Title: Hydrocortisone Nanosuspensions for Ophthalmic Delivery: A Comparative Study between Microfluidic Nanoprecipitation and Wet Milling

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Source: *Journal of Controlled Release, 149, 175-181 (2011)*

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Recently, drug nanosuspensions have shown a potential for ophthalmic delivery. In this study, a hydrocortisone (HC) nanosuspension (NS) was developed using microfluidic nanoprecipitation as a recent, simple and cost-effective bottom-up technique of drug nanonization. For comparison, a second HC NS was prepared by top-down wet milling procedures. The produced nanosuspensions were characterized for particle size, shape and zeta potential. HC nanosuspensions of approximately 300 nm particle size were produced by adjusting experimental conditions of the two processing techniques. Results of X-ray diffraction and differential scanning calorimetry revealed that HC maintained the crystalline structure upon milling, while predominant amorphous particles were generated after precipitation. Ocular bioavailability of HC nanosuspensions was assessed in albino rabbits using HC solution as a control. A sustained drug action was maintained up to 9 h for the nanosuspensions compared to 5 h for the

drug solution. The precipitated and milled NS achieved comparable AUC0–9h values of 28.06 ± 4.08 and 30.95 ± 2.2, respectively, that were significantly ($P < 0.05$) higher than that of HC solution (15.86 ± 2.7). After 2 months storage at room temperature, the milled HC NS showed good stability with no discernable changes in particle size, whereas the particle size of the precipitated HC NS increased to 440 nm.

Title: Design and Characterization of Transdermal Films Containing Ketorolac Tromethamine

Authors: G. Fetih[1], M. A. Ibrahim[2], M.A. Amin[3]

Source: *International Journal of PharmTech Research, 3 (1), 449-458, Jan-Mar (2011)*

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The objective of this work was to develop suitable film formulations of ketorolac tromethamine (KT) for transdermal use and to investigate the effect of film composition and permeation enhancers on the in-vitro release and skin permeation of the drug. Polyvinyl alcohol (PVA), sodium carboxymethylcellulose (NaCMC), and chitosan were used as film-forming polymers. The adhesive hydrophilic polymers plastoid® E35L (PL E35) and polyvinyl pyrrolidone (PVP) were added to improve bioadhesion. The permeation enhancers used were oleyl alcohol (OA), sodium glycocholate (NaGC) and propylene glycol (PG). Formulated films were characterized by measuring their mean thickness, mass, drug content, folding endurance and bioadhesion. In-vitro release was studied using the USP XXIII rotating paddle method and in-vitro permeation across hairless rat skin was studied using an in-vitro diffusion cell. Addition of PVP enhanced the drug release and permeation especially in case of chitosan, while Plastoid® E35L improved permeation only. Skin permeation of the drug was greatly improved by

the addition of permeation enhancers, the rank of their effectiveness was: sodium glycocholate (Na GC) > oleyl alcohol (OA) > propylene glycol (PG). The results obtained showed that these polymeric films can be a promising therapeutic system for the transdermal delivery of ketorolac.

Title: Design and Evaluation of Ciprofloxacin Hydrochloride Ocular Inserts

Authors: Mohamed A. Attia[1,2], Mohamed El-Azizi[1], Mohamed S. Hashish[1]

Source: *Int. J. PharmTech. Res., 3 (3), 1750-1763 (2011)*

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Ocular Conjunctivitis is one of the main causes of red eye syndrome. The present work focuses on the treatment of ocular conjunctivitis by using combined mechanisms:

(1) Formulation of ocular inserts to provide prolonged and sustained release system of the drug.

(2) Use of therapeutic agent, as ciprofloxacin hydrochloride in combination with the polymers used. The selected polymers were methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), and Eudragit RS100 (ERS 100). The developed ocular inserts were evaluated for physic-chemical, mechanical, drug release, drug permeability, and In-vivo characteristics. The ocular inserts showed desired delivery of the drug to the ocular tissue of the rabbit's eye. In-vivo studies showed that ciprofloxacin hydrochloride had a significant effect on reduction of induced ocular conjunctivitis.

Title: Novel Optimization of Shape, Swelling and Release Behaviors of Tolmetin Sodium Loaded Alginate Microbeads

Authors: A.K. Hussein[1], G. Fetih[2]

Source: *J. Drug Del. Sci. Tech., 21 (2) 165-174 (2011)*

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In the design of oral delivery, alginates (Alg) have attracted increasing attention. However, due to their hydrophilic character incorporation of small hydrophilic drugs such as tolmetin sodium (TOL) into Alg beads will not provide the desired regular shape as well as delayed drug release.

There is no study investigating the effect of methylcellulose (MC) and dual cross-linking (CaCl2 and glutaraldehyde, GA) on their shape, swelling and release behaviors. Hence this study aimed to evaluate the influence of MC and cross-linking agents on these behaviors of Alg microbeads prepared using the ionotropic gelation method compared with Alg microspheres prepared with w/o emulsion method. The results obtained display some interesting information. Both concentration of MC and type of cross-linking agent had dramatic effects on shape as well as swelling, erosion and release behaviors of the prepared microbeads. Swelling through ion-exchange process of Alg/MC blend single cross-linked microbeads was hindered in the case of dual cross-linked microbeads. The release of the drug from Alg/MC dual cross-linked microbeads was extended for

up to 12 h and the release mechanism was shifted from erosion type release to time-independent release process. Analgesic activity study indicated significantly different response patterns compared with plain TOL solution.

Title: Preparation, Charactarization and Anti-Inflammatory Activity of Celecoxib Chitosan Gel Formulations

Authors: M. El-Badry[1,2], G. Fetih[2]

Source: *J. Drug Del. Sci. Tech., 21 (2), 201-206 (2011)*

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This study was designed to evaluate the suitability of chitosan polymer as a vehicle for topical delivery system. celecoxib, which is a nonsteroidal anti-inflammatory drug, was incorporated into the gel vehicles in a concentration of 0.5 % w/v. Gels were prepared using three different concentrations and different molecular weights of chitosan. Viscosity, drug release from gels, permeation of drug through rat skin and anti-inflammatory activity of the drug were studied. In vitro release characteristics of the drug from different gels were carried out using dialysis membrane in phosphate buffer using a pH of 6.8. The results showed that, the gel form containing 1.0 % w/v medium molecular weight chitosan has superior drug release than other forms, whilst the gel form containing 2.0 % w/v high molecular weight chitosan shows the lowest amount of drug release. The release data were treated with various kinetic principles to assess the relevant parameters. The results revealed an inverse correlation between the percent drug release and the polymer concentration used. The results also showed that the release of drug from the prepared gels obeyed the Higuchi's diffusion model. The

permeation of drug through rat skin was carried out. The flux of drug is independent on the viscosity of the formulae. The anti-inflammatory activity of the drug in different gel formulations was studied using carrageenan-induced rat paw edema method. The results obtained show that there is excellent anti-inflammatory activity of the gel forms on rat paw edema.

Title: Pilot Randomized Trial for Treatment of Bacterial Vaginosis using In Situ Forming Metronidazole Vaginal Gel

Authors: Omar M. Shaaban[1], Gihan N. Fetih[3], Noura H. Abdellah[3], Sayed Ismail[3], Maggie A. Ibrahim[2], El-Sayed A. Ibrahim[3]

Source: *J. Obstet. Gynaecol. Res., 37 (7), 874-881, July (2011)*

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Aim: *To compare the efficacy of a novel vaginal delivery system for metronidazole (0.8% MTZ in situ gel) versus a conventional MTZ vaginal gel product in the treatment of bacterial vaginosis (BV).*

Material and Methods: *All consecutive patients who presented to a tertiary care hospital with symptoms suggestive of BV were approached to participate in the study. Forty-two eligible participants were randomly assigned to either MTZ in situ gel or a conventional vaginal gel product twice daily for 5 days. All participants were re-examined after one and 4 weeks of the beginning of treatment to ensure cure of infection and any side-effects.*

Results: *Demographic criteria of the participants were comparable in the two treatment groups. The cure rate after one week from the treatment was 85% in the in situ gel group and 71.4% in the conventional vaginal gel group (P = 0.294),*

while after 4 weeks, the cure rate showed significant difference in the in situ gel group as compared to the conventional vaginal gel group (16/20 [80%]) and (9/19 [47.4%]), respectively (P = 0.034).

Conclusion: *Pilot testing showed that in situ MTZ vaginal gel is more effective than the conventional vaginal gel for long-term cure of BV. These findings suggest a novel and efficient long-term treatment of BV.*

Title: Short Ligands Affect Modes of QD Uptake and Elimination in Human Cells

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Source: *ACS Nano, 5 (6), 4909-4918 (2011)*

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In order to better understand nanoparticle uptake and elimination mechanisms, we designed a controlled set of small, highly fluorescent quantum dots (QDs) with nearly identical hydrodynamic size (8-10 nm) but with varied short ligand surface functionalization. The properties of functionalized QDs and their modes of uptake and elimination were investigated systematically by asymmetrical flow field-flow fractionation (AF4), confocal fluorescence microscopy, flow cytometry (FACS), and flame atomic absorption (FAA). Using specific inhibitors of cellular uptake and elimination machinery in human embryonic kidney cells (Hek 293) and human hepatocellular carcinoma cells (Hep G2), we showed that QDs of the same size but with different surface properties were predominantly taken up through lipid raft-mediated endocytosis, however,

to significantly different extents. The latter observation infers the contribution of additional modes of QD internalization, which include X-AG cysteine transporter for cysteine-functionalized QDs (QD-CYS). We also investigated putative modes of QD elimination and established the contribution of P-glycoprotein (P-gp) transporter in QD efflux. Results from these studies show a strong dependence between the properties of QD-associated small ligands and modes of uptake/elimination in human cells.

Title: Dendrimers and Miktoarm Polymers Based Multivalent Nanocarriers for Efficient and Targeted Drug Delivery

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Source: *Chemical Communications, 47, 9572-9587 (2011), doi:10.1039/C1CC11981H*

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The delivery of biologically active agents to the desired site in the body and intracellular organelles is still a big challenge despite efforts made for more than five decades. With the elaboration of synthetic methodologies to branched and hyperbranched macromolecules such as miktoarm stars and dendrimers, the focus has shifted to nanocarriers able to release and direct drug molecules to a desired location in a controlled manner. We present here recent developments in the field of targeted drug delivery with a focus on two specific macromolecular nanocarriers, dendrimers and miktoarm stars, and provide examples of these nanocarriers tested in different biological systems. A particular attraction of miktoarm stars is their versatility in achieving superior drug loading within their self-assembled structures. Advantages of dendrimers over linear polymers are that

the former provide a platform for development of multivalent and multifunctional nanoconjugates, in addition to their ability to accommodate a large number of molecules inside, or at their surfaces.

Title: Physicochemical Characterization and Dissolution Properties of Meloxicam-Gelucire 50/13 Binary Systems

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Source: *Sci. Pharm., 79, 375-386 (2011), doi:10.3797/scipharm.1101-22*

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A solid dispersion of Meloxicam (MX), a poorly soluble, non steroidal anti-inflammatory drug, and Gelucire 50/13 was prepared by spray drying. Spherical microparticles were yielded with smooth surfaces as observed by scanning electron microscopy. According to differential scanning calorimetry and powder X-ray diffractometry analysis, MX was transformed from the crystalline state to the amorphous state as confirmed by the disappearance of its melting peak and the crystalline peaks. The dissolution tests at pH 7.4 revealed that the dissolution rate of encapsulated MX was 2.5-fold higher than that of the corresponding physical mixture and fourfold higher than the drug alone, respectively. The microparticles prepared at a ratio of 1:4 (drug/Gelucire) exhibited a 4-fold higher anti-inflammatory activity on the paw edema of rats in comparison to the drug alone. All in all, this work reveals that spray drying is a suitable technique for preparation of solid dispersions with improved biopharmaceutical and pharmacological characteristics of MX.

Title: Enhancement of Dissolution and the Anti-Inflammatory Effect of Nimesulide, Using Liquisolid Compact for Oral Application

Authors: M. A. Hassan[1,2], H. M. El-Saghir[1]

Source: *Bull. Pharm. Sci., Assiut University, 34 (1), 1-8 (2011)*

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Nimesulide is a poorly soluble drug, the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them the technique of liquisolid compacts which is a promising one. The liquisolid compacts were prepared using 20 mg nimesulide, Avicel PH102 as a carrier, and Aerosil 200 as a coating material in a ratio of 20:1, as well as AC-DI-SOL as a disintegrant in a concentration of 5% from the total weight of the compact. The liquids used include PEG400, PG, and a mixture of these solvents with Tween 80. From the results obtained it is concluded that the suitable loading factor (L_f) is 0.2 which gave good flowability and compressibility. Friability, hardness, disintegration time and the dissolution rate were carried out. All the liquisolid compacts showed higher dissolution rate than the conventional tablets. The liquisolid compacts containing the PEG400 showed the highest dissolution rate than the other preparations. The effect of different concentrations of drug on the dissolution rate

was studied, and it was observed that 20% of drug gave the maximum dissolution rate, and no significant increase of the dissolution rate with increasing the drug concentration. Conventional tablets and liquisolid compacts containing PG and PEG400 were tested for their anti-inflammatory effects using paw oedema test. liquisolid compacts exhibited a pronounced inhibition of swelling than that of conventional tablets. In conclusion liquisolid compact of nimesulide can be used as a technique to improve the dissolution rate and the anti-inflammatory effect of nimesulide

Title: Mucoadhesive Buccal Patches of Lornoxicam: II– In-vivo Evaluation and Clinical Efficacy

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Lornoxicam is a NSAID of the oxicam class and it has the same side effects of this group when taken orally. In attempts to avoid the systemic side effects of lornoxicam (e.g. gastric irritation) and to achieve sustained release of the drug, several buccal patch formulations containing lornoxicam were prepared using different polymers and were evaluated for in-vitro characteristics in part I of this study. In the current study, the selected formulations (based on the previous in-vitro data) are evaluated for in-vivo performance using experimental animals and clinical efficacy on human volunteers. Pharmacokinetic parameters were assessed following application of the selected patches in rabbits. A comparative clinical study was conducted on patients with post-operative pain and edema following maxillofacial operations. The results of the in-vivo animal experiment showed that lornoxicam formulated in different buccal patches was successfully delivered to the systemic circulation and showed high absolute bioavailability of lornoxicam. The clinical study results revealed that sodium carboxy methyl cellulose (NaCMC, 3%) formulation applied to the buccal mucosa was slightly better or equally effective to the orally administered commercial oxicam product

(Feldene Flash® tablets) in reducing pain level, swelling and tenderness within a period of 4 days with no observed side effects. These findings suggest that lornoxicam administered in this buccal patch may present a potential therapeutic use as a strong anti-inflammatory and analgesic agent.

Title: Enhancement of Solubility and Dissolution Rate of Domperidone by Utilizing Different Techniques

Authors: E. H. Ibrahim, T. H. El-Faham, F.A. Mohammed, N. S. El-Eraky

Source: *Bull. Pharm. Sci., Assiut University, 34 (2), 105-120 (2011)*

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The aim of this study was to enhance solubility and dissolution of water insoluble antiemetic drug, domperidone, with three different techniques viz., solid dispersion, melt granulation, and liquisolid compacts techniques. Solid dispersion and melt granulation systems at 1:1, 1:2 and 1:3 drug to polymer ratios were prepared. Several liquisolid formulations containing various ratios of drug: liquid vehicle (ranging from 5% to 50% w/w) were formulated. The IR spectroscopy, scanning electron microscopy (SEM), X-ray powder diffractometry (XRD) and differential scanning calorimetry (DSC) were used to examine the physical state of the drug. Furthermore, the solubility and the in-vitro dissolution of the drug from the different systems were studied. The in-vitro dissolution study showed that the percent of the drug dissolved from solid dispersions containing 3 parts of each of PF-127, PEG 6000, Myrj 52 or PEG 4000 is 54.3, 48.98, 43.37, and 43.2% after 6 hrs respectively, compared to only 8% dissolved of drug alone. There is a highly significant difference in % of domperidone dissolved from solid dispersion, melt granulation, and liquisolid compacts systems compared to drug alone ($P< 0.001$), also the difference between solid dispersion system compared to the other systems

was highly significant (P< 0.001). It can be concluded that domperidone aqueous solubility and dissolution were markedly improved via solid dispersion technique with PF-127 prepared by solvent evaporation method compared to other methods used. The data from the (SEM), (XRD) and (DSC) revealed absence of crystalline structure for domperidone in its solid dispersion with Pluronic F-127 (1:3) drug to polymer ratio. Also, the IR spectra indicated the absence of well defined interaction.

Title: Formulation and Evaluation of Meclizine HCl Orally Disintegrating Tablets

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Source: *Bull. Pharm. Sci., Assiut University, 34 (2), 141-148 (2011)*

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Recent advances in novel drug delivery system aims at achieving better patient compliance. One of these advances is the formulation of orally dissolving tablets (ODTs) which dissolve instantaneously, releasing the drug, within a few seconds without the need of water. The main objective of this paper was to prepare and develop ODTs of Meclizine (MZ HCl) with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age for easy administration. Meclizine HCl is an anti-emetic drug used for management of dyspepsia, heartburn, epigastric pain, nausea, and vomiting. The interaction of meclizine and used excipients was studied using differential scanning calorimetry (DSC). The ODTs were prepared by direct compression method. The effect of varying concentrations of different superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time and dissolution rate was studied. The prepared tablets were

evaluated for hardness, friability, disintegration time and in-vitro drug release. DSC studies revealed that no interaction between the drug and the used excipients. All tablets had hardness in the range 4.2-5.6 kp and friability less than 1%. Weight variation and drug content of all formulations were within official limit according to BP. In-vitro drug release study of ODTs tablets showed that more than 90% of the drug was released within 10 min. Palatability test by 12 volunteers showed acceptable taste and mouth feel. Thus, results obtained conclusively demonstrated successful rapid disintegration of the formulated tablets and acceptable palatability.

Title: Design and Evaluation of Novel pH-Sensitive Chitosan Nanoparticles for Oral Insulin Delivery

Authors: Makhlof A.[1,2], Tozuka Y.[2], Takeuchi H.[2]

Source: *Eur. J. Pharm. Sci., 42, 445-451 (2011)*

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Chitosan nanoparticles (CS NPs) have been commonly regarded as potential carriers for the mucosal delivery of therapeutic peptides because of their biocompatibility, bioadhesion and permeation enhancing properties. However, they have limited colloidal stability and readily dissociate and dissolve in the acidic gastric conditions. In the current study, CS NPs were formulated by ionic cross-linking with hydroxypropyl methylcellulose phthalate (HPMCP) as a pH-sensitive polymer and evaluated for the oral delivery of insulin. In vitro results revealed a superior acid stability of CS/HPMCP NPs with a significant control over insulin release and degradation in simulated acidic conditions with or without pepsin. Furthermore, fluorescently-labeled CS/HPMCP NPs showed a 2- to 4-fold improvement in the intestinal mucoadhesion and penetration compared to CS/TPP NPs as evidenced by quantitative fluorescence analysis and confocal microscopy. After s.c. injection to rats, no significant difference in the hypoglycemic effect of insulin solution or insulin-loaded CS/HPMCP NPs was observed, confirming the physico-chemical stability and biological activity of the entrapped peptide. Following peroral administration, CS/HPMCP NPs increased

the hypoglycemic effect of insulin by more than 9.8 and 2.8 folds as compared to oral insulin solution and insulin-loaded CS/tripolyphosphate (TPP) NPs, respectively.

Title: In-vitro and In-vivo Evaluation of WGA-Carbopol Modified Liposomes as Carriers for Oral Peptide Delivery

Authors: Makhlof A.[1,2], Fujimoto S.[2], Tozuka Y.[2], Takeuchi H.[2]

Source: *Eur. J. Pharm. Biopharm., 77, 216-224 (2011).*

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Surface modification of liposomal nanocarriers with a novel polymer-lectin conjugate was proposed for enhancing the systemic uptake of encapsulated peptide and protein therapeutics after oral administration. Wheat germ agglutinin (WGA) was covalently attached to carbopol (CP) using the carbodiimide method. The prepared WGA-CP conjugate retained the biological cell binding activity of WGA without any evidence of cytotoxicity to Caco-2 monolayers. Cationic liposomes in the size range of 100 nm were prepared by the lipid film hydration method followed by probe sonication and surface modification with negatively charged WGA-CP. The uptake of WGA-CP liposomes by Caco-2 cells was significantly higher than non-modified or CP liposomes. The uptake was dependent on the surface concentration of WGA, temperature, and incubation period, and was significantly inhibited in the presence of chlorpromazine and 10-fold excess of free WGA. These results suggest the involvement of active transport mechanism for the cellular uptake of the modified liposomes, mediated mainly by binding of WGA to its specific cell

membrane receptors. Dual channel confocal microscopy confirmed the simultaneous association and internalization of the polymer conjugate and the liposomal carrier by Caco-2 cells and intestinal membrane of rats. In addition, the pharmacological efficacy of calcitonin, a model peptide drug, was enhanced by more than 20 and 3 folds following peroral administration of calcitonin-loaded WGA-CP liposomes as compared to non-modified and CP liposomes, respectively.

Title: Poly(Glycerol Adipate-co-ω-Pentadecalactone) Spray-Dried Microparticles as Sustained Release Carriers for Pulmonary Delivery

Authors: Hesham Tawfeek[1,2], Sayed Khidr[2], Eman Samy[2], Sayed Ahmed[2], Mark Murphy[1,3], Afzaal Mohammed[4], Anjum Shabir[4], Gillian Hutcheon[1], Imran Saleem[1]

Source: *Pharm. Res., DOI 10.1007/s11095-011-0433-6 (2011)*

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Purpose *The aim of this work was to optimize biodegradable polyester poly(glycerol adipate-co-ω-pentadecalactone), PGAco-PDL, microparticles as sustained release (SR) carriers for pulmonary drug delivery.*

Methods *Microparticles were produced by spray drying directly from double emulsion with and without dispersibility enhancers (L-arginine and L-leucine) (0.5–1.5%w/w) using sodium fluorescein (SF) as a model hydrophilic drug.*

Results *Spray-dried microparticles without dispersibility enhancers exhibited aggregated powders leading to low fine particle fraction (%FPF) (28.79±3.24), fine particle dose (FPD) (14.42±1.57 μg), with a mass median aerodynamic*

diameter (MMAD) 2.86±0.24 µm. However, L-leucine was significantly superior in enhancing the aerosolization performance (L-arginine:% FPF 27.61±4.49–26.57±1.85; FPD 12.40±0.99–19.54±0.16 µg and MMAD 2.18±0.35–2.98±0.25 µm, L-leucine:%FPF 36.90±3.6–43.38±5.6; FPD 18.66±2.90–21.58±2.46 µg and MMAD 2.55±0.03–3.68±0.12 µm). Incorporating L-leucine (1.5%w/w) reduced the burst release (24.04±3.87%) of SF compared to unmodified formulations (41.87±2.46%), with both undergoing a square root of time (Higuchi's pattern) dependent release. Comparing the toxicity profiles of PGA-co-PDL with L-leucine (1.5%w/w) (5 mg/ml) and poly(lactide-co-glycolide), (5 mg/ml) spray-dried microparticles in human bronchial epithelial 16HBE14o- cell lines, resulted in cell viability of 85.57±5.44 and 60.66±6.75%, respectively, after 72 h treatment.

Conclusion *The above data suggest that PGA-co-PDL may be a useful polymer for preparing SR microparticle carriers, together with dispersibility enhancers, for pulmonary delivery.*

Title: Factor-Inhibiting Hypoxia-Inducible Factor (FIH) Catalyses the Post-Translational Hydroxylation of Histidinyl Residues within Ankyrin Repeat Domains

Authors: Ming Yang[1], Rasheduzzaman Chowdhury[1], Wei Ge[1], Refaat B. Hamed[1,2], Michael A. McDonough[1], Timothy D. W. Claridge[1], Benedikt M. Kessler[3], Matthew E. Cockman[3], Peter J. Ratcliffe[3], Christopher J. Schofield[1]

Source: *FEBS Journal, 278, 1086-1097 (2011), doi:10.1111/j.1742-4658.2011.08022.x*

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Factor-inhibiting hypoxia-inducible factor (FIH) is an Fe(II) / 2-oxoglutarate-dependent dioxygenase that acts as a negative regulator of the hypoxiainducible factor (HIF) by catalysing b-hydroxylation of an asparaginyl residue in its C-terminal transcriptional activation domain (CAD). In addition to the hypoxia-inducible factor C-terminal transcriptional activation domain (HIF-CAD), FIH also catalyses asparaginyl hydroxylation of many ankyrin repeat domain-containing proteins, revealing a broad sequence selectivity. However, there are few reports on the selectivity of FIH for the hydroxylation of specific residues. Here, we report that histidinyl residues within the ankyrin repeat domain of tankyrase-2 can be hydroxylated by FIH. NMR and crystallographic

analyses show that the histidinyl hydroxylation occurs at the b-position. The results further expand the scope of FIH-catalysed hydroxylations.

Title: The 2-Oxoglutarate-Dependent Oxygenase JMJD6 Catalyses Oxidation of Lysine Residues to give 5S-Hydroxylysine Residues

Authors: Monica Mantri[1], Nikita D. Loik[1], Refaat B. Hamed[1,2], Timothy D. W. Claridge[1], James S. O. McCullagh[1], Christopher J. Schofield[1]

Source: *ChemBioChem, 12, 531-534 (2011), doi: 10.1002/cbic. 201000641*

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Amino acid analyses reveal that JMJD6-catalysed hydroxylation of RNA-splicing regulatory protein fragments occurs to give hydroxylysine products with 5S stereochemistry. This contrasts with collagen lysyl hydroxylases, which give 5R-hydroxylated products. The work suggests that more than one subfamily of lysyl hydroxylases has evolved and illustrates the importance of stereochemical assignments in proteomic analyses.

Title: Stereoselective C–C Bond Formation Catalysed by Engineered Carboxymethylproline Synthases

Authors: Refaat B. Hamed[1,2], J. Ruben Gomez-Castellanos[1], Armin Thalhammer[1], Daniel Harding[1], Christian Ducho[1], Timothy D. W. Claridge[1], Christopher J. Schofield[1]

Source: *Nature Chemistry, 3, 365-371 (2011), doi: 10.1038/nchem. 1011 (2011)*

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The reaction of enol(ate)s with electrophiles is used extensively in organic synthesis for stereoselective C–C bond formation. Protein-based catalysts have had comparatively limited application for the stereoselective formation of C–C bonds of choice via enolate chemistry. We describe protein engineering studies on 5-carboxymethylproline synthases, members of the crotonase superfamily, aimed at enabling stereoselective C–C bond formation leading to N-heterocycles via control of trisubstituted enolate intermediates. Active site substitutions, including at the oxyanion binding site, enable the production of substituted N-heterocycles in high diastereomeric excesses via stereocontrolled enolate formation and reaction. The results reveal the potential of the ubiquitous crotonase superfamily as adaptable catalysts for the control of enolate chemistry.

Title: Photoactivable Peptides for Identifying Enzyme–Substrate and Protein–Protein Interactions

Authors: Dante Rotili[1,2], Mikael Altun[3], Refaat B. Hamed[1,4], Christoph Loenarz[1], Armin Thalhammer[1], Richard J. Hopkinson[1], Ya-Min Tian[3], Peter J. Ratcliffe[3], Antonello Mai[2], Benedikt M. Kessler[3], Christopher J. Schofield[1]

Source: *Chem. Commun., 47, 5, 1488-1490 (2011), doi: 10.1039 /c0cc04457a*

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Photoactivated cross-linking of peptides to proteins is a useful strategy for identifying enzyme–substrate and protein–protein interactions in cell lysates as demonstrated by studies on the human hypoxia inducible factor system.

Title: Antimicrobial Antioxidant Daucane Sesquiterpenes from Ferula hermonis Boiss

Authors: Zedan Zeid Ibraheim[1], Wael M. Abdel-Mageed[1], Huanqin Dai[2], Hui Guo[2], Lixin Zhang[2], Marcel Jaspars[3]

Source: *Phytother. Res. (2011), doi: 10.1002/ptr.3609*

Address: [1]Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut, Egypt, [2]Chinese Academy of Sciences Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100190, P.R. China, [3]Department of Chemistry, University of Aberdeen, AB24 3UE, Scotland, UK

*Seventeen daucane sesquiterpenoid esters, including a new one (**4**), were isolated from the root of Ferula hermonis Boiss. The structures of the isolated compounds were elucidated on the basis of spectroscopic evidence and correlated with known compounds. The relative stereochemistry of the new compound was determined using 2D NOESY and the most stable and the lowest energy conformation was determined using molecular modelling. The antimicrobial activity was evaluated by determination of MIC using the broth microdilution method against six bacterial strains and one fungal strain (Pseudomonas aeruginosa PAO1, Escherichia coli, Bacillus subtilis ATCC6633, Mycobacterium bovis BCG Pasteur, Mycobacterium tuberculosis H37Rv, Staphylococcus aureus ATCC6538 and Candida albicans SC5314). There was a significant indication that compounds **15**, **16**, **17** demonstrated potent activity against Gram +ve (S.*

aureus, B. subtilis), as well as Mycobacterium strains M. bovis BCG and M. tuberculosis H37Rv. None of the isolated compounds exhibited a significant antifungal activity. In the antioxidant study using the DPPH assay method, the highest radical scavenging activity was observed for compounds ***15***, ***16***, ***17***.

Title: In Vitro Effects of Some Herbs Used in Egyptian Traditional Medicine on Viability of Protoscolices of Hydatid Cysts

Authors: Doaa A. Yones[1], Gamal A. Taher[2], Zedan Z. Ibraheim[3]

Source: *Korean J. Parasitol., 49 (3), 255-263 (2011), doi: 10.3347/kjp.2011.49.3.255*

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The present work evaluated the effects of alcoholic extracts of salvia (Salvia officinalis), thyme (Thymus vulgaris), and 2 pure compounds (thymol and menthol) on the viability of Echinococcus granulosus protoscolices in vitro. Four different concentrations of each extract (2,500, 1,500, 1,000, and 500 μg/ml) and 3 different concentrations each of thymol and menthol (50, 10, and 1 μg/ml) were used. Concentration of 2,500 μg/ml of both extracts showed a significant protoscolicidal activity on the 6th day. Complete loss of viability of protoscolices occurred with 500 μg/ml concentration of both extracts at day 6 and day 7 post-treatment (PT), respectively. Pure compounds, i.e., menthol and thymol, showed potent effects with 50 μg/ml concentration at day 2 and day 5 PT, respectively. These effects were compared with those of albendazole sulfoxide (800 μg/ml), a commonly used treatment drug for hydatidosis. Krebs-Ringer solution and the

hydatid cystic fluid at a ratio of 4:1 was a good preservative solution which kept the protoscolices viable for 15 days.

Title: Methyl Jasmonate Induced Accumulation of Biologically Active Phenolic Compounds in Cell Cultures of Emex spinosa (L.) Campd.

Authors: Ahmed M.A. Abd El-Mawla[1,2], Zedan Z. Ibraheim[1]

Source: *Spatula DD., 1 (2), 67-71 (2011), doi: 10.5455/spatula. 20110508114925*

Address: [1]Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt, [2]Department of Pharmacognosy, Faculty of Pharmacy, Taif University, Taif 21974, Saudi Arabia

BACKGROUND: *Cell suspension cultures were established from the aerial parts of Emex spinosa cultivated on MS medium.*

METHODS: *The changes in cells weight and phenolics content (anthraquinones and flavonoids) were followed between day zero and 12. The effect of methyl jasmonate on their production was studied.*

RESULTS: *The linear increase in fresh weights was found to be parallel to both anthraquinones and flavonoids production. Cell suspension cultures treated with 100ml methyl jasmonate showed a significant increase in level of both anthraquinones and flavonoids. The enhancements of phenolics were: 7 fold in chrysophanol, 10 fold in physcion, 15 fold in aloe-emodin, 9 fold in aloe-emodin-8-O-glucoside, 6 fold in emodin-8-O-glucoside, 17 fold in kaempferol-3-O-rutinoside and 11 fold in quercetin-3-O-rutinoside (rutin).*

CONCLUSION: *The present study indicated that the methyl jasmonate affected positively production of phenolic compounds in cell cultures of E. spinosa.*

Title: Hydroxy Vasntine, A New Pyrroloquinazoline Alkaloids Trisulcus (Forssk) Nees

Authors: Mohamed A. El-Shanawany, Hanaa M. Sayed, Sabrin R. M. Ibrahim, Marwa A. A. Fayed

Source: *J. Nat. Prod. Plant Resour., 1 (4), 80-85 (2011)*

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*Hydroxy vasntine (**1**), a new pyrroloquinazoline alkaloidsalong with two known compounds: 7-hydroxy vasicine (**2**) and 7-hydroxy vasicine (**3**) were isolated from the aerial parts of Anisotes trisulcus (Forssk) Nees (Acanthaceae). Their structures were established by UV, IR, ID NMR, in addition to mass spectroscopic data and comparison with literature data. The different fractions were evaluated for their cytotoxic activity using the brine shrimp bioassay.*

Title: A New Xanthone From the Roots of Centaurium spicatum

Authors: Mohamed A. El-Shanawany[1], Gamal A. Mohamed[2], Alaa M. Nafady[2], Sabrin R.M. Ibrahim[1], Mohamed M. Radwan[3,5], Samir A. Ross[3,4]

Source: *Phytochemistry Letters, 4, 126-128 (2011)*

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*The chloroformic fraction of the roots of Centaurium spicatum L. afforded one new xanthone named 1,5,8-trihydroxy-3,6,7-trimethoxyxanthone (**1**) together with six known xanthones (**2–7**), one of them isolated for the first time from a plant source (**2**). One secoiridoid glucoside (**8**) was also isolated. The structures of the isolated compounds were established based on 1D and 2D (^1H–^1H COSY, HMQC, and HMBC) NMR spectroscopy, in addition to high resolution mass spectrometry. The isolated compounds were tested for their antimicrobial and antiprotozoal activities. Compound **6** displayed moderate antifungal activity*

against Candida krusei and Cryptococcus neoformans with IC_{50} values of 12.8 and 17.9 μg/ml respectively.

Title: Cinnamyl Alcohols and Methyl Esters of Fatty Acids from Wedelia prostrata callus Cultures

Authors: Ahmed M. A. Abd El-Mawla[1], Salwa F. Farag[1], Till Beuerle[2]

Source: *Natural Product Research, 25 (1), 45-52 (2011), doi: 10.1080/14786419.2010.482937*

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*Two methyl esters of fatty acids, namely octadecanoic acid methyl ester (methyl stearate) (**1**) and hexadecanoic acid methyl ester (methyl palmitate) (**2**), in addition to four cinnamyl alcohol derivatives, sinapyl alcohol (**3**), coniferyl alcohol (**4**), p-coumaryl alcohol (**5**) and coniferyl alcohol 4-O-glucoside (coniferin) (**6**), were isolated from callus cultures of Wedelia prostrata. The structure of coniferin was established by spectroscopic and chemical methods, while the other compounds were identified by gas chromatography – mass spectrometry and thin layer chromatography in comparison with standards.*

Title: Elicitation of Trigonelline and 4-Hydroxy-isoleucine with Hypoglycemic Activity in Cell Suspension Cultures of Trigonella foenum graecum L.

Authors: Ahmed M. A. Abd El-Mawla[1,2], Husam Eldien H. Osman[3]

Source: *The Open Conference Proceedings Journal, 2, 80-87 (2011)*

Address: [1]Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt, [2]Department of Pharmacognosy, Faculty of Pharmacy, Taif University, Taif 21974, Saudi Arabia,
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Cell suspension cultures of Trigonella foenum graecum L. (fenugreek) were initiated from the cotyledon portions of sterile germinated seeds and maintained on MS medium supplemented with 2,4-dichlorophenoxy acetic acid (2, 4-D) (1 mg/l), kinetin (0.1 mg/l) and sucrose (5%). The changes in cell mass and both trigonelline and 4- hydroxyisoleucine content were followed between days zero and 12. The linear increase in fresh weight was found to be parallel to both trigonelline and 4-hydroxyisoleucine production. Cell suspension cultures treated with 100 µM methyl jasmonate (MJ) for 24 hours showed a noticeable increase in the level of trigonelline and 4-hydroxyisoleucine. The marked improvement in the histological and electron microscopically pictures of pancreas of STZ-diabetic rats fed with extract of cells treated with MJ is coincided with more effective and

significant hypoglycemic activity than that for seeds extract. The extract of cultured cells treated with MJ lowered blood glucose from 284 ± 7.4 to 123 ± 8.1 units and increased the insulin level from 4.42 ± 0.23 µU/ml to a high level 8.33 ± 0.41 µU/ml.

Title: HPLC Analysis and Role of the Saudi Arabian Propolis in Improving the Pathological Changes of Kidney Treated with Monosodium Glutamate

Authors: Ahmed M. A. Abd El-Mawla[1,2], Husam Eldien H. Osman[3]

Source: *Spatula DD, 1 (3), 119-127 (2011), doi: 10.5455/spatula.20110803105445*

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Background: *Monosodium glutamate is commonly used in our foods and reported many physiological effects. Propolis is a natural product widely used in folk medicine due to its bioactive compounds. It is considered one of the richest sources of phenolic acids and flavonoids.*

Methods: *The phenolic acids and flavonoids content of Saudi Arabian propolis was determined by HPLC analysis. Three groups of albino rats were used in the present study for histological and histochemical studies. Group 1 (control group) received 0.9% NaCL, group 2 was given monosodium glutamate (6 mg/g bw) and group 3 received monosodium glutamate (6 mg/g body weight) and propolis (50 mg/kg body weight).*

Results: *The HPLC analysis of the Saudi Arabian propolis revealed presence of predominant phenolic acids; trans-cinnamic, p-coumaric, caffeic, ferulic, sinapic, and flavonoids; apigenin, kaempferol, quercetin, rutin. The rats administered orally with the monosodium glutamate (6 mg/g body weight) and propolis (50 mg/kg body weight) for 8 weeks showed a significant protective effect of propolis in prevention monosodium glutamate induced toxic pathological changes in kidney of the rats.*

Conclusion: *The presence of phenolic compounds in the Saudi Arabian propolis is coincided with its role in improving the histological and ultrastructural pictures of kidney treated with monosodium glutamate.*

Title: Induction of Biologically Active Flavonoids in Cell Cultures of Morus nigra and Testing their Hypoglycemic Efficacy

Authors: Ahmed M. A. Abd El-Mawla[1,2], Khaled M. Mohamed[2], Ashraf M. Mostafa[3]

Source: *Sci. Pharm., 79, 951-961 (2011), doi: 10.3797/scipharm.1101-15*

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The antidiabetic activity of both leaves and MJ-treated cell cultures of Morus nigra was evaluated after their oral administration to streptozotocin - induced diabetic rates. The antidiabetic activity of extracts from leaves given to streptozotocin (STZ) - diabetic rats for 10 days increased with increasing doses of leaves extract up to 500 mg/kg/day. The administration of 500 mg/kg/day of leaves extract reduced the concentration of glucose from 370 ± 7.31 mg/dl (control) to 154 ± 6.27 mg/dl and a significant increase in the insulin level from 11.3 ± 0.31 μU/ml (control) to 14.6 ± 0.43 μU/ml was recorded.

Cell suspension cultures were established from the young leaves of Morus nigra cultivated on modified MS medium supplemented with 2.0 mg/l 1-naphthaleneacetic acid (NAA), 0.2 mg/l 6-(furfurylamino)-purine (kinetin). The

changes in cells weight and flavonoids content were followed between day zero and 12. The linear increase in fresh weight was found to be parallel to flavonoids production. Cell cultures treated with 100 μM methyl jasmonate for 24 hours showed a noticeable increase in level of flavonoids and significant and more effective hypoglycemic activity than that for extract from leaves. The major flavonoids were isolated by TLC and HPLC and identified as rutin, quercetin, Morusin and cyclomorusin by co-chromatography and mass spectrometry in comparison to samples of authentic reference compounds.

Title: Effects of Gum acacia Aqueous Extract on the Histology of the Intestine and Enzymes of Both the Intestine and the Pancreas of Albino Rats Treated with Meloxicam

Authors: Ahmed M. A. Abd El-Mawla[1,2], Husam Eldien H. Osman[3]

Source: *Pharmacognosy Research, 3 (2), 114-121 (2011)*

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Background: *Non-steroidal anti-inflammatory drugs (NSAIDs) cause gastrointestinal damage both in the upper and lower gastrointestinal tract, in addition to their undesirable side effects on the pancreas. Meloxicam like all NSAIDs has damaging effects on the gastrointestinal tract including perforations, ulcers and bleeding.*

Objective: *The present work describes the effects of Gum acacia aqueous extract on the histology of intestine and enzymes of both intestine and Pancreas of albino rats treated with Meloxicam.*

Materials and Methods: *This study was performed on four groups of equally weighed male rats, each group included ten animals; the first group was received a diet containing 0.2 mg/kg bw meloxicam per day; the second was given 1gm gum*

acacia per day in its diet; the third was given meloxicam followed by gum in the same doses per day; while the fourth group (control rats) was placed on a normal diet and water. All rats were received their diet for a period of 21 days.

Results: *A considerable protective effect of Gum acacia aqueous extract on the histology of intestine of albino rats treated with meloxicam was recorded. In addition, the study displayed a significant increase (P<0.001) in the intestinal enzymes; lipase, amylase, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) in the 1st and 3rd groups animals while these enzymes were significantly decreased (P<0.001) in the 2nd group when compared with the 4th control group.*

Conclusion: *This study concluded that gum acacia provides a protection and defense against the harmful effects of meloxicam therapy used as one of the novel anti-Cox-1 and Cox-2 NSAIDs.*

Title: Role of Propolis in Improving Male Rat Fertility Affected with Aluminum Chloride Cytotoxicity

Authors: Alsayed Ali Mahran[1], Ahmed Hassan Abdel-Rahman Al-Rashidy[2], Ahmed Mohamed Ahmed Abd El-Mawla[3,4]

Source: *Spatula DD, 1 (4), 189-198 (2011), doi: 10.5455/spatula.20111122065544*

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AIM: *Aluminum chloride ($AlCl_3$) is commonly used in daily life but it can be induce reproductive toxicity. Propolis has been reported to be important antioxidant. Therefore, the present study aimed to investigate the protective effects of propolis against reproductive toxicity of aluminum chloride ($AlCl_3$) in male rats.*

METHODS: *Sixty male albino rats were divided into three equal groups, the first served as negative control, the second received $AlCl_3$ (34 mg/kg bw, 1/25 LD_{50}), the third received $AlCl_3$ and treated with propolis (50 mg/kg bw.). Treatment was continued for 70 days.*

RESULTS: *$AlCl_3$ caused a decrease in body and testes weights and testosterone hormone. In addition, histological changes as damages within the seminiferous tubules and vascular degeneration of the germ cells and Sertoli cells cytoplasm*

were observed. On the other hand, electron microscopy study showed changes in the testis seminiferous tubules such as atrophy of the tubular membrane, mitochondria, endoplasmic reticulum, Golgi apparatus and nucleus. Our results revealed that propolis alleviated the reproductive toxic effects of $AlCl_3$.

CONCLUSION: *Treatment with propolis alleviates $AlCl_3$-associated hazards and protects the testicular tissues from $AlCl_3$ toxicity.*

Title: GC-MS studies of Crinum asiaticum L. Leaves and Flowers

Authors: John Refaat[1], Mohamed S. Kamel[1], Mahmoud A. Ramadan[2], Ahmed A. Ali[2]

Source: *Research J. Pharmacognosy and Phytochemistry, 3 (5), 232-235 (2011)*

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From the lipid fraction of Crinum asiaticum L. leaves, six saturated straight chain hydrocarbons, two sterols as well as thirteen fatty acids were isolated and identified. The isolation and identification of these compounds were based on GLC/MS technique. Most of these compounds are reported here for the first time either in this species or in Crinums generally. On the other hand, GLC/MS analysis of the volatile oil of its flowers, for the first time among Crinums, resulted in the isolation of ten components, eight of which were identified. Unsaturated fatty acids and phenols were found to prevail in the leaves and flowers' volatiles, respectively.

Title: Analgesic, Anti-Inflammatory and Antimicrobial Activities of Crinum augustum Rox. and Crinum asiaticum L.

Authors: John Refaat[1], Mohamed S. Kamel[1], Mahmoud A. Ramadan[2], Ahmed A. Ali[2]

Source: *Research J. Pharmacognosy and Phytochemistry, 3 (6), 289-296 (2011)*

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Many Crinum species are traditionally used in different parts of the world for various local pains, inflammatory processes and microbial infections. In the present study, the total ethanolic extracts of C. augustum Rox. bulbs and C. asiaticum L. leaves were fractionated separately into five fractions each. The resulting fractions (400 mg/Kg, orally) of the total extract of C. augustum Rox. bulbs were evaluated for their analgesic and anti-inflammatory effects in mice using the hot plate and carrageenan-induced paw oedema tests versus acetyl salicylic acid (ASA) (100 mg/Kg, orally) and indomethacin (15 mg/Kg, orally), respectively. Fractions II, III and ASA showed the highest analgesic effects, whereas; II, III, IV and indomethacin were the highest anti-inflammatory ones at that tested doses. On the other hand, a comparative study of the antimicrobial activities of the total extracts of both plants together with their fractions (at 5, 10 and 50 mg/ml) showed inhibitory effects on S. aureus and E. coli, especially at

50 mg/ml. In addition, the per oral LD_{50} of the total extract of C. augustum Rox. bulbs were determined to be 1.6 g/Kg in mice.

Title: Phytochemical and Biological Studies of Adiantum capillus-veneris L.

Authors: Zedan Z. Ibraheim, Amany S. Ahmed, Yaser G. Gouda

Source: *Saudi Pharmaceutical Journal, 19 (2), April (2011)*

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*Chromatographic fractionation of the alcoholic extract of the dried fronds of Adiantum capillus-veneris L. (Adiantaceae) yielded seven compounds: Four triterpenoidal compounds belonging to adiantane and filicane groups were isolated from the hexane fraction and identified as isoadiantone (**1**); isoadiantol-B (**2**); 3-methoxy-4-hydroxyfilicane (**3**) and 3,4-dihydroxyfilicane (**4**) and three flavonoids were isolated from the ethyl acetate fraction and identified as: quercetin (**5**), quercetin-3-O-glucoside (**6**) and quercetin-3-O-rutinoside (rutin) (**7**). The identification of the isolated compounds has been established through their physical, chemical and spectroscopic methods including IR, ^{1}H-NMR, ^{13}C-NMR, HSQC, HMBC, NOESY and MS. Biological studies of the total alcoholic extract, hexane fraction and some of the isolated compounds showed an anti-inflammatory activity while the hypoglycemic study of the total alcoholic extract showed a significant activity.*

Title: Macro- and Micromorphology of the Leaf, Stem, Stem Bark and Flower of Vangueria edulis Cultivated in Egypt

Authors: D. W. Bishay, E. Y. Backheet, Y. G. Gouda, S. M. Moustafa

Source: *Bull. Pharm. Sci., Assiut University, 34 (1), 53-76 (2011)*

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Vangueria edulis belongs to Rubiaceae which includes about 620 genera with almost 13000 species which is widely distributed but mainly tropical. Biological studies showed that some species of the genus Vangueria showed antimicrobial activity, reported to have anthelmintic action and antiplasmodial activity and fed to cattle suffering from East Coast Fever. No detailed information could be traced concerning the macro- and micromorphology of the plant. This provoked the authors to carry out this study to identify the drug in both entire and powdered forms.

Title: Efficient Regioselective Three-Component Domino Synthesis of 3-(1,2,4-Triazol-5-yl)-1,3-thiazolidin-4-ones as Potent Antifungal and Antituberculosis Agents

Authors: Serry A. El Bialy[1], Maria M. Nagy[2], Hamdy M. Abdel-Rahman[3]

Source: *Arch. Pharm. Chem. Life Sci., 344, 821-829 (2011), DOI: 10.1002/ardp.201100001*

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In research for promising antibacterial and antifungal compounds, a series of 2-aryl 3-[1,2,4]triazol-5-yl 4-thiazolidinones ***1*** *were synthesized by a domino reaction of 5-amino-1H-[1,2,4]triazoles* ***3****, aromatic aldehydes, and* α*-mercaptoacids in boiling toluene in the presence of molecular sieves 4 Å. Of the twenty novel 3-[1,2,4]triazol-5-yl 4-thiazolidinone derivatives, four compounds 2-benzo[d][1,3]dioxol-6-yl-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (****1i****), 2-(4-chlorophenyl)-5-methyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (****1p****), 2-benzo[d][1,3]dioxol-6-yl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (****1s****), 2-benzo[d][1,3]dioxol-6-yl-5-methyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (****1t****) exhibited MICs of 4 mg/mL or less versus*

Mycobacterium tuberculosis. Moreover, these compounds were screened against Candida albicans. Compounds ***1p***, ***1s*** *gave MICs of 1 mg/mL or less, and were fungicidal. Finally, compound 1s was evaluated against an expanded fungal panel and showed good activity against Cryptococcus neoformans. In addition, compound 1s also appeared to be fungicidal against Aspergillus arrhizus, with MIC <1 mg/mL.*

Title: Novel Microwell-based Spectrophotometric Assay for Determination of Atorvastatin Calcium in its Pharmaceutical Formulations

Authors: Tanveer A Wani[1], Nasr Y Khalil[1], Hamdy M Abdel-Rahman[2], Ibrahim A Darwish[1]

Source: *Chemistry Central Journal, 5, 57 (2011), doi:10.1186/1752-153X-5-57*

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The formation of a colored charge-transfer (CT) complex between atorvastatin calcium (ATR-Ca) as a n-electron donor and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a π-electron acceptor was investigated, for the first time. The spectral characteristics of the CT complex have been described, and the reaction mechanism has been proved by computational molecular modeling. The reaction was employed in the development of a novel microwell-based spectrophotometric assay for determination of ATR-Ca in its pharmaceutical formulations. The proposed assay was carried out in 96-microwell plates. The absorbance of the colored-CT complex was measured at 460 nm by microwellplate absorbance reader. The optimum conditions of the reaction and the analytical procedures of the assay were established. Under the optimum conditions, linear relationship with good correlation coefficient (0.9995) was found between the absorbance and the concentration of ATR-Ca in the range of 10-150 μg/well. The limits of detection and quantitation were 5.3 and 15.8

µg/well, respectively. No interference was observed from the additives that are present in the pharmaceutical formulation or from the drugs that are co-formulated with ATR-Ca in its combined formulations. The assay was successfully applied to the analysis of ATR-Ca in its pharmaceutical dosage forms with good accuracy and precision. The assay described herein has great practical value in the routine analysis of ATR-Ca in quality control laboratories, as it has high throughput property, consumes minimum volume of organic solvent thus it offers the reduction in the exposures of the analysts to the toxic effects of organic solvents, and reduction in the analysis cost by 50-fold. Although the proposed assay was validated for ATR-Ca, however, the same methodology could be used for any electron-donating analyte for which a CT reaction can be performed.

Title: Synthesis, Biological Evaluation and Molecular Modeling Study of Substituted 1,2,4-Triazole-3-Acetic Acid Derivatives

Authors: Hend A. A. Abd El-Wahab, Hamdy M. Abdel-Rahman, Gamal-Eldin S. Alkaramany, Mahmoud A. El-Gendy

Source: *Der Pharma Chemica, 3 (6), 540-552 (2011)*

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*A series of 1,2,4-triazole-3-acetamides **3a-b**, 1-acylated-1,2,4-triazole-3-acetamides **4a-b**, ethyl 5-(2-substitutedacetamido)-1H-1,2,4-triazole-3-acetates **6, 7, 8**, ethyl 1- substituted (carbamoyl and thiocarbamoyl)-5-amino-1H-1,2,4-triazole-3-acetates **9a-j** and ethyl 5-(3(4-chlorophenyl)ureido-1H-1,2,4-triazol-3-acetate **10** were synthesized. The obtained compounds were evaluated for their anti-inflammatory. Most of the tested compounds exhibited significant anti-inflammatory activities with compounds **9a-j** were better than indomethacin. None of the tested compounds showed significant antitumor activity. Finally docking of selected compounds was performed to COX-2 and COX-1 enzymes in order to rationalize the obtained anti-inflammatory results and to predict the selectivity of the synthesized compounds.*

Title: Amantadine Amides Prodrugs as Hepatic Delivery Systems to Enhance its Activity Against HCV

Authors: Tarek Aboul-Fadl[1,2], Mahmoud M. Sheha[2], Adel S. El-Azab[2], Hatem A. Abdel-Aziz[1]

Source: *Digest Journal of Nanomaterials and Biostructures, 6 (4), 1675-1683 (2011)*

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*To enhance the activity of amantadine against HCV, its amide prodrugs with thiazolidine-4-carboxylic acid derivatives (**6-9**) and bile acids (**10** and **11**) were designed and synthesized. In vitro kinetic stability of amide prodrugs **8** and **10** were investigated in aqueous buffer solution with variable pH values (1.2, 4.5. 6.8, 7.4. 8.0) and in biological fluids of 90% human plasma and rat liver homogenate at 37°C. In vivo release of the parent drug from these prodrug was investigated in mice with the thioazolidine-4-carboxylic acid amide **8** as representative of these delivery systems. Results from the in vivo distribution study indicated that the level of amantadine increased significantly in liver from **8** when compared to amantadine itself. The study suggested the synthesized delivery systems is promising carrier to enhance the hepatic bioavailability of amantadine.*

Title: Schiff Bases of Indoline-2,3-dione: Potential Novel Inhibitors of Mycobacterium Tuberculosis (Mtb) DNA Gyrase

Authors: Tarek Aboul-Fadl[1,2], Hatem A. Abdel-Aziz[1], Mohammed K. Abdel-Hamid[2], Tilal Elsaman[1], Jane Thanassi[3], Michael J. Pucci[3]

Source: *Molecules, 16, 7864-7879 (2011), doi: 10.3390/molecules16097864*

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In the present study a series of Schiff bases of indoline-2,3-dione were synthesized and investigated for their Mtb gyrase inhibitory activity. Promising inhibitory activity was demonstrated with some of these derivatives, which exhibited IC_{50} values ranging from 50-157 µM. The orientation and the ligand-receptor interactions of such molecules within the Mtb DNA gyrase A subunit active site were investigated applying a multi-step docking protocol using Molecular Operating Environment (MOE) and Autodock4 docking software. The results revealed the importance of the isatin moiety and the connecting side chain for strong interactions with the enzyme active site. Among the tested compounds the terminal aromatic ring benzofuran showed the best activity. Promising new

leads for developing a novel class of Mtb gyrase inhibitors were obtained from Schiff bases of indoline-2,3-dione.

Title: (Z)-Ethyl 2-cyano-2-{2-[5,6-dimethyl-4-(thiophen-2-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]-hydrazinylidene}acetate

Authors: Hoong-Kun Fun[1], Madhukar Hemamalini[1], Hatem A. Abdel-Aziz[2], Tarek Aboul-Fadl[2,3]

Source: *Acta Cryst., E67, o2145-o2146 (2011), doi: 10.1107/S1600536811028911*

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In the title compound, $C_{17}H_{16}N_6O_2S$, an intramolecular N—H…O interaction generates an S(6) ring. The pyridine ring makes a dihedral angle of 71.38 (11)° with the thiophene ring. In the crystal, molecules are linked by a pair of N—H…N hydrogen bonds, forming an inversion dimer. The dimers are stacked in columns along the b axis through weak intermolecular C—H…N hydrogen bonds.

Title: Microwave-Assisted One-Step Synthesis of Fenamic Acid Hydrazides from the Corresponding Acids

Authors: Tarek Aboul-Fadl[1,3], Hatem A. Abdel-Aziz[1], Adnan Kadi[1], Ahmed Bari[1], Pervez Ahmad[1], Tilal Al-Samani[1], Seik Weng Ng[2]

Source: *Molecules, 16, 3544-3551 (2011), doi: 10.3390/molecules16053544*

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A facile and efficient method for synthesis of fenamic acid hydrazides from their acids in one-step reaction under microwave irradiation and solvent-free conditions was developed. Compared with the two-step conventional heating method, the process was simple, the reaction time was very short and the yields were almost quantitative.

Title: Microwave-Assisted Solution-Phase Synthesis and DART-Mass Spectrometric Monitoring of a Combinatorial Library of Indolin-2,3-dione Schiff Bases with Potential Antimycobacterial Activity

Authors: Tarek Aboul-Fadl[1,2], Hatem A. Abdel-Aziz[1], Adnan Kadi[1], Pervez Ahmad[1], Tilal Elsaman[1], Mohamed W. Attwa[1], Ibrahim A. Darwish[1,3]

Source: *Molecules, 16, 5194-5206 (2011), doi: 10.3390/molecules16065194*

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*A combinatorial library composed of eleven hydrazides **A-K** and eleven indolin-1,2-dione derivatives **1-11** has been designed to formally generate sublibraries of 22 mixtures, **M1-M22** comprising of 121 Schiff bases, **A-K(1-11)**. The designed library has been synthesized by the solution-phase method and microwave-assisted synthetic techniques. The formation of individual compounds of each mixture was confirmed by Direct Analysis in Real Time (DART) as ionization technique connected to an Ion Trap as a mass detector. The synthesized mixtures were evaluated for their antimycobacterial activity against four*

Mycobacterium strains; M. intercellulari, M. xenopi, M. cheleneoi and M. smegmatis. Variable antimycobacterial activity was revealed with the investigated mixtures and maximum activity was shown by ***M8****,* ***M10****,* ***M11****, and* ***M15*** *with MIC values of 1.5, 3.1, 6.2 and 0.09 µg/mL, respectively. Application of the indexed method of analysis on these active mixtures revealed that compounds* ***D8****,* ***D10*** *and* ***D11*** *may contribute to the activity of the tested mixtures.*

Title: Cell Screening Assay for Identifying Inhibitors of Eosinophil Proliferation

Authors: Jessica J. Kempe-Dustin[1], Tarek Aboul-Fadl[2,3], Clarissa Christensen[1], Robert Palais[4], Krishna Parsawar[5], Gerald J. Gleich[1,6], Lori A. Wagner[1]

Source: *Drug Dev. Res., 72, 353-360 (2011), DOI: 10.1002/ddr.20438*

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The purpose of this study was to develop a cell-based screening assay for identification of small molecules for the treatment of asthma. Eosinophils are leukocytes that contribute to the pathology of asthma. Lidocaine inhibits interleukin-5 (IL-5)-mediated survival and activation of human eosinophils, and it is able to replace inhaled glucocorticoids for the treatment of asthma; however, lidocaine has many side effects, including anesthesia. Therefore, a collection of commercial and novel, synthesized lidocaine analogues were investigated for

inhibitory activity of the IL-5-stimulated proliferation of TF-1 cells, a $CD34^+$, cytokine-dependent, erythroleukemic cell line model for eosinophil growth. Among 74 investigated compounds, 10 were more potent inhibitors of cell proliferation than lidocaine (average IC_{50} = 223 µM), with IC_{50} values ranging within 1-119 µM. This cell-based assay is an effective method for screening chemical compounds and has revealed promising lead compounds for the treatment of asthma.

Title: Synthesis of Substituted Dihydropyrimidines as Hypotensive Agents

Authors: Salah A. Abdel-Aziz[1], Nawal A. El-Koussi[2], Hoda Y. Hassan[2], Adel F. Youssef[2], Magda M. Yousri[3]

Source: *Bull. Pharm. Sci., Assiut University, 34 (2), 159-179 (2011)*

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*A series of Dihydropyrimidines (DHPMs) with variable substituents at four positions in pyrimidine nucleus (**I-IV**), were prepared and tested for their calcium channel blocker and hypotensive effect using amlodipine as a reference compound. Molecular alignment revealed a direct correlation between fitting and in-vitro rat ileum relaxation. A pharmacophore was developed for compounds with hypotensive and/or calcium channel blocking activity. Series **IV** showed hypotensive and calcium antagonist effect, while series **I** and **II** showed calcium antagonist activity without hypotensive action. Series **III** were devoid of either effect.*

Title: Design and Synthesis of some New Theophylline Derivatives with Bronchodilator and Antibacterial Activities

Authors: Alaa M. Hayallah, Walid A. Elgaher, Ola I. Salem, Abdel Alim M. Abdel Alim

Source: *Arch Pharm. Res., 34 (1), 3-21 (2011). DOI 10.1007/s12272-011-0101-8.*

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Methylxanthines especially theophylline have been recognized as potent bronchodilators for the relief of acute asthma for over 65 years. Recently, it was found that bacterial infection plays a role in asthma pathogenesis. Accordingly, the present work involves the synthesis of 6-(4-(un)substituted phenyl)thiazolo[2,3-f]theophyllines **2a-g** *and different series of 8-(1,2,4-triazol-3-ylmethylthio)theophyllines* **6-9**. *The chemical structures of the target compounds were proved by IR, ^{1}H NMR, ^{13}C NMR, EI-MS and HRMS spectroscopic techniques along with elemental analyses. The bronchodilator activity of fifteen compounds was determined in vivo by acetylcholine induced bronchospasm in anaesthetized guinea pigs. Results revealed that all compounds showed moderate to good activity; in addition, five compounds exhibited a bronchodilator activity nearly similar to that of aminophylline as a standard. The antibacterial activity of all the target compounds was investigated in vitro against both Gram-positive and Gram-negative bacterial strains. Results revealed that some compounds showed more potent antibacterial activity than ampicillin as a standard. Acute*

toxicity study for four target compounds revealed that none of these derivatives showed significant toxicity up to 300 mg/kg. It was found that compound **8c** *combined both promising bronchodilator and antibacterial activities. This compound could be subjected for further investigations as a new possible candidate in the treatment of bronchial asthma.*

Title: Design, Synthesis, and Antimicrobial Activity of Newl 1,4-disubstituted Octahydroquinoxaline-2,3-diones

Authors: Mostafa A. Hussein

Source: *Bull. Korean Chem. Soc., 32 (5), 1511-1518, (2011), DOI 10.5012/bkcs.2011.32.5.1511*

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*A series of 1,4-disubstituted octahydroquinoxaline-2,3-dione derivatives was prepared through two steps reaction. The latter involves the formation of N,N-disubstituted cyclohexane-1,2-diamine derivatives (**1a-j**) through reductive alkylation of 1,2-cyclohexanediamine with different aldehydes in presence of sodium cyanoborohydride. Fusion of compounds (**1a-j**) with diethyl oxalate affording the target compounds (**2a-j**). Elucidation of structures of compounds (**2a-j**) was based upon different spectral data as well as the elemental methods of analyses. In addition, mass spectrometry and X-ray diffraction analyses were carried out. Moreover, the lipophilicity of the target compounds as expressed from the Clog P. Most of the test compounds (**2a-j**) showed weak to moderate antibacterial and antifungal activities against most of the used bacterial and fungal strains in comparison to chloramphenicol and clotrimazole as reference drugs respectively.*

Title: Synthesis, Anti-inflammatory, Analgesic, and Antibacterial Activities of Some Triazole, Triazolothiadiazole, and Triazolothiadiazine Derivatives

Authors: Mostafa A. Hussein[1], Refaat M. Shaker[2], Mohammed A. Ameen[2], Mohammed F. Mohammed[2]

Source: *Arch. Pharm. Res., 34 (8), 1239-1250 (2011), DOI 10.1007/s12272-011-0802-z.*

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The current work is concerned with synthesis of new 1,2,4-traizoles, 1,3,4-thiadiazoles, and 1,3,4-thiadiazines derivatives. Derivatives ***3a-i*** *were obtained by condensation of 4-amino-3-(4-pyridine)-5-mercapto-1,2,4-triazole* ***1*** *with the appropriate aldehyde. Compounds* ***4a-i*** *were synthesized in a one pot reaction involving compounds* ***3a-i****, formaldehyde and morpholine. Condensation of compound* ***1*** *with the appropriate acids 4-substituted phenacyl bromide gave compounds* ***6a-d*** *and* ***8a-f*** *respectively. The chemical structures of the newly synthsized derivatives were elucidated using different spectral and elemental methods of analyses. All compounds were evaluated for their anti-inflammatory activity and the most potent derivatives were tested for their analgesic activity using indomethacin as a reference drug. In addition, ulcerogenicity and* LD_{50} *for the most active compounds were evaluated. Moreover, The antibacterial activities of the newly synthesized derivatives were investigated.*

Title: Synthesis and Antimicrobial Activity of New Substituted Dihydropyrimidine Derivatives

Authors: Mostafa A. Hussein[1], Samia G. Abdel Moty[1], Salah A. Abdel Aziz[2], Mahrous A. Abou-Salim[3]

Source: *Bull. Pharm. Sci., Assiut University, 34 (1), 37-52 (2011)*

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A new series of ethyl 6-methyl-4-(substituted)phenyl-2-(substituted)-phenacyl-thio-1,4-dihydropyrimidine-5-carboxylate ***(2a-x)*** *was prepared by reaction of ethyl 1,2,3,4-tetrahydro-6-methyl-4-(substituted)phenyl-2-thioxopyrimidine-5-carboxy-late* ***1(a–d)*** *with phenacyl bromides. Compounds* ***1(a–d)*** *were synthesized using the principle of Bignelli condensation by one pot reaction of the appropriate araldehyde, ethyl acetoacetate and thiourea in acidic medium. Confirmation of the chemical structure of the synthesized compounds* ***(2a-x)*** *was substintiated by different spectral data IR, ^{1}H-NMR, MS in addition to their microanalyses. The newly synthesized compounds were evaluated for their antimicrobial activities. The antibacterial and antifungal testing identified compounds* ***2b, 2e, 2k, 2l, 2m, 2n, 2o, 2p, 2q, 2r*** *and* ***2x*** *as the most effective*

agents in comparison to Chloramphenicol and Clotrimazole as reference antibacterial and antifungal drugs respectively.

Title: Synthesis and Biological Evaluation of Some Benzimidazo-1,2,4-Triazole Derivatives as Antimicrobial and Anti-Inflammatory Agents

Authors: Anber F. Mohammed, Mostafa A. Hussein, Samia G. Abdel-Moty, Abdel-Alim M. Abdel-Alim

Source: *Bull. Pharm. Sci., Assiut University, 34 (1), 77-92 (2011)*

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Three new series of N'-(aryl or heteroarylmethylidene)-2-(1H-1,2,4-triazolo[2,3-a]benzimidazol-2-ylsulfanyl) acetohydrazides ***(4a-k)****, N'-(α-arylethylidene)-2-(1H-1,2,4-triazolo[2,3-a]benzimidazol-2-ylsulfanyl) acetohydrazides* ***(5a-d)****, and 2-([[5-(alkyl or aralkylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl]sulfanyl)-1H-1,2,4-triazolo[2,3-a]benzimidazoles* ***(7a-e)*** *were synthesized. Reaction of compound* ***(1)*** *with methyl bromoacetate afforded* ***(2)****, which when refluxed with hydrazine hydrate yielded* ***(3)****. The latter was condensed with aromatic aldehydes and substituted acetophenones to afford compounds* ***(4a-k)*** *and* ***(5a-d)*** *respectively. Treatment of compound* ***(3)*** *with carbon disulfide in the presence of potassium hydroxide resulted in the formation of* ***(6)****. The latter was alkylated with the appropriate alkyl or aralkyl halides to afford compounds* ***(7a-e)****. The purity of all new compounds was checked by TLC and elucidation of their structures was confirmed by IR, ^{1}HNMR, and mass spectrometry along with elemental microanalyses. All the target compounds were evaluated for their in-vitro antimicrobial and in-vivo anti-inflammatory activities*

in comparison with ampicillin, fluconazole, and indomethacin as reference drugs respectively. In addition to molecular docking of compound **5c** *was performed.*

Title: Design, Synthesis and Antidiabetic Activity of Some New 4-Amino (or 6-Oxo)-2-Methyl/ Benzylthio (or Substituted Amino) Pyrimidine Derivatives

Authors: Salah A. Abdel-Aziz[1], Mostafa A. Hussein[2], I. T. Abdel-Raheem[3]

Source: *Bull. Pharm. Sci., Assiut University, 34 (2), 149-158 (2011)*

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A new series of 4-amino-5-cyano-2-methyl/benzylthio (or substituted amino) 6-substituted phenyl pyrimidines ***5a-l****, and 2-methyl/benzylthio (or substituted amino)-5-cyano-1,6-dihydro-6-oxo-4-(substitutedphenyl) pyrimidines* ***6a-l*** *was prepared. The reaction of S-methyl (or benzyl) isothiourea salts* ***1a,b*** *with benzylidenemalononitriles* ***2a-c*** *afforded compounds* ***5a-f****. Reaction of compounds* ***5a-c*** *(R= methylthio) with the appropriate amines* ***4a,b*** *(cyclohexylamine or 2-phenylethylamine) afforded 4-amino-2-substituted amino-5-cyano-6- (substituted phenyl) pyrimidines* ***5g-l****. On the other hand, reaction of S-methyl (or benzyl) isothiourea salts* ***1a,b*** *with ethyl α-cyanocinnamates* ***3a-c*** *afforded compounds* ***6a-f****. Reaction of compounds* ***6a-c*** *(R= methylthio) with the appropriate amines* ***4a,b*** *afforded 2-substituted amino-5-cyano-4-oxo-6- (substituted phenyl) pyrimidines*

6g-l. *The purity of the new compounds was checked by TLC and elucidation of their structures was confirmed by IR, ^{1}H-NMR, and mass spectrometry along with elemental microanalyses. All the target compounds were evaluated for their in-vivo antidiabetic effects in rates in comparison with metformin as a reference drug.*

Title: Dual Separation Mode for Simultaneous Determination of Antihypertensive Drug Combinations by High-Performance Liquid Chromatography

Authors: Sameh Ahmed, Noha N. Atia, Niveen A. Mohamed

Source: *Talanta, 84, 666-672 (2011)*

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A simple, reproducible and efficient dual separation mode high performance liquid chromatographic (HPLC) method was developed for simultaneous determination of antihypertensive drug combinations including; hydrochlorothiazide (HCTZ), valsartan (VAL), amiloride (AML) and captopril (CAP). The newly developed Platinum™ column, which provides a dual-mode separation with its polar and non-polar sites, was used for rapid separation of these co-administered drugs. Good resolution was obtained when Platinum™ column was used compared with C18 column. Additionally, simple isocraticmodewith mobile phase containing methanol and 0.02 mole L^{-1} phosphate buffer adjusted to pH 3.0 (45:55, v/v) was used for separation. The flow rate was 0.5m$Lmin^{-1}$ and effluent was monitored at 270 nm. All the investigated drugs were completely separated within less than 6 min. The linearity range obtained for the developed HPLC method was 0.5–100 µgmL^{-1} with detection limits of 0.13–1.2 µgmL^{-1} for all the studied drugs. The method was validated in accordance with the requirements of ICH guidelines and shown to be suitable for

intended applications. The method was successfully used for determination of the studied drugs in pure form and pharmaceutical dosage forms without prior need for separation. The method is valuable for quality control laboratories for simultaneous determination of these co-administered antihypertensive drugs in binary, ternary and quaternary mixtures.

Title: Selective Chemiluminescence Method for Monitoring of Vitamin K Homologues in Rheumatoid Arthritis Patients

Authors: Sameh Ahmed[1], Naoya Kishikawa[2], Kaname Ohyama[2], Takahiro Imazato[3], Yukitaka Ueki[3], Naotaka Kuroda[2]

Source: *Talanta, 85, 230–236 (2011)*

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Vitamin K is a fat-soluble vitamin involved in blood coagulation and bone metabolism. The detection and monitoring of vitamin K homologues in rheumatoid arthritis (RA) patients is a challenging problem due to the smaller concentrations of vitamin K and the presence of several interfering medications. Therefore, this study aimed to develop a new highly sensitive and selective chemiluminescence (CL) method designated to quantify vitamin K homologues in plasma of RA patients including phylloquinone (PK, vitamin K_1), menaquinone-4 (MK-4, vitamin K_2) and menaquinone-7 (MK-7, vitamin K_2). The method was based on the unique photochemical properties of vitamin K homologues that were exploited for selective luminol CL reaction. The correlation coefficients of 0.998 or more were obtained in the concentration ranges of 0.1–100 ngmL^{-1} vitamin K homologues. The detection limits were 0.03–0.1 ngmL^{-1} in human plasma for

vitamin K homologues. The developed HPLC-CL system was successfully applied for selective determination of vitamin K homologues in plasma of RA patients. The developed method may provide a useful tool for monitoring vitamin K homologues in different clinical studies such as RA, osteoporosis and hepatocellular carcinoma in which vitamin K is intervented.

Title: Chemometric Methods for the Simultaneous Determination of Some Water-Soluble Vitamins

Authors: Abdel-Maaboud I. Mohamed, Horria A. Mohamed, Niveen A. Mohamed, Marwa R. El-Zahery

Source: *Journal of AOAC International, 94 (2), 467-481 (2011)*

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*Two spectrophotometric methods, derivative and multivariate methods, were applied for the determination of binary, ternary, and quaternary mixtures of the water-soluble vitamins thiamine HCl (**I**), pyridoxine HCl (**II**), riboflavin (**III**), and cyanocobalamin (**IV**). The first method is divided into first derivative and first derivative of ratio spectra methods, and the second into classical least squares and principal components regression methods. Both methods are based on spectrophotometric measurements of the studied vitamins in 0.1 M HCl solution in the range of 200–500 nm for all components. The linear calibration curves were obtained from 2.5–90 mg/mL, and the correlation coefficients ranged from 0.9991 to 0.9999. These methods were applied for the analysis of the following mixtures: (I) and (II); (I), (II), and (III); (I), (II), and (IV); and (I), (II), (III), and (IV). The described methods were successfully applied for the determination of vitamin combinations in synthetic mixtures and dosage forms from different manufacturers. The recovery ranged from 96.1±1.2 to 101.2±1.0% for derivative methods and 97.0±0.5 to 101.9±1.3% for multivariate methods. The results of the*

developed methods were compared with those of reported methods, and gave good accuracy and precision.

Title: An Efficient One-Pot Reaction for Selective Fluorimetric Determination of Cefpodoxime and its Prodrug

Authors: Niveen A. Mohamed, Hanaa M. Abdel-Wadood, Sameh Ahmed

Source: *Talanta, 85, 2121–2127 (2011)*

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Cefpodoxime proxetil (CFP), an oral third-generation cephalosporin, is a prodrug that is de-esterified in vivo to its active metabolite, cefpodoxime acid (CFA). Therefore, this study aimed to develop a facile and efficient one-pot reaction for selective and sensitive determination of CFA and its prodrug (CFP). The method was based on single-step reaction between CFP or CFA and 1,2-naphthoquinone-4-sulfonate (NQS) as a selective derivatizing reagent in alkaline medium without heating, extraction or reduction steps as usual for NQS derivatization reactions. The fluorescence of the formed NQS-derivative was monitored directly at emission wavelength of 440 nm after excitation at 330 nm. The method can easily be implemented in plating facilities by operators and/or incorporated in on-line derivatization reaction. The correlation coefficients of 0.9991 and 0.9984 were obtained in the concentration ranges of 50–2000 ng mL^{-1} for CFA and CFP, respectively. The detection limits were 9.17 and 9.48 ng mL^{-1} for CFA and CFP, respectively. The method was validated in accordance with the requirements of ICH guidelines and shown to be suitable for their efficient and sensitive determinations. The developed method was successfully

applied for selective determination of CFP in pure form and in pharmaceutical dosage forms as well as CFA in human urine after single dose of CFP without prior need for separation. The method is valuable for quality control laboratories for monitoring of CFP and its active metabolite CFA.

Title: Determination of Memantine in Rat Plasma by HPLC-Fluorescence Method and its Application to Study of the Pharmacokinetic Interaction Between Memantine and Methazolamide

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Source: *Biomed. Chromatogr. (2011), doi: 10.1002/bmc.1648*

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A sensitive high-performance liquid chromatographic method with fluorescence detection was developed to determine memantine (MT) in rat plasma. The method consists of pre-column labeling of MT with 4-(4,5-diphenyl-1H-imidazol-2-yl)benzoyl chloride (DIB-Cl) and a clean-up step with solid-phase extraction. A good separation of DIB-MT was achieved within 12 min on an octadecylsilica (ODS) column (150x4.6 mm i.d.; 5 μm) with a mobile phase of acetonitrile–water (70:30, v/v). The calibration curve prepared with fluoxetine as an internal standard showed good linearity in the range of 10–400 ng/mL (r= 0.999). The limits of detection and quantitation at signal-to-noise ratios of 3 and 10 were 2.0 and 6.6 ng/mL, respectively. The method was shown to be reliable

with precisions of <5% for intra-day and <9% for inter-day as relative standard deviation. The fluorescence property and reaction yield of authentic DIB-MT were also examined. The proposed method was successfully applied to study the pharmacokinetic interaction between MT and methazolamide.

Title: Spectrofluorimetric Determination of Some Water-Soluble Vitamins

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Source: *Journal of AOAC International, 94 (6), 1758-1769 (2011)*

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Two simple and sensitive spectrofluorimetric methods were developed for determination of three water-soluble vitamins (B_1, B_2, and B_6) in mixtures in the presence of cyanocobalamin. The first one was for thiamine determination, which depends on the oxidation of thiamine HCl to thiochrome by iodine in an alkaline medium. The method was applied accurately to determine thiamine in binary, ternary, and quaternary mixtures with pyridoxine HCl, riboflavin, and cyanocobalamin without interference. In the second method, riboflavin and pyridoxine HCl were determined fluorimetrically in acetate buffer, pH 6. The three water-soluble vitamins (B_1, B_2, and B_6) were determined spectrofluorimetrically in binary, ternary, and quaternary mixtures in the presence of cyanocobalamin. All variables were studied in order to optimize the reaction conditions. Linear relationship was obeyed for all studied vitamins by the proposed methods at their corresponding λ_{exc} or λ_{em}. The linear calibration curves were obtained from 10 to 500 ng/mL; the correlation ranged from 0.9991 to 0.9999. the suggested procedures were applied to the analysis of the investigated vitamins in their laboratory-prepared mixtures and pharmaceutical dosage forms

from different manufacturers. The RSD range was 0.46-1.02%, which indicates good precision. No interference was observed from common pharmaceutical additives. Good recoveries (97.6 ± 0.7 – 101.2 ± 0.8%) were obtained. Statistical comparison of the results with reported methods shows excellent agreement and indicates no significant difference in accuracy and precision.

Title: Non-Invasive In situ Identification and Band Assignments of Diazepam, Flunitrazepam and Methadone Hydrochloride with FT-Near-Infrared Spectroscopy

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Source: *Forensic Science International, 206, 87-91 (2011), doi:10.1016/j.forsciint.2010.06.029*

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Near-infrared spectroscopy (NIR) has evolved into an important rapid, direct and non-invasive technique in drugs analysis. In this study, the suitability of NIR spectroscopy to identify two benzodiazepine derivatives, diazepam and flunitrazepam, and a synthetic opiate, methadone hydrochloride, inside USP vials and probe the solid-state form of diazepam presents in tablets has been explored. The results show the potential of NIR spectroscopy for rapid, in situ and non-destructive identification of drugs.