Figure 5a

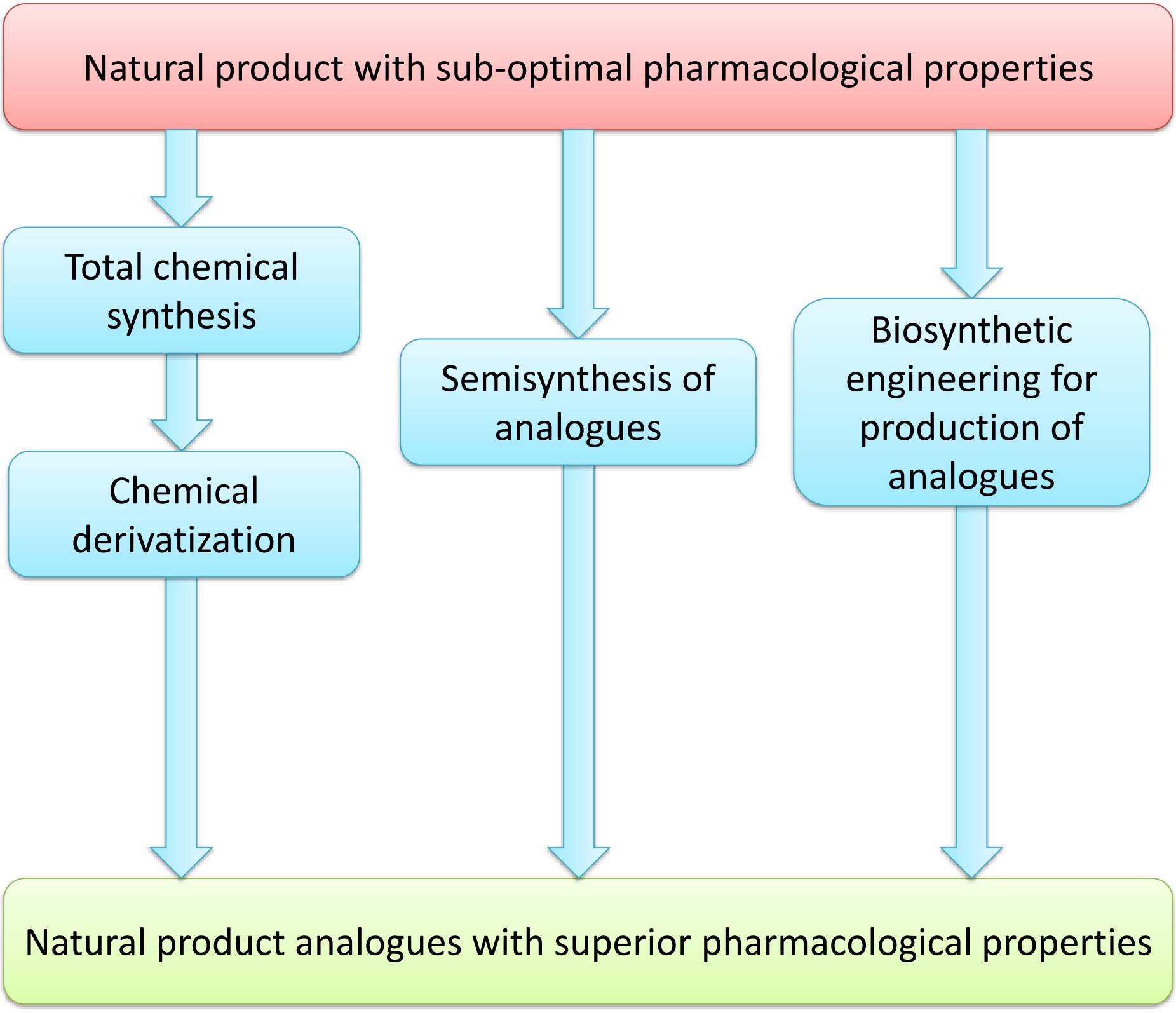
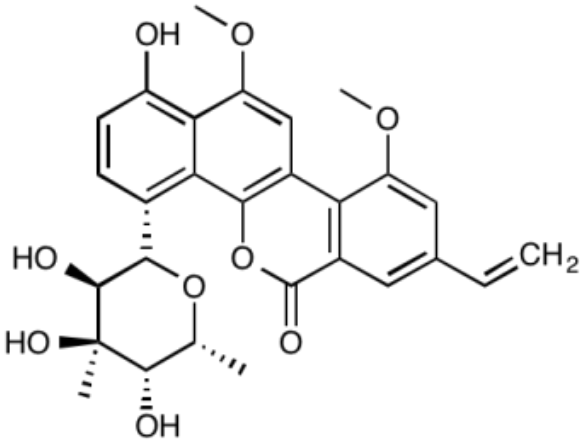

Natural product with sub-optimal pharmacological properties
Total chemical synthesis
Chemical derivatization
Semisynthesis of analogues
Biosynthetic engineering for production of analogues
Natural product analogues with superior pharmacological properties

Figure 5b



Chrysomycin A

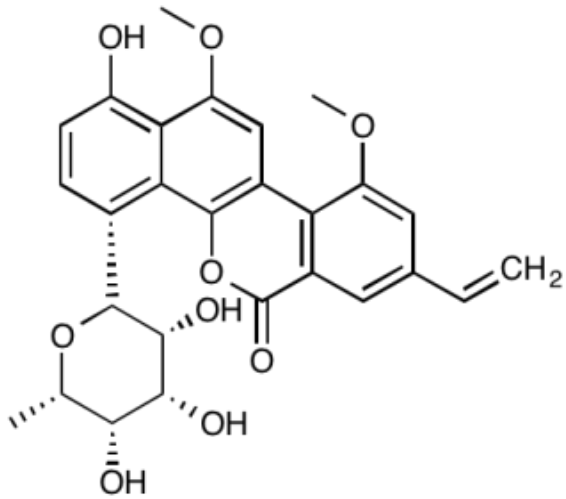
Chrysomycin A was identified as a hit in a highthroughput screen against multi-drug-resistant tuberculosis strains

↓

A 10-step scalable synthesis of chrysomycin A was developed, which also afforded the synthesis of 33 new analogues

↓

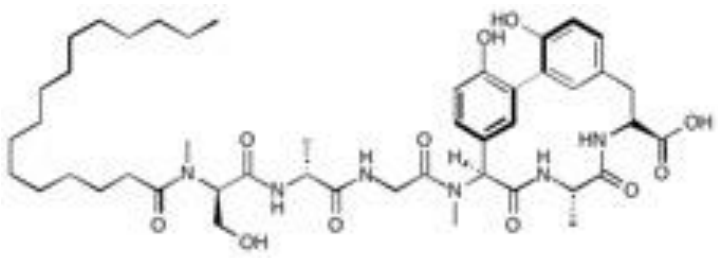
(+)-64, representing one of the new analogues, exhibited 5-fold stronger activity against multi-drug-resistant tuberculosis strains



(+)-64

Wu F, Zhang J, Song F, Wang S, Guo H, Wei Q, Dai H, Chen X, Xia X, Liu X, Zhang L, Yu JQ, Lei X. Chrysomycin A Derivatives for the Treatment of Multi-Drug-Resistant Tuberculosis. ACS Cent Sci. 2020 Jun 24;6(6):928-938. doi: 10.1021/acscentsci.0c00122. Epub 2020 May 4. PMID: 32607440; PMCID: PMC7318084.

Figure 5c

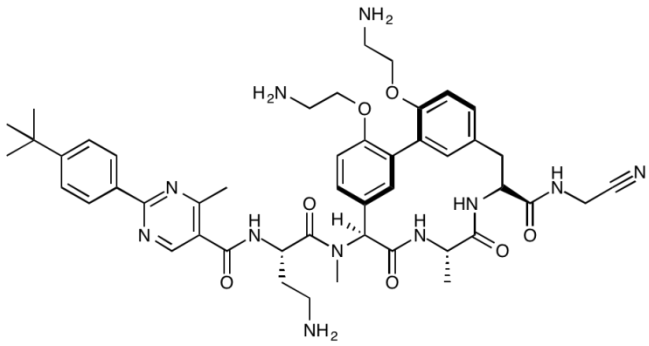


Arylomycin A-C_{16}

Arylomycins represent a class of NP antibiotics with weak activity and limited spectrum

Chemical derivatization of arylomycin A-C16 led to the discovery of G0775, which had more potent, broad-spectrum activity against Gram-negative bacteria

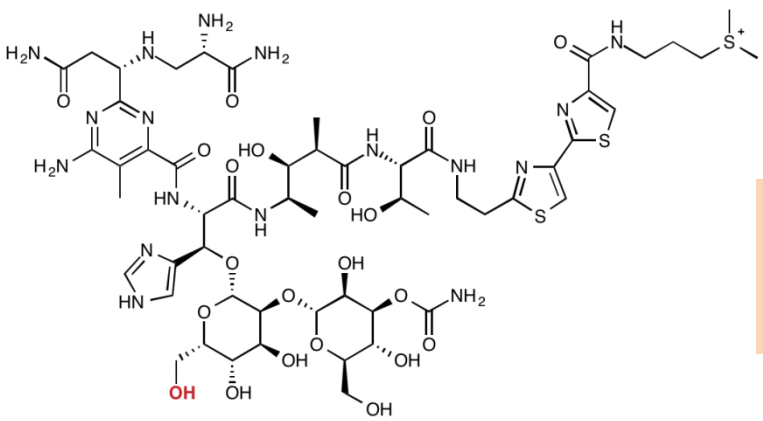
G0775 exhibits unprecedented molecular mechanism of action and activity against multidrug-resistant Gram-negative clinical isolates in vitro and in vivo



G0775

Smith, P.A., Koehler, M.F.T., Girgis, H.S. et al. Optimized arylomycins are a new class of Gram-negative antibiotics. Nature 561, 189–194 (2018). https://doi.org/10.1038/s41586-018-0483-6

Figure 5d



Bleomycin A2 (BLM A2)

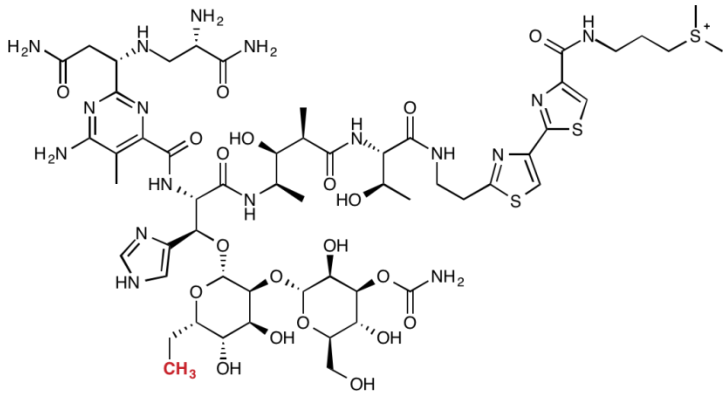
Streptomyces mobaraensis DSM40847 is identified by genome mining as a new bleomycin producer

↓

Targeted manipulation of the biosynthetic pathway of bleomycin in *S. mobaraensis* led to the production of 6′-deoxy-BLM A2

↓

6′-deoxy-BLM A2 exhibited more rapid DNA cleavage than bleomycin A2



6´-deoxy-Bleomycin A2 (6´-deoxy-BLM A2)

Hindra, Yang D, Teng Q, Dong LB, Crnovčić I, Huang T, Ge H, Shen B. Genome Mining of Streptomyces mobaraensis DSM40847 as a Bleomycin Producer Providing a Biotechnology Platform To Engineer Designer Bleomycin Analogues. Org Lett. 2017 Mar 17;19(6):1386-1389. doi: 10.1021/acs.orglett.7b00283.