ORGANICKÁ SYNTÉZA PŘÍRODNÍCH LÁTEK JAKO NÁSTROJ PROTI ANTIBIOTICKÉ REZISTENCI

Přírodovědecká fakulta

Univerzita Palackého v Olomouci

ONDŘEJ KOVÁČ

Antibiotická rezistence v ČR: Jak společně zastavit nezastavitelné

19.11.2025

Kontakt: ondrej.kovac@upol.cz; https://kovaclab.com/

Antibiotická rezistence: globální hrozba 21. století

Operace

Transplantace

Dialýza

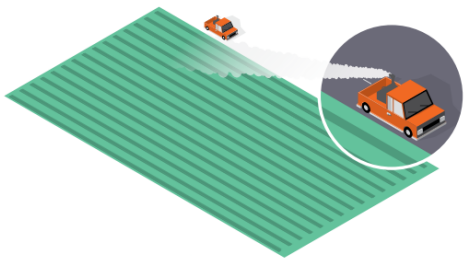
Chronická onemocnění

Sepse

Antibiotická rezistence

Onkologická péče

Veterinární medicína/
Hospodářství

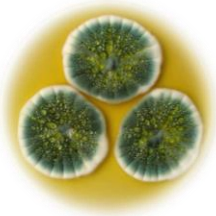


Zemědělství

https://www.cdc.gov/drugresistance/biggest-threats.html
Lancet **2022**, *399*, 629–655

Příroda: náš nejlepší chemik

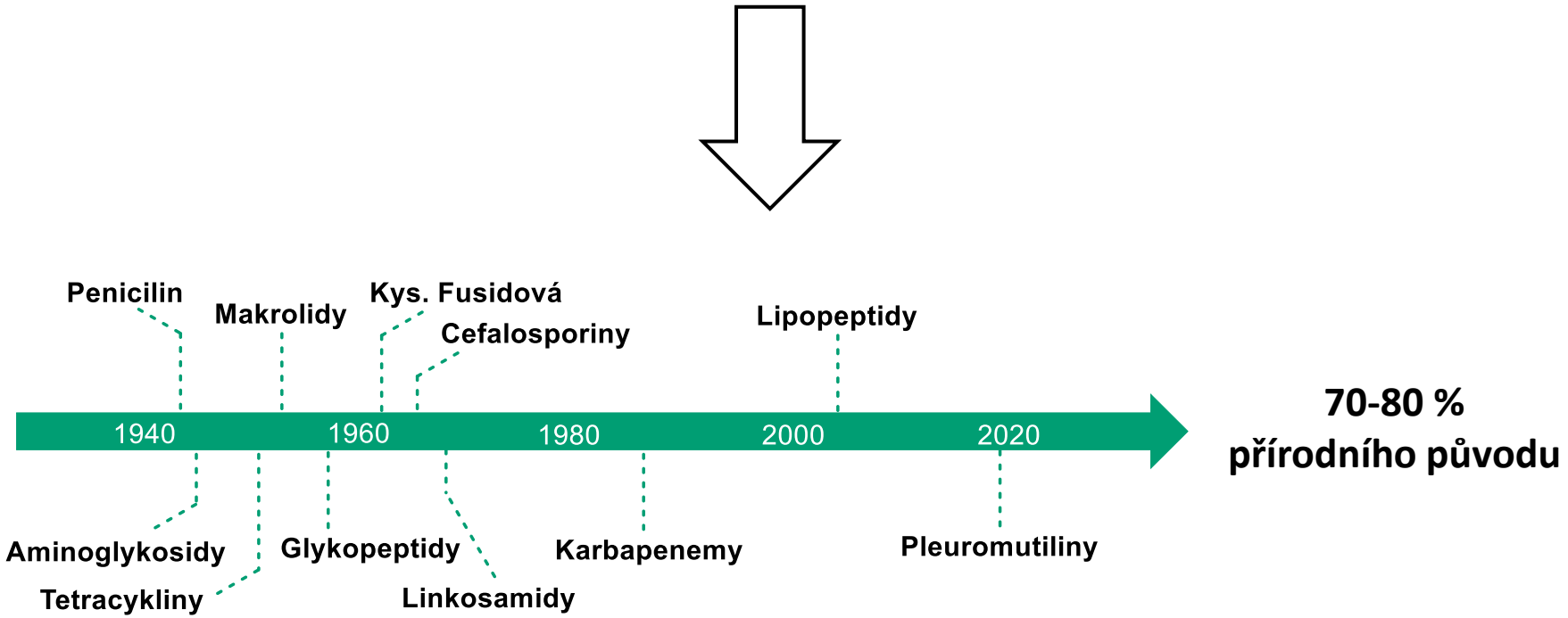
Kitasatospora spp.



Penicilium spp.

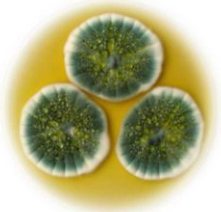
Omphalina spp.

Streptomyces spp.

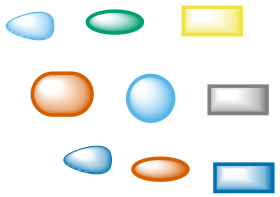


Nat. Rev. Chem. **2021**, *5*, 726–749
Curr. Opin. Biotechnol. **2022**, *78*, 102783

Příroda jako řešení ATB rezistence?

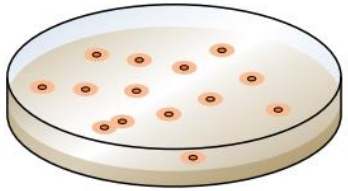


Izolace



Přírodní produkty

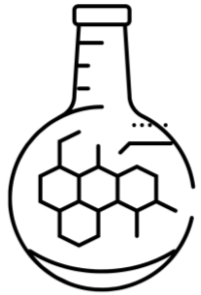
Testování



Antimikrobiální testy

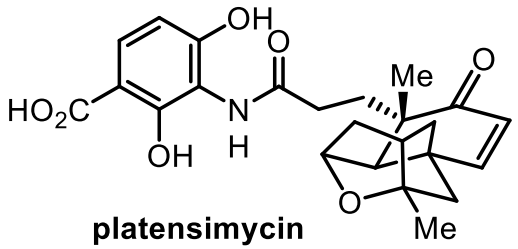
Nové ATB

Inspirace



Organická syntéza

Testování



platensimycin
[inhibice FabF]

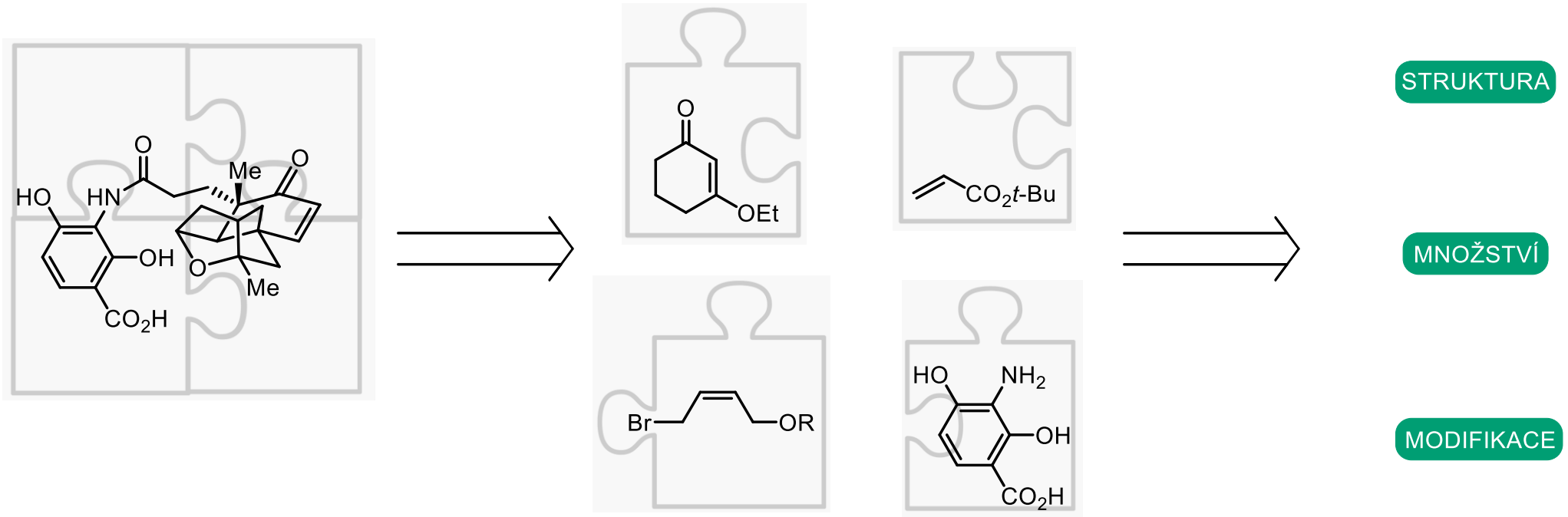
Izolace

1-2 mg / 10-20 L fermentační kultury

Nové ATB

Nat. Rev. Chem. **2021**, *5*, 726–749
Nature **2006**, *441*, 358–361

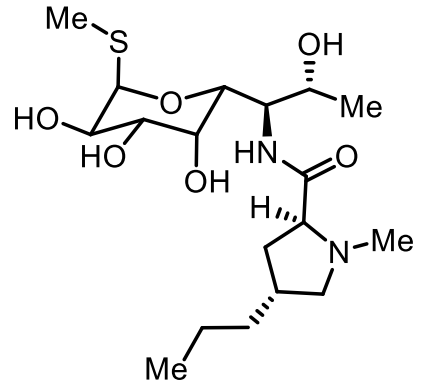
Organická syntéza = molekulární puzzle

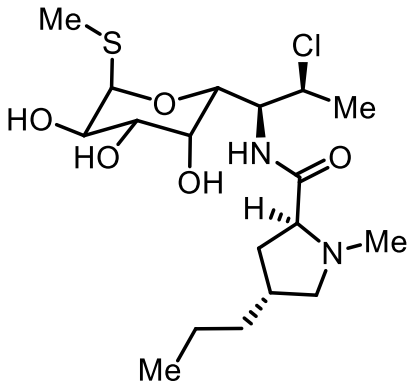


J. Am. Chem. Soc. **2009**, *131*, 16905–16918

Příběh Iboxamycinu (2021)

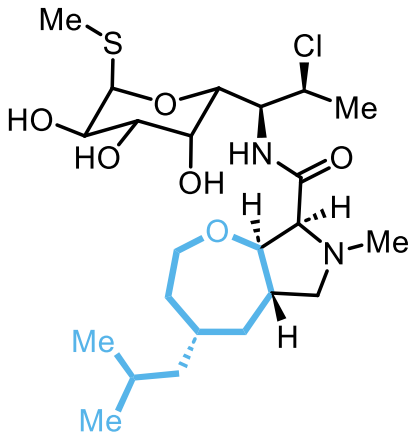
Lincomycin (FDA 1964)





Clindamycin (FDA 1970)

Syntéza + modifikace

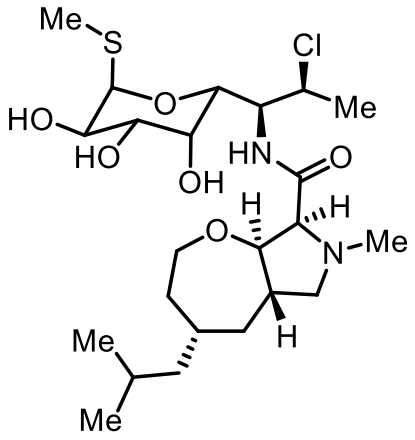


- ESKAPE
- Potlačení rezistence
- Nové vazebné místo
- Myší modely

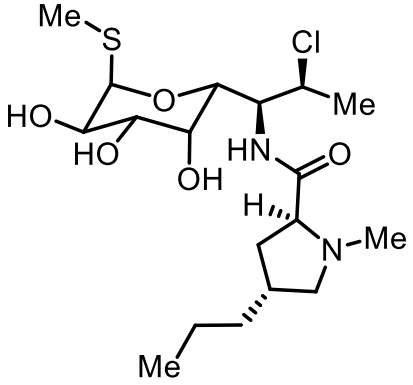
Gram-pozitivní bakterie → Zvýšení aktivity → **Gram-negativní bakterie**

Nature **2021**, *599*, 507–512

Příběh Iboxamycinu (2021)



Iboxamycin (IBX)



Clindamycin (CLI)

a

	Species	Strain description	IBX	CLI
Gram-positive	*S. aureus*	ATCC 29213	0.06	0.125
	S. aureus	Clinical; MDR, *c-ermA*	1	>256
	S. aureus	Clinical; *msrA*	0.06	0.125
	S. aureus	Clinical; *cfr*	2	>128
	S. epidermidis	Clinical; *cfr*	8	>128
	S. haemolyticus	Clinical; LNZ-R, MEC-R	0.06	2
	S. pneumoniae	Clinical; *c-ermB*	0.25	256
	S. pneumoniae	ATCC 700673; MDR	0.5	>64
	S. pyogenes	ATCC 19615	0.03	0.06
	E. faecalis	ATCC 29212; *lsaA*	0.06	16
	E. faecalis	Clinical; *c-ermB*	1	>256
	E. faecium	Clinical; VRE, *vanA*	1	>64
	C. difficile	ATCC 700057	0.25	8
Gram-negative	*B. fragilis*	ATCC 25285	0.5	1
	E. coli	ATCC 25922	8	>128
	K. pneumoniae	ATCC 10031	0.25	8
	K. pneumoniae	Clinical; FQ-R	8	>128
	K. oxytoca	Clinical	8	>128
	A. baumannii	ATCC 19606	4	>128
	P. aeruginosa	ATCC 27853	128	>128
	H. influenzae	ATCC 9007	0.5	8
	N. gonorrhoeae	Clinical	0.125	2

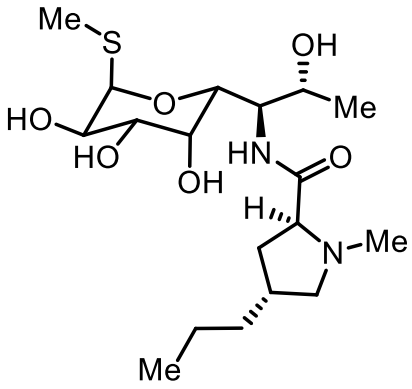
b

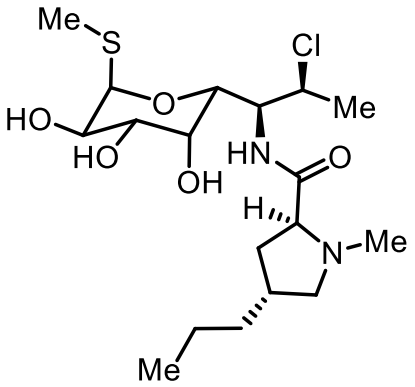
Species	Strain description	IBX	CLI	CTR	LEVO	AZM	DOXY	LNZ	VAN
S. aureus	ATCC BAA-1707; MRSA	0.06	0.125	64	>128	1	0.25	2	1
S. aureus	Clinical; MRSA	0.06	0.25	>128	1	1	64	2	2
S. aureus	ATCC 700699; *c-ermA*	2	>128	>128	32	>128	16	2	8
S. aureus	Clinical; *cfr*	2	>128	128	8	>128	0.25	16	>64
S. pneumoniae	Clinical; MLS_B	0.25	>64	1	0.25	>64	2	4	2
S. pyogenes	MMX 946; *c-ermB*	0.25	>256	≤0.03	0.5	>64	0.125	1	0.5
E. faecalis	Clinical; VRE	1	>256	>256	128	>128	16	2	>128
E. faecalis	Clinical; VRE	2	>256	>256	64	>128	1	16	>128
E. faecium	Clinical; VRE, LNZ-R	≤0.06	>64	>256	128	8	16	64	>256
E. faecium	Clinical; VRE	1	>256	>256	128	>128	0.25	4	>128

Nature **2021**, *599*, 507–512

Příběh BT-33 (2025)

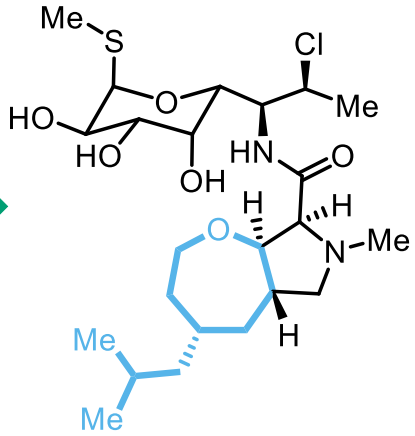
Lincomycin (FDA 1964)





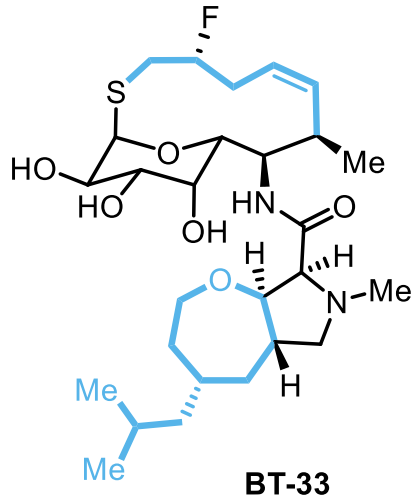
Clindamycin (FDA 1970)

Syntéza + modifikace



Iboxamycin (IBX)

Syntéza + modifikace

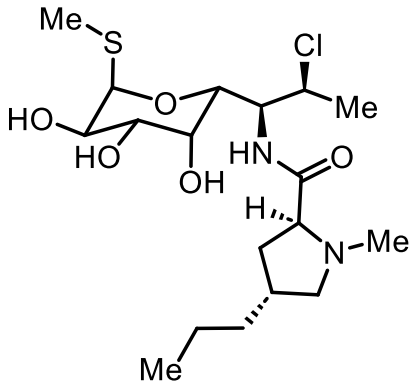


BT-33

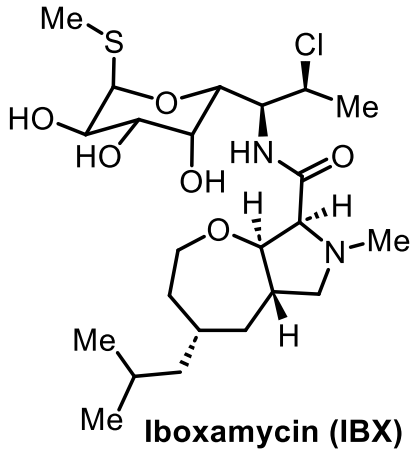
- **Potlačení rezistence**
- **Vyšší poločas rozpadu**
- **Myší modely**
- **Pre-klinické studie**

Nat. Chem. **2025**, *17*, 582–589
J. Am. Chem. Soc. **2024**, *146*, 29135–29139

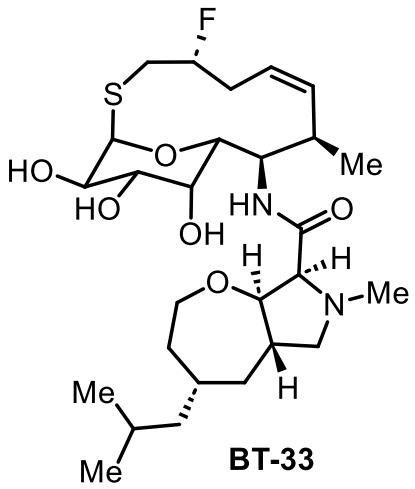
Příběh BT-33 (2025)



Clindamycin (CLI)



Iboxamycin (IBX)



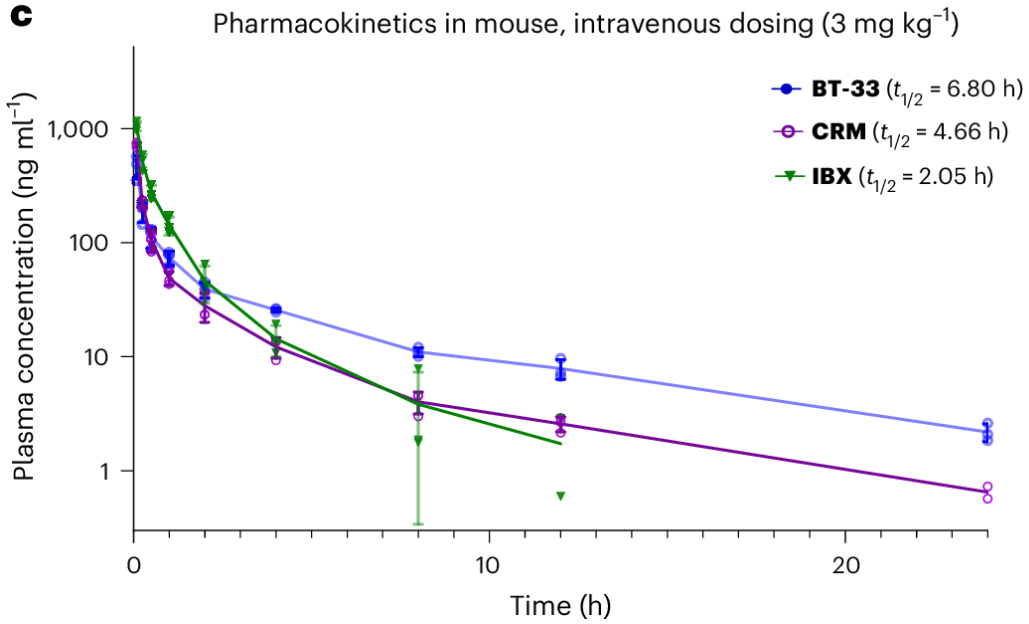
BT-33

a

Species	Isolate description	CLI	IBX	CRM	BT-33
S. aureus	*cfr*	>32	1	0.5	0.25
S. aureus	*c-ermA*	>32	4	0.5	0.25
S. aureus	*ermA, vgaA, lnuA*	>32	8	0.5	0.25
S. epidermidis	LZD-R, *ermA*	>32	>32	4	2
S. pneumoniae	*c-ermB*	>32	0.25	≤0.06	≤0.06
S. pyogenes	*c-ermB*	>32	0.25	≤0.06	≤0.06
E. faecalis	*lsaA*, VRE	>32	2	0.25	0.25
E. faecium	VRE	>32	4	0.125	≤0.06
E. coli	CRE	>32	16	2	2
E. coli	MDR	>32	16	8	4
K. pneumoniae	FQR	>32	8	4	2
A. baumannii	CRAB	>32	8	8	1
A. baumannii	CRAB	>32	32	8	4
P. aeruginosa	ATCC 27853	>32	>32	4	1

MIC (μg ml^{-1})	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32

c

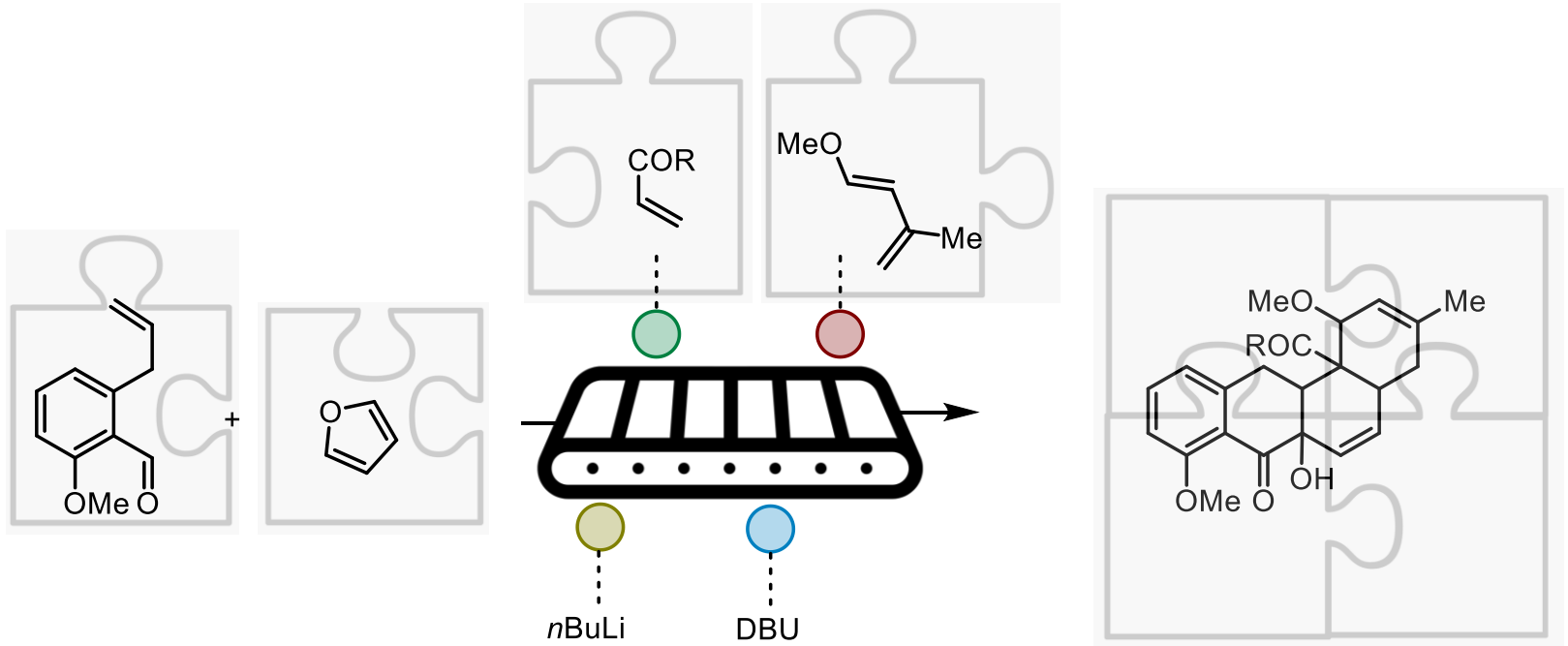


Nat. Chem. **2025**, *17*, 582–589

Náš přístup – Molekulární pásová výroba

Jednoduché výchozí látky

Komplexní molekula

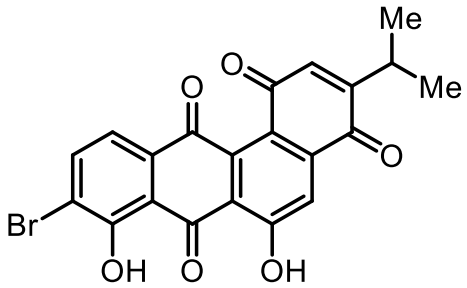


STRUKTURA

MNOŽSTVÍ

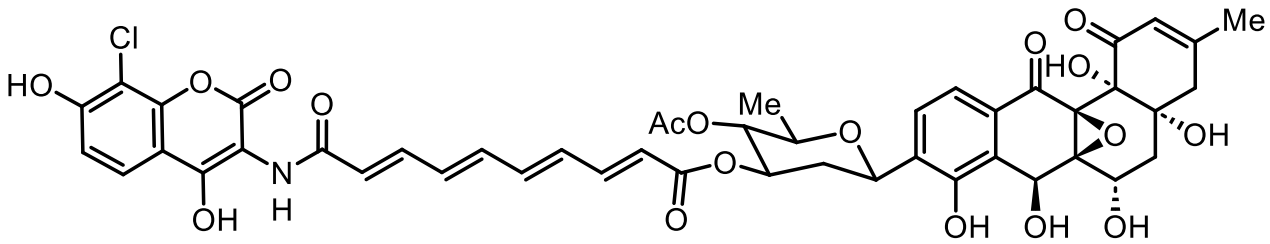
MODIFIKACE

nocardiopsistin D



- MIC = 0,098 μg/mL
- *anti*-MRSA, *anti*-VRSA

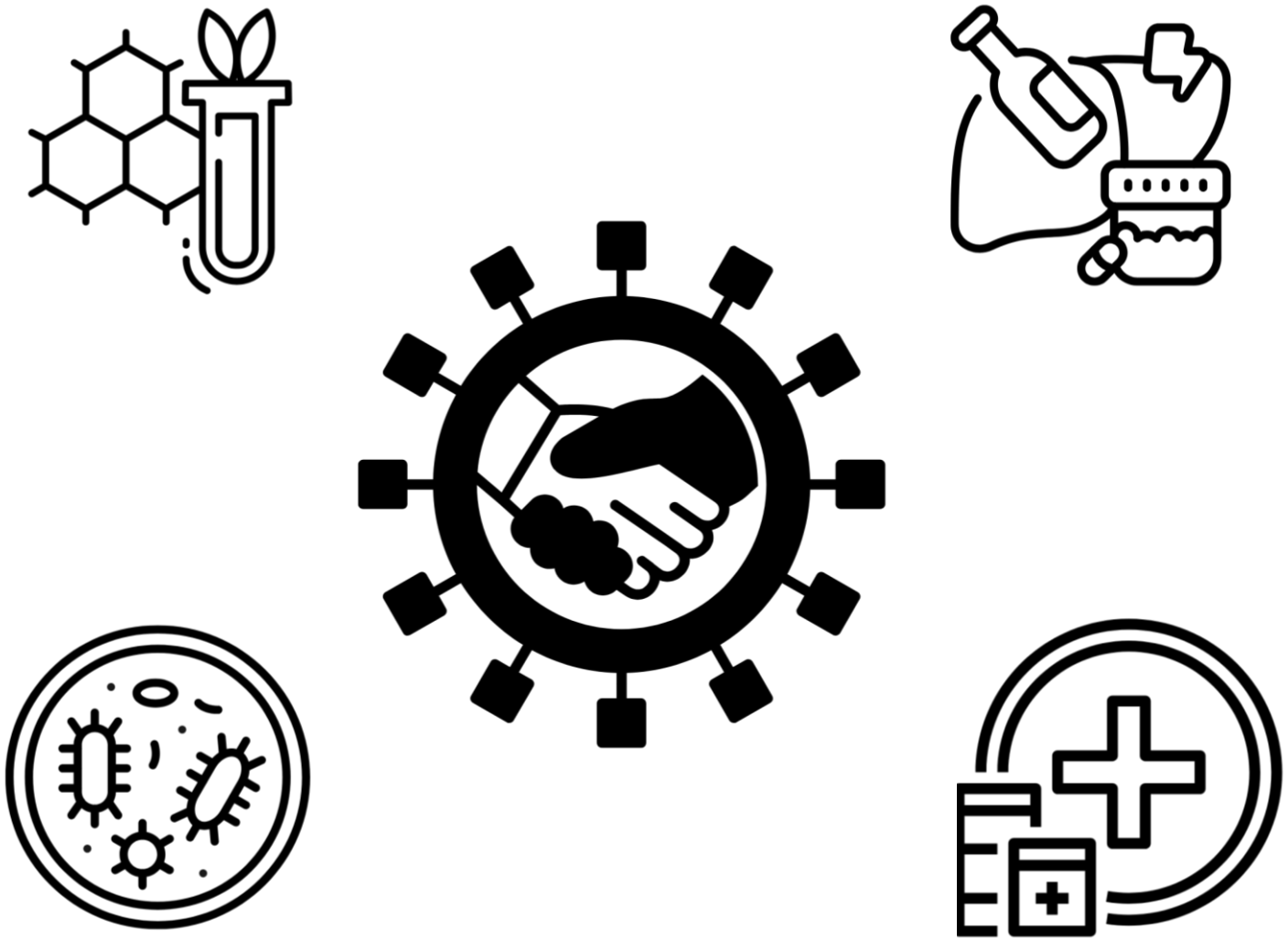
simocyclinone D8 (SD8)



- MIC = 4 μg/mL
- nový mechanismus účinku (DNA gyrasa)

Org. Lett. **2022**, *24*, 7900–7904; *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1202–1204; *Science* **2009**, *326*, 1415–1418

Bez spojení disciplín nová antibiotika nevzniknou



KováčLab 2025

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