ALLEGATO B

UNIVERSITÀ DEGLI STUDI DI MILANO
selezione pubblica per n.1 posto/i di Ricercatore a tempo determinato ai sensi dell'art.24, comma 3, lettera b) della Legge 240/2010 per il settore concorsuale 03/C1 - CHIMICA ORGANICA, settore scientifico-disciplinare CHIM/06 - CHIMICA ORGANICA presso il Dipartimento di SCIENZE PER GLI ALIMENTI, LA NUTRIZIONE E L'AMBIENTE, (avviso bando pubblicato sulla G.U. n. 17 del 02-03-2021) Codice concorso 4577

Michail Christodoulou
CURRICULUM VITAE

INFORMAZIONI PERSONALI (NON INSERIRE INDIRIZZO PRIVATO E TELEFONO FISSO O CELLULARE)

COGNOME	**CHRISTODOULOU**
NOME	**MICHAIL**
DATA DI NASCITA	20-12-1980

WORK EXPERIENCE

01/05/2017 – 30/04/2020 – Milan, Italy
ASSISTANT PROFESSOR (RTD-A) – University of Milan, Department of Pharmaceutical Sciences.

16/02/2015 – 28/04/2017 – Modena, Italy
RESEARCH GRANT (POST-DOCTORAL RESEARCHER) – University of Modena and Reggio Emilia, Department of Life Sciences. Project "Design and development of CDK2 and EGFR type III allosteric inhibitors as anticancer drugs" AIRC IG15993.

01/04/2013 – 15/02/2015 – Milan, Italy
RESEARCH GRANT (POST-DOCTORAL RESEARCHER) – University of Milan, Department of Chemistry. New technologies in Organic Synthesis: Flow Chemistry in the multistep synthesis of pharmaceutical and natural compounds.

01/04/2011 – 31/03/2013 – Milan, Italy
RESEARCH GRANT (POST-DOCTORAL RESEARCHER) – University of Milan, Department of Organic and Industrial Chemistry. New technologies in Organic Synthesis: Flow Chemistry in the multistep synthesis of pharmaceutical and natural compounds.

EDUCATION
06/04/2018
Italian National Scientific Qualification for Associate Professor in Organic Chemistry (Abilitazione Scientifica Nazionale, SC 03/C1 - CHIMICA ORGANICA, SSD CHIM/06 - Chimica organica, Seconda (II) Fascia).

19/10/2005 – 16/12/2010 – Athens, Greece
DOCTOR'S DEGREE IN ORGANIC CHEMISTRY – Agricultural University of Athens
PhD thesis title: Synthesis of novel bioactive molecules and evaluation of their biological activity.

24/11/2003 – 09/03/2005 – Patras, Greece
MASTER'S DEGREE IN MEDICINAL CHEMISTRY – University of Patras, Departments of Chemistry and Pharmaceutical Chemistry
Master thesis title: Synthesis of internally guanylated and incorporating tetrazole moieties in the secondary amines of polyamine analogs and conjugates for medical application

28/09/1999 – 18/12/2003 – Patras, Greece
BACHELOR'S DEGREE IN CHEMISTRY – University of Patras, School of Sciences – Department of Chemistry
Bachelor thesis title: Synthesis of non-peptidic derivatives of histamine as antagonists of angiotensin II.

PUBLICATIONS

- Scopus Author ID: 25222774400
- ORCID ID: 0000-0002-5098-3143

My overall scientific production is of 59 peer reviewed articles on international journals (h-index: 16. Citations: 926 - Scopus database 13/03/2021), 8 oral communications and 16 poster presentations on international and national congresses.

Articles:

1) G. Facchetti, **M. S. Christodoulou**, L. Barragán Mendoza, F. Cusinato, L. Dalla Via and I. Rimoldi "Biological Properties of New Chiral 2-Methyl-5,6,7,8-tetrahydroquinolin-8-amine-based Compounds" ***Molecules*** 2020, *25*, 5561.

2) M. Bellini, B. Riva, V. Tinelli, M. A. Rizzuto, L. Salvioni, M. Colombo, F. Mingozzi, A. Visioli, L. Marongiu, G. Frascotti, **M S. Christodoulou**, D. Passarella, D. Prosperi and L. Fiandra "Engineered Ferritin Nanoparticles for the Bioluminescence Tracking of Nanodrug Delivery in Cancer" ***Small*** 2020, *16*, 2001450.

3) G. Facchetti, **M. S. Christodoulou**, E. Binda, M. Fusè and I. Rimoldi "Asymmetric Hydrogenation of 1-aryl substituted-3,4-Dihydroisoquinolines with Iridium Catalysts Bearing Different Phosphorus-Based Ligands" ***Catalysts*** 2020, *10*, 914.

4) I. Durmaz Sahin, **M. S. Christodoulou**, E. Akhan Guzelcan, A. Koyas, C. Karaca, D. Passarella and R. Cetin-Atalay "A small library of chalcones induce liver cancer cell death through Akt phosphorylation inhibition" ***Scientific Reports*** 2020, *10*, 11814.

5) E. Corsini, G. Facchetti, S. Esposito, A. Maddalon, Isabella Rimoldi and **M. S. Christodoulou** (co-corresponding author) "Antiproliferative effects of chalcones on T-cell acute lymphoblastic leukemia-derived cells: Role of PKCβ" ***Arch Pharm***. 2020, *353*, e2000062.

6) **M. S. Christodoulou**, S. Giofrè, E. M. Beccalli, F. Foschi and G. Broggini "Divergent Conversion of 4-Naphthoquinone-substituted 4*H*-Isoxazolones to Different Benzo-fused Indole Derivatives" ***Org. Lett***. 2020, *22*, 2735−2739.

7) **M. S. Christodoulou**, F. Nicoletti, K. Mangano, M. A. Chiacchio, G. Facchetti, I. Rimoldi, E. M. Beccalli and S. Giofrè "Novel 3,3-disubstituted oxindole derivatives. Synthesis and evaluation of the anti-proliferative activity" ***Bioorg. Med. Chem. Lett***. 2020, *30*, 126845.

8) M. L. Di Paolo, **M. S. Christodoulou**, A. M. Calogero, L. Pinzi, G. Rastelli, D. Passarella, G. Cappelletti and L. Dalla Via "2-Phenyloxazole-4-carboxamide as a Scaffold for Selective Inhibition of Human Monoamine Oxidase B" ***ChemMedChem*** 2019, *14*, 1641-1652.

9) E. Colombo, M. Biocotino, G. Frapporti, P. Randazzo, **M. S. Christodoulou**, G. Piccoli, L. Polito, P. Seneci and D. Passarella "Nanolipid-Trehalose Conjugates and Nano-Assemblies as Putative Autophagy Inducers" ***Pharmaceutics*** 2019, *11*, 422.

10) G. Facchetti, S. Pellegrino, R. Bucci, D. Nava, R. Gandolfi, **M. S. Christodoulou** and I. Rimoldi "Vancomycin-Iridium (III) Interaction: An Unexplored Route for Enantioselective Imine Reduction" ***Molecules*** 2019, *24*, 2771.

11) G. Fumagalli, L. Polito, E. Colombo, F. Foschi, **M. S. Christodoulou**, F. Galeotti, D. Perdicchia, I. Bassanini, S. Riva, P. Seneci, A. García-Argáez, L. Dalla Via and Daniele Passarella "Self-assembling Releasable Thiocolchicine−Diphenylbutenylaniline Conjugates" ***ACS Med. Chem. Lett***. 2019, *10*, 611-614.

12) D. Quaglio, N. Zhdanovskaya, G. Tobajas, V. Cuartas, S. Balducci, **M. S. Christodoulou**, G. Fabrizi, M. Gargantilla, E.-M. Priego, Á. Carmona Pestaña, D. Passarella, I. Screpanti, B. Botta, R. Palermo, M. Mori, F. Ghirga and M.-J. Pérez-Pérez "Chalcones and Chalcone-mimetic Derivatives as Notch Inhibitors in a Model of T-cell Acute Lymphoblastic Leukemia" ***ACS Med. Chem. Lett***. 2019,*10*, 639-643.

13) S. Giofrè, E. M. Beccalli, F. Foschi, C. La Rosa, L. Lo Presti and **M. S. Christodoulou** "Chemo- and Regioselective Palladium(II)-Catalyzed Aminoarylation of *N*-Allylureas Providing 4-Arylmethyl Imidazolidinones" ***Synthesis*** 2019, *51*, 3462-3470.

14) E. Bonandi, F. Foschi, C. Marucci, F. Dapiaggi, M. Sironi, S. Pieraccini, **M. S. Christodoulou**, F. de Asís Balaguer, J. F. Díaz, N. Zidar and Daniele Passarella "Synthesis of Thicolchicine-Based Conjugates: Investigation towards Bivalent Tubulin/Microtubules Binders" ***ChemPlusChem*** 2019, *84*, 98-102.

15) M. Vidakovic, J. Marinello, M. Lahtela-Kakkonen, D. Matulis, V. Linkuvienė, B. Y. Michel, R. Navakauskienė, **M. S. Christodoulou**, D. Passarella, S. Klimasauskas, C. Blanquart, M. Cuendet, J. Ovadi, S. Poulain, F. Fontaine-Vive, A. Burger and N. Martinet "New Insights into the Epigenetic Activities of Natural Compounds" ***OBM Genetics*** 2018, *2*(3), doi: 10.21926/obm.genet.1803029.

16) L. Carlino, **M. S. Christodoulou** (co-first authorship), V. Restelli, F. Caporuscio, F. Foschi, M. S. Semrau, E. Costanzi, A. Tinivella, L. Pinzi, L. Lo Presti, R. Battistutta, P. Storici, M. Broggini, D. Passarella and G. Rastelli "Structure–Activity Relationships of Hexahydrocyclopenta[*c*]quinoline Derivatives as Allosteric Inhibitors of CDK2 and EGFR" ***ChemMedChem*** 2018, *13*, 2627-2634.

17) **M. S. Christodoulou**, S. Giofrè, G. Broggini, A. Mazza, R. Sala, and E. M. Beccalli "Divergent Palladium- and Platinum-Catalyzed Intramolecular Hydroamination/Hydroarylation of *O*-Propargyl-2-aminophenols"

Eur. J. Org. Chem. 2018, 6176-6184.
18) G. Fumagalli, G. Giorgi, M. Vágvölgyi, E. Colombo, **M. S. Christodoulou**, V. Collico, D. Prosperi, F. Dosio, A. Hunyadi, M. Montopoli, M. Hyeraci, A. Silvani, G. Lesma, L. Dalla Via and D. Passarella "Heteronanoparticles by Self-Assembly of Ecdysteroid and Doxorubicin Conjugates To Overcome Cancer Resistance" ***ACS Med. Chem. Lett.*** 2018, *9*, 468-471.
19) R. Gandolfi, G. Facchetti, **M. S. Christodoulou**, M. Fusè, F. Meneghetti and I. Rimoldi "Cascade Reaction by Chemo- and Biocatalytic Approaches to Obtain Chiral Hydroxy Ketones and *anti* 1,3-Diols" ***ChemistryOpen*** 2018, *7*, 393-400.
20) **M. S. Christodoulou**, S. Giofrè, G. Broggini, L. Dalla Via, A. Mazza and E. M. Beccalli "Copper-Catalyzed Alkoxylation as Key Step to Convert Isatin to Oxazinoindol-2-one Derivatives" ***ChemistrySelect*** 2018, *3*, 4361-4365.
21) **M. S. Christodoulou** (co-corresponding author), F. Dapiaggi, F. Ghiringhelli, S. Pieraccini, M. Sironi, M. Lucafò, D. Curci, G. Decorti, G. Stocco, C. S. Chirumamilla, W. Vanden Berghe, P. Balaguer, B. Y. Michel, A. Burger, E. M. Beccalli, D. Passarella and N. Martinet "Imidazo[2,1-*b*]benzothiazol Derivatives as Potential Allosteric Inhibitors of the Glucocorticoid Receptor" ***ACS Med. Chem. Lett.*** 2018, *9*, 339-344.
22) F. Ricci, L. Carrassa, **M. S. Christodoulou**, D. Passarella, B. Michel, R. Benhida, N. Martinet, A. Hunyadi, E. Ioannou, V. Roussis, L. Musso, S. Dallavalle, R. Silvestri, N. Westwood, M. Mori, C. Ingallina, B. Botta, E. Kavetsou, A. Detsi, Z. Majer, F. Hudecz, S. Bősze, B. Kaminska, T. V. Hansen, P. Bertrand, C. M. Athanassopoulos and G. Damia "A High-throughput Screening of a Chemical Compound Library in Ovarian Cancer Stem Cells" ***Comb. Chem. High Throughput Screen.*** 2018, *21*, 50-56.
23) G. Fumagalli, B. Stella, I. Pastushenko, F. Ricci, **M. S. Christodoulou**, G. Damia, D. Mazza, S. Arpicco, C. Giannini, L. Morosi, F. Dosio, P. A. Sotiropoulou and D. Passarella "Heteronanoparticles by self-Assembly of Doxorubicin and Cyclopamine Conjugates" ***ACS Med. Chem. Lett.*** 2017, *8*, 953-957.
24) **M. S. Christodoulou** (co-first authorship), F. Caporuscio, V. Restelli, L. Carlino, G. Cannazza, E. Costanzi, C. Citti, L. Lo Presti, P. Pisani, R. Battistutta, M. Broggini, D. Passarella and G. Rastelli "Probing an Allosteric Pocket of CDK2 with Small Molecules" ***ChemMedChem*** 2017, *12*, 33-41.
25) G. Fumagalli, **M. S. Christodoulou** (co-first authorship), B. Riva, I. Revuelta, C. Marucci, V. Collico, D. Prosperi, S. Riva, D. Perdicchia, I. Bassanini, A. García-Argáez, L. Dalla Via and D. Passarella "Self-assembled 4-(1,2-diphenylbut-1-en-1-yl)aniline based nanoparticles: podophyllotoxin and aloin as building blocks" ***Org. Biomol. Chem.*** 2017, *15*, 1106-1109.
26) J. Marangon, **M. S. Christodoulou**, F. V. M. Casagrande, G. Tiana, L. Dalla Via, A. Aliverti, D. Passarella, G. Cappelletti and S. Ricagno "Tools for the rational design of bivalent microtubule-targeting drugs" ***Biochem. Biophys. Res. Commun.*** 2016, *479*, 48-53.
27) A. S. Moriello, L. Luongo, F. Guida, **M. S. Christodoulou**, D. Perdicchia, S. Maione, D. Passarella, V. Di Marzo and L. De Petrocellis "Chalcone Derivatives Activate and Desensitize the Transient Receptor Potential Ankyrin 1 Cation Channel, Subfamily A, Member 1 TRPA1 Ion Channel: Structure-Activity Relationships *in vitro* and Anti-nociceptive and Anti-inflammatory Activity *in vivo*" ***CNS Neurol. Disord. - Drug Targets*** 2016, *15*, 987-994.
28) **M. S. Christodoulou** (co-corresponding author), M. Zarate, F. Ricci, G. Damia, S. Pieraccini, F. Dapiaggi, M. Sironi, L. Lo Presti, A. N. García-Argáez, L. Dalla Via and D. Passarella "4-(1,2-diarylbut-1-en-1-yl)isobutyranilide derivatives as inhibitors of topoisomerase II" ***Eur. J. Med. Chem.*** 2016, *118*, 79-89.
29) C. Marucci, **M. S. Christodoulou**, S. Pieraccini, M. Sironi, F. Dapiaggi, D. Cartelli, A. M. Calogero, G. Cappelletti, C. Vilanova, S. Gazzola, G. Broggini and D. Passarella "Synthesis of Pironetin-Dumetorine Hybrids as Tubulin Binders" ***Eur. J. Org. Chem.*** 2016, 2029-2036.
30) R. Navakauskiene, M. Mori, **M. S. Christodoulou** (co-first authorship), A. Zentelyte, B. Botta, L. Dalla Via, F. Ricci, G. Damia, D. Passarella, C. Zilio and N. Martinet "Histone demethylating agents as potential *S*-adenosyl-L-methionine-competitors" ***Med. Chem. Commun.*** 2016, *7*, 1245-1255.
31) G. Fumagalli, D. Mazza, **M. S. Christodoulou**, G. Damia, F. Ricci, D. Perdicchia, B. Stella, F. Dosio, P. A. Sotiropoulou and D. Passarella "Cyclopamine–Paclitaxel-Containing Nanoparticles: Internalization in Cells Detected by Confocal and Super-Resolution Microscopy" ***ChemPlusChem*** 2015, *80*, 1380–1383.
32) **M. S. Christodoulou**, M. Mori, R. Pantano, R. Alfonsi, P. Infante, M. Botta, G. Damia, F. Ricci, P. A. Sotiropoulou, S. Liekens, B. Botta and D. Passarella "Click Reaction as a Tool to Combine Pharmacophores: The Case of Vismodegib" ***ChemPlusChem*** 2015, *80*, 938–943.
33) M. Stucchi, S. Cairati, R. Cetin-Atalay, **M. S. Christodoulou**, G. Grazioso, G. Pescitelli, A. Silvani, D. C. Yildirim and G. Lesma "Application of the Ugi reaction with multiple amino acid-derived components: synthesis and conformational evaluation of piperazine-based minimalist peptidomimetics" ***Org. Biomol. Chem.*** 2015, *13*, 4993–5005.
34) **M. S. Christodoulou** (co-first authorship), F. Calogero, M. Baumann, A. N. García-Argáez, S. Pieraccini, M. Sironi, F. Dapiaggi, R. Bucci, G. Broggini, S. Gazzola, S. Liekens, A. Silvani, M. Lahtela-Kakkonen, N. Martinet, A. Nonell-Canals, E. Santamaría-Navarro, I. Baxendale, L. Dalla Via and D. Passarella "Boehmeriasin A as new lead compound for the inhibition of Topoisomerases and SIRT2" ***Eur. J. Med. Chem.***

2015, *92*, 766–775.
35) S. Borrelli, D. Cartelli, F. Secundo, G. Fumagalli, **M. S. Christodoulou**, A. Borroni, D. Perdicchia, F. Dosio, P. Milla, G. Cappelletti and D. Passarella "Self-Assembled Squalene-based Fluorescent Hetero-Nanoparticles" ***ChemPlusChem*** 2015, *80*, 47–49.
36) S. Borrelli, **M. S. Christodoulou**, I. Ficarra, A. Silvani, G. Cappelletti, D. Cartelli, G. Damia, F. Ricci, M. Zucchetti, F. Dosio and D. Passarella "New class of squalene-based releasable nanoassemblies of paclitaxel, podophyllotoxin, camptothecin and epothilone A" ***Eur. J. Med. Chem.*** 2014, *85*, 179–190.
37) P. S. Colombo, G. Flamini, **M. S. Christodoulou**, G. Rodondi, S. Vitalini, D. Passarella and G. Fico "Farinose alpine *Primula* species: Phytochemical and morphological investigations" ***Phytochemistry*** 2014, *98*, 151–159.
38) **M. S. Christodoulou**, A. Sacchetti, V. Ronchetti, S. Caufin, A. Silvani, G. Lesma, G. Fontana, F. Minicone, B. Riva, M. Ventura, M. Lahtela-Kakkonen, E. Jarho, V. Zuco, F. Zunino, N. Martinet, F. Dapiaggi, S. Pieraccini, M. Sironi, L. Dalla Via, O. M. Gia and D. Passarella "Quinazolinecarboline alkaloid evodiamine as scaffold for targeting topoisomerase I and sirtuins" ***Bioorg. Med. Chem.*** 2013, *21*, 6920–6928.
39) **M. S. Christodoulou**, N. Fokialakis, D. Passarella, A. N. García-Argáez, O. M. Gia, I. Pongratz, L. Dalla Via and S. A. Haroutounian "Synthesis and biological evaluation of novel tamoxifen analogues" ***Bioorg. Med. Chem.*** 2013, *21*, 4120–4131.
40) F. Calogero, S. Borrelli, G. Speciale, **M. S. Christodoulou**, D. Cartelli, D. Ballinari, F. Sola, C. Albanese, A. Ciavolella, D. Passarella, G. Cappelletti, S. Pieraccini and M. Sironi "9-Fluorenone-2-Carboxylic Acid as a Scaffold for Tubulin Interacting Compounds" ***ChemPlusChem*** 2013, *78*, 663–669.
41) E. Riva, M. Mattarella, S. Borrelli, **M. S. Christodoulou**, D. Cartelli, M. Main, S. Faulkner, D. Sykes, G. Cappelletti, J. S. Snaith and D. Passarella "Preparation of Fluorescent Tubulin Binders" ***ChemPlusChem*** 2013, *78*, 222–226.
42) C. Peruzzotti, S. Borrelli, M. Ventura, R. Pantano, G. Fumagalli, **M. S. Christodoulou**, D. Monticelli, M. Luzzani, A. L. Fallacara, C. Tintori, M. Botta and D. Passarella "Probing the Binding Site of Abl Tyrosine Kinase Using in Situ Click Chemistry" ***ACS Med. Chem. Lett.*** 2013, *4*, 274–277.
43) **M. S. Christodoulou**, F. Zunino, V. Zuco, S. Borrelli, D. Comi, G. Fontana, M. Martinelli, J. B. Lorens, L. Evensen, M. Sironi, S. Pieraccini, L. Dalla Via, O. M. Gia and D. Passarella "Camptothecin-7-yl-methanthiole: Semisynthesis and Biological Evaluation" ***ChemMedChem*** 2012, *7*, 2134–2143.
44) **M. S. Christodoulou**, N. Fokialakis, S. Nam, R. Jove, A.-L. Skaltsounis and S. A. Haroutounian "Synthesis and *In Vitro* Biological Evaluation of Novel Pyrazole Derivatives as Potential Antitumor Agents" **Med. Chem.** 2012, *8*, 779–788.
45) F. Colombo, C. Tintori, A. Furlan, S. Borrelli, **M. S. Christodoulou**, R. Dono, F. Maina, M. Botta, M. Amat, J. Bosch and D. Passarella "'Click' synthesis of a triazole-based inhibitor of Met functions in cancer cells" ***Bioorg. Med. Chem. Lett.*** 2012, *22*, 4693–4696.
46) R. Gaggeri, D. Rossi, **M. S. Christodoulou**, D. Passarella, F. Leoni, O. Azzolina and S. Collina "Chiral Flavanones from *Amygdalus lycioides* Spach: Structural Elucidation and Identification of TNFalpha Inhibitors by Bioactivity-guided Fractionation" ***Molecules*** 2012, *17*, 1665–1674.
47) **M. S. Christodoulou**, F. Colombo, D. Passarella, G. Ieronimo, V. Zuco, M. De Cesare and F. Zunino "Synthesis and biological evaluation of imidazolo[2,1-*b*]benzothiazole derivatives, as potential p53 inhibitors" ***Bioorg. Med. Chem.*** 2011, *19*, 1649–1657.
48) **M. S. Christodoulou**, S. Liekens, K. M. Kasiotis and S. A. Haroutounian "Novel pyrazole derivatives: Synthesis and evaluation of anti-angiogenic activity" ***Bioorg. Med. Chem.*** 2010, *18*, 4338–4350.
49) **M. S. Christodoulou**, K. M. Kasiotis, N. Fokialakis, I. Tellitu and S. A. Haroutounian "PIFA-mediated synthesis of novel pyrazoloquinolin-4-ones as potential ligands for the estrogen receptor" ***Tet. Lett.*** 2008, *49*, 7100–7102.

Reviews:
1) **M. S. Christodoulou**, E. M. Beccalli, F. Foschi and S. Giofrè "Pd-Catalyzed Domino Reactions Involving Alkenes To Access Substituted Indole Derivatives" ***Synthesis*** 2020, *52*, 2731-2760.
2) **M. S. Christodoulou**, E. M. Beccalli and S. Giofrè "Palladium-Catalyzed Benzodiazepines Synthesis" ***Catalysts*** 2020, *10*, 634.
3) E. M. Beccalli, G. Broggini, **M. S. Christodoulou** and S. Giofrè "Transition Metal-Catalyzed Intramolecular Amination and Hydroamination Reactions of Allenes" ***Adv. Organomet. Chem.*** 2018, *69*, 1-71.
4) E. Bonandi, **M. S. Christodoulou**, G. Fumagalli, D. Perdicchia, G. Rastelli and D. Passarella "The 1,2,3-triazole ring as a bioisostere in medicinal chemistry" ***Drug Discov. Today*** 2017, *22*, 1572–1581.
5) G. Cappelletti, D. Cartelli, **M. S. Christodoulou** and D. Passarella "Microtubule-Directed Therapeutic Strategy for Neurodegenerative Disorders: Starting From the Basis and Looking on the Emergences" ***Curr. Pharm. Des.*** 2017, *23*, 784–808.
6) G. Fumagalli, C. Marucci, **M. S. Christodoulou**, B. Stella, F. Dosio and D. Passarella "Self-assembly drug conjugates for anticancer treatment" ***Drug Discov. Today*** 2016, *21*, 1321–1329.

7) D. Perdicchia, **M. S. Christodoulou**, G. Fumagalli, F. Calogero, C. Marucci and D. Passarella "Enzymatic Kinetic Resolution of 2-Piperidineethanol for the Enantioselective Targeted and Diversity Oriented Synthesis" ***Int. J. Mol. Sci.*** 2016, *17*, 17.
8) C. Marucci, G. Fumagalli, F. Calogero, A. Silvani**, M. S. Christodoulou**, N. Martinet and D. Passarella "Natural Products and Cancer Stem Cells" ***Curr. Pharm. Des.*** 2015, *21*, 5547–5557.
9) **M. S. Christodoulou** (co-first authorship), A. Thomas, S. Poulain, M. Vidakovic, M. Lahtela-kakkonen, D. Matulis, P. Bertrand, E. Bartova, C. Blanquart, E. Mikros, N. Fokialakis, D. Passarella, R. Benhida and N. Martinet "Can we use the epigenetic bioactivity of caloric restriction and phytochemicals to promote healthy ageing?" ***Med. Chem. Commun.*** 2014, *5*, 1804–1820.
10) P. A. Sotiropoulou, **M. S. Christodoulou**, A. Silvani, C. Herold-Mende and D. Passarella "Chemical Approaches to targeting drug resistance in cancer stem cells" ***Drug Discov. Today*** 2014, *19*, 1547–1562.

ORAL PRESENTATIONS as speaker

1) "**Divergent reactivity of terminal alkynes under transition metals catalysis**" 5th CHAOS meeting, Taragona (Spain), 19th-21st September, 2018.
2) "**Intramolecular transition-metals catalyzed hydroarylation processes for the synthesis of pyranoquinolines**" XXXVIII Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana, Milan (Italy), 9th-13th September, 2018.
3) "**Povarov reaction for the synthesis of cylcopenta[c]quinoline deerivatives as allosteric modulators of the CDK2 protein**" 4 International Workshop on Pericyclic Reactions and Synthesis of Hetero- and Carbocyclic Systems, Milan (Italy), 28th-30th June, 2017.
4) "**Synthesis and biological evaluation of novel Vismodegib analogues**" 2nd Working Group Meeting of COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Budapest (Hungary), 27th-28th March, 2014.
5) "**Structural Modifications of Natural Products. Synthesis and Biological Evaluation**" 1st Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Milano (Italy), 3rd-5th July, 2012.
6) "**Novel heterocyclic molecules as p53 inhibitors: Synthesis and biological activity evaluation**" Meeting of 2 and 3 Working groups – CM0602 Action: Inhibitors of Angiogenesis: Design, Synthesis and Biological Exploitation, Dublin (Ireland), 7th-9th May, 2010.
7) "**Synthesis of p53 inhibitors**" 3rd Workshop – CM0602 COST Action: Inhibitors of Angiogenesis: Design, Synthesis and Biological Exploitation, Favignana (Italy), 16th-18th October, 2009.
8) "**Results of COST STS mission in Bilbao. Collaboration between AUA-UPV**" 4 Meeting of the working group D28/008/03: Natural Products as a Source for Discovery, Synthesis, and Application of New Pharmaceuticals, Athens (Greece), 17th March, 2007.

POSTER PRESENTATIONS

1) Maria Luisa Di Paolo, **Michael S. Christodoulou**, Alessandra M. Calogero, Luca Pinzi, Giulio Rastelli, Daniele Passarella, Graziella Cappelletti and Lisa Dalla Via, **"**A New scaffold for selective inhibition of human monoamine oxidase B**"**, 24th World Congress on Advances in Oncology and 24th International Symposium on Molecular Medicine**"**, Sparta (Greece), 10th-12th October, 2019.
2) **Michael S. Christodoulou**, E. M. Beccalli and S. Giofrè, "Ruthenium-catalyzed ring transformation of 4,4-disubstituted isoxazolin-5-ones to different heterocyclic systems", XXXIX Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana, Torino (Italy), 8th-12th September, 2019.
3) **Michael S. Christodoulou** and Daniele Passarella, "Two synthetic approaches for the synthesis of boehmeriasin A", Final Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, La Laguna, Tenerife (Spain), 13th-14th December, 2018.
4) **Michael S. Christodoulou**, F. Calogero, R. Bucci, F. Dapiaggi, D. Passarella, "Convenient Synthesis of enantiopure Boehmeriasin A", 1st Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature – from natural products chemistry to drug discovery, Rome (Italy), 5th–6th October, 2015.
5) **Michael S. Christodoulou**, G. Fumagalli, P. A. Sotiropoulou, F. Dosio, D. Mazza, and D. Passarella, "Self-assembled Squalene-based Fluorescent Hetero-Nanoparticles", 2nd Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells & CIBICAN Conference on Molecular Pharmacology and Mechanisms of New Anticancer Drugs, Puerto de la Cruz, Tenerife (Spain), 14th-15th October, 2014.
6) C. Marucci, **M. Christodoulou**, R. Bucci, D. Passarella, "Design and Synthesis of Dumetorine-Pironetin hybrids", XXXIX "A. Corbella" International Summer School, Gargnano (Italy), 15th-20th June, 2014.

7) **Michael S. Christodoulou**, T. Kokkola, E. Jarho, N. Martinet, M. Lahtela-Kakkonen and D. Passarella, "Evodiamine and Camptothecin as Scaffolds for Targeting Sirtuins", Epigenetics: From Bench To Bedside, COST Conference, Athens (Greece), 5th-8th May, 2014.
8) **Michael S. Christodoulou**, P. A. Sotiropoulou, G. Damia, M. Botta and D. Passarella, "Novel Vismodegib analogues: synthesis and biological evaluation", 2nd Working Group Meeting-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Warsaw (Poland),19th-20th September, 2013.
9) **Michael S. Christodoulou** and D. Passarella, "Modifying the Camptothecin scaffold: Synthesis and biological evaluation" 1st Working Group Meeting-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Porto (Portugal), 21st–22nd February, 2013.
10) **Michael S. Christodoulou** and D. Passarella, "Camptothecin scaffold modification: synthesis and biology", Chemistry and Biology in Action: Joint meeting of COST actions TD0905-Epigenetics: from bench to bedside, CM0804-Chemical Biology with Natural Products and CM1106-Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Salerno (Italy), 5th-6th November, 2012.
11) **M. Christodoulou**, K. Kasiotis, and S. Haroutounian, "Small sized heterocyclic molecules: Synthesis and antitumor properties", 1st Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Milano (Italy), 3rd-5th July, 2012.
12) **Michael S. Christodoulou** and D. Passarella, "Synthesis and biological evaluation of imidazolo[2,1-*b*]benzothiazole derivatives, as potential p53 inhibitors", COST CM0602 - Inhibitors of angiogenesis: design, synthesis and biological exploitation (ANGIOKEM), Smolenice (Slovakia), 11th-14th June, 2011.
13) **Michael S. Christodoulou**, E. N. Tzanetou, and S. A. Haroutounian, "Novel Pyridinyl Acetamides and Acrylamides as Potential Antiangiogenesis Agents", 14th Hellenic Symposium on Medicinal Chemistry, Thessalonica (Greece), 23th-25th April, 2010.
14) **Michael S. Christodoulou**, K. M. Kasiotis and S. A. Haroutounian, "PIFA MEDIATED SYNTHESIS OF NOVEL PYRAZOLOQUINOLIN-4-ONES", 2nd Hellenic Symposium in Organic Synthesis: From Chemistry to Biology, Medicine and Material Science, Athens (Greece), 19th–21st April, 2007.
15) **M. Christodoulou**, C. M. Athanassopoulos, T. Garnelis and D. Papaioannou, "Applications of *Na,Nω* Ditritylated Bisamides to the Synthesis of Internally Guanylated Polyamines and of Polyamine Analogs Incorporating Tetrazole Moieties", 6th International Conference of Medicinal Chemistry: Drug Discovery and Design, Patra (Greece), 10th–12th March, 2005.
16) C. Athanassopoulos, T. Garnelis, E. Pantazaka, **Michalis Christodoulou** and D. Papaioannou, "EFFICIENT GUANYLATION OF *Na,Nω* DITRITYLATED POLYAMINES AT THE SECONDARY AMINO FUNCTIONS", 8th Conference of Chemistry Greece - Cyprus: Chemistry, Quality of life and education, Thessalonica (Greece), 10th–13th December, 2004.

TEACHING ACTIVITY

Academic year 2019 – 2020. University of Milan
Professor with contract responsible for the "Laboratory of Organic Chemistry" of the course "Chemical safety and Toxicological Environmental Sciences" (Total hours: 32).

Academic year 2018 – 2019. University of Milan
Professor responsible for the "Laboratory of Organic Chemistry" of the course "Chemical safety and Toxicological Environmental Sciences" (Total hours: 32).

Academic year 2017 – 2018. University of Milan
Professor responsible for the "Laboratory of Organic Chemistry" of the course "Chemical safety and Toxicological Environmental Sciences" (Total hours: 32).

01/04/2009 – 30/06/2009. Agricultural University of Athens
ASSISTANT IN ORGANIC CHEMISTRY. Assisting the Professor to the laboratory of Organic Chemistry to supervise the undergraduate students during the experiments. (Total hours: 84).

01/10/2008 – 20/12/2008. Agricultural University of Athens
ASSISTANT IN GENERAL AND INORGANIC CHEMISTRY. Assisting the Professor to the laboratory of General and Inorganic Chemistry to supervise the undergraduate students during the experiments. (Total hours: 54).

01/03/2008 – 30/06/2008. Agricultural University of Athens
ASSISTANT IN ORGANIC CHEMISTRY. Assisting the Professor to the laboratory of Organic Chemistry to supervise the undergraduate students during the experiments. (Total hours: 84).

01/10/2007 – 28/02/2008. Agricultural University of Athens
ASSISTANT IN GENERAL AND INORGANIC CHEMISTRY. Assisting the Professor to the laboratory of General and Inorganic Chemistry to supervise the undergraduate students during the experiments. (Total hours: 54).

01/04/2007 – 30/06/2007. Agricultural University of Athens
ASSISTANT IN ORGANIC CHEMISTY. Assisting the Professor to the laboratory of Organic Chemistry to supervise the undergraduate students during the experiments. (Total hours: 84).

01/03/2006 – 31/05/2006. Agricultural University of Athens
ASSISTANT IN ORGANIC CHEMISTRY. Assisting the Professor to the laboratory of Organic Chemistry to supervise the undergraduate students during the experiments. (Total hours: 84).

Supervising Undergraduate students:

- *As main supervisor:*

1) Alessia Pirola. "Sviluppo e validazione di metodi spettrometrici per la quantificazione di sostanze contenute nei dispositivi medici e per la loro rilevazione dopo assorbimento percutaneo" A.A.: 2018-2019. Degree in Chemical safety and Toxicological Environmental Sciences.
2) Gaetano F. Gnatta. "Aggregation-induced emission luminogens: Synthesis and characterization" A.A.: 2017/2018. Degree in Biotechnology.

- *As a co-supervisor:*

1) Tommaso Ruggiero. "Sintesi di calconi e addizione di boro enantioselettiva mediante un catalizzatore chirale a base di Cu(II)" A.A.: 2018/2019. Degree in Chemistry.
2) Eleonora Binda. "SINTESI DI 2-FENIL-OSSAZOLO-4-CARBOSSAMMIDI" A.A.: 2016/2017. Degree in Chemistry.
3) Alessio Garabelli. "REAZIONE DI POVAROV PER LA PREPARAZIONE DI COMPOSTI A SCHELETRO 3a,4,5,9b-TETRAIDRO-3*H*-CICLOPENTA[*c*]CHINOLINICO" A.A.: 2015/2016. Degree in Chemistry.
4) Ilaria Ordan. "SINTESI DI ANALOGHI SEMPLIFICATI DELL'ACIDO MARTINELLICO" A.A.: 2015/2016. Degree in Chemistry.
5) Eleonora Colombo. "LA REAZIONE DI POVAROV PER LA SINTESI DI COMPOSTI FARMACOLOGICAMENTE UTILI" A.A.: 2014/2015. Degree in Chemistry.
6) Lorenzo Cogliati. "Sintesi di composti a scheletro tetraidrociclopenta-chinolinico" A.A.: 2014/2015. Degree in Chemistry.
7) Francesca Ghiringhelli. "SINTESI DI DERIVATI IMIDAZO [2,1-*b*] BENZOTIAZOLICI" A.A.: 2013/2014. Degree in Chemistry.

Supervising Master's students:

- *As a co-supervisor:*

1) Benedetta Ricci. "Synthesis of new topoisomerase and tubulin binders: tamoxifen and pironetin as leads" A.A.: 2019/2020. Degree in Chemistry.
2) Alessio Di Natale. "COPPER CATALYSIS AND ORGANOCATALYSIS AS TOOLS FOR INTRAMOLECULAR SYNTHESIS OF AZA-HETEROCYCLES" A.A.: 2018/2019. Degree in Pharmaceutical Chemistry and Technology.
3) Arianna Villa. "REAZIONI MULTICATALITICHE DI IDROARILAZIONE INTRAMOLECOLARE: STRATEGIE PER LA SINTESI DI PIRANO-CHINOLINE E SISTEMI ETEROPOLICICLICI CORRELATI" A.A.: 2016/2017. Degree in Pharmaceutical Chemistry and Technology.
4) Serena Saltini. "SINTESI DI COMPOSTI POLIETEROCICLICI FUNZIONALIZZATI ATTRAVERSO REAZIONI DOMINO" A.A.: 2016/2017. Degree in Pharmaceutical Chemistry and Technology.
5) Eleonora Colombo. "Synthesis of chalcones and Ixabepilone analogues as tubulin binders" A.A.: 2016/2017. Degree in Chemistry.
6) Stefano Frizzarin. "Triazoles and hexahydrocyclopenta[c]quinolines as scaffolds in the synthesis of Hsp90 and CDK2 inhibitors" A.A.: 2016/2017. Degree in Chemistry.
7) Alessia Altea. "Synthesis of Trisubstituted Triazoles as Potential Hsp90 Inhibitors" A.A.: 2015/2016. Degree in Industrial Chemistry.

MEMBER OF ORGANIZING AND SCIENTIFIC COMMITTEES

- Member of the Scientific Committee: "Meeting dedicated to Early Career Investigators COST Action CM1407 – Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery", Brussels (Belgium), 18th-19th February, 2019.
- Member of the Scientific Committee: "Final Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery", La Laguna, Tenerife

(Spain), 13th-14th December, 2018.

- 3rd Training School of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, La Laguna, Tenerife (Spain), 10th-12th December, 2018.
- Member of the Scientific Committee: "5th MC/WG Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery", Salini Resort (Malta), 1st-2nd March, 2018.
- Member of the Scientific Committee: "4th Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery", Lisbon (Portugal), 21st-22nd September, 2017.
- Member of the Scientific Committee: "2nd Training School, Synthesis, isolation and structural elucidation of bioactive compounds, of COST Action CM 1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery", Lisbon (Portugal), 18th-20th September, 2017.
- Member of the Organizing Committee: "4th Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells", Chioggia (Italy), 10th-11th March, 2016.
- Group Coordinator: "Training School-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells", Lisbon (Portugal), 23rd-25th November, 2015.
- Member of the Organizing and Scientific Committee: "Targeting Hedgehog Signaling in Cancer Stem Cells. Focused Joint-meeting for ESRs", Barcelona (Spain), 19th-20th January, 2015.
- Member of the Organizing Committee: "1st Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells", Milano (Italy), 3rd-5th July, 2012.

CONFERENCES, WORKSHOPS AND SYMPOSIA

- XXXIX Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana, Torino (Italy), 8th-12th September, 2019.
- Final Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, La Laguna, Tenerife (Spain), 13th-14th December, 2018.
- 3rd Training School of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, La Laguna, Tenerife (Spain), 10th-12th December, 2018.
- 5th CHAOS meeting, Taragona (Spain), 19th-21st September, 2018.
- XXXVIII Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana, Milan (Italy), 9th-13th September, 2018.
- 5th MC/WG Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, Salini Resort (Malta), 1st-2nd March, 2018.
- 4th Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, Lisbon (Portugal), 21st-22nd September, 2017.
- 4th International Workshop on Pericyclic Reactions and Synthesis of Hetero- and Carbocyclic Systems, Milan (Italy), 28th-30th June, 2017.
- Working Group 1st meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, Rome (Italy), 7th April, 2017.
- 3rd Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, Krakow (Poland), 2nd-3rd March, 2017.
- Nanomedicine Symposium CEN@UniMiB: Towards translation and European Networking, Milan (Italy), 18th October, 2016.
- 2nd Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, Madrid (Spain), 4th-5th April, 2016.
- 4th Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Chioggia (Italy), 10th-11th March, 2016.
- Training School-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Lisbon (Portugal), 23rd-25th November, 2015.
- 1st Meeting of COST Action CM1407: Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery, Rome (Italy), 5th-6th October, 2015.
- 3rd Working Group Meeting-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Athens (Greece) 26th-27th March, 2015.
- Targeting Hedgehog Signaling in cancer Stem Cells Focused Joint-meeting for ESRs, Barcelona (Spain), 19th-20th January, 2015.
- 2nd Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells & CIBICAN Conference on Molecular Pharmacology and Mechanisms of New Anticancer Drugs, Puerto de la Cruz, Tenerife (Spain), 14th-15th October, 2014.

- Epigenetics: From Bench To Bedside, COST Conference, Athens (Greece), 5th–8th May, 2014.
- 2nd Working Group Meeting-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Budapest (Hungary), 27th–28th March, 2014.
- 2nd Working Group Meeting-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Warsaw (Poland), 19th–20th September, 2013.
- 1st Working Group Meeting-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Porto (Portugal), 21st–22nd February, 2013.
- Chemistry and Biology in Action: Joint meeting of COST actions TD0905-Epigenetics: from bench to bedside, CM0804-Chemical Biology with Natural Products and CM1106-Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Salerno (Italy), 5th–6th November, 2012.
- 1st Workshop-COST Action CM1106: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells, Milano (Italy), 3th–5th July, 2012.
- COST CM0602 - ANGIOKEM: Inhibitors of Angiogenesis: Design, Synthesis and Biological Exploitation, Smolenice Castle (Slovakia) 11th–14th June, 2011.
- Training School – Inhibitors of Angiogenesis: design, synthesis and biological exploitation, Rhodes (Greece), 27th–30th September, 2010.
- 3rd European Workshop in Drug Synthesis, Siena (Italy), 23rd–27th May, 2010.
- Meeting of 2nd and 3rd Working groups – CM0602 Action: Inhibitors of Angiogenesis: Design, Synthesis and Biological Exploitation, Dublin (Ireland), 7th–9th May, 2010.
- 3rd Workshop – CM0602 COST Action: Inhibitors of Angiogenesis: Design, Synthesis and Biological Exploitation, Favignana (Italy), 16th–18th October, 2009.
- Meeting of the CM0602 COST Action: Inhibitors of Angiogenesis: Design, Synthesis and Biological Exploitation, Athens (Greece), 14th March, 2009.
- 4th Meeting of the working group D28/008/03: Natural Products as a Source for Discovery, Synthesis, and Application of New Pharmaceuticals, Athens (Greece), 17th March, 2007.
- 2nd Hellenic Symposium in Organic Synthesis: From Chemistry to Biology, Medicine and Materials Science, Athens (Greece), 19th–21st April, 2007.
- 6th Conference of Medicinal Chemistry: Drug Discovery and Design, Patra (Greece), 10th–12th March, 2005.
- 8th Conference of Chemistry Greece - Cyprus: Chemistry, Quality of life and education, Thessalonica (Greece), 10th–13th December, 2004.
- 1st Hellenic Symposium in Organic Synthesis: From Chemistry to Biology, Medicine and Materials Science, Athens (Greece), 4th–6th November, 2004.
- 4th Hellenic Forum on Bioactive Peptides, Patra (Greece), 22nd–24th April, 2004.
- 5th Conference of Medicinal Chemistry: Drug Discovery and Design, Patra (Greece), 11th–13th March, 2004.
- 4th Conference of Medicinal Chemistry: Drug Discovery and Design, Patra (Greece), 13th–14th March, 2003.

PARTICIPATION IN RESEARCH PROJECTS

2019
LINEA 2 "DOTAZIONE ANNUALE PER ATTIVITÀ ISTITUZIONALI" AZIONE A2. Title: "Synthesis of novel tamoxifen analogs as selective Topoisomerase II inhibitors". Project leader: Michail Christodoulou.

2018
LINEA 2 "DOTAZIONE ANNUALE PER ATTIVITÀ ISTITUZIONALI" AZIONE A2. Title: "Development of organometallic complexes for asymmetric catalysis". Project leader: Michail Christodoulou.

2017
LINEA 2 "DOTAZIONE ANNUALE PER ATTIVITÀ ISTITUZIONALI" AZIONE A2. Title: "Development of peptide based hybrid catalysts for asymmetric catalysis". Project leader: Sara Pellegrino.

16/03/2015 – 15/03/2019
COST Action CM1407 "Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery".
28/03/2012 – 27/03/2016
COST Action CM1106 "Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells".

07/06/2007 – 06/06/2011
COST Action CM0602 "Inhibitors of Angiogenesis: Design, Synthesis and Biological Exploitation".

VISITING SCHOLAR AND VISITING RESEARCHER

03/10/2020 – 05/12/2020
Short Term Scientific Mission, University Of Patras, Greece.

04/11/2013 – 14/11/2013
Short Term Scientific Mission, Mind the Byte, S.L., Barcelona, Spain.

13/02/2011 – 12/04/2011
Short Term Scientific Mission, Università degli Studi di Milano, Italy.

01/03/2010 – 30/06/2010
Short Term Scientific Mission, Università degli Studi di Milano, Italy.

02/09/2009 – 31/01/2010
Coordinated Continuative Collaboration with Università degli Studi di Milano, Italy.

27/04/2009 – 27/05/2009
Short Term Scientific Mission, Università degli Studi di Milano, Italy.

14/11/2006 – 14/12/2006
Short Term Scientific Mission, University of the Basque Country, Bilbao, Spain.

MEMBER OF THE EDITORIAL BOARD AND REVIEWER PANEL

- Current Medicinal Chemistry and Medicinal Chemistry (Bentham Science).
- EC Pharmacology and Toxicology (ECPT) https://www.ecronicon.com/ECPP-EB.php
- Journal of Targeted Drug Delivery http://sciaeon.org/targeted-drug-delivery/editorial-board
- Guest Editor of the Special Issue "Towards the Transition Metal Catalysis in Organic Synthesis" of the journal ***Catalysts***.
- Guest Editor of the Special Issue "Drug Discovery and Development Based on Native/Engineered Microorganisms" of the journal ***Molecules***.

INSTITUTIONAL RESPONSABILITIES

2017 - 2020
Member of the Faculty board of “Pharmaceutical Chemistry and Technology”, “Chemistry”, “Biotechnology” and “Chemical safety and Toxicological Environmental Sciences” degree

2017 – 2019
Member of the board of teacher of the PhD course of “Pharmaceutical Science”

MEMBER OF:

Italian Society of Chemistry (Società Chimica Italiana) - Division of Organic Chemistry.

RECOGNITIONS

2016
Seal of excellence for the project proposal 747516, Novel Chemoenzymatic Generation of Unnatural Spirotetronates (CHEMGENSPIR), submitted under the Horizon 2020’s Marie Skłodowska-Curie actions call H2020-MSCA-IF-2016. Although, the project was not funded.

NATIONAL AND INTERNATIONAL COLLABORATIONS (Ongoing)

National:

- Prof. Lisa Dalla Via, Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Italy. Biological evaluation of compounds targeting the Human Monoamine Oxidase A and B and Topoiserases I and II.
- Prof. Claudia Binda, Department of Biology and Biotechnology, University of Pavia, Italy. Co-crystallization of synthetic molecules with the Human Monoamine Oxidase A and B proteins.
- Prof. Graziella Cappelletti, Department of Biosciences, University of Milan, Italy. Biological evaluation of compounds targeting the microtubules.
- Prof. Emanuela Corsini, Department of Environmental Science and Policy, University of Milan, Italy. Biological evaluation of compounds targeting the Receptor for Activated C kinase 1 and the Protein Kinase Ca/b.
- Prof. Giulio Rastelli, Department of Life Sciences, University of Modena and Reggio Emilia, Italy. Molecular modelling studies for synthetic compounds towards the Human Monoamine Oxidase A and B, Carbonic Anhydrases, Estrogen Receptors and Heat shock Protein 90.
- Dr. Mattia Mori, Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Italy. Molecular modelling studies for synthetic compounds towards the Notch1 protein.
- Prof. Daniele Passarella, Department of Chemistry, University of Milan. Synthesis of synthetic or hybrid compounds and nanoparticles with biological activity.
- Dr. Isabella Rimoldi, Department of Pharmaceutical Sciences, University of Milan. Synthesis of complexes for asymmetric hydrogenation.

International:

- Prof. Irem Durmaz Sahin, School of Medicine, Koc University, Turkey. Biological evaluation of compounds targeting the Akt protein phosphorylation.
- Prof. Constantinos Athanassopoulos, Department of Chemistry, University of Patras, Greece. Development of hybrid molecules with biological activity.

RESEARCH ACTIVITY

As a researcher in Organic Chemistry, my research activity is focused on four main research areas:
1) Synthesis and Structure–Activity Relationships (SARs) studies of natural compounds and synthetic analogues targeting biologically relevant enzymes and receptors.
2) Development of novel metal- and bio- catalytic methodologies for the preparation of polyheterocycles or fused heterocycle scaffolds with potential biological activity.
3) Isolation of natural compounds from plants, their characterization based on spectroscopic data and investigation of their potential biological activity.
4) Development of delivery systems of biologically active molecules based on nanoparticles.

1) Synthesis and Structure–Activity Relationships (SARs) studies of natural compounds and synthetic analogues targeting biologically relevant enzymes and receptors.
In my early academic years, my work was focused on the synthesis of topoisomerase inhibitors. Topoisomerases are enzymes involved in several cellular processes, such as transcription, replication and recombination, and the importance of their cellular role is underscored by the fact that they are the target of several anticancer chemotherapeutic agents and antibiotics. Both intercalation and inhibition of topoisomerases by intercalating drugs can impair DNA replication and transcription, preventing the cell growth. Topoisomerases are classified into two types: type I enzymes cleave one DNA strand and pass either one or two strands through the break before resealing it, while type II cleave both DNA strands in concert and pass another double strand through the break followed by relegation of the double strand break.
In this field, camptothecin, a naturally occurring pentacyclic quinoline alkaloid isolated from *Camptotheca acuminata* acts as a selective poison of topoisomerase I by forming a ternary complex with topoisomerase I and DNA. A promising strategy to improve the efficiency of camptothecin, which shows poor aqueous solubility, consists of developing analogues, which form a more stable cleavable complex and thus allow the conversion of single strand breaks into lethal doublestrand breaks. In this context, we designed the introduction of a methylenthiol (CH_2SH) group at position 7 of the camptothecin scaffold to promote an increase in bioavailability. Moreover, the thiol group could potentially enable new possible interactions with the biological target through the generation of disulfide bonds. Cellular studies and molecular modelling analysis indicated that the 7-modified camptothecin derivatives fully maintained the biological activity and

the same drug–target interactions of the natural compound. This conclusion was, also, supported by biochemical characterization, indicating a similar ability to induce DNA damage. These observations supported the view that position 7 is favorable for the introduction of suitable side chains without detrimental effects. (**Article N. 43**)

Searching for new scaffolds that inhibit the topoisomerases, we have seen that tamoxifen, apart from its main competitive inhibition of estrogens to the estrogen receptor (ER), can induce apoptosis in both ER-a-positive and ER-a-negative breast cancer cells through several distinct pathways including the inhibition DNA topoisomerases. In this scenario, a collection of compounds, structurally related to tamoxifen, were designed and synthesized as potential anticancer agents targeting topoisomerases. The McMurry coupling reaction was used as the key synthetic step in the preparation of these analogues and the structural assignment of *E*, *Z* isomers was determined on the basis of 2D-NOESY experiments. The compounds were evaluated for their antiproliferative activity on breast cancer (MCF-7), cervix adenocarcinoma (HeLa) and biphasic mesothelioma (MSTO-211H) human tumor cell lines and showed good inhibition in the low micromolar range. The biological studies on the molecular mechanism responsible for cytotoxicity highlighted the ability of the compounds to inhibit the relaxation activity mediated by topoisomerase II, thus suggesting the nuclear enzyme as a potential intracellular target. (**Article N. 39**)
Based on the scaffold of the most active abovementioned tamoxifen analogues, a second generation was synthesized with the McMurry coupling reaction to be the key synthetic step. The new compounds, characterized by the triarylskeleton substituted with the isobutyramide moiety, were found to be cytotoxic in the micromolar range in two human tumor cell lines, MCF-7 and HeLa and two human ovarian cancer cell lines (A2780 and OVCAR5). Further biological experiments pointed out topoisomerase II as a possible intracellular target responsible for the cytotoxicity and the occurrence of cell death through the activation of the intrinsic apoptotic pathway was, also, proved. (**Article N. 28**)

The similarities between camptothecin and evodiamine, a naturally occurring quinazolincarboline alkaloid, prompted as to synthesize a series of evodiamine analogs and examine their inhibition abilities against the topoisomerases. The synthesized evodiamine analogs, bearing different substituents at position 5 were tested for their antiproliferative activity on H460, MCF-7 and HepG2 cell lines showing low potency. Also, the activity of these derivatives as potential inhibitors of Topoisomerase I showed that they were unable to affect the catalytic activity of the nuclear enzyme. At the same time, the scaffold similarities of the evodiamine derivatives with the indole derivatives EX-527 which is a well-known sirtuin inhibitor drew our attention to test the prepared molecules against SIRT1, SIRT2 and SIRT3. Sirtuins are involved in DNA damage signaling and different DNA repair pathways. Five of the obtained compounds showed good selective inhibitory activity towards SIRT2 with the *S* enantiomers to be slightly more active. Three of them showed high selectivity towards SIRT2 over SIRT1 and SIRT3. In total, the obtained results suggested evodiamine as a new potential scaffold for the design of sirtuins inhibitors. (**Article N. 38**)

Continuing our effords for the synthesis and biological evaluation of natural compounds, we have seen that Boehmeriasin A, a naturally occurring phenanthroquinolizidine alkaloid, first isolated from the aqueous ethanolic extract of *Boehmeria siamensis* Craib (Urticaceae) possesses a strong *in vitro* cytotoxic activity, higher than taxol, against 12 cell lines from 6 panels of cancer including breast, kidney, prostate, colon, lung cancer and leukemia and restrains the expression of a series of genes related to cell proliferation and cell cycle regulation, although, with an unclear mechanism of action. In this case, we developed two synthetic approaches to obtain the racemic mixture and the pure enantiomers of boehmeriasin A. The anti-proliferative activity in three cancer cell lines (CEM, HeLa and L1210) and two endothelial cell lines (HMEC-1, BAEC) indicated a promising activity at the nanomolar range. Virtual screening with the Hurakan software identified topoisomerases as a possible target. The biological evaluation against topoisomerases permitted to identify the interaction with DNA. Moreover, structural similarities of boehmeriasin A with known sirtuin inhibitors drove us to test the compound against SIRT1 and SIRT2. Interestingly, the compounds showed an activity against SIRT2 These results offered new suggestions for the design and practical synthesis of new topoisomerase and SIRT-2 inhibitors based on the boehmeriasin A scaffold. (**Article N. 34**)

Continuing my research in the field of protein inhibitors, I focused my attention to the preparation of tubulin binders. Tubulin is a dimeric protein, whose (α, ß) heterodimers selfassemble in a head-to-tail fashion to form protofilaments and microtubules (MTs). MTs are key components of the cytoskeleton, and play a fundamental role in cell division and in many fundamental processes for cell function such as cell shape maintenance, cell motility, and morphology. The kinetics and dynamics of MTs polymerization and depolymerization regulate their biological functions. Interfering with this mechanism, either by stabilizing or destabilizing MTs, results in cytotoxic effects on duplicating cells, which are blocked in different phases of mitosis and eventually undergo apoptosis (programmed cell death). MTs are thus the target of many

anticancer drugs that exert their cytotoxic action during the cell-division process. In this area, fluorenone derivatives have generated interest because of their use in several diverse fields ranging from drugs to materials science. Initial modelling studies proposed that the introduction of a hydrophobic group at position 7 of the 9-fluorenone-2-carboxylic acid generated compounds that interact better with the tubulin. Then a group of compounds was synthesized and the antiproliferative activity on two different human cancer cell lines indicated moderately good activity. Fluorescent microscopy and flow cytometry confirmed the interference of the most active compound with the tubulin function. (**Article N. 40**)
In the same field of investigating tubulin inhibitors, we designed a novel hybrid structure by merging the pharmacophores of two natural products; pironetin which is a α-tubulin binder and dumetorine. The presence of three stereogenic centers in the designed scaffold, provided us the opportunity to produce eight stereoisomers that might interact in different manners with the biological target. After the synthesis of all eight stereoisomers, the biological studies revealed that the obtained compounds influence tubulin polymerization albeit with modest inhibition properties. Docking studies confirmed a reasonable level of tubulin binding interactions with the synthesized compounds. (**Article N. 29**)

Another key protein investigated was the tumor suppressor protein p53, which plays a critical role in cellular response to a variety of stresses including DNA damage. Taking into consideration the scaffold of pifithrin-β, which sensitizes wild-type p53 tumor cells to paclitaxel (PTX) and vinca alkaloids, we synthesized a collection of compounds as potential p53 inhibitors. The biochemical and biological evaluations showed that compounds with a tetrahydrobenzothiazole scaffold acted as inhibitors of the p53 transcriptional activity and were effective in enhancing paclitaxel-induced apoptosis. In contrast, in spite of the increased cytotoxic potency, selected compounds with a benzothiazole scaffold were not able to modulate the transcriptional activity of p53, as indicated by lack of change of p21 expression. The therapeutic potential of the compounds of the former series in combination with taxanes was confirmed in a human tumor xenograft model. (**Article N. 47**)

In parallel the smoothened (SMO) protein which is part of the Hedgehog (Hh) signaling pathway drew my attention. The synthetic compound vismodegib is a smoothened (SMO) antagonist that inhibits the Hedgehog (Hh) signaling pathway. This is achieved by preventing SMO translocation to the primary cilium. In this field, we substituted the amide bond presented in the Vismodegib structure with a bioisosteric 1,2,3-triazole ring (**Review N. 4**). Based on modelling studies we created a small library of 1,4-diphenyl-1,2,3-triazole derivatives, with the aim to obtain a new class of Hedgehog pathway inhibitors. The biological evaluation on three cancer cell lines, murine leukemia cells (L1210), CEM and HeLa and two endothelial cell lines, human microvascular endothelial cells (HMEC-1) and bovine aortic endothelial cells (BAEC), showed effective activity of some compounds. One compound showed interesting activity on glioblastoma cells and seems to block cells in S phase similarly to Vismodegib. (**Article N. 32**)

Recently, I focused my attention to the synthesis of Monoamine oxidases (MAOs) inhibitors. MAOs are flavin adenine dinucleotide (FAD)-containing enzymes, catalyzing the oxidative deamination of neurotransmitter amines and a wide variety of amine xenobiotics, including therapeutic drugs. The two MAO-A and MAO-B isoforms are established pharmacological targets for various neurological, psychiatric, and neurodegenerative diseases. MAO-A inhibitors have therapeutic utility mainly as anxiolytics and antidepressants, whereas MAO-B inhibitors are typically used for the treatment of Parkinson's disease. In this context, after a screening campaign of a large library of natural and synthetic compounds, we identified the 2-phenyloxazole as a promising scaffold for developing new MAOs inhibitors. Subsequently, we prepared a small library of new 2-phenyloxazole-4-carboxamides variously substituted at the phenyl ring and bearing an amide group at position 4. For all the derivatives, the biological evaluations highlighted their ability to inhibit selectively the hrMAO-B activity. Kinetic analysis provided evidence for a competitive mode of inhibition, and notably, for the most interesting compound, the inhibitory effect was confirmed in NGF-differentiated PC12 cell lysates. Furthermore, molecular modelling studies provided insight into the structural determinants responsible for the anti-MAO-B activity and selectivity. (**Article N. 8**)

In the search of enzyme inhibitors as anticancer drugs, the finding of allosteric inhibitors is considered a challenging approach. Cyclin-dependent kinase (CDK) family are key regulatory proteins that can become deregulated in certain types of cancer. Recently, an inactive conformation of cyclin-dependent kinase 2 (CDK2) with an open allosteric pocket was identified in a series of complexes with 8-anilino-1-naphthalene sulfonate (ANS), proposing immediately the ANS pocket as a potential site to accommodate type III allosteric inhibitors. Based on virtual screening, an appropriate hexahydrocyclopenta[*c*]quinoline scaffold was identified as a tool to probe the relevance of the allosteric inhibition of CDK2. This finding prompted us to developed a stereoselective method for the synthesis of this hexahydrocyclopenta[*c*]quinoline derivative and detailed studies of the regio- and stereochemistry of the entire preparation provided valuable allosteric

probes, whose binding modes within the CDK2 allosteric pocket were predicted using docking and MD simulations. Two different biological experimental approaches confirmed the interaction with the CDK2 allosteric pocket and mutagenesis experiments were performed to probe the effect of mutations in the allosteric pocket confirming the predicted binding site. The outcome provided could shed light on the allosteric modulation of the CDK2 activity with type III ligands. (**Article N. 24**)
Continuing the abovementioned discovery of a type III allosteric modulator of the cyclin-dependent kinase 2 (CDK2) characterized by a hexahydrocyclopenta[*c*]quinolone scaffold, three different series of derivatives were synthesized and biologically evaluated. Docking of the synthesized compounds into the allosteric pocket of CDK2 allowed the elucidation of structure–activity relationships (SARs). Moreover, the reported CDK2 allosteric inhibitors were tested on the wild-type epidermal growth factor receptor (EGFR) kinase domain and its clinically relevant T790M/L858R mutant, leading to the identification of active compounds. (**Article N. 16**)

In addition, after a screening of a library of 1200 natural and synthetic compounds we identified a new moiety bearing the imidazo[2,1-*b*]benzothiazole and imidazo[2,1-*b*]-benzoimidazole skeleton as a new scaffold for the inhibition of the glucocorticoid receptor (GCR) activity. Initial modeling studies of the most active compound on the crystallographic structure of the GCR ligand binding domain provided three novel structures, which were synthesized and further evaluated for their antagonist action mechanism against GCR in the presence of dexamethasone (DEX). The biological evaluation of the synthesized novel molecules did not show a classic antagonism against GCR but rather a reverse GCR transactivation, illustrated with a reduced expression of the GILZ gene. However, in contrast to mifepristone (RU486), our molecules failed to displace DEX in ligand binding assays. Taking into account all the experimental data, we concluded that our novel analogues hold promise as a novel class of anti-inflammatory GCR modulator compounds with decreased GCR transactivation properties. Most importantly, given that they bind to the GCR but do not displace the reference ligand DEX their allosteric binding is the most likely explanation. (**Article N. 21**)

Another approach to combat cancer progression is based on the inhibition of angiogenesis. Several molecules containing various azaheterocyclic rings, including the pyrazole moiety, were designed, synthesized and investigated as potent inhibitors of angiogenesis. In this scope, we envisioned the synthesis of novel fused pyrazolo[4,3-*c*]quinolone derivatives combining in a single molecule the known pharmacophore quinoline ring with a substituted pyrazole. This was achieved through the PIFA [phenyliodine(III) bis(trifluoroacetate)] mediated ring closure of the appropriate trisubstituted pyrazole derivatives to form the fused pyrazolo[4,3-*c*]quinoline ring system. The anti-angiogenic activity of these compounds was evaluated by using *in vitro* assays for endothelial cell proliferation and migration, and in the chicken chorioallantoic membrane (CAM) assay. Molecules containing the fused pyrazolo[4,3-*c*]quinoline motifs emerged as potent anti-angiogenic compounds, which also had the ability to inhibit the growth of MCF-7 and Hela *in vitro*. (**Article N. 48**)

2) Development of novel metal- and bio- catalytic methodologies for the preparation of polyheterocycles or fused heterocycle scaffolds with potential biological activity.
Another scientific area of interest is the development of efficient and user-friendly methods for the formation of carbon–nitrogen, carbon–oxygen and carbon–carbon bonds for the synthesis of polyheterocycles or fused heterocycle scaffolds with potential biological activity. Considering the reaction processes, the development of domino reactions that involve C_C and/or C-heteroatom bonds formation could emerged as an attractive strategy. Each reaction in the tandem catalysis may be initiated by a change in conditions (e. g. change in temperature) or by the addition of a new reagent but compared with the traditional stepwise-mediated synthetic approaches, the one-pot procedures show significant advantages. Due to the time and reagents saving in purifying the single synthetic steps, as well as the reduction of the costs of the synthetic paths, this methodology is highly atom economic and environmentally benign in a practical fashion.
Moreover, the use of copper catalysts in the C-heteroatom bond formation instead of the widespread palladium catalysis is supported by economic and environmental attributes. In this context, we developed a synthetic method for the construction of [6, 5,6]-tricyclic isatin derivatives. This scaffold is present in pharmaceutical active compounds such as the aldole reductase inhibitors, in compounds showing anti-inflammatory activity, in molecules acting as selective human $ß_3$-adrenergic receptor agonists, as potential antipsychotic compounds, as anticancer compounds and also as compounds with antiproliferative activity through the cannabinoid receptors CB_1 and CB_2. Starting from 5,7-dibromoisatin we developed a new pathway for the synthesis of oxazinoindole-2-one derivatives, in which the alkoxylation/arylation process was developed as a one-pot procedure using the tandem copper-palladium catalysis, providing 5-(hetero)aryl substituted oxazinoindole-2-ones. Preliminary biological evaluation for some of the compounds showed inhibition in the low micromolar range on the A2780 MSTO-211H tumor cell lines. (**Article N. 20**)

Continuing our research in the synthesis of fused heterocycles with potential biological activity, we

developed a fruitful divergent cyclization of terminal alkynes arising from 2-aminophenols depending on the transition metal employed. The interest of this strategy was due to the rapid access to different heterocyclic scaffolds starting from the same building block. From *O*-propargyl-2-aminophenols bicyclic 3-methylene-1,4-benzoxazines were obtained from the hydroamination, and the formation of a new C–N bond, under the $Pd(PPh_3)_4$ catalysis, whereas *N*-Boc-8-amino-(2*H*)-benzopyrans were afforded through hydroarylation, and the formation of a new C-C bond, using $PtCl_2$ as catalyst. The subsequent functionalization of *N*-Boc-8-amino-(2*H*)-benzopyrans paved the way for the synthesis of the tricyclic pyrano[3,2-*h*]quinolones, a scaffold which in the literature presents antiproliferative and antioxidant activities useful in the treatment of the Alzheimer's disease and promising metalchelating properties. (**Article N. 17**)

Afterwards, we worked on the synthesis of polyheterocycles through the formation of more than one bond in a single step. This method represents a rapid and economical way to obtain functionalized substrates with further applications. In particular, we developed an aminoarylation process of *N*-allylureas in the presence of aryltributylstannanes, performed under ligand-free Pd-catalysis, by using the H_2O_2 as oxidant. The reaction was chemo- and regioselective, affording the imidazolidinones as the exclusive ring obtained. (**Article N. 13**)

Recently, we were intrigued by the oxindole scaffold, which is present in a large family of natural and unnatural compounds endowed with biological activities. Among them, 3,3-disubstituted oxindole derivatives are recognized as valuable compounds for drug discovery. More specifically, oxindoles bearing an amino group at the 3-position are belonging to a variety of pharmacological active molecules, such as the gastrin/CCK-B receptor antagonist AG-041R, the vasopressin VIb receptor antagonist SSR-149415 and the HIV protease inhibitors. In this field, we synthesized 3,3-disubstituted oxindole derivatives bearing a nitrogen atom at the C-3 position starting from 3-alkyl oxindole. In this case, we were able to obtain the compounds through a metal free pathway. These derivatives were tested in five human tumor cell lines (PC3, MCF7, SW620, MiaPaca2 and A375) and on primary cells (PBMCs) from healthy donors providing compounds with strong anticancer effect in all cancer lines on the low micromolar range. (**Article N. 7**)

At the same time, we were interested on the functionalization of the 4*H*-isoxazol-5-one scaffold, which by ring opening, could be considered a versatile building block in organic synthesis. Specifically, the isoxazolinone ring can be converted into either acylic compounds, such as azadienes and alkynes, or heterocyclic structures, such as pyridines, azirines, imidazoles, 1,3-oxazines, pyrazin-2-ones, and piperidines. In this field, we envisioned the 4-(1,4-naphthoquinone)-substituted 4*H*-isoxazol-5-ones as possible precursors of new benzo-fused indoles, because benzo-fused indole moieties are key structural blocks in many biologically natural or synthetic compounds. Among them, benzo[*f*]indole-4,9-diones play a relevant role due to their pronounced biological antibacterial, antiviral, antifungal, anticancer, and anti-inflammatory activities and benzo[*g*]indole derivatives have shown anticancer, anti-inflammatory, and antipsychotic activities. Starting from easily prepared 4,4-disubstituted 4*H*-isoxazol-5-ones bearing a 1,4-naphthoquinone moiety we synthesized different types of benzoindolyl products depending on the different reaction conditions. The decarboxylative ring opening/ring closure promoted by catalytic $[Ru(p\text{-cymene})_2Cl_2]_2$ yielding benzo[*f*]indole-4,9-diones and, alternatively, the hydrogenation reactions provided the conversion of 4-(1,4-naphthoquinone)-substituted isoxazol-5-ones to benzo[*g*]indole compounds, with the level of reduction depending on the substituents present on the ring. These strategies represented a valuable alternative to the methods already reported in the literature for the preparation of benzo-indoles and provide wide possibilities to use the 4*H*-isoxazol-5-ones as building blocks to access heterocyclic products. (**Article N. 6**)

Biocatalysis is a powerful tool for the stereoselective preparation of many chiral compounds. Chiral molecules are strategic building blocks in the synthesis of many pharmaceutical and agricultural compounds. In this context, we envisioned a chemo-enzymatic cascade approach for the stereoselective synthesis of hydroxy ketones and the corresponding 1,3-diols. Starting with α,ß-unsaturated compounds, a cascade reaction by a new class of tridentate *N*,*N*,*O* ligands with copper(II) complexes for the asymmetric ß-borylation was performed, followed by deprotection to the corresponding keto–alcohols, which then were bioreduced by yeasts. The biotransformation set up with *Rhodotorula rubra* allowed (*R*)-keto–alcohols and (*S*,*S*)-diols to be obtained with up to 99%*ee* and up to 99%*de* in favor of the anti enantiomers. (**Article N. 19**)

Moreover, In the last decades, the development of hybrid catalysts that combine the advantages of chemical catalysts and biocatalysis, has launched an original approach, allowing high selectivity and specificity to be merged with a wide scope of reactivity and substrates. Recently it was found that several biological effects of vancomycin (Van), a front-line glycopeptide antibiotic produced by *Streptomyces orientalis* and active

against Gram positive infections, are related to its ability to bind both Cu(II) and Zn(II) metal ions under physiological/neutral conditions. In this case, we developed a hybrid catalyst generated from the interaction of the steric hindered and rigid vancomycin with Ir(III) metal complex. The conformational rearrangement of vancomycin, caused by the complexation with IrCp*, was evinced by several analytical techniques such as MALDI-TOF, UV, Circular dichroism (CD), Raman IR, and NMR. The capability of this new hybrid catalyst to reduce different cyclic imines was evaluated in aqueous media under mild reaction conditions affording the reaction products with moderate to appreciable enantioselectivity. (**Article N. 10**)

3) Isolation of natural compounds from plants, their characterization based on spectroscopic data and investigation of their potential biological activity.

An important activity during my research years was devoted to the isolation and structural elucidation of plant-derived natural compounds. In particular, the extraction and purification of phytocomponents from the *Amygdalus lycioides* Spach branchlets resulted in the isolation of four chiral flavanones: (*2R*,*3R*)-Taxifolin, (*2R*,*3R*)-aromadendrin, (*S*)-5,7,3',5'-tetrahydroxyflavanone and (*S*)-naringenin. The isolation of the phytocomponents was performed by a direct purification of the crude extract *via* semi-preparative HPLC and the characterization of the structures of these compounds were obtained by comparison of the measured $[\alpha]_D$, 1D and 2D NMR and HRESI-MS spectra with values in the literature. The dose dependent activity of (*S*)-naringenin, exerted *in vitro* on human peripheral blood mononuclear cells (hPBMC), as well as its *in vivo* efficacy, highlights its potential use in inflammatory conditions associated with increased Tumour Necrosis Factor alpha (TNFα) production. (**Article N. 46**)

Moreover, I worked on the investigation of epicuticular and tissue flavonoids, the volatiles and the glandular trichome structure of the leaves of four species of *Primula L.* that grow in the Italian Eastern Alps. *Primula albenensis* Banfi and Ferlinghetti, *P. auricula* L., *P. farinosa* L., *P. halleri* Gmelin produce farinose exudates that are deposited on the leaf surface as filamentous crystalloids. Apart from the already known compounds, a new flavone, the 3,5-dihydroxyflavone, was isolated from the acetone extract of leaf farinas and three new flavonol glycosides, 3'-*O*-(ß-galactopyranosyl)-2'-hydroxyflavone, isorhamnetin 3-*O*-a-rhamnopyranosyl-(1→3)-*O*-[a-rhamnopyranosyl-(1→6)]-*O*-ß-galactopyranoside and quercetin 3-*O*-a-rhamnopyranosyl-(1→3)-*O*-[a-rhamnopyranosyl-(1→6)]-*O*-ß-galactopyranoside were isolated from the MeOH extract of the leaves. All the structures were elucidated based on their ^{1}H and ^{13}C NMR data and 2D NMR techniques, as well as on HPLC–MS. The leaf-volatiles emitted by these *Primula* species were mainly sesquiterpene hydrocarbons, with the exception of *P. albenensis*, which produced almost exclusively a non-terpene derivative. (**Article N. 37**)

4) Development of delivery systems of biologically active molecules based on nanoparticles.

The availability of a potent drug is often not sufficient to guarantee high activity, due to pharmacokinetic and bioavailability limitations. In order to exploit the pharmacological activity, the majority of the compounds should reach the site of action in appropriate concentrations. Many factors may cause a decrease in the intracellular drug concentration. A site selective delivery of drugs to their sites of action could result in greater therapeutic effects and potentially minimize side-effects. Nanoparticles can be preferentially delivered to the tumor site thanks to the enhanced permeation and retention (EPR) effect, whereas the lymphatic system is usually deficient. In addition to that, nanotechnologies can improve drug properties in several ways: by controlling release and distribution, by enhancing drug absorption by mucosa or cells and by protecting the drug from degradation. The concept of lipid-drug conjugates has gained considerable attention in recent years, and they are usually obtained by a covalent coupling of the drug to biocompatible lipid moieties. Among them, squalene, a natural precursor of many steroids, showed the ability, when linked to biologically active compounds, to achieve a spontaneous formation of nanoassemblies in water. Thus, squalene protects the drugs from environment damaging factors and, in some cases, improves their pharmacokinetic profile by decreasing the toxicity of the associated drugs with an increase in their therapeutic index.

In this context, we initially developed a class of squalene-based conjugate compounds of paclitaxel, podophyllotoxin, camptothecin and epothilone joined by different linkers. The obtained compounds self-assemble and form nanoassemblies that were characterized. The *in vitro* activity of the compounds highlighted the importance of the disulfide bond in the linker. In total, the results acquired, indicated a good starting point for the construction of nanoassemblies bearing a disulfide bridge. (**Article N. 36**)

Next, we moved to the preparation of squalene-based fluorescent heteronanoparticles by mixing a paclitaxel–squalene conjugate and a fluorescein–squalene conjugate, in order to trace the delivery of the nanoassemblies and to demonstrate the internalization of the drug. The formation of self-assembled heteronanoparticles was confirmed by using the quasielastic light scattering (QELS) technique. The internalization in A549 human lung carcinoma cells was verified by microscopy analysis and paclitaxel in

nanoassemblies maintains its ability to target microtubules. (**Article N. 35**)

Then, taking into consideration the results of the above mentioned heteronanoparticles, we demonstrated the possibility of forming hetero-nanoparticles containing two different drugs. Moreover, a ternary combination with the addition of a dye-squalene conjugate was used to permit the observation of the cellular internalization. In this case, hetero-nanoparticles generated by self-assembly of cyclopamine-, a natural alkaloid acting as Hedgehog signaling pathway (Hh) inhibitor, and paclitaxel-squalene conjugates showed a combined efficacy in the treatment of three different cancer cell lines, OVCAR5 (ovarian cancer cell) and #83 and #110 (ovarian tumor-initiating cells). The use of ternary combination with the addition of a dye-squalene conjugate secured the obtainment of fluorescent nanoparticles that permitted the observation of the cellular internalization by confocal microscopy and super-resolution dSTORM (direct stochastic optical reconstruction microscopy). Altogether, we presented that the two drugs do not influence each other's activity and it may be possible to trace these nanoparticles in the cells by imaging. (**Article N. 31**)

Afterwards, we moved our interest to new self-assembly inducers with particular attention to the ones that possess an antiproliferative activity to make possible the obtainment of self-assembling dual drugs. In this case, we considered the use of the hydrophobic moiety of 4-(1,2-diphenylbut-1-en-1-yl)aniline, a tamoxifen analog, which we recently demonstrated to have antiproliferative activity on different human tumor cell lines. (**Article N. 28**) The expected self-assembly ability of this structure could derive from the π-stacking interactions among the aromatic rings of the adjacent molecules, forming a hydrophobic core and exposing the polar moieties toward the aqueous environment. Aloin was first selected because of its hydrophilic structure in order to test the self-assembly properties of amphiphilic conjugates and podophyllotoxin, a lipophilic antiproliferative compound, in order to prove the ability of 4-(1,2-diphenylbut-1-en-1-yl)aniline to induce self-assembly also in a totally lipophilic conjugate. The obtained nanoparticles were characterized by dynamic light scattering (DLS), transmission electron microscopy (TEM) and nanoparticle tracking analysis (NanoSight). The obtained results showed the ability of the 4-(1,2-diphenylbut-1-en-1-yl)aniline scaffold to induce self-assembly on different types of conjugates containing aloin or podophyllotoxin, opening the possibility to prepare a plethora of 4-(1,2-diphenylbut-1-en-1-yl)aniline based conjugates containing different anticancer drugs as building blocks and suitable linkers to induce drug release after cell internalization. (**Article N. 25**)

Subsequently, pursuing our interest in self-assembled squalene heteronanoparticles, we investigated the combination of cyclopamine (CYP, Hedgehog pathway inhibitor) and doxorubicin (DOXO) conjugates with the aim to demonstrate the formation of hetero-NPs that could improve the performance given by the use of the simple parental drugs. In this case, the selection of doxorubicin−squalene conjugate was selected because it was shown to improve the anticancer efficacy and the therapeutic index of DOXO. The formation of hetero-NPs combining cyclopamine− and doxorubicin−squalene derivatives was demonstrated by DLS characterization and showed that the NPs are narrow monodisperse and stable for 4 weeks. The *in vitro* biological evaluation confirmed that the cytotoxic activity of the parental drugs is maintained and the efficacy of the nanoformulated drugs is higher than the single combination of the conjugates. Importantly, the *in vivo* experiments showed that cyclopamine−doxorubicin NPs not only reduce tumor growth but also significantly decrease the toxicity of chemotherapy in mice, allowing the administration of higher doses of chemotherapy, potentially eliminating the more resistant tumor cells and therefore leading to a treatment that is more effective. (**Article N. 23**)

Afterwards, driven by the fact that many tumor cells show resistance to drugs we considered the formation of self-assembled heteronanoparticles as a promising approach to overcome this problem. In this scenario, we planned the preparation of some ecdysone conjugates containing the squalene tail to be combined with the known squalenoylated doxorubicin and investigate their ability to form heteronanoparticles (H-NPs) toward the treatment of doxorubicin resistant cell lines. Ecdysone derivatives were used due to their chemo-sensitizing effect on MDR cancer cells. The nanosuspensions were characterized by dynamic light scattering (DLS) and transmission electron microscopy (TEM). DLS analysis confirmed the formation of nanoassemblies in aqueous medium. The biological evaluation on A2780ADR cell line confirmed not only the maintenance of the activity of the parental drug but at least partially the ability to overcome cancer resistance. The *in vitro* cell uptake was demonstrated, and the involvement of an endosomal-mediated pathway was suggested. (**Article N. 18**)

At the same time, we designed the synthesis of new self-assembling conjugates characterized by the presence of a self-immolative linker in order to improve the release of the active drug inside the cell induced by lipase cleavage. The previously reported 4-(1,2-diphenylbut-1-en-1-yl)aniline (**Article N. 25**) was used as

a self-assembling inducer, a *p*-hydroxylbenzyl alcohol as the self-immolative linker and aminothiocolchicine as the prototype drug. The successful formation of nanoparticles was established by means of dynamic light scattering (DLS) measurements, atomic force microscopy (AFM) and fluorescence microscopy. The release of the thiocolchicine derivative was demonstrated *in vitro* in the presence of porcine pancreatic lipase and Celite-supported lipase. The antiproliferative activity of the NPs obtained was demonstrated on two human cancer cell lines (HeLa and MCF-7). These results showed the possibility to modulate the characteristics of the self-assembled nanoparticles that depend on the self-assembling inducer, the self-immolative linker, and the drug. (**Article N. 11**)

Data	13-03-2021	Luogo	Milano