Année de publication : 2022

Zucolotto Cocca L.H., Pelosi A., Sciuti L.F., M. G. Abegão L., Kamada K., Piguel S., Renato Mendonça C., De Boni L. (2022 Feb 15)

Two-photon brightness of highly fluorescent imidazopyridine derivatives: Two-photon and ultrafast transient absorption studies

Journal of Molecular Liquids : 348 : 118379 : DOI : 10.1016/j.molliq.2021.118379

Résumé

Imidazopyridine derivatives are unnatural purines isosteres and have been idealized and synthesized in the last decades, given their great applicability in several science areas. For instance, they may present potential to be used as fluorescent bioprobes on DNA or RNA spectroscopic studies. Furthermore, their synthesis can be performed to incorporate different peripheral structures in the central imidazopyridine scaffold, modeling and increasing the optical properties. Aiming applications as fluorescent probes as molecular liquids at the therapeutic window, thanks to the considerable emissive characteristics of this class of compound, optical spectroscopic studies considering nonlinear optical properties were performed on two distinct classes of N3-MEM-3H-imidazo[4,5-b]pyridine derivatives. The presented results exposed exceptionally high fluorescence quantum yields and two-photon absorption effects at the therapeutic window. The two-photon absorption spectra revealed a particular contribution of a higher excited state in some imidazopyridine derivatives containing naphthalene group. The excited state was confirmed by femtosecond time resolved spectroscopy. The obtained two-photon brightness shows substantial values for all compounds, with the potential to be used as fluorescent probes induced by two-photon excitation.

Clelia Mathieu, Quentin Chamayou, Thi Thanh Hyen Luong, Delphine Naud, Florence Mahuteau-Betzer, Mouad Alami, Elias Fattal, Samir Messaoudi, Juliette Vergnaud-Gauduchon (2022 Feb 5)

Synthesis and antiproliferative activity of 6BrCaQ-TPP conjugates for targeting the mitochondrial heat shock protein TRAP1.

European journal of medicinal chemistry : 229 : 114052 : DOI : 10.1016/j.ejmech.2021.114052

Résumé

A series of 6BrCaQ-C-TPP conjugates 3a-f and 5 was designed and synthesized as a novel class of TRAP1 inhibitors. Compound 3a displayed an excellent anti-proliferative activity with mean GI values at a nanomolar level in a diverse set of human cancer cells (GI = 0.008-0.30 μM) including MDA-MB231, HT-29, HCT-116, K562, and PC-3 cancer cell lines. Moreover, the best lead compound 6BrCaQ-C-TPP induces a significant mitochondrial membrane disturbance combined to a regulation of HSP and partner protein levels as a first evidence that his mechanism of action involves the TRAP-1 mitochondrial Hsp90 machinery.

Sounderya Nagarajan, Florent Poyer, Laura Fourmois, Delphine Naud-Martin, Kadda Medjoubi, Andrea Somogyi, Gabrielle Schanne, Lucas Henry, Nicolas Delsuc, Clotilde Policar, Helene C Bertrand, Florence Mahuteau-Betzer (2022 Jan 25)

Cellular detection of a mitochondria targeted brominated vinyl triphenylamine optical probe (TP-Br) by X-ray fluorescence microscopy.

Chemistry (Weinheim an der Bergstrasse, Germany) : Accepted Article : DOI : 10.1002/chem.202104424

Résumé

Triphenylamine (TP) derivatives such as two-branch cationic vinylbenzimidazolium triphenylamine TP-2Bzim are promising turn-on fluorescent probes suitable for two-photon imaging, labelling mitochondria in live cells. Here, we designed two TP-2Bzim derivatives as bimodal probes suitable for X-ray fluorescence imaging. The conjugation of the TP core with a rhenium tricarbonyl moiety in the TP-RePyta probe altered the localisation in live cells from mitochondria to lysosomes. The introduction of bromine on the TP core generated the TP-Br probe retaining good photophysical properties and mitochondria labeling in live cells. The influence of calcium channels in the uptake of TP-Br was studied. Synchrotron Radiation X-ray Fluorescence (SXRF) imaging of bromine enabled the detection of TP-Br and suggested a negligible presence of the probe in an unbound state in the incubated cells, a crucial point in the development of these probes. This study paves the way towards the development of TP probes as specific organelle stainers suitable for SXRF imaging.

Florence Mahuteau-Betzer, Marie Auvray, Frédéric Bolze, Delphine Naud-Martin, Matthieu Poulain, Margaux Bossuat, Gilles Clavier (2022 Jan 21)

On the road for more efficient biocompatible two-photon excitable fluorophores.

Chemistry (Weinheim an der Bergstrasse, Germany) : Accepted Article : DOI : 10.1002/chem.202104378

Résumé

Red to NIR absorption and emission wavelengths are key requirements for intravital bioimaging. One of the way to reach such excitation wavelengths is to use two-photon excitation. Unfortunately, there is still a lack of two-photon excitable fluorophores that are both efficient and biocompatible. Thus, we design a series of biocompatible quadrupolar dyes in order to study their ability to be used for live-cell imaging, and in particular for two-photon microscopy. Hence, we report the synthesis of 5 probes based on different donor cores (phenoxazine, acridane, phenazasiline and phenothiazine) and the study of their linear and non-linear photophysical properties. TD-DFT calculations were performed and were able to highlight the structure-property relationship of this series. All these studies highlight the great potential of three of these biocompatible dyes for two-photon microscopy, as they both exhibit high two-photon cross-sections (up to 3 650 GM) and emit orange to red light. This potential was confirmed through live-cell two-photon microscopy experiments, leading to images with very high brightness and contrast.

Gatin A., Duchambon P., Rest G.v.d., Billault I., Sicard-Roselli C. (2022 Jan 21)

Protein Dimerization via Tyr Residues: Highlight of a Slow Process with Co-Existence of Numerous Intermediates and Final Products

International Journal of Molecular Sciences : 23 : 1174 : DOI : 10.3390/ijms23031174

Résumé

Protein dimerization via tyrosine residues is a crucial process in response to an oxidative attack, which has been identified in many ageing-related pathologies. Recently, it has been found that for isolated tyrosine amino acid, dimerization occurs through three types of tyrosine–tyrosine crosslinks and leads to at least four final products. Herein, considering two protected tyrosine residues, tyrosine-containing peptides and finally proteins, we investigate the dimerization behavior of tyrosine when embedded in a peptidic sequence. After azide radical oxidation and by combining UPLC-MS and H/D exchange analyzes, we were able to evidence: (i) the slow kinetics of Michael Addition Dimers (MAD) formation, i.e., more than 48 h; (ii) the co-existence of intermediates and final cyclized dimer products; and (iii) the probable involvement of amide functions to achieve Michael additions even in proteins. This raises the question of the possible in vivo existence of both intermediates and final entities as well as their toxicity and the potential consequences on protein structure and/or function.

Pelosi A.G., Zucolotto Cocca L.H., Abegão L.M., Sciuti L.F., Piguel S., De Boni L., Mendonça C.R. (2022 Jan 1)

Influence of electron-withdrawing groups in two-photon absorption of imidazopyridines derivatives

Dyes and Pigments : 198 : 109972 : DOI : 10.1016/j.dyepig.2021.109972

Résumé

This work investigates the influence of different electron-withdrawing groups (Cl, Br, fluorobenzonitrile), on the two-photon absorption cross-section of six imidazo[4,5-b]pyridine derivatives. The two-photon absorption cross-section spectra were obtained by ultra-fast Z-scan technique from 470 nm up to 700 nm. The Sum-Over-States approach was applied to model the two-photon absorption spectra, using a three-level energy system. Photophysical properties, such as transition dipole moment, the difference of permanent dipole moments, and anisotropy coefficient were determined through the analysis of one-photon absorption spectra, solvatochromism, and fluorescence anisotropy, respectively. Besides, the excited state absorption spectra were measured through ultra-fast transient absorption, allowing the excited state lifetime and spectral position determination. Two-photon absorption cross-sections of about 160 GM were observed when two electron-withdrawing groups are linked to the imidazo[4,5-b]pyridine core, elucidating a path to achieve high optical nonlinearities in imidazopyridine derivatives. Furthermore, a increase in the two-photon cross-section was observed when chloride is linked at the C-6 position (90 GM) instead of the C-5 position (50 GM), which is related to the proximity of a higher excited state.

Année de publication : 2021

Nils-Jørgen Knudsen Dal, Martin Speth, Kerstin Johann, Matthias Barz, Claire Beauvineau, Jens Wohlmann, Federico Fenaroli, Brigitte Gicquel, Gareth Griffiths, Noelia Alonso-Rodriguez (2021 Nov 29)

The zebrafish embryo as an in vivo model for screening nanoparticle-formulated lipophilic anti-tuberculosis compounds.

Disease models & mechanisms : Online ahead of print : DOI : 10.1242/dmm.049147

Résumé

With the increasing emergence of drug-resistant Mycobacterium tuberculosis strains, new and effective antibiotics against tuberculosis (TB) are urgently needed. However, the high frequency of poorly water-soluble compounds among hits in high-throughput drug screening (HTS) campaigns is a major obstacle in drug discovery. Moreover, in vivo testing using conventional animal TB models such as mice is time-consuming and costly, and represents a major bottleneck in lead compound discovery and development. Here, we report the use of the zebrafish embryo TB model, to evaluate the in vivo toxicity and efficacy of five poorly water-soluble nitronaphthofuran derivatives, which were recently identified to possess anti-tuberculosis activity in vitro. To aid solubilization compounds were formulated in biocompatible polymeric micelles (PM). Three of the five PM-formulated nitronaphthofuran derivatives showed low toxicity in vivo, significantly reduced bacterial burden and improved survival in infected zebrafish embryos. We propose the zebrafish embryo TB-model as a quick and sensitive tool for evaluating in vivo toxicity and efficacy of new anti-TB compounds during early stages of drug development. Thus, this model is well suited to pinpoint promising compounds for further development.

Piguel S., Le Bescont J., Mouawad L., Boddaert T., Bombard S. (2021 Nov 1)

Photoactivatable small-molecule inhibitors for light-controlled TAM kinase activity

ChemPhotoChem : 5 : 989-994 : DOI : 10.1002/cptc.202100131

Résumé

The TAM kinase family arises as a promising therapeutical target for cancer therapy, auto-immune, and viral diseases. In this study, we report the first photoactivatable caged inhibitors of Tyro3 and Mer. This strategy enables spatial and temporal control of the biological activity of the inhibitor upon irradiation with UV light. We describe the design, the synthesis, the photocleavage properties, and the inhibitory activity of four Tyro3 and Mer photoactivatable small molecules. The proof of concept on the TAM kinase family was achieved in vitro , since irradiation by UV light restored the full inhibitory activity of two prodrugs.

Laura Fourmois, Florent Poyer, Aude Sourdon, Delphine Naud-Martin, Sounderya Nagarajan, Rahima Chennoufi, Eric Deprez, Marie-Paule Teulade-Fichou, Florence Mahuteau-Betzer (2021 Jul 15)

Modulation of cellular fate of vinyl triarylamines through structural fine tuning: to stay or not to stay in the mitochondria?

Chembiochem : a European journal of chemical biology : 22 : 2457-2467 : DOI : 10.1002/cbic.202100168

Résumé

Mitochondria is involved in many cellular pathways and dysfunctional mitochondria are linked to various diseases. Hence efforts have been driven to design mitochondria-targeted fluorophores for monitoring the mitochondria status. However, the factors that govern the mitochondria-targeted potential of dyes are not well-understood. In this context, we synthesized analogues of the TP-2Bzim probe belonging to the vinyltriphenylamine (TPA) class and already described for its capacity to bind nuclear DNA in fixed cells and mitochondria in live cells. These analogues (TP-1Bzim, TP n -2Bzim, TP 1+ -2Bzim, TN-2Bzim) differ by the cationic charge, the number of vinylbenzimidazolium branches and the nature of the triaryl core. Using microscopy, we demonstrated that the cationic derivatives accumulate in mitochondria but do not reach mtDNA. Under depolarisation of the mitochondrial membrane, TP-2Bzim and TP 1+ -2Bzim translocate to the nucleus in direct correlation with their strong DNA affinity. This reversible phenomenon emphasizes that these probes can be used to monitor ΔΨ m variations.

Marc Lavigne, Olivier Helynck, Pascal Rigolet, Rofia Boudria-Souilah, Mireille Nowakowski, Bruno Baron, Sébastien Brülé, Sylviane Hoos, Bertrand Raynal, Lionel Guittat, Claire Beauvineau, Stéphane Petres, Anton Granzhan, Jean Guillon, Geneviève Pratviel, Marie-Paule Teulade-Fichou, Patrick England, Jean-Louis Mergny, Hélène Munier-Lehmann (2021 Jul 7)

SARS-CoV-2 Nsp3 unique domain SUD interacts with guanine quadruplexes and G4-ligands inhibit this interaction.

Nucleic Acids Research : 49 : 7695–7712 : DOI : 10.1093/nar/gkab571

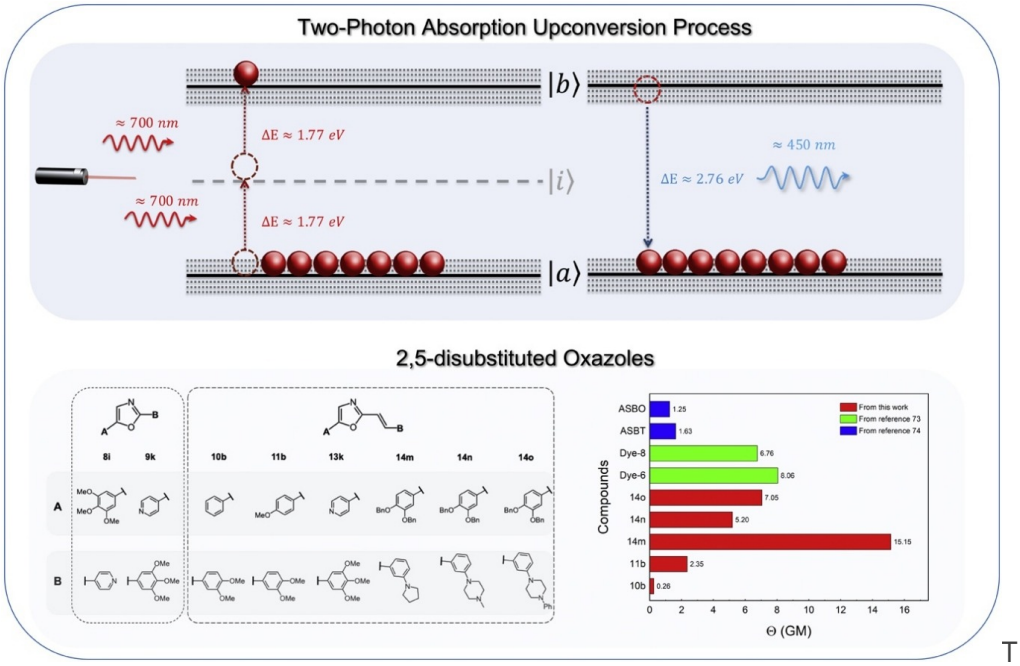
Résumé

The multidomain non-structural protein 3 (Nsp3) is the largest protein encoded by coronavirus (CoV) genomes and several regions of this protein are essential for viral replication. Of note, SARS-CoV Nsp3 contains a SARS-Unique Domain (SUD), which can bind Guanine-rich non-canonical nucleic acid structures called G-quadruplexes (G4) and is essential for SARS-CoV replication. We show herein that the SARS-CoV-2 Nsp3 protein also contains a SUD domain that interacts with G4s. Indeed, interactions between SUD proteins and both DNA and RNA G4s were evidenced by G4 pull-down, Surface Plasmon Resonance and Homogenous Time Resolved Fluorescence. These interactions can be disrupted by mutations that prevent oligonucleotides from folding into G4 structures and, interestingly, by molecules known as specific ligands of these G4s. Structural models for these interactions

are proposed and reveal significant differences with the crystallographic and modeled 3D structures of the SARS-CoV SUD-NM/G4 interaction. Altogether, our results pave the way for further studies on the role of SUD/G4 interactions during SARS-CoV-2 replication and the use of inhibitors of these interactions as potential antiviral compounds.

Abegão L.M., Santos F.A., Piguel S., Rodrigues J.J., Mendonça C.R., De Boni L. (2021 Apr 15)
The ability of 2,5-disubstituted oxazole dyes derivatives to generate two-photon upconversion photoluminescence and its brightness evaluation
Journal of Photochemistry and Photobiology A: Chemistry : 411 : 113214 : DOI : 10.1016/j.jphotochem.2021.113214

Résumé



The brightness study of emissive compounds is one of the fundamental spectroscopic characterizations. In this work, we assessed the brightness values of eight 2,5-disubstituted oxazole dyes derivatives by combining linear and nonlinear spectroscopic parameters. The range of the brightness values obtained is from 0.26 GM to 15.15 GM. The highest value belongs to compound 14 m, which, compared to previously investigated compounds of similar π-conjugation length, is at least two times higher. Brightness values were determined in the spectral region between 700 nm–720 nm, revealing this class of dyes' potential to be used as photoluminescence bioprobes excited by two-photons.

Sylvie Gory-Fauré, Rebecca Powell, Julie Jonckheere, Fabien Lanté, Eric Denarier, Leticia Peris, Chi Hung Nguyen, Alain Buisson, Laurence Lafanechère, Annie Andrieux (2021 Mar 12)

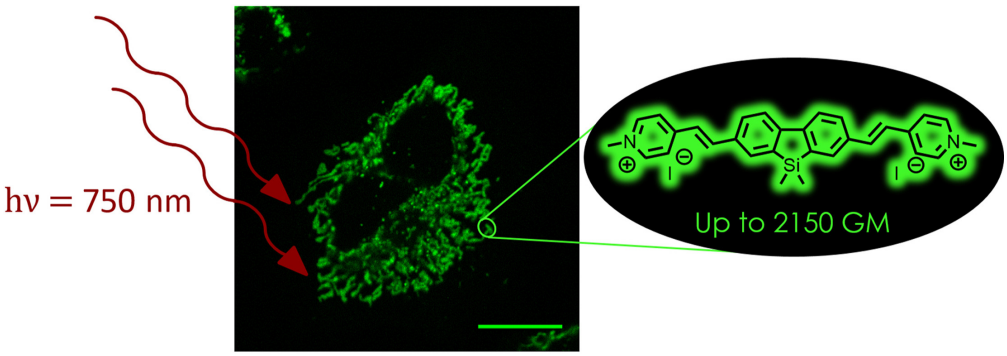
Pyr1-Mediated Pharmacological Inhibition of LIM Kinase Restores Synaptic Plasticity and Normal Behavior in a Mouse Model of Schizophrenia.
Frontiers in pharmacology : 12 : 627995 : DOI : 10.3389/fphar.2021.627995

Résumé

The search for effective treatments for neuropsychiatric disorders is ongoing, with progress being made as brain structure and neuronal function become clearer. The central roles played by microtubules (MT) and actin in synaptic transmission and plasticity suggest that the cytoskeleton and its modulators could be relevant targets for the development of new molecules to treat psychiatric diseases. In this context, LIM Kinase – which regulates both the actin and MT cytoskeleton especially in dendritic spines, the post-synaptic compartment of the synapse – might be a good target. In this study, we analyzed the consequences of blocking LIMK1 pharmacologically using Pyr1. We investigated synaptic plasticity defects and behavioral disorders in MAP6 KO mice, an animal model useful for the study of psychiatric disorders, particularly schizophrenia. Our results show that Pyr1 can modulate MT dynamics in neurons. In MAP6 KO mice, chronic LIMK inhibition by long-term treatment with Pyr1 can restore normal dendritic spine density and also improves long-term potentiation, both of which are altered in these mice. Pyr1 treatment improved synaptic plasticity, and also reduced social withdrawal and depressive/anxiety-like behavior in MAP6 KO mice. Overall, the results of this study validate the hypothesis that modulation of LIMK activity could represent a new therapeutic strategy for neuropsychiatric diseases.

Auvray M., Bolze F., Clavier G., Mahuteau-Betzer F. (2021 Mar 1)
Silafluorene as a promising core for cell-permeant, highly bright and two-photon excitable fluorescent probes for live-cell imaging
Dyes and Pigments : 187 : 109083 : DOI : 10.1016/j.dyepig.2020.109083

Résumé



In this study, we report the synthesis, linear and non-linear photophysical studies and live-cell imaging of two two-photon activatable probes based on a silafluorene core: SiFluo-V and SiFluo-L. Thanks to their quadrupolar (A-π-D-π-A) design, these probes exhibit respectively good to impressive two-photon cross-sections (from 210 GM to 2150 GM). TD-DFT

calculations support the experimental evidence that SiFluo-L displays far better two-photon absorption properties than SiFluo-V. Moreover, SiFluo-L possesses all requirements for bioimaging as it is water soluble, cell-permeant and presents a low cytotoxicity (IC80 ≥ 10 µM). It labels mitochondria in live-cell imaging at low laser power with high brightness, contrast and photostability. This study demonstrates that silafluorene is a promising core to develop new two-photon fluorophores for live-cell imaging.

Thomas Barbot, Veronica Beswick, Cédric Montigny, Éric Quiniou, Nadège Jamin and Liliane Mouawad (2021 Feb 4)

Deciphering the mechanism of inhibition of SERCA1a by sarcolipin using molecular simulations

Frontiers in Molecular Biosciences : 7 : 606254 : DOI : 10.3389/fmolb.2020.606254

Résumé

SERCA1a is an ATPase calcium pump that transports Ca2+ from the cytoplasm to the sarco/endoplasmic reticulum lumen. Sarcolipin (SLN), a transmembrane peptide, regulates the activity of SERCA1a by decreasing its Ca2+ transport rate, but its mechanism of action is still not well understood. To decipher this mechanism, we have performed normal mode analysis in the all-atom model, with the SERCA1a-SLN complex, or the isolated SERCA1a, embedded in an explicit membrane. The comparison of the results allowed us to provide an explanation at the atomic level for the action of SLN that is in good agreement with experimental observations. In our analyses, the presence of SLN locally perturbs the TM6 transmembrane helix and as a consequence modifies the position of D800, one of the key metal-chelating residues. Additionally, it reduces the flexibility of the gating residues, V304 and E309 in TM4, at the entrance of the Ca2+ binding sites, which would decrease the affinity for Ca2+. Unexpectedly, SLN has also an effect on the ATP binding site more than 35 Å away, due to the straightening of TM5, a long helix considered as the spine of the protein. The straightening of TM5 modifies the structure of the P-N linker that sits above it, and which comprises the 351DKTG354 conserved motif, resulting in an increase of the distance between ATP and the phosphorylation site. As a consequence, the turn-over rate could be affected. All this gives SERCA1a the propensity to go toward a Ca2+ low-affinity E2-like state in the presence of SLN and toward a Ca2+ high-affinity E1-like state in the absence of SLN. In addition to a general mechanism of inhibition of SERCA1a regulatory peptides, this study also provides an insight into the conformational transition between the E2 and E1 states.

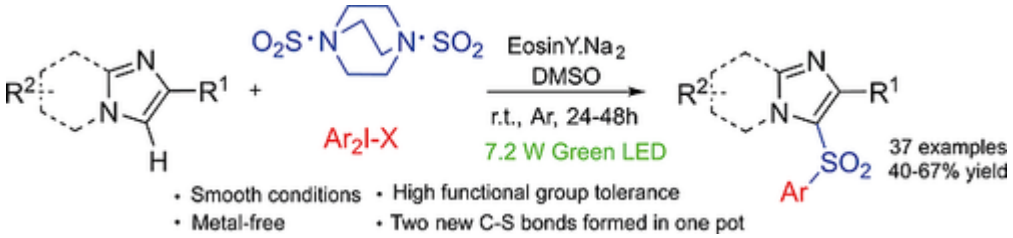
Année de publication : 2020

Breton-Patient C., Naud-Martin D., Mahuteau-Betzer F., Piguel S. (2020 Nov 15)

Three-component C-H bond sulfonylation of imidazoheterocycles via visible-light organophotoredox catalysis.

European Journal of Organic Chemistry : 2020 : 6653-6660 : DOI : 10.1002/ejoc.202001219

Résumé



The first entirely visible-light photoredox catalyzed sulfonylation of imidazoheterocycles has been developed. This transformation demonstrates an efficient C-H functionalization for the straightforward synthesis of novel C-3 sulfonylated imidazoheterocycles from various imidazopyridines and diaryliodonium salts with different electronic and steric properties and easy handled DABCO- bis (sulfur dioxide). The reaction proceeds in moderate to good yields under mild conditions at room temperature using the inexpensive organophotocatalyst EosinY.Na 2 and shows a high functional group tolerance (37 examples).