

Dott. Antimo Gioiello (English version)

Research Interest

General areas of interest are: *Synthetic and medicinal chemistry (natural products, steroids, heterocyclic compounds), Drug discovery, Flow chemistry, Microwave-assisted synthesis, Solid supported reagents and scavengers, Process/reaction optimisation, Design of Experiments, Robotics and automation, Reaction mechanisms.*

Focussing on a multi-disciplinary approach, my research activities are centred on the design and synthesis of biologically active molecules for nuclear receptors, GPCRs, and a variety of enzymes as therapeutic targets in CNS disorders, cancer, liver, and metabolic diseases. The compounds employed as investigative tools are the basis for exploring the pharmacological and therapeutic relevance of biological targets in collaboration with a wide range of national and international research groups. A primary aspect of my research is the development of synthetic methodologies which encompass the effective and efficient use of knowledge in investigating new reactions, the design and implementation of new processing methods for solving challenges associated with compound library building and large scale preparations. To these aims, advanced synthetic tools and enabling technologies such as flow apparatus, microwave reactors, solid supported reagents and scavengers are associated with automation to improve the speed, efficiency, safety and cost of specific chemical transformations.

Main Research Topics

- Bile acid-responsive nuclear and membrane receptors including FXR, TGR5, PXR, CAR and VDR;
- Steroid-activated nuclear receptors such as DAF-12;
- Steroid chemistry, characterization and analysis;
- Flow chemistry;
- Process and reaction optimization of bioactive compounds, key intermediates and building blocks by using design of experiments in both batch and flow conditions;
- Reaction, reactivity and mechanisms of diazo compounds.

Key Collaborations

- Intercept Pharmaceuticals, New York (USA)
- Servier, Paris (France)

- Department of Chemistry, Durham University, Durham (UK)
- Institute for Applied Synthetic Chemistry, Vienna University of Technology, Vienna (Austria)
- Department für Pharmazeutische Chemie, Universität Wien, Vienna (Austria)
- Faculty of Pharmacy, Gazi University, Gazi (Turkey)
- Italian Institute of Technology, Genova (Italy)
- Dipartimento di Chimica 'G. Ciamician', University of Bologna, Bologna (Italy)
- Dipartimento di Farmacia, University of Parma, Parma (Italy)
- Dipartimento di Farmacia, University of Naples Federico II, Napoli (Italy)

Invited Lectures

1. **Gioiello, A.;** Macchiarulo, A.; Guerrieri, E.; Carotti, A.; Rizzo, G.; Adorini, L.; Pellicciari, R. "New potent and selective FXR agonists: design, synthesis and modeling of norcholanylamine derivatives." Nuove Prospettive in Chimica Farmaceutica (IV Meeting). S. Margherita di Pula (Italy), May 6-7, **2010**.
2. **Gioiello, A.** "Novel explorations with bile acids. Case studies in organic and medicinal chemistry." X Laboratorio di Metodologie Sintetiche in Chimica Farmaceutica. Siena (Italy), February 13-17, **2011**.
3. **Gioiello, A.;** Macchiarulo, A.; Sabbatini, P.; Venturoni, F.; Nuti, R.; Rizzo, G.; Adorini, L.; Roda, A.; Pellicciari R. "Avicholic acid: a primary bile acid from birds on the route to potent and selective TGR5 ligands." XXIV Congresso Nazionale della Società Chimica Italiana. Lecce (Italy), September 11-16, **2011**.
4. **Gioiello, A.;** Macchiarulo, A.; Pellicciari, R. "Bile Acid Derivatives: An Emerging Class of Compounds in Inflammation and Metabolic Disorders." XXII Congresso Nazionale della Chimica Farmaceutica della Società Chimica Italiana (XXII National Meeting on Medicinal Chemistry). Roma (Italy), September 10-13, **2013**.

Recent Publications

1. **Gioiello, A.;** Venturoni, F.; Natalini, B.; Pellicciari, R. "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.
2. Natalini, B.; Sardella, R.; Camaioni, E.; Macchiarulo, A.; **Gioiello, A.;** Carbone, G.; Pellicciari, R. "Derived Chromatographic Indices as Effective Tools to Study the Self-Aggregation Process of Bile Acids." *J. Pharm. Biol. Anal.* **2009**, *50*, 613-621.

3. Natalini, B.; Sardella, R.; **Gioiello, A.**; Carbone, G.; Dawgul, M.; Pellicciari, R. "Side-chain Modified Bile Acids: Chromatographic Separation of 23-Methyl Epimers." *J. Sep. Sci.* **2009**, *32*, 2022-2033.
4. Thomas, C.; **Gioiello, A.**; Noriega, L.; Strehle, A.; Oury, J.; Rizzo, G.; Macchiarulo, A.; Yamamoto, H.; Matak, C.; Pruzanski, M.; Pellicciari, R.; Auwerx, J.; Schhons, K. "TGR5-Mediated Bile Acid Sensing Controls Glucose Homeostasis." *Cell Metab.* **2009**, *10*, 167-177.
5. **Gioiello, A.**; Khamidullina, A.; Fulco, M. C.; Venturoni, F.; Zlotsky, S.; Pellicciari, R. "New One-pot Synthesis of Pyrazole-5-carboxylates by 1,3-Dipole Cycloadditions of Ethyl Diazoacetate with α -methylene Carbonyl Compounds." *Tetrahedron Lett.* **2009**, *50*, 5978-5980.
6. Pellicciari, R.; **Gioiello, A.**; Macchiarulo, A.; Thomas, C.; Rosatelli, E.; Natalini, B.; Sardella, R.; Pruzanski, M.; Roda, A.; Pastorini, E.; Schoonjans, K.; Auwerx, J. "Discovery of 6 α -Ethyl-23(S)-methyl-cholic Acid (S-EMCA, INT-777) as a Potent and Selective Agonist for the TGR5 Receptor, a Novel Target for Diabesity." *J. Med. Chem.* **2009**, *52*, 7958-7961.
7. Marinella, R.; Natalini, B.; Andrisano, V.; Seraglia, R. **Gioiello, A.**; Pellicciari, R. "Thermal and Catalytic Reactions of Ethyl Diazopyruvate with [60]Fullerene." *Tetrahedron* **2010**, *66*, 7329-7332.
8. **Gioiello, A.**; Sabbatini, P.; Rosatelli, E.; Macchiarulo, A.; Pellicciari, R. "Divergent and Stereoselective Synthesis of Dafachronic Acids." *Tetrahedron* **2011**, *67*, 1924-1929.
9. **Gioiello, A.**; Macchiarulo, A.; Carotti, A.; Filipponi, P.; Costantino, G.; Rizzo, G.; Adorini, L.; Pellicciari, R. "Extending SAR of bile acids as FXR ligands: Discovery of 23-N-(carbocinnamyloxy)-3 α ,7 α -dihydroxy-6 α -ethyl-24-nor-5 β -cholan-23-amine." *Biorg. Med. Chem.* **2011**, *19*, 2650-2658.
10. Pellicciari, R.; Camaioni, E.; Gilbert, A. M.; Macchiarulo, A.; Bikker, J. A.; Shah, F.; Bard, J.; Costantino, G.; **Gioiello, A.**; Robertson, G. M.; Sabbatini, P.; Venturoni, F.; Liscio, P.; Carotti, A.; Bellocchi, Cozzi, A.; Wood, A.; Gonzales, C.; Zaleska, M. M.; Ellingboe, J. W.; Moroni, F. "Discovery and characterization of novel potent PARP-1 inhibitors endowed with neuroprotective properties: From TIQ-A to HYDAMTIQ" *Med. Chem. Comm.*, **2011**, *2*, 559-565.
11. Natalini, B.; Sardella, S.; **Gioiello, A.**; Rosatelli, E.; Ianni, F.; Camaioni, E.; Pellicciari, R. "Fast chromatographic determination of the bile salt critical micellar concentration." *Anal. Bioanal. Chem.* **2011**, *401*, 267-274.
12. **Gioiello, A.**; Venturoni, F.; Marinozzi, M.; Natalini, B.; Pellicciari, R. "Exploring the Synthetic Versatility of the Lewis Acid Induced Decomposition Reaction of r-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.

13. Pols, T. W. H.; Nomura, M.; Harach, T.; Lo Sasso, G.; Oosterveer, M. H.; Thomas, C.; Rizzo, G.; **Gioiello, A.**; Adorini, L.; Pellicciari, R.; Auwerx, J.; Schoonjans, K. "TGR5 Activation Inhibits Atherosclerosis by Reducing Macrophage Inflammation and Lipid Loading" *Cell Metab.* **2011**, *14*, 747-757.
14. **Gioiello, A.**; Sardella, R.; Rosatelli, E.; Sadeghpour, B. M.; Natalini, B.; Pellicciari, R. "Novel Stereoselective Synthesis and Chromatographic Evaluation of E-Guggulsterone" *Steroids* **2012**, *77*, 250-254.
15. Venturoni, F.; **Gioiello, A.***; Sardella, R.; Natalini, B.; Pellicciari, R. "Continuous Flow Synthesis and Scale-up of Glycine- and Taurine-Conjugated Bile Salts" *Org. Biomol. Chem.* **2012**, *10*, 4109-4115.
16. Pellicciari, R.; **Gioiello, A.**; Sabbatini, P.; Venturoni, F.; Nuti, R.; Colliva, C.; Rizzo, G.; Adorini, L.; Pruzanski, M.; Roda, A.; Macchiarulo, A. "Avicholic Acid: a Lead Compound from Birds on the Route to Potent and Selective TGR5 Modulators" *ACS Med. Chem. Lett.* **2012**, *3*, 273-277.
17. Macchiarulo, A.; **Gioiello, A.**; Pellicciari, R. "TGR5 Agonists in Development" Chapter 10 in *New Therapeutic Strategies for Type 2 Diabetes*; Editor: Rob M Jones. RSC Publishing, **2012**, 270-305.
18. Sardella, R.; **Gioiello, A.**; Ianni, F.; Venturoni, F.; Natalini, B. "HPLC/ELSD analysis of amidated bile acids: an Effective and Rapid Way to Assist Flow Chemistry Processes" *Talanta*, **2012**, *100*, 364-371.
19. **Gioiello, A.***; Rosatelli, E.; Nuti, R.; Macchiarulo, A.; Pellicciari, R. "Patented TGR5 Modulators: a Review (2006- present)" *Expert Opin. Ther. Patents* **2012**, *22*, 1399-1414.
20. Macchiarulo, A.; Carotti, A.; Cellanetti, M.; Sardella, R.; **Gioiello, A.** "Navigations of Chemical Space to Further the Understanding of Polypharmacology in Human Nuclear Receptors" *Med. Chem. Comm.* **2013**, *4*, 216-227.
21. Sabbatini, P.; Filipponi, P.; Sardella, R.; Natalini, B.; Nuti, R.; Macchiarulo, A.; Pellicciari, R.; **Gioiello, A.*** "Synthesis and Quantitative Structure-Property Relationships of Side Chain-Modified Hyodeoxycholic Acid Derivatives" *Molecules* **2013**, *18*, 10497-10513.
22. Russo, S.; Incerti, M.; Tognolini, M.; Castelli, R.; Pala, D.; Iftiin, H.-M.; Giorgio, C.; De Franco, F.; **Gioiello, A.**; Vicini, P.; Barocelli, E.; Rivara, S.; Mor, M.; Lodola, A. "Synthesis and Structure-Activity Relationships of Amino Acid Conjugates of Cholanolic Acid as Antagonists of the EphA2 Receptor" *Molecules* **2013**, *18*, 13043-13060.
23. **Gioiello, A.***; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R. "Building a Sulfonamide Library by Eco-Friendly Flow Synthesis" *ACS Comb. Sci.* **2013**, *15*, 235-239.

24. Macchiarulo, A.; **Gioiello, A.**; Thomas, C.; Pols, T. W. H.; Nuti, R.; Ferrari, C.; Giacchè, N.; De Franco, F.; Pruzanski, M.; Auwerx, J.; Schoonjans, K.; Pellicciari, R. "Probing the Binding Site of Bile Acids in TGR5" *ACS Med. Chem. Lett.* **2013**, 4, 1158-1162.

Communications to Congresses

1. Natalini, B.; Sardella, R.; **Gioiello, A.**; Carbone, G.; Pellicciari, R. "Side-chain modified bile acids: chromatographic evaluation of the epimer separation". Nuove Prospettive in Chimica Farmaceutica (III Meeting). Castelvechio Pascoli (Lucca, Italy), February 13-14, **2009**.
2. Pellicciari, R.; **Gioiello, A.**; Macchiarulo, A.; Thomas, C.; Rosatelli, E.; Schoonjans, K.; Adorini, L.; Pruzanski, M.; Auwerx, J. "Discovery of selective TGR5 modulators and their use in unraveling molecular features of bile acid recognition site". Joint EASL-AASLD Monothematic Conference: Nuclear Receptors and Liver Disease. Vienna (Austria), February 27-Marzo 1, **2009**.
3. Pellicciari, R., Macchiarulo, A., **Gioiello, A.**, Rosatelli, E., Thomas, C., Auwerx, J. "Targeting genomic (FXR) and nongenomic (TGR5) bile acids receptor pathways for metabolic disorders: discovery, S.A.R. and molecular modeling of potent and selective bile acids derivatives". 237th ACS National Meeting, Division of Medicinal Chemistry. Salt Lake City (USA), March 22-26, **2009**.
4. Sabbatini, P.; **Gioiello, A.**; Khamidullina, A.; Pellicciari, R. "A new divergent synthesis of dafachronic acids from bile acids". Hungarian-Austrian-Czec-German-Greek-Italian,-Polish-Slovak-Slovenian Joint Meeting on Medicinal Chemistry. Budapest (Hungary), June 24-27, **2009**.
5. Rosatelli, E.; **Gioiello, A.**; Macchiarulo, A.; Thomas, C.; Rizzo, G.; Adorini, L.; Auwerx, J.; Pellicciari, R. "Novel body modified bile acid derivatives as TGR5 modulators". Hungarian-Austrian-Czec-German-Greek-Italian,-Polish-Slovak-Slovenian Joint Meeting on Medicinal Chemistry. Budapest (Ungheria), June 24-27, **2009**.
6. **Gioiello, A.**; Venturoni, F.; Khamidullina, A.; Natalini, B.; Pellicciari, R. "Exploring the reactions of ethyl diazoacetate: new approaches to biologically active compounds". XXIII Congresso Nazionale della Società Chimica Italiana. Sorrento (Italy), July 5-10, **2009**.
7. Venturoni, F.; **Gioiello, A.**; Khamidullina, A.; Marinozzi, M.; Pellicciari, R. "On route to biologically active compounds: BF₃·Et₂O induced decomposition of α -diazo- β -hydroxy- β -aryl ester in acetonitrile". III International Symposium on Advances in Synthetic and Medicinal Chemistry. Kiev (Ukraine), August 23-27, **2009**.

8. **Gioiello, A.**; Venturoni, F.; Marinozzi, M.; Pellicciari, R. "Lewis acid-promoted decomposition of α -dialdo- β -hydroxy esters as a wealthy source of useful synthetic intermediates. Novel explorations with isatin". 239th National Meeting & Exposition – American Chemical Society (ACS). San Francisco (CA, USA), March 21-25, **2010**.
9. Pellicciari, R.; Macchiarulo, A.; **Gioiello, A.**; Thomas, C.; Rosatelli, E.; Schoonjans, K.; Auwerx, J. "Targeting TGR5 in diabetes: focus on S-EMCA (INT-777) a potent and selective bile acid mimetic agonist". 239th National Meeting & Exposition – American Chemical Society (ACS). San Francisco (CA, USA), March 21-25, **2010**.
10. Sabbatini, P., **Gioiello, A.**, Macchiarulo, A., Rosatelli, E., Rizzo, G., Adorini, L., Thomas, C., Auwerx, J., Pellicciari, R. "Sulfonate bile acid derivatives as potent and selective modulators of TGR5, a new target for diabetes". XXVIII Camerino-Cyprus-Noordwijkerhout symposium - Trekking through receptor chemistry. Camerino (Italy), May 16-20, **2010**.
11. Venturoni, F.; **Gioiello, A.**; Marinozzi, M.; Pellicciari, R. "On the route to biologically active heterocycles-containing compounds: Novel explorations with cyclic α -dialdo- β -hydroxy ketones". XXI International Symposium on Medicinal Chemistry (EFMC-ISMC 2010). Brussels (Belgium), September 5-9, **2010**.
12. Natalini, B., Sardella, R., **Gioiello, A.**, Rosatelli, E., Nuti, R., Camaioni, E., Macchiarulo, A., Pellicciari, R. "Chromatographic hydrophobicity index: a highthroughput tool to estimate the critical micellar concentration of bile acids". XX Meeting on Medicinal Chemistry. Abano Terme (Padova, Italy), September 12-16, **2010**.
13. Natalini, B.; Ianni, F.; Sardella, R.; **Gioiello, A.**; Sabbatini, P.; Filipponi, P.; Pellicciari, R. "Chromatographic evaluation of the 25(R,S)-methyl-bishomo-hyodeoxycholic acid epimers". XIX Convegno Interregionale (TUMA 2010). Ancona (Italy), September 30 –October 1, **2010**.
14. **Gioiello, A.**; Macchiarulo, A.; Guerrieri, E.; Carotti, A.; Rizzo, G.; Adorini, L.; Pellicciari, R. "New potent and selective FXR agonists: design, synthesis and modeling of norcholanylamine derivatives". Nuove Prospettive in Chimica Farmaceutica (IV Meeting). S. Margherita di Pula (Italy), May 6-7, **2010**.
15. Guerrieri, E.; **Gioiello, A.**; Macchiarulo, A.; Carotti, A.; Rizzo, G.; Adorini, L.; Pellicciari, R. "Design, synthesis, molecular modeling and biological activity of chenodeoxycholic acid carbamate derivatives as potent and selective FXR agonists". X Sigma-Aldrich Young Chemists Symposium (SAYCS). Pesaro (Italy), October 18-20, **2010**.

16. Pellicciari, R.; Macchiarulo, A.; **Gioiello, A.**; Thomas, C.; Rosatelli, E.; Filipponi, P.; Carotti, A.; Nuti, R.; Shapiro, D.; Rizzo, G.; Roda, A.; Adorini, L.; Pruzanski, M.; Schoonjans, K.; Auwerx, J. "Deconstructing bile acid signaling pathways". 241st ACS National Meeting & Exposition. Anaheim (CA, USA), March 27-31, **2011**.
17. Pellicciari, R.; **Gioiello, A.**; Camaioni, E.; Macchiarulo, A.; Gilbert, A.; Bikker, J.; Costantino, G.; Robertson, G. M.; Venturoni, F.; Carotti, A.; Bellocchi, D.; Cozzi, A.; Wood, A.; Gonzales, C.; Ellingboe, J.; Moroni, F. "HYDAMTIQ: A New, Potent PARP-1 Inhibitor with Neuroprotective Properties". 241st ACS National Meeting & Exposition. Anaheim (CA, USA), March 27-31, **2011**.
18. Rosatelli, E.; **Gioiello, A.**; Macchiarulo, A.; Venturoni, F.; Giacchè, N.; Nuti, R.; Thomas, C.; Auwerx, J.; Pellicciari, R. "Synthesis, molecular modelling and activity of C23-substituted cholic acid derivatives as TGR5 modulators". Convegno Interregionale TUMA. Perugia (Italy), June 31-July 1, **2011**.
19. **Gioiello, A.**; Macchiarulo, A.; Sabbatini, P.; Venturoni, F.; Nuti, R.; Rizzo G.; Adorini L.; Roda, A.; Pellicciari, R. "Avicholic Acid: A Primary Bile Acid from Birds on the Route to Potent and Selective TGR5 Ligands". XXIV Congresso Nazionale della Società Chimica Italiana. Lecce (Italy), September 11-16, **2011**.
20. Carotti, A.; **Gioiello, A.**; Macchiarulo, A.; Marinozzi, M.; Liscio, P.; Sabbatini, P.; Rizzo G.; Adorini L.; Pellicciari, R. "Targeting the FXR Nuclear Receptor through a Virtual Screening Approach". XXIV Congresso Nazionale della Società Chimica Italiana. Lecce (Italy), September 11-16, **2011**.
21. Natalini, B.; Sardella, R.; **Gioiello, A.**; Rosatelli, E.; Ianni, F.; Camaioni, E.; Pellicciari, R. "Fast Chromatographic Determination of the Unconjugated Bile Salt Critical Micellar Concentration". XIV International Meeting on Recent Development in Pharmaceutical Analysis. Pavia (Italy), September 21-24, **2011**.
22. Sabbatini, P.; Camaioni, E.; Bellocchi, D.; Costantino, G.; Moroni, F.; **Gioiello, A.**; Pellicciari, R. "Design, Synthesis and S.A.R. Studies of Isoquinolin-1(2H)-ones as Selective PARP-2 Inhibitors". Nuove Prospettive in Chimica Farmaceutica (NPCF6). Riccione (Italy), April 15-17, **2012**.
23. Natalini, B.; Ianni, F.; Sardella, R.; Lisanti, A.; Venturoni, F.; **Gioiello, A.**; Pellicciari, R. "Analisi HPLC/ELSD di Acidi Biliari Amidati: un Approccio Efficace per Assistere Processi Sintetici a Flusso Continuo". XXXI Congresso Interregionale TUMA 2012. Francavilla al Mare (Italy), June 18-20, **2012**.
24. **Gioiello, A.**; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R. "Eco-sustainable Synthesis of Bioactive Sulfonamides: from Batch to Flow Approach". XXI National Meeting on Medicinal Chemistry. Palermo (Italy), July 17-20, **2012**.

25. **Gioiello, A.**; Sardella, R.; Rosatelli, E.; Natalini, B.; Pellicciari, R. "Novel stereoselective synthesis and chromatographic evaluation of guggulsterones, the bioactive constituents of the hypolipidemic guggulipid". XXI National Meeting on Medicinal Chemistry. Palermo (Italy), July 17-20, **2012**.
26. Macchiarulo, A.; Aguilera, L. S.; Nuti, R.; Carotti, A.; **Gioiello, A.**; Entrena Gaudix, A.; Pellicciari, R. "Molecular Docking and High-Throughput Molecular Dynamics to Detect and Analyze the Binding Site Properties of DAF-12 Orthologs in Parasitic Nematodes". XIX EuroQSAR Symposium. Vienna (Austria), August 26-30, **2012**.
27. **Gioiello, A.**; Sabbatini, P.; Ogawa, A.; Sardella, R.; Passeri, D.; Natalini, B.; Robertson, G. M.; Macchiarulo, A.; Sommer, R.; Pellicciari, R. "Unraveling the Molecular Basis for DAF -12 Activation: Diastereoselective Synthesis and SAR Studies of Dafachronic Acid Derivatives". EFMC-ISMC, XXII International Symposium on Medicinal Chemistry. Berlino (Germany), September 2-6, **2012**.
28. Mangiavacchi, F.; Di Schino, L.; Filipponi, P.; **Gioiello, A.**; Santi, S. "Translating Batch Selenium-Catalyzed Cyclizations into Flow Mode". Cardiff (UK), **2013**.
29. Gioiello, A.; Cerra, B.; Setchell, K. D.; Pellicciari, R. "Synthesis of 3 β ,7 α -Dihydroxy- Δ^5 -cholenoic Acid Derivatives: 'Atypical' Bile Acid Metabolites and Useful Biomarkers to Detect 3 β -HSDH Deficiency". VI Nuove Prospettive in Chimica Farmaceutica (NPCF 6). Rimini (Italy), April 15-17, **2013**.
30. Mostarda, S.; Filipponi, P.; Rosatelli, E.; Venturoni, F.; Pellicciari, R.; Gioiello, A. "On the Route to Flow Glucuronidation: Design of Experiments and Koenigs-Knorr Reaction Optimization". XXII Congresso Nazionale della Chimica Farmaceutica della Società Chimica Italiana (XXII National Meeting on Medicinal Chemistry). Roma (Italia), September 10-13, **2013**.

Teaching Activity A.A. 2013-14

Laboratory of extractive and synthetic preparation of drugs (9 CFU, IV° CTF).

Support activities for teaching course in medicinal chemistry (9 CGU, III° CTF).