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Modelling lethality and teratogenicity of zebrafish (*Danio rerio*) due to β-lactam antibiotics employing the QSTR approach

Presented by

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https://scholar.google.com/citations?user=brQXNwUAAAAJ&hl=en

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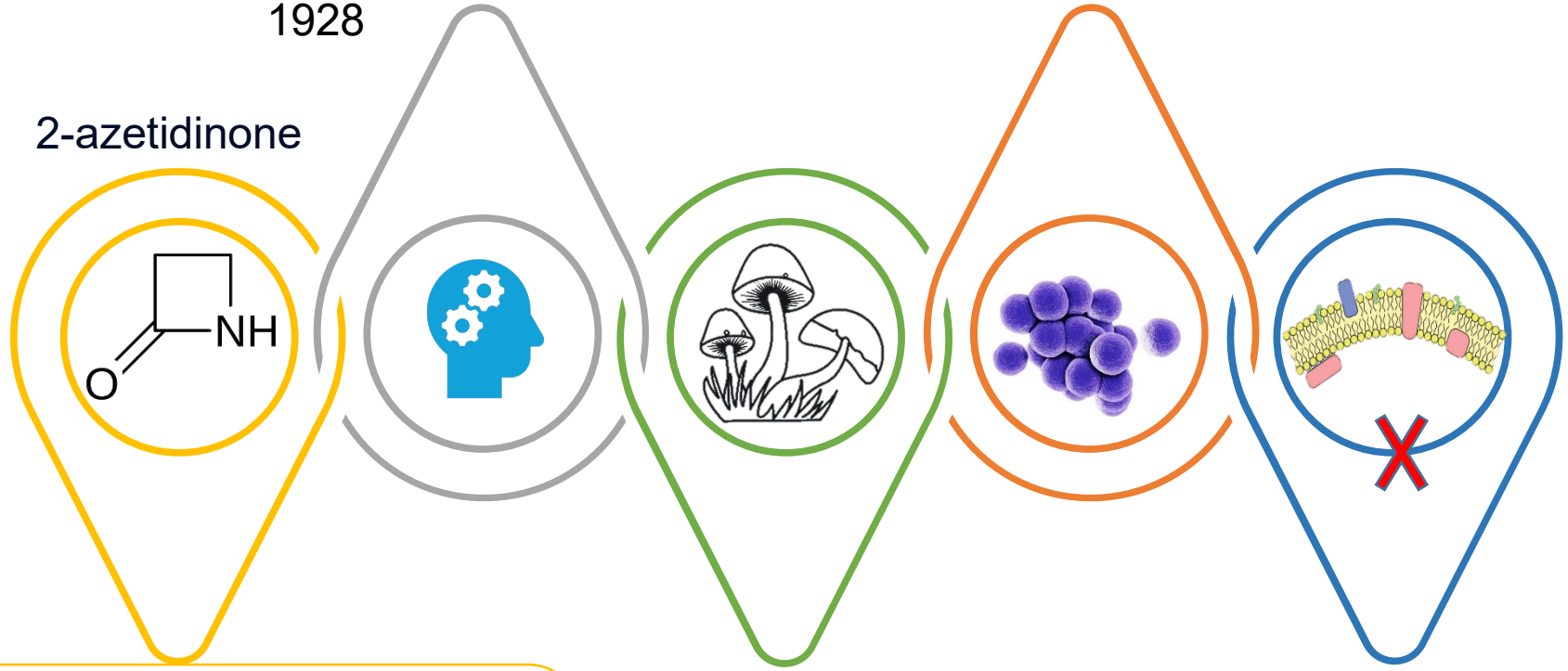
Introduction

What is β-lactam?

Sir Alexander Fleming, 1928

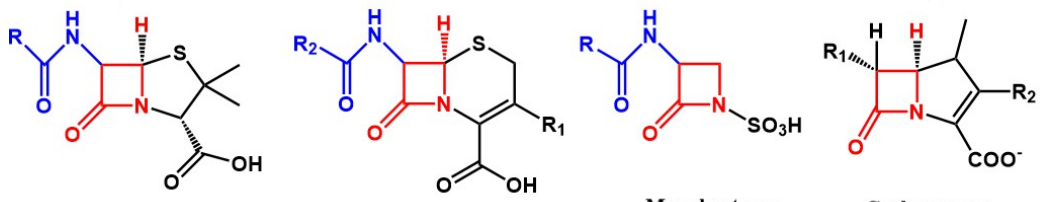
Staphylococcus bacteria

2-azetidinone



Penicillium notatum

Acts by interfering with the synthesis of the **bacterial cell wall peptidoglycan**



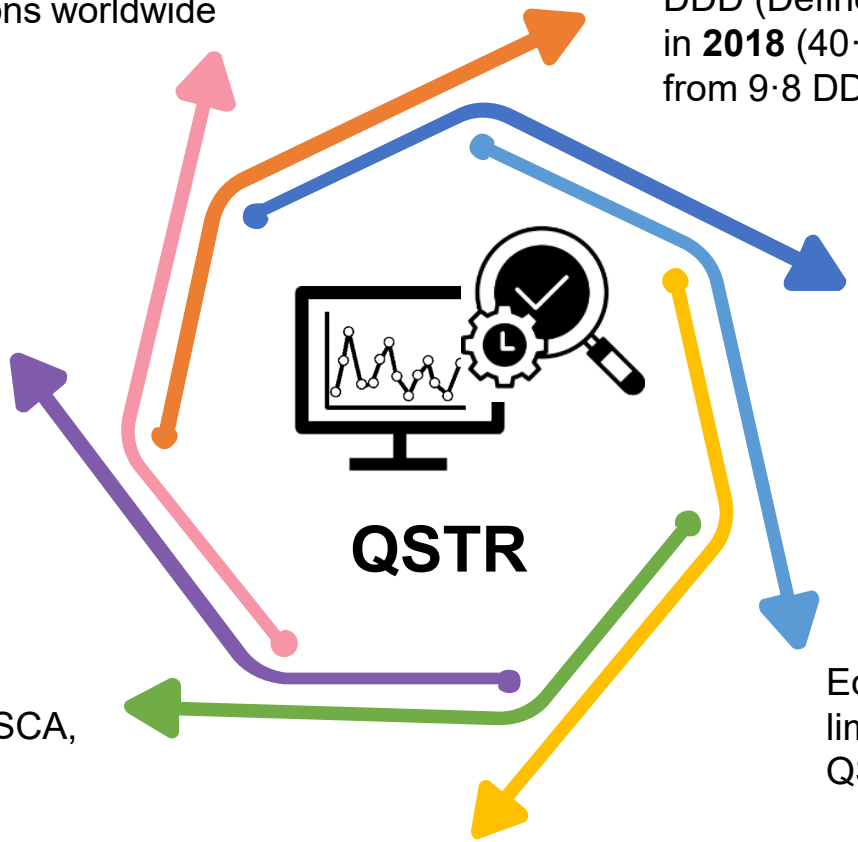
Core structure of beta-lactam antibiotics

Introduction

β-lactam antibiotics are one of the most effective and consumed medications worldwide

A recent study by Browne et al. in 2021 showed that antibiotic consumption was 14·3 DDD (Defined Daily Dose)/1000 patients/day in **2018** (40·2 billion DDD), an increase of **46%** from 9·8 DDD/1000 patients/day **in 2000**.

Advantages of zebrafish (*Danio rerio*) embryos: high fertility and reproduction rate, their transparent property and their phenotypic properties can be easily identified, genetic resemblance with human, more susceptible to drugs and pollutants than the mature fish → **OECD 236 guidelines**



The residual fractions of β-lactams and their metabolites in ecosystems exhibit numerous hazardous effects

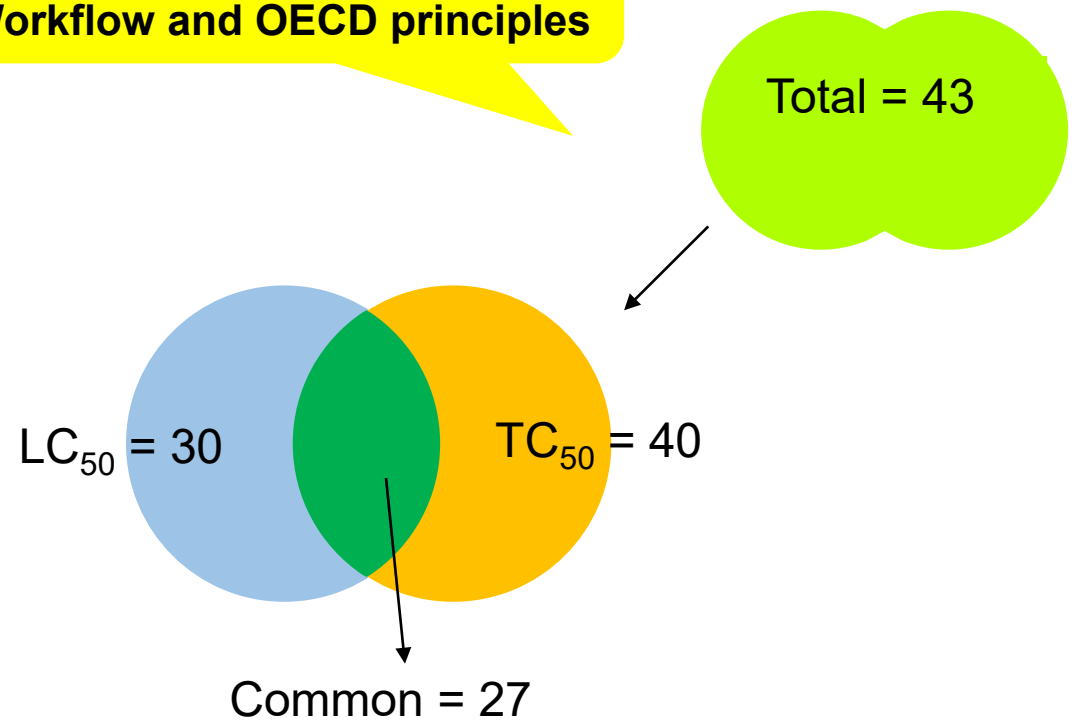
International organizations propose some new regulations: ECHA, US TSCA, CEPA etc.

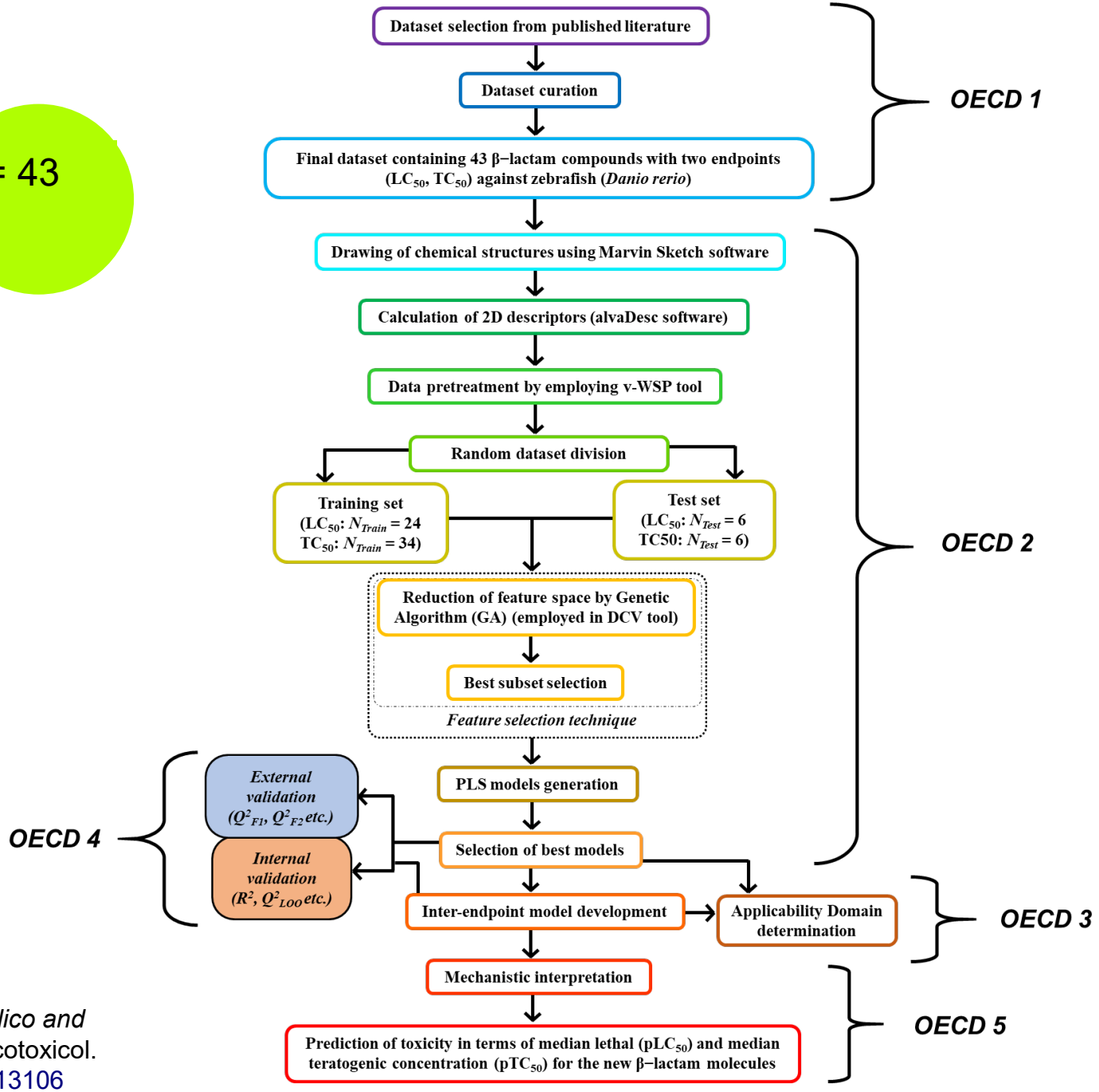
Ecotoxicity data of β-lactams are quite limited, and hence it's a subject of QSTR study.

Require lots of resources and time, and are also reliant on an enormous quantity of test animals

Materials and methods

Workflow and OECD principles





Y. Han et al., *Hazard assessment of beta-lactams: Integrating in silico and QSTR approaches with in vivo zebrafish embryo toxicity testing*, Ecotoxicol. Environ. Saf. 229 (2022), pp. 113106. doi:10.1016/j.ecoenv.2021.113106

Results and discussions

Models' results

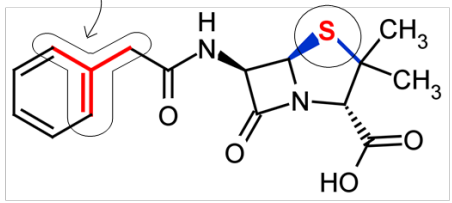
	Model endpoint	Model Eq.	No. of Desc.	N-Train : N-test	LVs	Internal metrics				External metrics			
						R^2	Q^2_{LOO}	MAE_{Train}	$RMSE_C$	Q^2_{F1}	Q^2_{F2}	MAE_{Test}	$RMSE_P$
single endpoint models	Lethal conc. (pLC_50)	**pLC_50 (molar)** = 0.24751 - 1.23436*nThiophenes + 1.37757*minaasC + 0.45837*B09[O-O] + 0.82527*minssS	4	24, 6 Total = 30	3	0.75	0.616	0.147	0.218	0.684	0.684	0.183	0.212
	Teratogenic conc. (pTC_50)	**pTC_50 (molar)** = 2.23315 - 9.71107*Eta_sh_x + 1.27553*(C-043) - 0.04204*SsNH2 + 0.52521*minaasC	4	34, 6 Total = 40	2	0.631	0.54	0.285	0.351	0.607	0.581	0.22	0.301
inter-endpoint models	**pLC_50** = *f* (pTC_50)	**pLC_50** = 0.60336 - 0.34386*(C-019) - 0.76698*(H-049) - 0.19548*(O-057) + 0.81293***pTC_50**	3, 1	21, 6 Total = 27	3	0.84	0.703	0.145	0.176	0.76	0.745	0.149	0.167
	pTC_50 = *f* (pLC_50)	**pTC_50** = -0.54584 + 0.44531*(C-019) + 0.66524*MaxaasC + 0.45035*B06[C-S] + 0.91521***pLC_50**	3, 1	22, 5 Total = 27	3	0.768	0.606	0.182	0.259	0.678	0.639	0.194	0.211

Results and discussions: **Important structural features**

Minimum (min) electron accessibility for

Carbon atom (C) with 2 aromatic bonds (aa) and 1 single bond (s) ***minaasC***

Sulphur atom (S) with 2 single bonds (ss) ***minssS***



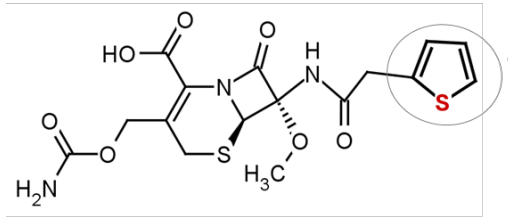
Penicillin G (# 22)

minaasC = 0.872 ↑

minssS = 1.424 ↑

pLC_{50} = 2.481 ↑

One thiophene moiety is present

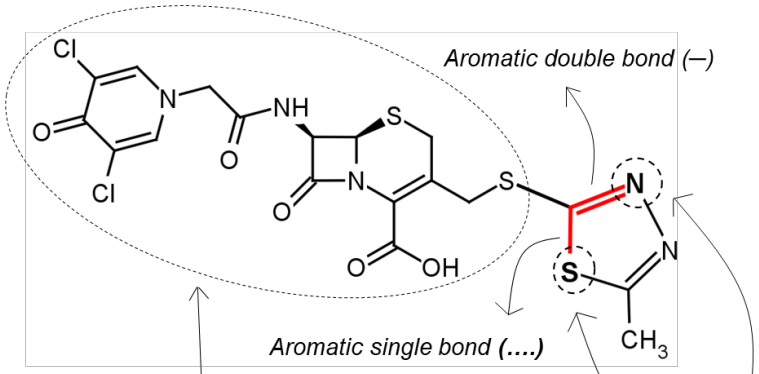


Cefoxitin (# 10)

nThiophenes = 1 ↑

pLC_{50} = 1.547 ↓

One C-043 featured (X–CR…X) carbon atom is present



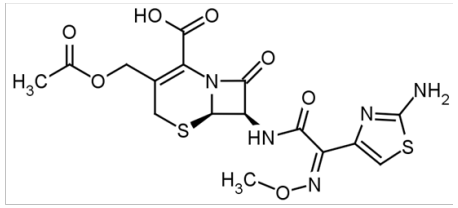
Cefazedone (# 33)

C-043 = 1 ↑

pTC_{50} = 3.699 ↑

X (= N, S atom)

No C-043 featured carbon atom is present



Cefotaxime (# 8)

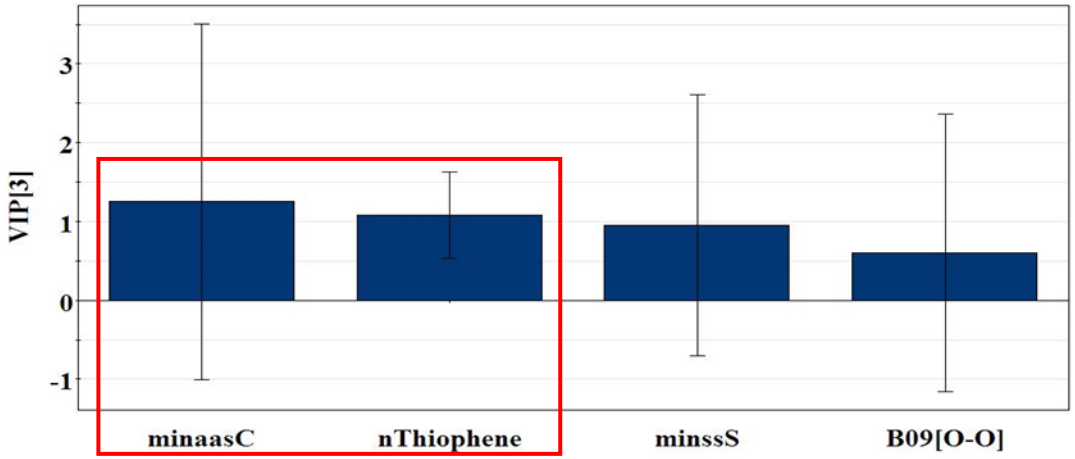
C-043 = 0 ↓

pTC_{50} = 1.523 ↓

a)

VIP Plot of **pLC_{50} (*single*)** model

VIP[Comp. 3]

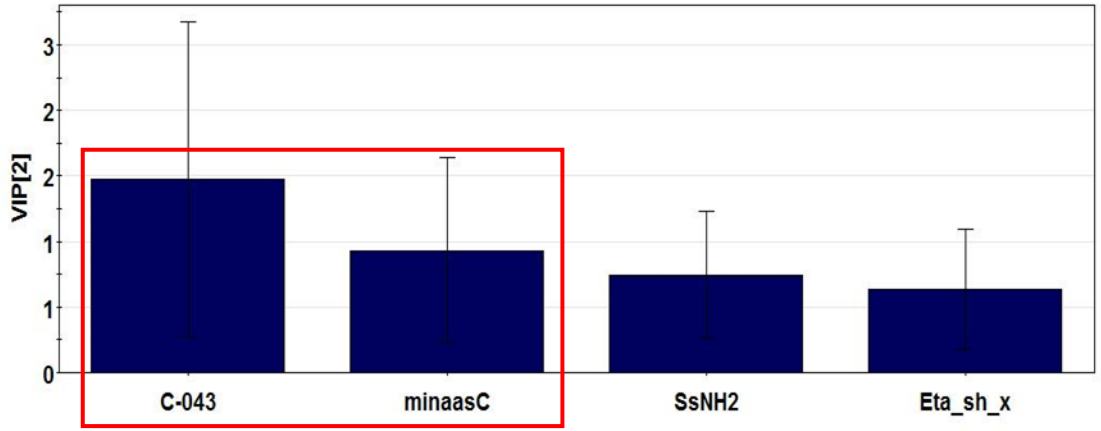


\+ — **Descriptors** \+ \+

b)

VIP Plot of **pTC_{50} (*single*)** model

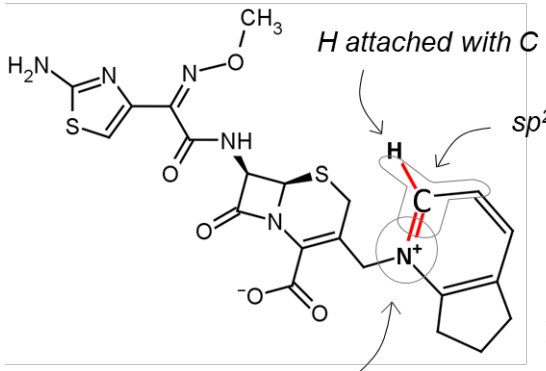
VIP[Comp. 2]



\+ \+ — —

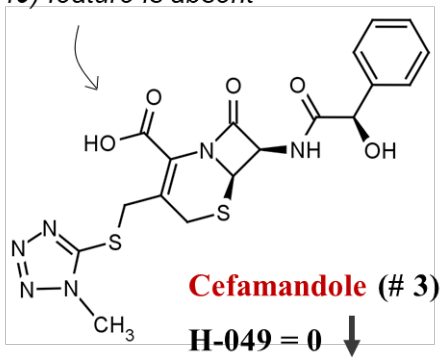
Results and discussions: **Important structural features**

Formal bond order of C with N is 2.
So, formal oxidation number is 2 (C^2)



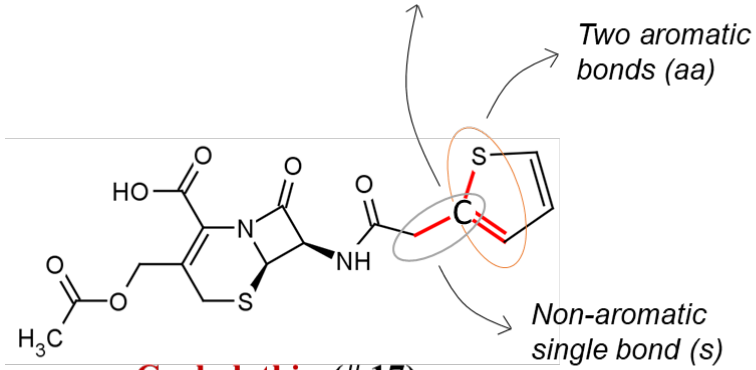
Cefpirome (# 11)
H-049 = 1 ↑
pLC_{50} = 1.804 ↓

(H-049) feature is absent



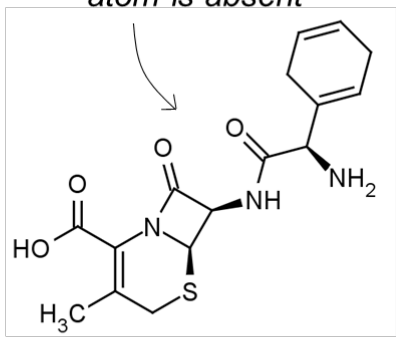
Cefamandole (# 3)
H-049 = 0 ↓
pLC_{50} = 2.495 ↑

Maximum electron accessibility for this C-atom (Maxaas)



Cephalothin (# 17)
MaxaasC = 0.886 ↑
pTC_{50} = 2.538 ↑

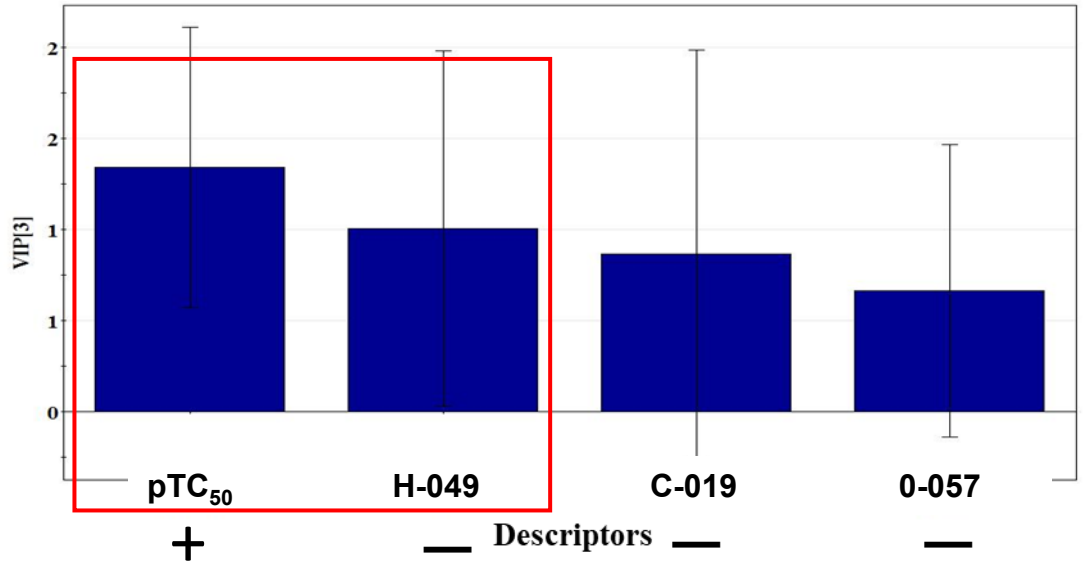
aas featured C-atom is absent



Cefradine (# 13)
MaxaasC = 0 ↓
pTC_{50} = 1.706 ↓

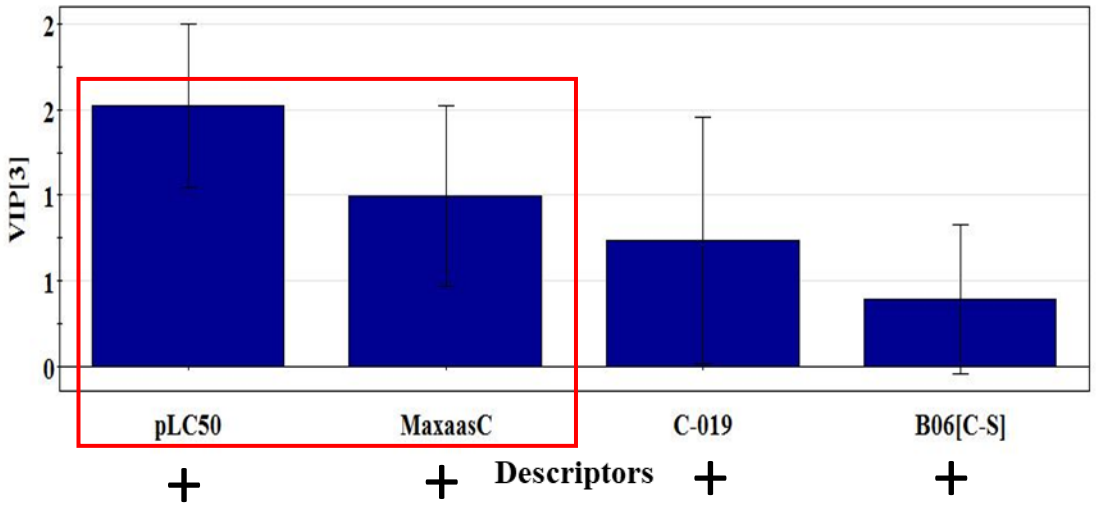
c)

VIP Plot of **pLC_{50} (*inter*)** model



d)

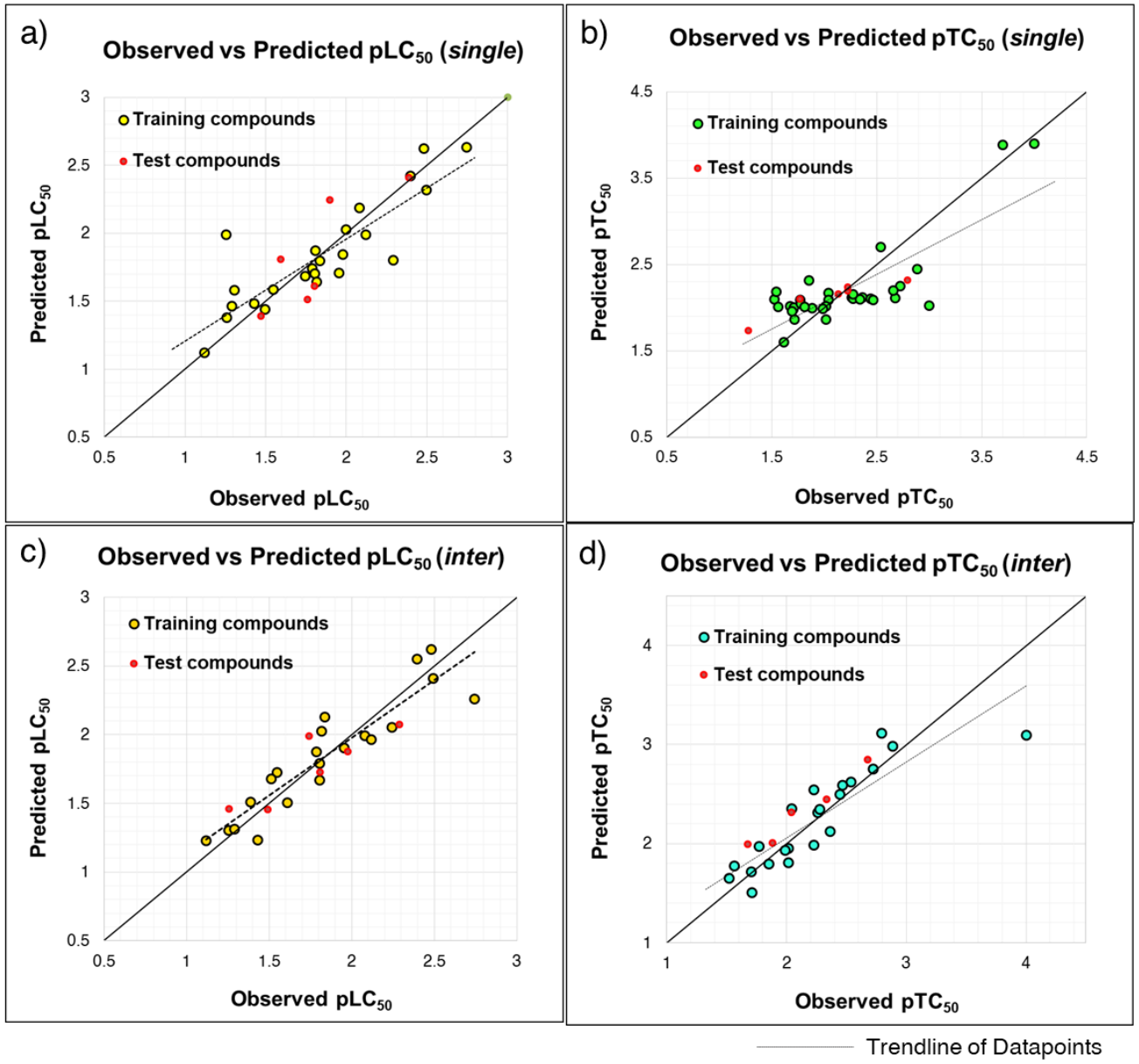
VIP Plot of **pTC_{50} (*inter*)** model



Results and discussions

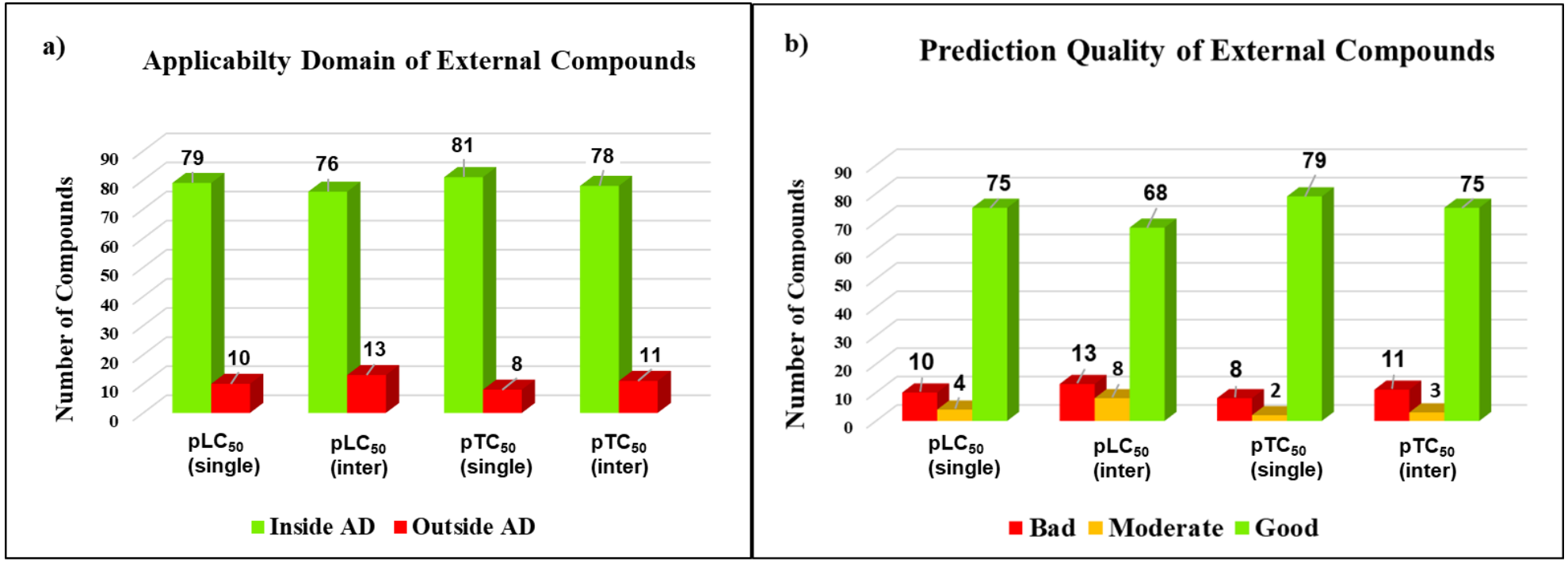
Scatter Plots

It shows how well the predicted values (along the Y-axis) and the observed values (along the X-axis) are correlated, indicating the goodness-of-fit of the model.



Observed and Predicted pLC_{50} and pTC_{50} values are in Molar (M) scale.

External set prediction



Total number of external β-lactam compounds ($N_{External}$) = 89

85 – 91 %

Inside AD

76 – 89 %

Good predictions

Roy, K., Ambure, P. and Kar, S., 2018. How precise are our quantitative structure–activity relationship derived predictions for new query chemicals?. ACS omega, 3(9), pp.11392-11406.

Conclusion

- The QSTR models developed employing two toxicity endpoints, namely median lethal (LC_{50}) and median teratogenic concentration (TC_{50}) against zebrafish (*Danio rerio*) for a set of 30 and 40 β-lactam compounds respectively.
  - The LC_{50} and TC_{50} are **proportionally correlated** to each other.
    - Developed models demonstrate statistical validity, resilience, and strong predictive performance.
    - The vital structural attributes of β-lactams responsible for influencing toxicity. The structural attributes that enhance the toxicity of β- lactams may be removed, and those that reduce the toxicity may be included in the final structure while designing a new molecule.
    - If predictions point out harmful effects, their use and emission should be restricted to our surrounding aquatic environment.
- Ultimately help to achieve the ideas behind green chemistry and the **3Rs** (*Refinement, Replacement, and Reduction*) by minimization of testing of animals.

Thank you