



Research Activity:

a. Development of neuroprotective agents

- Design and synthesis of metabotropic glutamate receptors
- Design and synthesis of new PARP inhibitors
- Design and synthesis of new tankyrase inhibitors
- Design and synthesis of new inhibitors involved in the kynurenine pathway

b. Characterization of genomic and non genomic bile acid pathways

- Design and synthesis of modulators of the FXR and DAF-12 nuclear receptors
- Design and synthesis of TGR5 membrane receptor modulators
- Synthesis, characterization and analysis of steroidal compounds

c. New synthetic reactions by means of diaxocarbonyl compounds

d. Development of chromatographic methods of analysis

- New chiral selectors in the ligand-exchange chromatography
- Development of new chiral stationary phases
- Derived chromatographic indices in the evaluation of the hydrophilic/hydrophobic balance of bile acids

International collaborations:

- Prof. Michael Lämmerhofer, Institute of Pharmaceutical Sciences, University of Tübingen, Tübingen, Germany.
- Prof. Wolfgang Lindner, Department of Analytical Chemistry, University of Vienna, Vienna, Austria.
- Prof. Erden Banoglu, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Gazi University, Ankara, Turkey.
- Prof. Semen Zloty, Ufa State Petroleum Technical University, Ufa (Russia)
- Prof. Oliver Werz, Institute of Pharmacy, Friedrich-Schiller-University Jena, Jena, Germany.
- Prof. Joaquín María Campos, Departamento de Química Farmacéutica y Orgánica, Facultad de Farmacia, Granada, Spain.
- Dr. Maria Luisa Ruiz del Castillo, Instituto de Ciencia y Tecnología de Alimentos y Nutrición (ICTAN), Consejo Superior de Investigaciones Científicas (CSIC) Madrid, Spain.

- Prof.ssa Federica Pellati, Dipartimento di Scienze della Vita, Università degli Studi di Modena e Reggio Emilia, Modena.
- Dr. Vincenzo Formica, Medical Oncology Unit - Internal Medicine Department "Tor Vergata" University Hospital, Roma.
- Prof. Roberto Mandrioli, Dipartimento di Scienze per la Qualità della Vita (QuVi), Università di Bologna.
- Prof. Carlo Bertucci, Dipartimento di Farmacia e Biotecnologie (FaBiT), Università di Bologna, Bologna.
- Prof.ssa Laura Mercolini, Dipartimento di Farmacia e Biotecnologie (FaBiT), Università di Bologna, Bologna.
- Prof. Beniamino Cenci Goga, Dipartimento di Medicina Veterinaria, Università degli Studi di Perugia, Perugia.
- Dr. Alessandro Di Michele, Dipartimento di Fisica e Geologia, Università degli Studi di Perugia, Perugia.
- TES Pharma, Corciano (Perugia) (Italia)
- Intercept Pharmaceuticals, New York (USA)
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- Institute for Applied Synthetic Chemistry, Vienna University of Technology, Vienna (Austria)
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Publications (2009-2013)

1. B. Natalini, R. Sardella, E. Camaioni, A. Macchiarulo, A. Gioiello, G. Carbone, R. Pellicciari, "Derived chromatographic indices as effective tools to study the self-aggregation process of bile acids" *J. Pharm. Biomed. Anal.* **2009**, *50*, 613-621.
2. A. Gioiello, F. Venturoni, B. Natalini, R. Pellicciari, "BF₃•Et₂O-Induced Decomposition of Ethyl 2-Diazo-3-hydroxy-3,3-diarylpropanoates in Acetonitrile: A Novel Approach to 2,3-Diaryl β-Enamino Ester Derivatives" *J. Org. Chem.* **2009**, *74*, 3520-3523.
3. B. Natalini, R. Sardella, G. Carbone, A. Macchiarulo, R. Pellicciari, "The effect of the copper(II) salt anion in the Chiral Ligand-Exchange Chromatography of amino acids" *Anal. Chim. Acta* **2009**, *638*, 225-233.
4. M.C. Fulco, M. Marinozzi, B.E. Çaliskan, R. Sardella, B. Natalini, R. Pellicciari, "Synthesis and Chromatographic Resolution of Conformationally Constrained Analogues of Homotaurine" *Tetrahedron* **2009**, *65*, 8756-8762.
5. B. Natalini, R. Sardella, A. Gioiello, G. Carbone, M. Dawgul, R. Pellicciari, "Side-chain Modified Bile Acids: Chromatographic Separation of 23-Methyl Epimers" *J. Sep. Sci.* **2009**, *32*, 2022-2033.
6. R. Pellicciari, A. Gioiello, A. Macchiarulo, C. Thomas, E. Rosatelli, B. Natalini, R. Sardella, M. Pruzanski, A. Roda, E. Pastorini, K. Schoonjans, J. Auwerx, "Discovery of 6α-Ethyl-23(S)-methylcholic Acid (S-EMCA, INT-777) as a Potent and Selective Agonist for the TGR5 Receptor, a Novel Target for Diabetes" *J. Med. Chem.* **2009**, *52* (24), 7958-7961.
7. B. Natalini, R. Sardella, N. Giacchè, S. Palmiotto, E. Camaioni, M. Marinozzi, A. Macchiarulo, R. Pellicciari, "Chiral ligand-exchange separation and resolution of extremely rigid glutamate analogs: 1-aminospiro[2.2]pentyl-1,4-dicarboxylic acids" *Anal. Bioanal. Chem.* **2010**, *397*, 1997-2011.
8. M. Roberti, B. Natalini, V. Andrisano, R. Seraglia, A. Gioiello, R. Pellicciari, "Thermal and Catalytic Reactions of Ethyl Diazopyruvate with [60]Fullerene" *Tetrahedron* **2010**, *66*, 7329-7332.

9. B. Natalini, N. Giacchè, R. Sardella, F. Ianni, A. Macchiarulo, R. Pellicciari, "Computational studies for the elucidation of the enantiomer elution order of amino acids in Chiral Ligand-Exchange Chromatography" *J. Chromatogr. A* **2010**, *1217*, 7523-7527.
10. B. Natalini, R. Sardella, S. Massari, F. Ianni, O. Tabarrini, V. Cecchetti, "Synthesis and chromatographic enantioresolution of anti-HIV quinolone derivatives" *Talanta* **2011**, *85*, 1392-1397.
11. B. Natalini, R. Sardella, A. Macchiarulo, M. Marinozzi, E. Camaioni, R. Pellicciari, "Mechanistic aspects and applications of chiral ligand-exchange chromatography" in *Advances in Chromatography*, E. Grushka, N. Grinberg, Eds, Taylor&Francis, Boca Raton, FL, vol. 49, 71-134 (2011)
12. B. Natalini, R. Sardella, A. Gioiello, E. Rosatelli, F. Ianni, E. Camaioni, R. Pellicciari, "Fast chromatographic determination of the bile salt critical micellar concentration" *Anal. Bioanal. Chem.* **2011**, *401*, 267-274.
13. A. Gioiello, F. Venturoni, M. Marinozzi, B. Natalini, and R. Pellicciari, "Exploring the Synthetic Versatility of the Lewis Acid Induced Decomposition Reaction of α -Diazo- β -hydroxy Esters. The Case of Ethyl Diazo(3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetate" *J.Org. Chem.* **2011**, *76*, 7431-7437.
14. A. Gioiello, R. Sardella, E. Rosatelli, B.M. Sadeghpour, B. Natalini, and R. Pellicciari, "Novel stereoselective synthesis and chromatographic evaluation of E-guggulsterone" *Steroids* **2012**, *77*, 250-254.
15. B. Natalini, R. Sardella, "Chromatographic separation and analysis: chiral ion and ligand exchange stationary phases", in *Comprehensive Chirality*, G. Tranter (Ed.), Elsevier, vol. 8.8, 115-152 (2012). ISBN: 9780080951676
16. B. Natalini, "La Ricerca in Chimica Farmaceutica ed in Tecnologia Farmaceutica", in *La Chimica in Umbria tra Passato e Futuro*, AUR-Rapporti, Perugia, 261-282 (2011). (
17. R. Sardella, F. Ianni, B. Natalini, G. P. Blanch, M. L. Ruiz del Castillo, "Rapid Detection of D-amino Acids in Cheese with a Chiral Ligand-Exchange Chromatography System", *Curr. Anal. Chem.* **2012**, *8*, 319-327. **IF 1.809**
18. B. Natalini, R. Sardella, F. Ianni, "Cromatografia chirale a scambio di ligandi. Una vecchia tecnica per nuovi studi computazionali". *La Chimica e L'Industria* **2012**, *4*, 98-103.
19. M. Marinozzi, A. Carotti, E. Sansone, A. Macchiarulo, E. Rosatelli, R. Sardella, B. Natalini, G. Rizzo, L. Adorini, D. Passeri, F. De Franco, M. Pruzanski, R. Pellicciari, "Pyrazole[3,4-e][1,4]thiazepin-7-one derivatives as a novel class of Farnesoid X Receptor (FXR) agonists" *Bioorg. Med. Chem.* **2012**, *20*, 3429-3445.
20. F. Venturoni, A. Gioiello, R. Sardella, B. Natalini, R. Pellicciari, "Continuous flow synthesis and scale-up of glycine- and taurine-conjugated bile salts" *Org. Biomol. Chem.* **2012**, *10*, 4109-4115 (DOI: 10.1039/c2ob25528f).
21. R. Sardella, A. Macchiarulo, A. Carotti, F. Ianni, M.E. García Rubiño, B. Natalini, "Chiral mobile phase in ligand-exchange chromatography of amino acids: Exploring the copper(II) salt anion effect with a computational approach", *J. Chromatogr. A* **2012**, *1269*, 316-324. (DOI: 10.1016/j.chroma.2012.08.018)
22. R. Sardella, A. Gioiello, F. Ianni, F. Venturoni, B. Natalini, "HPLC/ELSD analysis of amidated bile acids: An effective and rapid way to assist continuous flow chemistry processes", *Talanta* **2012**, *100*, 364-371 (DOI: 10.1016/j.talanta.2012.07.092)
23. R. Sardella, F. Ianni, N. Giacchè, A. Lisanti, P. Conti, A. Pinto, L. Tamborini, B. Natalini, "Ligand-exchange enantioresolution of dihydroisoxazole amino acid derivatives acting as glutamatergic modulators", *Trends Chrom.* **2012**, *7*, 43-56.

24. R. Sardella, M. Marinozzi, F. Ianni, A. Lisanti, B. Natalini, "Simultaneous diastereo- and enantioseparation of Farnesoid X Receptor (FXR) agonists with a quinine carbamate-based chiral stationary phase", *Anal. Bioanal. Chem.* **2013**, *405*(2), 847-862 (DOI: 10.1007/s00216-012-6348-1).
25. B. Natalini, C. Santi, "Risonanza Magnetica Nucleare" in *Principi di Analisi Farmaceutica*, a cura di V. Cavrini, V. Andrisano, 3a Ed. 2013, Soc. Editrice Esculapio, Bologna, 393-412 [ISBN: 978-88-7488-529-9].
26. B. Natalini, R. Sardella, F. Ianni, "Enantioseparations by High Performance Liquid Chromatography based on Chiral Ligand Exchange", in *Chiral Separations - Methods in Molecular Biology, Methods and Protocols*, 2nd Edition, G.K.E. Scriba (Ed.), Humana Press Inc., New York, (J.M. Walker, ser. Ed.), vol. 970, 191-208 (2013). DOI:10.1007/978-1-62703-263-6_11.
27. B. Natalini, R. Sardella, F. Ianni, M. E. García-Rubiño, A. Conejo-García, M. del Carmen Núñez, M. A. Gallo, J. M. Campos, "Chromatographic Enantioresolution of Six Purine Derivatives Endowed with Anti-Human Breast Cancer Activity", *Chromatographia* **2013**, *76*(9-10), 475-482. (DOI: 10.1007/s10337-013-2398-6)
28. M. Marinozzi, A. Carotti, R. Sardella, F. Buonerba, F. Ianni, B. Natalini, D. Passeri, G. Rizzo, R. Pellicciari, "Asymmetric synthesis of the four diastereoisomers of a novel non-steroidal farnesoid X receptor (FXR) agonist: Role of the chirality on the biological activity", *Bioorg. Med. Chem.* **2013**, *21*, 3780-3789.
29. R. Sardella, A. Lisanti, M. Marinozzi, F. Ianni, B. Natalini, G. P. Blanch, M. L. Ruiz del Castillo, "Combined monodimensional chromatographic approaches to monitor the presence of D-amino acids in cheese", *Food Control* **2013**, *34*, 478-487. (if-2012=2,738)
30. P. Sabbatini, P. Filipponi, R. Sardella, B. Natalini, R. Nuti, A. Macchiarulo, R. Pellicciari, A. Gioiello, "Synthesis and Quantitative Structure-Property Relationships of Hyodeoxycholic Acid Derivatives", *Molecules* **2013**, *18*, 10497-10513.

Communications (2009-2013)

1. A. Gioiello, F. Venturoni, A. Khamidullina, B. Natalini, R. Pellicciari, "Exploring the reaction of ethyl diazoacetate: new approaches to biologically active compounds", XXIII Congresso Nazionale della SCI, Sorrento (NA), 169 (2009).
2. M.C. Fulco, R. Sardella, M. Marinozzi, B.E. Caliskan, B. Natalini, R. Pellicciari, "Synthesis and chromatographic enantioresolution of conformationally constrained homotaurine analogues", XXIII Congresso Nazionale della SCI, Sorrento (NA), 181 (2009).
3. N. Giacchè, R. Sardella, A. Macchiarulo, M. Dawgul, B. Natalini, R. Pellicciari, "A new computational model to predict the elution order in the Chiral Ligand-Exchange Chromatography (CLEC) of amino acids", XXIII Congresso Nazionale della SCI, Sorrento (NA), 177 (2009).
4. B. Natalini, R. Sardella, A. Macchiarulo, M. Marinozzi, N. Giacchè, R. Pellicciari, "Molecular Modelling Studies in the Chiral Ligand-Exchange Chromatography of Amino Acids". XIII Int. Meeting on Recent Developments in Pharmaceutical Analysis, Milan, Italy, 60 (2009).
5. B. Natalini, R. Sardella, A. Gioiello, G. Carbone, R. Pellicciari, "Side-chain modified bile acids: chromatographic evaluation of the epimer separation". Nuove Prospettive in Chimica Farmaceutica – III Meeting/Workshop. Castelvechio Pascoli, 114 (2009).
6. Natalini, R. Sardella, N. Giacchè, F. Ianni, E. Camaioni, A. Macchiarulo, M. Marinozzi, R. Pellicciari, "Chiral ligand-exchange separation and resolution of extremely rigid glutamate

analogues: 1-aminospiro[2.2]pentyl-1,4-dicarboxylic acids". XVI International Symposium on Separation Science, Roma, P11, 86 (2010).

7. B. Natalini, R. Sardella, A. Gioiello, E. Rosatelli, R. Nuti, E. Camaioni, A. Macchiarulo, R. Pellicciari, "Chromatographic hydrophobicity index: a high-throughput tool to estimate the critical micellar concentration of bile acids". XX National Meeting on Medicinal Chemistry, Abano Terme (PD), P97, 195 (2010).
8. B. Natalini, N. Giacchè, R. Sardella, F. Ianni, A. Macchiarulo, R. Pellicciari, "Computational studies for the elucidation of the enantiomer elution order in chiral ligand-exchange chromatography". XX National Meeting on Medicinal Chemistry, Abano Terme (PD), P98, 196 (2010).
9. B. Natalini, F. Ianni, R. Sardella, A. Gioiello, P. Sabbatini, P. Filipponi, R. Pellicciari, "Chromatographic evaluation of the 25-(*R,S*)-methyl-bishomo-hyodeoxycholic acid epimers". XXIX Convegno Interregionale Toscana-Umbria-Marche-Abruzzo, Ancona, OR20 (2010).
10. B. Natalini, R. Sardella, A. Macchiarulo, F. Ianni, R. Pellicciari, "Descriptive structure-separation relationship studies in the enantioseparation of amino acids". Nuove Prospettive in Chimica Farmaceutica – IV Meeting/Workshop. S. Margherita di Pula (CA), (2010).
11. B. Natalini, R. Sardella, N. Giacchè, F. Ianni, A. Macchiarulo, R. Pellicciari, "Computational studies on ligand-exchange systems operating with chiral additives". XXIX Convegno Interregionale Toscana-Umbria-Marche-Abruzzo, Ancona, OR10 (2010).
12. B. Natalini, R. Sardella, F. Ianni, M.E. Garcia Rubiño, A. Carotti, A. Macchiarulo, R. Pellicciari, "Mechanistic investigations on a ligand-exchange system operating with a chiral mobile phase". V Meeting Nuove Prospettive in Chimica Farmaceutica, Trieste, 28 (2011).
13. B. Natalini, R. Sardella, A. Carotti, F. Ianni, M.E. García Rubiño, A. Macchiarulo, R. Pellicciari, "The effect of the Cu(II) salt anion in a ligand-exchange system operating with a chiral mobile phase". XXIV Congresso Nazionale della SCI, Lecce, 438 (2011).
14. B. Natalini, F. Ianni, R. Sardella, F. Venturoni, A. Gioiello, R. Pellicciari, "HPLC/ELSD analysis of conjugated bile acids: a way to assist flow chemistry processes". XXIV Congresso Nazionale della SCI, Lecce, 450 (2011).
15. F. Venturoni, A. Gioiello, R. Sardella, B. Natalini, R. Pellicciari, "Development of an Efficient Continuous Flow Synthesis of Glyco- and Tauro-Conjugated Natural and Semi-Synthetic Bile Acids". XXIV Congresso Nazionale della SCI, Lecce, 464 (2011).
16. B. Natalini, R. Sardella, A. Gioiello, E. Rosatelli, F. Ianni, E. Camaioni, R. Pellicciari, "Fast chromatographic determination of the unconjugated bile salt critical micellar concentration". 14th Int. Meeting RDPA 2011, Pavia, OC20 (2011).
17. B. Natalini, R. Sardella, F. Ianni, M. E. García-Rubiño, A. Conejo-García, M. C. Núñez, J. M. Campos, "Chromatographic enantioresolution of six 2- and 6-substituted (*R,S*)-9-(2,3-dihydro-1,4-benzoxathin-2- or -3-ylmethyl)-9*H*-purines endowed with anti-human breast cancer activity". 14th Int. Meeting RDPA 2011, Pavia, P084 (2011).
18. R. Sardella, F. Ianni, A. Lisanti, B. Natalini, G.P. Blanch, M.L. Ruiz del Castillo, "Fast determination of amino acids in cheese extracts with a coated chiral ligand-exchange chromatography stationary phase". *Em. J. Food Agric.* **2012**, *24*, 117 (ChimALSi-2012, P-151).
19. B. Natalini, F. Ianni, R. Sardella, A. Lisanti, F. Venturoni, A. Gioiello, R. Pellicciari, "Analisi HPLC/ELSD di acidi biliari amidati: un approccio efficace per assistere processi sintetici a flusso continuo". XXXI TUMA 2012, Francavilla a Mare (CH) (2012).
20. R. Sardella, F. Ianni, A. Lisanti, B. Natalini, "Ruolo della fase mobile nell'enantioseparazione con fasi stazionarie chirali a base polisaccaridica". XXXI TUMA 2012, Francavilla a Mare (CH) (2012).

21. B. Natalini, R. Sardella, F. Ianni, N. Giacchè, P. Conti, A. Pinto, L. Tamborini, "Ligand-exchange enantioresolution of dihydroisoxazole amino acid derivatives". 21st National Meeting on Medicinal Chemistry, Palermo, 122 (2012).
22. A. Gioiello, R. Sardella, E. Rosatelli, B. Natalini, R. Pellicciari, "Novel stereoselective synthesis and chromatographic evaluation of guggulsterones, the bioactive constituents of the hypolipidemic guggulipid". 21st National Meeting on Medicinal Chemistry, Palermo, 131 (2012).
23. A. Gioiello, P. Sabbatini, A. Ogawa, R. Sardella, D. Passeri, B. Natalini, G. Robertson, A. Macchiarulo, R. Sommer, R. Pellicciari, "Unraveling the molecular basis for DAF-12 activation: diastereoselective synthesis and SAR studies of dafachronic acid derivatives". ISMC 2012, Berlino (Germany), 89 (2012).
24. F. Ianni, A. Lisanti, R. Sardella, M. Marinozzi, B. Natalini, "Role of the mobile phase composition in the chromatographic enantioseparation of pharmacologically relevant compounds". 7th AltUN Annual Meeting, Perugia (Italy), 25 (2013).
25. G. Fodaroni, M. Burico, A. Gaetano, L. Mattoli, B. Natalini, R. Seraglia, P. Traldi, "*Cynara scolymus* leaves: metabolomic fingerprinting as an effective analytical tool in stability studies". 31st IMMS 2013, Palermo, 87 (2013).
26. P. Sabbatini, P. Filippini, R. Sardella, B. Natalini, R. Nuti, A. Macchiarulo, R. Pellicciari, A. Gioiello, "Side chain modified HDCA derivatives: synthesis, CMC determination and molecular modelling studies". XXII National Meeting on Medicinal Chemistry, Roma, 111 (2013).
27. G. Marcelli, A. Carotti, B. Natalini, M. Marinozzi, "Environmentally friendly, sequential, one-pot synthesis of N-aryl-5-aminopyrazoles from anilines" 13^o SAYCS, Riccione (RM), 51 (2013)

Didactic Activity (2013-2014)

Medicinal Chemistry and Toxicol. I for the Master Degree in Pharmacy