Discovery of Highly Potent, Orally Active CCR5 Antagonist TAK-652 as an Anti-HIV-1 Agent

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In course of our work developing CCR5 antagonists as backup compounds to TAK-779 for injection, we discovered the potent, orally active compound **1** with a tertiary amino group. Based on our previous experience, we designed 1-benzazepine derivatives containing sulfoxide and heteroaryl groups as new polar substituents, and performed chemical modifications of this series. As a result, it was found that *S*-sulfoxide compounds containing an imidazolyl group exhibited highly potent CCR5 antagonistic activities. From further investigation, we discovered 1-isobutyl-1-benzazocine derivative TAK-652 as a remarkably potent and orally bioavailable anti-HIV-1 agent. We describe the design, synthesis, and biological evaluation of sulfoxide compounds containing [6,7]- to [6,10]-fused ring nuclei.