SYNTHESIS, ANTIVIRAL AND ANTIBACTERIAL ACTIVITIES OF ISATIN MANNICH BASES

Dharmarajan Sriram*, Tanushree Ratan Bal, Perumal Yogeeshwari

Medicinal Chemistry Research Laboratory, Pharmacy Group, Birla Institute of Technology and Science, Pilani – 333031, India

Abstract. HIV is the most significant risk factor for many opportunistic infections like tuberculosis, hepatitis, bacterial infections etc. We designed an isatin lead compound as a novel non-nucleoside reverse transcriptase inhibitor with broad-spectrum chemotherapeutic properties for the effective treatment of AIDS and AIDS-related opportunistic infections. Compound 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(N²,3'-((4'-amino-5'-trimethoxybenzyl)pyrimidin-2'-yl)imino-1'-(5-chloroisatinyl)]methyl]-N¹-piperazinyl]-3-quinoline carboxylic acid (14) emerged as the most potent broad-spectrum chemotherapeutic agent active against HIV, HCV, M. tuberculosis and various pathogenic bacteria.

Acquired immunodeficiency syndrome (AIDS), due to infection with the human immunodeficiency virus (HIV), has become a worldwide epidemic. HIV infection, which targets the monocytes expressing surface CD4 receptors, eventually produces profound defects in cell-mediated immunity. Overtime, infection leads to severe depletion of CD4 T-lymphocytes (T-cells) resulting in opportunistic infections (OIs) like tuberculosis (TB), fungal, viral, protozoal and neoplastic diseases and, ultimately, death. TB is the most commonOI in people with AIDS and it is the leading cause of death among people with AIDS. Co-infection of hepatitis C virus (HCV) and HIV is quite common, mainly because these infections share the same parenteral, sexual and
vertical routes of transmission. Although classical OIs are now rarely seen, the toxicity of antiretroviral drugs, as well as liver diseases caused by HCV, represents an increasing cause of morbidity and mortality among HIV-positive patients. Predisposing liver damage results in a higher rate of hepatotoxicity by antiretroviral drugs, which may limit the benefit of HIV treatment in some individuals. Logically, it appears that an ideal drug for HIV/AIDS patients should suppress HIV replication, thereby acting as an anti-HIV drug, as well as possess efficacy against OIs like TB, hepatitis and other bacterial infections. Earlier works in our laboratory have led to the identification of various isatinimino derivatives exhibiting broad-spectrum chemotherapeutic properties. Continuing to develop broad-spectrum chemotherapeutics, we undertook the present study to design, synthesize and evaluate isatin analogues, which may suppress HIV replication in addition to inhibiting opportunistic microorganisms.

**Design**

To qualify as a non-nucleoside reverse transcriptase inhibitor (NNRTI), the compound should interact specifically with a non-substrate binding site of the reverse transcriptase (RT) of HIV-1, and inhibit the replication of HIV-1 at a concentration that is significantly lower than the concentration typically observed to affect normal cell viability. Based on this concept, more than thirty different classes of NNRTI's may be considered. Although the NNRTI's seemingly belong to widely diverging classes of compounds, closer inspection reveals that most have some common features, that is a carboxamide or (thio) urea entity (‘body’), surrounded by two hydrophobic, mostly aryl moieties (‘wings’), one of which is often substituted by a halogen.