# TS149: additional project notes

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## Contents

# 1 summary

10 most promising drugs (sorted by relevance - top is most promsing):

- zafirlukast
- ebselen derivatives
- diethylstilbestrol
- dienestrol
- curcumin
- 2,3-Dichloro-1,4-naphthoquinone
- nifedipine
- hexachlorophene
- 2,2',4,4'-Tetrahydroxybenzophenone
- mefenamic acid

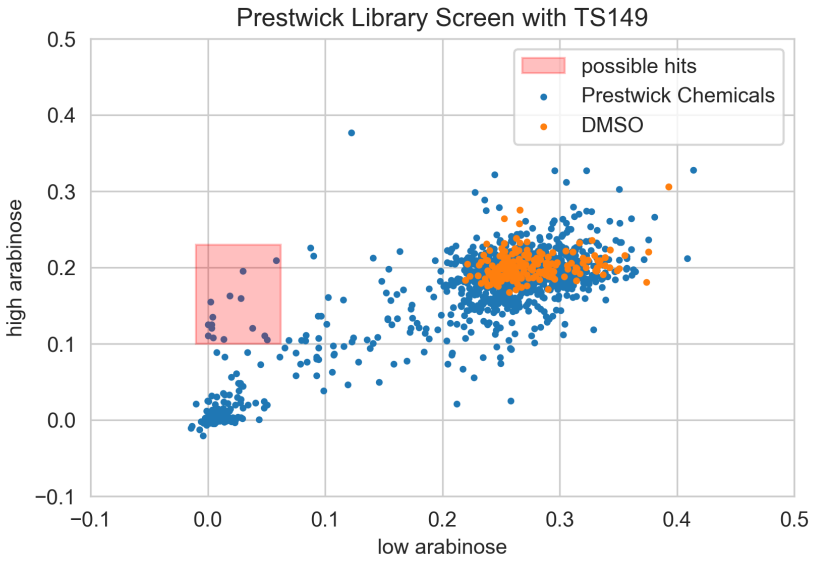
→ further experiments necessary, e.g.
- dose-response tests with TS149
- docking simulation with ASADH
- PCR to see if and which genes are upregulated?

Ranking of the other 14, less promising drugs (sorted by relevance - top is most promsing):

- haloprogin
- primaquine diphosphate
- bromocryptine mesylate
- saquinavir mesylate
- nomegestrol acetate
- reserpine
- thiorphan
- raclopride
- metixene hydrochloride
- 3,5-Pyrazoledicarboxylic acid monohydrate
- DL-2,3-Diaminopropionic acid monohydrochloride
- N-Iodosuccinimide
- phthaldialdehyde
- rosmarinic acid

# 2 drugscreen

## 2.1 Hits




| PCL number | Name | Class | Effect |
|---|---|---|---|
| 756* | Diethylstilbestrol | Endocrinology | |
| 798* | Dienestrol | Endocrinology | |
| 1033 | Nomegestrol acetate | Endocrinology | Contraceptive |
| 603 | Zafirlukast | Respiratory | Antiasthmatic |
| 54 | Mefenamic acid | Central Nervous System | Analgesic |
| 479 | Raclopride | Central Nervous System | |
| 193* | Oxolinic acid | Metabolism | Antibacterial |
| 780* | Cinoxacin | Metabolism | Antibacterial |
| 318 | Quinacrine dihydrochloride hydrate | Infectiology | Antihelmintic |
| 720* | Cefuroxime sodium salt | Infectiology | Antibacterial |
| 1118* | Cefepime hydrochloride | Infectiology | Antibacterial |
| 1250* | Cefpodoxime proxetil | Infectiology | Antibacterial |
| 1274* | Ceftibuten | Infectiology | Antibacterial |
| 555 | Nifuroxazide | Infectiology | Antibacterial |
| 792 | Propidium iodide | Infectiology | Antibacterial |
| 1100 | Toltrazuril | Infectiology | Anticoccidial |

* estrogen-receptor agonists colored in green, quinolones colored in blue, ß-lactams colored in yellow

### 2.1.1 Diethylstilbestrol and dienestrol

**OD values drug screen**

mean low/high: 0.0041 / 0.135
low Arabinose: 0.0043 0.0018 0.0041
high Arabinose: 0.1854 0.135 -0.0038
755 Diethylstilbestrol C18H20O2 268.3589 Store at room temperature 56-53-1 Endocrinology Prestw-756 10D07

mean low/high: 1E-04 / 0.125
low Arabinose: 1E-04 -0.0016 0.0043
high Arabinose: 0.125 0.2482 -0.0022
797 Dienestrol C18H18O2 266.34296 Store at room temperature 84-17-3 Endocrinology Prestw-798 10H09

**Notes**

- compounds are synthetic nonsteroidal estrogens and used to treat menopausal symptoms
- both have a very similar chemical structure
- both are inhibiting growth of Mtb: MIC > 64µM (Sebastián et al., 2017)
- both have antimicrobial effect against Corynebacterium ammoniagenes and Streptococcus pneumoniae (Sebastián et al., 2017)

**References**

Maier, L., Pruteanu, M., Kuhn, M., Zeller, G., Telzerow, A., Anderson, E. E., Brochado, A. R., Fernandez, K. C., Dose, H., Mori, H., Patil, K. R., Bork, P., & Typas, A. (2018). Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*, *555*(7698), 623–628. https://doi.org/10.1038/nature25979

Sebastián, M., Anoz-Carbonell, E., Gracia, B., Cossio, P., Ainsa, J. A., Lans, I., & Medina, M. (2017). Discovery of antimicrobial compounds targeting bacterial type FAD synthetases. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *33*(1), 241–254. https://doi.org/10.1080/14756366.2017.1411910

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### 2.1.2 Nomegestrol acetate

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0505 / 0.1052 |
| low Arabinose: | 0.0199 0.1012 0.0505 |
| high Arabinose: | 0.1052 0.1266 0.0799 |

1032 Nomegestrol acetate C23H30O4 370.49315 Store at room temperature 58652-20-3 Endocrinology Contraceptive Prestw-1033 13H04

**Notes**

- nomegestrol acetate is anagonist of progesteron receptors and used as a contraceptive
- no paper about antimicrobial effect or ASADH binding found yet

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### 2.1.3 Zafirlukast

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0582 / 0.2094 |
| low Arabinose: | 0.0582 0.2321 0.0514 |
| high Arabinose: | 0.212 0.2094 0.1959 |

602 Zafirlukast C31H33N3O6S 575.68916 Store at room temperature 107753-78-6 Respiratory Antiasthmatic Prestw-1364 08E04

**Notes**

- Zafirlukast acts as an antagonist of leukotriene receptors and is usedto treat asthma
- purified ASADH from streptococcus pneumoniae and vibrio cholerae was inhibited! (Thangavelu, 2016)
- inhibits growth of Mtb and Mycobacterium smegmatis (because of inhibition of lsr2-binding....but can't be the only reason!) (Pinault et al., 2013)
- usually does not inhibit growth of E.coli bacteria (Gerits et al., 2017; Pinault et al., 2013), but worked for TESEC strain because of deletion of tolC?!
- some derivatives with smaller chemical structures were synthesised already with better potency and less toxicity for epithelial cells (Chandrika et al., 2019)

**References**

Pinault, L., Han, J.-S., Kang, C.-M., Franco, J., & Ronning, D. R. (2013). Zafirlukast inhibits complexation of lsr2 with DNA and growth of mycobacterium tuberculosis. *Antimicrobial Agents and Chemotherapy*, *57*(5), 2134–2140. https://doi.org/10.1128/aac.02407-12

Chandrika, N. T., Fosso, M. Y., Alimova, Y., May, A., Gonzalez, O. A., & Garneau-Tsodikova, S. (2019). Novel zafirlukast derivatives exhibit selective antibacterial activity against porphyromonas gingivalis. *MedChemComm*, *10*(6), 926–933. https://doi.org/10.1039/c9md00074g

Gerits, E., der Massen, I. V., Vandamme, K., Cremer, K. D., Brucker, K. D., Thevissen, K., Cammue, B. P., Beullens, S., Fauvart, M., Verstraeten, N., & Michiels, J. (2017). In vitro activity of the antiasthmatic drug zafirlukast against the oral pathogens porphyromonas gingivalis and streptococcus mutans. *FEMS Microbiology Letters*, fnx005. https://doi.org/10.1093/femsle/fnx005

Thangavelu, B. (2016). *Development of selective inhibitors against metabolic enzymes involved in aspartate pathway for antibiotic development* (Doctoral dissertation). The University of Toledo

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### 2.1.4 Mefenamic acid

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0382 / 0.1203 |
| low Arabinose: | 0.0382 0.3367 0.0162 |
| high Arabinose: | 0.0773 0.1483 0.1203 |

53 Mefenamic acid C15H15NO2 241.2923 Store at room temperature 61-68-7 Central Nervous System Analgesic Prestw-54 01F05

**Notes**

- inhibits cyclooxygenase-2 (COX-2) and used to treat mild to moderate pain
- positive influence of COX-2 inhibition on the severity and outcome of *S. pyogenes* infection in mice (Goldmann et al., 2010)
- weak antimicrobial action of tolfenamic acid and niflumic acid, two other COX-2 inhibitors (Sebastian et al., 2017). (have a highly similar chemical structure as the hit compound mefenamic acid: Fenamates)

- The influence of niflumic acid on the $PGE_2$ levels in with *Mtb* infected mice and the disease severity was evaluated in study (Moreno et al., 2002). It was shown that a treatment with niflumic acid in a later phase of infection was reducing the number of *Mtb* in the lungs. The author J. Rangel Moreno is explaining this effect with the modulation of the immune system via changed $PGE_2$ levels.
- all 6 fenamates were inhibiting cell growth of TS149 (in high and low arabionse; exept of mefenamic acid: inhibition just in low arabinose)

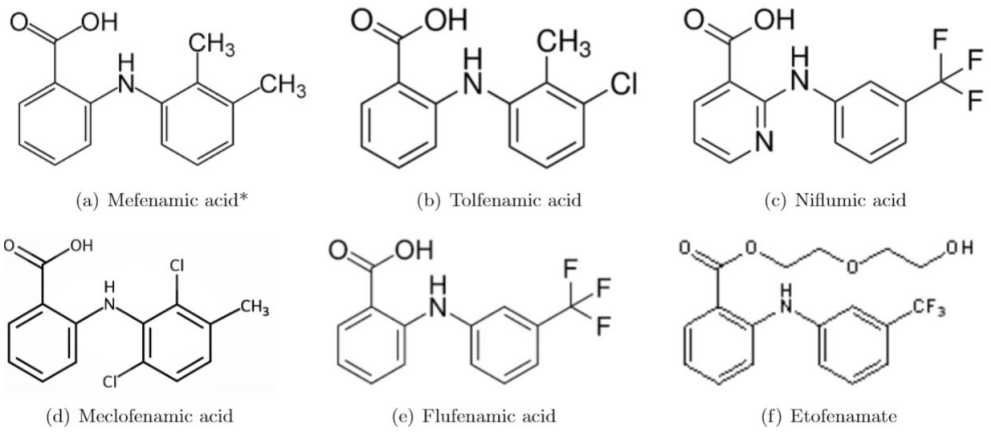


Figure 1: Chemical structures of the 6 fenamate derivatives *Hitcompound

**References**

Moreno, J. R., Garcia, I. E., de la Luz Garcia Hernandez, M., Leon, D. A., Marquez, R., & Pando, R. H. (2002). The role of prostaglandin e2 in the immunopathogenesis of experimental pulmonary tuberculosis. *Immunology*, *106*(2), 257–266. https://doi.org/10.1046/j.1365-2567.2002.01403.x

Sebastian, M., Anoz-Carbonell, E., Gracia, B., Cossio, P., Ainsa, J. A., Lans, I., & Medina, M. (2017). Discovery of antimicrobial compounds targeting bacterial type FAD synthetases. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *33*(1), 241–254. https://doi.org/10.1080/14756366.2017.1411910

Goldmann, O., Hertzén, E., Hecht, A., Schmidt, H., Lehne, S., Norrby-Teglund, A., & Medina, E. (2010). Inducible cyclooxygenase released prostaglandin e2 modulates the severity of infection caused by streptococcus pyogenes. *The Journal of Immunology*, *185*(4), 2372–2381. https://doi.org/10.4049/jimmunol.1000838

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### 2.1.5 Raclopride

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0689 / 0.1045 |
| low Arabinose: | 0.0592 0.0689 0.0971 |
| high Arabinose: | 0.0777 0.1045 0.1381 |

478 Raclopride C15H20Cl2N2O3 347.24425 Store at room temperature 84225-95-6 Central Nervous System Prestw-1325 06H10

**Notes**

- antagonist of D2 dopamine receptors

- when labeled with 11C, is suitable and widely used for quantitative imaging of dopamine D2 receptors (D2R) in the brain striatum with PET
- no paper about antimicrobial effect or ASADH binding found yet

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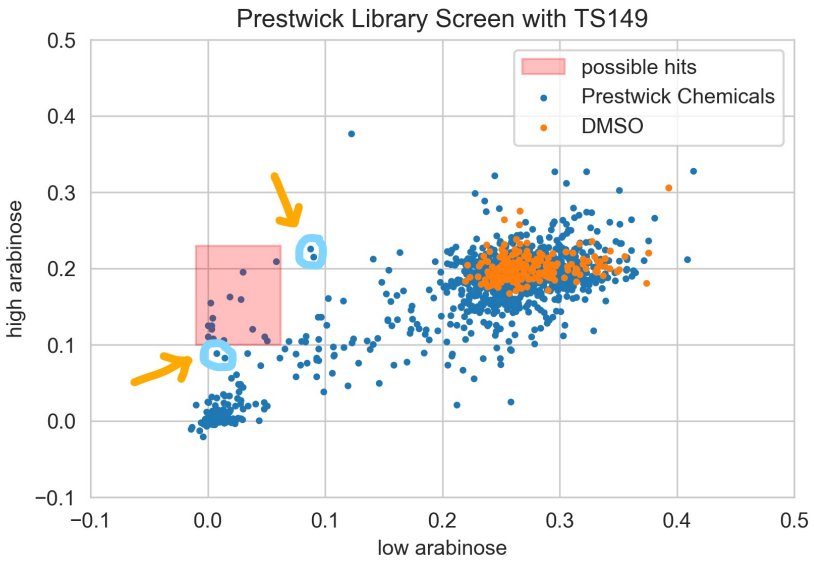
## 2.2 other "hits" outside the red box




### 2.2.1 Haloprogin

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0076 / 0.0888 |
| low Arabinose: | 0.0021 0.2448 0.0076 |
| high Arabinose: | 0.0888 0.1186 0.023 |

401 Haloprogin C9H4Cl3IO 361.39503 Store at room temperature 777-11-7 Central Nervous System Anesthetic Prestw-1269 06A03

**Notes**

- antifungal drug used to treat athlete's foot and other fungal infections
- mechanism of action is unknown, but it is thought to be via inhibition of oxygen uptake and disruption of yeast membrane structure and function
- effecive against some Gram-positive bacteria (Harrison et al., 1970)

**References**

Harrison, E. F., Zwadyk, P., Bequette, R. J., Hamlow, E. E., Tavormina, P. A., & Zygmunt, W. A. (1970). Haloprogin: A topical antifungal agent. *Applied Microbiology*, *19*(5), 746–750. https://doi.org/10.1128/aem.19.5.746-750.1970

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### 2.2.2 Saquinavir mesylate

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0144 / 0.0828 |
| low Arabinose: | 0.0144 0.0126 0.0765 |
| high Arabinose: | 0.1138 0.0416 0.0828 |

1113 Saquinavir mesylate C39H54N6O8S 766.96463 Store at +4°C 149845-06-7 Immunology Antiviral Prestw-1114 14H05

**Notes**

- used to tread HIV (inhibitor of the human immunodeficiency virus type 1 (HIV-1) protease)
- no literature about antibacterial effect or ASADH-interaction found

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### 2.2.3 Thiorphan

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0903 / 0.215 |
| low Arabinose: | 0.2389 0.0903 0.0642 |
| high Arabinose: | 0.18 0.2214 0.215 |

632 Thiorphan C12H15NO3S 253.32225 Store at room temperature 76721-89-6 Gastroenterology Antidiarrheal Prestw-633 08H04

**Notes**

- Antidiarrheal: inhibitor of membrane metalloendopeptidase (enkephalinase)
- no literature about antibacterial effect or ASADH-interaction found

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### 2.2.4 Reserpine

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0876 / 0.2256 |
| low Arabinose: | 0.0496 0.2679 0.0876 |
| high Arabinose: | 0.2294 0.2256 0.1885 |

874 Reserpine C33H40N2O9 608.69475 RT 50-55-5 Central Nervous System Antipsychotic Prestw-875 11H06

**Notes**

- used for the treatment of high blood pressure as an adrenergic blocking agent
- reduces antibiotic resistances (Viveiros et al., 2002)

**References**

Viveiros, M., Portugal, I., Bettencourt, R., Victor, T. C., Jordaan, A. M., Leandro, C., Ordway, D., & Amaral, L. (2002). Isoniazid-induced transient high-level resistance in mycobacterium tuberculosis. *Antimicrobial Agents and Chemotherapy*, *46*(9), 2804–2810. https://doi.org/10.1128/aac.46.9.2804-2810.2002

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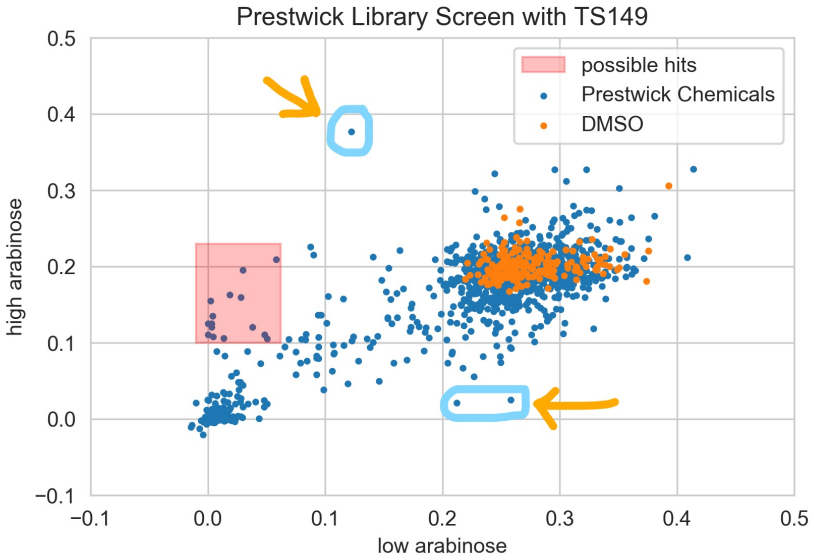
## 2.3 are the outlayers errors or special?




### 2.3.1 Primaquine diphosphate

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.2581 / 0.0253 |
| low Arabinose: | 0.0473 0.2581 0.3537 |
| high Arabinose: | 0.0253 0.0218 0.0388 |

475 Primaquine diphosphate C15H27N3O9P2 455.34474 Store at room temperature 63-45-6 Infectiology Antimalarial Prestw-476 06H07

**Notes**

- antimalarial
- Primaquine's mechanism of action is not well understood. It may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite. Also, although its mechanism of action is unclear, primaquine may bind to and alter the properties of protozoal DNA
- primaquine derivatives inhibit Mycobacterium tuberculosis growth!! (Pavić, Perković, et al., 2018)

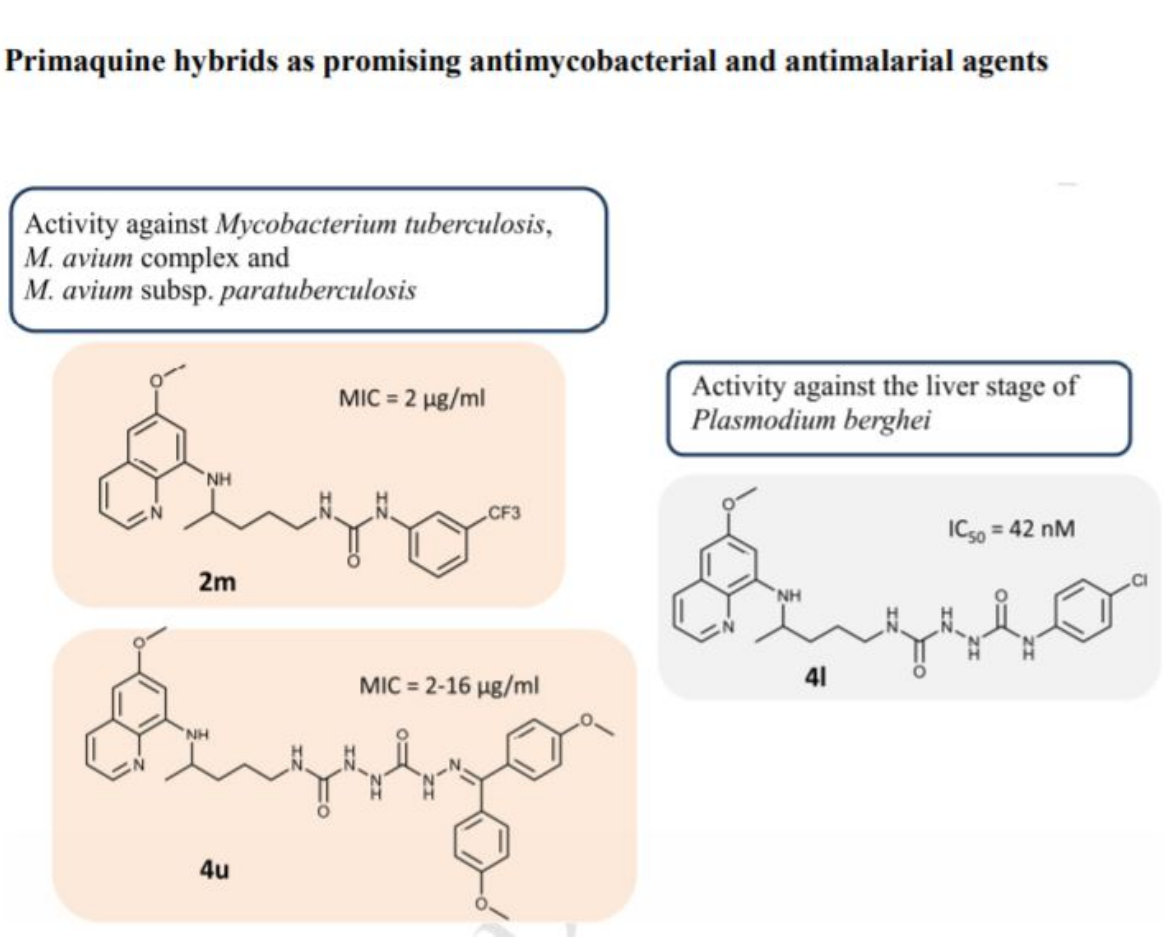



Figure 2: Pavić, Perković, et al., 2018; Pavić, Rajić, et al., 2018

**References**

Pavić, K., Perković, I., Pospıšilová, Š., Machado, M., Fontinha, D., Prudêncio, M., Jampilek, J., Coffey, A., Endersen, L., Rimac, H., & Zorc, B. (2018). Primaquine hybrids as promising antimycobacterial and antimalarial agents. *European Journal of Medicinal Chemistry*, *143*, 769–779. https://doi.org/10.1016/j.ejmech.2017.11.083

Pavić, K., Rajić, Z., Michnová, H., Jampılek, J., Perković, I., & Zorc, B. (2018). Second generation of primaquine ureas and bis-ureas as potential antimycobacterial agents. *Molecular Diversity*, *23*(3), 657–667. https://doi.org/10.1007/s11030-018-9899-z

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### 2.3.2 Metixene hydrochloride

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.2124 / 0.0213 |
| low Arabinose: | 0.0048 0.2699 0.2124 |
| high Arabinose: | 0.0075 0.0213 0.0391 |

490 Metixene hydrochloride C20H24ClNS 345.93798 Store below 0°C 1553-34-0 Central Nervous System Antiparkinsonian Prestw-491 07B02

**Notes**

- anticholinergic antiparkinsonian agent, potently inhibits binding of quinuclidinyl benzilate (QNB) to the muscarinic receptor

- no paper about antimicrobial effect or interaction with ASADH found

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### 2.3.3 Bromocryptine mesylate

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.1225 / 0.3768 |
| low Arabinose: | 0.0659 0.2048 0.1225 |
| high Arabinose: | 0.1363 0.4095 0.3768 |

120 Bromocryptine mesylate C33H44BrN5O8S 750.71533 Store at +4°C 22260-51-1 Central Nervous System Antiparkinsonian Prestw-121 02E02

**Notes**

- oral dopamine receptor agonist labeled for the treatment of type 2 diabetes mellitus and used to help reduce symptoms of Parkinson's disease
- no paper about antimicrobial effect or interaction with ASADH found

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## 3 tested literature compounds

### 3.0.1 3,5-Pyrazoledicarboxylic acid monohydrate

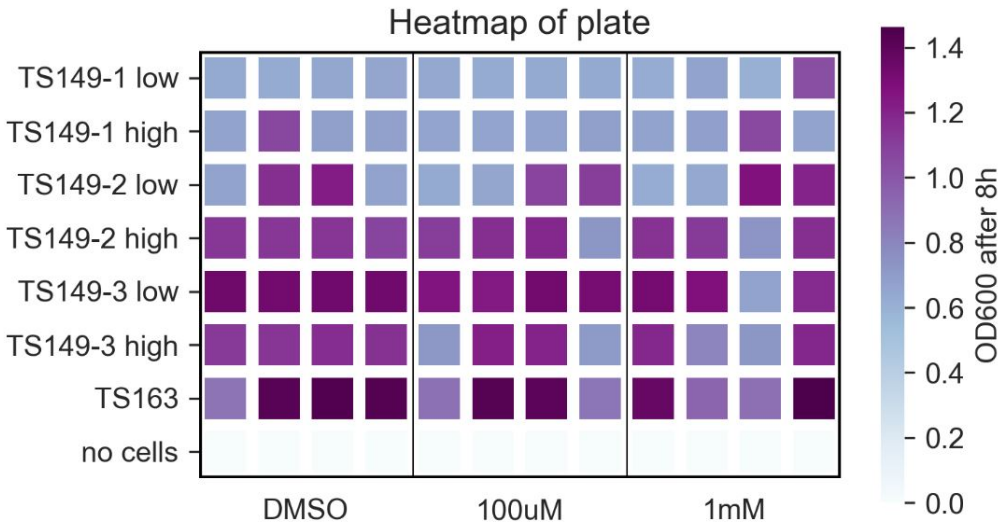
**Notes**

- "consistent H-bonding interaction with highly conserved active site residues"
- "remains bound to key active residues of Mtb-ASADH"

**References**

Kumar, R., Garg, P., & Bharatam, P. (2015). Pharmacoinformatics analysis to identify inhibitors of Mtb-ASADH. *Journal of Biomolecular Structure and Dynamics*, *34*(1), 1–14. https://doi.org/10.1080/07391102.2015.1005137

**Effect on TS149**



### 3.0.2 Curcumin

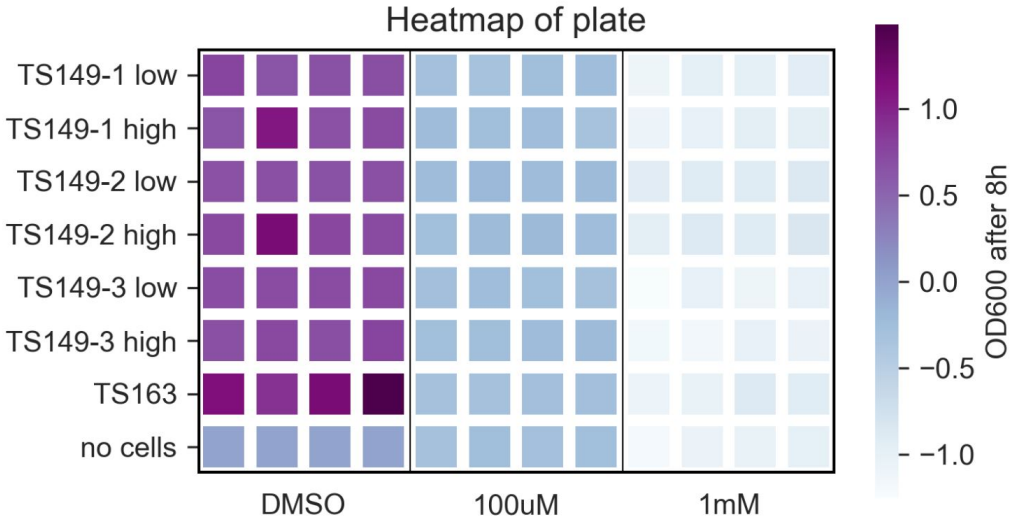
**Notes**

- "capable of binding within the binding site of ASD"
- "high degree of hydrogen bonding with ASD"
- "Curcumin another most active compound that could be further investigated and validated to be used as an ASD inhibitor and can be utilized against Mycobacterium infection in the near future"

**References**

Khan, S., Somvanshi, P., Bhardwaj, T., Mandal, R. K., Dar, S. A., Wahid, M., Jawed, A., Lohani, M., Khan, M., Areeshi, M. Y., & Haque, S. (2017). Aspartate-ß-semialdeyhyde dehydrogenase as a potential therapeutic target of mycobacterium tuberculosis h37rv: Evidence from in silico elementary mode analysis of biological network model. *Journal of Cellular Biochemistry*, *119*(3), 2832–2842. https://doi.org/10.1002/jcb.26458

**Effect on TS149**




### 3.0.3 Rosmarinic acid

**Notes**

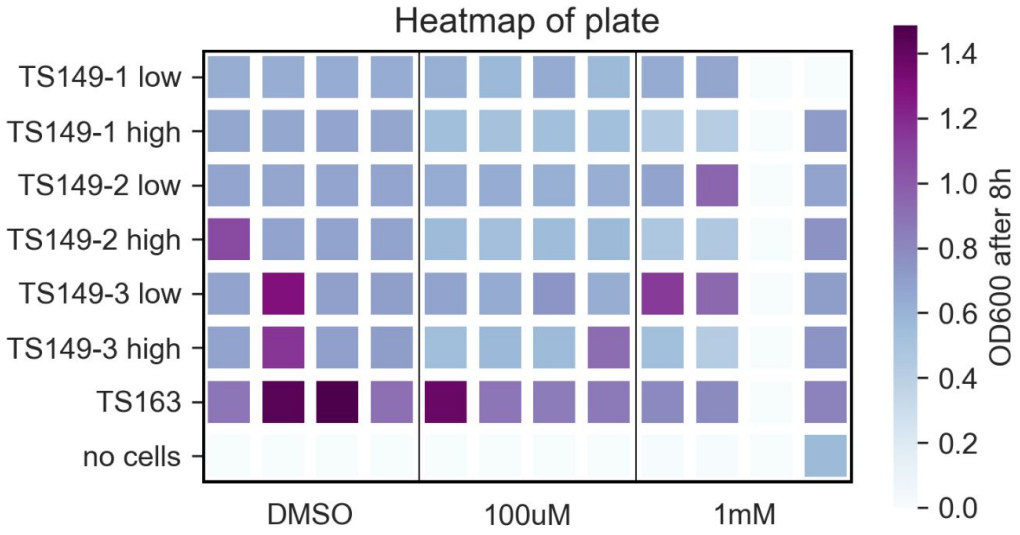
- "Rosmarinic acid was considered as the most effective inhibitor by performing molecular docking"
- "undergoes a high degree of hydrogen bonding with ASD"

**References**

Khan, S., Somvanshi, P., Bhardwaj, T., Mandal, R. K., Dar, S. A., Wahid, M., Jawed, A., Lohani, M., Khan, M., Areeshi, M. Y., & Haque, S. (2017). Aspartate-ß-semialdeyhyde

dehydrogenase as a potential therapeutic target of mycobacterium tuberculosis h37rv: Evidence from in silico elementary mode analysis of biological network model. *Journal of Cellular Biochemistry*, *119*(3), 2832–2842. https://doi.org/10.1002/jcb.26458

**Effect on TS149**

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### 3.0.4 DL-2,3-Diaminopropionic acid monohydrochloride

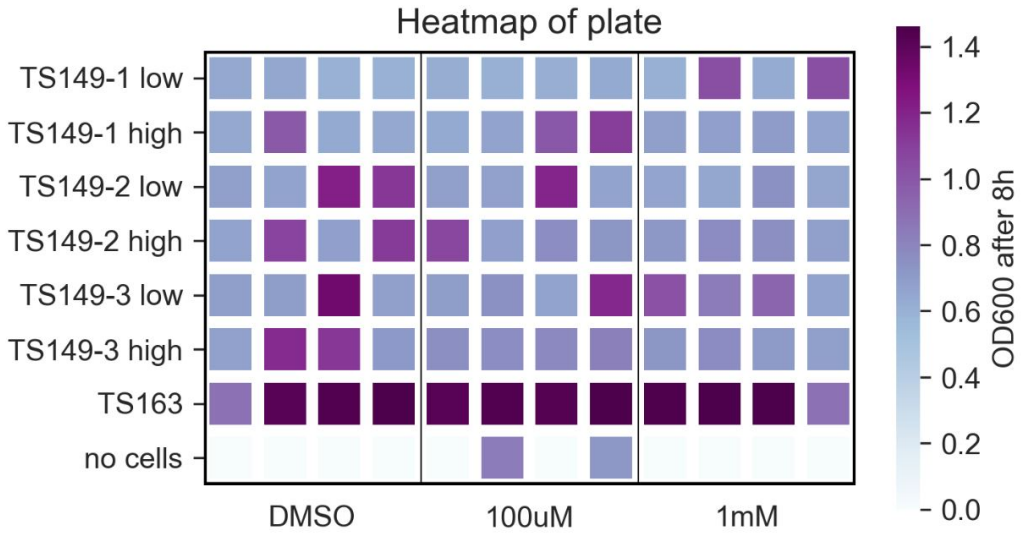
**Notes**

- "do not show appreciable selectivity between the bacterial forms of ASADH"
- "has a Ki in the low millimolar range for both spASADH and vcASADH, with a very high ligand efficiency of ¿0.5, and already shows selectivity (¿40:1) for bacterial versus fungal ASADHs"

**References**

Gao, G., Liu, X., Pavlovsky, A., & Viola, R. E. (2010). Identification of selective enzyme inhibitors by fragment library screening. *Journal of Biomolecular Screening*, *15*(9), 1042–1050. https://doi.org/10.1177/1087057110381383

**Effect on TS149**

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### 3.0.5 2,2',4,4'-Tetrahydroxybenzophenone

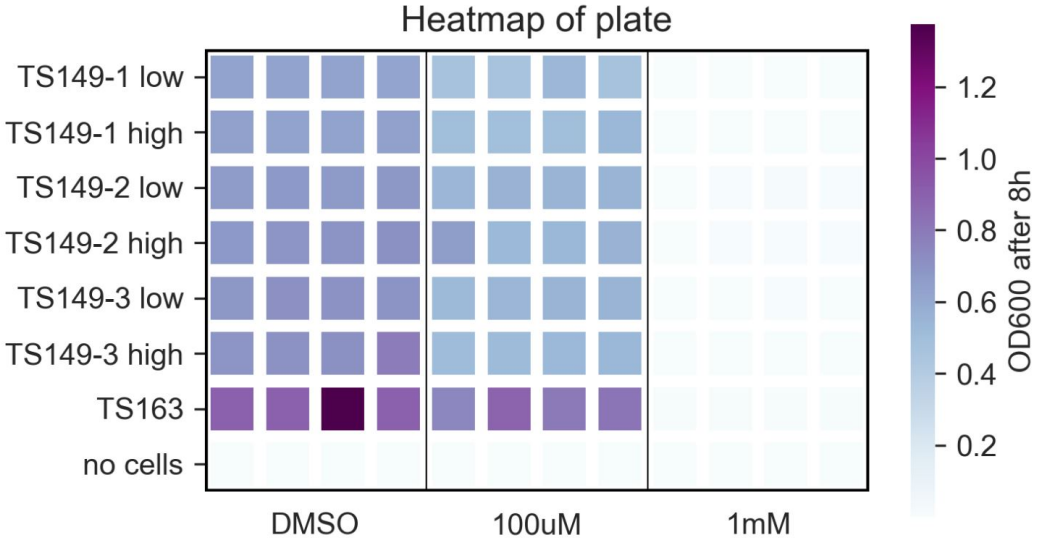
**Notes**

- very low Ki for vcASADH
- "Increasing the number of hydroxyl groups that decorate the ring structure from 1 to 4 produces a further 10-fold improvement in affinity while maintaining the LE"
- derivative "4-Hydroxybenzophenone" has low Ki values for spASADH, vcASADH, cdASADH

**References**

Gao, G., Liu, X., Pavlovsky, A., & Viola, R. E. (2010). Identification of selective enzyme inhibitors by fragment library screening. *Journal of Biomolecular Screening*, *15*(9), 1042–1050. https://doi.org/10.1177/1087057110381383

**Effect on TS149**



### 3.0.6 N-Iodosuccinimide

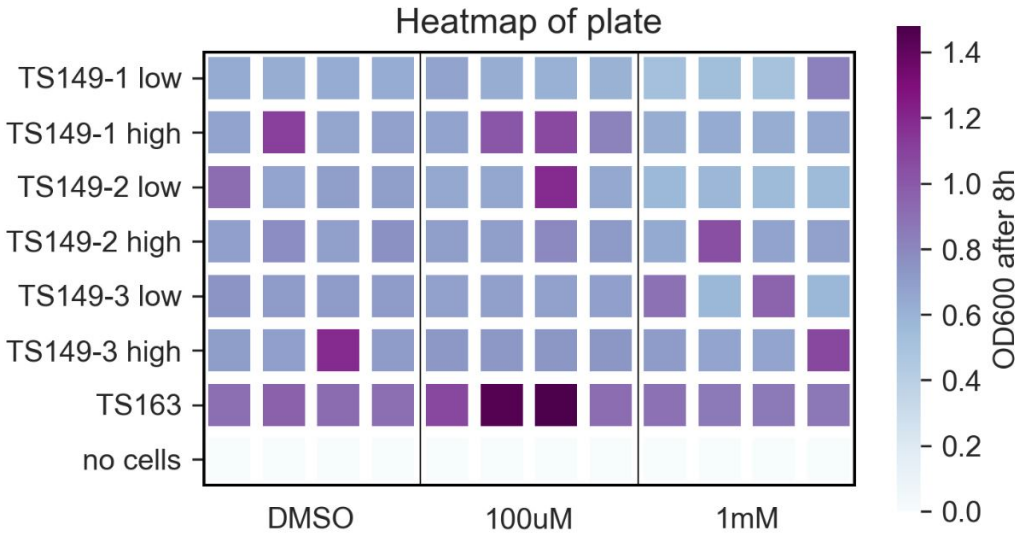
**Notes**

- very low Ki for vcASADH and spASADH
- also pretty low Ki for cdASADH

**References**

Gao, G., Liu, X., Pavlovsky, A., & Viola, R. E. (2010). Identification of selective enzyme inhibitors by fragment library screening. *Journal of Biomolecular Screening*, *15*(9), 1042–1050. https://doi.org/10.1177/1087057110381383

**Effect on TS149**




### 3.0.7 2,3-Dichloro-1,4-naphthoquinone

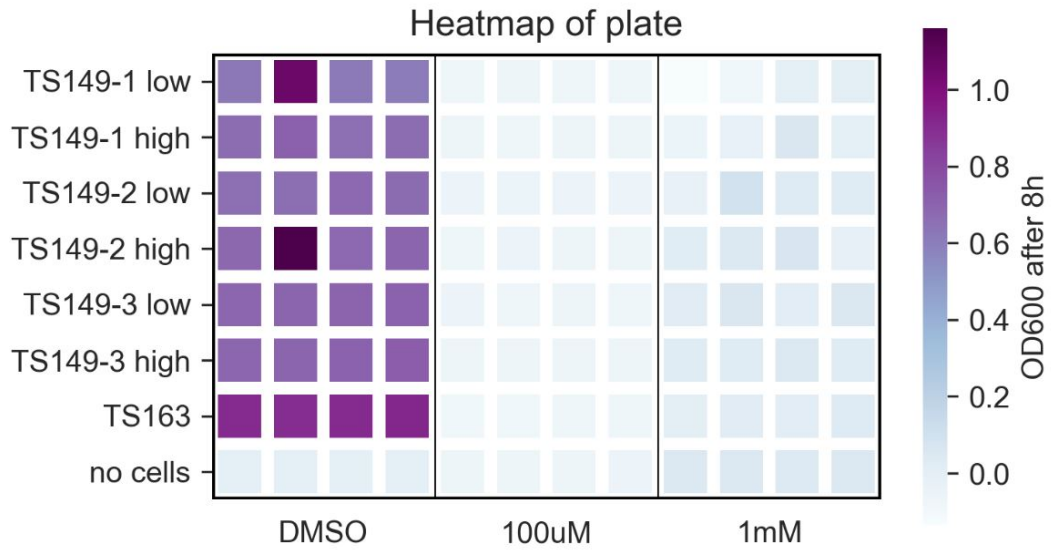
**Notes**

- fungal ASADH inhibitor

**References**

Dahal, G. P., & Viola, R. E. (2018). A fragment library screening approach to identify selective inhibitors against an essential fungal enzyme. *SLAS DISCOVERY: Advancing the Science of Drug Discovery*, *23*(6), 520–531. https://doi.org/10.1177/2472555218767844

**Effect on TS149**

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### 3.0.8 Phthaldialdehyde

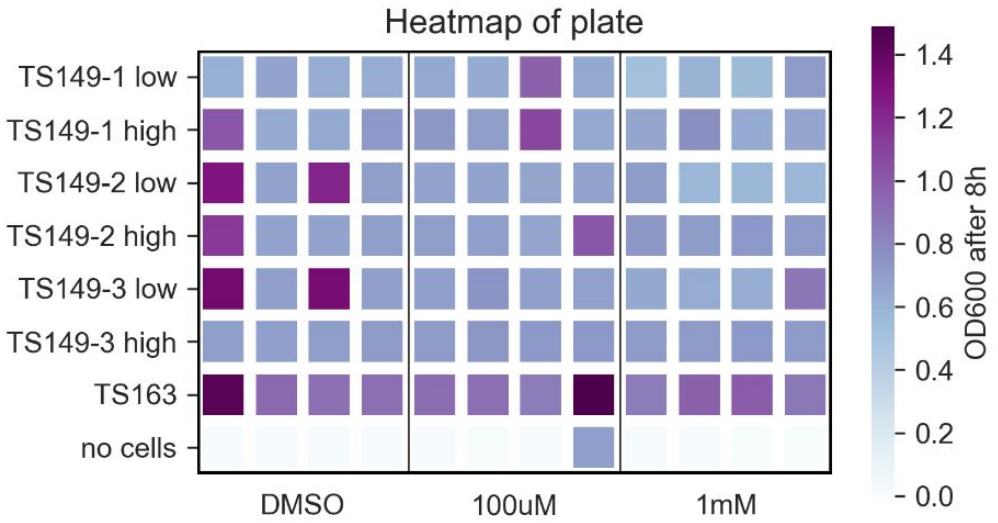
**Notes**

- fungal ASADH inhibitor

**References**

Dahal, G. P., & Viola, R. E. (2018). A fragment library screening approach to identify selective inhibitors against an essential fungal enzyme. *SLAS DISCOVERY: Advancing the Science of Drug Discovery*, *23*(6), 520–531. https://doi.org/10.1177/2472555218767844

**Effect on TS149**



# 4 other interesting compounds

## 4.1 ASADH thesis Viola

(Thangavelu, B. (2016). *Development of selective inhibitors against metabolic enzymes involved in aspartate pathway for antibiotic development* (Doctoral dissertation). The University of Toledo):

- Nifedipine
- Ebselen
- Hexachlorophene

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### 4.1.1 Ebselen

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0091 / 0.0132 |
| low Arabinose: | 0.0081 0.0292 0.0091 |
| high Arabinose: | 0.0132 0.1594 0.0064 |

739 Ebselen C13H9NOSe 274.18278 Store at 2-8°C 60940-34-3 Metabolism Anti-inflammatory Prestw-740 10B11

**Notes**

- 'While ebselen itself is too reactive to serve as an enzyme inhibitor, with some structural modifications that decrease reactivity, could possibly provide a selective enzyme inhibitor' (Thangavelu, 2016)
- 'This reactivity is a great disadvantage in terms of specificity towards a target enzyme. In an attempt to moderate its reactivity, the ebselen molecule was modified and its structure was extended so that it will exhibit increased affinity towards modification of only the active site cysteine of ASADH. This specificity will be achieved through two different approaches: 1) decreasing the reactivity of ebselen molecule by replacing "Se" with either a "S" atom or a carbonyl group 2) use of in-silico methods to model ebselen derivatives with different functional groups that can interact with the active site residues.' (Mutthamsetty, 2017)
- evidence for inhibition of ASADH (Mutthamsetty, 2017; Thangavelu, 2016)
- inhibits mtb growth (Gustafsson et al., 2016; Kanvatirth et al., 2019)
- analogs are synthesised already and work against mtb (Gustafsson et al., 2016)

**References**

Thangavelu, B. (2016). *Development of selective inhibitors against metabolic enzymes involved in aspartate pathway for antibiotic development* (Doctoral dissertation). The University of Toledo

Mutthamsetty, V. (2017). *Design and synthesis of amino acid-based inhibitors against key enzymes* (Doctoral dissertation). The University of Toledo (Chapter 4.7 ff.)

Kanvatirth, P., Jeeves, R. E., Bacon, J., Besra, G. S., & Alderwick, L. J. (2019). Utilisation of the prestwick chemical library to identify drugs that inhibit the growth of mycobacteria

(S. J. Shin, Ed.). *PLOS ONE*, *14*(3), e0213713. https://doi.org/10.1371/journal.pone.0213713

Gustafsson, T. N., Osman, H., Werngren, J., Hoffner, S., Engman, L., & Holmgren, A. (2016). Ebselen and analogs as inhibitors of bacillus anthracis thioredoxin reductase and bactericidal antibacterials targeting bacillus species, staphylococcus aureus and mycobacterium tuberculosis. *Biochimica et Biophysica Acta (BBA) - General Subjects*, *1860*(6), 1265–1271. https://doi.org/10.1016/j.bbagen.2016.03.013

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### 4.1.2 Nifedipine

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0926 / 0.058 |
| low Arabinose: | 0.0926 0.4312 0.0662 |
| high Arabinose: | 0.058 0.0109 0.0732 |

62 Nifedipine C17H18N2O6 346.34281 "Store at room temperature Very light sensitive" 21829-25-4 Cardiovascular Antianginal Prestw-63 01G04

**Notes**

- used to manage angina, high blood pressure, Raynaud's phenomenon, and premature labor
- inhibits Sp-ASADH and Vc-ASADH (Thangavelu, 2016)
- no paper about antimicrobial effect found

**References**

Thangavelu, B. (2016). *Development of selective inhibitors against metabolic enzymes involved in aspartate pathway for antibiotic development* (Doctoral dissertation). The University of Toledo

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### 4.1.3 Hexachlorophene

**OD values drug screen**

| | |
|---|---|
| mean low/high: | 0.0055 / 0.0083 |
| low Arabinose: | 0.0055 0.0084 0.0049 |
| high Arabinose: | 0.0105 0.007 0.0083 |

1199 Hexachlorophene C13H6Cl6O2 406.90957 Store at -20°C 70-30-4 Infectiology Antiseptic Prestw-1472 15H11

**Notes**

- an organochlorine compound that was once widely used as a disinfectant and used to prevent or treat skin infections
- inhibits Sp-ASADH and Vc-ASADH (Thangavelu, 2016)
- has some antibacterial effect (Vorherr et al., 1988)
- inhibits corona-virus species (Cao et al., 2015)
- inhibits thrombocytopenia syndrome virus (SFTSV) (Yuan et al., 2019)

## References

Thangavelu, B. (2016). *Development of selective inhibitors against metabolic enzymes involved in aspartate pathway for antibiotic development* (Doctoral dissertation). The University of Toledo

Vorherr, H., Vorherr, U. F., & Moss, J. C. (1988). Comparative effectiveness of chlorhexidine, povidone-iodine, and hexachlorophene on the bacteria of the perineum and groin of pregnant women. *American Journal of Infection Control*, *16*(4), 178–181. https://doi.org/10.1016/0196-6553(88)90031-4

Cao, J., Forrest, J. C., & Zhang, X. (2015). A screen of the NIH clinical collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Research*, *114*, 1–10. https://doi.org/10.1016/j.antiviral.2014.11.010

Yuan, S., Chan, J. F.-W., Ye, Z.-W., Wen, L., Tsang, T. G.-W., Cao, J., Huang, J., Chan, C. C.-Y., Chik, K. K.-H., Choi, G. K.-Y., Cai, J.-P., Yin, F., Chu, H., Liang, M., Jin, D.-Y., & Yuen, K.-Y. (2019). Screening of an FDA-approved drug library with a two-tier system identifies an entry inhibitor of severe fever with thrombocytopenia syndrome virus. *Viruses*, *11*(4), 385. https://doi.org/10.3390/v11040385

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## 4.2 Interesting figures from papers

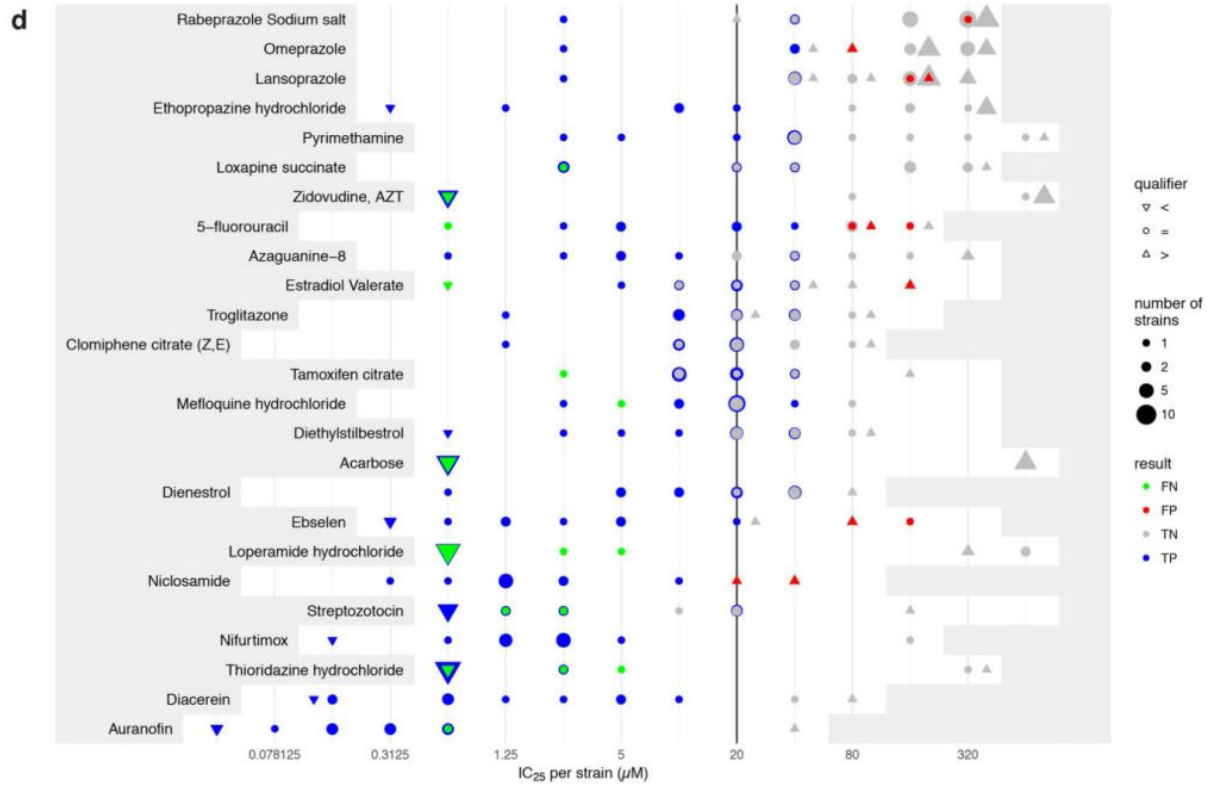



Figure 3: Maier, L., Pruteanu, M., Kuhn, M., Zeller, G., Telzerow, A., Anderson, E. E., Brochado, A. R., Fernandez, K. C., Dose, H., Mori, H., Patil, K. R., Bork, P., & Typas, A. (2018). Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*, *555*(7698), 623–628. https://doi.org/10.1038/nature25979 'Figure 5 d, IC25s of 25 drugs in up to 27 individual strains (see also a, b). The white area indicates the drug concentration range tested for each drug. Symbol sizes depict the number of strains with a particular IC25, symbol colours indicate categorization into false negative, false positive, true negative and true positive, and symbol shapes qualify whether actual IC25s were determined or IC25 was deemed to be higher or lower than the highest or lowest concentration tested, respectively. Vertical line indicates the drug concentration used in screen (20 M). IC25s for all drug–strain pairs are listed in Supplementary Table 4. Particular drugs were responsible for false negatives in our screen (acarbose, loperamide, thioridazine), presumably owing to drug decay'

| **Shortlisted Drugs (*M. tuberculosis*)** | **Liquid MIC (μM)** | **$IC_{50}$ (μM) HepG2 cells** |
|---|---|---|
| Ebselen | 18.51 | 45 |
| Clomiphene | 7.59 | 35 |
| GBR 12909 | 26.64 | 55 |
| Raloxifen | 22.10 | 20 |
| Tamoxifen | $\geq$ 100 | 30 |
| Auranofin | 0.27 | 3 |
| Pentamidine | 10.51 | 3.5 |
| Tripelennamine | 49.3 | >250 |
| Florfenicol | 25.4 | >250 |

Figure 4: Kanvatirth, P., Jeeves, R. E., Bacon, J., Besra, G. S., & Alderwick, L. J. (2019). Utilisation of the prestwick chemical library to identify drugs that inhibit the growth of mycobacteria (S. J. Shin, Ed.). *PLOS ONE*, *14*(3), e0213713. https://doi.org/10.1371/journal.pone.0213713, Table 4. 'MIC determination of selected drugs against M. tuberculosis H37Rv.'

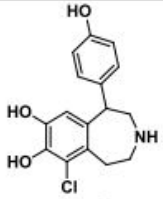
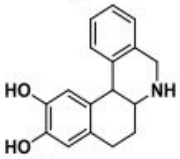
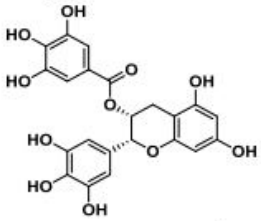
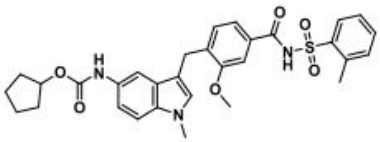
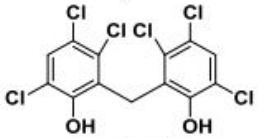
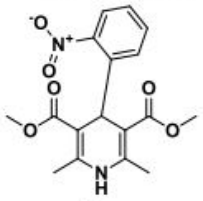
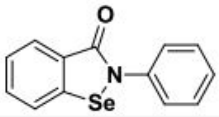
| Compound Name | Structure | $K_i$ value in µM *Sp* ASADH | *Vc* ASADH |
|---|---|---|---|
| Fenoldopam |  | 140±2.5 | 18±2.5 |
| Dihydrexidine |  | 35±7 | 27±4 |
| Epigallocatechin gallate |  | 34±5 | 8.9±0.8 |
| Zafirlukast |  | 21±2.3 | 10.8±0.6 |
| Hexachlorophene |  | 8.8±0.9 | 7.0±0.5 |
| Nifedipine |  | 7.6±1.2 | 18±0.5 |
| Ebselen |  | 0.66±0.03 | 2.0±0.06 |

Figure 5: Thangavelu, B. (2016). *Development of selective inhibitors against metabolic enzymes involved in aspartate pathway for antibiotic development* (Doctoral dissertation). The University of Toledo, Table 2.2 "Kinetic Evaluation of NIHCC Library"