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NOVEL HIV- PROTEASE INHIBITORS CONTAINING β-HYDROXYETHER AND -THIOETHER DIPEPTIDE ISOSTERE SURROGATES: MODIFICATION OF THE P3 LIGAND.

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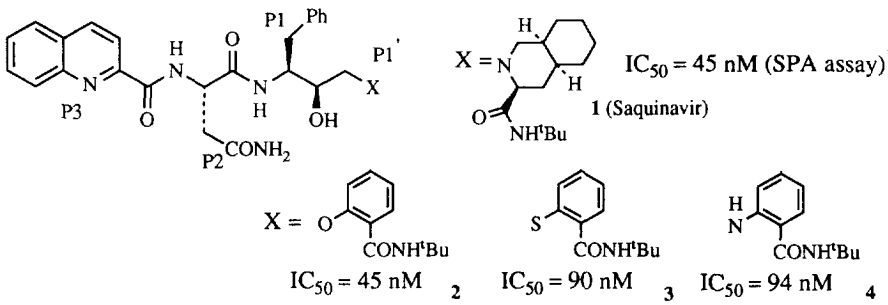
Abstract: Studies involving modifications to the P3 position of previously described HIV-protease inhibitors[1] containing β-hydroxyether and thioether dipeptide isostere replacements led to the discovery of pseudopeptides **8o** and **8p** with improved antiviral activites.

During the course for the search for effective anti-HIV agents, the literature has uncovered a wide range of pseudopeptides designed specifically to inhibit the critical virus encoded protease.[2] Although these chemical agents resemble the transition states believed to form during the hydrolysis of the gag and gag-pol polyproteins[3] many successful inhibitors incorporate unnatural conformationally restricted ligands. Providing resistance to hydrolysis from endogenous proteases, the introduction of these amino acid substitutes generally leads to agents with improved pharmacokinetic properties. A most noteable example Ro 31-8959, Saquinavir (**1**),[4] undergoing clinical evaluation, incorporates cis-decahydroisoquinoline and 2-quinolinylcarbonyl ligands for the P1' and P3 binding regions, respectively. Subsequently, we[1,5] and others[6] have shown that potent HIV-protease inhibitors and effective antiviral agents can be obtained by substituting the synthetically complex decahydroisoquinoline moiety with relatively simple aromatic ligands (e.g. **2-4**).



In this paper we now wish to report on an attempt to improve the potency of our lead compounds by describing the syntheses and enzyme and antiviral activities resulting from transformations to the 2-quinolinylcarbonyl (P3) ligand in our compounds

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The majority of the compounds (**Table**) in this study were prepared directly from the known amines **5**.[1] These intermediates were used to prepare the carbamates **6** through with the aid of BOP reagent[7] and a suitably *N*-protected form of asparagine. Following deprotection, the resulting amines **7** are condensed with a variety of acids to provide the target compounds **8**. The sulfonamides (**8c** and **d**) were prepared from the same intermediates **7** with 2-naphthalene sulfonyl chloride in the presence of triethylamine.

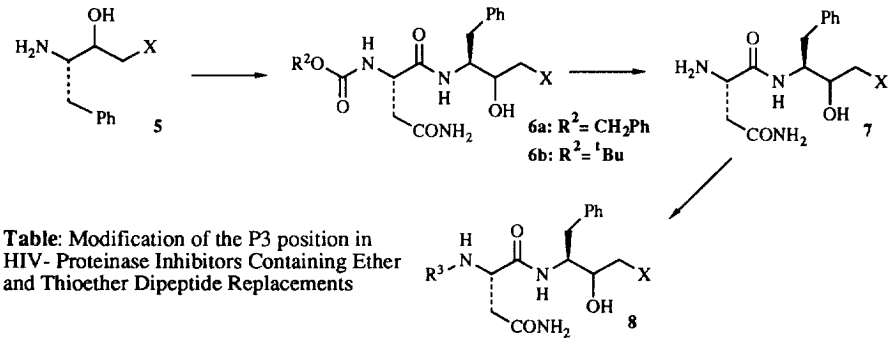
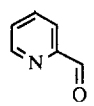
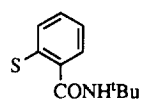
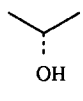
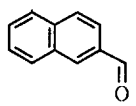
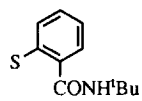
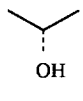
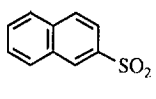
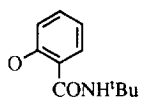
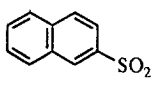
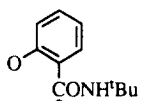
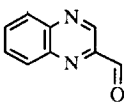
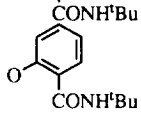
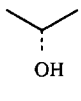
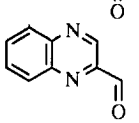
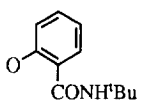
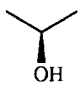
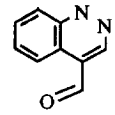
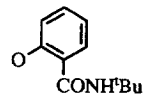
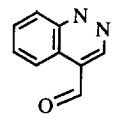
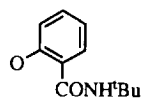
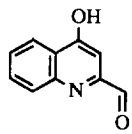
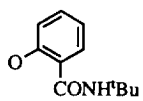
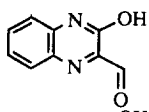
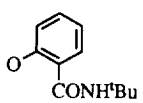
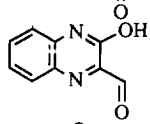
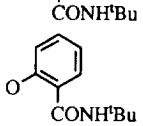
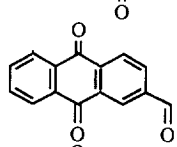
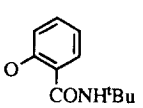
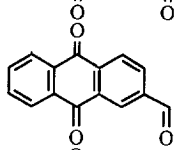
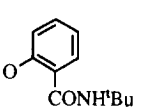
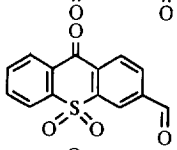
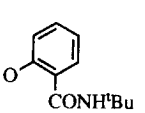
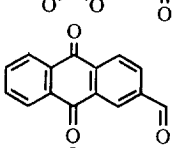
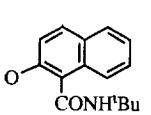
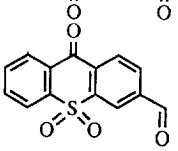
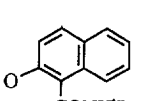


Table: Modification of the P3 position in HIV- Proteinase Inhibitors Containing Ether and Thioether Dipeptide Replacements

Entry	R^3	X	Carbinol Configuration	Enzyme IC_{50} (nM)[a,b]	Antiviral ID_{50} (μM)[b,c]
8a				Not Active	Not Tested
8b				390	13.4
8c				425	Not Active
8d				42% at 500 nM	Not Active
8e				100	0.61
8f				63	0.63

	R^3	X	Carbinol Configuration	Enzyme IC_{50} (nM)[a,b]	Antiviral ID_{50} (mM)[b,c]
8g				500	13.4
8h				130	9.3
8i				410	11.2
8j				35% at 500 nM	10.6
8k				36% at 500 nM	Not Active
8l				90	2.3
8m				41	0.33
8n				44	0.55
8o				62	0.16
8p				60	0.10

[a]Tested at a maximum concentration of 500 nM of Inhibitor. Compounds that have an IC_{50} greater than 500 nM but show inhibition at this concentration are also indicated in the Table. [b]See ref. 1 for experimental conditions. [c]Antiviral activity against the HTLV-III strain of HIV-I in CEM cell lines.

In this study compounds that displayed activity at 500 nM in the enzyme assay were then tested as antiviral agents. As can be seen from the Table the pyridyl compound **8a** proved to be inactive in the enzyme assay probably through loss of hydrophobic binding with the enzyme. Some of the activity was recovered in the naphthyl analogues (**8b-d**), although they were still clearly less active than the previously reported quinolinyl analogues (eg **2**),[1] suggesting that the nitrogen atom in the bicyclic P3 ligands plays a role in providing optimal potency. The importance of this nitrogen atom was confirmed through the enzyme and antiviral activities of the quinoxalyl analogues (**8e** and **f**) which were as potent as their quinolinyl counterparts. The cinnolinyl (**8g** and **h**) and the hydroxylated quinolinyl and quinoxalyl molecules (**8i-k**) were much less active and were not considered for further studies. In contrast, success was attained through the tricyclic derivatives (**8l-p**) some of which were as active as our lead inhibitors in the enzyme assay. Interestingly, unlike compounds containing quinolinyl (e.g. **2**) and quinoxalyl ligands (e.g., **8f**) there is a distinct preference for a (*S*)-alcohol configuration particularly with respect to antiviral activity (**8l** vs **8m**). Furthermore, antiviral activity can be further enhanced by substituting the salicylyl ligands in the P1' region with the corresponding 3-alkoxy naphthalene-2-carboxamides (**8o** vs **8m** and **8p** vs **8n**). Compounds **8o** and **p** displayed improved antiviral activities over our previously reported best antiviral agent (ID = 0.24 uM).[1] These results suggest that improvements in antiviral activity may be obtained in these compounds through judicious choice of P3 and P1' ligands possibly a result of increased hydrophobic interactions with the S3 and S1' binding regions in the enzyme. Further attempts to improve upon the potency of these compounds will be reported in due course.

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