# Picornavirus Inhibitors: Trifluoromethyl Substitution Provides a Global Protective Effect against Hepatic Metabolism

Guy D. Diana,*,† Patrick Rudewicz,‡ Daniel C. Pevear,† Theodore J. Nitz,† Suzanne C. Aldous,† David J. Aldous,† David T. Robinson,⊥ Tandy Draper,† Frank J. Dutko, Christopher Aldi,∥ Guy Gendron,# R. Christopher Oglesby,@ Deborah L. Volkots,§ Michael Reuman,‡ Thomas R. Bailey,† Richard Czerniak,‡ Tracey Block,@ Robert Roland,¶ and James Oppermann‡

*Research Division Sanofi Winthrop, Inc., Collegeville, Pennsylvania 19426*

*Received October 6, 1994*®

Several modifications of the oxazoline ring of WIN 54954, a broad spectrum antipicornavirus compound, have been prepared in order to address the acid lability and metabolic instability of this compound. We have previously shown that the oxadiazole analogue **3** displayed comparable activity against a variety of rhinoviruses and appeared to be stable to acid. A monkey liver microsomal assay was developed to examine the metabolic stability in vitro of both compounds, and it was determined that WIN 54954 displayed 18 metabolic products while **3** was converted to *8* products. Two major products of **3** were determined by LC-MS/MS to be monohydroxylated at each of the terminal methyl groups. Replacement of the methyl on the isoxazole ring with a trifluoromethyl group, while preventing hydroxylation at this position, did not reduce the sensitivity of the molecule to microsomal metabolism at other sites. However, the (trifluoromethyl)oxadiazole **9** not only prevented hydroxylation at this position but also provided protection at the isoxazole end of the molecule, resulting in only two minor products to the extent of 4%. The major product was identified as the monohydroxylated compound **23**. The global metabolic protective effect of trifluoromethyl group on the oxadiazole ring was further demonstrated by examining a variety of analogues including heterocyclic replacements of the isoxazole ring. In each case, the trifluoromethyl analogue displayed a protective effect when compared to the corresponding methyl analogue.

In the course of our synthetic efforts to develop a compound for the treatment of the common cold resulting from human rhinovirus infections, we have been confronted with the extensive metabolism of our most promising compounds. WIN 54954 (**1**)[1,2] did not demonstrate a therapeutic effect when administered orally to patients infected with human rhinovirus-16, -39, and -50,[3] although a prophylactic effect was seen against coxsackievirus A21.[4] This compound resulted in the formation of a relatively large number of metabolites, primarily resulting from hydrolysis of the oxazoline ring. In order to address this problem, a replacement for the oxazoline ring was required which would maintain the antiviral activity and yet be resistant to extensive metabolism, thus decreasing the rate of clearance from plasma. We had previously shown that the tetrazole analogues displayed activity comparable to the oxazoline counterparts[5] and that the tetrazole ring was hydrolytically stable. WIN 61605 (**2**) which emerged from this series as a potential clinical candidate,[6] was found to cause hepatoxicity when administered to beagles, and further development of this compound was terminated.

A continued search for a suitable replacement for the oxazoline ring resulted in the synthesis of the 5-methyloxadiazole analogue **3**[7] (WIN 61893) which was shown to be more potent than the oxazoline and tetrazole predecessors. Since it was our contention that metabolism was a key issue for these drugs, an in vitro liver microsomal assay was initiated to study their metabolic stability. In order to determine the nature of the metabolic products as well as the areas on the molecules which were susceptible to metabolic degradation, mass spectral analysis of the products from the microsomal assay was utilized. This information was critical for the design of analogues which would be resistant to metabolism in this assay and subsequently demonstrate lower plasma clearance in vivo.

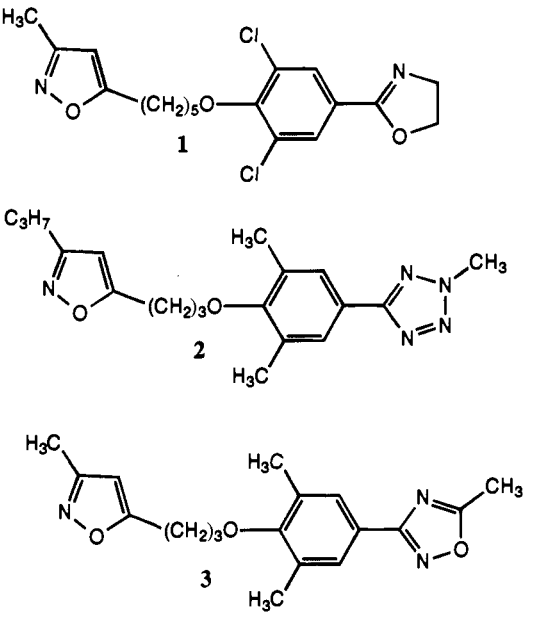



**Figure 1.** WIN 54954, compound **2**, and compound **3**.

† Viro Pharma, Inc., Collegeville, PA.
‡ Sanofi Winthrop, Collegeville, PA.
⊥ Sanofi Winthrop, Alnwick, U.K.
§ Pfizer, Groton, CT.
@ Nycomed, Inc., Rensselaer, NY.
∥ P.O. Box 2211, Schenectady, NY.
# Procyte, Seattle, WA.
¶ General Electric Silicones, Waterford, NY.
® Abstract published in *Advance ACS Abstracts*, March 15, 1995.

0022-2623/95/1838-1355$09.00/0 

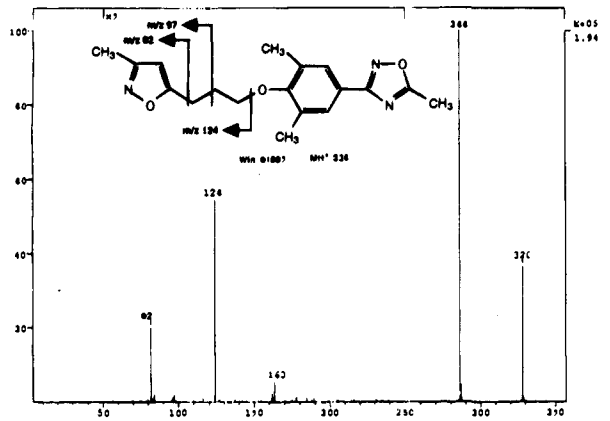


**Figure 2.** LC-MS/MS of compound **3**, showing the fragmentation patern. The parent ion is present at 328. The peak at 286 results from the fragmentation of the oxadiazole ring and the ion at 124 results from cleavage of the ether bond. Ions at 97 and 82 are due to further fragmentation of the aliphatic chain.

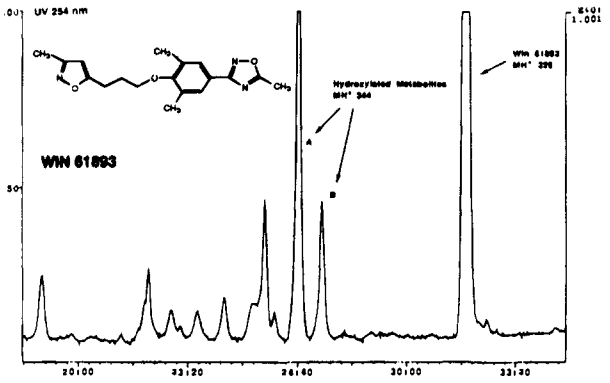



**Figure 3.** The product spectrum of the liver microsomal products of compound **3**. Two major peaks at $MH^+$ of 344 are the result of monohydroxylation (products A and B).

## Monkey Liver Microsomal Assay

In vivo studies with **1** (Figure 1) had demonstrated that monkey was the species which most closely approximated the metabolism of the compound in humans. Compounds were incubated with microsomes prepared from monkey liver at 37 °C for 30 min, and samples were analyzed by HPLC (see the Experimental Section). HPLC analysis indicated that there were approximately 18 products from WIN 54954 as compared to 8 for compound **3**. Although the extent of metabolism of compound **3** was reduced, the rate of metabolism was not markedly different from **1** (half-life of 27 vs 20 min, respectively). In the absence of the co-factor NADP, no metabolism of **3** occurred in the in vivo incubations, suggestive of cytochrome P450-dependent metabolism. Therefore, although the microsomal instability of compound **3** was reduced, this level of stability was not considered sufficient to advance this compound for further evaluation.

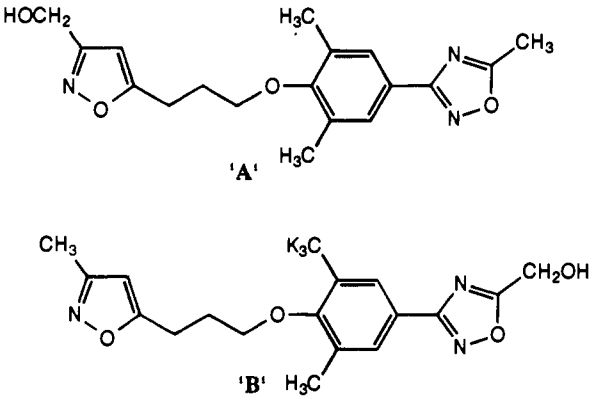


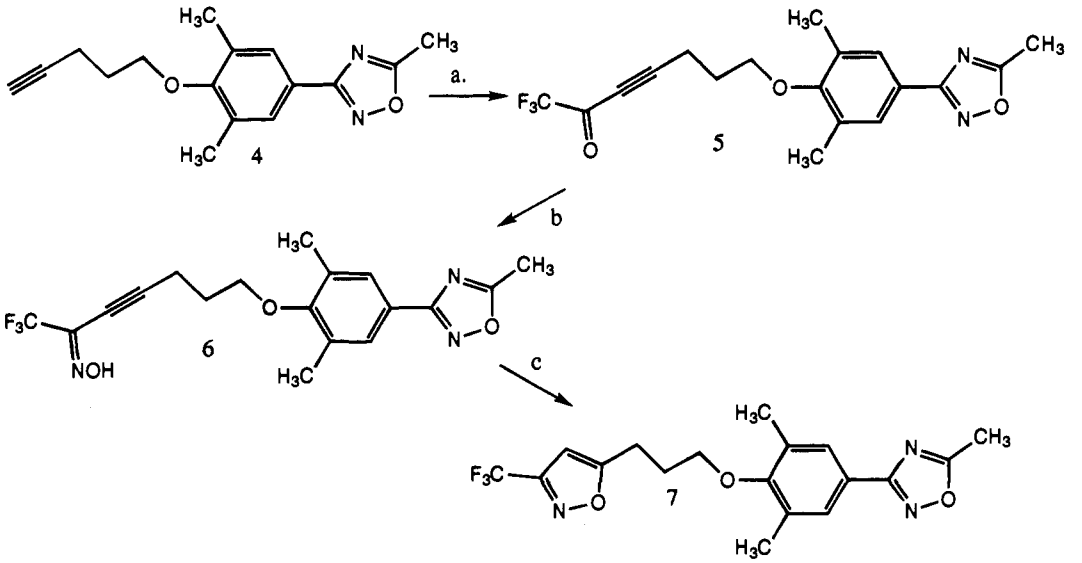

**Figure 4.** Metabolic products resulting from the exposure of **3** to monkey liver microsomes for 30 min.

The objective at this point was to synthesize an analogue of **3** which would have comparable activity with enhanced metabolic stability. The approach taken was to determine the nature of the metabolic products of **3** as well as the major sites of metabolism and to block these positions by conventional means. In order to achieve this goal, a product ion mass spectrometry technique was utilized.

## Mass Spectrometry

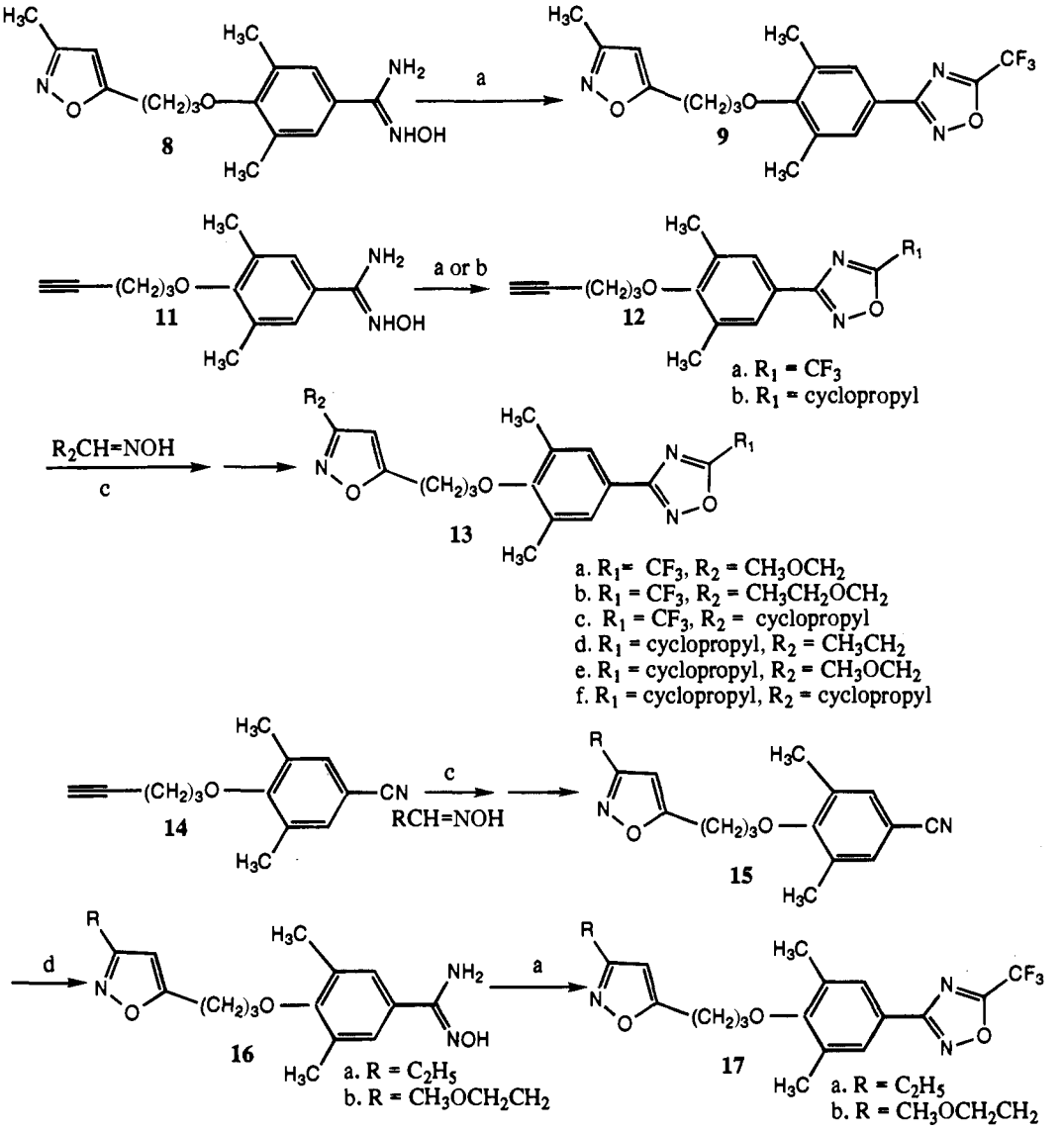
The LC-MS/MS of **3** is shown in Figure 2. In addition to the parent ion at $MH^+$ of 328, a strong ion was

**Scheme 1**[a]




[a] (a) *n*-BuLi, THF, −78 °C; $CF_3CO_2Et$; $BF_3{\cdot}Et_2O$; (b) $NH_2OH$, KOH; (c) $C_6H_6$, heat.

**Scheme 2**[a]




[a] (a) TFAA, pyridine; (b) cyclopropanecarbonyl chloride, pyr; (c) NCS, DMF; (d) $NH_2OH$, $K_2CO_3$, EtOH.

observed at 286, resulting from the fragmentation of the oxadiazole ring. Cleavage of the C–O ether bond provided the ion at 124, and further fragmentation of the aliphatic chain generated ions at 97 and 82. With the fragmentation pattern of **3** established, the product ion MS of the liver microsomal product was examined in a similar fashion. In addition to numerous minor products, two major monohydroxylated products, A and B, in the ratio of 3:1 were observed (Figure 3) with ions at $MH^+$ at 344. The identity of metabolite B was established as follows. The product ion spectrum for metabolite B was identical to that for WIN 61893 with the exception of the parent peak at 344. This located the site of hydroxylation as the methyl group on the oxadiazole ring and the product as shown in Figure 4, which is the only one that would give the daughter ions at 286 (−58), 124, and 97.

The product ion spectrum for metabolite A showed a +16 fragment for all of the daughter ions when compared to the spectra for **3**. Consequently, product A was assigned the structure shown in Figure 4 whose synthesis has been previously reported.[7] The structures of both A and B were confirmed by co-elution with known material.

Analysis of the metabolic products of **3** indicated that hydroxylation occurred to a greater extent on the methyl group attached to the isoxazole ring. Consequently, a trifluoromethyl group was initially introduced at this position to replace the methyl group in an effort to prevent metabolic hydroxylation and consequently the extent of metabolism. The synthesis of this compound is shown in Scheme 1. Treatment of the anion of acetylene **4**[7] with ethyl trifluoroacetate and boron trifluoride etherate provided ketone **5** in 20% yield. Conversion of **5** to the corresponding oxime **6** followed by heating in refluxing benzene[9] gave the (trifluoromethyl)isoxazole **7**. The isomeric (trifluoromethyl)-oxadiazole **9** was also prepared as described in Scheme 2, from amidoxime **8**.[7]

The result of incubation of compound **7** with monkey liver microsomes for 30 min is shown in Figure 5. Three major metabolites were observed, two of which from MS–MS were consistent with monohydroxylation ($MH^+$ 398) and one which had a mass ion consistent with dihydroxylation ($MH^+$ 414). The ion spectrum of one of the monohydroxylated metabolites, C, is shown in Figure 6. The observed fragmentation pattern elimi-

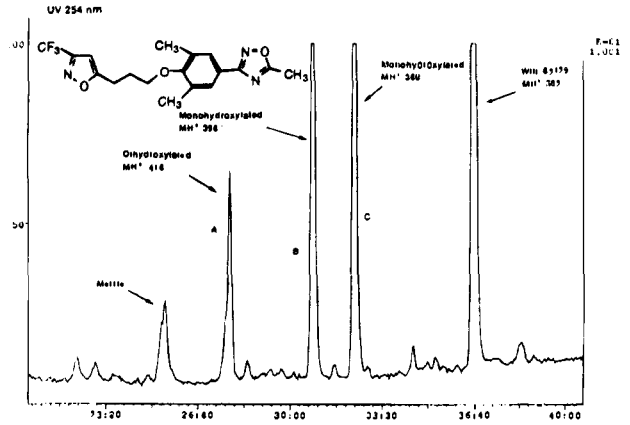


**Figure 5.** LC-MS analysis of the products resulting from the 30 min incubation of **7** with monkey liver microsomes. Two monohydroxylated and one dihydroxylated products are present at 398 and 414, respectively.

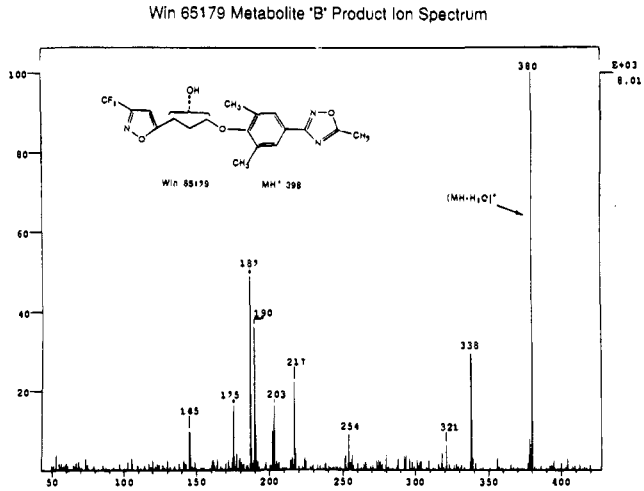



**Figure 6.** The ion spectrum of metabolite C from the incubation of compound **7**.

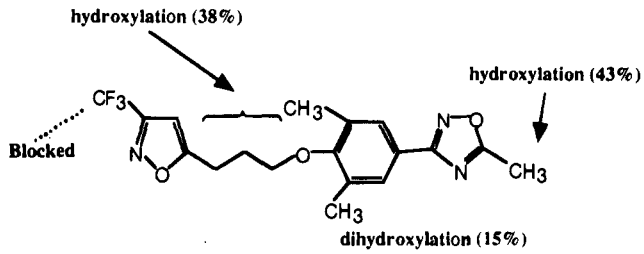



**Figure 7.** Summary of the biotransformation of compound **7**.

nated the possibility of the hydroxyl being located at the oxadiazole ring since the peak at 380 resulted from loss of water as well as from fragmentation of the oxadiazole ring as seen in compound **3**. The ion at 203 may have resulted from the right hand portion of the molecule via cleavage of the C–O bond within the chain.

The biotransformation of compound **7** is summarized in Figure 7. Of the metabolic products characterized, 43% resulted from hydroxylation of the methyl group attached to the oxadiazole ring, 38% was attributed to monohydroxylation of the chain, and 15% to dihydroxylation. The rate of metabolism of **7** was not different from that of **3**. In summation, blocking the metabolism of the methyl group on the isoxazole ring did not appear to affect the overall metabolic stability of the molecule.

The results of the metabolic transformation of **9** were

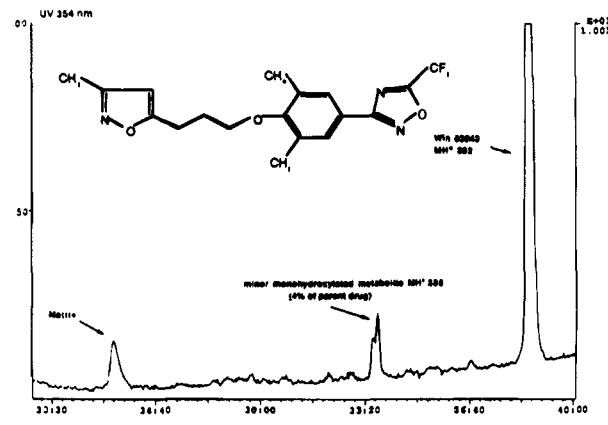


**Figure 8.** LC-MS analysis of the metabolic transformation of **9** showing one major peak at $MH^+$ 382 corresponding to the parent compound and one minor peak.

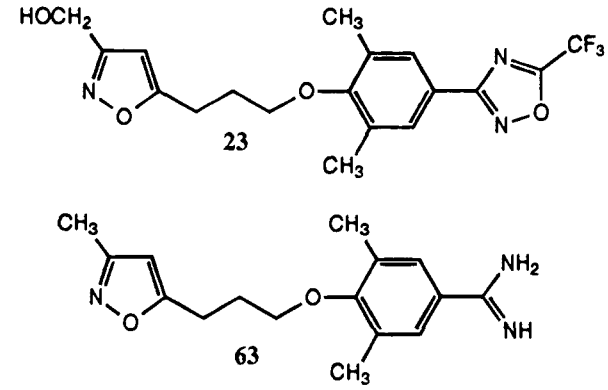
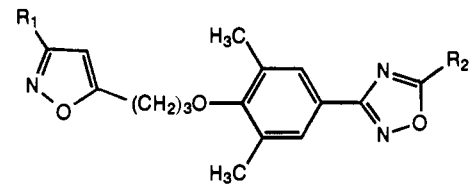



**Figure 9.** Metabolic conversion product of compound **9** found in trace amounts.

**Table 1.** Global Protective Effect of the Trifluoromethyl Group against in Vitro P450 Metabolism



| compound | $R_1$ | $R_2$ | $T_{1/2}$ (min) |
|---|---|---|---|
| **3**[a] | $CH_3$ | $CH_3$ | 27 |
| **9** | $CH_3$ | $CF_3$ | >150 |
| **10**[a] | $C_2H_5$ | $CH_3$ | 11 |
| **17a** | $C_2H_5$ | $CF_3$ | >150 |
| **49**[a] | $CH_3OCH_2$ | $CH_3$ | 30 |
| **13a** | $CH_3OCH_2$ | $CF_3$ | 95 |
| **13b** | $C_2H_5OCH_2$ | $CF_3$ | >150 |
| **23** | $HOCH_2$ | $CF_3$ | >150 |
| **27** | $CH_3SO_2CH_2$ | $CF_3$ | >150 |
| **26** | $CH_3SOCH_2$ | $CF_3$ | >150 |
| **7** | $CF_3$ | $CH_3$ | 33 |

[a] See ref 7.

quite different and are shown in Figure 8. After incubation for 30 min, approximately 96% of the parent compound was recovered unchanged, and of the remaining 4%, the principle metabolic product was a monohydroxylated derivative which was identified by product ion MS as **23** (Figure 9). In addition, traces of amidine **63** were also identified. A comparison of the gradient HPLC profiles of WIN 54954 (**1**) and **9** are shown in Figure 10.

Having established the global protective effect of the

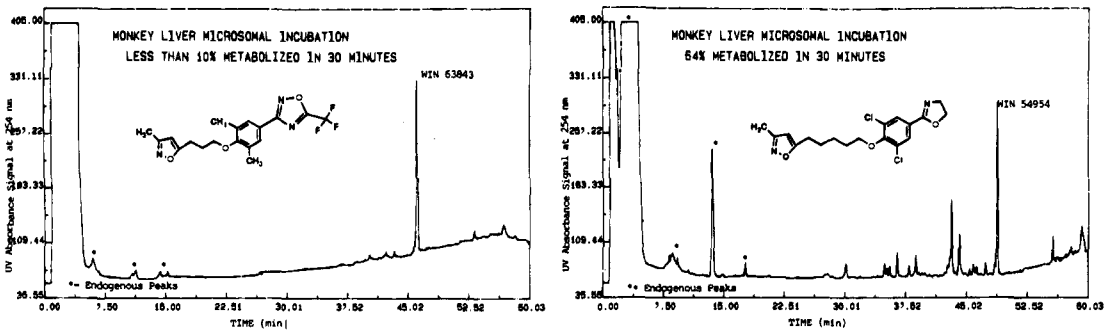
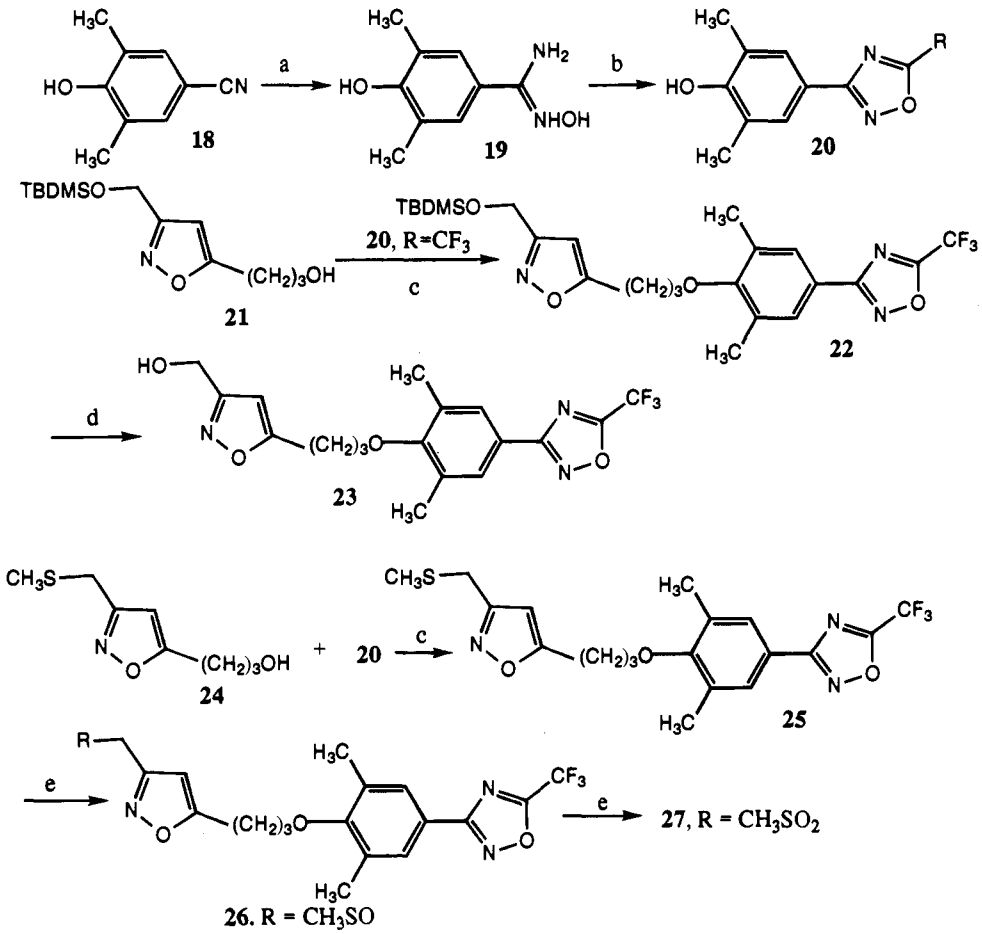



**Figure 10.** A comparison of the gradient HPLC profiles of WIN 54954 and compound **9**.

**Scheme 3**[a]



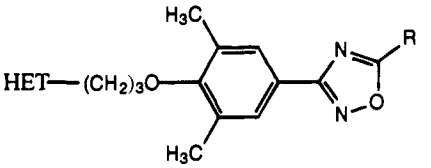

[a] (a) $NH_2OH$, EtOH; (b) $(CF_3CO)_2O$, pyr; (c) DEAD, triphenylphosphine, THF; (d) 1 N HCl, THF; (e) oxone, $Al_2O_3$, $CH_2Cl_2$, heat.

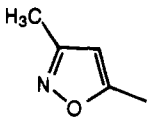
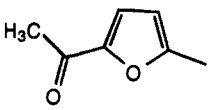
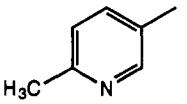
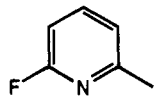
trifluoromethyl group attached to the oxadiazole ring, the general significance of this observation was explored. Several analogues with various substituents on the isoxazole ring[6] were synthesized as shown in Schemes 2 and 3. Amidoxime **11** was treated with cyclopropanecarbonyl chloride or TFAA to give the appropriate oxadiazole **12**. The isoxazoles **13** and **17** were obtained by a [3 + 2] cycloaddition of the derived nitrile oxide.[10] The hydroxymethyl analogue **23** was prepared by the procedure outlined in Scheme 3. Conversion of nitrile **18** to amidoxime **19** followed by acylation with TFAA provided oxadiazole **20** which was coupled[11] with alcohol **21** to give **22**. Removal of the TBDMS group was accomplished with 1 N HCl. The methylthio, methyl sulfoxide, and methyl sulfone analogues were prepared as shown. Oxidation of the methyl sulfide analogue with oxone[12] at room temperature gave **26**. Further oxidation of **26** in refluxing chloroform gave **27**.

The half-life values for several analogues of **3** which were incubated with liver microsomes are shown in Table 1. A comparison was made between the methyl- and (trifluoromethyl)oxadiazole. In every case, the trifluoromethyl analogues displayed significantly greater stability than the methyloxadiazole. Of particular interest were the methoxymethyl analogues **49** and **13a**. One might anticipate that the ether linkage would be a point of metabolic cleavage. However, the trifluoromethyl group afforded protection, and the compound remained essentially unchanged after a 30 min incubation. The corresponding ethyl ether **13b** was also protected.

The effect of replacement of the isoxazole ring with other heterocycles is shown in Table 2. Acetylfuran **30**

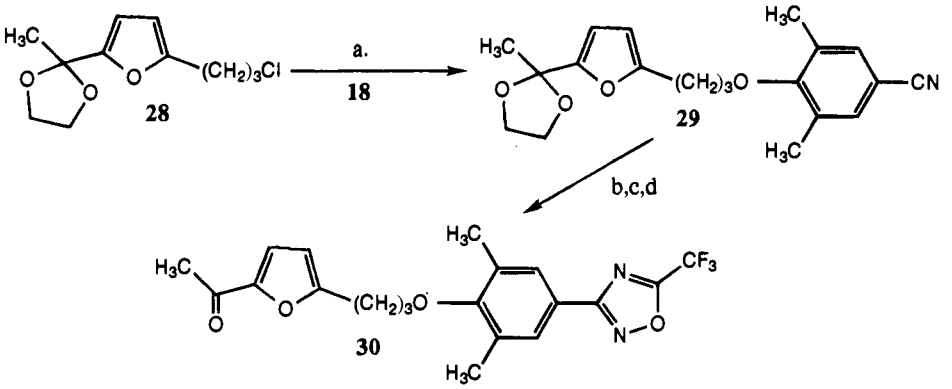
**Table 2.** Global Protective Effect of the Trifluoromethyl Group against in Vitro P450 Metabolism



| compound | HET | R | T1/2(min) |
|---|---|---|---|
| 3 |  | $CH_3$ | 30 |
| 9 | | $CF_3$ | >150 |
| 60[a] |  | $CH_3$ | 37 |
| 30 | | $CF_3$ | 63 |
| 61 |  | $CH_3$ | 82 |
| 36 | | $CF_3$ | 118 |
| 62 |  | $CH_3$ | 17 |
| 39 | | $CF_3$ | >150 |

[a] See ref 8.

**Scheme 4**[a]



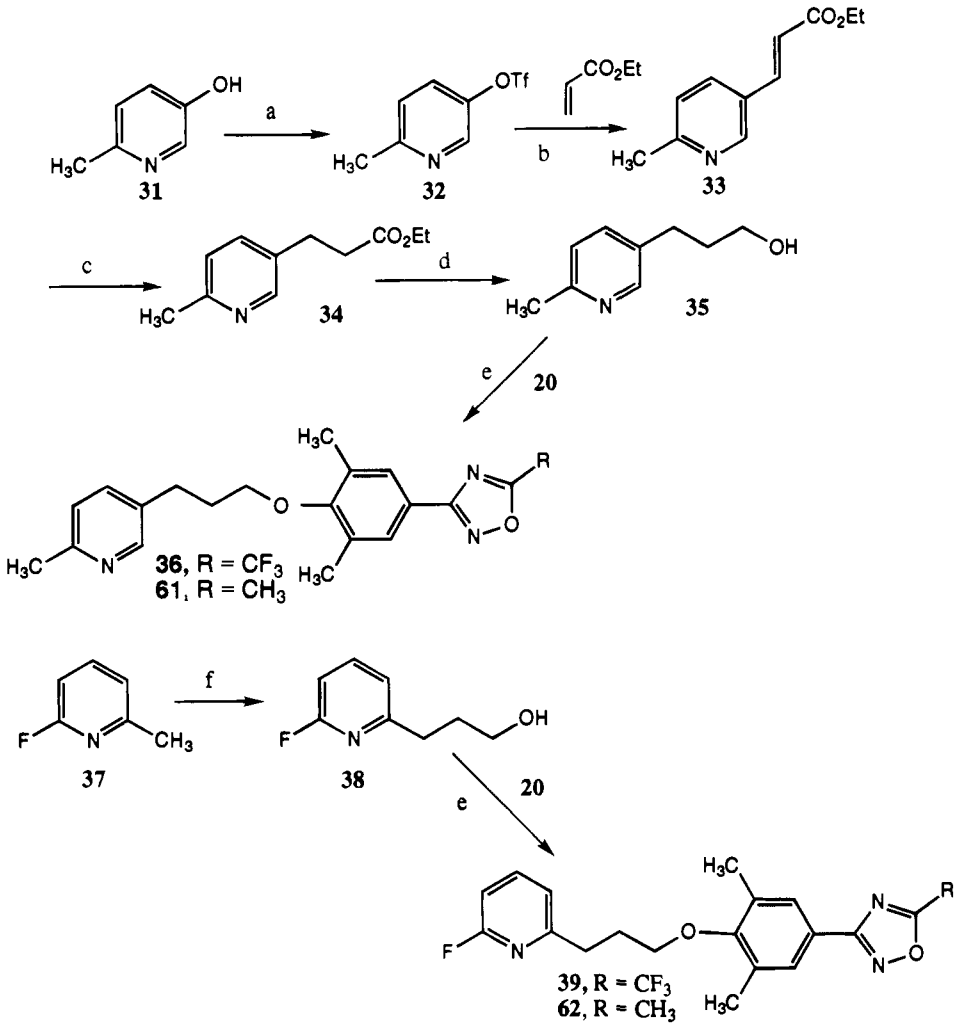
[a] (a) $K_2CO_3$, NMP, 105 KI, 60 °C; (b) $NH_2OH$, KOH; (c) TFAA, pyr; (d) HCl/$H_2O$.

was prepared from chloropropylfuran **28**[8] and 3,5-dimethyl-4-hydroxylbenzonitrile followed by conversion of the resulting nitrile **29** to **30** as shown in Scheme 4. The pyridine analogues **36** and **39** were prepared according to the procedure outlined in Scheme 5. The hydroxypyridine **31** was converted to triflate **32** which was cross-coupled with ethyl acrylate to give the pyridyl acrylate **33**. Successive reductions of **33** and **34** provided the pyridylpropanol **35** which was converted to **36** by reaction with phenol **20**. Although the number of examples is limited, it would appear that global protection is also afforded to the molecule regardless of the nature of the heterocycle (Table 2). These specific examples were chosen because of our interest in the antipicornavirus activity associated with these series of compounds. The least dramatic effect was seen with the acetylfuran where the difference in the half-lives of the respective analogues is less than 2-fold. This was also the case with 2-methylpyridine; however, the methyl analogue **61** was relatively stable when compared to the respective analogues in the other heterocyclic examples.

The global protective effect was not restricted to the trifluoromethyl group. The incorporation of cyclopropyl (Scheme 6), difluoromethyl, carboxamide, and ethoxy substituents into the 5-position of the oxadiazole ring also provided protection against P450 metabolism (Table 3). However, the difluoroethyl (**58**) and trifluoroethyl (**59**) analogues, prepared according to Scheme 7, were not protective. The protective effect of the cyclopropyl group, which was comparable to the trifluoromethyl analogue (Table 4), was of particular interest. All of the analogues, with the exception of the ethyl analogue **13d**, exhibited enhanced stability in the microsomal assay.

In order to assess the abilities of the in vitro metabolic assays to select compounds which would demonstrate improved pharmacokinetic performance in vivo, **9** and **1** were administered intravenously (10 mg/kg) to beagle dogs and the pharmacokinetic parameters calculated

**Scheme 5**[a]




[a] (a) $Tf_2O$, pyr; (b) DMF, $PdCl_2$ $(Ph_3P)_2$, LiCl; (c) Pd/C, $H_2$, 50 psi; (d) LAH, ether; (e) DEAD, triphenylphosphine; (f) LDA, ethylene oxide.

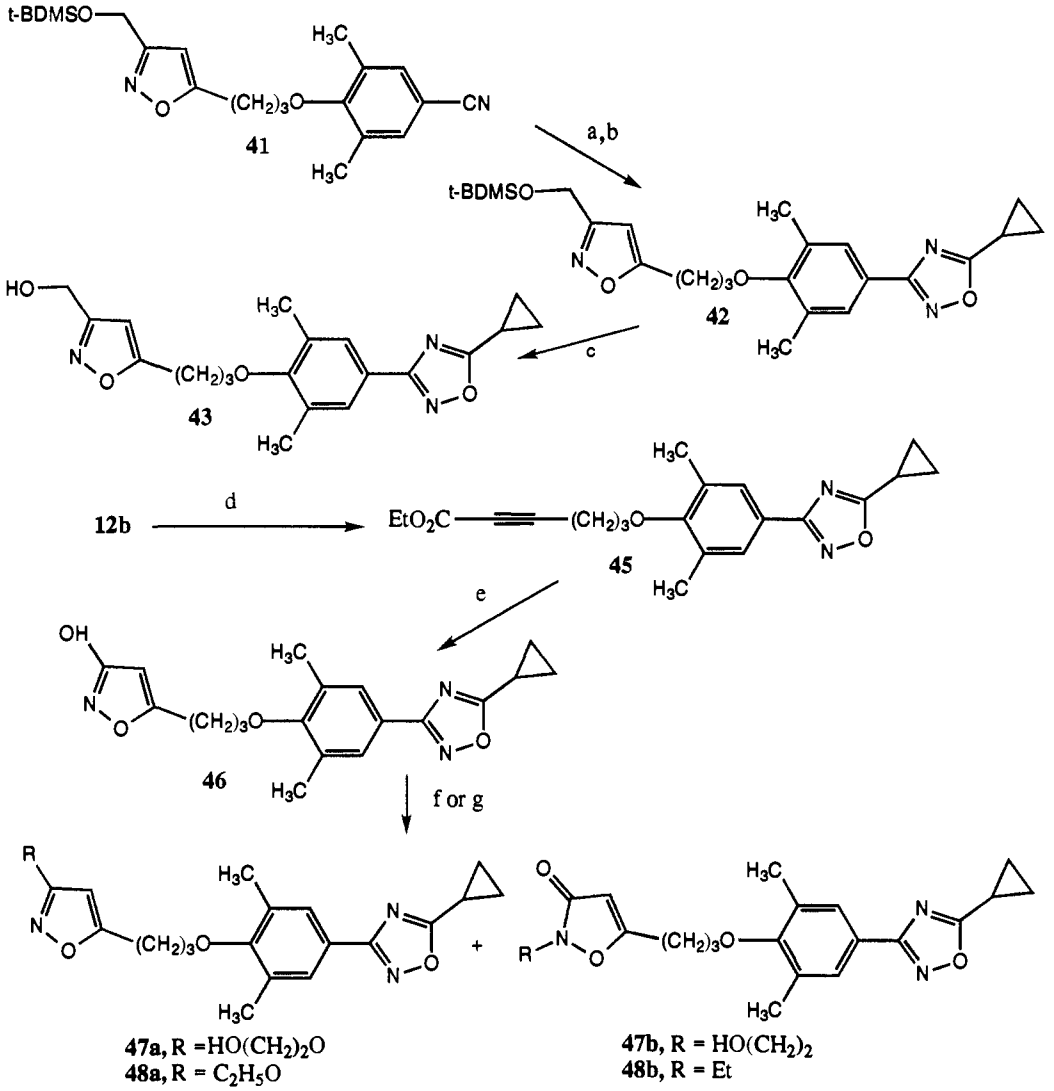
(see Table 5). Compound **9** demonstrated a greater than two fold increase in AUC compared to **1**, as well as a 4-fold increase in terminal elimination half-life and a 2–3-fold decrease in the plasma clearance values. In summary, compound **9** displayed a superior pharmacokinetic profile consistent with reduced hepatic clearance indicating a good correlation between the in vitro metabolism assays and in vivo pharmacokinetic performance.

## Discussion

One of the most interesting results of this study isthe radical difference in the protective effect of the trifluoromethyl group depending upon its location on the molecule. Despite the relatively high degree of hydroxylation of the methyl group on the isoxazole ring in compound **3**, little, if any, effect was seen on the number of metabolic products resulting from blocking this position with a trifluoromethyl group. Hydroxylation had occurred at other sites in the molecule. Conversely, the trifluoromethyl group in **9** blocked the secondary site of metabolism and in addition imparted global protection to the entire molecule. The lack of a protective effect of the difluoroethyl **58** and trifluoroethyl **59** while the cyclopropyl analogue **56** imparted global protection suggests that the protection was not simply a protective effect resulting from the replacement of hydrogen with fluorine.

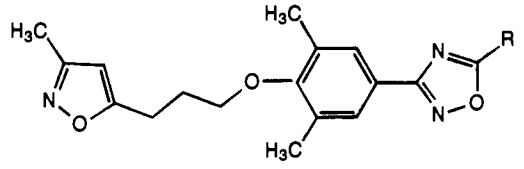
In order to determine if electrostatics, particularly in the area of the oxadiazole ring, play a significant role in the inhibition of the metabolism process, we have determined the electrostatic potential of the methyl (**3**), trifluoromethyl (**9**), difluoromethyl (**57**), carboxamide (**51b**), ethoxy (**55**), and cyclopropyl (**56**) analogues. The results are shown in Figures 11 and 12. The metabolically unstable methyl analogue **3** exhibited a positive lobe at the upper surface of the methyl group. On the other hand the carboxamide (**51b**) and ethoxy (**55**) analogues displayed a build up of a negative potential at this location when compared to the methyl analogue. In contrast, the cyclopropyl analogue (**56**) displays a potential similar to **3**; however, the potential is somewhat distorted. The olefinic-like character of the cyclopropyl ring with respect to its ability to conjugate with neighboring p orbitals[13–17] is not addressed by the methodology used to calculate electrostatic potentials.[18] Due to the protective nature of the cyclopropyl group, one would have expected an electrostatic potential map more closely related to that of the trifluoromethyl analogue, if electrostatics played a significant role in this case. The potential map for the difluoromethyl analogue **57** is conformationally dependent and as a

**Scheme 6**[a]




[a] (a) $NH_2OH$, EtOH, $K_2CO_3$; (b) cyclopropanecarbonyl chloride, pyr; (c) 1 N HCl, THF; (d) *n*-BuLi, $ClCO_2Et$; (e) $NH_2OH$·HCl, EtOH, NaOH; (f) $BrCH_2CH_2OH$, $K_2CO_3$, acetone; (g) $C_2H_5Br$, NaOH.

**Table 3.** Inhibition of in Vitro P450 Metabolism

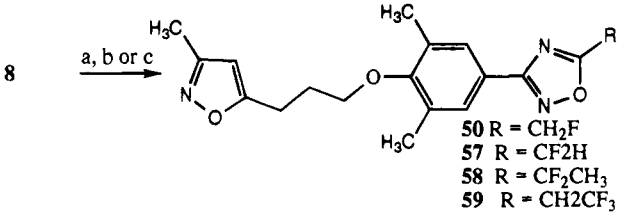


| compd | *R* | $T_{1/2}$ (min) |
|---|---|---|
| **3** | $CH_3$ | 27 |
| **9** | $CF_3$ | >150 |
| **50** | $CH_2F$ | 14 |
| **51b** | $CONH_2$ | 138 |
| **52**[a] | $CCl_3$ | 11 |
| **53** | CN | 17 |
| **54**[a] | $OCH_3$ | 33 |
| **55**[a] | $OC_2H_5$ | >150 |
| **56** | cyclopropyl | 134 |
| **57** | $CF_2H$ | 85 |
| **58** | $CF_2CH_3$ | 66 |
| **59** | $CH_2CF_3$ | 32 |

[a] See ref 7.

result may vary, the variation being a function of proton position. However, the presence of a positive lobe similar to the methyl analogue may account for the

**Scheme 7**[a]

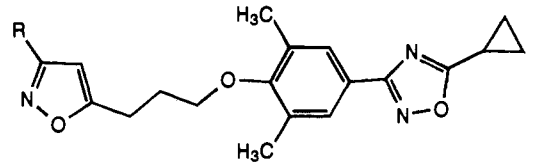



[a] (a) RCOOEt, 90 °C; (b) $CF_3CH{=}\overline{CSCH_2CH_2CH_2S}$, AgOTf, $C_6H_6$, heat; (c) RCOCl, pyridine.

slightly reduced level of protection when compared to **59**. The potential maps for the difluoroethyl **58** and trifluoroethyl **59** analogues (Figure 13) were similar to the methyl analogue **3** and not to the trifluoromethyl analogue **9**.

A remaining unknown is the role of electrostatics in the binding process. Since it has been shown with **3** that metabolism occurs at both ends of the molecule, one might envision that the hydroxylation occurs in stages. Initially, the phenyl end of the molecule may bind, exposing the isoxazole end to the P450 active site. Subsequently, a reorientation of the molecule may take

**Table 4.** Global Protective Effect of the Cyclopropyl Group



| compd | R | $T_{1/2}$ (min) |
|---|---|---|
| **56** | $CH_3$ | >150 |
| **13d** | $C_2H_5$ | 54 |
| **13f** | cyclopropyl | >150 |
| **43** | $HOCH_2$ | >150 |
| **13e** | $CH_3OCH2$ | >150 |
| **48** | $CH_3CH_2O$ | >150 |
| **47** | $HOCH_2CH_2O$ | >150 |

**Table 5.** Comparison of the Pharmacokinetic Parameters of Compounds **9**[a] and 1 in Fasted Beagle Dogs following iv administration

| | **9**[b,c] | 1[b,d] |
|---|---|---|
| half-life (h) | 27 | 7 |
| AUC (ng h/mL) | 11753 | 4911 |
| (std dev) | 4130 | 1021 |
| CL (L/h/kg) | 0.77 | 1.91 |

[a] Compounds were administered at 10 mg/kg. [b] $n = 4$. [c] Compound was formulated as an intralipid solution. [d] Compound was formulated as a PEG:400-ethanol (95:5) solution.

place, exposing the other end to the active site of P450. However, the electronic environments of the isoxazole and the oxadiazole rings in these molecules are completely different since the latter is linked to the phenyl ring, thereby affording the opportunity for conjugation with consequent dispersion of charge throughout the conjugated system of any inductive effect of the trifluoromethyl group. The (trifluoromethyl)isoxazole, however, offers no possibility for conjugation, thereby transferring the induction over a smaller system. In the case of **9**, the compound might only be able to bind in an allowed orientation due to the charged environment around the oxadiazole and phenyl rings, while exposing the protected (trifluoromethyl)oxadiazole ring to the active site. The situation with **7** may result from the less electrostatically charged environment of the isoxazole ring which offers no hinderance to binding in either mode. Consequently, the change in binding preference may be entirely dependent upon the difference in the electrostatic environments of the two molecules. There are several other possible explanations for this phenomenon which, without the availability of X-ray crystallography, are simply hypotheses.

We have shown that certain analogues in this series of compounds are resistant to P450 metabolism which may be attributed to a lack of binding. Computational results suggest that steric bulk and electrostatics may be responsible for this lack of binding. Although there are numerous examples of the resistance of the trifluoromethyl group to metabolic degradation[19] and examples of the protective effect of fluorine at sites distal to the location of fluorine on a molecule,[20,21] to our knowledge, this is the first example of an extensive global protective effect occurring at positions distantly remote from the protected one.

## Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 20SX FTIR. NMR spectra were acquired in the indicated solvent on a JEOL-FX270, a General Electric QE-300, or a Bruker-AC200 FTNMR. HETCOR ($^1H-^{13}C$ correlation) and DEPT experiments were utilized to assist in peak assignments. Mass spectra were recorded on a Nermag R10/10 coupled to a Varian 3400 Gas Chromatograph or on a JEOL JMS-01SC spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, or Quantitative Technologies Inc., Whitehouse, NJ. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Thin layer chromatography (TLC) was performed on E. Merck 1×3, Kieselgel 60 F-254 plates. Flash chromatography, medium-pressure liquid chromatography (MPLC), and dry flash chromatography were performed as previously indicated.[7] High-boiling solvents (DMF, NMP) were stage-dried over molecular sieves, chloroform was passed through a column of silica gel 60 and dried ($Na_2SO_4$) prior to use, and THF and ether were distilled from sodium benzophenone ketyl. Organic extracts were dried with $MgSO_4$ unless otherwise noted. All moisture-sensitive reactions were performed in dried glassware under a nitrogen or argon atmosphere.

**Computational Chemistry.** The bioactive conformation of analogue **9** bound to HRV-14 has been determined crystallographically. This conformation was used for all modeled compounds. Each analogue was constructed in the modeling package Sybyl[18] by modification of the basic structure of analogue **9** using the standard tools and fragments found in Sybyl. The individual structures were submitted for charge calculation within Sybyl, utilizing the QCPE MOPAC[22] command. The charges were calculated in the semiempirical package MOPAC, specifying the AM1 method and the "precise" convergence criteria suggested by Dewar.[23] The MOPAC charges were retrieved and used to generate isopotential maps via the potential command in Sybyl. Three color-coded potential levels were used to generate the contours of the map; surface points with a potential of −1 kcal/mol are shown in blue, the null (nodal) points with a potential of 0 kcal/mol are colored yellow, and surface points with a potential of 1 kcal/mol are shown in red.

**Liver Microsomes Incubation Procedure.** The individual compounds (25 μM) were incubated in unstoppered Erlenmeyer flasks (10 mL) at 37 °C for 30 min with microsomes isolated from monkey liver homogenate. Each incubation flask contained glucose-6-phosphate (1.5 mg/mL), $NADPHNa_4$ (0.95 mg/mL), $MgCl_2$ (1.0 M, 5.0 μL/mL), niacinamide (1.50 mg/mL), G-6-P dehydrogenase (1.50 units/mL), sufficient microsomal suspension, and phosphate buffer (pH 7.4, 0.1 M) to achieve a final protein concentration of 2.0 mg/mL in a total volume of 3 mL. At appropriate intervals, 1 mL aliquots of the incubate were extracted twice with 6 volumes of hexane. The extracts were combined and reduced in volume. The dried extracts were analyzed by HPLC.

**Thermospray LC-MS/MS.** The thermospray LC-MS/MS experiments were done using a Finnigan MAT TSQ 700 triple quadrupole mass spectrometer equipped with a TSP 2 ion source. The operating conditions were as follows: vaporizer, 90 °C; ion source temperature, 200 °C, repeller voltage, 50 V. For the collision-induced dissociation (CID) experiments, argon was used as the collision gas at a pressure of 1 mTorr. The collision energy (quadrupole 2 offset voltage) was 25 eV ($E_{lab}$).

A Varian 9010 multisolvent delivery system equipped with a Varian 9050 UV detector were used for the chromatographic separation. A Supelcosil LC-18-DB (4.6 × 150 mm, 4 particle size) and a Brownlee $C_{18}$ (4.6 × 30 mm) guard column were used for the chromatographic separation. The mobile phases were 0.1 M ammonium acetate in water (A) and acetonitrile (B). The flow rate used was 1.2 mL/min with a linear gradient of 0 min, 5% B→5 min, 5% B→40 min, 85% B→50 min, 85% B→60 min, 5% B. The microsomal incubation mixture (50 μL) was injected onto the HPLC column. The effluent passed through the UV detector (254 nm) and then to the mass spectrometer.

**In Vivo Data.** All research involving animals described in this publication was performed in accord with the Sterling Winthrop Pharmaceuticals Research Division (SWPRD) Policy On Animal Use and all national and federal legislation. All

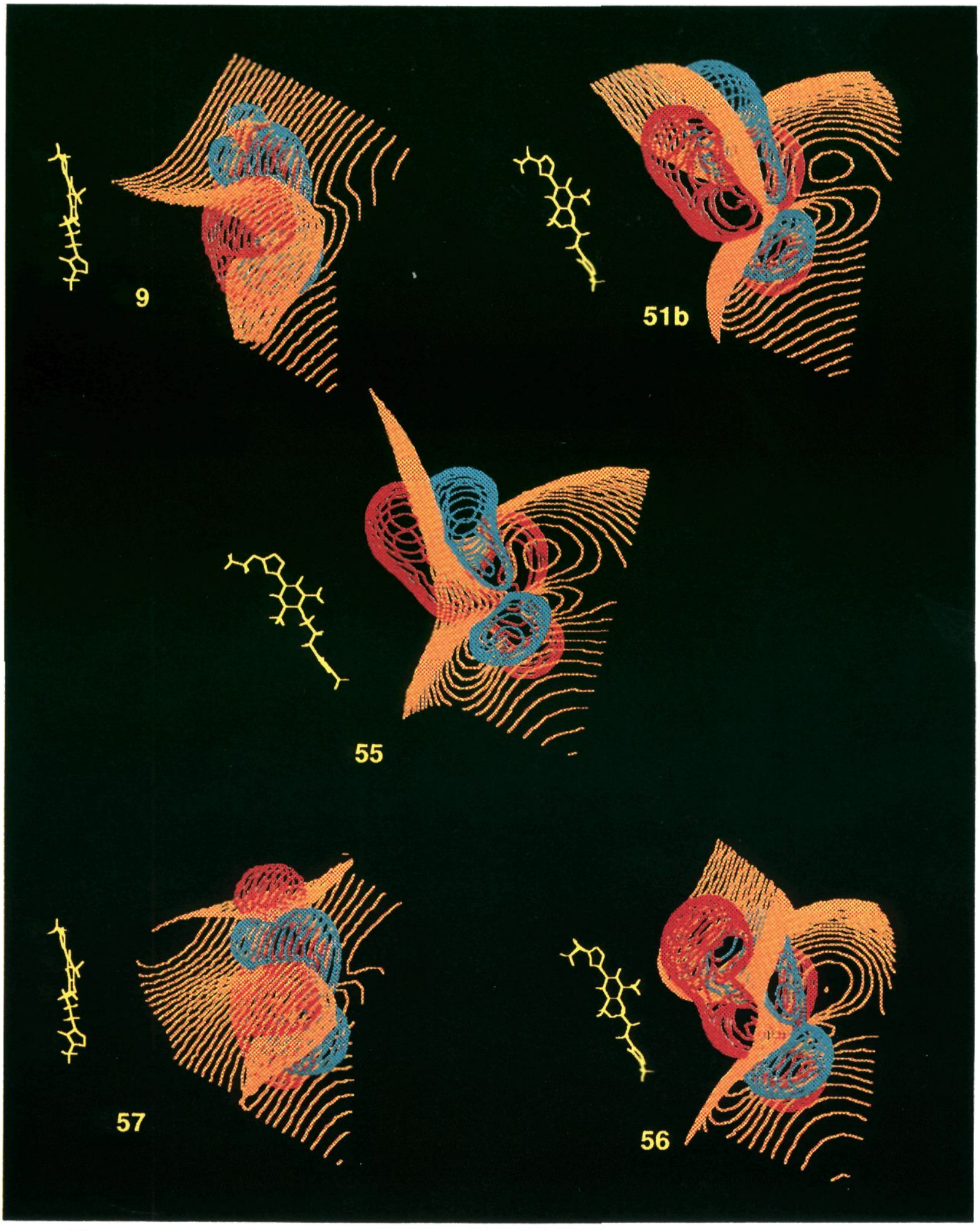



**Figure 11.** Electrostatic potential maps for compounds **9**, **51b**, **55**, **56**, and **57**.

SWPRD animal facilities and programs are accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). Compound **9** was formulated in PEG 400 solution (10 mg/mL) for intravenous infusion over a 20 min period to beagle dogs (Marshall Farms Inc.). Compound **1** was administered as an Intralipid (Kabivitrum UK Ltd, Uxbridge) emulsion (20 mg/mL) in a bolus dose. Plasma samples containing **9** (1 mL) were extracted with hexane and reduced to dryness under a stream of nitrogen at 50 °C and redissolved in methanol (100 $\mu$L). Plasma concentrations of **9** were determined using a Hewlett-Packard Model 5890 GC equipped with an electron capture detector and a Hewlett-Packard Model 7673A auto-injector. The injection port, column oven, and detector were held at 280, 230, and 280 °C, respectively. Aliquots (1 $\mu$L) were chromatographed onto a glass column packed with 3% OV-25 on Supelcoport 100/120 mesh (4 ft × 2 mm i.d.). The argon−methane (95:5, high purity) carrier gas flow was 30 mL/min. The retention time for **9** was approximately 1.5 min and the assay validated to a minimum quantifiable level of 50 ng/mL. The calibration curve was linear over the range 50−2000 ng/mL, and recoveries were all greater than 76%. Samples containing **1** (1 mL) were analyzed by reverse-phase HPLC on a Partisil ODS-3 column with a mobile phase of methanol−sodium acetate (0.025 M, pH 5.7)−

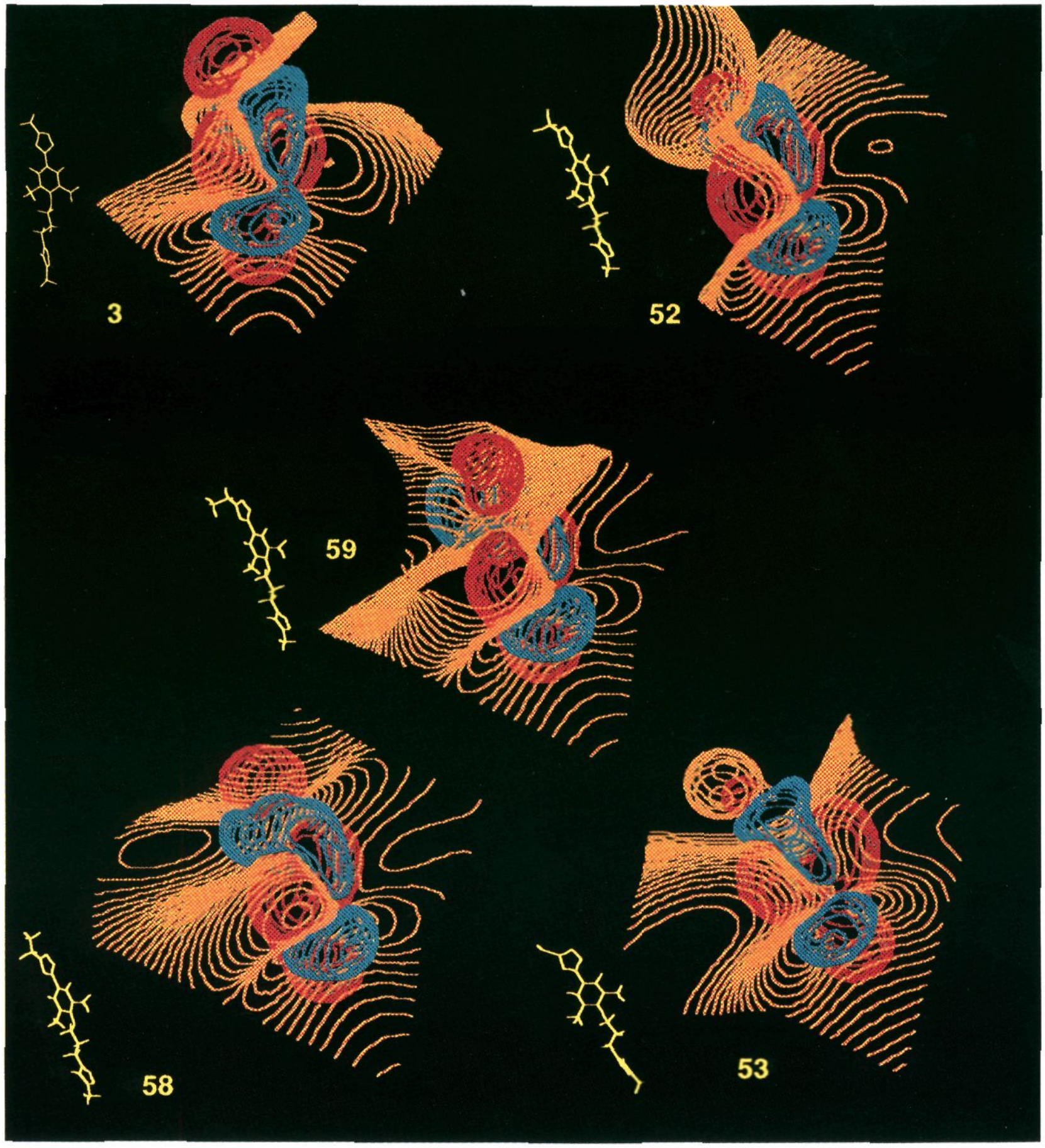



**Figure 12.** Electrostatic potential maps for compounds **3**, **52**, **53**, **58**, and **59**.

tetrahydrofuran (8:2.1:10) with UV absorption detection at 254 nm. Plasma samples were buffered to pH 10 and extracted into hexane. The retention time of **1** was 7.3, and the assay was validated to a minimum quantifiable level of 20 ng/mL.

**Pharmacokinetic Calculations.** Peak plasma concentrations of **9** and **1** ($C_{max}$) and the time of their occurrence ($t_{max}$) were obtained by inspection. Plasma concentrations less than minimum quantifiable level were ignored in the calculation of mean values. Pharmacokinetic parameters (half-life, CL) were determined from plasma profiles by model independent methods. Areas under the curves were determined by the trapezoidal rule.

**1,1,1-Trifluoro-7-[2,6-dimethyl-4-[3-(5-methyl-1,2,4-oxadiazolyl)]phenoxy]hept-3-yn-2-one (5).** To a chilled (−70 °C) solution of **4** (2.0 g, 7.4 mmol) in THF (50 mL) was added 2.0 *M* *n*-BuLi (3.7 mL, 7.4 mmol) followed by ethyl trifluoroacetate (1.1 g, 7.7 mmol). This mixture was stirred at −70 °C for 10 min, and $BF_3$·$Et_2O$ was added (1.5 mL, 11.9 mmol). The mixture was stirred an additional 4 h at −70 °C and then allowed to warm to room temperature overnight. The reaction was quenched with saturated $NH_4Cl$ (20 mL), diluted with water, extracted with ether, dried ($Na_2SO_4$), and concentrated in vacuo to give an oil. Column chromatography (20−40% ether in hexane) gave 497 mg of **5** which was used as is without further purification: MS CI *m/z* $(MH)^+$ 367.

**3-[3,5-Dimethyl-4[[3-[3-(trifluoromethyl)-5-isoxazolyl]-propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (7).** To a stirred solution of **5** (497 mg, 1.36 mmol) and $NH_2OH$·HCl (509 mg, 7.32 mmol) in glacial acetic acid (10 mL) was added 1 M HCl (1 mL). After 48 h, additional 1 M HCl (1 mL) and $NH_2$-OH·HCl (1.00 g, 14.4 mmol) were added. After 1 week, the mixture was poured into water, extracted with ether, dried ($Na_2SO_4$), and concentrated to give 470 mg of **6** as an oil which was heated in benzene at reflux for 18 h. The cooled reaction mixture was diluted with $CH_2Cl_2$, washed with 1.5 *M* $KHCO_3$ and water, and filtered through a short column of silica gel to give an oil which was crystallized from methanol at dry ice temperature to give **16** mg of **7**. The mother liquor was treated

with Darco, concentrated, and crystallized. The solid obtained was further purified by preparative TLC on silica gel using $CHCl_3$ to give 92 mg (18%) of pure **7** as a white solid: mp 62–64.5 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.73 (s, 2H), 6.34 (s, 1H), 3.88 (t, $J$ = 5.7 Hz, 2H), 3.16 (t, $J$ = 7.4 Hz, 2H), 2.63 (s, 3H), 2.32 (s, 6H), 2.26 (m, 2H). Anal. ($C_{18}H_{18}F_3N_3O_3$) C, H, F. N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (9).** To a solution of amidoxime **8**[7] (4.38 g, 14.4 mmol) in dry pyridine (8 mL) was added TFAA (4.07 mL, 28.8 mmol) at a rate to maintain a gentle reflux. After cooling to room temperature, the reaction mixture was diluted with water, chilled with an ice bath, and filtered. The solids obtained were washed with water, dissolved in methylene chloride, dried and filtered through a short column composed of an upper layer of Florisil and a lower layer of silica gel. There was obtained 5.10 g of a pale yellow solid which was purified by flash chromatography (15% ethyl acetate in hexane) to give 4.76 g (86.5%) of pure **9** as a white crystalline solid: mp 61–62 °C (methanol); IR (KBr, $cm^{-1}$) 1607, 1472, 1452, 1419, 1378, 1318, 1211, 1176, 1157, 1110, 1046, 992, 926; $^1H$ NMR ($CDCl_3$) $\delta$ 7.77 (s, 2H), 5.90 (s, 1H), 3.88 (t, $J$ = 6.1 Hz, 2H), 3.02 (t, $J$ = 7.5 Hz, 2H), 2.33 (s, 6H), 2.28 (s, 3H), 2.26 (m, 2H); $^{13}C$ NMR (ppm) 172.19, 168.85, 165.52 (q, $J_{CF}$ = 44.3 Hz), 159.76, 159.16, 132.04, 128.40, 120.17, 115.99 (q, $J_{CF}$ = 273.7 Hz), 101.77, 70.71, 28.26, 23.34, 16.29, 11.36. Anal. ($C_{18}H_{18}F_3N_3O_3$) C, H, N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-(4-pentyn-1-yloxy)phenyl]-1,2,4-oxadiazole (12a)** was prepared according to the procedure given for **9**. From **11**[7] (7.40 g, 30.0 mmol), pyridine (9.0 mL), and TFAA (8.50 mL, 60.0 mmol) was obtained 6.42 g (65.9%) of pure **12a** as a pale yellow oil. Crystallization from methanol provided a white solid: mp 47.5–48 °C; IR (KBr, $cm^{-1}$) 3321, 2122, 1472, 1422, 1380, 1321, 1209, 1167, 1150, 1110, 1044, 991, 919, 895, 860, 784, 768, 753, 646, 617; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 3.93 (t, $J$ = 6.0 Hz, 2H), 2.51 (dt, $J$ = 4.2 and 2.6 Hz, 2H), 2.35 (s, 6H), 2.20 (m, 3H). Anal. ($C_{16}H_{15}F_3N_2O_2$) C, H, N.

**5-Cyclopropyl-3-[3,5-dimethyl-4-(4-pentyn-1-yloxy)phenyl]-1,2,4-oxadiazole (12b)** was prepared according to the procedure given for **9**. From **11**[7] (5.00 g, 20.3 mmol), pyridine (75 mL), and cyclopropylcarbonyl chloride (2.77 mL, 30.5 mmol) was obtained 3.98 g (66.2%) of pure **12b** as a nearly colorless oil which solidified upon standing: mp 45–46 °C (methanol); IR (KBr, $cm^{-1}$) 3267, 1578, 1524, 1420; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 3.91 (t, $J$ = 6.1 Hz, 2H), 2.50 (dt, $J$ = 6.9 and 2.6 Hz, 2H), 2.33 (s, 6H), 2.18–2.32 (m, 1H), 1.96–2.09 (m, 3H), 1.14–1.37 (m, 4H). Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

**General Procedure for the Syntheses of 13a–c and 15b.** To a solution of NCS (1.8–2.5 equiv) in dry DMF or NMP (1.6–3.0 mL/mmol of NCS) and 1–2 drops of pyridine was added dropwise a solution of oxime (1.8–2.5 equiv) in the same solvent (0.40–0.80 mL/mmol of oxime). The internal temperature was maintained at 25–30 °C with a 25 °C water bath. After 1 h at room temperature, a solution of **12a** (1 equiv) in the same solvent (0.80 mL/mmol of **12a**) was added. The reaction mixture was heated to 85–90 °C, and a solution of TEA (1.8–2.5 equiv) in the same solvent (0.80–1.6 mL/mmol of TEA) was added dropwise over 45–90 min. After an additional h at 85–90 °C, the mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic phases were washed with 10% $KHSO_4$, water, and brine, dried, and concentrated in vacuo. The crude products were purified by chromatography (15–40% ethyl acetate in hexanes).

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-[[3-[3-(methoxymethyl)-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (13a).** From methoxyacetaldehyde oxime (1.10 g, 12.3 mmol) and **12a** (2.00 g, 6.17 mmol) was obtained 1.78 g (70.1%) of pure **13a** as a colorless oil: IR (NaCl film, $cm^{-1}$) 1604, 1471, 1421, 1321, 1212, 1177, 1159, 1110, 993; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 6.13 (s, 1H), 4.51 (s, 2H), 3.89 (t, $J$ = 6.1 Hz, 2H) 3.40 (s, 3H), 3.07 (t, $J$ = 7.6 Hz, 2H), 2.34 (s, 6H), 2.24 (m, 2H); $^{13}C$ NMR (ppm) 172.91, 168.86, 165.95 (q, $J_{CF}$ = 45.3 Hz), 161.38, 159.13, 132.03, 128.43, 120.21, 116.08 (q, $J_{CF}$ = 276.8 Hz), 100.30, 70.63, 65.82, 58.47, 28.23, 23.45, 16.30. Anal. ($C_{19}H_{20}F_3N_3O_4$) C, H, N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-[[3-[3-(ethoxymethyl)-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (13b).** From ethoxyacetaldehyde oxime (1.27 g, 12.3 mmol) and **12a** (2.00 g, 6.17 mmol) was obtained 926 mg (35.3%) of pure **13b** as a white powder following crystallization from methanol: mp 24–25 °C; IR (NaCl film, $cm^{-1}$) 1604, 1472, 1421, 1321, 1209, 1177, 1159, 1111, 993; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 6.14 (s, 1H), 4.56 (s, 2H), 3.89 (t, $J$ = 6.1 Hz, 2H), 3.56 (q, $J$ = 7.0 Hz, 2H), 3.07 (t, $J$ = 7.6 Hz, 2H), 2.34 (s, 6H), 2.24 (m, 2H), 1.24 (t, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (ppm) 172.80, 168.87, 165.70 (q, $J_{CF}$ = 45.3 Hz), 161.75, 159.16, 132.06, 128.44, 120.21, 116.20 (q, $J_{CF}$ = 274.3 Hz), 100.44, 70.66, 66.28, 63.93, 28.24, 23.47, 16.32, 15.03. Anal. ($C_{20}H_{22}F_3N_3O_4$) C, H, N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-[[3-(3-cyclopropyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (13c).** From cyclopropanecarboxaldehyde oxime (0.48 g, 5.6 mmol) and **12a** (0.92 g, 2.8 mmol) was obtained 0.90 g (82%) of pure **13c** following crystallization from ethanol: white needles, mp 63.5–65 °C; IR (KBr, $cm^{-1}$) 1604, 1447, 1320, 1222, 1202, 1155; $^1H$ NMR ($CDCl_3$) $\delta$ 7.77 (s, 2H), 5.70 (s, 1H), 3.86 (t, $J$ = 6.1 Hz, 2H), 2.99 (t, $J$ = 7.6 Hz, 2H), 2.32 (s, 6H), 2.20 (m, 2H), 1.98 (dt, $J$ = 5.0 and 3.5 Hz, 1H), 1.07–0.99 (m, 2H), 0.83–0.75 (m, 2H); $^{13}C$ NMR (ppm) 172.13, 168.92, 166.49, 159.22, 132.11, 128.48, 120.23, 118.10 (q, $J_{CF}$ = 273.8 Hz), 98.50, 70.75, 28.30, 23.46, 17.37, 7.97, 7.39. Anal. ($C_{20}H_{20}F_3N_3O_3$) C, H, N.

**4-[[3-[3-(Methoxyethyl)-5-isoxazolyl]propyl]oxy]-3,5-dimethylbenzonitrile (15b).** From 3-methoxypropionaldehyde oxime (1.94 g, 18.8 mmol) and **14**[7] (2.20 g, 10.3 mmol) was obtained 0.89 g (40.4%) of recovered **14** and 1.51 g (46.5%) of pure **15b** as a colorless oil. Crystallization from ethanol provided fine white needles of **15b**: mp 64–65 °C; IR (KBr, $cm^{-1}$) 2223, 1603, 1479, 1222, 1115, 994, 820; $^1H$ NMR ($CDCl_3$) $\delta$ 7.32 (s, 2H), 5.99 (s, 1H), 3.85 (t, $J$ = 6.1 Hz, 2H), 3.67 (t, $J$ = 6.5 Hz, 2H), 3.38 (s, 3H), 3.01 (t, $J$ = 7.6 Hz, 2H), 2.92 (t, $J$ = 6.5 Hz, 2H), 2.28 (s, 6H), 2.20 (m, 2H); $^{13}C$ NMR (ppm) 172.08, 161.66, 159.59, 132.83, 132.50, 119.00, 107.44, 101.41, 70.84, 70.35, 58.70, 28.19, 26.74, 23.36, 16.23. Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

**General Procedure for the Syntheses of 13d,e,f.** To a chilled (0 °C) solution of oxime (2.5 equiv) in dry DMF (15 mL) was added NCS (2.5 equiv) in 1 portion. After 1–2 h, **12b** (1 equiv) was added and the whole heated to 80 °C. A solution of TEA (2.5 equiv) in dry DMF (5 mL) was added dropwise over 90 min. The mixture was heated an additional 18 h. Workup and purification as described for **13a** provided the pure products.

**5-Cyclopropyl-3-[3,5-dimethyl-4-[[3-(3-ethyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (13d).** From propionaldehyde oxime (0.43 g, 5.9 mmol) and **12b** (0.70 g, 2.4 mmol) there was obtained 0.58 g (67%) of pure **13d** as a colorless oil: IR (NaCl film, $cm^{-1}$) 1603, 1581, 1421; $^1H$ NMR ($CDCl_3$) $\delta$ 7.70 (s, 2H), 5.92 (s, 1H), 3.85 (t, $J$ = 6.1 Hz, 2H), 3.02 (t, $J$ = 7.6 Hz, 2H), 2.67 (q, $J$ = 7.5 Hz, 2H), 2.31 (s, 6H), 2.27–2.14 (m, 3H), 1.30–1.18 (overlapping t, $J$ = 7.5 Hz, and m, 7H). Anal. ($C_{21}H_{25}N_3O_3$) C, H, N.

**5-Cyclopropyl-3-[3,5-dimethyl-4-[[3-[3-(methoxymethyl)-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (13e).** From methoxyacetaldehyde oxime (0.82 g, 9.3 mmol) and **12b** (1.10 g, 3.72 mmol) there was obtained 726 mg of **13e** as a colorless oil. This material was added to 200 mg of **13e** obtained from a similar run from **12b** (502 mg, 1.70 mmol). Crystallization from methanol provided 207 mg of pure **13e**: mp 44–45 °C; IR (KBr, $cm^{-1}$) 1601, 1578, 1424; $^1H$ NMR $CDCl_3$ $\delta$ 7.70 (s, 2H), 6.12 (s, 1H), 4.51 (s, 2H), 3.86 (t, $J$ = 6.1 Hz, 2H), 3.40 (s, 3H), 3.06 (t, $J$ = 7.6 Hz, 2H), 2.31 (s, 6H), 2.26–2.10 (m, 3H), 1.36–1.22 (m, 4H). Anal. ($C_{21}H_{25}N_3O_4$) C, H, N. An additional 336 mg of pure **13e** was obtained from the mother liquor for a combined yield of 543 mg (26.1%).

**5-Cyclopropyl-3-[3,5-dimethyl-4-[[3-(3-cyclopropyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (13f).** From cyclopropanecarboxaldehyde oxime (539 mg, 6.33 mmol) and **12b** (750 mg, 2.53 mmol) there was obtained 579 mg (60.4%)

of pure **13f** as a colorless oil which solidified upon standing: mp 59–60 °C (methanol); IR (KBr, $cm^{-1}$) 1604, 1576, 1421; $^1H$ NMR ($CDCl_3$) $\delta$ 7.67 (s, 2H), 5.67 (s, 1H), 3.84 (t, $J$ = 6.1 Hz, 2H), 2.96 (t, $J$ = 7.6 Hz, 2H), 2.28 (s, 6H), 2.24–2.09 (m, 3H), 2.0–1.90 (m, 1H), 1.30–1.16 (m, 4H), 1.05–0.88 (m, 2H), 0.80–0.76 (m, 2H). Anal. ($C_{22}H_{25}N_3O_3$) C, H, N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-[[3-(3-ethyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (17a).** A mixture of **15a**[7] (2.01 g, 7.50 mmol), ethanol (20 mL), $NH_2OH$·HCl (2.61 g, 37.5 mmol), and finely divided $K_2CO_3$ (5.20 g, 37.5 mmol) was refluxed for 18 h. The mixture was filtered hot, the filter cake was washed with ethanol, and the combined filtrates were concentrated in vacuo to give 2.57 g of crude amidoxime **16a** as a pasty yellow solid. This material was dissolved in pyridine (2.3 mL), and TFAA (2.1 mL, 15 mmol) was added dropwise. The mixture was refluxed for 1 h, cooled to room temperature, diluted with water, and extracted with methylene chloride (3×). The combined organic phases were washed with 1 N HCl, water, and brine, dried, and concentrated in vacuo. The pale yellow oil obtained (2.15 g) was chromatographed ($CH_2Cl_2$) to give 2.10 g (70.7%) of pure **17a** as a white solid: mp 57–58 °C (methanol); IR (KBr, $cm^{-1}$) 1603, 1467, 1321, 1228, 1241, 1157, 994; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 5.92 (s, 1H), 3.88 (t, $J$ = 6.1 Hz, 2H), 3.02 (t, $J$ = 7.6 Hz, 2H), 2.69 (q, $J$ = 7.6 Hz, 2H), 2.33 (s, 6H), 2.20 (m, 2H), 1.27 (t, $J$ = 7.6 Hz, 3H); $^{13}C$ NMR (ppm) 172.11, 168.90, 165.25, 159.21, 132.08, 128.45, 120.20, 116.02 (q, $J_{CF}$ = 273.6 Hz), 100.44, 70.75, 28.29, 23.44, 19.57, 16.33, 12.64. Anal. ($C_{19}H_{20}F_3N_3O_3$) C, H, N.

**5-Trifluoromethyl-3-[3,5-dimethyl-4-[[3-[3-(methoxyethyl)-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (17b).** Sodium (442 mg, 19.2 mmol) was dissolved in dry methanol (20 mL) contained in an addition funnel. This solution was added dropwise to a solution of $NH_2OH$·HCl (1.34 g, 19.2 mmol) in dry methanol (10 mL). A fine white precipitate formed. After 1 h, a solution of **15b** (1.21 g, 3.85 mmol) in dry methanol (5 mL) was added and the mixture heated at reflux for 2.5 h. The hot reaction mixture was filtered, the filter cake was washed with methanol, and the combined filtrates were concentrated in vacuo. The white oily solid obtained (**16b**) was dissolved in pyridine (4 mL), and TFAA (1.63 mL, 11.6 mmol) was added at a rate to maintain a gentle reflux. The mixture was heated at reflux for an additional 30 min, cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic phases were washed with 10% $KHSO_4$, water, and brine, dried, and concentrated in vacuo to give 2.27 g of a yellow oil. Flash chromatography (30% ethyl acetate in hexanes) provided 1.28 g (78.0%) of pure **17b** as a colorless oil. Crystallization from methanol gave a white solid: mp 36.5–37 °C; IR (KBr, $cm^{-1}$) 1607, 1325, 1210, 1171, 1155, 1117, 1016, 996; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 6.00 (s, 1H), 3.88 (t, $J$ = 6.1 Hz, 2H), 3.68 (t, $J$ = 6.5 Hz, 2H), 3.38 (s, 3H), 3.03 (t, $J$ = 7.6 Hz, 2H), 2.93 (t, $J$ = 6.5 Hz, 2H), 2.34 (s, 6H), 2.23 (m, 2H); $^{13}C$ NMR (ppm) 172.26, 168.91, 161.64, 159.20, 132.10, 128.46, 120.21, 101.38, 70.74, 70.58, 58.70, 28.25, 26.76, 23.45, 16.36. Anal. ($C_{20}H_{22}F_3N_3O_4$) C, H, N.

**4-[3-[5-(Trifluoromethyl)-1,2,4-oxadiazolyl]]-2,6-dimethylphenol (20).** A mixture of phenol **18**[7] (10.1 g, 68.3 mmol), dry ethanol (400 mL), $NH_2OH$·HCl (23.7 g, 341 mmol), and finely divided $K_2CO_3$ (47.0 g, 341 mmol) was refluxed with efficient stirring for 20 h. The hot reaction mixture was filtered and the filter cake washed with hot ethanol. The combined filtrates were concentrated in vacuo to give 17.9 g of crude amidoxime as a glassy, tan solid. The crude amidoxime was dissolved into pyridine (85 mL), and TFAA (28.5 mL, 200 mmol) was added at a rate to maintain a gentle reflux. The reaction mixture was heated an additional hour and stirred at room temperature for 18 h. The cooled reaction mixture was diluted with ice/water (500 mL). The tan solid which formed was filtered and washed repeatedly with water, dissolved into $CH_2Cl_2$ (230 mL), dried, and filtered through a short column of Florisil. There was obtained 13.2 g (75.2%) of pure **20** as a white solid: mp 114–5 °C (white needles, hexane); IR (KBr, $cm^{-1}$) 3433, 1604, 1462, 1320, 1167, 944; $^1H$ NMR ($CDCl_3$) $\delta$ 7.80 (s, 2H), 5.10 (s, 1H), 2.30 (s, 6H); $^{13}C$ NMR (ppm) 168.98, 164.74 (q, $J_{CF}$ = 43.7 Hz), 155.76, 128.26, 123.89, 116.51, 115.97 (q, $J_{CF}$ = 274.1 Hz), 15.71. Anal. ($C_{11}H_9F_3N_2O_2$) C, H, N.

**[[3-[5-[3-[4-[3-[5-(Trifluoromethyl)-1,2,4-oxadiazolyl]]-2,6-dimethylphenoxy]propyl]isoxazolyl]]methoxy]dimethyl(dimethylethyl)silane (22).** A solution of **21**[7] (1.00 g, 3.67 mmol), **20** (1.04 g, 4.04 mmol), and TPP (1.06 g, 4.04 mmol) in dry THF (10 mL) was chilled to 0 °C. A solution of DEAD (0.61 mL, 1.0 mmol) in dry THF (15 mL) was added dropwise over 20 min. The solution was stirred for 30 min at 0 °C and 18 h at room temperature, diluted with water, and extracted with ethyl acetate (2×). The combined organic phases were washed with 10% NaOH and brine, dried, filtered through a pad of silica gel 60, and concentrated in vacuo to give 3.44 g of yellow oil. Chromatography (10% ethyl acetate in hexanes) provided 1.73 g (83.6%) of pure **22** as a colorless oil: IR (NaCl, film, $cm^{-1}$) 1604, 1472, 1320, 1212; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 6.12 (s, 1H), 4.74 (s, 2H), 3.87 (t, $J$ = 6.1 Hz, 2H), 3.05 (t, $J$ = 7.5 Hz, 2H), 2.33 (s, 6H), 2.24 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H). Anal. ($C_{24}H_{33}F_3N_3O_4Si$) C, H, N.

**5-[3-[4-[3-[5-(Trifluoromethyl)-1,2,4-oxadiazolyl]]-2,6-dimethylphenoxy]propyl]-3-isoxazolemethanol (23).** A solution of **22** (0.75 g, 1.5 mmol), THF (60 mL), and 1 N HCl (7.5 mL) was stirred at room temperature for 18 h and then diluted with water (100 mL). The pH was adjusted to pH 7 (pH paper) with solid $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic phases were washed with brine, dried, and concentrated in vacuo to give 0.73 g of yellow oil which was purified by chromatography (50% ethyl acetate in hexanes) to provide 0.58 g (100%) of pure **23** as a white solid: mp 92–3 °C (white needles from ethanol); IR (KBr, $cm^{-1}$) 3298, 3206, 1606, 1465, 1321, 1208, 1156, 1042; $^1H$ NMR ($CDCl_3$) $\delta$ 7.77 (s, 2H), 6.13 (s, 1H), 4.74 (s, 2H), 3.88 (t, $J$ = 6.1 Hz, 2H), 3.06 (t, $J$ = 7.6 Hz, 2H), 2.33 (s, 6H), 2.27 (m, 3H); $^{13}C$ NMR (ppm) 173.09, 168.88, 163.57, 159.14, 132.07, 128.47, 120.25, 99.94, 70.66, 57.08, 28.28, 23.52, 16.36. Anal. ($C_{18}H_{18}F_3N_3O_4$) C, H, N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-[[3-[3-[(methylthio)methyl]-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (25).** A solution of DEAD (1.42 mL, 9.01 mmol) in THF (5 mL) was added dropwise to a chilled (0 °C) solution of **24**[7] (1.53 g, 8.19 mmol), **20** (2.33 g, 9.01 mmol), and TPP (2.36 g, 9.01 mmol) in THF (15 mL). The solution was stirred for 18 h at room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic phases were washed with 10% NaOH, water, and brine, dried, and filtered through a pad of silica gel 60 to give a yellow solid (7.26 g) which was taken up into hot $CH_2Cl_2$. Upon cooling, white needles crystallized out and were removed by filtration. The mother liquor was concentrated in vacuo to a yellow oil (6.54 g) which was further purified by MPLC (20% ethyl acetate in hexanes followed by a second chromatography with 10% ethyl acetate in hexanes). There was obtained 2.93 g (83.7%) of pure **25** as a pale yellow oil which crystallized as white flakes from methanol: mp 45–45.5 °C; IR (1% KBr, $cm^{-1}$) 1602, 1469, 1422, 1320, 1204, 1153, 992; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 6.11 (s, 1H), 3.88 (t, $J$ = 6.1 Hz, 2H), 3.65 (s, 2H), 3.06 (t, $J$ = 7.6 Hz, 2H), 2.34 (s, 6H), 2.24 (m, 2H), 2.06 (s, 3H); $^{13}C$ NMR (ppm) 172.98, 168.89, 165.51 (q, $J_{CF}$ = 43.1 Hz), 161.61, 159.16, 132.09, 128.47, 120.24, 116.02 (q, $J_{CF}$ = 273.7 Hz), 100.71, 70.65, 28.34, 28.21, 23.54, 16.36, 15.12, 12.41. Anal. ($C_{19}H_{20}F_3N_3O_3S$) C, H, N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4-[[3-[3-[(methylsulfenyl)methyl]-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (26).** A mixture of **25** (1.87 g, 4.37 mmol), wet alumina (4.4 g), $CH_2Cl_2$ (22 mL), and oxone (2.69 g, 4.37 mmol) was stirred at reflux for 2 h and room temperature for 18 h, filtered, and concentrated in vacuo to a white solid (2.35 g). Flash chromatography (50% ethyl acetate in hexanes followed by 10% methanol in $CH_2Cl_2$) provided 1.83 g (94.3%) of pure **26** as a white solid: mp 103–103.5 °C (methanol); IR (KBr, $cm^{-1}$) 1604, 1472, 1418, 1321, 1205, 1172, 1025, 993; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (s, 2H), 6.24 (s, 1H), 4.13 (d, $J$ = 13.7 Hz, 1H), 3.91 (d, $J$ = 13.7 Hz, 1H), 3.89 (t, $J$ = 6.0 Hz, 2H), 3.10 (t, $J$ = 7.6 Hz, 2H), 2.58 (s, 3H), 2.34 (s, 6H), 2.28 (m, 2H); $^{13}C$ NMR (ppm) 173.87, 168.86, 165.56 (q, $J_{CF}$ = 44.0 Hz), 159.09, 154.45,

132.02, 128.46, 120.27, 115.99 (q, $J_{CF}$ = 273.9 Hz), 102.36, 70.58, 49.37, 37.98, 28.10, 23.57, 16.31. Anal. ($C_{19}H_{20}F_3N_3O_4S$) C, H, N.

**5-(Trifluoromethyl)-3-[3,5-dimethyl-4[[3-[3-[(methylsulfonyl)methyl]-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (27).** A mixture of **26** (0.65 g, 1.5 mmol), wet alumina (1.5 g), $CHCl_3$ (5 mL), and oxone (2.7 g, 4.4 mmol) was refluxed for 10 h and stirred at room temperature for 96 h. The mixture was filtered and concentrated in vacuo to a white solid (0.67 g, 100%). Crystallization from methanol provided **27** as tiny white needles: mp (122.5–123 °C; IR (KBr, $cm^{-1}$) 1601, 1443, 1311, 1211, 1169; $^1H$ NMR ($CDCl_3$) $\delta$ 7.79 (s, 2H), 6.34 (s, 1H), 4.34 (s, 2H), 3.89 (t, $J$ = 6.0 Hz, 2H), 3.11 (t, $J$ = 7.6 Hz, 2H), 2.91 (s, 3H), 2.34 (, 6H), 2.28 (m, 2H); $^{13}C$ NMR (ppm) 174.46, 168.86, 165.60 (q, $J_{CF}$ = 44.0 Hz), 159.06, 154.09, 132.02, 128.49, 120.32, 116.00 (q, $J_{CF}$ = 273.9 Hz), 102.34, 70.51, 52.09, 39.69, 28.09, 23.61, 16.33. Anal. ($C_{19}H_{20}F_3N_3O_5S$) C, H, N.

**3,5-Dimethyl-4-[[3-[2-[5-(2-methyl-1,3-dioxolanyl-2-yl)-furanyl]]propyl]oxy]benzonitrile (29).** A mixture of **18**[7] (1.3 g, 8.9 mmol), **28**[7] (2.1 g, 8.9 mmol), finely divided $K_2CO_3$ (1.2 g, 8.9 mmol), dry NMP (35 mL), and KI (0.15 g, 0.9 mmol) was heated at 60 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (160 mL). The organic phase was washed with water (6 × 200 mL), dried, and concentrated in vacuo to dryness. Flash chromatography (10% ethyl acetate in hexanes) afforded 2.7 g (89%) of pure **29** as a pale yellow oil: IR (NaCl film, $cm^{-1}$) 2225; $^1H$ NMR ($CDCl_3$) $\delta$ 7.28 (s, 2H), 6.20 (d, $J$ = 3.4 Hz, 1H), 5.94 (d, $J$ = 3.4 Hz, 1H), 4.00 (m, 2H), 3.80 (t, $J$ = 6.2 Hz, 2H), 2.85 (t, $J$ = 7.4 Hz, 2H), 2.27 (s, 6H), 2.16 (m, 2H), 1.69 (s, 3H). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

**1-[5-[3-[4-[3-[5-(Trifluoromethyl)-1,2,4-oxadiazolyl]]-2,6-dimethylphenoxy]propyl]-2-furanyl]ethanone (30).** A mixture of **29** (2.1 g, 63 mmol), ethanol (40 mL), $NH_2OH$·HCl (4.0 g, 31 mmol), and finely divided $K_2CO_3$ (2.2 g, 31 mmol) was refluxed for 3 h. After the mixture was cooled to room temperature, the solids were filtered and the mother liquor was concentrated in vacuo. The crude amidoxime obtained was dissolved in pyridine (35 mL), and TFAA (3.4 mL, 24 mmol) was added slowly. The mixture was heated at 50 °C for 1 h, cooled to room temperature, diluted with 1 N HCl (100 mL), and extracted with ethyl acetate (150 mL). The organic phase was washed with water (2 × 100 mL), dried, and concentrated in vacuo to dryness. MPLC (10% ethyl acetate in hexanes) provided 0.53 g (26%) of pure **30** as a white solid: mp 67–68 °C; IR (1% KBr) 1662, 1656, 1510, 1352, 1209, 1030; $^1H$ NMR ($CDCl_3$) $\delta$ 7.77 (s, 1H), 7.14 (d, $J$ = 3.4 Hz, 1H), 6.25 (d, $J$ = 3.4, 1H), 3.87 (t, $J$ = 6.2 Hz, 2H), 3.04 (t, $J$ = 7.4 Hz, 2H), 2.45 (s, 3H), 2.33 (s, 3H), 2.26 (m, 2H), 1.61 (s, 6H). Anal. ($C_{20}H_{19}F_3N_2O_4$) C, H, N.

**Trifluoromethanesulfonic Acid, 6-methyl-3-pyridyl Ester (32).** To a chilled (0 °C) solution of 6-methyl-3-pyridinol (**31**, 5.0 g, 46 mmol) in dry pyridine (23 mL) was added dropwise triflic anhydride (8.6 mL, 51 mmol) at a rate to maintain a reaction temperature of 0–2 °C. The mixture was stirred at 0 °C for 15 min and room temperature for 18 h. The volatiles were removed in vacuo, and residue obtained was partitioned between ether and water. The organic phase was washed with water and brine, dried, and concentrated in vacuo to give 9.7 g (90%) of **32** which was used as is without further purification: $^1H$ NMR ($CDCl_3$) $\delta$ 8.42 (s, 1H), 7.48 (d, $J$ = 8.8 Hz, 1H), 7.22 (d, $J$ = 8.8 Hz, 1H), 2.59 (s, 3H); MS CI $m/z$ 242 ($MH^+$).

**6-Methyl-3-pyridinepropenoic Acid, Ethyl Ester (33).** A DMF solution (20 mL) of **32** (4.8 g, 20 mmol), ethyl acrylate (4.3 mL, 40 mmol), TEA (8.3 mL, 60 mmol), LiCl (2.5 g, 60 mmol), and bis(triphenylphosphine)palladium(II) chloride (0.12 g, 0.17 mmol) was heated at 100 °C for 96 h. The cooled reaction mixture was partitioned between water and ethyl acetate. The organic phase was washed with water (4 × 100 mL) and brine, dried, and concentrated in vacuo. Chromatography (25% ethyl acetate in hexanes) provided 2.61 g (67%) of **33** which was used as is without further purification: $^1H$ NMR ($CDCl_3$) $\delta$ 8.58 (s, 1H), 7.72 (d, $J$ = 8.2 Hz, 1H), 7.59 (d, $J$ = 16.0 Hz, 1H), 7.42 (d, $J$ = 16.0 Hz, 1H), 7.18 (d, $J$ = 8.2 Hz, 1H), 4.13 (q, $J$ = 7.1 Hz, 2H), 2.57 (s, 3H), 1.32 (t, $J$ = 7.1 Hz, 3H).

**6-Methyl-3-pyridinepropanoic Acid, Ethyl Ester (34).** A mixture of **33** (2.61 g, 13.4 mmol), ethyl acetate (100 mL), and 10% palladium on carbon (1.0 g) was shaken on a Paar apparatus with an initial hydrogen pressure of 50 psi. After 35 psi of hydrogen had been consumed, the mixture was filtered through Supercel and concentrated in vacuo. There was obtained 2.2 g (83%) of **34** which was used without further purification: $^1H$ NMR ($CDCl_3$) $\delta$ 8.31 (s, 1H), 7.37 (d, $J$ = 7.5 Hz, 1H), 7.02 (d, $J$ = 7.5 Hz, 1H), 4.11 (q, $J$ = 7.1 Hz, 2H), 2.87 (dd, $J$ = 6.6 and 6.1 Hz, 2H), 2.56 (dd, $J$ = 6.6 and 6.1 Hz, 2H), 2.47 (s, 3H), 1.32 (t, $J$ = 7.1 Hz, 3H).

**6-Methyl-3-pyridinepropanol (35).** Neat **34** (2.60 g, 13 mmol) was added dropwise to a chilled (0 °C) suspension of LAH (0.55 g, 14 mmol) in dry THF (50 mL). The pale green reaction mixture was stirred for 40 min, treated sequentially with water (0.5 mL), 10% NaOH (0.5 mL), and water (1.5 mL), filtered, concentrated, and dried in vacuo to give 1.77 g (90%) of **35** which was used without further purification: $^1H$ NMR ($CDCl_3$) $\delta$ 8.31 (s, 1H), 7.40 (d, $J$ = 7.5 Hz, 1H), 7.05 (d, $J$ = 7.5 Hz, 1H), 3.67 (t, $J$ = 6.6 Hz, 2H), 2.71 (t, $J$ = 7.5 Hz, 2H), 2.53 (s, 3H), 1.89 (m, 2H).

**5-[3-[4-[3-[5-(Trifluoromethyl)-1,2,4-oxadiazolyl]]-2,6-dimethylphenoxy]propyl]-2-methylpyridine (36).** Neat DEAD (1.7 g, 10 mmol) was added dropwise to a chilled (0 °C) $CH_2Cl_2$ (15 mL) solution of **35** (0.53 g, 3.7 mmol), **20** (1.3 g, 5.0 mmol), and TPP (2.6 g, 10 mmol). After stirring at room temperature for 24 h, the reaction mixture was concentrated in vacuo to dryness. The residue was partitioned between water and ethyl acetate. The organic phase was extracted with 1 M methanesulfonic acid. The combined aqueous extracts were basified with 1 M NaOH and extracted with ethyl acetate. The combined organic phases were dried and concentrated in vacuo to give 0.50 g of solid. MPLC (25% ethyl acetate in hexanes) provided 0.20 g (10%) of pure **36** as a white solid: mp 67–69 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 8.38 (s, 1H), 7.71 (s, 2H), 7.43 (d, $J$ = 8.3 Hz, 1H), 7.02 (d, $J$ = 8.3 Hz, 1H), 3.81 (t, $J$ = 6.6 Hz, 2H), 2.81 (t, $J$ = 7.5 Hz, 2H), 2.73 (s, 3H), 2.29 (s, 6H), 2.10 (m, 2H). Anal. ($C_{20}H_{20}F_3N_3O_2$·0.25$H_2O$) C, H, N.

**6-Fluoro-2-pyridinepropanol (38).** A solution of LDA·THF (14.8 mL of 1.5 M in cyclohexane) was added dropwise to a cold (−78 °C) THF (40 mL) solution of 2-fluoro-6-methylpyridine (**37**, 3.0 g, 27 mmol). After stirring at −78 °C for 20 min, 7.5 M ethylene oxide in THF (4 mL) was added. The reaction was allowed to stir to room temperature, diluted with water (100 mL), and extracted with ether (50 mL). The organic phase was washed with water (3 × 50 mL), dried ($Na_2SO_4$), and concentrated in vacuo to dryness. MPLC (15% ethyl acetate in hexane) afforded 1.1 g (27%) of pure **38** as a clear yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 7.72–7.58 (m, 1H), 7.03 (dd, $J$ = 7.1 and 2.1 Hz, 1H), 6.72 (dd, $J$ = 8.3 and 2.7 Hz, 1H), 3.65 (t, $J$ = 6.3 Hz, 2H), 2.61 (t, $J$ = 5.4 Hz, 2H), 2.02–1.79 (m, 2H).

**2-Fluoro-6-[3-[4-[3-[5-(trifluoromethyl)-1,2,4-oxadiazolyl]]-2,6-dimethylphenoxy]propyl]pyridine (39).** A $CH_2Cl_2$ (10 mL) solution of DEAD (1.5 g, 5.6 mmol) was added dropwise to a chilled (0 °C) $CH_2Cl_2$ (15 mL) solution of **38** (0.53 g, 3.7 mmol), **20** (0.95 g, 3.9 mmol), and TPP (0.97 g, 5.6 mmol). After stirring at room temperature for 12 h, the reaction mixture was concentrated in vacuo to dryness and filtered through a short column of silica gel 60 (25% ethyl acetate in hexane). MPLC (25% ethyl acetate in hexane) provided 0.61 g (45%) of pure **39** as clear oil which solidified upon standing: mp 58–60 °C (hexane); $^1H$ NMR ($CDCl_3$) $\delta$ 7.77 (s, 2H), 7.74 (m, 1H), 7.10 (dd, $J$ = 7.3 and 2.2 Hz, 1H), 6.78 (dd, $J$ = 8.2 and 2.8 Hz, 1H), 3.87 (t, $J$ = 6.3 Hz, 2H), 3.01 (t, $J$ = 8.1 Hz, 2H), 2.33 (s, 6H), 2.26 (m, 3H). Anal. ($C_{19}H_{17}F_4N_3O_2$) C, H, N.

**4-[[3-[3-[[[Dimethyl(dimethylethyl)silyl]oxy]methyl]-5-isoxazolyl]propyl]oxy]-3,5-dimethylbenzonitrile (41).** To a chilled (0 °C) $CH_2Cl_2$ (25 mL) solution of **18**[7] (773 mg, 5.26 mmol), **21**[7] (1.43 g, 5.26 mmol), and TPP (1.38 g, 5.26 mmol) was added dropwise over 30 min a solution of DEAD (915 mg, 5.26 mmol) in $CH_2Cl_2$ (5 mL). The solution was

stirred at 0 °C for 30 min and at room temperature for 18 h, afterwhich it was washed with water, 2.5 M NaOH, and brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was triturated in ether to remove the bulk of the triphenylphosphine oxide, the filtrate concentrated in vacuo, and the residue purified by chromatography (15% ethyl acetate in hexanes) to give 1.73 g (82.2%) of pure **41** as a colorless oil: IR (NaCl film, $cm^{-1}$) 2226, 1601; $^1H$ NMR ($CDCl_3$) $\delta$ 7.32 (s, 2H), 6.11 (s, 1H), 4.74 (s, 2H), 3.85 (t, $J$ = 6.1 Hz, 2H), 3.04 (t, $J$ = 7.5 Hz, 2H), 2.28 (s, 6H), 2.19 (m, 2H), 1.82 (s, 9H), 0.93 (s, 6H). Anal. ($C_{22}H_{32}N_2O_3Si$) C, H, N.

**5-[3-[4-[3-(5-Cyclopropyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]propyl]-3-isoxazolemethanol (43).** A mixture of **41** (1.22 g, 3.05 mmol), ethanol (30 mL), $NH_2OH$·HCl (1.06 g, 15.2 mmol), and finely divided $K_2CO_3$ (2.10 g, 15.2 mmol) was refluxed for 5 h and filtered. The filter cake was washed with ethanol, and the combined filtrates were concentrated in vacuo to give 1.30 g of the amidoxime as a white solid. A portion of this material (0.47 g, 1.1 mmol) was dissolved into in pyridine (20 mL), and cyclopropanecarbonyl chloride (0.15 mL, 1.6 mmol) was added. The mixture was heated at 90 °C for 26 h. The pyridine was removed in vacuo and the residue partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×). The combined organic phases were washed with 3 N HCl (2×) and brine, dried ($Na_2SO_4$), and concentrated in vacuo to yield 0.61 g of a yellow oil. Chromatography (35% ethyl acetate in hexanes) provided 0.25 g (62%) of pure **43** as a colorless oil. Crystallization from $CH_2Cl_2$ and hexanes provided **43** as a white solid: mp 80–81 °C; IR (KBr, $cm^{-1}$) 3409, 1599, 1575, 1359, 1208, 1048; $^1H$ NMR ($CDCl_3$) $\delta$ 7.70 (s, 2H), 6.12 (s, 1H), 4.75 (d, $J$ = 5.9 Hz, 2H), 3.86 (t, $J$ = 5.9 Hz, 2H), 3.06 (t, $J$ = 7.5 Hz, 2H), 2.31 (s, 6H), 2.27–2.19 (m, 3H), 2.03 (t, $J$ = 5.9 Hz, 1H), 1.31–1.22 (m, 4H). Anal. ($C_{20}H_{23}N_3O_4$) C, H, N.

**6-[4-[3-(5-Cyclopropyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]hex-2-ynoic Acid, Ethyl Ester (45).** To a cold (−78 °C), dry THF solution (20 mL) of **12b** (1.30 g, 4.41 mmol) was added dropwise $n$-BuLi (2.30 mL, 2.3M in hexane) over 15 min. After an additional 30 min at −78 °C, ethyl chloroformate (0.63 mL, 6.6 mmol) was added and the mixture warmed gradually to 0 °C over 2 h. The reaction was quenched with saturated $NH_4Cl$ and extracted with ethyl acetate (3×). The combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo to give a colorless oil (2.05 g). Chromatography (10–20% ethyl acetate in hexanes) provided 1.38 g (85.0%) of pure **45** as a colorless oil: IR (NaCl, film, $cm^{-1}$) 2234, 1711, 1582, 1255, 1207, 1079, 1031; $^1H$ NMR ($CDCl_3$) $\delta$ 7.68 (s, 2H), 4.20 (q, $J$ = 7.1 Hz, 2H), 3.88 (t, $J$ = 5.9 Hz, 2H), 2.64 (t, $J$ = 7.0 Hz, 2H), 2.30 (s, 6H), 2.20 (m, 1H), 2.06 (m, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H), 1.25–1.20 (m, 4H); MS CI $m/z$ 369 ($MH^+$). Anal. ($C_{21}H_{24}N_2O_4$·0.25$H_2O$) C, H, N.

**5-[3-[4-[3-(5-Cyclopropyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]propyl]-3-isoxazolol (46).** A mixture of **45** (810 mg, 2.20 mmol), ethanol (15 mL), $NH_2OH$·HCl (400 mg, 5.76 mmol), and 10% NaOH (5 mL) was stirred at room temperature for 24 h (after 8 h, a solution was obtained). Water (6 mL) was added, and the mixture was acidified with concentrated HCl to pH 2 (pH paper) and extracted with ether (4×). The combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo to a white solid. Chromatography (50% ethyl acetate in hexanes) provided 0.55 g (70%) of pure **46** as a white solid: mp 155–156 °C (ethyl acetate and hexanes); IR (KBr, $cm^{-1}$) 3300–2400, 1623, 1580, 1524, 1360, 1208, 1049; $^1H$ NMR ($CDCl_3$) $\delta$ 7.70 (s, 2H), 5.76 (s, 1H), 3.83 (t, $J$ = 6.2 Hz, 2H), 2.96 (t, $J$ = 7.6 Hz, 2H), 2.31 (s, 6H), 2.20 (m, 3H), 1.35–1.20 (m, 4H). Anal. ($C_{19}H_{21}N_3O_4$) C, H, N.

**5-[3-[4-[3-(5-Cyclopropyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]propyl]-3-(isoxazolyloxy)ethanol (47a) and 5-[3-[4-[3-(5-Cyclopropyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]propyl]-2-(hydroxyethyl)-3*H*-isoxazol-3-one (47b).** A mixture of **46** (0.75 g, 2.1 mmol), dry acetone (25 mL), finely divided $K_2CO_3$ (0.24 g, 1.7 mmol), and 1-bromoethanol (0.19 mL, 2.7 mmol) was heated at reflux for 5 h, filtered, and concentrated in vacuo to give a pinkish red oil (1.1 g). Dry flash chromatography (50% ethyl acetate in hexanes followed by ethyl acetate) provided 0.51 g of impure **47a**. Elution with 3% methanol in $CH_3Cl_2$ gave 0.48 g (57%) of pure **47b** as a pale yellow oil. Pure **47a** was obtained by dry flash chromatography (hexane to 50% ethyl acetate in hexanes): yield 0.31 g (37%); mp 64–65 °C (ether and hexanes); IR (1% KBr, $cm^{-1}$) 3440, 1617, 1578, 1508, 1461, 1343, 1210; $^1H$ NMR ($CDCl_3$) $\delta$ 7.70 (s, 2H), 5.72 (s, 1H), 4.35 (m, 2H), 3.97 (m, 2H), 3.85 (t, $J$ = 6.1 Hz, 2H), 2.95 (t, $J$ = 7.6 Hz, 2H), 2.31 (s, 6H), 2.29–2.16 (m, 3H), 1.55 (s, 1H), 1.33–1.21 (m, 4H). Anal. ($C_{21}H_{25}N_3O_5$) C, H, N. For **47b**: mp 117–118 °C ($CH_2Cl_2$ and hexanes); IR (1% KBr, $cm^{-1}$) 3401, 1655; $^1H$ NMR ($CDCl_3$) $\delta$ 7.70 (s, 2H), 5.60 (s, 1H), 4.02 (m, 2H), 3.97 (m, 2H), 3.85 (t, $J$ = 5.7 Hz, 2H), 2.84 (t, $J$ = 7.1 Hz, 2H), 2.30 (s, 6H), 2.29–2.13 (m, 3H), 1.55 (s, 1H), 1.33–1.21 (m, 4H). Anal. ($C_{21}H_{25}N_3O_5$) C, H, N.

**5-Cyclopropyl-3-[3,5-dimethyl-4-[[3-(3-ethoxy-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (48a) and 5-[3-[4-[3-(5-Cyclopropyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]propyl]-2-ethyl-3*H*-isoxazol-3-one (48b).** A mixture of **46** (0.30 g, 0.85 mmol), dry acetone (25 mL), finely divided $K_2CO_3$ (0.24 g, 1.7 mmol), and ethyl iodide (0.18 mL, 2.2 mmol) was heated at 50 °C for 18 h, filtered, and concentrated in vacuo to give a pinkish solid. Chromatography (50% ethyl acetate in hexanes) provided 0.19 g of slightly impure **48a** and 0.12 g (37%) of pure **48b** as a colorless oil. Pure **48a** was obtained by chromatography ($C_{18}$ silica gel, 20% water in methanol): yield 0.14 g (43%); mp 70–71 °C (methanol); IR (1% KBr, $cm^{-1}$) 1621, 1576, 1460, 1359, 1209; $^1H$ NMR ($CDCl_3$) $\delta$ 7.69 (s, 2H), 5.66 (s, 1H), 4.28 (q, $J$ = 7.1 Hz, 2H), 3.84 (t, $J$ = 6.1 Hz, 2H), 2.94 (t, $J$ = 7.6 Hz, 2H), 2.32 (s, 6H), 2.21 (m, 3H), 1.40 (t, $J$ = 7.1 Hz, 3H), 1.33–1.21 (m, 4H). Anal. ($C_{21}H_{25}N_3O_5$) C, H, N. For **48b**: mp 59–60 °C (ether and hexanes); IR (1% KBr, $cm^{-1}$) 1681; $^1H$ NMR ($CDCl_3$) $\delta$ 7.71 (s, 2H), 5.55 (s, 1H), 3.90 (q, $J$ = 7.1 Hz, 2H), 3.85 (t, $J$ = 6.0 Hz, 2H), 2.84 (t, $J$ = 7.5 Hz, 2H), 2.31 (s, 6H), 2.29–2.13 (m, 3H), 1.29 (t, $J$ = 7.1 Hz, 3H), 1.33–1.21 (m, 4H). Anal. ($C_{21}H_{25}N_3O_5$) C, H, N.

**5-(Fluoromethyl)-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (50)** was prepared according to the procedure given for **9**. From **8** (3.07 g, 10.1 mmol), pyridine (4.0 mL), and fluoroacetyl chloride (1.96 g, 20.2 mmol) was obtained 1.59 g (45.6%) of pure **50** as a white solid: mp 80–80.5 °C (methanol); IR (KBr, $cm^{-1}$) 1604, 1586, 1473, 1444, 1423, 1380, 1353, 1289, 1207, 1072, 1042, 1006, 921, 902, 807, 748; $^1H$ NMR ($CDCl_3$) $\delta$ 7.76 (s, 2H), 5.89 (s, 1H), 5.60 (d, $J_{HF}$ = 46.2 Hz, 2H), 3.86 (t, $J$ = 6.1 Hz, 2H), 3.01 (t, $J$ = 7.6 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H); $^{13}C$ NMR (ppm) 172.90 (d, $J_{CF}$ = 25.2 Hz), 172.25, 168.33, 159.76, 158.59, 131.77, 128.19, 121.33, 101.76, 74.33 (d, $J_{CF}$ = 176.0 Hz), 70.67, 28.26, 23.36, 16.29, 11.39. Anal. ($C_{18}H_{20}FN_3O_3$) C, H, N.

**3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole-5-carboxylic acid ethyl ester (51a)** was prepared according to the general procedure given for **9**. From **8** (6.06 g, 20.0 mmol), pyridine (30 mL), and ethyl oxalyl chloride (4.5 mL, 40 mmol) there was obtained 5.23 g (67.8%) of pure **51a** as a white solid: mp 105–106 °C (ethyl acetate/hexanes); IR (KBr, $cm^{-1}$) 1756, 1605, 1465, 1445, 1417, 1378, 1301, 1213; $^1H$ NMR ($CDCl_3$) $\delta$ 7.82 (s, 2H), 5.90 (s, 2H), 4.57 (q, $J$ = 7.1 Hz, 2H), 3.87 (t, $J$ = 6.1 Hz, 2H), 3.02 (t, $J$ = 7.5 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H), 1.49 (t, $J$ = 7.1 Hz, 3H); $^{13}C$ NMR (ppm) 172.20, 169.11, 166.33, 159.71, 158.79, 154.14, 131.79, 128.31, 120.87, 101.73, 70.65, 63.84, 28.23, 23.32, 16.22, 13.97, 11.34. Anal. ($C_{20}H_{23}N_3O_5$) C, H, N.

**3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole-5-carboxamide (51b).** Finely divided **51a** (3.08 g, 8.00 mmol) was added to 10% ethanolic ammonia (80 mL). After 15 min, a solution was obtained and a fine precipitate started to form. After 4 h, the mixture was filtered, and the solids obtained were washed with cold ethanol to give 2.35 g (82.5%) of pure **51b** as a fine white powder: mp 177–8 °C (isopropyl acetate); IR (KBr, $cm^{-1}$) 3320, 3160, 1707, 1607, 1469, 1445, 1418, 1331, 1205, 1052; $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.63–8.50 (br, 2H), 7.73 (s, 2H), 6.17 (s, 1H), 3.87 (t, $J$ = 6.0 Hz, 2H), 2.96 (t, $J$ = 7.5 Hz, 2H), 2.30 (s, 6H), 2.20 (s, 3H),

2.12 (m, 2H); $^{13}$C NMR (ppm) 172.14, 169.30, 167.77, 159.35, 158.36, 154.39, 131.77, 127.70, 120.80, 101.92, 70.60, 27.80, 22.61, 15.92, 10.92. Anal. ($C_{18}H_{20}N_4O_4$) C, H, N.

**3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole-5-carbonitrile (53).** To a chilled (0 °C) suspension of **51b** (1.60 g, 4.50 mmol) and dry pyridine (11.2 mL) in dry THF (27 mL) was added TFAA (1.90 mL, 13.5 mmol). The mixture was stirred at 0 °C for 4 h and at room temperature for 18 h, diluted with water (100 mL), and extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with 1 N HCl (3×) and brine, dried, and concentrated in vacuo. The red solid obtained (1.67 g) was chromatographed (MPLC, 20% ethyl acetate in hexanes) to give 1.38 g (90.8%) of pure **53** as a white solid: mp 93–4 °C (ethyl acetate and hexanes); IR (KBr, cm$^{-1}$) 1606, 1565, 1464, 1443, 1421, 1333, 1266, 1211, 1043; $^1$H NMR ($CDCl_3$) $\delta$ 7.76 (s, 2H), 5.90 (s, 1H), 3.87 (t, $J$ = 6.1 Hz, 2H), 3.02 (t, $J$ = 7.5 Hz, 2H), 2.34 (s, 6H), 2.28 (s, 3H), 2.22 (m, 2H); $^{13}$C NMR (ppm) 172.14, 169.19, 159.76, 159.39, 151.36, 132.20, 129.44, 119.61, 106.23, 101.78, 70.73, 28.24, 23.32, 16.33, 11.37. Anal. ($C_{18}H_{18}N_4O_3$) C, H, N.

**5-Cyclopropyl-3[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (56)** was prepared according to the procedure given for **9**. From **8** (0.86 g, 2.8 mmol), pyridine (1.0 mL), and cyclopropanecarbonyl chloride (0.51 mL, 5.7 mmol) was obtained 0.71 g (71.0%) of pure **56** as a white solid: mp 85–88 °C (methanol); IR (KBr, cm$^{-1}$) 1608, 1578, 1419, 1343, 1211, 1050, 922, 768; $^1$H NMR ($CDCl_3$) $\delta$ 7.70 (s, 2H), 5.88 (s, 1H), 3.84 (t, $J$ = 6.0 Hz, 2H), 3.01 (t, $J$ = 7.5 Hz, 2H), 2.31 (s, 6H), 2.28 (s, 3H), 2.24 (m, 3H), 1.27 (m, 4H); $^{13}$C NMR (ppm) 181.24, 172.28, 167.88, 159.71, 158.07, 131.43, 127.98, 122.28, 101.72, 70.60, 28.24, 23.36, 16.24, 11.36, 9.92, 7.70. Anal. ($C_{20}H_{23}N_3O_3$) C, H, N.

**5-(Difluoromethyl)-3-[3,5-dimethyl-4[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (57).** A suspension of **8** (7.58 g, 25 mmol) and ethyl difluoroacetate (25 mL) was heated at 100 °C with an oil bath. After 30 min, a solution was obtained. The solution was heated for 4 h, during which time a fine white solid was deposited, cooled to room temperature, and concentrated in vacuo. The residue obtained was suspended into $CH_2Cl_2$ (10 mL) and filtered. The white solid obtained was washed with $CH_2Cl_2$. The combined filtrates were concentrated in vacuo to a yellow oil (9.87 g). MPLC (20% ethyl acetate in hexanes) provided 5.05 g (55.6%) pure **57** as a white solid: mp 70–70.5 °C (methanol); IR (KBr, cm$^{-1}$) 1601; $^1$H NMR ($CDCl_3$) $\delta$ 7.77 (s, 2H), 6.86 (t, $J_{HF}$ = 52.2 Hz, 1H), 5.90 (s, 1H), 3.87 (t, $J$ = 6.1 Hz, 2H), 3.02 (t, $J$ = 7.6 Hz, 2H), 2.33 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H); $^{13}$C NMR (ppm) 172.29, 169.32 (t, $J_{CF}$ = 30.0 Hz), 168.55, 159.85, 158.94, 131.98, 128.36, 120.73, 105.77 (t, $J_{CF}$ = 243.6 Hz), 101.85, 70.74, 28.31, 23.40, 16.35, 11.45. Anal. ($C_{18}H_{19}F_2N_3O_3$) C, H, N.

**5-(α,α-Difluoroethyl)-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (58).** (Diethylamino)sulfur trifluoride (3.63 mL, 27.5 mmol) was added dropwise to freshly distilled ethyl pyruvate (2.90 g, 25.0 mmol) at 0 °C. After stirring for 18 h at room temperature, the solution was chilled with an ice bath and water (2.5 mL) was added dropwise. After 15 min, the mixture was partitioned between water (25 mL) and ether (15 mL). The ethereal phase was washed with water and brine, dried, and filtered through a short column of Florisil. Careful concentration of the ethereal solution obtained (130 mmHg, cold water bath) provided 2.10 g (60.9%) of pure ethyl 2,2-difluoropropanoate as a pale yellow oil free of ether: IR (NaCl film, cm$^{-1}$) 1770, 1322, 1177, 1151, 1017, 942; $^1$H NMR ($CDCl_3$) $\delta$ 4.33 (q, $J$ = 7.1 Hz, 2H), 1.81 (t, $J_{HF}$ = 18.9 Hz, 3H), 1.36 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (ppm) 164.36 (t, $J_{CF}$ = 32.9 Hz), 115.13 (t, $J_{CF}$ = 247.5 Hz), 62.80, 21.35 (t, $J_{CF}$ = 25.4 Hz), 13.86.

A mixture of **8** (1.52 g, 5.00 mmol), the above ester (2.07 g, 15.0 mmol), and dry NMP (0.50 mL) was heated at 105 °C for 22 h. The cooled reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with water (2 × 25 mL) and brine, dried, and concentrated in vacuo to a brown oil (1.62 g). MPLC (15% ethyl acetate in hexanes) provided 755 mg (39.9%) of pure **58** as white solid: mp 64–65 °C (methanol); IR (1% KBr, cm$^{-1}$) 1605, 1209, 1151; $^1$H NMR ($CDCl_3$) $\delta$ 7.77 (s, 2H), 5.90 (s, 1H), 3.87 (t, $J$ = 6.1 Hz, 2H), 3.02 (t, $J$ = 7.6 Hz, 2H), 2.33 (s, 6H), 2.28 (s, 3H), 2.27 (m, 2H), 2.17 (t, $J_{HF}$ = 18.6 Hz, 3H); $^{13}$C NMR ppm 172.28, 171.81 (t, $J_{CF}$ = 34.7 Hz), 168.42, 159.82, 158.81, 131.88, 128.33, 120.97, 114.82 (t, $J_{CF}$ = 241.1 Hz), 101.82, 70.72, 28.30, 23.39, 23.18 (t, $J_{CF}$ = 25.2 Hz), 16.32, 11.43. Anal. ($C_{19}H_{21}F_2N_3O_3$) C, H, N.

**5-(β,β,β-Trifluoroethyl)-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (59).** A mixture of **8** (4.55 g, 15.0 mmol), dry THF (45 mL), 2-(trifluoroethylidenyl)-1,3-dithiane[24] (3.60 g, 18.0 mmol), and silver trifluoroacetate (7.3 g, 33 mmol) was refluxed in the dark for 22 h, cooled to room temperature, and filtered. The green filter cake was washed with ethyl acetate (4 × 20 mL). The combined filtrates were concentrated in vacuo. The concentrate was dissolved into $CH_2Cl_2$ (50 mL) and washed with water (3 × 25 mL), 0.1 M $NaHCO_3$ (25 mL, freshly prepared), and brine, dried, and filtered through a short column of Florisil. The yellow paste obtained (5.39 g) was purified by MPLC (40% ethyl acetate in hexanes). There was obtained, in order of elution, recovered dithiane (1.05 g), **9** (430 mg, 7.5%), pure **59** (730 mg, 12.3%), and impure **59** (1.92 g). The latter fraction was subjected to two chromatographies (25% ethyl acetate in hexanes) which provided an additional 1.49 g of pure **59** for a total yield of 2.22 g (38%): mp 84–85 °C (white flakes from methanol); IR (1% KBr, cm$^{-1}$) 1610, 1422, 1380, 1252, 1241, 1156; $^1$H NMR ($CDCl_3$) $\delta$ 7.75 (s, 2H), 5.89 (s, 1H), 3.86 (t, $J$ = 6.0 Hz, 2H), 3.84 (q, $J_{HF}$ = 9.5 Hz, 2H), 3.01 (t, $J$ = 7.5 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H); $^{13}$C NMR (ppm) 172.31, 169.48 (q, $J_{CF}$ = 4.0 Hz), 168.65, 159.84, 158.62, 131.82, 128.22, 123.07 (q, $J_{CF}$ = 277.5 Hz), 121.35, 101.84, 70.71, 32.78 (q, $J_{CF}$ = 33.8 Hz), 28.30, 23.42, 16.35, 11.46. Anal. ($C_{19}H_{20}F_3N_3O_3$) C, H, N.

**2-Methyl-5-[3-[4-[3-(5-methyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]propyl]pyridine (61)** was prepared according to the procedure given for **36**. From **35** (0.53 g, 3.5 mmol) and 4-[3-(5-methyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenol[7] (0.72 g, 3.5 mmol) there was obtained 0.53 g (44%) of pure **61**: mp 66–69 °C (*tert*-butyl methyl ether, ether, and hexanes); $^1$H NMR ($CDCl_3$) $\delta$ 8.37 (s, 1H), 7.76 (, 2H), 7.42 (d, $J$ = 8.3 Hz, 1H), 7.09 (d, $J$ = 8.3 Hz, 1H), 3.82 (t, $J$ = 6.6 Hz, 2H), 2.81 (t, $J$ = 7.5 Hz, 2H), 2.65 (s, 3H), 2.57 (s, 3H), 2.31 (s, 6H), 2.16 (m, 2H). Anal. ($C_{20}H_{23}N_3O_2$·0.5$H_2O$) C, H, N.

**2-Fluoro-6-[3-[4-[3-(5-methyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenoxy]propyl]pyridine (62)** was prepared according to the procedure given for **39**. From **38** (0.50 g, 3.2 mmol) and 4-[3-(5-methyl-1,2,4-oxadiazolyl)-2,6-dimethylphenol[7] (0.66 g, 3.2 mmol) there was obtained 0.55 g (55%) of pure **59**: mp 54–56 °C (isopropyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.71 (s, 2H), 7.91 (m, 1H), 7.10 (dd, $J$ = 7.3 and 2.2 Hz, 1H), 6.77 (dd, $J$ = 8.2 and 2.8 Hz, 1H), 3.85 (t, $J$ = 6.3 Hz, 2H), 3.01 (t, $J$ = 7.8 Hz, 2H), 2.64 (s, 3H), 2.30 (s, 6H), 2.23 (m, 2H). Anal. ($C_{19}H_{20}FN_3O_2$) C, H, N.

## References


(1) Diana, G. D.; Cutcliffe, D.; Oglesby, R. C.; Otto, M. J.; Mallamo, J. P.; Akullian, V.; McKinlay, M. A. Synthesis and Structure-Activity Studies of Some Disubstituted Phenylisoxazoles against Human Picornaviruses. *J. Med. Chem.* **1989**, *32*, 450–455.

(2) Woods, M. G.; Diana, G. D.; Rogge, M. C.; Otto, M. J.; Dutko, F. J.; McKinlay, M. A. In Vitro Activity and In Vivo Activities of WIN 54954, a New Broad Spectrum Antipicornavirus Drug. *Antimicrob. Agents Chemother.* **1989**, *33*, 2069–2074.

(3) Turner, R. B.; Hayden, F. G. Efficacy of Oral WIN 54954 for the prophylaxis of Experimental Rhinovirus Infections. *Antiviral Res. Suppl.* **1992**, *17S* (1), Abstract no. 91.

(4) Schiff, G. M.; Sherwood, J. R.; Young, E. C.; Mason, L. J.; Prophylactic Efficacy of WIN 54954 in Prevention of Experimental Human Coxsackie Virus A21 Infection and Illness. *Antiviral Res. Suppl.* **1992**, *17S* (1), Abstract no. 92.

(5) Bailey, T. R.; Diana, G. D.; Kowalczyk, P. J.; Akullian, V.; Eissenstat, M. A.; Cutcliffe, D.; Mallamo, J. P.; Carabateas, P. M.; Pevear, D. C. Antirhinoviral Activity of Heterocyclic Analogs of WIN 54954. *J. Med. Chem.* **1992**, *35*, 4628–4633.

(6) Diana, G. D.; Cutcliffe, D.; Volkots, D. L.; Mallamo, J. P.; Bailey, T. R.; Vescio, N.; Oglesby, R. C.; Nitz, T. J.; Wetzel, J.; Giranda, V.; Pevear, D. C.; Dutko, F. J. Antipicornavirus Activity of Tetrazole Analogues Related to Disoxaril. *J. Med. Chem.* **1993**, *36*, 3240–3250.
(7) Diana, G. D.; Volkots, D.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. Oxadiazoles as Ester Bioisosteric Replacements in Compounds Related to Disoxaril. Antirhinovirus Activity. *J. Med. Chem.* **1994**, *37*, 2421–2436.
(8) Bailey, T. R.; Diana, G. D.; Mallamo, J. P.; Vescio, N.; Draper, T. L.; Carabateas, P. M.; Long, M. A.; Giranda, V.; Dutko, F. J.; Pevear, D. C. An Evaluation of the Antirhinovirus Activity of Acylfuran Replacements for 3-methylisoxazole. Are 2-Acetylfurans Bioisosters for 3-methylisoxazoles? *J. Med. Chem.* **1994**, *37*, 4177–4184.
(9) Linderman, R. J.; Kirollos, K. S. An Efficient Method for the Synthesis of Trifluoromethyl Substituted Heterocycles. *Tetrahedron Lett.* **1989**, *30*, 2049–2052.
(10) Torsell, K. B. G. Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis, VCH Publishers Inc.: New York, 1988.
(11) Mitsunobu, O. The Use of Diethyl Azidodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1 and references cited therein.
(12) Greenhalgh, R. P. Selective Oxidation of Phenyl Sulfides to Sulphoxides or Sulphones Using Oxone and Wet Alumina. *Synlett.* **1992**, 235–6.
(13) Music, J. F.; Matsen, F. A. Molecular Orbital Theory and Spectra of Monosubstituted Benzenes. V. Styrenes, Phenylacetylenes and Phenylcyclopropane *J. Am. Chem. Soc.* **1950**, *72*, 5256–5262.
(14) Cromwell, N. H.; Hudson, G. V. The Steric Requirements for Three-Ring Carbonyl Hyperconjugation *J. Am. Chem. Soc.* **1953**, *75*, 872–874.
(15) Mahrbacher, R. S.; Cromwell, N. H. Cyclopropyl Ketones. I. Synthesis and Spectra of 1-Aroyl-2-arylcyclopropanes. *J. Am. Chem. Soc.* **1957**, *79*, 401–408.
(16) Daubin, W. G.; Berezin, G. H. The Ultraviolet Spectra of Cyclopropyl Conjugated Ketones. *J. Am. Chem. Soc.* **1967**, *89*, 3449–3452.
(17) Van-Catledge, F. A.; Boerth, D. W.; Kao, J. On Conformational Sensitivity in the Ultraviolet Spectra of Cyclopropyl Ketone and Olefins. *J. Org. Chem.* **1982**, *47*, 4096–3000.
(18) Sybyl 6.3, Tripos Associates, Inc., St. Louis, MO.
(19) Park, K.; Kitteringham, N. R. Effects of Fluorine Substitution on Drug Metabolism: Pharmacological and Toxicological Implications *Drug Metab. Rev.* **1994**, *26*, 605–643.
(20) Swaminathan, S.; Siddiqui, A. U.; Pinkerton, N. G.; Wilson, W. K.; Schroeper, G. J. Inhibitors of Sterol Synthesis: 3β-Hydroxy-25,26,26,26,27,27-Heptafluoro-5α-Cholestan-15-one, an Analog of Potent Hypocholesterolemic Agent in which Its Major Metabolism is Blocked *Biochem. Biophys. Res. Commun.* **1994**, *201*, 168–173.
(21) Banni, K.; Toru, T.; Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Hazato, A. Kurozumi, S. Synthesis of Chemically Stable Prostacyclin Analogs. *Tetrahedron* **1983**, *39*, 3807–3819.
(22) MOPAC (QCPE program no. 455) 5.0, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, IN.
(23) Dewar, M. J.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A New General Purpose Quantum Mechanical Molecular Model *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909. Dewar, M. J. Applications of Quantum Mechanical Molecular Models to Chemical Problems. Part 70: Quantum Mechanical Molecular Models *J. Phys. Chem.* **1985**, *89*, 2145–2151.
(24) Solberg, J.; Benneche, T.; Undheim, K. 2-(2,2,2-Trifluoroethylidene)-1,3-dithianes. New Intermediates for the preparation of $CF_3$-containing Compounds. *Acta Chem. Scand.* **1989**, *43*, 69–73.

JM940648K