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BMS Derivatives C7-Linked to β-Cyclodextrin and Hyperbranched Polyglycerol Retain Activity against R5-HIV-1_{NLAD8} Isolates and Can Be Deemed Potential Microbicides

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Abstract: Amides from indole-3-glyoxylic acid and 4-benzoyl-2-methylpiperazine, which are related to entry inhibitors developed by Bristol-Myers Squibb (BMS), have been synthesized with aliphatic chains located at the C7 position of the indole ring. These spacers contain an azido group suitable for the well-known Cu(I)-catalyzed (3+2)-cycloaddition or an activated triple bond for the nucleophilic addition of thiols under physiological conditions. Reaction with polyols (β-cyclodextrin and hyperbranched polyglycerol) decorated with complementary click partners has afforded polyol–BMS-like conjugates that are not cytotoxic (TZM.bl cells) and retain the activity against R5-HIV-1_{NLAD8} isolates. Thus, potential vaginal microbicides based on entry inhibitors, which can be called of 4th generation, are reported here for the first time.

The term "microbicides" originally designated medicinal drugs targeting sexually transmitted diseases in general. With the advent of the AIDS pandemic, it is more commonly used for chemicals that can be applied topically to the vagina or rectum to kill, neutralize, or block HIV-1 as well as other viruses or pathogens, as a prophylactic treatment. Microbicides can be formulated as gels, creams, films, suppositories, tablets, or as slow-release sponges or vaginal rings,[1] which may or may not have spermicidal activity. HIV continues to spread, mainly in sub-Saharan Africa; every year around 380,000 young women are infected.[1] According to the WHO and the International Partnership for Microbicides (IPM), increased availability of microbicides would greatly empower women to protect themselves,[1b,c] as the consent or even knowledge of their sexual partner is not required.

First-generation microbicides, which were surfactants such as nonoxynol-9 and savvy gel (a betaine), and 2nd generation microbicides, such as carraguard (a natural sodium polysaccharidesulfate) and PRO2000 (a polynaphthalenesulfonate) were soon shown to be inefficient. Indeed, many were contraindicated as they produced vaginal irritation so virus entry was then enhanced. The addition of anti-HIV drugs, either entry inhibitors (ENIs), nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside RTIs (NNRTIs), integrase inhibitors (INIs), or protease inhibitors (PIs), to gels, creams, and rings was soon considered.[2] These so-called third-generation microbicides (Figure 1, first row) have proved more successful, but only a gel containing 1% of a tenofovir prodrug (a commercially available RTI taken orally as tenofovir disoproxil fumarate or as tenofovir alafenamide, which are usually mixed with other RTIs or with RTIs and INIs in a single pill) and a vaginal ring with dapivirine (a known NNRTI) have reached Phase III clinical trials.[2] Unfortunately, a very recent report indicates that this last approach reduces risk of transmission by only 29%, whereas the other microbicides mentioned "had no evident effect".[2a] Fortunately, research into dendrimers,[2e] electrospun fibers, probiotics, and mixtures of different types of anti-HIV drugs[1d] is in progress.

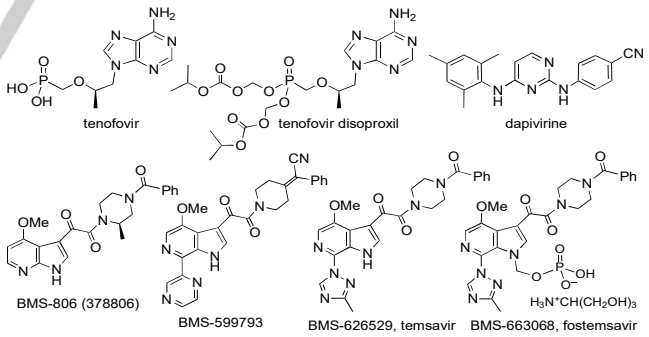


Figure 1. Molecular structures of RTIs used as microbicides (first row) and of representative entry inhibitors (ENIs, second row).

For two decades, Bristol-Myers Squibb has been investigating several indole-glyoxamides[3] as ENIs, mainly in the first of the three steps into which the entry process may be subdivided: virus attachment, coreceptor binding, and membrane fusion. Many of these glyoxamides (see Figure 1) were highly active, in the nM range, but posed pharmacokinetic or toxicity issues. However, very recently, fostemsavir,[4] a prodrug of temsavir, has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). BMS-599793, an IPM microbicide, deserves to be highlighted as well.[5]

In this context, a few years ago we started a project aimed at linking BMS derivatives to polyhydroxylic gels (**1**). The idea was that the resulting gels and creams may block HIV-1 at the initial stage of its life cycle and that the viruses would be bound to such an easily removable product. If 3 ± 1 BMS-type units could be anchored to each polymer molecule, the antiviral activity could be potentiated by simultaneous binding of the trimeric gp120.[6] Here we report on the syntheses and screenings of these "prototypes" of microbicides, which we call of fourth generation. We recognize that optimized inhibitors, such as the BMSs shown in Figure 1, could surpass the present "prototypes", if they too can be appropriately linked to standard vaginal gels, but here we aim to demonstrate proof-of-concept.

We started our work by preparing series of simple indole-glyoxamides, hoping to obtain structures of type **1** (Figure 2). We were aware of the SAR studies by BMS indicating that large substituents at N1, C4, C5, and C6 of the indole system were poorly tolerated,[3] and there are very recent computational and X-ray studies showing how BMS derivatives interact with the binding site(s) of gp120.[7] Cocrystal structures of trimeric HIV-1 envelope glycoprotein (Env) with BMS-806 and with BMS-529[7c] as well as with BMS-818251 and with BMS-814508[7d] indicated that the more appropriate point of attachment is C7.

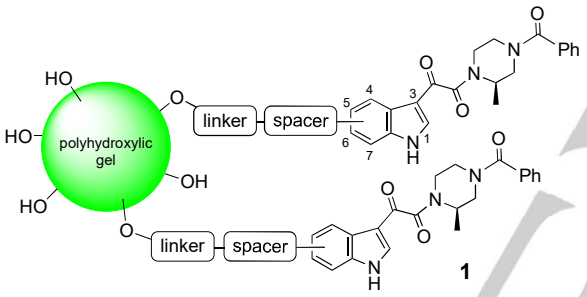
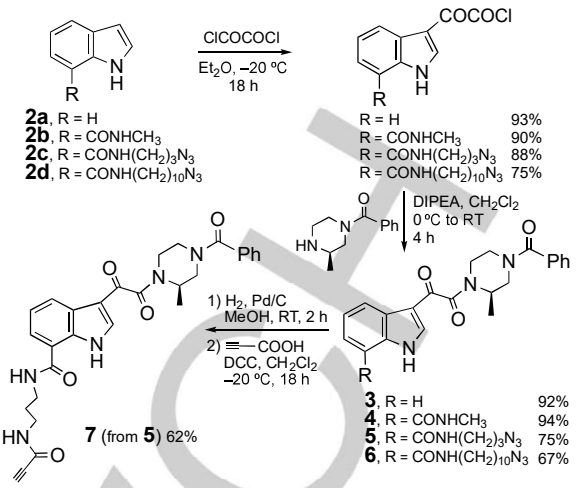


Figure 2. BMS-like derivatives conjugated to a polyol model.

From indole (**2a**) and indole-7-carboxamides **2b–d** we synthesized BMS analogues **3–6** shown in Scheme 1, by means of the known procedure for the integration of the piperazine moiety onto C3 of the indole ring.[3] Compounds **3**[3c,6,8] and **4**[9] were prepared to be used as additional reference samples in the tests. Compounds **5** and **6** have spacers of three and ten methylenes, respectively, and the terminal azido groups required for the linkage via an azide–alkyne cycloaddition.[10] We also prepared **7** from **5** by reduction of the azido group to amine, followed by its acylation with propynoic acid (propiolic acid). Compound **7** may not only be useful for a CuAAC reaction,[10] but also for the addition of N- or S-nucleophiles[11] to the conjugated triple bond.

The toxicity of these compounds was tested using TZM.bl cells and the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, indicating that none of them was cytotoxic at 1–100 μM concentrations in aqueous DMSO (1% v/v).

Also, as a preliminary work, the entry inhibition of **3–6** was examined with two types of HIV-1 stocks (see Figure 3), namely, the CCR5-tropic R5-HIV-1_{NLAD8} laboratory isolate obtained by transient transfection with the pNL(AD8) plasmid and the NL4-3 strain, an X4-monotropic laboratory isolate, by comparison with a known carbosilane-polysulfonate dendrimer (G2-S16, active as ENI in the nM range).[12] See Supporting Information. We applied



Scheme 1. Synthesis of **3–7**. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole, DIPEA = diisopropylethylamine, and DCC = dicyclohexylcarbodiimide..

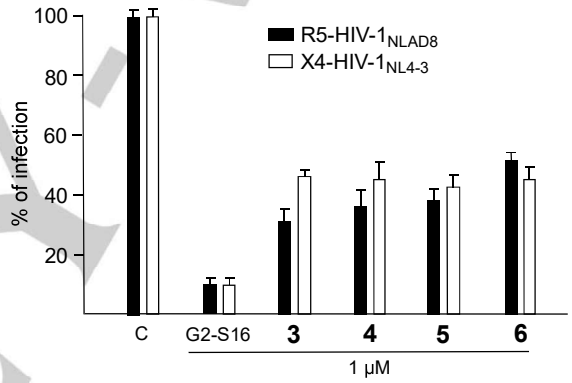


Figure 3. Percentage of infection after incubation at 37 °C of TZM.bl cells with 1 μM solutions of **3–6** for 1 h (in relation to non-treated cells, see C = control of infection) and then with R5 or X4 viruses for 3 h. The carbosilane-polysulfonate dendrimer G2-S16 (16 sulfonate groups), a known ENI,[12] was used as the reference.

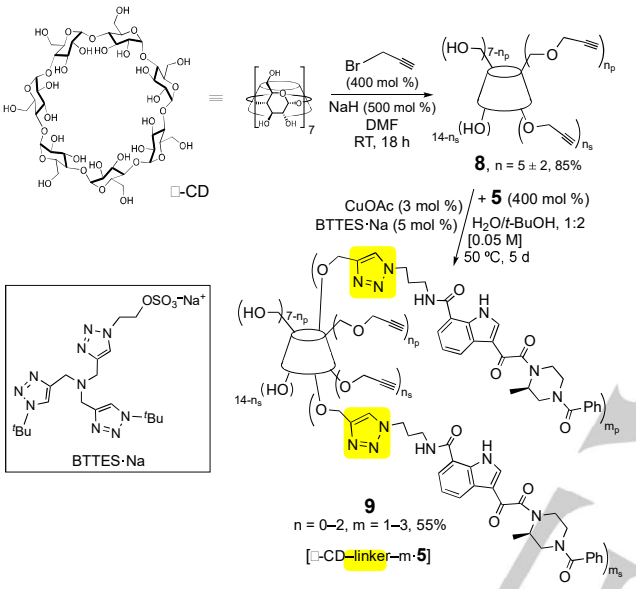
the luciferase activity assay to monitor infection of TZM.bl cells. Although the R5 virus infection (i.e., via interaction with CD4 and CCR5 coreceptors) is much more efficient[13] than the X4 virus infection (i.e., via interaction with CD4 and CXCR4 coreceptors), when enough sample was available, we often examined both strains for the sake of comparison.

It can be observed in Figure 3 that with **3–6** the percentages of infection, from three measurements for each compound at 1 μM in aqueous DMSO (1% v/v), were reduced to 40% as a mean value. The more active sample against R5 viruses appeared to be the C7-unsubstituted sample **3** (31 ± 6%), whereas the less active was **7**, the substrate with the longest-chain substituent at C7.

Although the antiviral activity of these simple BMS derivatives, under the indicated conditions, is lower than that of the BMS compounds highlighted in Figure 1, it seems it would suffice, in the future, to use temsavir analogs with appropriate spacers/pre-linkers to improve our results.

As a polyol model we chose β-cyclodextrin (β-CD). Its reaction with an excess of propargyl bromide (3-bromo-1-propyne) in NaH/DMF at rt, to produce a relatively homogeneous poly-propargylated mixture was systematically studied. Although the

polypropargylation of β-CD has been reported by using 2100 mol % of $BrCH_2C{\equiv}CH$ and NaH,[14] it was essential for us to maintain the hydrophilic nature of the samples. Thus, several experiments with 200–800 mol % of reagents were undertaken. As shown in Scheme 2, with 500 mol % of NaH and 400 mol % of propargyl bromide, the MALDI-TOF/TOF mass spectra indicated that the major product included five propargyl groups, followed by tetrasubstituted and hexasubstituted compounds. The yield of the final sample (**8**, 85%) and its homogeneity (5 ± 2 propargyl groups) were optimum under these conditions. It was not important to establish how many primary (of 7) and secondary (of 14) hydroxy groups did react: the point was and is to introduce a sufficient number of potential linkers into suitable polyols.



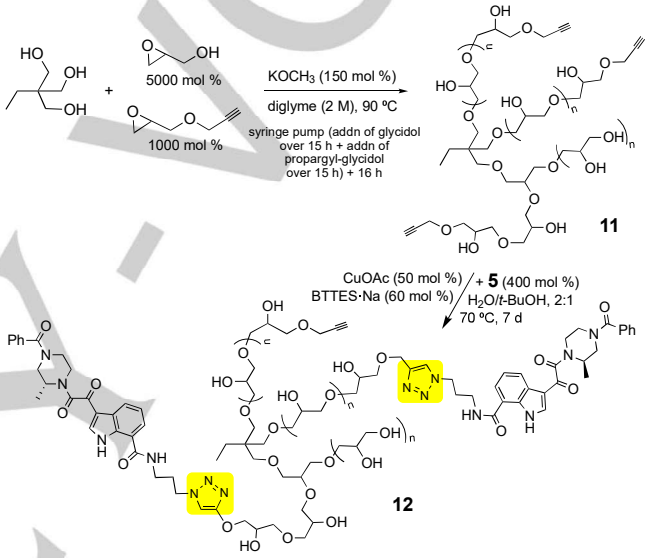
Scheme 2. Synthesis of **8**, a mixture of oligopropargylated β-CDs, and conjugation with **5**, to afford **9**; n_p and n_s = number of propargyl groups linked to primary and secondary OH groups, respectively; m_p and m_s = number of BMS-type unities linked to primary and secondary OH groups. CuOAc = copper(I) acetate.

The reaction of **8** with an excess of **5** in the presence of Cu(I)[10,15] required previous exhaustive optimization. As models, we chose the monoazide of β-cyclodextrin and, on the other hand, the morpholine amide of propynoic acid and 1-hexyne. We compared Cu(I) sources and ligands,[15] using as small as possible amounts of $CuSO_4$/sodium ascorbate, CuOAc, or $Cu_2(OTf)_2{\cdot}C_6H_6$. At rt and 0.05 M concentrations in water or aq ^{t}BuOH, the optimal conditions turned out to be 3 mol % of CuOAc and 5 mol % of the sodium tris(triazolyl)ethylsulfate BTTES·Na.The surfactant nature of BTTES·Na was clearly an advantage in this case.

When these optimized conditions were applied to **8** and **5**, we had only to increase the reaction time and temperature to reach good conversions (oligo-substitution). In this way, **9** was obtained as a mixture comprising one β-CD scaffold randomly decorated with 2 ± 1 BMS-like substituents.

Similarly, a sample with a spacer of ten methylene groups (**10**), instead of three methylenes, was prepared from **8** and **6** in 63% yield (**10**, n = 0–3, m = 1–4, see the Supporting Information). As no significant differences were noted between **9** and **10** regarding the toxicity and anti-HIV-1 activity (see below), we continued our studies with **9**, that is, with the shorter length spacer.

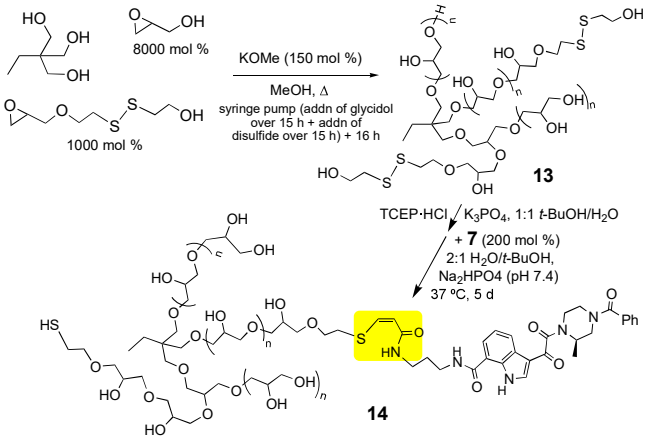
Our next step was the propargylation of hyperbranched polyglycerol (HPG). It is known that the biocompatibility and absence of toxicity of HPG are excellent.[16] We formed a copolymer of *rac*-glycidol and propargylated glycidol (Scheme 3), added in a 5:1 ratio, from 2-ethyl-2-(hydroxymethyl)-1,3-propanediol as the initiator, following the reports of Frey et al.[17] We previously optimized the method by checking different bases (KHDMS, CsOH, NaH, $KOCH_3$), variable excesses of glycidols, two solvents (THF in a microwave synthesizer at 90 ºC and diglyme in a vial at 90 ºC as well), and different addition times. We used our best conditions to prepare **11** (Scheme 3). The MALDITOF-TOF/TOF mass spectrum of the sample (**11**) showed the most intense $[M + Na]^+$ peaks between *m/z* 727.8 and 1338.5, mean MW ≈ 1100. Concentrations were based on this mean value.



Scheme 3. Synthesis of **11**, an oligomer/polymer mixture made from *rac*-glycidol and propargylated glycidol. CuAAC reaction of **11** with an excess of **5** to afford **12**.

This sample, after training experiments to optimize the CuAAC with a model (benzyl azide, azidomethylbenzene), was treated with **5** (400 mol %) for 7 days at 70 ºC in the presence of 50 mol % of Cu(I) and 60 mol % of BTTES·Na to afford, after an appropriate workup, a yellowish viscous oil (**12**), as shown in Scheme 3. The filtrates from the precipitation and purification of **12** were combined, diluted with water, and extracted with EtOAc to recover unreacted **5**. The MALDI-TOF/TOF analysis of **12** (Supporting Information) indicated main peaks at *m/z* values between 907.8 and 1612.4 (mean MW ≈ 1300).

We also prepared a different HPG derivative, decorated with thiol groups, in accordance with the procedure reported by Kim et al.[18] After heating the starting triol with KOMe/MeOH and evaporation to dryness, the solid was solved in diglyme at 90 ºC and a huge excess of *rac*-glycidol (Scheme 4) was added over 16 h. The disulfide arising from glycidyl chloride and disulfide of 2-sulfanylethanol (2-mercaptoethanol) was also introduced via a syringe pump. The S–S bond of the the mixture (**13**) was cleaved with tris(carboxyethyl)phosphine (TCEP) and, after precipitation with acetone, the crude product was subjected to a conjugate addition to the activated triple bond of **7** at physiological pH, without any special catalyst.



Scheme 4. Synthesis of **13**, an oligomer/polymer mixture made from *rac*-glycidol and a disulfide derivative of *rac*-glycidol. Reduction to the thiol derivative with TCEP [$P(CH_2COOH)_3$] and addition to the activated alkyne **7** under physiological conditions to afford **14**.

The toxicity of **9**, **10**, **12**, and **14** was evaluated against TZM.bl cells (Figure 4). None was cytotoxic at concentrations below 100 μM or, in the case of **9** and **10**, below 50 μM.

β-Cyclodextrin, its propargylated derivative **8**, HPG, its propargylated derivative **11**, and its disulfide **11** were also evaluated. None was cytotoxic at 100 μM concentrations and none showed anti-HIV-1 activity either (results not included in Figures 4 and 5 for the sake of simplicity).

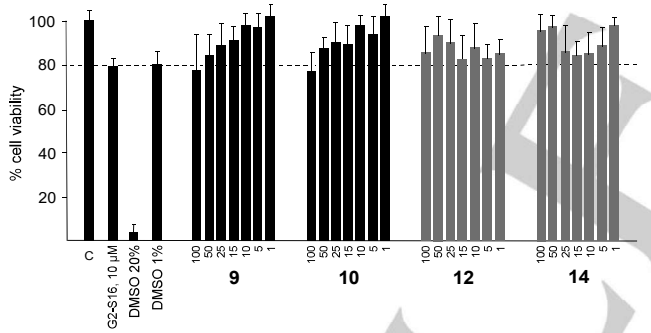


Figure 4. Cytotoxicity of samples **9**, **10**, **12**, and **14** against TZM.bl cells, at different concentrations (from 100 μM to 1 μM) in 1% aqueous DMSO (v/v). C = control; dendrimer G2-S16 = the reference.[12]

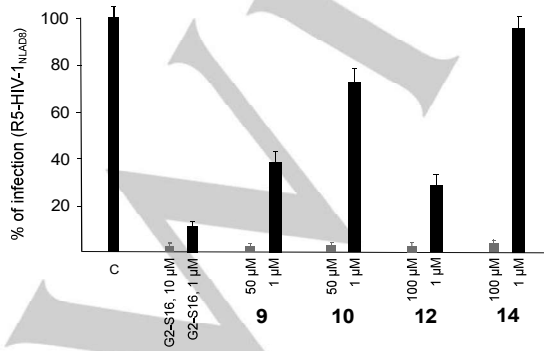


Figure 5. Synthesis of **13**, an oligomer/polymer mixture made from *rac*-glycidol and a disulfide derivative of *rac*-glycidol. Reduction to the thiol derivative with TCEP [$P(CH_2COOH)_3$] and addition to the activated alkyne **7** under physiological conditions to afford **14**.

The antiviral activity of **9**, **10**, **12**, and **14** against R5 isolates was finally evaluated as mentioned above: first at their non-toxic concentrations and then at 1 μM (Figure 5). To our delight, at their non-toxic concentrations, all were almost as active as the reference dendrimer (which has 16 sulfonate ions per molecule). Furthermore, **9** and **12** were still as much active at 1 μM as **4** and **5** and only slightly less active than the C7-unsubstituted compound, **3** (Figure 3). In other words, the antiviral performance of the BMS-type structures at blocking gp120 of HIV-1 does not disappear when they are attached to polyol scaffolds through C7-amide groups.

In summary, the cytotoxicities of the C7-substituted BMS-derived samples that we screened appear to be very low, with non-toxic maximum concentrations relatively very high (50–100 μM), which is a clear advantage from a pharmacological point of view. Anti-HIV-1 activities of samples **9** and **12** are also noteworthy, showing inhibitions similar to those of their precursors after only 1 h of incubation at 37 ºC, when they are later treated for 3 h with HIV-1. The fact that these inhibition percentages occur using the R5 isolate, which is responsible for the HIV-1 primoinfection, is of key importance for any ENI-type vaginal microbicide. Moreover, there is room for improvement, once the proof-of-concept has been demonstrated: we will attempt to derivatize more active BMS compounds (such as BMS-626529 or BMS-828251), to prepare oligo-substituted scaffolds of much higher MW (in order to increase the gel properties), and to submit them for screening against a large panel of HIV-1 strains.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 4th generation microbicides • HIV entry inhibitors • BMS-type drugs • click chemistry • hyperbranched polyglycerol

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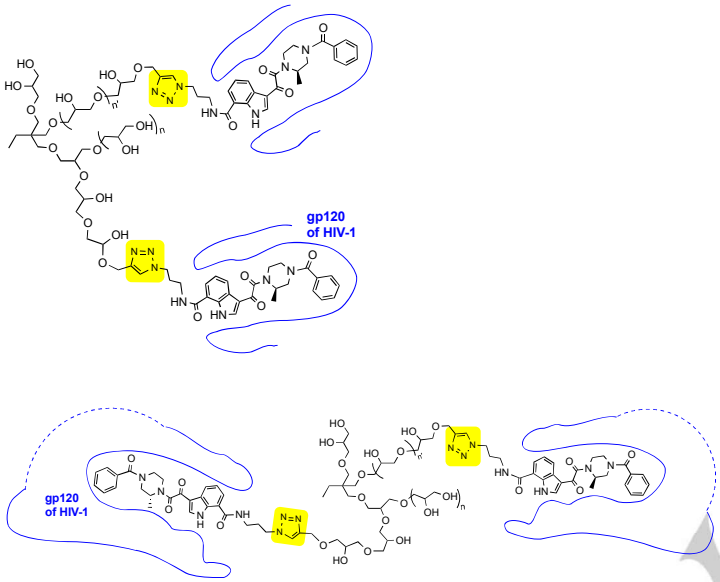

Entry inhibitors similar to those reported by Bristol-Myers Squibb have been linked, through the C7 position of their indole ring, to β-cyclodextrin or hyperbranched polyglycerols by means of click reactions. They are not cytotoxic at all at 50–100 μM and two of them maintain anti-HIV-1 activity in vitro, against R5-HIV-1_{NLAD8} Isolates, in the low μM range. This paves the way for the development of a new generation of vaginal microbicides.