

Human Immunodeficiency Virus-Reverse Transcriptase and Hepatitis C Virus RNA-Dependent RNA Polymerase Inhibition Activities of Fullerene Derivatives

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Introduction

Human immunodeficiency virus (HIV) infection is one of the major causes of morbidity and mortality in the world. There are two major targets for anti-HIV agent, *i.e.*; HIV-protease and HIV-reverse transcriptase (HIV-RT). Molecular modeling studies revealed that C₆₀-core could be fit to the hydrophobic substrate-binding site of HIV-protease. Indeed, some fullerene derivatives inhibited HIV-protease.¹

Hepatitis C virus (HCV) is the major etiological virus of non-A and non-B hepatitis. An estimated 2-3% of the world population is chronically infected with HCV. HCV infection causes severe liver disease and can lead to the development of hepatocellular carcinoma.

Both HIV and HCV are RNA virus and have similar enzymes. For example, HIV-RT and HCV RNA-dependent RNA polymerase (HCV-RP) are RNA-dependent polymerase, which are essential for the virus replication.

The biological effects of fullerene and its derivatives are of interest. We intend to develop fullerene derivatives as a new type of lead compound to be used as medicine and have reported that the anionic fullerene derivatives show interesting antioxidant activities² and the cationic derivatives, alkylated C₆₀-bis(*N,N*-dimethylpyrrolidinium iodide), have excellent anti-bacterial and antiproliferative activities.³

In this report, we studied the HIV-RT and HCV-RP inhibition activities of anionic (**1**), cationic (**2-4**), and amino acid types (**5**) of fullerene derivatives (Fig. 1).

Experiments

We previously reported the preparation of fullerene derivatives, **1** to **5**.⁴ HIV-RT and HCV-RP inhibition activities were examined according to Dhanak *et al.*⁵ and Choo *et al.*⁶ respectively.

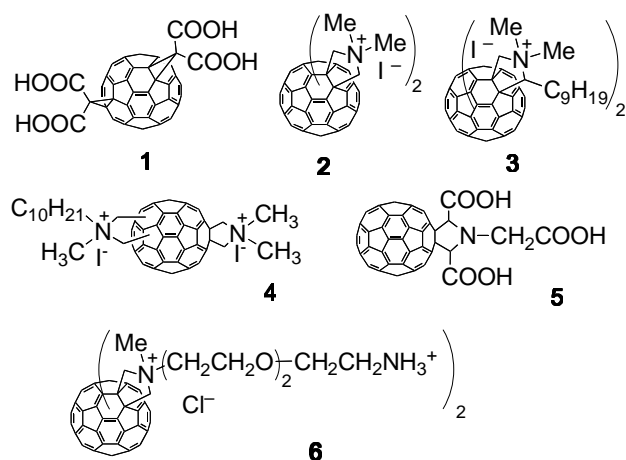


Fig. 1 Structure of fullerene derivatives

Results and Discussion

HIV-RT inhibition

HIV-RT inhibition activity of fullerene derivatives is listed in Table 1. All examined fullerene derivatives were effective than non-nucleoside analog of HIV-RT inhibitor, nevirapine (IC₅₀ 23 μM).⁶ Especially, the amino acid type fullerene derivative, **5**, strongly inhibited HIV-RT.

Recently, Bosi *et al.* reported anti-HIV activity of fullerene derivatives, **6** (Fig. 1).⁷ They speculated that the mechanism is HIV-polymerase inhibition without experimental evidence. Our HIV-RT inhibition result serves another possible mechanism of the anti-HIV activity.

Table 1 HIV-RT inhibition activity of fullerene derivatives

Fullerene	1	2	3	4	5
IC ₅₀ (μM)	1.2	1.0	0.5	8.9	0.029

HCV-RP inhibition

Among examined fullerene derivatives, cationic derivatives were effective than others and an addition of long alkyl chain into fullerene derivative depressed the activity (Table 2). The HCV-RP inhibition effect of the three regio isomers, 2(t-2), 2(t-3), and 2(t-4) was not significantly different. These findings indicate that it is not necessary to separate the regio isomers to study HCV-RP inhibition activities.

Table 2 HCV-RP inhibition activity of fullerene derivatives

Fullerene	1	2(t-2)	2(t-3)	2(t-4)	3	4	5
IC ₅₀ (μM)	3.0	0.27	0.31	0.34	1.6	1.8	2.0

We are now investigating the mechanism of enzymes inhibition.

In conclusion, the data obtained from this study indicate that the fullerene derivatives are new and effective lead compound for anti-HIV and anti-HCV agents.

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