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Charline J. J. Gerard, Ludovic Lépée, Clément Pinètre, Hugo Cercel, Clément Brandel, et al.. Co-crystallization of Praziquantel: conglomerate and racemic compound nucleation rates. ISIC2023, Sep 2023, Glasgow (Ecosse), United Kingdom. hal-04233725

HAL Id: hal-04233725

<https://hal.science/hal-04233725v1>

Submitted on 9 Oct 2023

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Co-crystallization of Praziquantel : conglomerate and racemic compound nucleation rates

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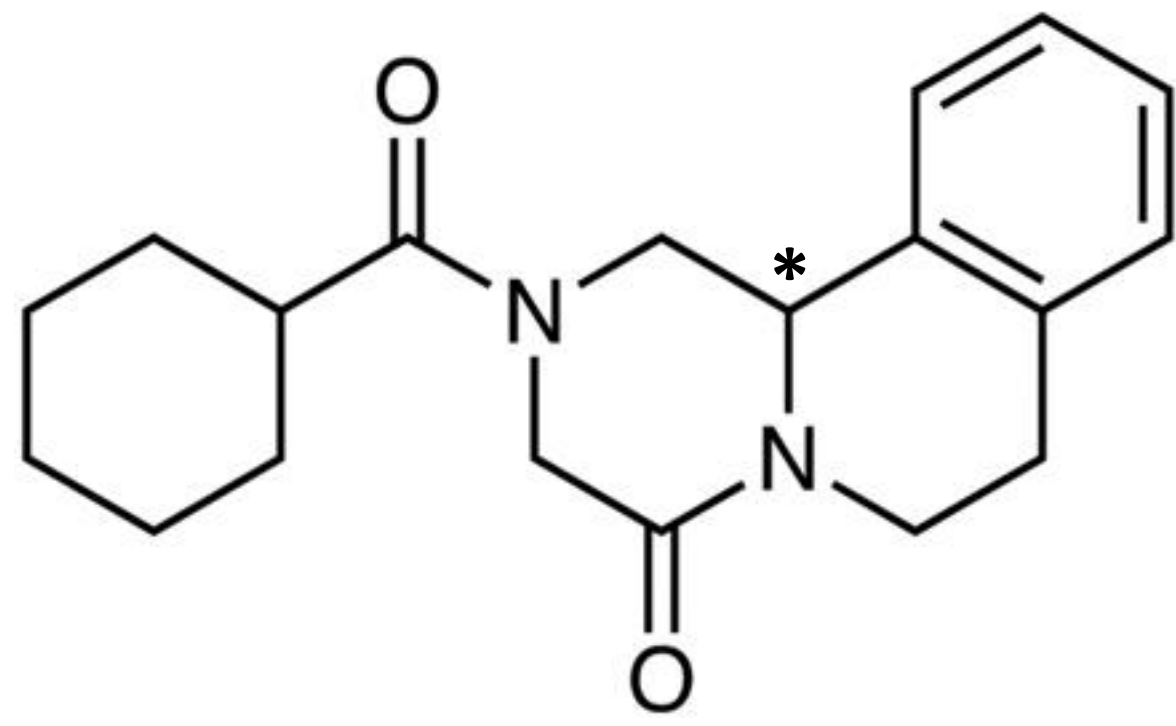
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INTRODUCTION

Praziquantel (PZQ)

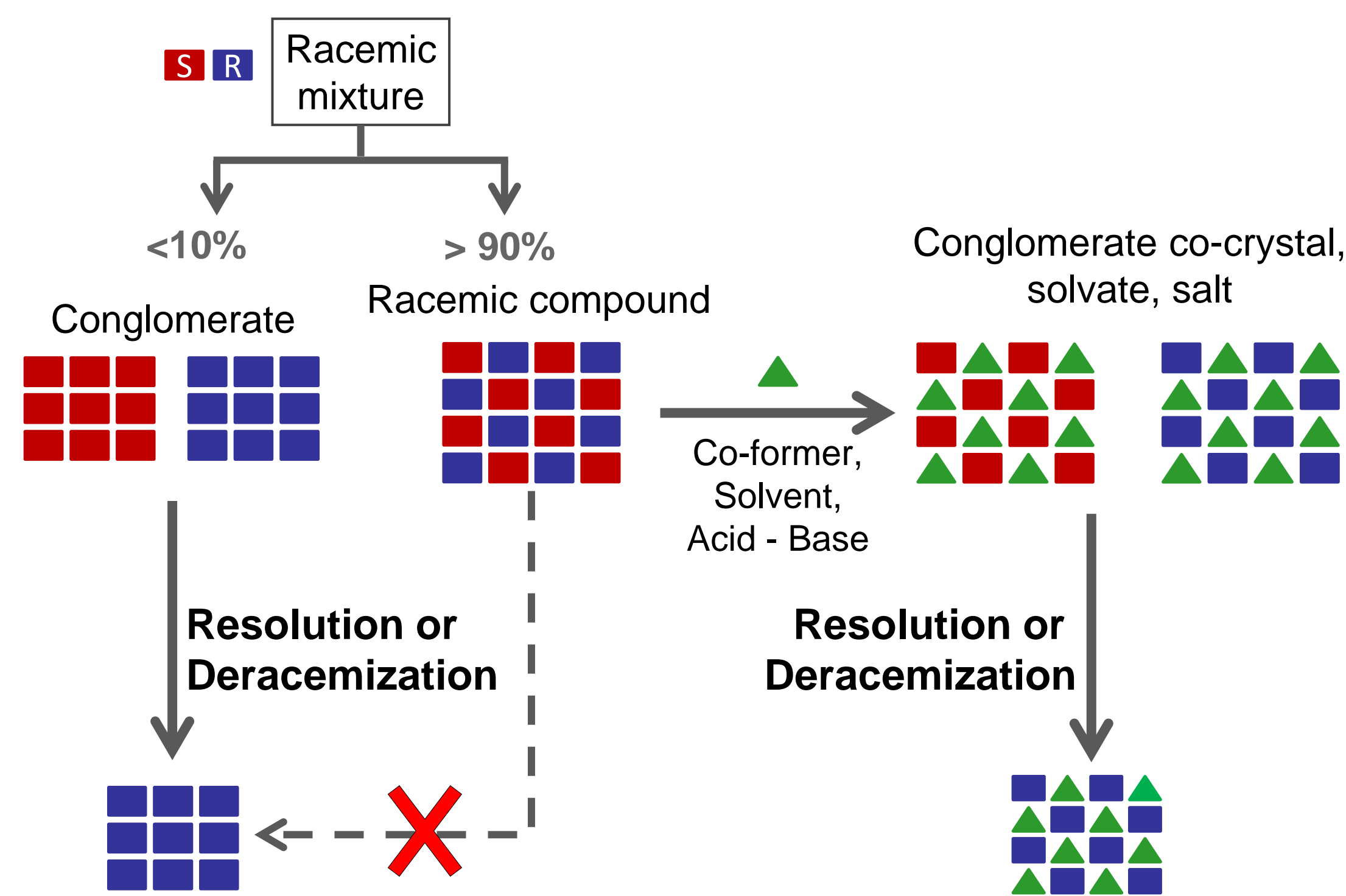
Racemic compound



Compound	S- form	R- form
Praziquantel	Bitter taste	Parasitic worm treatment

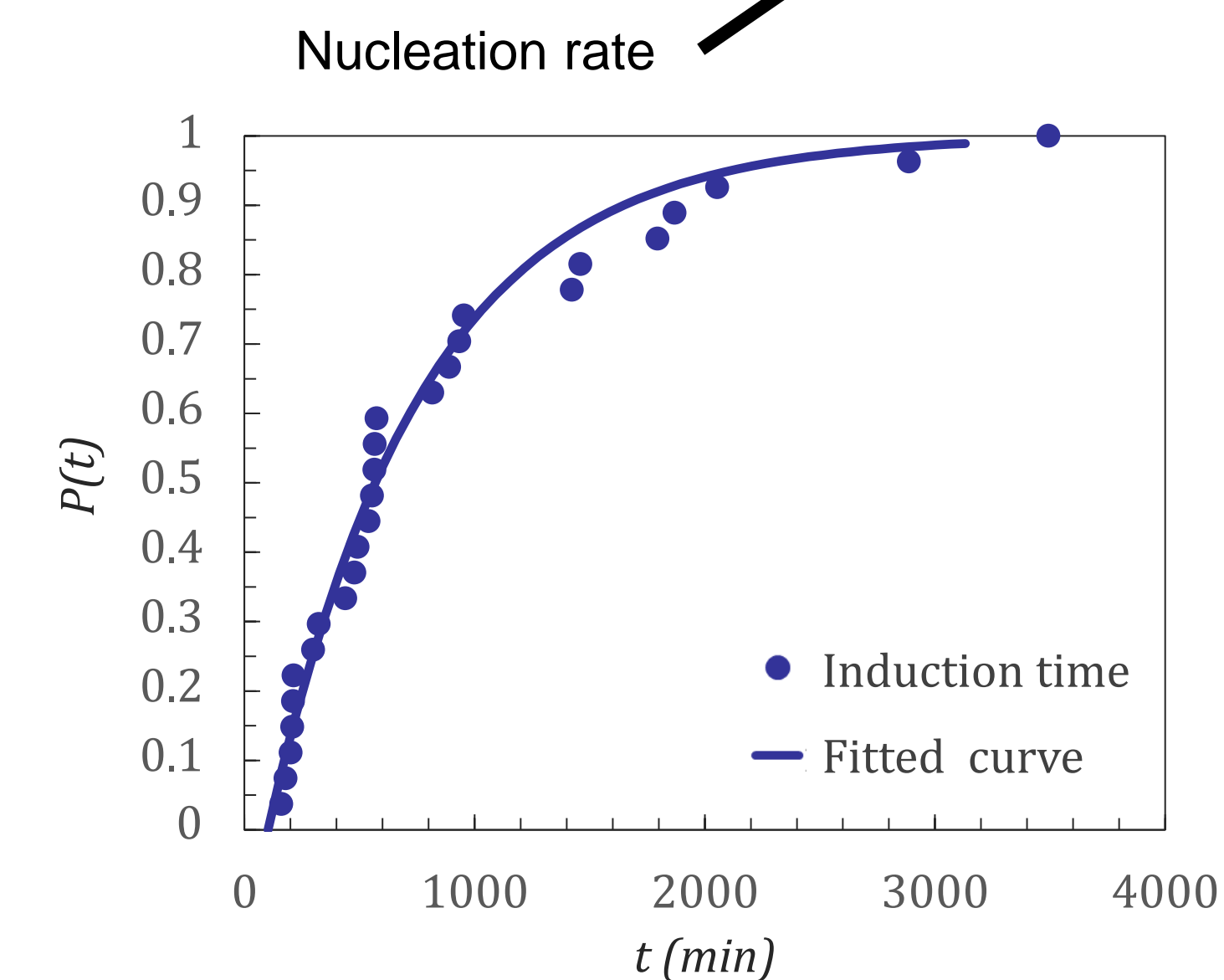
- Many marketed racemic products switched to enantiopure
- New chiral API are predominantly marketed as enantiopure

Co-crystallization of APIs



Probability distribution of induction times [1]

$$P(t) = 1 - \exp(-JV(t - t_g))$$



OBJECTIVES

Crystallization behavior of chiral molecules

This system offers the opportunity to study crystallization kinetics of conglomerate and racemic compounds in similar conditions as the same components are involved (PZQ – VA – EtOH)

Nucleation rate J and growth time t_g measurements regarding the supersaturation and the molar fraction of the co-former VA

SYSTEM PRESENTATION

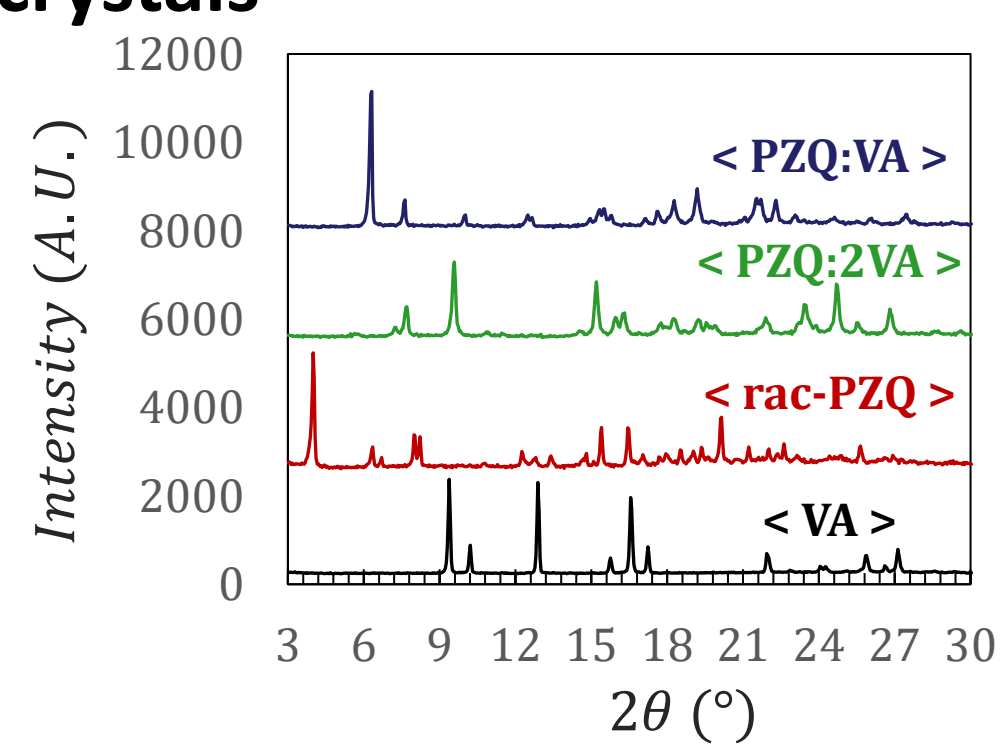
PZQ + VA form two co-crystals [3]

PZQ:VA co-crystal

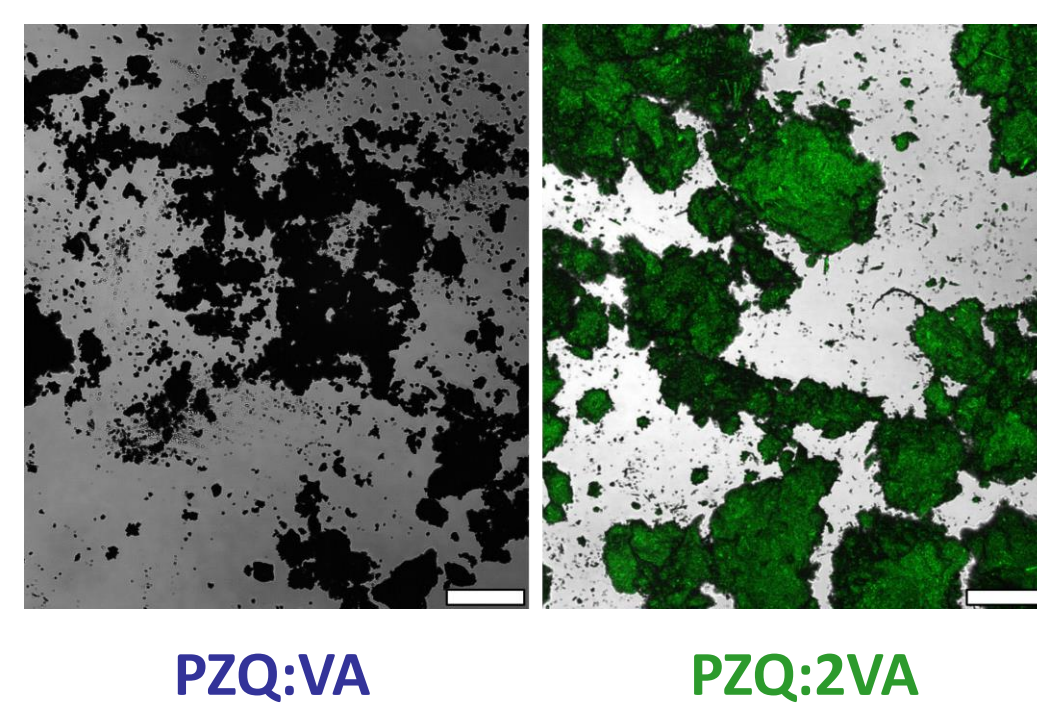
Racemic
Equimolar

PZQ:2VA co-crystal

Conglomerate
Non equimolar

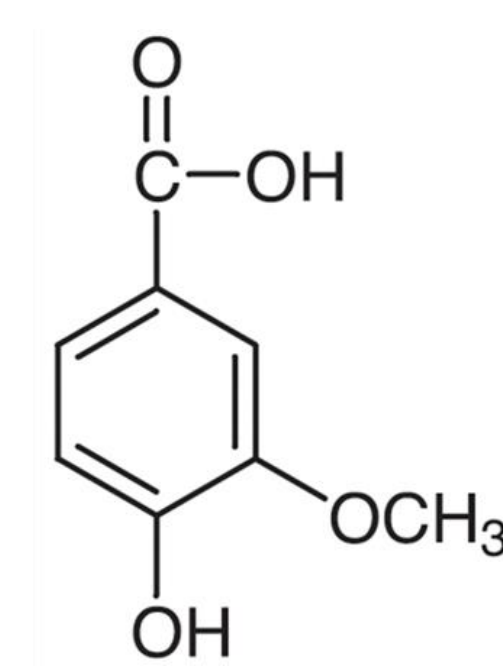


SHG-Microscopy

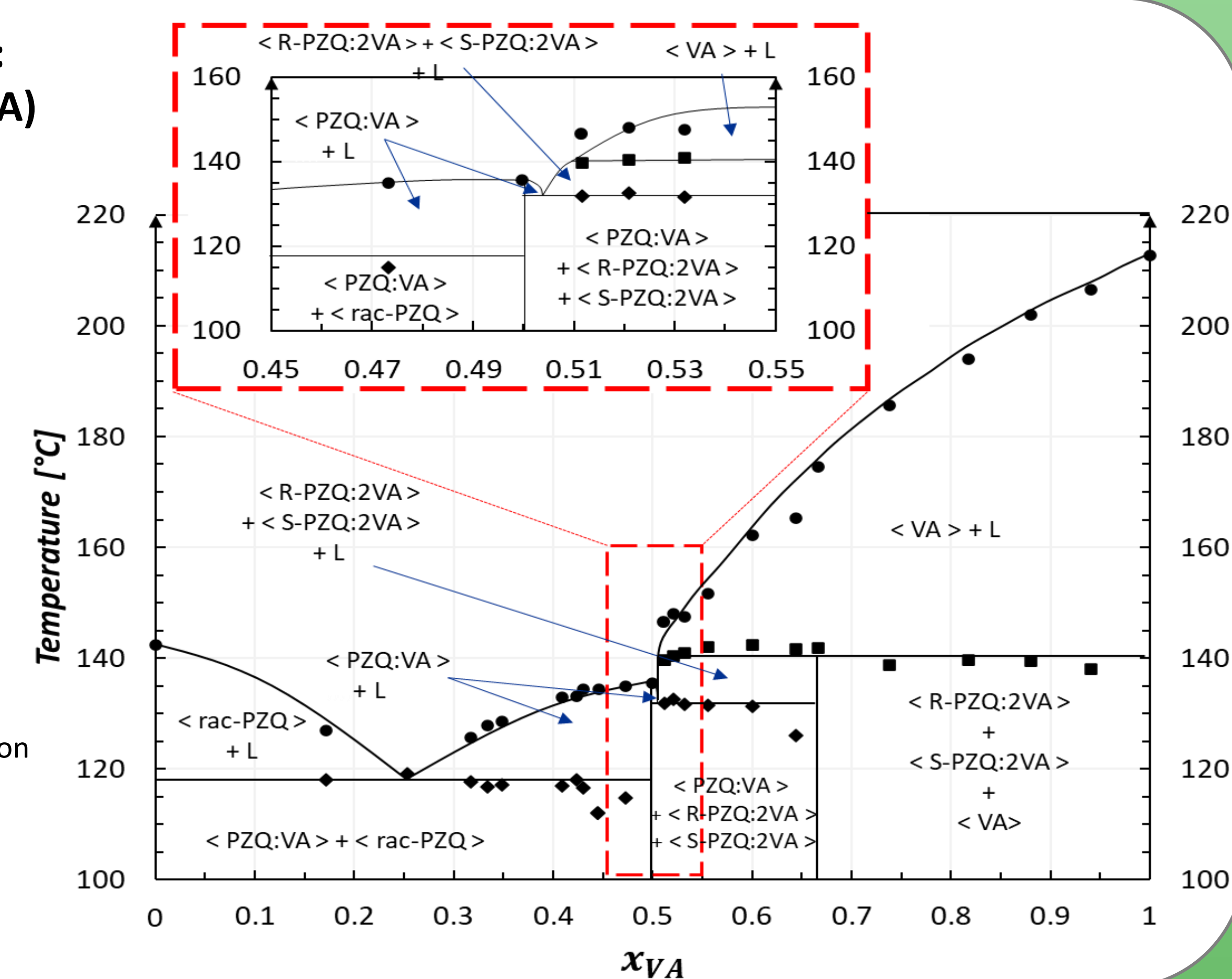


PHASE DIAGRAM

Co-former [2]: Vanillic acid (VA)

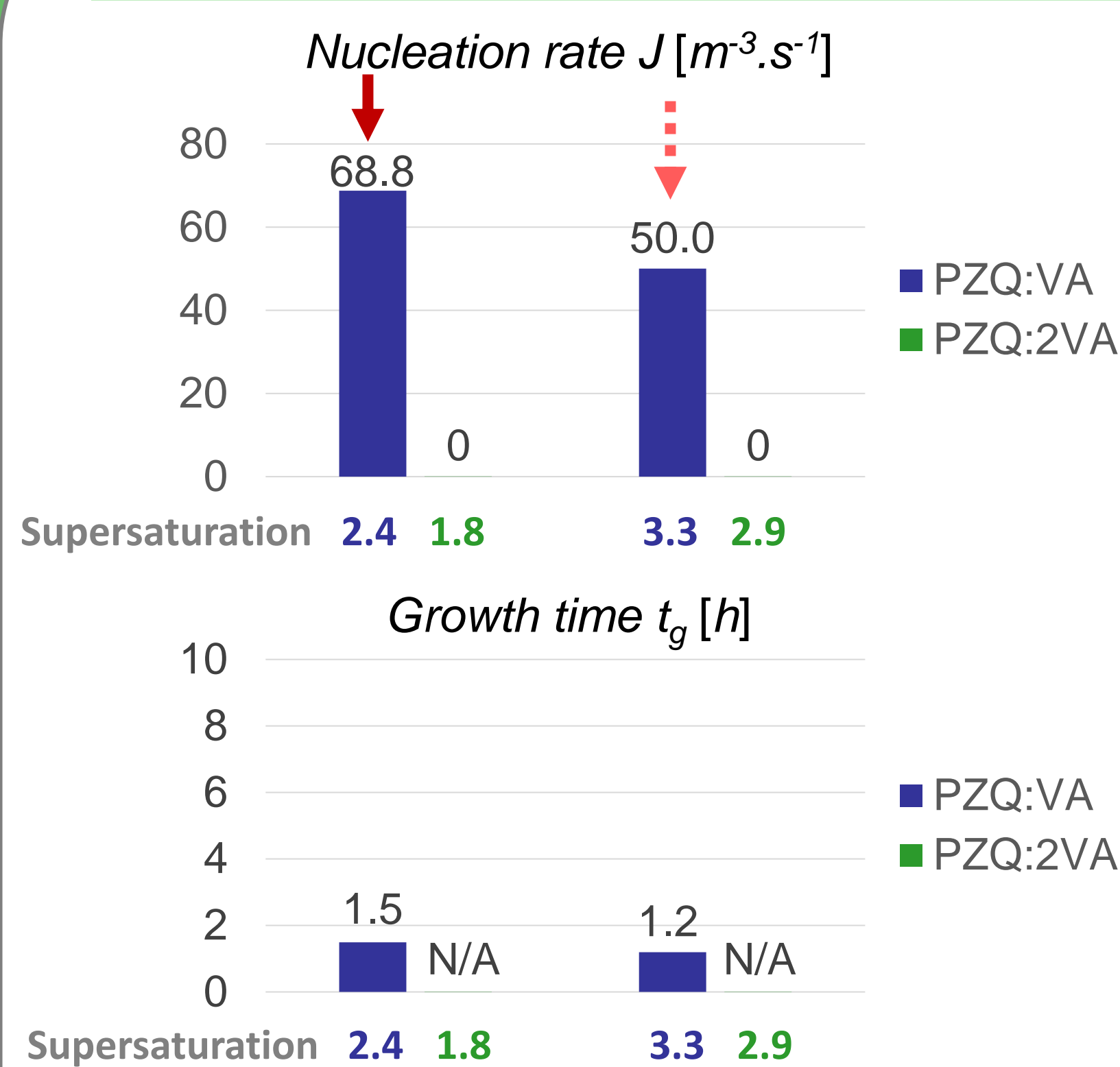


Isolethal binary section
[R-PZQ] = [S-PZQ]



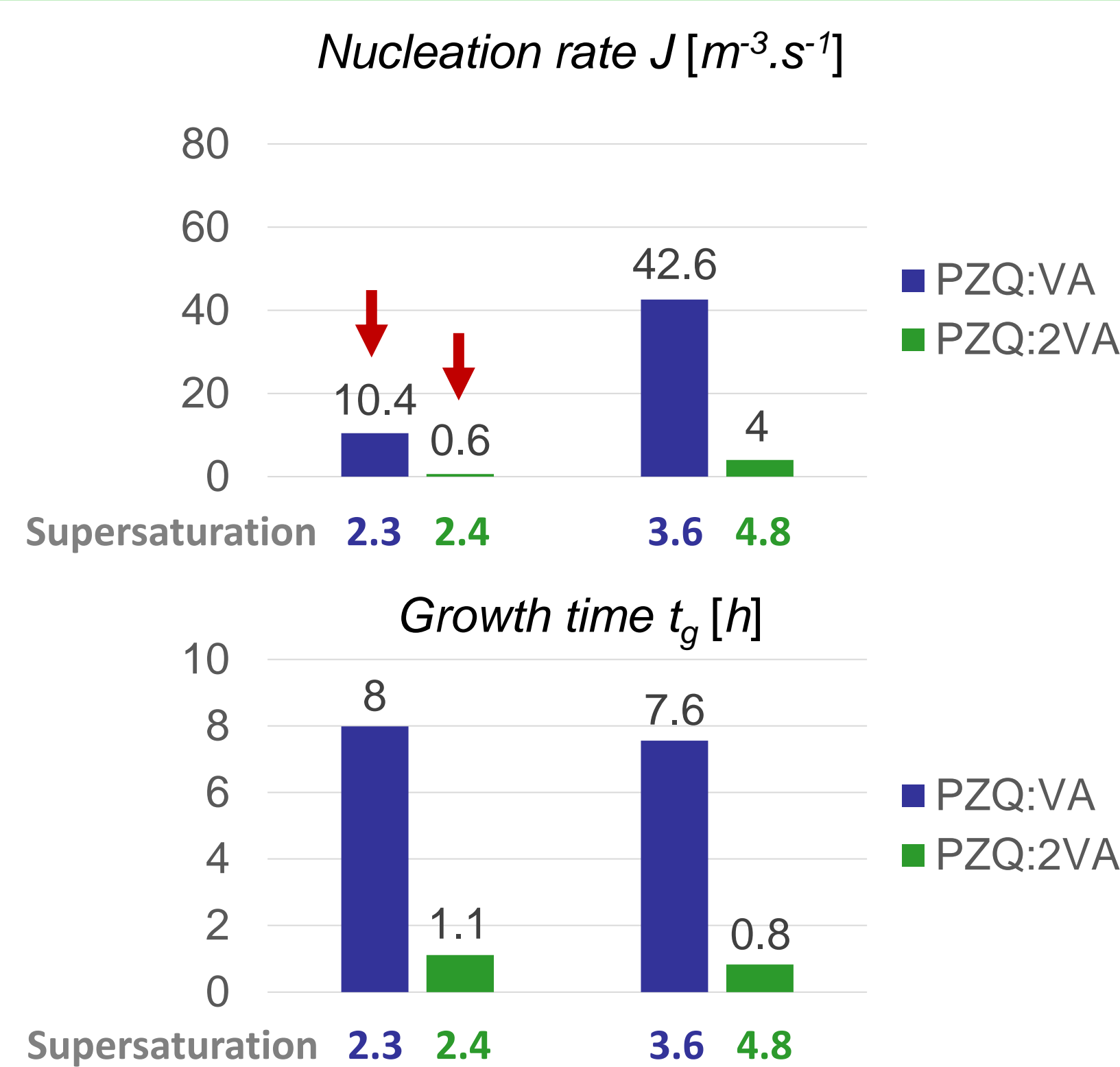
RESULTS

Stable racemic compound ($y_{VA} = 0.5$)



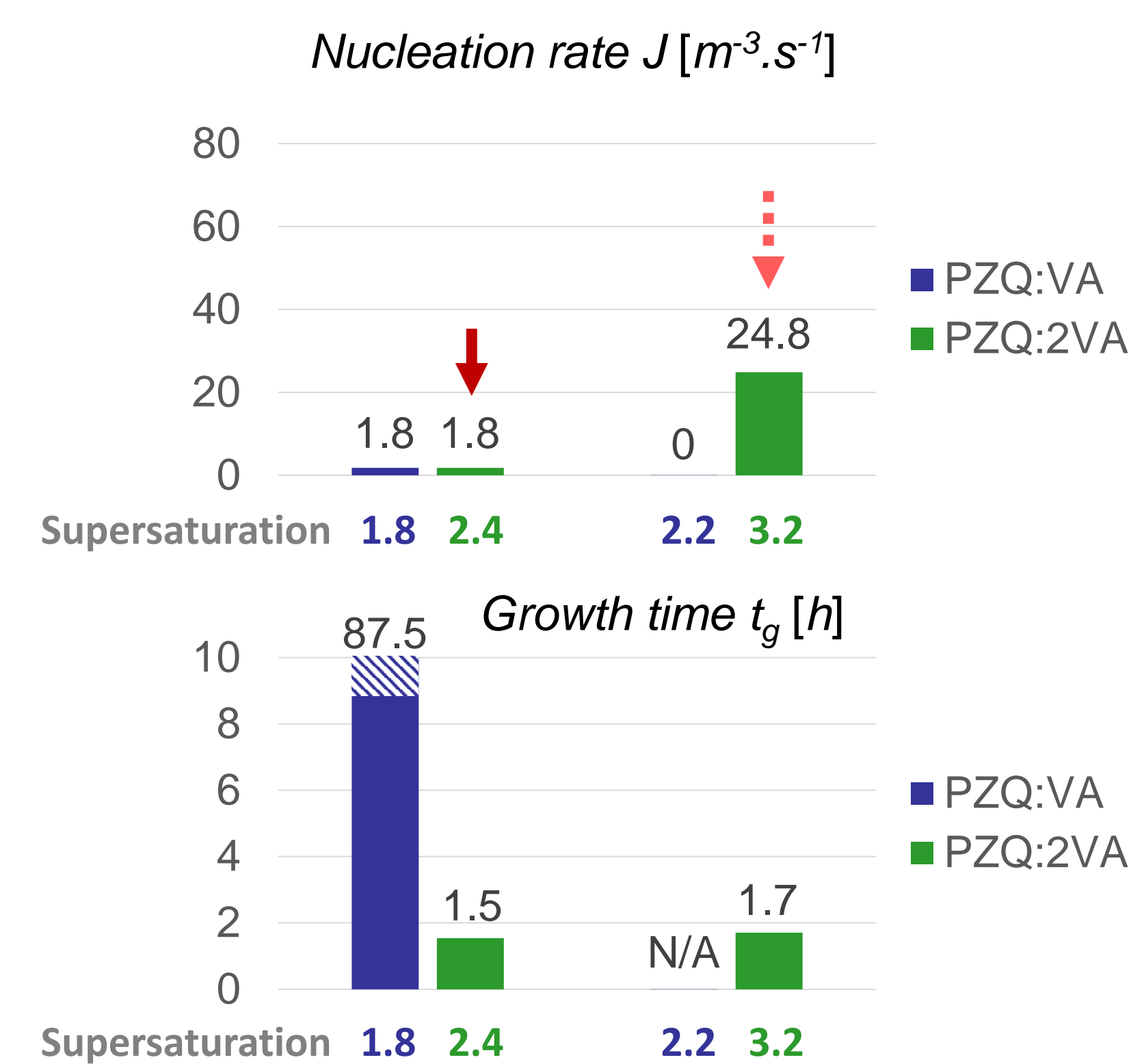
When the racemic co-crystal is the stable phase, the conglomerate co-crystal does not nucleate

Stable conglomerate ($y_{VA} = 0.67$)



When the conglomerate co-crystal is the stable phase, there is a competition between the two co-crystals : PZQ:2VA grows faster but the nucleation rate of PZQ:VA is higher

Conglomerate co-crystal enhancement ($y_{VA} = 0.8$)



In excess of co-former, the conglomerate co-crystal is favored, with higher nucleation rate and shorter growth time

CONCLUSION

The nucleation rate of the conglomerate co-crystal is lower : at identical supersaturation ($\beta = 2.4/3.2$) the nucleation rate of PZQ:2VA is much lower than that of PZQ:VA
At $y_{VA} = 0.67$, despite a shorter growth time of PZQ:2VA, the nucleation rate of PZQ:VA remains higher even though it is metastable

The nucleation of the racemic compound is generally favored, with a significantly higher nucleation rate

The conglomerate co-crystal needs higher supersaturation to nucleate and prevent the crystallization of the racemic compound

If both forms can nucleate, the racemic compound is favored

This system opens routes toward direct enantiomeric resolution of PZQ via preferential crystallization of the PZQ:2VA conglomerate cocrystal

[1] Jiang, S., & ter Horst, J. H. (2011). Crystal nucleation rates from probability distributions of induction times. *Crystal growth & design*, 11(1), 256-261

[2] Devogelaer, J. J. et al. (2021). Cocrystals of Praziquantel: Discovery by Network-Based Link Prediction. *Crystal Growth & Design*, 21(6), 3428-3437

[3] Gerard, C. J. J. et al. (to be published). Phase diagrams of Praziquantel and Vanillic acid cocrystals: racemic compound and conglomerate system