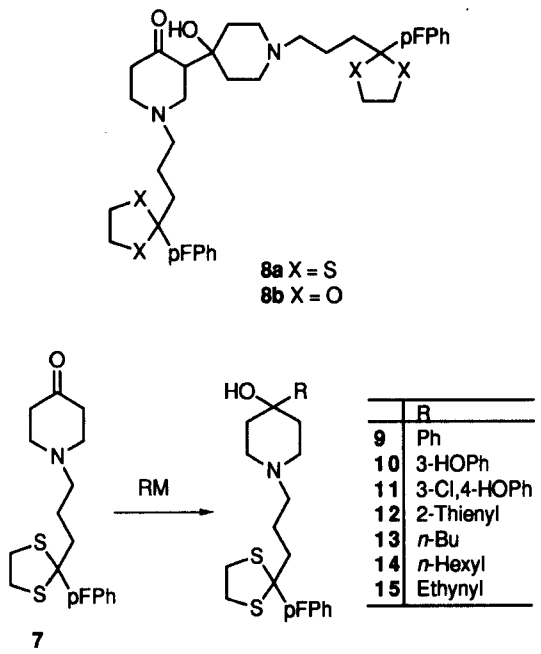
Addition of Grignard reagents to the carbonyl group of *N*-substituted 4-piperidones is a well precedented way to synthesize 1-alkyl-4-aryl-4-hydroxypiperidines. A variety



Scheme 1

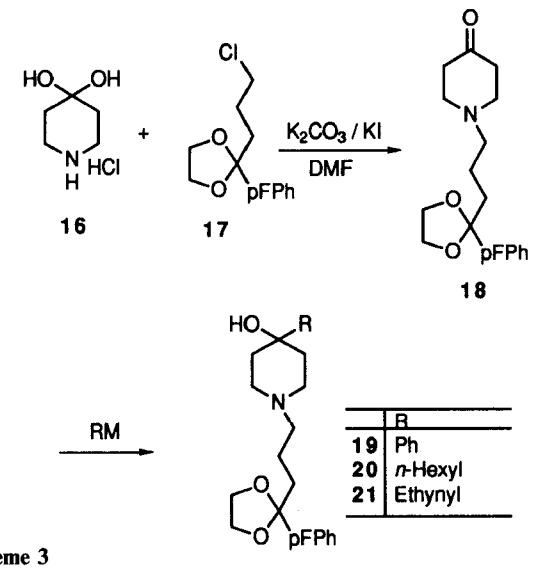
of compounds of this type have been generated using this reaction.[5,6] Surprisingly, aliphatic and aromatic Grignard reagents do not add to **7** under a variety of reaction conditions in which the temperature, solvent, Grignard concentration, and Grignard/ketone ratio were varied (Scheme 2, M = MgX). The only product isolated from these reactions was the aldol self condensation product **8a**. A variety of organolithium reagents, however, add to the carbonyl group of **7** to give haloperidol thioketal derivatives **9–13** and **15** in fair yield, in accord with the previously reported addition of organolithium reagents to 1-alkyl-4-piperidones.[7–10] Both butyllithium, a very basic alkyllithium reagent, and the much less basic ethynyllithium add to give **13** and **15**, respectively (Scheme 2, M = Li). None of the aldol condensation product **8a** was observed in the preparations of these compounds, although addition reactions of organolithium reagents are known to be more prone to enolization/condensation problems than Grignard reagents.[11] Haloperidol ethanedithioketal derivatives with alkyl, aryl and ethynyl substituents on position 4 of the piperidine ring have been obtained directly from **7** and the corresponding organolithium reagents by what appears to be a general synthesis of these types of compounds. For **10** and **11** the aryllithium reagents were prepared in situ by literature precedented metal–halogen exchange of the corresponding aromatic bromide and butyllithium without protection of the hydroxy group.[12]

The results with the lithium reagents suggest that the aldol condensation side-reaction might not be related to the intrinsic basicity of the organometallic reagents. As there



Scheme 2

are a number of examples of Grignard additions to piperidones,[5,6] it was felt that the thioketal moiety might be the cause of the difficulties associated with addition to **7**. We therefore synthesized compound **18**, which is analogous to **7** except that the thioketal has been replaced by a ketal. It was synthesized in good yield (75%) by direct alkylation of 4-piperidone **16** by chloride **17** (Scheme 3) rather than by a previously reported three-step synthesis that gives **18** in 30% yield.[13,14] In contrast to thioketal **7**, **18** undergoes an addition reaction with phenylmagnesium bromide to give **19** in moderate yield (55%) without detectable formation of the corresponding aldol condensation product. Reaction of **18** with phenyllithium rather than phenylmagnesium bromide did not increase the yield (45%) of the desired addition product. The yield of the desired adduct is lower (26%), and the aldol condensation product **8b** (34%) is also isolated, in reactions of **18** with the aliphatic Grignard reagent hexylmagnesium chloride. Ethynyllithium gave the addition product in 44% yield.



Scheme 3

These observations have led us to conclude that the thioketal is responsible for the failure of Grignard reactions with **7** [compare reaction of phenylmagnesium bromide with **7** (0%) and with **18** (55%)]. In an effort to determine whether this effect is general, 1-benzylpiperidin-4-one (**22**) was reacted with phenylmagnesium bromide in the presence and absence of thioketal **23** (Scheme 4). The thioketal had no effect on the yield of adduct **24**. The effect of the thioketal is thus intramolecular rather than intermolecular. One explanation for the reactivity of **7** consistent with this conclusion is that the magnesium atom of the Grignard reagent forms a chelate with the dithioketal sulfur atoms and the piperidine nitrogen atom. Formation of this complex could facilitate deprotonation of the piperidinone, possibly via a 1,3-intramolecular process, to give the enolate species. This possibility led us to examine addition of Grignard reagents to **7** in the presence of excess magnesium chloride in the hope that magnesium ions would prevent formation of such a chelate and so increase the amount of the desired product. The results for thioketal **7** were dramatic. The aromatic Grignard reagent, phenylmagnesium bromide, added to the carbonyl group of **7** in excellent yield (85%). Indeed, even the aliphatic Grignard reagent, hexylmagnesium chloride, provided addition product **14** in fair yield

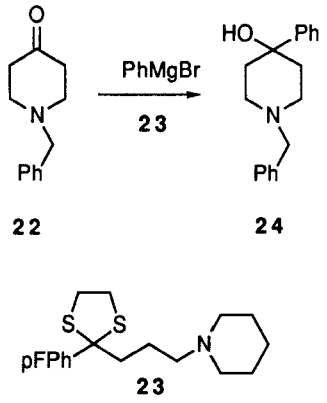
Table 1. Yields of Addition and Aldol Condensation Products

Ketone	Reagent Type[a]	Addition Product (%)	Aldol Product (%)[b]
7	A	**9** (40)	**8a** (n.d.)
7	B	**9** (0)	**8a** (42)
7	C	**9** (85)	**8a** (0)
7	A	**10** (50)	**8a** (n.d.)
7	A	**11** (58)	**8a** (n.d.)
7	A	**12** (59)	**8a** (n.d.)
7	A	**13** (29)	**8a** (< 10)
7	B	**14** (0)	**8a** (52)
7	C	**14** (43)	**8a** (8)
7	A	**15** (28)	**8a** (0)
18	A	**19** (45)	**8b** (n.d.)
18	B	**19** (55)	**8b** (n.d.)
18	C	**19** (72)	**8b** (n.d.)
18	B	**20** (26)	**8b** (34)
18	C	**20** (37)	**8b** (16)
18	A	**21** (44)	**8b** (n.d.)

[a] A: Organolithium reagents, B: Grignard reagents, C: Grignard reagents›$MgCl_2$

[b] n.d.: not detected.

(43%). The yields of the products from addition of phenyl- and hexylmagnesium bromide to ketal **18** also increased in the presence of magnesium chloride (Table 1), but to a lesser extent. Thus, it appears that the thioketal sulfurs bind the magnesium ion more strongly than the ketal oxygens because, in the absence of magnesium salt, Grignard reagents do not add to **7** at all but add to **18** in low to moderate yields. The lithium ion does not appear to form an analogous chelate because organolithium reagents add equally well to the carbonyl of the ketal and thioketal precursors.



Scheme 4

Table 2. Inhibitory Activities of the Haloperidol Analogues Against the HIV-1 Protease

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
6	> 500	**12**	100
7	> 500	**13**	210
8a	270	**14**	32
8b	> 500	**15**	> 500
9	60	**19**	360
10	110	**20**	> 500
11	28	**21**	> 500

The ketals and thioketals synthesized in this study have been assayed as potential in vitro inhibitors of the HIV-1 protease by previously described procedures (Table 2).[2]

The best inhibitors among the compounds tested are **11** and **14**, both of which have IC_{50} values of approximately 30 μM. None of the present derivatives is a better inhibitor of the protease than the parent compound **2** (IC_{50} 15 μM), but some informative trends in the activities of the derivatives are evident. First, compounds that contain the thioketal moiety are clearly superior to those with a ketal function as inhibitors of the protease (cf compounds **9** and **19**, or **14** and **20**), presumably because the thioketal function is more lipophilic. The results also indicate that a lipophilic group at position 4 of the piperidine ring is essential for activity. The lipophilic group can be an aromatic ring, as in compounds **9**–**12**, or a moderately large aliphatic group, as in compound **14**. The crucial role of lipophilicity in binding of the inhibitors is in accord with the fact that hydrophobic interactions appear to dominate the binding interactions of the protease with other classes of molecules.[15] These results provide information of use in the design of further haloperidol-derived inhibitors of the HIV-1 protease.

In summary, we have developed a general synthesis of haloperidol ethanedithioketal derivatives suitable for the preparation of inhibitors of the HIV protease through the addition of organolithium reagents to piperidone **7**. In addition, we have discovered that the thioketal moiety of **7** adversely effects the addition of Grignard reagents and have shown that this adverse effect can be overcome by adding magnesium salts to the reaction medium. Although the effect of the magnesium salt is not general, its is important here because the thioketal function contributes significantly to the activity of haloperidol-derived HIV-1 protease inhibitors. The relative biological activities of the compounds described here demonstrate the importance of hydrophobic interactions in the binding of inhibitors to the HIV-1 protease.

Melting points were determined with a Thomas capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained at 300 and 75 MHz respectively on a GE QE-300 instrument. Infrared spectra were run on a Nicolet 5DX FT-IR. Mass spectra were measured with a VG-70 mass spectrometer which was equipped with a Hewlett-Packard 5890A gas chromatograph. Satisfactory HRMS obtained for **6, 7, 8a, 9–15, 18–21, 23**: $m/z \pm 0.0020$. Elemental analyses were performed by the Microanalysis Laboratory, University of California, Berkeley. Satisfactory microanalyses obtained for **18, 19, 21**: C ± 0.30, H ± 0.21, N ± 0.34. The silica gel used in column chromatography was from Aldrich (Merck, 70–230 mesh). TLC was performed on Analtech silica gel-60 F-254 plates. THF and Et_2O were dried by refluxing over sodium/benzophenone.

4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-4′-fluorobutyrophenone (5):
A mixture of 4-chloro-4′-fluorobutyrophenone (2.8 g, 14 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (2 g, 14 mmol), K_2CO_3 (1.93 g, 14 mmol) and KI (100 mg) in DMF (40 mL) was heated under reflux for 16 h. After cooling the mixture was washed with H_2O and dried (K_2CO_3). The solvent was evaporated and the residue was purified by column chromatography (silica gel, EtOAc). The title compound was obtained as a colorless oil (2.3 g, 54%).

IR (NaCl): ν = 2959 (s), 2812 (m), 1687 (s, C=O), 1602 (s), 1504 (m), 1230 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.68 (t, 4H, CH_2CH_2N of piper.), 1.94 (m, 2H, $CH_2CH_2CH_2$), 2.43 (t, 2H, $CH_2C=O$), 2.51 (m, 4H, CH_2CH_2N of piper.), 2.97 (t, 2H, CH_2N chain), 7.12 (t, 2H, J = 8 Hz, FCCH), 8.00 (dd, J = 5, 8 Hz, FCCHCH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0 ($CH_2CH_2CH_2$), 34.7 (CH_2CH_2N of piper.), 36.1 ($CH_2C=O$), 51.2, 51.7 (CH_2N), 64.1 (OCH_2), 107.2 (spiro), 115.5 (d, J = 12 Hz, FCCH), 130.5 (d, J = 8 Hz, FCCHCH), 133.5 ($CH_2C=OC$), 165.5 (d, J = 254 Hz, FC), 198.4 (C=O).

MS (CI): m/z (%) = 308 (M+H, 100), 169 (65), 156 (87).

2-[3-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)propyl]-2-(4-fluorophenyl)-1,3-dithiolane (6):
A solution of **5** (154 mg, 0.5 mmol), 1,2-ethanedithiol (168 mL, 2 mmol) and $BF_3 \cdot Et_2O$ (565 μL, 5 mmol) in MeOH (5 mL) was stirred at r.t. for 2 h. It was then diluted with EtOAc (50 mL) and aq K_2CO_3 was added. The organic phase was washed with H_2O and dried (K_2CO_3). After column chromatography (silica gel, EtOAc), the title compound was obtained as a colorless oil. Yield: 163 mg (84.6%).

IR (NaCl): ν = 2952 (s), 2812 (m), 1602 (s), 1503 (m), 1230 (s), 1096 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (quint, 2H, $CH_2CH_2CH_2$), 1.70 (t, 4H, CH_2CH_2N of piper.), 2.05–2.43 (m, 8H, CH_2N, $NCH_2CH_2CH_2$), 3.16–3.41 (m, 4H, SCH_2CH_2S), 3.93 (s, 4H, OCH_2CH_2O), 6.97 (t, 2H, J = 8.5 Hz, FCCH), 7.66 (dd, 2H, J = 5, 8 Hz, FCCHCH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 ($CH_2CH_2CH_2$), 34.7 (CH_2CH_2N of piper.), 39.2, 43.7 (SCH_2CH_2S, $NCH_2CH_2CH_2$), 51.2, 51.6 (CH_2N), 64.1 (OCH_2), 76.6 (CPhF), 107.2 (spiro), 114.5 (d, J = 18 Hz, FCCH), 128.8 (d, J = 8 Hz, FCCHCH), 140.8 (FCCHCHC). 165.5 (d, J = 254 Hz, FC).

MS (CI): m/z (%) = 384 (M+H, 95), 324 (57), 156 (100).

1-[4,4-Ethylenedithio-4-(4-fluorophenyl)butyl]-4-piperidinone (7):
A mixture of **6** (120 mg, 0.32 mmol), 6 N HCl (1 mL) and dioxane (5 mL) was heated under reflux for 1 h. After cooling to r.t. the

solution was diluted with H_2O, treated with K_2CO_3 and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated and the residue was purified by column chromatography. Compound **7** was obtained as a colorless oil (100 mg, 92.1 %).

IR (NaCl): ν = 3029 (w), 2959 (s), 2812 (m), 1715 (s, C=O), 1448 (m), 1349 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 (m, 2 H, $CH_2\underline{CH_2}CH_2$), 2.05–2.42 (m, 8 H, $C\underline{H_2}C=O$, $NC\underline{H_2}CH_2C\underline{H_2}$), 2.59–2.69 (m, 4 H, NCH_2 piper.), 3.20–3.43 (m, 4 H, SCH_2CH_2S), 6.99 (t, 2 H, J = 8.5 Hz, FCCH), 7.68 (dd, 2 H, J = 5, 8 Hz, FCCHC$\underline{H}$).

MS (CI): m/z (%) = 264 (M + H, 100), 165 (40), 123 (65), 112 (86).

3-[1-[4,4-Ethylenedithio-4-(4-fluorophenyl)butyl-4-hydroxy-4-piperidyl]-1-[4,4-ethylenedithio-4-(4-fluorophenyl)butyl]]-4-piperidinone (8a):

4-Chlorophenylmagnesium bromide (0.064 mol, 3 M in Et_2O) was added to a solution of **7** (217 mg, 0.064 mmol) in THF (3 mL) at − 78 °C. The mixture was stirred at r.t. for 16 h and then treated with sat. aq NH_4Cl before it was extracted with EtOAc and the extract was dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/acetone, 10:1). Compound **8a** was obtained as a colorless oil (225 mg, 52 %).

IR (NaCl): ν = 3260 (w, br, OH), 1715 (m, C=O), 1602, 1503 (s, Ar), 1229 cm^{-1} (m, C–O).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.60 (m, 8 H, $CH_2C\underline{H_2}$ CH_2, $C\underline{H_2}CH_2N$), 2.10–2.75 (m, 19 H, $C\underline{H_2}N$, CH_2S, $CH_2C=O$, $>CHC=O$), 3.20–3.45 (m, 8 H, SCH_2CH_2S), 5.48 (s, br, 1 H, OH), 6.90–7.05 (m, 4 H, FCCH), 7.60–7.70 (dd, 4 H, J = 5, 8 Hz, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 25.5, 28.0, 36.1, 36.2, 39.2, 39.3, 41.6, 43.7, 48.7, 49.2, 53.1, 54.1, 56.9, 58.0, 70.0, 73.2, 73.5 for aliphatic carbons.

MS (CI): m/z (%) = 679 (M + H, 0.3), 661 (M + H–H_2O, 3.5), 340 (53), 280 (35), 199 (60), 164 (100), 112 (100).

2-(4-Fluorophenyl)-2-[3-(4-hydroxy-4-phenyl-1-piperidyl)propyl]-1,3-dithiolane (9):

Method A: A solution of **7** (102 mg, 0.3 mmol) in Et_2O (15 mL) was added very slowly to a solution of PhLi (0.72 mmol in 2 mL Et_2O) at − 78 °C. The solution was warmed to r.t., stirred for 16 h, and then refluxed for 2 h. The mixture was poured onto ice and extracted with EtOAc. The solvent was evaporated. Column chromatography (silica gel, EtOAc/acetone, 10:1) gave **9** (50 mg, 40 %).

Method B: $MgCl_2$ (95 mg, 1 mmol) was heated under vacuum with a flame. After cooling to r.t. a solution of **7** (100 mg, 0.289 mmol) was added. The suspension was cooled to − 78 °C and PhMgBr (3 M in Et_2O, 0.6 mmol) was added. The mixture was stirred at − 78 °C for 15 min and at r.t. for 1 h. Aq NH_4Cl solution was added to the mixture and was stirred for 10 min. The mixture was extracted with EtOAc and the organic phase was dried ($MgSO_4$). Column chromatography gave **9** (106 mg, 85 %).

IR (NaCl): ν = 3409 (br,OH), 3051 (w), 2945 (m), 2819 (w), 1602 (m), 1511 (s), 1265 (m), 1230 (s), 773 (m), 738 (s), 709 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (m, 2 H, $CH_2C\underline{H_2}CH_2$), 1.63 (d, 4 H, eq. $C\underline{H_2}CH_2N$, $NCH_2CH_2C\underline{H_2}$), 2.02 (t, 2 H, ax. $C\underline{H_2}CH_2N$), 2.32–2.39 (m, 4 H, ax. $CH_2C\underline{H_2}N$, CH_2N chain), 2.69 (d, 2 H, eq. $CH_2C\underline{H_2}N$), 3.20–3.40 (m, 4 H, SCH_2), 6.96 (t, 2 H, J = 8.5 Hz, FCCH), 7.26, 7.34, 7.50 (m, 5 H, Ph), 7.67 (dd, 2 H, J = 5, 8 Hz, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3 ($CH_2\underline{C}H_2CH_2$), 38.4 ($\underline{C}H_2CH_2N$ of piper.), 39.3 ($\underline{C}H_2CH_2CH_2N$), 43.8, 49.4 ($CH_2N$), 58.2 ($SCH_2$), 71.2 (COH), 73.5 (> C–PhF), 114.5 (d, J = 21 Hz, FC$\underline{C}$H), 130.5 (d, J = 8 Hz, FCCH$\underline{C}$H), 124.5, 126.9, 128.3, 148.3 (Ph), 128.8 ($\underline{C}$HCHCF), 140.8 ($\underline{C}$CHCHCF), 165.5 (d, J = 254 Hz, FC).

MS (CI): m/z (%) = 418 (M + H, 100), 400 (M + H–H_2O, 23), 358 (42), 190 (99).

2-(4-Fluorophenyl)-2-[3-(4-hydroxy-4-(2-thienyl)-1-piperidyl)propyl]-1,3-dithiolane (12):

2-Thienyllithium (0.32 mL, 0.32 mmol) was added to THF (4 mL) and cooled to − 78 °C. A solution of **7** (102 mg, 0.3 mmol) in THF (4 mL) was added slowly at − 78 °C. The mixture was allowed to warm up to r.t. and was then stirred for 3.5 h before it was poured onto ice, extracted with EtOAc, and dried ($MgSO_4$). The solvent was evaporated. Column chromatography (silica gel, hexane/EtOAc, 5:3) provided **12** as a slightly yellow oil (75 mg, 59 %).

IR (NaCl): ν = 3416 (br, OH), 2945 (m), 1595 (m), 1504 (s), 1230 (s), 738 (s), 702 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (m, 2 H, $CH_2C\underline{H_2}CH_2$), 1.89 (d, 4 H, eq. $C\underline{H_2}CH_2N$, $NCH_2CH_2C\underline{H_2}$), 2.11 (t, 2 H, ax. $C\underline{H_2}CH_2N$), 2.29–2.42 (m, 4 H, ax. $CH_2C\underline{H_2}N$, CH_2N chain), 2.61 (d, 2 H, eq. $CH_2C\underline{H_2}N$), 3.20–3.42 (m, 4 H, SCH_2), 6.94–7.01 (m, 4 H, FCCH, SCCHCH), 7.19 (m, 1 H, SC$\underline{H}$=CH), 7.66 (m, 2 H, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3 ($CCH_2\underline{C}H_2CH_2$), 39.2 ($\underline{C}H_2CH_2N$ of piper.), 39.5 ($\underline{C}H_2CH_2CH_2N$), 43.7, 49.4 ($CH_2N$), 58.0 ($SCH_2$), 70.2 (COH), 73.5 (> C–PhF), 114.5 (d, J = 21 Hz, FC$\underline{C}$H), 128.8 (d, J = 8 Hz, FCCH$\underline{C}$H), 140.7 ($\underline{C}$CHCHCF), 162.1 (d, J = 254 Hz, FC), 121.9, 123.9, 126.8, 153.7 (thienyl).

MS (CI): m/z (%) = 424 (M + H, 45), 406 (M + H–H_2O, 40), 196 (thienyl-OHpipN^+ = CH_2, 100), 178 (40), 112 (41).

2-(4-Fluorophenyl)-2-[3-[4-hydroxy-4-(3-hydroxyphenyl)-1-piperidyl]propyl]-1,3-dithiolane (10):

A solution of BuLi (2.5 M, 4.5 mmol) was added to a solution of 3-bromophenol in Et_2O (4 mL) at − 78 °C. The mixture was stirred at r.t. for 16 h. Compound **7** (102 mg, 0.3 mmol) in Et_2O (5 mL) was added at − 78 °C and the mixture was stirred at r.t. for 16 h. The mixture was poured onto ice and extracted with EtOAc, and the extract was dried ($MgSO_4$). The solvent was evaporated. Column chromatography (silica gel, EtOAc) gave **10** as a colorless oil (63 mg, 50.0 %).

IR (NaCl): ν = 3409 (br, OH), 2945 (m), 1602 (m), 1503 (s), 738 (s), 702 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (m, 4 H, $CH_2C\underline{H_2}CH_2$, eq. $C\underline{H_2}CH_2N$), 2.02 (t, 2 H, $NCH_2CH_2C\underline{H_2}$), 2.25–2.44 (m, 6 H, ax. $C\underline{H_2}CH_2N$, ax. $CH_2C\underline{H_2}N$, CH_2N chain), 2.70 (d, 2 H, eq. $CH_2C\underline{H_2}N$), 3.20–3.40 (m, 4 H, SCH_2), 6.58, 6.84–6.93, 7.09 (d, m, t, 6 H, FCCH, PhOH), 7.60 (m, 2 H, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6 ($CH_2\underline{C}H_2CH_2$), 37.5 ($\underline{C}H_2CH_2N$ of piper.), 39.3 ($\underline{C}H_2CH_2CH_2N$), 43.7, 49.2 ($CH_2N$), 58.1 ($SCH_2$), 71.1 (COH), 73.3 (> CPhF), 114.6 (d, J = 21 Hz, FC$\underline{C}$H), 128.8 (d, J = 8 Hz, FCCH$\underline{C}$H), 140.6 ($\underline{C}$CHCHCF), 165.1 (d, J = 254 Hz, FC), 112.5, 115.8, 129.5, 149.5, 156.7, 159.9 (PhOH).

MS (CI): m/z (%) = 434 (M + H, 45), 416 (M + H–H_2O, 15), 374 (35), 206 (HOC_5H_4HO-pipN^+ = CH_2, 100), 190 (99).

2-[3-[4-(3-Chloro-4-hydroxyphenyl)-4-hydroxy-1-piperidyl]propyl]-2-(4-fluorophenyl)-1,3-dithiolane (11):

From 4-bromo-2-chlorophenol (207.5 mg, 1 mmol) **11** was obtained as a colorless oil (82 mg, 58.5 %) using the same procedure as for **10**.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (m, 2 H, $CH_2C\underline{H_2}CH_2$), 1.65 (d, 2 H, eq. $C\underline{H_2}CH_2N$), 2.05 (t, 2 H, $NCH_2CH_2C\underline{H_2}$), 2.25–2.40 (m, 6 H, ax. $C\underline{H_2}CH_2N$, ax. $CH_2C\underline{H_2}N$, CH_2N chain), 2.70 (d, 2 H, eq. $CH_2C\underline{H_2}N$), 3.20–3.40 (m, 4 H, SCH_2), 6.95 (t, J = 8 Hz, 2 H, FCCH), 7.25, 7.45 (3 H, ClPhOH), 7.70 (dd, J = 5, 8 Hz, 2 H, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 ($CH_2\underline{C}H_2CH_2$), 38.4 ($\underline{C}H_2CH_2N$ of piper.), 39.3 ($\underline{C}H_2CH_2CH_2N$), 43.8, 49.3 ($CH_2N$), 58.1 ($SCH_2$) (70.8 (COH), 73.5 (> CPhF), 114.6 (d, J = 21 Hz, FC$\underline{C}$H), 128.9 (d, J = 6 Hz, FCCH$\underline{C}$H), 141.7 ($\underline{C}$CHCHCF), 165.1 (d, J = 254 Hz, FC), 116.0, 116.1, 119.8, 124.7, 125.6, 150.3 (ClPhOH).

MS (EI): m/z (%) = 467 (M, 70), 449 (M–H_2O, 11), 408 (28), 240 (100), 222 (42), 205 (47).

2-[3-(4-Butyl-4-hydroxy-1-piperidyl)propyl]-2-(4-fluorophenyl)-1,3-dithiolane (13):
From **7** (100 mg, 0.298 mmol) and BuLi (0.3 mmol) using the procedure (Method A) for **9**, **13** was obtained as an oil (34 mg, 29%).

IR (NaCl): ν = 3416 (w, br, OH), 3058 (w), 2938 (s), 1602 (w), 1504 (s), 1272 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, 3H, CH_3), 1.26–1.61 (m, 12H, $NCH_2\underline{CH_2}\underline{CH_2}$, $\underline{CH_2}CH_2N$, CH_2 in Bu), 2.20–2.35 (m, 6H, $NC\underline{H_2}CH_2C\underline{H_2}$, ax. $CH_2C\underline{H_2}N$), 2.52 (d, 2H, eq. $CH_2C\underline{H_2}N$), 3.20–3.40 (m, 4H, SCH_2), 6.95 (t, J = 8 Hz, 2H, FCCH), 7.70 (dd, J = 5, 8 Hz, 2H, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 23.2, 24.9, 25.4 ($CH_2\underline{C}H_2CH_2$), 36.8, 39.2 ($\underline{C}H_2CH_2CH_2N$), 42.6, 49.4 ($CH_2N$), 58.2 ($SCH_2$), 69.4 (COH), 73.5 (>CPhF), 114.4 (d, J = 21 Hz, FC$\underline{C}$H), 128.8 (d, J = 6 Hz, FCCH$\underline{C}$H), 140.8 ($\underline{C}$CHCHCF), 161.6 (d, J = 247 Hz, FC).

MS (EI): m/z (%) = 397 (M^+, 28), 379 (M-18, 70), 338 (34), 152 (100).

2-(4-Fluorophenyl)-2-[3-(4-hexyl-4-hydroxy-1-piperidyl)propyl]-1,3-dithiolane (14):
From $MgCl_2$ (95 mg, 1 mmol), **7** (92 mg, 0.27 mmol) and hexylmagnesium chloride (0.5 mmol) using Method B for **9**, **14** was obtained as an oil (49 mg, 43%).

IR (NaCl): ν = 3438 (br, OH), 3051 (w), 2931 (s), 1602 (w), 1504 (s), 1265 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, 3H, CH_3), 1.24–1.65 (m, 16H, $NCH_2\underline{CH_2}\underline{CH_2}$, $\underline{CH_2}CH_2N$, CH_2 in hexyl), 2.20–2.53 (m, 8H, $NC\underline{H_2}CH_2C\underline{H_2}$, $CH_2C\underline{H_2}N$), 3.20–3.40 (m, 4H, SCH_2), 6.95 (t, J = 8 Hz, 2H, FCCH), 7.70 (dd, J = 5, 8 Hz, 2H, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 22.7, 25.3, 29.8, 31.8, 36.7, 39.2, 42.9, 43.7, 49.4 (CH_2N), 58.2 (SCH_2), 69.4 (COH), 73.5 (>C–PhF), 114.6 (d, J = 21 Hz, FC$\underline{C}$H), 128.9 (d, J = 6 Hz, FCCH$\underline{C}$H), 140.8 ($\underline{C}$CHCHCF), 161.6 (d, J = 247 Hz, FC).

MS (EI): m/z (%) = 425 (M^+, 5),366 (12), 348 (14), 198 (67), 180 (100).

2-[3-(4-Ethynyl-4-hydroxy-1-piperidyl)propyl]-2-(4-fluorophenyl)-1,3-dithiolane (15):
From **7** (100 mg, 0.298 mmol) and ethynyllithium–ethylenediamine complex (92 mg, 1 mmol) using the procedure (Method A) for **9**, **15** was obtained as an oil (34 mg, 29%).

IR (NaCl): ν = 3304 (m, ethynyl H–C), 2952 (w), 2310 (w), 1504 (s), 1265 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 (m, 2H, $NCH_2\underline{CH_2}CH_2$), 1.75–1.90 (m, 4H, piper. $\underline{CH_2}CH_2N$), 2.25–2.45 (m, 6H, $NC\underline{H_2}CH_2C\underline{H_2}$, ax. $CH_2C\underline{H_2}N$), 2.49 (s, 1H, ethynyl H), 2.52 (d, 2H, eq. $CH_2C\underline{H_2}N$), 3.20–3.40 (m, 4H, SCH_2), 6.95 (t, J = 8 Hz, 2H, FCCH), 7.70 (dd, J = 5, 8 Hz, 2H, FCCHC$\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3 ($CH_2\underline{C}H_2CH_2$), 41.1 ($\underline{C}H_2CH_2CH_2N$), 43.6, 49.9 ($CH_2N$), 52.9, 57.7 ($SCH_2$), 66.4 (COH), 72.6 (ethynyl), 73.4 (>CPhF), 87.0 (ethynyl), 114.5 (d, J = 21 Hz, FC$\underline{C}$H), 128.8 (d, J = 6 Hz, FCCH$\underline{C}$H), 140.7 ($\underline{C}$CHCHCF), 161.6 (d, J = 246 Hz, FC).

MS (EI): m/z (%) = 365 (M^+, 13), 306 (44), 179 (32), 138 (100).

1-[4,4-Ethylenedioxy-4-(4-fluorophenyl)butyl]-4-piperidinone (18):
The piperidone hydrochloride monohydrate **16** (921 mg, 6 mmol) was suspended in DMF (15 mL) with K_2CO_3 (1.66 g, 12 mmol) and the chloroketal **17** (1.47 g, 6 mmol) and the mixture was stirred overnight at r.t. It was then refluxed for 1 h and subsequently cooled to r.t., filtered and evaporated under reduced pressure. The residue purified by flash column chromatography (silica gel, EtOAc) gave the title compound as a solid (1.39 g, 75.4%). It could be recrystallized from CH_2Cl_2/hexane for analysis. mp 64.5–65 °C (Et_2O/hexane) Lit.[14] 63 °C.

IR ($CHCl_3$): ν = 3023, 2959, 2899, 2812, 2777, 1715, 1602, 1504 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.55–1.60 (m, 2H, $NCH_2\underline{CH_2}CH_2$), 1.90–1.95 (m, 2H, $NCH_2CH_2C\underline{H_2}$), 2.40–2.45 (m, 6H, 3 × $NC\underline{H_2}$), 2.69 (t, 4H, J = 6 Hz, 2 × $C\underline{H_2}CO$), 3.74–3.79, 4.00–4.04 (2 × m, 2 × 2H, OCH_2CH_2O), 7.02 (t, 2H, J = 9 Hz, 2 × C$\underline{H}$CF), 7.42 (dd, 2H, J = 5.5, 8.8 Hz, 2 × C$\underline{H}$CHCF).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.40, 38.11, 41.06, 52.85, 56.99, 64.38, 109.80, 114.65 (d, J = 21 Hz), 127.35 (d, J = 7.6 Hz), 138.26, 162.76 (d, J = 246 Hz), 209.09.

MS: m/z (%) = 307 (27), 264 (24), 167 (37), 112 (100).

Addition of Organometallics to Piperidone 18; General Procedure:
The ketone was dissolved in THF under Ar and the solution was cooled to 0 °C. The organometallic reagent was then added dropwise and the solution was stirred at 0 °C for 1 h and at r.t. for a further h. It was then quenched with sat. aq NH_4Cl and diluted with EtOAc. The organic layer was separated and washed with brine, dried and evaporated. The residue was purified by flash column chromatography, eluant as specified.

The additions to **18** employing $MgCl_2$ as an additive were performed in the same way as described in the general procedure above, except that anhydr. $MgCl_2$ (3 equiv, heated under vacuum) was included in the THF solution of **18**.

2-(4-Fluorophenyl)-2-[3-(4-hydroxy-4-phenyl-1-piperidyl)propyl]-1,3-dioxolane (19):
This compound was prepared by the general procedure from **18** and PhMgBr (55%) or PhLi (44.8%; 56.5% based on unrecovered starting material). It was also prepared using $MgCl_2$ as an additive (72%). (Eluant: EtOAc). It could be recrystallized from CH_2Cl_2/Et_2O/hexane for analysis. mp 110–110.5 °C (CH_2Cl_2/Et_2O/hexane).

IR ($CHCl_3$): ν = 3592, 3009, 2952, 2924, 2889, 2819, 2777, 1602, 1504 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.54–1.62 (m, 2H, $NCH_2\underline{CH_2}CH_2$), 1.68 (d, 2H, J = 12.3 Hz, 2 × eq. $C\underline{H_2}CH_2N$), 1.88–1.90 (m, 2H, $NCH_2CH_2C\underline{H_2}$), 2.09 (dt, 2H, J = 4, 13 Hz, 2 × ax. $C\underline{H_2}CH_2N$), 2.31–2.42 (m, 4H, $NC\underline{H_2}CH_2CH_2$ and 2 × ax. CH_2N), 2.70–2.74 (m, 2H, 2 × eq. $C\underline{H_2}N$), 3.71–3.75, 3.96–4.01 (2 × m, 2 × 2H, OCH_2CH_2O), 6.99 (t, 2H, J = 8.7 Hz, 2 × C$\underline{H}$CF), 7.22–7.49 (m, 7H, 2 × C$\underline{H}$CHCF and C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.02, 38.30, 38.41, 49.34, 58.49, 64.40, 71.02, 109.97, 114.76 (d, J = 21 Hz), 124.47, 126.75, 127.43 (d, J = 7.6 Hz), 128.15, 138.34, 148.46, 162.31 (d, J = 246 Hz).

MS: m/z (%) = 385 (M^+, 1), 367 (M–H_2O, 3), 342 (8), 322 (5), 190 ($C_{12}H_{16}NO$, 100), 172 ($C_{12}H_{12}N$, 27), 123 (C_7H_4FO, 13).

2-(4-Fluorophenyl)-2-[3-(4-hexyl-4-hydroxy-1-piperidyl)propyl]-1,3-dioxolane (20):
Prepared by the general procedure from **18** and hexylmagnesium bromide (26%). The aldol condensation product **8b** was also isolated (34.3%). The reaction was also performed in the presence of $MgCl_2$ as an additive to give **20** (37.3%) and **8b** (16.5%). (Eluant: acetone).

20: IR ($CHCl_3$): ν = 3599, 3009, 2931, 2861, 2819, 2777, 1602, 1504 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.90 (m, 3H, CH_3), 1.28–1.69 [m, 16H, 2 × $NCH_2\underline{CH_2}COH$, $NCH_2\underline{CH_2}CH_2$ and $CH_3(\underline{CH_2})_5$], 1.84–1.89 (m, 2H, $NCH_2CH_2C\underline{H_2}$), 2.23–2.35 (m, 4H, $NC\underline{H_2}CH_2CH_2$ and 2 × ax. CH_2N), 2.57–2.61 (m, 2H, 2 × eq. $C\underline{H_2}N$), 3.72–3.77, 3.98–4.02 (2 × m, 2 × 2H, OCH_2CH_2O), 6.99 (t, 2H, J = 8.7 Hz, 2 × C$\underline{H}$CF), 7.40 (dd, 2H, J = 5.6, 8.6 Hz, 2 × C$\underline{H}$CHCF).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.01, 21.10, 22.56, 22.70, 29.77, 31.79, 36.77, 38.43, 42.93, 49.44, 58.51, 64.48, 69.40, 110.01, 114.81 (d, J = 21 Hz), 127.40 (d, J = 7.7 Hz), 138.42, 162.40 (d, J = 247 Hz).

MS: m/z (%) = 393 (M^+, 22), 374 (40), 198 (100).

3-[1-[4,4-Ethylenedioxy-4-(4-fluorophenyl)butyl]4-hydroxy-4-piperidyl]-1-[4,4-ethylenedioxy-4-(4-fluorophenyl)butyl]-4-piperidinone **(8b)**:

IR ($CHCl_3$): ν = 3227, 2988, 2959, 2869, 2619, 1729, 1602, 1504 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.62 (m, 6H, 2 × $NCH_2\underline{CH}_2CH_2$ and 2 × eq. $NCH_2\underline{CH}_2COH$), 1.74–1.94 (m, 6H, 2 × $NCH_2CH_2\underline{CH}_2$ and 2 × ax. $NCH_2\underline{CH}_2COH$), 2.16–2.63 (m, 12H, 6 × $\underline{CH}_2N$), 2.71–2.82, 2.92–2.98, 3.15–3.20 (3 × m, 3 × 1H, 3 × CHCO), 3.73–3.77, 3.98–4.03 (2 × m, 2 × 4H, 2 × $OCH_2\underline{CH}_2O$), 5.60 (brd s, 1H, OH), 6.97–7.04 (m, 4H, 4 × $C\underline{H}CF$), 7.38–7.43 (m, 4H, 4 × $C\underline{H}CHCF$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.92, 21.03, 21.22, 36.18, 36.27, 38.02, 38.39, 41.64, 48.65, 49.27, 52.95, 54.17, 57.06, 57.84, 58.35, 60.26, 64.44, 70.00, 109.73, 109.96, 114.75 (d, J = 21 Hz), 114.88 (d, J = 22 Hz), 127.41 (d, J = 8.5 Hz), 138.17, 138.39, 162.33 (d, J = 246 Hz), 162.39 (d, J = 246 Hz).

MS (CI): m/z (%) = 615 (M^+ + 1, 13), 309 (100), 264 (52), 167 (59).

2-[3-(4-Ethynyl-4-hydroxy-1-piperidyl)propyl]-2-(4-fluorophenyl)-1,3-dioxolane (21):

The ketone **18** (123 mg, 0.40 mmol) was added to a THF (3 mL) suspension of lithium acetylide–ethylenediamine complex (110 mg, 1.2 mmol) under Ar at 0 °C. The reaction mixture was then stirred at 0 °C for 1 h and at r.t. for a further 2 h. It was quenched with sat. aq NH_4Cl and diluted with EtOAc. The organic layer was separated, washed with brine, dried and evaporated and the residue was purified by flash column chromatography (silica gel, EtOAc) to give some starting ketone (40 mg) and the title compound as a solid (57 mg, 42.7%; 63.3% based on unrecovered starting material). It was recrystallized from CH_2Cl_2/hexane for analysis. mp 80–86 °C (CH_2Cl_2/hexane).

IR ($CHCl_3$): ν = 3592, 3304, 3009, 2952, 2889, 2819, 1602, 1504 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43–1.48 (m, 2H, $NCH_2C\underline{H}_{-2}CH_2$), 1.70–1.84 (m, 6H, $NCH_2CH_2\underline{CH}_2$ and 2 × $NCH_2\underline{CH}_2C$), 2.20–2.27 (m, 4H, $NC\underline{H}_2CH_2CH_2$ and 2 × ax. CH_2N), 2.40 (s, 1H, CCH), 2.50–2.60 (m, 2H, 2 × eq. $C\underline{H}_2N$), 3.54 (br s, 1H, OH), 3.64–3.68, 3.90–3.94 (2 × m, 2 × 2H, $OCH_2\underline{CH}_2O$), 6.92 (t, 2H, J = 8.7 Hz, 2 × $C\underline{H}CF$), 7.33 (dd, 2H, J = 5.5, 8.6 Hz, 2 × $C\underline{H}CHCF$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.87, 38.24, 38.68, 49.75, 57.88, 64.30, 65.83, 72.32, 87.25, 109.84, 114.66 (d, J = 21 Hz), 127.35 (d, J = 7.6 Hz), 138.24, 162.21 (d, J = 246 Hz).

MS: m/z (%) = 333 (6), 332 (18), 167 (16), 138 (100).

2-(4-Fluorophenyl)-2-[3-(1-piperidyl)propyl]-1,3-dithiolane (23):

A mixture of piperidine (0.85 g, 10 mmol), 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (2 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol), and KI (1.66 g, 10 mmol) in DMF (20 mL) was heated at 50 °C for 16 h. H_2O and EtOAc were then added and the organic phase was separated, washed with brine (3 ×), and dried ($MgSO_4$). Solvent removal and purification of the residue by silica gel column chromatography (EtOAc) gave 1.67 g (61%) of the ketal corresponding to the title thioketal as a colorless oil.

IR (NaCl): ν = 3395 (br, OH), 2938 (m), 1609 (m), 1504 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.41 (m, 2H, 4-CH_2 in piper.), 1.53–1.58 (m, 6H, $C\underline{H}_2CH_2N$, chain $CH_2C\underline{H}_2CH_2$), 1.86 (t, 2H, J = 9 Hz, $C\underline{H}_2$-ketal), 2.24 (t, 2H, J = 8 Hz, chain $CH_2C\underline{H}_2N$), 2.31 (m, 4H, piper. $CH_2C\underline{H}_2N$), 3.75–3.77, 3.98–4.00 (2 m, 4H, ketal), 6.99 (t, 2H, J = 7 Hz, FCCHC$\underline{H}$C), 7.38–7.43 (m, 2H, FCC$\underline{H}$CHC).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 24.4, 25.9, 38.5, 54.5, 59.2, 64.4, 110.0, 114.8 (d, J = 12 Hz), 127.4 (d, J = 8 Hz), 162.4 (J = 254 Hz).

A solution of the ketal (548 mg, 1.87 mmol), 1,2-ethanedithiol (283 mg, 3 mmol) and $BF_3 \cdot Et_2O$ in dry MeOH (10 mL) was stirred at r.t. for 16 h. H_2O and EtOAc were added and the organic phase was separated, washed with brine, and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by silica gel column chromatography (EtOAc). The title compound (347 mg, 57%) was obtained as a colorless oil.

IR (NaCl): ν = 3390 (br, OH), 2861 (m), 1598 (m), 1499 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.56 (m, 8H, piper. $CH_2CH_2CH_2$, chain $CH_2C\underline{H}_2CH_2$), 2.19–2.34 (m, 8H, $C\underline{H}_2N$, $C\underline{H}_2$-thioketal), 3.19–3.27, 3.32–3.41 (2 m, 4H, thioketal), 6.96 (t, J = 7 Hz, 2H, FCCHC$\underline{H}$C), 7.64–7.68 (m, 2H, FCC$\underline{H}$CHC).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5, 25.3, 26.0, 39.2, 43.9, 54.5, 58.9, 73.6, 114.5 (d, J = 12 Hz), 128.9 (J = 8 Hz), 140,9, 161.7 (J = 254 Hz).[16]

Investigation of the Effect of Thioketal 23 on Grignard Reactions:

To a solution of 1-benzyl-4-piperidinone (192 mg, 1 mmol) with or without thioketal **23** (1 mmol), PhMgBr (1.5 equiv.) was added at 0 °C. After 10 min the mixture was allowed to warm to r.t. and stirred for 1 h. The mixture was quenched with silica gel and purified by column chromatography (silica gel, hexane/EtOAc, 1:1). Compound **24** was obtained as a white solid (82% in the absence, and 73% in the presence, of **23**); mp 105–107 °C (Lit.[17] 107–109 °C).

Bioassay:

The activities of the haloperidol derivatives as inhibitors of the HIV-1 protease were evaluated as previously reported for haloperidol itself.[2]

This work was supported by National Institutes of Health Grant GM 39552. Mass spectra were obtained in the Bio-organic, Biomedical Mass Spectrometry Facility (A. Burlingame, Director) supported by grants RR 01614.

(1) Huff, J.R. *J. Med. Chem.* **1991**, *34*, 2305.
(2) DesJarlais, R.L.; Seibel, G.L.; Kuntz, I.D.; Furth, P.S.; Alvarez, J.C.; Ortiz de Montellano, P.R.; DeCamp, D.L.; Babé, L.M.; Craik, C.S. *Proc. Natl. Acad. Sci.* **1990**, *87*, 6644.
(3) Rutenber, E.; Fauman, E.B.; Fong, S.; Furth, P.S.; Ortiz, de Montellano, P.R.; Meng, E.; Kuntz, I.D.; DeCamp, D.L.; Salto, R.; Craik, C.; Stroud, R.M. manuscript in preparation.
(4) Janssen, P.A.J., van de Westeringh, C.; Jageneau, A.H.M.; Demoen, P.J.A.; Hermans, K.F.; van Daele, G.H.P.; Schellekens, K.H.L.; van der Eycken, C.A.M.; Niemegeers, C.J.E. *J. Med. Pharm. Chem.* **1959**, *1*, 281.
(5) Harper, N.J.; Simmonds, A.B.; Wakama, W.T.; Hall, G.H.; Vallance, D.K. *J. Pharm. Pharmacol.* **1966**, *18*, 150.
Harper, N.J.; Simmonds, A.B. *J. Pharm. Pharmacol.* **1964**, *16*, 150.
Harper, N.J.; Simmonds, A.B. *J. Med. Pharm. Chem.* **1959**, *1*, 181.
(6) Ziering, A.; Berger, L.; Heineman, S.D.; Lee, J. *J. Org. Chem.* **1947**, *12*, 894.
(7) Lee, J.; Ziering, A.; Heinemann, S.D.; Berger, L. *J. Org. Chem.* **1947**, *12*, 885.
(8) Berger, L.; Ziering, A.; Lee, J. *J. Org. Chem.* **1947**, *12*, 905.
(9) Casy, A.F.; Iorio, M.A.; Pocha, P. *J. Chem. Soc. (C)* **1967**, 942.
(10) Takai, H.; Obase, H.; Terannishi, M.; Karasawa, A.; Kubo, K.; Shuto, K.; Kasuya, Y.; Hashikami, M.; Karashima, N.; Shigenobu, K. *Chem. Pharm. Bull.* **1985**, *33*, 1129.
(11) Wakefield, B.F. *Organolithium Methods*; Academic Press: London, 1988.
(12) Meek, D.W.; Dyer, G.; Workman, M.O. *Inorg. Synth.* **1976**, *16*, 168.
Kozikowski, A.P.; Cheng, X.-M. *J. Org. Chem.* **1984**, *49*, 3240.
(13) The analogous synthesis was not available for the thioketal **7** because the required halothioketal underwent a novel rearrangement reaction:
Sui, Z.; Furth, P.S.; De Voss, J.J. *J. Org. Chem.* **1992**, *57*, 6658.
(14) Vincent, S.H.; Shambhu, M.B.; Digenis, G.A. *J. Med. Chem.* **1980**, *23*, 75.
(15) Meek, T.D. *J. Enzyme Inhib.* **1992**, *6*, 65.
(16) A crystal structure has been obtained for the hydrochloride salt of this compound (M. Olmstead, Z. Sui, and P.R. Ortiz de Montellano, unpublished)
(17) Boggiano, B.G.; Petrow, V.; Stephenson, O.; Wild, A.M. *J. Chem. Soc.* **1959**, 1143.