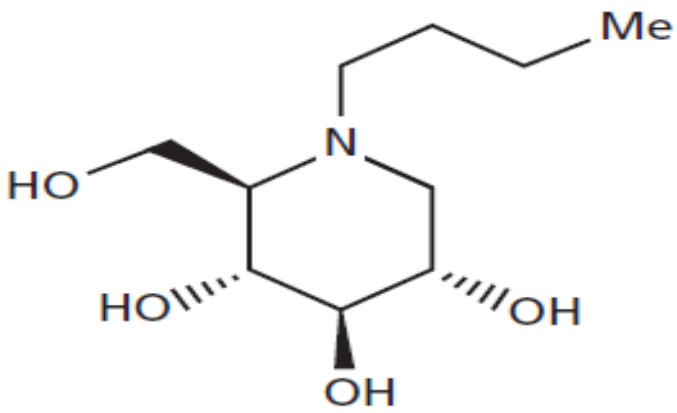
Antiviral agents

Inhibitors of other targets

Inhibitors of other targets

- *N* ***-Butyldeoxynojirimycin is a carbohydrate*** that inhibits **glycosidases —enzymes that catalyse** the trimming of carbohydrate moieties linked to viral proteins.
- If this process is inhibited, too many carbohydrate groups end up attached to a protein, resulting in the protein adopting a different conformation.



N-Butyldeoxynojirimycin

Maraviroc

- **Maraviroc was approved as a CCR5 chemokine receptor antagonist** in 2007 and is the first anti-HIV agent to act on a molecular target on the host cell rather than the virus.
- It was developed from a compound that had potent activity, but which blocked HERG ion channels,a potassium ion channel.
- This ion channel is best known for its contribution to the electrical activity of the heart that coordinates the heart's beating.
- Agents which block these channels often have toxic cardiac side effects and so a large number of analogues were synthesized to find a potent compound which did not block the HERG ion channels.
- Maraviroc was the result. It is an example of an agent that works by blocking protein–protein interactions between a viral protein and a host cell protein

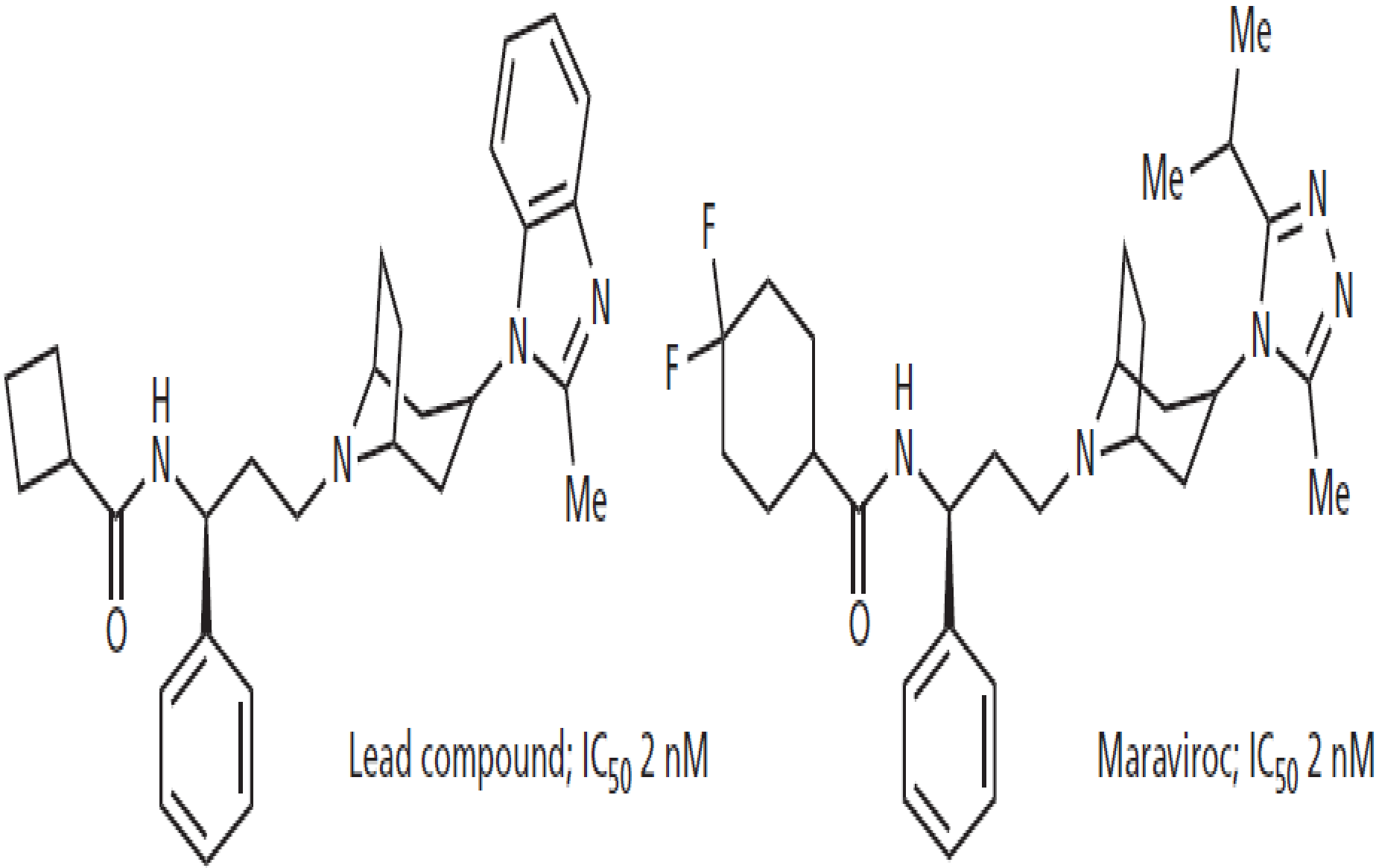


FIGURE 20.37 Comparison of meraviroc and the lead compound from which it was developed.

Raltegravir as Integrase Inhibitor

- Th e first integrase inhibitor to reach the market in 2007 was **raltegravir.**
- **The keto-enol system** is important for activity as it acts as a chelating group for two magnesium ion cofactors in the enzyme's active site.

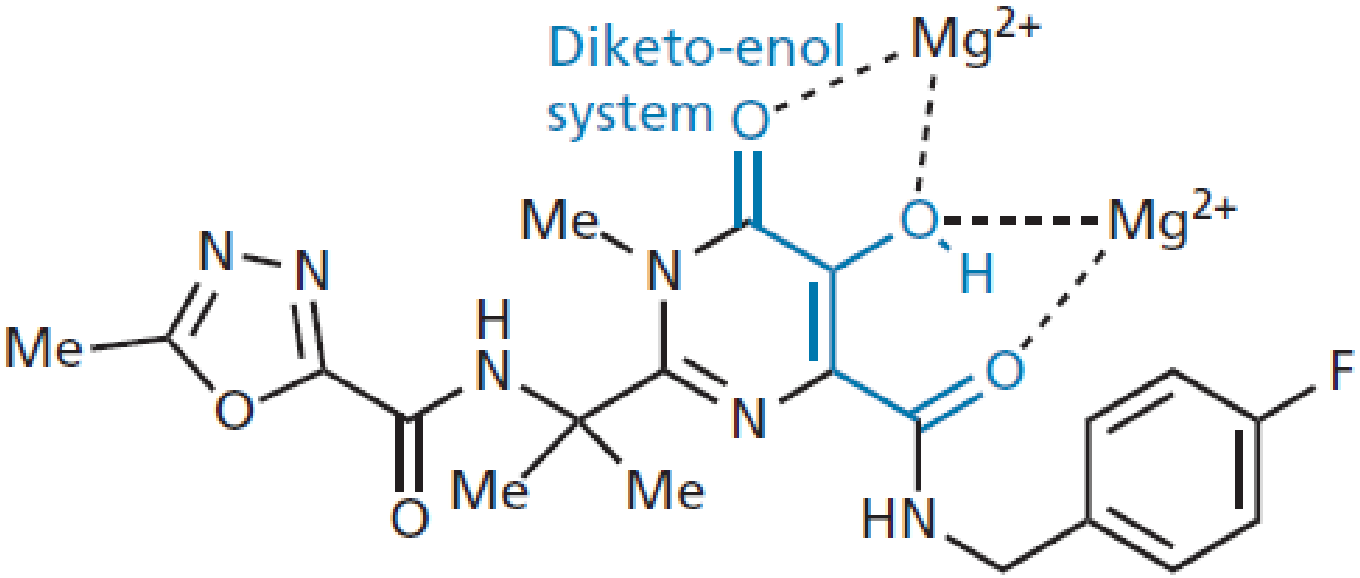


FIGURE 20.38 The integrase inhibitor raltegravir acting as a metal ion chelator.

Antiviral drugs acting against RNA viruses

Antiviral drugs acting against RNA viruses: flu virus
Structure and life cycle of the influenza virus

- Influenza (or flu) is an airborne, respiratory disease caused by an RNA virus which infects the epithelial cells of the upper respiratory tract.
- The nucleocapsid of the flu virus contains (−) ssRNA and a viral enzyme called **RNA polymerase**
- Surrounding the nucleocapsid there is a membranous envelope derived from host cells which contains two viral glycoproteins called **neuraminidase** (NA) and **haemagglutinin (HA).**
- **The latter acquired** its name because it can bind virions to red blood cells and cause haemagglutination.

Antiviral drugs acting against RNA viruses: flu virus
Structure and life cycle of the influenza virus

- The mucosal secretions are rich in glycoproteins and glycolipids which bear a terminal sugar substituent called **sialic acid (also called *N -acetylneuraminic acid).***
- ***NA (also called sialidase) is*** an enzyme which cleaves sialic acid from these glycoproteins and glycolipids , thus degrading the mucus layer and allowing the virus to reach the surface of epithelial cells.
- Once the virus reaches the epithelial cell, adsorption takes place whereby the virus binds to cellular glycoconjugates that are present in the host cell membrane, and which have a terminal sialic acid moiety.
- The viral protein HA is crucial to this process. Like NA, it recognizes sialic acid but, instead of catalysing the cleavage of sialic acid from the glycoconjugate, HA binds to it .

Antiviral drugs acting against RNA viruses: flu virus
Structure and life cycle of the influenza virus

- Once the virion has been adsorbed, the cell membrane bulges inwards taking the virion with it to form a vesicle called an **endosome —a process called receptor mediated endocytosis .**
- **The pH in the endosome then decreases,** causing HA in the virus envelope to undergo a dramatic conformational change whereby the hydrophobic ends of the protein spring outward and extend towards the endosomal membrane.
- After contact, fusion occurs and the RNA nucleocapsid is released into the cytoplasm of the host cell.
- Disintegration of the nucleocapsid releases viral RNA and viral RNA polymerase, which both enter the cell nucleus.

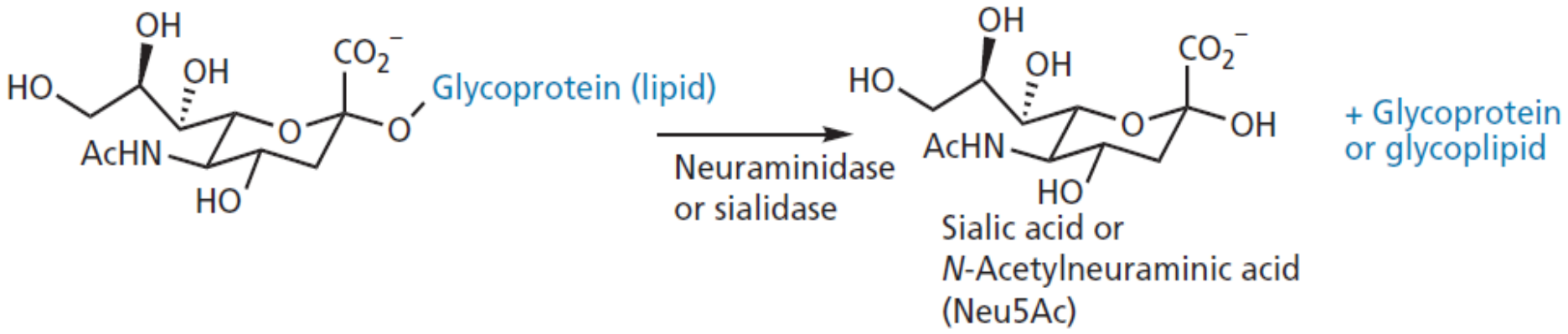


FIGURE 20.39 Action of neuraminidase (sialidase).

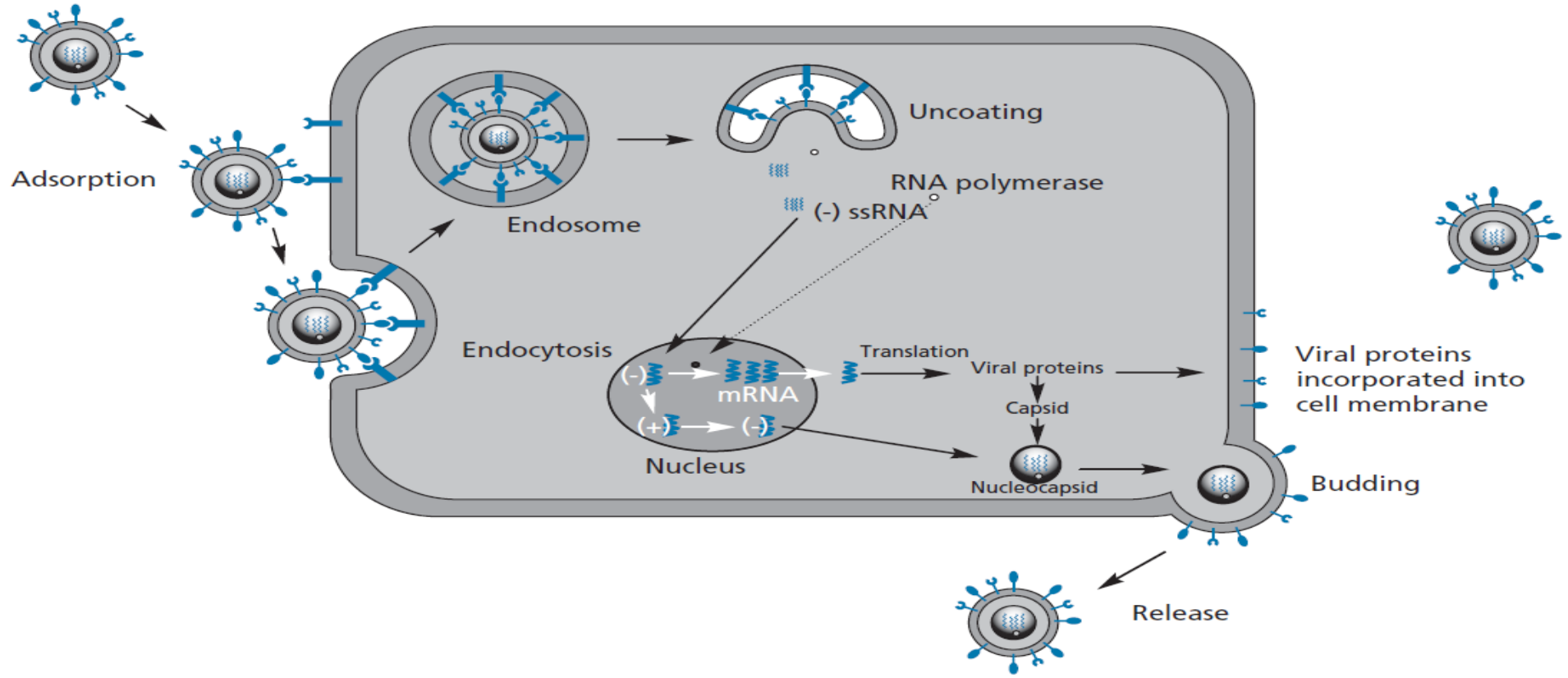


FIGURE 20.40 Life cycle of the influenza virus in a host epithelial cell.

Antiviral drugs acting against RNA viruses: flu virus
Structure and life cycle of the influenza virus

- Viral RNA polymerase now catalyses the copying of (−) viral RNA to produce (+) viral RNA, which departs the nucleus and acts as the mRNA required for the translation of viral proteins. Copies of (−) viral RNA are also produced in the nucleus, then exported into the cytoplasm.
- Capsid proteins spontaneously self-assemble in the cytoplasm with incorporation of (−) RNA and newly produced RNA polymerase to form new nucleocapsids.
- Meanwhile, the freshly synthesized viral proteins HA and NA are incorporated into the membrane of the host cell.
- Newly formed nucleocapsids then move to the cell membrane and attach to the inner surface. HA and NA move through the cell membrane to concentrate at these areas and host cell proteins are excluded

Antiviral drugs acting against RNA viruses: flu virus
Structure and life cycle of the influenza virus

- Budding then takes place and a new virion is released. NA aids this release by hydrolysing any interactions that take place between HA on the virus and sialic acid conjugates on the host cell membrane.
- As HA and NA are on the outer surface of the virion, they can act as antigens (i.e. molecules which can be potentially recognized by antibodies and the body's defence systems).
- In theory, it should be possible to prepare vaccines which will allow the body to gain immunity from the flu virus.
- Such vaccinations are available, but they are not totally protective and they lose what protective effect they have with time. This is because the flu virus is adept at varying the amino acids present in HA and NA, thus making these antigens unrecognizable to the antibodies which originally recognized them—a process called **antigenic variation**

Antiviral drugs acting against RNA viruses: flu virus
Structure and life cycle of the influenza virus

- The reason it takes place can be traced back to the RNA polymerase enzyme, which is a relatively error-prone enzyme and means that the viral RNA which codes for HA and NA is not consistent.
- Variations in the code lead to changes in the amino acids present in NA and HA, which results in different types of flu virus based on the antigenic properties of their NA and HA.
- There are three groups of flu virus, classified as A, B, and C. Antigenic variation does not appear to take place with influenza C and occurs slowly with influenza B.
- With influenza A, however, variation occurs almost yearly.
- If the variation is small, it is called **antigenic drift .**
- If it is large, it is called **antigenic shift**
- **and it is this that** can lead to the more serious epidemics and pandemics.

Ion channel disrupters: adamantanes

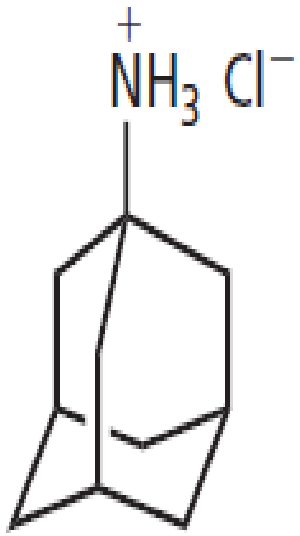
Amantadine and rimantadine

Ion channel disrupters: adamantanes
Amantadine and rimantadine

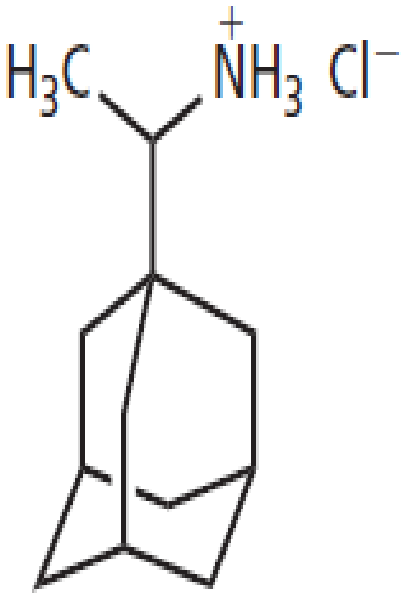
- **Amantadine and rimantadine** are related adamantanes with similar mechanisms of action and can inhibit viral infection in two ways.
- At low concentration (<1 μg/ml), they inhibit the replication of influenza A viruses by blocking a viral ion channel protein called **matrix (M2) protein .**
- **At higher concentrations** (>50 μg/ml), the basic nature of the compounds becomes important and they buff er the pH of endosomes to prevent the acidic environment needed for HA to fuse the viral membrane with that of the endosome.
- These mechanisms inhibit penetration and uncoating of the virus

Ion channel disrupters: adamantanes
Amantadine and rimantadine

- Unfortunately, the virus can mutate in the presence of amantadine to form resistant variants. Amantadine binds to a specific region of the M2 ion channel, and resistant variants have mutations which alter the width of the channel.
- Work has also been carried out in an attempt to find an analogue which might affect the ion channel and pH levels at comparable concentrations.
- This has focused on secondary and tertiary amines with increased basicity, as well as alteration of the structure to reduce activity for the ion channel.
- The rationale is that resistant flu variants are less likely to be produced if the drug acts on two different targets at the same time.
- Rimantadine was approved in 1993 as a less toxic alternative to amantadine for the treatment of influenza A. Unfortunately, neither agent is effective against influenza B as this virus does not contain the matrix (M2) protein.
- Side effects are also a problem, possibly owing to effects on host cell ion channels.



Amantadine



Rimantadine

Neuraminidase inhibitors

Neuraminidase inhibitors

- **Structure and mechanism of neuraminidase:**
- NA is a mushroom-shaped tetrameric glycoprotein anchored to the viral membrane by a single hydrophobic sequence of some 29 amino acids.
- As a result, the enzyme can be split enzymatically from the surface and studied without loss of antigenic or enzymic activity.
- X-ray crystallographic studies have shown that the active site is a deep pocket located centrally on each protein subunit.

Neuraminidase inhibitors

- The most important interactions involve the carboxylate ion of sialic acid, which is involved in ionic interactions and hydrogen bonds with three arginine residues, particularly with Arg-371.
- There are three other important binding regions or pockets within the active site.
- The glycerol side chain of sialic acid at C-6 fills one of these pockets, interacting with glutamate residues and a water molecule by hydrogen bonding.
- The hydroxyl group at C-4 is situated in another binding pocket, interacting with a glutamate residue.
- Finally, the acetamido substituent at C-5 fits into a hydrophobic pocket which is important for molecular recognition.

Neuraminidase inhibitors

- This pocket includes the hydrophobic residues Trp-178 and Ile-222 which lie close to the methyl carbon (C-11) of sialic acid, as well as the hydrocarbon backbone of the glycerol side chain.

- The glycosidic OH at C-2 is also shifted from its normal equatorial position to an axial position where it points out of the active site and can form a hydrogen bond to Asp-151, as well as an intramolecular hydrogen bond to the hydroxyl group at C-7.

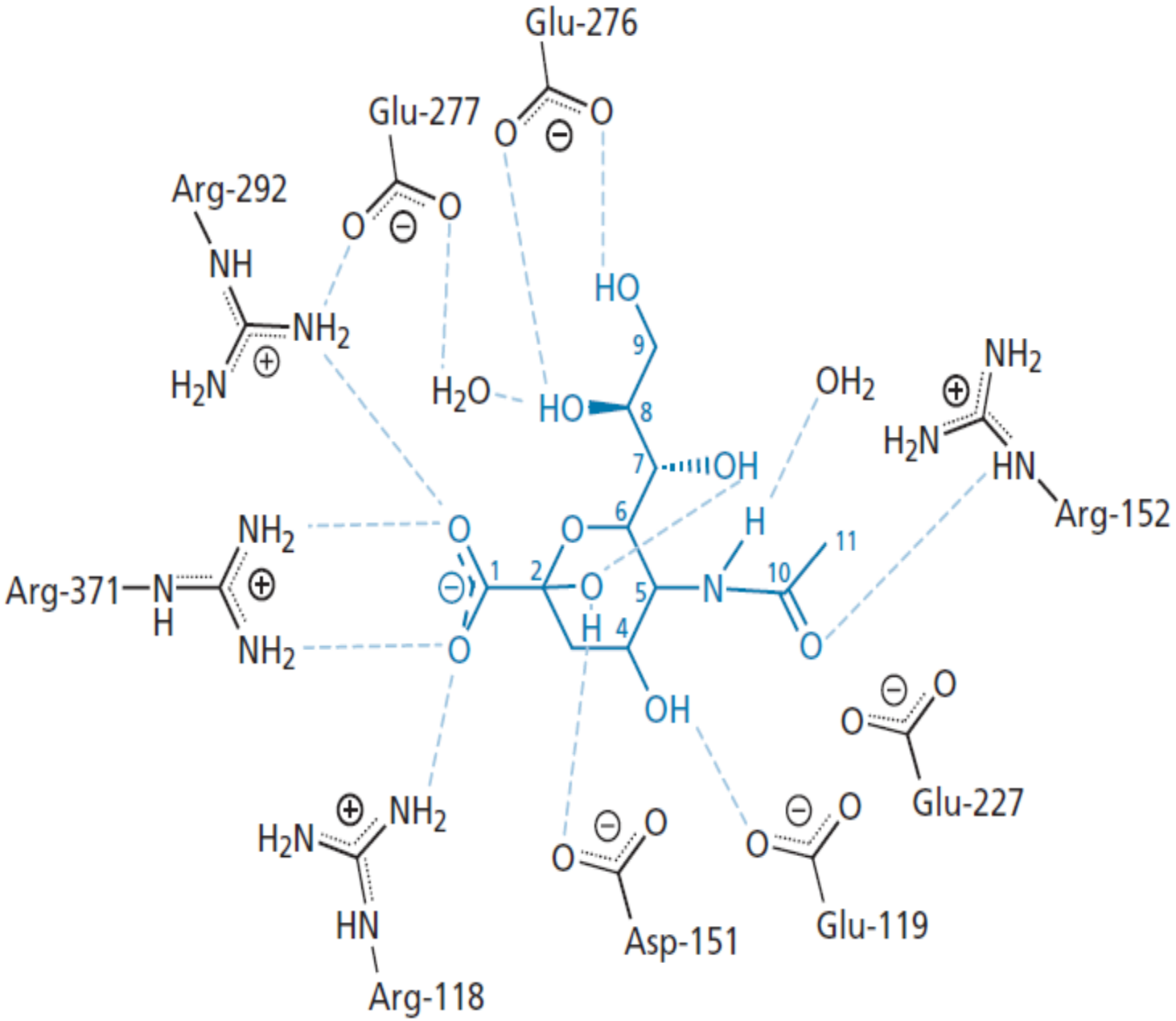


FIGURE 20.42 Hydrogen bonding interactions between sialic acid and the active site of neuraminidase.

Neuraminidase inhibitors

- The inhibitor was crystallized with the enzyme and studied by X-ray crystallography and molecular modelling to show that the same binding interactions were taking place with the exception of the missing hydroxyl group at C-2.
- Unfortunately, this compound also inhibited bacterial and mammalian sialidases and could not be used therapeutically. Moreover, it was inactive *in vivo*
- The most important result from these studies was the discovery that the binding region normally occupied by the 4-OH of sialic acid could also interact with an aminium or guanidinium ion.
- As a result, sialic acid analogues having an amino or guanidinyl group at C-4, instead of a hydroxyl group, were modelled in the active site to study the binding interactions and to check whether there was room for the groups to fit.

Transition-state inhibitors: development of zanamivir

Transition-state inhibitors: development of zanamivir

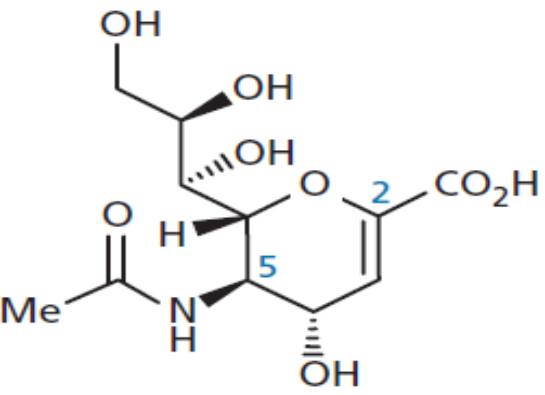
- The transition state has a planar trigonal centre at C-2 and so sialic acid analogues containing a double bond between positions C-2 and C-3 were synthesized to achieve that same trigonal geometry at C-2.
- The discovery of the inhibitor **2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid (*Neu5Ac2en*)**
- In order to achieve the required double bond, the hydroxyl group originally present at C-2 of sialic acid had to be omitted, which resulted in lower hydrogen bonding interactions with the active site.

Transition-state inhibitors: development of zanamivir

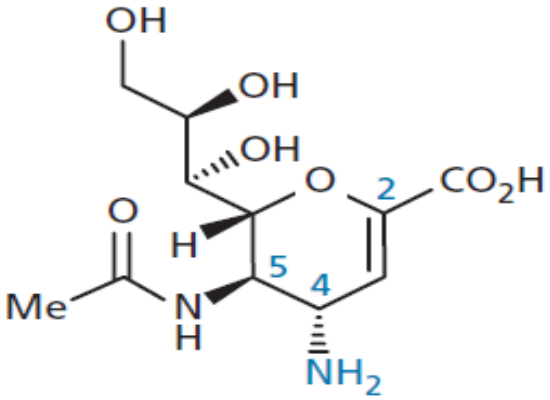
- These modelling studies were favourable and so the relevant structures were synthesized and tested for activity. **4-Amino-Neu5Ac2en contains the** aminium group and was found to be more potent than Neu5Ac2en
- Moreover, it was active in animal studies and showed selectivity against the viral enzyme, implying that the region of the active site which normally binds the 4-hydroxyl group of the substrate is different in the viral enzyme from comparable bacterial or mammalian enzymes.
- Molecular modelling studies had suggested that the larger guanidinium group would be capable of even greater hydrogen bonding interactions, as well as favourable van der Waals interactions.

Transition-state inhibitors: development of zanamivir

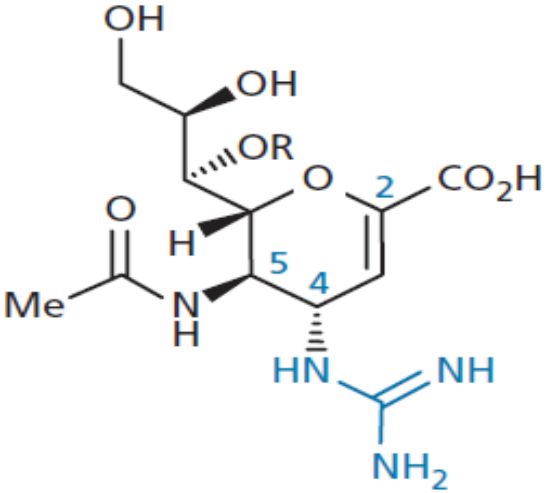
- The relevant structure **zanamivir ; was, indeed, found to be a more** potent inhibitor having a 100-fold increase in activity.
- Moreover, the larger guanidinium group was found to expel a water molecule from this binding pocket which is thought to contribute a beneficial entropic effect.
- Zanamivir is a slow-binding inhibitor with a high binding affinity to influenza A NA



Neu5Ac2en
K_i (M) 4×10^{-6}; IC_{50} 5–10 μM



4-Amino-Neu5Ac2en
K_i (M) 4×10^{-8}



Zanamivir (Relenza); R=H
K_i (M) 3×10^{-11}
Laninamivir (Inavir); R=Me

- It was approved by the US FDA in 1999 for the treatment of influenza A and B, and was marketed by Glaxo Wellcome and Biota.
- Unfortunately, the polar nature of the molecule means it has poor oral bioavailability (<5%), and it is administered by inhalation.

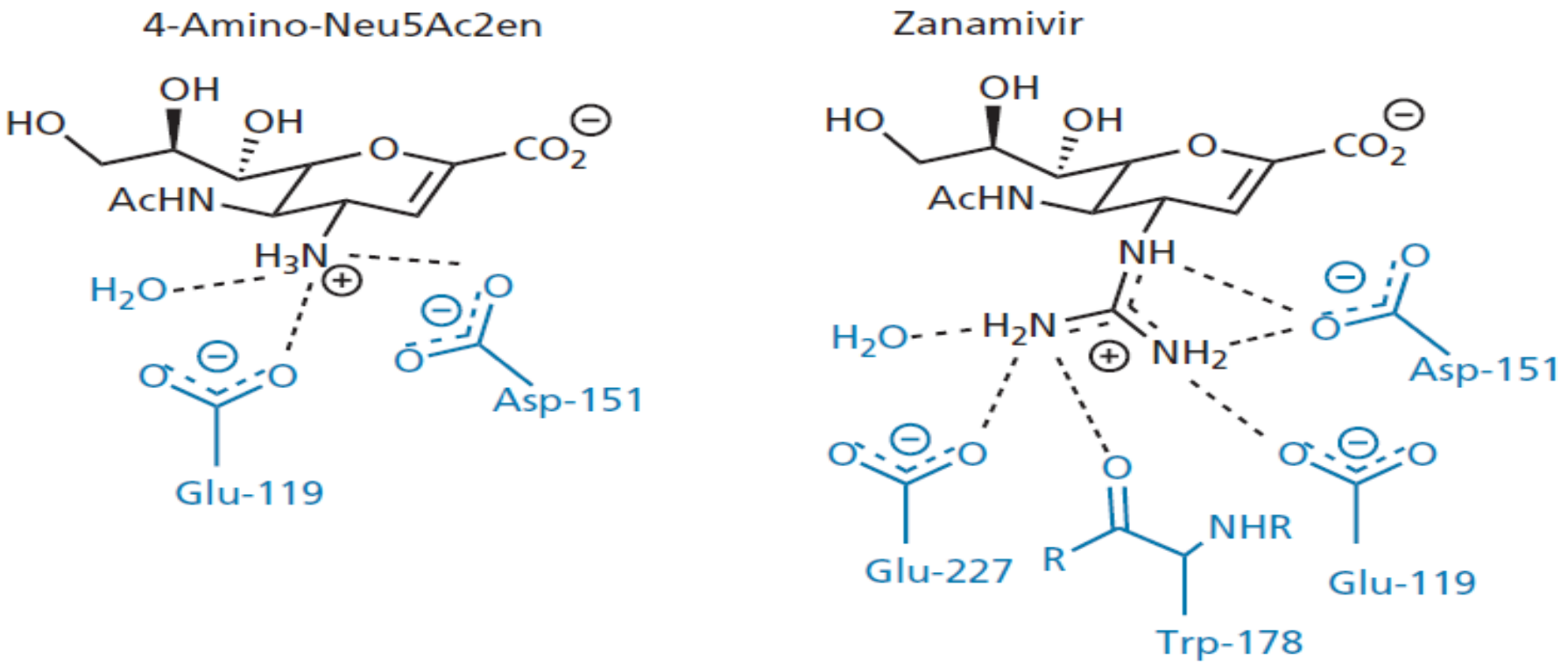


FIGURE 20.45 Binding interactions of aminium and guanidinium moieties at C-4 with the active site of neuraminidase.

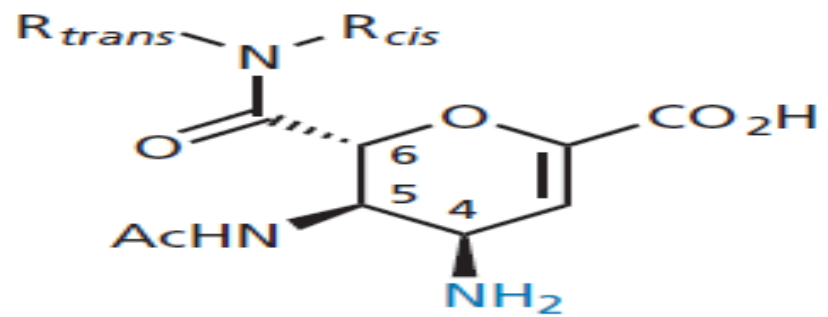
Transition-state inhibitors: 6-carboxamides

Transition-state inhibitors: 6-carboxamides

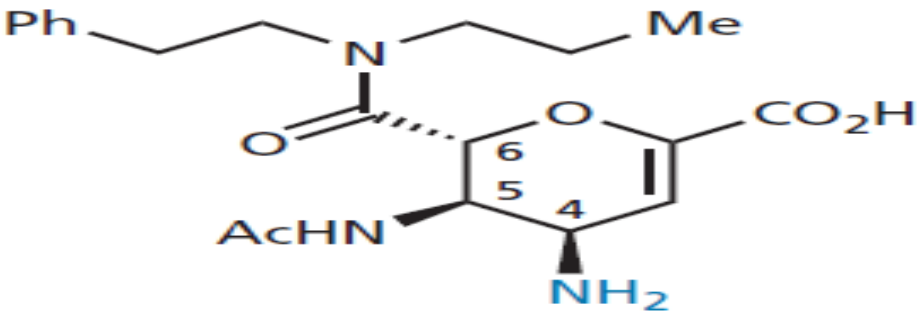
- A problem with the inhibitors (zanamivir) is their polar nature.
- The glycerol side chain is particularly polar and has important binding interactions with the active site. However, it was found that it could be replaced by a carboxamide side chain with retention of activity.
- A series of 6-carboxamide analogues was prepared to explore their structure–activity relationships.
- Secondary carboxamides (where R *cis* = *H) showed similar weak* inhibition against both A and B forms of the NA enzyme.
- Tertiary amides having an alkyl substituent at the *cis position* resulted in a pronounced improvement against the A form of the enzyme, with relatively little effect on the activity against the B form. Thus, tertiary amides showed a marked selectivity of 30–1000-fold for the A form of the enzyme.
- Good activity was related to a variety of different sized R *trans substituents larger than methyl.*
- *but the size of* the R *cis group was more restricted and optimum activity* was achieved when R *cis was ethyl or n -propyl.*

Transition-state inhibitors: 6-carboxamides

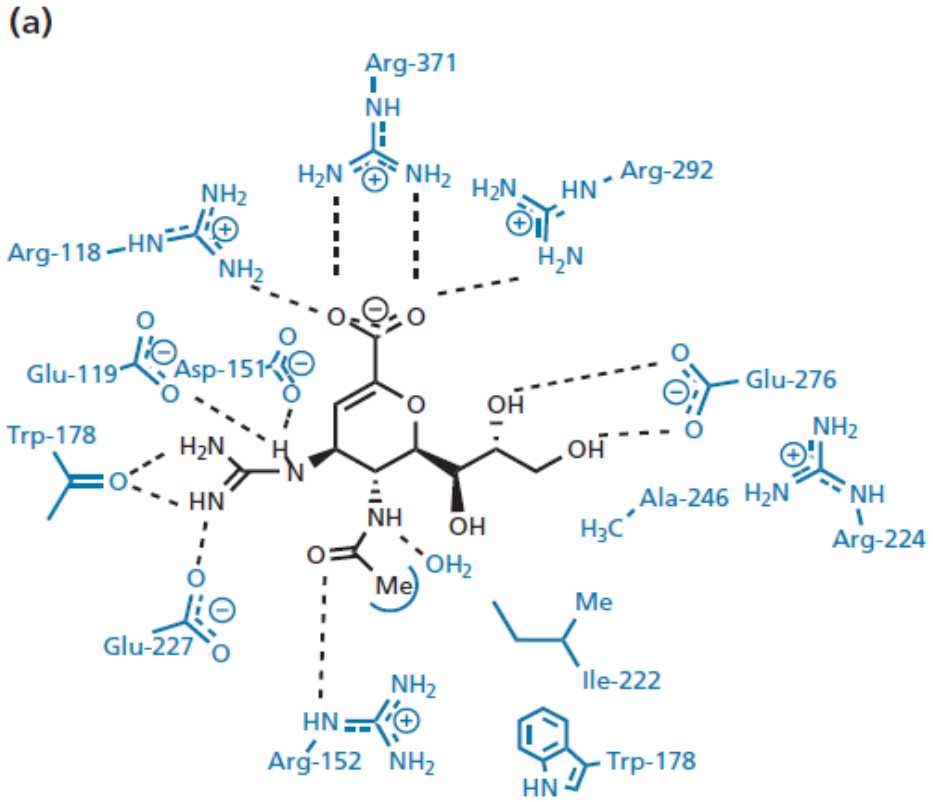
- The 4-guanidinium analogues are more active than corresponding 4-amino analogues but the improvement is slightly less than that observed for the glycerol series, especially where the 4-amino analogue is already highly active.
- Crystal structures of the carboxamide (I)bound to both enzymes A and B were determined by X-ray crystallography
- The dihydropyran portion of the carboxamide (I) binds to both the A and B forms of the enzyme in essentially the same manner as observed for zanamivir.
- The important binding interactions involve the carboxylate ion, the 4-amino group, and the 5-acetamido group—the latter occupying a hydrophobic pocket lined by Trp-178 and Ile-222.
- However, there is a significant difference in the region occupied by the carboxamide side chain.
- In the sialic acid analogues, the glycerol side chain forms intermolecular hydrogen bonds to Glu-276. These interactions are not possible for the carboxamide side chain.



6-Carboxamides



I



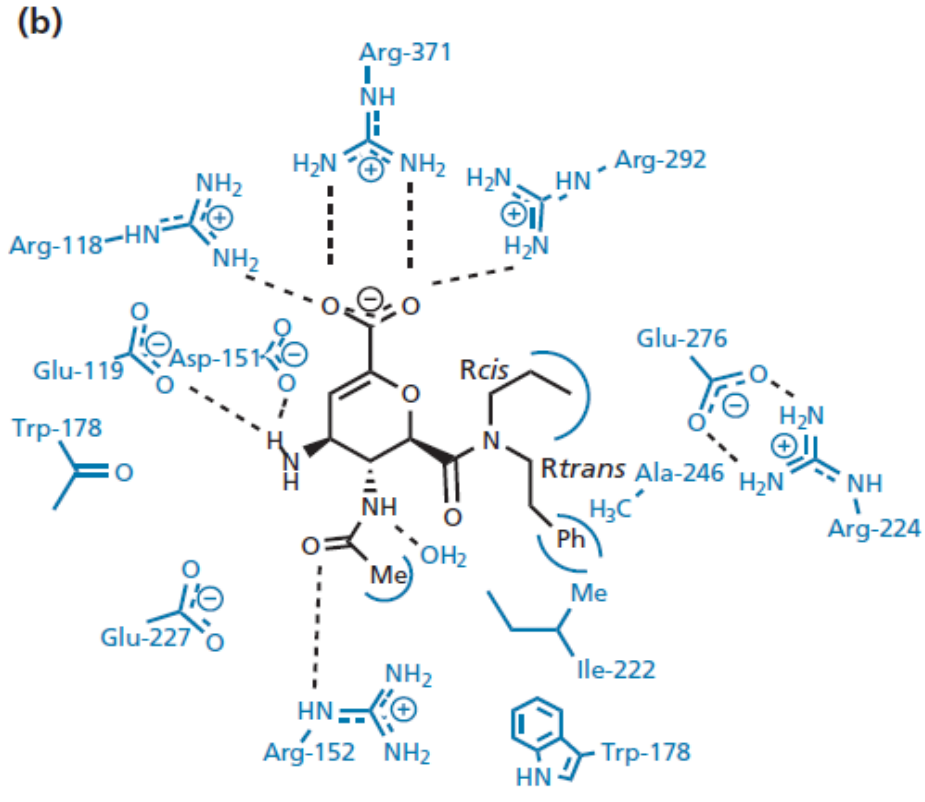


FIGURE 20.47 Binding interactions of zanamivir and carboxamides; (**a**) binding of zanamivir to the active site; (**b**) binding of carboxamide (I) to the active site.

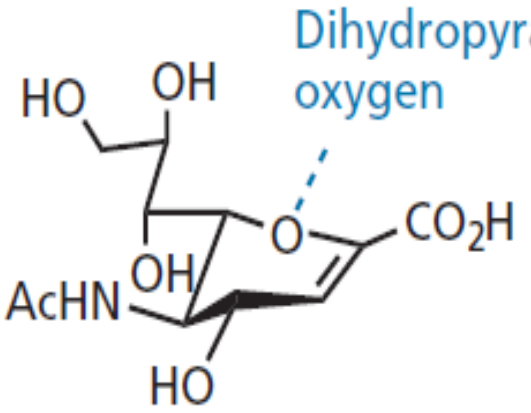
Carbocyclic analogues: development of oseltamivir (Tamiflu)

Carbocyclic analogues: development of oseltamivir

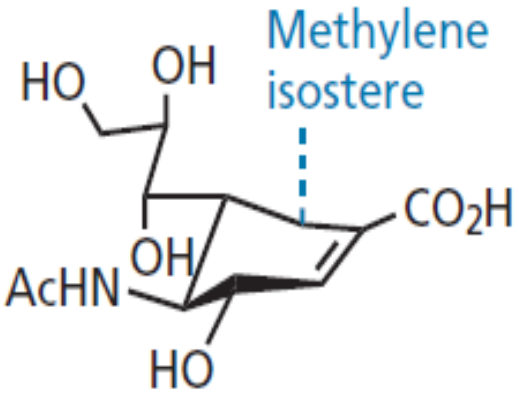
- The dihydropyran oxygen of Neu5Ac2en and related inhibitors have no important role to play in binding these structures to the active site of NA. Therefore, it should be possible to replace it with a methylene isostere to form carbocyclic analogues such as structure I
- This would have the advantage of removing a polar oxygen atom which would increase hydrophobicity and potentially increase oral bioavailability. Moreover, it would be possible to synthesize cyclohexene analogues, such as structure II, which more closely match the stereochemistry of the reaction's transition state than previous inhibitors

Carbocyclic analogues: development of oseltamivir

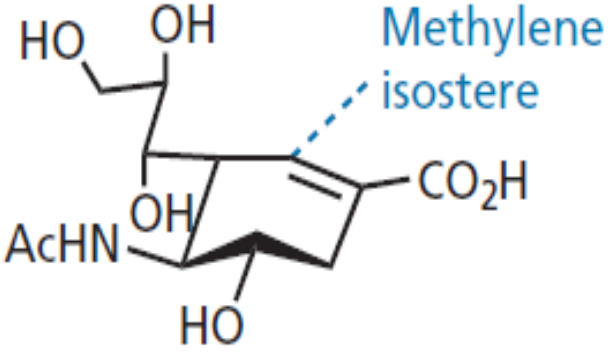
- Such agents might be expected to bind more strongly and be more potent inhibitors.
- Structures I and II were synthesized to test this theory, and it was discovered that structure II was 40 times more potent than structure I as an inhibitor
- As the substituents are the same, this indicates that the conformation of the ring is crucial for inhibitory activity. Both structures have half-chair conformations, but these are different owing to the position of the double bond.



Neu5Ac2en



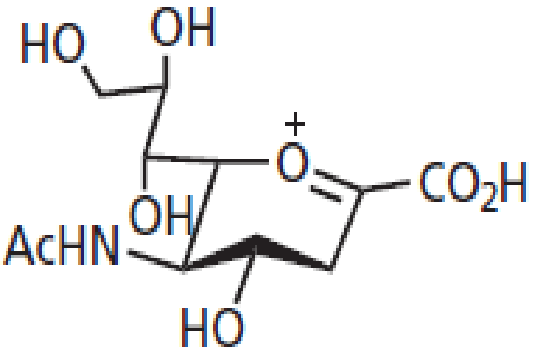
(I) IC_{50} 850 μM



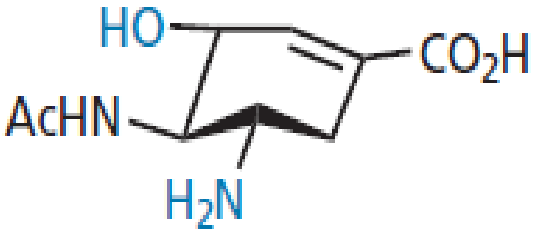
(II) IC_{50} 20 μM

Carbocyclic analogues: development of oseltamivir

- It was now planned to replace the hydroxyl group on the ring with an amino group to improve binding interactions ,
- and to remove the glycerol side chain to reduce polarity.
- In its place, a hydroxyl group was introduced for two reasons.
- Firstly, the oxonium double bond in the transition state is highly polarized and electron deficient, whereas the double bond in the carbocyclic structures is electron rich.
- Introducing the hydroxyl substituent in place of the glycerol side chain means that the oxygen will have an inductive electron-withdrawing effect on the carbocyclic double bond and reduce its electron density.
- Secondly, adding the hydroxyl group meant that it would be possible to synthesize ether analogues which would allow the addition of hydrophobic groups to fill the binding pocket previously occupied by the glycerol side chain



Reaction intermediate



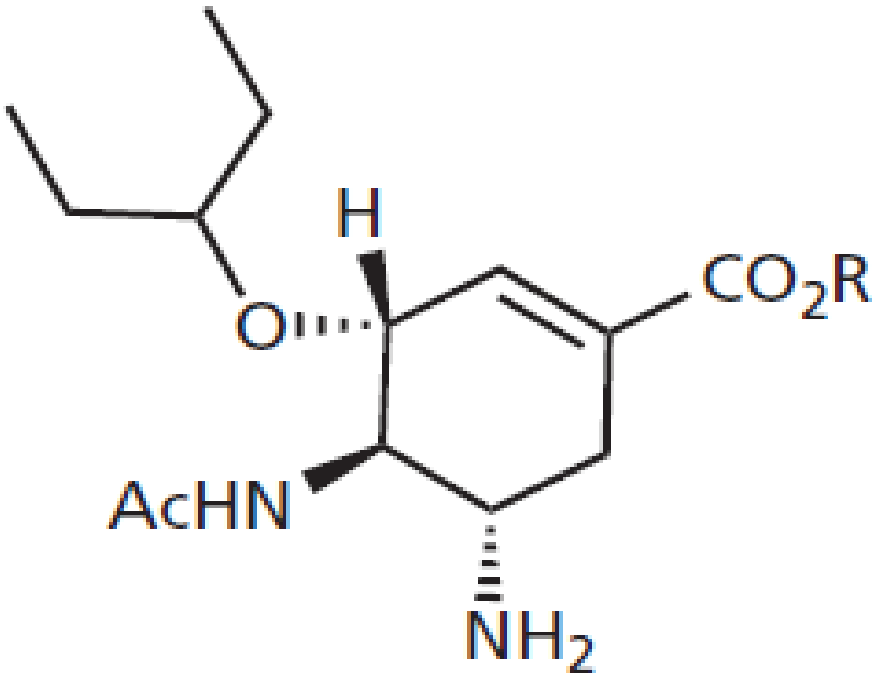
(III) IC_{50} 6.3 μM

(IV) Inactive

- The resultant structure III was synthesized and proved to be a potent inhibitor. In contrast, the isomer IV failed to show any inhibitory activity.
- A series of alkoxy analogues of structure III was now synthesized in order to maximize hydrophobic interactions in the region of the active site previously occupied by the glycerol side chain
- For linear alkyl chains, potency increased as the carbon chain length increased from methyl to *n –propyl*
- Although longer chains than propyl increase hydrophobic interactions, there is a downside in that there is partial exposure of the side chain to water outside of the active site.

Carbocyclic analogues: development of oseltamivir

- Branching of the optimal propyl group was investigated ,There was no increase in activity when methyl branching was at the β-position, but the addition of a methyl group at the α-position increased activity by 20-fold
- The optimal side chain proved to be a pentyloxy side chain (R = CH(Et) 2).
- Replacing the amino group with a guanidine group improves activity, as with the sialic acid series. However, the improvement in activity depends on the type of alkyl group present on the side chain, indicating that individual substituent contributions may not be purely additive, as a guanidinium group is not required to achieve low nanomolar inhibition.
- Oseltamivir (Tamiflu) is the ethyl ester prodrug for the treatment of influenza A and B.
- It is taken orally and is converted by esterases in the gastrointestinal tract.



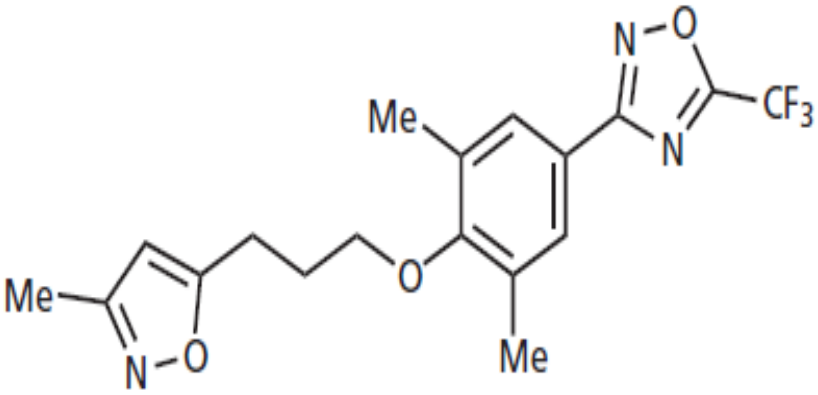
R=H GS 4071

R=Et Oseltamivir (Tamiflu)

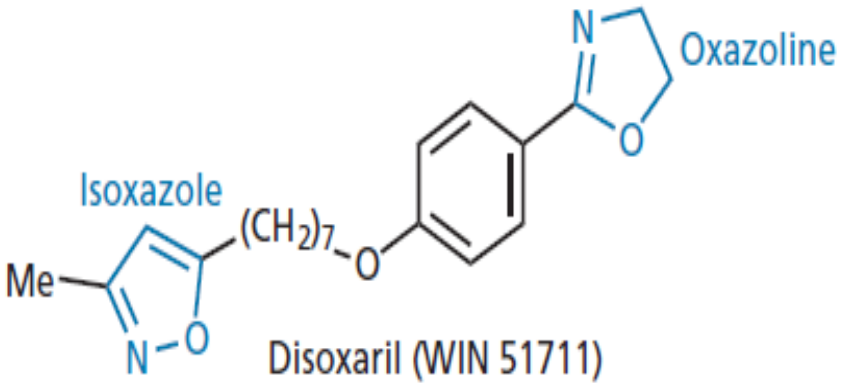
Antiviral drugs acting against RNA viruses: cold virus

Antiviral drugs acting against RNA viruses: cold virus

- The agents used against flu are ineffective against colds, as these infections are caused by a different kind of virus called a rhinovirus.
- There are at least 89 serotypes of **human rhinoviruses** (HRV) and they belong to a group of viruses called the **picornaviruses which include the polio, hepatitis A,** and foot and mouth disease viruses.
- On the canyon floor there is a pore which opens into a hydrophobic pocket within the VP1 protein. This pocket is either empty or occupied by a small molecule called a **pocket factor**
- A variety of drugs having antiviral activity are thought to mimic the pocket factor by displacing it and binding to the same hydrophobic pocket.
- The drugs concerned are called **capsid-binding agents and are characteristically** long-chain hydrophobic molecules. Like the pocket factor, they stabilize the capsid by locking it into a stable conformation and preventing the conformational changes required for uncoating.



Pleconaril



Disoxaril (WIN 51711)

- **Pleconaril is one such drug that has** undergone phase III clinical trials which demonstrate that it has an effect on the common cold. It is an orally active, broad-spectrum agent which can cross the blood–brain barrier. Th e drug may also be useful against the enteroviruses that cause diarrhoea, viral meningitis, conjunctivitis, and encephalitis, as these viruses are similar in structure to the rhinoviruses.
- The development of pleconaril started when a series of isoxazoles were found to have antiviral activity. This led to the discovery of **disoxaril which entered** phase I clinical trials, but proved to be too toxic

- the oxazoline and phenyl rings were roughly coplanar and were located in a hydrophilic region of the pocket near the pore leading into the centre of the virion
- Th e hydrophobic isoxazole ring binds into the heart of the hydrophobic pocket and the chain provides suffi cient flexibility for the molecule to bend round a corner in the pocket
- Structure-based drug design was carried out to find safer and more eff ective antiviral agents. For example, the chain cannot be too short or too long, or else there are steric interactions.
- Placing additional hydrophobic groups on to the phenyl ring improves activity against the HRV2 strain, because increased interactions are possible with a phenylalanine residue at position 116 rather than leucine.

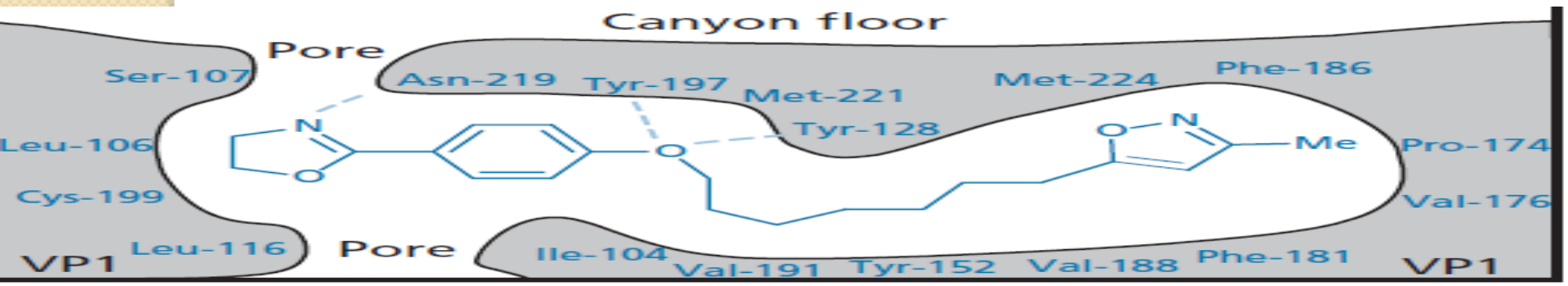


FIGURE 20.54 Binding of disoxaril (possible hydrogen bonds shown as dashed lines).

Antiviral drugs acting against RNA viruses: hepatitis C

Antiviral drugs acting against RNA viruses: hepatitis C

- Hepatitis C virus (HCV) is a positive-stranded RNA virus that was discovered in 1989. It is a blood-borne virus that affects an estimated 170 million people worldwide, but many of those infected with the agent are unaware of the fact as they do not experience any symptoms.
- However, the virus can cause serious liver damage, cancer, and, in the long term, death.
- In May 2011, two new drugs with a more selective mode of action were approved for the treatment of hepatitis C— **boceprevir and telaprevir**

Antiviral drugs acting against RNA viruses: hepatitis C

- The life cycle of the virus within the host cell includes the synthesis of a 3000-amino acid polyprotein, which is cleaved into individual viral proteins by a viral protease enzyme called **HCV NS3-4A protease . This is a serine** protease containing a catalytic triad of Asp, His, and Ser
- Having identified the target and the active site, it was decided to design an inhibitor that could interact with the active site, but would not undergo the enzyme catalysed reaction.
- A series of peptide structures was studied where the susceptible amide bond was replaced with a keto amide group in the expectation that the serine residue in the active site would react with the ketone carbonyl group rather than the amide carbonyl group.

Antiviral drugs acting against RNA viruses: hepatitis C

- As a ketone group undergoes nucleophilic addition rather then nucleophilic substitution, no bond cleavage results and a reversible covalent bond is formed between the inhibitor and the active site.
- A series of peptide structures containing the ketoamide group was screened, leading to the identification of an undecapeptide which reacted as planned and showed good activity as an inhibitor.

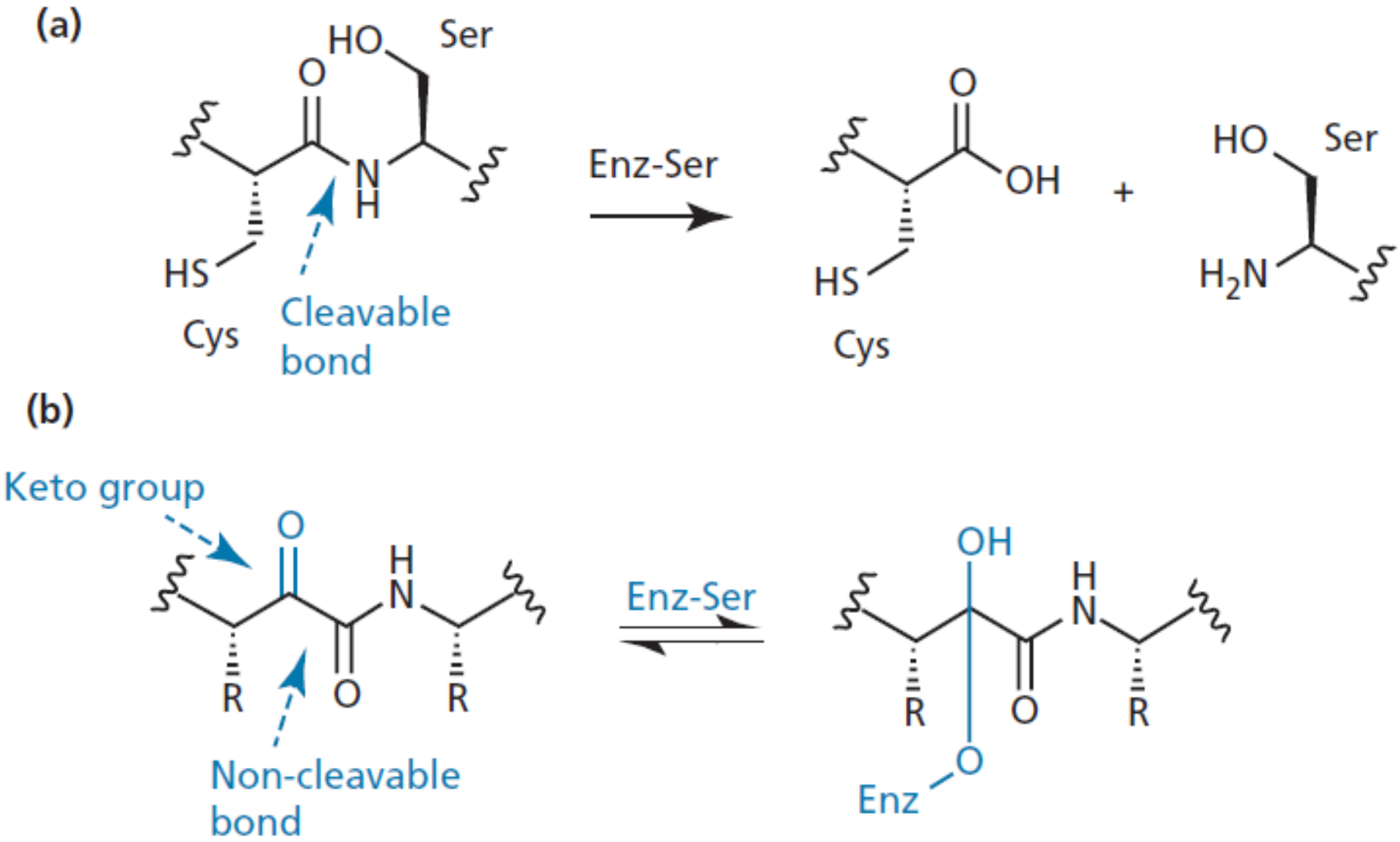


FIGURE 20.57 Design of protease inhibitors for HCV NS3-4A protease. (**a**) Normal enzyme-catalysed reaction. (**b**) Interaction of inhibitors with an active site serine residue.

Broad-Spectrum Antiviral Agents

Broad-spectrum antiviral agents

- **Agents acting against cytidine triphosphate synthetase**
- Cytidine triphosphate is an important building block for RNA synthesis and so blocking its synthesis inhibits the synthesis of viral mRNA.
- The fi nal stage in the biosynthesis of cytidine triphosphate is the amination of uridine triphosphate—a process that is catalysed by the enzyme cytidine triphosphate synthetase
- **Cyclopentenyl cytosine** is a carbocyclic nucleoside that is converted in the cell to the triphosphate, which then inhibits this final enzyme in the biosynthetic pathway

Broad-spectrum antiviral agents

- **Agents acting against S-adenosylhomocysteine hydrolase**
- Th e 5'-end of a newly transcribed mRNA is capped with a methyl group in order to stabilize it against phosphatases and nucleases, as well as enhancing its translation.
- *S -adenosylhomocysteine hydrolase is an intracellular* enzyme that catalyses this reaction and many viruses need it to cap their own viral m-RNA
- **3-Deazaneplanocin A** is an analogue of cyclopentenyl cytosine, and acts against a range of RNA and DNA viruses by inhibiting *S -adenosylhomocysteine hydrolase.*

Ribavirin

Ribavirin

- Ribavirin is a synthetic nucleoside that induces mutations in viral genes and is used against hepatitis C infection
- It was the first synthetic, non-interferon-inducing broad-spectrum antiviral nucleoside and can inhibit both RNA and DNA viruses by a variety of mechanisms, although it is only licensed for hepatitis C and respiratory syncytial virus.
- Its dominant mechanism of action appears to be depletion of intracellular pools of GTP by inhibiting **inosine-5'-monophosphate dehydrogenase .**
- **Phosphorylation of ribavirin results in** a triphosphate which inhibits **guanyl transferase and** prevents the 5' capping of mRNAs. The triphosphate can also inhibit **viral RNA-dependent RNA polymerase .**
- Owing to these multiple mechanisms of action, resistance is rare.
- The drug's main side effect is anaemia and itis a suspected **teratogen**

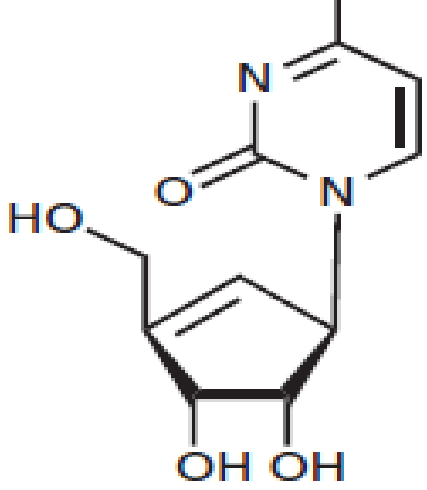
Interferons

Interferons

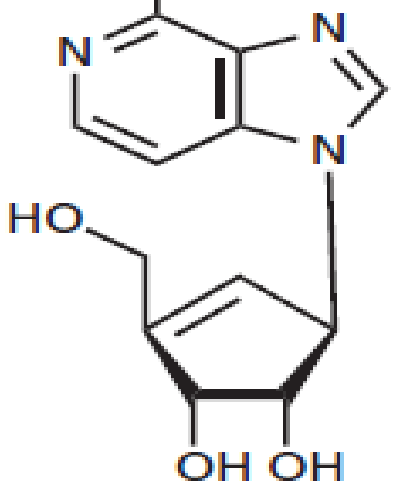
- Interferons are small natural proteins that were discovered in 1957 and which are produced by host cells as a response to ‘foreign invaders’.
- Once produced, interferons inhibit protein synthesis and other aspects of viral replication in infected cells. In other words, they shut the cell down.
- This can be described as an intracellular immune response.
- Administering interferons to patients has been seen as a possible approach to treating flu, hepatitis, herpes, and colds.
- There are several interferons which are named according to their source: α-interferons from lymphocytes, β-interferons from fibroblasts, and γ-interferons from T-cells.

Interferons

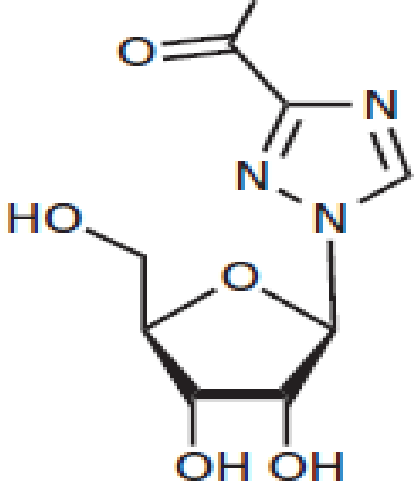
- α-Interferon (also called **alferon or IFN-alpha) is** the most widely used of the three types.
- In the past, it was difficult and expensive to isolate interferons from their natural cells, but recombinant DNA techniques allow the production of genetically engineered interferons in larger quantities.
- Interferon production in the body can also be induced by agents known as **immunomodulators .**
- **One such** example is **avridine** which is used as a vaccine adjuvant for the treatment of animal diseases such as foot and mouth.
- **Imiquimod also induces** the production of α-interferon, as well as other cytokines that stimulate the immune system. It is effective against genital warts.



Cyclopentenyl cytosine

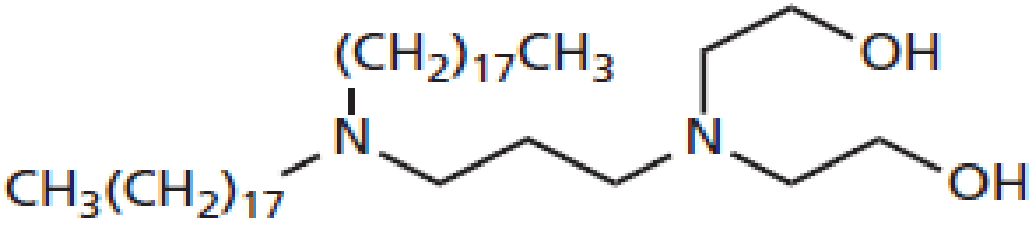


3-Deazaneplanocin A

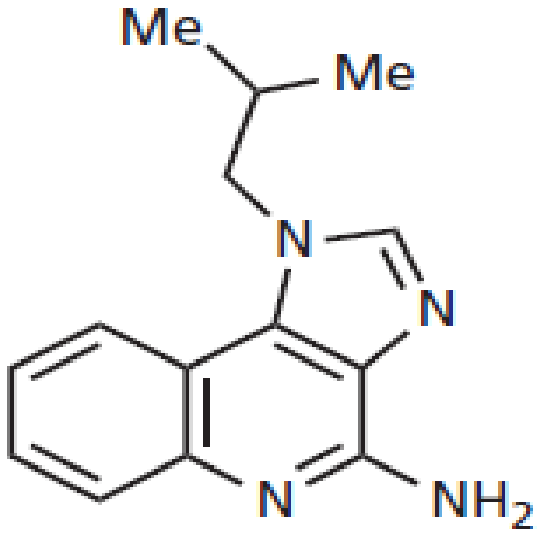


Ribavirin

FIGURE 20.60 Broad-spectrum antiviral agents.



Avridine



Imiquimod

FIGURE 20.61 Immunomodulators.

Antibodies and ribozymes

- Antibodies that recognize a virion-specific antigen will bind to that antigen and mark the virus out for destruction by the body's immune system
- **Palivizumab is a** humanized monoclonal antibody which was approved in 1998 for the treatment of respiratory syncytial infection in babies
- It blocks viral spread from cell to cell by targeting a specific protein of the virus
- It has been possible to identify sites in viral RNA that are susceptible to cutting by **ribozymes —enzymatic** forms of RNA.
- One such ribozyme is being tested in patients with hepatitis C and HIV.
- Ribozymes could be generated in the cell by introducing genes into infected cells—a form of gene therapy.