**Abstract**

Recombinant HIV integrase was used to test three new clones against the enzyme, with a third clone being used as a control. The assay was performed in a biochemical assay with nanomolar potency. S/GSK1349572 inhibited HIV replication in a clade- and subtype-independent manner. The IC50 value for the wild type virus NL432 was 0.52 nM. In cellular assays, the potency shift extrapolated to 100% human serum was 75-fold, resulting in a 6.4 nM concentration for S/GSK1349572. This is the first report of an integrase inhibitor that is active against HIV-1 from thirteen subtype B clinical isolates.

**Results and Discussion**

Table 1. Inhibition of Recombinant HIV Integrase and HIV Replication by S/GSK1349572

<table>
<thead>
<tr>
<th>Integrase</th>
<th>NC50 (nM)</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/GSK1349572</td>
<td>0.52</td>
<td>0.52</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0.65</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Methods**

The study was conducted in cell-based assays with the use of PBMCs and Molt-4 cells. The effect of S/GSK1349572 on viral DNA integration was measured by measuring HIV integrase strand transfer inhibition in biochemical assay, by viral DNA species quantification, and in cell based HIV replication assays. Analysis of viral mechanism: Mechanistic studies examined the effect of S/GSK1349572 on viral DNA integration using quenched-polypeptide (QCP) assay. The results showed that S/GSK1349572 inhibited HIV replication in a clade- and subtype-independent manner. The IC50 value for the wild type virus NL432 was 0.52 nM. In cellular assays, the potency shift extrapolated to 100% human serum was 75-fold, resulting in a 6.4 nM concentration for S/GSK1349572. This is the first report of an integrase inhibitor that is active against HIV-1 from thirteen subtype B clinical isolates.

**Conclusions**

S/GSK1349572 is a potent inhibitor of HIV integrase in vitro and cell-based HIV replication assays. The mechanism of action of S/GSK1349572 was confirmed by measuring HIV integrase strand transfer inhibition in biochemical assay, by viral DNA species quantification, and in cell-based HIV replication assays. S/GSK1349572 inhibited HIV replication in a clade- and clinical-isolate independent fashion. S/GSK1349572 had limited cross-resistance to RAL- and ELV-resistant mutants. In vitro passage studies showed that S/GSK1349572 leads to a less diverse resistance profile with lower fold change.

**Acknowledgements**

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**References**