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

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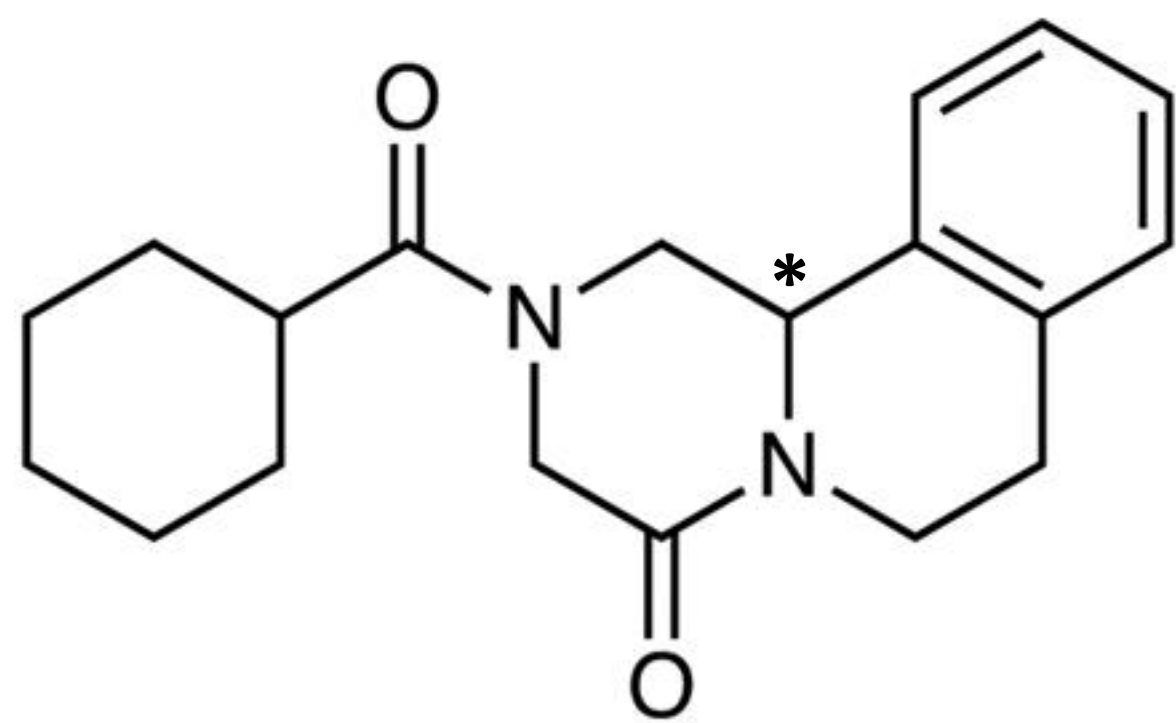
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## INTRODUCTION

### Praziquantel (PZQ)

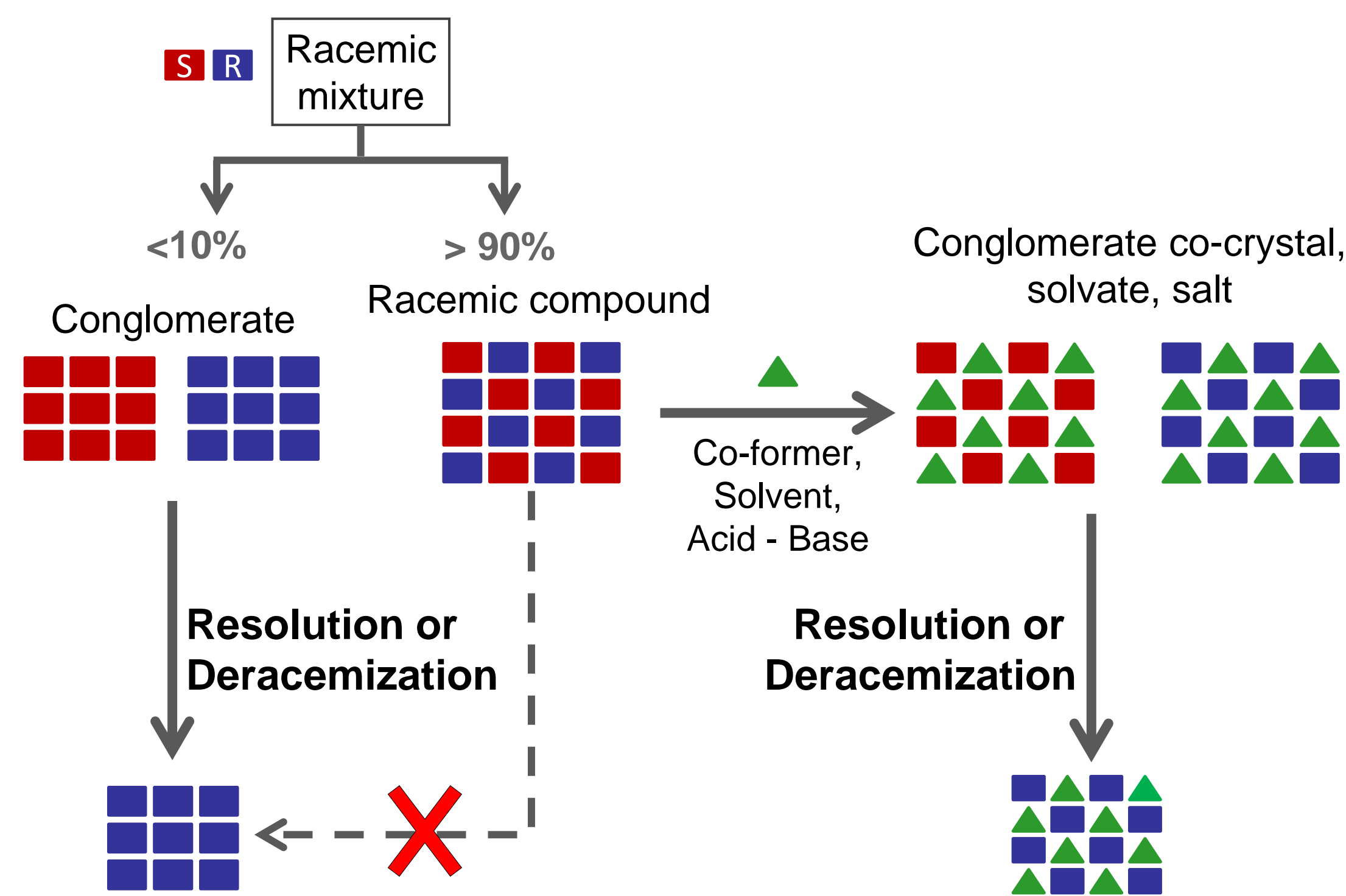
Racemic compound



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

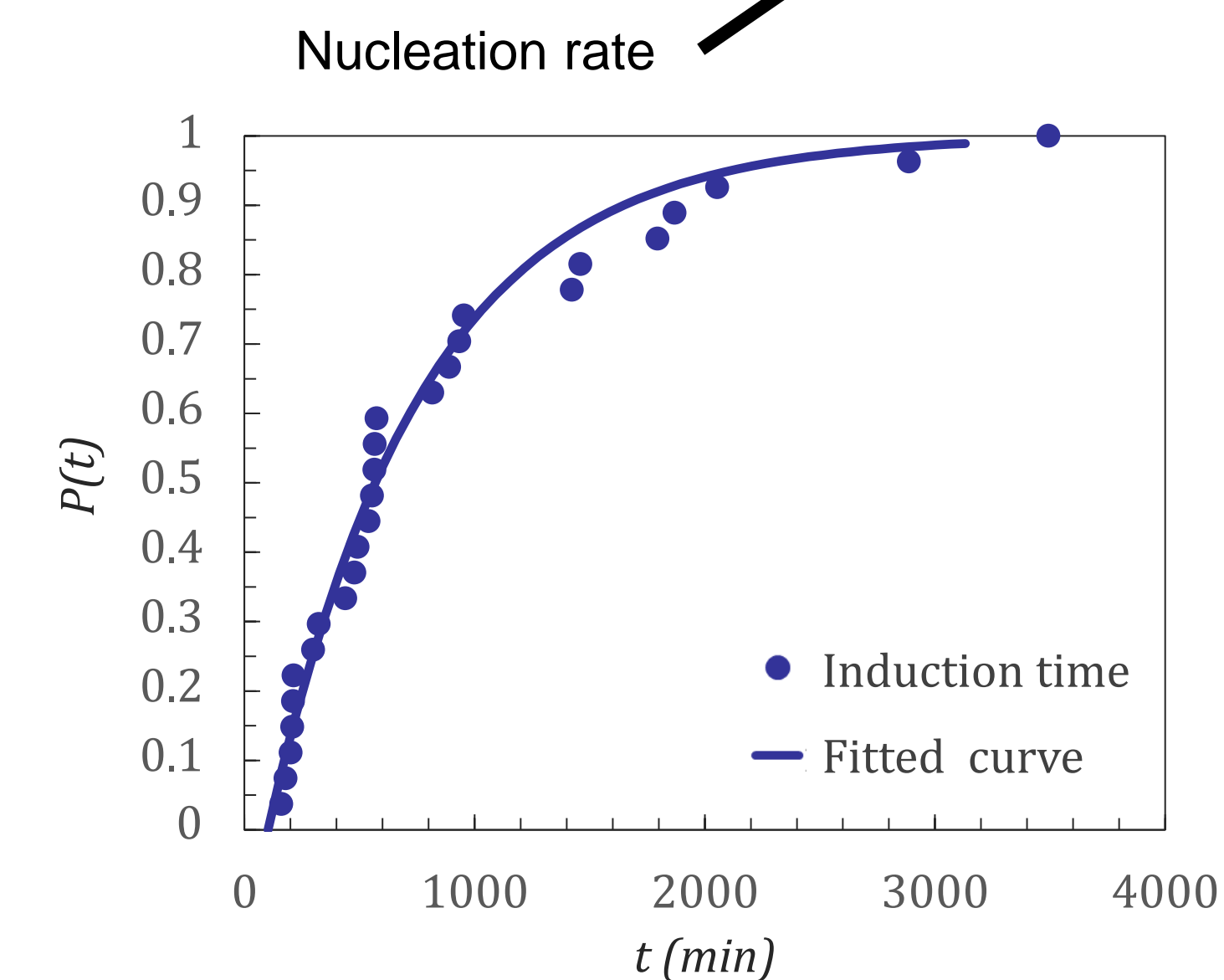
- Many marketed racemic products switched to enantiopure
- New chiral API are predominantly marketed as enantiopure

### 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

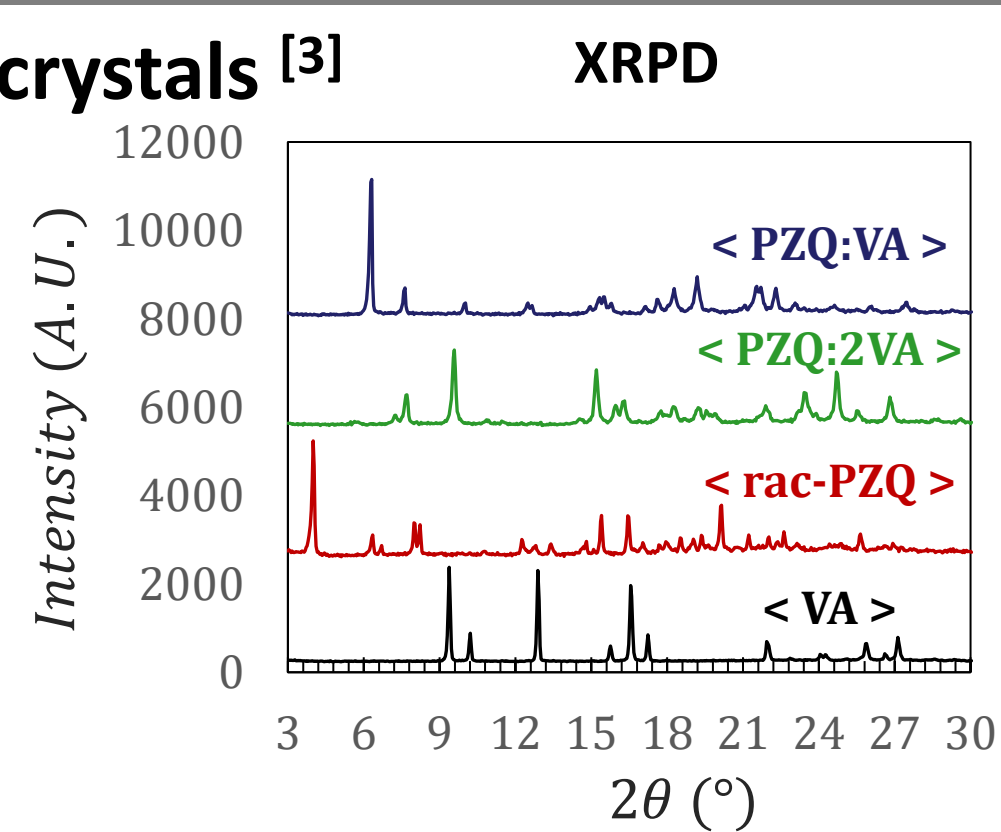
### PZQ + VA form two co-crystals [3]

#### PZQ:VA co-crystal

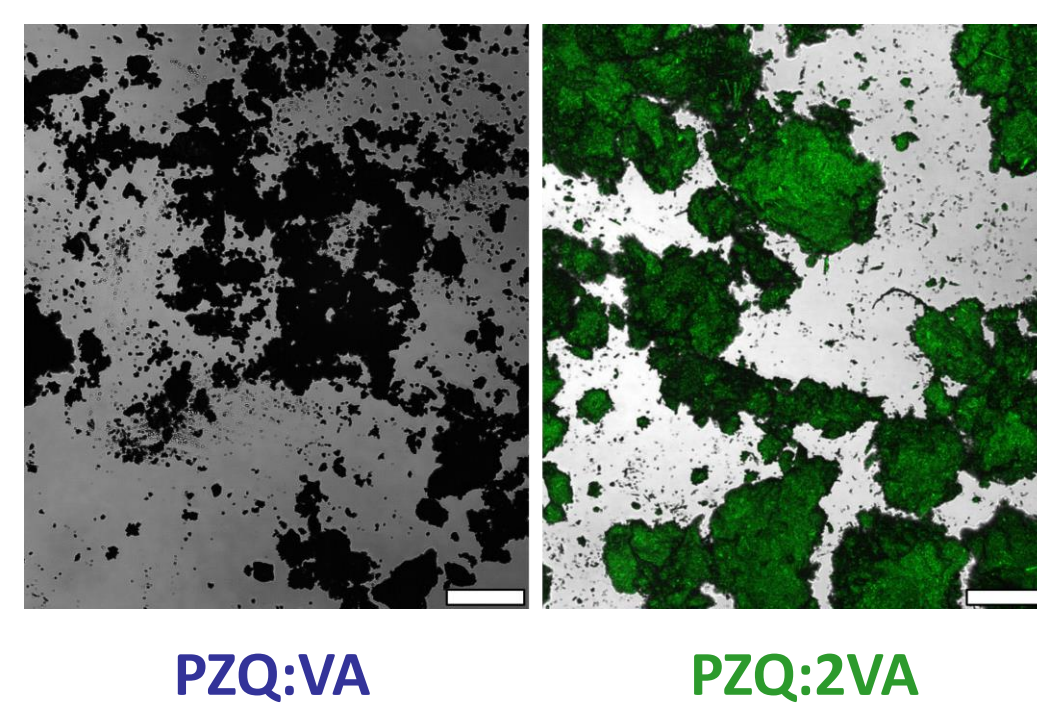
Racemic  
Equimolar

#### PZQ:2VA co-crystal

Conglomerate  
Non equimolar

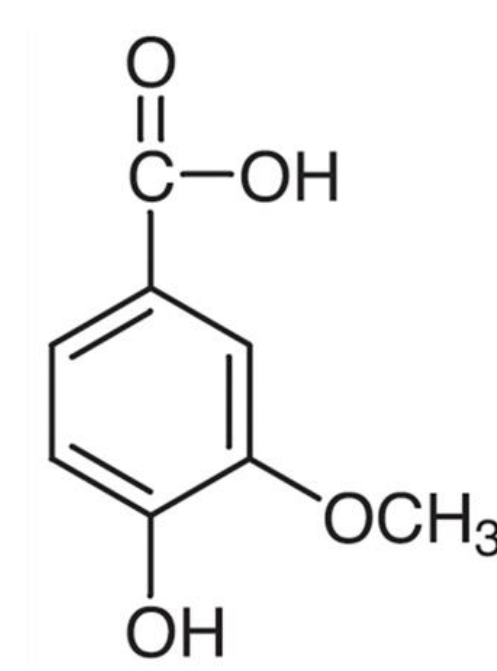


### SHG-Microscopy

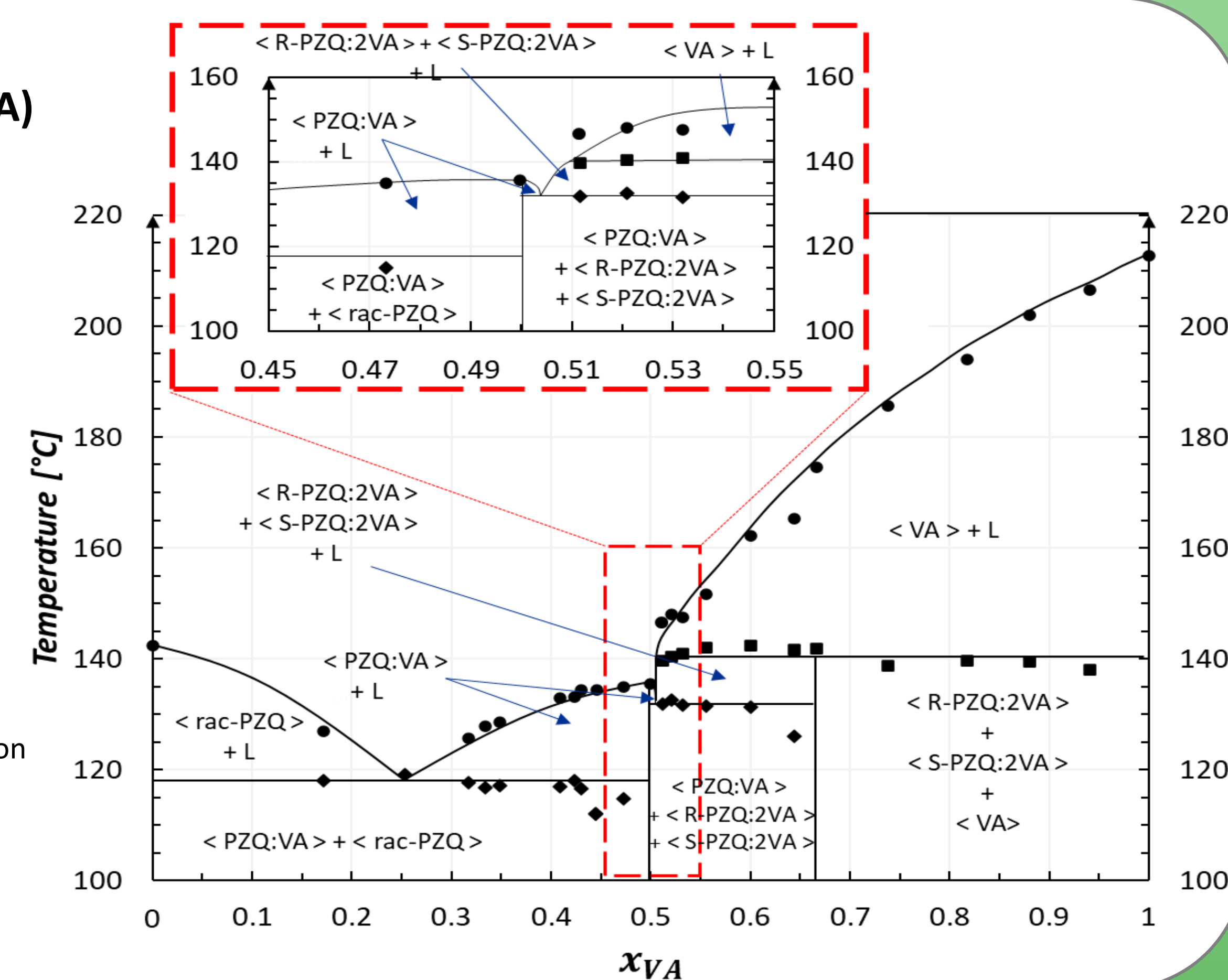


## PHASE DIAGRAM

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

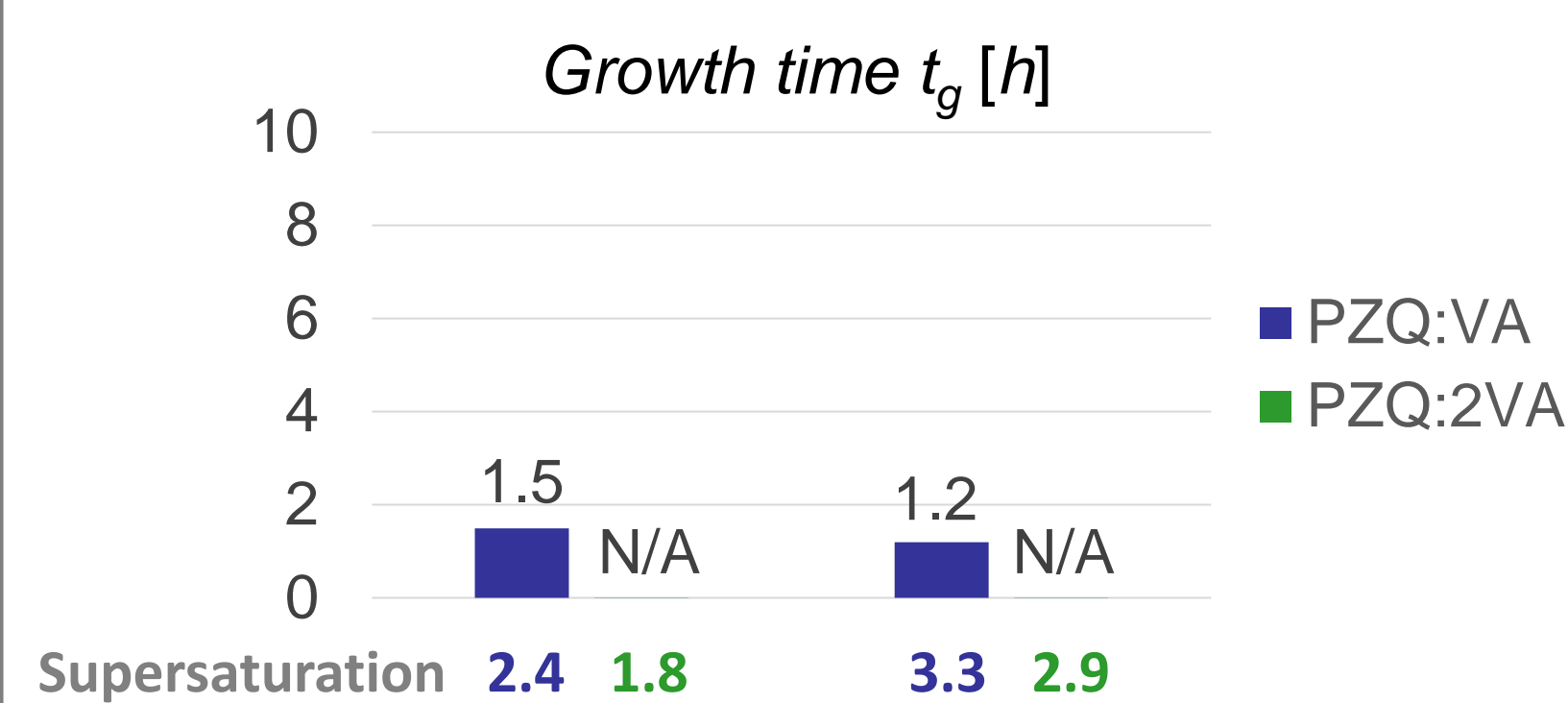
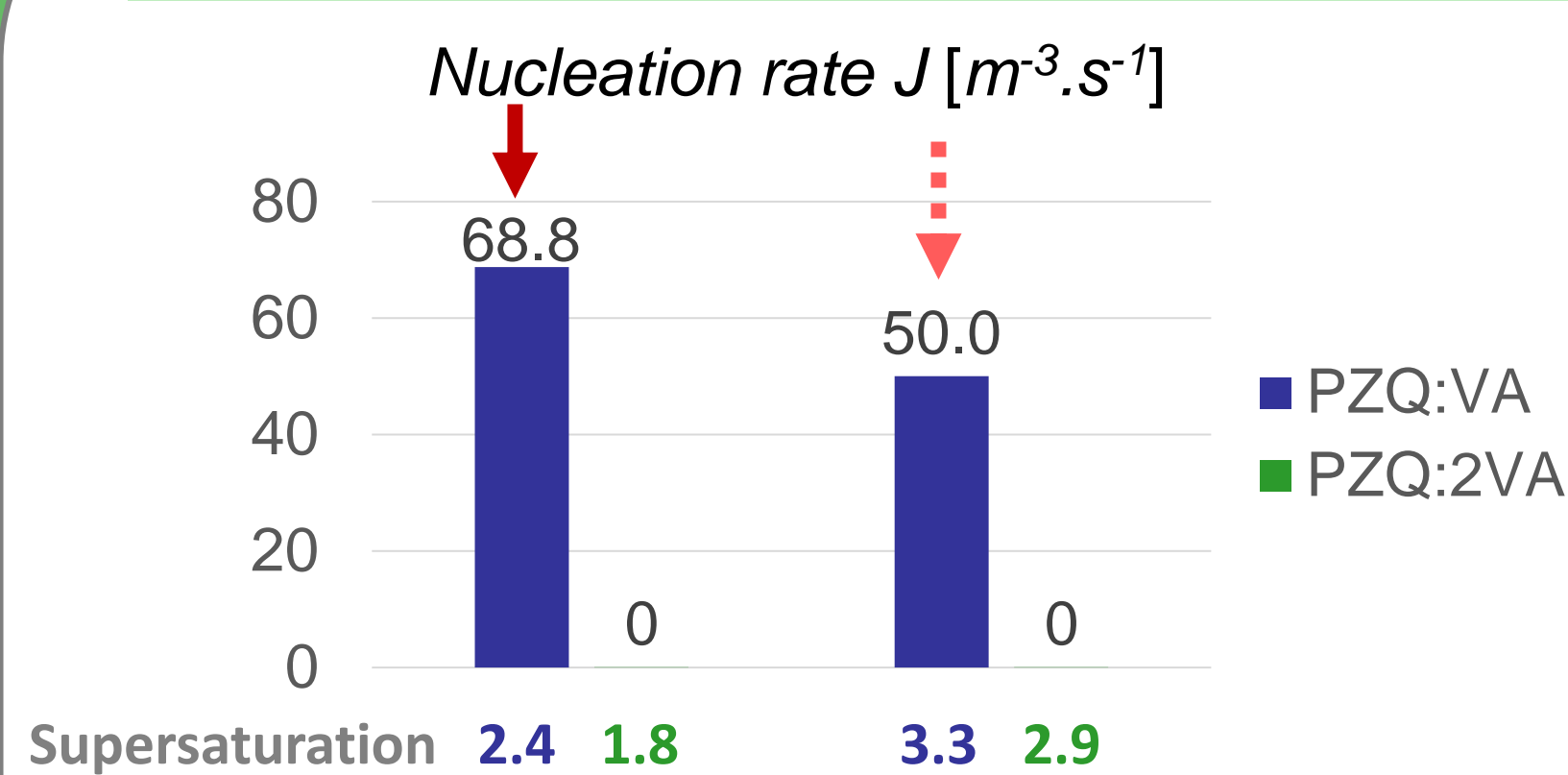


Isolethal binary section  
[R-PZQ] = [S-PZQ]



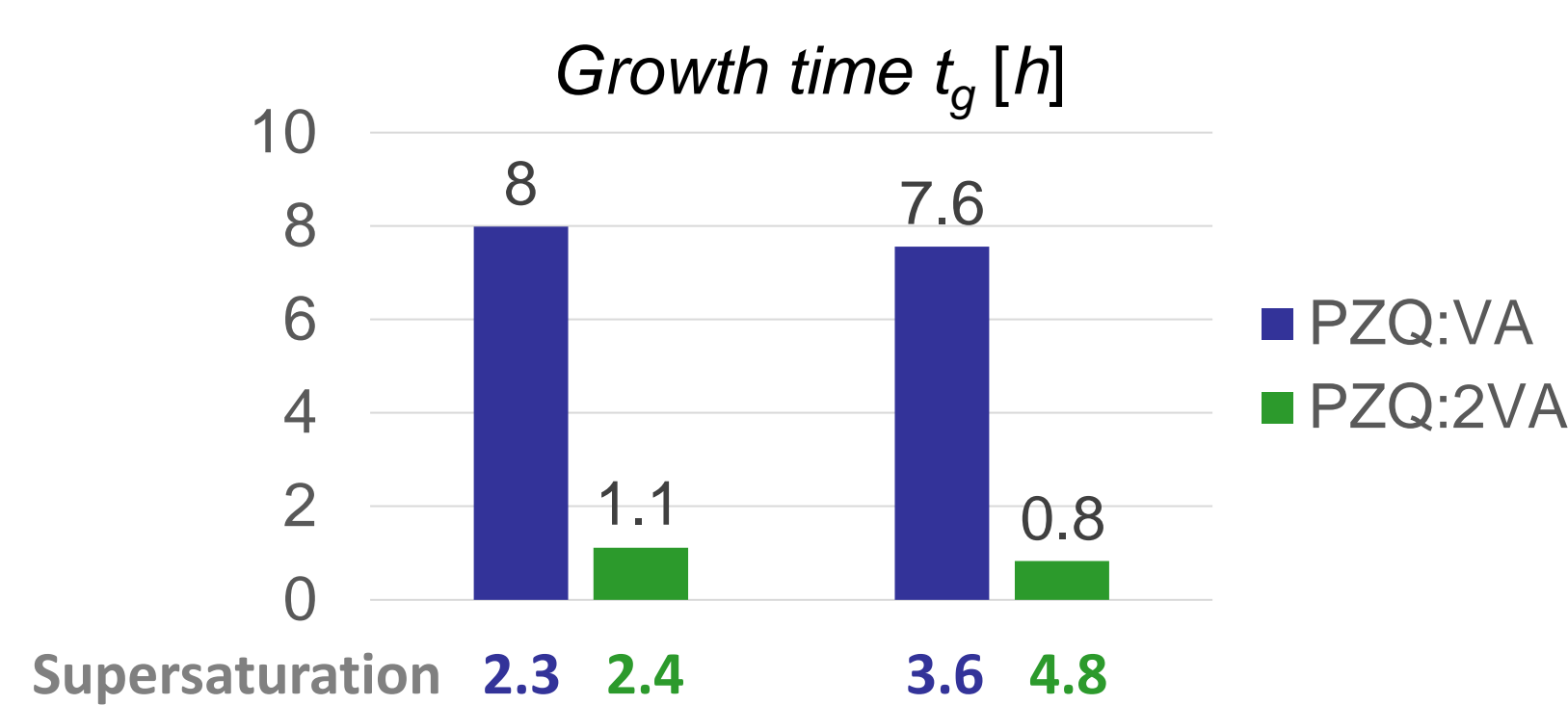
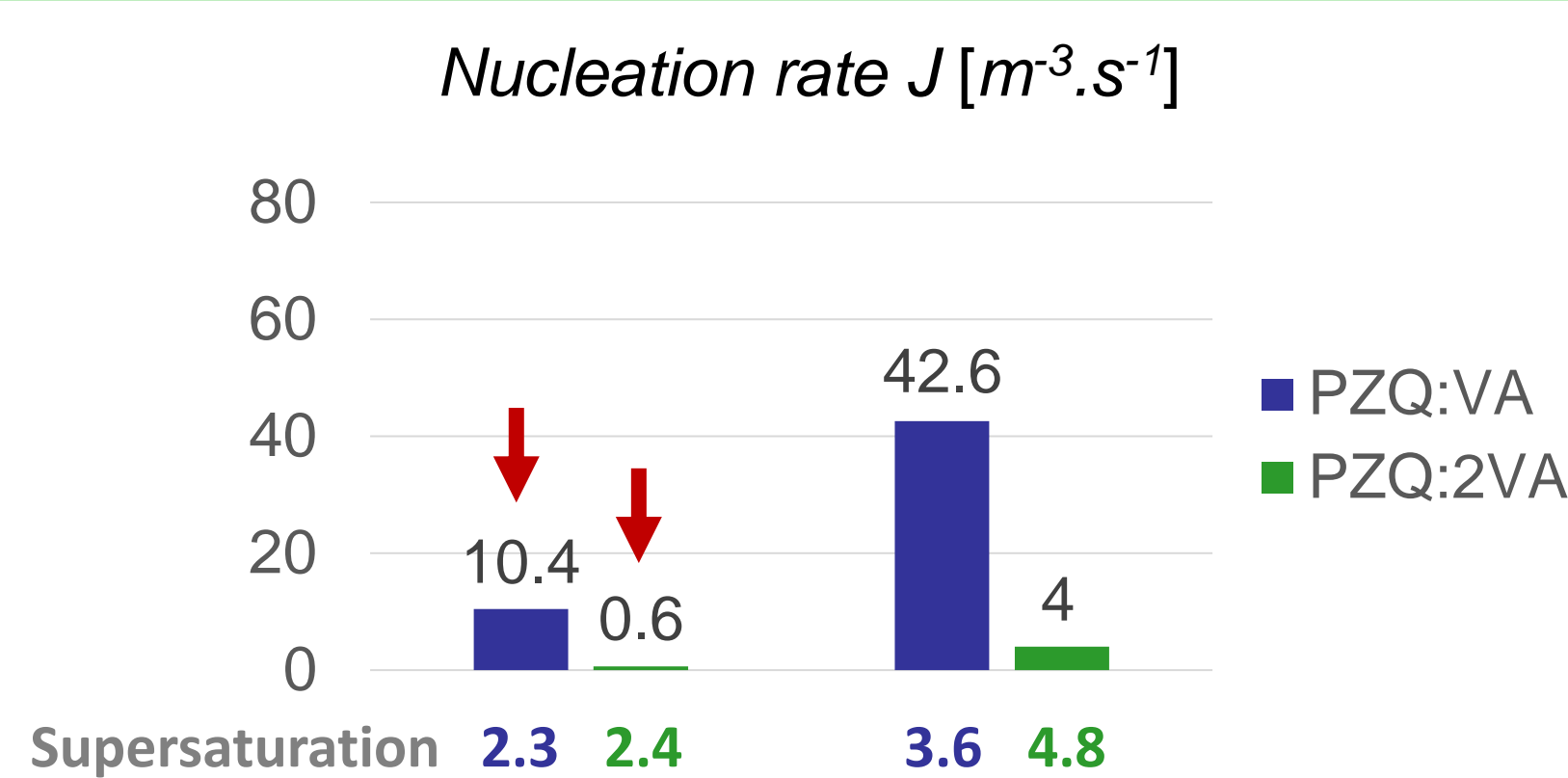
## RESULTS

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



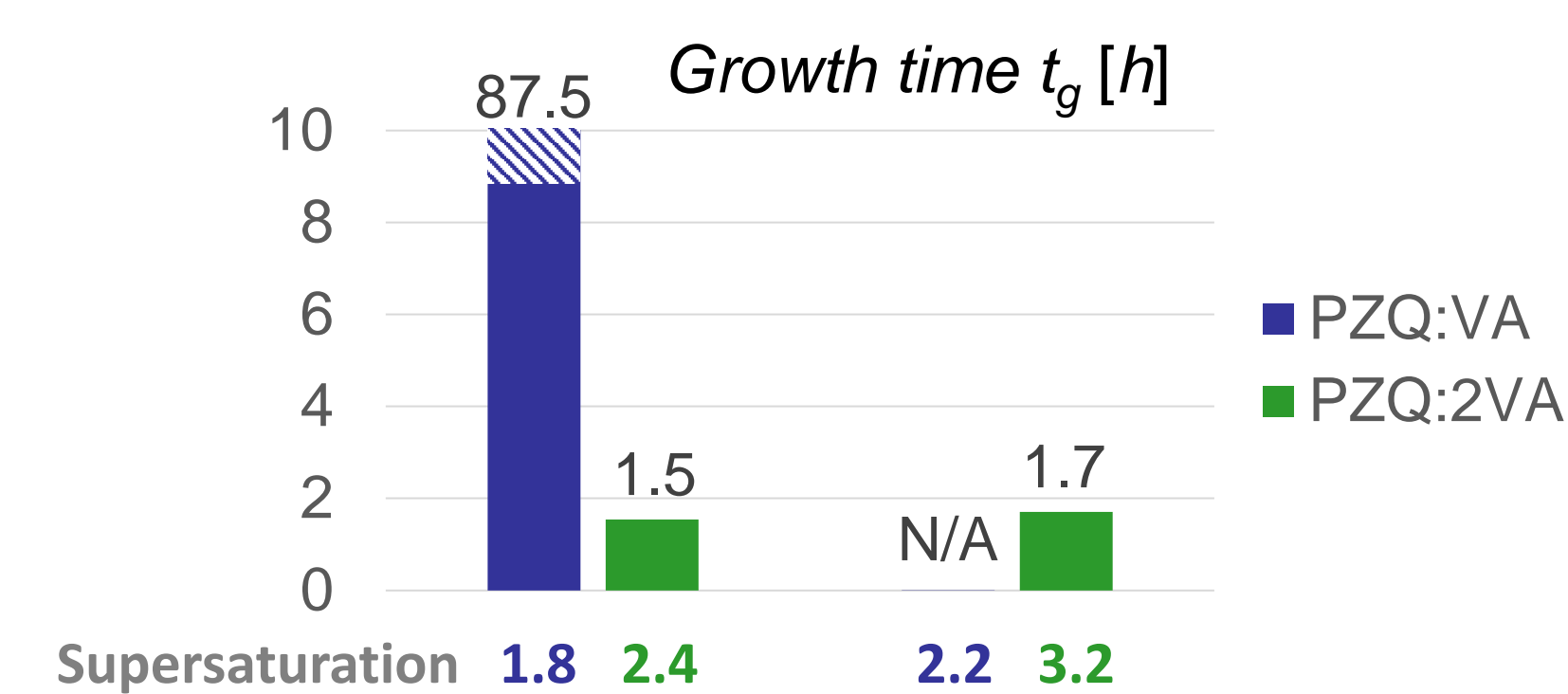
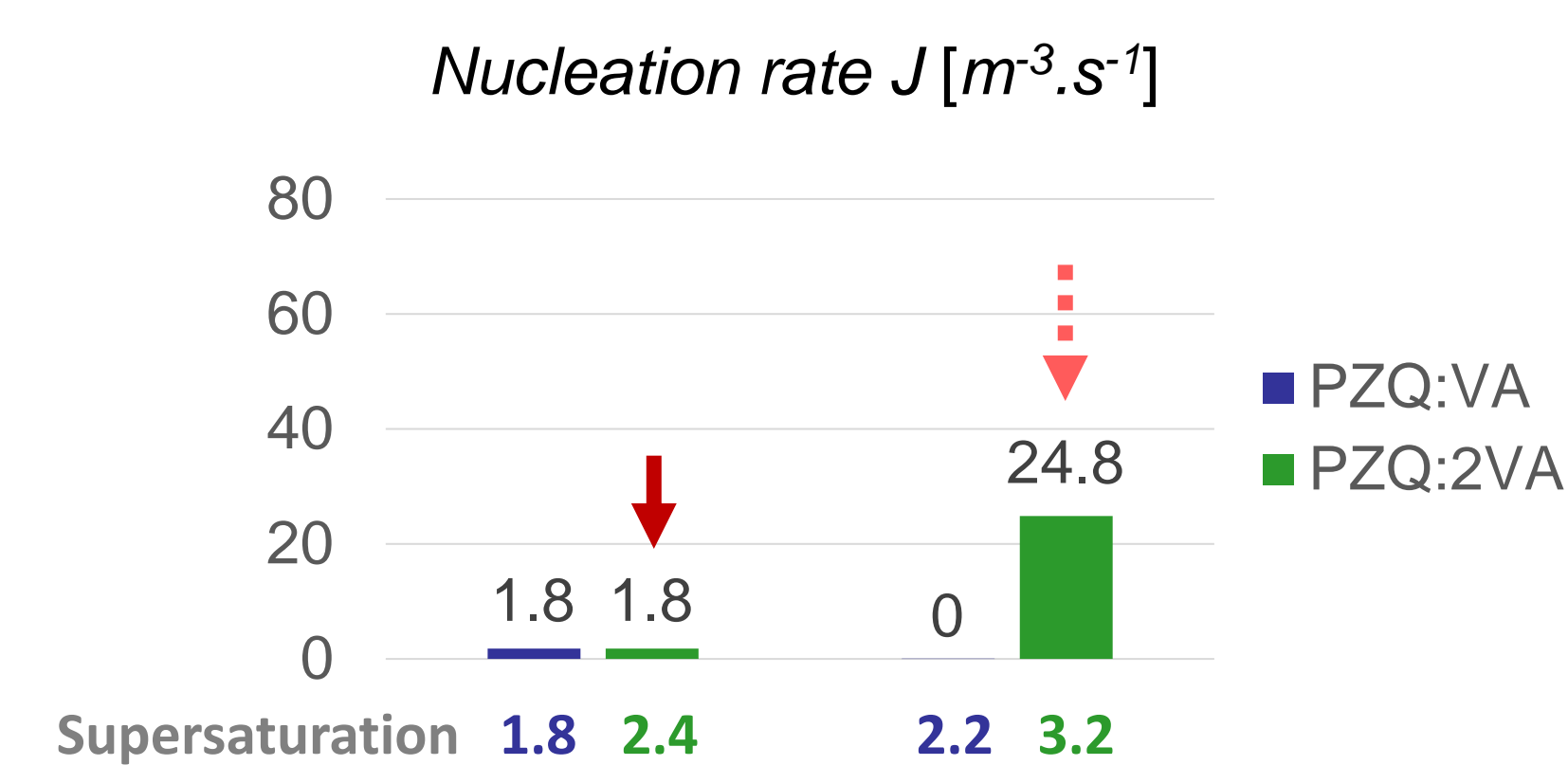
When the racemic co-crystal is the stable phase, the conglomerate co-crystal does not nucleate

### 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