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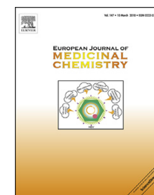
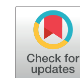


Review article

# Recent updates for designing CCR5 antagonists as anti-retroviral agents



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The healthcare system faces various challenges in human immunodeficiency virus (HIV) therapy due to resistance to Anti-Retroviral Therapy (ART) as a consequence of the evolutionary process. Despite the success of antiretroviral drugs like Zidovudine, Zalcitabine, Raltegravir WHO ranks HIV as one of the deadliest diseases with a mortality of one million lives in 2016. Thus, there emerges an urgency of developing a novel anti-retroviral agent that combat resistant HIV strains. The clinical development of ART from a single drug regimen to current triple drug combination is very slow. The progression in the structural biology of the viral envelope prompted the discovery of novel targets, which can be demonstrated a proficient approach for drug design of anti-retroviral agents. The current review enlightens the recent updates in the structural biology of the viral envelope and focuses on CCR5 as a validated target as well as ways to overcome CCR5 resistance. The article also throws light on the SAR studies and most prevalent mutations in the receptor for designing CCR5 antagonists that can combat HIV-1 infection. To conclude, the paper lists diversified scaffolds that are in pipeline by various pharmaceutical companies that could provide an aid for developing novel CCR5 antagonists.

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## 1. Introduction

Incommensurate with the stats of WHO, HIV is one of the deadliest infections contributing to a total of 36.7 million infections until December 2016 amongst which 1.8 million were diagnosed in 2016 itself. In 2016 itself, 19.5 million people underwent anti-retroviral treatment summing up to US$ 11 billion. In the vicinity of 2000 and 2016, new HIV infections fell by 39%, and HIV-related demises reduced by 33% with 13.1 million lives spared because of ART in a similar period. There is no cure for HIV disease [1]. In any case, successful antiretroviral (ARV) medications can control the infection and help anticipate transmission so individuals with HIV, and those at considerable hazard, may have an improved life expectancy. Hence, the global community has committed to expanding the access to antiretroviral therapy (ART) including diagnosing 90% of all people with HIV infection, providing treatment to 90% of the total diagnosed and assuring 90% of the treated to achieve virologic suppression by 2020 [1].

The sequential evolution of HIV can be described as around 1930's the retroviral infection transmitted to humans for the first time from chimpanzees. The lack of scientific techniques made it difficult and taking almost 50 years to discover CD4 as HIV receptor. The slow advancement in science and healthcare fields led to the discovery of Zidovudine as the first agent in anti-retroviral therapy. Combination therapy of Zalcitabine and Zidovudine was initiated in 1991. AZT resistance was reported in 1993. The first protease inhibitor Saquinavir was approved in 1995. Enfuvirtide, a fusion inhibitor was approved in 2003. TRIM-5$\alpha$ was discovered as a target in 2005 [2]. Maraviroc gained approval in 2007. The current first-line therapy for HIV varies according to different age groups: 1) Adults: Tenofovir Disoproxil Fumarate (TDF) + Lamivudine or Emtricitabine (XTC) + Efavirenz (EFV) as a fixed dose combination. 2) Adolescents: TDF + XTC + EFV a FDC 3) Pregnant women: TDF + XTC + EFV 4) Children: abacavir (ABC) + lamivudine (3 TC) [1].

For adults, adolescents, and children $\geq$ five years, advanced HIV disease are defined as a CD4 cell count < 200 cells/mL or a WHO clinical stage 3 or 4 events at presentation for care. The infection of HIV can be categorized into two varieties HIV-1 and HIV-2. Today, HIV 1, along with its less widespread accompaniment HIV-2, infects more than 30 million people worldwide. HIV-1 primarily infects the humans by weakening the innate and adaptive immune rendering the infected person susceptible to various other infections and certain types of cancer by majorly targeting $CD4^+$ T cells. The structural studies of HIV acknowledged that the virus consists of a viral core and an envelope. The outer envelope consists of spikes comprise trimers of non-covalently linked heterodimers consisting of the surface glycoprotein gp120 and the transmembrane glycoprotein gp41 [3–5]. The glycoprotein subunits gp120 and gp41 are cleaved at Golgi Apparatus from a single subunit gp160 which in turn is synthesized in the viral mitochondria. Now for combating HIV, one needs a systematic stepwise study of the life cycle of HIV.

### 1.1. HIV life cycle

The life cycle of HIV is organized into various steps as represented in Fig. 1. **Viral attachment:** The gp120 of the viral envelope and $CD4^+$ cells interacts and forms a bridging sheet between the interior and exterior domains of gp120, facilitating the binding of the HIV-1 virus to $CD4^+$ cells. [6–8]**Viral Fusion:** The involvement of co-receptors incorporates the fusion peptide into the cytoplasm from the amino terminus of gp41 ending into the fusion of the viral envelope to the host cell membrane [9–11]. **Uncoating:** The fusion of viral envelope to host cell membrane is succeeded by the partial dissolution of viral core capsid which results in the release of viral genomic material into the cytoplasm [12,13]. **Reverse Transcription:** The viral genomic material consists of viral RNA which is reverse transcribed to viral DNA by Reverse Transcriptase enzyme which is a heterodimer of p66 and p41 with two active sites. **Nuclear import**: The viral DNA then is imported into the host cell nucleus by various nuclear importers. **Integration:** The imported viral DNA is incorporated into host cell DNA via integrase enzyme.

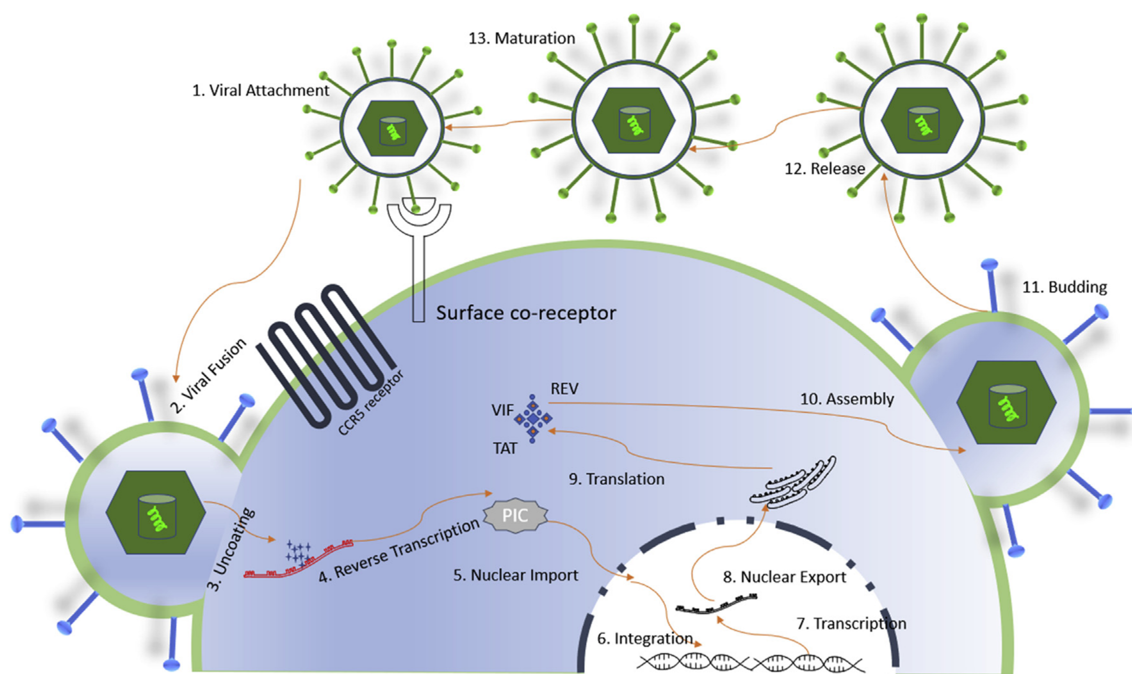


**Fig. 1.** HIV-1 Life Cycle, 1. Viral attachment, 2. Viral Fusion, 3. Uncoating, 4. Reverse Transcription, 5. Nuclear import, 6. Integration, 7. Transcription, 8. Nuclear export, 9. Translation, 10. Assembly, 11. Budding, 12. Release, 13. Maturation.

**Transcription:** The host cell DNA along with integrated viral genomic material is transcribed into host cell RNA. **Nuclear export**: The transcribed RNA is then exported via various nuclear exporters. **Translation:** These exported RNA's are translated into proteins of capsid, nucleocapsid, and matrix that assemble over cell surface as an immature HIV. **Assembly:** During the process of assembling the synthesized proteins of capsid, nucleocapsid, and matrix assembles to form the functional parts of virus-like plasma membrane and other intercellular membranes. **Budding:** The assembled immature HIV buds convert into mature HIV and infect surrounding cells. The process of budding requires the formation of structural proteins like capsid, matrix, and nucleocapsid which are synthesized from precursor polypeptide Gag. **Release:** The assembled structure forms a new virus attached to the CD4 cell which then detaches from the host cell to form a new free virus. This step is called the release of the virus. **Maturation:** The stage of maturation includes the formation of new virions to get ready to infect other immune cells.

## 2. Anti-retroviral therapy

The classical anti-retroviral therapy includes drugs from two different classes like Reverse Transcriptase Inhibitors and Protease Inhibitors. Reverse transcriptase inhibitors inhibit the process of reverse transcription at stage IV of HIV replication. They are categorized into two categories: A) reverse transcriptase inhibitors with nucleosidic structure- Lamivudine, Zidovudine, Tenofovir (Fig. 2.) and B) non-nucleosidic reverse transcriptase inhibitors like Efavirenz, Nevirapine, Delavirdine, Etravirine as shown in (Fig. 3.). Protease Inhibitors like Saquinavir, Ritonavir, Indinavir (Fig. 4.) inhibit the process of budding and thus block the stage X and retard the production of mature HIV.

The classical anti-retroviral therapy was initiated as a mono or a dual therapy with a combination of two drugs from two different classes. But, both mono and dual therapy faced repercussion due to resistance. Hence to overcome these insufficiencies of the treatment a combination of three drug regimen known as Highly Active Anti-Retroviral Therapy (HAART) was initiated in 1996. The combination includes TWO Nucleosidase Reverse Transcriptase Inhibitors ONE Non-Nucleosidase Reverse Transcriptase inhibitor OR ONE Protease Inhibitors. But recently incidences of Highly Active Retroviral Therapy resistance are reported which states the significance of the development of new molecules that treat resistant strains of HIV. Resistance is not the only reason for the emergence of novel anti-retroviral agents but the concomitant long-term metabolic side effects due to fat metabolism.

## 3. Recently discovered targets for HIV therapy

Combating HIV is a tough task but with the advancement into insights of viral structure rewarded into exceptional targets that can be a potential target that serves to be treatment pathways for HIV infection. Some of the targets that could be focused on future Anti-Retroviral Therapy are **Inhibitors of viral cell attachment:** This is the rate-limiting step for retroviral infection and inhibits the first step of virion attachment to host cells. The most promising agents include negatively charged heparan sulfate proteoglycans, that binds with positively charged moieties of the viral envelope [14]. **Entry inhibitors:** These drugs inhibit the viral entry into the cell via blocking the fusion of virus into host cell membrane. These drugs can be categorized into three categories: *I. gp120-CD4 binding:* The agents of this class are free to bind to either gp120 or CD4 and induce conformational changes in gp120-CD4 to avoid the fusion of the virus. These agents need to be negatively charged and the efficient one could be polyanionic compounds, bis-azo

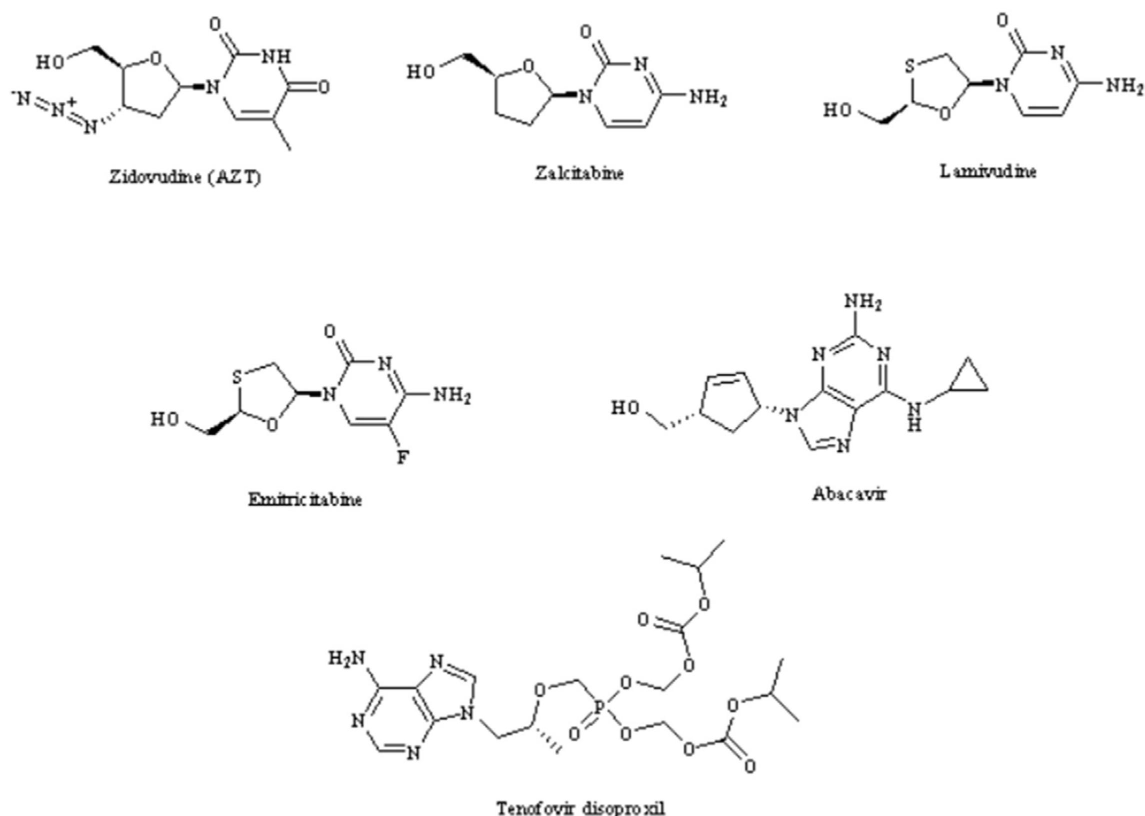


**Fig. 2.** Nucleoside reverse transcriptase inhibitors.

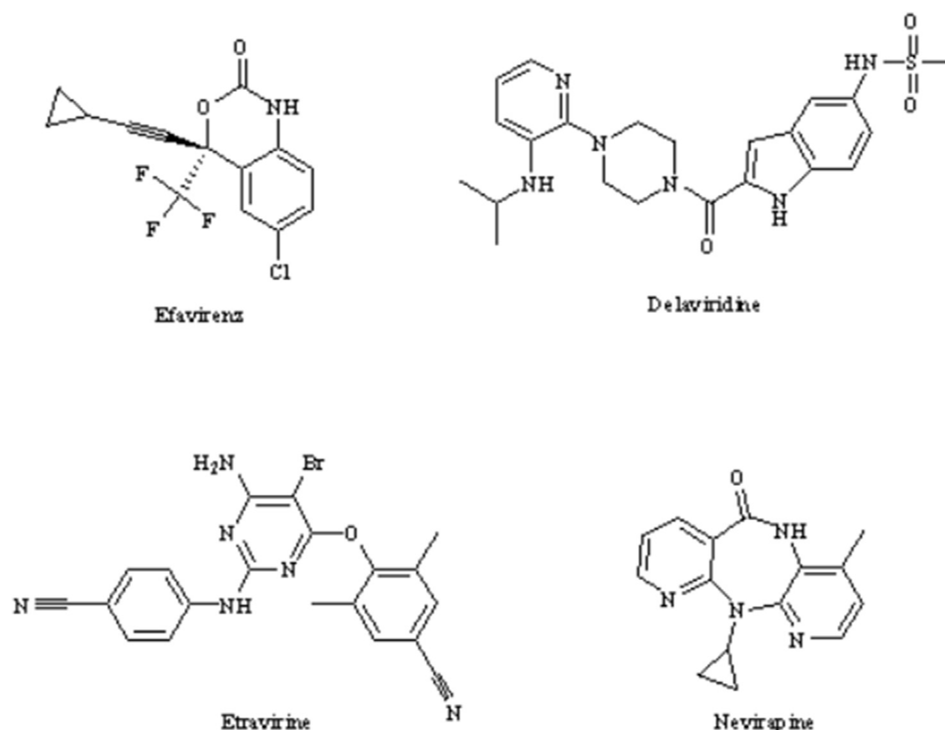


**Fig. 3.** Non-nucleoside reverse transcriptase inhibitors.

compounds like FP-21399 [7]. *II. Gp120 co-receptor blockers:* These agents intervene the HIV virus interaction with the CD4 surface co-receptors. The co-receptors that are targeted belongs to a 7 trans-membrane GPCR and bind to the chemotactic chemokines that produce cell signals and continue the immune response further. The selectivity of HIV-1 to bind to specific co-receptor determines its tropism that is if HIV-1 binds to CCR5 co-receptor it is known as R5 Tropic HIV-1 if it binds to CXCR 4 co-receptor it is called as X4 Tropic HIV-1 and a Dual-Tropic HIV if it proceeds through both CCR5/CXCR4 co-receptor [15]. The agents that act upon CCR5 are RANTES, MIP-1α, and MIP-1β, Maraviroc, Aplaviroc, Vicriviroc, Cenicriviroc, Nifeviroc (Fig. 5.) [16–18]. The agents acting upon CXCR4 are plerixafor, ALX40-4C (Fig. 6), T22 and other highly cationic compounds. [19–22] A distamycin analog NSC651016 blocks both CCR5/CXCR4 receptors [23]. *III. Gp41 fusion blockers:* These agents block the final fusion stage which is induced by conformational changes in gp41 trimer [24]. Only a few molecules are available like Ivermectin and a Betulinic acid derivative RPR 103611 (Fig. 7.) is thought to be inhibiting gp41 fusion [25]. **Uncoating Inhibitors:** Targeting the uncoating process inhibits the third step of HIV life cycle, and blocks the release of virions into the cytoplasm. To target uncoating, the viral capsid needs to be targeted like TRIM 5α. TRIM 5α was isolated from rhesus macaques [26] that recognize assembled capsid structure to accelerate uncoating and hence TRIM 5α agonists are potential agents for blocking uncoating [27]. Example- PF 3450074 mimics Cyclosporine A (Fig. 8.) and causes a premature viral core uncoating and inhibits HIV-1 replication [28,29]. **Nuclear Import Inhibitors:** This class of drug inhibits the translocation of the viral cDNA into host cell nucleus so that the viral cDNA doesn't incorporate into host cell DNA. These drugs inhibit step IV of HIV life cycle. Importin B is one of the nuclear-importing protein which on inhibition produces blockade of NLS bearing cargo proteins which in turn results in the inhibition of Impα/β dependent transport Example- Ivermectin as depicted in Fig. 7. **Integrase Inhibitors:** These agents inhibit the strand transfer reaction of cDNA to cellular DNA. The blocking is achieved by the removal of terminal dinucleotide from 3′ end through the inhibition of the interaction of a protein integrase. This integrase enzyme integrates viral cDNA to host chromosome with that of the LONG TERMINAL REPEAT sequence [30]. Di-keto integrase inhibitors blocks the nuclear import and accumulate viral cDNA in the cytoplasm [31]. Example- Raltegravir, Elvitegravir as shown in Fig. 9. **VIF deregulation:** VIF stands for Virion Infectivity Factor which can be downregulated by incorporating VIF Inhibitors which in turn antagonize incorporation of APOBEC3G that causes HIV-1 degradation via 26 S proteasome [32,33]. VIF also may inhibit the negative cellular factor's activity and lead to blockade of formation of infectious virions [34,35]. **Nuclear Export Inhibitors:** These agents inhibit the post-transcriptional nuclear export of the mRNA to the cytoplasm and block the assembly formation on the cell surface and blocks the infection of HIV to another cell due to immature budding. **Assembly Blockers:** These agents include various accessory and regulatory viral proteins like TAT. Viral Transactivator Protein, TAT is a viral regulatory protein that is involved in the process of transcription which initiates U3 promoter and blocks HIV maturation. TAT is needed by spliced mRNA while unspliced mRNA demands the need of Rev-dependent mRNA export [36,37].

## 4. Detailed insights into viral entry process

The HIV-1 virus structure is comprised of viral envelope and viral core. The viral envelope is made up of two different subunits gp120 and gp41 which are generated at Golgi bodies from gp160 which in turn is synthesized in mitochondria [3–5]. The HIV-1 envelope spikes comprise of trimers that are covalently linked heterodimers of a surface glycoprotein gp120 and a trans-membrane glycoprotein gp41. Upon activation, the spikes initiate a series of conformational changes that lead to bridging sheet formation between interior and exterior domains of gp120 and finally

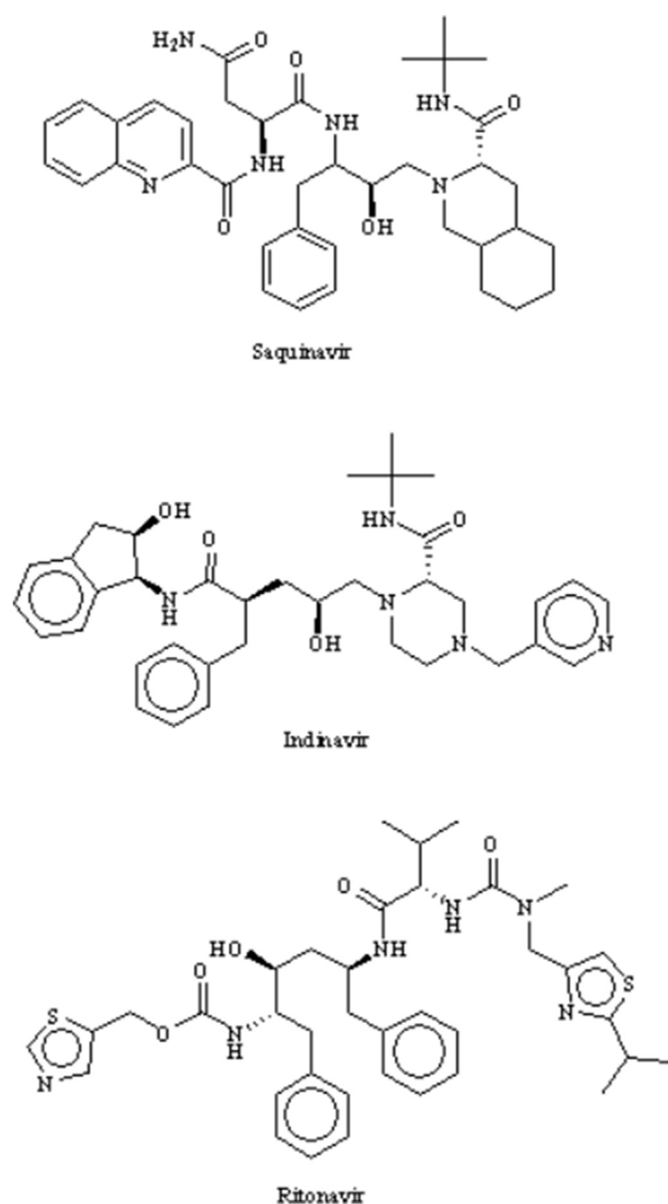


**Fig. 4.** Protease inhibitors.

outreaching the binding site onto the proximal side and opens up the HIV-1 binding sites [6–8]. Once the binding sites of V3 loop gp120 are exposed it initiates the attachment of HIV-1 to the host cells (CD4+T cells and macrophages). The host cells bind to HIV via the surface co-receptors present on the cell membrane. The binding of viral envelope via gp120 to the cell surface co-receptor causes the insertion of fusion peptide from the amino terminus of gp41 and precipitates the rearrangements of the trimerized amino-carboxy terminal within gp41-repeat heptad sequences. This results in the formation of a pre-fusion intermediate as an extended coiled-coil and relocation of fusion peptides from distal to the proximal position and results into destabilization which was thought earlier but recent studies proved that the flexible core of gp120 brings about conformational changes without destabilizing the gp41 trimers. The extended coiled-coil then transforms to a six-helix hairpin structure [9–11], and the C and N terminal heptads come into association and transmembrane gp41 come into close proximity and facilitates actual merger and form a fusion pore utilizing two $CD4^+$ cells and four-six co-receptors of CD4 cells.

## 5. Insights of CCR5 Co-receptor as a potential target as HIV-1 entry inhibitors

Chemokine family of receptors are thought to be chemo-attractant amongst which certain receptors of CC chemokine family are involved in HIV-1 infection. The entry of HIV-1 is facilitated via two major surface co-receptors CCR5 and CXCR4 amongst which CCR5 is preferred in 51% of HIV-1 infection cases. Depending upon the co-receptor selectivity the tropism of the virus is determined that is whether it is R5 tropic or X4 tropic [38]. Thus, for targeting R5 tropic HIV-1 virus CCR5 could be targeted. CCR5 co-receptor targeting is a major focus due to its higher expression over cell surface and it regulates cell signaling. To target CCR5 determining its structural features, biological functions and mechanism of cell signaling are essential.

Chemokine receptors are members of the family of seven transmembranes spanning G-protein coupled receptor that consists of about 340–370 amino acids. The chemokines are categorized into four different classes depending on the number and spacing of cysteine residue in N terminus of the receptor namely, C (XCR1), CC (CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10), CXC (CXCR1, CXCR2, CXCR3, CXCR4, CXCR5 and CXCR6), $CX_3C$ ($CX_3CR1$) and four decoys of ACKRs (ACKR1, ACKR2, ACKR3/CXCR7 and ACKR4) [39]. Both consists of seven hydrophobic transmembrane domains with an intracellular C terminal tails that comprise of structural motifs and an extracellular N terminal segment. Chemokine receptors consist of cysteine residues in all four extracellular domains. It also consists of a conserved DRY-LAVHA sequence in the second intracellular loop and a short third intracellular loop comprising of positively charged residues [40].

CCR5 is a CC chemokine receptor which is expressed on resting T-lymphocytes, macrophages and immune dendritic cells. CCR5 comprises of 352 amino acids with a 71% of similarity in sequence identity with CCR2 [41,42]. Both CCR2 and CCR5 lie in a close proximity to chromosome 3p21. The conserved TXP sequence of the second transmembrane domain of CCR5 is the structural determinant in receptor activation utilizing rhodopsin structure as a template. CCR5 also consists of a disulfide bridge between second and third extracellular loops. The existence of two additional cysteine residues that form additional disulfide bonds between N-terminus and third extracellular loop. These additional cysteine disulfide bonds bring structural constraints on the extracellular loop and stabilize conformation which catalyzes ligand binding [43]. Alanine mutation at extracellular cysteine results in reduced cell surface expression, chemokine binding, and impaired HIV co-receptor function. It consists of several tyrosine residues adjacent to acidic amino acids which get post-translationally modified to sulfated tyrosine which induces negative charges that enable it to interact with gp120 and natural ligands. CCR5 contains two sulfated moieties at Tyr10 and Tyr14 at the amino terminus. It also bears negatively charged sites that interact with conserved residues in the C4/V3 stem region of gp120 [44,45].

### 5.1. CCR5 signaling

CCR5 is also modified at Ser-6 by O-glycosylated link which is essential for CCR5 binding. Certain palmitoylated cysteine residues are found in the vicinity of hydrophobic and positively charged amino acids in carboxy-amino terminal [46,47]. Palmitoylation is found at three cysteine residues at 321, 323 and 324 positions. CCR5 palmitoylation enhances the ligand simulated endocytosis Protein Kinase C mediated CCR5 phosphorylation [48–50]. But the absence of palmitoylation doesn't affect HIV-1 entry. CCR5 dimerization was postulated to be essential for CCR5 signaling wherein both αi and βγ dimers of CCR5 regulates secondary messenger like adenyl

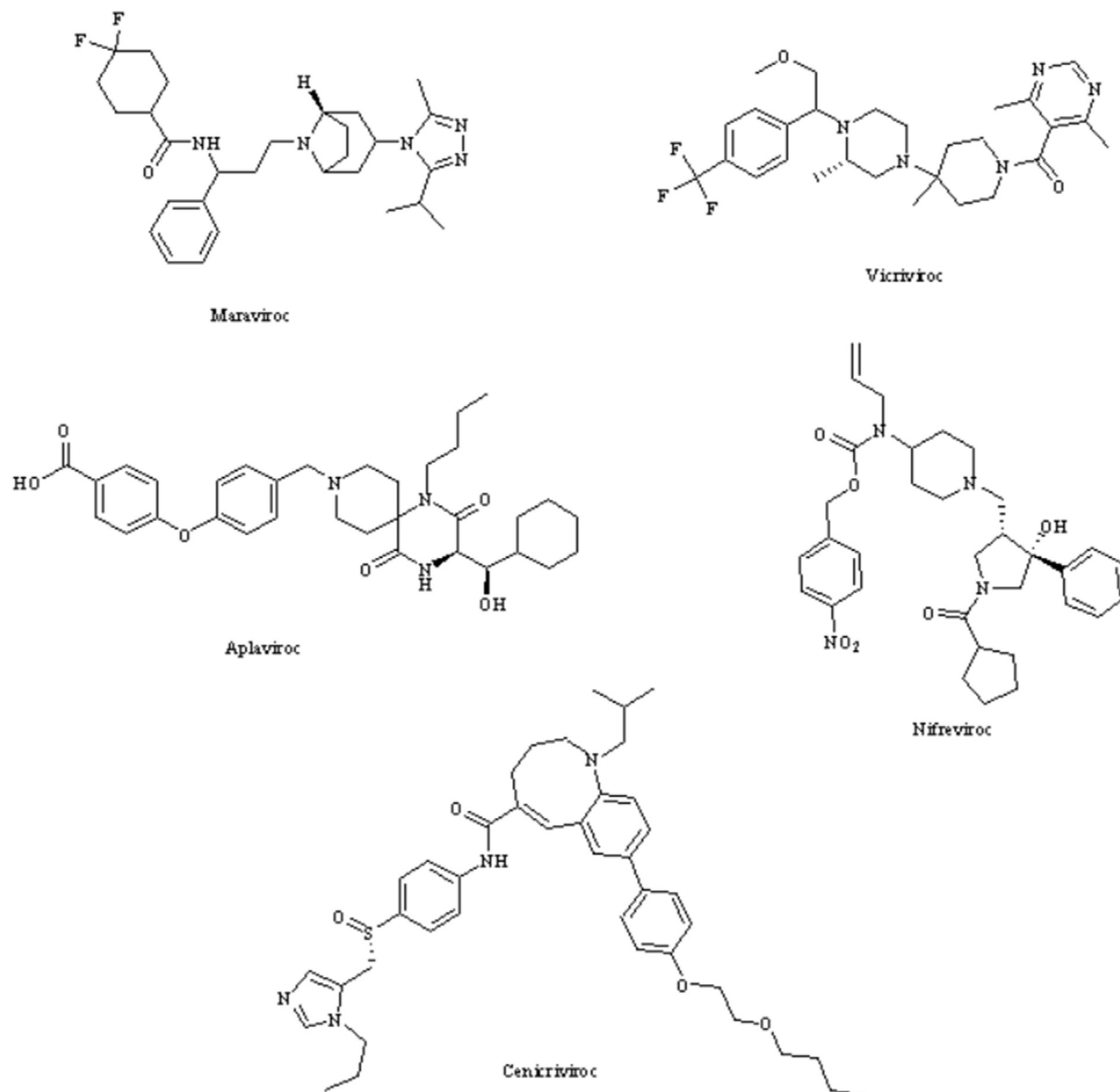


**Fig. 5.** CCR5 antagonists.

cyclase or phospholipase Cβ which leads to calcium mobilization and phosphoinositol-1,4,5-triphosphate [51,52]. The subsequent release of Gβγ subunits leads to chemotaxis. The further activation of phospholipase Cβ leads to the release of diacylglycerol which in turn activates PKC. Certain, CCR5 natural ligands like RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted), MIP-1α and MIP-1β (Macrophage Inhibitory Protein) activates phosphatidylinositol 3-kinase (PI3K) and Rho A that co-ordinate and reorganize actin cytoskeleton to facilitate cell motility. The T-cell induction via CCR5 leads to activation of two focal adhesion kinase FAK and PYK [53] that plays important role in cell motility. Ligand binding to CCR5 may lead to secondary messenger activated kinases that mediate serine-threonine protein kinases known as G-Protein coupled Receptor Kinase (GRK) leading to agonist-induced CCR5 phosphorylation via GRK2 and GRK3. GRK and PKC mediated phosphorylation occurs only of serine at 336, 337, 342 and 349 at carboxyl amino terminals and never occurs over tyrosine or threonine residues [54]. Three phosphorylated CCR5 has a high binding affinity for β Arrestin 1 and β Arrestin 2 which induces cellular signaling via MAP Kinase and activates ERK1/2 and JNK/SAPK. β Arrestin induces clathrin mediated cell internalization and endocytosis and hence mediate HIV-1 entry [50].

### 5.2. CCR5 ligands

The natural ligands for CCR5 like RANTES, Macrophage Inhibitory Protein 1-α and Macrophage Inhibitory Protein 1-β that are agonistic to CCR5 which upon binding induces signaling cascade via G-protein coupled receptor and co-ordinate leukocyte trafficking and recruit immune effector cells to infected or inflamed cells and initiate an adaptive immune response [16]. Five diversified scaffolds as CCR5 antagonist are designed to date- Maraviroc, Vicriviroc, Aplaviroc, INCB009471 and Cenicriviroc as shown in Table 1. Aplaviroc was a small molecule CCR5 antagonist that was developed by GlaxoSmithKline as a spiro diketopiperazine moiety that efficiently inhibits HIV infection with a half-life of more than 100 h [55]. Aplaviroc was halted at Phase IIB because of severe hepatotoxicity observed to the patient under Aplaviroc therapy [56,57].

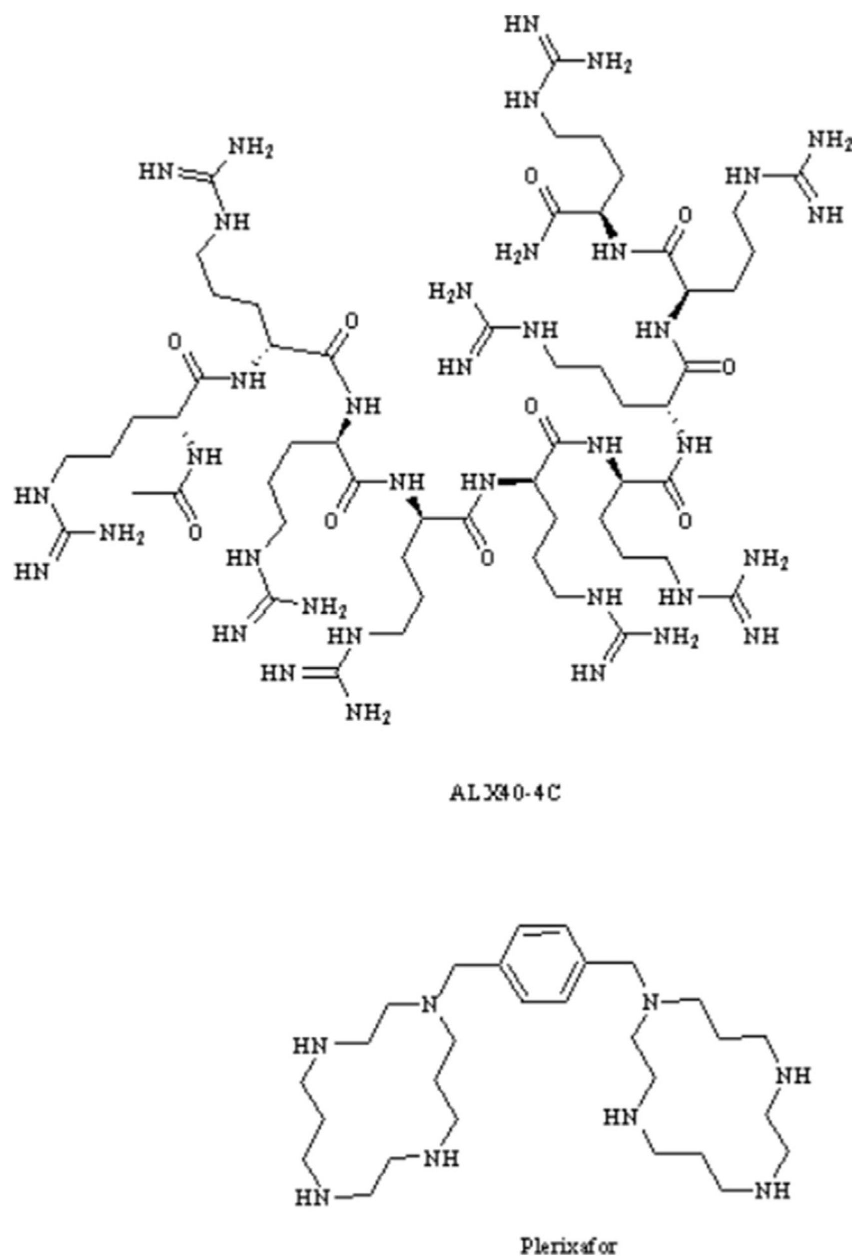


**Fig. 6.** CXCR4 antagonists.

This provided an insight for designing molecules that have sufficient binding efficiency for CCR5. TAK-779 was the first low molecular weight non-peptide that antagonize RANTES. TAK 779 was a quaternary anilide molecule that was under investigation by Takeda Pharmaceuticals for HIV treatment [23]. The development of TAK-779 was terminated due to poor oral bioavailability. The identification of TAK-779 was followed by two diverse moieties TAK-220 and TAK-652. TAK-652 was given the name of Cenicriviroc and is in Phase III trials. Maraviroc is the first and the only licensed antagonist listed as an entry inhibitor that targets CCR5 by Pfizer. Maraviroc binds reversibly to the co-receptor and induces conformational changes that block its interaction with the V3 loop of gp120 [58]. Maraviroc is an orally bioavailable CCR5 antagonist that is metabolized by CYP3A4 that received FDA approval in 2007 [59]. Another CCR5 antagonist is Vicriviroc which was initiated by Schering-Plough that non-competitively binds at the CCR5 allosteric site [60]. Vicriviroc was developed vicriviroc from SCH-C, an oxyimino-piperidino-piperidine amide which was discontinued due to HERG inhibitory activity [55]. Vicriviroc also failed because it was not able to prove its superiority over combination antiretroviral therapy. The progress of development of Vicriviroc was halted at Phase II as patients experienced vicriviroc bound viral entry. The other reason for stalling Vicriviroc development was increased liver malignancy.

### 5.3. CCR5 binding of maraviroc

The binding of Maraviroc to CCR5 provides an insight for designing of novel moieties. The focus over amino acid interaction acknowledges binding scopes to CCR5. These interactions are based on previous studies are described below [61–65]. The ligand binds at the bottom of the pocket at helices of I, II, III, V, VI and VII of the seven transmembrane helices. The nitrogen of tropane is protonated and is indulged in salt bridge interaction with Glu-283 as

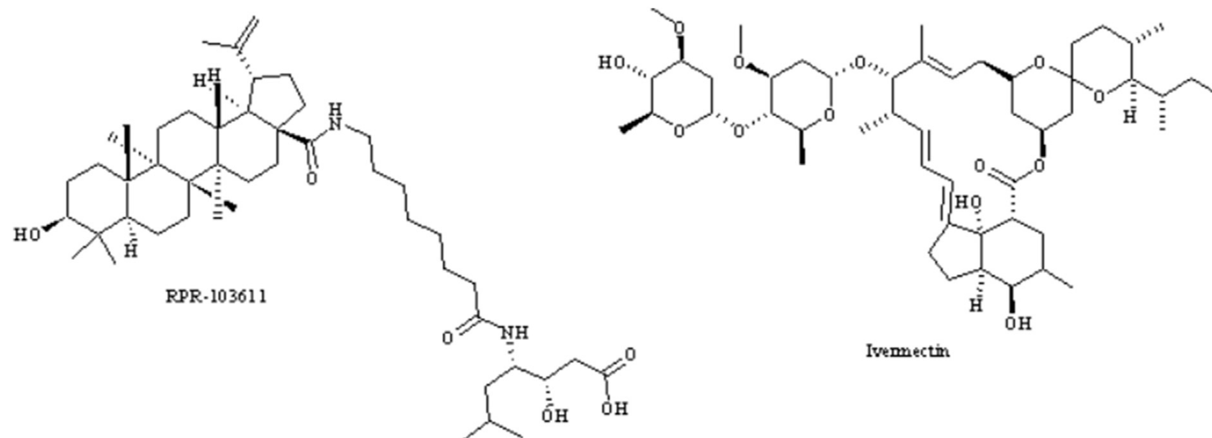


**Fig. 7.** GP41 interaction blocker and nuclear import inhibitor.

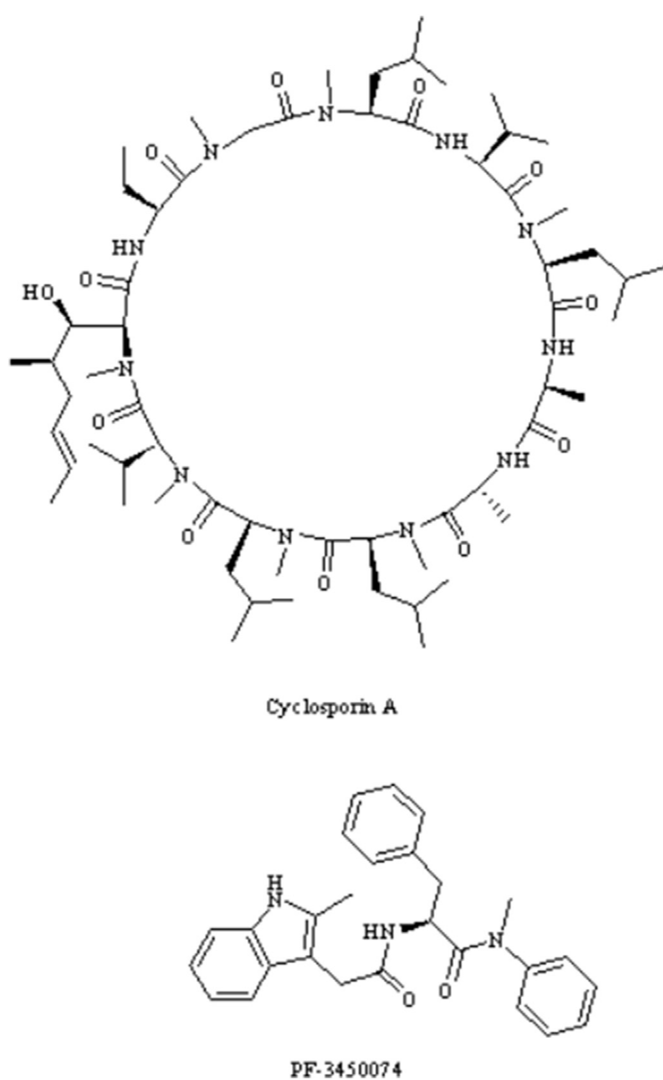


**Fig. 8.** Uncoating inhibitors.

shown in Fig. 10. The carboxamide nitrogen forms a hydrogen bond with Tyr-251. The carbon chain between two nitrogens is correlated with the positions of Glu-283 and Tyr-283. The amine moiety of triazole forms a hydrogen bond with Tyr-37. The two fluorine atoms of difluorocyclohexane form two hydrogen bonds with Thr-195 and Thr-259. The phenyl ring forms a hydrophobic interaction with five residues of Tyr-108, Phe-109, Phe-112, Trp-248, and Tyr-251.

### *5.4. Other CCR5 antagonists and its interaction with CCR5 receptor*

As discussed earlier in Section 5.2 there were certain molecules that were developed but did not transform to a drug. These are Aplaviroc, Vicriviroc, Cenicriviroc, TAK-779. The interaction of Aplaviroc, Vicriviroc, TAK- 779 is discussed further in the article.

The binding pockets of CCR5 consist of some key residues that are involved in the interactions of small molecule CCR5 antagonists like Maraviroc (MVC), Aplaviroc (APL), Vicriviroc (VVC), TAK-779, TAK-220. The two important amino acid residues namely Lys26 and Lys191 in the extracellular loop are involved in interaction with the CCR5 antagonist. The residues of transmembrane domain are also involved in the interaction with antagonists which are listed above in this section. There are two hydrophobic pockets with aromatic residues of Leu33, Tyr37, Phe79 and Trp86 in the transmembrane helices 1 and 2. The residues of Thr105, Tyr108, Phe109, Ile198 and Tyr251 are present in transmembrane helices 3, 5 and 6 [39]. The central binding sites consists of a negatively charged centre Glu283 surrounded by positive hydrogen bond donating residues Thr105, Tyr108, Tyr251, and Thr284. All the CCR5 antagonists i.e. MVC, APL, VVC, TAK-779 and TAK-220 interact with the negatively charged carboxylate of Glu283 utilizing the basic nitrogen present in the structure. The strength of interaction with Glu283 differs widely in all the CCR5 antagonists with the strongest with MVC and weakest with TAK-779.

APL additionally interacts with the carboxyl group of Lys191 or Lys26 in extracellular loop 2. The aromatic side chain interacts with Phe109 and Trp86. The elongated shape of APL also allows alternative interaction of peripheral positively charged functional groups with negatively charged Glu283 [58]. But certain specific interactions like Phe108, Tyr251, Tyr37 of MVC discussed above were silent for APL. The hydroxyl group of APL interacts with Thr195 forming a hydrogen bond. The cyclohexane ring of APL interacts with Ile198. Aplaviroc consists of tertiary butyl group that interacts with multiple aromatic residues. Thus, the key interactions of APL with CCR5 are Trp86, Phe109, Ile198 and Glu283 [58].

TAK-779 consists of a bicyclic functional group containing a phenyl ring that interacts with Tyr108 forming T-shaped $\pi$-$\pi$ stacking and with Tyr86. TAK-779 forms hydrogen bond with Thr284 utilizing tetrahydropyran and hydrophobic interaction is

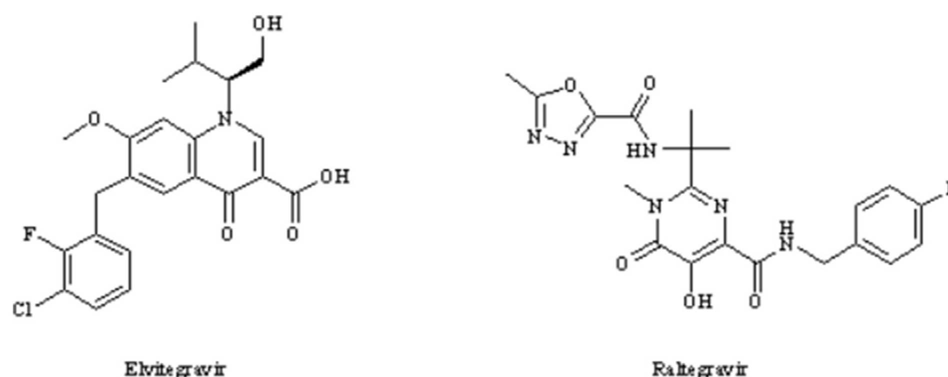


**Fig. 9.** Integrase inhibitors.

**Table 1**
CCR5 antagonist and its activities.

| Molecules | Activity |
|---|---|
| Maraviroc | $IC_{50}$ of 5.2 nm |
| Vicriviroc | $IC_{50}$ of 0.91 nm |
| Aplaviroc | $IC_{50}$ of 0.4 nm |
| Nifreviroc | $IC_{50}$ of 2.9 nm |
| Cenicriviroc | $IC_{50}$ of 0.25 nm |

observed with Tyr37 and Trp86. The quaternary nitrogen does not interact with Glu283 due to steric hindrance causing increased distance of the methyl group and positively charged nitrogen. The methyl group on the phenyl ring interacts with Ile198 [58]. Thus, TAK-779 has strong interactions with Trp86, Ile198 and Tyr108. It also interacts weakly with Glu283, Thr195, Phe109, Trp248 and Tyr251.

Vicriviroc also interacts with multiple residues of the receptor. VVC consists of trifluoromethyl phenyl group that interacts by a strong hydrophobic interaction with Ile198. The phenyl group is also thought to be interacting with Tyr108 via T-shaped aromatic $\pi$-$\pi$ stacking. The tertiary nitrogen of VVC interacts via strong electrostatic interaction with Glu283. The piperazine ring interacts strongly with Tyr251. Thus, the most important interactions of VVC are Tyr108, Tyr251, Glu283 and Ile198 [58].

TAK-220 interacts strongly with Glu-283 via salt bridge interaction because of its structural flexibility due to the presence of more number of rotatable bonds. The 3-chloro-4-methyl phenyl

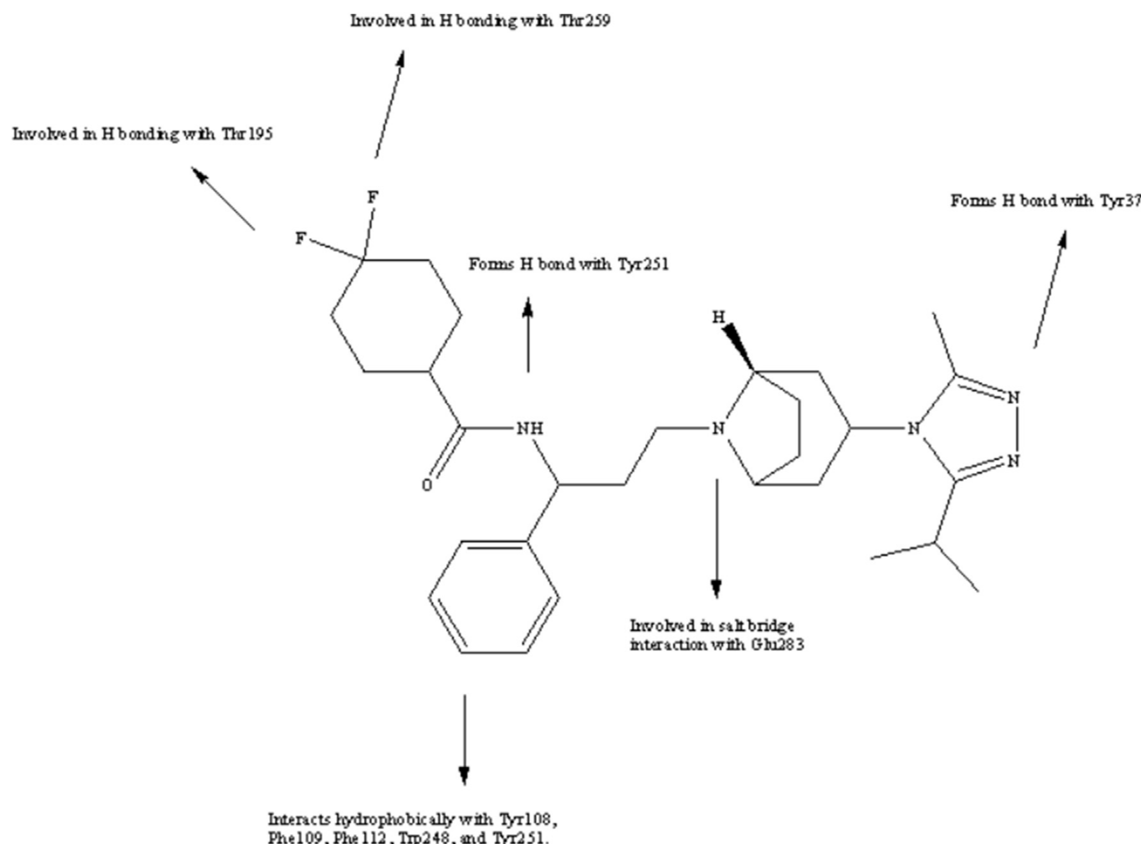


**Fig. 10.** Maraviroc-CCR5 binding.

ring of TAK-220 resembles the phenyl ring of MVC and has similar hydrophobic interactions. The residues of Trp86, Tyr108, Trp248, Tyr251, Thr195 and Met287 have weak interactions with TAK-220. Ile198 is also thought to have a strong interaction with TAK-220. Additionally the helical bundle of CCR5 interacts with TAK-220 through Phe109, Trp248 and Tyr251 [58].

### 5.5. Maraviroc resistance

Maraviroc resistance is observed either due to clinical bypass of the tropism of R5 to X4 tropism by HIV-1 or by the induced ability of the virus to bind with a ligand rebound CCR5 [66–70]. Previous studies revealed that resistance to small molecule CCR5 antagonist doesn't develop cross-resistance to all other molecules. Maraviroc (MVC) resistant strain showed cross-resistance to TAK-779 but remained sensitive to Vicriviroc and Aplaviroc. The instant development of MVC resistance is due to mutations in the V3 loop and the mutations in V4 loop determine the magnitude of resistance. The critical residues for resistant virus to ascertain drug bound configuration of CCR5 lies within N-terminus. Due to tyrosine mutants Y10A, Y14A, and Y15A, all the essential interactions were pounded and thus strongly inhibited the ability of the resistant envelope to use the drug-bound receptor. This suggests that Tyr10, Tyr14 and Tyr15 are involved in resistance. The single amino acid changes H88A, H181A, F182A, P183A, W190A, and C269A significantly increased MVC sensitivity and hence notifies that Histidine 88, Histidine 181, Phenylalanine 182, Proline 183, Tryptophan 190 and Cysteine 269 are significant for resistance [71].

The mutations reported to be responsible for HIV-1 resistance within the N terminus are (Y3A, Q4A, Y10A, D11A, Y14A, Y15A, N24A, and Q27A), within ECL1 are (H88A, Q93A, and N98A), ECL2 (S179A, H181A, F182A, P183A, Q186A, Y187A, F189A, and W190A), and within ECL3 are (E262A, N267A, N268A, C269A, and N273A) [71]. MVC resistant envelope shows a generally unassuming alteration in CCR5 engagement contrasted with that of MVC Sensitive envelope which is portrayed by an expanded dependence on Tyr14, Tyr15, Glu18 and Asp-11 in the CCR5 N terminus. MVC resistant envelope turned out to be basically dependent on sulfated tyrosine residues on Tyr3, Tyr10, and Tyr-14, in the CCR5 N terminus [70]. MVC Resistant envelope turned out to be fundamentally dependent on His88 and His181 in the CCR5 ECL1 and ECL2 areas, individually. Past investigations uncovered novel connections with charged components of the CCR5 ECL1 and ECL2 regions that are required for the recognition of drug bound CCR5 by MVC resistant envelope. Mutagenesis studies mapped the safe changes in MVC resistant envelope to amino acids Thr316 and Val323 in the V3 stem of gp120. The Thr316 resistant change is accounted for to be close to the tip of the V3 loop and probably assumes a part in binding to the ECLs, while the Val323 resistant transformation is at the V3 stem of CCR5 N-end interface [70]. The structural predictions proposed that the Val323 resistance mutation in the MVC resistant V3 stem may prompt a more scattered or less unbending V3 loop structure with a modified CCR5 binding cavity, which may allow altered interactions amongst V3 and the N terminus of drug bound CCR5.

### 5.6. Mutations in CCR5 receptors and its effect on the efficiency of various CCR5 antagonists

There are 1021 mutation data points determined for over 100 residue positions of all 13 discovered chemokines [39]. Various specific point mutations have been reported for the G-protein coupled receptor CCR5. These mutations have a diverse effect on various small molecule CCR5 antagonists like Maraviroc, Aplaviroc, Vicriviroc and TAK-779. These suggest that different small molecule antagonists have different interactions with CCR5 within the conserved regions of the receptor. Thus, the conformational changes produced by different antagonist binding are independent of each other and thus prove the observed minimal cross-resistance amongst the discovered molecules. The reported mutations can be listed as K26A in the N-terminus, where Lysine is transformed to Alanine [72]. The transmembrane helix I is reported to have mutations at two different positions of Y37A, Y37F, L33A. Wherein, for Y37A the tyrosine residue is mutated to alanine, for Y37F tyrosine residue at position 37 is mutated to phenylalanine, and for L33A Lysine residue of position 33 is mutated to Alanine. The transmembrane helix II have mutations at two different positions of F79A and W86A [73]. Here, the phenylalanine at 79th position is mutated to alanine and tryptophan at 86 is mutated again to alanine. The transmembrane helix three is also reported to have mutations over four different positions of T105A, Y108A, Y108F, F109A and F113A which implies that threonine at 105 is mutated to alanine, tyrosine at 108 is mutated to two different substrates of alanine and phenylalanine, the phenylalanine at 109 is mutated to alanine and the phenylalanine at 113 is again substituted to alanine [73]. The mutations are also observed in transmembrane helix five in which Y251A and Y251F are reported, which implies that tyrosine at the position of 251 can be substituted to two different amino acids of phenylalanine and alanine. The extracellular loop remained more conserved and only one mutation of K191A was reported in the extracellular loop II, which indicates the mutation of lysine with alanine is observed at position 191. The seventh transmembrane helix is also not spared from getting mutated where mutation at two different positions are reported. These are E283A and T284A which correspond to the residues of glutamic acid and threonine both of which are mutated to alanine residues.

The effect of these mutations varies widely for binding of every small molecule antagonists. Certain of the mutations led to drastic depletion of activity of few molecules whereas the other mutations did not matter for drug affinity and efficiency. The mutation E283A results in a 5.5 folds decrease in activity of TAK-779 whereas the same mutation resulted in the depletion of activity by 12,109 times in vicriviroc [73]. Another mutation of W86A had a minimal effect of 83 folds in MVC and highest of 1367 folds in SCH-C. The mutation of Y37A had a comparatively lower effect on the efficiencies with least of 0.6 folds in APL to the greatest of 395 folds in vicriviroc. F109A is also another mutation that has a wide range of decrease in efficiency of different candidates with a highest effect on APL of 2620 folds decrease in activity and the least of 0.6 in MVC. Other mutations like Y37A, I198A, W248A, Y251A affect the affinity and efficiency of only Aplaviroc whereas the mutations at W86A, Y108A, I198A affected maraviroc, vicriviroc and TAK-779 as discussed by Labrecque J. *et al.*

### 5.7. SAR studies of CCR5 antagonists

Based upon the structure based pharmacophore alignment of CCR5 ligands the essential features required for the therapeutic activity are 1) one basic feature e.g. basic nitrogen of MVC for interaction with Glu283, 2) one aromatic moiety e.g. triazole ring of MVC 3) one hydrophobic feature e.g. phenyl ring of MVC 4) second hydrophobic feature e.g. difluoro cyclohexane ring of MVC [39]. This pharmacophoric alignment and SAR studies discussed by Arimont Marta *et al.* help in the future development of novel CCR5 antagonists. The distribution of aromatic and hydrophobic features is symmetrical around the cationic feature in the centre. The spatial distribution of the aromatic, hydrophobic and cationic features of Vicriviroc, Aplaviroc, SCH-C, TAK-779 resemble the spatial distribution of maraviroc [74–78]. The structure activity relationship for CCR5 antagonist is derived from the various in affinity and potency of CCR5 ligands like MVC, APL, VVC, SCH-C, TAK-779, TAK-220, AK-

317, and AK-530 as shown in (Fig. 11) [39].

Modifications at aromatic pyridine ring in the structures of Vicriviroc, SCH-C, Aplaviroc cannot be done by substituting various electron withdrawing groups, as there is an observed decrease in affinities for these ligands. The seven-membered ring of TAK-779 is preferable over six membered rings and the optimal distance between the phenyl ring with quaternary nitrogen or positive charge is one carbon linker which reveals a strong π-π interaction with Trp86 [23,79]. The conformational arrangement which consists of relative distance and directions of cationic aromatic and hydrophobic is very much essential for CCR5 binding. The hydrophobic benzene ring in TAK-220 is favourable for increasing the affinity for CCR5. This reassures the importance of the hydrophobic feature. The modification at the linker of piperidine ring and benzene ring of TAK-220 decreases the affinity which implies that the flexibility of aromatic benzene ring is essential for targeting minor pocket of CCR5 [80]. The triazole and difluorohexyl ring replacement of maraviroc by benzimidazole and aromatic phenyl ring respectively, are tolerable to give similar activities [81–83]. A 290 fold decrease in activity is observed when the tetra hydro

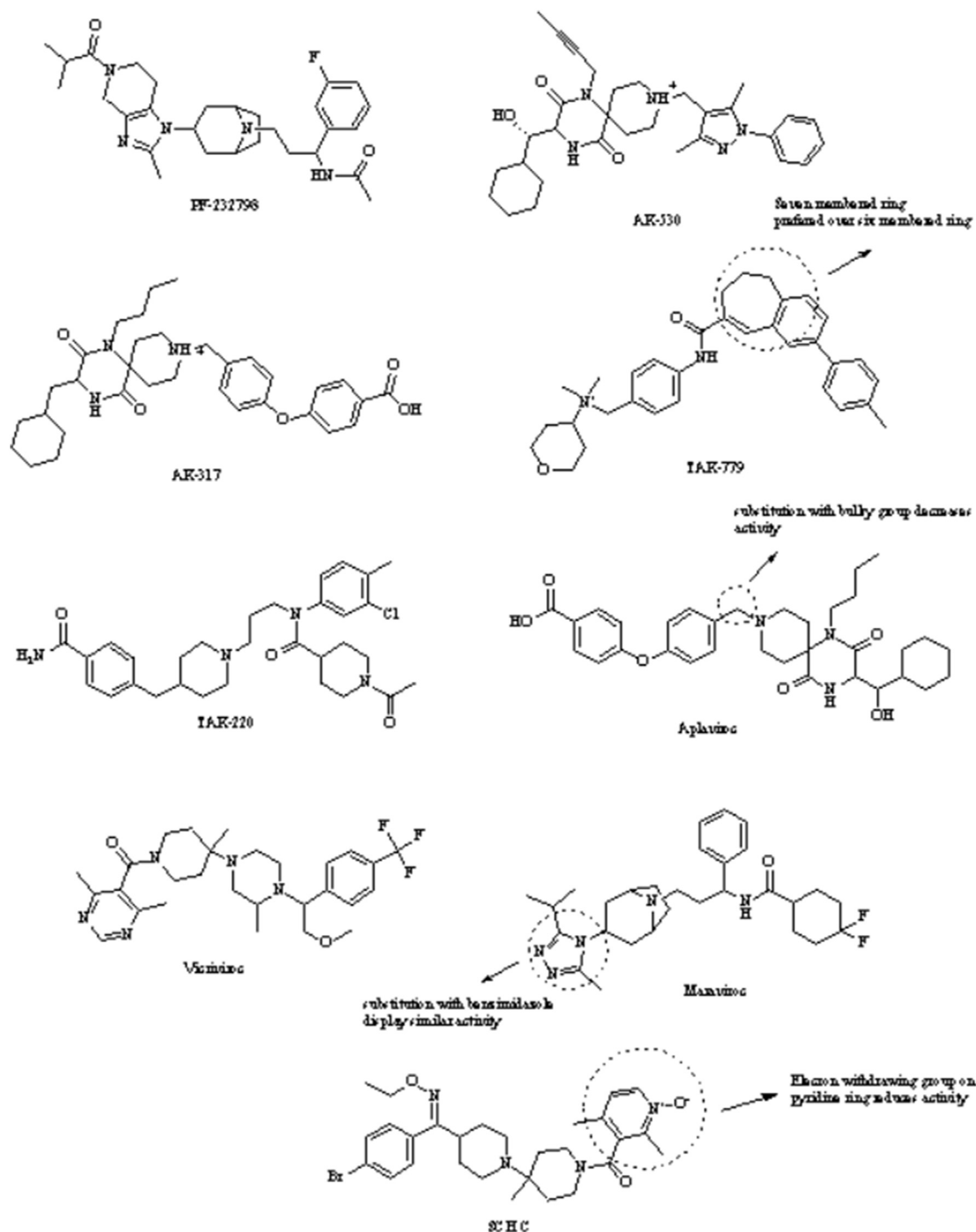


**Fig. 11.** SAR studies of CCR5 antagonists.

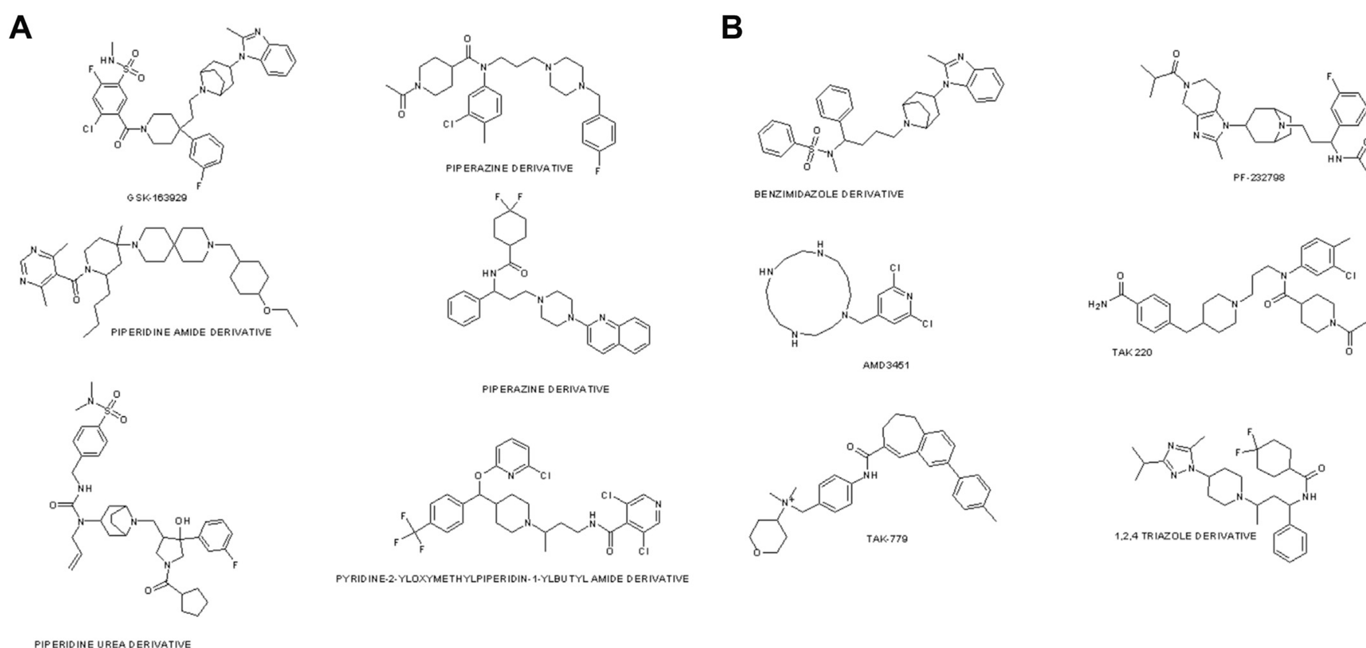


**Fig. 12.** Diversified scaffolds for designing novel anti-retroviral agents. Fig. 12a. GSK-163929, Piperazine derivatives, Piperidine amide and urea derivatives. Fig. 12b. AMD 3451, PF-232798, Benzimidazole and 1,2,4-triazole derivatives.

pyridinoimidazole is replaced by aromatic phenyl ring because of the reason that the aromatic bulky interactions of tetra hydro pyridine with Trp86 favours the affinity and efficiency of PF-232798 [84].

### 5.8. Current diversified scaffolds for targeting CCR5

There are certain molecules that are under pipeline upon which this paper would throw some light and would be further helpful in the development of CCR5 antagonist (Fig. 12.). The most potent amongst the discussed is imidazo-piperidine derivative and has an advantage of being more potent than MVC and can also combat resistant HIV-1 infection. Some of these scaffolds like 4,4 disubstituted piperidine derivative scaffold by GlaxoSmithKline showed reliable results with an $IC_{50}$ value of 4.26 nM can be an important lead. Another moiety that is an oral CCR5 antagonist candidate that is an Imidazo-piperidine drug candidate by Pfizer with an activity of $IC_{50}$ of 2 nM with a retained activity over the CC185 resistant strain of HIV-1. Two series by GSK of 2-phenyl-1,4-diaminobutane (DAB) and 2-methyl-2-phenyl-1,4-diaminobutane (MDAB) showed excellent anti-HIV activity with $IC_{50}$ of 8 nM on Peripheral Blood Lymphocyte (PBL). A ligand was designed utilizing bio-isosterism of Maraviroc generated a carboxamide moiety with an $IC_{50}$ of 14.4 nM in RATNES binding assay. TAK-220 is another lead that consists of piperidine-4-carboxamide by Toriba Therapeutics reached clinical phase I but have no development further [64]. Merck also worked and obtained a lead to a series of 1,3,3,4 tetra substituted pyrrolidine that furnished nifreviroc with an $IC_{50}$ of 2.9 nM [85]. Some short existing scaffolds of 1,2,4 triazole, 1-amido-1-phenyl-3-piperidinyl butane [86], pyridine-2-yloxymethylpiperidin-1-ylbutyl amide, pyridine-2-ylmethylaminopiperidin-1-ylbutyl amide [87] with variable activity having $IC_{50}$ ranging between 0.25 and 75 nM. Roche provided another lead molecule of diazaspiro (5,5) undeca-2-one [88] with an excellent potency of 30 nM. GSK again harbored a lead of *p*-cyanobenzyl [89] derivative that was reported to be toxic. Roche has another moiety into the pipeline with a scaffold of octahydro-pyrrole-(3,4-c) pyrrole with an $IC_{50}$ of 6.17 nM in 2012. Schering-Plough produced an Indane derivative from SAR studies of Vicriviroc has an anti-HIV-1 activity with $IC_{50}$ of 0.16 nM. Roche ended up in the lead of hexahydropyrrol (3,4-c) pyrrole [90] through HTS having an $IC_{50}$ of 7 nM [6,7].-fused 1-benzazepine to a [6,8]-fused-1-benzazocine optimisation resulted in the generation of Cenicriviroc which dually blocks CCR5/CCR2 that is in phase IIb trials. Novartis disclosed another novel CCR5/CCR2 dual antagonist lead of an indole derivative through HTS activity. An N-pyridinylmethyl cyclam AMD3451 [91] was the first CCR5/CXCR4 dual inhibitor with $IC_{50}$ of 1.2 μM. Pyrazolopyrimidine [92] is also a hit for the CCR5/CXCR4 dual inhibitor.

## 6. Conclusion

The current combinatorial anti-retroviral therapy of HAART suffers from major disadvantages due to day to day evolution of the virus into a drug-resistant strain which demands novel anti-retroviral therapy that combats HIV-1 and its resistance. This review presented the problem associated with the current HAART therapy and focused on the alternative pathways and techniques that might become a potential route for combating HIV-1 resistance. CCR5 is a promising target for inhibiting HIV-1 infection at a very early stage of viral life cycle. Even though CCR5 is a potential target for restricting infection, it suffers from a setback of resistance. Hence, designing novel CCR5 Antagonists that interact with conserved residues or sequences of amino acids in the CCR5 active pocket or novel dual antagonist of CCR5/CXCR4 co-receptors could serve as a highly effective therapy for resistant HIV-1 infection. Thus, the novel CCR5 antagonist could serve the purpose of combating viral resistance with efficient potency as the major advantage over Maraviroc which is the only CCR5 antagonist available in the market.

## Conflicts of interest

Authors confirm that this article content has no conflicts of

interest.

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