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Benzenepropanamine Analogues as Non-detergent Microbicidal Spermicide for Effective Pre-exposure Prophylaxis

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Abstract : According to UNAIDS 2013 estimate nearly 52% of all individuals living with HIV are now women of reproductive age (15–44 years). Seventy-five percent cases of HIV acquisition are through heterosexual contacts and sexually transmitted infections (STIs), attributable to unsafe sexual behaviour. Each year, an estimated 500 million people acquire atleast one of four STIs: chlamydia, gonorrhoea, syphilis and trichomoniasis. Trichomonas vaginalis (TV) is exclusively sexually transmitted in adults, accounting for 30% of STI cases and associated with pelvic inflammatory disease (PID), vaginitis and pregnancy complications in women. TV infection resulted in impaired vaginal milieu, eventually favoring HIV transmission. In the absence of an effective prophylactic HIV vaccine, prevention of new infections has become a priority. It was thought worthwhile to integrate HIV prevention and reproductive health services including unintended pregnancy protection for women as both are related with unprotected sex. Initially, nonoxynol-9 (N-9) had been proposed as a spermicidal agent with microbicidal activity but on the contrary it increased HIV susceptibility due to surfactant action. Thus, to accomplish an urgent need of novel woman controlled non-detergent microbicidal spermicides benzenepropanamine analogues have been synthesized. At first, five benzenepropanamine-dithiocarbamate hybrids have been synthesized and evaluated for their spermicidal, anti-Trichomonas and anti-fungal activities along with safety profiling to cervicovaginal cells. In order to further enhance the scope of above study benzenepropanamine was hybridized with thiourea as to introduce anti-HIV potential. The synthesized hybrid molecules were evaluated for their reverse transcriptase (RT) inhibition, spermicidal, anti-Trichomonas and antimicrobial activities as well as their safety against vaginal flora and cervical cells. simulated vaginal fluid (SVF) stability and pharmacokinetics of most potent compound versus N-9 was examined in female Newzealand (NZ) rabbits to observe its absorption into systemic circulation and subsequent exposure in blood plasma through vaginal wall. The study resulted in the most promising compound N-butyl-4-(3-oxo-3-phenylpropyl) piperazin-1-carbothioamide (29) exhibiting better activity profile than N-9 as it showed RT inhibition (72.30 %), anti-Trichomonas (MIC, 46.72 µM against MTZ susceptible and MIC, 187.68 µM against resistant strain), spermicidal (MEC, 0.01%) and antifungal activity (MIC, 3.12–50 µg/mL) against four fungal strains. The high safety against vaginal epithelium (HeLa cells) and compatibility with vaginal flora (lactobacillus), SVF stability and least vaginal absorption supported its suitability for topical vaginal application. Docking study was performed to gain an insight into the binding mode and interactions of the most promising compound, N-butyl-4-(3-oxo-3-phenylpropyl) piperazin-1-carbothioamide (29) with HIV-1 Reverse Transcriptase. The docking study has revealed that compound (29) interacted with HIV-1 RT similar to standard drug Nevirapine. It may be concluded that hybridization of benzenepropanamine and thiourea moiety resulted into novel lead with multiple activities including RT inhibition. A further lead optimization may result into effective vaginal microbicides having spermicidal, anti-Trichomonas, antifungal and anti-HIV potential altogether with enhanced safety to cervico-vaginal cells in comparison to Nonoxynol-9.

Keywords : microbicidal, nonoxynol-9, reverse transcriptase, spermicide
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