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Pyrazole NNRTIs 4: Selection of UK-453,061 (lersivirine) as a Development Candidate

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ABSTRACT

We prepared three discreet cohorts of potent non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) based on the recently reported 3-cyanophenoxypyrazole lead **3**. Several of these compounds displayed very promising anti-HIV activity in vitro, safety, pharmacokinetic and pharmaceutical profiles. We describe our analysis and conclusions leading to the selection of alcohol **5** (UK-453,061, lersivirine) for clinical development.

The UN estimates that 33 million people were living with HIV infection in 2007.[1] There remains an urgent need for new and improved medicines to treat HIV infection. The most valuable new therapies will suppress drug-resistant viruses, cause fewer side effects than existing agents and be conveniently used in highly active antiretroviral therapy (HAART). Non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) remain a cornerstone of HAART despite the recent introduction of new classes of anti-HIV agents including a viral entry inhibitor, CCR5 antagonist and HIV integrase inhibitor.[2] We set out to identify a novel NNRTI with a broad spectrum of activity against HIV with clinically significant drug resistance mutations in reverse transcriptase (RT) whilst reducing the required dose and pill burden, minimising the risk of side effects and drug–drug interactions and hence improving tolerability and the ease of compliance when compared to existing NNRTIs.

We recently reported the design, synthesis and characterisation of the benzylpyrazole **1,** a novel prototype NNRTI which was designed to incorporate the excellent broad spectrum activity of the experimental drug capravirine whilst seeking to achieve an improved pharmaceutical, pharmacokinetic and pre-clinical safety profile.[3] We have also described the initial optimisation and further development of this lead to the phenoxypyrazole **2** and a successful effort to improve the ligand-lipophilicity efficiency (LLE)[4] of the series leading to the advanced lead 3-cyanophenoxypyrazole **3** (Fig. 1).[5,6]

We now sought to further improve both the antiviral activity and the pharmacokinetic profile of the 3-cyanophenoxypyrazole

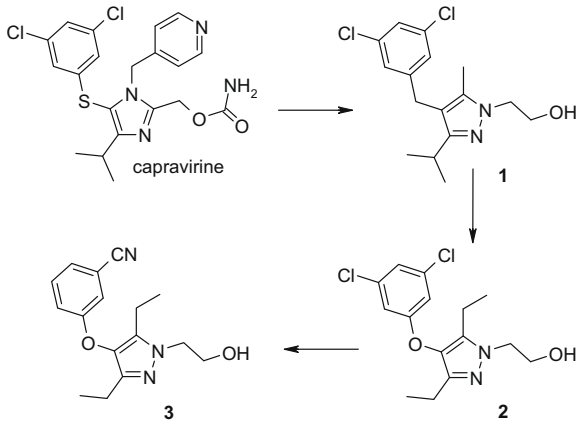

Figure 1. Evolution of lead pyrazole inhibitor **3**.

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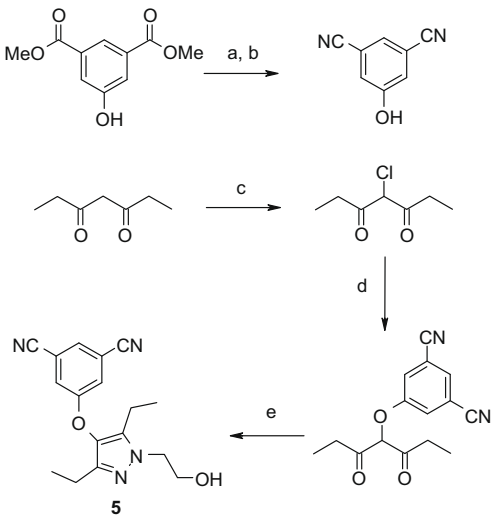


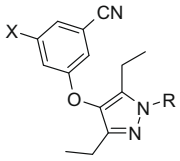
Scheme 1. Synthesis of compound **5**. Reagents and conditions: (a) 0.880 g/mL NH_3 in H_2O, 71%; (b) $POCl_3$, MeCN, 96%; (c) Bu_4NBr, TMS–Cl, DMSO, MeCN, 68%; (d) Cs_2CO_3, 3,5-dicyanophenol, acetone, 47%; (e) 2-hydroxyethylhydrazine, AcOH, 71%.

series. The 3-cyanophenoxy group was identified as a ligand-lipophilicity efficient replacement for the 3,5-dichlorophenoxy substituent through an exploration of the SAR enabled by parallel chemistry using readily available phenols.[6] We anticipated that adding a small substituent, and in particular fluorine, chlorine, methyl or nitrile to the 5-position of the phenoxy group of the lead **3** would give greater inhibition of RT based on our earlier findings in the related benzylpyrazole series.[5] We also speculated that these modifications might improve resilience to mutations within the NNRTI binding pocket through more optimal interactions with the highly conserved W229 and neighbouring resides which has been proposed by Stuart, Stammers and co-workers for an analogue of emivirine[7] and for capravirine.[8] Once we were convinced of the merits of these designs we undertook the synthesis of the requisite phenols and utilised these in the previously established route to prepare the target pyrazoles as illustrated for compound **5** in Scheme 1.

We prepared the *N*-hydroxyethyl pyrazoles **4–7**, and also the corresponding unsubstituted parent compounds **9–12**, and *N*-aminoethylpyrazoles **14–17** as our previous work suggested that these might also show good activity.[5] The in vitro profiles of these three cohorts of compounds are shown in Table 1 along with the unsubstituted forerunners **3**, **8** and **13**. It was immediately clear that our objective of improving potency against wild type RT had been successful with all compounds except parent **9** displaying improved activity over the lead **3**. The alcohols **4–7**, unsubstituted pyrazole **12** and amines **16** and **17**, in particular were potent inhibitors of RT and this translated into very potent antiviral activity in cell culture. It is interesting to note that the addition of substituents to the 5-position of the phenoxy group does not seem to alter the relative activities towards the various mutant RT enzymes; indeed the spectrum appears remarkably consistent across representatives of this family of compounds (Table 2).

Although compound **12** shows excellent ligand efficiency (LE)[9] it has a lower LLE and is too lipophilic for good metabolic stability within this class of inhibitors. Compound **12** retains activity against a panel of mutant RT enzymes but is less impressive against the most clinically important K103N mutant (Table 2) and also displays increased cytotoxicity relative to the alcohols **4–7**. The amines **16** and **17** are stable in microsomes[10] and hepatocytes but further in vitro profiling suggested a likely reduced ther-

Table 1
Profiles of 3-cyanophenoxypyrazole derivatives



Compound	X	R	*c*log *P*	log D	RT IC_{50}[a] (μM)	LE[b]	LLE[c]	AV_{50}[a] (nM)	AV_{90} (nM)	CC_{30}[a] (μM)	HLM $T_{1/2}$[a] (min)	Microsomal free fraction[a]	Predicted Cl_u (mL/min/kg)[a]	Dofetilide binding[a]
Efavirenz	—	—	—	—	0.0084	—	—	0.6	1.2	>2	—	—	—	—
Capravirine	—	—	3.53	—	0.093	0.47	3.50	1.4	2.4	>1	7.5	—	—	—
3	H	CH_2CH_2OH	2.7	2.7	0.35	0.43	3.76	—	—	—	27	80%	50	
4	F	CH_2CH_2OH	2.8	2.9	0.081	0.45	4.29	5.7	25	>30	44	—	⩽30	0%@25μM
5	CN	CH_2CH_2OH	2.1	1.8	0.119	0.43	4.92	4.0	25	>30	73	—	8	0%@25μM
6	Cl	CH_2CH_2OH	3.4	3.3	0.034	0.48	4.07	0.94	5.4	>30	67	—	109	—
7	Me	CH_2CH_2OH	3.2	3.2	0.042	0.47	4.18	0.30	3.0	>30	17	—	—	—
8	H	H	3.4	—	0.89	0.47	2.65	—	—	—	37	—	—	—
9	F	H	3.5	—	1.0	0.44	2.50	—	—	18	—	—	—	—
10	CN	H	2.8	2.8	0.24	0.46	3.82	17	59	>30	>120	—	<19	IC_{50} 9.8μM
11	Cl	H	4.1	—	0.13	0.51	2.79	3.0	18	2.4	—	—	—	IC_{50} 39μM
12	Me	H	3.9	3.8	0.074	0.53	3.23	0.89	6.7	1.4	38	—	—	IC_{50} 100μM
13	H	$CH_2CH_2NH_2$	2.8	1.2	0.6	0.41	3.42	—	—	—	>120	50%	—	—
14	F	$CH_2CH_2NH_2$	2.9	1.5	0.26	0.42	3.69	28	131	<30	>120	—	<18	84%@20μM 96%@60μM
15	CN	$CH_2CH_2NH_2$	2.2	0.9	0.31	0.40	4.31	22	100	>30	>120	—	<7	64%@30μM 92%@100μM
16	Cl	$CH_2CH_2NH_2$	3.5	2.0	0.043	0.47	3.87	8.3	24	30	>120	—	<33	88%@25μM
17	Me	$CH_2CH_2NH_2$	3.3	1.5	0.040	0.47	4.10	0.67	3.5	>30	>120	40%	<30	52%@5μM

[a] AV_{50} and AV_{90} are antiviral IC_{50} and IC_{90}, respectively, in cell culture in SupT1 cells infected with the RF strain of HIV. CC_{30} = the 30% cytotoxic concentration of the compound in cell culture in SupT1 cells. HLM = human liver microsome preparation. Cl_u = unbound clearance from human hepatocyte experiments. Dofetilide binding = in vitro displacement of radiolabelled dofetilide from the HERG channel. Details of in vitro assays have been reported separately.[11,12,13]

[b] Ligand efficiency (LE) is the binding energy per heavy atom (kcal mol^{-1}) = $-1.4 \log (RT\ IC_{50})$/number of heavy atoms.[9]

[c] Ligand-lipophilicity efficiency (LLE) = $-\log (RT\ IC_{50}) - c\log P$.[4]

Table 2
IC_{50} fold-resistance of selected pyrazoles versus RT enzymes[a] bearing NNRTI resistance mutations cf. wild type

	Efavirenz	**3**	**4**	**5**	**6**	**12**	**17**
K103N	44	2.3	1.8	1.6	1.2	3.1	2.4
Y181C	2.2	1.5	2.7	1.6	3.2	1.1	2.6
F227L	0.4	4.7	5.0	4.7	3.6	3.3	5.0
V106A	1.8	15	14	1.4	3.4	4.8	3.7
Y188C	0.8	0.3	0.6	0.4	0.2	0.1	0.4
K101E	3.8	9.4	5.6	5.0	6.2	4.4	6.2
P236L	2.8	0.4	0.9	1.3	1.1	0.4	1.8
V108I	1.0	11	7.6	6.8	4.8	4.4	9.3
L100I	5.6	2.9	4.3	4.5	13	5.0	5.9
L234I	2.5	11	12	5.2	8.9	1.5	7.5

[a] Details of in vitro assays have been reported separately.[13]

apeutic window compared to the alcohols **4**–**7** with respect to off target pharmacology as assessed in wide ligand profiling (data not shown) and ion channel selectivity indicated in a dofetilide binding assay.[11] The alcohol **7** was vulnerable to metabolism in microsomes presumably due to its increased lipophilicity and introduction of a vulnerable benzylic methyl group. Replacing the methyl group in **7** with a chlorine atom to give compound **6** improves resistance to oxidative metabolism but the log *D* of the resulting molecule is too high leading to unacceptably fast glucuronidation as determined in human hepatocytes. Finally we chose alcohol **5** over the equipotent but slightly more lipophilic congener **4** due to its improved metabolic stability. Thus alcohol **5** was chosen for further development on the basis of its compelling overall in vitro profile. Subsequent studies also showed improvements, notably reduced clearance and increased half life, in the in vivo pharmacokinetic profile in rats for alcohol **5** compared to the earlier lead **3** (Table 3).[12]

Compound **5** demonstrated excellent activity against large panels of wild type and drug-resistant HIV consistent with the encouraging profile demonstrated against the isolated RT enzymes shown above.[13] Compound **5** can be readily prepared in multi-gram quantities by virtue of the efficient and concise synthetic route. The compound also has good aqueous solubility and formulation characteristics which enable further in vivo evaluation. Clinical trials evaluating the potential of **5** (UK-453,061, lersivirine) to treat HIV infection are proceeding and further progress will be reported in due course.[14]

Table 3
Rat pharmacokinetic data for key compounds (2 mg/kg, iv)

Compound	**3**	**5**
Cl (mL/min/kg)	>100	25.9
Vd (l/kg)	1.3	1.6
$T_{1/2}$ (h)	0.1	1.6

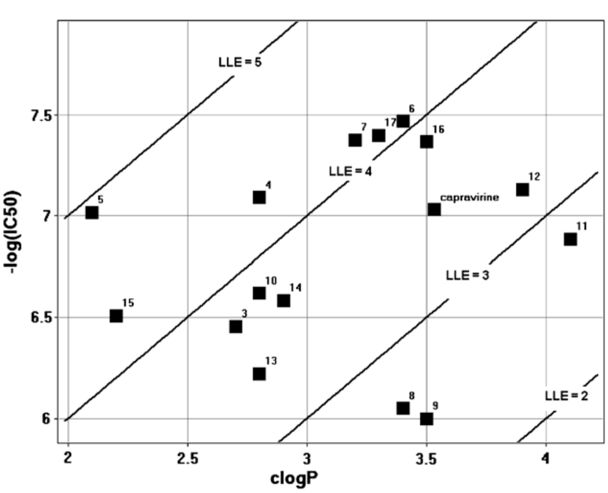


Figure 2. Plot of $-\log(\text{RT IC}_{50})$ against $c\log P$ for pyrazole series. The 45° lines indicate equal values of LLE.

In conclusion we have vindicated our design strategy; combining excellent broad spectrum anti-HIV activity, an encouraging pre-clinical safety profile, and a high quality pharmacokinetic and pharmaceutical profile through focusing on attaining the necessary excellent physical properties. The improvements made in LLE which ultimately drove this success and allowed selection of alcohol **5** can be seen in Figure 2. We have subsequently applied our learning about the benefits of employing cyanohalo- and dicyanophenoxy substituents discovered in this work to provide further novel NNRTI series and will publish additional results shortly.[15]

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