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Potent HIV Protease Inhibitors Containing a Novel (2-Phenylsulfanyl-1-Hydroxyethyl)amide Isostere

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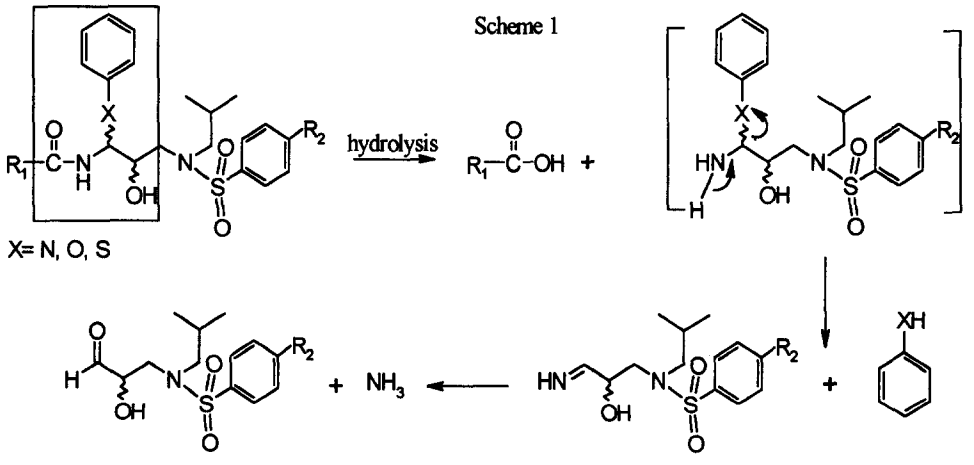
Abstract : Based on the concept of bioisosterism, we report the design and synthesis of new protease inhibitors. These new compounds incorporate in their backbone the synthon 2-N-Acyl-2-Phenylsulfanyl-1-Hydroxyethyl (I) which confers on the resulting compounds both *in vitro* activity on MT_4 infected cells and HIV-1 protease inhibition properties. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Over the last 10 years, significant progress has been made in the treatment of patients infected by HIV, in part due to the clinical use of an increasing number of anti-HIV drugs. Combination therapy should be exercised cautiously, because it might eventually, for multiply-resistant virus, result in final drug failure[1]. Therefore, the development of new active drugs remains a high priority in anti-HIV research. In this paper we report the synthesis of new HIV protease inhibitors. Chemical structures are based on the introduction of the (2-Phenylsulfanyl-1-Hydroxyethyl)amide synthon (I) into appropriate backbones.

Stable N-acyl phenylalanine bioisosteres in which the methylene group has been replaced by various atoms (nitrogen, oxygen, sulfur) have been described in the literature.[2,3] Indeed, acylation of the amino group provides stabilization of the molecule by delocalizing the nitrogen electrons into the peptide bond. As already reported by Kingsbury et al,[4,5] when these bioisosteres are submitted to enzymatic or chemical hydrolysis, release of aniline or phenol or thiophenol occurs according to a mechanism shown in Scheme 1.

Scheme 1



Substituents R_1 and R_2 were selected by analogy with the chemical structure of the new protease inhibitor

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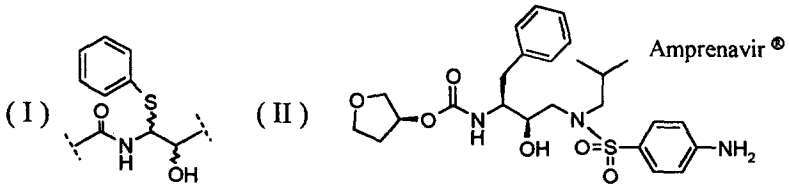
Amprenavir®[6] (II). The synthesis of new pseudo-peptides which contain the (2-Phenylsulfanyl-1-Hydroxyethyl)amide synthon are described in this paper. Their synthesis are achieved through the formation ketone intermediates **2a-c.** For this purpose two synthetic routes were used (scheme 2). The first utilizes allylamine as starting material, while the second one uses allylisocyanate.

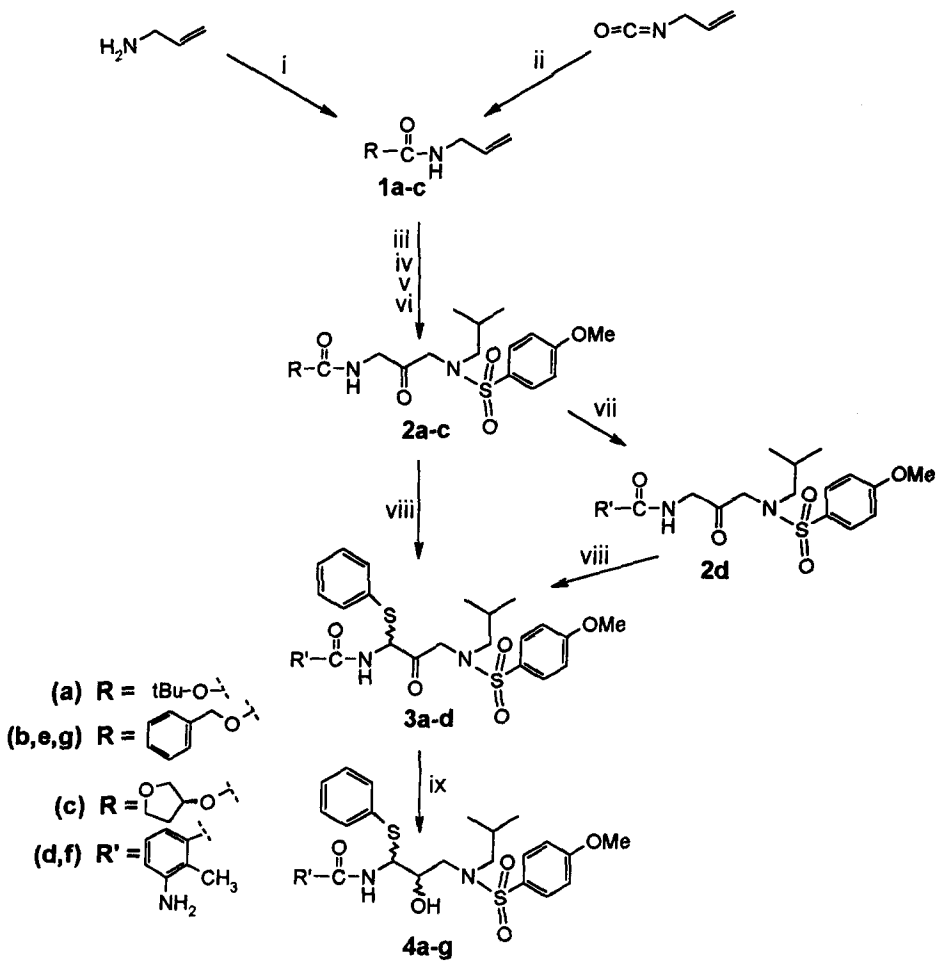


Oxidation of N-allylcarbamate precursors **1a-c** with MCPBA[7] led to the corresponding epoxides. Selective opening of these latter using isobutylamine in methanol, followed by N-sulfonylation[8] in acetonitrile, result in the isolation of the corresponding N-substituted sulfonamido-hydroxypropylene derivatives. Oxidation of these intermediates using Swern conditions[9] gave to the corresponding ketones **2a-c** in good yields. After Boc deprotection of **2a**, the resulting free amine function was coupled (using BOP[10]) to 3-amino-2-methylbenzoic acid, leading to **2d**. Introduction of phenylsulfanyl group was achieved using S-phenylbenzenethiosulfonate[11] as reagent in the presence of lithium diisopropylamide (LDA). The corresponding intermediates **3a-c** were isolated. Only monosulfenylation was observed in these experimental conditions. In contrast, as we have previously reported[12], the use of sodium hydride or the mixture of n-butyllithium/sodium hydride (1/1) leads to diphenylsulfanyl derivatives. The last step of the synthesis required specific reduction of the α-phenylsulfanyl ketone intermediates. As reported, reduction of α-phenylsulfanyl ketone with $Zn(BH_4)_2$, and Super Hydride®[13,14], led respectively to the anti and syn corresponding alcohols. Reduction of compounds **3a-d** with $NaBH_4$ or $Zn(BH_4)_2$ produced a mixture of syn-anti products **4a-d** in a 1:1 ratio. In contrast when Super Hydride® was used to reduce **3b** a 7:3 ratio in favor of the syn product **4b** was obtained as already reported for syn-selective reduction[15] of α-phenylsulfanyl ketones with Super Hydride®. Ratio syn-anti product determination were based on the different values of ^1H NMR chemical shift of the NH protons (a doublet peak at 5.55 ppm for the anti product, and at 5.66 ppm for the syn product). NMR data of compounds **4a-g** are given under reference 18.

The anti-HIV activity of these new bioisosteres was assayed in an HIV cytopathic assay[16] in MT_4 cells infected by HIV-BRU, and also by an HIV-1 inhibition assay on recombinant protease[17]. Compounds **4b-d** tested as diastereoisomeric mixtures, demonstrate remarkable *in vitro* anti-HIV activities ranging from EC_{50}= 0.1 to 1μM (infected MT_4 cells), and IC_{50}= 10nM to 1μM (antiprotease inhibition).

These results clearly indicate that the synthesis of (2-Phenylsulfanyl-1-Hydroxyethyl)amide pseudo-peptides represents a promising approach for the design of new anti-HIV compounds.

Scheme 2



Reagents: (i) Boc_2O, CH_2Cl_2, (1a); Cbz_2O, CH_2Cl_2, (1b); (ii) S(+)-3-Hydroxytetrahydrofuran, TEA, DMAP, CH_2Cl_2, (1c); (iii) MCPBA, CH_2Cl_2; (iv) $iBuNH_2$, MeOH; (v) 4-Methoxybenzenesulfonyl chloride, K_2CO_3, CH_3CN; (vi) TFAA, DMSO, TEA, CH_2Cl_2; (vii) 1) TFA, CH_2Cl_2, 2) BOP, TEA, 3-Amino-2-methylbenzoic acid; (viii) $PhSSO_2Ph$, LDA, $ClCH_2CH_2Cl$, (3a-d); (ix) Super hydride, THF; (4b,d), $NaBH_4$, EtOH, (4a,c,e,f); $Zn(BH_4)_2$, THF, (4g).

Acknowledgments

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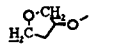
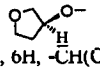
[18] **4a** : ^{1}H NMR (CDCl3) δ 0.7-0.9 (2d, 6H, -CH(C$\underline{H}_3$)C$\underline{H}_3$), 1.6-1.8 (2s, 9H, -Boc), 1.6-1.8 (m, 1H ,-C$\underline{H}$(CH$_3$)CH$_3$), 2.8-3.0 (2d, 2H, -C$\underline{H}_2$-CH(CH$_3$)CH$_3$), 3.0-3.4 (m, 2H, -CH(OH)-C$\underline{H}_2$-), 3.79 (2s, 4H, -OC$\underline{H}_3$, -CH(O$\underline{H}$)), 3.9-4.1 (m, 1H, -C$\underline{H}$(OH)-), 4.9-5.0 (m, 1H, -C$\underline{H}$-SPh), 5.15-5.35 (2d, 1H, -N$\underline{H}$), 6.8-7.7 (m, 9H, Ar). MS (FAB$^+$): 525 (M+H).

4b,e,g : ^{1}H NMR (CDCl3) δ 0.8-1.0 (2d, 6H, -CH(C$\underline{H}_3$)C$\underline{H}_3$), 1.7-1.9 (m, 1H ,-C$\underline{H}$(CH$_3$)CH$_3$), 2.9-3.1 (2d, 2H, -C$\underline{H}_2$-CH(CH$_3$)CH$_3$), 2.9-3.4 (m, 2H, -CH(OH)-C$\underline{H}_2$-), 3.86 (2s, 4H, -OC$\underline{H}_3$, -CH(O$\underline{H}$)), 4.0-4.2 (m, 1H, -C$\underline{H}$(OH)-), 4.9-5.1 (m, 3H, -C$\underline{H}_2$-Ph, -C$\underline{H}$-SPh), 5.5-5.7 (2d, 1H, -N$\underline{H}$), 6.9-7.9 (m, 12H, Ar). MS (FAB$^+$): 559 (M+H).

7c : ^{1}H NMR (CDCl3) δ 0.7-0.9 (2d, 6H, -CH(C$\underline{H}_3$)C$\underline{H}_3$), 1.6-1.7 (m, 1H ,-C$\underline{H}$(CH$_3$)CH$_3$), 1.7-2.1 (m, 2H, ), 2.6-2.9 (2dd, 2H, -C$\underline{H}_2$-CH(CH$_3$)CH$_3$), 2.9-3.4 (m, 2H, -CH(OH)-C$\underline{H}_2$-), 3.4-3.9 (m, 8H, -OC$\underline{H}_3$,  , -CH(O$\underline{H}$)), 4.05-4.15 (m, 1H, -C$\underline{H}$(OH)-), 4.9-5.1 (m, 2H, -C$\underline{H}$-SPh, ), 5.4-5.6 (2d, 1H, -N$\underline{H}$), 6.9-7.8 (m, 9H, Ar). MS (FAB$^+$): 539 (M+H).

4d,f : ^{1}H NMR (CDCl3) δ 0.6-0.9 (2d, 6H, -CH(C$\underline{H}_3$)C$\underline{H}_3$), 1.65-1.9 (m, 1H ,-C$\underline{H}$(CH$_3$)CH$_3$),1.9-2.05 (2s, 3H, -C$\underline{H}_3$) 2.65-3.0 (2dd, 2H, -C$\underline{H}_2$-CH(CH$_3$)CH$_3$), 3.0-3.5 (m, 2H, -CH(OH)-C$\underline{H}_2$-), 3.86 (2s, 4H, -OC$\underline{H}_3$, -CH(O$\underline{H}$)), 4.05-4.2 (m, 1H, -C$\underline{H}$(OH)-), 5.45-5.6 (m, 1H, -C$\underline{H}$-SPh), 6.5-6.6 (2d, 1H, -N$\underline{H}$), 6.6-7.7 (m, 12H, Ar). MS (FAB$^+$): 558 (M+H).