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3-Iodo-4-phenoxypyridinones (IOPY's), a New Family of Highly Potent Non-nucleoside Inhibitors of HIV-1 Reverse Transcriptase

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Abstract—Building upon the potent anti-HIV-1 activities observed for the 3-dimethylamino-4-benzylpyridinone **2**, and the corresponding 4-aryloxypyridinone analogue **3**, a concise and efficient route to the 3-iodo-4-aryloxypyridinones **14a–c** (IOPY's) was developed. This involved reaction of the 4-hydroxy substituted pyridinone **10** with the requisite dichloroiodobenzene reagent **11**. IOPY compound **14c** is active at $IC_{50} = 1–45$ nM against wild type HIV-1 and a panel of six major simple/double HIV mutant strains.

The introduction of highly active antiretroviral therapy (HAART) involving the use of drug combinations to treat AIDS has had a dramatic impact on the morbidity and mortality of individuals infected by the human immunodeficiency virus (HIV).[1,2] However, in spite of this success there are continuing problems of toxicity and drug resistance, including the emergence of multi-drug-resistant strains of HIV-1.[3,4] It is thus important to continually develop more potent and less aggressive drugs for the treatment of HIV. In this context, non-nucleoside reverse-transcriptase inhibitors (NNRTIs) are finding increasing use in multi-drug regimens.[5] At present, only three molecules of this family, nevirapine (Viramune), delavirdine (Rescriptor) and efavirenz (Sustiva), are approved for the treatment of HIV infected patients.[6]

A contribution from our laboratories to this effort was the discovery that 3-amino-4-arylthiopyridinones[7] of general structure **1** (Fig. 1) are potent inhibitors of wild type HIV-1 reverse transcriptase. Preliminary SAR on this series has led to the identification of the 3-dimethylamino-4-benzylpyridinone **2** as a promising lead compound.[8] As part of an extensive optimisation programme on this new family of HIV-1 RT inhibitors,

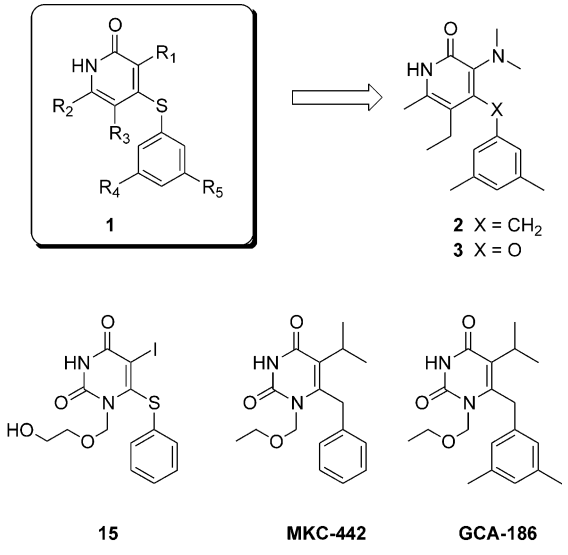

Figure 1.

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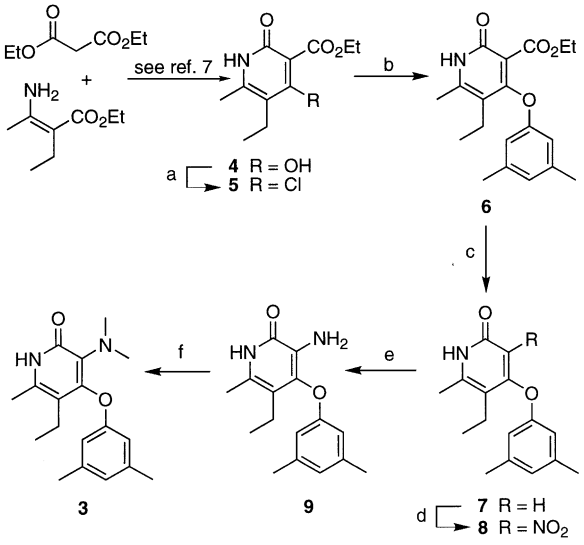
we wanted to evaluate the potential of compound **3**, the corresponding aryloxypyridinone analogue of **2**. In a further, and larger context, our objective was to develop a synthetic route which would give easy and rapid access to a wide range of aryloxypyridinone analogues which are modified at the C-3 position. The development of such an approach based upon the reaction of 4-hydroxy-2-pyridinones with hypervalent iodine reagents leading to a highly potent lead compound **14c** in the aryloxypyridinone series is the subject of the present communication.

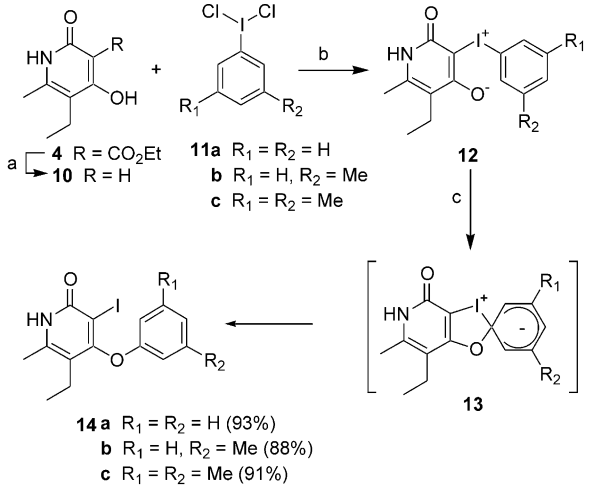
Chemistry

4-Thioarylpyridinones **1** are prepared by condensation of a requisite 4-chloropyridinone with a thiophenol derivative in a Michael addition/retro-Michael process.[7] This transformation is dependent upon the presence of an electron withdrawing (ester or nitro) substituent at the C-3 position of the pyridinone ring. Following this strategy, the 4-chloro-3-carbethoxy-2-pyridinone **5** was reacted with the potassium anion of 3,5-dimethylphenol in refluxing DMF[9] (Scheme 1). The derived condensation product **6** (94%) was then heated in aqueous HCl to effect hydrolyse–decarboxylation to giving the intermediate **7** (86%). Treatment of **7** with fuming nitric acid in acetic acid afforded the 3-nitropyridone **8** (55%). Reduction of the nitro group using tin(II) chloride dihydrate in ethyl acetate provided amine **9** (70%), which was subsequently converted to the target *N,N*-dimethyl substituted benzyloxypyridinone **3** under reductive alkylation conditions [HCHO (37 wt. % in water), $NaBH_3CN$, MeCN; 85%]. Overall, eight steps were required to obtain **3**, and although the yield of certain operations were high the conversion of **4** to **5** on reaction with $POCl_3$ (average yield 40%) has proven difficult to optimise.[7]



Scheme 1. (a) $POCl_3$, $BnEt_3NCl$, MeCN, reflux (30–60%); (b) potassium phenolate (1 equiv), DMF, reflux (94%); (c) 2N HCl, reflux (86%); (d) HNO_3 (3 equiv), AcOH, 5–90 °C (55%); (e) $SnCl_2{\cdot}2H_2O$ (5 equiv), EtOAc, reflux (70%); (f) HCHO (10 equiv), $NaBH_3CN$ (3 equiv), CH_3CN, reflux (85%).

Thus, as a general approach for subsequent analogue synthesis this route did not appear sufficiently attractive for our needs. For this reason, our attention was focused to a report by Kappe and El-Mariah concerning the reaction of 4-hydroxyquinolin-2-ones with (dichloroiodo)benzene.[10] In this transformation both an aryloxy and an iodo substituent are introduced adjacent to each other on the pyridinone nucleus in essentially a single operation. Applying this methodology (Scheme 2), it was found that the reaction of 4-hydroxypyridinone **10** with the (dichloroiodo)arenes **11a–c**, prepared by reaction of iodobenzene, 3-methyliodobenzene or 3,5-dimethyliodobenzene with chlorine gas, gave direct access to the 3-iodo-4-phenoxy substituted pyridinones **14a–c** in excellent yields. The first step in this process involves formation of the aryliodonium ylides **12a–c**, which on heating rearranges via the spiro-Meisenheimer[11] intermediates **13a–c**, to the observed product. This result was highly promising, as the presence of the iodo substituent at C-3 in compounds **14** opens up a broad range of opportunities to introduce diverse substituents at C-3 [particularly by halogen–metal exchange, Pd(0) and Cu^+ based coupling techniques]. Pertinent to the present report, the formation of compounds **14** provided the opportunity to evaluate the influence of the iodine at the C-3 position on anti-HIV activity in the pyridinone series.



Scheme 2. (a) 2 N HCl, reflux; (b) Na_2CO_3, H_2O, rt; (c) DMF, reflux.

Table 1. Activity (IC_{50}, μM) versus HIV-1[12]

Compd	LAI	SI[b]	K103N	Y181C
3	0.004	25,000	0.050	0.158
7	0.500	200	nd	nd
8	0.004	2500	0.100	0.158
14a	0.0016	63,000	0.040	0.316
14b	0.0016	19,900	0.032	0.051
14c	0.0013	9000	0.003	0.020
2	0.008	12,500	0.032	0.100
MKC442	0.008	1260	0.8	2
GCA-186[a]	0.001	52,000	0.04	0.18

[a]Literature values.[14]
[b]SI is the ratio of 50% cytotoxic concentration to IC_{50}.

Table 2. Activity (IC_{50}, μM) versus HIV-1[12]

Compd	LAI	K103N	K100I	Y181C	Y188L	K103N + K100I	K103N + Y181C
14c	0.0013	0.003	0.006	0.020	0.045	0.020	0.040
2	0.008	0.032	0.05	0.1	0.3	nd	0.8
Nevirapine	0.032	6.3	> 10	10	> 10	> 10	> 10
Delavirdine	0.063	2.5	2.5	1.9	1.3	> 10	> 10
Efavirenz	0.001	0.040	0.040	0.002	0.2	> 10	0.040

Anti-HIV-1 Test Results and Discussion

Compounds **3** and **14a–c** were evaluated for their anti-HIV activity,[12] and the results were compared to those for lead compound **2** (Table 1). To obtain a clear indication of the potential worth of the aryloxypyridinones, and in particular the 3-iodo substituted compounds **14a–c**, a comparison was also made to the related HEPT analogues MKC-442[13] and GCA-186,[14] and to the three currently used NNRTI type drugs, nevirapine, delavirdine and efavirenz (Table 2).

In an initial screen against wild-type HIV-1 and the two major mutant strains Y181C and K103N,[15] it was found that replacement of the bridging CH_2 group in **2** by an oxygen atom does not result in either a net gain or loss in activity. Both pyridinones **2** and **3** were found to be 10 times more active than MKC-442, but in the more direct comparison with GCA-186 (literature values),[14] which also possesses the 3,5-dimethyl substitution in the phenyl ring, one sees that all three compounds are comparable in activity. Thus, the CH_2 for O exchange is acceptable, indicating that we can incorporate this modification in further analogue studies. Looking next at the three iodo substituted pyridinone analogues **14a–c**. Nanomolar range activities were again observed for these molecules against the LAI strain. This result contrasts sharply with the only marginal activity reported for the corresponding iodo-HEPT compound **15** ($IC_{50} = 3.6\,\mu M$).[16] Noteworthy was the observation that introduction of the methyl groups on the phenyl ring in compounds **14** resulted in a considerable improvement in the activities against the two mutant strains, and in particular K103N (**14c**; $IC_{50} = 0.003\,\mu M$). Indeed **14c** is 10 times more active against this major mutant than either compound **2** or GCA-186. A further 5–10 times improvement in activity was also observed against the Y181C mutant.

The presence of the iodine atom in the aryloxpyridinones **14a–c** thus has a positive impact on activity (contrary to earlier indications).[16] The exact nature of the contribution of the iodine atom to the binding of these NNRTI type molecules in RT is not understood at present, but the hydrophobic properties of this substituent, its polarisability and/or its effective volume are three factors which may favour binding, and thus distinguish compounds **14** from the corresponding compound **7** ($IC_{50} = 0.50\,\mu M$) in which this group is absent.

In light of the interesting activities found for **14c**, it was tested against a larger panel of HIV-1 mutant strains (Table 2). It is immediately seen that, relative to lead molecule **2**, there is a significant gain in activity against all the mutant strains, and in particular a 20-fold improvement in activity against the K103N + Y181C double mutant. In addition, with the exception of the values found for the Y181C mutant, this molecule has a much better profile in vitro than efavirenz, the current NNRTI standard in combination therapy. Note in particular that efavirenz is inactive against K103N + K100I, and that both efavirenz and **14c** remain equipotent against the K103N + Y181C double mutant.

Compound **14c** thus represents an interesting new lead molecule for the development of pyridinone based anti-HIV agents. This avenue of research is actively being persuaded, as is the original objective of using the iodo substituent in these pyridinones as a 'handle' to introduce varied and diverse functionality at C-3 of the pyridinone ring.

Acknowledgements

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