Molecular Docking Studies of Royleanone Diterpenoids from Plectranthus spp. as P-Glycoprotein Inhibitors

The development of multidrug resistance (MDR) is a major cause of failure in cancer chemotherapy. Several abietane diterpenes with antitumoral activities have been isolated from Plectranthus spp. such as 6,7-dehydroroyleanone (DHR, 1) and 7α-acetoxy-6β-hydroxyroyleanone (AHR, 2). Several royleanone derivatives were prepared through hemisynthesis from natural compounds 1 and 2 to achieve a small library of products with enhanced anti-P-glycoprotein activity. Nonetheless, some derivatives tend to be unstable. Therefore, to reason such lack of stability, the electron density based local reactivity descriptors condensed Fukui functions and dual descriptor were calculated for several derivatives of DHR. Additionally, molecular docking and molecular dynamics studies were performed on several other derivatives to clarify the molecular mechanisms by which they may exert their inhibitory effect in P-gp activity. The analysis on local reactivity descriptors was important to understand possible degradation pathways and to guide further synthetic approaches toward new royleanone derivatives. A molecular docking study suggested that the presence of aromatic moieties increases the binding affinity of royleanone derivatives toward P-gp. It further suggests that one royleanone benzoylated derivative may act as a noncompetitive efflux modulator when bound to the M-site. The future generation of novel royleanone derivatives will involve (i) a selective modification of position C-12 with chemical moieties smaller than unsubstituted benzoyl rings and (ii) the modification of the substitution pattern of the benzoyloxy moiety at position C-6.

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Contributors: Isca, V. M., Ferreira, R. J., Garcia, C., Monteiro, C. M., Dinic, J., Holmstedt, S., André, V., Pesic, M., Dos Santos, D. J., Candeias, N. R., Afonso, C. A., Rijo, P.
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A concise synthesis of carbasugars isolated from Streptomyces lincolnensis

(−)-Quinic acid was used as a starting material in the hemisynthesis of two epimeric carbasugars isolated from Streptomyces lincolnensis. Previous 10–12 steps syntheses for the carbasugars have been herein shortened to 4–6 steps by using quinic acid as a chiron, based on a regioselective reduction step, with stereoinversion of a tertiary center. Both C-5 epimers of (1R, 2R, 3R)-5-(hydroxymethyl)cyclohexane-1,2,3-triol were obtained in up to 76% overall yield.

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DOIs:

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Surface Stabilization and Dissolution Rate Improvement of Amorphous Compacts with Thin Polymer Coatings: Can We Have It All?

The distinction between surface and bulk crystallization of amorphous pharmaceuticals, as well as the importance of surface crystallization for pharmaceutical performance, is becoming increasingly evident. An emerging strategy in stabilizing the amorphous drug form is to utilize thin coatings at the surface. While the physical stability of systems coated with pharmaceutical polymers has recently been studied, the effect on dissolution performance as a function of storage time, as a further necessary step toward the success of these formulations, has not been previously studied. Furthermore, the effect of coating thickness has not been elucidated. This study investigated the effect of these polymer-coating parameters on the interplay between amorphous surface crystallization and drug dissolution for the first time. The study utilized simple tablet-like coated dosage forms, comprising a continuous amorphous drug core and thin polymer coating (hundreds of nanometers to a micrometer thick). Monitoring included analysis of both the solid-state of the model drug (with SEM, XRD, and ATR FTIR spectroscopy) and dissolution performance (and associated morphology and solid-state changes) after different storage times. Stabilization of the amorphous form (dependent on the coating thickness) and maintenance of early-stage intrinsic dissolution rates characteristic for the unaged amorphous drug were achieved. However, dissolution in the latter stages was likely inhibited by the presence of a polymer at the surface. Overall, this study introduced a versatile coated system for studying the dissolution of thin-coated amorphous dosage forms suitable for different drugs and coating agents. It demonstrated the importance of multiple factors that need to be taken into consideration when aiming to achieve both physical stability and improved release during the shelf life of amorphous formulations.

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Organisations: Materials Science and Environmental Engineering, Research group: Chemistry & Advanced Materials, University of Helsinki, University of Otago, Danmarks Tekniske Universitet, DTU Informatik
Contributors: Novakovic, D., Peltonen, L., Isomäki, A., Fraser-Miller, S. J., Nielsen, L. H., Laaksonen, T., Strachan, C. J.
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Synthetic Design of Asymmetric miRNA with an Engineered 3′ Overhang to Improve Strand Selection

We developed a novel miRNA design that significantly improves strand selection within the RISC complex by engineering the 3′ end by adding extra nucleotides. Addition of seven nucleotides at the 3′ ends of the miR or miR* strand resulted in a thermodynamic asymmetry at either of the two ends, which resulted in selective RISC recruitment, as demonstrated by a stem-loop PCR experiment. Such selective recruitment was also corroborated at the protein level by western blot analysis. To investigate the functional effect because of selective recruitment, we performed apoptosis and metastasis studies using human colon carcinoma cells (HCT116)and human osteosarcoma cells (MG63). These experiments indicated that

recruitment of the miR strand is responsible for inducing apoptosis and inhibiting the invasiveness of cancer cells. Recruitment of the miR* strand, on the other hand, had the opposite effect. To the best of our knowledge, our strand engineering strategy is the first report of improved strand selection of a desired miRNA strand by RISC without using any chemical modifications or mismatches. We believe that such structural modifications of miR34a could mitigate some of the off-target effects of miRNA therapy and would also allow a better understanding of sequence-specific gene regulation. Such a design could also be adapted to other miRNAs to enhance their therapeutic potential.

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Metabolic profiling of water-soluble compounds from the extracts of dark septate endophytic fungi (DSE) isolated from scots pine (Pinus sylvestris L.) seedlings using UPLC–orbitrap–MS
Endophytes are microorganisms living inside plant hosts and are known to be beneficial for the host plant vitality. In this study, we isolated three endophytic fungus species from the roots of Scots pine seedlings growing on Finnish drained peatland setting. The isolated fungi belonged to dark septate endophytes (DSE). The metabolic profiles of the hot water extracts of the fungi were investigated using Ultrahigh Performance Liquid Chromatography with Diode Array Detection and Electron Spray Ionization source Mass Spectrometry with Orbitrap analyzer (UPLC–DAD–ESI–MS–Orbitrap). Out of 318 metabolites, we were able to identify 220, of which a majority was amino acids and peptides. Additionally, opine amino acids, amino acid quinones, Amadori compounds, cholines, nucleobases, nucleosides, nucleotides, siderophores, sugars, sugar alcohols and disaccharides were found, as well as other previously reported metabolites from plants or endophytes. Some differences of the metabolic profiles, regarding the amount and identity of the found metabolites, were observed even though the fungi were isolated from the same host. Many of the discovered metabolites have been described possessing biological activities and properties, which may make a favorable contribution to the host plant nutrient availability or abiotic and biotic stress tolerance.

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Contributors: Tienaho, J., Karonen, M., Muilu–Mäkelä, R., Wähälä, K., Denegri, E. L., Franzén, R., Karp, M., Santala, V., Sarjala, T.
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Synthesis of 6,12-disubstituted methanodibenzo[b,f][1,5]dioxocins: Pyrrolidine catalyzed self-condensation of 2′-Hydroxyacetophenones

The preparation of unprecedented 6,12-disubstituted methanodibenzo[b,f][1,5]dioxocins from pyrrolidine catalyzed self-condensation of 2′-hydroxyacetophenones is herein described. This method provides easy access to this highly bridged complex core, resulting in construction of two C-O and two C-C bonds, a methylene bridge and two quaternary centers in a single step. The intricate methanodibenzo[b,f][1,5]dioxocin compounds were obtained in up to moderate yields after optimization of the reaction conditions concerning solvent, reaction times and the use of additives. Several halide substituted methanodibenzo[b,f][1,5]dioxocins could be prepared from correspondent 2′-hydroxyacetophenones.

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INT=msee,"Riihonen, Vesa"
INT=msee,"Vale, João R."

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Understanding Dissolution and Crystallization with Imaging: A Surface Point of View

The tendency for crystallization during storage and administration is the most considerable hurdle for poorly water-soluble drugs formulated in the amorphous form. There is a need to better detect often subtle and complex surface crystallization phenomena and understand their influence on the critical quality attribute of dissolution. In this study, the interplay between surface crystallization of the amorphous form during storage and dissolution testing, and its influence on dissolution behavior, is analyzed for the first time with multimodal nonlinear optical imaging (coherent anti-Stokes Raman scattering (CARS) and sum frequency generation (SFG)). Complementary analyses are provided with scanning electron microscopy, X-ray diffraction and infrared and Raman spectroscopies. Amorphous indomethacin tablets were prepared and subjected to two different storage conditions (30 °C/23% RH and 30 °C/75% RH) for various durations and then dissolution testing using a channel flow-through device. Trace levels of surface crystallinity previously imaged with nonlinear optics after 1 or 2 days of storage did not significantly decrease dissolution and supersaturation compared to the freshly prepared amorphous tablets while more extensive crystallization after longer storage times did. Multimodal nonlinear optical imaging of the tablet surfaces after 15 min of dissolution revealed complex crystallization behavior that was affected by both storage condition and time, with up to four crystalline polymorphs simultaneously observed. In addition to the well-known α- and ?-forms, the less reported metastable ?- and ?-forms were also observed, with the ?-form being widely observed in samples that had retained significant surface amorphousness during storage. This form was also prepared in the pure form and further characterized. Overall, this study demonstrates the potential value of nonlinear optical imaging, together with more established solid-state analysis methods, to understand complex surface crystallization behavior and its influence on drug dissolution during the development of amorphous drugs and dosage forms.

General information

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EXT="Isomäki, Antti"
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Source ID: 85054882971
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Crystallization Kinetics of an Amorphous Pharmaceutical Compound Using Fluorescence-Lifetime-Imaging Microscopy

Pharmaceutical scientists are increasingly interested in amorphous drug formulations especially because of their higher dissolution rates. Consequently, the thorough characterization and analysis of these formulations are becoming more and more important for the pharmaceutical industry. Here, fluorescence-lifetime-imaging microscopy (FLIM) was used to monitor the crystallization of an amorphous pharmaceutical compound, indomethacin. Initially, we identified different solid indomethacin forms, amorphous and γ- and α-crystalline, on the basis of their time-resolved fluorescence. All of the

studied indomethacin forms showed biexponential decays with characteristic fluorescence lifetimes and amplitudes. Using this information, the crystallization of amorphous indomethacin upon storage in 60 °C was monitored for 10 days with FLIM. The progress of crystallization was detected as lifetime changes both in the FLIM images and in the fluorescence-decay curves extracted from the images. The fluorescence-lifetime amplitudes were used for quantitative analysis of the crystallization process. We also demonstrated that the fluorescence-lifetime distribution of the sample changed during crystallization, and when the sample was not moved between measuring times, the lifetime distribution could also be used for the analysis of the reaction kinetics. Our results clearly show that FLIM is a sensitive and nondestructive method for monitoring solid-state transformations on the surfaces of fluorescent samples.

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Increased survival rate by local release of diclofenac in a murine model of recurrent oral carcinoma

Despite aggressive treatment with radiation and combination chemotherapy following tumor resection, the 5-year survival rate for patients with head and neck cancer is at best only 50%. In this study, we examined the therapeutic potential of localized release of diclofenac from electrospun nanofibers generated from poly(d,l-lactide-co-glycolide) polymer. Diclofenac was chosen since anti-inflammatory agents that inhibit cyclooxygenase have shown great potential in their ability to directly inhibit tumor growth as well as suppress inflammation-mediated tumor growth. A mouse resection model of oral carcinoma was developed by establishing tumor growth in the oral cavity by ultrasound-guided injection of 1 million SCC-9 cells in the floor of the mouth. Following resection, mice were allocated into four groups with the following treatment: 1) no treatment, 2) implanted scaffolds without diclofenac, 3) implanted scaffolds loaded with diclofenac, and 4) diclofenac given orally. Small animal ultrasound and magnetic resonance imaging were utilized for longitudinal determination of tumor recurrence. At the end of 7 weeks following tumor resection, 33% of mice with diclofenac-loaded scaffolds had a recurrent tumor, in comparison to 90%-100% of the mice in the other three groups. At this time point, mice with diclofenac-releasing scaffolds showed 89% survival rate, while the other groups showed survival rates of 10%-25%. Immunohistochemical staining of recurrent tumors revealed a near 10-fold decrease in the proliferation marker Ki-67 in the tumors derived from mice with diclofenac-releasing scaffolds. In summary, the local application of diclofenac in an orthotopic mouse tumor resection model of oral cancer reduced tumor recurrence with significant improvement in survival over a 7-week study period following tumor resection. Local drug release of anti-inflammatory agents should be investigated as a therapeutic option in the prevention of tumor recurrence in oral squamous carcinoma.

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Contributors: Will, O. M., Purcz, N., Chalaris, A., Heneweer, C., Boretius, S., Purcz, L., Nikkola, L., Ashammakhi, N., Kalthoff, H., Glüer, C. C., Wiltfang, J., Açil, Y., Tiwari, S.

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Source: Scopus
Source ID: 84991726470
Research output: Contribution to journal › Article › Scientific › peer-review

Indocyanine Green-Loaded Liposomes for Light-Triggered Drug Release
Light-triggered drug delivery systems enable site-specific and time-controlled drug release. In previous work, we have achieved this with liposomes containing gold nanoparticles in the aqueous core. Gold nanoparticles absorb near-infrared light and release the energy as heat that increases the permeability of the liposomal bilayer, thus releasing the contents of the liposome. In this work, we replaced the gold nanoparticles with the clinically approved imaging agent indocyanine green (ICG). The ICG liposomes were stable at storage conditions (4-22 °C) and at body temperature, and fast near-infrared (IR) light-triggered drug release was achieved with optimized phospholipid composition and a 1:50 ICG-to-lipid molar ratio. Encapsulated small molecular calcein and FITC-dextran (up to 20 kDa) were completely released from the liposomes after light exposure for 15 s. Location of ICG in the PEG layer of the liposomes was simulated with molecular dynamics. ICG has important benefits as a light-triggering agent in liposomes: fast content release, improved stability, improved possibility of liposomal size control, regulatory approval to use in humans, and the possibility of imaging the in vivo location of the liposomes based on the fluorescence of ICG. Near-infrared light used as a triggering mechanism has good tissue penetration and safety. Thus, ICG liposomes are an attractive option for light-controlled and efficient delivery of small and large drug molecules.

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Organisations: Department of Physics, Department of Chemistry and Bioengineering
Contributors: Lajunen, T., Kontturi, L., Viitala, L., Manna, M., Cramariuc, O., Róg, T., Bunker, A., Laaksonen, T., Viitala, T. , Murtomäki, L., Urtti, A.
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Cell-based bioreporter assay coupled to HPLC micro-fractionation in the evaluation of antimicrobial properties of the basidiomycete fungus Pycnoporus cinnabarinus

Context Identification of bioactive components from complex natural product extracts can be a tedious process that aggravates the use of natural products in drug discovery campaigns. Objective This study presents a new approach for screening antimicrobial potential of natural product extracts by employing a bioreporter assay amenable to HPLC-based activity profiling. Materials and methods A library of 116 crude extracts was prepared from fungal culture filtrates by liquid–liquid extraction with ethyl acetate, lyophilised, and screened against Escherichia coli using TLC bioautography. Active extracts were studied further with a broth microdilution assay, which was, however, too insensitive for identifying the active microfractions after HPLC separation. Therefore, an assay based on bioluminescent E. coli K-12 (pTetLux1) strain was coupled with HPLC micro-fractionation. Results Preliminary screening yielded six fungal extracts with potential antimicrobial activity. A crude extract from a culture filtrate of the wood-rotting fungus, Pycnoporus cinnabarinus (Jacq.) P. Karst. (Polyporaceae), was selected for evaluating the functionality of the bioreporter assay in HPLC-based activity profiling. In the bioreporter assay, the IC_{50} value for the crude extract was 0.10 mg/mL. By integrating the bioreporter assay with HPLC micro-fractionation, the antimicrobial activity was linked to LC-UV peak of a compound in the chromatogram of the extract. This compound was isolated and identified as a fungal pigment phlebiarubrone. Discussion and conclusion HPLC-based activity profiling using the bioreporter-based approach is a valuable tool for identifying antimicrobial compound(s) from complex crude extracts, and offers improved sensitivity and speed compared with traditional antimicrobial assays, such as the turbidimetric measurement.

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Original language: English
ASJC Scopus subject areas: Drug Discovery, Pharmacology, Pharmaceutical Science, Complementary and alternative medicine, Molecular Medicine
Keywords: Bioluminescent bacterial strain, Escherichia coli, Gram-negative bacteria, phlebiarubrone
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Source: Scopus
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Resveratrol interferes with the aggregation of membrane-bound human-IAPP: A molecular dynamics study

Amyloid aggregation of islet amyloid polypeptide (IAPP) in pancreatic tissues is a typical feature of type 2 diabetes mellitus. Resveratrol, a natural product extensively studied for its wide range of biological effects, has been shown to inhibit IAPP aggregation. However, the mechanism by which resveratrol inhibits IAPP aggregation is still far from complete elucidation. Now, an increasing knowledge of the mechanism of amyloid toxicity shifts the target of research towards the development of compounds which can prevent amyloid-mediated membrane damage rather than merely inhibit fiber formation. In this study we used all atom molecular dynamics to investigate the interaction of resveratrol with full-length human IAPP in a negatively charged membrane environment. Our results show that the presence of resveratrol induces the formation of secondary structures (sheets and helices) by inserting in a hydrophobic pocket between the interaction surface of two IAPP molecules in aqueous solution. On the other hand, resveratrol significantly perturbs the interaction of IAPP with negatively charged membranes by anchoring specific hydrophobic regions (23FGA25 and 32VGS34) of the

peptide and forming a stable 1:2 IAPP:resveratrol complex at the water/membrane interphase.

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Research output: Contribution to journal › Article › Scientific › peer-review

Integrated in vitro-in silico screening strategy for the discovery of antibacterial compounds
Multidrug-resistant bacterial infections are an increasing source of healthcare problems, and the research for new antibiotics is currently unable to respond to this challenge. In this work, we present a screening strategy that integrates cell-based high-throughput screening (HTS) with in silico analogue search for antimicrobial small-molecule drug discovery. We performed an HTS on a diverse chemical library by using an assay based on a bioluminescent Escherichia coli K-12 (pTetLux1) strain. The HTS yielded eight hit compounds with >50% inhibition. These hits were then used for structural similarity-based virtual screening, and of the 29 analogues selected for in vitro testing, four compounds displayed potential activity in the pTetLux1 assay. The 11 most active compounds from combined HTS and analogue search were further assessed for antimicrobial activity against clinically important strains of E. coli and Staphylococcus aureus and for in vitro cytotoxicity against human cells. Three of the compounds displayed antibacterial activity and low human cell cytotoxicity. Additionally, two compounds of the set fully inhibited S. aureus growth after 24 h, but also exhibited human cell cytotoxicity in vitro.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Department of Chemistry and Bioengineering, Research group: Industrial Bioengineering and Applied Organic Chemistry, Tampere University of Technology, Urban circular bioeconomy (UrCirBio), Centre for Drug Research, Division of Pharmaceutical Biosciences, Helsinki University, Division of Pharmaceutical Chemistry and Technology
Contributors: Nybond, S., Ghemtio, L., Nawrot, D. A., Karp, M., Xhaard, H., Tammela, P.
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Publication date: 1 Feb 2015
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Publication information
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Original language: English
ASJC Scopus subject areas: Drug Discovery, Molecular Medicine
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URLs:

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Source: Scopus
Source ID: 84923872765
Research output: Contribution to journal › Article › Scientific › peer-review

Pharmacokinetics of an injectable modified-release 2-hydroxyflutamide formulation in the human prostate gland using a semiphysiologically based biopharmaceutical model

The local distribution of 2-hydroxyflutamide (2-HOF) in prostate tissue after a single intraprostatic injection of a novel parenteral modified-release (MR) formulation in patients with localized prostate cancer was estimated using a semiphysiologically based biopharmaceutical model. Plasma concentration-time profiles for 2-HOF were acquired from a phase II study in 24 patients and the dissolution of the MR formulation was investigated in vitro. Human physiological values and the specific physicochemical properties of 2-HOF were obtained from the literature or calculated via established algorithms. A compartmental modeling approach was adopted for tissue and blood in the prostate gland, where the compartments were modeled as a series of concentric spherical shells contouring the centrally positioned depot formulation. Discrete fluid connections between the blood compartments were described by the representative flow of blood, whereas the mass transport of drug from tissue to tissue and tissue to blood was described by a one-dimensional diffusion approximation. An empirical dissolution approach was adopted for the release of 2-HOF from the formulation. The model adequately described the plasma concentration-time profiles of 2-HOF. Predictive simulations indicated that the local tissue concentration of 2-HOF within a distance of 5 mm from the depot formulation was approximately 40 times higher than that of unbound 2-HOF in plasma. The simulations also indicated that spreading the formulation throughout the prostate gland would expose more of the gland and increase the overall release rate of 2-HOF from the given dose. The increased release rate would initially increase the tissue and plasma concentrations but would also reduce the terminal half-life of 2-HOF in plasma. Finally, an in vitro-in vivo correlation of the release of 2-HOF from the parenteral MR formulation was established. This study shows that intraprostatic 2-HOF concentrations are significantly higher than systemic plasma concentrations and that increased distribution of 2-HOF throughout the gland, using strategic imaging-guided administration, is possible. This novel parenteral MR formulation, thus, facilitates good pharmacological effect while minimizing the risk of side effects.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Uppsala University, Tampere University Hospital, University of Gothenburg, Helsinki University Central Hospital, Päijät-Häme Central Hospital, LIDDS AB
Contributors: Sjögren, E., Tammela, T. L., Lennernäs, B., Taari, K., Isotalo, T., Malmsten, L. Å., Axén, N., Lennernäs, H.
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Pages: 3097-3111
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Peer-reviewed: Yes

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Volume: 11
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ISSN (Print): 1543-8384
Ratings:

Scopus rating (2014): CiteScore 7.6 SJR 1.641 SNIP 1.291
Original language: English
ASJC Scopus subject areas: Pharmaceutical Science, Molecular Medicine, Drug Discovery, Medicine(all)
Keywords: 2-hydroxyflutamide, drug delivery, Liproca Depot, physiological modeling, prostate cancer
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Source: Scopus
Source ID: 84906915553
Research output: Contribution to journal › Article › Scientific › peer-review

Role of the acyl groups in carbohydrate chains in cytotoxic properties of olivomycin A

A series of olivomycin A derivatives containing different combinations of the acyl residues in the carbohydrate chains was obtained. The formation of complexes of Mg 2+ -coordinated dimers of these compounds with double-stranded DNA was studied using spectral methods such as absorption, fluorescence and circular dichroism (CD) spectral analyses. There was a good correlation of the values of binding constants of complexes (antibiotic) 2 Mg 2+ -DNA, the quantum yields of fluorescence and changes of the induced CD spectra with topoisomerase I inhibition and cytotoxicity. We demonstrate that

the presence of the acyl groups in the saccharide residues of olivomycin A derivatives is absolutely necessary for a high cytotoxic potency of these antibiotics. On the basis of the experimental results and quantum chemical calculations, we presume that the acyl residue in the 4-O-position in the A-sugar residue is involved, to the most part, in the antibiotic-antibiotic interactions in the (olivomycin) 2 Mg 2+ dimers, whereas the O-acyl group in E-olivomicose residue largely participates in the formation of the (olivomycin) 2 Mg 2+ -DNA complexes.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Frontier Photonics, Russian Academy of Medical Sciences, Emanuel' Institute of Biochemical Physics, Russian Academy of Sciences, N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences
Contributors: Tevyashova, A. N., Durandin, N. A., Vinogradov, A. M., Zbarsky, V. B., Reznikova, M. I., Dezhenkova, L. G., Bykov, E. E., Olsufyeva, E. N., Kuzmin, V. A., Shtil, A. A., Preobrazhenskaya, M. N.
Number of pages: 8
Pages: 523-530
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Peer-reviewed: Yes

Publication information
Journal: JOURNAL OF ANTIBIOTICS
Volume: 66
Issue number: 9
ISSN (Print): 0021-8820
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Scopus rating (2013): CiteScore 3.7 SJR 0.712 SNIP 0.886
Original language: English
ASJC Scopus subject areas: Pharmacology, Drug Discovery
Keywords: Aureolic acid antibiotics, Cytotoxicity, Olivomycin A, Quantum chemical calculations, Spectroscopy, Structure-activity relationships, Topoisomerase I inhibitors
DOIs:

10.1038/ja.2013.39
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Source: Scopus
Source ID: 84884999183
Research output: Contribution to journal › Article › Scientific › peer-review

Protein-protein interactions: Inhibition of mammalian carbonic anhydrases I-XV by the murine inhibitor of carbonic anhydrase and other members of the transferrin family
The murine inhibitor of carbonic anhydrase (mICA), a member of the transferrin (TF) superfamily of proteins, together with human holo- and apoTF and lactoferrin (LF) were assessed as inhibitors of all catalytically active mammalian (h = human, m = murine) CA isoforms, from CA I to CA XV. mICA was a low nanomolar to subnanomolar inhibitor of hCAs I, II, III, VA, VB, VII and mCAs XV (K_I of 0.7-44.0 nM) and inhibited the remaining isoforms with K_I of 185.5-469 nM. hTF, apoTF, and hLF were inhibitors of most of these CAs but with reduced efficiency compared to mICA (K_I of 18.9-453.8 nM). Biacore surface plasmon resonance and differential scanning calorimetry experiments were also used for obtaining more insights into the interaction between these proteins, which may be useful for drug design of protein-based CA inhibitors.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), University of Calgary, CNR-INO, School of Management (JKK)
Contributors: Durdagi, S., Vullo, D., Pan, P., Kähkönen, N., Määttä, J. A., Hytönen, V. P., Scozzafava, A., Parkkila, S., Supuran, C. T.
Number of pages: 7
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Publication date: 14 Jun 2012
Peer-reviewed: Yes

Publication information
Journal: JOURNAL OF MEDICINAL CHEMISTRY
Volume: 55
Issue number: 11
ISSN (Print): 0022-2623
Ratings:

Scopus rating (2012): CiteScore 9.3 SJR 2.343 SNIP 1.75
Original language: English
ASJC Scopus subject areas: Molecular Medicine, Drug Discovery
DOIs:

10.1021/jm3004587
URLs:

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Source: Scopus
Source ID: 84862280022
Research output: Contribution to journal › Article › Scientific › peer-review

Baculovirus-mediated vascular endothelial growth factor-DΔNΔC gene transfer induces angiogenesis in rabbit skeletal muscle

Background: Occluded arteries and ischemic tissues cannot always be treated by angioplasty, stenting or by-pass-surgery. Under such circumstances, viral gene therapy may be useful in inducing increased blood supply to ischemic area. There is evidence of improved blood flow in ischemic skeletal muscle and myocardium in both animal and human studies using adenoviral vascular endothelial growth factor (VEGF) gene therapy. However, the expression is transient and repeated gene transfers with the same vector are inefficient due to immune responses. Methods: Different baculoviral vectors pseudotyped with or without vesicular stomatitis virus glycoprotein (VSV-G) and/or carrying woodchuck hepatitis virus post-transcriptional regulatory element (Wpre) were tested both in vitro and in vivo. VEGF-$D^{\Delta N\Delta C}$ was used as therapeutic transgene and lacZ as a control. In vivo efficacy was evaluated as capillary enlargement and transgene expression in New Zealand White (NZW) rabbit skeletal muscle. Results: A statistically significant capillary enlargement was detected 6days after gene transfer in transduced areas compared to the control gene transfers with baculovirus and adenovirus encoding β-galactosidase (lacZ). Substantially improved gene transfer efficiency was achieved with a modified baculovirus pseudotyped with VSV-G and carrying Wpre. Dose escalation experiments revealed that either too large volume or too many virus particles caused inflammation and necrosis in the target tissue, whereas 10^9 plaque forming units injected in multiple aliquots resulted in transgene expression with only mild immune reactions. Conclusions: We show the first evidence of biologically significant baculoviral gene transfer in skeletal muscle of NZW rabbits using VEGF-$D^{\Delta N\Delta C}$ as a therapeutic transgene.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), Ark Therapeutics Oy, Ita-Suomen yliopisto, University Central Hospital Kuopio
Contributors: Heikura, T., Nieminen, T., Roschier, M. M., Karvinen, H., Kaikkonen, M. U., Mähönen, A. J., Lesch, H. P., Rissanen, T. T., Laitinen, O. H., Airenne, K. J., Ylä-Herttuala, S.
Number of pages: 9
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Publication date: Jan 2012
Peer-reviewed: Yes

Publication information

Journal: JOURNAL OF GENE MEDICINE
Volume: 14
Issue number: 1
ISSN (Print): 1099-498X
Ratings:

Scopus rating (2012): CiteScore 5.3 SJR 0.841 SNIP 0.698
Original language: English
ASJC Scopus subject areas: Genetics, Molecular Biology, Molecular Medicine, Genetics(clinical), Drug Discovery
Keywords: Angiogenesis, Baculovirus, Gene therapy, Vascular endothelial growth factor
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Source: Scopus
Source ID: 84856190056
Research output: Contribution to journal › Article › Scientific › peer-review

Modification of olivomycin A at the side chain of the aglycon yields the derivative with perspective antitumor characteristics

A novel way of chemical modification of the antibiotic olivomycin A (1) at the side chain of the aglycon moiety was developed. Interaction of olivomycin A with the sodium periodate produced the key acid derivative olivomycin SA (2) in 86% yield. This acid was used in the reactions with different amines in the presence of benzotriazol-1-yl-oxy-

trispyrrolidino-phosphonium hexafluorophosphate (PyBOP) or diphenylphosphoryl azide (DPPA) to give corresponding amides. Whereas olivomycin SA was two orders of magnitude less cytotoxic than the parent antibiotic, the amides of 2 demonstrated a higher cytotoxicity. In particular, N,N-dimethylaminoethylamide of olivomycin SA showed a pronounced antitumor effect against transplanted experimental lymphoma and melanoma and a remarkably high binding constant to double stranded DNA. The therapeutic effects of this derivative were achievable at tolerable concentrations, suggesting that modifications of the aglycon's side chain, namely, its shortening to methoxyacetic residue and blocking of free carboxyl group, are straightforward for the design of therapeutically applicable derivatives of olivomycin A.

General information

Publication status: Published
MoE publication type: A2 Review article in a scientific journal
Organisations: Frontier Photonics, Russian Academy of Medical Sciences, N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences, Emanuel' Institute of Biochemical Physics, Russian Academy of Sciences
Contributors: Tevyashova, A. N., Shtil, A. A., Olsufyeva, E. N., Luzikov, Y. N., Reznikova, M. I., Dezhenkova, L. G., Isakova, E. B., Bukhman, V. M., Durandin, N. A., Vinogradov, A. M., Kuzmin, V. A., Preobrazhenskaya, M. N.
Number of pages: 7
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Publication date: 15 Dec 2011
Peer-reviewed: Yes

Publication information

Journal: BIOORGANIC AND MEDICINAL CHEMISTRY
Volume: 19
Issue number: 24
ISSN (Print): 0968-0896
Ratings:

Scopus rating (2011): CiteScore 5.4 SJR 1.137 SNIP 1.254
Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Medicine, Molecular Biology, Pharmaceutical Science, Drug Discovery, Clinical Biochemistry, Organic Chemistry
Keywords: Antibiotics, Antitumor activity, Aureolic acid, Chemical modifications, Drug-DNA complexes, Olivomycin A, Olivomycin SA
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URLs:

http://www.scopus.com/inward/record.url?scp=82255193979&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 82255193979
Research output: Contribution to journal › Review Article › Scientific › peer-review

Acetaldehyde-derived modifications on cytosolic human carbonic anhydrases

Acetaldehyde can generate modifications in several proteins, such as carbonic anhydrase (CA) II. In this study, we extended in vitro investigations on acetaldehyde adduct formation by focusing on the other human cytosolic CA enzymes I, III, VII, and XIII. High-resolution mass spectrometric analysis indicated that acetaldehyde most efficiently formed covalent adducts with CA II and XIII. The binding of up to 19 acetaldehydes in CA II is probably attributable to the high number of lysine residues (n=24) located mainly on the surface of the enzyme molecule. CA XIII formed more adducts (up to 25) than it contains lysine residues (n=16) in its primary structure. Acetaldehyde treatment induced only minor changes in CA catalytic activity in most cases. The present study provides the first evidence that acetaldehyde can bind to several cytosolic CA isozymes. The functional consequences of such modifications will be further investigated in vivo by using animal models.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), School of Management (JKK), Ita-Suomen yliopisto, CNR-INO, Tampere University Hospital
Contributors: Bootorabi, F., Jänis, J., Hytönen, V. P., Valjakka, J., Kuuslahti, M., Vullo, D., Niemelä, O., Supuran, C. T., Parkkila, S.
Number of pages: 9
Pages: 862-870
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Publication information

Journal: JOURNAL OF ENZYME INHIBITION AND MEDICINAL CHEMISTRY

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Issue number: 6
ISSN (Print): 1475-6366
Ratings:

Scopus rating (2011): CiteScore 3 SJR 0.487 SNIP 0.818
Original language: English
ASJC Scopus subject areas: Drug Discovery, Pharmacology
Keywords: Acetaldehyde, Adduct, Alcohol, Mass spectrometry, Modification
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Source: Scopus
Source ID: 81355149286
Research output: Contribution to journal › Article › Scientific › peer-review

Expression of MUC5AC in ocular surface epithelial cells using cationized gelatin nanoparticles

Decreased production of the mucin MUC5AC in the eye is related to several pathological conditions, including dry eye syndrome. A specific strategy for increasing the ocular levels of MUC5AC is not yet available. Using a plasmid specially designed to encode human MUC5AC, we evaluated the ability of hybrid cationized gelatin nanoparticles (NPs) containing polyanions (chondroitin sulfate or dextran sulfate) to transfect ocular epithelial cells. NPs were developed using the ionic gelation technique and characterized by a small size (95%). MUC5AC mRNA and protein were detected in conjunctival cells after in vitro transfection of the NPs. The in vivo administration of the NPs resulted in significantly higher MUC5AC expression in the conjunctiva compared to untreated control and naked plasmid. These results provide a proof-of-concept that these NPs are effective vehicles for gene therapy and candidates for restoring the MUC5AC concentration in the ocular surface.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Santiago de Compostela (USC), Biomaterials and Nanomedicine (CIBER BBN), Complejo Hospitalario Universitario de Santiago
Contributors: Konat Zorzi, G., Contreras-Ruiz, L., Párraga, J. E., López-García, A., Romero Bello, R., Diebold, Y., Seijo, B. , Sánchez, A.
Number of pages: 6
Pages: 1783-1788
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Peer-reviewed: Yes

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ISSN (Print): 1543-8384
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Scopus rating (2011): CiteScore 7.7 SJR 2.351 SNIP 1.532
Original language: English
ASJC Scopus subject areas: Molecular Medicine, Pharmaceutical Science, Drug Discovery
Keywords: dry eye, gene therapy, MUC5AC, nanoparticle, ocular surface
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Source: Scopus
Source ID: 80053545182
Research output: Contribution to journal › Article › Scientific › peer-review

Chemically modified gelatin as biomaterial in the design of new nanomedicines

The synthesis of new polymers has led to dramatic enhancements in the medical field. In particular, new chemical entities provided new prospects in tissue engineering, cellular therapy and drug delivery. However, significant efforts still need to be taken in consideration in order to achieve diverse clinical applications in these fields, which is challenging because of the lack of suitable materials with desired microstructure, permeability, degradation rates, products, and suitable mechanical properties. For these reasons some chemical strategies are focused in back to the nature approaches or, in other words, in improving the properties of natural polymers by chemical modifications. We report that by using a simple

chemical modification technique we can obtain new biomaterials, specifically suitable for biomedical applications. Concretely, we describe the chemical modification of gelatin and the suitable characteristics of the modified protein to develop new nanomedicines. This protein was selected because of its enormous potential in biomedicine, which is currently limited due to the difficulty of its use without toxic chemical crosslinkers. The modification of the protein was based on the transformation of the carboxylic group into amido groups after their reaction with polyamines, leading to a positively charged biopolymer. To cationize the gelatin two polyamines where used: ethylenediamine and spermine, the latter being one of the endogenous polyamines which has a very positive influence over cells. This modification was monitored by physico-chemical techniques such as NMR, spectrophotometry and potentiometry. With the most promising modified gelatins we were able to develop nanoparticles using the ionotropic gelation technique. In order to determine the ability of these new nanosystems to associate bioactive molecules we selected a model plasmid DNA. The developed nanosystems were characterized corroborating their ability to associate the genetic material. In conclusion, we were able to obtain a semi-synthetic biomaterial with tunable physico-chemical properties, which can be used to develop new nanosystems with the ability to associate genetic material. We therefore propose that the gelatin, with its chemical modification, provide a unique biomaterial for the development of new nanomedicines.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Santiago de Compostela (USC)
Contributors: Lopez-Cebral, R., Martn-Pastor, M., Evelin Parraga, J., Konat Zorzi, G., Seijoa, B., Sanchez, A.
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Publication date: May 2011
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Journal: MEDICINAL CHEMISTRY
Volume: 7
Issue number: 3
ISSN (Print): 1573-4064
Ratings:

Scopus rating (2011): CiteScore 2.2 SJR 0.37 SNIP 0.545
Original language: English
ASJC Scopus subject areas: Drug Discovery
Keywords: Chemically modified protein, Gelatin, Gene delivery, Nanomedicines, Nanoparticles
DOIs:

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URLs:

http://www.scopus.com/inward/record.url?scp=79955757101&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 79955757101
Research output: Contribution to journal › Article › Scientific › peer-review

Unity is strength

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Frontier Photonics, Univ Lille Nord de France, Lille University Hospital - CHRU, St. Philibert Hospital
Contributors: Maunoury, V., Mordon, S., Bulois, P.
Number of pages: 2
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Issue number: 2
ISSN (Print): 0009-3157
Ratings:

Scopus rating (2011): CiteScore 3.4 SJR 0.694 SNIP 0.866
Original language: English
ASJC Scopus subject areas: Pharmacology (medical), Oncology, Infectious Diseases, Pharmacology, Drug Discovery

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10.1159/000326914
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http://www.scopus.com/inward/record.url?scp=79953187666&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 79953187666
Research output: Contribution to journal › Letter › Scientific › peer-review

Ras regulates interleukin-1β-induced HIF-1α transcriptional activity in glioblastoma

We observed elevated levels of pro-inflammatory cytokine IL-1β in glioblastoma multiforme tumor samples. Since hypoxia-inducible factor-1α (HIF-1α) plays a crucial role in linking inflammatory and oncogenic pathways, we investigated the effect of IL-1β on HIF-1α expression in glioma cells under normoxia. IL-1β-mediated elevation of HIF-1α transcriptional activity was dependent on Ras-induced NF-κB activation, as IL-1β failed to induce NF-κB and HIF-1α activity in cells transfected with dominant negative RasN17. Increased Ras expression was accompanied by increased phosphorylation of Ras effectors AKT, ERK, JNK, and p38MAPK. While inhibition of these effectors individually failed to block the IL-1β-mediated increase in HIF-1α induction, co-inhibition of both AKT and ERK resulted in a significant decrease in IL-1β-induced HIF-1α activation. Interestingly, IL-1β elevated Wnt-1 expression in a Ras-dependent manner, and small interfering RNA (siRNA)-mediated knockdown of Wnt-1 decreased HIF-1α activity. Although Wnt-1-mediated HIF-1α was independent of the canonical Wnt/β-catenin signaling pathway, it regulated HIF-1α through NF-κB. siRNA-mediated HIF-1α knockdown attenuated elevated IL-1β mRNA levels induced upon IL-1β treatment. This was accompanied by increased interaction of HIF-1α with HIF responsive element on the IL-1β promoter upon IL-1β treatment, under normoxia. Our studies highlights for first time that (1) Ras is a key mediator of IL-1β-induced NF-κB and HIF-1α activation, under normoxia; (2) Wnt-1 regulates IL-1β-mediated HIF-1α induction via NF-κB; (3) Ras and Wnt-1 are intermediaries in the canonical IL-1β-NF-κB signaling pathway downstream of MyD88; and (4) IL-1β-induced HIF-1α drives a HIF-1α-IL-1β autocrine loop to maintain persistently elevated IL-1β level.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), National Brain Research Centre, Paras Hospitals
Contributors: Sharma, V., Dixit, D., Koul, N., Mehta, V. S., Sen, E.
Number of pages: 14
Pages: 123-136
Publication date: Feb 2011
Peer-reviewed: Yes

Publication information

Journal: JOURNAL OF MOLECULAR MEDICINE: JMM
Volume: 89
Issue number: 2
ISSN (Print): 0946-2716
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ASJC Scopus subject areas: Molecular Medicine, Drug Discovery, Genetics(clinical)
Keywords: Glioblastoma, HIF-1α, Hypoxia, IL-1β, Inflammation, NF-κB, Ras
DOIs:
10.1007/s00109-010-0683-5
URLs:
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Source: Scopus
Source ID: 79951676430
Research output: Contribution to journal › Article › Scientific › peer-review

Vilsmeier formylation of 2-carboxyindoles and preparation of O-benzylhydroxyureas on solid phase

The Vilsmeier formylation has been introduced for the solid-phase functionalization of five different 2-carboxyindoles. The aldehyde functionality has been utilized in the preparation of O-benzylhydroxyureas.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Helsinki University, Department of Pharmacy, Division of Pharmaceutical Chemistry, Division of Pharmacognosy, Viikki Drug Discov. Technol. Center, University of Tokyo
Contributors: Tois, J., Franzèn, R., Aitio, O., Laakso, I., Kylänlahti, I.

Number of pages: 4
Pages: 542-545
Publication date: Nov 2001
Peer-reviewed: Yes

Publication information
Journal: Journal of Combinatorial Chemistry
Volume: 3
Issue number: 6
ISSN (Print): 1520-4766
Original language: English
ASJC Scopus subject areas: Chemistry(all), Organic Chemistry, Discrete Mathematics and Combinatorics, Drug Discovery
DOIs:

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Source ID: 0035514539
Research output: Contribution to journal › Article › Scientific › peer-review

Recent advances in the preparation of heterocycles on solid support: A review of the literature

General information
Publication status: Published
MoE publication type: A2 Review article in a scientific journal
Organisations: University of Helsinki
Contributors: Franzén, R. G.
Number of pages: 20
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Publication date: May 2000
Peer-reviewed: Yes

Publication information
Journal: Journal of Combinatorial Chemistry
Volume: 2
Issue number: 3
ISSN (Print): 1520-4766
Original language: English
ASJC Scopus subject areas: Chemistry(all), Organic Chemistry, Discrete Mathematics and Combinatorics, Drug Discovery
DOIs:

10.1021/cc000002f
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Source: Scopus
Source ID: 0041037814
Research output: Contribution to journal › Review Article › Scientific › peer-review

Preparation of 5-substituted 2-carboxyindoles on solid support
The preparation of 5-substituted 2-carboxyindoles on solid support is reported. In the approach, the indole moiety is synthesized in solution phase, followed by nitro-group reduction, reductive amination and alkylation on solid support. The method provides a simple and convenient route for the preparation of 5-substituted 2-carboxyindoles with high purity and good yield. (C) 2000 Elsevier Science Ltd.

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Organisations: Div. Pharmaceutical Chem., Dept. P., University of Helsinki, Helsinki University
Contributors: Tois, J., Franzén, R., Aitio, O., Huikko, K., Taskinen, J.
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Utilization of Grignard reagents in solid-phase synthesis: A review of the literature

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Organisations: University of Helsinki
Contributors: Franzén, R. G.
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Investigation of the adducts formed by reaction of butenedioic acids with adenosine
Several genotoxic butenedioic acids present in chlorine-disinfected drinking water were allowed to react with adenosine, guanosine, and cytidine in aqueous solution. HPLC analyses, with detection at 254 and 310 nm, showed that clearly detectable products were formed only in the reactions with adenosine. The major products from the reactions between either 2-chloro-3- methyl-2-butenedioic acid (ox-MCF) or 2-chloro-3-(chloromethyl)-2- butenedioic acid (ox-CMCF) and adenosine were the same. This substance was isolated by C18 column chromatography and characterized by UV absorbance, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. It was identified as 3-(β-D-ribofuranosyl)-7-carboxy-7-formyl-8-[9'-(β-D-ribofuranosyl)-N ^{6}- adenosinyl]-1,N ^{6}-ethanoadenosine (cfεA,A). The yields of cfεA,A in reactions performed at pH 7.4 and 37 °C were 0.7% and 0.3% with ox-MCF and ox-CMCF, respectively.

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Contributors: Franzén, R., Morita, M., Tanabe, K., Takagi, H., Shibata, Y.
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Mutational spectra of Salmonella typhimurium revertants induced by chlorohydroxyfuranones, byproducts of chlorine disinfection of drinking water

The base substitution specificities of 3-chloro-4-(dichloromethyl)-5- hydroxy-2(5H)-furanone (MX), 3-chloro-4-(chloromethyl)-5-hydroxy-2(SH)- furanone (CMCF), 3,4-dichloro-5-hydroxy-2(5H)-furanone (MCA), and chloromalonaldehyde (CMA), a putative breakdown product of MCA, were examined in the hisG46 gene and in the hisG428 gene of Salmonella typhimurium using allele specific oligonucleotide hybridization. Although the compounds are structurally closely related, they induced substantially different mutation spectra: MCA and CMA caused primarily GC → AT transitions in the hisG46 allele (target sequence CCC), in particular, at the second position of the codon in strain TA100. In TA100 the mutation spectrum of MCA was similar to that of CMA. The mutational specificity of MCA can be explained as a consequence of misincorporation opposite to cyclic ethene adducts identical to those formed by the carcinogen vinyl chloride. The spectra induced by MX and CMCF in TA100 were almost identical but distinctively different from the spectra of MCA and CMA. Both compounds induced primarily GC → TA transversions, in particular, at the second position of the codon, and to a lesser extent in the first position of the codon. An identical site bias is induced by carcinogens such as polycyclic aromatic hydrocarbons and heterocyclic amines as a consequence of formation of (noncyclic) guanosine adducts. In hisG428 (target sequence TAA) MX induced again primarily GC → TA transversions in Tyr tRNA genes (supC/M) and, to a lesser extent, intragenic AT → TA transversions (TAA → AAA). The possible involvement of guanosine and adenosine adducts in the mutational specificity of MX is addressed.

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Contributors: Knasmuller, S., Zöhrer, E., Kronberg, L., Kundi, M., Franzen, R., Schulte-Hermann, R.
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Synthesis of chlorinated 5-hydroxy 4-methyl-2(5H)-furanones and mucochloric acid

An improved procedure for the synthesis of chlorinated 5-hydroxy-4-methyl-2(5H)-furanones is described. By this method also carbon-labelled (^{13}C and ^{14}C at C-3) hydroxyfuranones, including mucochioric acid, can be prepared. Each step of the method was examined in an effort to optimize both the yield and the purity of the compounds.

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