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Design of boronic acid-attributed carbon dots on inhibits HIV-1 entry

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The development of gp120 targeted human immunodeficiency virus (HIV) drug has improved antiretroviral therapies owing to its effects on attachment to target cells. Some currently available antiretroviral therapies that act by inhibiting viral infection still have limited on the toxicity issues; therefore, novel approaches to treat and prevent HIV infections are still needed. Here, we introduce carbon dot nanoparticles as a new strategy for preventing HIV-1 infection via interaction with gp120 and subsequent elimination of target cell interaction. Carbon dots (diameter: ~2 nm) exhibiting a graphene-like structure were prepared by pyrolysis of citric acid and further associated with boronic acid-containing molecules. Specific peaks on Fourier transform infrared spectroscopy and X-ray photoelectron spectroscopy indicated successful modification of the carbon dots by boronic acid. The lower cytotoxic effects of this carbon-based material were evaluated using WST-1 assays. The existence of boronic acid moieties on the edge of carbon dots enhanced the inhibitory activity by suppressing syncytium formation. These findings provide a basis for further studies of carbon dot-based applications in HIV prevention and therapy.

Introduction

Human immunodeficiency virus (HIV) is a widely investigated virus that remains a serious challenge for the pharmaceutical, medical, and biotechnological fields owing to its association with high mortality rates.[1, 2] In recent decades, considerable efforts have been made in an attempt to develop medicines and vaccines to minimize the harmful effects of HIV infection. Notably, several therapeutic strategies, including combination antiretroviral therapy (cART) and highly active antiretroviral therapy (HAART), have been developed to prevent further spread of HIV.[3-5] However, despite improvements in antiviral therapy, on the common cases, the disease has not yet been completely controlled.[6]

Rapid interactions with the current host and spread to new hosts are major concerns associated with the handling of HIV.[7] Moreover, others major challenges, such drug resistance, toxicity, poor access to reservoirs, complicating side effects of multidrug treatment, the limited role of the drug in HIV prevention, have restricted the development of innovative approaches to the treatment of HIV infection.[8, 9] Nonspecific interactions and suboptimal efficacy have also led to the failure of several antiviral drugs during clinical trials.[10, 11] Thus, novel approaches are needed to treat and study HIV.

The viral infection cycle encompasses several important steps; the initial step of HIV infection is binding of the gp120 receptor on the viral envelope to a surface protein on the target cell. This receptor is heavily glycosylated, containing complex-type oligosaccharides and high mannose-type structures. Therefore, researchers have focused on the development of antiviral drugs based on the concept of gp120-targeted entry inhibition by presenting particular molecules as gp120-binding agents.[12-15] For example, the boronic acid moieties, where may selectively and reversibly react with either 1,2- or 1,3-cis diols to produce a boronate diester complex such as those on gp120 and saccharides, has emphasized the applicability of boronic acid materials as antiretroviral agents that may effectively inactivate HIV infections. Some studies in the field of medicinal chemistry have demonstrated that boronic acid as a crucial part on carbohydrate-based sensors and catalysis of reactions involving carbohydrate derivatives owing to the strong affinity of boronic acid for carbohydrates,[16-18] and this may apply in prevention or treatment of HIV infection.

Antiviral drugs have generally been designed to specifically target either viral protein or cellular protein, and a major aim of antiviral drug discovery is minimizing problems with drug administration. In order to fulfil this need, many studies have begun focusing on the use of nanoparticles.[19, 20] Utilization of drug-conjugated nanoparticles has been informed to be more

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favorable than directly active drug owing to the attraction of the drug to the target due to the presence of multiple active sites on the nanoparticle.[21, 22] To date, many types of nanoparticles have been developed for use as drug delivering agents for HIV therapeutics based on noble metals,[23-25] polymers,[26-28] composite materials,[29-32] and lipids.[33, 34] However, these nanoparticles have shown limited effects due to inertness of the starting material, toxicity, colloidal stability, and complicated fabrication methods. Thus, utilization of carbon based nanoparticles, like carbon dots (Cdots), have received considerable attention as potential nanoparticles for drug delivery in clinical applications. Cdots on form graphene-like nanostructure has been shown to have promising good result in the fields of sensing, catalysts, bio-imaging, solar energy, optoelectronics, fluorescent ink, and drug delivery.[35-41] Moreover, Cdots also exhibit excellent photostability and tunable photoluminescence and are colloidally stable, cost effective, eco-friendly, nontoxic, biocompatible, chemically inert and, making them more reliable than conventional nanostructures.

To date, several studies have reported the use of carbon-based materials for HIV treatment.[42-45] Zhang et al. recently reported the potency of both graphene and graphene oxide, which induced conformational changes and aggregation of fragments of the viral R protein.[44] Unfortunately, the validation of Cdots potency to inhibit viral entry has not been improved as a therapeutic strategy for the treatment or prevention of HIV infections. Therefore, in this study, we report a method for the preparation of Cdots as an entry inhibitor to prevent HIV infection. Preparation of Cdots was carried out by pyrolysis of citric acid (CA) to produce a graphene-like structure with abundant of hydroxyl and carboxylate sites on the surface. These sites were then further modified with boronic acid by conjugating Cdots with carboxyl phenylboronic acid (CBBA) to block viral entry. These findings provide important information regarding the characteristics, toxicity, and inhibitory activity of Cdots for further clinical applications.

Experimental section

Materials

4-Dimethylaminopyrid (DMAP); 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC); 4-carboxy-3-chlorobenzeneboronic acid (CBBA, 97 %) were purchased from Sigma-Aldrich (Milwaukee, WI, USA). Sodium hydroxide and citric acid anhydrous (CA) were purchased from Showa Kako Corp. (Osaka, Japan). All chemicals were used directly without further purification.

Synthesis of Carbon dots (Cdots)

Cdots were prepared by following previous work with some modifications.[39] Experimentally, two hundreds mg of CA (200 mg) was calcined at 250 °C for 30 min. The process will produce the CA orange indicating carbonization process to form graphitic nanostructures or Cdots. Once cooled to room temperature, Cdots was added with NaOH solution (0.5 M) until the pH of the solution to be neutral. Then, the solution further dialyzed on membrane with a molecular-weight cut off (MWCO) of 1000 Da to narrows the size distribution of the Cdots and remove small molecules.

Preparation of CBBA-Attributed Cdots (CBBA-Cdots). In further attributing process, 10 mL of CBBA solution (0.3 mg/mL was added with 2.4 mg of DMAP under magnetic stirring until clearly dissolved and then added with 3.1 mg of EDC. After keep on the mixing process for 30 minutes, the solution was mixed 5 mL of Cdots and continuing with stirrer process for 24 h. The mixture was then passed on dialysis process for 24 h.

Cells

The Human acute T lymphoblastic leukemia cell lines (MT-4 and MOLT-4) were cultured in RPMI-1640 medium (GIBCO, USA) supplemented with 10% heat-inactivated fetal bovine serum (Sigma),1% Natrium bicarbonate, 100 U/mL penicillin G, and 100 µg/mL streptomycin (culture medium) and incubated for three days in CO_2 incubator. The Virus persistently infected on MT-4 cells (MT-4/HIV-1) which obtained from co-culture of HIV-1 infected peripheral blood mononuclear cell's (PBMCs) with uninfected PBMCs using stimulated phytohemagglutinin (PHA, 10 µg/mL). The co-culture is incubated in growth RPMI-1640 medium containing T cell growth factor cytokine, IL-2 for three days in CO_2 incubator. The virus stock was produced from supernatants of persistently infected MT-4 cells with the HIV-1 isolates from Surabaya, Indonesia.

Cytotoxicity assessment

Cell viability was quantified using the colorimetric WST-1 Cell Proliferation Reagent (Roche Applied Science, Switzerland). This assessment is based on a reduction of 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium sodium salt (WST-1) to a water-soluble formazan from living cells. In first step, the as-prepared Cdots and CBBA samples were dissolved in 1 mL of the RPMI-160 medium, then, added to MOLT-4 cells cultured in a 96 well plate with density of 2 x 10^5 cells/µL in 100 µL of sample dissolved medium. Teen µL of WST-1 reagents was subsequently added to each well and incubated for 24 h at 37 °C in CO_2 incubator. After the incubation, the viable cells were measured by the absorbance of each sample using a microplate reader at a wavelength of 450 nm. Cytotoxicity effect of Cdots and CBBA-Cdots were also evaluated on half of cytotoxic concentration (CC_{50}) analyzed with Origin software.

Antiviral assay (syncytia formation)

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Syncytia formation assay evaluated the antiviral activity of the as-prepared Cdots and CBBA samples. Here in, MT-4/HIV-1 cells and MOLT-4 cells were cultured in RPMI-1640 medium. The cells were cultured at 37 °C for 5 days. After the incubation, number of cells is further counted with hemocytometer. The MT4/HIV-1 cells (2 x 10^4 cells/µL) and MOLT-4 cells (4 x 10^5 cells/µL) were suspended in culture medium and placed in 96 well plates. Samples (Cdots or CBBA-Cdots) at specific concentrations were firstly mixed with MT4/HIV-1 cells and incubated for 30 minutes in a CO_2 incubator. The mixed sample was subsequently added with 4 × 10^5 cells/µL following incubation at 37 °C for 24 h in CO_2 incubator and using mixed of sample on cultured MOLT-4 as negative control (NC). After incubation, amount of produced syncytia were microscopically counted. The data were furnished in the percent of inhibition compared with negative control by below equation.

$$\% \text{ Inhibition} = \left[100 - \left(\frac{\text{NC} - \text{Syncytia on sample}}{\text{NC}}\right)\right] \text{ x } 100\ \%$$

Inhibiting activity was also evaluated on half concentration of inhibition (IC_{50}) value counted by Origin software.

Statistical Analysis

The statistical analysis, including Cytotoxic Concentration decreasing 50 % of cell viability (CC_{50}) and Inhibition Concentration inducing 50 % of cell viability were carried out using dose response mode on non-linear fitting curve of Origin®software (version 8.0724, OriginLab Inc., Northampton, MA). All data were performed in triplicate with comparison of mean using a Paired-Sample t-test.

Other characterizations

Physicochemical analysis obtaining dynamic light scattering (DLS) and zeta potential (ζ) were collected using Zetasizer Nanoseries 3000 HS of Malvern instrument. Transmission electron microscopy (TEM) images of samples were prepared by layering Cdots solution onto copper grids (200-mesh) coated with a thin Formvar-carbon film and removing the solvent by drying at room temperature. High-resolution of TEM image (HR-TEM) was got using a Tecnai G2 F20 instrument (Philips, Holland). X-ray diffraction (XRD) patterns were prepared using a Rigaku 18 kW rotating anode source X-ray diffractometer with the Cu Ka1 line (l = 1.54 Å). Atomic Force Microscopy (AFM) images was resulted using an scanning probe SPM-9600 (Shimadzu Co., Japan) at ambient temperature, X-ray photoelectron (XPS) spectra were obtained using VG ESCA scientific theta probe spectrometer equipped with an Al Kα (1486.6 eV) X-ray source and pass energy of 28 eV. Fourier transform infrared (FTIR) spectra was performed using by FTIR spectroscopy (Shimadzu, Japan).

Results and Discussion

Structural and morphological characterization of Cdots.

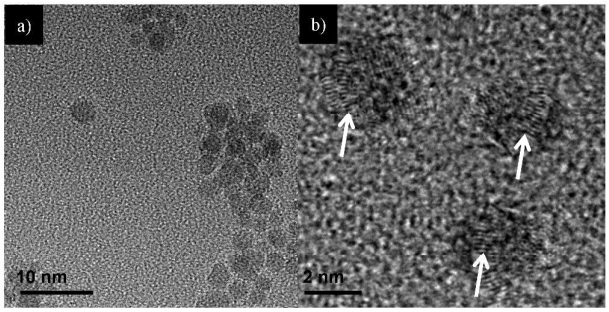

Figure 1. TEM image of as-prepared Cdots (a) and its high magnification image performed with high-resolution TEM (b). White arrays show lattice finger of graphene like structure on Cdots.

The morphologies and particle sizes of Cdots were firstly investigated by electron microscopy. The TEM images shown in Figure 1a demonstrated that Cdots were nearly spherical, with particle sizes of less than 5 nm. These data were further confirmed by atomic force microscopy (AFM; (Figure S1 in the Supporting Information). A histogram of the AFM data showed that Cdots were typically about 2 nm in size. Moreover, HR-TEM analysis (Figure 1b) showed that the Cdots exhibited a lattice finger structure, indicating the presence of carbon crystals surrounding the amorphous phase. Further physicochemical analysis (Tabel 1) using DLS also showed that

Table 1. Physicochemical properties of prepared nanoparticles*

Type	Hydrodynamic Diameter (nm)	Polydispersity Index	ζ (mV)
Cdots	2.8 ± 1.1	1.4 ± 0.08	-55.4 ± 8.2
CBBA-Cdots	6.2 ± 0.8	0.9 ± 0.02	-90.9 ± 7.01

* each data presented as mean ± SD (n=3).

the hydrodynamic diameter of Cdots was 2.8 nm, similar to the data obtained from AFM.

During the synthesis of Cdots, the pyrolysis of CA induces carbonization, producing a crystal phase in the form of the observed graphene-like structure. Further high-magnification HR-TEM images allowed us to determine the distance between the carbon atoms in the lattice (0.34 nm). Moreover, XRD analysis (Figure 2a) showed that the diffractogram pattern of Cdots had a broad peak at 2θ (range: 20–30°), confirming the graphitic structure based on JCPDS26-1076, with d-spacing at a higher intensity (006) of 0.335 nm. This result was consistent with the above HR-TEM images and also similar to the results of some previous studies on indentifying the crystal structure of Cdots.[37, 46, 47] This findings were further supported by Raman measurements (Figure 2b), where the G-band peak significantly appeared at 1582 cm^{-1}, representing the formation of sp_2-hybridized carbon atoms.. Moreover, a D-band peak was also recorded at 1332 cm^{-1}, associated with vibration of the sp^3-hybridized carbon as atoms at the edge of

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the crystal. This peak supported that the Cdots formed a crystal graphene-like structure. The higher intensity D-band indicated the formation of bonds at the edge, yielding the amorphous phase, or bonds at the terminal end of the carbon plane, which would contribute to the water solubility of the Cdots.

Surface modification of Cdots

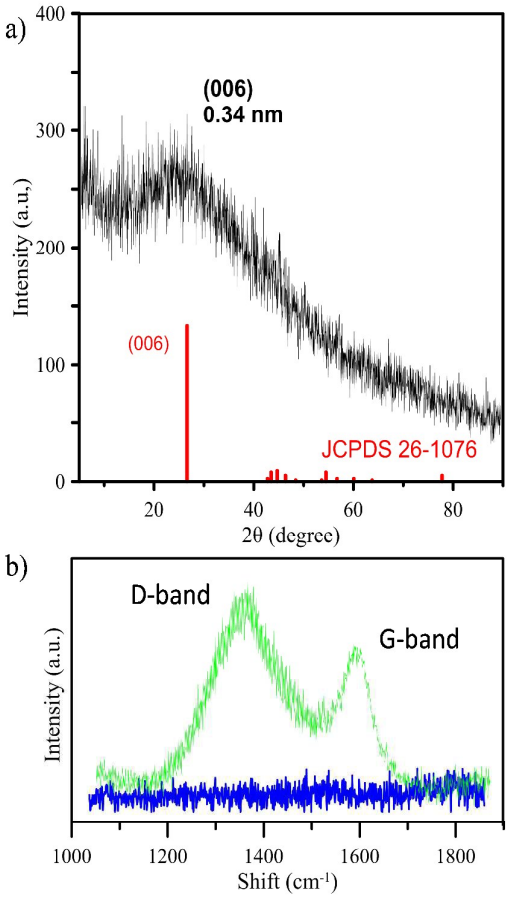
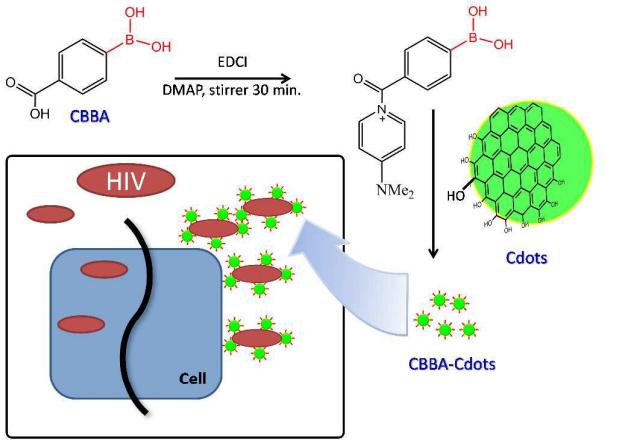


Figure 2. (a) Diffractogram pattern of Cdots. (b) its Raman spectra of Cdots (green line) and citric acid (yellow line).

Based on the results of previous studies, boronic acid containing-material has positive effects on the selectivity of glycopeptides and on glycoprotein enrichment. Therefore, introducing CBBA onto Cdots is critical and guarantees a specific interaction between Cdots and HIV, which is covered abundantly by glycoprotein. As illustrated in Scheme 1, introducing CBBA onto Cdots was accelerated via the EDCI/DMAP reagents, which activated the carboxylate moiety of CBBA before reacting specifically with the hydroxyl sites presented on Cdots.

The obtained CBBA-Cdots were then investigated further using X-ray photoelectron spectroscopy (XPS; Figure 3a–d), which revealed the existence of atoms, namely carbon (around 286 eV), oxygen (around 531 eV), and boron (around 193 eV). Deconvolution of high-resolution C1 XPS spectra yielded peaks at 285.4 (i) and 286.5 eV (ii), which indicated C-C/C=C (graphite) and C-O species, respectively, on Cdots. The carbon spectrum also showed a peak at 288.2 eV (iii) for -C=O (ester) on boronic acid-conjugated Cdots.[48] Further deconvolution of O1 XPS spectra yielded peaks at 531.3 (iv), 532.7 (v), and 533 eV (vi), assigned to H-O, C-O, and B-O on CBBA-Cdots,



Scheme 1. Schematic illustration of conjugating CBBA onto Cdots and further mechanism on inhibition entry.

respectively.[49-51] Moreover, the appearing a peak on 193.7 eV for B-O species strongly indicates successfully conjugation of CBBA onto Cdots.[52] Moreover, the appearance of a peak at 193.3 eV for the B-O species strongly indicated successful conjugation of CBBA onto Cdots.[53] Functional group analyses using Fourier transform infrared (FTIR) spectroscopy were carried out to further support our characterization of CBBA-Cdots. When FTIR spectra of CBBA-Cdots were compared with bare Cdots (Figure 3e), the presence of CBBA conjugated onto Cdots was demonstrated by specific peaks at 1572 (1), 1080 (2), 758 (3), and 680 cm^{-1} (4), which were assigned to the stretching vibrations of the B-OH, B-C, C-H, and C-C bonds of CBBA, respectively, consistent with previous studies.[53, 54] However, the FTIR data also yielded several peaks, including peaks at 3448.84 (5), 2852.81 (6), and 1414.93 (7), assigned to O-H, C-H, and C=O, respectively, for Cdots. Lastly, we obtained the zeta potential values for Cdots and CBBA Cdots from our physicochemical analysis (Table 1) to determine whether CBBA was successfully conjugated to Cdots. The existence of boronic acid sites from CBBA on the surface of nanoparticles was observed by the decrease in the zeta potential value to -90.9 eV.

Cytotoxicity assay

In order to evaluate the potential utility of CBBA-Cdots in biological applications, we assessed the toxicity of the obtained CBBA-Cdots in MOLT-4 human leukemia cells using WST-1 assays, as shown in Figure 4a. After 24 h incubation with both Cdots and CBBA-Cdots, MOLT-4 cells proliferated as

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rapidly as untreated cells (control), even the concentrations was raised up to 300 µg/mL. The figure also show that average percent cell viability at each concentration was greater than 80%, confirming the absence of cytotoxic effects for both Cdots and CBBA-Cdots in human cells. Further analysis on proving low toxicity of this nanomaterial was determined by CC_{50} values, where both Cdots and CBBA-Cdots perform high CC_{50} values on 2901.2 and 1991.9 µg/mL, respectively (Figure S2 in the Supporting Information). These high CC_{50} values supported that both Cdots and CBBA-Cdots could be applied safely under the conditions used in this study.

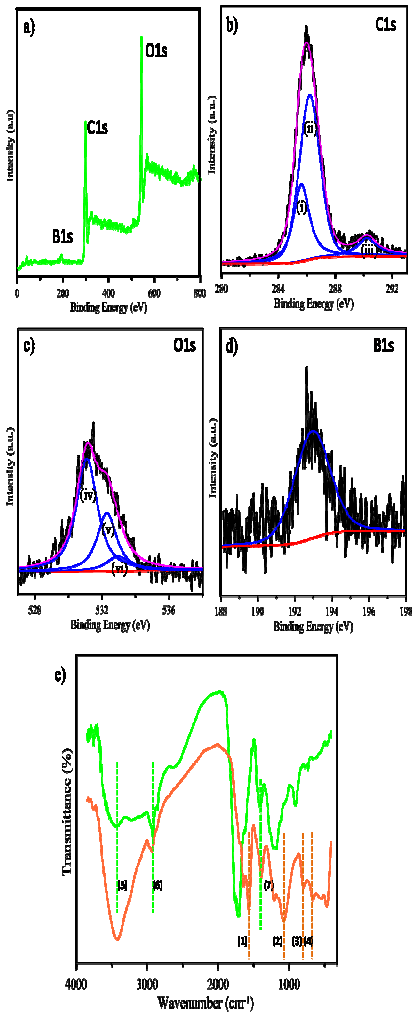

Figure 3. XPS spectrum of Cdots on (a) full scan range, (b) the C1s spectrum, (c) the O1s spectrum, and (d) the B1s spectrum. (e) FTIR spectra of Cdots (green line) and CBBA-Cdots (red line).

Evaluation of anti-HIV efficacy in vitro

During HIV-1 infection, HIV entry into target cells is initiated through binding of gp120 overexpressed on the virus with the surface receptor CD4 and the co-receptor CXCR4 or CCR5 on the cell surface. Insertion of the virus onto cell is affected by the viral protein, cell killing is induced by syncytium production. As a common condition, the spread of HIV can take on virus-to-cell and cell-to-cell pathways. Unlike the former pathway, transitions of the virus from the infected cell to the normal cell on directly contact was confirmed as more efficiently way via virological synapse process.[55, 56] However, both of the pathways includes a binding of gp120 to surface receptor of targeted cell

In this study, we examined the HIV inhibitory activity of Cdots and CBBA-Cdots by setting the infection on cell-to-cell way and counting the numbers of syncytia produced after a 24-h incubation of cultured MT4/HIV-1 and MOLT-4 cells with nanoparticles. Basically, syncytial formation is not equal to cell-to-cell pathway, but it represents the interaction between

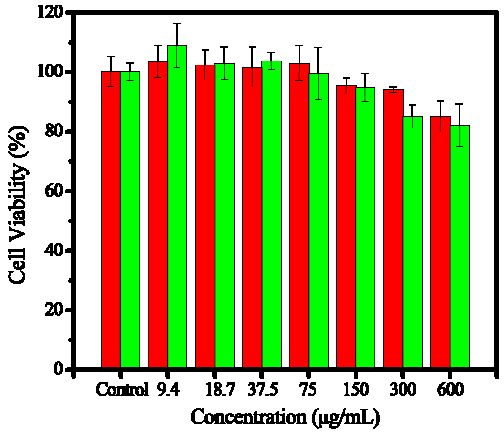

Figure 4. Cell viability evaluation using WST-1 assay of MOLT-4 cells after 24 h treatment with Cdots (red) and CBBA-Cdots (green) compared negative control. All data perform in the format mean ± SD (n=3).

gp120 and CD4/CXCR4 during the pathway. Therefore, syncytia formation assay is a useful method for the screening of inhibitors for viral cell-to-cell transmission. On the investigation, the Cdots were first incubated with MT4/HIV-1 cells to allow preliminary interaction with gp120 of the virus before addition of MOLT-4 cells. Observation by microscopy showed that incubation with Cdots (300 µg/mL) did not effectively prevent the formation of syncytia, similar to the results of the negative control (Figure a-d). In contrast, CBBA-Cdots efficiently bound to gp120 on the virus, thereby preventing the binding of MOLT-4 cells and blocking infection. Accordingly, when high concentrations of CBBA-Cdots were used, no syncytia were found on the cultured cells. Formation of tetravalent boronate diester cyclic complex from reaction between boronic acid site of CBBA-Cdots to 1,2-*cis* diols sites on Gp120 was predicted as responsible factor on this phenomena. We further analyzed the potency of Cdots on the inhibition of HIV infection by varying the concentrations of Cdots (Figure 5e). Conjugation of CBBA onto Cdots significantly increased the inhibitory capacity of Cdots at high concentrations (greater than 75 µg/mL), whereas the

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inhibitory effects were decreased at lower concentrations. However, Figure 4b also proves that Cdots, itself, performs ability on prevents HIV infection, even at low concentrations. This phenomena was caused by the existence of hydroxyl and carboxylate functional groups on the edges of Cdots that may facilitate the occurrence of non-covalent interactions, such hydrogen bonding, with molecules expressed on the viral envelope, including gp120, gp41, and transmembrane subunits, thus conferring Cdots with their observed inhibitory activity. This finding also confirm that increasing inhibitor ability was mainly caused by the existence of boronic acid site on CBBA-Cdots. Further improving inhibitor ability showed by the IC_{50} values, where both Cdots and CBBA-Cdots showed very different value, namely 9506.3 and 26.7 μg/mL, respectively (Figure S3 in the Supporting Information); thus, CBBA-Cdots had a significantly lower IC_{50} than Cdots (with probability value $p < 0.05$. These findings supported that the conjugated boronic acid functioned synergistically to prevent HIV infection.

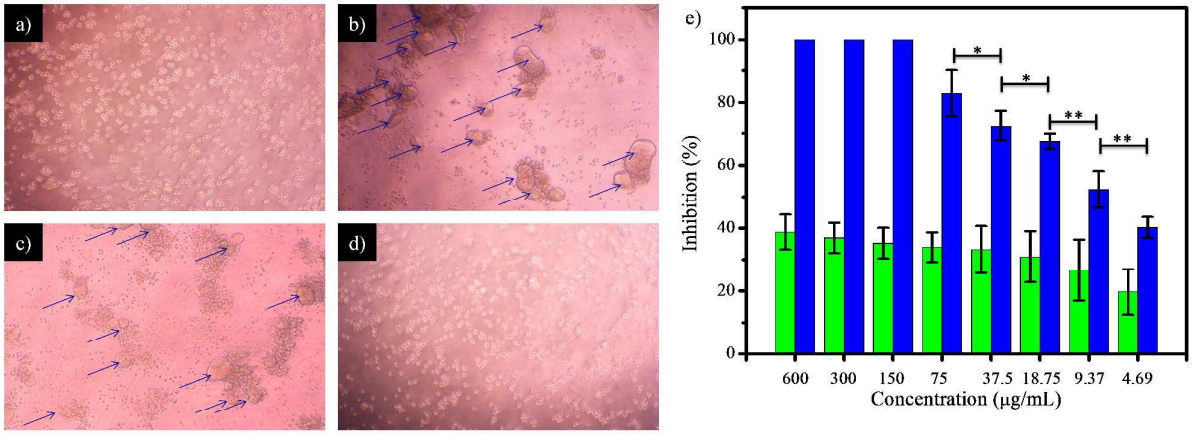

Figure 5. Microscopic images consisting mix of cultured MOLT-4 cell and Cdots as positive control (a); mix of cultured MOLT-4 cell and MT-4/HIV as negative control; mix of cultured MOLT-4 cell, MT-4/HIV, and 300 μg/mL of Cdots (c); mix of cultured MOLT-4 cell, MT-4/HIV, and 300 μg/mL of CBBA-Cdots(d). All data performs after 24 h incubation. Blue arrays indicate position of obtained syncytia. (e) Inhibition intensity 0f Cdots (green) and CBBA-Cdots (blue) against MT4/HIV-1 cells over 24 h incubation. All data perform in the format mean ± SD (n=3).*$p < 0.05$, **$p < 0.01$.

Conclusion

In this study, we investigated the antiviral effects of synthetic Cdots and CBBA-Cdots on HIV. Our findings showed that these synthetic nanoparticles, which formed graphene-like structures, inhibited HIV entry. In vitro analysis of the cytotoxicity of Cdots and CBBA-Cdots revealed that these nanoparticles could be safely applied, even at high concentration and after modification with CBBA. Furthermore, conjugation of Cdots with CBBA increased the inhibitory effects of the nanoparticles on HIV infection by preventing binding with the target cell. These data support the potential applications of Cdots and CBBA-Cdots in the clinical setting. The mechanism through which CBBA-Cdots prevent HIV infection may also be further developed to establish a dual-effect HIV drug for prevention and therapy by loading currently available HIV drugs onto the graphene scaffold of Cdots.

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Competing interests

The authors have declared that no competing interest exists.

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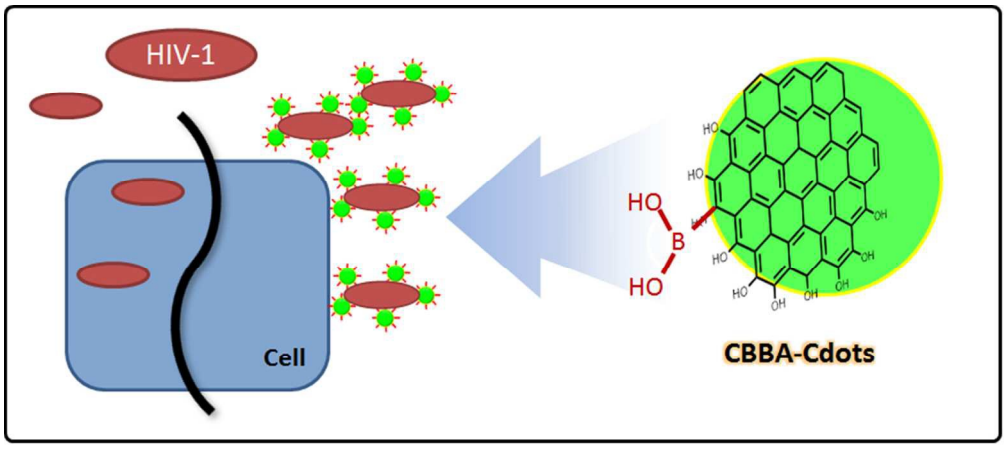

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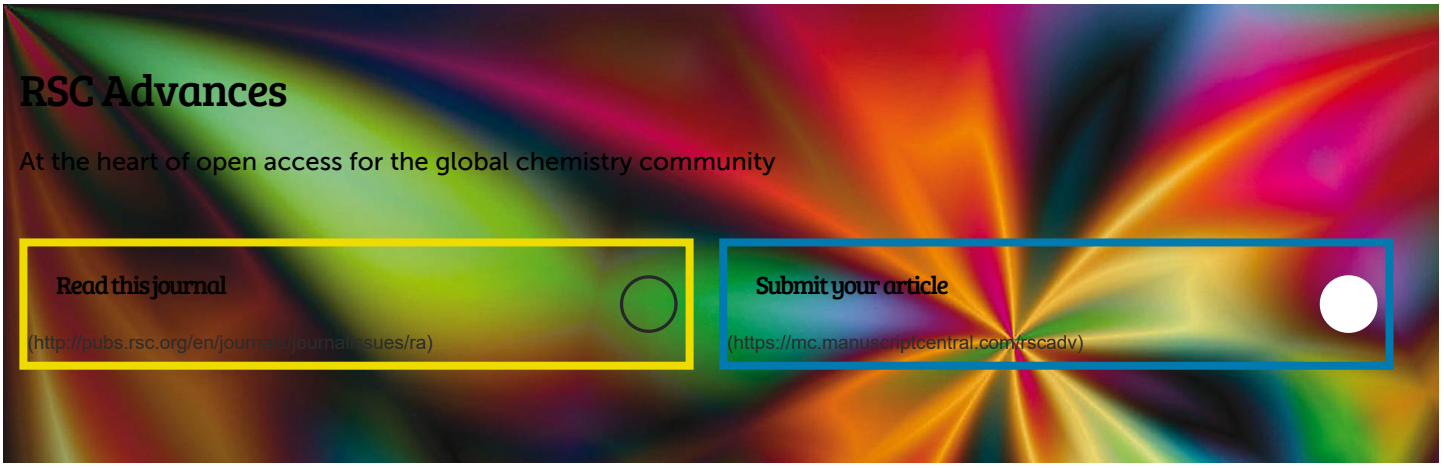

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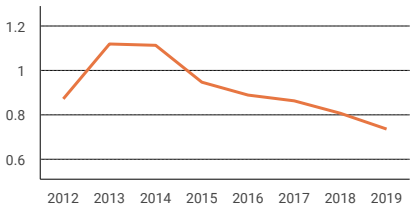

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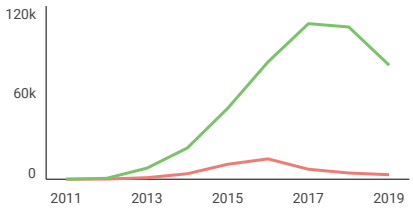

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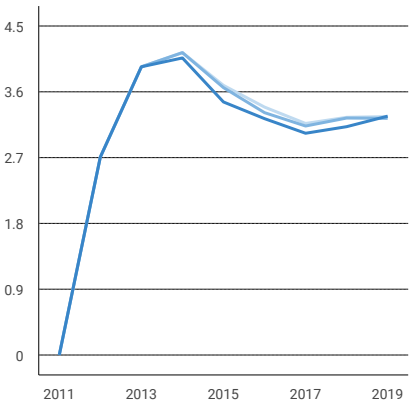

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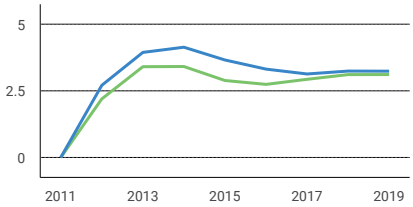

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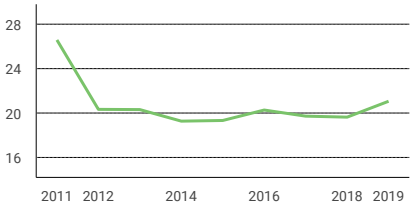

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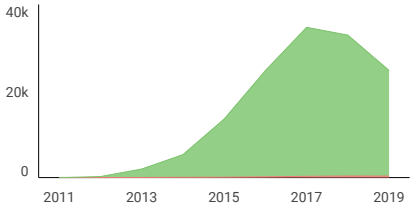

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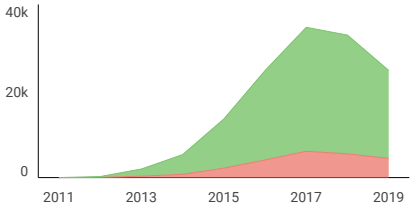

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