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Therapeutic potential of peptidomimetics as antiviral agents: short review on recent progress

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Abstract

The tug of war between viruses and humans existed for millions of years. The defensive mechanisms and rapid evolution of these viruses have made it difficult for researchers to progress in antiviral drug discovery. Therefore, this paper is intended to give an overview on reported drug targets via an insight on viral pathogenesis and the peptidomimetic-drugs reported till date against three most globally prevalent and deadly viruses: SARS-CoV-2, HIV, and HCV. The reason for selective illustration in this review is attributed to the proven record of antecedents reporting wide scope of peptidomimetics in development of antiviral drugs highlighting the ease of rapid mobilization of peptidomimetics for treatment of emerging viruses.

Introduction:

RNA viruses affecting humans cause devastating mortality and morbidity rates. These microorganisms lack ribosomes, hence require host cell to synthesize proteins and replicate itself, therefore we can term this microorganism as an obligate parasite. This viral protein synthesis plays a vital role in viral life cycle and thus its inhibition is one of the main targets in Anti-viral drug discovery. However, drug discovery in the field of virology requires continuous efforts due to the constant mutation and re-emergence of these deadly pathogens [1, 2]. Though a variety of antiviral drugs and vaccines are commercially available, yet there is always a new urge for more potent molecules. Moreover, the pandemics like Spanish flu (1918), SARS (2003) and the most recent COVID-19 (2019) are the three major outbreaks which caused and still causing adverse effects on humankind. It is important to note that, COVID-19 has caused more than 3 million deaths worldwide till date. According to recent statistics released by WHO, deaths due to viral infections has gradually decreased over last two decades (Figure 1), the success can be majorly attributed to development of effective anti-viral regimens and therapies [3, 4].

In development of antiviral drugs, it is important to understand fundamentals of chemical biology of virus and its interactions with host cell. The main strategies to combat viral infections are vaccines (for prevention) and antiviral agents/antibodies (for treatment). Classification of antiviral drugs is based on their chemical structure, target site, and mode of action. From the portal of entry to the spread of infection, there are multiple targets identified by researchers to interrupt or block the pathogenesis of virus, namely: Entry/Fusion inhibitors, inhibitors of viral genome replication, inhibitors of viral protein synthesis etc [5, 6].

Peptidomimetic molecules are the desirable alternatives to the peptide structures, they mimic the native peptides in 3D space in either transition (or) ground-state and produce the same biological effect as parent peptides. Apart from circumventing the ADME problems associated with natural peptides, these peptidomimetic molecules have enhanced pharmacokinetic properties over natural peptides, therefore exhibit better bioavailability at the target site, the main advantage for peptidomimetic molecules over peptides is attributed to the ability to resist protease-mediated decomposition. In other words, it is a process to incorporate peptide features into a nonpeptide scaffold. It is important to mention that the development of peptidomimetic molecules needs knowledge of conformation, topology and electronic orientation of native peptide molecule. Further, tight binding of peptides at the active site of enzymes calls for large surface area and high functionality around the molecules, therefore highly functionalized peptidomimetic molecules can have more interaction at the active site of an enzyme. Past decade has been a milestone in development of antiviral peptidomimetic drugs. Initially, a peptidomimetic drug candidate is based on the native peptide, mimicking its protein interaction (or) structure (or) function, which later modified in laboratory to overcome blood-brain barrier and enhance bioavailability, reduce drug elimination, and induce stability [7, 8].

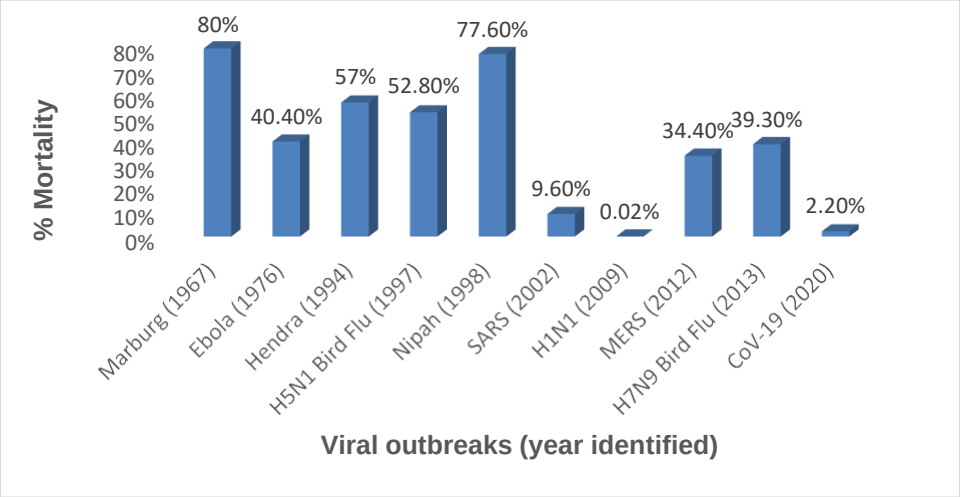

Figure 1: Yearly viral outbreaks and respective mortality rates (as per WHO)

Literature review and Discussion:

Peptidomimetics targeting anti-HIV drugs.

HIV is one of the deadly viruses causing immunodeficiency in human. Though pathology of this virus is well known, yet its vaccine or treatment is elusive to researchers, reason being the development of latent reservoirs of HIV soon after infection and rapid mutation of the virus. In the past decade broadly active neutralizing antibodies (bnAbs) were identified to be prophylactic against HIV infection in preclinical stage. However their efficacy is questioned at mucosal entry point in humans. Among HIV therapeutics, peptidomimetic based therapeutics for entry/fusion inhibitors, Protease inhibitors, integrase inhibitors, are discussed in present paper [9, 10].

Entry/Fusion inhibitors:

The entry inhibitors are more advantageous over other classes of inhibitors because this class of inhibitors blocks viral infection at the stage of invasion without any effect on human cell. Based on the point of entry, the inhibitors target Env gp120, gp41, host receptor CD4 and coreceptors CCR5, CXCR4. The only FDA approved gp41 inhibitor is enfuvirtide, commercialized as Fuzeon. This fuzeon is a peptidomimetic of gp41 C-terminal heptad repeat (CHR), it prevents the formation stable 6- helix bundle (6HB) and thus blocks the fusion of viral with human target cell membrane. Due to rapid mutations and HIV gp41 structural dynamics it is difficult to develop gp41 inhibitors. However, recently in the year 2020, *T. Kobayakawa et.al* reported a dimerized peptidomimetic small inhibitors with a PEG linker targeting a 34-mer peptide fragment in gp41 viral receptor (Figure 2.a) [11, 12].

Human CD4, also known as T-cells are the entry-level targets for human immunodeficiency virus (HIV), *Neffe and Meyer* resolved this issue by developing a peptidomimetic ligand of a peptide NMWQKVGTPL whose binding affinity and efficiency of interaction towards CD4 cells was enhanced by synthetically modifying its chemical structure, thereby blocking the interaction of these cells with viral glycoprotein gp120 and thus providing an entry level defensive mechanism against the virus. On the other hand*, L. K. Tsou et al.* developed a proteomimetic inhibitor, that binds to the viral glycoprotein gp120, thereby inhibiting its interaction with human CD4.

Viral chemokine coreceptors and important targets for genesis of HIV infection, CXCR4 and CCR5 are a part of gp120. Few peptidomimetic-based CXCR4 antagonists were developed namely, T140 developed in the year 1998 is a 14-mer peptide molecule competitively binds to CXCR4 and blocks the entry of X4-HIV-1 entry. FC131, a comparably more potent CXCR4 antagonist was developed in the year 2003. POL-3026 and POL-6326 are conformationally constrained mimetics based on b-hairpin structure of polyphemusin II. Further, though maraviroc is the first antagonists developed against CCR5 receptor which is a non-peptidic CCR5 ligand, there was a considerable development in peptidomimetic based drugs. *M. Saitz et.al* in the year 2010 developed a structural mimic to helical CCR5 epitope (Figure 2.b). Other CCR5 inhibitor aminooxypentane-RANTES (AOP-RANTES) which is a more potent derivative of RANTES and inhibits the HIV entry into target cell [13-15].

Protease Inhibitors

HIV protease is the most viable biological target for developing therapeutics against HIV., as they block viral replication and hinder its infection in human cells. Structurally, this HIV protease enzyme consists of b-sheet and a-helical segments in a curved tubular shape. Though few non-peptide leads were developed earlier, yet the idea of

peptidomimetic based anti-HIV therapeutics introduced in 1990 has instigated many researchers to develop in it. Finally in the year 1996, first peptidomimetic based protease inhibitor, Saquinavir was approved by FDA. Later other peptidomimetic molecules, namely: nelfinavir, amprenavir, ritonavir and indinavir were commercialized into the market. These first generation drugs mimic the tetrahedral transition-state of native peptide and has hydroxyethylene and hydroxyethylamine bonds as the peptidomimetic scaffold which enhanced its potency and addressed the issue of viral resistance compared to the previous drugs. However, the first generation drugs exhibited various pharmacokinetic impediments eventually leading to virological failure [16, 17].

The shortcomings of first-generation drugs due to inherent peptide-like structures were combated by their reduction in second-generation drugs with an emphasis on enhanced antiviral activity. It is important to mention that the failure in treatment with first-generation drug, ritonavir was due to mutation at V82, which is caused by the interaction of thiazolyl P3 ligand with V82. This problem of ritonavir was overcome by lopinavir. Later replacement of aza-dipeptide bond with hydrazine and introduction of pyridylbenzyl moiety enhanced the antiviral activity of Atazanavir over first generation drugs. Introduction of 1-Phenylpropyl and m-sulfonamide at C3 and C6 position respectively enhanced the potency and antiviral activity over all the first-generation drugs. Moreover, the impediment of water solubility of firs-generation Amprenavir was resolved by synthesizing its prodrug Fosamprenavir, similarly, introduction of chiral bis-tetrahydrofuran instead of monosubstituted tetrahydrofuran in Amprenavir enhanced the viral enzyme inhibition over this first-generation drug (Figure 2.c) [18, 19].

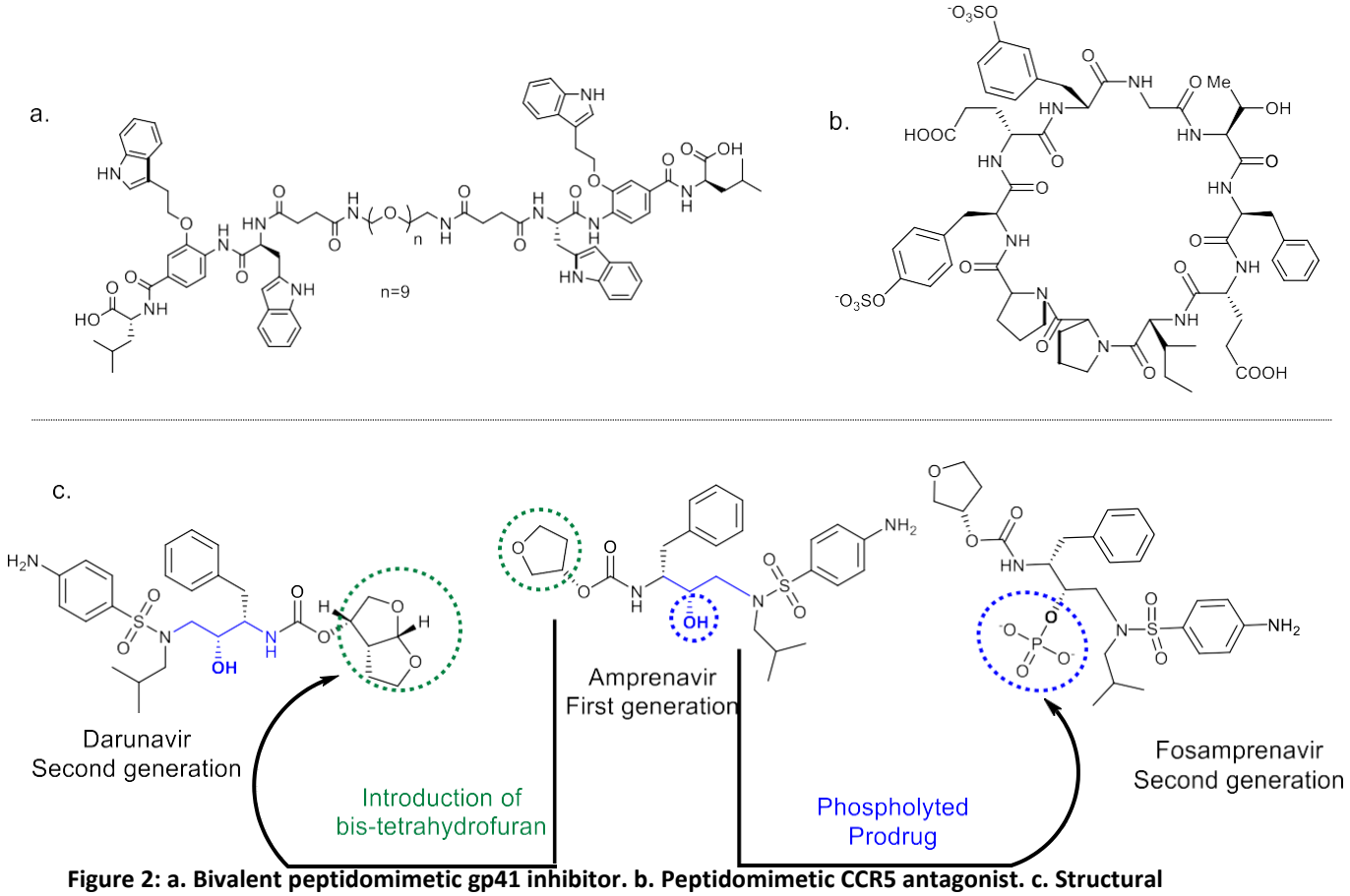

Figure 2: a. Bivalent peptidomimetic gp41 inhibitor. b. Peptidomimetic CCR5 antagonist. c. Structural modification of Amprenavir to obtain second generation drugs.

Integrase (IN) inhibitors

HIV integrase is an enzyme which belongs to the family polynucleotide transferases and integrates viral DNA into human cell's chromosomal genome. Integrase enzyme integrated the viral DNA into the human DNA in two steps: 1. Viral DNA preparation with recessed 3'-OH termini. 2. Integration of recessed DNA into human DNA. Therefore, these IN inhibitors are also known as integrase strand transfer inhibitors (INSTIs), which are becoming more common

in antiretroviral therapy. Thought FDA approved small molecule-based drugs and peptides were developed as IN inhibitors, yet peptidomimetic based molecules stand as novel avenue for development of IN inhibitors, especially to interfere with the interaction between cofactor, LEDGF/p75-Integrase interaction [20, 21].

Peptidomimetic targeting SARS-CoV-2

The ongoing pandemic, SARS-CoV-2 which cause coronavirus disease, COVID-19 called for an alarming situation urging for immediate identification of vaccines and concerned antiviral treatment. So far, remdesivir and convalescent plasma are the only authorized clinical drugs prescribed for recovery from this virus. In this context, peptidomimetic-based inhibitors could be more efficient alternatives over small molecule-based drugs due to better tolerance. Generally, in SARS-CoV-2 infection, the S protein attachment, S1 and S2 conformational changes, insertion of fusion peptide (FP), rearrangement, six-helix bundles (6HB) formation, and viral proteases are vital drug targets whose activity can be blocked by designing peptidomimetic-based inhibitors and prevent any further infection. Further, we can categorize the anti-SARS-CoV-2 drugs into: Viral entry inhibitors, viral protease inhibitors while viral replicase inhibitors for the same are still under progress.

Entry inhibitors

SARS-CoV-2 attaches to the human ACE2 cells with its spike glycoprotein, S-protein, exactly mentioning it is the S1 subunit of S-protien which binds to ACE2 cells. Therefore, the S protein-mediated viral attachment and entry are expected to be the main targets in developing neutralizing antibodies or vaccines or therapeutics [22, 23].

Protease inhibitors

After the initial attachment, the serine protease TMPRSS2 of host cell is responsible for proteolytic cleavage of viral S-protein and the exposed S2 subunit allows the fusion between viral and human cell-membrane. It is this S2 subunit that contains fusion peptides, heptad repeat region 1 (HR1) and, heptad repeat region 2 (HR2). These HR1 and HR2 play a vital role in drawing the host and viral cell membranes to proximity, in turn aiding in fusion, releasing viral genome into host (human) cytoplasm. Thus, peptidomimetic molecules which block this fusion are derived from the HR1 or HR2 domain of viral S protein and most of the molecules are under preclinical trials. Camostat is a peptidomimetic TMPRSS2 protease inhibitor, along with inhibiting the entry of vesicular stomatitis virus (VSV), a virus that harbors SARS-CoV-2. After entry, the release of viral genome, the ribosome initiated the viral replication aided by release of polypeptides by viral proteases. At this stage, a combination of peptidomimetic drugs, Lopinavir/ritonavir is used as regimen to inhibit the activity of viral proteases. In the process of further exploration for effective peptide-based antiviral agent against this, SARS-CoV-2, it was identified that protease nsp5 ($3CL^{pro}$ or M^{pro}) is an important target to develop effective antiviral agents, which received major attention from the researchers, however, peptide-based antiviral agents have the problem of proteolytic degradation which could be overcome by peptidomimetics. The active site of nsp5 contains a Cys-His catalytic dyad, here cys145 acts a nucleophile, while His41 acts as the general acid/base. With a long b-strand on one end and loop residues 189-191 on other side, the substrate binding pocket is situated between domain I and II. Glu66 is an important residue for substrate recognition and binding, which forms active site of a monomer of M^{pro}. It is important to note that the M^{pro} binding site is a most conserved site with least drug resistance, which proved the interest of many chemical biologist to synthesize substrates with best fit for this active site. Effective M^{pro} inhibitors structurally contain a peptidomimetic molecule with four components: M^{pro} S1 site, M^{pro} S2 site, a highly variable tail region and Warhead (Figure 3.a). Beginning in early 2000, Yang H, Xie W, Xue X, Yang K, Ma J, et al. in 2005 and Xue et al. in 2008 designed a peptidomimetic irreversible inhibitors, N3 and 13b respectively (Figure 3.b), against CoV M^{pro} proteases, (the main enzymes for processing polypeptides from viral RNA), with low cellular toxicity. In 2016, T. Pillaiyar et al. reported four peptidomimetic inhibitors against $3CL^{pro}$ also known as M^{pro}, wherein the a part of selective substrate was replaced by “warhead” groups like aldehydes, halomethyl ketones, epoxy ketones and Michael acceptors, thereby making the peptidomimetic inhibitors more selective to the specific site of $3CL^{pro}$ (Figure 3.c) [24, 25].

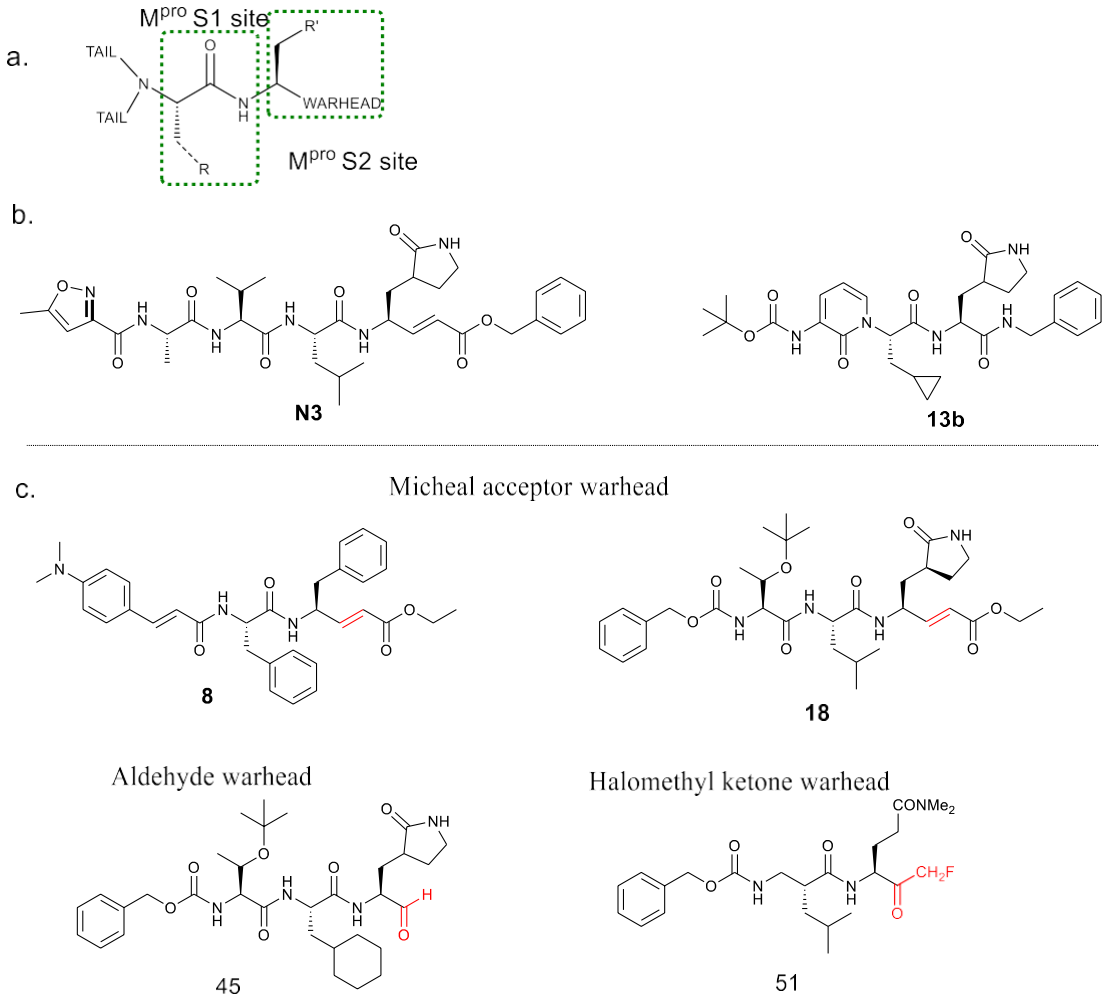

Figure 3: Anti- SARS-CoV peptidomimetic drugs.

Peptidomimetics targeting HCV

Hepatitis C virus (HCV) is a global health problem affecting more than 185 million humans worldwide. It causes chronic liver disease, leading to hepatocellular carcinoma in worst cases. It is important to note the disease goes unnoticed till the stage of liver damage because this disease is generally asymptomatic till the development of viral reservoirs in liver. HCV is the main cause of HCC (hepatocellular carcinoma) and cirrhosis, which may lead to an urge for liver transplantation in many cases. The open reading frame in the RNA of this small, enveloped virus, encodes for a polyprotein precursor which on post translation transcends into viral polyprotein. The post-translational structural and non-structural proteins are synthesized by ribosome. The gene order of structural and non-structural proteins as reported in the literature has the gene order s 5'-C-E1-E2-NS2-NS3-NS4A-NS4B-NSSA-NSSB-3'. Earlier interferon-based therapy has proved to be an ineffective method of treatment in most of the patients causing many side effects. This triggered the development of alternative treatment regimens with more efficacy and better rate of tolerance in patients. The anti-HCV drugs can be categorized into two: 1. DAAs - Direct-acting target viral proteins driving HCV lifecycle. 2. HTAs – Host cell targets required for viral replication. Table 1 depicts the viral and host targets and their respective functions along with the selective drug classes. In this review we will focus only on those DAAs and HTAs which have peptidomimetic based drugs as anti-HCV agents [26, 27].

DAAs		**HTAs**	
Function (*Virus protein*)	Drug class	Function (*Host protein/ cell*)	Drug class

Envelope gylcoproteins (*E1, E2*)	Neutralizing antibodies	Viral entry (*CD81*)	Antibodies and small-molecule inhibitors
Viroporin (*p7*)	Imino sugars	Viral entry (*SCARB1*)	
Serine protease (*NS3A, NS4A*)	Peptidomimetics	Viral entry (*OCLN*)	
Membrane remodeling (*NS4B*)	Small-molecule inhibitors	Viral entry (CLDN1)	
RNA replication (*NS5A*)	Peptidomimetics	NS5A cofactor (*Cyclophilin A*)	Peptoids- Cyclosporin A derivatives
RdRP (*NS5B*)	Nucleoside/non-nucleoside inhibitors	Viral RNA stabilization (*miR122*)	Oligonucleotides

Table 1: Anti-HCV drug targets and concerned drug class.

Serine protease (NS3A, NS4A) Inhibitors:

The trypsin-like serine protease present in NS3 protein of hepatitis C virus is responsible to process viral polyprotiens and is one of the top three drug targets against HCV. This NS3 is a bifunctional protein with serine protease activity at 5'end and NTPase (or) helicase activity at 3' end. During the replication of viral genome (RNA), the NS3 helicase hydrolyzed NTP serves as energy source aiding in unwinding of double-stranded RNA in a 3' to 5' direction. While the exact function of helicase is unknown, few researchers believe that helicase might initiate RNA synthesis. Hence, both serine and helicase end of the NS3 protease of virus is important in its replication. It is also important to note that NS4 is a cofactor that regulates NS3 enzymatic activity by localizing it on the outer leaflet of ER membrane. The NS3 protease inhibitors synthesized are aimed to either behave as competitive inhibitors (blocking the active site) or allosteric inhibitors (interfere in conformational changes). There are three classes of drugs used as NS3A inhibitors: peptidomimetics, oligopeptides and macrocycles, Table 2 shows the approved drugs under these three categories.

Apart from the above approved drugs, few potent molecules were reported in past decade. Recently, in 2020, *A. Omar and M. Elfaky, S. Arnold* inspected the crystal structure of NS3-NS4 complex and developed a peptidomimetic imidazole scaffold (Figure 4.a) inspired by the kink region of NS4A region which showed promising activity against NS3 region. In 2019, *I.Meewan, X. Zhang, S. Roy et.al* developed Tryptophan-based peptidomimetic molecule (Figure 4.b) in 4 steps which exhibited good binding activity as HCV NS3/4A protease inhibitors [28]. In 2017*, A. Portela, T.Barros, C.Lima et.al* synthesized isosorbide based peptidomimetic molecule with furan as heterocyclic substituent (Figure 4.c) was selectively potent against HCV NS3/4A protease. In 2014, *A. Lampa, S. Bergman, S. Gustafsson et.al* reported aryl acyl sulfonamides (Figure 4.d) as HCV NS3/4A protease inhibitors with pyrimidinyloxyphenylglycine and 4-(trifluoromethyl)phenyl as side chains. In 2009, *M. Sellstedt and F. Almqvist* synthesized rigid tricyclic peptidomimetic scaffold (Figure 4.e) which is expected to exhibit biological activity a [29-31].

Peptidomimetics	Oligopeptides	Macrocycles (*)
Boceprevir Telaprevir Narlaprevir	Asunaprevir Faldaprevir	Ciluprevir (P_1–P_3) Danoprevir (P_1–P_3) Glecaprevir (P1–P3) Voxilaprevir (P1–P3) Paritaprevir (P1–P3) Simeprevir (P1–P3) Vaniprevir (P2–P4) Grazoprevir (P2–P4)

(*): Individual amino acid sidechain that interacts with the binding pockets of the protease.

Table 2: FDA approved anti-serine protease drugs.

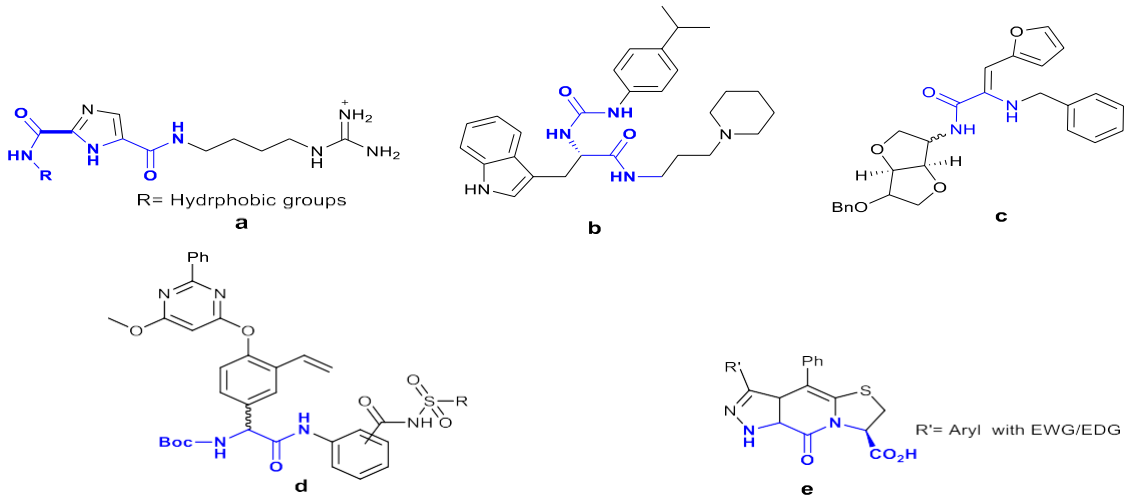

Figure 4: Potent serine protease inhibitor peptidomimetic molecules.

RNA replication (NS5A) Inhibitors:

NS5A is a non-structural phosphoprotein which involves in multiple roles for viral lifecycle in host cell, these include cellular functions, complex interactions, and viral replication. This protein is localized to ER membrane and exists in phosphorylated form. This protein is mainly composed of 3 domains (I, II, III) and four functional regions (A, B, C, D), wherein domain I is involves in RNA replication aided by RNA dependent RNA polymerase, while the domains II and III are mainly involved generating viral particles. Moreover, previous studies mention that viral NSA5A protein interacts with cyclophilin A which is key for RNA replication. On the other hand, it is domain III of viral NS5A which is important for viral genome packaging and assembly [32]. Due its vital role in viral lifecycle NS5A is identified as a key drug target to inhibit viral activity. Previous literature illustrates. four mode of action for these inhibitors: block signaling with viral components , block viral genome replication and assembly, block NS5A oligomer functions, redistribute the NS5A proteins localized in ER region to cytoplasmic lipid droplets, this is accompanied by the inhibition of viral activity. It is to be noted that, the chemical structure of NS5A inhibitors has a specific pattern, consisting of central non-peptidic planar linker with peptidomimetic chain (heterocycle + cap) on either side of linkers containing hetero/homo dimer structures (Figure 5.a). Though there are FDA approved drugs against this target, yet further potent drugs are under clinical trials as depicted in Table 3 [33, 34]

FDA approved drugs	Molecules under clinical trials
Daclatasvir	IDX719
Elbasvir	ACH-3102
Ledipasvir	GSK-2336805
Ombitasvir	ACH-2928
Pibrentasvir	BMS824393
Velpatasvir	ACH-3102
Ritonavir	PPI668

Table 3: NS5A inhibitors

Apart from above mentioned FDA approved drugs and those under clinical trials, there has been a good progress I development of new potent molecules in recent past. In 2020, *B. Liu, K. Gai, H. Qin et.al.*developed a potent molecule by incorporating 4-silapiperidine group attached to N-phenylpyrrolidines planar core and N-phenylpyrrolidines cap (Figure 5.b), as pangenotypic NS5A inhibitor. In the same year W.Kazmierski, S.Baskaran, J.Walker, designed and developed GSK2818713 which is inspired from first-genration drug daclatasvir having biphenyl core (Figure 5.c),. In 2019, *V.Ramdas, R. Talwar and M. Banerjee et.al* developed a homodimeric molecule with a tricyclic core (Figure 5.d), wherein it was identified through SAR studies that the planar structure of central core is responsible for pangenotypic (active against all genotypes) and substituted imidazole enhanced the antiviral activity. In 2018, In 2017, *I. Kang, S.Hsu, H.Yang et.al* developed a orally bioavailable NS5A inhibitor (Figure 5.e) as potent and selective

anti-HCV molecule. Presence of substituted thiazole and a carboxamide link between thiazole and pyrrolidine heterocyclic rings enhanced the activity over lead molecule. *S.Giroux, J.Xu, T.J.Reddy et.al.* in the year 2013 designed and developed an analogue of Daclatasvir by 2 structural modifications, replacement of one of the imidazole ring with thienoimidazole and modifying biraryl linker to a monoaryl linker (Figure 5.f) [35-38].

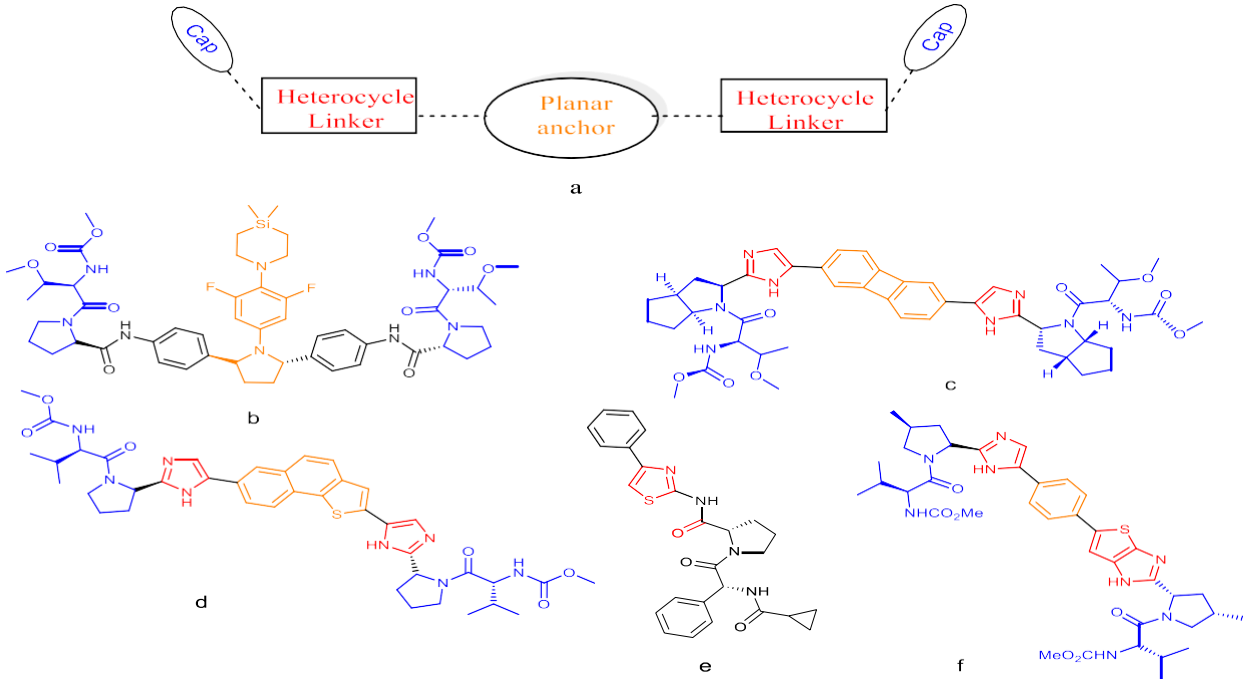

Figure 5: Potent NS5A inhibitor peptidomimetic molecules

Conclusion and perspective

The discovery of effective antiviral drugs is a challenge due to the emergence and re-emergence of viruses. In the present pandemic , more potent anti-viral molecules can be generated by virtual screening methods and structure-based designs. Since most of the early phase of the viruses are in latent stage, it is difficult to prevent infections in early stages as in HIV. Hence, effective inhibitors for later stage of viral lifecycle is vital in antiviral drug development. As observed in the literature most of the peptidomimetic molecules are designed by initial confirmation of active binding sites. This allows the researchers to tailor the chemical structure of molecules by incorporating essential groups and eliminating non-essential groups so that the final molecules are a good fit at the active sites. For example, the second-generation anti-HIV peptidomimetic drugs, Fosamprenavir and Darunavir were inspired from the first-generation drug Amprenavir by its structural modification. Similarly, incorporation of warheads in anti-SARS-CoV potent molecules is another tailoring strategy adopted by the researchers to enhance their potency. Potent NS5A molecules also gives us a perspective that, observing the chemical pattern of the lead molecule and its further tailoring allows researchers to design and develop molecules with good interaction and fit with receptor.

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