ISATIN ANTI-HIV AGENT: A REVIEW

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ABSTRACT

HIV-AIDS remains among the world’s great public health challenges. Worldwide resurgence of HIV is due to major problem outbreak of multi drug resistant HIV mutants can gain a competitive advantage over with respect to virus and become the dormant quasispecies. Thus, there is persuasive need for anti-HIV drugs with improved properties such as, enhanced activity against MDR strains, reduced toxicity, shortened duration of therapy, low dose frequency, rapid mechanism of action and most important it will have been executing conformational adaptability and to increase flexibility to penetrate host cells and exert anti-retroviral effects in the intra and extra cellular environment.

Indoline-2,3-dione (Isatin) derivatives are reported to show anti-HIV activities accordingly, isatin is a versatile lead molecule for designing of potential anti-HIV agent. The current review tracing isatin derivatives with potential anti-HIV activity.

KEYWORDS: Isatin, Isatin analogues, Isatin binding proteins, Potential anti-HIV activity.

INTRODUCTION

Isatin was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acid. It forms red needles with M.P 201-202°C. In nature, isatin is found the roots and the leaves of the plant, Strobilanthes cusia (Nees) Kuntze of the Acanthaceae family that is widely distributed in northern and central China, have been used in traditional Chinese medicine to treat a variety of ailments caused by microorganisms and virus. Isatin has been known for about 150 years and has been recently found, like oxindole and endogenous polyfunctional heterocyclic compounds, to exhibit biological activity in mammals. Isatin and its analogs are inconstant substrates, which can be used for the synthesis.
of numerous heterocyclic compounds. Isatin and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different biological activities being anti-HIV. It is synthetically and having capable of moving freely in all direction. The carbonyl group at position-2 is adjacent to the hetero atom and is stabilized by resonance, thus it behaves as typical amide in its properties. It readily undergoes aromatic substitution reaction at C-5, N-alkylation via anions, and ketonic reaction at the C-3 carbonyl groups. If the 5th position is already occupied then electrophilic attack takes place at 7th position. Isatin and its derivatives can confer nucleophilic attack at positions C-2 and/or C-3. The chemo-selectivity of these reactions depends on the nature of nucleophile, substituent, solvent and temperature employed. Nucleophilic substitution at position C-2 in isatin, leads to the opening of the heterocyclic ring. This process may be followed by an intra-molecular or by an inter-molecular cyclization. The initial products obtained can relieve further reaction in the presence of a second nucleophilic group to give cyclization products. In the past few decades, Isatin and its derivatives have received much attention due to their chemotherapeutic values. This review covers updated information on the most active isatin derivatives that have been reported to show considerable anti-HIV activates. From those results, ideas for future molecular modifications leading to compounds with greater favorable pharmacological properties may be derived. So far, modifications of the isatin ring have proven highly effective with improved potency and lesser toxicity. The present review highlights the recently synthesized isatins possessing anti-HIV activities.

![Fig.1 Isatin]

**Some common routes to synthesis of substituted isatin derivatives**

**The Sandmeyer isatin synthesis**

The method developed by Sandmeyer is the oldest and the most frequently used for the synthesis of isatin. It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75%
overall yield. The method applies well to anilines with electron-withdrawing substituents, such as 2-fluoroaniline, and to some heterocyclic amines, such as 2-aminophenoxathine.

I) Synthesis of Substituted isonitroso acetanilide from substituted aniline

\[
\begin{align*}
&\text{P-Substituted aniline} &\text{Substituted isonitrosoacetanilide} \\
&\begin{array}{c}
R \quad \text{NH}_2 \\
\text{Cl}_3\text{CH(OH)}_2 \\
\text{NH}_2\text{OH.HCl}
\end{array} &
\begin{array}{c}
R \quad \text{NOH} \\
\text{N} \\
\text{O}
\end{array}
\end{align*}
\]

Where R= H, Cl, F, Br, CH\textsubscript{3}.

II) Synthesis of 5-substituted isatin from substituted isonitrosoacetanilide

\[
\begin{align*}
&\text{Substituted isatin.} \\
&\begin{array}{c}
R \quad \text{N} \\
\text{O}
\end{array} &
\begin{array}{c}
\text{R} \quad \text{NOH} \\
\text{H}_2\text{SO}_4
\end{array}
\end{align*}
\]

Where R= H, Cl, F, Br, CH\textsubscript{3}.

Review on Anti-HIV Activity of Isatin:
Teitz et al.\textsuperscript{[3]} had been reported that N-methylisatin-\(\beta\)-4',4'-diethyl thiosemicarbazone and N-allyl-\(\beta\)-4',4''-diallyl thiosemicarbazone have shown inhibition of HIV by their action on reverse transcriptase and viral structural proteins.

\[
\begin{align*}
&\begin{array}{c}
\text{N} \\
\text{N} \\
\text{H}
\end{array} &
\begin{array}{c}
\text{S} \\
\text{C}_2\text{H}_5 \\
\text{C}_2\text{H}_5
\end{array} \\
\text{CH}_3 \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]

Pandeya S.N.et al.\textsuperscript{[4]} have been reported isatin as antibacterial, antiungal and anti-HIV. Investigations of antimicrobial activity of compounds were done by an agar dilution method against 26 pathogenic bacteria, 8 pathogenic fungi and anti-HIV activity against replication of HIV in MT-4 cells.
Sriram et al.\textsuperscript{[5]} designed, synthesized and evaluated novel amino-pyrimidinimino-isatin derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors. Compound presented below found as the most potent broad-spectrum agent active against HIV, HCV, \textit{Mycobacterium tuberculosis} and various pathogenic bacteria.

Bal et al.\textsuperscript{[6]} synthesized and evaluated anti-HIV activity of isatin β-thiosemicarbazone derivatives. On the basis of pharmacophoric modelling studies a series of isatin β-thiosemicarbazone derivative was synthesized and evaluated for their anti-HIV activity in HTLV-III\textsubscript{B} strain in the CEM cell line. The synthesized compounds have shown significant anti-HIV activity.

\begin{align*}
R_1 & = \text{H, -CH}_3 \\
R_2 & = \text{H}
\end{align*}
Ghosh et al.\textsuperscript{[7]} designed and synthesized a series of novel HIV-1 protease inhibitors incorporating oxyindoles as the P’2-ligands. The effects of substituents, spirocyclic rings, and ring sizes have been investigated. A number of inhibitors exhibited low nanomolar inhibitory potencies against HIV protease.

Kumari et al.\textsuperscript{[8]} carried out Rhodium (II) acetate-catalyzed stereoselective synthesis, SAR and anti-HIV activity of novel oxindoles bearing cyclopropane ring. The trans isomers interacted well with HIV-1 RT through H-bonding with amino acids, like Lys101, Lys103, His235, Tyr318, constituting the non-nucleoside inhibitor binding pocket (NNIBP) during docking experiments. However, the compounds showed very little activity when subjected to \textit{in vitro} anti-HIV-1 screening using β-galactosidase assay.

Kang et al.\textsuperscript{[9]} have designed a series of Isatin-β-thiosemicarbazone as potent herpes simplex virus inhibitors type-1 (HSV-1) and type-2 (HSV-2) in a plaque reduction assay. Their cytotoxicity was examined using human rhabdomyosarcoma cells (RD cells). Several derivatives of isatin-β-thiosemicarbazone exhibited significant and selective antiviral activity with low cytotoxicity. It was found that the thiourea group at thiosemicarbazone and the NH functionality at isatin were essential for their antiherpetic activity.

P. Selvam et al.\textsuperscript{[10]} studied design, Synthesis and anti-HIV activity of Novel Isatine-Sulphonamides and the compounds were tested for anti-HIV activity against the replication of HIV-1 (III\textsubscript{B}) in MT-4 cells.
Aliasghar et al.\textsuperscript{[12]} have reported bis-Schiff base of isatin as antibacterial, antifungal, and antiviral activity.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) \centering{\includegraphics[width=0.8\textwidth]{isatin_diagram.png}};
\end{tikzpicture}
\end{center}

Where, $X=\text{CH}_2\text{-O-}, \text{-C=O}$

$R_1=\text{H, Bn}$

$R_2=\text{H, F}$

**CONCLUSION**

Development of resistance to existing drugs is a constantly growing phenomenon that has concerned researchers throughout the world, and now has reached alarming levels for HIV. This combined with the recent decline in the development of new drugs to combat them can be anticipated to lead to infectious diseases lacking ready treatment regimens. New drugs for anti-HIV are heavily needed. Unfortunately, there are few new drugs in the pipeline, making it un-likely that new compounds available to respond to the pressing need. Isatin is a flexible lead molecule for potential bioactive agents. and its derivatives were reported to possess potent anti-HIV activity. In the mean time no isatin derivative clinically used in anti-HIV therapy, however, research hopefully continue to shed light on ways to increase the therapeutic efficacy and specificity of isatins. As we understand more about its function and sites of action we may be able to develop new pharmacological agents to mimic or counteract its activity.
REFERENCES


