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Posters

Antonio Elías Kuri Pineda, Med chem (Los Angeles) 2018, Volume 8
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Biotransformation study of the synthetic cannabinoid JWH-007

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The cannabinoid substances group can be subdivided into three subgroups called: phytocannabinoids, endogen cannabinoids and synthetic cannabinoids. All of these have the ability of modulate the activity of the receptors CB1 and CB2, which are part of the physiological endocannabinoid system. Research on synthetic cannabinoids has had different scopes, focusing primarily on the understanding of the physiological function of the CB1 receptor. However, some of these compounds have started to be used as psychoactive substances, so the focus of their study has been channeled towards their toxic effects, their pharmacokinetics and how they can be detected in users. In this study, we present an approach to phase I-biotransformation of the compound JWH-007, which is a strong agonist of the CB1 receptors and it is reported by its use as a psychoactive substance due to the effects caused by its administration. In that sense, we first synthesized the compound with an alkylation reaction SN2 followed by an acylation reaction Friedel-Crafts. Once purified and chemically characterized, an *in vitro* biotransformation study was carried out in a controlled system that includes CYP2C9, and the subsequent determination of the chemical structures of the products generated by Mass Spectroscopy. Our data suggests that some of these Phase I-metabolites retain their biological activity, since they have an important affinity for the CB1 receptor. In that way, the determination of the kinetic parameters of the enzymatic process allows to conclude the chemical structures of the main Phase I-metabolites and their catalysis speed. The chosen *in vitro* biotransformation system is ideal for the initial study of the metabolism of compounds of biological interest. This, in turn, opens can lead to later research in more complex system such as cell lines or animals. The knowledge of the key points in the biotransformation of the compound is essential in the pharmacological study of CB receptors, which are still being explored as a therapeutically alternative and more recently because of their value as molecular targets of new drugs.

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Matteo Dal Prà, Med chem (Los Angeles) 2018, Volume 8
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Fluorinated anti-tubulin phenyl-pyrroloquinolinones: *In vitro* and *in vivo* anticancer properties

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Tricycle Phenyl-Pyrroloquinolinones (PPyQs) are a class of compounds that have showed interesting *in vitro* and *in vivo* anti-proliferative activity acting as tubulin polymerization inhibitors by binding at the colchicine site into β-tubulin. The major initial focus on introducing fluorine into biologically active compounds is to improve their metabolic stability by blocking potential reactive positions with fluorine. In an attempt to reduce the oxidative metabolism of 7-PPyQs and at the same time to possibly maintain the excellent pharmacodynamic, we designed the synthesis of some compounds 12-15 and 19, monofluoro-phenyl derivatives of the earlier 3-ethyl-7-PPyQ 20 and 3-benzoyl-7-PPyQ 21. Of the new compounds synthesized, potent cytotoxicity (low and sub-nanomolar GI_{50} values) was observed with 12 and 13, both more potent than 20, in both leukemic and solid tumor cell lines. Neither compound 12 nor 13 induced significant cell death in normal human lymphocytes, suggesting that the compounds may be selectively active against cancer cells. In particular, 13 was a potent inducer of apoptosis in the A549 and HeLa cell lines. With both compounds, induction of apoptosis was associated with dissipation of the mitochondrial transmembrane potential and production of reactive oxygen species, indicating that cells followed the intrinsic pathway of apoptosis. Experiments carried out in a mouse syngeneic model demonstrated high antitumor activity of 13, which significantly reduced the tumor mass at doses four-ten times lower than that required for the CA-4P used as reference compound. Finally, molecular docking and metabolic stability studies of the newly synthesized compounds will be reported.

Biography

Matteo Dal Prà has completed his PhD at the University of Padova, School of Medicine, Department of Pharmaceutical and Pharmacological Sciences.

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Notes:

Meysun Ibrahim Abdullah et al., Med chem (Los Angeles) 2018, Volume 8
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LC/ESI/QT of studies of the leaves extract of *Kitaibelia balansae* species

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The traditional Turkish medicine includes many compounds with variations in their chemical and physical properties. In this work, compounds present in the leaves and flower of *Kitaibelia balansae* extracted with solvents of different polarities were screened out and their structures were characterized by liquid chromatography/electrospray ionization mass spectrometry in negative ion mode. 67 compounds were observed in the leaves extract, 35 of which were recognized and identified as flavonoids. The naphthodianthrones, hiperforin and hypericin were almost the major compounds in the leave extract. Catechin, epicatechin, myricetin, quercitrin, isoquercetin, kaempferol, apigenin, and chlorogenic acid were also present in these extracts together with other compounds. However, up to date to our knowledge there is no research on *Kitaibelia balansae* species has been conducted.

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Luminita Confederat et al., Med chem (Los Angeles) 2018, Volume 8
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Development of new polymeric systems with potential applications in chronic wound treatment

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Statement of the Problem: Chronic wounds represent an important issue in medical practice taking into account their impact on patient's quality of life, the difficulty of their care and the costs involved. Based on their specific characteristics and biological properties, chitosan and hyaluronic acid have attracted the researchers' interest in developing new systems with medical applications. The purpose of this study was the development of some new polymeric systems, hydrogel type, with potential use in chronic wounds treatment.

Materials & Methods: The developed systems were obtained using chitosan hydrogel 5%, bentonite 5% and hyaluronic acid solution 1%. The proportion of chitosan-bentonite hydrogel and hyaluronic acid solution ranged between 95%-5% and 40%-60%. In these formulations the arginine 2% was included. The obtained hybrid hydrogels were characterized in terms of pH and morphology using Scanning Electron Microscopy (SEM). The presence of arginine in the polymer matrix was proved by Fourier-Transformed Infrared Spectroscopy (FT-IR).

Findings: There were obtained seven new hybrid hydrogels based chitosan-bentonite-hyaluronic acid-arginine, whose pH varied between 4.72 and 5.33. The presence of the active substance was proved by IR spectroscopy and the morphology was analyzed by SEM.

Conclusion & Significance: The systems developed represent a step in the attempt to improve chronic wound management, targeting the tissue regeneration and the risk of local infections.

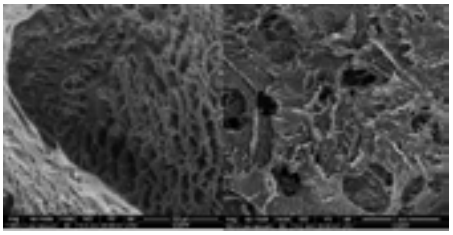

Fig SEM images of hydrogels obtained

Recent Publications

1. Giri T K, Thakur A, Ajazuddin A A, Badwaik H and Tripathi D K (2012) Modified chitosan hydrogels as drug delivery and tissue engineering systems: present status and applications, Acta Pharmaceutica Sinica B, 2 (5):439-449.
2. Debats I B J G, Wolfs T G A M, Gotoh T, Cleutjens J P M, Peutz-Kootstra CJ and Van der Hulst R (2009) Role of arginine in superficial wound healing. Nitric Oxide 15:147-156.
3. Mogoşanu GD and Grumezescu (2014) AM Natural and synthetic polymers for wounds and burns dressing, International Journal of Pharmaceutics, 463 (2):127-136.
4. Stern R and Maibach H I (2008) Hyaluronan in skin: aspects of aging and its pharmacologic modulation, Clinics in Dermatology, 26: 106-122.
5. Mayet N, Choonara Y E, Kumar P, Tomar L K, Tyagi C, Du Toit LC and Pillay V (2014) A Comprehensive Review of Advanced Biopolymeric Wound Healing Systems, Journal of Pharmaceutical Sciences, 103 (8): 2211-2230.

Biography

Luminita Confederat is a young researcher and a PhD student at the "Gr. T. Popa" University of Medicine and Pharmacy, Iasi. She has expertise in the field of Pharmaceutical Chemistry, Pharmaceutical Technology and Analytical Techniques. Her research area concerns the use of biopolymers in medicine, targeting the improvement of pharmacokinetic profile of the drugs included in polymeric matrix as well as the benefits represented by the pharmacological properties of some polymers in the management of diseases likes diabetes and chronic wounds.

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Mihaela-Iustina Avram et al., Med chem (Los Angeles) 2018, Volume 8
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Characterization and biological evaluation of new polymeric systems with potential applications in chronic wound treatment

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Statement of the Problem: Recent data indicate that chronic wounds account for almost 4% of total health system costs, and that this proportion is increasing. The common chronic skin and soft tissue wounds include the diabetic food ulcer, the pressure ulcer and the venous and arterial leg ulcers. Prevention of bacterial infection is important in severe cases because it is associated with septic shock, the major cause of death.

Materials & Methods: New hybrid hydrogels based on chitosan-hyaluronic acid-bentonite which have incorporated arginine (2%) as active substance, have been developed. The proportion of chitosan-bentonite hydrogel and hyaluronic acid solution ranged between 95%-5% and 40%-60%. Arginine is a basic alpha-amino acid which is known that enhances wound collagen synthesis and wound breaking strength during normal and impaired healing. The hybrid hydrogels have been studied in terms of swelling degrees and porosity. The antimicrobial study using Gram positive and Gram negative bacterial strains and *in vitro* antioxidant assays were performed. In order to correlate the intensity of the biological effect with arginine concentration, *in vitro* kinetic release of active agent was also performed.

Findings: The swelling degree is depending on concentration of chitosan and hyaluronic acid as well as on concentration of arginine and is ranged between 200% and 300% after 60 min. The presence of arginine in the polymeric matrix has as result increasing of the porosity degree. The porosity degree is an important characteristic of polymeric membranes used in the treatment of wounds, since it influences the exudate absorption, the rate of colonization and the angiogenesis process. Arginine improved also the biological effects of the polymeric matrix based on chitosan-hyaluronic acid-bentonite.

Conclusion & Significance: The features and biological effects of the developed hybrid hydrogels recommended them as new therapeutic alternatives in the treatment of chronic wounds.

Recent Publications

1. Cervini-Silva J, Ramírez-Apan MT, Kaufhold S, Ufer K, Palacios E and Montoya A (2016) Role of bentonite clays on cell growth, Chemosphere, 149: 57-61.
2. Giri TK, Thakur A, Ajazuddin AA, Badwaik H and Tripathi DK (2012). Modified chitosan hydrogels as drug delivery and tissue engineering systems: present status and applications, Acta Pharmaceutica Sinica B, 2 (5): 439-449.
3. Mogoşanu GD and Grumezescu AM (2014) Natural and synthetic polymers for wounds and burns dressing, International Journal of Pharmaceutics, 463 (2): 127-136.
4. Morton LM and Phillips TJ (2016) Wound healing and treating wounds: Differential diagnosis and evaluation of chronic wounds, Journal of the American Academy of Dermatology, 74 (4): 589-605.
5. Smith R G (2008) Enzymatic debriding agents: an evaluation of the medical literature. Ostomy/wound management, 54.8: 16-34.

Biography

Mihaela-Iustina Avram has completed her PhD at Grigore T Popa University of Medicine and Pharmacy, Romania. She is involved in the activities and she wants to discover new models with potential therapeutic applications. She conducted this study of the biological characterization and evaluation of hybrid hydrogels after intense and long-term research in the field. Developed hybrid hydrogels are recommended as new therapeutic alternatives for the treatment of chronic wounds.

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Tamas Lorincz et al., Med chem (Los Angeles) 2018, Volume 8
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Pharmacologic ascorbate and ferroptosis

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Pharmacologic (mM) concentration of ascorbate induces oxidative stress through the Fenton reaction. Cancer cells are known to show higher sensitivity towards ROS as normal cells. The mechanism of the induced cytotoxicity is still to be elucidated and involves oxidative stress, glutathione depletion, lipid peroxidation, the elevation of labile iron pool and caspase independency. In the frame of a large scale screening experiment to explore chemical compounds with killing effect on tumor cells a new chemical compound, erastin was identified which could induce cell death (ferroptosis) of RASmutant tumor cells. The morphology, biochemistry and genetics of ferroptosis differs considerably from other cell death types, such as apoptosis, necrosis, and autophagy and show high similarity as listed above which lead us to hypothesize that ferroptosis (at least partly) is responsible for ascorbate induced cytotoxicity in cancer cells.

Recent Publications

1. Tamás Lőrincz, Katalin Jemnitz, Tamás Kardon, József Mandl, András Szarka
2. Ferroptosis is Involved in Acetaminophen Induced Cell Death
3. Pathology Oncology Research 21:(4) pp. 1115-21. (2015)
4. Tamás Lőrincz, András Szarka
5. The determination of hepatic glutathione at tissue and subcellular level
6. Journal of Pharmacological and Toxicological Methods 88: pp. 32-39. (2017)
7. Szilvia Z Tóth, Tamás Lőrincz, András Szarka
8. Concentration Does Matter: The Beneficial and Potentially Harmful Effects of
9. Ascorbate in Humans and Plants
10. Antioxidants and Redox Signaling [Epub ahead of print] (2017)
11. Area of research interest: cell death, *in vitro* toxicology, antitumor pharmacology

Biography

Tamas Lorincz has an MSc. degree in biochemical engineering and is a PhD candidate in the group lead by Professor Dr. Andras Szarka at Budapest University of Technology and Economics. Tamás Lőrincz received a Gedeon Richter Plc. Talentum PhD. scholarship in 2014 and the New National Excellence Program scholarship of the Hungarian Ministry of Human Capacities in 2017.

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Notes:

Katarzyna Gach-Janczak et al., Med chem (Los Angeles) 2018, Volume 8
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In vitro and *in vivo* activity of opioid cyclopeptide with mu/delta agonist profile

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Centrally acting opioid agonists, such as morphine, are the most widely used analgesics for the treatment of severe pain. Among the three types of classic opioid receptors, mu, delta and kappa, the mu receptor was identified as primarily responsible for the pain-relieving effects but also responsible for a number of undesired side effects, including sedation, respiratory depression, inhibition of gastrointestinal transit, tolerance and physical dependence. In the previous decades, chemists and pharmacologists focused on obtaining analogs with high selectivity for one opioid receptor type. More recently, the development of compounds with mixed opioid profile is gaining a lot of interest eg. synergistic antinociceptive effects in response to the mu and delta receptor activation were observed in several *in vivo* studies. In this study we have shown that the replacement of the tyrosine residue in the mu-selective opioid ligand Tyr-c[D-Lys-Phe-Asp]NH_2 with 2',6'-dimethyltyrosine (Dmt) produced a cyclopeptide Dmt-c[D-Lys-Phe-Asp]NH_2 with mu-delta opioid receptor profile. This new analog showed improved antinociception in the hot-plate test as compared to the parent peptide but also significantly inhibited the gastrointestinal transit. Using the bioluminescence resonance energy transfer (BRET) assay it was shown that this analog was biased toward β-arrestin. To the best of our knowledge, it is the first reported β-arrestin biased opioid analog of a peptide structure. Our data are in accordance with earlier reports indicating that various *in vivo* activities of opioid agonists arise not only from the activation of one or more opioid receptors, but also from promoting G-protein or β-arrestin pathways.

Biography

Katarzyna Gach-Janczak has been working in the Department of Biomolecular Chemistry at Medical University of Lodz since 2006, first as a PhD student, then as an Assistant and now as an Assistant Professor. In May 2010, she defended her Doctoral thesis. She completed her Post-doctoral training in the Laboratory of Neuronal and Neuroendocrine Differentiation and Communication, University of Rouen (France). Her area of scientific interests is bidirectional. She is searching for new analgesics based on the structure of the endogenous opioid peptides and studying synthetic heterocyclic compounds as potential anticancer agents. She has published 43 research papers in international journals.

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e-Poster

Jose Ignacio Bueso-Bordils et al., Med chem (Los Angeles) 2018, Volume 8
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Obtention of minimum inhibitory concentration prediction equations for antibacterial quinolones versus two gram-positive and two gram-negative pathogenic bacteria

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The search for new molecules with therapeutic activity is a laborious process with an elevated economic cost. To find a new therapeutic activity for a compound which is provided with pharmacological and toxicological information mean an important saving of money and time which improves its pharmaceutical development as a new drug. Among the different methods used for this purpose, molecular topology has showed to be a useful tool to find quantitative relationships between chemical structure and activity. In this work, a multilinear regression analysis has been carried out in order to look for functions capable of accurately predicting a series of biological properties of a group of quinolones, widely used nowadays because of their broad spectrum activity, well tolerance profile and advantageous pharmacokinetic properties. In order to establish quantitative relationships, it is necessary to numerically describe the chemical structure of compounds by means of topological indices. The studied activities were minimum inhibitory concentration of 50 against *Proteus vulgaris* and *Staphylococcus epidermidis;* and minimum inhibitory concentration of 90 against *Clostridium perfringens* and *Haemophilus influenzae*. The species targeted in this study are very common human pathogens. Intercorrelation, Y-randomization and cross-validation by using leave-one-out test were also performed in order to assess the stability and the prediction ability of the functions selected.

Biography

Jose Ignacio Bueso-Bordils has completed his PhD from CEU Cardenal Herrera University. He is an Associate Professor at CEU Cardenal Herrera University. He has published three papers in reputed international journals, including *European Journal of Medicinal Chemistry*.

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Accepted Abstracts

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Chemical analysis of gallstones of district Peshawar and Mardan by atomic absorption spectrophotometer

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Gall bladder cancer [GBC] is a highly fatal malignancy. Regions of high prevalence of gallstones [GS] have shown to have higher rates of GBC, which is now a recognized risk factor for GBC. In these regards, heavy metal toxicity has also been reported to associate with GBC. It is also known that over the time heavy metals can accumulate in the biliary system and hence in the GS. An effort therefore at recognizing and avoiding potential risk factors for GBC occurrence is paramount. The present study was aimed to determine the chemical composition and heavy metal occurrence in gallstones. For this purpose, Gallstones were collected from patient admitted in Ali medical center and Mardan Medical complex, Mardan for surgical treatment (cholesistectomy), and also interviewed the GBC patients dietary pattern, nutritional status, lifestyle and non-dietary habits, a closed ended questionnaire was prepared. Biological samples including blood, hair, nails, were collected from the patients. We reported quantitative and qualitative chemical analysis of gallstone. The major element involved in the formation of gallstone is Ca (Calcium), Cholesterol, and the bile pigment, Mn (manganese), Fe (iron), Co (cobalt), Cu (cupper) were also the minor components of gallstones. These heavy metals determination were carried out with highly sensitive technique using Atomic Absorption Spectrophotometer (AAS). This study is involved different type of gallstones i.e. cholesterol, pigment stone, and the missed stone. Results revealed that ratio of cholesterol stone is greater as compared to pigment stone and mixed stone. Cholesterol level 54% mixed stone 40% and the pigment stone is 6% according to experimental results and also with contribution of the minor component like Fe, Mn, Co, Cu. A total of 54% of cholesterol gallstones were found in our study with the female predominance.

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Novel dihalo-substituted thiocarbamides as standalone agents to combat deadly tuberculosis: Design synthesis and bioevaluation

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Studies carried out in the field of TB biochemistry have revealed that M. tuberculosis is unique among most bacteria, therefore, several drugs require activation *in situ* to produce the inhibitory effect. Impelled by the fact, it was envisaged to develop and screen newer dihalo-substituted thiocarbamide derivatives as an analog of ethionamide against strains of *Mycobacterium tuberculosis* (Mtb). The chemical modification approach was chosen in the hope that it may provide information in the identification of some new targets. There are several known targets which are involved in the synthesis of some specific protein or mycolic acid for which InhA is the key enzyme. Various thiocarbamide drugs (ETH, TAC, ISO and C26) act via different final targets upon metabolic activation by the EthA protein inhibiting the biosynthesis of mycolic acid. Some novel dihalo-substituted thiocarbamide derivatives were synthesized and structures of these derivatives were established on the basis of IR, 1H and 13C-NMR and mass spectral data. All the dihalo-substituted thiocarbamide derivatives were tested *in-vitro* for antimycobacterial activity against *Mycobacterium tuberculosis* (ATCC-25177) by well diffusion method and MIC by serial dilution method. Results of the antitubercular screening disclosed that some of the derivatives showed moderate to good antitubercular potential. Among all the tested derivatives, two viz., 1-(3,4-Dichlorophenyl)-1-(furan-2-ylmethyl)-3-phenylthiourea and 1-(3,4-Dichlorophenyl)-3-phenyl-1-(1-(thiophen-2-yl)ethyl)thiourea displayed MIC values of 25µg/mL and one compound 1-(3-Chloro-4-fluorophenyl)-3-phenyl-1-(1-(thiophen-2-yl)ethyl)thiourea exhibited MIC value of 12.5µg/ml against *Mycobacterium tuberculosis* (ATCC-25177).

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Novel diterpene derivatives induced apoptosis in human lung cancer cell lines in p53 independent mechanism

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Lung cancer has been identified as the most lethal form of cancer today. We designed and screened 16 diterpene derivatives for their cytotoxic activties in H1299 human large cell lung carcinoma cells that are null for p53, normal lung epithelial cell lines (NL-20). Our data indicated that Diterpene derivatives 9 and 15 decreased cell proliferation and induced apoptosis in H1299 lung cancer cells more than normal lung epithelial NL-20 cells. Flow cytometric analysis showed that both Diterpene derivatives 9 and 15 arrested the H1299 cells in G1 phase which is further confirmed by increased expression level of p21. Moreover, both diterpene derivatives increased caspase-9 activitiy and the induction of apoptosis was significantly reduced after treating cells with caspase-9 inhibitor LEHD-CHO. Both Diterpene derivatives increased Caspase 3 activities and induced Parp-1 cleavage in H1299 cells. Based on previous results, we have identified two novel diterpenes derivatives which provoked apoptosis lung cancer cells by arresting cells in G1 phase and increasing caspase-9 and caspase-3 activities. The above findings demonstrate that diterpene derivative 9 and 15 induces apoptosis in H1299 cells in p53-indpendent mechanisms which merits further development.

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High-throughput virtual screening of chalcone compounds against diverse targets-development and use of a specific chalcone virtual library

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The chalcone family of compounds are well-known for their different therapeutic properties including anti-inflammatory, anti-microbial or anti-cancer activities, although the mechanism in many cases is not well understood. The generation of a virtual library mimicking the aldol condensation was effected with a view to expansion with aliphatic side chains as a result of alkyl halide reactivity. This virtual library was based on a very specific set of criteria with respect to substituents and with availability of the starting materials (substituted acetophenones and benzaldehyde derivatives) from suppliers for actual experimental work. The resulting 8063 compounds in the library were subjected to semiempirical AM1 geometry optimizations with the use of Gaussian 09, prior to virtual screening (docking using Autodock Vina) against 17 targets including HIV-1 integrase, MRSA pyruvate kinase, HSP09, COX-1, COX-2, ALR2, MAOA and AMOB, acetyl choline esterase A and B and PLA2 (including more than one enzymatic structure where conformers are available). The choice of targets related to the existence in the literature of similar compounds to those in this library having experimental activities against these targets. Lead compounds have been identified, and molecular dynamics has provided information about the strength of binding in several cases.

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Molecular docking study and structure-based design of novel camptothecin analogues used as topoisomerase I inhibitor

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This paper involves the molecular docking study on the inhibition of Human topoisomerase I (top1) which is the molecular target of a diverse set of anti-cancer compounds by Glycinate, camptothecin and its analogs. Their reaction mechanisms involving their interaction to a transient top1-DNA covalent complex, in order to inhibit the resealing of a single-strand nick created by the enzyme to relieve superhelical tension in duplex DNA, were confirmed using Quantum computational techniques in ICM-Pro Molsoft program. Our research findings on this reaction inquiry of the human top1-DNA complex bound with camptothecin analogs were helpful in improving the activities of top1 poisons through a structure based computational drug design. our results indicate that the Pi-Pi interactions of the camptothecin drugs with DNA as a result of its planner nature and the presence of some fragments on the lactone E-ring were directly responsible for its stable ternary complex with topo 1. The molecular docking result of our study shows Morpholinodoxorubicin (-32.835 kcal/mol), 9-Amino-20-RS-Camptothecin (-28.792 kcal) and Camptothecin Lysinate HCl (-28.224 kcal) best inhibit topo 1 when compared with other NSC compounds within our data set. These compounds were further utilized in designing new potent antitumor compounds by attaching potent fragments to the lactone ring of the compounds. Most of these compounds were reported to be more active than the parent structure, some of which includes CLD-12, CLD-7, CD-9 with a binding affinity of -40.307kcal/mol, -36.743kcal/mol and -36.072kcal/mol respectively. At the end of our study, we were able to optimize potent novel compounds that can be used to inhibit topoisomerase 1 enzyme.

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Synthesis, anti-bacterial activity and molecular docking of novel pyrazole conjugates

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A novel series of pyrazole conjugates were synthesized using molecular hybridization approach through Vilsmeier-Haack reaction. The structure elucidation of the synthesized compounds was established using 1HNMR, 13CNMR, IR and elemental analyses. All compounds were tested for antimicrobial activity against two Gram positive bacteria (Methicillin-resistant *Staphylococcus aureus, Staphylococcus aureus)* and four Gram negative bacteria *(Escherichia coli, Salmonella typhimurium, Klebsiella pneumonia* and *Pseudomonas aeruginosa)*. Among the compounds tested, 3-(2,4-dichlorophenyl)-1-(2,4-dinitrophenyl)-1pyrazoyl)methylene)hydrazinecarbothioamide (3a) and 2-((3-(2-chlorophenyl)-1-(2,4-dinitrophenyl)-1H-pyrazol-4-yl)methyleneamino)thiazolidin-4-one (4b) emerged as the most cogent antimicrobial compounds with minimum bacterial concentration (MBC) of 0.08, 0.08, 0.16 and 0.16 µg/mL against MRSA and *S. aureus* respectively. Molecular docking studies of the compounds into the crystal structure of topoisomerase II and topoisomerase IV suggested that compounds 3a and 4b preferably interact with the target through hydrogen bonding.

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Electromembrane extraction combined with capillary electrophoresis for the determination of metoclopramide and ondansetron in urine samples

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Electromembrane extraction (EME) is a sample preparation technique in pharmaceutical, chemical, clinical and environmental analysis. This technique uses electro-migration across artificial liquid membranes for selective extraction of analytes and sample enrichment from complex matrices. This method has many advantages such as simplicity, rapid, low-cost, low LOD, high pre-concentration factor and high recovery. In the present work, simultaneous pre-concentration and determination of two basic drugs namely metoclopramide (MCP) and ondansetron (OSN) were studied using EME as a suitable extraction method, followed with capillary electrophoresis (CE) using ultraviolet (UV) detection as separation technique. The drugs were extracted from 4 ml sample solutions, through a supported liquid membrane (SLM) consisting 2-nitrophenyloctylether (NPOE) impregnated in the walls of a polypropylene hollow fiber, and into a 20 mL acidic aqueous acceptor solution resent inside the lumen of the hollow fiber with a potential difference applied over the SLM. The variables of interest, such as chemical composition of the organic liquid membrane, stirring speed, extraction time and voltage, pH of donor and acceptor phases and salt effect in the EME process were investigated and optimized. Under optimal conditions NPOE as SLM, stirring rate of 1000 rpm, 200 V potential differences, 20 min as the extraction time, acceptor phase HCl (pH 1.0) and donor phase HCl (pH 1.5). After the microextraction process, the extracts were analyzed by CE with optimum conditions phosphate running buffer (pH 2.0), applied voltage of 20 kV and 25°C. Under the optimum conditions, limits of detection (LOD) and quantification (LOQ) for MCP and OSN were 2.31-2.68 and 7.72-8.91 ng mL-1 respectively. Pre-concentration factor and RSD for five replicates of each drug were calculated to be 200 and 4.06-3.93 respectively. Finally, the applicability of this method was studied by the extraction and determination of these drugs in urine samples with recovery percentages of 87–92%.

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Chemical fertilizers and its effect on the quality of groundwater in the Tadla irrigated plain; Morocco

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In Morocco, irrigated perimeters are threatened by diffuse nitric pollution of groundwater, which reduces the potential of water resources which are of good quality, thus creating a health risk for the population and socioeconomic developments in the country. Control of this pollution requires sufficient knowledge of the causes and mechanisms responsible for this problem. The Beni Mellal-Khénifra region suffers from the misuse of agrochemical inputs coupled with agricultural intensification and heavy pumping of groundwater, which is making water in the region of poor quality. Despite decades of efforts to reduce the release of pollutants into the environment, nutrient enrichment of aquatic environments remains an important issue, especially phosphates released into the environment, which come from agricultural sources (Fertilizers) and industrial wastes, human excreta and detergents or phosphate washed, and nitrates that turn into nitrites causing diseases that are in some cases fatal in newborns. In this context, this study has achieved to determine the effects of the use of fertilizers on the water quality of the Tadla aquifer, by carrying out various analyzes such as nitrates, nitrites and phosphates, whose results have allowed extracting polluted areas and unpolluted areas.

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Synthesis of dihydroquinoline carboxamide derivatives, as anti-tubercular agents

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Quinoline derivatives have wide applicability in various fields of medicinal, industrial, bio-organic and synthetic organic chemistry. Sodium trifluromethanesulfonate, and glacial acetic acid efficiently catalyzed the synthesis of dihydroquinoline via Friedländer annulation. The synthesized dihydroquinoline analogues coupled with different amines by the use of coupling reagent gave dihydroquinoline carboxamide derivatives in moderate to good yields. The synthesized compounds were evaluated for the anti-tubercular activity and cytotoxic activities. The structure of all the novel compounds were confirmed using 1H NMR, 13C NMR and mass spectral techniques.

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Sorption affinities of chromium on natural phosphate and its derivative hydroxyapatite

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Moroccan natural phosphate and its converted hydroxyapatite were used to develop an effective adsorbent suitable for the removal of trivalent and hexavalent chromium from aqueous solution. The converted hydroxyapatite was prepared from natural phosphate and characterized using various techniques of characterization. Thus, the adsorption of Cr (III) and Cr2O72- ions were investigated to understand the adsorptive selectivity of two chromium oxidative degrees on natural phosphate and its derivative apatite using batch system at room temperature. The sorption results showed a high affinity of natural phosphate for the Cr2O72- than c-HAP contrary to Cr (III) adsorption related to the presence of silica groups present in natural phosphate while the converted apatite has a good affinity for Cr (III) ions. The adsorption behavior of both adsorbent fitted the Langmuir and Freundlich isotherm models implying that the adsorption mostly occurred through a heterogeneous binding of metal to the surface of the adsorbent.

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Novel drug discovery approaches for cancer metabolism: old paradigm with new perspective

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Cancer still remains the second leading cause of death in the world after heart disease and cardiovascular complications. Moreover, survivors of cancer still continue to suffer from symptoms of pain, fatigue, and depression despite existing treatment advances for cancer treatment. Even though numerous pharmacological therapies have been developed in the past decade, the advantage of new treatment options remains important in the fight against this deadly disease. It is now well understood that protein kinases play key roles in the growth and survival of cancer cells by regulating their onset of DNA synthesis, their response to DNA damage and their entry, progression, and exit from mitosis. Clinical validations prove that protein kinases are an attractive class of therapeutic drug targets for cancer as demonstrated with the recent approval of six protein kinase inhibitors. The Warburg effect describes the particular reliance of cancer cells on glycolysis for energy. Increased glycolysis and acid resistance have been postulated to be an essential part of carcinogenesis, conferring a significant growth advantage as well as promoting typical tumor progression. Targeting accelerated glycolysis in cancer cells is a new promising modality for treatment of cancer. Inhibition of glycolysis can be done without significant side effects, and such treatment will be additive to most known cancer therapies. Recent studies show that Methyl Jasmonate reveals promising results for treatment of cancer. During the presentation the role of Aerobic Glycolysis for tumor growth and small molecule drug discovery and development efforts as well as their therapeutic applications for oncological indications will be highlighted.

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Synthesis of 2-substituted pyrazolines as potential antimalarial and antimicrobial agents

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A novel series of 2-substituted pyrazolines were synthesized and evaluated for *in vitro* antimalarial efficacy against chloroquine sensitive (MRC-2) as well as chloroquine resistant (RKL9) strains of *Plasmodium falciparum*. Compounds were confirmed by elemental analyses, IR, 1H NMR and 13C NMR spectral data. Compounds 5o (IC50=0.032 μM for MRC-2 and IC50=0.209 μM for RKL-9) displayed better antiplasmodial activity than chloroquine. The antibacterial and antifungal evaluations were also conducted, compounds 5d and 5k exhibited better antibacterial activity against *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* than ciprofloxacin. Antifungal activity of compound 5n against A. niger (MIC-3.36 μg/ml) and C. albicans (MIC-6.9 μg/ml) was found to be better than the standard drug fluconazole.

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Role of dynamic nonprime binding of sampatrilat for the development of domain selective inhibitors

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Sampatrilat is a vasopeptidase inhibitor that inhibits both angiotensin I-converting enzyme (ACE) and neutral endopeptidase. ACE is a zinc dipeptidyl carboxypeptidase that contains two extracellular domains (nACE and cACE). In this study the molecular basis for the selectivity of sampatrilat for nACE and cACE was investigated. Enzyme inhibition assays were performed to evaluate the *in vitro* ACE domain selectivity of sampatrilat. The inhibition of the Cdomain (Ki=13.8 nM) by sampatrilat was 12.4-fold more potent than that for the N-domain (171.9 nM), indicating differences in affinities for the respective ACE domain binding sites. Interestingly, replacement of the P2 group of sampatrilat with an aspartate abrogated its C-selectivity and lowered the potency of the inhibitor to activities in the micromolar range. The molecular basis for this selective profile was evaluated using molecular modeling methods. We found that the C-domain selectivity of sampatrilat is due to occupation of the lysine side chain in the S1 and S2 subsites and interactions with Glu748 and Glu1008, respectively. This study provides new insights into ligand interactions with the nonprime binding site that can be exploited for the design of domain selective ACE inhibitors.

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Drug discovery from edible plants based on GLP-1R disease target

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The glucagon-like peptide-1 receptor (GLP-1R) is expressed in many tissues and has been implicated in diverse physiological functions, such as energy homeostasis and cognition. GLP-1 analogs are approved for treatment of type 2 diabetes and are undergoing clinical trials for other disorders, including neurodegenerative diseases. GLP-1 analog therapies maintain chronically high plasma levels of the analog and can lead to loss of spatiotemporal control of GLP-1R activation. To avoid adverse effects associated with current therapies, we characterized positive modulators of GLP-1R signaling. We screened extracts from edible plants using an intracellular cAMP biosensor and GLP-1R endocytosis assays. Galanal B and a new compound (N55) were isolated from Hedychium coronarium (HC) and Trigonella foenum-graecum (fenugreek) respectively as active principles for modulating glucagon-like-peptide-1 GLP-1 activity. The first total syntheses of both natural products and their analogue were finished for structure elucidation and SAR study. These findings identify a new class of modulators of GLP-1R signaling and suggest that GLP-1 is a viable target for drug discovery.

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Lyso-DGTS lipid isolated from microalgae enhances PON1 activities *in vitro* and *in vivo*, increases PON1 penetration into macrophages and decreases cellular lipid accumulation

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High-density lipoprotein (HDL) plays an important role in preventing atherosclerosis. The antioxidant effect of HDL is mostly associated with paraoxonase 1 (PON1) activity. Increasing PON1 activity using nutrients might improve HDL function and quality and thus, decrease atherosclerotic risk. We previously isolated and identified a novel active compound, Lyso-DGTS (C20:5, 0) from *Nannochloropsis* sp. ethanol extract. In the present study, its effect on PON1 activities was examined and the mechanism by which the compound affects PON1 activity was explored. Lyso-DGTS elevated recombinant PON1 (rePON1) lactonase and esterase activities in a dose- and time-responsive manner, and further stabilized and preserved rePON1 lactonase activity. Incubation of lyso-DGTS with human serum for 4 h at 37˚C also increased PON1 lactonase activity in a dose-responsive manner. Using tryptophan-fluorescence-quenching assay, lyso-DGTS was found to interact with rePON1 spontaneously with negative free energy G=-22.87 KJ/mol at 25˚C). Thermodynamic parameters and molecular modeling calculations showed that the main interaction of lyso-DGTS with the enzyme is through a hydrogen bond with supporting van der Waals interactions. Furthermore, lyso-DGTS significantly increased rePON1 influx into macrophages and prevented lipid accumulation in macrophages stimulated with oxidized low-density lipid dose-dependently. *In-vivo* supplementation of lyso-DGTS to the circulation of mice fed a high-fat diet via osmotic mini-pumps implanted subcutaneously significantly increased serum PON1 lactonase activity and decreased serum glucose concentrations to the level of mice fed a normal diet. Our findings suggest a beneficial effect of lyso-DGTS on increasing PON1 activity and thus, improving HDL quality and atherosclerotic risk factors.

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Plant macromolecule from different species of Boraginaceae family and its anticancer efficacy

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The 13C NMR experiments of water-soluble high-molecular preparations from different species of *Boraginaceae* family *Symphytum asperum, S. caucasicum, S. officinale, S. grandiflorum* and *Anchusa italica* were carried out and simulated 13C NMR spectrum was calculated for 2-hydroxy-3-(3',4'-dihydroxyphenyl)-propionic acid residue (I) of the corresponding polyether using ACD/CNMR Version 1.1 program. Signal positions in the 13C NMR spectrum of this hypothetical structure (I) coincided satisfactory with the experimental values. According to 13C, 1H NMR, APT, 2D heteronuclear $^{1}H/^{13}C$ HSQC and 2D DOSY experiments the main structural element of these preparations was found to be a regularly substituted by 3,4-dihydroxyphenyl and carboxyl groups polyoxyethylene backbone, namely poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDPGA). The repeating unit of this polymer is 3-(3,4-dihydroxyphenyl)glyceric acid residue. Most of the carboxylic groups of PDPGA from *A. italica and S. grandiflorum* are methylated. PDPGA is endowed with intriguing pharmacological properties as anticomplementary, antioxidant, anti-inflammatory, burn and wound healing effect. The synthesis of racemic monomer of PDPGA 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)propionic acid (DDPPA) was carried out via Sharpless asymmetric dihydroxylation of trans-caffeic acid derivatives using a potassium osmate catalyst. The PDPGA and DDPPA exerted anti-cancer efficacy *in vitro* and *in vivo* against human prostate cancer (PCA) cells via targeting androgen receptor, cell cycle arrest and apoptosis without any toxicity, together with a strong decrease in prostate specific antigen level in plasma. However, our results showed that anticancer efficacy of PDPGA is more effective compared to its synthetic monomer. Overall, this study identifies PDPGA as a potent agent against PCA without any toxicity, and supports its clinical application.

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Effiacy of amygdalin (vitamin B17) as natural anti-tumor drug

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Cancer is the disease type which may lead to death. There were different risk factors that increases the rate of cancer development, these factors may include genetic, inherited, environmental, and life important strategy in treatment of this disease; chemotherapy infusion has various side effects. The style factors. There were different strategies in the treatment of cancer. Chemotherapy is one of the new trends in treatment of cancer using natural chemotherapy. Most studies assume that vitamin B17 has ability to kill the malignant cell, to prevent it from spreading it to other organs and this help to control cancer, on the other hand healthy cells doesn't have effect with this therapy. Some researchers indicate vitamin B17 injection may be effective on healthy cells due to the toxic effect of cyanide which present is in composition of vitamin B17, also, they found toxic effects of vitamin B17 can be released if taken orally from its natural sources due to the action of gut bacteria.

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