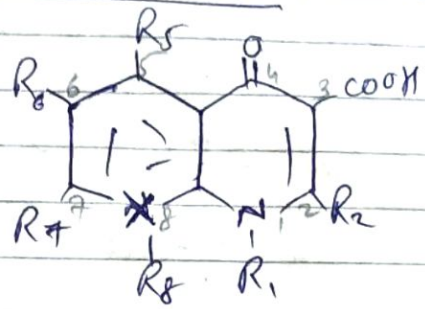
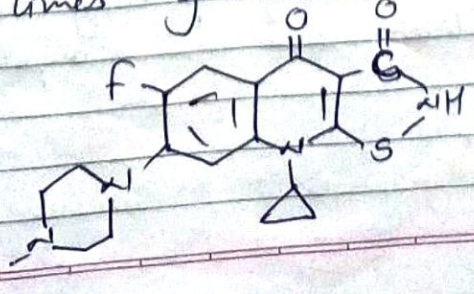
SAR of Quinolones [6M]



- At C_1 (1^{st} position):
  - Substituents at position can be ethyl, butyl, cyclopropyl, difluorophenyl which results in potent compound
  - Fluorine addition at ∝1 - 1 cyclopropyl or at 1- butyl gives compound with improved activity against gram positive bacteria
  - Replacement of hydrogen at C-2

- At C_2 (2^{nd} position):
  - Replacing hydrogen at C_2 is generally disadvantageous.
  - But, some derivatives containing C-1, C_2 ring have shown possess notable activity.
  Eg: Prulifloxacin

- At C_3 (3^{rd} position):
  - Modification of C_3 carboxylic acid leads to decrease in antibacterial activity.
  - Replacement of carboxylic acid & isothiazolo group give more active isothiazolo quinolone which is 4-10 times greater in in-vitro antibacterial activity

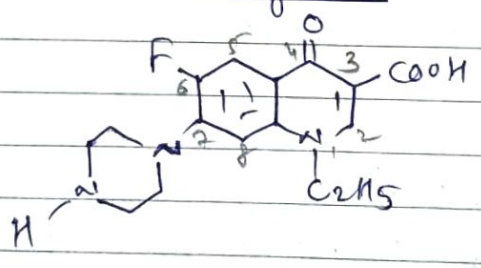


Isothiazolo quinolone

- At C_4 (4^{th} position):
  - The oxo group of quinolones nucleus appear to be essential for antibacterial activity.
  - Its replacement with 4-thioxo or sulphonyl group leads to loss of activity.
- Studies have shown that 1,4-

- At C_5 (5^{th} position):
  - Introduction of group at C_5 position has been proven beneficial in terms of antibacterial activity.
  - The order of activity is
    $NH_2, CH_3 > F, H > OH$

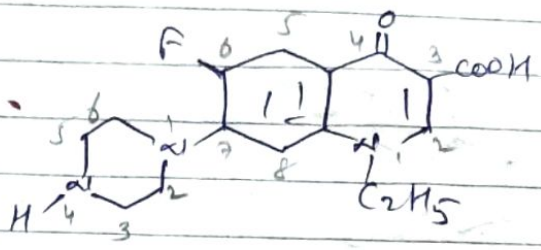
- At C_6 (6^{th} position):
  Incorporation of fluorine at 6^{th} position greatly improve antibacterial activity by increasing lipophilicity of molecule which improves drug penetration through bacterial cell wall.
  Eg: Norfloxacin



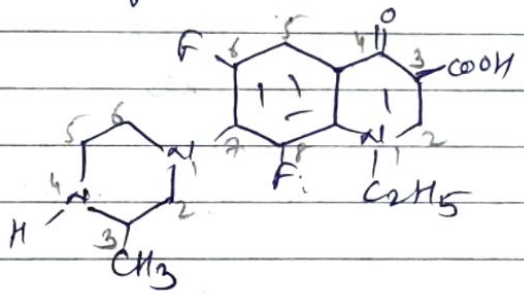
  The order of activity is: $F > Cl, Br$
  $CH_3 > CaL$

- At C_7 (7^{th} position)
  - Introduction of piperazin moiety at C_7 position is essential for controlling potency and spectrum.
  - Other aminopyrrolidines also are compatible for activity.
  - Eg: Enoxacin

Enoxacin

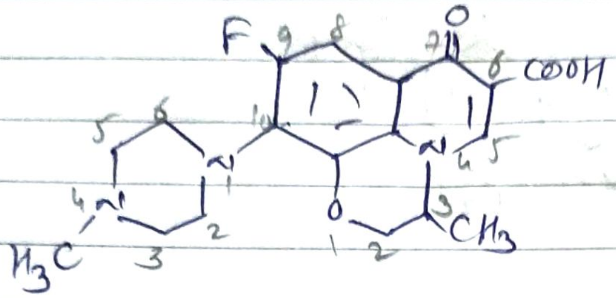


- At C_8 (8th position)
- The fluoro substitute offer good potency against gram negative pathogens while methoxy moiety is active against gram positive bacteria
- Order of activity is: F, Cl, O CH_3 > H
  CF_3 > methyl, vinyl
- Halogen at C_8 position improves oral absorption.
- Eg: Lomefloxacin



- Studies have shown that 1,4-dihydro-4-oxo-3-pyridine carboxylic acid moiety is essential for antibacterial activity.
- Alkyl substitution at 1st position is essential for activity
- Lower alkyl compounds generally have greater potency - methyl, ethyl, cyclopropyl
- Ring condensation at 1-8, 5-6, 7-6 & 7-8 position also lead to active compound. Eg: Ofloxacin

Ofloxacin



ANTI-VIRAL AGENTS

Baltimore Classification

- Antiviral agents are agents that cures & control the viral infection.
- This agent have narrow spectrum and have limited efficacy
- Viruses represent separate & unique class of infection.
- Its most simple as compared to typical bacterial structure, virus possesses simple chemical composition, lack of metabolic enzyme, lacks of protein synthesizing system. It contain only 1 type of nucleic a either DNA or RNA
- Viruses utilize host cell machinery for their multiplication & growth & it depend upon host cell metabolism i.e protein synthesis, enzyme system etc
- Unlike bacteria viruses does not depend on nutrient media to grow, they can replicate only in host cell & may be animal, plant or bacteria
- Viruses are considered intracellular parasite that utilize biochemical system & nutrient product of host cell to sustain their life
- Virus cell include small pox, influenza flu, polio, rabbis, yellow fever

Viral replication:

Virus → adsorption → penetration → uncoating → transcription → translation → assembling → release of new virus.

Adsorption

Virion invent host cell, the reactive site on capsid bind & their complementary on host cell. The viral particle encapsulated by host cell

cytoplasm form vacuoles.

Uncoating:
The genetic material passes into host cell and leaving the capsid outside the host cell

Synthesis of viral component:
The viral genome enter in cytoplasm or neoplasm and starts to utilize host nucleic acid compon system for the synthesis of whole viral protein and produce viral genomes.

Release of virus:
The viral nucleic a and capsid protein are synthesized in diff part of host cell by ribosomes.
The RNA is synthesized by viral genome and host cell are unable to differentiate b/w the viral & cell directed order

The large no. of synthesis of viral particles brought together assembling into new virions and later release from host cell by budding process.

Anti-viral agents

For designing anti-viral agents the viral replication step is utilized at the basis for designing anti-viral agent.
Eg: Amantidine hydrochloride inhibit viral penetration & uncoating of influenza while idoxuridine inhibit viral DNA synthesis

Due to several reason a single drug is utilized as anti-viral agent & clinically utilized. not

Development of anti-viral agent

The following problems are consider in development of new anti-viral agents:

- Lack of satisfactory experimental models.
- Use of wrong virus
- Narrow spectrum activity
- Limitation of their uses due to severe toxicity.
- Difficulty in clinical assessment.

Classification:

I Nucleoside reverse transcriptase inhibitors (NRTI).

1. Purine nucleoside & nucleotide

Eg: Acyclovir
Gancyclovir
Valacyclovir
Pencyclovir
Famcyclovir
Vidarabine

2 Pyrimidine nucleoside & nucleotide

Eg: Idoxuridine — Lamivudine
Pseudo, Cidofovir — Zidovudine
Trifluridine — Zalcitabine

3 Thiosemi carbazole

Eg Methisazone

4 Adamantane amines. (inhibition of early stage of viral replication)

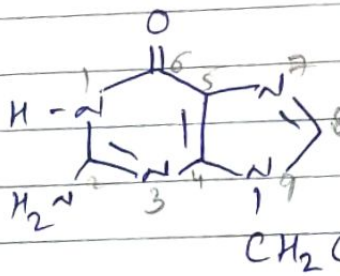
Eg: Amantadine, Tromantadine.
Rimantadine
Somantadine

II Non-nucleotide reverse transcriptase inhibitors
Eg: Nevirapine
Delavirdine
Loviride
Emivirine
Efavirenz

III HIV protease inhibitor.
Eg: Saquinavir
Indinavir
Ritonavir
Nelfinavir

IV Miscellaneous agent.
Eg: Foscarnet sodium
Ribavirin

Acyclovir



$CH_2OCH_2CH_2-OH$

2-amino-9[(2-hydroxyethoxy)methyl]-1H-purine-6-(9H) one

It is widely used antiviral agent specially on herpes infection, it prevent viral application in infected cell. It is extremely selective & low toxicity.

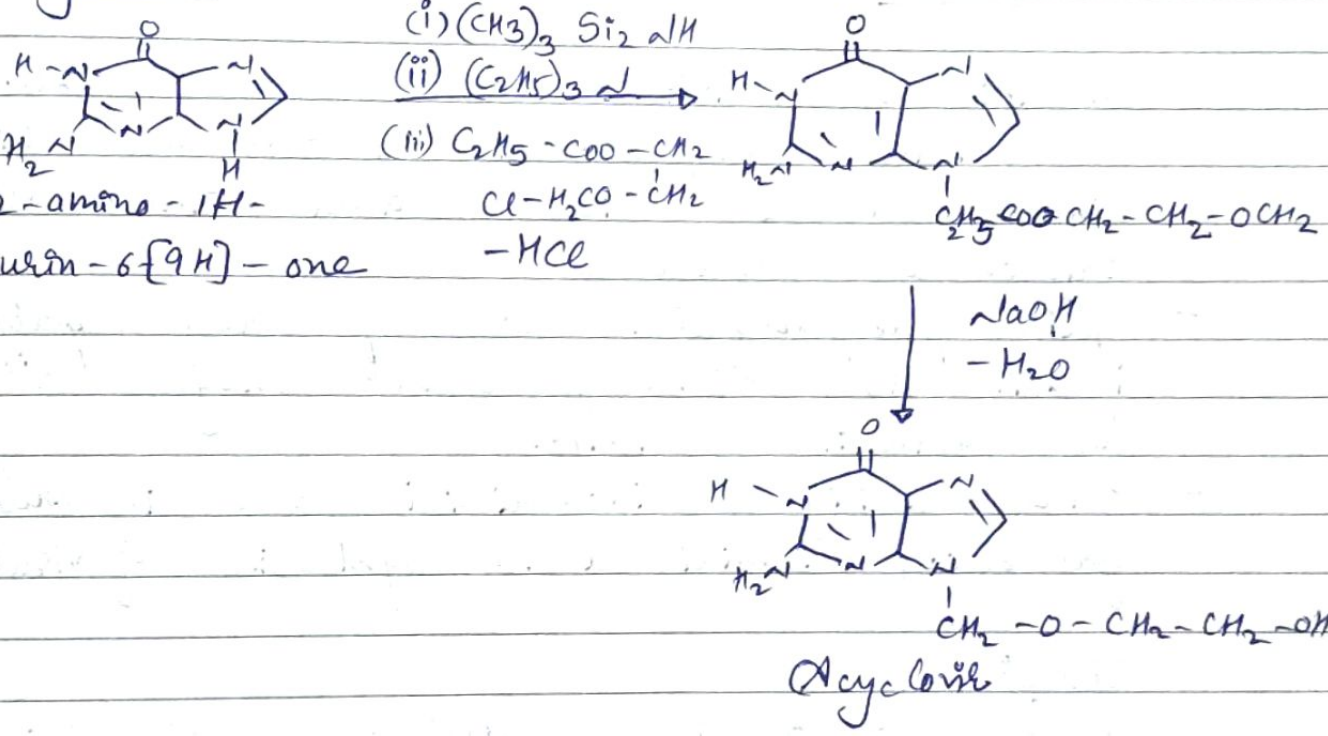
MOA:
Acyclovir is converted by viral thymidine kinase into acyclovir monophosphate & is then converted into acyclovir triphosphate by host cell kinase enzyme

Acyclovir triphosphate competitively inhibit & inactivate HSV (Herpes Simplex Virus) specified DNA polymerase prevent further viral DNA synthesis without affecting on normal cellular processes

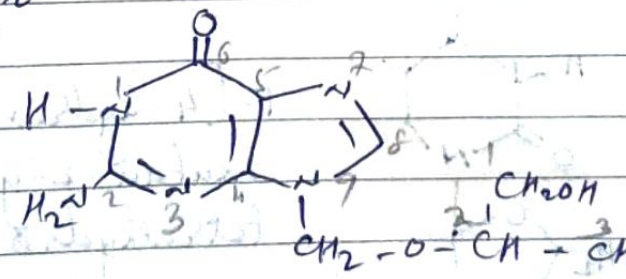
Uses:

Drug of choice for prophylaxis as well as in treatment of HSV particularly type - I including chronic & recurrent mucocutaneous herpes, i & ii genital herpes & herpes simplex encephalitis.

Synthesis:

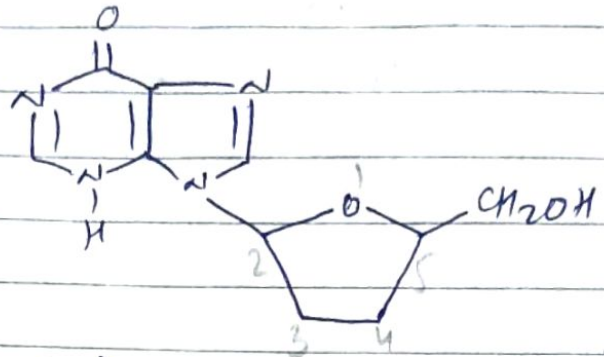


✱ Ganciclovir



2-amino-9[(1,3-dihydroxy propan-2-yl oxy) methyl]-1H-purin-6-(9H) one

Didanosine



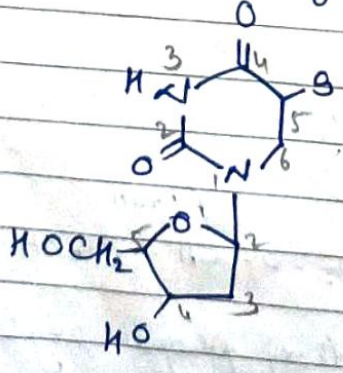
9 (5-(hydroxy methyl) tetrahydro furan-2-yl) 3H-purine-6-(9H) one

3/3

Idoxuridine

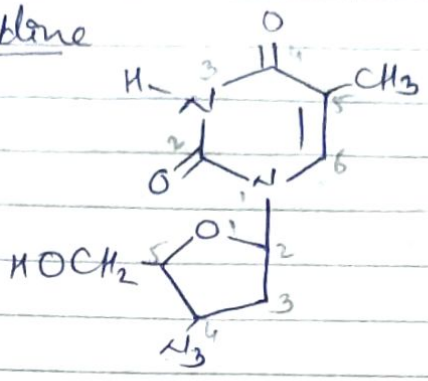
- It act as antiviral agent against DNA virus
- Idoxuridine phosphorylated by enzyme thiamidine kinase enzyme which convert into active triphosphate derivative
- This phosphorylated form of drug capable to inhibit HSV DNA polymerase enzyme is required for synthesis of DNA
- The ability of idoxuridiric a c is substitute for deoxy thiamidic a in synthesis of viral DNA.

Uses:
In the treatment of HIV of eyelid, conjunctiva, cornea



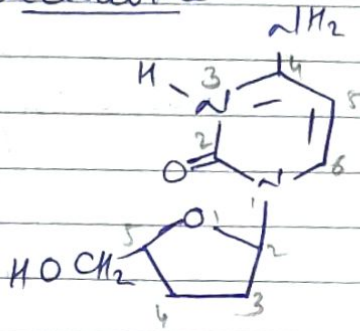
1-[4-hydroxy-(5-hydroxymethyl) oxalan-2-yl] 5-iodo-1,2,3,4-tetrahydro pyrimidin-2,4-dione

Zidovudine



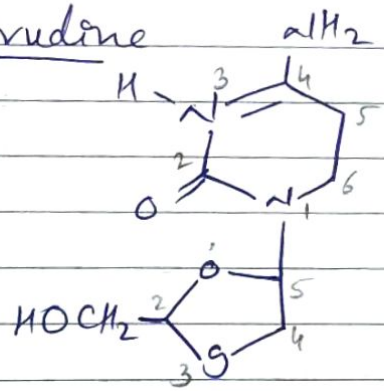
1-[4-azido-5(hydroxymethyl) tetrahydro furan-2-yl]5-methyl pyrimidine-2,4-[1H,3H]-dione

Zalcitabine



4-amino-[1-(5-hydroxymethyl) tetrahydrofuran-2-yl] pyrimidin-2[1H]-one

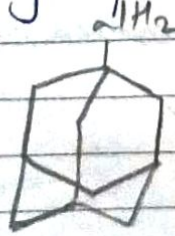
Lamivudine



4-amino-[1-(2-hydroxymethyl) 1,3-oxathiolan-5-yl] pyrimidin-2(1H)-one

Amantadine

Amantadine & it's methyl derivative inhibit uncoating of viral RNA within infected host body will thereby prevent it's replication.



1-aminoadamantane

Rimantadine

- It interfere with the viral uncoating by inhibiting the release of specific protein
- It is more effective than amantadine

α-methyl-1-adamantane methyl amine

N-{2-[4-(3-(propan-2-yl amino) pyridin-2-yl) piperazin-1-yl] carbonyl} 1H indol-1-yl methane sulphonamide

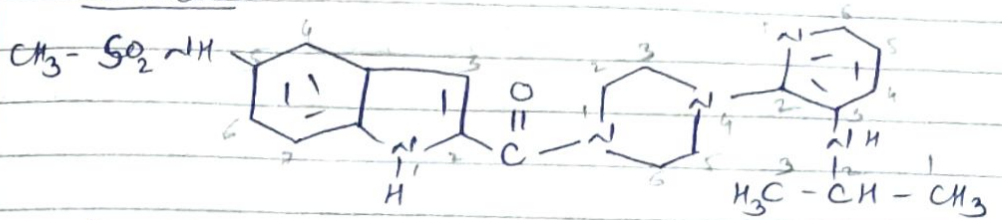
Non-nucleotide reverse transcriptase inhibitors (NNRTI)

It is the class of antiviral drug that develope

- Generally, they are hydrophobic molecule & are bind to the allosteric binding site & is hydrophobic in nature.
- Since, the allosteric binding site separate from substrate binding site.
- NNRTI are non-competitive reversible inhibitors.
- NNRTI's doesn't bind to the active site of polymerase but less conserved pocket near the active site P66 sub-domain. Hereby, their binding results in conformational change in reverse transcriptase that disturb's positioning of residue that bind DNA and results into inhibition of polymerization.

Delavirdin

Delavirdin



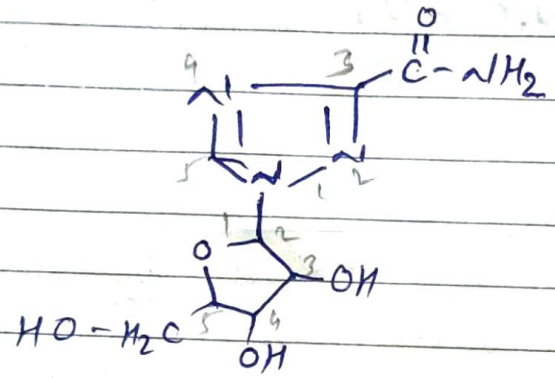
1- [2-(4-(3-propan-2-yl amino) pyridin-2-yl) piperazin-1-yl] carbonyl] 1H-indol-5-yl methane

HIV- Protease inhibitor [PI's]

- These agents have short life ∴ of resistance develop c in a short time of period.
- When PI's & RTI are used in combination in the antiviral activity & viral resistance developed slowly
- Large amts. of viral polyproteins synthesized in infected host cells. This proteins are break down into various functional viral components by protease enzyme
- Protease inhibitor bind to the active site of protease enzymes & interferes c the cleaving/ function
- All protease ~~inbt~~ inhibitors are potent inhibitor of CYP3A4
- Eg: Saquinavir, Indinavir, Ritonavir.

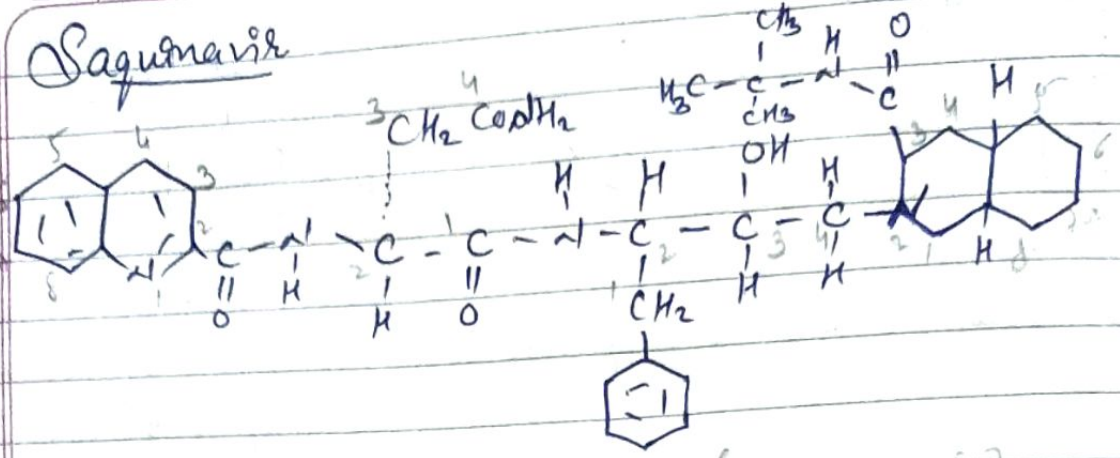
Ribavirin

It is ribonucleic analogue (guanosine) used to inhibit viral RNA synthesis as well as viral mRNA capine. It is a prodrug & when metabolize, the metabolites have structural resemblence to purine RNA nucleotide & it is capable to interfere to RNA metabolism & is essential for RNA replication



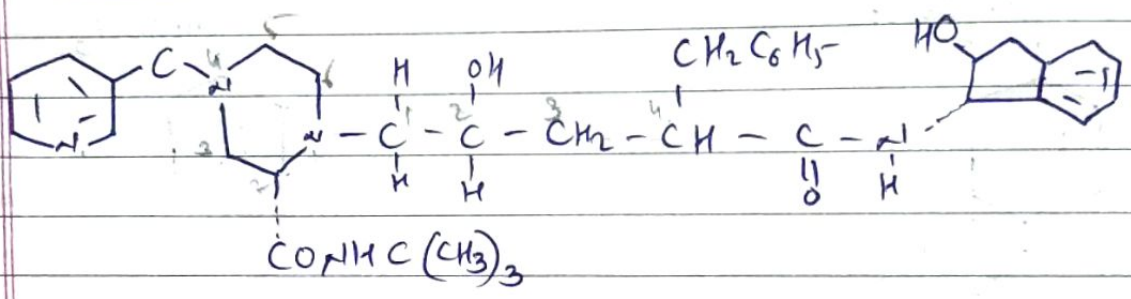
1 - [3,4-dihydroxy-5-(Hydroxymethyl) oxalin-2-yl]-[1H]-1,2,4- triazole - 3- carboxamide

✡ Saquinavir



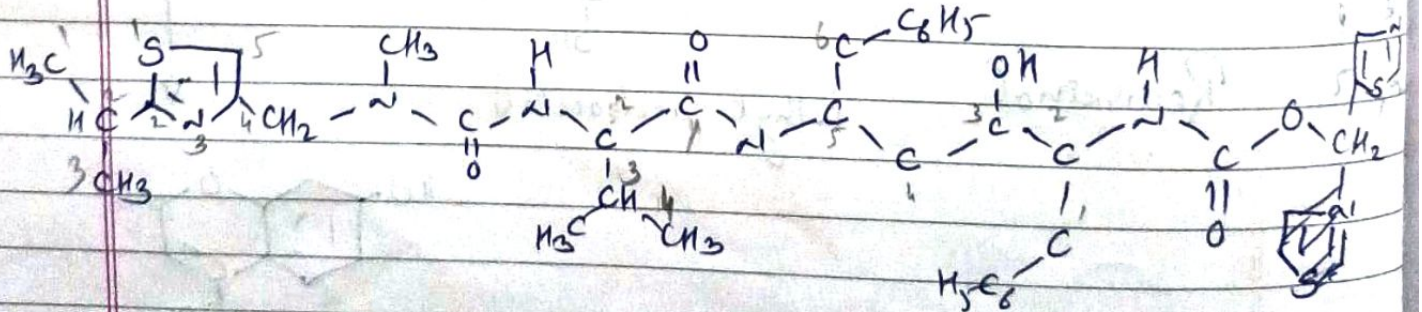
N-(1-(4-(3-tert butyl carbonyl)-octahydroisoquinolin-2(1H)-yl)-3-hydroxy-1-phenylbutan-2-ylamino)-4-amino-1,4-dioxobutan-2-yl) quinoline-2-carboxamine

✡ Indinavir



1-(4 benzyl-2-hydroxy-5-(2-hydroxy-2,3-dihydro-1H-inden-1-yl-amino)-5-oxopentyl)-N-tert butyl-4 (pyridin-3-yl methyl) piperazine-2-carboxamide

✡ Ritonavir



1,3-thiazol-5-yl methyl-N [3-hydroxy-5 [3-methyl-2 ((methyl (2-propan-2-yl) 1,3-thiazol-4-yl) methyl) carbamoyl) amino] butanamide] 1,6-diphenyl-2-yl carbamate.