Synthesis of benzo-, pyrido-, thieno- and imidazo-fused N-hydroxy-4-oxopyrimidine-2-carboxylic acid derivatives

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N-Hydroxy-4-oxoquinazoline-2-carboxamide derivatives (cyclic hydroxamic acids) and related pyrido- and thieno-substituted analogues, as well as a N-hydroxyhypoxanthine-2-carboxamide, were synthesised for the first time, by means of a four-step sequence that involves a smooth reaction of aminohydroxamates with methyl trimethoxacetate. Other strategies were unsuccessful.

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**Figure 1.** Raltegravir and two examples of congeners. N-Hydroxypyrimidin-4-one derivatives proposed as alternative candidates.

Raltegravir (Isentress, MK-0518), developed by Merck, is the first HIV-1 integrase inhibitor (INI) approved by the FDA.\textsuperscript{1} Raltegravir and its congeners (Figure 1),\textsuperscript{1b,c} elvitegravir (Gilead) and S/GSK candidates have similar pharmacophoric elements and mechanism of action.\textsuperscript{1d,e}

The interest of some of us in hydroxamates\textsuperscript{2a} and the well-known chelating power of hydroxamic acids,\textsuperscript{2b} prompted us to propose alternative candidates based on the replacement of the C-OH group of raltegravir by a N-OH group, which would enhance the acidity of the OH proton and would improve the coordination with magnesium ions. Thus, we designed N-hydroxypyrimidinone derivatives shown in Figure 1 (bottom). The challenge was to develop a general approach, as simple as possible, to these unknown molecules.

The strategies analyzed by us at the beginning of our project are summarised in Scheme 1. In the first approach (a), we envisaged the N-oxidation of N3 of 4-amino-pyrimidines and of N1 of adenine,\textsuperscript{3} where the \(\pi\)-electron-donating ability of the amino group is crucial for the formation of the N-oxide. The subsequent deamination, either enzymatically or via diazotization,\textsuperscript{3} should afford the desired N-hydroxy pyrimidones (cyclic hydroxamic acids). While 2-cyano derivatives of adenine and adenosine (Scheme 1, top, \(X = \text{CN}\))\textsuperscript{3} gave the N-oxide in acceptable conversions (with a large excess of \(m\)-CPBA in CH\textsubscript{2}Cl\textsubscript{2}, as the reagent of choice among eight reagents examined), the corresponding methyl ester (\(X = \text{COO}Me\)) and amide (\(X = \text{CONH}CH\textsubscript{2}H\textsubscript{2}F = \text{CONH-4-FBn}\)) did not. In other words, a slight increase in the steric hindrance at position 2 hampered the N-oxidation. Although we achieved the conversion of

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X = CN to X = COOMe with NaOMe in MeOH at 50 ºC, the methoxy group could not be replaced by the 4-fluorobenzylarnino group (a substitution that was very easy when the N-oxide substituent was absent). Moreover, whereas deamination of adenine derivatives (to obtain hypoxanthine derivatives) was quite efficient in our hands, either with adenosine deaminase or via nitrosation, the N-oxide derivatives did not react. In short, the route via formation of N-oxides is not feasible.

Approach b involved a ring opening–closing process by using hydroxylamine (or a protected derivative of it, such as NH\textsubscript{2}OBr or NH\textsubscript{2}OTf) to attack the oxazines of Scheme 1. We prepared the corresponding imidazooxazines by treating the 2-amino carboxylic acid with a large excess of CIDOCOOCMe and DPEA in CH\textsubscript{3}CN. Opening with hydroxylamine derivatives gave mixtures coming from the attack of the hydroxylamines at the diverse electrophilic positions. Moreover, heating the open compounds in Ac\textsubscript{2}O gave rise to degradation compounds.

According to disconnection e, the hydroxamates (PG = Bn or PG = 4-methoxybenzyl = PMB), prepared from the amino ester, benzylamine or 4-methoxybenzylamine, and Li[N(SiMe\textsubscript{3})\textsubscript{2}] (LiHMDS), were heated with dimethyl oxalate and NaOEt\textsuperscript{7} in search of direct cyclisation. Only starting material was recovered. Heating with MeOCCO-CONH-4-FBn was also unsuccessful. With CIDOCOOCMe and DPEA or in pyridine, mainly the O-acylation occurred. On the other hand, with K\textsubscript{2}CO\textsubscript{3} or with DMAP, NHIDOCOOCMe derivatives were obtained, but their cyclisation to N-hydroxyimidazolinones under several dehydrating conditions did not take place.

Among all the approaches that we attempted only that one indicated as d in Scheme 1 turned out to be productive. Although the reaction of vicinal amino carboxamides with alkyl orthoformates such as CH\textsubscript{2}OR\textsubscript{3} is classical\textsuperscript{8} and orthoesters such as methyl 2,2,2-trimethoxyacetate\textsuperscript{9} have been used with vicinal diamines or aminophenols,\textsuperscript{9e} there are no reported precedents, according to a SciFinder search, of the reaction of amino hydroxamates with this oxalic acid orthoester. We first examined the conversion of amino ester 1a (methyl anthranilate) to benzo hydroxamate 2a (Scheme 2). An excess of a strong base such as LiHMDS was required.\textsuperscript{10} With a stronger base such as LDA the reaction was even faster.\textsuperscript{10} Without strong base the reaction did not progress, even in refluxing 1,4-dioxane. The more general conditions starting from amino esters 1a–e, the analogous pyridines 1g and 1h and the methyl 5-aminoimidazole-4-carboxylate 1k\textsuperscript{11} are shown in Scheme 2, which gave rise to good-to-excellent yields of hydroxamates of type 2 (in the case of 1e, a mixture was obtained, but 2e and 2f were readily separated by column chromatography). On the other hand, owing to the decomposition of amino esters 1i and 1j in strong basic media, we prepared 2i and 2j by the standard coupling of the corresponding amino acids with O-(4-methoxybenzyl)hydroxylamine (NH\textsubscript{2}OPMB) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).\textsuperscript{12}

We then subjected 2a and (MeO)\textsubscript{2}COOMe excess to an screening of solvents, acid catalysts, temperatures, and reaction times. Most relevant results are shown in Table 1.

![Scheme 1. Retrosynthetic analysis of N-hydroxypyrimidin-4-ones.](image)

![Scheme 2. Amino hydroxamates 2a–k.](image)

**Table 1.** Survey of cyclisation conditions\textsuperscript{a}

| Entry | n | Catalyst (mol%) | Solvent | Temp. (ºC) Time (h) | Yield (%) |
|-------|---|-----------------|---------|---------------------|-----------|
| 1     | 2.5 | – | DME | 90 | 15 | ≤ 1 |
| 2     | 2.0 | TsOH (10) | CH-CN | 20 | 4 | 95 |
| 3     | 2.5 | BF\textsubscript{2}Et\textsubscript{3}O (10) | CH-CN | 20 | 4 | 97 |
| 4     | 2.5 | BF\textsubscript{2}Et\textsubscript{3}O (10) | CH-CN | 80 | 0.5 | 96 |
| 5     | 2.5 | Sc(OH\textsubscript{2}) (10) | CH-CN | 20 | 4 | 96 |
| 6     | 2.5 | Sc(OH\textsubscript{2}) (10) | CH-CN | 80 | 0.5 | 95\textsuperscript{d} |
| 7     | 2.5 | TsOH (10) | CH-CN | 80 | 0.5 | 98 |
| 8     | 2.5 | TsOH (10) | DME | 90 | 0.5 | 98 |
| 9     | 2.5 | TsOH (10) | dioxane | 90 | 0.5 | 97 |
| 10    | 2.5 | TsOH (10) | toluene | 90 | 3 | 97 |
| 11    | 2.5 | AcOH | 90 | 0.5 | 98 |
| 12    | 2.0 | TsOH (2) | CH-CN | 80 | 4 | 98 |

\textsuperscript{a} From 1 mmol of 2a in 10 mL of solvent.

\textsuperscript{b} TsOH means commercially available 4-toluensulfonic acid–hydrate.

\textsuperscript{c} Scandium trifluoromethanesulfonate of 99% purity. In trials with 1 mol% of TIOH, under the conditions of entry 1, only a conversion of 10% was noted after 72 h. Thus, the activity of Sc(OH\textsubscript{2}) is not due to the possible content of TIOH as impurity.

\textsuperscript{d} The O–PMB bond was cleaved under these conditions: the yield refers to PMB-deprotected 3a.
Acid catalysis was required, as expected for an orthoester, to achieve the complete conversion of 2a to 3a. Not only TSOH and Lewis acids were active, in several solvents (see entries 2–10 of Table 1), but also weaker acids such as AcOH could be used (entry 11). With 2 mol% of TSOH in refluxing CH3CN (entry 12), the cyclisation occurred in 4 h.

This cyclisation or condensation is general, as it could be applied to 2-amino hydroxamates 2h–f, to aminopyridines 2g and 2h and to thiophene derivatives 2i and 2j, as indicated in Table 2, with some adaptations. Afterwards, the esters of 3a–j were transformed to carboxamides 4a–j,15 which were subjected to the cleavage of the O–PMB bond with TFA, to give the desired cyclic hydroxamic acids, 5a–j.

| Table 2. From amino esters 2a–j to quinazolones 5a–f, pyridopyrimidinones 5g and 5h and thienopyrimidinones 5i and 5j. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Entry | Step 1 | Yield (%) | Step 2 | Yield (%) | Step 3 | Yield (%) |
| 1 | 2a to 3a | 95–98 | 3a to 4a | 91 | 4a to 5a | 95 |
| 2 | 2b to 3b | 98 | 3b to 4b | 86 | 4b to 5b | 92 |
| 3 | 2c to 3c | 92 | 3c to 4c | 87 | 4c to 5c | 90 |
| 4 | 2d to 3d | 85 | 3d to 4d | 85 | 4d to 5d | 90 |
| 5 | 2e to 3e | 89 | 3e to 4e | 89 | 4e to 5e | 95 |
| 6 | 2f to 3f | 91 | 3f to 4f | 93 | 4f to 5f | 97 |
| 7 | 2g to 3g | 90 | 3g to 4g | 85 | 4g to 5g | 87 |
| 8 | 2h to 3h | 85 | 3h to 4h | 85 | 4h to 5h | 92 |
| 9 | 2i to 3i | 92 | 3i to 4i | 70 | 4i to 5i | 90 |
| 10 | 2j to 3j | 90 | 3j to 4j | 75 | 4j to 5j | 92 |

*See Scheme 2 for the substituents (groups/rings). 
15 Similar results in refluxing THF. 
15 The CONHOMe group at position 4 of the aromatic ring was also cleaved to CONH2.

120 mol% of TSOH H2O was required in this case, owing to the basicity of the 2-aminopyridine moiety. Refluxing AcOH was not sufficient whereas heating at 140 °C (MW) gave rise to degradation. On the other hand, heating overnight with 10 mol% of BF3, at 80 °C in a closed vial, caused an almost complete disappearance of 2g (to give in 80% isolated yield the desired 3g). 
* This cyclisation was performed in refluxing AcOH.
15 For 2h in refluxing CH3CN.
15 With 220 mol% of 4-FBnNH2 and dropwise addition of 200 mol% of LDA, in THF at –78 °C, stirring for 4 h. Heating with 4-FBnNH2 (as in entries 1–8) gave rise to decarboxylation.

Finally, we obtained N-hydroxyhypoxanthine 5k16 in three high-yielding steps from 2k as detailed in Scheme 3.

Samples of the molecules thus prepared (5a, 5e, 5f and 5k) were tested as inhibitors of the 3'-processing and strand transfer activities of HIV-1 integrase at a single 10 µM concentration, with regard to raltegravir;16 unfortunately, no activity was observed. They also appeared to be inactive for concentrations up to 10 µM in an HIV-1 antiviral, single-round-of-infection assay.16

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9. Compound 5sc: mp 262.5–264.0 °C (dec); 1H NMR (400 MHz, DMSO-d6) δ 4.46 (d, J = 6.1 Hz, 2 H), 5.36 (s, 2 H), 7.19 (m, 4 H), 7.39 (m, 4 H), 8.28 (s, 1 H), 9.36 (m, J = 6.1 Hz, 1 H), 12.05 (s, 1 H); 13C NMR (100.6 MHz, DMSO-d6) δ 41.3, 45.7, 115.0 (d, J = 3.0 Hz), 115.5 (d, J = 21.4 Hz), 115.5 (d, J = 21.5 Hz), 123.5, 129.1 (d, J = 8.2 Hz), 129.7 (d, J = 8.4 Hz), 132.6 (d, J = 3.0 Hz), 134.3 (d, J = 3.0 Hz), 141.7, 144.9, 149.1, 153.4, 160.2, 161.2 (d, J = 24.2 Hz), 161.6 (d, J = 24.40 Hz); HRMS (ESI, m/z), calc for C_{22}H_{23}F_{6}N_{4}O_{3} [(M+H)^{+}] 412.1216, found 412.1204.

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12. Regarding 2-carboxyl or 2-carbonyl derivatives of pyrimidin-4-ones, 75 patents can be found via SciFinder from 2000 to 2010 aimed at treating diverse diseases.
Graphical abstract

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