Compounds acting against HIV

Imidazo[1,2-a]pyridines as non-nucleoside reverse transcriptase inhibitors (NNRTIs)

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HIV drug targets

Viral enzymes:

- Reverse Transcriptase
- Protease
- Integrase
Reverse Transcriptase

Two types of inhibitors: NRTIs and NNRTIs
Inhibitor Modes of action

NRTI

NNRTI
NNRTIs in HIV treatment

- Non-competitive allosteric inhibitors of reverse transcriptase

- Form part of first-line treatment regimen of HAART, eg. nevirapine, efavirenz

- Potent, highly selective anti-HIV agents

- Structurally diverse

- Generally good safety profile
Imidazo[1,2-a]pyridines

\[ \text{Res Act} = 41\% \]
\[ \text{IC}_{50} = 29\text{ uM (RT)} \]
\[ \text{IC}_{50} = 41\text{ uM (PBMC)} \]

Hit compound identified from an enzymatic RT screen – poorly active in whole cell anti-HIV assay
Reverse transcriptase assay

Compounds showing < 20% residual activity in enzymatic assay were submitted to SRI for whole-cell anti-HIV infectivity assay.
Hit to Lead Development

H
halogen
methyl
cyano
alkoxy

alkyl
branched alkyl
cycloalkyl
phenyl
halogenated phenyl

alkyl
branched alkyl
cycloalkyl
aromatic
Lead compound identified
Lead optimisation

- **Res Act = 18%**
  - $IC_{50} = 7 \mu M$
  - MAGI $IC_{50} = 3 \mu M$

- **Res Act = 57%**
  - $IC_{50} = 5 \mu M$
  - MAGI $IC_{50} = 0.6 \mu M$

- **Res Act = 11%**
  - $IC_{50} = 5 \mu M$
  - MAGI $IC_{50} = 0.6 \mu M$

- **Res Act = 3%**
  - $IC_{50} = 2 \mu M$
  - MAGI $IC_{50} = 0.2 \mu M$

- **Res Act = 94%**
  - $IC_{50} = 8 \mu M$
  - MAGI $IC_{50} = 0.6 \mu M$

- **Res Act = 20%**
  - $IC_{50} = 15 \mu M$
  - MAGI $IC_{50} = 0.8 \mu M$

- **Res Act = 4%**
  - $IC_{50} = 1.5 \mu M$
  - MAGI $IC_{50} = 0.18 \mu M$

- **Res Act = 12%**
  - $IC_{50} = 7 \mu M$
  - MAGI $IC_{50} < 0.6 \mu M$

- **Res Act = 5%**
  - $IC_{50} = 3.5 \mu M$
  - MAGI $IC_{50} = 0.18 \mu M$
Summary: Activity improvement

IC₅₀ = 29 uM (RT)
IC₅₀ = 41 uM (PBMC)
cf. Nevirapine
IC₅₀ = 0.67 uM (RT)
IC₅₀ = 0.033 uM (PBMC)

IC₅₀ = 4.4 uM (RT)
IC₅₀ = 0.16 uM (PBMC)
IC₅₀ = 0.41 uM (MAGI)
cf. Nevirapine
IC₅₀ = 0.67 uM (RT)
IC₅₀ = 0.033 uM (PBMC)

IC₅₀ = 3.5 uM (RT)
IC₅₀ = 0.18 uM (MAGI)
cf. Nevirapine
IC₅₀ = 0.67 uM (RT)
IC₅₀ = 0.10 uM (MAGI)
Conclusions

- A compound possessing anti-HIV activity similar to that of FDA-approved nevirapine was developed
- Acts as a non-nucleoside reverse transcriptase inhibitor
- Compound shows good cell permeability
- Quantitative structure activity relationship (QSAR) developed for the compound series