Chimica Farmaceutica e Tossicologica I

Corso di Laurea Magistrale a Ciclo Unico in Chimica e Tecnologia Farmaceutiche

SAPIENZA
UNIVERSITÀ DI ROMA

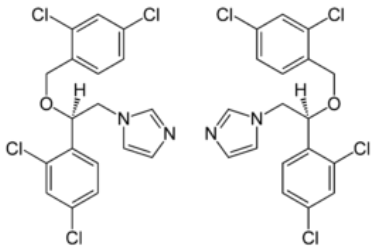
Prof. Rino Ragno
Dipartimento di Chimica e Tecnologie del Farmaco

Chimica Farmaceutica Sistematica

Farmaci Antifungini Azolici Sintesi

Sezione 6.3.2.1.0.0.25

Farmaci Antifungini Azolici

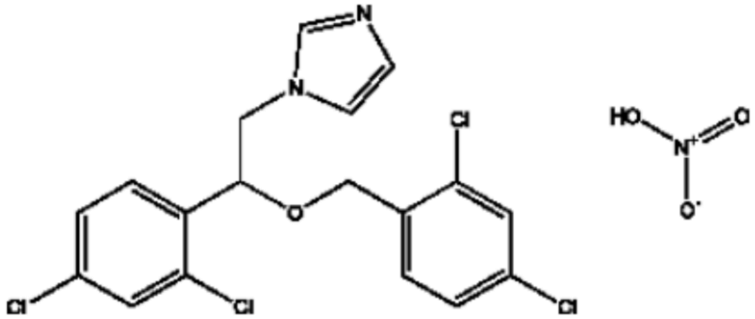


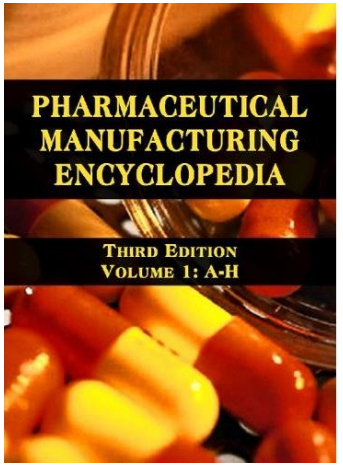
6.3.2.1.0.0.26

MICONAZOLE NITRATE Synthesis

Chemical Name:

1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl] imidazole mononitrate.





Manufacturing Process

Imidazole is reacted with ω-bromo-2,4-dichloroacetophenone and that product reduced with sodium borohydride.

A suspension of 10.3 parts of the α-(2,4-dichlorophenyl)imidazole-1-ethanol thus obtained and 2.1 parts of sodium hydride in 50 parts of dry tetrahydrofuran is stirred and refluxed for 2 hours. After this reaction time, the evolution of hydrogen is ceased.

Then there are added successively 60 parts dimethylformamide and 8 parts of 2,4-dichlorobenzyl chloride and stirring and refluxing are continued for another 2 hours.

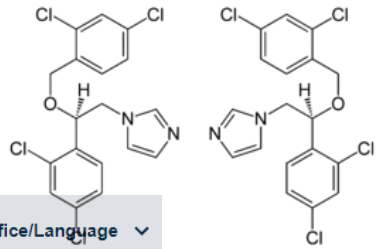
The tetrahydrofuran is removed at atmospheric pressure. The dimethylformamide solution is poured onto water.

The product, 1-[2,4-dichloro-β-(2,4-dichlorobenzyloxy)phenethyl]imidazole, is extracted with benzene.

The extract is washed with water, dried, filtered and evaporated in vacuo. From the residual oily free base, the nitrate salt is prepared in the usual manner in 2-propanol by treatment with concentrated nitric acid, yielding, after recrystallization of the crude solid salt from a mixture of 2-propanol, methanol and diisopropyl ether, 1-[2,4-dichloro-β-dichlorobenzyloxy)phenethyl]imidazole nitrate; melting point 170.5°C.

Farmaci Antifungini Azolici

6.3.2.1.0.0.27



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pn=CN101486680A

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CN101486680B Method for industrial production of miconazole nitrate

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Bibliographic data

Applicants	TAIZHOU COLLEGE +
Inventors	BIN HE; FUYOU PAN; QIUMEI YAN +
Classifications	
IPC	***C07D233/64; A61P31/10;***
Priorities	CN200910096171A·2009-02-18
Application	CN200910096171A·2009-02-18
Publication	CN101486680B·2011-08-31
Published as	**CN101486680A;** CN101486680B

No drawings found. Please consult other publications of this patent family in "Available in", if displayed above.

EN ZH

Method for industrial production of miconazole nitrate

Abstract

The invention provides an industrialized production method of miconazole nitrate, pertaining to the technical field of medicine synthesis. The method solves such problems as complex technology, comparatively low yield and purity, and the like in the existing industrialized production method of the miconazole nitrate. The industrialized production method of the miconazole nitrate includes the following steps: a. N-alkylation reaction; b. reducing reaction; c. O-alkylation reaction. The industrialized production method has the advantages of simple technology, no requirement for extracting any intermediate product, high yield and purity, etc.

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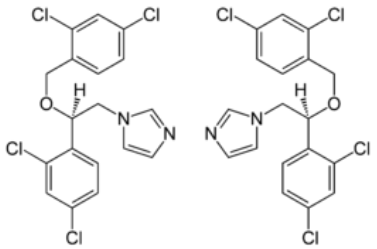


6.3.2.1.0.0.28

Manufacturing Process

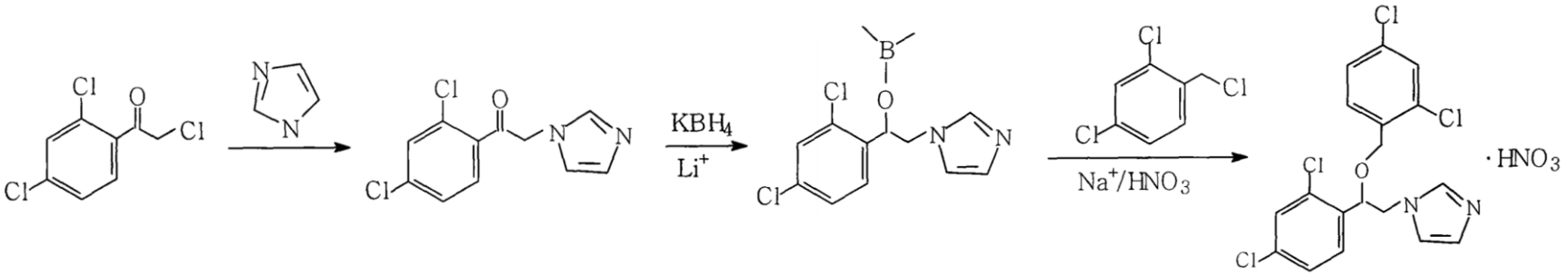
Imidazole is reacted with ω-**bromo**-2,4-dichloroacetophenone and that product reduced with **sodium** borohydride.

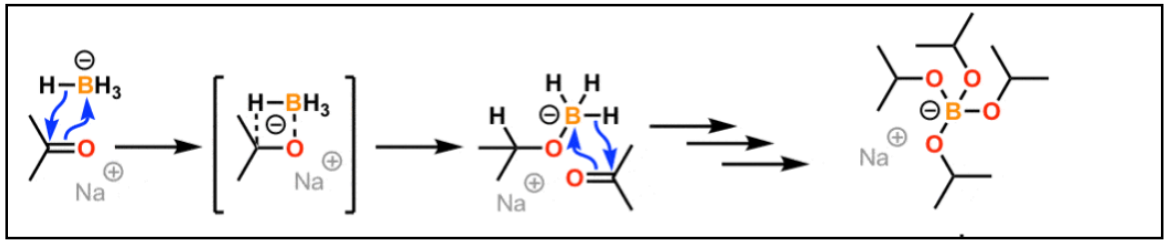
A suspension of 10.3 parts of the α-(2,4-dichlorophenyl)imidazole-1-ethanol thus obtained and 2.1 parts of sodium hydride in 50 parts of dry tetrahydrofuran is stirred and refluxed for **2 hours**. After this reaction time, the evolution of hydrogen is ceased.

Then there are added successively 60 parts dimethylformamide and 8 parts of **2,4-dichlorobenzyl chloride** and stirring and refluxing are continued for another 2 hours.

The tetrahydrofuran is removed at atmospheric pressure. The dimethylformamide solution is poured onto water.

The product, 1-[2,4-dichloro-β-(2,4-dichlorobenzyloxy)phenethyl]imidazole, is extracted with benzene.





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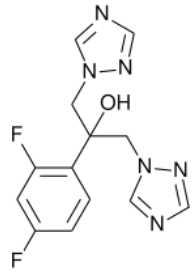


6.3.2.1.0.0.29

FLUCONAZOLE Synthesis

Chemical Name:

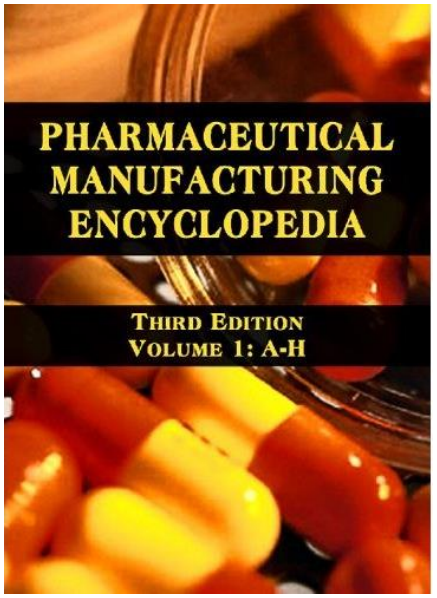
1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-

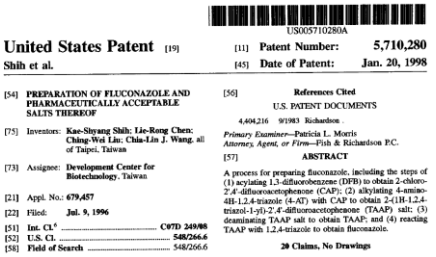
Manufacturing Process

141.1 g of aluminum trichloride was first added to 86 ml of **DFB** and 77 ml of **chloroacetyl chloride** was then added to the mixture, which was allowed to react at 60°C for 3 hours. After the reaction mixture had cooled down, 500 g of cold water was added. The mixture was stirred for about 20 min and then filtered to afford about 158.5 g of **2-chloro-2',4'-difluoroacetophenone** in solid form (91% yield).

A solution of 158.5 g of **2-chloro-2',4'-difluoroacetophenone** and 88.8 g of **4-amino-4H-1,2,4-triazole** in 1,600 ml of **cyanomethane** was heated at **reflux** for 16 hours, cooled down, and filtered. The solid thus obtained was then washed with 500 ml of ethyl ether once to afford **2-(1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone salt**. The crude product obtained was dissolved in 1,320 ml of 1.5 N hydrochloric acid. To the solution thus obtained, an aqueous solution (330 ml) of sodium nitrite (58.2 g) was dropwise added and the mixture was allowed to react for 30 min. Aqueous ammonium was then used to adjust the reaction mixture to a neutral pH. The solid was precipitated and filtered to afford 159 g of **2-(1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone** (yield about 80%), which had a water content of about 10%.

4 g of **4-amino-4H-1,2,4-triazole**, 57.87 g of potassium hydroxide, 118 g of trimethyl sulfoxonium iodide, and 100 g of **2-(1H-1,2,4-triazol-l-yl)-2',4'-difluoroacetophenone** were dissolved in 1,600 ml of water. The solution was heated at 70°C to react for 16 hours. Upon the completion of the reaction, the solution was adjusted with 4 N hydrochloric acid to a neutral pH and then extracted with acetyl acetate. The organic layer was collected, dried with 30 g of anhydrous calcium dichloride, decolorized with 15 g of active charcoal, and finally filtered off solid residues. The filtrate was concentrated to afford 99.3 g of the crude product (yield 72%). The crude product was further recrystallized from 500 ml of a solvent mixture of acetyl acetate and n-hexane (2:1) to afford 66.3 g of the Fluconazole in the form of white solid (yield 48%).





US005710280A

United States Patent [19]
Shih et al.

[11] Patent Number: 5,710,280
[45] Date of Patent: Jan. 20, 1998

[54] PREPARATION OF FLUCONAZOLE AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

[75] Inventors: Kao-Shyang Shih; Lie-Rong Chen; Ching-Wei Liu; Chia-Lin J. Wang, all of Taipei, Taiwan

[73] Assignee: Development Center for Biotechnology, Taiwan

[21] Appl. No.: 679,457

[22] Filed: Jul. 9, 1996

[51] Int. Cl.[6] C07D 249/08
[52] U.S. Cl. 548/266.6
[58] Field of Search 548/266.6

[56] References Cited
U.S. PATENT DOCUMENTS
4,404,216 9/1983 Richardson .
Primary Examiner—Patricia L. Morris
Attorney, Agent, or Firm—Fish & Richardson P.C.

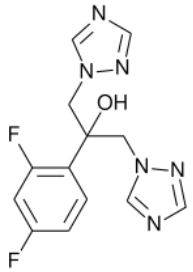
[57] ABSTRACT

A process for preparing fluconazole, including the steps of (1) acylating 1,3-difluorobenzene (DFB) to obtain 2-chloro-2',4'-difluoroacetophenone (CAP); (2) alkylating 4-amino-4H-1,2,4-triazole (4-AT) with CAP to obtain 2-(1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone (TAAP) salt; (3) deaminating TAAP salt to obtain TAAP; and (4) reacting TAAP with 1,2,4-triazole to obtain fluconazole.

20 Claims, No Drawings

Farmaci Antifungini Azolici

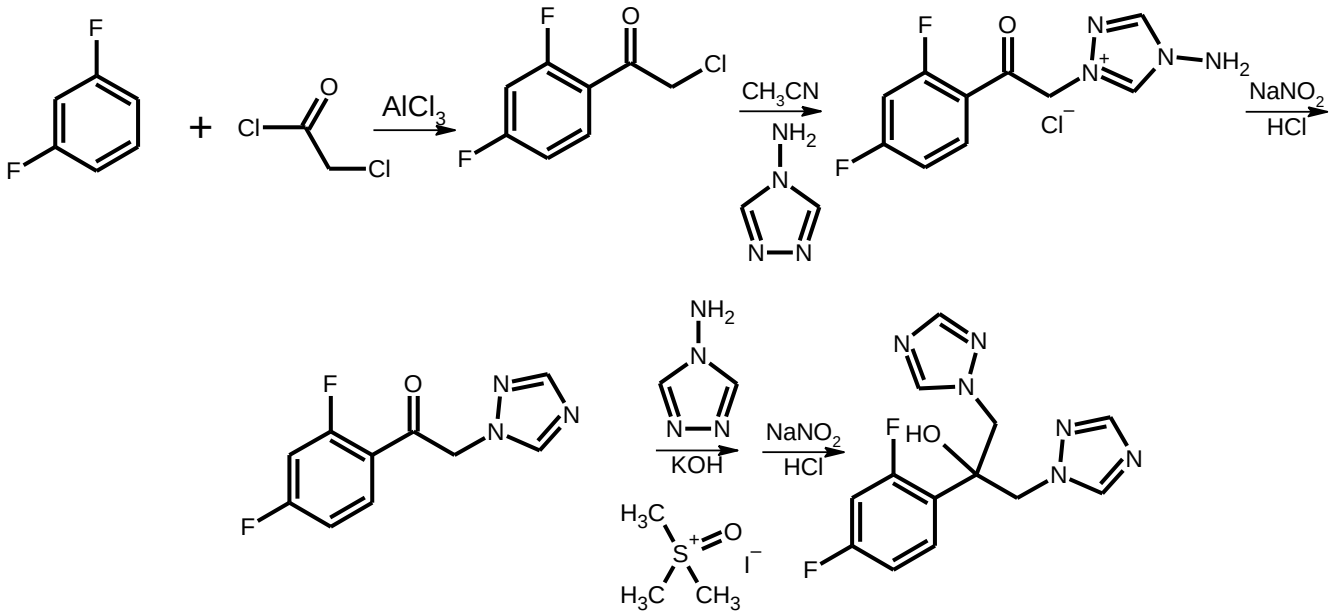
6.3.2.1.0.0.29b

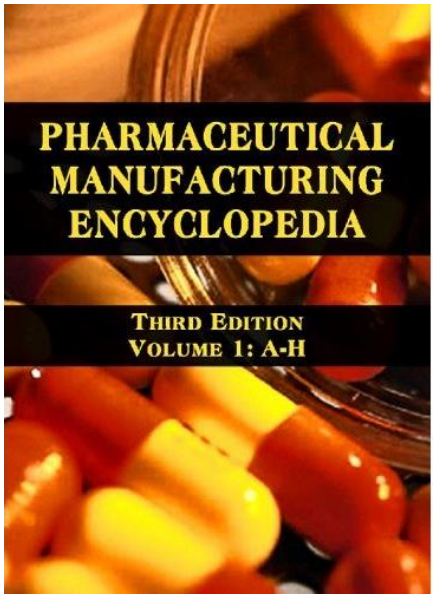


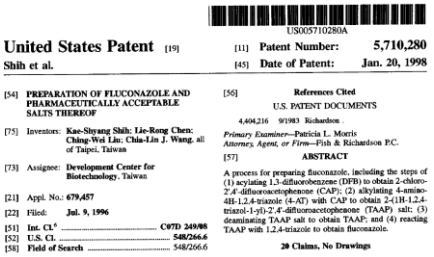
FLUCONAZOLE Synthesis

Chemical Name:

1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-







US005710280A

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[73] Assignee: Development Center for Biotechnology, Taiwan

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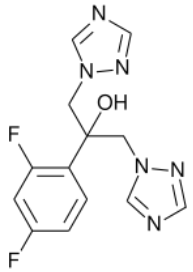
20 Claims, No Drawings

Farmaci Antifungini Azolici



6.3.2.1.0.0.29c

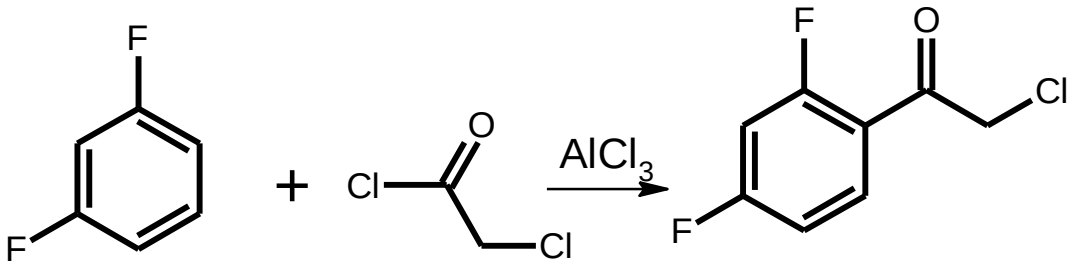
FLUCONAZOLE Synthesis

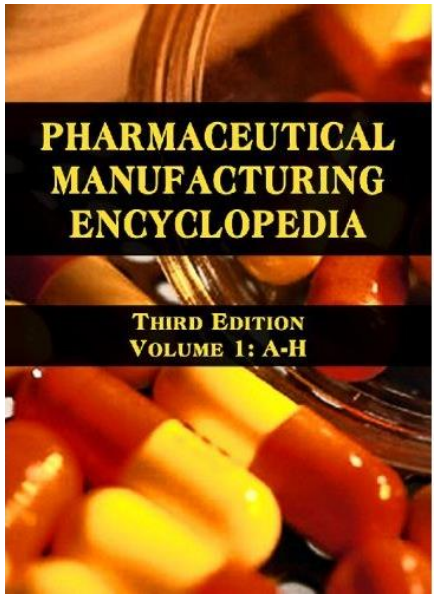
Chemical Name:

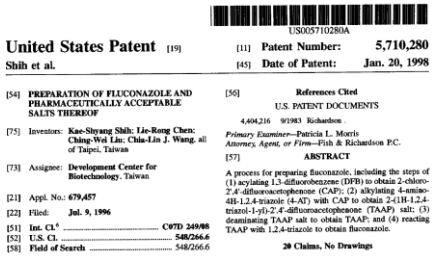
1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-

141.1 g of aluminum trichloride was first added to 86 ml of **DFB**

- 77 ml of **chloroacetyl chloride** was then added to the mixture, which was allowed to react at 60°C for 3 hours
- After the reaction mixture had cooled down,
- 500 g of cold water was added and stirred for about 20 min
- Separation by filtering afforded about 158.5 g of **2-chloro-2',4'-difluoroacetophenone** in solid form (91% yield).







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20 Claims, No Drawings

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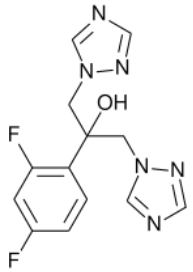


6.3.2.1.0.0.29d

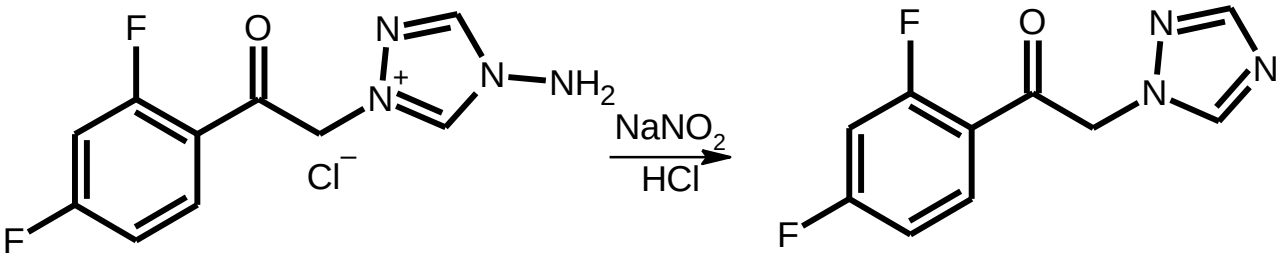
FLUCONAZOLE Synthesis

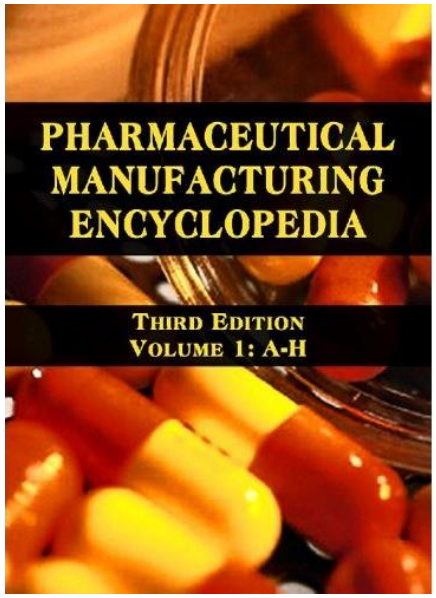
Chemical Name:

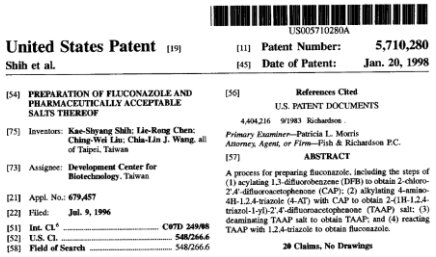
1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-

A solution of 158.5 g of **2-chloro-2',4'-difluoroacetophenone** and 88.8 g of **4-amino-4H-1,2,4-triazole** in 1,600 ml of **cyanomethane** was heated at **reflux** for 16 hours,

- The reaction was then cooled down
- Solid and liquid were separated by filtration
- The solid was then washed with 500 ml of ethyl ether once to afford **2-(4-amino-1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone salt**.







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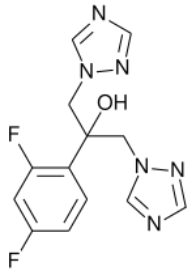


6.3.2.1.0.0.29e

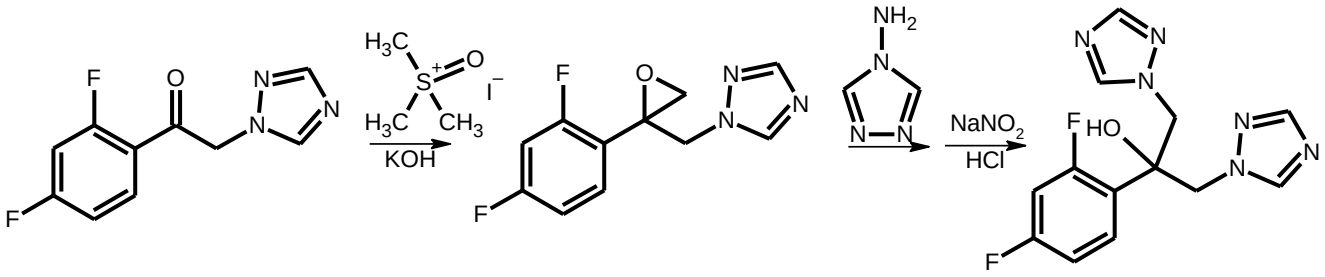
FLUCONAZOLE Synthesis

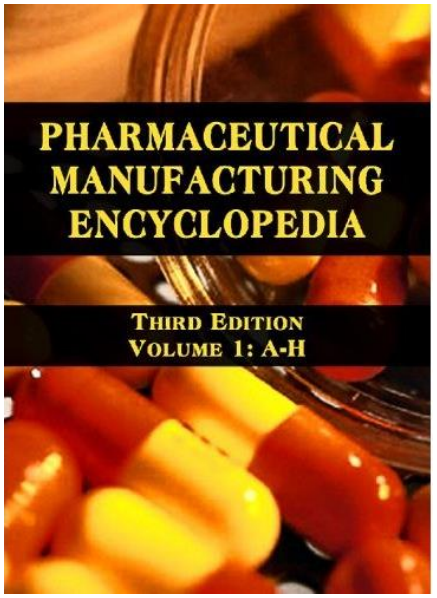
Chemical Name:

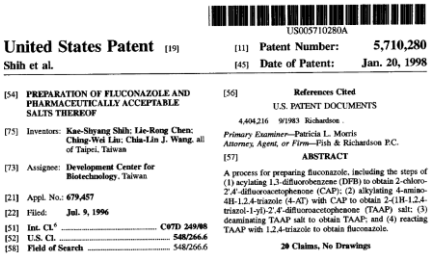
1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-

4 g of **4-amino-4H-1,2,4-triazole**, 57.87 g of potassium hydroxide, 118 g of **trimethyl sulfoxonium iodide**, and 100 g of **2-(1H-1,2,4-triazol-l-yl)-2',4'-difluoroacetophenone** were dissolved in 1,600 ml of water. The solution was heated at 70°C to react for 16 hours.

- Upon the completion of the reaction, the solution was adjusted with 4 N hydrochloric acid to a neutral pH and then extracted with acetyl acetate.
- The organic layer was collected, dried with 30 g of anhydrous calcium dichloride, decolorized with 15 g of active charcoal, and finally filtered off solid residues.
- The filtrate was concentrated to afford 99.3 g of the crude product (yield 72%).
- The crude product was further recrystallized from 500 ml of a solvent mixture of acetyl acetate and n-hexane (2:1) to afford 66.3 g of the Fluconazole in the form of white solid (yield 48%).







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[52] U.S. Cl. 548/266.6
[58] Field of Search 548/266.6

[56] References Cited
U.S. PATENT DOCUMENTS
4,404,216 9/1983 Richardson .

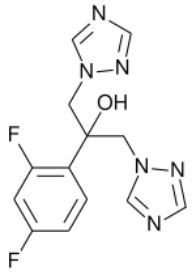
Primary Examiner—Patricia L. Morris
Attorney, Agent, or Firm—Fish & Richardson P.C.

[57] ABSTRACT

A process for preparing fluconazole, including the steps of (1) acylating 1,3-difluorobenzene (DFB) to obtain 2-chloro-2',4'-difluoroacetophenone (CAP); (2) alkylating 4-amino-4H-1,2,4-triazole (4-AT) with CAP to obtain 2-(1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone (TAAP) salt; (3) deaminating TAAP salt to obtain TAAP; and (4) reacting TAAP with 1,2,4-triazole to obtain fluconazole.

20 Claims, No Drawings

Farmaci Antifungini Azolici



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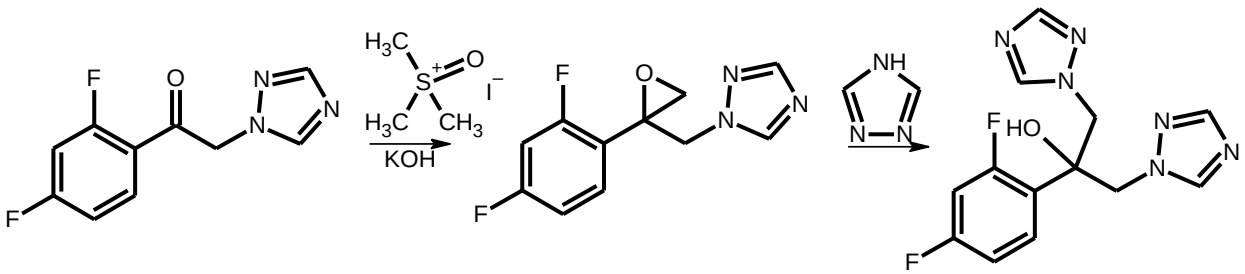
FLUCONAZOLE Synthesis

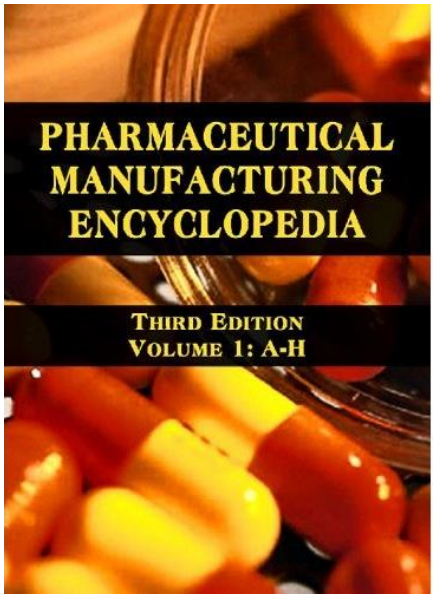
Chemical Name:

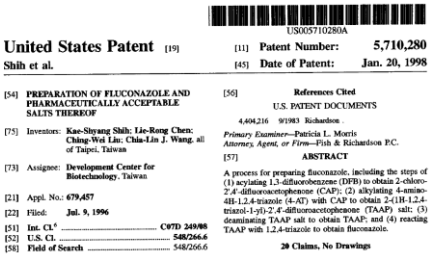
1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-

4 g of **1,2,4-triazole**, 57.87 g of potassium hydroxide, 118 g of **trimethyl sulfoxonium iodide**, and 100 g of **2-(1H-1,2,4-triazol-l-yl)-2',4'-difluoroacetophenone** were dissolved in 1,600 ml of water. The solution was heated at 70°C to react for 16 hours.

- Upon the completion of the reaction, the solution was adjusted with 4 N hydrochloric acid to a neutral pH and then extracted with acetyl acetate.
- The organic layer was collected, dried with 30 g of anhydrous calcium dichloride, decolorized with 15 g of active charcoal, and finally filtered off solid residues.
- The filtrate was concentrated to afford 99.3 g of the crude product (yield 72%).
- The crude product was further recrystallized from 500 ml of a solvent mixture of acetyl acetate and n-hexane (2:1) to afford 66.3 g of the Fluconazole in the form of white solid (yield 48%).







US005710280A

United States Patent [19]
Shih et al.

[11] Patent Number: 5,710,280
[45] Date of Patent: Jan. 20, 1998

[54] PREPARATION OF FLUCONAZOLE AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

[75] Inventors: Kao-Shyang Shih; Lie-Rong Chen; Ching-Wei Liu; Chia-Lin J. Wang, all of Taipei, Taiwan

[73] Assignee: Development Center for Biotechnology, Taiwan

[21] Appl. No.: 679,457

[22] Filed: Jul. 9, 1996

[51] Int. Cl.[6] C07D 249/08
[52] U.S. Cl. 548/266.6
[58] Field of Search 548/266.6

[56] References Cited
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4,404,216 9/1983 Richardson .

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20 Claims, No Drawings

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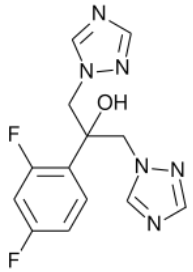

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Dimethylsulfonium Methylide, a Reagent for Selective Oxirane Synthesis from Aldehydes and Ketones

E. J. Corey and Michael. Chaykovsky

Cite this: *J. Am. Chem. Soc.* 1962, 84, 19, 3782–3783

Publication Date: October 1, 1962

https://doi.org/10.1021/ja00878a046

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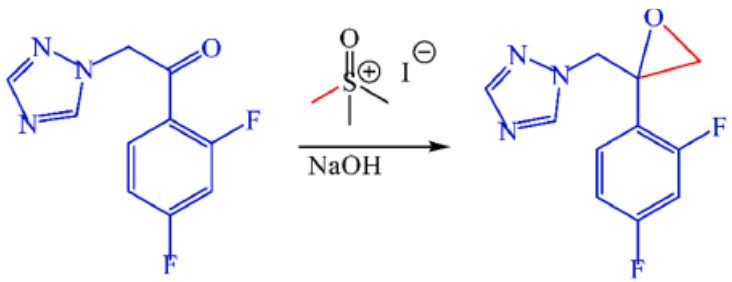
Journal of the American Chemical Society

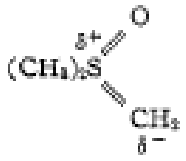
For the **fluconazole** synthesis, an epoxide ring is the key intermediate achieved by well-known **Corey-Chaykovsky** epoxidation with **trimethyl sulfoxonium iodide (TMSI)** reagent employed as the **ring closer**



DIMETHYLSULFONIUM METHYLIDE, A REAGENT FOR SELECTIVE OXIRANE SYNTHESIS FROM ALDEHYDES AND KETONES

Sir:

As a result of the general synthetic utility of dimethyloxosulfonium methylide (alternatively dimethylsulfoxonium methylide) (I) as a reagent for the addition of methylene to double bonds which are receptive to nucleophiles,[1] a study of the related dimethylsulfonium methylide (II) seemed appropriate despite indications that sulfonium ylides derived from non-stabilized carbanions are subject to rapid spontaneous decomposition[2] while those in a highly stabilized condition, *e.g.*, 9-fluorenyl derivatives,[3] are of very limited synthetic import. This report summarizes the first returns of such an investigation including a practical method for the generation of the ylide II in a reasonably stable condition and the application of this substance as a reactive but *exceedingly selective* methylene transfer agent.



I

II

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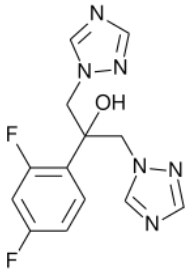

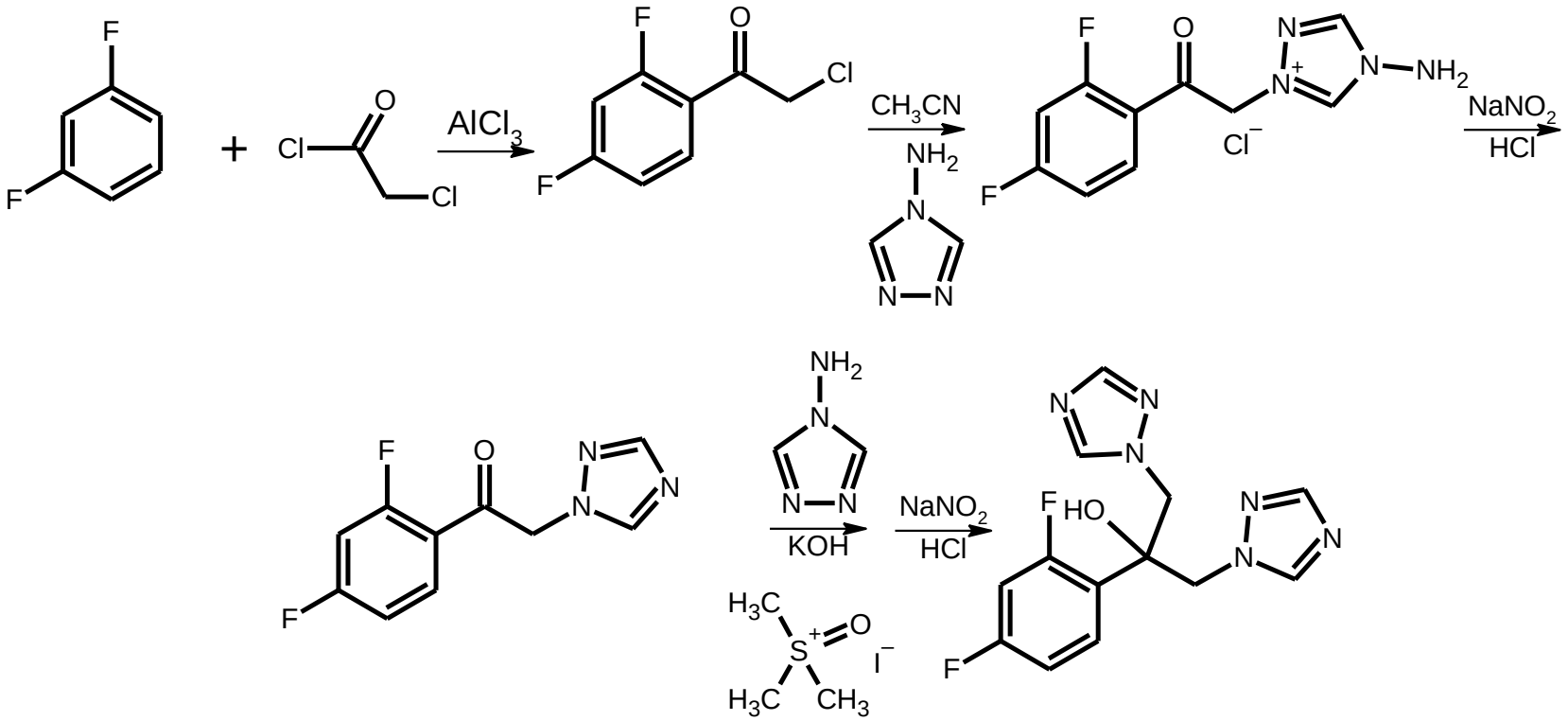

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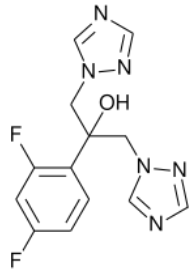

(1) is Friedel-Crafts acylation, which can be conducted using DFB and chloroacetyl chloride as the starting materials in the presence of a catalyst such as aluminum trichloride. An organic solvent such as dichloromethane is added to the reaction mixture to slowly reduce the heat emitted during the reaction. CAP can be produced at a yield of about 97% or higher and the crude product can be used in the subsequent nitrogen alkylation reaction without further purification.

(2) This step involves reacting 4-AminoTriazole (4-AT) with CAP in the presence of a suitable solvent such as acetonitrile. The yield of TAAP (triazoloaminoacetophenone) salt, obtained after filtration, can be as high as about 95%. 4-AT is used as the starting material of this step to avoid any isomerization during the reaction.

(3) The TAAP salt obtained from step (2) is subjected to deamination with an acid and sodium nitrite. The yield of free TAP (triazoloacetophenone) thus obtained after precipitation and filtration can be about 85% or higher. The acid used in the step can be a diluted hydrochloric acid solution, for example, 1.5N hydrochloric acid.

(4) Fluconazole is obtained in a single-step epoxidation/ring-opening reaction. The yield can reach about 50% or greater. More specifically, the reaction of TAP, and trimethylsulfoxonium iodide (Me_3SOI) can be conducted in a basic aqueous solution at a temperature of about 40°-100° C. (e.g., about 60°-80° C. or about 70° C.) for about 3–20 hours (e.g. 12-18 hours or about 16 hours). Both aqueous solvents and other aprotonic solvents such as N,N-dimethylformamide, dimethyl sulfoxide, and hexamethylphosphoramide can be used. Examples of a suitable base include, but are not limited to, sodium hydroxide, potassium hydroxide, sodium carbonate, and potassium carbonate.

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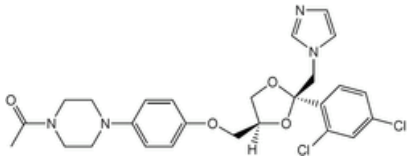
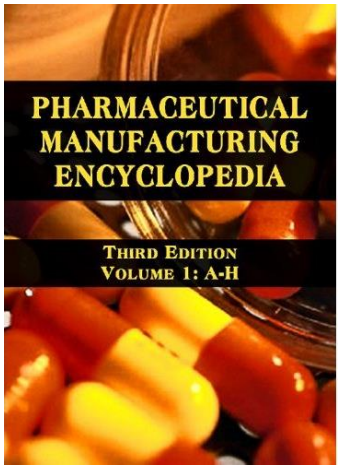


6.3.2.1.0.0.33

KETOCONAZOLE Synthesis

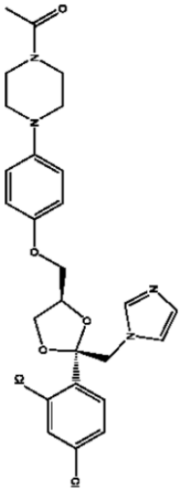
Chemical Name: 1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine



Manufacturing Process

(A) A mixture of 33.8 parts of **4-(4-piperazinyl)phenol dihydrobromide**, 11.2 parts of **acetic acid anhydride**, 42 parts of potassium carbonate and 300 parts of **1,4-dioxane** is stirred and refluxed for 3 days. The reaction mixture is filtered and the filtrate is evaporated. The solid residue is stirred in water and **sodium hydrogen carbonate** is added. The whole is stirred for 30 minutes. The precipitated product is filtered off and dissolved in a diluted hydrochloric acid solution. The solution is extracted with trichloromethane. The acid aqueous phase is separated and neutralized with ammonium hydroxide. The product is filtered off and crystallized from ethanol, yielding 5.7 parts of 1-acetyl-4-(4-hydroxyphenyl)piperazine; MP 181-183°C.

(B) A mixture of 2.4 parts of **1-acetyl-4-(4-hydroxyphenyl)piperazine**, 0.4 part of **sodium hydride** dispersion 78%; 75 parts of **dimethylsulfoxide** and 22.5 parts of **benzene** is stirred for one hour at 40°C. Then there are added 4.2 parts of **cis-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl methane sulfonate** and stirring is continued overnight at 100°C. The reaction mixture is cooled and diluted with water. The product is extracted with **1,1'-oxybisethane**. The extract is dried, filtered and evaporated. The residue is crystallized from 4-methyl-2-pentanone. The product is filtered off and dried, yielding 3.2 parts (59%) of cis-1-acetyl-4-[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxyl phenyl]piperazine; MP 146°C.



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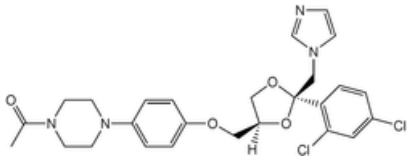
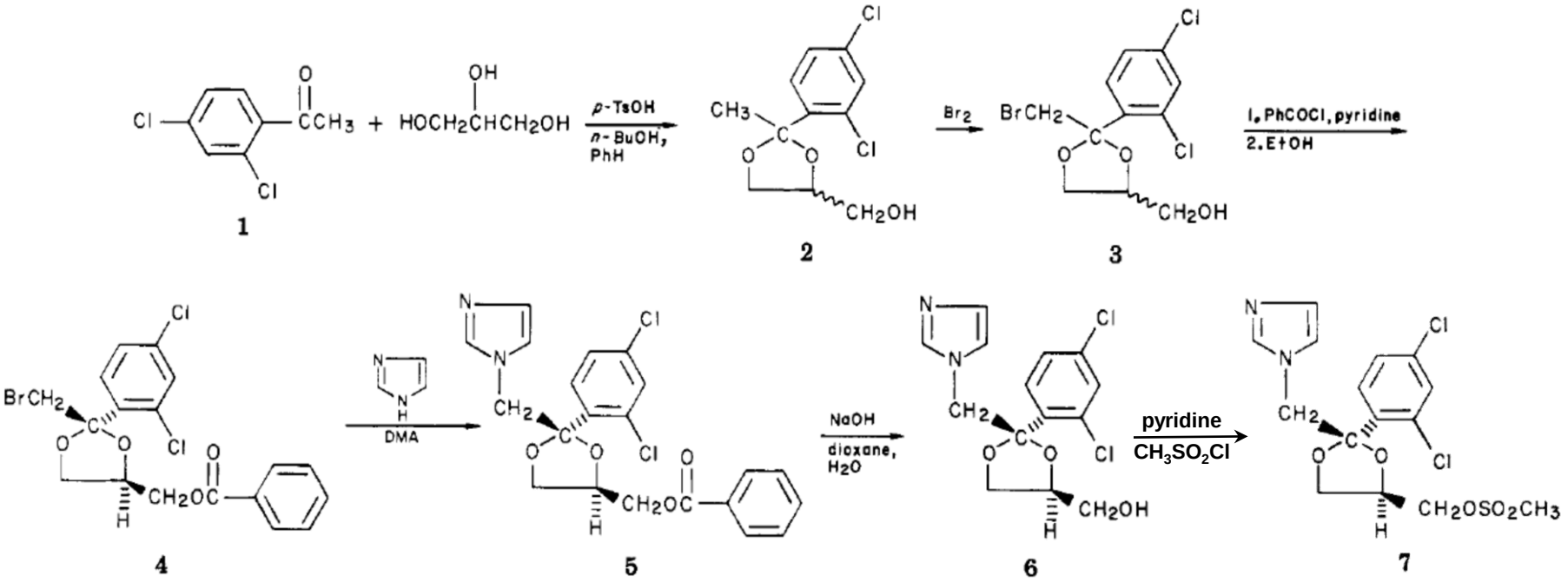


Antimycotic Imidazoles. Part 4. Synthesis and Antifungal Activity of Ketoconazole, a New Potent Orally Active Broad-Spectrum Antifungal Agent

J. Heeres,* L. J. J. Backx, J. H. Mostmans, and J. Van Cutsem

Janssen Pharmaceutica, Research Laboratoria, B-2340 Beerse, Belgium. *Received February 1, 1979*



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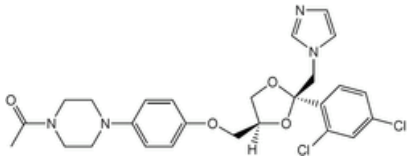
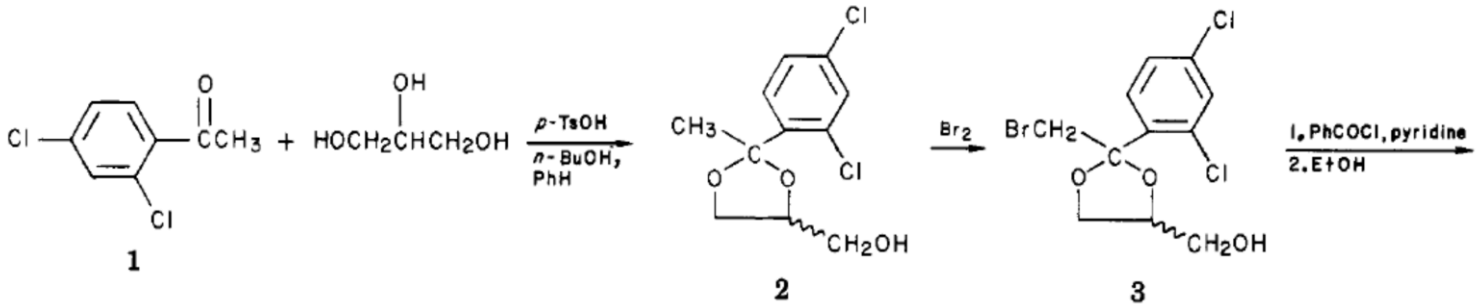


In this regard, the main changes are evident in Janssen's (1981) antifungal **ketoconazole**, the first drug containing a heterocyclic **dioxolane** functional group, replacing the ketone with a new long-tail structure.

The synthesis, starting from **2,4-dichloroacetophenone**. Ketalization with glycerine was performed in a **benzene-1-butanol** medium with azeotropic removal of water in the presence of a catalytic amount of **p-toluenesulfonic** acid. Without isolation, the ketal **2** was **brominated** at 30 °C to **bromoketal 3.**



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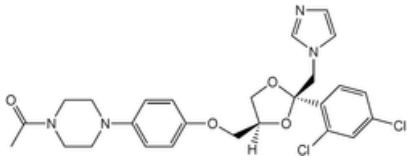
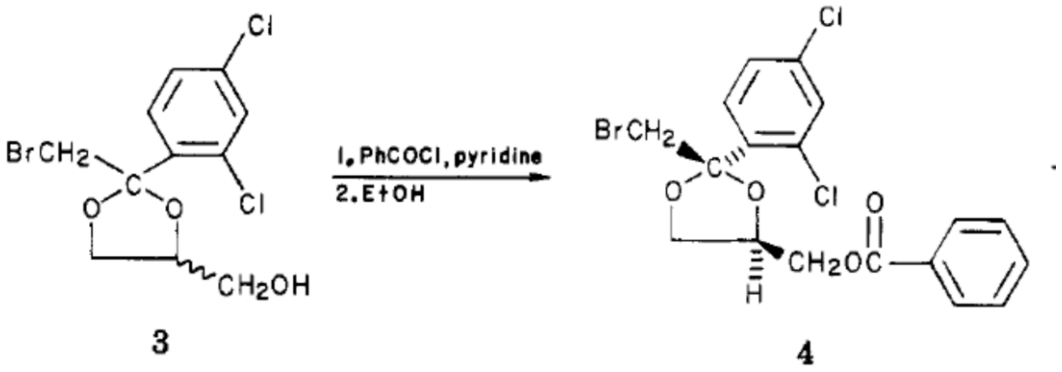


Benzoylation of **3** in **pyridine** afforded the ester as a cis/trans mixture, from which the cis form **4** could be isolated by crystallization from EtOH. The pure trans isomer could be obtained by liquid chromatography of the mother liquor.



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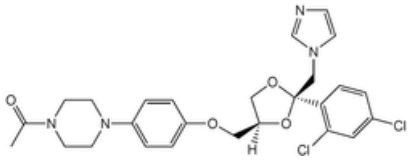
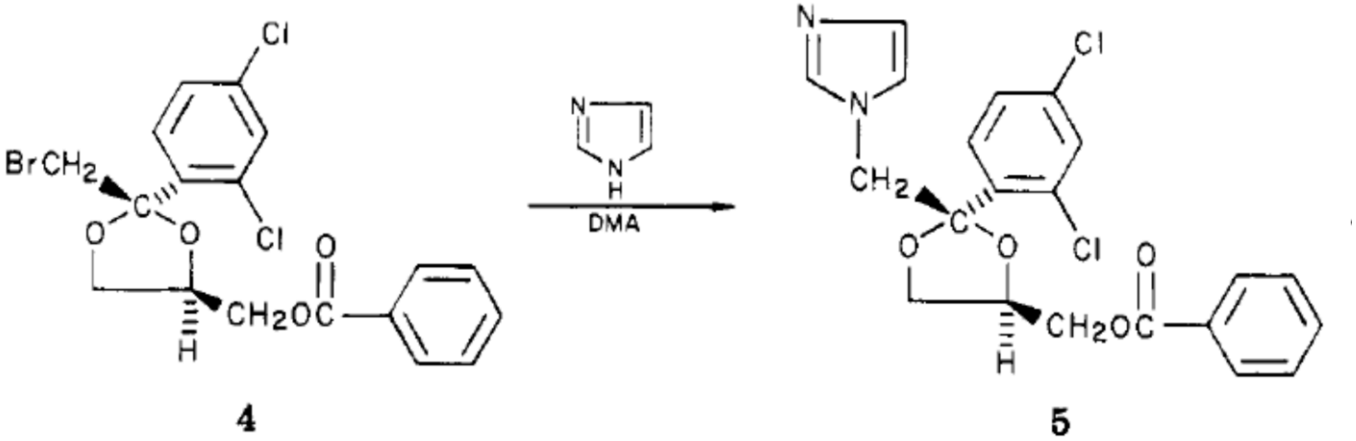


Coupling of bromoketal **4** in dry DMA (**Dimethylacetamide**) with **imidazole** gave the imidazole derivative **5.**



4 **5**

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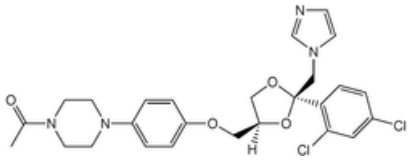
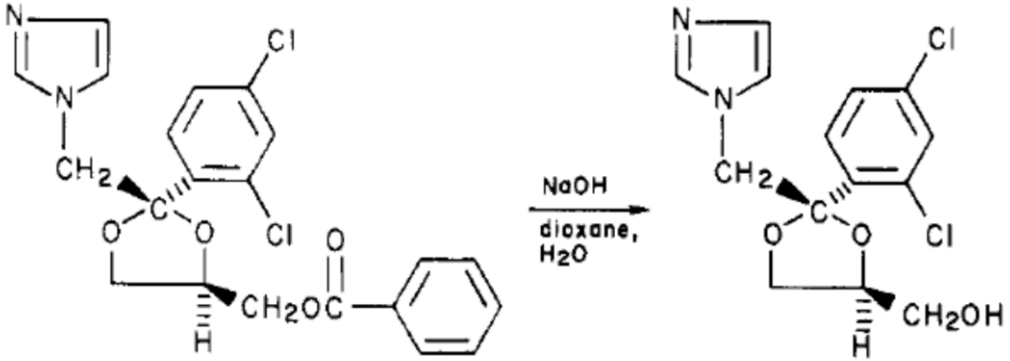


The ester ***5*** was saponified at reflux with NaOH in dioxane-water medium to the alcohol **6.**



5 **6**

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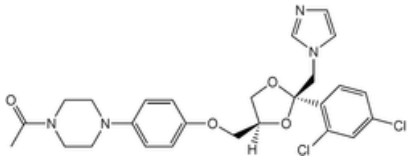
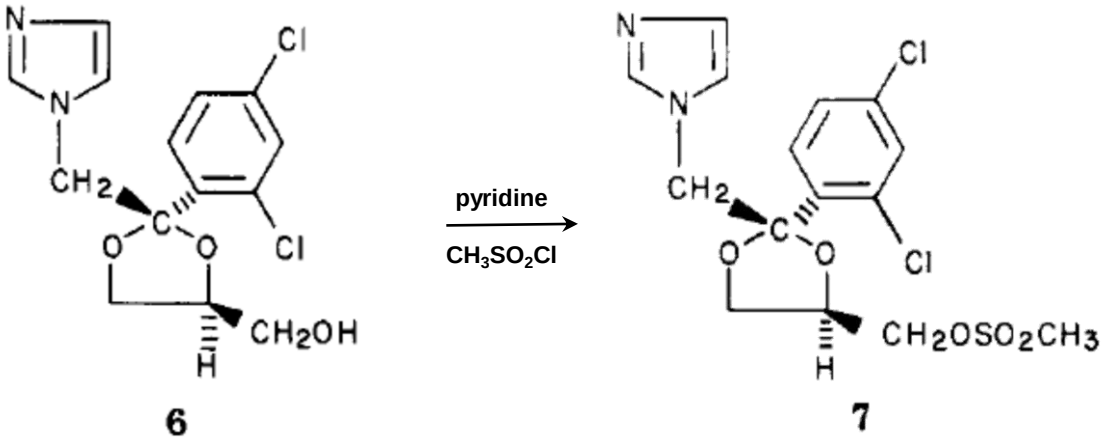


Alcohol **6** was converted to **methanesulfonate 7**



6 **7**

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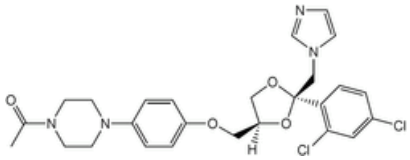

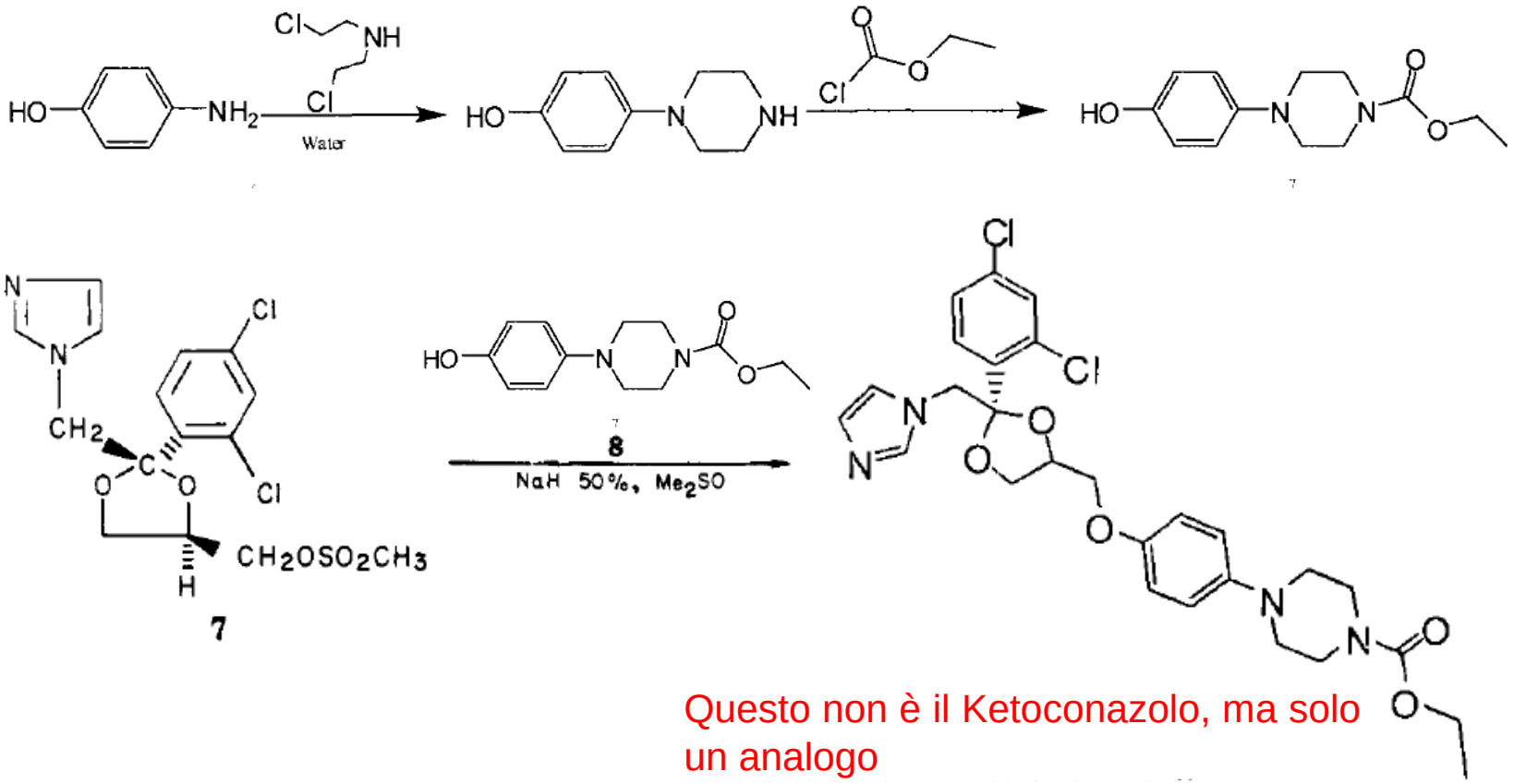

Questo non è il Ketoconazolo, ma solo un analogo

Farmaci Antifungini Azolici

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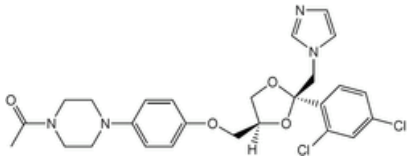

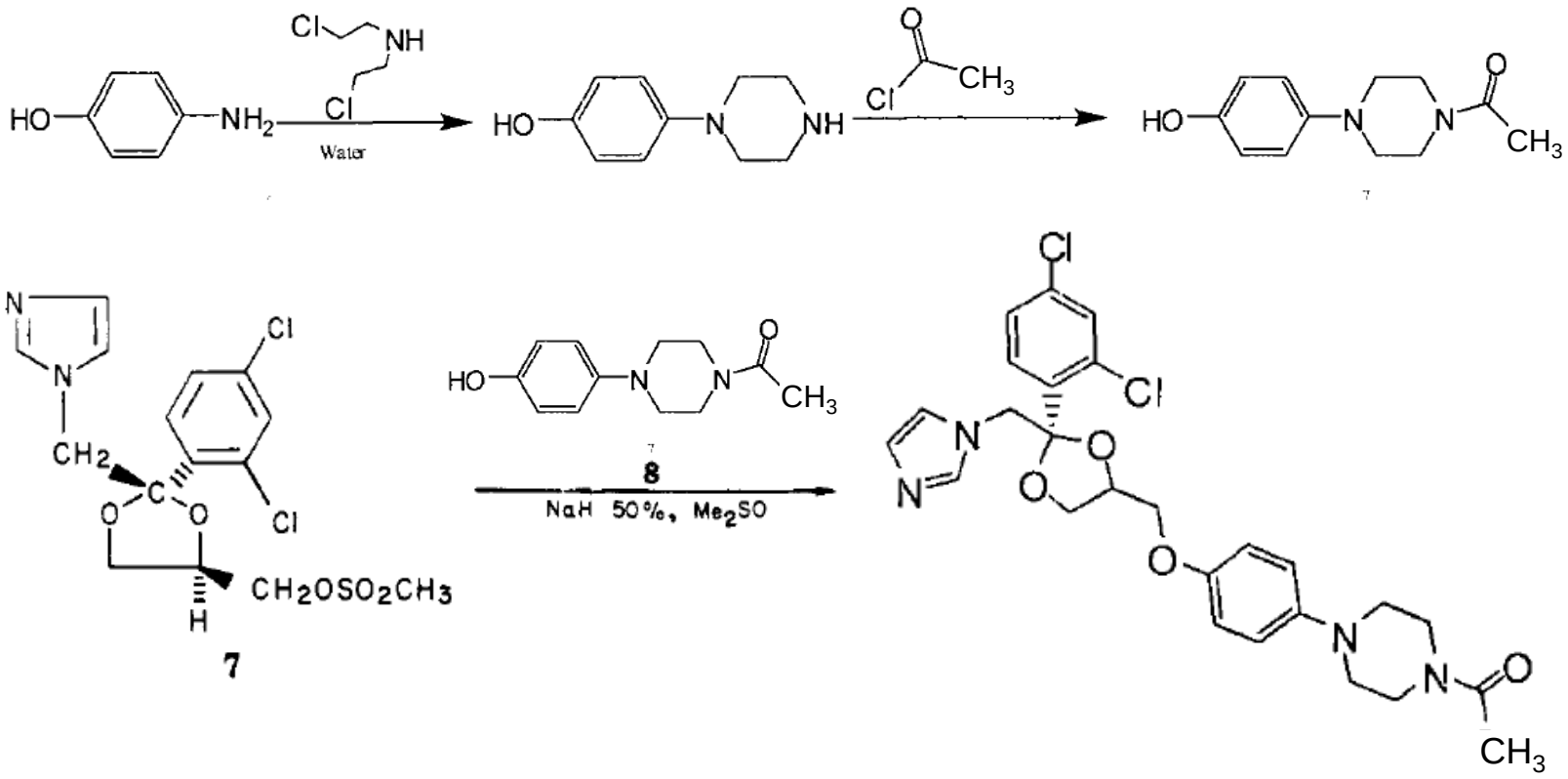

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Journal of Medicinal Chemistry

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Synthetic Approaches to New Drugs Approved during 2018

Andrew C. Flick, Carolyn A. Leverett, Hong X. Ding, Emma McInturff, Sarah J. Fink, Christopher J. Helal, Jacob C. DeForest, Peter D. Morse, Subham Mahapatra, and Christopher J. O'Donnell*

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Journal of Medicinal Chemistry

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Perspective

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Synthetic Approaches to the New Drugs Approved During 2015

Andrew C. Flick,[†] Hong X. Ding,[‡] Carolyn A. Leverett,[†] Robert E. Kyne, Jr.,[§] Kevin K. -C. Liu,[∥] Sarah J. Fink,[⊥] and Christopher J. O'Donnell*[,†]

ACS Publications

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

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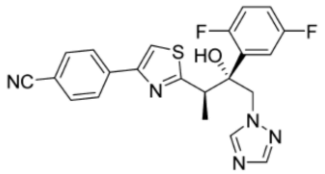
Voriconazole (30)



8 Isavuconazole

Isavuconazonium Sulfate (**Cresemba**). Isavuconazonium sulfate is a **broad spectrum antifungal agent** that was codeveloped by Basilea Pharmaceutica and Astellas Pharma, which obtained its first approval by the United States FDA for the treatment of invasive **aspergillosis** and invasive **mucormycosis**, available as both oral and intravenous formulations.

Isavuconazonium sulfate is a **water-soluble prodrug**, which is rapidly hydrolyzed by esterases (mainly **butylcholinesterase**) in plasma into the active moiety **isavuconazole** (**BAL-4815**) and an inactive cleavage product (BAL-8728).

Isavuconazole inhibits cytochrome P450 (CYP)-dependent enzyme lanosterol 14-α-demethylase (CYP51) and thereby inhibits the synthesis of ergosterol, a key component of the fungal cell membrane.

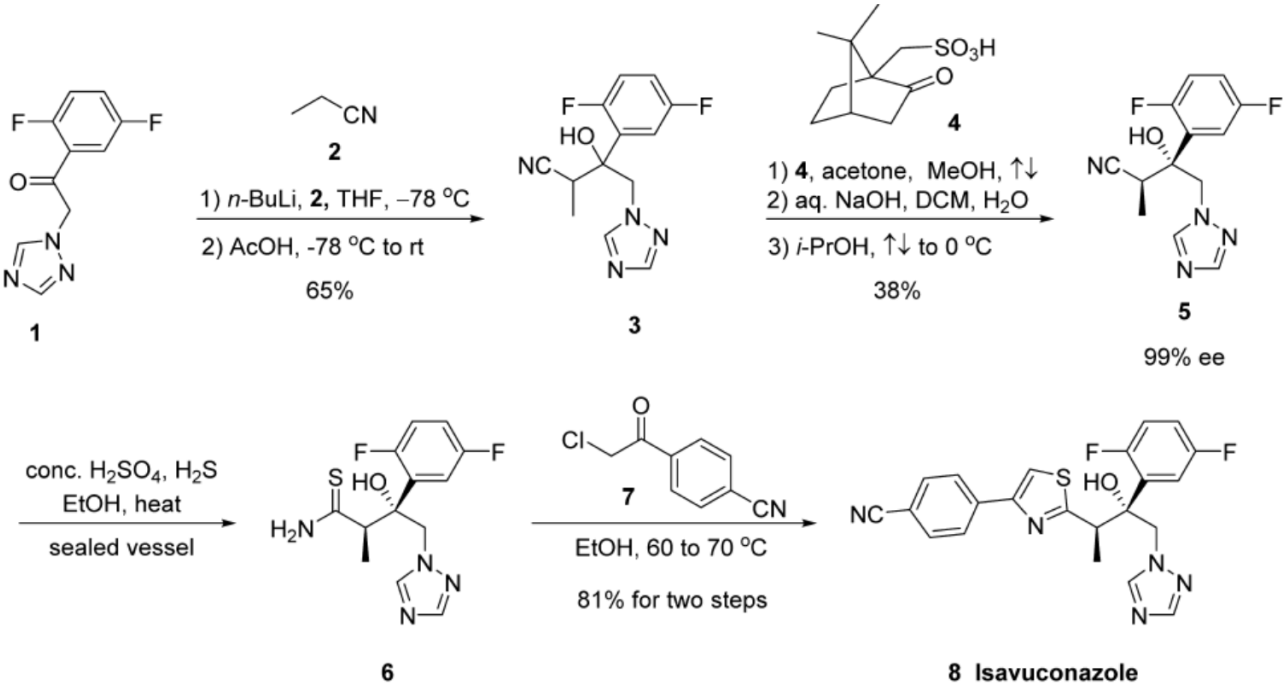
Isavuconazole displayed potent **fungistatic** or **fungicidal** activity in vitro against a **broad range of clinically important yeasts and molds**, namely *Candida* spp., *Cryptococcus* spp., *Trichosporon* spp., *Geotrichum capitatum*, *Pichia* spp., *Rhodotorula* spp., *Saccharomyces cerevisiae*, *Aspergillus* spp., and most species known to cause mucormycosis (*Mucorales* mucorales). This broad range of antifungal activity renders this drug more clinically appealing compared to other azoles with narrower indications. Furthermore, isavuconazole does not require a cyclodextrin vehicle due to its water solubility, and currently does not require therapeutic drug monitoring.

Isavuconazole has displayed improved safety and tolerability compared to voriconazole. As a prodrug, the structure of isavuconazonium sulfate consists of two parts: the active moiety isavuconazole and a water-soluble, prodrug side chain. Several papers have been published on the synthesis of isavuconazonium sulfate, and the approach to enantiomerically pure isavuconazole has been reported through three different synthetic strategies.

Farmaci Antifungini Azolici

6.3.2.1.0.0.42

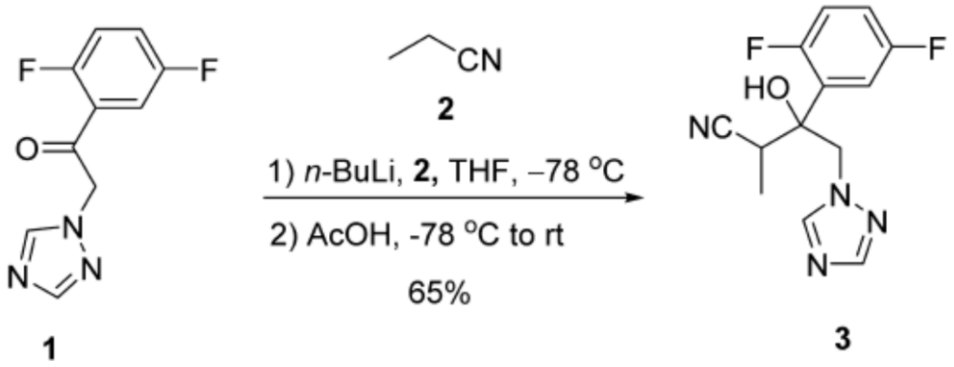
The synthesis of active moiety **isavuconazole** was started with commercial **1-(2,5-di*fl*uorophenyl)-2-(1*H*-l,2,4-triazol-l- yl)ethanone** (1).
Triazole 1 was treated with *n*-BuLi followed by exposure to propionitrile (2) and acidic quench to give racemic alcohol 3 in 65% yield.
Resolution of this racemic alcohol was facilitated through the use of camphor derivative 4 to provide alcohol 5 in 38% yield and **99% ee**.
Nitrile 5 was then treated with concentrated H_2SO_4 and H_2S to furnish thioamide 6, and this was followed by a cyclization reaction involving **4-(2-chloroacetyl)-benzonitrile** (7) which gave rise to **isavuconazole** in **81%** yield across the two-step sequence.



Farmaci Antifungini Azolici

6.3.2.1.0.0.42

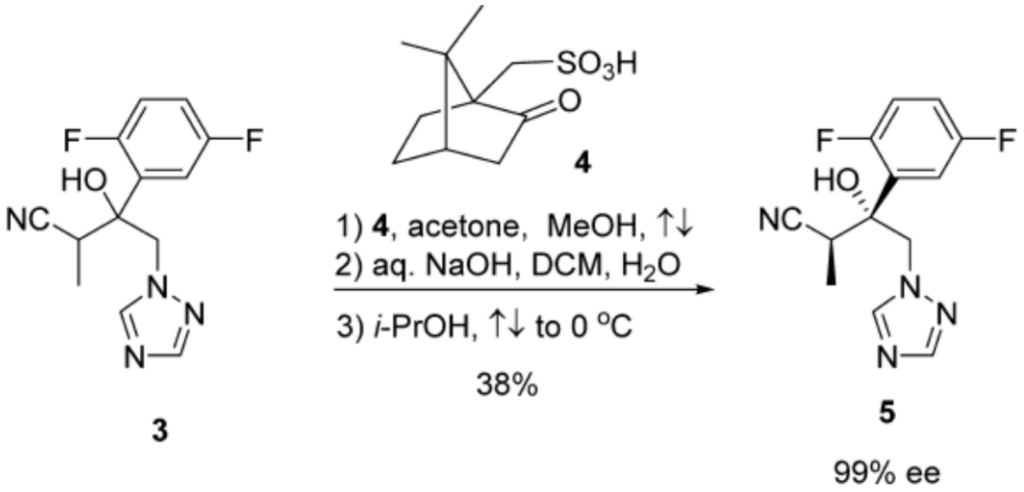
The synthesis of active moiety **isavuconazole** was started with commercial **1-(2,5-di*fl*uorophenyl)-2-(1*H*-l,2,4-triazol-l- yl)ethanone** (1). Triazole 1 was treated with *n*-BuLi followed by exposure to propionitrile (2) and acidic quench to give racemic alcohol 3 in 65% yield.



Farmaci Antifungini Azolici

6.3.2.1.0.0.42

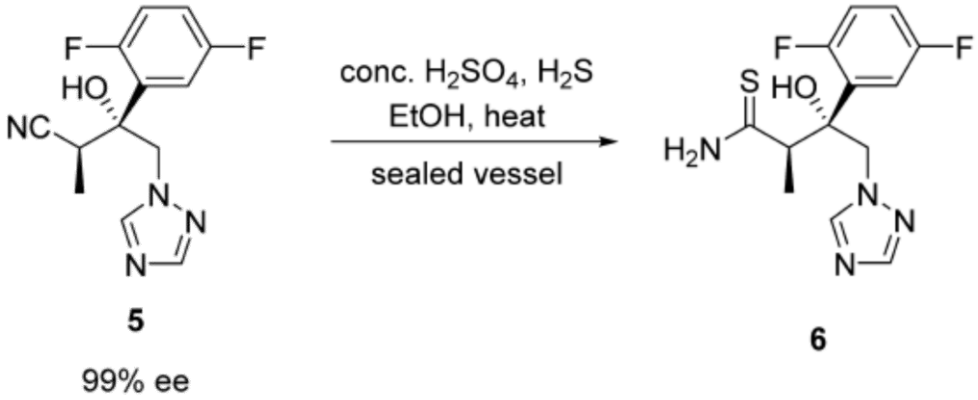
Resolution of this racemic alcohol was facilitated through the use of camphor derivative 4 to provide alcohol 5 in 38% yield and **99% ee**.



Farmaci Antifungini Azolici

6.3.2.1.0.0.42

Nitrile 5 was then treated with concentrated H_2SO_4 and H_2S to furnish thioamide 6



5

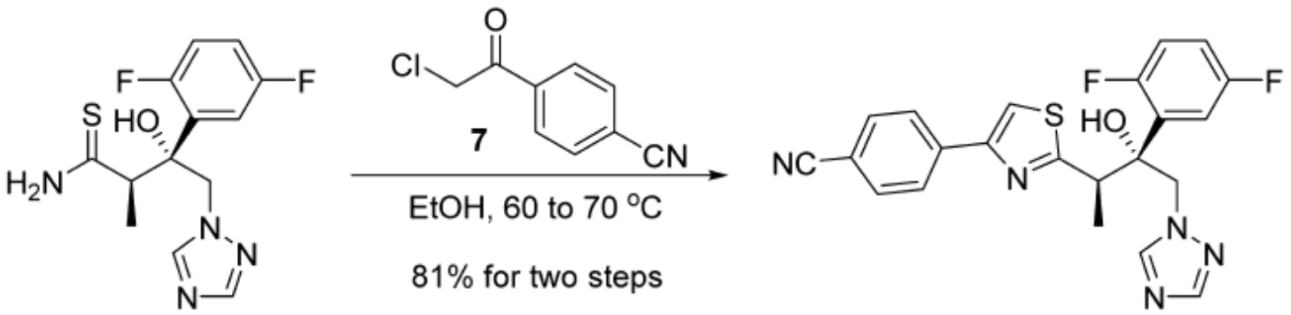
99% ee

6

Farmaci Antifungini Azolici

6.3.2.1.0.0.42

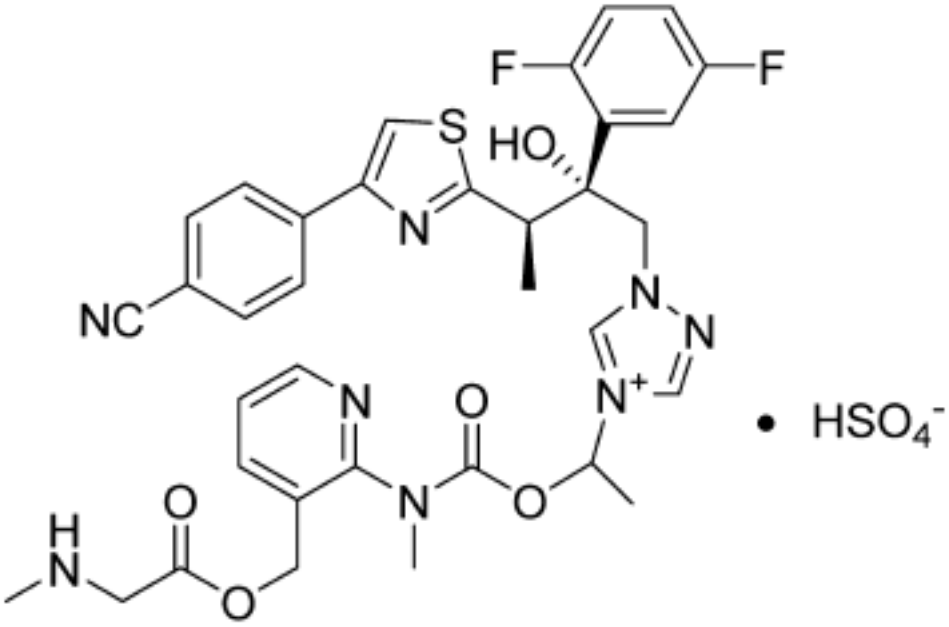
thioamide 6 was followed by a cyclization reaction involving **4-(2-chloroacetyl)-benzonitrile** (7) which gave rise to **isavuconazole** in **81%** yield across the two-step sequence.



6 **8 Isavuconazole**

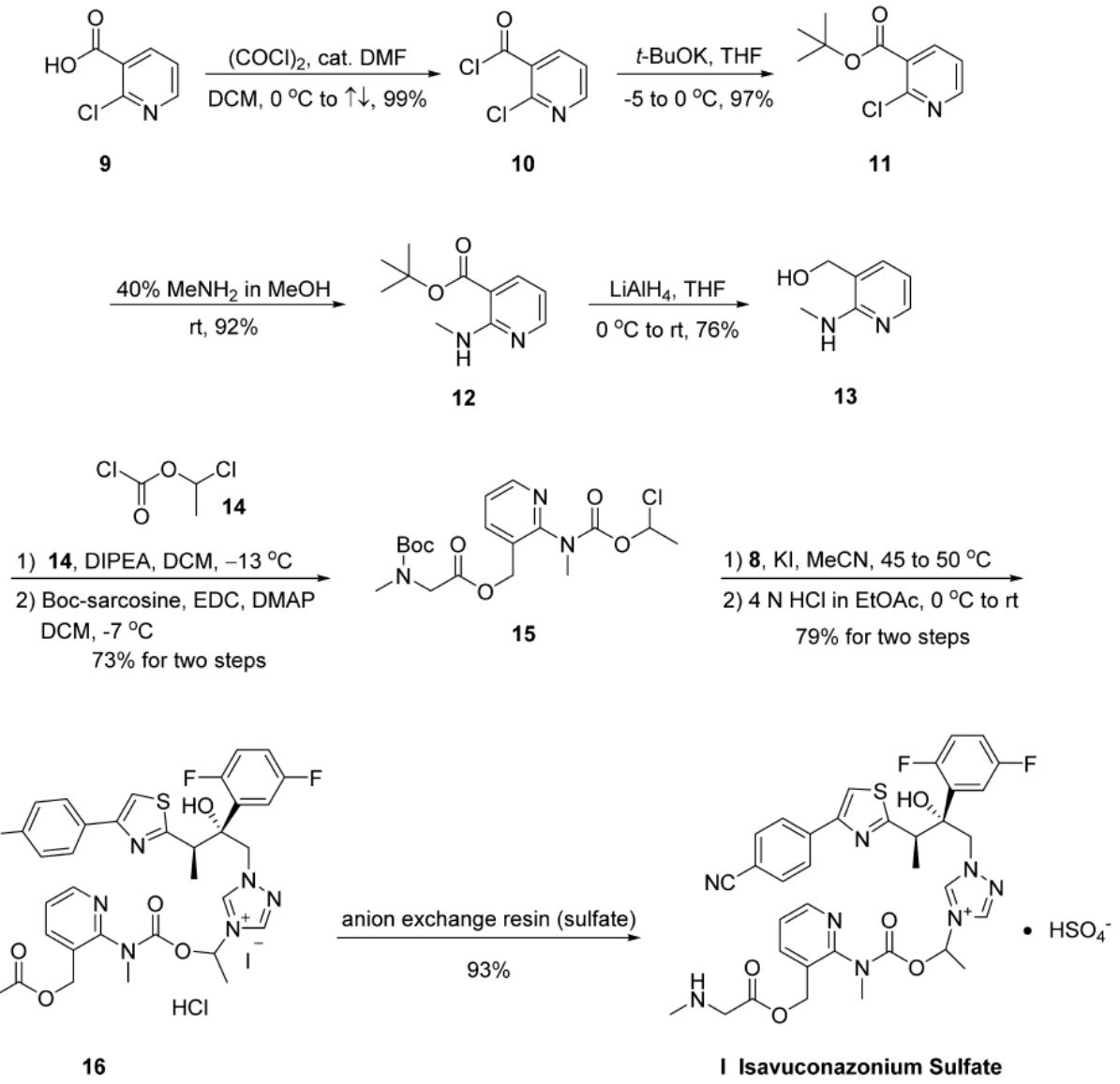
Farmaci Antifungini Azolici

6.3.2.1.0.0.44



I Isavuconazonium Sulfate

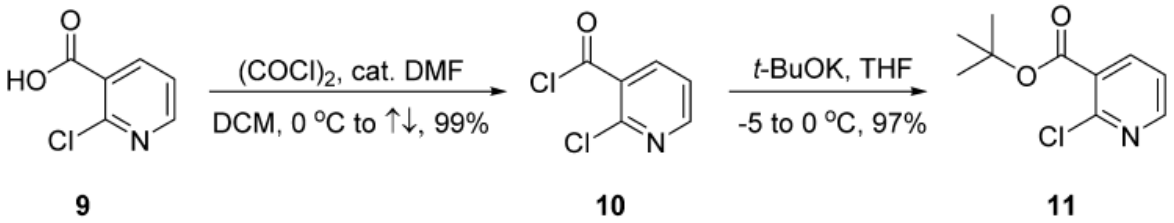
Farmaci Antifungini Azolici



Farmaci Antifungini Azolici

6.3.2.1.0.0.43

The preparation of water-soluble side chain 15 was initiated from commercially available **2-chloronicotinic acid** (9), which was converted to the corresponding *tert*-butyl ester 11 via acid halide 10 in excellent yield for the two-step protocol.

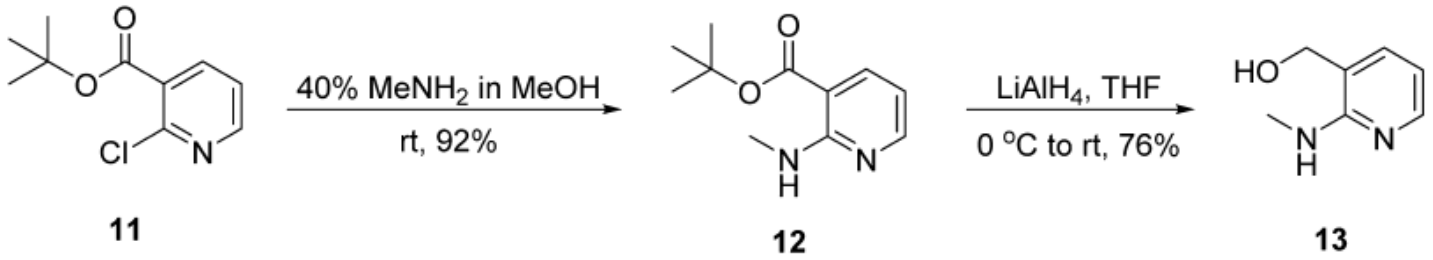


9 **10** **11**

Farmaci Antifungini Azolici

6.3.2.1.0.0.43

Subjection of pyridyl chloride 11 to methanolic methylamine furnished aminopyridine 12 in 92% yield, and this compound was subsequently reduced with lithium aluminum hydride to give aminoalcohol 13 in 76% yield.

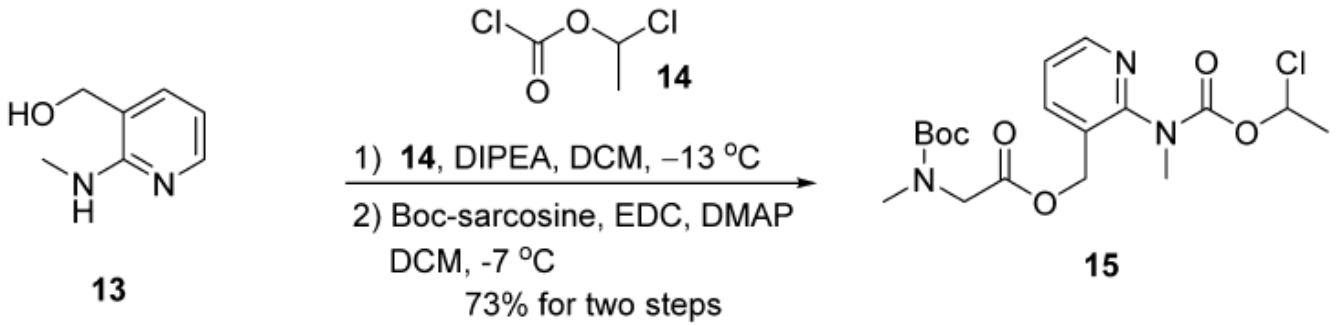


11 12 13

Farmaci Antifungini Azolici

6.3.2.1.0.0.43

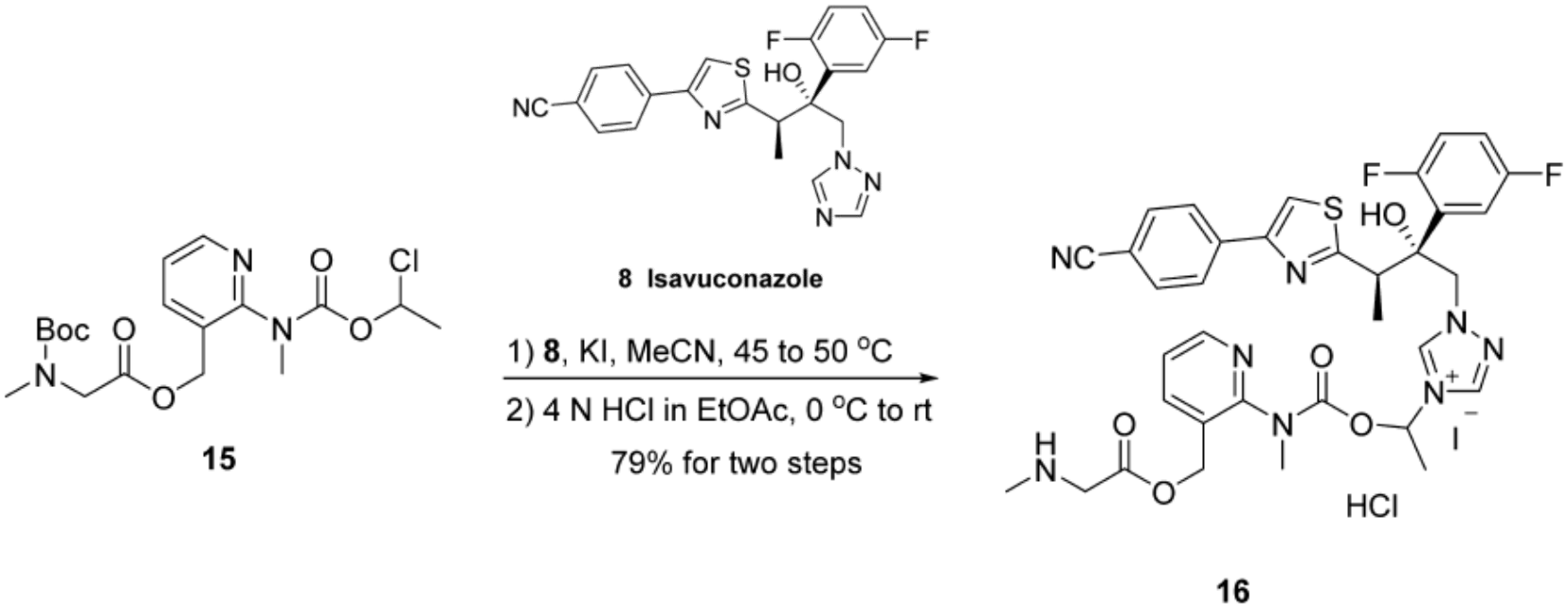
Next, N-acylation of 13 with 1-chloroethyl chloroformate (14) followed by treatment with *N*-Boc-sarcosine under esterification conditions delivered chloroethyl ester 15 in 73% yield.



Farmaci Antifungini Azolici

6.3.2.1.0.0.43

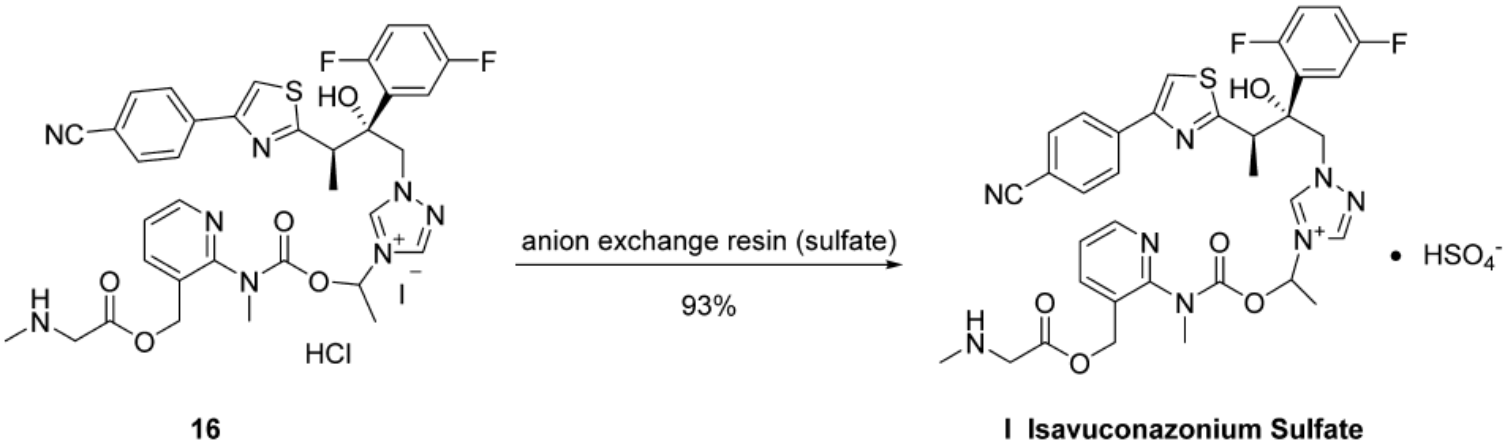
The union of the aminopyridyl side chain 15 with thiazoloalcohol 8 was facilitated by reacting the two compounds in the presence of KI in acetonitrile, and this alkylation was followed by removal of the Boc group with hydrochloric acid to give rise to isavuconazonium iodide hydrochloride (16) in 79% yield.



Farmaci Antifungini Azolici

6.3.2.1.0.0.43

Finally, isavuconazonium sulfate (I) was prepared from 16 using an anion exchange resin in 93% yield to finish the construction of the API.



16 **I Isavuconazonium Sulfate**

Farmaci Antifungini Azolici

6.3.2.1.0.0.44

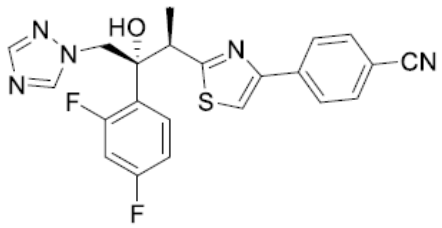
Fosravuconazole L-lysine ethanolate (F-RVCZ) is an orally administered, broad-spectrum antifungal drug approved in Japan for the treatment of onychomycosis in 2018.

F-RVCZ is a prodrug of ravuconazole with improved solubility and oral bioavailability. Originally discovered by Eisai, **ravuconazole** was licensed to Bristol-Myers Squibb (BMS) for worldwide development, excluding Japan, in 1996.

However, BMS terminated development of the drug in 2004, and Eisai reacquired the worldwide development, manufacturing, and marketing rights.

The antifungal activities of **ravuconazole**, like other azole drugs, derive from the inhibition of ergosterol biosynthesis and block the 14α-demethylation pathway present in many strains of yeasts and molds. The lowering of ergosterol levels leads to accumulation of 14α-methyl sterols, which impairs normal structure and functions of cell membranes, ultimately resulting in growth inhibition or death of fungal cells.

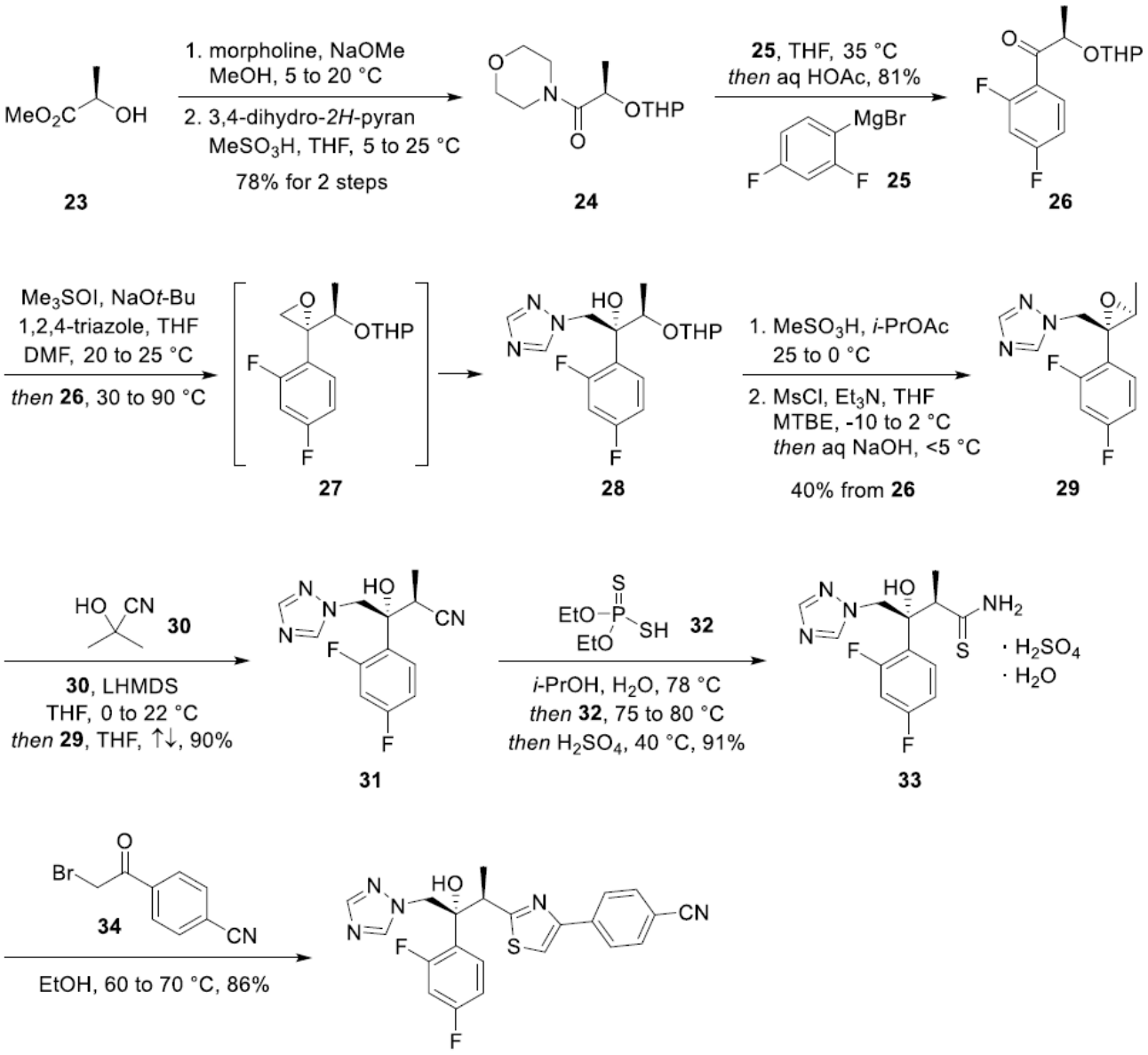
F-RCVZ exhibited higher efficacy (higher initial cure rates and lower recurrence rates), an improved safety-profile (lower hepatic functional disorders), and improved dosing regimen (once daily for 12 weeks) over existing standards of care such as terbinafine and itraconazole.



Ravuconazole (35)

Farmaci Antifungini Azolici

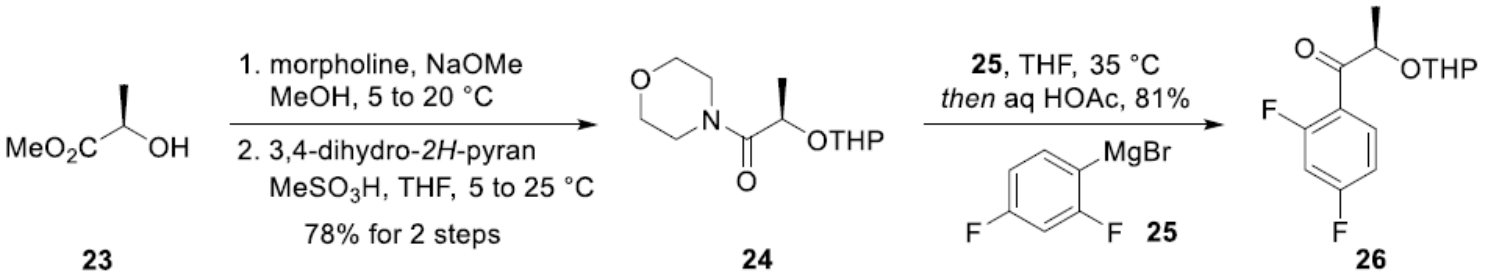
6.3.2.1.0.0.44



Farmaci Antifungini Azolici

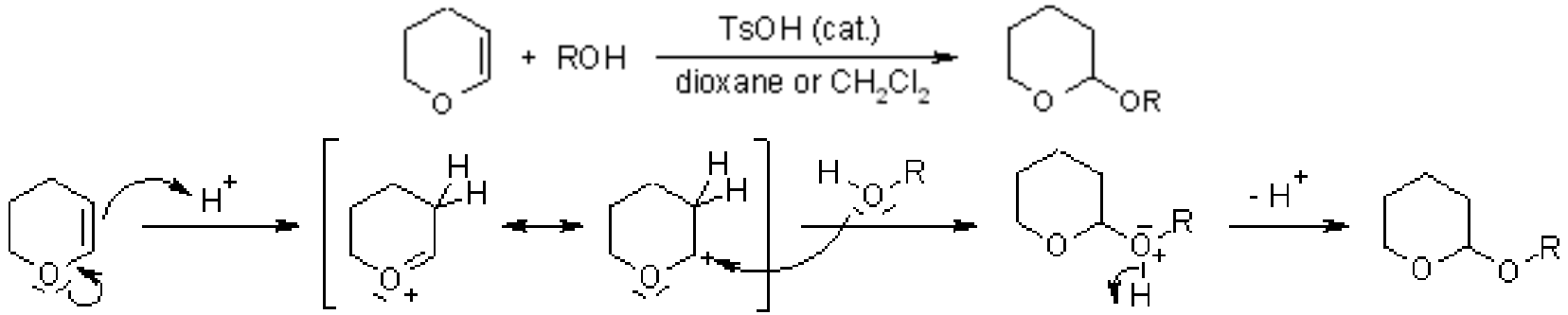
6.3.2.1.0.0.44

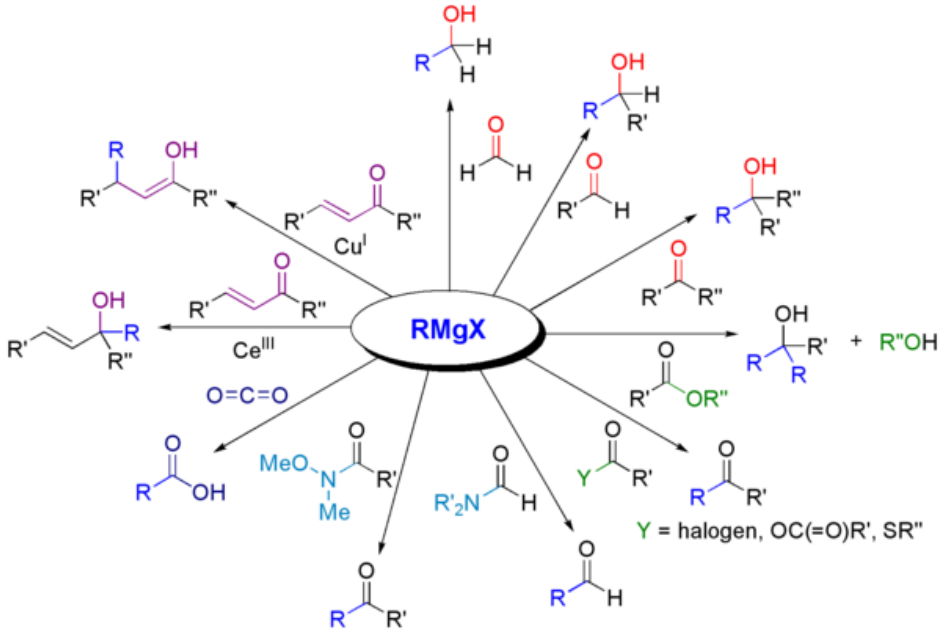
In addition to several disclosures describing the gram-scale synthesis of ravuconazole and related precursors, **a robust plant-scale preparation has been described by researchers at BMS**. This route utilized lactate 23 as a starting material for the preparation of arylpropanone 26. First, methyl ester 23 was converted to a morpholine amide in the presence of catalytic sodium methoxide. The alcohol was subsequently protected to generate tetrahydropyranyl ether 24. Use of **real-time infrared reaction monitoring allowed for safe formation of Grignard reagent 25** from the corresponding bromide, which was then reacted with amide 24 to furnish aryl ketone 26 after aqueous acetic acid quench.



Farmaci Antifungini Azolici

6.3.2.1.0.0.44

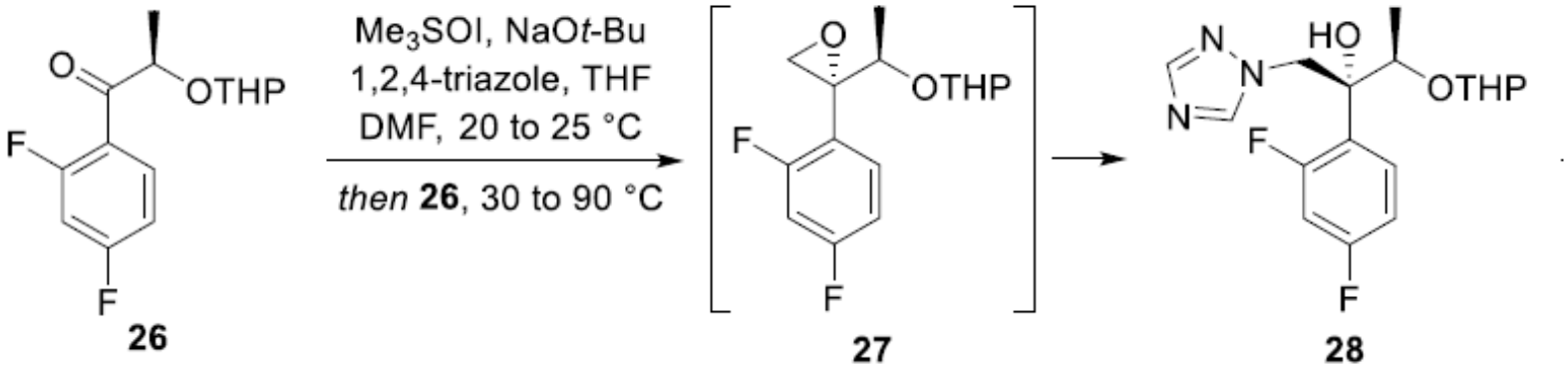




Farmaci Antifungini Azolici

6.3.2.1.0.0.44

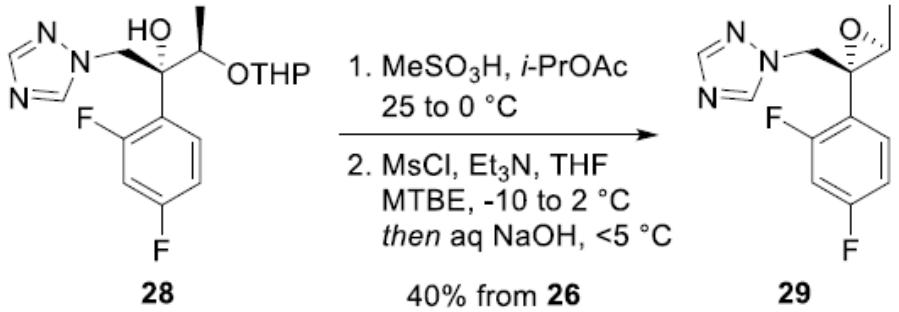
Corey−Chaykovsky epoxidation and subsequent epoxide opening were performed in a single-step, telescoped process. Once epoxidation was complete, heating the reaction mixture to 90 °C triggered a triazole-mediated epoxide-opening sequence to form alcohol 28. The stereochemical outcome of the epoxide-forming step is dictated by the adjacent chiral center, providing 27 in 8.6:1 dr.



Farmaci Antifungini Azolici

6.3.2.1.0.0.44

Removal of the tetrahydropyranyl protecting group within 28 generated an intermediate diol which was converted to trisubstituted epoxide 29 via selective mesylation of the secondary alcohol.

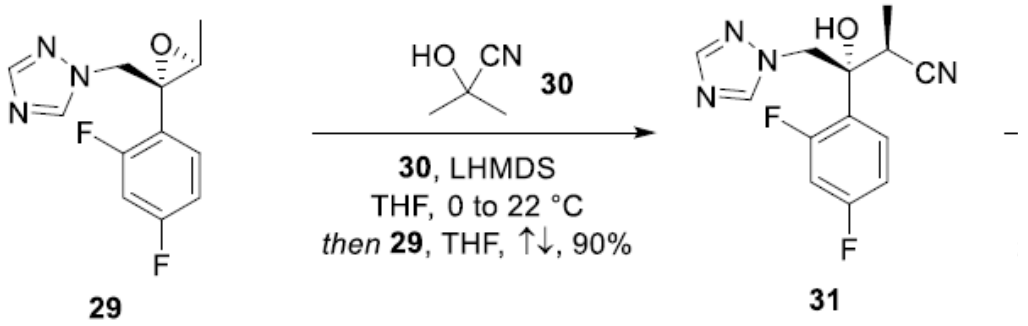


28 40% from **26** **29**

Farmaci Antifungini Azolici

6.3.2.1.0.0.44

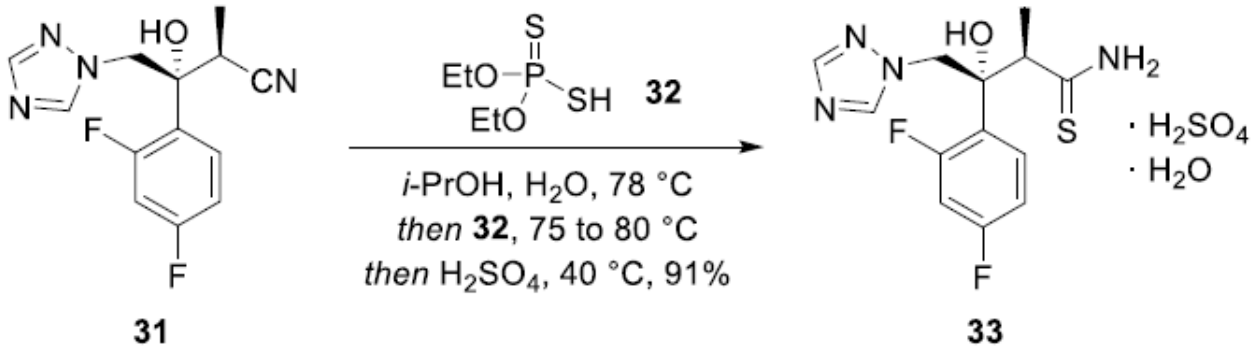
Generation of lithium cyanide *in situ* from acetone cyanohydrin 30 and **LHMDS (lithium hexamethyldisilazide**) followed by subsequent addition to epoxide 29 delivered the α-cyano alcohol 31 in 90% yield



Farmaci Antifungini Azolici

6.3.2.1.0.0.44

31 was subsequently converted to thioamide monohydrate salt 33 by treatment with **diethyl dithiophosphate** 32 and sulfuric acid.

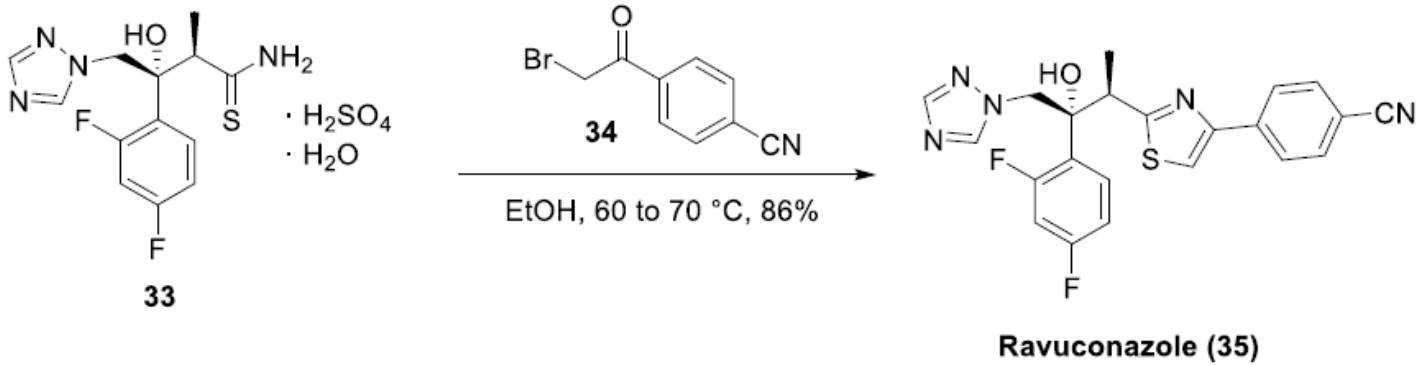


31 **33**

Farmaci Antifungini Azolici

6.3.2.1.0.0.44

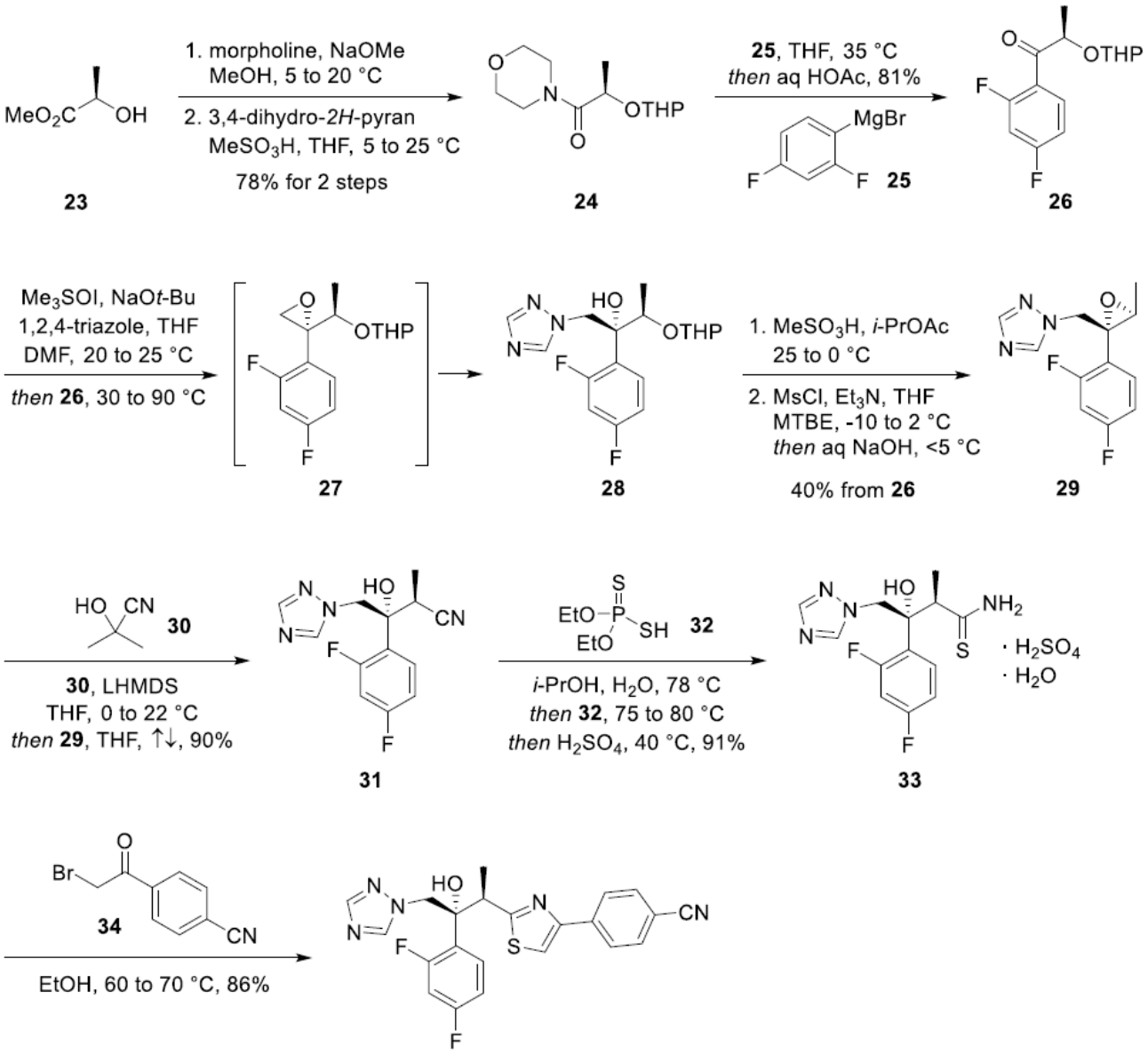
Condensation of the thioamide 33 with 2-bromo-4′-cyanoacetophenone 34 in hot ethanol resulted in thiazole formation which completed the preparation of **ravuconazole**



Ravuconazole (35)

Farmaci Antifungini Azolici

6.3.2.1.0.0.50



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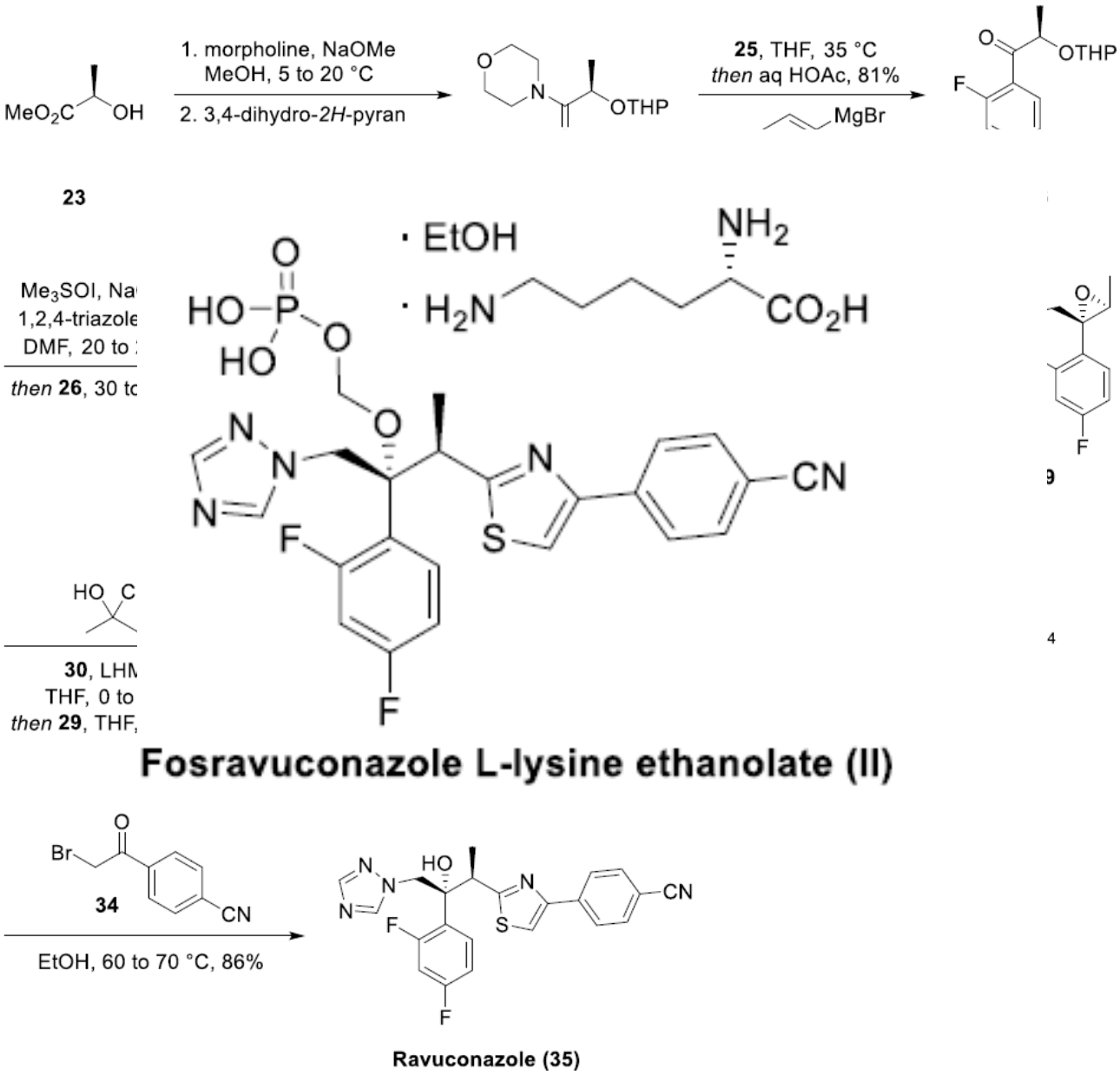

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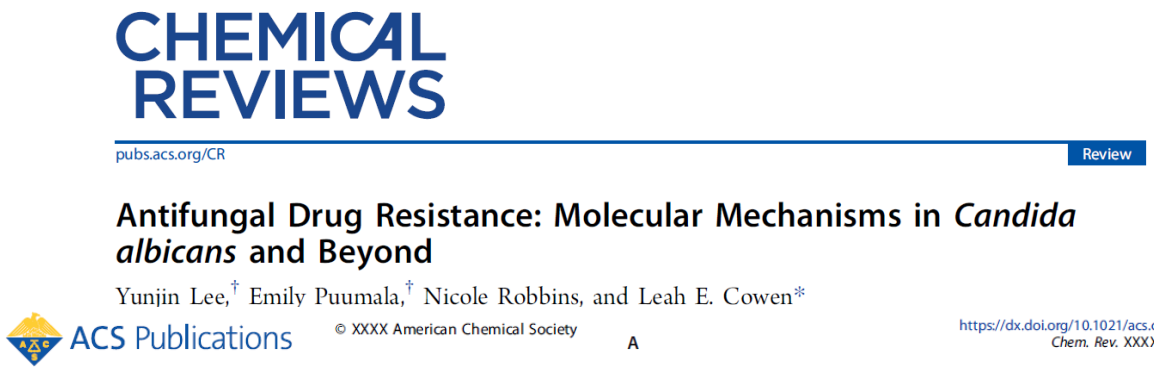


Fungal infections are a major contributor to infectious disease-related deaths across the globe. *Candida* species are among the most common causes of invasive mycotic disease, with *Candida albicans* reigning as the leading cause of invasive candidiasis.

Given that **fungi are eukaryotes** like their human host, the number of unique molecular targets that can be exploited for antifungal development remains limited. Currently, there are only three major classes of drugs approved for the treatment of invasive mycoses, and the efficacy of these agents is compromised by the development of drug resistance in pathogen populations. Notably, the emergence of additional drug-resistant species, such as *Candida auris* and *Candida glabrata*, further threatens the limited armamentarium of antifungals available to treat these serious infections. Here, we describe our current arsenal of antifungals and elaborate on the resistance mechanisms *Candida* species possess that render them recalcitrant to therapeutic intervention. Finally, we highlight some of the most promising therapeutic strategies that may help combat antifungal resistance, including combination therapy, targeting fungal-virulence traits, and modulating host immunity. Overall, a thorough understanding of the mechanistic principles governing antifungal drug resistance is fundamental for the development of novel therapeutics to combat current and emerging fungal threats.

Farmaci Antifungini Azolici

6.3.2.1.0.0.51

Molecular mechanisms of antifungal drug resistance.

(A) Resistance to **polyenes** is primarily mediated by the **depletion of the target ergosterol through loss-of-function mutations in ergosterol biosynthesis genes**. This leads to the production of alternate sterols, which do not e*ff*ectively interact with polyenes and therefore are not extracted from the fungal cell membrane.

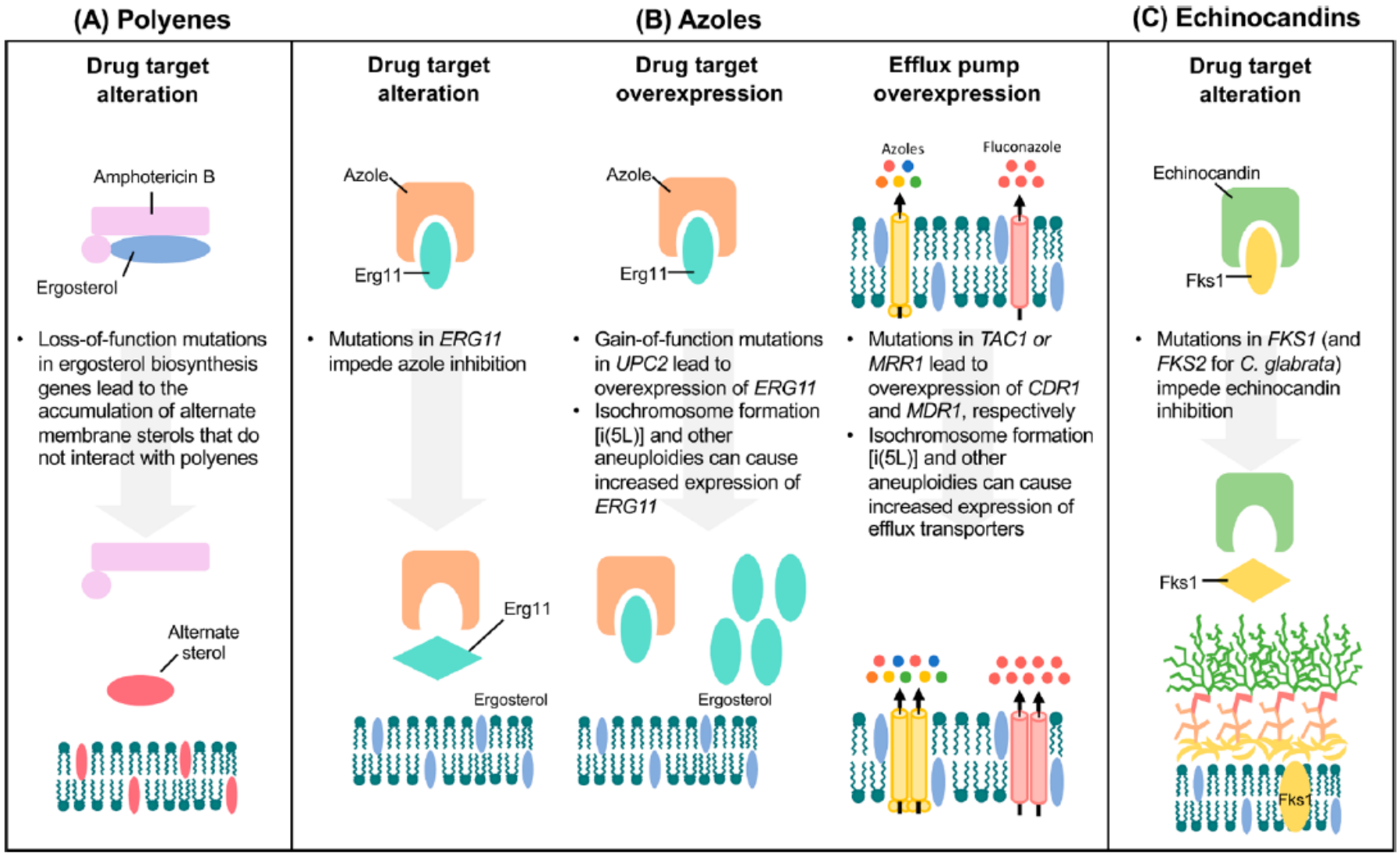
(B) Resistance to **azoles** can occur through

- substitutions to the azole target, Erg11, which leads to lower drug-binding affinity for the lanosterol demethylase enzyme (left panel).
- Overexpression of the drug target can occur through gain-of-function mutations in the transcriptional activator, *UPC2*, or through the formation of aneuploidies, such as [i(5L)], which directly increase the copy number of *ERG11* (middle panel).
- Azole resistance is also acquired through the upregulation of ABC transporters (yellow), including Cdr1 and Cdr2, by activating mutations in speci*fi*c transcription factors (*TAC1* in *C. albicans* and *C. auris* and *PDR1* in *C. glabrata*).
- Additionally, overexpression of the MF transporter (pink), Mdr1, through activating mutations in the transcriptional factor, *MRR1*, confers azole resistance (right panel). Efflux pumps can also be overexpressed through aneuploidy formation.

(C) Resistance to **echinocandins** primarily involves mutations in *FKS* genes that encode the catalytic subunit of the drug target (1,3)-*β*-D-glucan synthase. For *C. albicans* and *C. auris*, mutations conferring echinocandin resistance occur in *FKS1*, while for *C. glabrata*, mutations occur in both *FKS1* and its paralogue *FKS2*.

Farmaci Antifungini Azolici

6.3.2.1.0.0.52



Farmaci Antifungini Azolici

6.3.2.1.0.0.53

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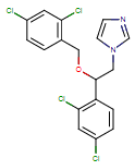
- Enzymes (11)
- Carriers (1)
- Transporters (1)

Miconazole

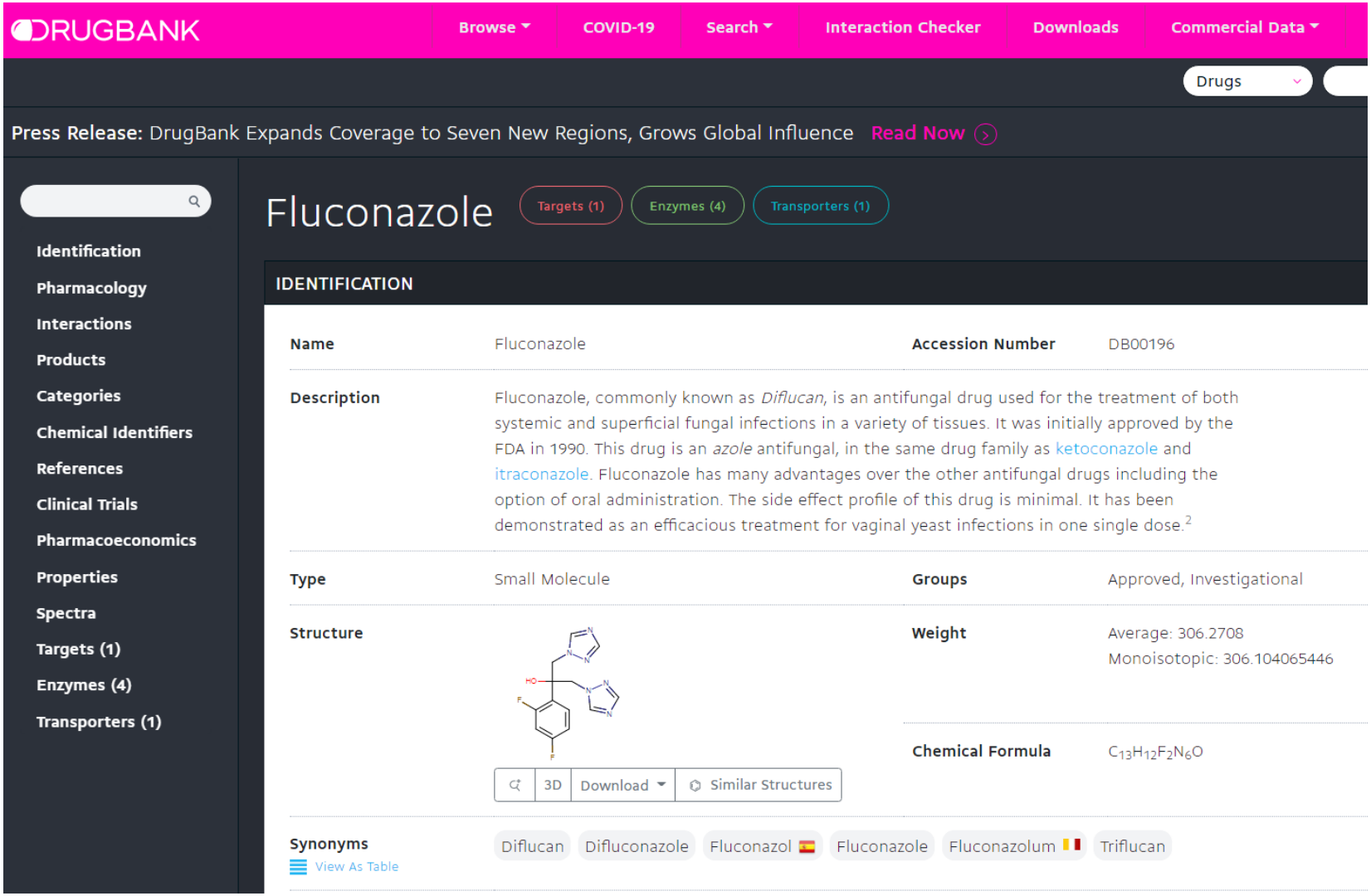
Targets (8) | Enzymes (11) | Carriers (1) | Transporters (1)

IDENTIFICATION

Name	Miconazole	**Accession Number**	DB01110
Description	Miconazole is a broad-spectrum azole antifungal with some activity against Gram-positive bacteria as well.[3] It is widely used to treat mucosal yeast infections, including both oral and vaginal infections; although intravenous miconazole is no longer available, a wide variety of suppositories, creams, gels, and tablet-based products are available.[13,14,15,16,17] Miconazole is thought to act primarily through the inhibition of fungal CYP450 14α-lanosterol demethylase activity.[3,4] Miconazole was first synthesized in 1969 and first granted FDA approval on January 8, 1974, for sale by INSIGHT Pharmaceuticals as a topical cream.[12,13] It is currently available as a variety of prescription and over the counter products. Despite having been in clinical use for an extended period, resistance to miconazole among susceptible organisms is relatively low.[3]		
Type	Small Molecule	**Groups**	Approved, Investigational, Vet approved
Structure	 3D Download Similar Structures	**Weight**	Average: 416.129 Monoisotopic: 413.986023908
		Chemical Formula	$C_{18}H_{14}Cl_4N_2O$

Farmaci Antifungini Azolici

6.3.2.1.0.0.54



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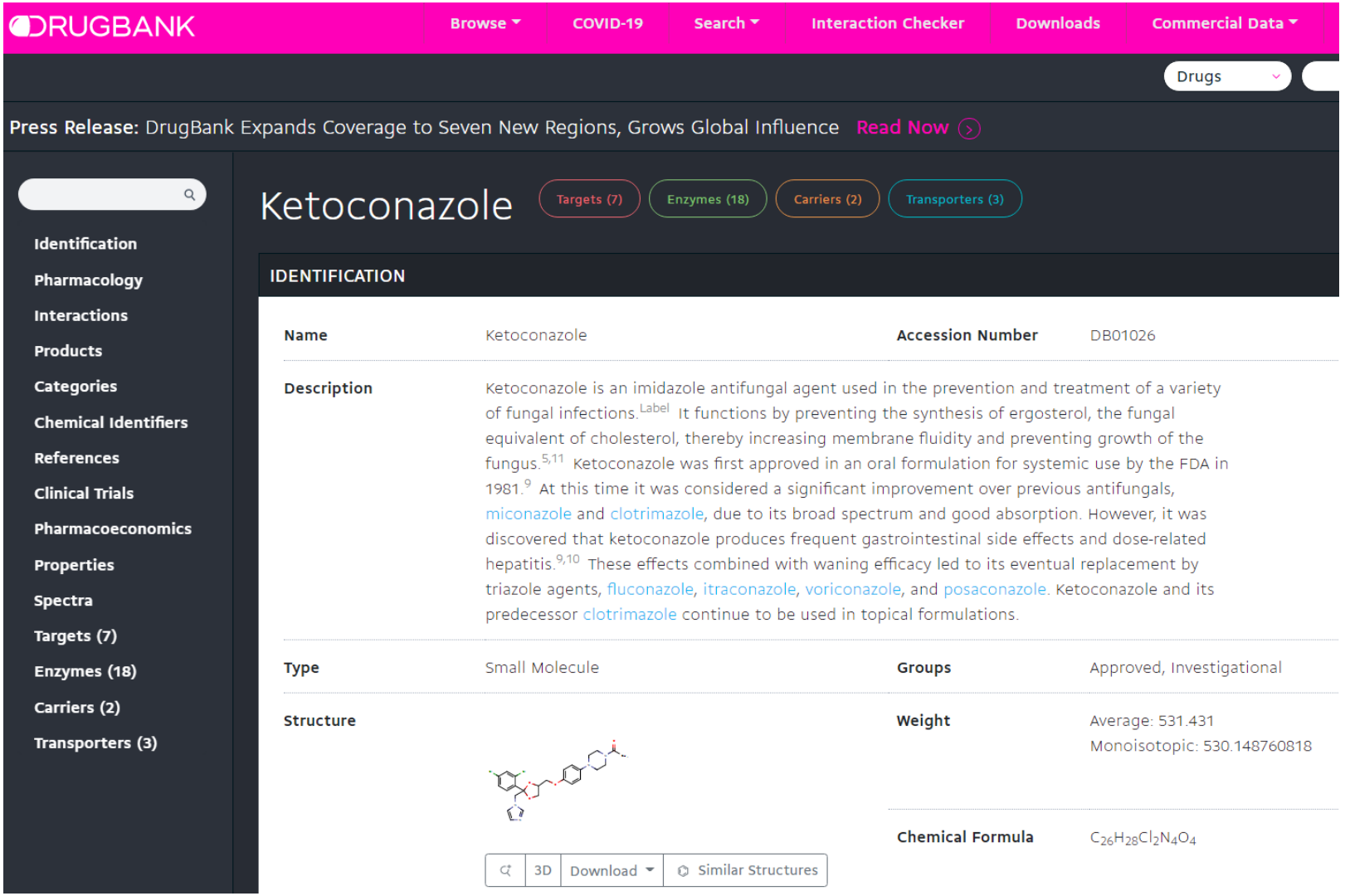

Farmaci Antifungini Azolici

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Biofilm eradication and antifungal mechanism of action against *Candida albicans* of cationic dicephalic surfactants with a labile linker

Emil Paluch[1]✉, Jakub Szperlik[2], Łukasz Lamch[3], Kazimiera A. Wilk[3] & Ewa Obłąk[4]✉

Scientific Reports | (2021) 11:8896 | https://doi.org/10.1038/s41598-021-88244-1 nature portfolio

The mentioned groups of amphiphilic substances are characterized by the presence of a weak, hydrochloride cationic center readily undergoing deprotonation, as well as a stable, strong quaternary ammonium group and alkyl chains capable of strong interactions with fungal cells. Strong fungicidal properties and the role in creation and eradication of biofilm of those compounds were discussed in our earlier works, yet their mechanism of action remained unclear. It was shown that investigated surfactants induce strong oxidative stress and cause increase in cell membrane permeability without compromising its continuity, as indicated by increased potassium ion (K^+) leakage. Thus experiments carried out on the investigated opportunistic pathogen indicate that the mechanism of action of the researched surfactants is different than in the case of the majority of known surfactants. Results presented in this paper significantly broaden the understanding on **multifunctional cationic surfactants** and their mechanism of action, as well as suggest their possible future applications as surface coating antiadhesives, **fungicides and antibiofilm agents in medicine or industry**.

Farmaci Antifungini Azolici

6.3.2.1.0.0.56