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Short Communication

Evaluation of anti-HIV activity of 5-(2-phenyl-3′-indolal)-2-thiohydantoin

Sibel Suzen, Erdem Buyukbingol *

Department of Pharmaceutical Chemistry, Faculty of Pharmacy (ECZACILIK), Ankara University, Tandogan, 06100 Ankara, Turkey

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Abstract

The anti-HIV activity of the previously synthesized 5-(2-phenyl-3′-indolal)-2-thiohydantoin **I** was evaluated. The compound, containing two structural moieties found in highly active anti-HIV agents, exhibited poor activity and rather high cytotoxicity.

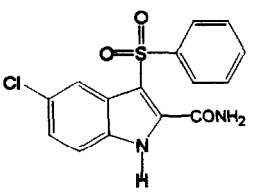
Keywords: Anti-HIV activity; Indole; Thiohydantoin

1. Introduction

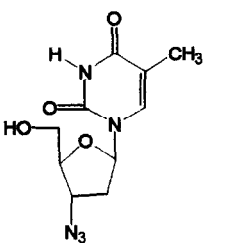
Development of effective pharmaceuticals for immunodeficiency syndrome (AIDS) is of high priority. One of the first reverse transcriptase (RT) inhibitors to emerge in AIDS treatment was 3′-azido-3′-deoxythymidine (AZT) [1], a synthetic nucleoside analogue of thymidine. Intracellular phosphorylation of this compound leads to triphosphate nucleosides which then act as RT substrates to terminate chain reactions [2].

Although AZT is effectively used in HIV-related infections [3], its clinical effectiveness has been limited by serious side effects [4–6] and the appearance of AZT-resistant strains of HIV [7]. The clinical efficacy of AZT [1,8,9] for the treatment of HIV has stimulated the design and evaluation of structurally related compounds. Thus, identification and development of novel nucleoside and non-nucleoside HIV-selective compounds are required to further elucidate the molecular mechanism underlying HIV-inhibitory activity as well as to identify novel compounds having potential for an improved therapeutic index.

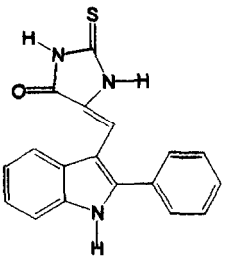
The non-nucleoside analogue compounds have chemical structures greatly different from those of nucleoside analogues [10]. The non-nucleoside inhibitors (NNIs) of HIV-1 reverse transcriptase have also been studied extensively in the laboratory and clinic as antiviral agents for the treatment of AIDS [11]. Williams and co-workers identified 5-chloro-3-(phenylsulfonyl)-indole-2-carboxamide (L-737,126) as a potent NNI of wild type HIV RT with activity against certain RTs from clinically relevant resistant mutant viruses [12]. Low nanomolar concentrations of L-737,126 inhibit the HIV-1 RT enzyme in vitro. Modification of the non-nucleoside inhibitor of HIV-1 RT nevirapine (Vira mune) by incorporation of a 2-indolyl substitutent conferred activity against



L-737,126



AZT



Compound I

* Corresponding author. Fax: +90 312 222 6543; e-mail: erdem@pharmacy.ankara.edu.tr

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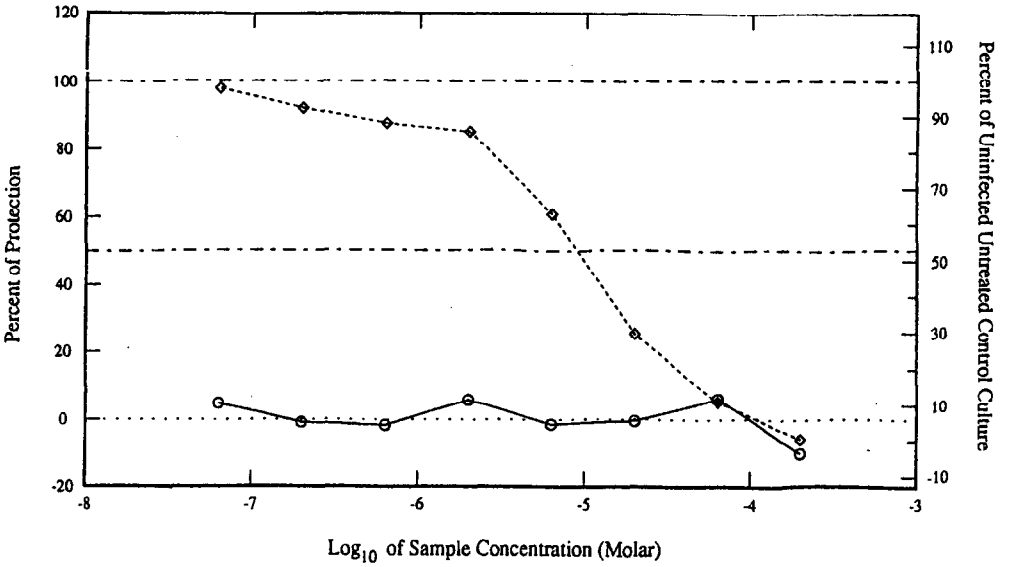

Fig. 1. In vitro anti-HIV screening result of compound I: – · · –, 100% and 50% reference lines; · · ·, viral cytopathic effect; – O –, infected treated culture; - ◇ -, uninfected treated culture.

several mutant forms of the enzyme [13]. On the other hand, the hydantoin ring (2,4-imidazolidinedione) as the nucleobase related to the thymidine part of AZT was reported as an alternative for inhibitor design for the improvement of the inhibitors with respect to development of new RT inhibitors [14]. On the basis of that concept, in this study the anti-HIV activity of the previously synthesized [15] indolalhydantoin derivative **I** was evaluated.

2. Experimental

The procedure [16] used in the National Cancer Institute's test for agents active against HIV is designed to detect agents acting at any stage of the virus reproductive cycle. The assay basically involves the killing of T4 lymphocytes by HIV. Small amounts of HIV are added to cells, and two cycles of virus reproduction are necessary to obtain the required cell killing. Agents that interact with virions, cells, or virus gene-products to interfere with viral activities will protect a cell from cytolysis. Compounds that degenerate or are rapidly metabolized in the culture conditions may not show activity in this screen. All tests were compared with at least one positive (e.g. AZT-treated) control done at the same time under identical conditions. Compound **I** was dissolved in dimethyl sulfoxide, then suitably diluted in cell culture medium. T4 lymphocytes were added and after a brief interval HIV-1 was added. Cultures were incubated at 37°C in a 5% carbon dioxide atmosphere for 6 days. The tetrazolium salt XTT was added to all wells. Individual wells were analysed spectrophotometrically to quantitate formazan production, and in addition were viewed microscopically to detect viable cells and confirm protective activity. Drug-treated virus-infected cells were compared with drug-treated non-infected cells and with other appropriate controls on the same plate.

Table 1
Activity against HIV-1 and growth inhibitory properties of 5-(2-phenyl-3′-indolal)-2-thiohydantoin

Dose (M)	Percent of protection	Percent of control	
		Infected	Uninfected
6.35×10^{-8}	4.83	10.54	97.91
2.00×10^{-7}	−0.95	5.11	92.42
6.34×10^{-7}	−1.74	4.36	88.12
2.00×10^{-6}	5.81	11.46	85.86
6.33×10^{-6}	−1.52	4.57	63.05
2.00×10^{-5}	−0.54	5.49	29.48
6.32×10^{-4}	6.27	11.89	10.97
2.00×10^{-4}	−9.99	−3.39	0.54

Data were reviewed in comparison with other tests done at the same time and a determination about activity was made. The results of testing are shown in Fig. 1 and Table 1.

3. Results and discussion

Herein we report the results of the anti-HIV assay of 5-(2-phenyl-3′-indolal)-2-thiohydantoin which contains two structural moieties that can be found in highly active anti-HIV agents such as AZT and L-737,126. This compound was first synthesized for the investigation of its aldose reductase inhibitor activity [15]. It should be noted (Table 1) that compound **I** was very poorly active and exhibited a rather strong cytotoxicity. Despite this result the compound still shows prospects of producing novel indolalhydantoin derivatives with more promising activity against HIV. On the other hand, the observed cytotoxicity could be pursued in order to obtain anti-proliferative agents. Therefore, for both reasons the synthesis of suitably substituted derivatives is in progress.

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