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Synthesis of New 7-Membered α-Phenylthio Cyclic Oxamides: HIV Inhibitors.

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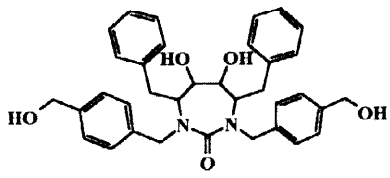
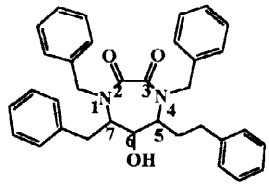
Abstract : Based on the concept of bioisosterism, we report the computer design and the synthesis of original 7-membered α-phenylthio cyclic oxamides with potent anti HIV-1 properties.

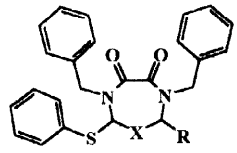
Knowledge of the HIV protease (HIV. PR) mechanism of action and substrate specificity has been extensively used to design a variety of transition state-based inhibitors with inhibition constant in the nanomolar or subnanomolar range.[1-4] A representative structure of these inhibitors is the computer designed seven-membered ring urea **1** in which the carbonyl oxygen mimics the hydrogen-bonding features of a key structural water molecule.[5] Structural studies of DMP 323 **1** with HIV-1 protease revealed that the carbonyl of the cyclic urea moiety hydrogen bonds to the residues (Ile 50 and Ile50') of the enzyme while the diol moiety is hydrogen bonded to the two catalytic aspartic acid residues (Asp25 and Asp25').[5] Consequently, cyclic oxamide structures such as **2**, containing complementary groups able to mimic the above mentioned electrostatic interactions, have been synthesized and their Van der Waals interactions to the active site of HIV-1 protease studied.[6]



DMP 323
1



Cyclic oxamide
2



3 R=S-Ph, X= C=O
4 R=S-Ph, X= C=N-OH
5 R=S-Ph, X= CH -OH

Phenylthio cyclic oxamide

One of the classical isosteres of methylene is the sulfur heteroatom.[7] We have speculated that the replacement of a benzyl by a phenylthio group at the 5 and 7 position of **2**, could provide additional binding energy without drastically affecting the interactions with HIV protease active site. Molecular modeling showed that compound **5** correctly match the preferred low energy conformation of **2** (fig. 1).

In this paper we wish to report the possible synthetic strategies leading to the phenylthio cyclic oxamide bioisosters **3**, **4** and **5**. The synthesis of such phenylthio cyclic oxamides represents a real synthetic challenge since arylthioaminal groups are known to be chemically unstable if not stabilized by the presence of an α carbonyl function.[8] Nevertheless, this specific chemical instability of α-phenylthio oxamide

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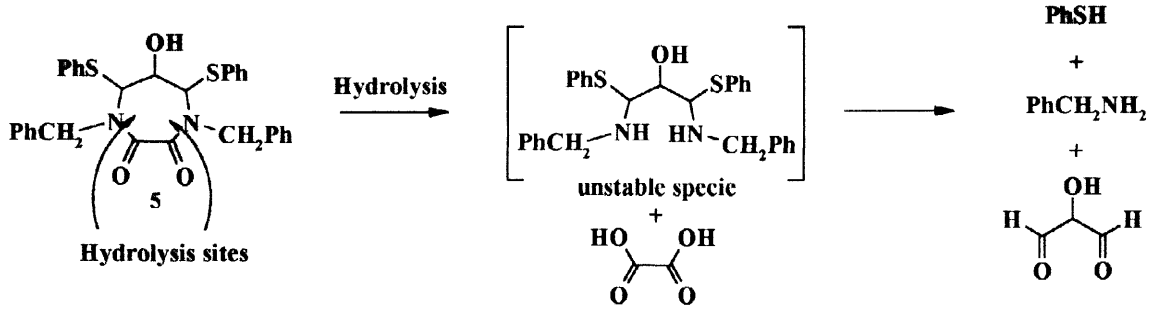
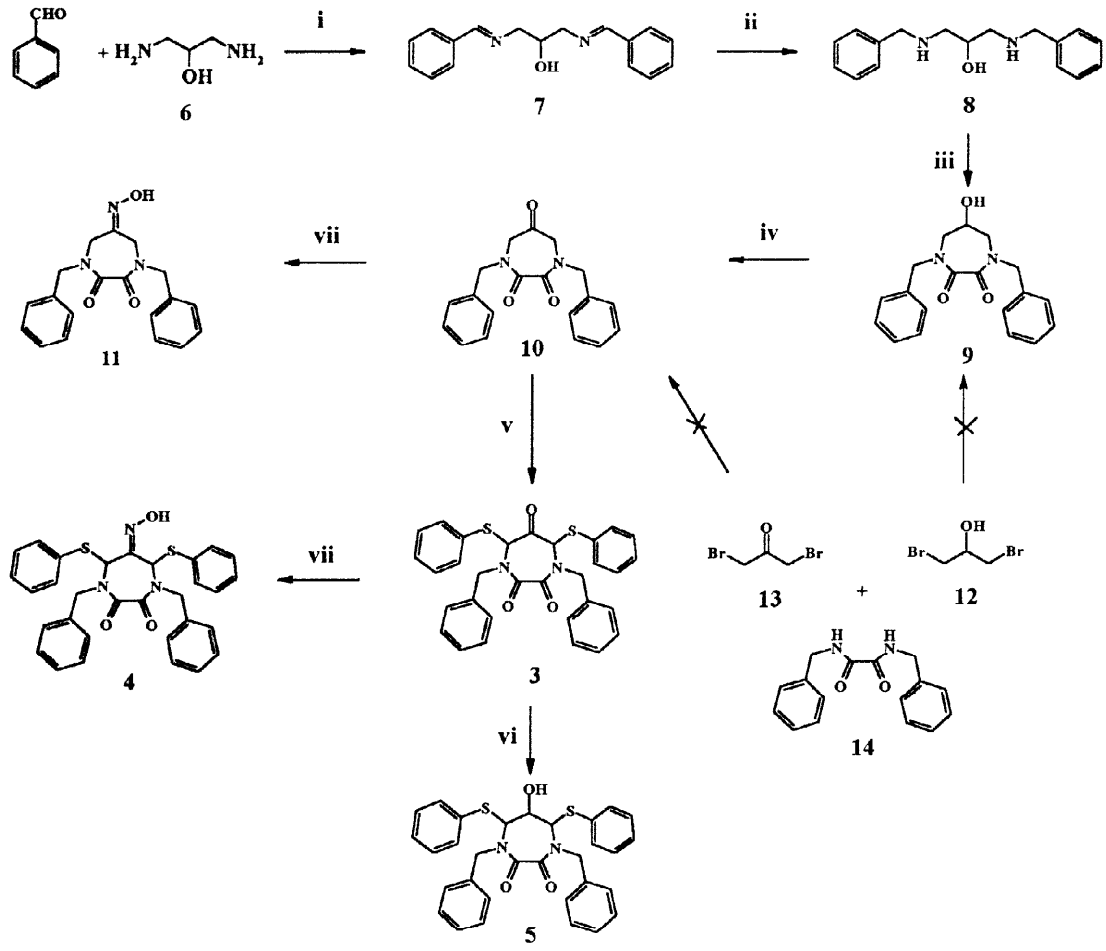
derivatives such as **3**, **4** and **5** could be a means to design a novel class of HIV protease inhibitors. Indeed, following the example of chemical hydrolysis, enzymatic cleavage of derivative **5** could generate the release of the toxophoric drug thiophenol (scheme 1) as already reported in the case of other phenylthio substrates.[9]



Scheme 1

Several synthetic routes have been investigated. The formation of the key intermediates **9** or **10** through the condensation of 1,3 dibromo-2-hydroxypropane **12** or 1,3-dibromoacetone **13** respectively with dibenzyloxalylamide **14** failed. Therefore the synthesis was achieved through the synthetic pathway shown in scheme 2. Benzaldehyde was condensed with 1,3 diamino-2-hydroxypropane **6** in the presence of sodium sulfate in methylene chloride.[10] The resulting crude imine **7** was reduced with sodium borohydride in ethanol to the corresponding 1,3 di(*N*-benzylamino)-2-hydroxypropane **8** which was obtained in quantitative yield after purification by flash column chromatography.[11] Addition to intermediate **8** of 1 equivalent of oxalyl chloride in methylene chloride led to the expected 6-hydroxy cyclic oxamide **9** in 23% yield.[6] After purification, compound **9** was oxidized using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[12] to give the corresponding cyclic ketone **10** in 60% yield. Others oxidizing conditions (Swern conditions)[13] did not improve the yield of the key intermediate **10**. The structure of compound **10** was confirmed both by NMR and MS analysis and by the formation of the corresponding oxime **11** with hydroxylamine hydrochloride.[14] Sulfenylation of the cyclic keto-oxamide **10** represents the limiting step of the synthesis. It was achieved using two experimental conditions: condensation of diphenyldisulfide[15] or condensation of *S*-phenyl benzenethiosulfonate[16] in the presence of butyllithium and sodium hydride. In both cases degradation products were observed and the diphenylthio derivative **3** was obtained in yields up to 30%. Besides spectral data, oxime derivative **4** confirmed the structure of **3**. 1,4-dibenzyl-5,7-bisphenylsulfanyl-[1,4]diazepane-2,3,6-trione **3** was reduced with sodium triacetoxyborohydride.[17] However, in this experimental condition, phenylthio group was lost and derivative **5** was isolated in only 30% yield. Other reducing agents such as $NaBH_4$, BMS, DIBAL, led to degradation products. It should be noted that, at ambient temperature ^1H NMR signals of cyclic oxamides **3**, **4** and **5** broaden. As already reported, this might be due to the high barrier of inversion of the seven membered ring system but also to the presence of different diastereoisomers.[6,18] Structural data (NMR, MS) of phenylsulfanyl cyclic oxamides **3**, **4**, and **5** are reported under reference

19. The stereochemistry of compounds **3** and **4** could exist as a mixture of cis meso and trans racemic forms, whereas for compound **5** as a mixture of 2 meso and one racemic possible forms. Further NMR experiments are in progress in order to elucidate the relative stereochemistry of these compounds. Anti-HIV activity of compounds **3**, **4** and **5** on infected MT_4 cells has been investigated. Compound **5** elicited a good anti HIV activity (EC_{50}=0,5 μM).



Scheme 2 : *Reagents*:(i) Na_2SO_4, CH_2Cl_2; 93 %; (ii) $NaBH_4$, EtOH; quantitative; (iii) $(COCl)_2$, Et_3N, CH_2Cl_2; 23 %; (iv) TEMPO, KBr, NaOCl (pH = 8), CH_2Cl_2, $NaHCO_3$ sat.; 60 %; (v) $PhSSO_2Ph$, NaH, $ClCH_2CH_2Cl$; 30 %; (vi) $NaB(OAc)_3H$, THF; 30 %; (vii) NH_2OH, HCl, Et_3N, CH_2Cl_2; 44 % (**11**); 43 % (**4**).

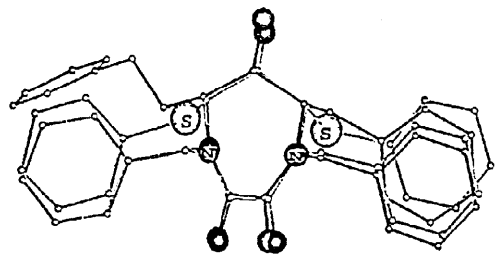


Fig. 1: Overlapped oxamide **2** and phenylthio oxamide **5** in their preferred low energy conformation calculated from GenMol Software.[20] There is an extremely good fit (95%) between the two analogues.

Acknowledgments

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References and Notes

1. Thaisrivongs, S. *Ann. Rep. Med. Chem.*, **1994**, *29*, 133-144.
2. De Lucca, G.; Liang, J.; Aldrich, P.; Calabrese, J.; Cordova, B.; Klabe, R.; Rayner, M.; Chang, C. *J. Med.Chem.*, **1997**, *40*, 1707-1719.
3. Hultén, J.; Bonham, N.M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Aqvist, J.; Classon, B.; Danielson, U.H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med.Chem.*, **1997**, *40*, 885-897.
4. Bäckbro, K.; Löwgren, S.; Österlund, K.; Atepo, J.; Unge, T.; Hultén, J.; Bonham, N.M.; Schaal, W.; Karlén, A.; Hallberg, A. *J. Med.Chem.*, **1997**, *40*, 898-902.
5. Lam, P.; Jadhav, P.; Eyermann, P.; Hodge, C.; Ru, Y.; Bacheler, L.; Meek, J.; Otto, M.; Rayner, M.; Wong, Y.; Chang, C.; Weber, P.; Jackson, D.; Sharpe, T.; Erickson-Vitanen, S. *Science*, **1994**, *263*, 380-384.
6. Jadhav, P.K.; Man, H-W. *Tetrahedron Lett.*, **1996**, *37*, 1153-1156.
7. Burger, A. **1970**. *In* "Medicinal Chemistry" (Burger A., ed.), 3rd ED., Wiley, New York.
8. Kingsbury, W.; Boehm, J.; Metha, R.; Grappel, S.; Gilvarg, G. *J. Med. Chem.* **1984**, *27*, 1747-1751.
9. Kingsbury, W.; Boehm, J.; Perry, J.; Gilvarg, C. *Proc. Natl. Acad. Sci. USA*, **1984**, *81*, 4573.
10. Stork, G.; Leong, A.; Touzin, A. *J. Org. Chem.*, **1976**, *41*, 3491-3493.
11. Jackson, W.; Jacobs, H.; Matthews, B.; Jayatilake, G.; Watson, K. S. *Tetrahedron Lett.*, **1990**, *31*, 1447-1450.
12. Anelli, P.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.*, **1987**,*52*, 2559-2562.
13. Mancuso, A.; Swern, D. *Synthesis*, **1981**, 165-185.
14. Feldman, P. Tetrahedron Lett., **1991**, *32*, 875-878.
15. Hiroi, K.; Miura, H.; Kotsuji, K.; Sato, S. *Chemistry Letters*, **1981**, 559-562.
16. Trost, B.; Hiroi, K.; Kurosumi, S. *J. Am. Chem. Soc.* **1975**, *97*, 438-440.
17. Abdel-Magid, A.; Maryanoff, C.; Carson, K. *Tetrahedron Lett.*, **1990**, *31*, 5595-5598.
18. Isaksson, R.; Liljefors, T. *J. Chem. Soc. Perkin Trans. 2*, **1981**, *10*, 1344-1350.
19. Compound **3**: MS (NOBA) : $(M+H)^+$ = 539. ^{1}H NMR 250 MHz ($CDCl_3$) δ : 7,2 (m, 20 H, C*H*$_{arom}$); 4,9 (s, 2 H, C*H*-S-Ph); 4,6 (dd, 4 H, N-C*H*$_2$-Ph : AB spectrum, J_{gem} = 14,4 Hz). ^{13}C NMR 250 MHz ($CDCl_3$) δ : 192,5 (CHCOCH); 162,6 (N-CO); 134,3 and 134,1 and 131,8 and 129,8 and 129,8 and 129,1 and 128,7 (C$_{arom}$); 70,5 (N-CH-S); 52,6 (N-CH$_2$-Ph). IR (NaCl ν cm^{-1}):1724 (C=O ketone); 1676 (C=O amide). Anal.($C_{31}H_{26}N_2O_3S_2$): C, H, N.

    Compound **4**: MS (NOBA): $(M+H)^+$ =553. ^{1}H NMR 250 MHz ($CDCl_3$) δ :7,2(m, 20H, CH$_{arom.}$); 5,4(m, 2H, C*H*-SPh) 4-4,5(m, 4H, Ph-C*H*$_2$-N); 3,8(m, 1H, C=NO*H*). IR (NaCl ν cm^{-1}): 3324 (N-OH); 1682 (C=O amide). Anal.($C_{31}H_{27}N_3O_3S_2$): C, H, N.

    Compound **5**: MS (NOBA): $(M+H)^+$ = 541, $[(M+SPh)+H]^+$ =433. ^{1}H NMR 250 MHz ($CDCl_3$) δ :7,2(m, 20H, CH$_{arom.}$); 5,2(m, 2H, C*H*-SPh); 4,5(m, 4H, Ph-C*H*$_2$-N); 3,5(m, 1H, C*H*-OH). IR (NaCl ν cm^{-1}): 3365 (OH); 1659 (C=O amide) Anal.($C_{31}H_{28}N_2O_3S_2$): C, H, N.
20. Pèpe, G.; Siri, D. *J. Mol. Graphics* **1990**, *71*, 93.