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SYNTHESIS OF NEW NON-NUCLEOSIDE INHIBITORS OF HIV-1.

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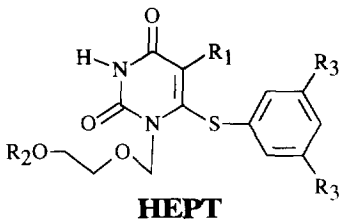
Abstract: Some new 4-arylthio-pyridinones which are related to non-nucleoside RT inhibitors of HIV-1 exhibited significant antiviral activities in cell culture. They have been synthesized from different β-keto esters.

The reverse transcriptase (RT) of human immunodeficiency virus type 1 (HIV-1) has been, up to date, one of the main target aimed to search for drugs that may be useful for chemotherapeutic intervention in acquired immunodeficiency syndrome (AIDS).[1] The currently approved antiretroviral compounds (AZT, ddI, ddC, D4T) are nucleoside analogs which all inhibit competitively RT enzyme leading to chain termination during the process of reverse transcription. Unfortunately, the clinical usefulness of these drugs is limited by side effects, toxicities and drug resistance.[2] Several specific non-nucleoside reverse transcriptase inhibitors (NNRTIs), first discovered by random screening (HEPT, TIBO, αAPA, nevirapine, BHAP...) have also been evaluated in monotherapy protocols in clinical trials. However, these trials had to be discontinued due to the rapid emergence of viral resistance.[2,3] Yet, at the present time and to our knowledge, it is generally considered that the use of the NNRTIs in combination with other agents (nucleosides, protease inhibitors...) remains a viable alternative in AIDS chemotherapy.[3]

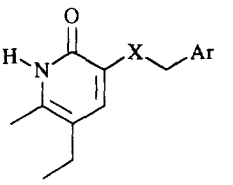
Recently we have discovered in our laboratory[4] a new family of pyridinone NNRTIs **1** which retain some of the structural features of HEPT[5] on one hand and of pyridinones

developed by the Merck Research Laboratories[6] on the other hand.



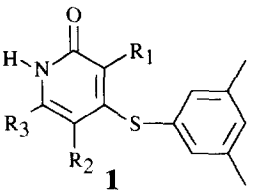
HEPT

R_1 = Me, Et, iPr...
R_2 = Me, Ph...
R_3 = H, Me



Pyridinones

X = NH, CH_2
Ar = 4,7-dichlorobenzoxazole, benzoxazole



1

a $R_1 = NO_2$, COOEt...; R_2 = Me; R_3 = H

b $R_1 = NO_2$, COOEt...; R_2 = Et; R_3 = Me

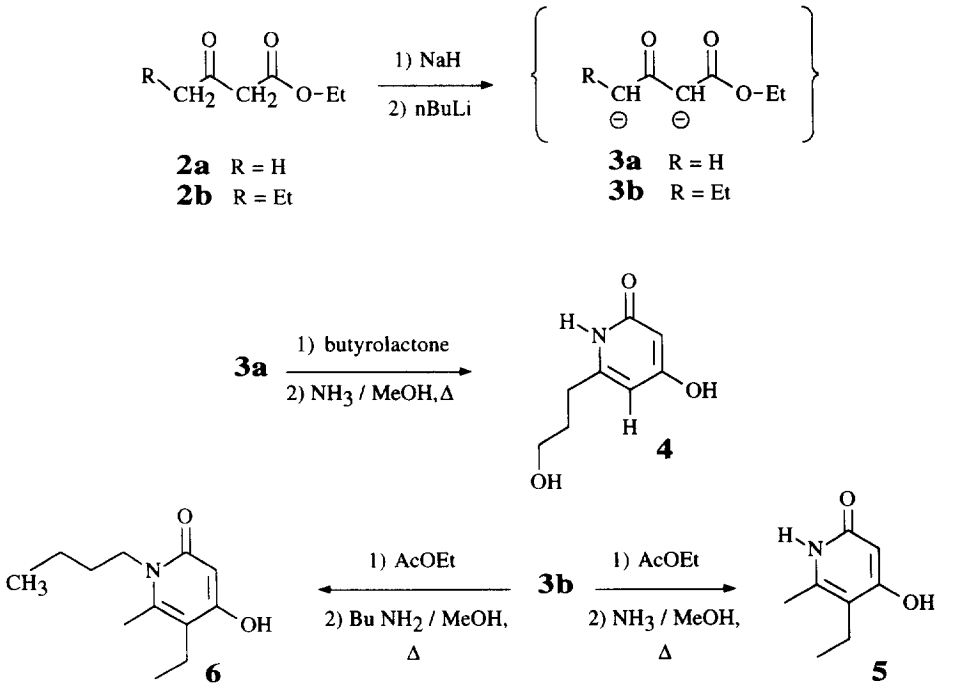
The synthesis of pyridinones **1** has been described previously.[4] The present paper presents an alternative route to this type of compounds allowing a convenient access to new modifications at positions 5 (R_2) and 6 (R_3) as well as preliminary anti HIV activities in vitro.

Synthesis and biological results

Condensation of the dianion[7] of the commercially available ethyl acetoacetate (**2a**) or ethyl butyrylacetate (**2b**) with either butyro lactone or ethyl acetate led to diketo ester intermediates that could be treated, without purification, with methanolic ammonia to give substituted pyridinones **4**[8] or **5**[4] in 40-50 % overall yield after column chromatography (Scheme 1). The synthesis of **5** was performed previously in three steps from ethyl 2-ethylacetoacetate *via* its aminocrotonate derivative which was condensed with the sodium salt of diethyl malonate[4]. The present synthesis allows numerous potential variations at N-1, 5 and 6 positions. For example, cyclisation with butylamine of the α-pyrone resulting from condensation of **3b** with AcOEt afforded substituted pyridinone **6**[9]. Furthermore, the dianion of ethyl acetoacetate (**2a**) can give access, in principle[7], to any variation at R_2 in pyridinones **1**.

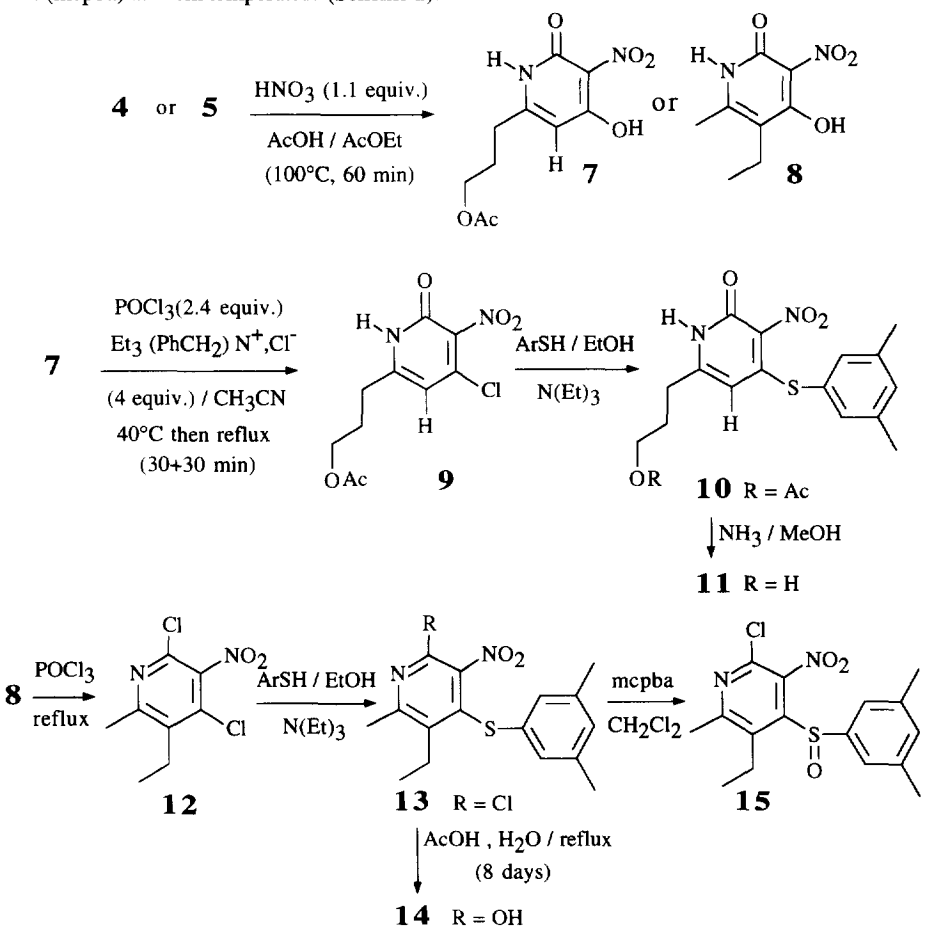
We have shown before[4] that the simultaneous presence of nitro or carbethoxy at position 3 and thiophenyl functions at position 4 in pyridinones **1** were a requisite for antiviral

activity, therefore these functions had to be introduced in **4** and **5**. Previous experience in this series showed that introduction of a nitro function at position 3 could be readily obtained in a large excess of 53% HNO_3 (density of 1.33) at 80°C for 15 min. in 80% yield. However we show here that the same nitration can also be obtained with 1.1 equivalent of fuming 100% HNO_3 (density of 1.52) in a mixture of acetic acid and ethyl acetate (4 : 1 in volume). These conditions specifically led to **7**[10] from **4** and to **8**[11] from **5** (Scheme 2) without any side product observed when nitration of **4** was performed in a large excess of 53% HNO_3. As described previously[4] for related compounds, monochlorination at position 4 in **7** led specifically to the 4-chloro derivative **9**[12] (2.4 equiv. of $POCl_3$, 4 equiv. of benzyl triethyl ammonium chloride, in CH_3CN). Nucleophilic substitution by a thiophenyl group of the chlorine atom in **9** was carried out in ethanol at room temperature and led to **10**[13] in good yield which, in turn was deacetylated with ammonia in methanol to give **11**.[14] However, in the case of 5,6-disubstituted pyridinone **8**, and in the same conditions, the yield of the monochlorination was low (≤ 20 %).



Scheme 1

Therefore we treated **8** in boiling $POCl_3$ to obtain dichloropyridine **12**[15] in high yield. As already known[16] for related compounds, nucleophilic substitution of the chlorine atom by a thiophenyl group occured exclusively at position 4. But hydrolysis of the remaining 2-chlorine atom proved difficult since 0.1N boiling HCl and O.1N boiling NaOH, led to the cleavage of the thiophenyl ether substituent. Fortunately, slow conversion of **13**[17] to **14** was performed cleanly in boiling acetic acid in the presence of a 2 equivalents of water. Finally, sulfoxide derivative **15**[18] was obtained from **13** in CH_2Cl_2 with 1.1 equivalent of m-chloroperbenzoic acid (mcpba) at room temperature (Scheme 2).



Scheme 2

This work shows that funtionalized pyridinones can be obtained from β-ketoesters and that the dichlorination route is an alternative strategy to pyridinones **1**, especially when 5,6-disubstituted pyridinones can hardly be monochlorinated and only in low yield.

Antiviral activities were measured in CEM SS cells infected with HIV-1 (LAI strain)[19](Table 1).

Compounds	IC_{50} (μM)	CC_{50} (μM)
10	1	>1
11	8.10^{-1}	>1
13	8.10^{-2}	>1
14	6.10^{-3}	>10
15	3	8
AZT	3.10^{-3}	$>10^{2}$

The 50% inhibitory concentration (IC_{50}) is the concentration of a compound conferring 50% protection; the 50% cytotoxic dose (CC_{50}) is the concentration at which the viability of mock-infected cells was reduced by half.

Table 1. *In vitro* anti HIV-1 activity of compounds **10-15**

As shown in the table, compound **14** was efficient at nanomolar concentration and had the most potent antiviral activity (selectivity index > 1600). Increasing the length of the substituent chain at position 6 (**10, 11**) led to a diminution but not an abolition of the anti-HIV-1 activities. The reduced activity of sulfoxide **15**, as compared to **13** suggests a possible interaction of the sulfur with the target protein or a steric hindrance with the oxygen atom. In conclusion, these compounds constitute an interesting new family of NNRTIs that deserve further SAR studies , which are ongoing in our laboratory, to improve their selectivity index.

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8. **4**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 10.88 (s, 1H, NH), 10.30 (s, 1H, OH), 5.59 (d, *J* = 2.2 Hz, 1H, H-5), 5.33 (d, *J* = 2.2 Hz, 1H, H-3), 4.52 (t, *J* = 5.1 Hz, 1H, OH), 3.38 (q, *J* = 6.4 Hz, 2H, $\underline{CH_2}OH$), 2.38 (t , *J* = 7.6 Hz, 2H, $\underline{CH_2}$-pyrid.), 1.67-1.30 (m, 2H, CH_2).mp 260°C, yield 22%. Anal. ($C_8H_{11}NO_3$) C, H, N.
9. **6**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 10.36 (s, 1H, OH), 5.57 (s, 1H, H-3), 3.87 (t, *J* = 7.6 Hz, 2H, $\underline{CH_2}$-N-pyrid.), 2.35 (q, *J* = 7.3 Hz, 2H, $\underline{CH_2}$-pyrid.), 2.29 (s, 3H, CH_3-pyrid.), 1.47-1.27 (m, 4H, 2xCH_2), 1.92 (m, 6H, 2xCH_3).mp 228°C, yield 32%. Anal. ($C_{12}H_{19}NO_2$) C, H, N.
10. **7**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 12.29 (s, 1H, NH), 11.90 (s, 1H, OH), 5.86 (s, 1H, H-5), 4.00 (t, *J* = 6.3 Hz, 2H, $\underline{CH_2}$-OAc), 2.53 (m, 2H, $\underline{CH_2}$-pyrid.), 1.97 (s, 3H, $\underline{CH_3}$-CO), 1.89 (m, 2H, CH_2). mp 150°C, yield 71%. Anal. ($C_{10}H_{12}N_2O_6$) C, H, N.
11. **8**[4] was obtained here in 89% yield on heating only 1.1 equivalent of 100% HNO_3 in a mixture of ethyl acetate/ acetic acid (1:4 in volume) in an oil bath preheated at 100°C.
12. **9**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 12.03 (s, 1H, NH), 6.49 (s, 1H, H-5), 4.01 (t, J = 6.2 Hz, 2H, $\underline{CH_2}$-OAc), 2.60 (t, J = 7.5 Hz, 2H, $\underline{CH_2}$-pyrid.), 1.98 (s, 3H, $\underline{CH_3}$-CO), 1.90 (m, 2H, CH_2). mp 120°C, yield 76%. Anal. ($C_{10}H_{11}N_2O_5Cl$) C, H, N.
13. **10**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 12.51 (s, 1H, NH), 7.23 (s, 3H, phenyl), 5.43 (s, 1H, H-5), 3.87 (t, J = 6.3 Hz, 2H, $\underline{CH_2}$-OAc), 2.40 (t, J = 7.3 Hz, 2H, $\underline{CH_2}$-pyrid.), 2.31 (s, 6H, 2xCH_3), 1.92 (s, 3H, $\underline{CH_3}$-CO), 1.70 (m, 2H, CH_2). mp 196°C, yield 73%. Anal. ($C_{18}H_{20}N_2O_5S$) C, H, N.
14. **11**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 10.90 (s, 1H, NH), 10.25 (s, 1H, OH), 7.24 (s, 2H, phenyl), 7.21 (s, 1H, phenyl), 5.43 (s, 1H, H-5), 3.28 (m, 2H, $\underline{CH_2}$OH), 2.38 (t, J = 7.6 Hz, 2H, $\underline{CH_2}$-pyrid.), 2.31 (s, 6H, 2xCH_3), 1.50 (m, 2H, CH_2). mp 230°C, yield 93%. Anal. ($C_{16}H_{18}N_2O_4S$) C, H, N.
15. **12**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 2.86 (q, J = 7.5 Hz, 2H, $\underline{CH_2}$-pyrid.), 2.66 (s, 3H, CH_3-pyrid.), 1.14 (t, *J* = 7.5 Hz, $\underline{CH_3}CH_2$). mp 75-76°C, yield 81%. Anal. ($C_8H_8N_2O_2Cl_2$) C, H, N.
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17. **13**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 6.95 (s, 1H, phenyl), 6.85 (s, 2H, phenyl), 2.83 (q, *J* = 7.5 Hz, 2H, $\underline{CH_2}$-pyrid.), 2.61 (s, 3H, CH_3-pyrid.), 2.21 (s, 6H, 2xCH_3), 0.94 (t, J = 7.5 Hz, 3H, $\underline{CH_3}CH_2$). mp 84°C, yield 71%. Anal. ($C_{16}H_{17}N_2O_2ClS$) C, H, N.
18. **15**; ^{1}H-NMR (DMSO-d6, 200 MHz) δ: 7.41 (s, 2H, phenyl), 7.28 (s, 1H, phenyl), 2.75 (m, 2H, $\underline{CH_2}$-pyrid.), 2.57 (s, 3H, CH_3-pyrid.), 2.36 (s, 6H, 2xCH_3), 0.77 (t, J = 7.4 Hz, 3H, $\underline{CH_3}CH_2$).mp 132-134°C, yield 54%. Anal. ($C_{16}H_{17}N_2O_3ClS$) C, H, N.
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