**Антибиотики. β-лактамные антибиотики.**

Антибиотики представляют собой соединения, занимающие важное место в антибактериальной химиотерапии. Пенициллины были случайно открыты Александром Флемингом в 1929 году, а кристаллические пенициллины были получены Флори и его коллегами в 1940 году. В 1944 г. произошли важные события, такие как выделение сульфата стрептомицина из штаммов Streptomyces griseus и внедрение в клиническую практику многих биотехнологически приготовленных антибиотиков. В настоящее время синтетические и полусинтетические антибиотики получают из соединений, полученных биотехнологическим путем.

Антибиотики являются основными препаратами, применяемыми при лечении инфекционных заболеваний в медицине.

Примерно за 5000 лет до письменной истории в китайской литературе упоминается об использовании гнилых растений для лечения ран. Но научно, в исследованиях, проведенных Пастером и Жубером в 1877 году, было установлено, что два микроорганизма убивают друг друга. В 1889 г. Вюйемен использовал термин «антибиос», и таким образом появилось понятие «антибиотик». Этот термин до сих пор используется в современной медицине.

*Векман*Согласно научному постановлению: антибиотики образуются как вторичные метаболиты при метаболизме бактерий, грибов и актиномицетов и оказывают летальное действие на микроорганизмы. Однако многие антибиотики, используемые в настоящее время в клинической практике, синтезируются в виде вторичных метаболитов микроорганизмов, таких как грибы и бактерии.

Когда антибиотики группируются в соответствии с их химической структурой, они классифицируются в соответствии с механизмами действия на бактерии. Механизмы действия антибактериальных препаратов и антибиотиков изучены и разделены на следующие группы.

1) β-лактамные антибиотики

2) Аминогликозидные антибиотики

3) Антибиотики тетрациклиновой группы

4) Макролидные антибиотики

5) Антибиотики группы полипептидов

6) Антибиотики группы линкомицина

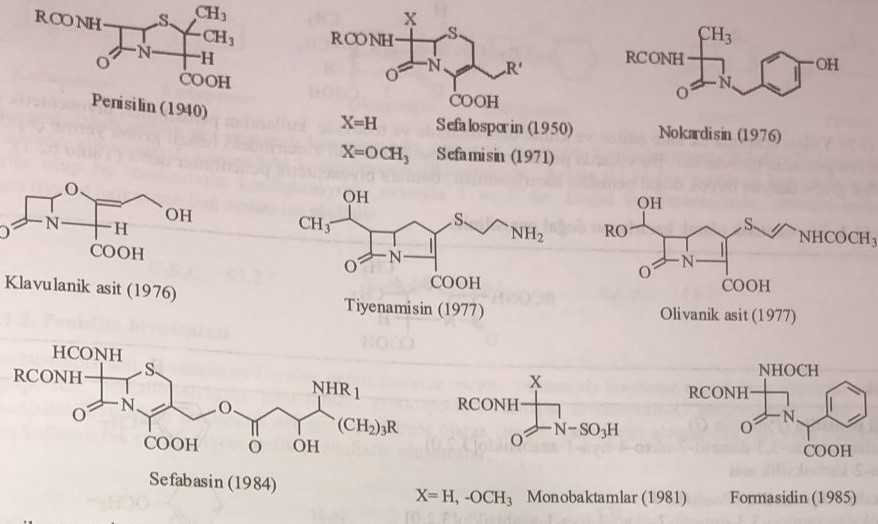
7) антибиотики группы хлорамфеникола

8) Антибиотики различного строения

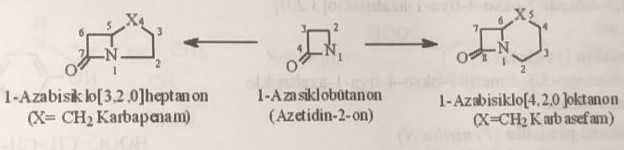
**β-лактамные антибиотики**

Эта группа соединений была введена в клиническую практику в 1929 г. бактериологом Александром Флемингом с выявлением антибактериального действия Penicillinum Notatum и в 1940 г. группой Флори с получением кристаллического пенициллина из Penicillinum notatum. В настоящее время многие антибиотики с β-лактамной структурой используются в клинике против различных бактериальных инфекций.

Химическая структура и дата изготовления этих соединений показаны ниже.

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Все эти природные соединения, полученные путем ферментации из различных микроорганизмов, имеют общую структуру β-лактама. То есть все соединения образуют структуру 1-азоциклобутана. Когда рассматриваются соединения, которые сохраняют эту основную структуру, и многие синтетические соединения, обнаруживается, что бета-лактамы имеют следующую основную структуру.



Помимо образования 1-азоциклобутаноновой структуры этих соединений существуют также конденсированные бициклические формы, сочетающиеся с пяти- или шестичленной гетероциклической или циклоалкановой структурой. Этими основными бициклическими структурами являются карбапенам, оксопенам, пенам и 1-азобицикло в соответствии с комбинацией –CH2-, -O-, -S- (метилен, окса, тиа) в качестве функциональной группы X. [4,2,0] Октаноны по-разному называются карбазепамом, оксозепамом и цефамом. Соединения, сохраняющие двойную связь между вторым и третьим состояниями, называются соответственно карбапенемами, оксопенемами, пенемами или карбазефемами, оксозепемами и цефемами.

Бета-лактамные антибиотики в основном изучаются в 4 группах.

1) Пенициллины: 1-азабицикло[3.2.0]гептаноны

2) Цефалоспорины: 1-азабицикло[4.2.0]октаноны

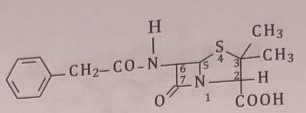
3) Монобактамы: 1-азациклобутаноны

4) Карбапенемы

**пенициллины**

**Природные пенициллины**

Группа пенициллина, первый представитель антибиотиков, пенициллин G, был получен группой Флори как вторичный метаболит из культуры Penicilium notatum и назван бензилпенициллином.



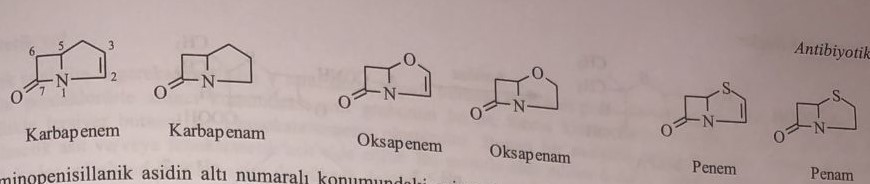
Пенициллины, полученные между 1940 и 1954 гг., внедренные в клиническую практику и применяемые в лечении, представляют собой производные пенициллина, полученные биосинтетически. За эти годы было получено много природных производных пенициллина, в которых бензильная группа в фенилуксусной боковой цепи пенициллина заменена на различные алкильные и арилалкильные группы. Эти пенициллины называются биосинтетическими пенициллинами.

Эти соединения были получены из культуры Penicillium notatum и Penicillium chrysogenum и введены в клиническую практику. Среди них пенициллин G и пенициллин V наиболее часто используются в клинике. Для приготовления инъекционного раствора этих производных используют соли натрия и калия. Новокаиновая соль бензилпенициллина — препарат депо-эффекта.![Text

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**Химия и номенклатура пенициллина**

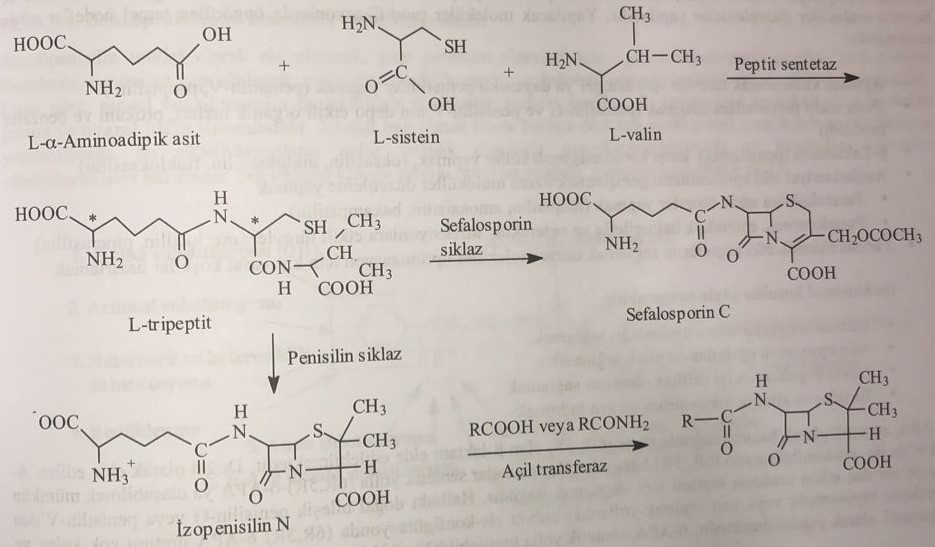
Основная структура бензилпенициллина представляет собой 6-амино-3,3-диметил-4-тиа-1-азобицикло[3.2.0]гептан-2-карбоновую кислоту, которая называется 6-аминопенициланской кислотой. Таким образом, путем добавления суффиксов пенициллин-6-амина пенициллин-6-амин к кольцевой системе, кольцевая система была названа пенам. Основными кольцевыми системами пенициллинов являются:



Асимметричный атом углерода в шестом положении 6-аминопеницилановой кислоты находится в R-конфигурации. Таким образом, во всех пенициллинах асимметрический атом углерода в шестом положении должен находиться в R-конфигурации. При этом атомы углерода во втором и пятом положениях асимметричны, их конфигурации S и R соответственно. В природном бензилпенициллине валентный угол тиазольного кольца, замещенного азетидиновым кольцом, следующий:

**Биосинтез пенициллина**

L-α-аминоадипиновая кислота конденсируется с L-цистеином и ферментом L-валинпептидсинтетазой с образованием трипептида. Из этого трипептида с помощью пенициллинциклазы образуются пенициллины, а с цефалоспоринциклазой – цефалоспорин-С. На заключительном этапе образуется бензилпенициллин, а в присутствии фенилуксусной кислоты образуются другие биосинтетические пенициллины.



**Молекулярная стабильность пенициллинов**

Пенициллин является стабильным соединением в нейтральной среде. В других средах подвергается гидролизу под действием кислоты и щелочи. Продукты деградации, образуемые пенициллиназой и пенициллинамидазой, которые действуют особенно в физиологических условиях, проявляют сходные свойства с продуктами деградации, образующимися при действии кислот и щелочей. Продуктами разложения являются 6-аминопеницилановая кислота, пенициллановая кислота и пениловая кислота. Особенно при пероральном применении он легко распадается на неактивную форму. В 1950-х и 1960-х годах были получены синтетические антибиотики, содержащие кислотоустойчивые производные β-лактамов.

![Diagram

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**Полусинтетические пенициллины**

В природных пенициллинах существует зависимость между рН среды и химической и биологической стабильностью антибиотика. Поскольку β-лактамное кольцо, которое является фармакофором, представляет активность, осуществляются трехуровневые молекулярные модификации, которые предотвращают как химическое, так и ферментативное расщепление этого кольца или стабилизируют β-лактамное кольцо. Основными мишенями молекулярных модификаций являются:

1) Получить pH-резистентные пенициллины для производных, которые будут использоваться перорально,

2) Для получения препаратов пролонгированного действия (пенициллин-G и пенициллин-V органические соли депо-эффекта, новокаиновые и бензатиновые пенициллины)

3) создать молекулы, защищенные от β-лактамаз (пенициллиназы) (оксациллин, диклоксациллин, флуклоксациллин)

4) Расширить спектр антибактериального действия

а) Получение эффективных производных против энтерококков (ампициллин, амоксациллин, бакампициллин)

б) Производные, эффективные в отношении синегнойных, энтерококковых бактерий (мезлоциллин, пиперациллин)

Химические условия оптимизации для улучшения фармакокинетических свойств следующие:

1) Обеспечение соответствия фармацевтическим препаратам

2) Для обеспечения оптимальности всасывания

3) Для обеспечения хорошей диффузии через липоидные барьеры

4) Свести к минимуму кумулятивную и аллергическую токсичность

При синтетическом получении 6-аминопеницилановой кислоты образуется β-лактам с транс-(6R,5S). В встречающейся в природе 6-аминопеницилановой кислоте она находится в цис-конфигурации (6R, 5R). Хотя существует химический способ производства, этот способ экономически не эффективен. 6-Аминопеницилановую кислоту удобнее получать в цис-конфигурации (6R,5R) одним из биосинтетических или полусинтетических путей с использованием природного пенициллина-G или пенициллина-V. 6-аминопеницилановая кислота производится как синтетическим, так и биосинтетическим путем.

**Биосинтетический путь**

При добавлении 0,001% иммобилизованной пенициллин-амидазы и 10% раствора аммиака для контроля pH к соединениям пенициллина G или пенициллина V происходит количественный гидролиз, и 6-аминопенициллиновая кислота дает фенилуксусную кислоту из пенициллина G или феноксиуксусную кислоту из пенициллина V.

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**Синтетический способ**

В синтезе как пенициллина G, так и пенициллина V карбоксильная группа в структуре защищена диметилдихлорсиланом. Затем с помощью пентахлорида фосфора лактимную форму амидной группы в шестом положении переводят в хлоридную форму. В присутствии бутанола или трет-бутанола получают трет-бутоксиазометин. В результате ее гидролиза одной молекулой воды получают 6-аминопеницилановую кислоту и фенилуксусную кислоту или феноксиуксусную кислоту. 6-аминопеницилановая кислота, полученная этим методом, не так чиста, как 6-аминопеницилановая кислота, полученная методом биосинтеза. В биосинтетическом пути продукт очень чистый, и этот метод экономически выгоден.

![Diagram, schematic

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**Молекулярная модификация бензилпенициллинов**

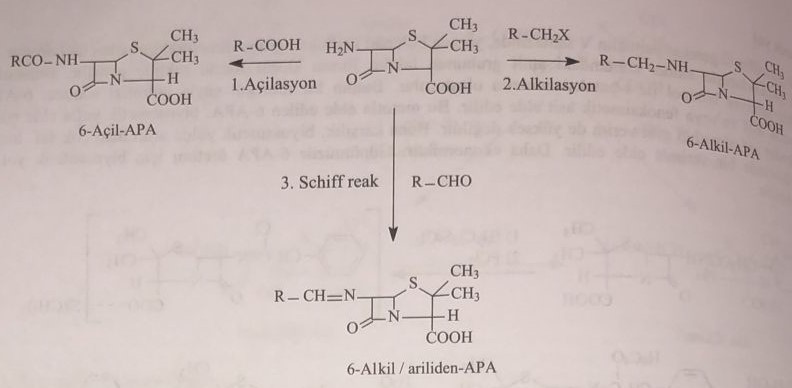
В качестве модели рассмотрен бензилпенициллин и получены его производные. Поэтому в молекуле бензилпенициллина замещение происходит по четырем основным функциональным группам: метиленовая в фенилуксусной кислоте, карбоксильная во втором положении, протон в пятом положении и 2,3-двойные связи в системе колец тиазола.

![Diagram, schematic

Description automatically 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**Производные аминогруппы в положении 6 6-аминопеницилановой кислоты**

Ацилирование, алкилирование и образование основания Шиффа на одной аминогруппе 6-аминопенициланской кислоты можно использовать для получения многих производных.



Среди этих трех производных производные 6-ациламинопенициловой кислоты обладают более высоким антибактериальным действием. Помимо мезиллена, алкил/арилиденовое (Шифф) основание и алкильные производные неэффективны или обладают меньшей антибактериальной активностью, чем при клиническом применении.

В результате комбинация аминогруппы в шестом положении обеспечивает активность. При сравнении пенициллина-V и пенициллина-G видно, что пенициллин-V более эффективен при пероральном приеме и более кислотоустойчив. Когда метиленовая группа в бензиле становится асимметричной, такие соединения, как фенетициллин и пропициллин, более эффективны при пероральном приеме.

![Diagram, schematic

Description automatically 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Фенициллин и пропициллин получают реакцией 2-феноксипропионовой и 2-феноксимасляной кислот с 6-аминопенициланской кислотой при катализе изобутилхлоркарбонатом и триэтиламином.

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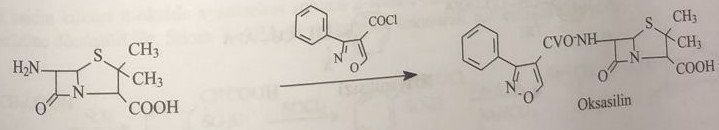
В 1960 году не было пенициллинового антибиотика, устойчивого к пенициллиназе, секретируемой Staphylococcus aureus. Поэтому лечить инфекционные заболевания, вызванные этой бактерией, было очень сложно. Для этого впервые проведена реакция ацилирования 6-аминопеницилановой кислоты по аминогруппе ароматическими карбоновыми кислотами и получены стабильные производные пенициллина, стерически защищающие β-лактамное кольцо от пенициллиназы.

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В этих соединениях установлено, что β-лактамное кольцо защищено за счет стерического эффекта боковой группы. Но спектр эффектов довольно узок, они мало отличаются с точки зрения клинической полезности и их применение ограничено.

Метициллин и нафциллин получают взаимодействием соответствующих хлорангидридов с 6-аминопенициловой кислотой в среде бикарбоната натрия или триэтиламина. В последние годы при синтезе этих соединений непосредственно получают изоксазоловые кислоты, которые вводят в реакцию с 6-аминопенициловой кислотой в среде изобутилхлоркарбоната и триэтиламина и получают с более чистым и высоким выходом.



![Diagram

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BiiP71FFUASAbulJHRRQIcPvCpJPu0UVBJGvUU9QN54oooLButNLH1oooAkT7ppE60UUCGt9001u1FFBI9e9C96KKChcncKcPumiigkaaehoooATPWlU/MKKKYCS9qT+GiiqKI2qVegooqCSCT71TRj5QaKKCxrMd3WmzdKKKAI16LVuEniiigCYdaVulFFACfw03aOuKKKAHikPWiigBmTuok+6aKKAIP4hSyfdNFFBRWYmou5oooAa3WnD7tFFAyu3So1oooKBqgb71FFBBG3+uRf4euPpzUdwgh37MjnPWiimBXDFbgqvygpuJXg5+vWoo5XjV9rsu0bgQeQfWiiqApyMZZJGf53jbCM3JUbSeD9RVCTTrO8hm8+ztpfLY7N0CHbhm6cf7K/lRRQAxvAfhy42l9DsNyOxR1t1VlLcMQQMjIAzS2fhvTPDEL2OlWUdjZxlisMQIUZYZx+dFFAwk6Gqr9KKKgoheqk1FFAFdu9QP3oopgVpe9Q7RRRVAf/9k=)

Для получения кислот, производных оксациллина, требуются специальные реакции. Для этого сначала получают соответствующий оксим бензальдегида. Путем пропускания из него газообразного хлора получают хлорид бензоксимовой кислоты. 5-метил-3-замещенный фенилизоксазол-4-карбоновую кислоту получают взаимодействием с этилацетоацетатом в среде метилата натрия, а затем с тионилхлоридом и хлорангидридом.

![Diagram

Description automatically 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NUVVZXWFlaY2RlZmdoaWpzdHV2d3h5eoOEhYaHiImKkpOUlZaXmJmaoqOkpaanqKmqsrO0tba3uLm6wsPExcbHyMnK0tPU1dbX2Nna4eLj5OXm5+jp6vHy8/T19vf4+fr/xAAfAQADAQEBAQEBAQEBAAAAAAAAAQIDBAUGBwgJCgv/xAC1EQACAQIEBAMEBwUEBAABAncAAQIDEQQFITEGEkFRB2FxEyIygQgUQpGhscEJIzNS8BVictEKFiQ04SXxFxgZGiYnKCkqNTY3ODk6Q0RFRkdISUpTVFVWV1hZWmNkZWZnaGlqc3R1dnd4eXqCg4SFhoeIiYqSk5SVlpeYmZqio6Slpqeoqaqys7S1tre4ubrCw8TFxsfIycrS09TV1tfY2dri4+Tl5ufo6ery8/T19vf4+fr/2gAMAwEAAhEDEQA/APuLy8tSNDnkdakoK55rkPRI1z3603qQKf0FIOOcZoEO2r360BMcjpQpyemKerYJpXAcq5GajdfmrO1zxJa+HY7OS7EzLdXUdnH5Me/EkjBU3ei7jWruw2Ov0pgN20bT0HWpMbuaVV280AQ+S5bB6Cp9tLkmkzt5oAY6fNmlwGU5pWkz2x70L25zQACMLyOlO5opM54ovYA/ipWXvTlUL160M/pTAYM04UnNLtzSAUrmlHFIq0r8AUAJxzmmeXu5HSpNuaVeDQAyMbWxUm3NLS/w0AN6ChelOXOKRmx+NAhV28+tN3UKmCads+WgYlFNk+VRSL+9pbADNUiqWwT0pGjxzQhKrkHAzTEOk46dKFG4Yqla65ZX2pX1jbXSTXdiY/tEK/ei38x5+u3P41dxtwOtAx4jwKa3BqSJciho+aVgEVVKjPWl6dOlG3tTgmOKYDV6U4ZpVUHg04x44FAEZpKeq0pO3igCMKxGRQGLHmn80m3LUwDBHFG2neXjmkY5GO9IBn8RpVXNC5B5p6tjNACdKKQ9KBmgA3UbuKRu9IBuGKAFVt3FSDgGmKu2jdQA2lQ7RmmSNyaI/u0APMvFM3buaaeuaVRu53YoGLuwtIelP2jHJyaToBjpQBC3embsU9ucivPviZ4q1rwvqXhC10m4sYk1zVBpsrXlu0vlZRm3gblz93GPemI79VaZlQP5e4hQ4AJUnI3YPHXFcf8ACvXL/wAQeA9MvtTuTeX8hmWWZgAWKzOvQcdFFZ3wx8f6j4qvvFenamLac6HeizGq6blIbsMucqCTtZO4DHBJ6dB1ug+HLHwzpcWnadFJDawliqPOZOWYsxJJJ5Yk9e9A0aO6orm7is7eWa4lSGCNGkeSQ4VVUZZiTwABzmnrnnNeYftJWd/qHwb12OxR5AjQSXKRDLfZllVpCB/FwOR6Uhm6Piz4daO0n33wsrqVIbe+ksJ1t7hnYKpWQrznOc9+3FaHhzxlpviuXVY9OlmkOmXTWU5miaILMqgkDIyeGqs2taDqnh23uTcWs2j3nkmDYdyt8ytEqr1J3bRx0xiua+F7IPF3xMTG1v8AhIWYj0PkQZH50rgem7vmZR0Bx0qGRhyO9LjC/rUb0xkLEryaj3g9OlSsdp+tRSR4JNADJO1NZsCng54HWmMvrQBG1QyOenapj3qtJjf70DIm+7xUDd6nbPeoJqBFf5dxz1pkzelSsuc1XkO3igdyvJncSKjYsQTUzN8tVmf5sUDIWzzmopOhqaT5W+tV5PloAryHkioZFGPepmbdk1XduTTQFeRipINVpF5LVYmbd061UkZo6bAhb7tVpV4qw3eoJGqQKcnFMb261PJ2qBu9NARPnvTOae3eoaYCt3qKT7lPbrTH27eetWlqJnlfxAj2+Jpj/eRD/wCOgf0oqX4jof8AhIFIXIMC/wAzRXXzGZ97qrNyKBkdak25GKb5eK4CmI1Kq5FOEeefSlHzc0EkTLluuDxgc4PPcjmuMv8A4teG9Pv9Rt7m6vIX04j7YzafMqW4Y8Fzt+6QQcn1rtZkG1ucdARnGefWvnHxc2s33iz4qjSJ4308iwh1S3jQNdSWvknzTEx43BN33genHNAHsvizS7vxJp+hvpYhuo4dTtNR83zQqNDG28FeOTg10+z94SAAPas3wfJpM3hfSv7CnS40aO2jitDuLMIwoADE87hjB9wa10VecnNIBy9BQ3el2Acik5oAFXIpdtAp/wA2OKAI2X5aaq7fxqUEng0bdvNACJHjNO9RTlOcGmyUAR8rwKXnbmnUY3DFMBilj0qRFPU0KNvFL83akA77vFJSc7uacM0AG2l5pcbuKbt2tjtQAvNJtp3A5HWkyT160AJ/FSSdqc3SkGaBCr0FPK9KYelCtigY54t2KZ0b3p7NTRSYEV1eQ2MLzXU8VtAv3pp3Eca/UlgKqaXr2la1I8WnapY6jIoyy2tzHMwX+9weKqePFjk8E+JElRXQ6ZdcbVYE+S/Y9x1rwz4RRPqvjL4apfWcHh640bw2k1k1uwaTW0lhRD8+QuEJLFDlgSSOKEI9m0PT7xfiN4uvJrOaGwuobFLa6kGUlZI5A4H/AH0tdUvCjjHHTFSR52L9PUn9cDNOK5GaYxq9qXbQMgU4UAJS0rUq96ACkZsUny7uetO/lQAymspJ4qQt6UlMBFyBzS9hTl+7UUkqp94496BE3YVEVJ6fjUZuosE7wVHWmzXRjjDocjdSGWAvpR0qu19HGcOcH71AuojJkSbgVyKAJ6KqfaSI0PPLVN5vsw96VwJeaTdVdbpY42DZb6daqtqSxySKVZNoXr3ouBpbsc0xm3VX+2K+Rt2c8e9S+YTwUwaLgGdvFPRjj2qrcPtmiUKN56ZqN7oKqgYLFtu0daLgXfpRuxWZ/aUjbgYWXacAN3pWurjdt2IV27s0DNLevduaRm75yKyJGl3QOFVWb26VNp80qrKJpPNO/wCXjGKQFpmSZioOWHavMvjF4SvvGGoeDIItDbV9O0/VTfXyl4wgiETJtwzLlsuDgZx1r0NpCLi4bd1UUkjStcRLuXLEDn3J6/lTuI4X4aeFdZ+HNzc+GlsheeFFme402+jljSS2R8sYZFPzNtYMQy9iK9ERMflXJ/D3xdP4w8H6fq88SQ3FwJCyR/c4kZQR9QAfxretb2TadzAHnpRcZoHjFVpriONvLb5iw+62NpHpg8GokkaWQlm47VzXjfxhZ+B/D+o69qQc2dlEWZYxlpckBY1HdmYge3WgCbS/DnhfStYupdL0vS7XVbcBp5LaFEmi8z1x93K5PvnNaWl6Lp2ltcyWlja2UtxIXlkhiRGlJ6ksOTXl1nD410eTUvFps9LuJ9bktXvNE3uZbaNAEG2UcO6odxB75rpZ/iR4ZhuTFceKdLjZWw5a8RDxywPzcH1HrSBHcxzDcUBzimXDeWpJ6jrXj+ofGw+F/iLDpGqrayeHdQgjmstatQfLieUsI0mJJUBvLIDDv711dh4m1W78c6/pNy1kdPsYYZImgRxI3mZYBjuwSAAM98UDOqjuFmXeDhab9oSXcq8kda888ReObjTdb0fwvpHky63qED3ry3nMFraxnDyPgnJLbQFyOf4hVC1+IOp6f4mufDGqR2iavcWsl7pl1EjLDOIz84ddzFXBx3PWqFc9S8wKtV2uCWIPSvFbf4zeILj4M3Pjz7Bp4mjiN2LIeYY/K8wxld/Z8gZ9q9G03VLm70WwnvBDHcS26zTLBnYrEA4GecDOPwpMZ0Rl98ConbcSQc1l/bDGpkMn7srxUf2uZYUG7J70hmjIyr1OCaY7YXk5qi03mPGd3zVNDcFlYE5Ip3AczcGqzd6imuSJMDpVT7e6OcDIHUUXAsyNt/Gq7KvzE1W/tJp8kDavpURu2ZsbWw38QouBPIy7RVeZd3IqrMzTSKQWA9PWoxeRxxld7OwNFyiWTqRUEnFI1wJGDD5RUa3UbZw4NNMBJKpy96luLqKIHJz6Cqa3HnMQoxTAZI1VppMsRVtiApJ6VUZkkJA6ikBX3bVpjVI2N3NMdcjjpTAheom61MeMVHzQBE33hSsoK8daG3bqXcQeetbITPPfHihdYiy2D5C/+hNRWr4otRNfQt/0y/8AZmorYzPtcZo25aq5mIOT0qRZ9zcdK4ymSldvNNLcUks4jGD3qJpVpEjnywwPTPoPofWsK6/sbQLu1Js7WzuNTnWyjaG1G+SRslV4XPPPWtnzl21xXj6Yf8JB4CA7+IIf/RU1AHZ2Njb2IeO2t4baMvuKW8QUFvfAxVpV565PtVS3n3c1Y82gCxt+XFYeteMNI8O3sNldXMj386l47Kzhe4nZB1fYi5Cj3rU8044JAz1H0OP1ry34e6iLH4wfE6DU5lh1W5uLWSy85gjSWKx4XYTwQCP0oA6if4ueFYbeCX+0ZNk92LGJltZmBnKg+X8q8Ng/dNaLeOdKj8VW/hppLltYni89LVbOXmM/xFigUKDweeCCK8z+Lt5Z3svhT+yLi2t7uTxfaNJciPfEZhGRllUgMQAo69qr6pDrDfGjyX1W3vtTk8J3sdpJaWxgCs0yhFwZDyWwc470riuek33xQ8OWDXLyXU81paS+RdX8FrJJawSZxtaZQVHPvx07V1McqTwxSxyLLDIodJIyCrKRkEYHoa8d+HWu6LpP7PFpFeSwQCx0qazvbZmAkNyQ6yR7RyzOxXjvvz3rs/g3pOpaF8JfCOn6sGi1C309VnjcnKHkhTnpgEDHbGKYHZfTpSk/LimoVk4znFNkkVeKBjlGOKkqs0o7Ukkp4y2KAJl3bj6VKM1XhlXvzTmnHakBPzTW71H5wPU4NNMi+5+lIRKrUCoHlHGOvvTfNPemMt+Zt4oEnWqrTZ+Ud6ej0hXJwSaWoVkwTTt+QKYXJKau3vTJZFUAnrVaWbawZW57rSC5e+lODYBqqlx5i5pnm/Nt5pgN1bTLfXtLu9OuzJ9kuo2gmEbtGWjb7y5XsRxWFD8P/Ct1pOm6OLZriDQpFkska9k+0WJCgLtkDbwMYGPQV0i9F/H+Vcl4dZv+FteOEH3PsG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В бензилпенициллинах проводят реакции алкилирования, аминирования, гидроксилирования, карбоксилирования и галогенирования для присоединения функциональной группы к метиленовой группе. Соединения, полученные галогенированием, являются химически неустойчивыми соединениями.

![Diagram, schematic

Description automatically 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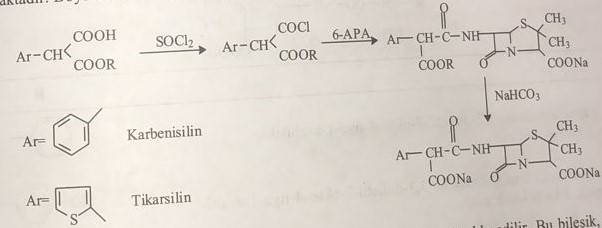
**Производные карбоновых и сульфокислот**

Эти соединения вошли в клиническую практику как производные пенициллина широкого спектра действия и парентерально эффективные, особенно против нозокомиальных инфекций, вызванных Pseudomonas aeruginosa. Карбенициллин, сульбенициллин и тикарциллин являются наиболее важными производными, вошедшими в клиническую практику. Эти соединения получают присоединением карбоксильной и сульфокислотной групп к метиленовой группе в бензилпенициллине.

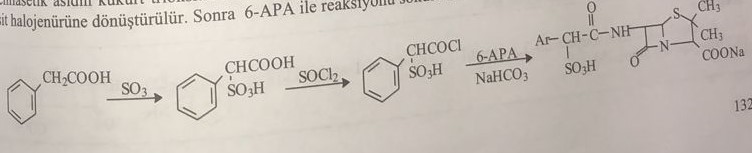
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Карбенициллин и тикарциллин получают хлорированием моноэфира арилмалоновой кислоты тионилхлоридом с последующей реакцией с 6-аминопеницилановой кислотой. Можно ацилировать непосредственно по аминогруппе 6-аминопенициланской кислоты моноэфирами арилмалоновой кислоты в присутствии изобутилхлоркарбоната и триэтиламина, что является методом активного сложного эфира с некоторыми патентными исследованиями. Таким образом осуществляется чистое и экономичное производство.



В результате взаимодействия фенилуксусной кислоты с триоксидом серы получается 2-фенил-2-сульфоуксусная кислота. Эти соединения превращаются в галогенангидрид тионилхлорида. Затем получают сульбенициллин взаимодействием с 6-аминопенициланской кислотой.



Карфециллин представляет собой фениловый эфир карбенициллина. Как и при синтезе карбенициллина тикарциллина, фенилмалоновую кислоту получают реакцией монофенилового эфира с 6-аминопенициланской кислотой.

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Величина МИК пенициллинов, полученных биосинтетически и синтетическим путем и используемых в клинической практике, указана в таблице ниже.

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**аминопенициллины**

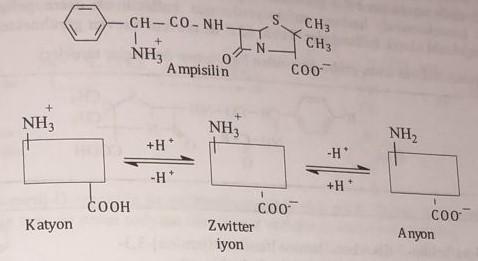
Эта группа соединений представляет собой производные, полученные в результате добавления аминогруппы к метиленовой группе в боковой цепи фенилуксусной кислоты. Фенильное кольцо может быть присоединено к метиленовой группе так же, как к аминогруппе.

![Diagram, letter

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Эти соединения были введены в клиническую практику в период с 1961 по 1972 г., широко используются ампициллин и амоксициллин. Спектр действия достаточно широкий, всасывание при пероральном приеме хорошее. Фармакокинетические свойства, такие как пероральная абсорбция и распределение в организме, усиливаются за счет этерификации карбоксильной группы во втором положении.

В зависимости от рН биологической среды они могут находиться в виде катионов, анионов и интерионов (цвиттер-ионов) за счет основных аминовых и карбоксильных функциональных групп во втором положении молекулы аминопенициллинов. На следующей схеме показан этот процесс:



1) Катион ампициллина образуется при рН желудка и всасывание снижается из-за ионизации препарата.

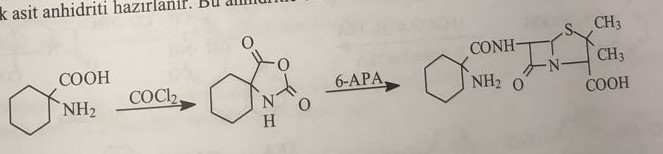
2) В тонком кишечнике образуется цвиттер-ион, всасывание препарата осуществляется путем активного транспорта.

3) Анион образуется путем депротонирования в нижних отделах тонкой и толстой кишки, поэтому всасывание препарата снижается и он выводится из организма с калом.

Для изменения этих ионизационных свойств аминопенициллинов и увеличения их всасывания были получены производные пролекарств.

Для получения этой группы пенициллинов необходимо сначала защитить аминогруппы, переносимые кислотным компонентом, образующим боковую группу, а затем соединить карбоксильную группу с 6-аминопеницилановой кислотой. Для этого в реакцию с метилацетоацетатом вводят аминогруппы D-фенилглицина, D-(4-гидроксифенил)глицина и D-(1,4-дигидрофенил)глицина. Используемая натриевая соль основания Шиффа называется солью Дейна. Затем эти соединения реагируют с 6-аминопенициловой кислотой в среде этилхлоркарбоната или изобутилхлоркарбоната и триэтиламина.

Среди аминопенициллинов молекула циклоцилина сохраняет амино- и карбоксильные группы в циклогексановом кольце. Для его синтеза сначала получают N-угольный ангидрид 1-амино-1-циклогексанкарбоновой кислоты в результате реакции с фосгеном или трифосгеном. Препарат получают в результате реакции 6-аминопеницилановой кислоты с этим ангидридом.



**Пролекарственные производные аминопенициллинов**

Эти препараты были синтезированы для устранения анионных свойств либо карбоксильной группы, либо катионных свойств аминогруппы производных аминопенициллина. Таким образом, устранена зависимость молекулы от перорального всасывания. При этом физико-химические свойства молекулы регулируются по фармацевтическим препаратам. Для этого карбоксильная группа этерифицируется до спирта. Аминогруппу также сделали неполярной путем ацилирования карбоновой кислотой.

**Производные по аминогруппе (ацилуреидные пенициллины)**

Алкилирование алкилирующими агентами, ацилирование кислотами и образование основания Шиффа с альдегидами возможны при рассмотрении химических реакций сочетания аминогруппы. Основание Шиффа алкилпроизводных этих продуктов обладает протоноакцепторными и косвенно катионообразующими свойствами. Однако в ацилпроизводных исчезают катионные свойства аминогруппы. Для него в качестве лекарственных препаратов используют только неполярные ацильные производные. Из этих соединений только ампициллин и амоксациллин являются препаратами, полученными в результате прямого ацилирования аминогруппы, которую они содержат в цепи, гетероциклическими карбоновыми кислотами и разработаны для применения при госпитальных инфекциях в целом. Применяется в клинике в виде инфузий и инъекций. Он показан в таблице:

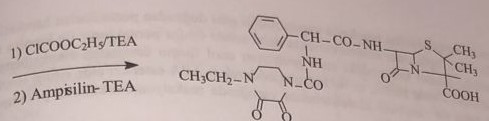
![Diagram, text, letter

Description automatically 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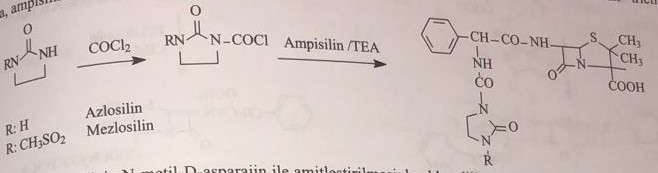
Активный эфир получают из апалилин 4-гидрокси-1,5-нафтиридин-3-карбоновой кислоты в среде этилхлоркарбоната и триэтиламина. Затем проводят реакцию с ампициллин-триэтиламиновой солью. При синтезе пиперациллина в первую очередь получают ацилированный фенилглицин путем соединения аминогруппы, полученной при взаимодействии 4-этил-2,3-диоксопиперазин-1-карбоксихлорида с фенилглицином, с 6-аминопенициланской кислотой. Это ацилирование происходит с помощью реагента переноса имидазолинонкарбоксилацила.

![Diagram

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Азлоцилин получают реакцией 1-хлоркарбонилимидазолидин-2-она с трифосгеном и ампициллином в триэтиламине. Мезлоцилин получают реакцией 1-хлоркарбонил-3-метилсульфонилимидазолидин-2-она, образующегося в результате реакции имидазолидин-2-она с метансульфонилхлоридом, а затем трифосгена с ампициллином в среде триэтиламина.



Аспоксициллин получают амидированием амоксициллина N-метил-D-аспарагином. Для этого н-метил-D-аспарагина хлорид вводят в реакцию с триэтиламиновой солью амоксациллина в среде безводного бикарбоната натрия.

![Diagram, timeline

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**Производные, полученные по карбоксильной группе**

Оральная абсорбция этих соединений, полученных путем этерификации карбоксильной группы различными спиртами, чрезвычайно высока, а их биодоступность клинически желательна. Эти производные называются диэфирными пролекарствами. Обычно используются ацилоксиспирты, этоксикарбонилоксиэтанол, бензоизофуран-3-оксо-1-ол, пивалоилоксиметанол для образования диэфиров.

![Text, letter

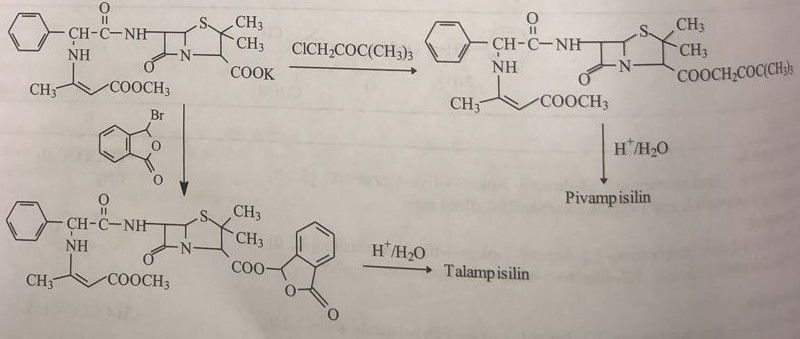
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AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAMjAyMzowMjoyNiAyMzo1NToyNAAyMDIzOjAyOjI2IDIzOjU1OjI0AAAAAAYBAwADAAAAAQAGAAABGgAFAAAAAQAAEZQBGwAFAAAAAQAAEZwBKAADAAAAAQACAAACAQAEAAAAAQAAEaQCAgAEAAAAAQAAH6QAAAAAAAAAYAAAAAEAAABgAAAAAf/Y/9sAQwAIBgYHBgUIBwcHCQkICgwUDQwLCwwZEhMPFB0aHx4dGhwcICQuJyAiLCMcHCg3KSwwMTQ0NB8nOT04MjwuMzQy/9sAQwEJCQkMCwwYDQ0YMiEcITIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIy/8AAEQgAmAEAAwEhAAIRAQMRAf/EAB8AAAEFAQEBAQEBAAAAAAAAAAABAgMEBQYHCAkKC//EALUQAAIBAwMCBAMFBQQEAAABfQECAwAEEQUSITFBBhNRYQcicRQygZGhCCNCscEVUtHwJDNicoIJChYXGBkaJSYnKCkqNDU2Nzg5OkNERUZHSElKU1RVVldYWVpjZGVmZ2hpanN0dXZ3eHl6g4SFhoeIiYqSk5SVlpeYmZqio6Slpqeoqaqys7S1tre4ubrCw8TFxsfIycrS09TV1tfY2drh4uPk5ebn6Onq8fLz9PX29/j5+v/EAB8BAAMBAQEBAQEBAQEAAAAAAAABAgMEBQYHCAkKC//EALURAAIBAgQEAwQHBQQEAAECdwABAgMRBAUhMQYSQVEHYXETIjKBCBRCkaGxwQkjM1LwFWJy0QoWJDThJfEXGBkaJicoKSo1Njc4OTpDREVGR0hJSlNUVVZXWFlaY2RlZmdoaWpzdHV2d3h5eoKDhIWGh4iJipKTlJWWl5iZmqKjpKWmp6ipqrKztLW2t7i5usLDxMXGx8jJytLT1NXW19jZ2uLj5OXm5+jp6vLz9PX29/j5+v/aAAwDAQACEQMRAD8A7nUdKur2dwt6YYWJJUZJ5UD/AB/OmNptpbus0+oSq6qFZ5JgNwDFhnPu36CoNCxaRadHb+TBG8kJz0R5FOc555Hc1aIgD749Medz1KxqD/4+RSAuwvO3zi0WI4xiSQA/+OgirIa7I+WKBfcyk/ptFIQqx6gT811bAegt2z+e/wDpU4ilxzctn2Vf8KAD7NKR/wAfk/5J/wDE037DGfvS3DH/AK7uv8iKAA2cSrkeYf8AelZv5ms+7eGN9g0+a524DMihgDjODk56Y7d6AEgtrCdmD6bDHIAGAeJckHv/AEqyLaCPiOGNP91QKADkDk5FI1MCM4xzTCMCkBXlkSIAuwXJAGT1J7VRt79biMeYvkyc/ITwcHse/wDnNAyrcXd4dz2kYdP4Mox35H3gR2zx+versEgmQkgggkHIoAsjJ4/WlPyrx2pjGMWzjjn3qJi+e1ADWzjNRnP4e1ADW9jTGYbeaBjARjFJn0oA1prWGZy0qs4/usxK/wDfPSnJDFFxHGiAf3VApkk6VOlICVQM81KOOlIRKB6mnAnOCaAF5PekO7PWgBG6dazLGYESW0i7J42y/XDE9SPx/Qj1oAiupGk1KKCHaska7zIVJwO47e3Ge4PaoL6K/ZnSKdN8kJEe0sgVwTyeuRyPy96AFW1uzbsr3kgdvMAC4IAJODkjdkAjv2pq2Uqy7/MKg5O1SeOB8uT2yM/jQBUudGae5MondQwIKnkc4BPX0H+e5d2bJ9lzPPxIFfbO6hvlI6A+uD+FAEWy2gvuZRu8v/lpIWI6885wODk+wqHUrixlsZQ9xbuqruK7wc45/pQAOZnZUs7jcq7DkMG43fNnPP3cVbsxN9nVbnHmqoDEfxHAyfzzQMsjlsg04jjG6mMYRzndyKjyM89aAEJBHtULjvmgBo24prY9KAIyfakBz2xQM3XbFM3c0ySRSe1Tpn6UgJV+tTKMjApASge9SUCAgjkc+1GRjOOaAGkj0qrcWUMz+YfMViMExyMmfrgigBkVvHbs3lhyWxku7OfzJNVb97hbi3MNv5i5OWAOU5Az15GCf50DGWl3cSSCKeHYxXdxxx8vr9T+VWWBJzQIjK1kCGPViks8WFj/AOWLYIyRnkY6juPagCc2Nuro6xIrJwm0Y29en5modQC/YJ1kY7WQpwMnnj+tAyq+qRIRG8cquVYgHHO0fN0P+c1PZXUV2kjIGGxynPemBbG0UuVoAa5GMioiTngfpQMbz6U1yQOgFADC4Vcll/Oqr31uhw1zAv1kA/rQAz7bE33JA/8A1zBb+VOjlDnGH/4FGw/mKBm+59qj+amSPVWJ61ZjU9zSAnVR61Oqgd6QiRQBUgxQA7dgcDrTST2FADPmzTZGYDp+NAFR7y2jbEl1Cp95BURuoWPy3EZHs4oAia+ij+8ZG5/gid/5A0wX6PxHDcn6wOv/AKEBQAjTS/8APtNj6p/8VTDK+eLebPuV/wAaAKskl8eEtYf+B3BH8lNMIupEKzRW6q3BAcv/AEFADPs7KCF8hf8Atl/9egLcDOJIRn0iP/xVAxfInbreSr/uIg/mDSi3kH3rudvqEH8lFMB/kbhjdIf+BkVH9jU8s0+fTz3H9aAEaxt/44g//XQlv51RuUS3uIEi0+JkkJDssQ+TlR/U/l+IYy6IYx0jQD2UUhQY4oAZj3pu3BzzQM1pp44QTJIiDuWbFVft9u/+qlEv/XIF/wD0HNBJMlyvULKfbymH8xUiXk+dq6fckf3i0YH/AKFn9KQFxHuSM+TEPYynP/oNS7rthhUgT3Llv0wKQDkjvj9+6tyPRLcg/mXP8qsiKQj/AI+HHuFX/CgQnkSMcNdTkenyj+QBo+wxZzunJ953/lmgBTaxEYKZ+pJqu2m2Zbd9jt8+pjGf5UASrGqLtRVX2UYphU560ARsvvTCo9aAI2CjqetQSyQRjLyoo/2mAoAqtqVgTgXluzeiyAn9KabyFh8olb3WFyP5UAJ9ojI+7L+MTf4VC946n5LK4kH+ztH/AKEwpjBLm4c/8ecif9dHX+hNSl7j/nlF/wB/D/8AE0AKrXWDiOIHP/PQn+gqBlv3f/j4t1A/6YMf/Z6AGsJFz51yOO4UKP1zUJkjzj+0CPoUP9KBjcwyYzeyyZ6bWxnr/dA9D+VMiW0llZI5ZWdPvAzSHHJHc+qn8qYExtoiMFcj3OaiFnbJIHW3iDjowQZH40DLGtXl3ZyRG0tBOXDbjsJIxjHT6n8qr2+oancaigayeK3+6+SPl4znnH0oJN6MDPJq0gUDrSADe2kRw9zCp9GcCpUvbUjKzxn/AHWBpCA6nAnASdj/ALFvIw/MLUyXsjoClrOc+qhf/QiKAJhNIW/49pQceq//ABVNaW+z+7tocf8ATScqf0U0DBftbD5/JT2GX/wpjrddpoPxiP8A8VQIge2uX5a+kT/rlGo/9CBpotXH3rueT/eKj+QFMBj2aMeZJ/wmYfyNRNp1qfvo0n/XV2f/ANCJpANFhZocpaQL9IwKXyol6RoP+AigCN5I1Ay6jJwMnqemKhkniRQWkUA5wc9aYEEt5BGG3PjaATwe/THr+HtRBcR3MXmRNuQkgH1oAfmnKNxoGSDqajk5Ixx60AZl3axJGGDvktg73L5B4PBz2yfwqra6VYso8uWWTYytljzuA4PTr8xP40DLwsYVO4A7s5zn1zn+ZqKHTbeBldUy6/xnqev4dz+dAFg9KYRmgY7WL77DNAGeZUl3ZMe35cY9QfWsltVV4Ema21GbKbmKyMoX5Q3Vccc4/CmSPkudRNqptdKuN52tiR2PBPI57gDr71v2FpFcpI15ptujrIQm5AcrgYPP4/lSA2IIooVxHGiD0UAVZXFAEgxThIudueeKQDZLmGNUdnBRmCBl5GScDp70xr6APKrHa0bBSCRkk9MAc80AVl1e2aFJCzAOFONpOMjIzx6A/lUCa3DOV8uN9rbSGbAyCyjpnP8AF6UAOe9lR5T5RljG3YEQgjPXOfbB6d6oRarfyRjdpkwYylTkEbV6hvcAccHOR0oETl9QeS3k8qNEK/vI/M5BI7/L26cVSX+2WjdN0SSlBtZxxuwvORkYJ3cD0H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Помимо получения этих сложных эфиров с использованием ампициллина, возможно также их получение непосредственно с использованием пенициллина. С использованием пенициллина G синтезируют первый соответствующий эфир, затем получают эфиры алкоксибензилпенициллина через енольную форму амидной группы в шестом положении с метанолом, н-пропанолом или изобутанолом в хинолиновой среде с пятихлористым фосфором. Это производное азометинхлорида гидролизуют водой с получением сложных эфиров 6-аминопенициловой кислоты, пивампициллин, талампициллин, бакампициллин и ленампициллин получают реакцией с фенилглицинхлоридом в среде изобутилхлоркарбоната.

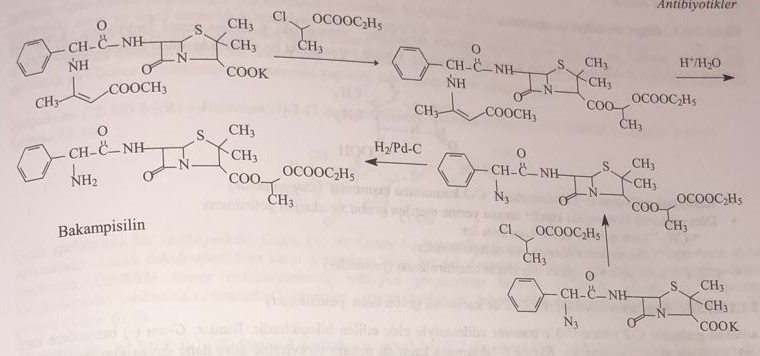
![Diagram

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HJzmnbqAFEg9adn3oArRW4iuHl3k7s8fU559atbh2NAC7vcUoYetADs470uaACl3UAGRQKAAtTd4yKAFyPWk/GgCEnB5NRswz1oAiZhnGelNyAKBjSwPeo3PvxTGMY/LVWRlBIoA3ioGDTGAwaBERpuKQhdoxSY5FAEijBpcCgBNozipAB+lAB3xS4H50AAQE4p+wAUAAFPxyKAF2jHek2gc0AGOc07HFACEDFN2jOaAFCDJNG0D8aAI3QVA6jrQBA6io6BjTzxSfwmmBGw4qBlBHSgZ//2f/hMehodHRwOi8vbnMuYWRvYmUuY29tL3hhcC8xLjAvADw/eHBhY2tldCBiZWdpbj0n77u/JyBpZD0nVzVNME1wQ2VoaUh6cmVTek5UY3prYzlkJz8+DQo8eDp4bXBtZXRhIHhtbG5zOng9ImFkb2JlOm5zOm1ldGEvIj48cmRmOlJERiB4bWxuczpyZGY9Imh0dHA6Ly93d3cudzMub3JnLzE5OTkvMDIvMjItcmRmLXN5bnRheC1ucyMiPjxyZGY6RGVzY3JpcHRpb24gcmRmOmFib3V0PSJ1dWlkOmZhZjViZGQ1LWJhM2QtMTFkYS1hZDMxLWQzM2Q3NTE4MmYxYiIgeG1sbnM6eG1wPSJodHRwOi8vbnMuYWRvYmUuY29tL3hhcC8xLjAvIj48eG1wOkNyZWF0b3JUb29sPldpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQ8L3htcDpDcmVhdG9yVG9vbD48eG1wOkNyZWF0ZURhdGU+MjAyMy0wMi0yNlQyMzo1NToyNi45NDE8L3htcDpDcmVhdGVEYXRlPjwvcmRmOkRlc2NyaXB0aW9uPjwvcmRmOlJERj48L3g6eG1wbWV0YT4NCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIC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При получении талампициллина и пивампициллина с использованием ампициллина калиевую соль ампициллина последовательно реагируют с 3-бромбензоизофуран-1-оном или пивалоилоксиметилхлоридом. Затем метилацетоацетат, защитную группу амина, гидролизуют и удаляют из молекулы.



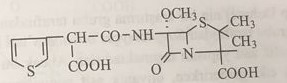
Баккампициллин синтезируется с использованием азидоциллина. 1-Хлорэтилэтоксикарбонат реагирует с калиевой солью азидоцилина. Затем азидную группу восстанавливают до амина. При этом синтез осуществляется с использованием калиевой соли ампициллина. Для этого калиевую соль ампициллина подвергают взаимодействию с этил-1-хлорэтилпропионатом с получением спиртовых биэфиров карбоксильных групп, затем гидролизуют и удаляют из молекулы метилацетоацетат, являющийся защитной группой.



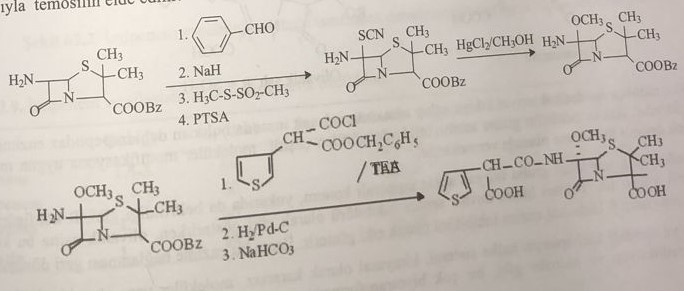
**Пенициллины субъединицы С-6**

Было обнаружено, что пенициллины ингибируют транспептидазу, которая обеспечивает перенос из D-аланин-D-аланинового участка пептидной цепи, формирующей клеточную стенку против бактерий. Установлено, что β-лактамаза, секретируемая бактериями, не влияет на цефалоспорины, сохраняющие α-метоксигруппу в седьмом положении от производных цефалоспоринов, и эта метоксигруппа защищает β-лактамное кольцо со стерической точки зрения. В 1981 году Слокомб и его коллеги открыли темозил. Темоциллин имеет период полувыведения 4-5 часов и является соединением широкого спектра действия, устойчивым к β-лактамазам. Это пенициллин с большим клиническим преимуществом по сравнению с карбенициллином и тикарциллином.

**Темоциллин:**(6S)-6-[2-карбокси-2-(3-тиенил)ацетамидо]-6-метокси-3,3-диметил-7-оксо-4-тиа-1-азабицикло[3.2.0]гептан 2- карбоновая кислота



При синтезе темоциллина эфир получают из 6-аминопенициланской кислоты. С бензальдегидом аминогруппа защищена путем получения амина из бензила. Затем при взаимодействии с метилметилтиосульфонатом тиоцианатную группу добавляют в шестое положение. Азометиновая структура расщепляется при нагревании п-толуола с сульфокислотой. Метоксигруппу добавляют в шестое положение с помощью хлорида ртути и метанола. Темоциллин получают реакцией полученного продукта с бензиловым эфиром 2-(3-тиенил)малонилхлорида.



**Другие модифицированные пенициллины**

Наиболее важными исследованиями, проведенными в этом отношении, являются производные, полученные путем молекулярных модификаций, которые получены путем сохранения основной функции β-лактама в молекулярной структуре пенама. Эти модификации в структуре пенама следующие:

![Diagram, schematic

Description automatically generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4R5aRXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIzOjAyOjI3IDAwOjI4OjUxAAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAM2MQAAkpIAAgAAAAM2MQAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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jny4ym0ZI9T0HtQBH4Zu4dI0OLTtRPkXNozo0bLkv8xIKf3s5/OsqTRriHRLNJ7WZpJ9W+2yQpGSY4yTwcdCBj8SaANi50xbbxPpFxYadP5MSyid41Y7Q6gL1PtXUY9aAFpQKAFIFFAFLbkYo8rI5oAcFPrTu3FADucUvvQAhxRkmgBc+tLuHrQAZHX+VZ93penXNw1zJaKZ2XazqWUt/vYOD+NADgieV5JiRogMGMrlcfTpU9rBDHGVgt0hQn7qRhQffigCyFx68dPb6ULnsT7+9ADsHGDzxRjH/6qADIpeMUAFFAFZUGc0/jFACcAU3owx3oAk96aQTwDQAgQ9zmnbM0AIUpdgoAeF4oKAjHrQAixKowo/GngUALimnhSfSgCNnbCkDrUhzjAoAY5KAE0K27vQAhk5ooA//ZAP/hMehodHRwOi8vbnMuYWRvYmUuY29tL3hhcC8xLjAvADw/eHBhY2tldCBiZWdpbj0n77u/JyBpZD0nVzVNME1wQ2VoaUh6cmVTek5UY3prYzlkJz8+DQo8eDp4bXBtZXRhIHhtbG5zOng9ImFkb2JlOm5zOm1ldGEvIj48cmRmOlJERiB4bWxuczpyZGY9Imh0dHA6Ly93d3cudzMub3JnLzE5OTkvMDIvMjItcmRmLXN5bnRheC1ucyMiPjxyZGY6RGVzY3JpcHRpb24gcmRmOmFib3V0PSJ1dWlkOmZhZjViZGQ1LWJhM2QtMTFkYS1hZDMxLWQzM2Q3NTE4MmYxYiIgeG1sbnM6eG1wPSJodHRwOi8vbnMuYWRvYmUuY29tL3hhcC8xLjAvIj48eG1wOkNyZWF0b3JUb29sPldpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQ8L3htcDpDcmVhdG9yVG9vbD48eG1wOkNyZWF0ZURhdGU+MjAyMy0wMi0yNlQyMzo1NTozMS42MDc8L3htcDpDcmVhdGVEYXRlPjwvcmRmOkRlc2NyaXB0aW9uPjwvcmRmOlJERj48L3g6eG1wbWV0YT4NCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIC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beXuEiGVGyPlkLAbfekB7Raail1p9vcxBvKmjWVPMG1trDIyPXn+lSCZlbeVyi8/dyeOTxj0riI/AviW4t187x7fiL+GOy02C3C/QYaro+GpuIf9L8U+Jrzu3/ABMFg+uPLRSM/WgDz/4ceJtK8ByS2gurSTw4umxbNRTSTb3cl0XYLbFQN00hRd3GSMjPXNeo+HJvEWs6odQv7VdB0gxlbfS5sSXM7HHzTMCQuDn5RyOcnsOT8F+D9O8P/F7XUBuryW10ezmt5NQupbl4mlluFlKNIzbNwjTO3HAxzXqcbe/JGSQAPehASbTnjp1HJ59QfWo7izivLd4J4YriBwVeKaNXRh6FSMH8amVgWPAH0pxbg4pgcLefDGPSfNuvCOqz+Frktua2jUz2L8dDA3CA4wTGVx6V5P8AETVb7VfFf9ieJ7T+xI47eGTVNc0uWa6shCWcw/uiNqEssp3y5UbR97GB9G89c8546+h964nS4R/wuLxLkZV9F08lMnb/AK26BGOnIyOnekBqeD9A0XRNOMmh+XLDeMXk1Iz+fJeEnmSSYks+SO/yjoAKt+IfEOmeFYYZ9SuBaieTy4owjSSytjOFRQSxxzx2qLSfBekeH9YuNT022k0+W4VlntbWZ0tZCf4zCDtDYwOAOlcLdXHmftQWCXPSDwu8umrszsk88rKy8feKYHXOO4oA6dfiVoNx4R1PxNa3E97pWmmVbnyLaQSxtHy6mNgGBA65qprHxY0zRfDnh3WTpmpXNlr08NvatHGqNG0uPKL7mG3IOe/Sk+Il5Yaj8L/iEljLbyvDp97FeNC2QLgQHeHx95hlRk9eK8c12xudN+FXwn1PUPFNxcW/9q6GyWckVvHBGMAnBVAx2qCMFuvpQB9QK5wc84/hznn3xx+tLuBwAOMV5t488dat4S1zTILe50qOO8vbS3trGdWe5uVZwszmQuFQLk467tuMjPHpXlnzHX0OehH8xQX0DaG7UhUA8VIsfHWkZfm60AMPSinGOigCoseBgcfhUiqI1z1pWXDcc0SISvHpQQMHXI61xniJU/4Wx4Fbofs2qDA/3IP8/hVrxd8SNE8CyNHqbXpmW2a7ZbOyluNkQJG5tgO0EggE4HBqr4hdW+JXw/kYeWXh1M7XOGXMEZIPuOvGelAHaBTsBHT0pkmI43ZztVVJJJwAO5/SrKqzRrhSOgxx+fNEcaySJFMgaKQ7XVx8pUnBznsefyoA4ZrvRdJ1jV/G82uWMeky2NvZvO0q+TH5UspLmQEjbmUA8ZGPeuwsJo761guIW3wyxrIj4+8pGQfyxXxjDJefCr4M30y77jwl4v027iKg/wDHjqQaRQB6JMqgYP8AEor6u1L4iaB4ZSytdT1Nbe7kto5FhWJ5XZcYDBUUk52mgSOmCkMadtOeTj8647/hZ1tcMP7P8P8AiTVf9qDSpI1+uZdopzeL/FN5xZ+A7mIH7ralqVvCPqQjOR+VAzsGX5eflGDyf8+9cRprbfjJrwyfm0Oxb8proVNJJ8Qrxl8uLwzpSgcrJcT3T898BYx+tYnhW31mz+MWuHWtStNRnfQLRleztWgRFFxcfLhnck5zzkdelAHpxUbcmsLxH4N0Txctn/a1hHePaMXgm3PHJESMEBkIOCOo6VrqzNHjNMZW7CgDL0/wX4e0vQ5NEtdItF0eV2eSxkj8yORmKli27JYnaMkmtKLQtMjtbe1TTbNLWAHyYVgXZFnrsGPl6nHpmplh+XJHNTQyAcd6AOW8TeBbrxVfMl1rjR6I89vO2mraIWVomD/JJn5dzKCcq3cV1qqvmOQoXcc/KAKX9KUNQNCbQO+aTim++aUN7UDF4opR9KKAKzEAep9B1pS3HcfhUcY3YUnG87eTgfQnt3/KvJrr4geKPFHh3xR4l8LrpcGk6TLdQWdteQtJJqH2ckTMWDgRglWVflbO0nvgUzM2vjFq0trpejW32Rr6yub9PtFpGw8y6aMh4rdR6PJtLHoERycAVycnh7Udc8U6Xa3Gs6g3iqGdr7V9Q0u5EVvpkMiBPs8eQwJYABVwCfmbIBAre01rjxppemeOfD8Jl1bV7OBLB74gwaNBKuZJAMdNwBPdvlXgFs9n4Z8J2fhXTFsrTfKxdpbi6n5muJj9+V27uenoo4HAqRox4/hbprKTdav4lvycj99rUyZ5IP8AqytdLpOk2+h6TBp1k0sUESsqs0hkfnvubJJ9zmr4jOOnt+QwP0x+VM2lc55OaBnAaj4S8F+GvA9h4J12f7bpWozC1t7XUJPMnnkZ8jbtXqGYkHHGe9eiQ4hAWEFEUbF2kqMDgY9sevvXCfFSyv7638ODTdHuNUuoNas7yRrYRqywxSBnG9iCM7hgA84Ndq037ozEbc4JUkZ5GQDgkZAxnnrQBZyxxz/9emswU8gE+/8A9aq5vAFGOSaj84yNnOe1AFDxZq2p6TpZudMsbe7MYd55by58mC1jVCxdyATzjHT61wvgfxJJ4q8exapLaNYNeeErGY2rnLRb7i4OCcD174PPIHSuk+I3hW/8ZaHb2Flq1vpca3CzXAuLYzpcKoO2NlDqdm7BPPO0A8Eg8zBd6V4V8RStqGs3+v8AiVtOhtL6KzsXlZUSWWQSPHED5eS5AyedtAHq8cfyjHSpNmGFcVH8WvDr+GbTWYrma5ivbp7GztooW+0XNwrFTFHGQDkFTnOAO5qxpfxGtJvEFtoWqWF54f1a7jM1pBqBiK3Kr97Y8bspZe65yKAOv4VSMj15qIr8wYBgOBwOuemK4ix+JGpeKbe9vvCWiw6vpVvK8EV1dXgt/troxDiBdjBgCCNzFQSMVymrfHSS+0Dwrq3h2ztLmHWtYi0WSLUtyzWVw5KsrKoIyhU8ZH1osB7J5y7QSQOcYIOc+nSnLID0rzXxR4q1rS/ih4P8NwNp8dlrcV08hlgZpYjBGHIX5xkPng44969G2gKUUFQD36igBx7moJZvLTluc1NtO3rUT24kHPNAE6SDYCTRUSx4XBOKKAK6TJHMCWwAwyQPr1/OvEvC+h+J/APhHxH4MtdAlu2mu706ZqcckQtTFcZIaYs24NHvbgBt2AcjPHr6wllIz16+9O/s8yJ8xwfYf5/SmJGf4F0KDwj4P0PQraZbmLS7OK2WbH3iqAMfz3cH2+tbyzbcDHQAfkMVUWF143E47kkn9TVjb8vByehpDLgPy5zTNw71Fltopw6ZIzQAyZvOXy8kL1xnuOh+tI9vujALFl7DsKc2Bz0pFZmx25oAFgO7djjtTYbVlZ2Jzu6DFTFgv3jxTxKo53UICCJXWePC9GXnHvwD7E4rxv8AZtR9Q8H+I4r4keIP+EjvF1NZeJPMLgRmQnnAVV24xXte9SASeP8AZrlPEXgPwtrWqSatc6NE2pyR+XLcwNJE8wAwBIEYBxjruBzTA828T3dnovxt8BeIYmhj8P79RsZLxNywwahKB87N1G/DDcO4rR+LGmnx546+HekaPOr3GmXs2oXtwpBFpbGDyxvIOAXbgKME7ST797HbQGzFg1nDLZKgRrRow0Wwdth+X9O/vWloOk2NnaNFp+mwaZbF8+TBbpCGPZiFAyRkgE0kJHknwO8RWPw5+HNj4W8Tv/ZOs6HJNbyWcsZZrgGV3R4AB+83g8AZ5x06nib34a6lpvw78PW+oaTfTXeo+Nv+Ehu9PtrVna0tHc/K5A4YIEzz9529K+qY4NmM7iFwRzyuOm09u35U6Ldjh2BOd2DgNkknj3PJx1NUM8S1zwLHofxg8A6n4d8MX406xivU1Ce1hkby0niVIgS57Y5xXtu0gDOM47A/1p5Qsu1ju4I57Z6kUBAp9B7ADtSAaBuHSnRpTtyinKQVyKQCNGtFBPqcUUAZEVuqtuP5VPtXafrRRQAm1FU+tQcRyrt6N296KKALYU4BPOajkjZ8gHFFFADFtm7ndUn2UMR1GPQ0UUAI1qCcHOPTNPW1HTtRRQBOkA24xQ1qrqVPAPXHBoooAZFp8cC4jXB/vd6sxoQOTn60UUALtxnJqF/3cbN2FFFAFaW6k8uNlGSxx16VZZn8vCnmiigCG5ke3RWPJJxRDMZskNjFFFADGuzuxjNFFFAH/9k=)

1) Перевод карбонила из второго положения в третье (изопенамы)

2) Замена атома серы в четвертом положении на метиленовую группу и кислород

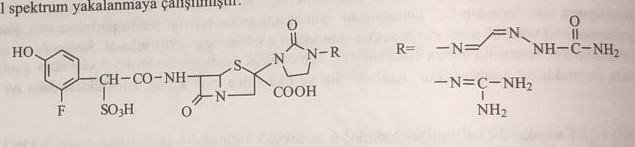
3)CH2 для карбапенама и кабапенемов

4)-O- для оксопенама (калавама) и оксопенемов

5)Получение производных (пенемов) с двойными связями между С-2 и С-3

**Соединения изопенама (пенициллины с карбоксильной группой, присоединенной к третьему углероду)**

Это соединения, полученные переносом карбоксильной группы на С-3 вместо С-2. В то же время они являются более стабильными соединениями в отношении β-лактамаз по сравнению с производными пенама. Клинические испытания моих двух образцов, представленных ниже, продолжаются. В этих примерах вместо С-2 одна из метильных групп в положении С-3 была заменена на карбоксильную группу, а другая метильная группа была заменена на группы 1,3-диазолидин-2-она. Но при замене группы –NH в структуре 1,3-диазолидин-2-она на другие гуанидиновые структуры были получены соединения с более широким антибактериальным спектром.



**Карбапенам и карбапенемовые пенициллины**

Тиенамицин, выделенный из Streptomyces Cattleya исследовательской группой MSD (Merck Sharp Dohme) в 1970 г., и оливановая кислота 7-оксо-(R)-1-азобицикло[3.2.0]гепт-2-ен-карбоновая кислота сохраняют свою структуру. Но биологические эффекты этих двух соединений совершенно разные. В то время как тиенамицин оказывает антибактериальное действие, оливановая кислота действует как ингибитор пенициллиназы и β-лактамазы. Основной структурой в этих производных является карбапенам, асимметричный атом углерода в восьмом положении находится в конфигурации тиенамовой (R) и в конфигурации оливановой кислоты (S).

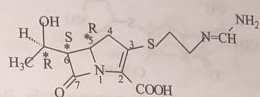
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 
Хотя тиенамицин обладает очень хорошим антибактериальным эффектом, он достаточно устойчив к ферменту дигидропептидазе, обнаруженному у человека. Но молекулярная структура пенициллиновой группы, подходящая для различных молекулярных модификаций, встречающихся в антибиотиках, позволяет синтезировать множество производных.

Как показано выше, восьмое положение, удерживающее спиртовую группу в боковой цепи тиенамицина, находится в конфигурации R, и при такой стерической структуре оно действует как ингибитор синтеза клеточной стенки бактерий, в то время как это положение в оливановой кислоте находится в конфигурации S. и действует как ингибитор β-лактамазы. Сочетание препарата с этим ферментом необратимо.

Тиенамицин и его карбапенамовая кольцевая система имеют химически прерывистую молекулярную структуру и подвергаются многим реакциям биотрансформации, таким как окисление, восстановление и гидролиз в биологической среде. По этой причине для более стабильных производных был проведен ряд структурно-активных исследований путем получения различных производных от карбоксильной группы во втором положении до боковой цепи в третьем положении и гидроксильной группы в восьмом положении. В этих исследованиях взаимосвязи между молекулярной структурой и активностью, проведенных для молекулы тиенамицина, молекулярная стабильность была достигнута за счет превращения аминогруппы в амид и сохранения активности в соединении. Таким образом, был получен имипенем со структурой N-формимидоилтиенамицина.

**Имипенем:**(5R,6S)-6-[(R)-1-гидроксиэтил]-3-(2-иминометиламиноэтилтио)-7-оксо-1-аза-бицикло[3,2,0]гепт-2-ен-2- карбоновая кислота

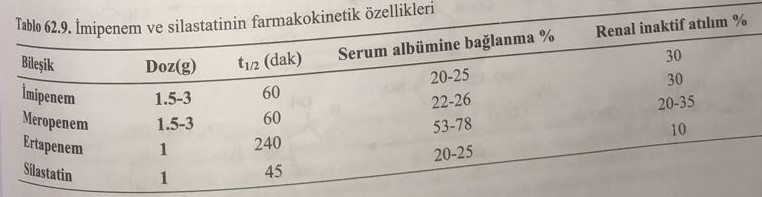


Это антибиотик широкого спектра действия. Они действуют против грам(+) и грам(-) бактерий. Он более устойчив к бета-лактамазам. Но он нестабилен по отношению к ферменту дигидропептидазе, его применяют в сочетании с ингибитором. Он используется в виде инфузии, особенно при инфекциях мочевыделительной системы. Для этого имипенем применяют в соотношении 1:1 с циластатином, ингибитором дигидропептидазы. Фармакокинетические свойства этого соединения перечислены в таблице ниже.

**Циластатин:**[R-[R\*,S\*(Z)]]-7-[2-Амино-2-карбоксиэтил)тио]-2-[[2,2-диметилциклопропил)карбонил]амино]-2-гептановая кислота

![Diagram

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generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4T0KRXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIzOjAyOjI3IDAwOjMxOjI0AAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAM4MwAAkpIAAgAAAAM4MwAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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tFgzKxluNsrlpAHAyd5cc4yMFm6Y60AT22lW0Gxk8zcpZlO88FsZ498D9all0uznnaeSImQ7SSHZQSCCDgHGRgc9e1ADF06zjDKltFhsq24btwwRznrwT+dSJYWwOBbQcekS+ufT15oAtJGsaBUVVUdAowBQ33eKAI6aevFMBrEVCQeoJFIBGUDlj+ZrPscf2hqWCDmZW4P/TNB/SgC/SUxje9IRQAUoNAHSquGHFVtKGNHsR6W8f/AKCKQFsNRznHSgBwX1NGMGgAIGKZgUANI9BTHwBluPrQBVkv7KM/Pd26f70qj+tRHVNOb7t/at/uzKf5GgCvNqtkOrTP/wBcreR//QVNMXU4JCBHb3pz62ki/wDoSigRL9pkA+TT7tv++F/9CYUxrq9PCaVMB6vNGP5MaABZL9utjbr/AL10f6IaVv7RbIWO0j+sjP8A+yigCIx6wf8Al6sVH/Xq7f8AtQUvkX5Hz30fP/PO3x/MmgZE9lcsOdTul/3EiH/slMGmtnL396//AG0C/wDoIFADjp0OMNLdt9buX/4qom0iycfPCZP+ujs38zTAYNF0pDkadaBvXyVz/KrEUEUC7YYkjXrtRQB+lADzTaAE70GgBvJpaAOozgg+9cVZ+LZIsWCWaf6P+6Dlyc7eM4/CkB0dnPeXahle3TIzzEzf+zCrhttQ/wCfy2H0tj/V6AIfsl6x+bUnH+5Cg/mDTxZz4ydSujx02xD/ANkoAGsQwO66um+kxX/0HFQNo1qSS0l431vZv/iqAHDS7EDabdX/AOujF/5k0h0rTgc/2fZ/9+F/woAcLW3j5jt4k/3UApxOOlADSaBQIWmmgBKQ0ANpp5FAyNqaaAI2J3fhTQcimA1jxSGgBuaTNACUmaQCUA80wP/Z/+Ex6Gh0dHA6Ly9ucy5hZG9iZS5jb20veGFwLzEuMC8APD94cGFja2V0IGJlZ2luPSfvu78nIGlkPSdXNU0wTXBDZWhpSHpyZVN6TlRjemtjOWQnPz4NCjx4OnhtcG1ldGEgeG1sbnM6eD0iYWRvYmU6bnM6bWV0YS8iPjxyZGY6UkRGIHhtbG5zOnJkZj0iaHR0cDovL3d3dy53My5vcmcvMTk5OS8wMi8yMi1yZGYtc3ludGF4LW5zIyI+PHJkZjpEZXNjcmlwdGlvbiByZGY6YWJvdXQ9InV1aWQ6ZmFmNWJkZDUtYmEzZC0xMWRhLWFkMzEtZDMzZDc1MTgyZjFiIiB4bWxuczp4bXA9Imh0dHA6Ly9ucy5hZG9iZS5jb20veGFwLzEuMC8iPjx4bXA6Q3JlYXRvclRvb2w+V2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NDwveG1wOkNyZWF0b3JUb29sPjx4bXA6Q3JlYXRlRGF0ZT4yMDIzLTAyLTI2VDIzOjU1OjMzLjgzMjwveG1wOkNyZWF0ZURhdGU+PC9yZGY6RGVzY3JpcHRpb24+PC9yZGY6UkRGPjwveDp4bXBtZXRhPg0KICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIC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Как и ингибиторы β-лактамазы, циластатин действует как субстрат, который конкурентно связывается с дегидропептидазой. Таким образом, он предотвращает ферментативную деградацию имипенема.

**Меропенем:**(5S,6S)-6-[(R)-гидроксиэтил]-3-[2-(диметиламинокарбонил)пирролидин-3-ил)тио-7-оксо-1-азабицикло[3,2,0]гепт-2- ен-2-карбоновая кислота

![Diagram

Description automatically generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4SImRXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIzOjAyOjI3IDAwOjMyOjU4AAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAM4MQAAkpIAAgAAAAM4MQAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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Вторым соединением из карбапенемовой группы β-лактамных антибиотиков является меропенем. Это производное используется в сочетании с ингибитором дегидропептидазы циластатином, таким как имипенем. Он устойчив к ферменту дегидропептидазе и обладает более сильным действием, чем имипенем.

Имипенем получают взаимодействием тиенамицина с формамидом. Поскольку тиенамицин не получают определенной степени чистоты путем ферментации, имипенем получают синтетическим путем.

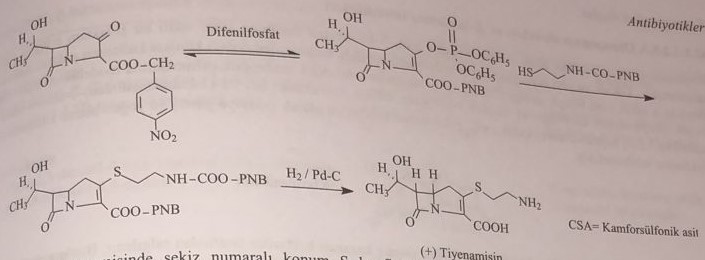
![Diagram

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Диэфиры 1,3-ацетондикарбоновой кислоты используют для синтеза тиенамицина. Основание Шиффа получают с первым бензиламином. После ацилирования этого продукта уксусным ангидридом кетоновая группа восстанавливается до бинарного спирта боргидридом натрия. Отсюда образуется лактонная структура, и это соединение разделяется на энантиомеры с D-камфосульфокислотой. Азетидиновое кольцо замыкается дициклогексилкарбодиимидом. В этом полученном производном диаминовую группу в первом положении сначала защищают н-бутилдиметилсилилхлоридом. Затем малоновую кислоту получают из п-нитробензилхлорида в моно(4-нитробензил)малонатный эфир, получая при этом карбапенамовое кольцо. Для этого метиленовую группу активируют реакцией диазопереноса. Затем термолизом получают кольцо 3-оксокарбапенама. Дифенилфосфатный эфир получают над енольной группой молекулы, енолизированной дифенилфосфатом. Боковая цепь тиенамицина присоединяется к молекуле с помощью 2-(4-нитробензилоксикарбониламино)этилмеркаптола. 4-нитробензилоксикарбонильная группа гидрируется палладий-углеродным катализом с образованием тиенамицина.

![Diagram

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В полученных тиенами восьмое состояние находится в S-конфигурации. Для получения активного изомера соединение подвергают взаимодействию с диэтилдиазодикарбоксилатом в среде трифенилфосфата с получением R-изомера.

![Diagram, schematic

Description automatically generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4R0SRXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIzOjAyOjI3IDAwOjM1OjU0AAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAMwMAAAkpIAAgAAAAMwMAAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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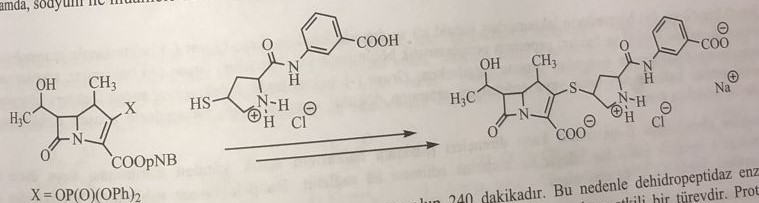
Меропенем синтезируется аналогично синтезу тиенамицина. Но при добавлении 2-(4-нитробензилоксикарбониламино)этилмеркаптола и 2-аминоэтилмеркапто в третье положение вместо 2-(4-нитробензилоксикарбониламино)этилмеркаптола используется 3-меркапто(2-диметиламинокарбонил)пирролидин, дифенилоксифосфатная группа удаляется , а 3-меркапто(2-диметиламинокарбонил)пирролидин конъюгирован в третьем положении в виде меркаптоэфира.

![Diagram

Description automatically 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Q3Vq8KSypbwx2/myK6ll8yTJXaFI4zWrefDuw8P6xow025urOPSdPOlW0cfllfJmRN+7KHccxo3PGR0p9r8M9Os/C+l6RHd3wfw2scul6jvQXUG3Me3cEClSh2kFTkUWQzk77xZN4k1vwbPqFnDbavo3i640S98nOx2+yTjcpPzBSrxnax71fsviNqaz/2RLHYWep3Hiq50RLyGIiJEWM3Bm2E/M7IMcnBZgx6Yrobf4b6bqml2MclzeRy292+vm5jdRJLeAf6xyVI/iI4A4qe8+DOgajLqMVxJfySarejVnuPtJWW3ukYKskLADyztUDj0pg0edeGtY1bwhZXFutxbTg/EJ7C+Z7YYkjnZDvUZxG2XUdz8xANaNn488WW+pPdXepWU+n2vi4eHZbNLEReZDJt8t9+75WUyKffHuM9V/wp/QI2ubNn1KcXF6uqTTS6hMZJLiIZRyd3XKqen8Iq5F8KfD+oSTJKl4Uv71dUnAvZcG5QJsk+91HH/fK+lAJGlpHiSPxBqF1ZDQ9UtpLX94JdV09obeSRZAqsjEnPOCCB9K47wNq2reFf+Ew0+98PTalqtvqv2+RdBIdbpbpd6OqSFQm1VAZcgjHTmvRdU0az17SrixvojPaykxOnmMpIBGDuUhs/Q1Fp+l2mgadLHZwbRK/mytLI8ryvsJ3O7MWY8DBJOO2KCjj5ta1TWfG1pps/2yx0rWvDd3MNLvYo0kgmSRIyTjOSQ/J6c1zPh66aT4c/Be7wFKXunoxVT8rPaSwsMk46nb1H4V6tceG9J1TUItTutPhm1CONoUuWLb1jf7yg56HA/IV578ULW08J2vg/SdHsoLCyXxJZGOOIH93/AKQOFyePvGkBymueNPEem6H4nhuNR1ax1mPSptR02+t7n7RZXccMoZ5IeAUwHCtERjngmrfxA8UDVNP+K9hDqv2mxXw/aapaw/aA6RHEjOVIxxuSM4z36V67pPhXRNKuJp7HR7GzludyzNFABvU4LKf9lickd6sWHgDwzYx3MNt4e0qCIQiFo47GIK8YYsEYbeVB5C9B1ApjPMNdjtLD4q61qQ1C8tXk8INfJNbXEheLZJKCyRltrFVcEDbtDD3zXntx40lbw740toPE80SQ6dpesWIttVMk0Z3bZgXJzuKr8yglQzEc19MQ6DpVvNDPHpVgk9uvkxyraxh1RSqABsZAwegpkekabHpETLpdiE8pcRC2QIoLcgDHTPOD3oGeEeLL9fDek/EbT7PWrv7NpE+l6rY779nkUSNGZV37juB2NlenzV2NrqN43xM8eR6A+l3F/Lb6ZdQx307pC4Ebo/KAscKExgenIr1BdLsoXdUs7ZQu0f6hORhTzxz1pzbFjllSKNGhOwbVxkHPU9fTv2oCx4f4q8Pyt44TUvGVz/ZRuvDrWVpd6TdzRQwXUUzyMiPwzEho3VW6lSMHAB7PwWnjbUNJ8PHVptIEM1lCNRjuLeT7Y0hhXcSQdm4uVPTPFegyD7PcSQqT5ZOGXPDcnGR3wOMmoDIyQCU/O4ZfvdCT1J9/8KBnhWizTr4L+Dl82VtdNv2srrH/ACzLQy26Of8AgYC+n7wV1PiNXX4o+DLmKGd1FvfW8sscEjRxF1jKbnAwuWRupHaty08F2Ph+xutIjlubrS52J+yXUu5E3M8h2EAEfMcjnjArbtYvsMZtVd5VjQKJJnLuV44JPXH580AeHeIfAOoa/wCPvGMtjDeLLHdWOp2Ud9HKun6g0MO2WF9wCMdwVd3JDbcZHNdL4uvpvEmh+DbmHT7zTtQPiGzcWt6hjmj2pI0ow33gELfMMjA69M+ryL5aRkchj93sMHAx3qo2m2810l46b54fkj3ksqhlYtgHgE7V568UAc7ZaBqun6Vqyarrt14ha5tnhjj+xxQmMFGG1fL27iSQMsaxPC3hfVtQ+G/hyyuL7VPC2o2NvFFci3SHe5VNm071cbSeRyPwr0JV3R7skHBPBxUcjDzMY/jxnJPUYNAHjvirwTr00njmOz0q41H+0LnTbyzu2eJftMsHl+Yx+bI4j64HXpTNY8C+JLrWNdvtO07yz/a1lrWnw3U8aR3jxQCKWNipOxiAcE98HNeyMv724B5KYwxHJ+tNWNWlmTACrg8Dr9aAPGZPBvi2+1q+vzokFsJvE1trkUbajA8gVYhHKr8HJPUcnrWlrngHV7+Pxhp9qtrNpHiiSK4eeWXbJp8oCLKCMfvBiMMvPB46c16dP80THOMcYHSoryMRqnO7cufmwcfSgDya1+HfiPQ/HmqeJ9Jns7drq7Xfbz3LmK6tfLUMjgJlZBIgkRhkfMQ2etWF+GuorqmtXEI0/Tk1Kyura7gtJ5Ps920uBHI8WwBHUZJdeWz2616S6jyV4HJwabGvyr75FA7XPNbH4e+IdJurW40zWNMt52sILHUfPtmlGYlKLNbkbSr7CAQ2R8oqzq3w5vr6LxRb22rWsdprF9BfxrLas7wyJ5ZIJD/MMxDHpuJrvmXCqcnvUVux+fPNAWseU+OPghqni7xNd6ta+IbWwFwsYkhewaQ7kjVM7i4JyFFFeq31yYbgoqqQAMbhmigR/9k=)

**Мое утро:**(4R,5S,6S)-3-[(3S,5S)-5-[(3-карбоксифенил)карбомоил]пирролидин-3-ил]сульфанил-6-[(1R)-1-гидроксиэтил]-4-метил -7-оксо-1-азо]азабицикло[3.2.0]гепт-2-ен-2-карбоновая кислота

Как и в синтезе эртапенема меропенема, аналогичного синтезу тиенамицина, диэтоксифосфатная группа в третьем положении объединена с 3-меркапто[2-(3-карбоксифенил)аминокарбонил]пирролидином вместо 3-меркапто(2-диметиламинокарбонил)пирролидина. , а к молекуле присоединена диэтоксифосфатная группа. Этилгексановая кислота далее реагирует с натрием в этилацетате с образованием соли.



Эртапенем имеет значительно более длительный период полувыведения (240 минут), чем имипенем. Поэтому дегидропептидазу применяют как парентерально, так и перорально без необходимости применения ингибитора фермента. Он показывает частичный эффект депо. Свойство связывания с белками меньше, чем у имипенема, и чувствительность к β-лактамазам наблюдается очень слабо. Эта группа антибиотиков используется особенно при смешанных инфекциях. В то время как имипенем и меропенем применяют внутривенно в дозе 1,5-3 г/сут, эртапенем применяют в дозе 1 г/сут. В частности, его не следует применять вместе с противовирусными препаратами, такими как ганцикловир. В это время наблюдаются сильные схватки.

**Производные оксопенама и ингибиторы β-лактамаз**

*Стрептомицеты оливковые* оливановая кислота, выделенная из, была получена как β-лактамное соединение, эффективное против фермента β-лактамазы. Он не имеет клинического применения из-за его токсических и необратимых свойств ингибитора ферментов. Однако исследования антибиотиков, ингибиторов β-лактамазы, используются при разработке новых соединений, устойчивых к β-лактамазам. В 1976 г. клавулановая кислота «3-(2-гидроксиэтилиден)-7-оксо-4-окса-1-азабицикло[3.2.0]гептан-2-карбоновая кислота», полученная из культуры Streptomyces clavuligerus, была включена в лечение в качестве β -ингибитор лактамазы, сделан и широко используется.

![Diagram, schematic

Description automatically generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4RwERXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIzOjAyOjI3IDAwOjM4OjAzAAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAMwMAAAkpIAAgAAAAMwMAAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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5OfSuh+F3w2ubG8j8VeJ4IE8R+QLaw0yDH2fQrXqsEXbzCOWYe4BpiEi8bfEq4ZTB8MEtl7C/12BD16nA4+lN+KWknxl4H8O6X4jsI7SfUtWtILyG1nEn2ZmZuY5BjDcL7ZxXp5Q+Wwz94cj15z+eay9Z8N6f4ka1Go2S3v2WXz4g7soSTghsKRkjA60AeO+EdS1/S/iJ4V8H+Ilku73Svtc9lrCjA1CzNuyI7cf6wfdZR0PNdvrPhn4h32rXbWfjjTdH05pGNvCuiCWVEyNoLvJg8e1dzJYpJNDNJFE00G7ypGUMybhhtpPIyOuOvegwvGBsO0f7IApAedr8OfGdw+br4rakcj7tnpNrFj6Zyart8F76bzVvviX4yucnIWG5it8n04TNem+W+5cO1Tpbnls8+tAHmWl/BTT/DepQeIrG/1nXvEenwz/YDr2rNLAZHRlwQF+XOcGus0HxdaaxfX2lPNG2r6XHD/aSW6uYY5XUnYsjKAxz269OBnNdH9nYqVDFQf7vH8q4T4peF9MPh+XXNTnvI9L0PzNZubGycRC9MUW5A5GD8rD1oA7WHb82do2tgtyR06cD1qdV3Lgdf++h+gryjQdM8T+KvANrrD+Kr7Ste1OxF1bw2QijtbcSDckZjZCzYG3cxOeuKTwjfzfE7xh41TVrq9h0vw9fro9rY2N08IZ0RWkmkaMqzOSxAGcYXpQM9af7xGGJUfd53H3xjpSfwgcHtnqD7duf19q+Z5/iFry62/wAPbjULxrb/AITJNBfVMlbh7JovP8reD9/goD1wck55rtPiHpNt8O/FHw6vfDdounvqWurpF/aWgIhu4JImyXQ/eIxu3/e5+Y4oC560dY0yGGSSTUrRIoQDLI06bUyCQWO4bc9s96XT9Ss9UgFzZXEN5bkkiS3lDoSCcgMuQcZH19a8B8E2t/Z+D/i1aaZ4d0+eybW9Ziaaa4EShQuQnl+WdwUZIGQPcV6l8D9q/BvwOF4U6NalSerfIDn8ec0AdwzfL0zmo2+XBxUy4PahlNAIryZaoVYk4AzVloix4p8UPlEnvQMotJluoHua8t8GzHxB8Z/iEdXhW4udHazs9LtrqMS/ZrZ4i+5FI43sOWHHavTUjJUk81ja14L0vX76K9ubd4tRjjEP2q0nkgkeMHIR2RgWAPTOcdsUEnD/AAfhMPiz4k2dqqHw1Ya4r6bHgNHBKYz5wh7DDnqvPNerRyegye2eapaLodroOmxafYWqW1pFnai88nqxJ5LHuTya0BCygY4NACruuBxxjrVlVCr7+tRW0JhzxyeTU/4UANwre5pPL3e1TbQBwKb17UAL5Xy5oKgLx1o3Y4py0AGz5apa5otn4i0PUdJ1CMyWN/bva3CrwxjcYYA9uKv7jSGgDzjwz4J8W+FdBsdAbXNNl0u1jFvBqn2eT7eYBgKpQny/MAAXOTjGdpqSL4dXeh+ItT1vw3rP9lyar5cl/aXdt9qieZVCCVAHVlYqBnOc+hr0D15wT1Pc0zyV6ZyDjPvjpmgDhE+C/h+48KzaNdC5lkuLz+05NW3ql2b3dkXAYD5TkAKo4A46ZrZs/A8Ees2+s6lqF5rmpWqSR2txdeUi23mcO0SKoG8jgswJAyAQDiulVcHpjtx6en09qf3J6seCTyT7UwON0P4V6Hoel6xp8LahNaavK818lzdtmWVzmRgQcgMOMKRW54f8N2HhXSLfS9LgNtp9su2GFpGk2LxwCxJxwO9aqdf0pzCgCJc0/wC91FLHjnNP3Uh7DQtLs9qVmApn2gL2zQMo7Svfimtj/wDVRRQSTxyDbin0UUDQ2SXYwqRZN3PaiigGHmBsgcYpdwC+9FFAhnXmlVjzRRQA4N2Y4NO3D60UUAG3v0phYrRRQA9W9qU9DRRQA1c1JRRQNDD94Yp6DJoooBiOB6cUixnr2oooBH//2Q==)

Пенициллин-гидролизующие ферменты секретируются особенно пенициллинрезистентными бактериями. Они называются пенициллиназа или β-лактамаза. Лактамазы продуцируют пенициллоевую кислоту путем расщепления лактамной структуры β-лактамных антибиотиков, аналогично гидролитическим реакциям в щелочных средах.

![Diagram

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Bot0qlQQPkOAGA5z3wTU2peINTs/i9oejLdKml3mj3d1LatGh/exyRhT5h56OeBgcc0AdPrnh2w8VaDqGj6pD52n30DQTqOG2n+IHswIDA+oFZHgH4fW/gWznEd1cXt/e+W97cy/Ks0qIFMnlg4Vm43YJ3EZ4ri/H3xospvh74nuPDeqXFjqtvo8+qaddyWoWOdI32mSJnBV13fKTwRkEetdZa/Ei1GjatdW9jqWqtotr5t1NbwII5HWNXkSNy2C2TyBwCpyScESK5268Ng1Iq5715LY/Hyxj8NadqmsaPqVq8lha3195MKtFbLM+xHVi+XRjyNuWwCcCtbxR8ZLPwrquuaf8A2FrGoS6NYR6ldPbRR7Bbtuy4Jf5sBW4HXHGcGqGehAHPWkZeeteZzfHC3t9Sazfw3q0Us1pDfWKyiMC7hkl8oSE7v3SgncWcDC881f0X4oHxR4Xm1fS9FkuGt764sLmN76FIYjCGLStPyuzhfmGevQdaVhnfp1xnNSdWrk/hv40fx54cXWW0qXSreaZ1tBNOHNxCpwJhgDCMc4zzgZrruOtUO45vSmhaUNntTqm5I3tS9OlJTZGBHFIAjkbk9AKVpFYjHFVGkfkDpTfmqrgWjJtbA6Upnwo71Ft8xcYpVUj5aLjCSYKw5yfSnq59etN8s/5FIsJORRcdx/mHoRUiSBge1V5I2XA61IMccc0XJLAXcoIGKXGKarngZ4oaT3ouMU5zSrncOaRcEinLSHcc+McGhT+NIE59qkVMUhkW0rk4xTgpYg7uanHzDnmnqnTinYBqxsre1TKpp2005QcVQCbTTmAUcnHvS89aG/2mKjoWXgj6HtQAzO7oOD71HJkZr5y134leIdBt/Hv2TxjNceING182WlaBNBbyNfRAxjZsSPzDu3v84PG0cV6Xr/x08PeGLx7XUvOD28kNvezW7xFLSaQLhSjOJHxvXJRWwTg46UDsd+iFm9+2akGWXO0gEZ+b+HPv0PQ1514g+Nul+H7zXYG0PXroaH5bahcQWqCKGNxuEwLONygY4Hzc8iqeq/Fbw/4Z8Ta/LLHqjy21hYsUkkSO1kWd9kOxWb5MseWbGBmgD02T7vJycZ+6ePTP1pi7lUYXPbcQcH3HHP8A9avO/EfxAt5tP0W41LStbsFm16Cyi+x3Cf67ja7OpAkiYH+EHpXFfEq7v7TxF8U0ttV1CFIPCsF/brHdyKkMyvKNyjd8qkLzjkjNA7nvLEt1Vl9SR0PpmkVWbIALH2Hr/gePxrh4fHL20eg6JZadP4g8QXOjR6g9usyx7YVCpvd2/iZ2wo755rm5vidoPjrUPCPk2WrRvqyahBBNHe/ZxazKjGZJVVvmZSMAjGDg8daBnrMj7e45Gfm4PoRj1qqW+bpzXlHwB8fXeu+B/DOlRQ3GuXNvZeZqWoyXOFtmaQ4SVmyWkIwdowcenf0Dxb4i/wCEXsYJhYz6hJcTiFRGVijiG0sXldjiNQATk5zgAcmgDaDevI9BTWyoBPfgccH/AOvnNeUWH7Q2lataWP2HS5ZdQuftY+yzXUcSs9vJsZYpDxIxOCAByK14/FUUvxEvLaPRdQbWE0Fb2NZbsLbyIZOI9gJAbfuBYgHigDvSvrSMo24rj/hJ4w1Lx54D07WtUslsp7kMyFZVZZkycMoA4x0OfTNdielBREVFMbmpGBprLTsBBIARg1WmGOBxVtx1qpJndSAh2mijc3rRQBLGvtiopLdy2Q3FWVcScAYFSMuBxSuYFaPGNucmngHtSquM4qRFORQO4i9OaVlJ5609kojb8qViSGOL5s5289688+PUbt4L0kW6LJOfEWl+Wsz7VZhcLjJAOBx1x716Sy/MAvG7j86wvF2paPpOjy32uRQNYWrxzgTRrIfNDfuggI5fcRt9yKQHJR/Du+8TeOPEXiDV1udAg1KxtbAWenagUuCYnZzK8sRwDg7VGSdpOSOlSJ4B1TTviDoV9p8klxpljpF5ZPd6levcXPmTyLIrNuGXAKKME9K7y3u5fscU1/E1lcNt8yB3DeWx6JknBb09e3TFLNcRpcJBI8STNkKjMu455JAPJAA544xVAfO+ofAfx3q0Mk5l0BNVudHutHvruS8nZ5mllRhLnyyEHyYEYOFB444r0XwR8N9b8M+Hdc8Lz3dmfDV3bSx2SrNJLc6e80ZEseCgDxh3crz174rvf7WsVvIrVr22W5aQQpC0yh9x6IB13EYwO4qlY+JTs1ee/m06GysrjbHLBdCRRCqqd02cCNiWPyk9171IjyLVvgH4u1/w8dLvtd0R4k0e102zWS2nlWzlh6yRAkfNIFXc5wwxtGQc12Gv/DPXPEGseKbqTWNK3a/oMWiuwhl+Vk8zMoGfukzSY7jatdRceKobk6L/AGRqWi3KXt2bY/aLzmXCsSsOwEtIHCjByMEndkCuc8K/Ee88Q+BbDWL260XRry41mTTvLuJWWCRI7poSkeW3GVgPlzxkc8CrC5geJ/gTrXie80S7HiWxsW03TraxMK2MrRXSwyrL+8XeMoxCgjPQH6VpxfA29TwzrHh9/FxNjq2sNqVzGNNSMSIxDNAQso+RyOQCMINoxkg9lp/xJ8K3+q2+mWviLTLjULicwQ2qThi8ijLRjtuGD8ueQrVJpnxC8OateXFjZ6zbS3NvDJNLEpbAjRtrtnGGCtnJGcY5oGX/AA/o97otvLDe6kuou7LsWO2NskCKiqqLHubC8Z+9/F9K1wvrXHab8SfD3iG9TQ9M1gw6tdwPPbL9jlU+WAf3o3xqpXI44wcVo+B/Fh8U6berOiQ6npd7Npl+kWdhniIDMmeQjBlYZ5wR6GpuB0ykbcU0kU36cUxs5xSAdu5oCDrTVU7galVfWgCNVUt6UjgD604x5PHFAh9eadgEj9Ogp6qOaXye+aPJx0NIAGPSlUjmmbTnFPVfzp2ARmFNOCM04rTfL3fWkAzzMd6hNwc+3rVryQO1RSWu7ODigCJL75jxx2q7G24A5qrDbhcAnOKuKduBjigZMlOFN3AdKRZDQUSr94cVMFPB7VApxg1YViy1Yrkh6CnLUW4mpeRigYv4UZPUHnt9aTJprPhhQM88+HPg/WvCur+Mb7VI7GIa3q8mpwva3DO8QZVUoSyrgjaORnqcc81Qk8B+KdI8aa9eaPfaOui69dfbLpr6zc3djIyhX8nA2urAZCk4BwcHofU1O4nnBPekFuFOQAPpx+P196B3PIPEfwl8Qa83xHW3u9Hjg8V2sNrFIzymS3WNNgdgqY5BJIz1xRefCTxHc69f6g91oMkF3plnplxZ3UcssTRwMxYEGM43Bm+b+HAPavYmjBwCMjOeaRowCDjtigDxOH4F6jp3huy0rT9RsbZLbxBFriWcnnS29tHHgrbQsxDbSRncQAO1XfGXwm1fxRrHi67t9V06CDXtGTRws0MjSRqu8+aSGAY/OwK4HavWzGOmPl9KVoxu6Dk5Pv8AX1oFY8zj+GWsWOtaF4h03VbOPXbDTF0m7SS1le2uYl5UhQwaNlYDnPOcVlL8E73Tbrwvc6TrFrHNo8t7cyyXFu5F1cXW7ew2kbVBbhfUCvX/ACwWGRnHT2phjHPGD6jg0FHiXw5+Auq/DC/0m40nXrFI47c2+qWsdrKIr8BspIE3fJKqkru6kHnNdj8RPBF740sNKjs9Uhs5NPv47xo7u3ae3uAFYCORAw5BII7ZAruPLXptG30A4pJBu5PJ9T1oA8CT9nHVI9H1DSL3XtI1nSryaefybvSnR7aaWRnM8Dq+UdcgDHoK7HR/hveaT44tdYl1WO8to9FXRTHPAxuXUHd5hYttBLdvc969FKAZ9KiAUDjjPpQOxx/wv8D3nw/8Lw6Nd6nDqcVuTHbtDbGHbHkkBssdzH16DbxjNdZ61K/AJFRKwyc0DGNmkP3cU9mHbrTGx0707gQuvXmq0inNWmUdjTNvfNICj+FFWdo9KKABYtvNKaVR6nFNaNj06VBzjlj3A44pY84HFP8A4dpp6qNuMU7AMyG6U1V+bpxTmj25xQjE8AYFMBWXv2rzX4z29wkfgaVQwtIfE+ntdMp+VFJYIWz2D7B9SK9MdsKVPQjBqjrGmWmu6bdWF/ALmzuUKSxkkZB7gjkEHkMOQQCMVIHzb8QPD/h/WvHnxXs73T3vdbOnWJ0qOFZGlW6aByDGBwrh9vPQDPYmpdP8J31x4ovNI8X2Wvah4kW9tLyxu7GJPs0qJFGFcXXlsYwpEm9S4zkYByK9z8N+CoPDmt6pqsOoaldXN/HFDP8AaZkZf3Y2x7SqKeFJHJ56nJrpNzbuCyj/AGSR/noKdwPmLWPB8W7xte2vhq7l1F/F1jdadcw6XMW+zI0LSSxERn5PlkJIIDY6c10Fr4Ue40Xx7AdE1zT4L/xUt9YmxsGiuIoyITHdJGykuqtFkqBkgkelfQKxiQAH61IsZXGGPHA5pAfP8fh7xDZr8PrnV9Ha6utM8R3F9cahpentHutjHIonkjJBieRn3mMcgrnAxUWm+EvEMfwh0DSX8N6kmo23i1NUmt2hVWWAXj3BlBLAY8t1465ZhX0J9n2jIwO3Axn2qERjPAx796q4rHgml+BvEEWnaaF8KXUc0fjmbX3D+QgFoXdkcnzOoDAbeoGcVL4L8D+NNP8AF3h/WdT8LMIrLTtRtbu3bUrdYQ0hR1WCJThUYLxxlixLE9a9/wB2/rzk7j9fWpBxnHHT9OlAzyf4Y6N4k0nVrzUvEuiLaaxqzO2p6o15AYbW3VT5NtAEZvkX5Dk4GcntWz8J9JkjHizXnR4o/EetzalbxyZz5G1Y4nP++ELjPOG55rupoI5onjkjWSNxtaNhlWX+6R0I9ulPjjCsMDAxgBeAB6YqQHKvrS7QO1K3C8UDmnYBtO7UbR6U7HtVaAManLTSDmn/AHVzSAMe1NGec1JxTe+KQAtL/OlGMUm7mi4DTnrTol70UFio4pAI/JxS7V288mkKlsGm7cNmgBdq9MU4AdKF5p3AHvQMcvUVIiq3GKjX3GamjUcHpQMXbtYDFSKwFHXvmk2jcKq4WJFHOaexOKYvSnnnii4xaiZSXzUyj1pdoPai47kSrU3KrShR2FGCTimIcvNEie9Nzto3c0FjeRSfhTnao1k9aBXFIHpUTCpZJAKY33eKBkLN81Iygrx1pGzyTTSxA60AMmUquc1BxU5bPWoJFy2RQO5E7HoTULdakkzTMetAXGr696jZtx4qXb2HFRCPaxNAXI2bHWkJ7ildQzYpjZUdeKVxi0VHvopgWVWl/iooqDnAru5NSL0ooqwGd6cqhC3GaKKQDZl3D0oWMFcHkHiiipAfMu4Ank8Yz27cUhX5etFFACx+lPYYYCiigB68jB6VEflbiiigA3bZMYqf0ooqgF/hpcbRxRRUgM3E8GnLRRVgOzik8w0UUAN8z5iCM0/OUFFFAAfvcUm7miikBI33aj96KKkBd3HrTs/LmiigBu8lqCSe9FFADx93IOMUp5xRRQA8/LgjimzSFVoooGOjmbYT7VKrM21s445FFFBRI7kAY4qbdt560UUASI25elK3DDFFFAxVYg880vmY5xRRVljGk3HpUfmc0UUEiOx/TNRRsWJFFFBJXuLhvMCjirSk7RRRQWRSE4OOKq+cW28cEUUUAMM3JGKf/ATRRQBXkf5ScVGW+QnHaiigCMSZ2nHUUxpMdBRRSAgkkPPFQeYWxRRUlBRRRVgf/9k=)

Важнейшей причиной развития резистентности к β-лактамным антибиотикам у бактерий является индукция секреции β-лактамаз. Этот процесс очень важен с клинической точки зрения. Фермент β-лактамаза вырабатывается генетическим кодом в хромосомах или путем образования резистентной плазмиды. β-лактамазы были классифицированы Сайксом и Мэтью:

1) Хромосомные (код с генетической информацией) β-лактамазы.

а) β-лактамазы I типа активны в отношении цефалоспоринов (цефалоспориназ)

б) β-лактамазы II типа активны в отношении пенициллинов (пенициллиназ)

в) β-лактамазы IV типа активны как в отношении пенициллинов, так и в отношении цефалоспоринов (лактамазы полиморф-1).

2) β-лактамазы, кодируемые резистентной плазмидой

а) β-лактамазы III типа активны в отношении пенициллина, цефалоспорина и монобактамов (полиморф-2-лактамазы)

б) β-лактамазы типа V активны в отношении пенициллина, цефалоспорина, монобактама и изоксазолилпенициллинов (мультифункциональные лактамазы).

Обычно лактамазы грам(+) бактерий локализуются внутри капсида и вне капсида, а у грам(-) бактерий локализуются в периплазматической части капсулы и бактериальной стенки по краю внутренней мембраны. В то время как грам(+) бактерии секретируют β-лактамазу, синтезированную в цитоплазме, непосредственно в окружающую среду, у грам(-) бактерий β-лактамаза высвобождается только при делении бактериальной клетки или вводится в инфекционную среду. Поэтому очень трудно лечить инфекционных больных, вызванных этими бактериями.

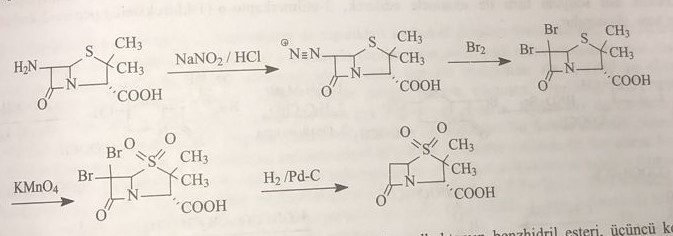
Устойчивость производных пенициллина к действию β-лактамаз обеспечивается защитой β-лактамного кольца со стерической точки зрения или сочетанием препарата с активным соединением, специфичным к β-лактамазе. Наиболее важные из этих соединений-ингибиторов β-лактамазы перечислены в таблице.

![Diagram, text

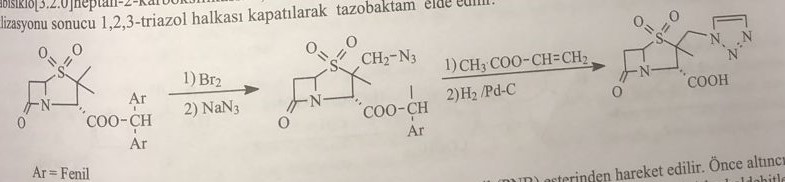
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Клавулановая кислота производится биотехнологически методом ферментации. Хотя и существует метод синтеза, экономически выгоднее получать соединение биотехнологическим путем. Три других ингибитора β-лактамаз получены синтетическим путем.

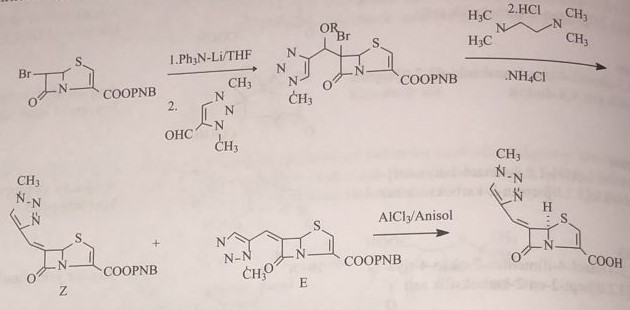
6-аминопеницилановая кислота используется для синтеза сульбактама. Для этого аминогруппу 6-аминопеницилановой кислоты сначала диазотируют азотной кислотой. Затем бромируют шестое состояние. Дибромпеницилановую кислоту реагируют с перманганатом (перманганатом) калия в среде уксусной кислоты и окисляют тиоэфирную группу до диоксидной группы. Дибромгруппа в шестом положении восстанавливается газообразным водородом при катализе Pd-C.



Сульбактам используется для синтеза тазобактама. Для этого бензгидриловый эфир сульбактама бромируют бромом по одной из метильных групп в третьем положении с образованием 3-азидометил-3-метил-7-оксо-4-тиа-1-азабицикло[3.2.0]гептан-2- карбоксил-4,4 с азидом натрия.-диоксид. Для этого тазобактам получают путем образования 1,2,3,-триазольного кольца в результате диенофильной циклизации из реакции с винилацетатом.



П-нитробензиловый (PNB) эфир 6-бромпенем-4-карбоновой кислоты используется для синтеза BRL 42715. Используя бром в первом состоянии, с литием получают литиевую соль трифениламина. В результате его реакции с 1-метил-1,2,3-триазол-4-карбальдегидом триазольный цикл присоединяется к шестому положению. Литий удаляют добавлением уксусной кислоты. Изомеры «Е» и «Z», полученные взаимодействием N,N,N,,N,-тетраметилэтилендиамина и хлорида аммония в среде диметилформамида в среде металлического цинка, разделяют кристаллизацией и очищают изомер Z. И продукт E изомеризуется. Е и Z разделяют перекристаллизацией. Этот изомер превращается в изомер Z при нагревании в среде хлорида алюминия/анизола.



**Пенемс**

Пенемы представляют собой соединения, образующие двойную связь между атомами углерода во втором и третьем положениях тиазольного кольца, и в отличие от карбапенемов сохраняют атом серы в четвертом положении. Вторым соединением в фазе III за пределами BRL-42715 является SCH-29482. Это соединение обладает очень широким ингибирующим действием на лактамазы. Он особенно активен в отношении лактамаз типа I и II. Активным изомером является изомер Z.

6-аминопеницилановая кислота используется для синтеза SCH-29482. На первом этапе из 6-аминопенициланской кислоты синтезируют 6-бромпеницилановую кислоту. В реакции с ацетальдегидом в среде этилмагнийбромида гидроксиэтильная группа присоединяется к шестому положению. Трихлорэтилхлоркарбонатом защищается гидроксильная группа в восьмом положении. Путем раскрытия тиазольного кольца 3-этилмеркаптопенем подвергают взаимодействию с этилксантогенатом и аллил-2-гидроксиацетатом и получают натриевую соль 3-этилмеркапто-6-(1-гидроксиэтил)пенем-2-карбоновой кислоты.

![Diagram

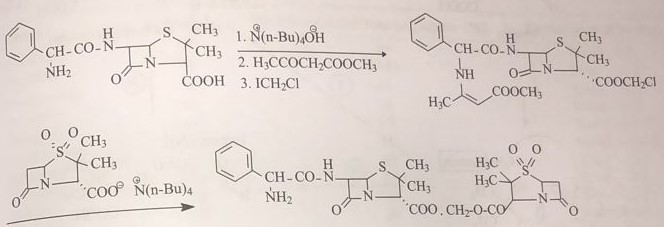
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AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAMjAyMzowMjoyNiAyMzo1NTo1MQAyMDIzOjAyOjI2IDIzOjU1OjUxAAAAAAYBAwADAAAAAQAGAAABGgAFAAAAAQAAEZQBGwAFAAAAAQAAEZwBKAADAAAAAQACAAACAQAEAAAAAQAAEaQCAgAEAAAAAQAAF5QAAAAAAAAAYAAAAAEAAABgAAAAAf/Y/9sAQwAIBgYHBgUIBwcHCQkICgwUDQwLCwwZEhMPFB0aHx4dGhwcICQuJyAiLCMcHCg3KSwwMTQ0NB8nOT04MjwuMzQy/9sAQwEJCQkMCwwYDQ0YMiEcITIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIy/8AAEQgAjgEAAwEhAAIRAQMRAf/EAB8AAAEFAQEBAQEBAAAAAAAAAAABAgMEBQYHCAkKC//EALUQAAIBAwMCBAMFBQQEAAABfQECAwAEEQUSITFBBhNRYQcicRQygZGhCCNCscEVUtHwJDNicoIJChYXGBkaJSYnKCkqNDU2Nzg5OkNERUZHSElKU1RVVldYWVpjZGVmZ2hpanN0dXZ3eHl6g4SFhoeIiYqSk5SVlpeYmZqio6Slpqeoqaqys7S1tre4ubrCw8TFxsfIycrS09TV1tfY2drh4uPk5ebn6Onq8fLz9PX29/j5+v/EAB8BAAMBAQEBAQEBAQEAAAAAAAABAgMEBQYHCAkKC//EALURAAIBAgQEAwQHBQQEAAECdwABAgMRBAUhMQYSQVEHYXETIjKBCBRCkaGxwQkjM1LwFWJy0QoWJDThJfEXGBkaJicoKSo1Njc4OTpDREVGR0hJSlNUVVZXWFlaY2RlZmdoaWpzdHV2d3h5eoKDhIWGh4iJipKTlJWWl5iZmqKjpKWmp6ipqrKztLW2t7i5usLDxMXGx8jJytLT1NXW19jZ2uLj5OXm5+jp6vLz9PX29/j5+v/aAAwDAQACEQMRAD8A9apprM1I2NVHnT7T5H/LQpvGemM4pCKcb3xZHVd6KMOCRywDAgY7bgtafJHSgAxhQMU8AYoANueMU8IMUALsGaXAFADJJ4IRuldVABJJ7D1p6skqZQgjJH4g4NADsH0FHTLNjFADfMiXaGZVLHC5I5PtQJoCDiWM4OD8w4JOP58UADywhMtKijdtzuHX0+tOC49aAIbpmjgLxxtIwxhR1PNVzNKbFZjG0TDl1I5UfjQA+1N2WIuFAGOxGM1b4AxQAyR44l3OcAkD8TUK3EUpKxHLDkjBBFMBHzz8lVmHUlaBldlXbVZximBVc1WbrQB1t7BLcIgimaPa2SVJGeCMfr+lQCG4TzJHuWBIztHIB/EfTt/OkBHPnyI/Mu3G/G7LKuR1PIAPTPSntbW5XBiTGMdKQivaW7GwjCzMQTvAfkEbs89zn606OJrFnnkuB5IBLAr0XLH/ANmH/fNAEq6nZyNtWXJxn7p6evSlbUbOFlV7hQXXcuehH1oAtrIrLuUgj1FQrqEBuHgO4OvbGc8Z4xQBJ9sh3bR5mQM48pv8KjmuHnjdLVX3gH5yuAp9MHGf880CK0xDyRw3MUimRGRyoLBlI5xgf0FSrcWliZGVZdhzk44BwX6de5oA0UkSQZRgwzjg0r42NnOMc4oAoztagwlpzG0ke2IkHkEqP5lfQ1CbKzMbMZWMZbbJ1w7bzx/30x9aAIHs7B59huXChWTytpzklmP6E9u1bFvGkVvHFGSUVQAT1NAytcajHb3RhcEADJb0GCf/AGWo336jbDYyxxyLhmB3NtI6exoAl+0vCyJcLy3CvGpIY/TqOnv9aR7ne6xRRuznk7gVAHqSf6ZoAqXEdxb2V0ZQZlJZ1KsSycZHp0Pp7Uv+ixMjpDKZXbgYIyQCf4voaYD7W/ivVygdDxgOME5UN/7MKLoO0EixsFkKkKx7HsaYzHeC+ErkTLsyNo3ZIHccjvVWRNRUDdIrfLztAGT2PI6UAVi170dTweSuOeff2x+tLGztEpkXa/cUAd4aoTxm7ZoJEdYupYd8dvx/pSASWwtpECGMKoOcL8vP4UG3t8nMEX/fApCIZLlLNkjCEx7C2EAGxVxk9egyOBUU+oWzL5UglUsVUgKp5JOBzkc4/wAcUANhjt5G8s+bGw4+dE/Lge1WBpsOCGdmySfmVD1/4DQBJ9jYWzRRXkyHnD4QkE9+lWViiD79i7+7bRk0AUlvd1/L5VrNKiqqF12gZ5J6keo/zinxXjBWK2UzZOfkK/8AsxHt0oAeszy3cTPaTRIqt80hTGTjA4Y+9WD9keQq3klycEHGSSP8KBCrLbRLxIigk8lup70tzLH9kkZmJQKdxTBOO/WgCncC1jZVlmkwig52qdoJ47eq/pTEFjuS2W4ch13JwuOMdOOvfI+tABtsCC/2tj8+3OR9706datWc8RaREvDOSdwBx8o44GAOP8aBlltjcMAc+tNJVfQUAULq5Zr2CGKIu0beY5JwANrD+tH2mcXij7NkFfvA8Drx+g5oAdPPO8EifZHyylfvr3/GrK7XiUMAceo70wI/KiVwyooIGBgf59KhnWORcSKrDrhhmgDPuLe3WN2W1iZgpIXYOT6VmfuyzxtaReYvIxFtyPp19aYypGIrhmBtZYSOucqPwptrYw2KyLDvxI5dtzluT9elAHoNMbpSAiJ4qHcCeaQhxRH6qDjpkdKb5MXeNemOnagBwiiyCEAwcjAxUnFADhjFRTx+dGFVsYOfY8f5P4UAPUKqhRyR1J70/AxQAmQwIK5qv/Zlu3UuQSxxn+8wYj8xQIP7MtikqbpMSpsbkcjAX09BU0FqkG9d5dGOdrnODkk/qf0oAkkt4JU2vGpGMdO1Iba2Lq/kx7l6NtGRQA0WVqCcQx8kHG0YGOmB26k/jTo7W3hO6OJEOMZVQOKBj8LmormNZoJI9xXepXK9RmgCCFBFHtJ3ZYnIGByewqTAU/WgA4b1+tV7mFnXEbbTkZxxuAI4J+mR+NMCo1hcYwl0wAJyN55HOBn2yPrioGsbsMjtcuxXO75zh/mz06DjigCYAmNS+N5UbgOmaryIOcGmMquMVXagDtzTHICkk4A5JNICFpEx95fTrUW9CcbhnPTNIQ4Oo707qc0AOwKXj0oAMg8YpQV6YoANwzwKcDuNAD9o9KSgQ4KOtLtBoGGOOlNyB2oEAAxkjFAw3ODQApUHk0xlXbzQMh+XFMwW6mgBduOhoI4/+vQBDOwiheVzhUUsx9AKpvfwhvLber527SvU8cfqKYFR9TtMIwkO2Q4RscMcgfzNQNf2/JDFgATkKSMDrTGDMGGQQQehqs9AHc9qqXaGSNVGfvqcjtgg0gKcmlQPuy0nzBlIz2Yknt7n6UxtKjGwxyyK8ahVOeOhHOMZ6/pSEPXTIlhMe98GPyznGcfl196uQqUjVWYuyqAWPc+tAEoxS8YoAABSHC9qADeM8CqH9qqYvMERxs34U5boeMeoxyO1ADzqYViuzO1lU/N1ySMj16U4aim0EI2SEJBOMFzgfX39qALFvcrMzJja6HkZz+tWD04oAaocDls/hSjPqPyoADk9TQOPSgAJ4qIyKRzQIYXUjimnPbj8KBjTuIxmkJIX1xQA2V08hzIVCBTuz0A71Qit4zbx/uonYKFdsc5HX9RTAY9nBj/UR8dPl6VTazhVdvkp0xnFMZHsWNAijCgYAqB6AOznlMUEkgUsVUsFHfA6VnyEXsaGRZIW3tHsJ5xnGR78DBHTNSBdJqKSeOIgO6rn1NAiTOaqTXxgWc+ST5YO1QeXOMjHHfkfhQBC2r7Si/ZnyzEHJ4UbsZPtgE5HAxSTa0YG2m3LYYL8rZycjpx7/wCOMjIBqRSLLErqQQwzkHIqSgBrsqIzHooycVFZbfKbaDw7E59zu/rQBYwPQUgjjGcIoz14oAUIiuWCgMeCQKfmgBM0yQv8pQZ+bkcdKAKss14JSI4gV569umPz5/KkWe8bbuQLknOUJxjp37/pQIi+134PzWoPyqcAEcnGV/DnnvUb3NzHIpkhBh2hmYIV28MSOTjsPzoGRG7ut8RW1Yq55Gw5T5gOT0PBJ49KfPfXEe7Fq3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**Комбинации ингибиторов β-лактамаз и производных пенициллина в качестве пролекарств**

С целью повышения фармакокинетических свойств активных производных пенициллина и цефалоспоринов его включают в лечение в комбинации с ингибиторами β-лактамаз. В частности, чаще применяют амоксациллин (Аугментин) с клавулановой кислотой. Сульбактам, тазобактам, BRL-42715 и SCH-29482 проявляют слабую антибактериальную активность. Однако против β-лактамаз типа II-V он особенно сочетается с ингибиторами β-лактамаз, кодируемыми как R-плазмида. С другой стороны, мономолекулярные пролекарства были получены методом активного эфира. К этой группе относится сультамициллин.

**Сультамициллин:**[2S-[2a(2R\*,5S\*),5a,6b(S\*)]]-6-[(аминофенилацетил)амино]амино]-3,3-диметил-7-оксо-4-тиа-1- [[(3,3-диметил-7-оксо-4-тиа-1-азабицикло[3.2.0]гепт-2-ил)карбонил]окси]метиловый эфир азабицикло[3.2.0]гептан-2-карбоновой кислоты S ,S-диоксид

При синтезе сультамициллина соль ампициллина получают с гидроксидом тетрабутиламмония. Аминогруппа защищена метилацетоацетатом. Затем готовят хлорметиловый эфир по карбоксильной группе ампициллина с йодхлорметаном. Полученное соединение подвергают взаимодействию с тетрабутиламмониевой солью сульбактама и получают диэфир сульбактама и ампициллина. Реакцией аминогруппы с п-толуолсульфокислотой защитную группу удаляют и одновременно получают тозилатную соль.



Сультамициллин представляет собой пролекарство, в котором ампициллин образует сложный диэфир по карбоксильным группам во втором положении с сульбактамом. Сначала в лечение включали лекарственную форму, полученную молярной смесью ампициллин/сульбактам (1:1). Эффект in vivo в этой структуре не всегда желаемого размера. Потому что наличие важных различий в кинетике абсорбции и элиминации обеих молекул свидетельствует о значительных рисках. Амфотерная природа ампициллина, особенно при пероральном применении, изменяется в зависимости от рН желудочно-кишечного тракта. В то же время, кроме различий в активности обоих препаратов, существуют и различия в периоде полувыведения. Для устранения этого фармакокинетического несоответствия сульбактам, Считалось, что его наносят на организм в виде комбинированного пролекарства с антибактериальным ампициллином в форме сложного диэфира, и таким образом был получен сультамицил, который заменил физические смешанные препараты ампициллин-сульбактам. Сультамициллин применяют внутрь в виде тозилатной соли. При приеме внутрь хорошо всасывается из желудочно-кишечного тракта. Биоабсорбция составляет 90%. Он быстро гидролизуется эстеразами крови и действует в форме ампициллина и сульбактама.

**Аллергия на пенициллин и механизм формирования.**

Поскольку транспептидаза не синтезируется в эукариотических клетках, β-лактамные антибиотики не оказывают на эти клетки фармакодинамического действия, поэтому эти препараты малотоксичны. Однако они вызывают аллергические реакции, реагируя с веществами пептидной структуры в организме.

В первые периоды внедрения в клинику пенициллина и его биосинтетических производных при парентеральном применении наблюдалась реактивность, развивающаяся вплоть до анафилактического шока. Комплекс β-лактам-пептид, образованный соединением пенициллоевой кислоты, образованной из β-лактамной структуры, со свободной аминогруппой пептидов, вызывает аллергические реакции в организме как аллерген. При этом наиболее реакционноспособной является пенициллиновая кислота, являющаяся одним из продуктов распада пенициллина, и она связывается с биополимерами быстрее, чем пенициллиновая кислота, а образующийся комплекс более стабилен. Основными аллергенными продуктами в комплексах конъюгации, представленных на схеме, являются:

1) Продукт конъюгации, образующийся при ацилировании аминогруппы белков крови пенициллоевой кислотой

2) Продукт конъюгации, образующийся в результате аминолиза β-лактамного кольца непосредственно с аминогруппой белка

3) Продукт конъюгации, образующийся при повторном замыкании тиазолидинового кольца после соединения пенициллиновой кислоты с аминогруппой белка.

![Diagram

Description automatically generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4TAIRXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIzOjAyOjI3IDAwOjQzOjAyAAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAMwMAAAkpIAAgAAAAMwMAAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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YjpTfNZeKl8li2dvNPWz3NuoArqzNxUixncCWqdodrcdaGhMmDu+YUADYCgL71TBkaHG3vWisZ27W696Psq4OOnegCrCiKMnrjmqfz/ap3T/V4A/GtNrWNuCuRT44VVdqLxQMrWsA5LtvJ5+lXQvA5pFjVfanBuDQO4ki7lxjdUaQHDcYPYVKr7sihm4oC4y3h8pTu+8eaWSIvhfxp3nKv8VOVvMXNAEXl9V9RTreNo1Ip1LG2XKfjQMiaPGRu60xbZd275umKtMu0Zqu9xtkC0CHxwrHxtokhWTg9KQTru+8tNNwmT81AEYtI1PHWpPIVv4ajkuBtBXpuwalSdQ1AxTCoXDL9KjEaqxx1qwzb6rSNsn2e2aAB49x56Uz7OqtUnmLux61FJNtYjb3oAcYhk1XmhVWzT/tS4ORtqJplm75xQA3plvSmLiY805u1B9utAB5Pp0pDFwacZNsJ/vVQ+0Pn73fmgaJZLeoWtVYH5aubldR34qGaaOMYDc0FFT7Oqt6USR8FaPtW6Qg9KY03zGgCH7L1z0xUBteKsNcMuB60hlG0560AU2t9tU7yCSRMo3ANXpZeajkmVRj1oAx5rWRsGodjKxyO1bvlq61VmhWgDFaTHtzSSSZwPWtBoVUE1C9srigCGMbFpsi55p5j8ohaY/WmgK8jKrbaryLuyKddLukz7VVabZVAI8arkUUxps80UAermFdo+7T0g4qqzGXawbAqws7Lx6VBmy1GmFxTWjWoTcNg1B9obnDcd6CS2IlyKf5XzH6VUSZ2b5W7VPZs7SNubpQA5gseDtoWVefmxROu41A1u27hWxjmgCaSdFHynce9RrMzSc8DFNiteeFOf9qrMdq24464oAb5m2lE3zCnxwuud1Bh3kY6d6AHg5XNQ+Zgt9atLD8oHpxUbQbWI9aAIPO+Ut+FNXcHjHrVprXcgX05py26nn0oAqjzCCCdoqIN82CckHFaZVcVXvryz0m0e7vJY7eGMZeSRtoHpn1J7CgDJ8QarH4f0q91S5V3tbOF53VBliFGePbI5PasDwj4j1bxJPbXL6fZtpN5ameO9s7lpSrZXbE3yjJ2sxPJ+7W//bWoal4dvtQ03R5JNqA2UN4AhvFJw3yBvlG3oW4Nct4R8EyaH44vb/RdKufDmh3FkyT6bPMAkt0WUo6ICwTA3AsODQB3Qt9wUYyccmnmFhxjbXPw+NzpMiW3iaybQpi20XKssllKe22XoufR/wAK1tY17T9G0v7bc3HmRkhY1tz5jzufurGv8TH7o+hNAFHxPax3ui3Oly3SW0upxS2Vu7t1d424X6feP0rmvhzf6roXhPSdAu/D99HrGnQJZkLB/or7QAJPN+6EIGcHnJrp9B0G5a8/t7Wgv9rSoyw28Xzx2ERPMaHux/ifucr2rol5yPT0oA80tfA8tz8TfFet6v4dhu7G9t7VLSSZony8SbTwWzglsZPpWXpvw/1Tw98K7jSbtrez1GGS6uLVba/MMeZHZ87kUnKA8LnB216/uxwelQTWdrfSRtPa29wYTmJp41cq3cqexoAq6Gxu9HsLhldGntIpHWYYcFkBIb355rUjtU52rRLtU5DHPv1qRZ12U0BLBCq5x1qQLzUFu+bj8Kssx2lh1xxQwGMtNjXmovtBZcnqOtLHIzLle9ICxS81WZn3ct2pqM24ZbigC18ueOtQef8AvzGF560rL1YdcVV2sWYlWzgYoAutJ0I6k4p8hZVJ9BVcRO2Cy96sMjbT7jFAFaO55G7qTgVeVF21mi2dGTd0z/erTVPSgChcSMsnH3VqNp9uFq9Jbbtx96hWx8zks2BQBVa6ZcKqrjPNO+1FXCnvU8lgq8r1qNbIMwLdqAGOxaJ9vy/N1qYMygYb61ZS3XAz0qRYVX+H5aBmfJcNH05BHLelSWJZpA5GeMCr/lqeVVdtNbhsDpQO4O3ytu9KyJFJmXaGCZPG3qa2wvmYFO8lRwOtAjEjhkbqjD/epfssm58ptHrW1tWkZVoAzDasFxjqactky5AGS3f0rQ7CjdnigZFGmIwCcnFVriF2YMu30rQK7VBquz7mxQMrLZFmQnqM5pslt8uPU1b89V49OKZJOq87qAKhsPXpUUlk3bpVt7vLKo702S5CsQzY4oAqLat320Sx7APl71MsymmzTBuFoAhaHcpI6nmqr2bY3DbjPNWhcBWCtUjyrj71AykY3YAfw1DNbEqQirmrUlwqsAOtOPagDJFjKp+72qI28qyZ/hxWzuWoJNrZoEZTRt2Xiq8sXX5WrXLKFIqFtuDQUYso2rUXzDmtmVY9v8NVrhV8sbaBleJ9yEVDO22M461L/Caqyx/NkM2O9AFRrroNtM+1K2RVgwDzPl9KqyWbFifl60ARyOpIqORSRkdKJYWReF5zTznyxnrQBUl+7VSWPKk1YklyzA9M1Wklzx2qkwK7I22int2opgesLZf7VONrtGRyaesysxw1L5gLY3VBkRiBdvPWhbdVBz0615l8VtZh0fxp4akuRqUumm0vJbu306SQtKsa7gQoK5AJ5KnjvWQ+satZ/D3wwk+qy/YfEGtLAL2O48yW2sZCWVfMBJD4Ur1OBxQI9ljaFjgSRgn0bmq8d9YLqBthfwC5bgQmRQxI9u9cZ448O2Gg+H7/AFfRNLhtNb0mznktBD8rSOYyu1gOX7nnpWB4kstMi+ApNosc9wbGCa3uUjDTyXbbTuDHneXOeexoA9Ug1qwur66s4b2F760G64t43/eRD3XvWRdfETw/ZKjPqHytdCyXZDIR5/8AcwF69q4HVPDuq6p4i1HXdKmWPxno8VkPLZ8JdKYcywuO6Mcge4rH1bWpNc8J+GL2SN9Me98XCZlmQeZCwlfcCG6kMuPwoA9mPiqxTxNHoRFymotAbja1uwCxjgsT2weK2F+bnGPxrynTftFv8b3S51NtRkOgGMTPCqYczAhBjjJC55rpZ/BguVaV9e1tv41VboIOvT5V5HtQBoal4sK+IBoWmWo1LVRD9pnVpPLitoj8qs7kMeWzwK5vXfiLrugzwR3GiW1tPLq0OmjzblmjdZV+WZGCZKg5yPWk/snVvCvxG1fW4bGfV9M1m1t4ZGs1DXFvLCGAUoWBYNuzntTfH/h3WPGlnokY0TzrS11WG8mguriPcYE+8GGeWJbIGencdKaA2x4qvm+KH/CORvZvYLpRvnYI5lyH2bCdwwDnPStC5+IXhqCRlm12xWRSQY1n3Nn0IHINYOneBbjSfig2v2WnWNppL6T9hZbcrG5l3795RFwRwq8+ldzFax2xPlRJGcdY02mmBzsnxM0BkcW11PeNx8ltaSyZ/wC+VqX/AITaKbb5Oia7OxUMANNdB+bBf51uyrPIyfMzKBjDNVuNdq49qVgOD1r4hahpdqso8LX8LSzx20U148UarJIyhCw3s2Mt6Vo6V4W828bUtenTVNSUgxpt/wBGtfaKPGC3+24OeoxVT4oWkk2k6bGu3bJrFgn/AJMKa6yKD55fm++aLCuXRvkByST3J61TmjKyHb1q/wBdoHXFNa2UsSW5pDM/Y1xbSQzokkbjDxyLuVl9CvevMbjwWI/icieH7tNDNppgvre2lQy2oleZ43/dlvk3KOq8ivW1jXbtrlbe3U/Fa8/2NDt//SiSgCmnjmbQfKtvFOnNpIJ2jUYyZrJz2AcZKH2kHHrWtqXijTdJS2kubgubw/6Mtupnef8A3AOX/DpW6Y02yROqyRsMMrD5SPQjvXm8FxbeG/jheS6mYbCyudDhttGklAjhjCMxuI4y33CTtJ9aAL2q/FTRbGxvLiQagn2S7hsZk+xuGillGUyGAwD65rUuvGiaf4q0nQH0m8a61SGSaGRWTYixgGUHLg/3RwD96uS+N2pabrfglzY3CyyPq+nxS3FuhZnCSiRsMF2vsUk4HTvU2oaa9n8ZPC9yt9qWswR6dfo9xcJujiaUJ5akxoFTe3vzQK56XIrsOOvanR20u3cep4rnfBev3154k8Q6RqdyrvYCCWM/ZGgfa4YMyA8MoK4Vu5ya7BZAoG7C/wCyOgp7DIre2MbfN6VO67l56U03C7uOmKgN0pGR2NIB7Wiv0anRW4jGGXNJ9rXgetSR3CtkUAO8lY+PWnrGv92qskzMygK2N1XN3yn+9QArR7RUchEaglu9QSTNGcfxEU0MZEG6gCzHIryD0qeRlqgpKXPHTFPnZmjI3dcUAWNy7d1OgkWQZrOkhlG5V3fMefoKu24KucLxigB9xIq4qKK6XmnzK8wIC9qjWzdY1Hr1oAa0zGRjnauKbFKm4KTuOMipWh8tiu3tTorf5g3tigBnnqeQ2SP4fSnrMXVvXHFI1kqtuDYJ5qQW/wAp5Zs8UAQrdbdkZ+8RmneZuY59alGn4ZSdwCVZFovHtQBS8x+zcVEszKZDndg1peSoBHrUP2ZY2J20AVGlkmZ+WHA4pVLKxLdQOK0Y4VODT/JX0FAGb5rNz7U6E7nU+tXmjVf4aWONTzQNEM/+rLVQVXkywXjFa5VfM/CoZfkOPWgoyWjJbHl9RzVeSEiMjy268Vt8LyWpHwBkdKAMSKGUgErwDTbiFpDIBWw3SmltpFAGSsLRr91qctvIyFttaBkVnOOtEn3TQBlMrbj8vaoArSOoEbY5zWvHhV+aq80iq2R0oAyWhaK5VtrbelX2xtO30qVvmXcOlRrIrcBuaAM5lbdz0qC4U9jt5rWkVahkVcUAYjEiRkLZJqJVaHhW4zzWxJHGrbhtyeKhlgjbqq5oGZtw7NgDpnmq7TMuQO1aTWq8/LUDW6t8oVcjmgZWjHmR/N61BOfLcoV4xmr2xgD8tU7yNmI5xQMqrOvNNZ14O6mSWsmTiomhZcZVqAHyN81QNt3mmqrecfmxTLjduFAEEkKtkjrVKW1YHIarjttzVdn+Y81QFKSMqTnrRVmRc80UAen/AGdlkAC1Ktq+5s1b+X71NMys1SYnP3Hg201LxJputzXFylzp6SxxRq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Свойство вызывать аллергическую реакцию присутствует у всех пенициллинов. У человека с аллергией на одно производное пенициллина может быть аллергия и на другие β-лактамные антибиотики. Это называется перекрестной аллергией. Люди, которые получали лечение пенициллином, более склонны к этой аллергии. Дети менее склонны к развитию аллергии, чем взрослые. Склонные к аллергии люди более склонны к развитию аллергии на пенициллин. Это аллергия I типа, обусловленная образованием антипенициллинового иммуноглобулина-антитела против конъюгационных антигенов, образующихся при соединении аминогрупп белков крови с пенициллином. Проявляется в виде отека, зуда и ангионевротического отека. Обычно проявляется через 2-30 минут после приема препарата. Глубина реакции доходит до анафилактического шока. Течение реакции I типа – тяжелое клиническое состояние. Аллергии, наблюдаемые в период от 1 до 72 часов после приема пенициллина, были очень легкими, после этих реакций не наблюдалось анафилактического шока.

Иногда быстрая реакция типа I приводит к анафилактическому шоку. Тошнота-рвота, боли в животе, отек слизистой оболочки рта и глотки, ларингит – это лишь первые симптомы анафилактического шока. Если не принять меры против этих симптомов, падает артериальное давление, сужаются бронхи и возникают обмороки. Эти симптомы приводят к смерти.

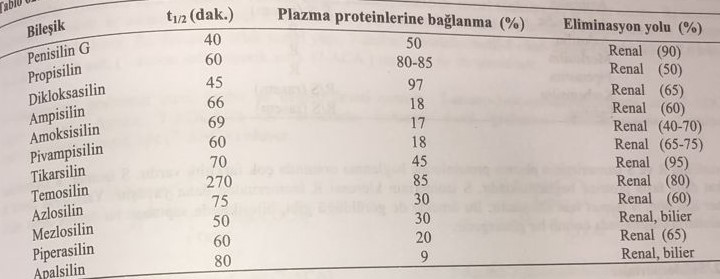
Аллергические реакции типа II и типа III представляют собой аллергии, проявляющиеся через 72 часа после приема препарата и основанные на взаимодействии антител IgG и IgM с пенициллин-аллергенным комплексом. Высыпания развиваются в виде эритемы и лихорадки. Аллергия этого типа может развиваться на все β-лактамные антибиотики. Из-за дерматологических симптомов ограничивается применение пенициллинов и цефалоспоринов в виде кремов, мазей и присыпок.

**Определение чувствительности к применению β-лактамных антибиотиков.**

Пациентам, которые будут клинически лечиться пенициллином и β-лактамными антибиотиками, рекомендуется пройти тест на чувствительность. Некоторые врачи совершают ошибку, проводя тестирование непосредственно с антибиотиками. Этот внутрикожный тест может вызвать серьезную аллергию. Поэтому раствор N-бензилпенцилилполилизина (PPL) используется в качестве тестового образца для определения чувствительности. Индекс надежности этого конъюгата выше, чем у теста чувствительности с другими β-лактамами и пенициллином-G. Тесты с этим аллергеном определяют аллергические реакции I типа. При реакциях типа II и типа III внутривенно или перорально вводят 1000–2000 МЕ (3–5 мг) пенициллина-G. Если пациент находится под наблюдением и никаких симптомов не наблюдается, то аллергической реакции нет.

**Биотрансформация и фармакокинетические свойства пенициллинов.**

Фармакокинетические свойства пенициллинов мало различаются в связи с тем, что их физико-химические свойства близки друг к другу. Период полувыведения из плазмы короткий, пропорциональный скорости деградации β-лактамазами. В таблице представлены фармакокинетические свойства некоторых пенициллинов.



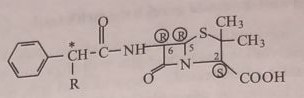
Существуют большие различия в связывании пенициллинов с белками плазмы. Ампициллин конъюгирован на 18%, тогда как изоксазолилпенициллины конъюгированы на 90%. Это очень хороший показатель устойчивости к лактамазам. Важное влияние на выбор врачом клинического применения препарата оказывают антилактамазные и бактериальные инфекции. В дополнение к клубочковой фильтрации важную роль в почечной элиминации пенициллинов играет петлевая секреция. Некоторые противоревматические и урикозурические препараты, обладающие кислотным механизмом транспорта, ингибируют реабсорбцию пенициллинов. Поэтому эти препараты нельзя применять вместе с пенициллинами.Реакции биотрансформации пенициллинов протекают параллельно с реактивностью β-лактамной кольцевой системы. Продуктом, образующимся в результате ферментативных или неферментативных первичных реакций, является пенициллоевая кислота. За этим веществом следует декарбоксилирование с образованием пенилоевой кислоты и реакция раскрытия тиазолидинового кольца. Ацилазы расщепляют 6-ациламиногруппу в некоторых производных пенициллина с образованием 6-аминопенициланской кислоты.

1) Ароматическое гидроксилирование и конъюгация (ускорение почечной элиминации) в производных, содержащих фенильную группу в боковой цепи, таких как бензилпенициллин и пропициллин.

2) Окисление метильной группы С5 изоксазольного кольца, как в изоксазолилпенициллинах. Таким образом, он образует более мощный антибактериальный метаболит (биоактивация).

**Хиральность пенициллинов (стереохимия пенициллинов).**

Исследованы конфигурация положений С-2, С-5 и С-6 в 6-аминопенициловой кислоте и угловая стереохимия бициклической структуры. Во многих полусинтетических производных пенициллина радикальная связь со структурой бензола образует четвертый асимметрический центр. Примером этого являются аминобензилпенициллины.



Было обнаружено, что из производных аминобензипенициллина R-изомер ампициллина более активен, чем S-изомер. Р-лактамное кольцо в молекуле представляет собой фармакофорную группу, обеспечивающую активность. Чем более стерически защищено β-лактамное кольцо, тем выше его антибактериальная активность. Установлено, что диастереомеры с четвертым хиральным центром в аминоацильной боковой цепи проявляют разные кинетические свойства. R- и S-изомеры пропициллина сильно различаются по связыванию с белками, а также по клиренсу и периоду полувыведения. Примеры четвертых асимметричных центродержателей приведены в таблице.

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Связывающие с белками плазмы свойства R- и S-изомеров темоциллина различны. Изомер S объединяет вдвое больше, чем изомер R. Клиренс изомера S медленнее, чем изомера R. Период полувыведения составляет 4 часа для R-изомера и 6 часов для S-изомера. Как видно из этих примеров, соединения обладают эффектом депо.