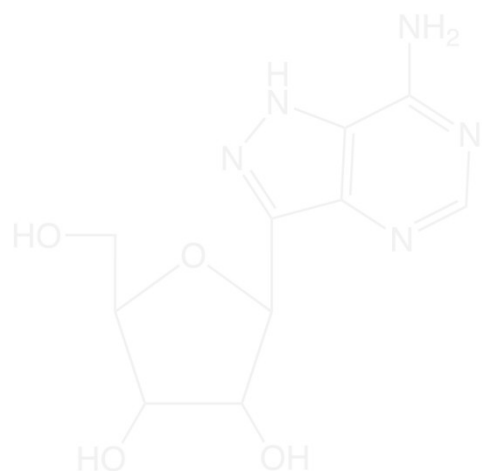
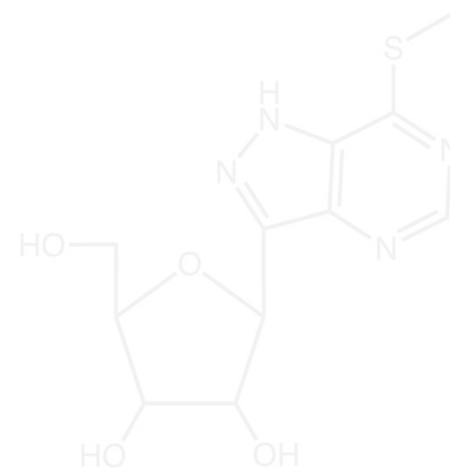
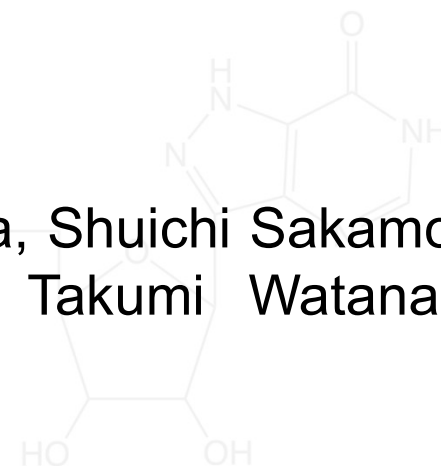




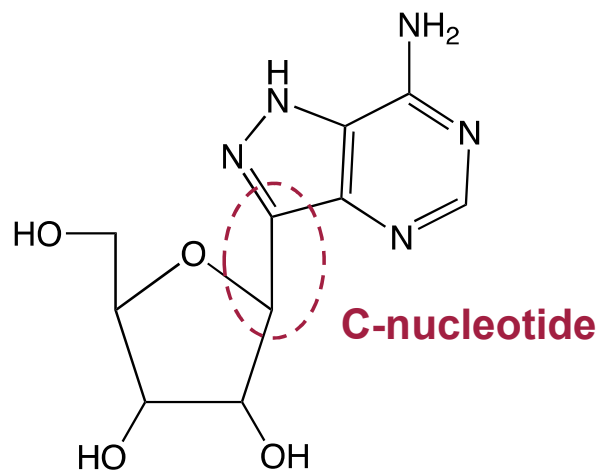
Formycin and its derivatives with diverse biological activities



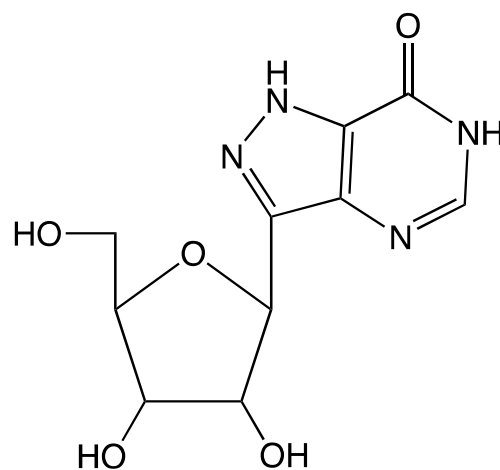
Naoki Takizawa, Hisashi Takada, Shuichi Sakamoto,
Ihomi Usami, Isao Momose, Takumi Watanabe,
Takao Shimizu



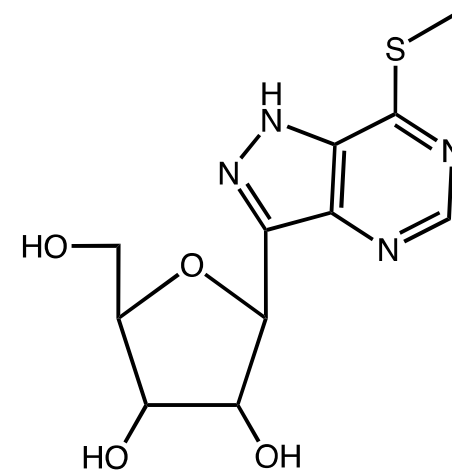
Formycin



Formycin A



Formycin B



Methyl-thio-formycin
(SMeFM)

Formycin A and Formycin B are natural products originally isolated by the Institute of Microbial Chemistry (BIKAKEN).
(J. Antibiotics, 17, 96-99 (1964))

Methyl-thio-formycin is a semisynthetic derivative of formycin A.

Anti-influenza virus activity of SMeFM

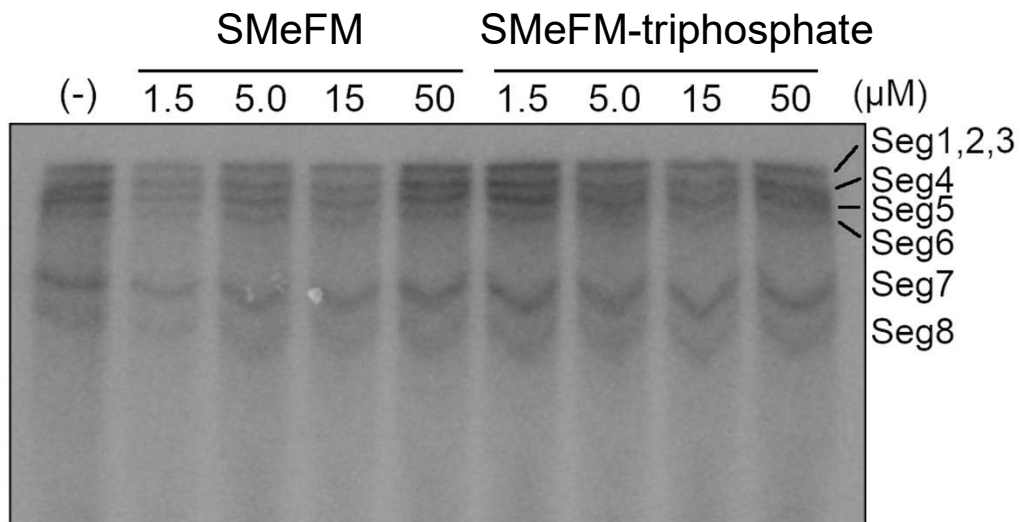
Strain	IC ₅₀ (nM)	Cell	CC ₅₀ (μM)	SI
A/WSN/33	34.1 ± 27.4	MDCK	14.6 ± 9.7	428.1
A/equine/2/Miami/63	43.8 ± 27.7			333.3
A/Kanagawa/ZC1802/2018 (H1N1pdm)	32.1 ± 5.0			454.8
A/Kanagawa/AC1877/2019 (H3N2)	23.6 ± 11.2			618.6
A/Kanagawa/IC1890/2019 (Xofluza resistance)	79.2 ± 26.6			184.3
A/Kanagawa/ZC1905/2019 (Tamiflu resistance)	55.4 ± 26.7			263.5
B/Lee/40	37.9 ± 26.6			385.2
B/Kanagawa/AC1807/2019 (Victoria)	60.0 ± 49.2			244.3
B/Kanagawa/IC1740/2018 (Yamagata)	47.8 ± 19.9	A549	20.8 ± 7.7	305.4
A/WSN/33	52.4 ± 1.1			396.9
A/WSN/33	24.4 ± 6.3	Calu-3	145.8 ± 41.5	5975

Takizawa N et al., Front. Microbiol. 13: 802671 (2022)

SMeFM exhibits potent anti-influenza virus activity

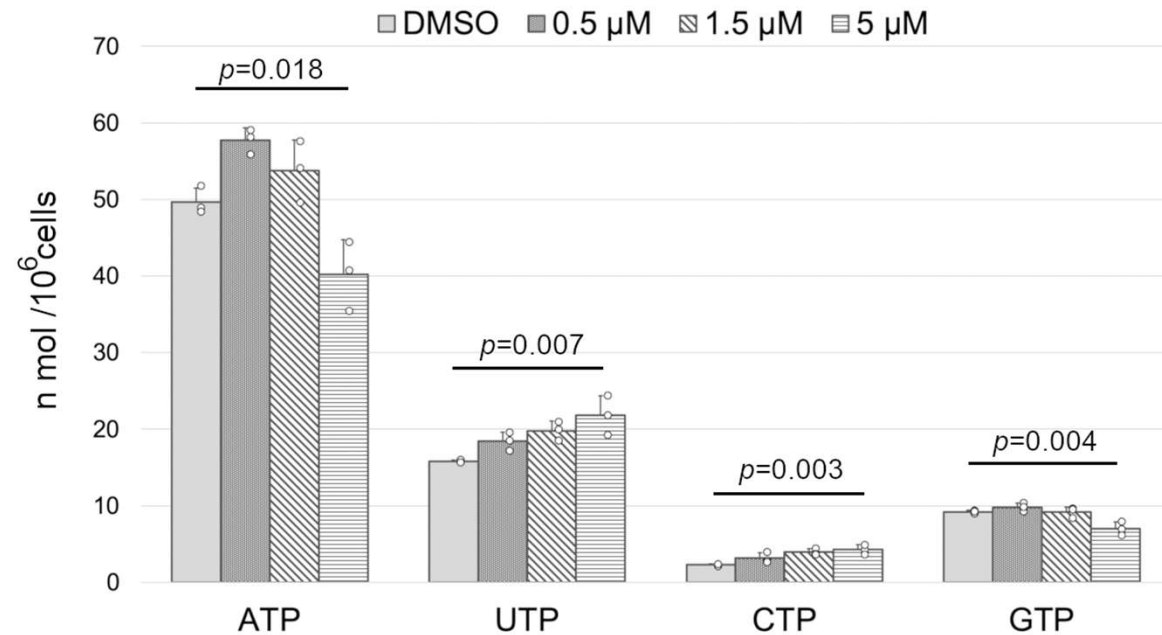
Inhibition of host factor(s) by SMeFM

In vitro viral RNA synthesis



SMeFM is not incorporated in viral RNA

Amount of NTPs in cells



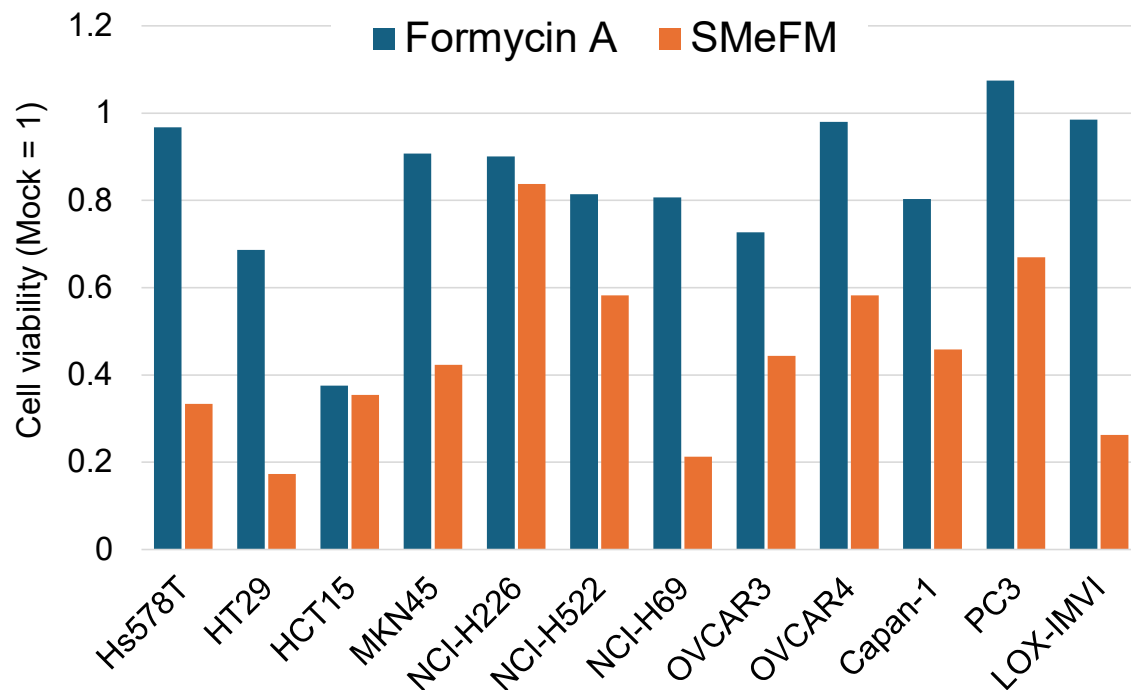
Purine nucleotides are reduced

Takizawa N et al., Front. Microbiol. 13: 802671 (2022)

SMeFM acts on host factor(s) rather than directly targeting viral proteins

Anti-tumor activity of formycins

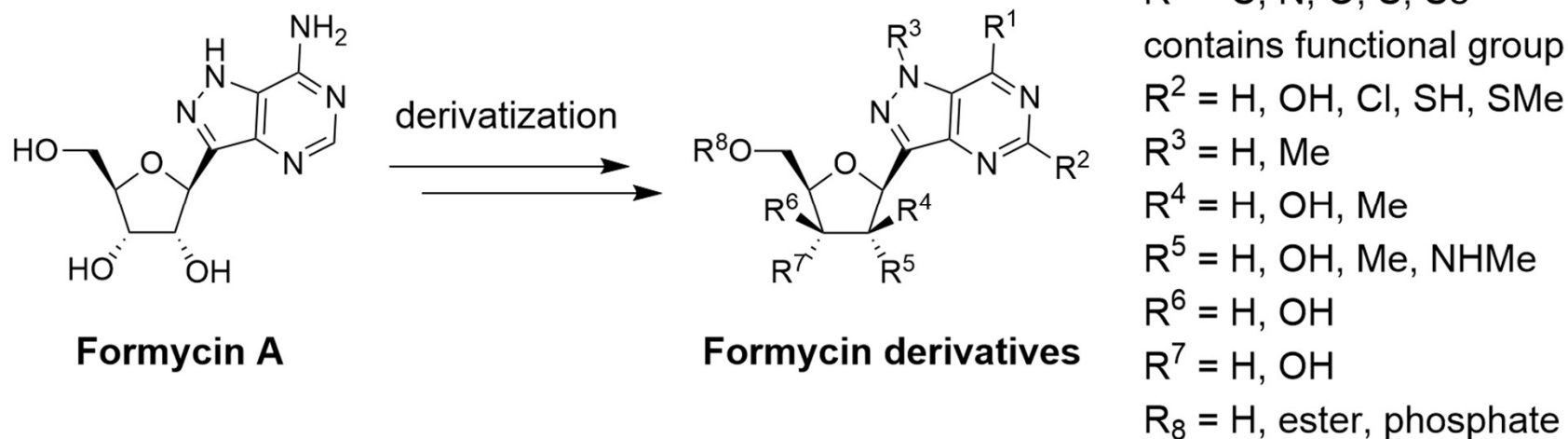
0.4 μ M, 72 h treatment (*in vitro*, MTT assay)



Cell Line	Cancer Type
Hs578T	Breast cancer (triple-negative breast cancer)
HT29	Colorectal cancer (colon adenocarcinoma)
HCT15	Colorectal cancer (colon adenocarcinoma)
MKN45	Gastric cancer (poorly differentiated adenocarcinoma)
NCI-H522	Lung cancer (Non-Small Cell Lung Cancer, adenocarcinoma)
NCI-H226	Lung cancer (Non-Small Cell Lung Cancer, squamous cell carcinoma)
NCI-H69	Lung cancer (Small Cell Lung Cancer, SCLC)
OVCAR4	Ovarian cancer (adenocarcinoma)
OVCAR3	Ovarian cancer (serous adenocarcinoma)
Capan-1	Pancreatic cancer (pancreatic ductal adenocarcinoma)
PC3	Prostate cancer (poorly differentiated adenocarcinoma, androgen-independent)
LOX-IMVI	Malignant melanoma

Formycin A and SMeFM exhibit antitumor activity

Formycin derivatives

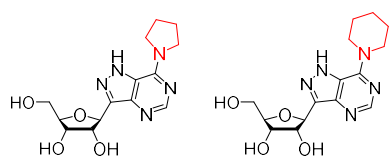
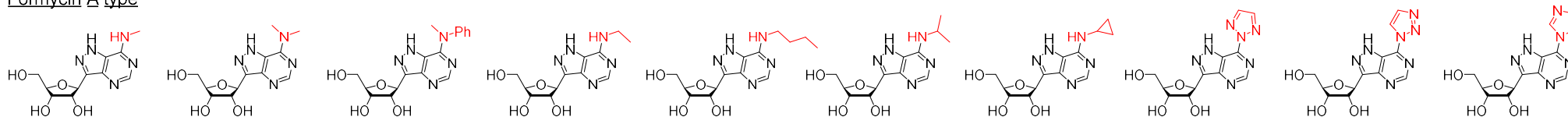


Semi-synthesis was performed using formycin A as the starting material, resulting in the production of over 60 types of derivatives.

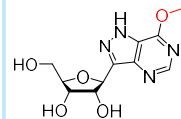
Takada H et al., Bioorg. Med. Chem. 57: 116613 (2022)

Formycin derivatives

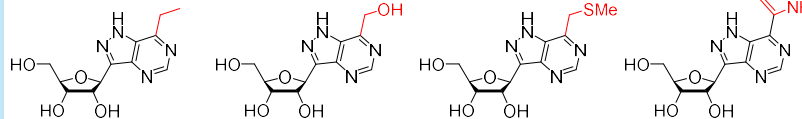
Formycin A type



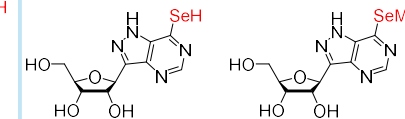
Formycin B type



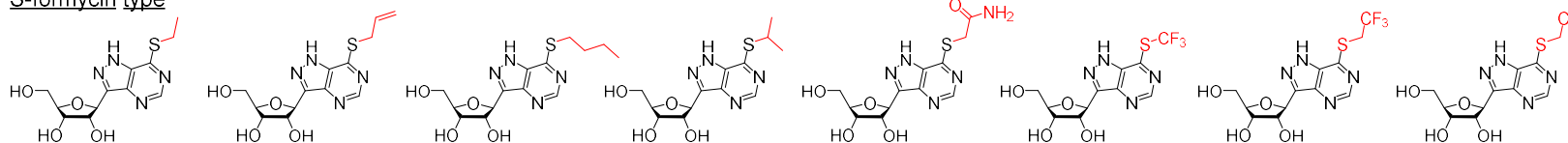
C-formycin type



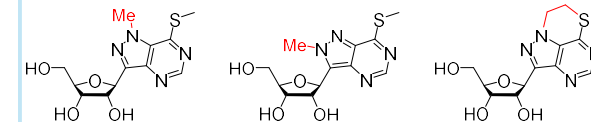
Se-formycin type



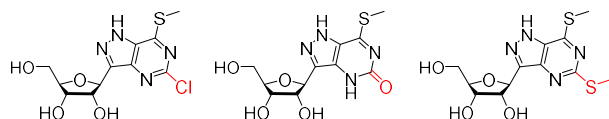
S-formycin type



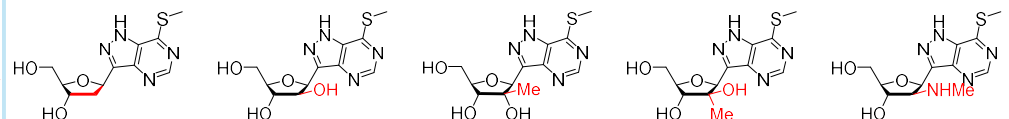
N¹ or N²-substituted type



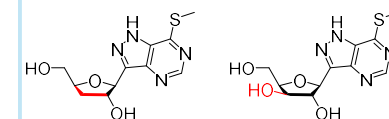
C⁵-substituted type



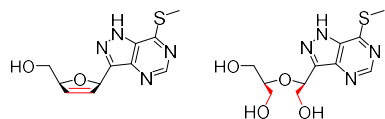
2'-modified compound



3'-modified compound

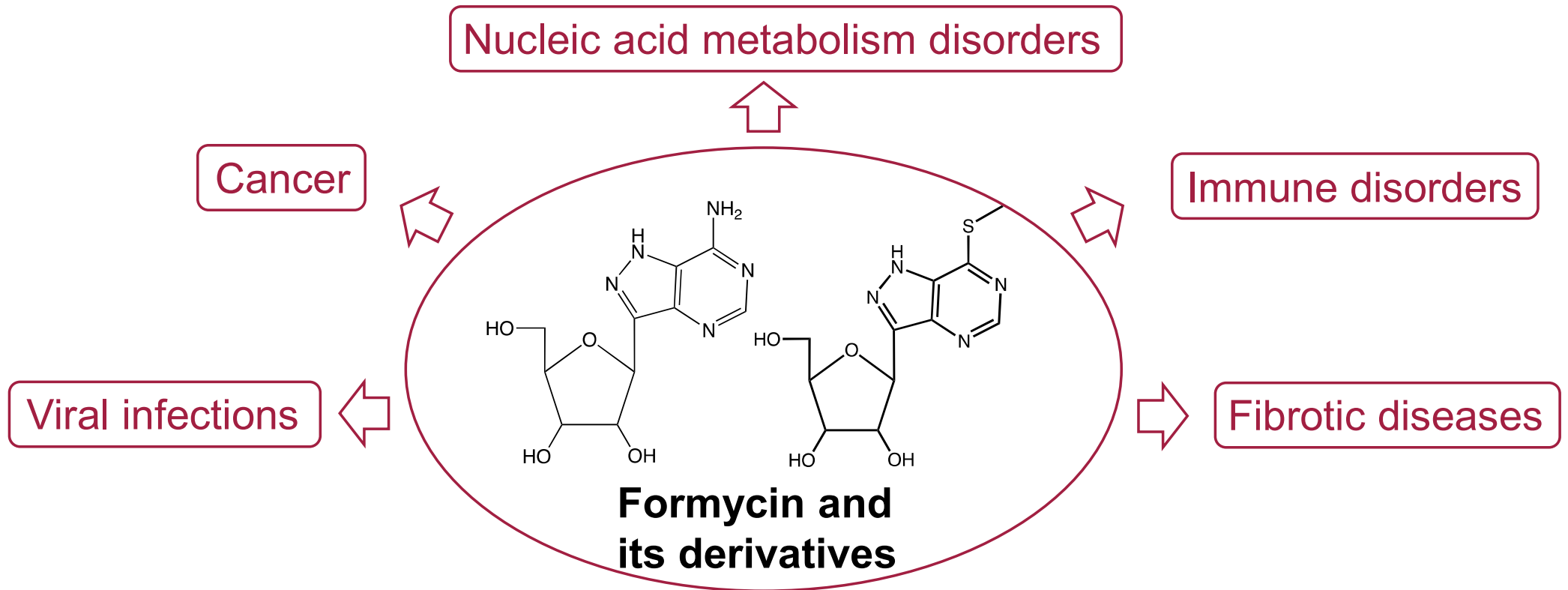


2', 3'-modified compound



Takada H et al., Bioorg. Med. Chem. 57: 116613 (2022)

Potential disease areas



Formycin and its derivatives may have therapeutic potential for a broad range of diseases, including viral infections, cancer, nucleic acid metabolism disorders, immune disorders, fibrotic diseases.