The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

# Diarylpentanoid BP-M345 acts as an antimitotic agent in NCI-H460 cell line

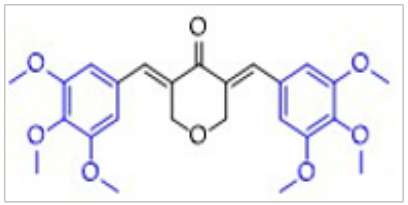
Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

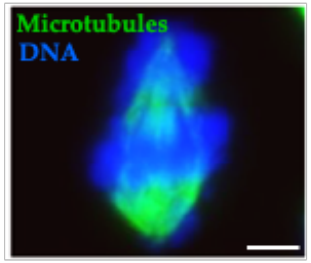
**Pedro Novais [1,†], Patrícia M. A. Silva [1,2,†], Joana Moreira [3,4], Andreia Palmeira [3,4], Isabel Amorim [5], Madalena Pinto [3,4], Honorina Cidade [3,4,*] and Hassan Bousbaa [1,*]**

[1] UNIPRO—Oral Pathology and Rehabilitation Research Unit, University Institute of Health Sciences (IUCS), CESPU, Rua Central de Gandra, 1317, 4585-116 Gandra, Portugal; pedro.ha.novais@gmail.com (P.N.), patricia.silva@cespu.pt (P.M.A.S.)
[2] TOXRUN—Toxicology Research Unit, University Institute of Health Sciences, CESPU, CRL, 4585-116 Gandra, Portugal;
[3] Interdisciplinary Centre of Marine and Environmental Research (CIIMAR), University of Porto, Edifício do Terminal de Cruzeiros do Porto de Leixões, Avenida General Norton de Matos, s/n, 4450-208 Matosinhos, Portugal; up201302558@edu.ff.up.pt (J.M.), apalmeira@ff.up.pt (A.P.), madalena@ff.up.pt (M.P.);
[4] Laboratory of Organic and Pharmaceutical Chemistry, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal;
[5] GreenUPorto (Sustainable Agrifood Production) Research Center, Faculty of Sciences, University of Porto, Rua do Campo Alegre, s/n, 4169-007 Porto, Portugal; mpamorim@fc.up.pt (I.A.);
- Corresponding author: hcidade@ff.up.pt (H.C.); hassan.bousbaa@iucs.cespu.pt (H.B.);
- † Authors contributed equally to this work.

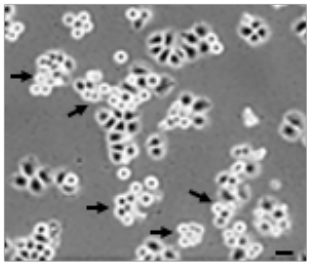
# Diarylpentanoid BP-M345 acts as an antimitotic agent in NCI-H460 cell line



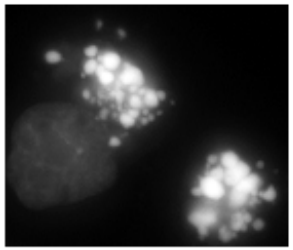
BP-M345




Chromosome misalignment



Mitotic arrest

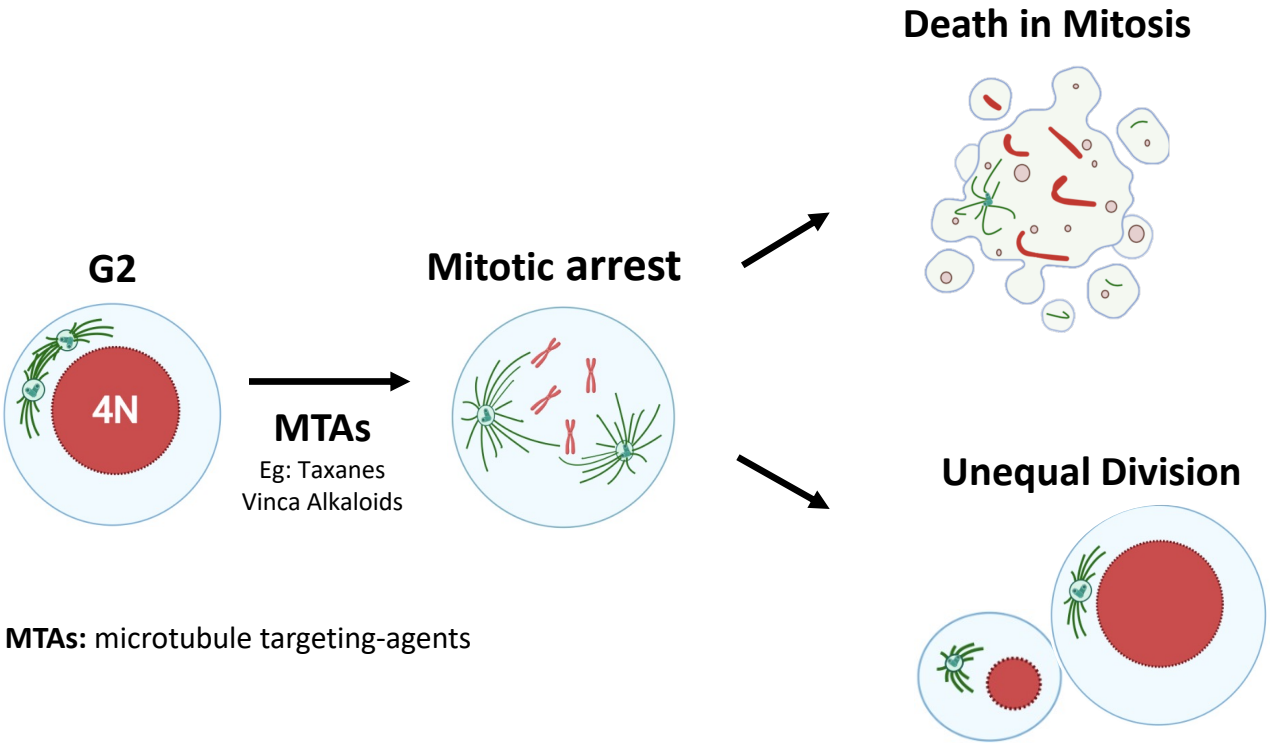


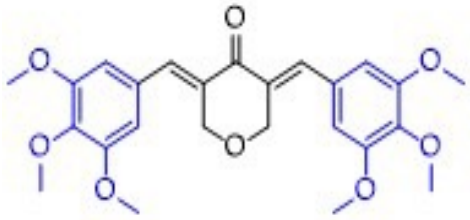
Tumor cell death

**Abstract:** Diarylpentanoids comprise a class of natural products and their synthetic analogues well known for their antitumor activity. Recently, the diarylpentanoid BP-M345 has been identified as a potent *in vitro* growth inhibitor of human colon cancer HCT116 cells expressing wt p53, with a $GI_{50}$ value of 0.17 µM, showing low toxicity in non-tumor HFF-1 cells. However, it was observed that BP-M345 has no effect on the inhibition of the p53-MDM2 interaction. Further insights into the mechanisms through which this compound could exert growth inhibitor activity were pursued. Considering that BP-M345 possesses 3,4,5-trimethoxyphenyl groups that have been much highlighted as playing crucial role in the interaction with tubulin in MTAs, it was hypothesized that this diarylpentanoid could also act as a antimitotic agent. Its antiproliferative activity was evaluated in human tumor cell line by sulforhodamine B assay. BP-M345 promoted a prolonged SAC-dependent mitotic arrest by interfering with mitotic spindle assembly, followed by massive apoptosis. The overall results indicate that the diarylpentanoid BP-M345 exerts its antiproliferative activity by inhibiting mitosis through microtubule perturbation and causing cancer cell death, highlighting its potential as antitumor agent. Additionally, docking poses and residues involved in the binding site of α,β-tubulin were predicted by docking studies.

**Keywords:** Antitumor; Apoptosis; BP-M345; Diarylpentanoid; Mitosis

# Introduction



BP-M345

**MTAs:** microtubule targeting-agents

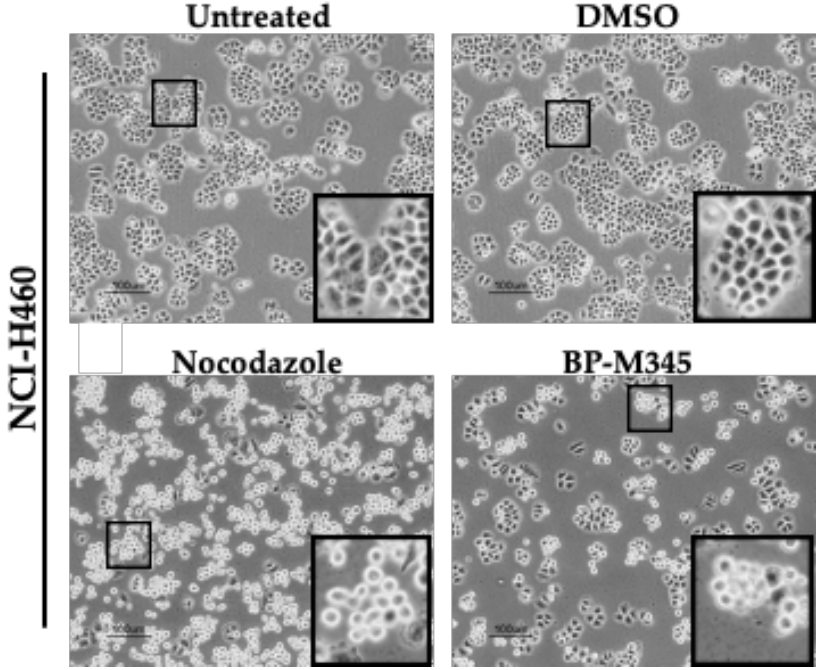
Created in BioRender

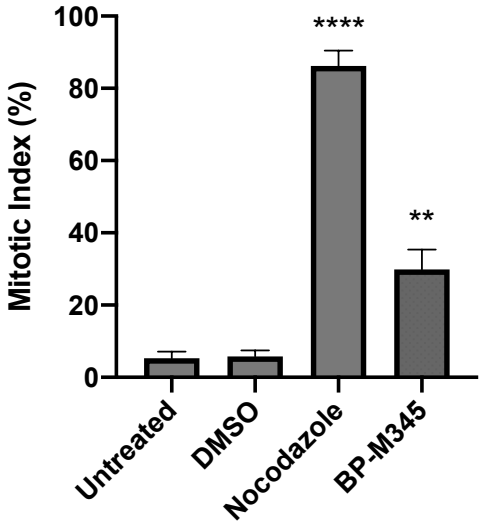
# Results and Discussion

## BP-M345 exhibits a potent tumor anti-growth activity and arrests cells in mitosis

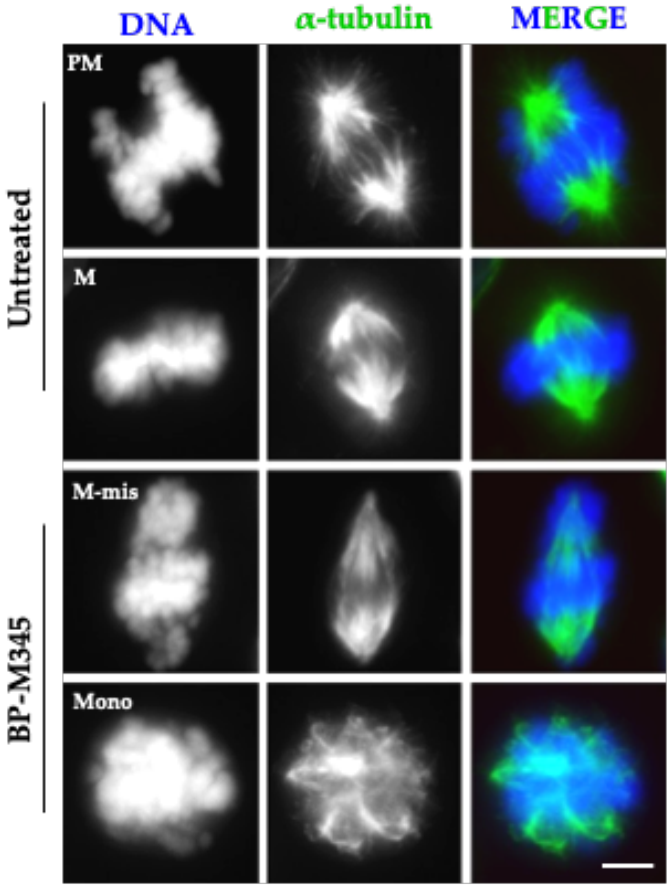
| $GI_{50}$ ($\mu$M) | | | |
|---|---|---|---|
| | A375-C5 | MCF-7 | NCI-H460 |
| BP-M345 | 0.24± 0.01 | 0.45± 0.06 | 0.37± 0.01 |
| Doxorubicin | 0.030± 0.04 | 0.028 ±0.01 | 0.028 ±0.01 |

$GI_{50}$ represents the concentration that causes 50% cell growth inhibition

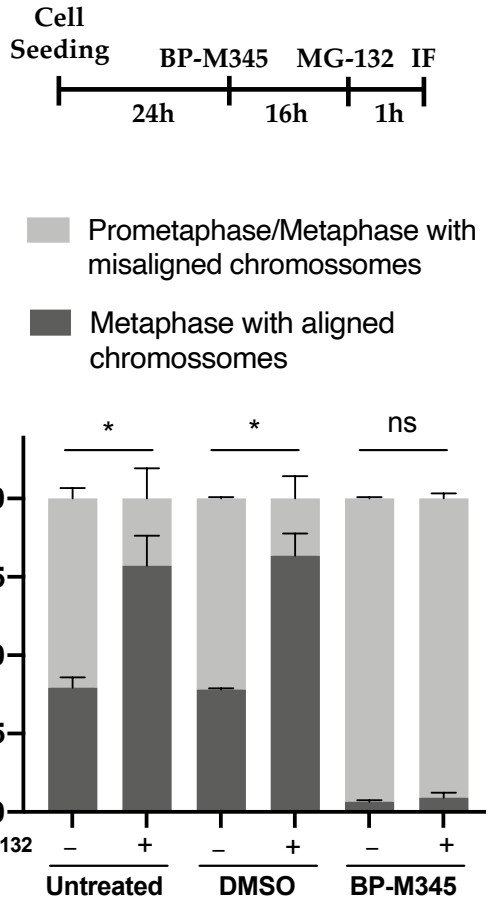


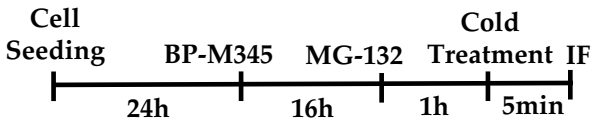
# BP-M345 disturbs mitotic spindle morphology and harms chromosome congression

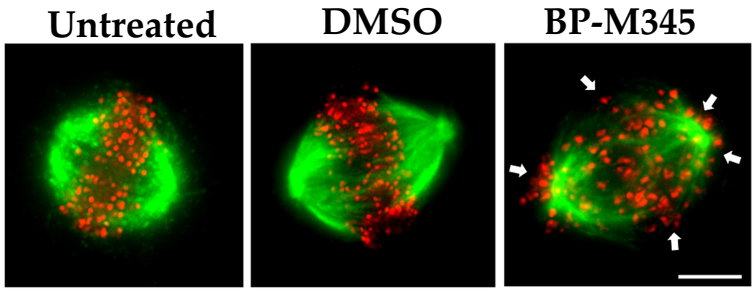


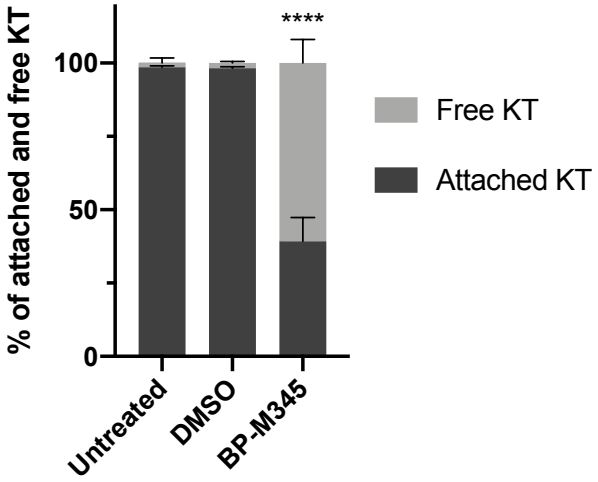

**PM:** Prometaphse
**M:** Metaphase
**M-mis:** Metaphase w/ Misaligned Chromosomes
**Mono:** Monopolar Spindle

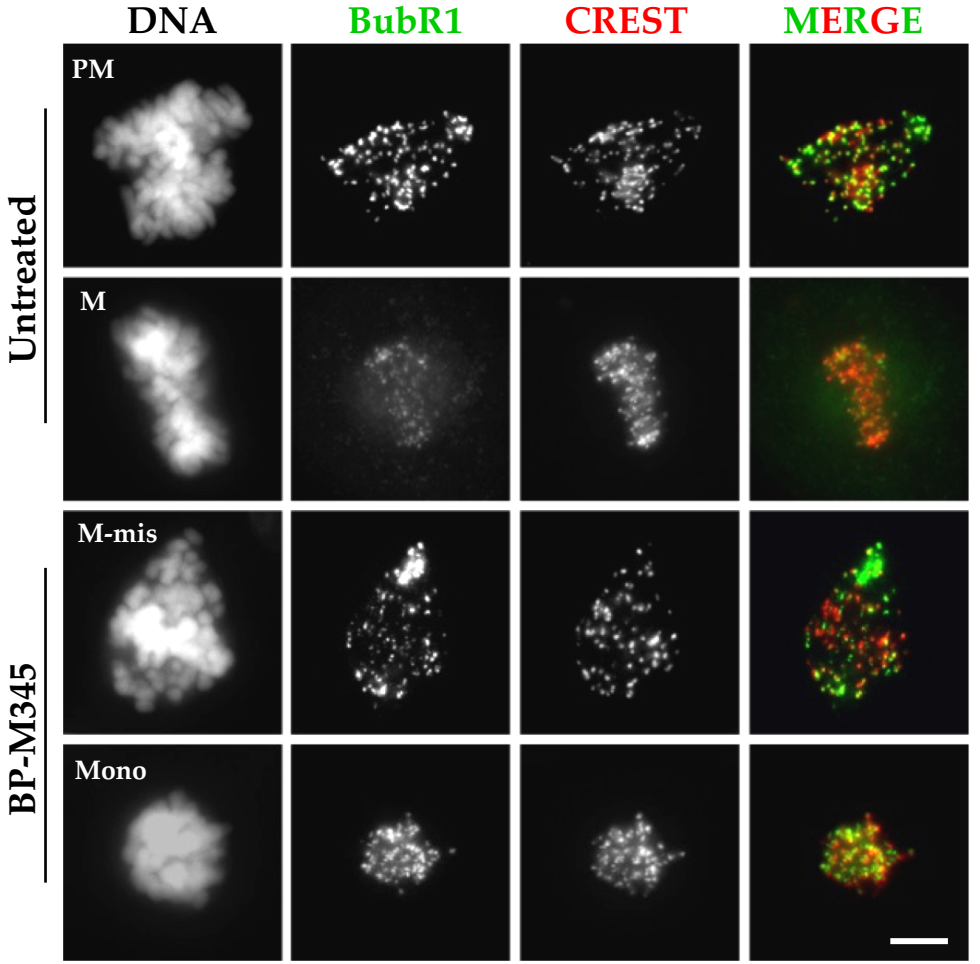


# BP-M345 interferes with the stability of kinetochore-microtubule attachments and promotes SAC activation



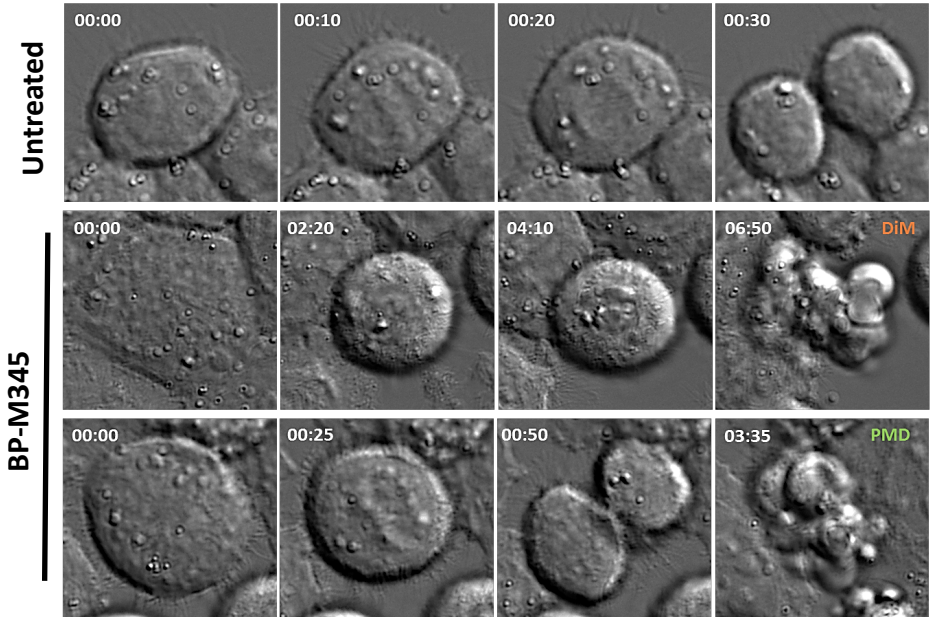



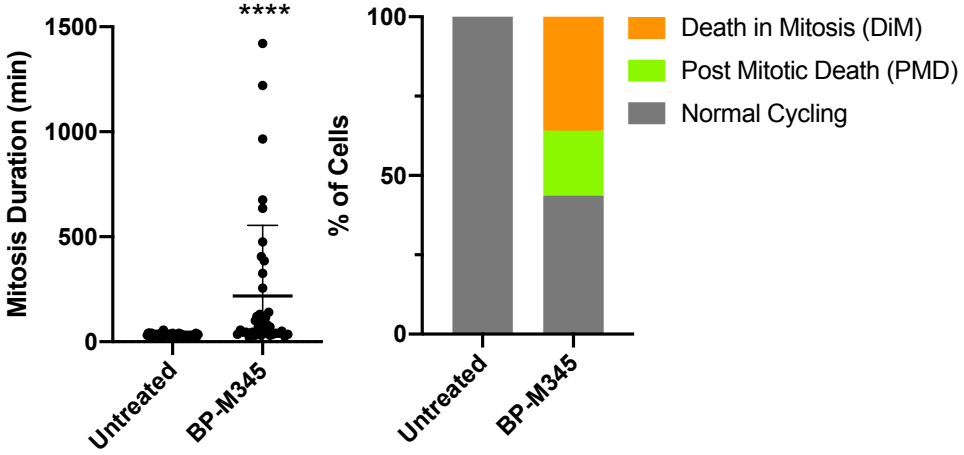



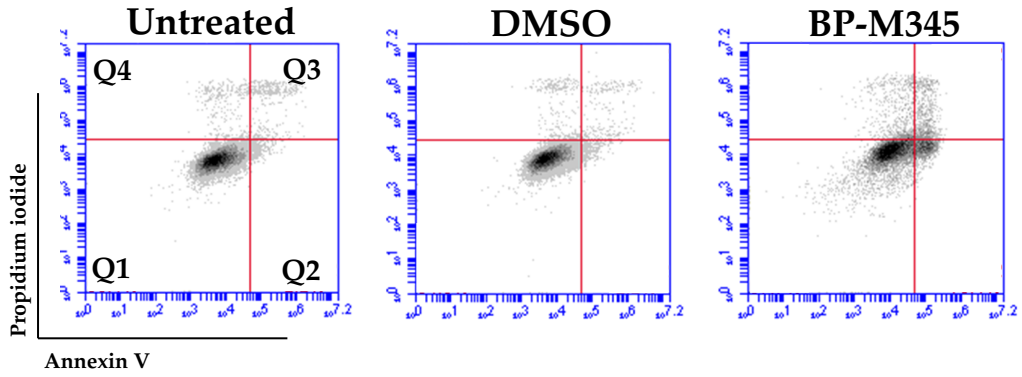



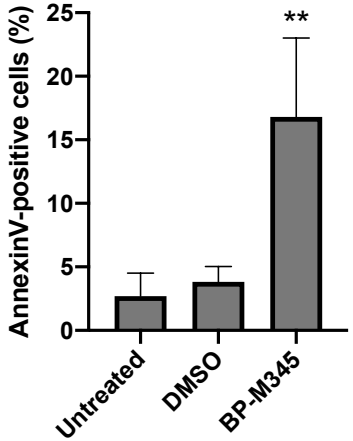

**PM:** Prometaphse
**M:** Metaphase
**M-mis:** Metaphase w/ Misaligned Chromosomes
**Mono:** Monopolar Spindle

# BP-M345 promotes tumor cell death mostly in mitosis by apoptosis



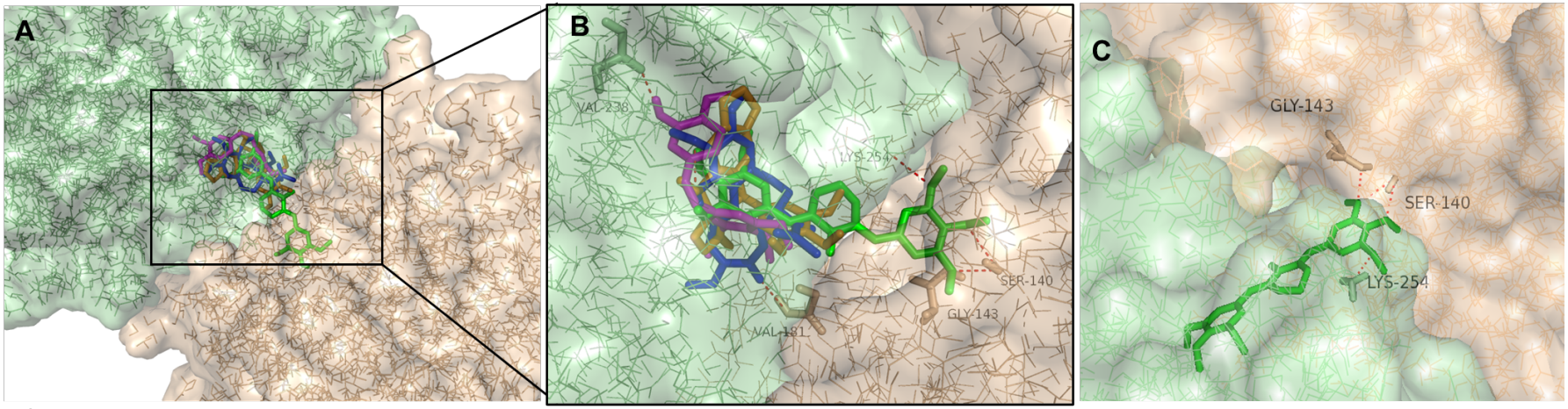



# Docking Studies

**Molecular docking model of BP-M345, colchicine, combretastatin A4, and podophyllotoxin with tubulin**

| Ligand | Docking Score (kcal mol−1) |
|---|---|
| Colchicine | −10.1 |
| Combretastatin A4 | −7.8 |
| Podophyllotoxin | −8.4 |
| BP-M345 | −8.7 |

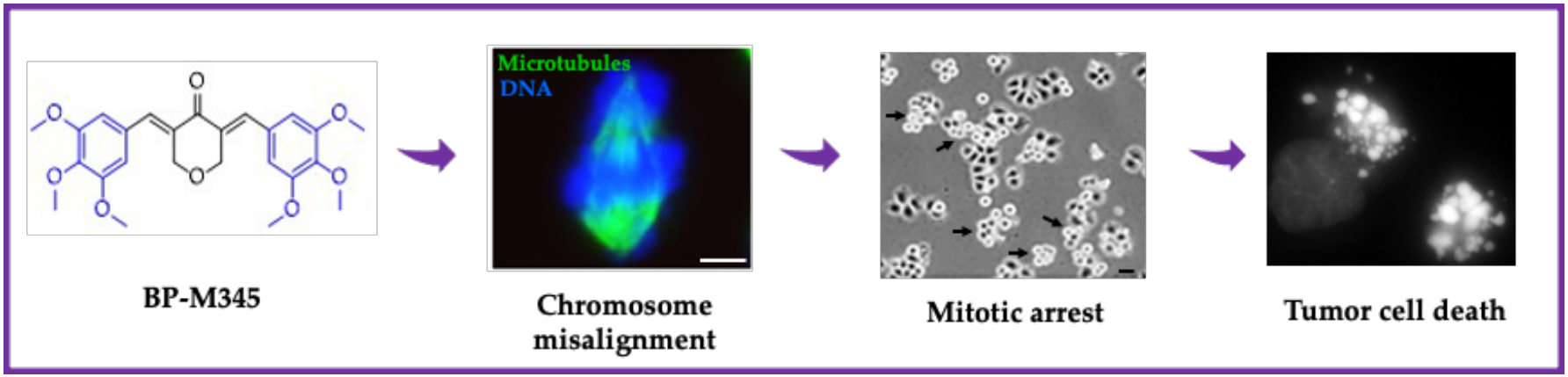
Compound **BP-M345 presented higher affinity** to tubulin than the known inhibitors combretastatin A4 and podophyllotoxin.




**α,β-tubulin binding site PDB: 4O2B**

**BP-M345** establishes three hydrogen interactions with **αGly-143**, **αSer-140**, and **βLis-154** and non-polar interactions with tubulin

# Conclusions




- Additional studies to determine its exact molecular targets
- Assessment of the safety profile and efficacy *in vivo*
- Investigate whether BP-M345 synergizes with current antimitotic drugs

# Acknowledgments

This research was funded by CESPU-Cooperativa de Ensino Superior Politécnico e Universitário Crl [grant number AntiMitoSphere_APSFCT_IINFACTS_2021 and ActivCHIRAL_PI2RL_IINFACTS_2021]. This research was partially supported by the Strategic Funding UIDB/04423/2020 and UIDP/04423/2020 (Group of Natural Products and Medicinal Chemistry, CIIMAR), through national funds provided by the FCT and ERDF, within the framework of the program PT2020 and the project PTDC/SAUPUB/28736/2017. Joana Moreira and Pedro Novais acknowledges their PhD grant (SFRH/BD/135852/2018 and BD/DCB/CESPU/02/202, respectively).