Antitubercular Natural Products and Synthetic Agents against Clinical Multidrug Resistant Isolates of *Mycobacterium tuberculosis*

Prasat Kittakoop
ประสาท กิตตะคุปต์

Chulabhorn Graduate Institute

Bioactive compounds

Natural products from plants and fungi

J. Nat. Prod. 2011, 74, 79-81
Phytochemistry 2011, 72, 816-820
Phytochemistry 2011, 72, 2062-2067
J. Nat. Prod. 2011, 74, 1650-1652
Eur. J. Org. Chem. 2011, 3809–3814
Planta Medica 2012, *78*, 582-588
Bioorg. Med. Chem. Lett. 2012, *22*, 2902-2905
Org. Biomol. Chem. 2012, *10*, 7220-7226
Planta Medica 2012, *78*, 1562-1567
RSC Adv. 2013, *3*, 1781-1788
Med. Chem. Commun. 2013, *4*, 1590-1596
J. Nat. Prod. 2013, *76*, 1824-1827
Planta Medica 2014, 80, 604-608
Eur. J. Org. Chem. 2014, 19, 3976–3980
Phytochemistry 2014, 108, 87-94
Mar. Drugs 2015, 13, 3567-3580
RSC Adv. 2015, *5*, 70595-70603
Phytochemistry 2016, 122, 126-138
Toxicology Reports 2017, 4, 165-171
Bioorg. Med. Chem. 2017, 25, 2868-2877
ChemistrySelect 2017, 2, 4969-4973
Phytochem. Lett. 2018, 24, 140-144
Chem. Biodivers. 2018, in press.
J. Microbiol. Biotechnol. 2018, in press.

Synthetic compounds

Green chemistry approach

Tetrahedron Lett. 2012, *53*, 2129–2131
RSC Adv. 2014, *4*, 13708-13718
Eur. J. Med. Chem. 2015, 89, 1-12
Angew. Chem. Int. Ed. 2016, 55, 3997-4001

WHO Report:

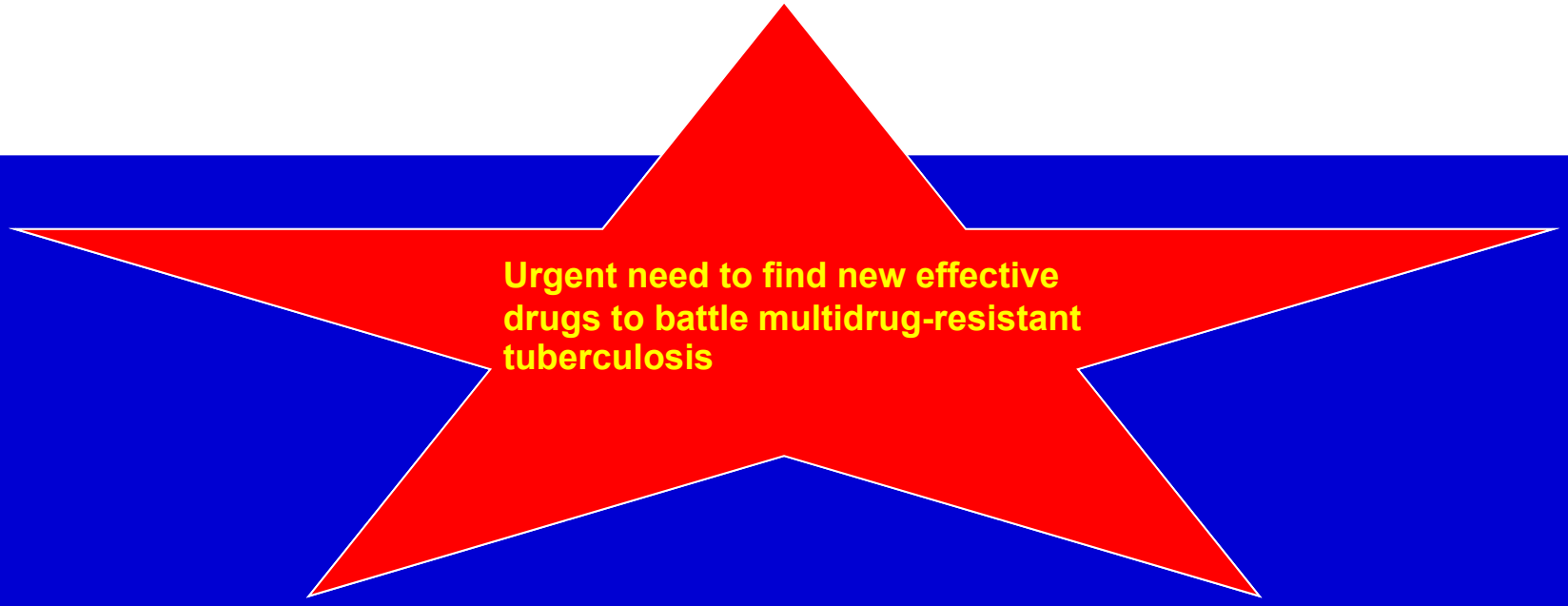
- Tuberculosis is the ninth leading cause of death worldwide

- In 2016, there were an estimated 1.3 million tuberculosis deaths among HIV-negative people and an additional 374,000 deaths among HIV-positive people.

- In 2016, an estimated 10.4 million people fell ill with tuberculosis

WHO Report:

- Drug-resistant tuberculosis is a continuing threat to the world community
- In 2016, there were 600,000 new cases with resistance to rifampicin drug
- In 2016, 490,000 cases had multidrug-resistant tuberculosis



Tuberculosis news in Thai newspaper:

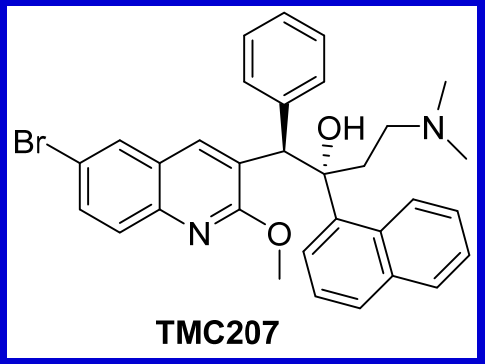
4 April 2018

In Thailand:

- **In 2016, there were 117,000 new cases**
  -with 4,700 cases with multidrug-resistant tuberculosis

♥Few first-line drugs: isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin

♥The last drug (rifampicin) approved for the treatment of tuberculosis was in 1960s



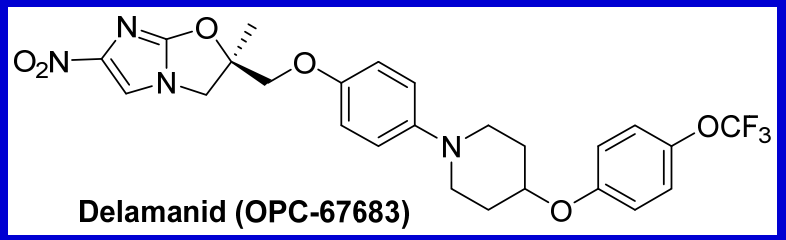
TMC207

♦TMC207: Approved in 2012

♦TMC207 is not only the first anti-TB drug in four decades, but also a new anti-TB drug with a new mechanism of action

♦Target: the proton pump of adenosine triphosphate (ATP) synthase of *Mycobacterium tuberculosis*

Science 2005, 307(5707), 223-227

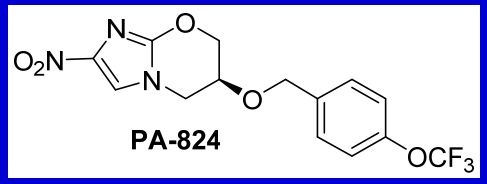


Delamanid (OPC-67683)

- Nitroimidazole
- Inhibits the synthesis of mycolic acids, a crucial component of the cell wall of the *Mycobacterium tuberculosis*

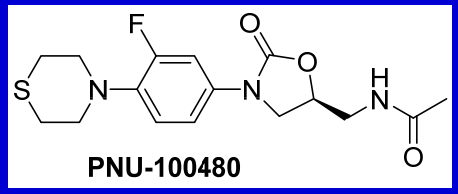
2014: Delamanid (OPC-67683) approved in European Commission for treatment of pulmonary MDR-TB in adult patients in the European Union
-Also in Japan and Korea

Anti-TB drug candidates currently in clinical trials



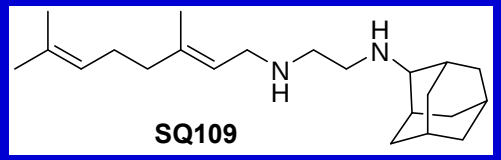
PA-824

♦Inhibition of mycolic acid biosynthesis



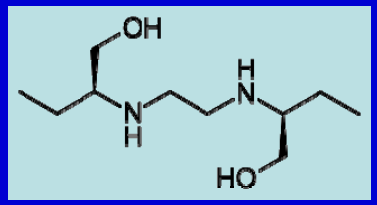
PNU-100480

♦Inhibition of an early step in the initiation phase of protein synthesis



SQ109

♦Inhibition of cell wall synthesis, targeting at a membrane transporter of trehalose monomycolate (MmpL3)



Ethambutol

An increasing number of MDR TB implies:

Mycobacterium tuberculosis may rapidly resist the new drugs that are redesigned from the existing chemical scaffolds of the currently used anti-TB drugs

Therefore, the search for anti-TB agents with new chemical scaffolds is important for anti-TB drug development

Alpinia galanga
Thai name “Kha” ข่า
Edible plant: Tom Yum

This plant root is used as a spice only in Thailand

http://www.the-than.com/samonpai/P/9.html

Tom Yum Kung
https://pairsu57.wordpress.com/2016/11/19/ต้มยำกุ้งน้ำข้น/

Tom Kha Kai

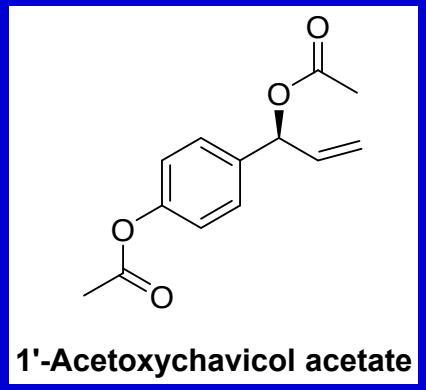
https://food.mthai.com/food-recipe/81171.html

Alpinia galanga

Thai name "Kha" ข่า

Edible plant: Tom Yum

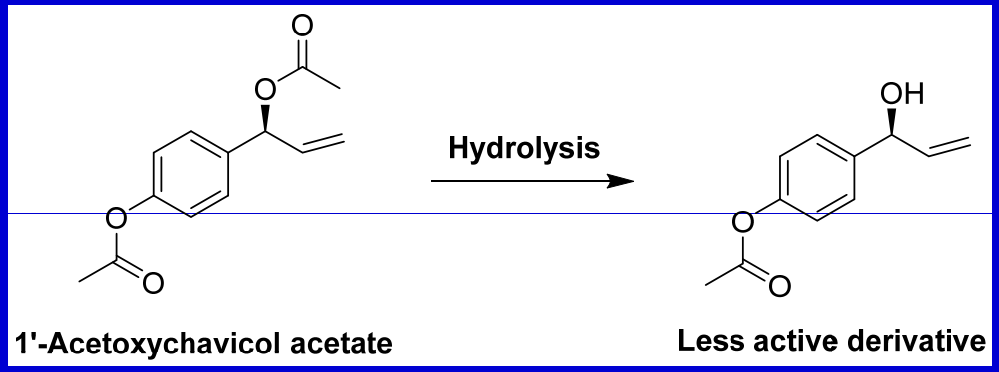
http://www.the-than.com/samonpai/P/9.html



1'-Acetoxychavicol acetate

Anti-tuberculosis activity against
Mycobacterium tuberculosis
MIC: 0.1-0.5 µg/mL

"1'-Acetoxychavicol acetate for tuberculosis treatment", US Patent no. 2002192262



1'-Acetoxychavicol acetate

Less active derivative

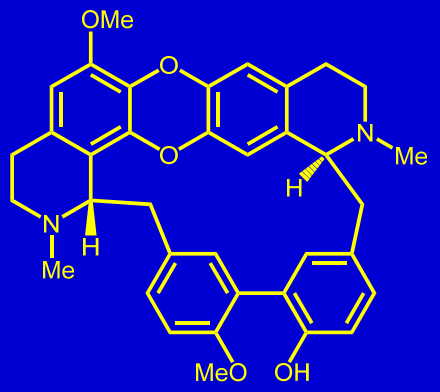
Tiliacora triandra

(Thai name: "Ya-Nang")

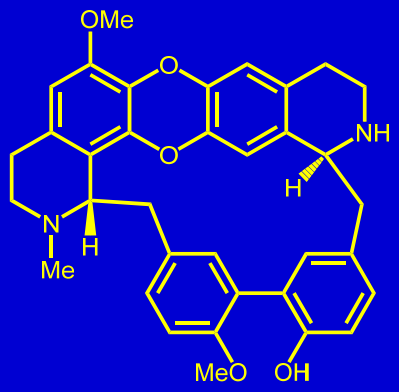
Leave: Edible, and used as food ingredient
Root: Traditionally used to treat fever

***Bioorg. Med. Chem. Lett.* 2012, *22*, 2902-2905**

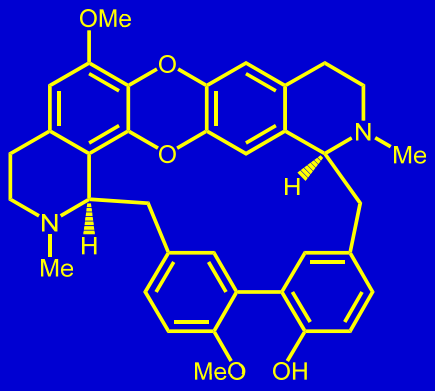
Antimycobacterial activity of bisbenzylisoquinoline alkaloids from *Tiliacora triandra* against multidrug-resistant isolates of *Mycobacterium tuberculosis*



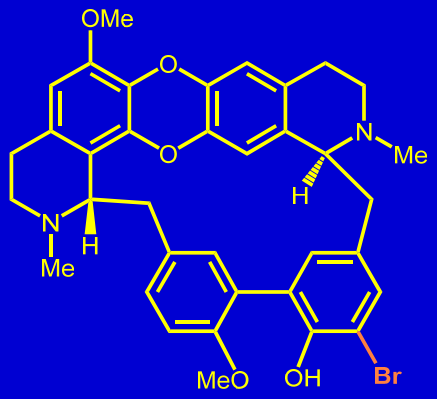
Tiliacorinine (1)



2'-Nortiliacorinine (2)



Tiliacorine (3)



13'-Bromo-tiliacorinine (4)

Bioorg. Med. Chem. Lett. 2012, *22*, 2902-2905

Antimycobacterial activity of bisbenzylisoquinoline alkaloids from *Tiliacora triandra* against multidrug-resistant isolates of *Mycobacterium tuberculosis*

Reference strains of *M. tuberculosis*	MIC value (μg/ml) of alkaloids			
	1	2	3	4
H37Ra	3.1	3.1	3.1	6.2
H37Rv	6.2	3.1	3.1	3.1
H37Rv-ETA-R ATCC 35830	3.1	6.2	3.1	3.1
H37Rv-PAS-R ATCC 35821	3.1	1.5	3.1	1.5
H37Rv-PZA-R ATCC 35828	6.2	6.2	6.2	3.1

H37Ra = Non-virulent strain; H37Rv = Virulent strain; H37Rv-ETA-R ATCC 35830 = Ethionamide resistant strain; H37Rv-PAS-R ATCC 35821 = *p*-Aminosalicylic acid resistant strain; and H37Rv-PZA-R ATCC 35828 = Pyrazinamide resistant strain

Bioorg. Med. Chem. Lett. 2012, *22*, 2902-2905

Antimycobacterial activity of bisbenzylisoquinoline alkaloids from *Tiliacora triandra* against multidrug-resistant isolates of *Mycobacterium tuberculosis*

Fifty-nine clinical isolates of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB)

MDR-TB isolates of *M. tuberculosis* (59 strains)	No. of strains	MIC value (μg/ml)			
		INH and RMP	EMB	SM	OFX
INH, RMP	12	2-≥ 8	≤ 2	≤ 2	≤ 2
INH, RMP, EMB	5	2-≥ 8	≥ 8	≤ 2	≤ 2
INH, RMP, SM	23	2-≥ 8	≤ 2	≥ 8	≤ 2
INH, RMP, EMB, SM	9	2-≥ 8	≥ 8	≥ 8	≤ 2
INH, RMP, EMB, OFX	1	2-≥ 8	≥ 8	≤ 2	≥ 4
INH, RMP, SM, OFX	1	2-≥ 8	≤ 2	≥ 8	≥ 4
INH, RMP, EMB, SM, OFX	8	2-≥ 8	≥ 8	≥ 8	≥ 4

MICs of isoniazid (INH), rifampin (RMP), ethambutol (EMB), streptomycin (SM), and ofloxacin (OFX) towards *Mycobacterium tuberculosis* isolates

Bioorg. Med. Chem. Lett. 2012, *22*, 2902-2905

Antimycobacterial activity of bisbenzylisoquinoline alkaloids from *Tiliacora triandra* against multidrug-resistant isolates of *Mycobacterium tuberculosis*

MICs of bisbenzylisoquinoline alkaloids for clinical multidrug-resistant isolates of *M. tuberculosis*

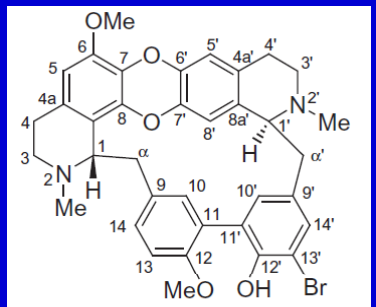
MDR-MTB isolates of *M. tuberculosis*	No. of strains	Tiliacorinine (**1**): No. of isolates for which MIC (μg/ml) is:			2′-Nortiliacorinine (**2**): No. of isolates for which MIC (μg/ml) is:				Tiliacorine (**3**): No. of isolates for which MIC (μg/ml) is:				13′-Bromo-tiliacorinine (**4**): No. of isolates for which MIC (μg/ml) is:		
		1.5	3.1	6.2	0.7	1.5	3.1	6.2	0.7	1.5	3.1	6.2	1.5	3.1	6.2
INH, RMP	12	2	6	4	–	2	7	3	–	3	6	3	5	7	–
INH, RMP, EMB	5	–	5	–	–	4	1	–	1	2	2	–	5	–	–
INH, RMP, SM	23	–	15	8		4	13	6	–	4	10	9	7	16	–
INH, RMP, EMB, SM	9	3	4	2	1	2	6	–	–	4	3	2	3	6	–
INH, RMP, EMB, OFX	1	–	1	–	–	1	–	–	–	1	–	–	1	–	–
INH, RMP, SM, OFX	1	–	1	–	–	–	1	–	–	–	1	–	–	1	–
INH, RMP, EMB, SM, OFX	8	1	5	2	–	5	3	–	–	4	2	2	4	4	–
Total	59	6	37	16	1	18	31	9	1	18	24	16	25	34	–

In general, four alkaloids gave the MIC value at 3.1 μg/ml against most multidrug-resistant mycobacterial isolates

Among the alkaloids tested, 13'-bromo-tiliacorinine (4) showed the MIC values at 1.5 (against 25 isolates) and 3.1 (against 34 isolates) μg/ml

Cytotoxicity toward normal cell line (MRC-5 cells):

Natural alkaloids 1-3: IC_{50} values of 3.13-3.87 μg/ml
Bromo derivative 4: IC_{50} value of 20.0 μg/ml



13'-Bromo-tiliacorinine (4)

Bioorg. Med. Chem. Lett. 2012, *22*, 2902-2905

Antimycobacterial activity of natural products and synthetic agents: pyrrolodiquinolines and vermelhotin as anti-tubercular leads against clinical multidrug resistant isolates of *Mycobacterium tuberculosis*, *Eur. J. Med. Chem.* 2015, *89*, 1-12

SCOPUS Citation: 33 times

Antimycobacterial activity:

-Various classes of natural products

-Synthetic compounds prepared by green chemistry approaches

The Twelve Principles of Green Chemistry

1. **Prevention**. It is better to prevent waste than to treat or clean up waste after it is formed.
2. **Atom Economy**. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemical Synthesis**. Whenever practicable, synthetic methodologies should be designed to use and generate substances that pose little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**. Chemical products should be designed to preserve efficacy of the function while reducing toxicity.
5. **Safer Solvents and Auxiliaries**. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.
6. **Design for Energy Efficiency**. Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks**. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives**. Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis**. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. **Design for Degradation**. Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. **Real-Time Analysis for Pollution Prevention**. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Anastas and Eghbali, Chem. Soc. Rev. 2010, 39, 301-312

2018 Green Chemistry Challenge Awards

♦Two winners optimized ***manufacturing processes for HIV drugs***. Synthesis of doravirine and nevirapine. By **using a common solvent for several transformations, the teams avoided multiple intermediate isolations,** and increased their chemical yields. "In both cases, the ***environmentally sustainable processes*** that were developed were also more economically attractive, which ***allowed a significant reduction in the cost of the drug***"

https://cen.acs.org/environment/green-chemistry/2018-Green-Chemistry-Challenge Awards/96/web/2018/10?utm_source=Newsletter&utm_medium=Newsletter&utm_campaign=CEN

An Organocatalyst from Renewable Materials for the Synthesis of Coumarins and Chromenes: Three-Component Reaction and Multigram Scale Synthesis

Green chemistry:
Renewable materials

Bovine tendons (เอ็นเนื้อ)
Food or waste from meat industry

Tendon hydrolysate: Oganocatalyst

Amino acids play an important role as organocatalysts for various reactions
(*Chem. Rev.* 2007, 107, 5471-5569; *Org. Biomol. Chem.* 2008, 6, 2047-2053)

Tendons are composed of various collagen fibers, which are proteins rich in hydroxyproline and proline (*Biochem. Biophys. Res. Commun.* 1973, 52, 106-114; *Biochem. J.* 1974, 1 39, 461-468)

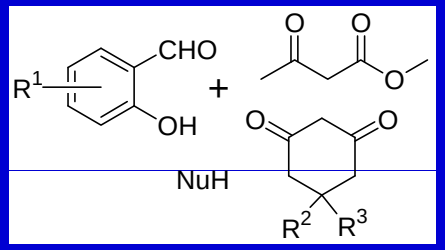
L-Proline and hydroxyproline are robust organocatalysts for many reactions
(*J. Am. Chem. Soc.* 2000, 122, 2395-2396; *Nature* 2008, 455, 304-308; *Org. Lett.* 2006, 8, 4653-4655)

RSC Advances 2014, 4, 13708-13718

An Organocatalyst from Renewable Materials for the Synthesis of Coumarins and Chromenes: Three-Component Reaction and Multigram Scale Synthesis

Bovine tendons

Acid hydrolysis



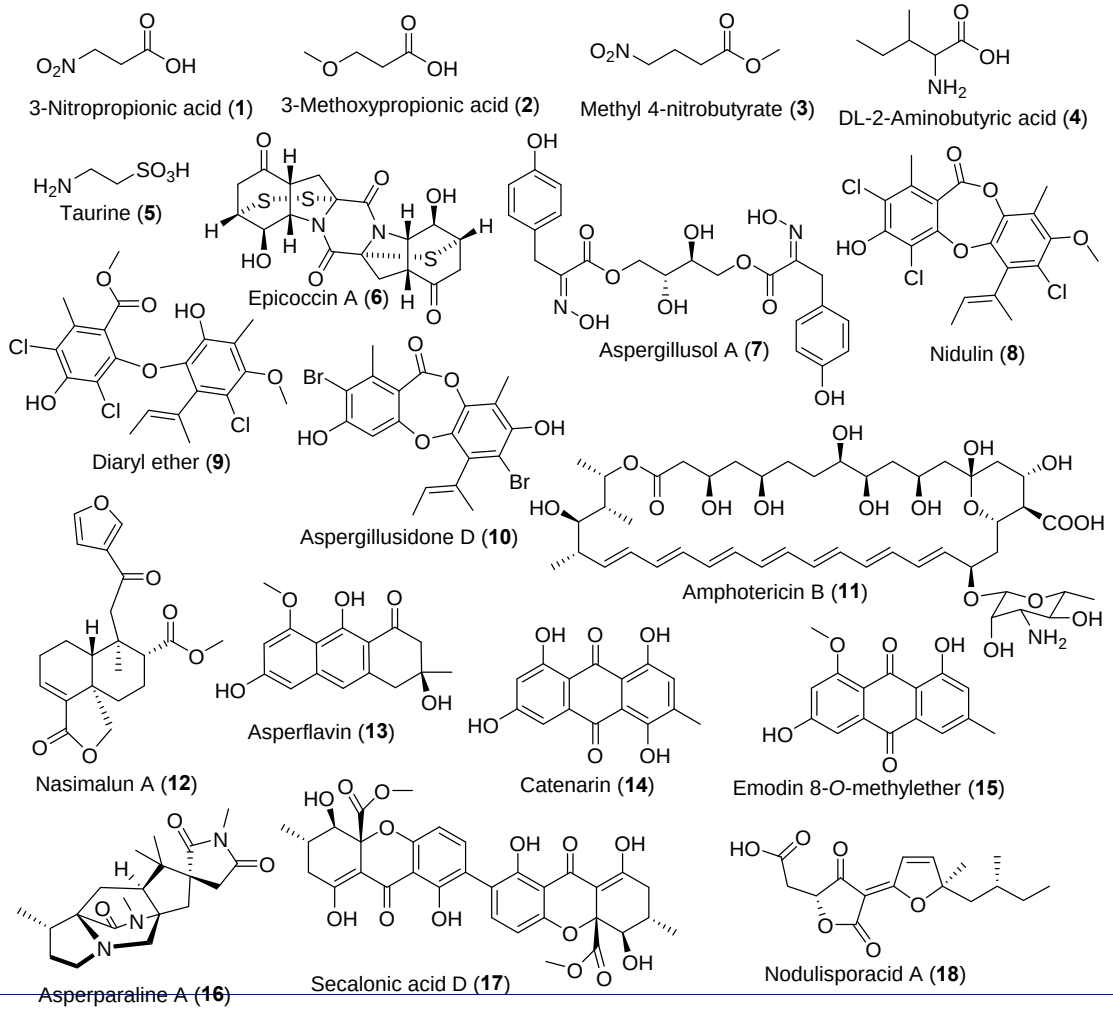
Solvent-free conditions or
Three-component reaction

Organocatalyst

Multigram scale synthesis

RSC Advances 2014, 4, 13708-13718

Antimycobacterial activity of natural products and synthetic agents: pyrrolodiquinolines and vermelhotin as anti-tubercular leads against clinical multidrug resistant isolates of *Mycobacterium tuberculosis*



Twenty-seven natural products were tested for anti-tubercular activity

Eur. J. Med. Chem. 2015, *89*, 1-12

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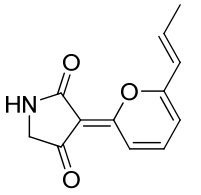
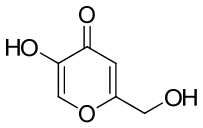
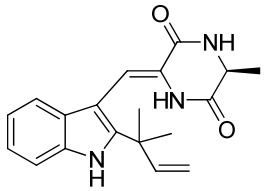


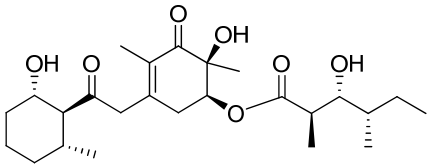
Vermelhotin (**19**)



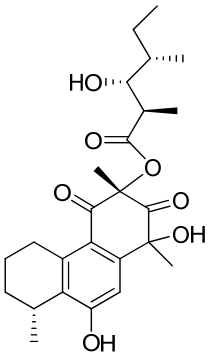
Kojic acid (**20**)



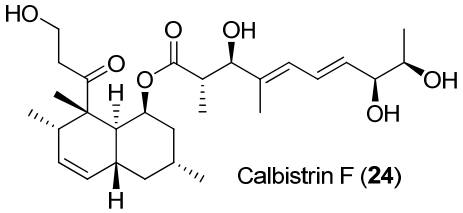
Neoechinulin A (**21**)



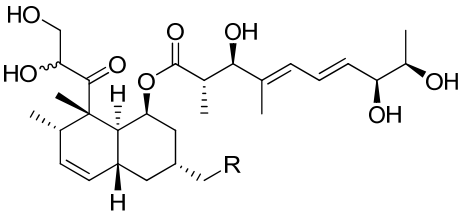
Dothideomycetone A (**22**)



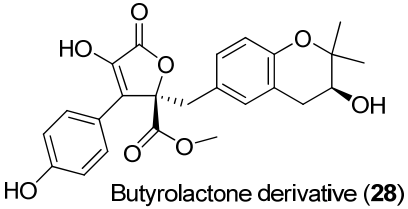
Dothideomycetide A (**23**)



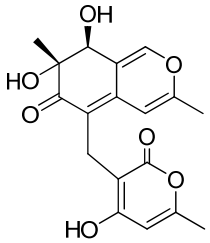
Calbistrin F (**24**)



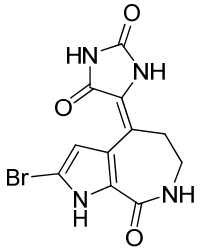
Calbistrin G, R = H (**25**)
Calbistrin H, R = OH (**26**)



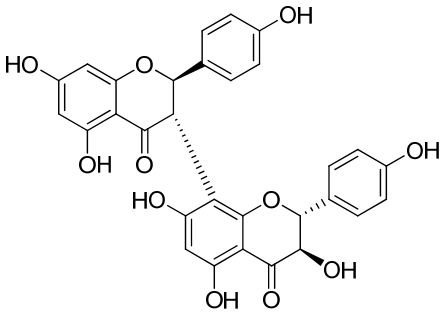
Butyrolactone derivative (**28**)



Dothideomynone B (**27**)



Axinohydantoin (**30**)



3",4',4"',5,5",7,7"-heptahydroxy-3,8-biflavanone (or known as GB1) (**29**)

Twenty-seven natural products were tested for anti-tubercular activity

Eur. J. Med. Chem. 2015, *89*, 1-12

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Vermelhotin

Isolated from an unidentified fungus CRI247-01

Phytochemistry 2008, 69: 2621-2626

Reference strains of *M. tuberculosis*	MIC value (µg/mL) of vermelhotin
H37Ra	3.1
H37Rv	6.2
H37Rv-ETA-R ATCC 35830	3.1
H37Rv-PAS-R ATCC 35821	3.1
H37Rv-PZA-R ATCC 35828	6.2

H37Ra = Non-virulent strain; H37Rv = Virulent strain; H37Rv-ETA-R ATCC 35830 = Ethionamide resistant strain; H37Rv-PAS-R ATCC 35821 = *p*-Aminosalicylic acid resistant strain; and H37Rv-PZA-R ATCC 35828 = Pyrazinamide resistant strain

Eur. J. Med. Chem. 2015, *89*, 1-12

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Vermelhotin

MDR TB isolates of *M. tuberculosis*	No. of strains	Vermelhotin : No. of isolates for which MIC (μg/mL) is:			
		1.5	3.1	6.2	12.5
INH, RMP	12	-	4	6	2
INH, RMP, EMB	5	-	3	2	-
INH, RMP, SM	23	1	11	10	1
INH, RMP, EMB, SM	9	-	4	5	-
INH, RMP, EMB, OFX	1	1	-	-	-
INH, RMP, SM, OFX	1	-	1	-	-
INH, RMP, EMB, SM, OFX	8	-	4	3	1
Total	59	2	27	26	4

Isoniazid (INH); rifampin (RMP); ethambutol (EMB); streptomycin (SM); ofloxacin (OFX)

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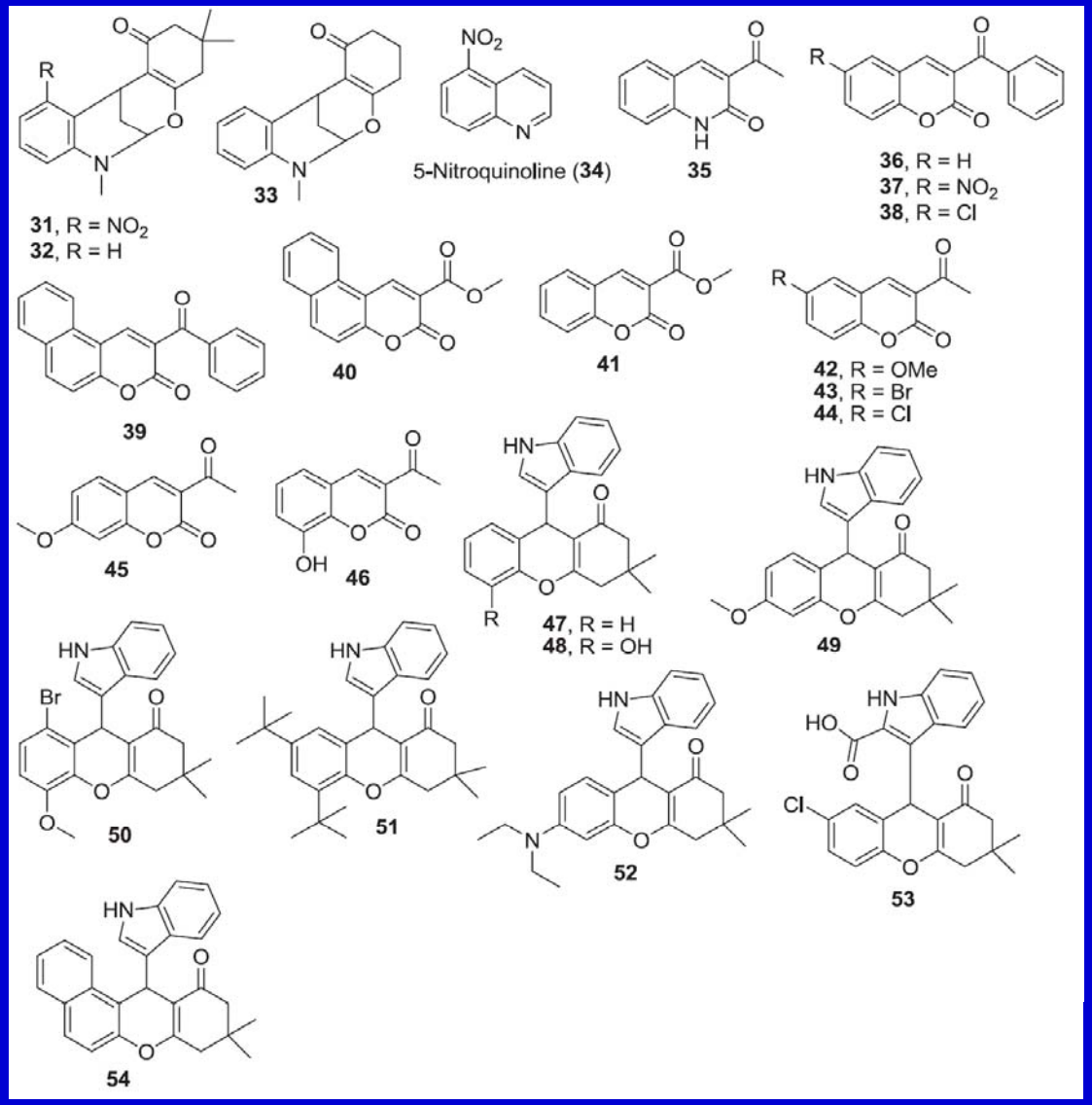

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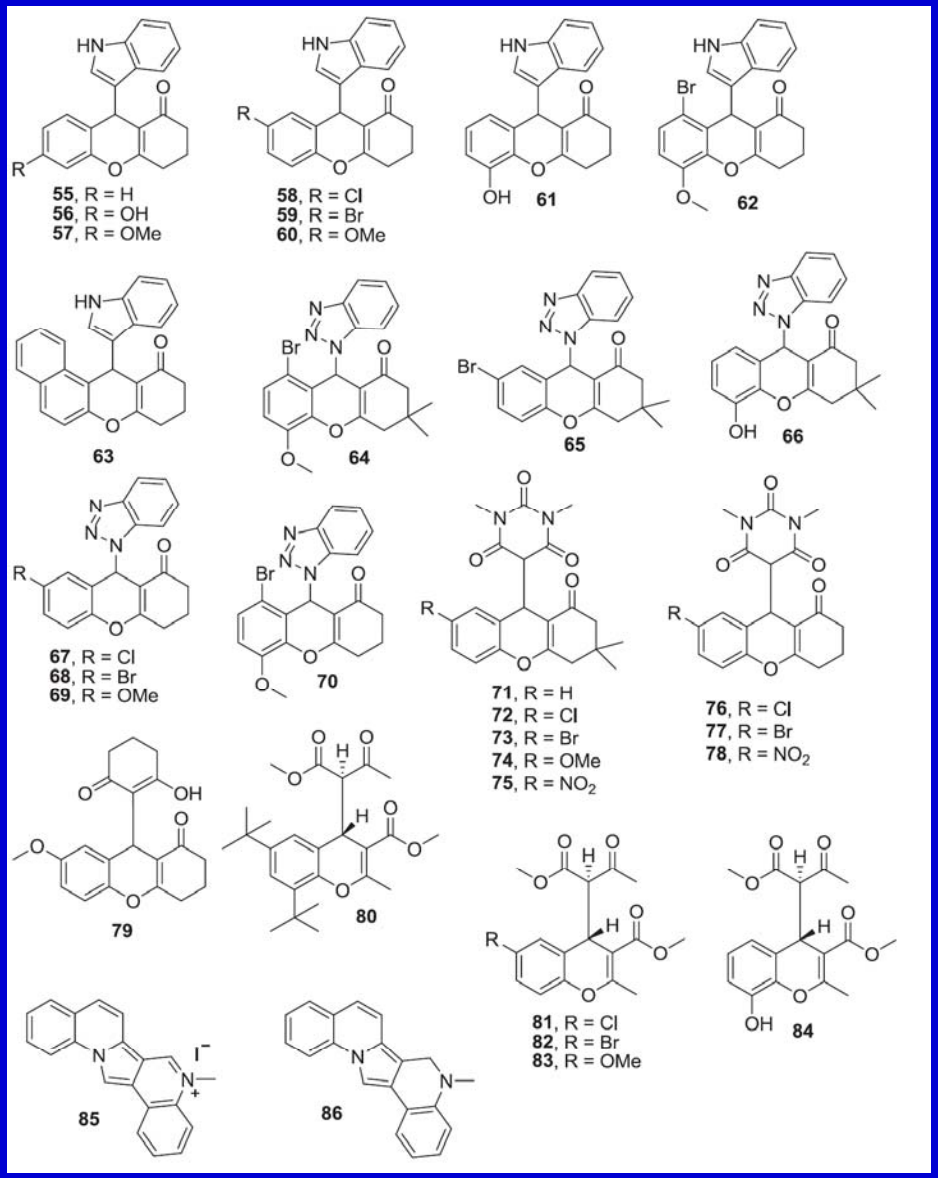

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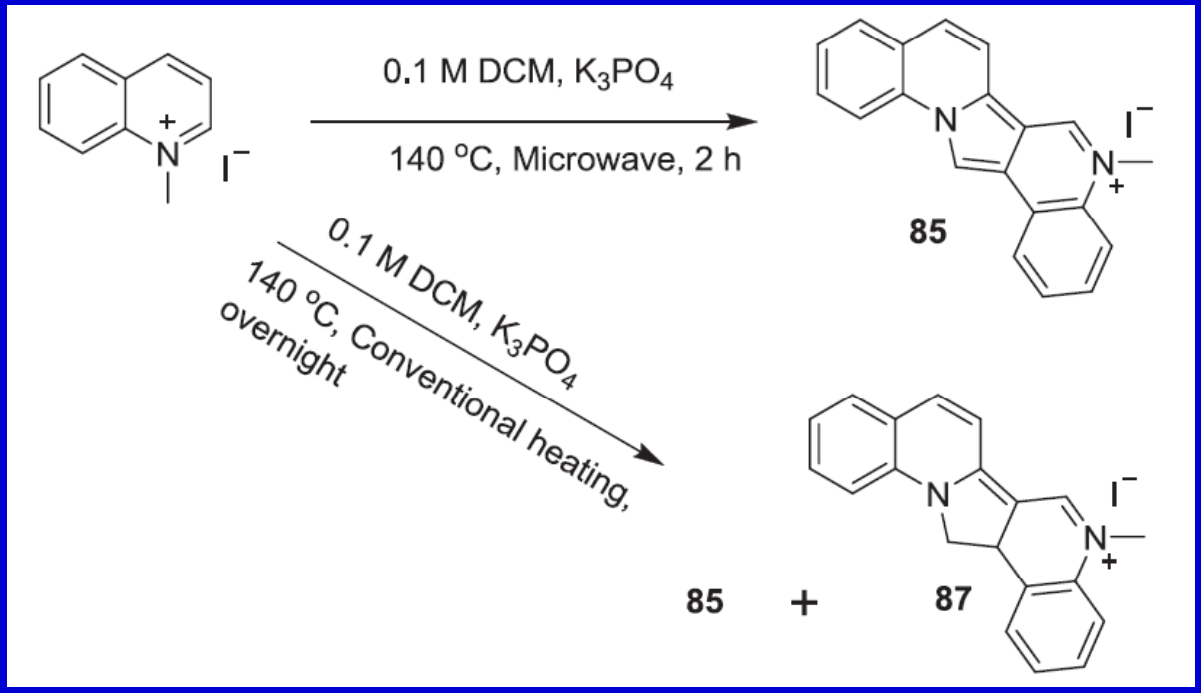

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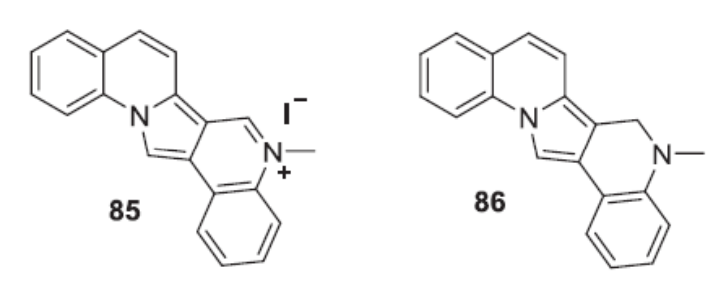
MIC values of compounds **85** and **86** for clinical multidrug-resistant isolates of *M. tuberculosis*.

MDR-TB isolates of *M. tuberculosis*	No. of strains	Compound **85**: No. of isolates for which MIC (μg/mL) is:					Compound **86**: No. of isolates for which MIC (μg/mL) is:				
		0.3	0.7	1.5	3.1	6.2	0.3	0.7	1.5	3.1	6.2
INH, RMP	12	2	1	3	6	–	2	1	2	7	–
INH, RMP, EMB	5	1	–	2	1	1	1	–	2	1	1
INH, RMP, SM	23	1	3	9	7	3	1	3	11	7	1
INH, RMP, EMB, SM	9	–	2	1	5	1	1	2	1	3	2
INH, RMP, EMB, OFX	1	–	–	–	1	–	–	–	–	1	–
INH, RMP, SM, OFX	1	–	–	–	1	–	–	–	1	–	–
INH, RMP, EMB, SM, OFX	8	–	–	2	5	1	–	–	3	4	1
Total	59	4	6	17	26	6	5	6	20	23	5



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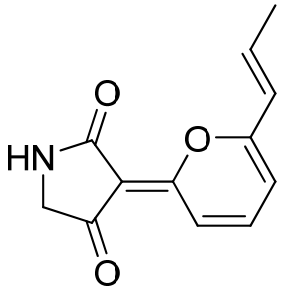
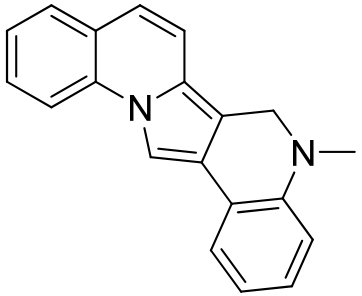


Vermelhotin (Natural product)

MIC 1.5-12.5 μg/mL against MDR TB



Synthetic compound

MIC 0.3-6.2 μg/mL against MDR TB

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Thank you for your attention