

## Prodrugs

- Albert** – 1958 г. : химични съединения, които се биотрансформират преди да окажат фармакологичен ефект.
- Harper** – 1959 г.: prodrug latency: химична модификация на биологичноактивни вещества, които се освобождават само при ензимна атака.
- Kupchan** – 1965 г.: включва в понятието и неензимно освобождаване на изходното съединение.
- Bodor** – 1981 г.: съединения, които претърпяват химична или ензимна хидролиза преди осъществяване на биологичното действие.

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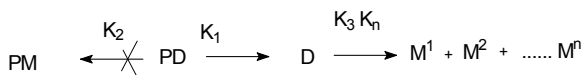
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**Prodrug** – неактивен прекурсор на лекарство, превръщайки се в неговата активна форма *in vivo* чрез нормален метаболитен процес

Следователно, създаване на лесно биотрансформирани се функционални групи.




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## Класификация

Два типа на база мястото на превръщане в крайната активна лекарствена молекула:  
 Тип I, тези които се превръщат вътреклетъчно (напр. противовирусните нуклеозидни аналози, статините);

Тип II, тези които се превръщат извънклетъчно, особено в храносмилателните течности или системното кръвообращение (напр. etoposide phosphate, valganciclovir, fosamprenavir).

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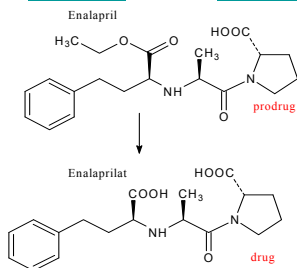
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## Примери:

Enalapril ----- esterase -----> enalaprilat;




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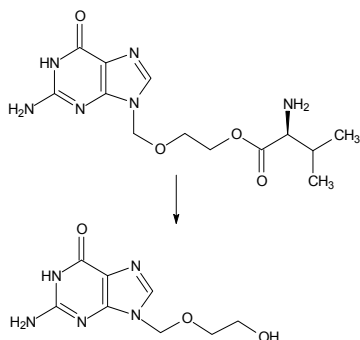


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Valacyclovir ----- esterase -----> acyclovir;




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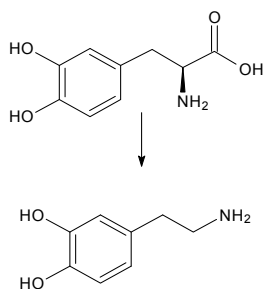


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Levodopa ----- DOPA decarboxylase -----> dopamine




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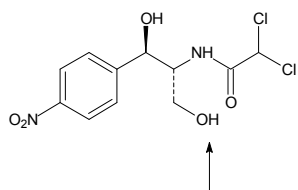
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[Chloramphenicol](#) succinate ester sodium salt е проdrug на chloramphenicol, приложение – интравенозно, защото чистият chloramphenicol е неразтворим във вода.

Chloramphenicol




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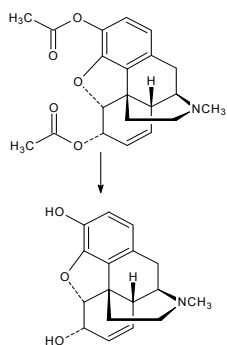


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[Heroin](#) ---- esterase → [morphine](#)




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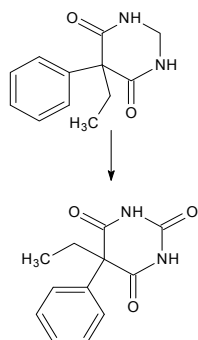


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[Primidone](#) ---- cytochrome P450 enzymes → [phenobarbital](#)




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## Prodrugs за подобряване мембранната пропускливост

Временно (обратимо) модифициране на неудобна функционална група, която е от значение за рецепторно или ензимно свързване, **но която пречи на лекарството да мине през клетъчните мембрани.**

Естери като **prodrugs**

-COOH, важна роля за връзката на лекарството с рецептора или ензима чрез йонна или водородна връзка, **но йонизираната група не може да премине през мастната клетъчна мембрана.**

**Отговор:** защита на киселинната функция, като **естер.**

**По-малко полярният естер може да премине през мастната мембрана на клетката.**

**Под действието на естерази – хидролизира обратно до свободна карбоксилна група.**

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**ACE – инхибитори prodrugs**, естерни прекурсори, които хидролизират от естерази до активни форми

- Enalapril -----→ Enalaprilat
- Perindopril ----→ Perindoprilat
- Trandolapril ---→ Trandolaprilat
- Cilazapril ----→ Cilazaprilat
- Quinapril --→ Quinaprilat
- Moexiptil----→ Moexiprilat
- Spirapril --→ Spiraprilat
- Fosinopril--→ Fosinoprilat

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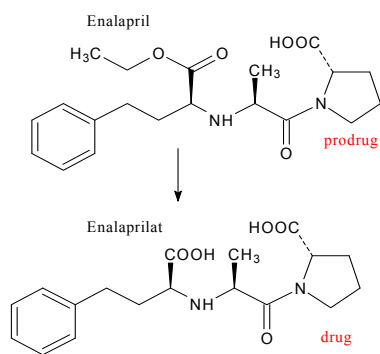
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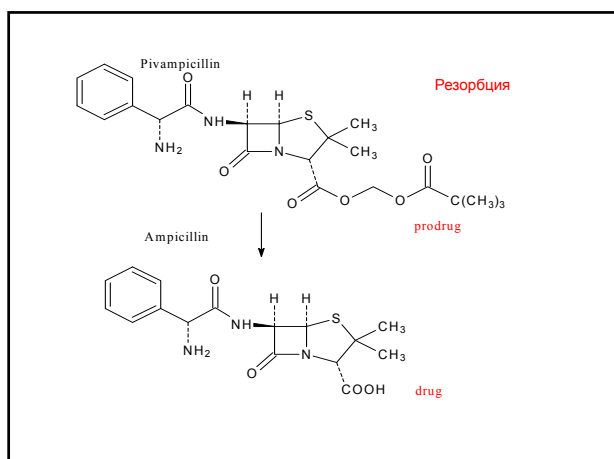
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### Важно

Естерите – чувствителни на хидролиза

**Решение** – включване в структурата на алкохола, **електрон-изтеглящи групи**.

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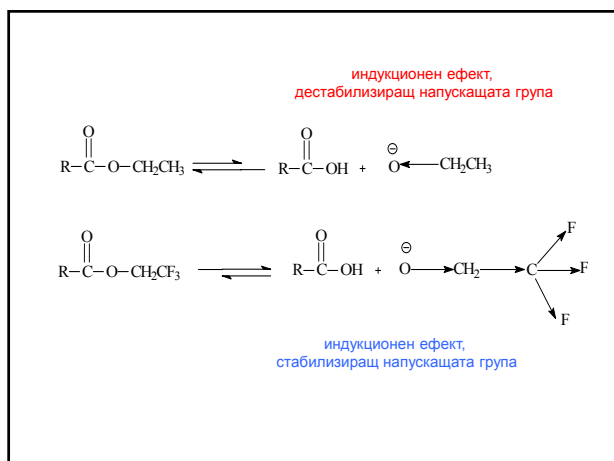
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## N-метиране

**N-дезметиране** - обикновена метаболитна реакция в черния дроб.

Полярни амини – **N-метиране** –  
редукция на полярността и  
подобряване мембранната  
пропускливост.

Сънотворни и антиепилептици – полза от  
тази реакция.

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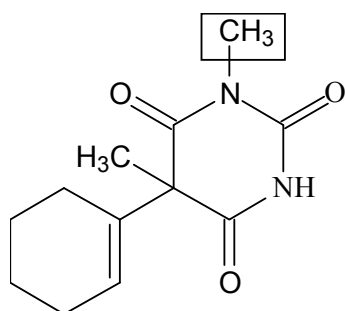
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## Hexobarbital (Hexobarbitone)




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## “Троянски кон” за мембрани протеини

Мембрани протеини – транспортират  
специфични субстанции в кръвта или  
**през** клетъчните мембрани.

Дизайн на **prodrugs** с предимство пред  
мембранните протеини в клетъчната  
мембрана, отговорни за мембрани  
амино киселини вътре в клетката.

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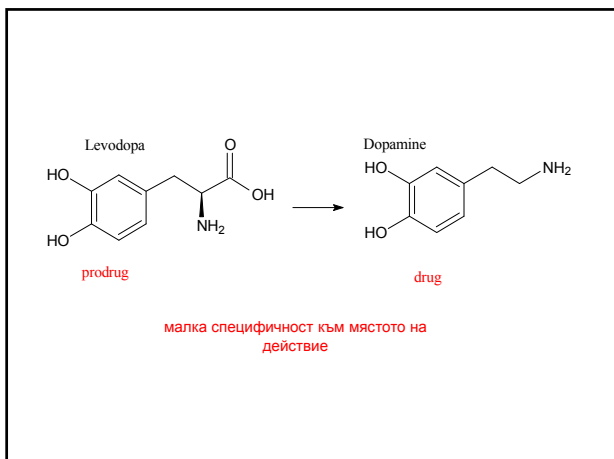
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**Dopamine** – много полярен, за преминаване през кръво-мозъчната бариера.

**Levodopa** – по-полярна, но аминокиселините я приемат, като такава за преминаване през бариерата.

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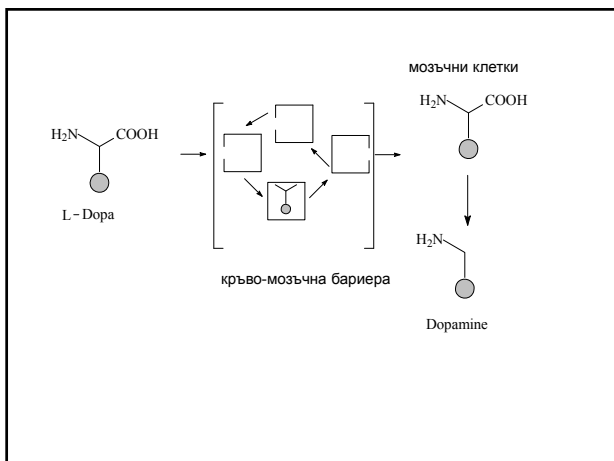
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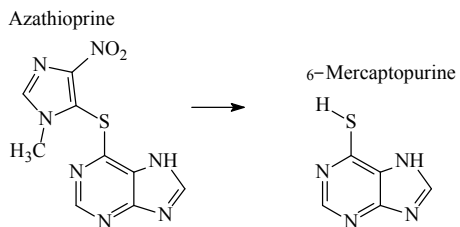
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**Prodrugs** за удължено лекарствено действие



Azathioprine е prodrug за 6-mercaptopurine

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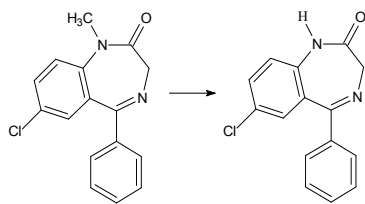
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Diazepam

Nordiazepam

Diazepam, като възможен prodrug на Nordiazepam

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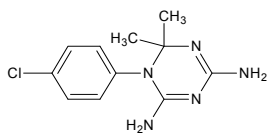
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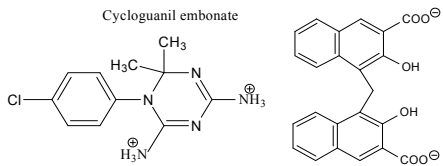
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**антималарен**

Cycloguanil



Cycloguanil embonate



активното лекарство е ограничено с голяма липофилна група

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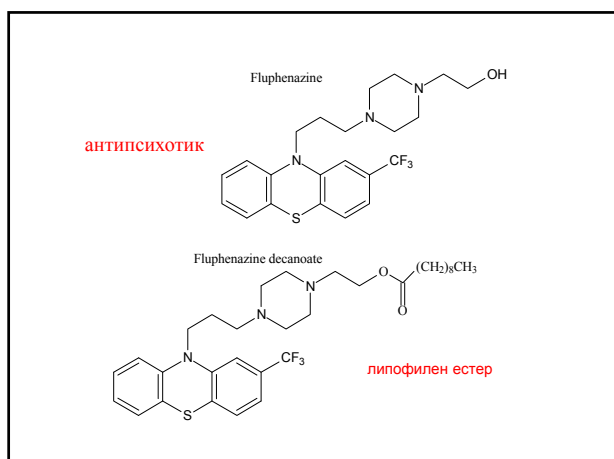
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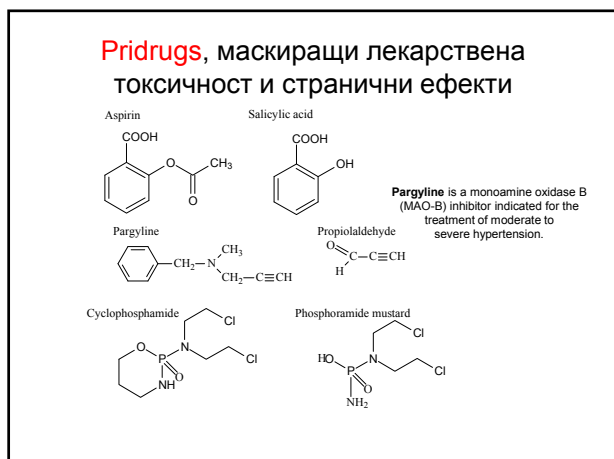
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Противовирусните лекарства: **Zidovudine**, **Acyclovir**, **Pencyclovir**

са не-токсични **prodrugs**, които показват селективна токсичност срещу вирусно инфектирани клетки, като се превръщат в токсични трифосфати.

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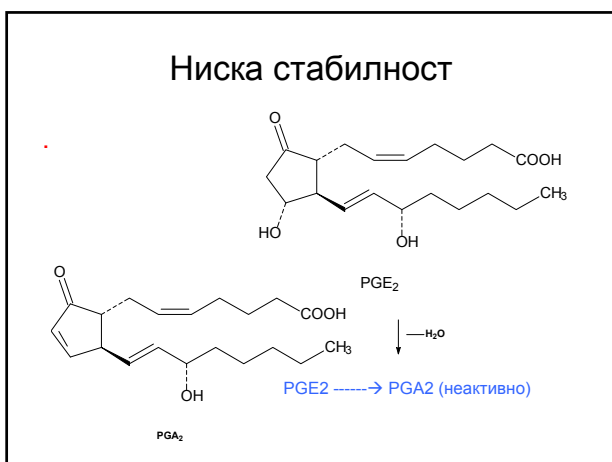
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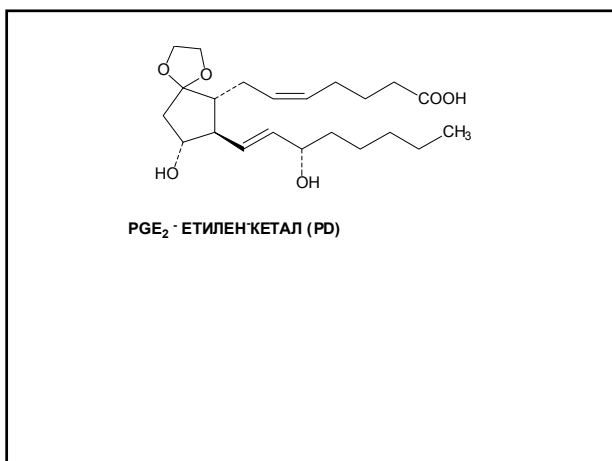
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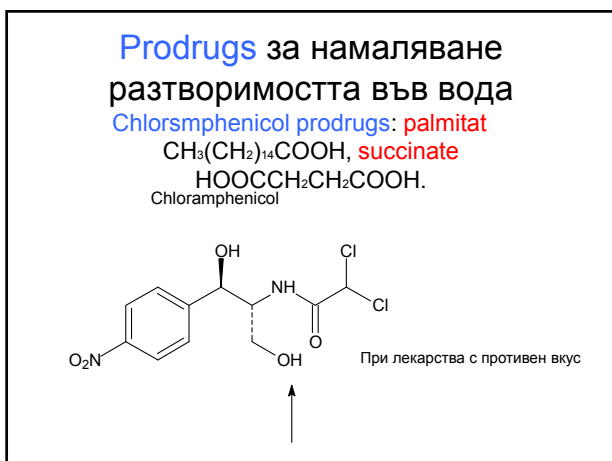
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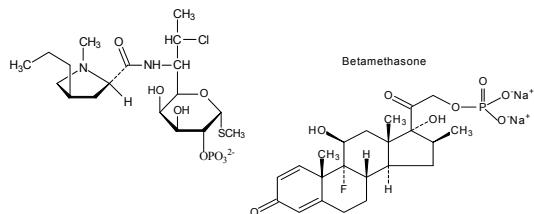
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## Prodrugs за подобряване разтворимостта във вода

Clindamycin phosphate




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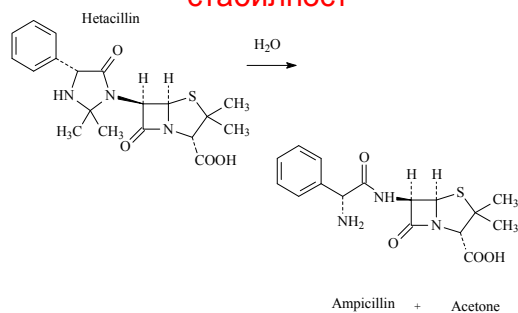
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## Prodrugs за увеличена химична стабилност



редукция на полярни групи - повишена кожна резорбция,  
скорост на проникване- по-висока

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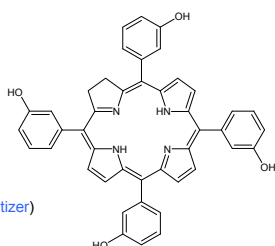
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## Prodrugs, които се активират от външно въздействие (спящи агенти)

Foscan (Temoporfin)




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Традиционните **prodrugs** са неактивни съединения, които се биотрасформират до активни.  
 Вариант на концепцията **prodrug** е "спящ агент".  
 Това е неактивно съединение, което единствено се превръща в активно лекарство от някои форми на външно въздействие. Напр. използването на фоточувствителни агенти, като **порфирини** или **хлорини** при лечението на тумори (фотодинамична терапия). Тези агенти имат малък ефект, но приложени интравенозно, се натрупват вътре в клетките и имат селективност към туморните клетки. Ако тези клетки се **облъчат**, **порфиринът** се активира и реагира с молекулен кислород до получаване на много токсичен атомен кислород, който атакува протеините и ненаситените липиди в клетъчната мембрана и формира хидрокси радикали, които реагират с DNA и резултатът е деструкция на клетката.  
**Foscan** е пример за **хлорин** фоточувствителен агент, клинично изпитан за лечение на някои тумори.

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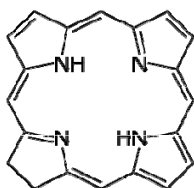
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Porphine,  
най-простия  
porphyrin



chlorin

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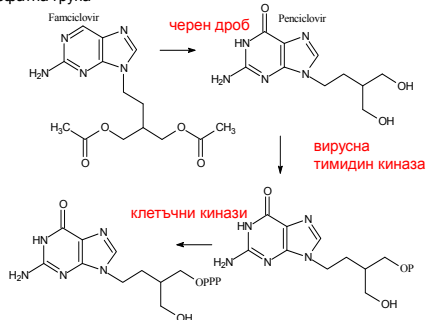
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## Prodrugs на Prodrugs

P = фосфатна група




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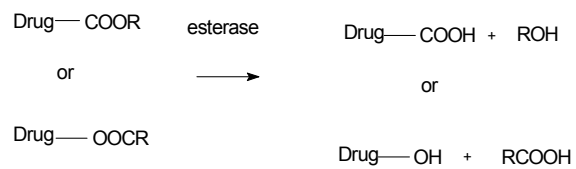
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## Prodrugs на функционални групи

### 1. Карбоксилони киселини и алкохоли Естери




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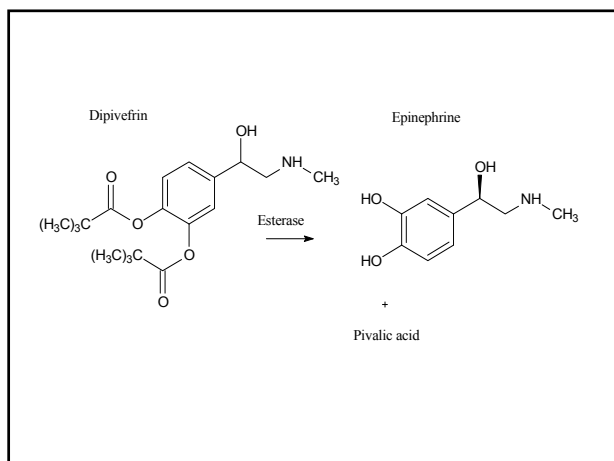
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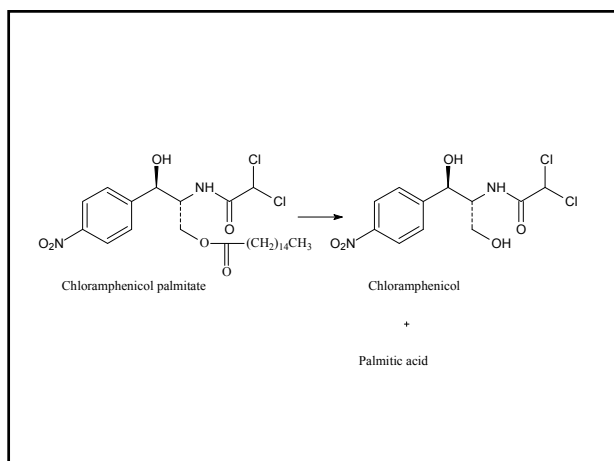
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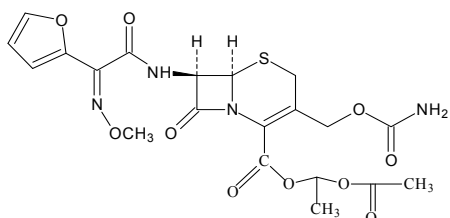
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## Cefuroxime Axetil (prodrug)

Cefuroxime Axetil - 1-(ацетилокси)этилов  
эстер на Cefuroxime




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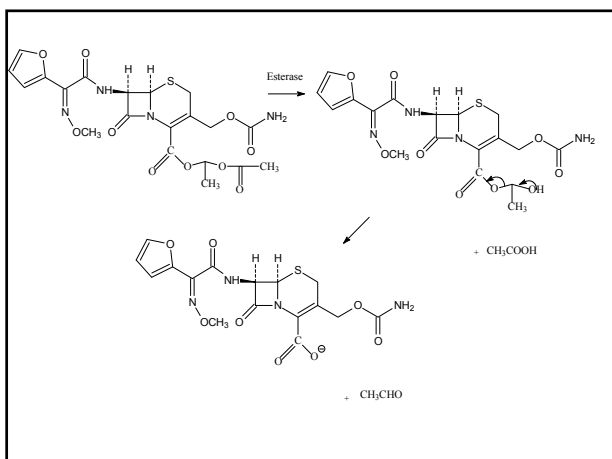
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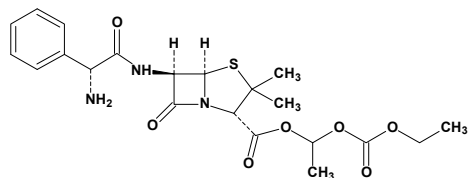
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## BACAMPICILLIN




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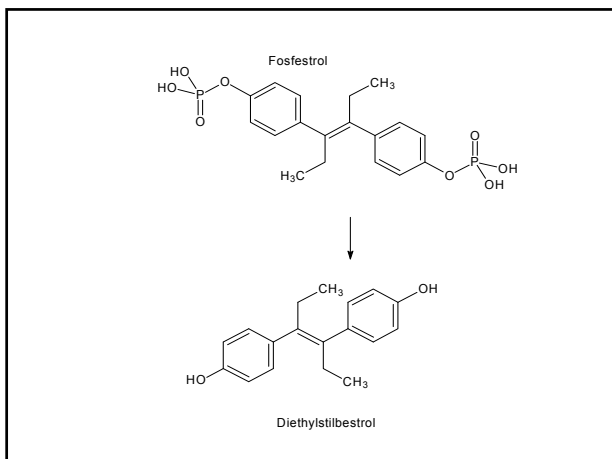
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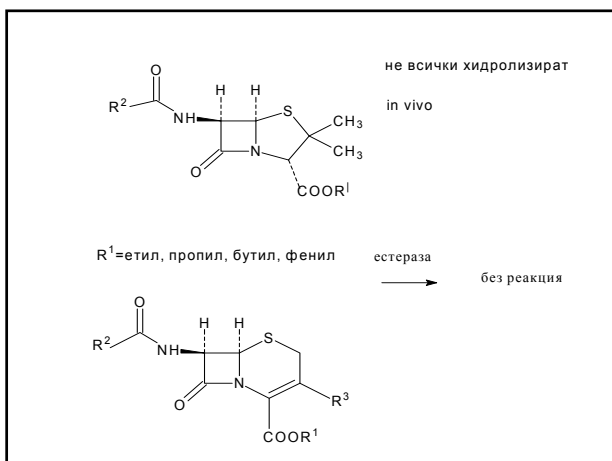
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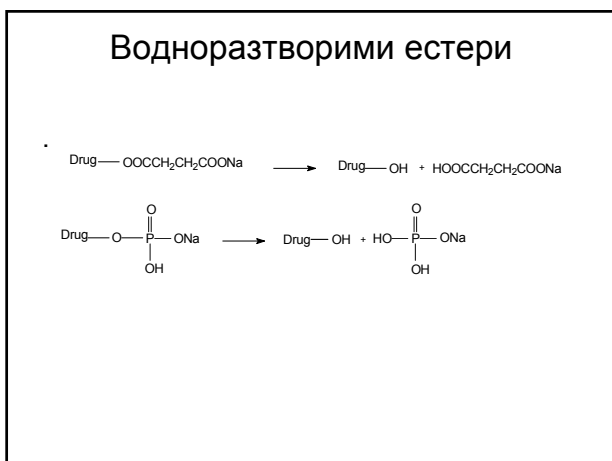
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### ЕСТЕРНИ АНАЛОЗИ НА АЛКОХОЛИ, КАТО PD

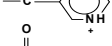
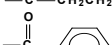
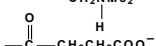
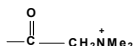
**DRUG – OH ----->DRUG-OX (PD)**

**X**

ЕФЕКТ НА РАЗТВОРИМОСТ ВЪВ ВОДА

НЕ СЕ УВЕЛИЧАВА

R = АЛИФАТЕН, АРОМАТЕН



УВЕЛИЧАВА СЕ

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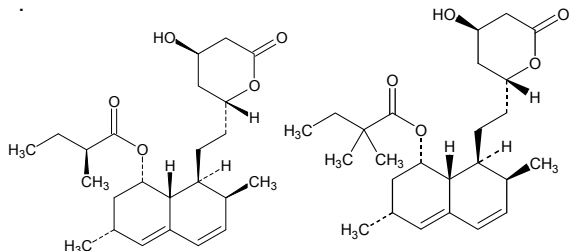
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**Lovastatin и Simvastatin** – лактонна фарма - хидролизират в черния дроб до бета-хидроксилни к-ни

Lovastatin

Simvastatin




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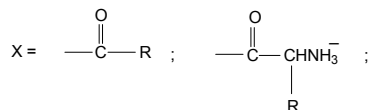
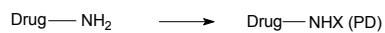
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### АМИНИ




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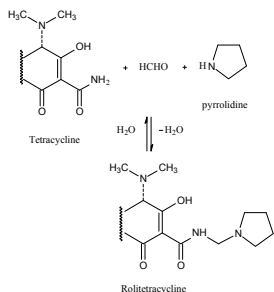
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## Манихови бази, като **prodrug**

Hetacillin → Ampicillin




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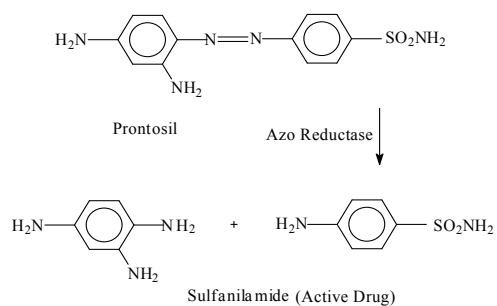
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## Азо - свързване




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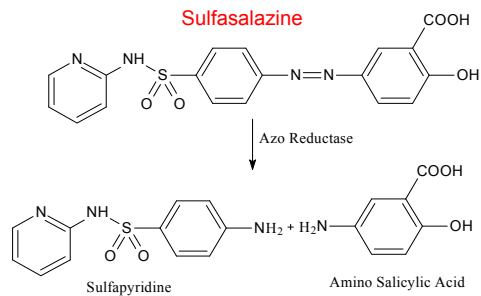
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## Sulfasalazine




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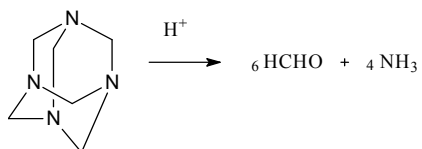
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## Карбонилни съединения

Methamine (Urotropin)



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