**Topically Applied Drugs**

**Definition:**
A topical medication is a medication that is applied to a particular place on or in the body, as opposed to systemically. (The word topical derives from Greek topikos, "of a place").

Most often this means application to body surfaces such as the skin or mucous membranes to treat ailments via a large range of classes including creams, foams, gels, lotions, and ointments.

**Commonly treated diseases**

- **Acne**
- Anaesthetics (pain relief)
- Actinic keratoses (precancerous patch of thick, scaly or crusty skin)
- Rosacea (redness of face)
- Impetigo (bacterial skin infection; affected 140 million in 2010)
- Furuncle (boils)
- Onychomycosis (fungal nail infection; ~10% adult population)
- Diaper rash
- Atopic dermatitis (inflammation of skin; ~20% population)
- Eczema (skin inflammation)
- Psoriasis (autoimmune disease, 2–4% population, no cure)
- Herpes/Shingles
- Melasma (dark skin discoloration)
- Androgenic alopecia (male–pattern hair loss)
- Glaucoma (increased eye pressure)
- Dry eye syndrome (upto 34% of elderly population)

**Disclaimer:**
This GM is primarily an overview of the synthetic efforts towards natural products based topically applied drugs. It is by no means a comprehensive coverage of all the literature surrounding the topic. The information contained herein is for informational purposes only and should NOT be used as a guideline for treatment.
Topically Applied Drugs

**miscellaneous**
- Ivermectin 2014; Galderma
- Alitretinoin 1999; Ligand
- Doxepin
- Flurouracil 1998; Upjohn
- Minoxidil 1988; hair
- Urea

**Pilocarpine**

Generic, WHO's list of essential medicines

- **Glaucoma**
  - (+)-Pilocarpine

  **Isolation:** Pilocarpus jaborandi (1875)
  **Activity:** glaucoma, hair growth
  **Total Syntheses:** Preobrashenks (1936), Dey, Chumachenko, DeGraw, Link, Noordam, Rapoport (x2), Buchi, Shapiro, Wang, Zhang, Davies

  *For different reasons it is desirable to make pilocarpine accessible by means of an organic chemical synthesis. So far the production of (+)-pilocarpine has been accomplished by extraction from vegetable material mainly consisting of the leaves of Pilocarpus microphyllus Stapf. This tropical shrub only grows in South America, especially in Brazil.*

  **Buchi:** JOC, 1993, 58, 62
  
  1. NaH; PhSeCl
  2. CpH, H2O2
  
  Only epoxide observed without CpH

  1. [(+)-Ipc2BrCl]
  2. EVE, Hg(OAc)2

  425 °C (FVP)
  95%

  29% (2 steps)

  cis:trans (3:2)

  47% Pd/C

  10% Py/C,H6

  61% in EtOH or EtOAc, trans isomer major product

  **Zhang:** JACS, 2002, 124, 8198

  1. K2CO3, MeOH, TosMIC gives <15%
  2. MeNH2 dry DCM:C6H6

  99% (2 steps)

  ee >99%

  **Davies:** Tetrahedron, 2009, 65, 8283

  1. [Rh(COD)Cl]2
  2. BINAP
  3. AgSbF6, rt

  92%

  dr >99:1, ee >98%

  3 steps
Retapamulin

Altabax®, GlaxoSmithKline, 2007–

Antibiotic

first new topical application antibiotic within the last 20 years

(+)-Pleuromutilin

Isolated: Pleurotus mutitus, Pleurotus passeckerianus (1951)

Activity: antibacterial against Gram-positive bacteria

Approaches: Kahn (1980, anionic oxy–Cope)
Paquette (1985–1988, late stage Michael)
Zard (2003, 8–endo–trig cyclisation)
Procter (2008–2009, RCM/SMI2 cascade)
Sorensen (2011, RCM, NHK)

Total Syntheses: Gibbons (1982, racemic, 31 steps)
Boeckman (1989, racemic, 27 steps)
Procter (2013, asymmetric, 34 steps)

SAR studies on pleuromutilin core


Commercial Route: WO 2010 056 855 A1, 2010

(+)-pleuromutilin

(prepared by fermentation)

2.2 g L⁻¹ after 6 days

Retapamulin, Altabax®

IC₅₀ (erythromycin–susceptible E. coli) = 0.33 µM

Gibbons: JOC, 1980, 45, 1540; JACS, 1982, 104, 1767

(+)-pleuromutilin

1. AcOCH₂CO₂H
   MeCl, DMAP
   11 steps
   62%

2. KOH, MeOH
   39%
   (2 steps)

(−)-pleuromutilin

Boeckman Jr.: JACS, 1989, 111, 8284

TsO

Me₂CuLi

Lefamulin, Nabirava

Phase III

From Robinson annelation

For a detailed discussion of this synthesis:
Maimone GM on Classic Terpene Synthesis

(±)-pleuromutilin

1. mCPBA
   2. BF₃·Et₂O,
   (CH₂O)₂ × rt
   89%
   (2 steps)

(−)-pleuromutilin


8 steps

25 steps

(+)-pleuromutilin

(Rom)
**Topically Applied Drugs**

**Common modifications of pleuromutilin core**

*Tet. Lett.*, 2011, 52, 4247 (Pfizer)

*Tetrahedron*, 1980, 36, 1807 (Sandoz)


**Spinosad (17:3 Spinosyn A:D)**

*JOC*, 2009, 74, 478 (GSK)

*JOC*, 2009, 74, 478 (GSK)

**Paquette (32 steps LLS, asymmetric): *JACS*, 1998, 120, 2543**

**More comprehensive discussion; Agrochemistry: Insecticides GM by Cherney**

**Roush (23 steps LLS, asymmetric): *PNAS*, 2004, 191, 11955**

**Conditions**

1. TMSOTI, Et$_3$N
2. mCPBA, DCM;
3. TBAF

**Yield**

- 1. TMSCl, LiHMDs
- 2. mCPBA, AcOH/Py, DCM
- 3. HCl

**562 g**

**Useful modification for Rubottom Oxidation**

**Spinosyn A**

Isolation: *Saccharopolyspora spinosa* (1991)

Activity: anti-insectidal (insecticide, Dow, 1997–)

Mupirocin
Bactroban; GlaxoSmithKline, Generic, WHO's list of essential medicines
Antibiotic

(+)-Pseudomonic acid A
Isolated: Pseudomonas fluorescens (1971)
Activity: against Gram–positive bacteria
Approaches: Mootoo, Honda, Sugawara
Total/Formal Syntheses: Kozikowski, Schonenberger, Raphael, Fleet, Sinay, Snider, Curran, Keck, Bates, Williams, Barrish, Nagarajan, DeShong, Willis, Sridhi, Marko


mupirocin prepared by fermentation 1–2 mg L⁻¹ after 24 h

Snider: JACS, 1982, 104, 1114

Mootoo (Approach): Tetrahedron, 1999, 55, 8303

Topically Applied Drugs

**Fusidic Acid**
Leo Pharma, 1962
Generic, WHO's list of essential medicines
Antibiotic

- Isoation: *Fusidium coccineum* (1960)
- Activity: against Gram-positive bacteria
- Approaches: Deslongchamps, Jung
- Total Syntheses (degradation ptl.): Dauben, Tanabe, Ireland

**SAR studies on Fusidic acid**

- Fusidic acid is an antibiotic that belongs to a group of its own, the fusidanes. The molecule has a steroid-like structure but does not possess any steroid activity.'
  
  *Br J Dermatol.*, 1998, 139, 37

- 'true' antibiotic

**Fusidic Acid**

- tetracyclic fusidane skeleton: chair–boat–chair (essential)
- Lipophilic side chain (dihydrofusidic acid has equivalent activity)
- OH groups can be replaced with other functional groups (keto, halogens sulfoxides, azides etc.)
- Carboxylic acid essential (gives rigidity but conformation of the chain is essential)
- Acetate important but can be exchanged by many other functionalities (O–acyl, S–acyl, ethers etc.)

**Dauben**: JACS, 1972, 94, 8593

9 steps from Hajo–Parrish ketone

- Towards synthesis of Fusidic acid degradation product

**Ireland**: JOC, 1977, 42, 1267

For Ireland Eschenmoser–Tanabe approach; Hermann GM on Robert Ireland

**Deslongchamps (Approach)**: JACS 2001, 123, 8210

- Correctly set all ABC ring stereocentres
  - Incorrect C3 stereochemistry

**WO 2012023081 A1**

Fusidic acid

Large scale production by batch fermentation

**Godtfredsen (Leo)**: Tetrahedron, 1979, 35, 2419

Similar rearrangements observed on using NBS and epoxides

more stable trans–anti–trans configuration
Calcitriol
Generic
Psoriasis

1,25-dihydroxycholecalciferol, 1,25-dihydroxyvitamin D₃

Isolation: Metabolite of vitamin D from chicken intestines (1971)
Activity: Increases the level of calcium (Ca²⁺) in the blood


1. DDQ
2. H₂O₂
3. Li/NH₄Cl

14% (3 steps)

Two step irradiation: 254 nm; 350 nm
50% (3 steps)

Dauben: *JACS*, 1982, 104, 5780

1. EtOH, Δ
2. NaOH

calcitriol
(8 steps)

Common methods for preparing vitamin D₃, calcitriol and its analogues

Calcitriol

Grundmann’s ketone

From Hajos–Parrish ketone

Mazur: *JACS*, 1975, 97, 6249

75% aq. dioxane
0.3 eq. pTsOH
80%

target these compounds instead

Target vitamin D₃


Vitamin D₃ degradation

Inhoffen–Lythgoe diol (Vitamin D₂ degradation)

Heck cross-coupling

25-hydroxy-Grundmann’s ketone

1. CO₂Me
2. LiAlH₄
3. NaOMe

89% (1 step)

1 mol% TsOH
1:1 dioxane/H₂O
64%
calcitriol

Vitamin D₃ degradation

25-hydroxycholesterol

Two step irradiation: 254 nm; 350 nm
50% (3 steps)

Dauben: *JACS*, 1982, 104, 5780

1. EtOH, Δ
2. NaOH

calcitriol
(8 steps)

Calcitriol

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From Hajos–Parrish ketone

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25-hydroxycholesterol

Two step irradiation: 254 nm; 350 nm
50% (3 steps)

Dauben: *JACS*, 1982, 104, 5780

1. EtOH, Δ
2. NaOH

calcitriol
(8 steps)
**Podophyllotoxin**

**Condylox®, Wartex®**

**Generic, WHO's list of essential medicines**

**Antimiotic**

(-)-Podophyllotoxin

*Isolation:* Podophyllum peltatum (1953)

*Activity:* anticancer

*Total/formal syntheses:* Gensler, Durst, Kaneko, Meyers, Vandewalle, Charton, Jones, Bhat, Berkowitz, Sherburn, Bach, Curran, Li, Murphy, Kraus, Caballero, Keaveney, Toste, Ishikawa, Poli, Rodrigo, Doyle, Linker, Maimone

Open chain increases anti–HIV activity

Hydrolysis to acid 500x less activity

More stable cis-2,3 lactone 100x less activity

Free OH/Phosphate appended to carbohydrates/ anilines with p-substitution

Reviews on SAR studies:

Common Synthetic approaches
- Fiedel–Crafts
- Michael addition

MeO

OH

OMe

MeO

OMe

plant tissue culture ~0.72 mg/L/day

Piperidine, tBuOH, 31°C, 5 d

podophyllotoxin

2.5:97.5

podophyllotoxin

picropodophyllotoxin

Major challenges: 1,2-cis geometry and trans lactone ring fusion

**Bhat:** *Tet. Lett.*, **1996**, 37, 4791

1. TFA
2. HgO
3. BF₃·Et₂O

25%

(-)-podophyllotoxin traditionally forming 1,2-cis junctions by acid catalysed cyclisation difficulty

**Steel (Approach):** *OBC*, **2007**, 5, 3201

MeO

OMe

OH

Ph

Si

TMS

OH

H

R

O

OMe

OMe

OTBS

(TMS)₂SiH, AIBN, C₆H₆, 80°C, 8 h

38%

(+)-podophyllotoxin (opposite enantiomer)

4 steps

6 steps

**Sherburn:** *JACS*, **2003**, 125, 12108

MeO

OMe

MeO

OMe

MeO

OMe

**Maimone:** *ACIE*, **2014**, 53, 3115

MeO₂C

OH

NH-DG

CO₂Me

1. LiEt₃BH
2. Protect

41%

(2 steps)

For initial Diels–Alder approaches;
*JOC*, **1980**, 45, 4538;
*JOC*, **1989**, 54, 4280

MeO

OMe

MeO

OMe

pictopodophyllotoxin

1. Me₂Si
2. nBuLi, MgBr₂

48%

(2 steps)

Pd(OAc)₂, ArI, K₂CO₃, tAmOH, 40% (8nO)₂PO₃H₂; TFA/H₂O

43% + 33% 4-epi

podophyllotoxin (5 steps)
Topically Applied Drugs

Selected oxahydrindene synthesis


White: JACS, 1995, 117, 1908

Crimmins (Total synthesis of (+)-Milbemycin D): JACS, 1996, 118, 7513

Spiroketal synthesis; Danishefsky: JACS, 1987, 109, 8117