Title: *In vitro* / *in vivo* Studies on the Improvement of the Dissolution Rate and Anti-inflammatory Effect of Meloxicam using Solvent Deposition Technique

Authors: M. A. Hassan

Source: *STP Pharma Pratiques, 18 (1), Janvier-Fevrier (2008)*

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Meloxicam, a new non-steroidal anti-inflammatory drug (NSAID), is a preferential inhibitor of cyclooxygenase-2 and has demonstrated potent analgesic and. anti-inflammatory activity after oral administration. The present work was carried by the preparation of meloxicam solid deposition by solvent deposition technique using different concentrations of microcrystalline cellulose (Avicel PH 101) as carrier material. The drug to the carrier ratio was 1:1, 1:5, 1:10, 1:20. The solvent deposition system (SDS) with drug to carrier ratio 1:20 showed the highest dissolution rate, and the SDSs showed higher dissolution rate when compared with physical mixture and drug alone. Differential scanning calorimetry (DSC) and infrared spectroscopy (IR) are used to investigate any change in crystal habit of meloxicam in SDSs and in the physical mixture. Drug alone, physical mixture (1:10) and SDS (1:10) were tested for its anti-inflammatory effect using paw oedema test. SDS (1:10) exhibited a pronounced inhibition of swelling than the drug alone and the physical mixture. Statistical analysis was carried out on the suppression of the swelling and showed

significant difference at 95% significance level between the formulations used in the test.

Title: Nanosizing of Hydrocortisone using Microfluidic Reactors

Authors: Hany S.M. Ali[1,2], P. York[1], N. Blagden[1]

Source: *Journal of Pharmacy and Pharmacology, Supplement 1, A-36 (2008)*

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Objectives: *The formulation of poor water-soluble drugs is a challenging problem within pharmaceutical development. Recently, formulation using nano particles was highlighted as showing great potential to improve the dissolution and solubility characteristic of poorly water soluble drugs. This enhancement of solubility is attributed to a massive increase in the overall specific surface area of such particles which is greater than that possible through micronisation (Muller R. H. et al 2001).*

One platform for nanoparticle formation is microfluidic reactors, and this technique involves liquid flows constrained in small-scale channels, with dimensions in the order of micrometers in scale (Whitesides G. M. 2006). The unique laminar flow regime within microfluidic devices (Weibel, D. B. and G. M. Whitesides 2006) presents an opportunity to use liquid liquid interfaces as templates for crystallisation for the production drug particles below 1um with well defined habit through a solvent drown out process.

The aim of this study *is to produce nano-sized particles of hydrocortisone, as a model of a hydrophobic drug, by controlled precipitation using a microfluidic*

technique. Experimental parameters for particle formation are multivariable and the critical parameters which are currently being examined include drug concentration, flow rate, diameters of the chips and inlet angles.

Methods: *Hydrocortisone solution (12 mg/ml, in ethanol) and water (antisolvent) were pumped at different (ml/min) flow rates, through a series of microreactors (Epigem Ltd, UK) with different channel diameters (0.1, 0.5 and 1mm) and inlet angles (10°, 25° and 50°). Precipitation (in the form of nanoparticles) was found to occur immediately. The particle size of the produced dispersions was determined by photon correlation spectroscopy (PCS) using a Zetasizer® NanoS (Malvern Instruments, UK). The effects of different drug concentrations, flow rates, internal diameters of the chips and inlet angles on drug particle size were studied.*

Results: *Nanodispersions of hydrocortisone (~200 ± 20nm) with narrow size distribution were obtained. Particle size decreased to less than 100 nm with increasing flow rate, especially, the rate of the antisolvent stream (Table 1). Decreasing drug concentration level resulted in larger particles. Sharper inlet angle and smaller internal diameters resulted in smaller drug particle size.*

Conclusions: *Nano-sized dispersions of hydrocortisone with narrow size distribution were successfully synthesized by controlled precipitation in microfluidic channels. Particle size can be influenced by modifying processing conditions and design of microfluidic devices.*

Title: Fluconazole-Loaded Liposomes for Ocular Delivery: Characterization and Antifungal Activity

Authors: F. S. Habib, E.A. Fouad, Dina F. Mohamed

Source: *Egypt. Pharm. J. (NRC), 7 (1), 11- 28 (2008)*

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Fluconazole loaded liposomes were prepared using reverse phase evaporation technique for ocular delivery of the drug. Characterization of fluconazole Iiposomes including; particle size and physical morphology were studied. The effects of different variables (cholesterol weight ratio and charge type) on the loading efficiency of liposomes as well as particle size were determined. Inclusion of cholesterol in liposomal formulations improved the encapsulation of fluconazole into liposomes at certain Phosphatidylcholine: Cholesterol (PC:Ch) weight ratios further increase in cholesterol content resulted in a decrease in the encapsulation percent of the drug. A significant increase in the encapsulation at ratio 7:3 was noticed. At ratio 7:6, the encapsulation significantly decreased. Incorporation of stearylamine (SA) into liposomes decreased the loading efficiency of fluconazole at ratio (PC: Ch: SA) 5: 5: 0.25 followed by insignificant increase in the entrapment of the drug into liposomes at ratio 5: 5: 0.5. On the other hand, addition of dicetyl phosphate (DP) into liposomes resulted in a significant increase in fluconazole encapsulation into liposomes at all tested (PC: Ch: DP) ratios. The loading efficiency of the neutral Iiposomes was found to be in between those of positively and negatively charged

liposomes. The particle size studies showed that, increasing cholesterol amount, led to an increase in the particle size. While increasing stearylamine and dicetyl phosphate led to decrease in the particle size of liposomes. An in-vitro study was done to know the effect of fluconazole loaded liposomes on different fungi isolated from eye.

Title: Preparation and Characterization of Albendazole Microparticles Prepared by Freeze-Drying Technique

Authors: Mahmoud El-Badry

Source: *Bull. Pharm. Sci., Assiut University, 31 (1), 123-135 (2008)*

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The aim of this work is preparation of albendazole (ABZ) microparticles with certain hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), and polyvinyl pyrrolidone (PVP) using freeze-drying technique. Microparticles of ABZ with these polymers were prepared in different ratios of 1:1, 1:2, and 1:4. Morphology of the prepared ABZ microparticles was studied using a scanning electron microscope. Spherical microparticles with smooth surface of ABZ were detected by this method. Physicochemical properties of drug alone and its freeze-dried microparticles were investigated using differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD). DSC and PXRD analysis showed that ABZ was transformed from the crystalline state to amorphous state by freeze-drying with the chosen polymers as confirmed by disappearance of its melting peak and characteristic crystalline peaks. Dissolution rate of ABZ from the prepared microparticles was determined and compared to its corresponding physical mixtures. Results showed that, the dissolution of freeze-dried microparticles was faster than the corresponding physical mixtures and drug alone. This indicates that, the freeze-drying technique improved ABZ dissolution. Moreover, it was found that the dissolution rate of the drug was affected by the polymer type and the ratio of ABZ to polymer.

Title: Liposomes as an Ocular Delivery System for Fluconazole: *In-Vivo* Study

Authors: F. S. Habib[1], E. A. Fouad[1], M. S. Abdel-Rahman[2], Dina Fathalla[1]

Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 249-263 (2008)*

Address: [1]Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt and [2]Department of Ophthalmology, Faculty of Medicine, Assiut University, Assiut, Egypt

The purpose of this study was to formulate topically effective controlled release ophthalmic fluconazole liposomal formulations using the reverse-phase evaporation technique. Soya bean phosphatidylcholine (PC) and cholesterol (Ch) in specific weight ratios were used. Selected formulations were tested for their in-vivo ocular antifungal effect. These included the neutral, the positively (using stearyl amine) and the negatively (using dicetyl phosphate) charged liposomes. A reproducible model of Candida keratitis in rabbits was performed and the effects of the prepared liposomes were better than a solution of fluconazole. The order of fluconazole liposomal formulations according to the time to achieve complete healing is arranged in a descending order: negatively charged liposomes > positively charged liposomes > neutral liposomes (7:4) > neutral liposomes (5:5) > fluconazole solution. The frequency of instillation was decreased; also, the time of ulcer healing was decreased. It was concluded that the use of liposomes as a drug delivery system could contribute to the enhancement of the effect of fluconazole in the eye.

Title: Liposomes as an Ocular Delivery System of Fluconazole: *In-Vitro* Studies

Authors: F. S. Habib, E. A. Fouad, Dina Fathalla

Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 293-311 (2008)*

Address: Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt

The purpose of this study was to formulate topically effective controlled release ophthalmic fluconazole liposomal formulations. Reverse-phase evaporation technique was used for the preparation of fluconazole liposomes consisting of phosphatidylcholine (PC) from soyabean and cholesterol (Ch) in weight ratios of (9:1), (7:2), (7:3), (7:4), (6:4), (7:6) and (5:5) with or without stearylamine (SA) or dicetyl phosphate (DP) as positive and negative charge inducers, respectively. The prepared liposomes were evaluated for their in-vitro release. The release mechanism was found to follow Higuchi and first order kinetics. Increasing cholesterol weight ratio in the prepared liposomal formulations progressively decreased the release of fluconazole from the vesicles. The positively charged liposomes showed slower rate of drug release compared to neutral ones. Negatively charged liposomes showed slight increase in the release rate and extent of fluconazole from the liposomal formulations 5:5:0.25 and 5:5:0.5; in comparison with neutral ones. Further increase in the amount of dicetyl phosphate 5:5:1 resulted in a significant decrease in the release rate.

Four fluconazole liposome eye drops were prepared. Physical stability study including, visual appearance, particle size and amount of drug leakage from liposome eye drops were studied. Approximately 82.82%, 76.55%, and 70.90% of fluconazole was retained in negative, positive and neutral liposomal ocular formulations up to a period of 24 weeks at 5°C.

Title: Mucoadhesive Drug Carriers and Polymers for Effective Drug Delivery

Authors: Makhlof A.[1,2], Werle M.[1], Takeuchi H.[1]

Source: *J. Drug Deliv. Sci. Technol., 18, 375-386 (2008)*

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The concept of mucoadhesion for the design of non-invasive drug delivery systems gained increasing attention in recent years. Within the current review, various mucoadhesive polymers, including poly(acrylates), chitosan, thiolated polymers and others, as well as their use in mucosal drug delivery are discussed. An emphasis has been put on the development of mucoadhesive formulations, and in particular on recently developed micro- and nanoparticulate systems. Moreover, the applications of the mucadhesive carrier systems for different administration routes such as the oral, nasal, pulmonary and ocular route are discussed.

Title: Cyclodextrins as Stabilizers for the Preparation of Drug Nanocrystals by the Emulsion Solvent Diffusion Method

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

Source: *Int. J. Pharm., 357, 280-285 (2008)*

Address: [1]Laboratory of Pharmaceutical Engineering, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan, [2]Current address: Department of Industrial Pharmacy, Assiut University, Assiut, Egypt

Cyclodextrins (CyDs) were employed as protective stabilizers for the preparation of surfactant-free nanocrystals of indomethacin (IMC) by using the emulsion solvent diffusion method. The effect of changing the type and concentration of CyDs on the formation of IMC nanocrystals was investigated. Dispersions were freeze-dried to characterize the size, shape, nanoparticle yield, crystallinity, and dissolution behavior of the obtained particles. Submicron-sized particles of IMC with average diameters in the range of 300-500 nm were obtained by incorporating α-, β-, or γ-CyD in the outer phase of the primary emulsions. Quantitative determination demonstrated that more than 80% of IMC was recovered as fine particles smaller than 0.8 μm. The powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) analyses of the freeze-dried samples confirmed the polymorphic change of IMC to the meta-stable form. A significant enhancement in the dissolution rate of IMC nanocrystals was observed when compared to the commercial powder.

Title: Fructose-amino Acid Conjugate and Other Constituents from *Cyperus rotundus* L.

Authors: Hanaa M. Sayed[1], Mahmoud H. Mohamed[2], Salwa F. Farag[1], Gamal A. Mohamed[2], Olanrewaju R. M. Omobuwajo[3], Peter Proksch[4]

Source: *Natural Product Research, 22 (17), 1487-97 (2008)*

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*Further phytochemical study on the aerial parts of Cyperus rotundus L. led to the isolation of a fructose-amino acid conjugate, N-(1-deoxy-α-D-fructos-1-yl)-L-tryptophan (**16**) and its tautomers, in addition to n-butyl-β-D-fructopyranoside (**1**), ethyl-α-D-glucopyranoside (**2**), adenosine (**3**), (-)-(E)-caffeoylmalic acid (**4**), vitexin (**5**), isovitexin (**6**), orientin (**7**), epiorientin (**8**), myricetin 3-O-β-D-galactopyranoside (**9**), luteolin 7-O-β-D-glucuronopyranoside-6''-methyl ester (**10**), chlorogenic acid (**11**), luteolin 4'-O-β-D-glucuronopyranoside (**12**), luteolin 7-O-beta-D-glucuronopyranoside (**13**), uridine (**14**) and ellagic acid (**15**). Their structures were elucidated on the basis of spectroscopic methods.*

Additionally, antioxidant and alpha-amylase inhibitory activities of some of the isolated phenolic compounds were carried out.

Title: Acanthomine A, A New Pyrimidine-β-carboline Alkaloid from the Sponge *Acanthostrongylophora ingens*

Authors: Sabrin R. M. Ibrahim[1], RuAngelie Ebel[2], Rainer Ebel[2], Peter Proksch[2]

Source: *Natural Product Communications, 3 (2), 175-178 (2008)*

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*Chemical investigation of the ethyl acetate extract of the sponge Acanthostrongylophora ingens afford two new alkaloids comprising of one pyrimidine-β-carboline alkaloid acanthomine A (**2**) and the norharman alkaloid 1-hydroxy-3,4-dihydronorharman (**3**), together with one known compound annomontine (**1**). Their structures were unambiguously established on the basis of NMR spectroscopy (^{1}H, ^{13}C, 1H-1H COSY, HMQC and HMBC) and mass spectrometry. This is the first report of this type of alkaloids from marine sponges. The isolated compounds were tested for cytotoxic activity using brine shrimp bioassay and different cancer cell lines.*

Title: Strepsiamide A-C, New Ceramides from the Marine Sponge *Strepsichordaia lendenfeldi*

Authors: Sabrin R. M. Ibrahim[1], Gamal A. Mohamed[2], Ehab S. Elkhayat[2], Yaser G. Gouda[1], Peter Proksch[3]

Source: *Natural Product Communications, 3 (2), 205-209 (2008)*

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*Investigation of the lipophilic extract of the Indonesian sponge Strepsichordaia lendenfeldi afforded three new ceramides, given the names strepsiamides A–C (**1–3**). The compounds showed cytotoxic activities against L5187Y and Hela cell lines. All structures were unambiguously established by 1D and 2D NMR spectroscopic and mass (EI-, APCI- and GC-MS) spectrometric data.*

Title: Callyaerin G, a New Cytotoxic Cyclic Peptide from Marine Sponge *Callyspongia aerizusa*

Authors: Sabrin R. M. Ibrahim[1], RuAngelie Edrada-Ebel[2], Gamal A. Mohamed[3], Diaa T. A. Youssef[4], Victor Wray[5], Peter Proksch[6]

Source: *ARKIVOC, xii, 164-171 (2008)*

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From the ethyl acetate fraction of the Indonesian sponge Callyspongia aerizusa new cyclic peptide named callyaerin G was isolated. Its structure was elucidated by extensive 1D and 2D NMR (1H NMR, TOCSY and ROESY) studies and mass spectrometric data (ESI- and FAB-MS). The stereochemistry was determined by Marfey`s analysis. Callyaerin G was found to exhibit cytotoxic activity when tested using different cancer cell lines.

Title: Diacarperoxides, Norterpene Cyclic Peroxides from the Sponge *Diacarnus megaspinorhabdosa*

Authors: Sabrin R.M. Ibrahim[1,2], Rainer Ebel[3], Victor Wray[4], Werner E. G. Müller[5], RuAngelie Edrada-Ebel[6], Peter Proksch[4]

Source: *J. Nat. Prod., 71, 1358–1364 (2008)*

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*Chemical investigation of the hexane extract of the sponge Diacarnus megaspinorhabdosa provided a series of new norterpene derivatives including three norditerpene cyclic peroxides, diacarperoxides A, B, and C (**1** to **3**), four norsesterterpene cyclic peroxides, diacarperoxides D to G (**4** to **7**), and the acyclic norsesterterpene diacardiol A (**8**). In addition, known norterpene peroxide congeners were also isolated, which included a known norsesterterpene cyclic*

*peroxide (**9**), nuapapuin A methyl ester (**10**), epimuqubilin B (**11**), methyl-2-epinuapapuinoate (**12**), and methyl diacarnoate A (**13**). The structures of the new compounds were established on the basis of one- and two-dimensional NMR spectroscopic studies (^{1}H, ^{13}C, COSY, HMQC, HMBC, and ROESY) as well as by mass spectrometric analyses. The relative configuration of chiral centers at C-2, C-3, and C-6 was assigned by established empirical rules. All compounds were valuated for their cytotoxic properties in vitro using several human as well as murine cancer cell lines.*

Title: Biosynthesis of Scopoletin and Scopolin in Cassava Roots during Post-Harvest Physiological Deterioration: The *E-Z*-Isomerisation Stage

Authors: Soad A.L. Bayoumi[1], Michael G. Rowan[1], Ian S. Blagbrough[1], John R. Beeching[2]

Source: *Phytochemistry, 69 (17), 2928-36 (2008)*

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Two to three days after harvesting, cassava (Manihot esculenta Crantz) roots suffer from post-harvest physiological deterioration (PPD) when secondary metabolites are accumulated. Amongst these are hydroxycoumarins (e.g. scopoletin and its glucoside scopolin) which play roles in plant defence and have pharmacological activities. Some steps in the biosynthesis of these molecules are still unknown in cassava and in other plants. We exploit the accumulation of these coumarins during PPD to investigate the E-Z-isomerisation step in their biosynthesis. Feeding cubed cassava roots with E-cinnamic-3,2',3',4',5',6'-d_5 acid gave scopoletin-d_2. However, feeding with E-cinnamic-3,2',3',4',5',6'-d_6 and E-cinnamic-2,3,2',3',4',5',6'-d_7 acids, both gave scopoletin-d_3, the latter not affording the expected scopoletin-d_4. We therefore synthesised and fed with E-cinnamic-2-d_1 when unlabelled scopoletin was biosynthesised. Solely the hydrogen (or deuterium) at C2 of cinnamic acid is exchanged in the biosynthesis of hydroxycoumarins. If the mechanism of E-Z-cinnamic acid isomerisation were photochemical, we would not expect to see the loss of deuterium which we

observed. Therefore, a possible mechanism is an enzyme catalysed 1,4-Michael addition, followed by sigma-bond rotation and hydrogen (or deuterium) elimination to yield the Z-isomer. Feeding the roots under light and dark conditions with E-cinnamic-2,3,2',3',4',5',6'-d_7 acid gave scopoletin-d_3 with no significant difference in the yields. We conclude that the E-Z-isomerisation stage in the biosynthesis of scopoletin and scopolin, in cassava roots during PPD, is not photochemical, but could be catalysed by an isomerase which is independent of light.

Title: Investigation of Biosynthetic Pathways to Hydroxycoumarins during Post-Harvest Physiological Deterioration in Cassava Roots by using Stable Isotope Labelling

Authors: Soad A.L. Bayoumi[1], Michael G. Rowan[1], John R. Beeching[2], Ian S. Blagbrough[1]

Source: *ChemBioChem, 9 (18), 3013-3022 (2008)*

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Cassava (Manihot esculenta Crantz) is an important starch-rich crop, but the storage roots only have a short shelf-life due to post-harvest physiological deterioration (PPD), which includes the over-production and polymerisation of hydroxycoumarins. Key aspects of coumarin secondary-metabolite biosynthesis remain unresolved. Here we exploit the accumulation of hydroxycoumarins to test alternative pathways for their biosynthesis. Using isotopically labelled intermediates (p-coumarate-2-^{13}C, caffeate-2-^{13}C, ferulate-2-^{13}C, umbelliferone-2-^{18}O and esculetin-2-^{18}O), we show that the major biosynthetic pathway to scopoletin and its glucoside, scopolin, in cassava roots during PPD is through p-coumaric, caffeic and then ferulic acids. An alternate pathway through 2',4'-dihydroxycinnamate and umbelliferone leads to esculetin and esculin. We have used C^{18}O$_2$-carboxylate-labelled cinnamic and ferulic acids, and feeding experiments under an atmosphere of ^{18}O$_2$, to investigate the o-hydroxylation and cyclisation steps. We demonstrate that the major pathway is through o-hydroxylation and not via a proposed spirolactone-dienone intermediate.

Title: Portulene, A New Diterpene from *Portulaca oleracea* L. Growing in Egypt

Authors: Ehab S. Elkhayat[1], Sabrin R. M. Ibrahim[2], Mohamed A. Aziz[3]

Source: Journal of Asian Natural Products Research, *10 (11), 1039-1043 (2008)*

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*Portulene (**1**), a new clerodene diterpene was isolated from the chloroform extract of Portulaca oleracea L. growing in Egypt, in addition to the known compounds lupeol (**2**), β-sitosterol (**3**) and β-sitosterol-3-O-β-D- glucopyranoside (**4**) which were reported for the first time from the title plant. The structures of the isolated compounds were unambiguously established through 1D, 2D and mass spectral data. Co-treatment of CCl_4 hepatic injured rats with 70% alcohol extract of P. oleracea significantly restored the hepatic marker enzymes and total bilirubin to near the normal values, which demonstrate the hepatoprotective potential of P. oleracea. In addition, the P. oleracea extract showed antimicrobial activity.*

Title: Mechanisms and Structures of Crotonase Superfamily Enzymes – How Nature Controls Enolate and Oxyanion Reactivity

Authors: Hamed R. B., Batchelar E. T., Clifton I. J., Schofield C. J.

Source: *Cell. Mol. Life Sci., 65, 2507-2527 (2008)*

Address: ---

Title: Thioester Hydrolysis and C-C Bond Formation by Carboxymethylproline Synthase from the Crotonase Superfamily

Authors: Batchelar E. T., Hamed R. B., Ducho C., Claridge T. D. W., Edelmann M. J., Kessler B., Schofield C. J.

Source: *Angew. Chem. Int. Ed., 47, 9322-9325 (2008)*

Address: ---

Title: Macro- and Micromorphology Studies of the Leaf, Stem and Stem Bark of *Ficus pandurata* Hance. Cultivated in Egypt

Authors: M. A. Ramadan[1], A. S. Ahmad[1], A. M. Nafady[2], A. I. Mansour[2]

Source: *Bull. Pharm. Sci., Assiut University, 31 (1), 1-28 (2008)*

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Ficus pandurata (Hance) Fiddle leaf fig (Family, Moraceae) is a tree indigenous to South Africa and cultivated in Egypt for its shade in public and private gardens. Previous investigations of Ficus species showed many medicinal uses; externally they have been used for treatment of leprosy, ulcers, itching, leucoderma and warts. Internally used as anti-inflammatory, to reduce fever, cure tuberculosis and against intestinal parasites. In the present work, the detailed macro-and micromorphological characters of the leaf, stem and stem bark of Ficus pandurata Hance were studied with the aim to find out the diagnostic elements of these organs, which facilitate their identification in both entire and powdered forms.

Title: Polyphenolic Compounds From the Leaves of *Schinus terebinthifolius* Raddi

Authors: Salwa F. Farag

Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 319-329 (2008)*

Address: Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, 71526, Assiut, Egypt

*Two quinic acid esters, 5-O-caffeoylquinic acid (**1**) and 5-O-coumaroylquinic acid (**2**); three myricetin glycosides, myricetin 3-O-α-L-rhamnopyranosyl (1'''→6'') β-D-galactopyranoside (**3**), myricetin 3-O-β-D-glucuronide (**4**), and myricetin 3-O-β-D-galactopyranoside (**5**); 1,6-digalloyl-β-D-glucose (**6**); and (+)-catechin (**7**) were isolated and identified for the first time from the leaves of Schinus terebinthifolius Raddi. Furthermore, investigation of tannic acid content was carried out by HPLC.*

Title: One Pot Synthesis of Tetrahydroquinoline-5-Thiones and Evaluation of Their Antimicrobial Activities

Authors: Aboul-Fetouh E. Mourad[1], Ashraf A. Aly[a], Hassan H. Farag[2], Mohamed F. Radwan[3] and Eman A. Beshr[3]

Source: *Journal of Chemical Research, April, 205-207, (2008)*

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The oxidation of 1,4-dihydropyridines (1 ,4-DHPs) to the corresponding pyridines occurs initially during the first pass metabolism in the liver. A variety of reagents has been utilised for this oxidative conversion: nitric acid, manganese dioxide-bentonite clay, chromium trioxide, potassium permanganate, pyridinium chlorochromate, ceric ammonium nitrate (CAN), clayfen, bismuth trinitrate, and ruthenium trichloride. However, most of these reactions require an extended period of time for completion, utilise strong oxidants in large excess, and give only modest yields of the products. Varma demonstrated that solid state oxidation of 1,4-DHPs using elemental sulfur yields the dehydro derivatives, whatever the 4-substituent is. Bagley reported that substituted arene- or heteroarene-carbonitriles can be converted into the corresponding thioamides, when treated with sodium sulfide solution in methanol at reflux. Subsequently, we have applied those conditions to 2-amino-4-aryl-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-

3-carbonitrile ***1a-d****, and we described the results herein. We also tested the activity of the obtained products as antimicrohial compounds. Having been interested in the synthesis of pyridines that carry heterocyclic substituents for some time, we now report the preparation of tetrahydroquinoline-5-thiones by a novel, efficient and facile procedure.*

Title: BACE1 Inhibitors: Optimization by Replacing the P1' Residue with Non-Acidic Moiety

Authors: Yoshio Hamada[1], Hamdy Abdel-Rahman[1], Abdellah Yamani[1], Jeffrey-Tri Nguyen[1], Monika Stochaj[1], Koushi Hidaka[1], Tooru Kimura[1], Yoshio Hayashi[1], Kazuki Saito[2], Shoichi Ishiura[3], Yoshiaki Kiso[1]

Source: *Bioorg. Med. Chem. Lett., 18, 1649-1653 (2008)*

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Recently, we reported potent BACE1 inhibitors KMI-429, -684, and -574 possessing a hydroxymethylcarbonyl isostere as a substrate transition-state mimic. These inhibitors showed potent inhibitory activities in enzymatic and cell assays, especially, KMI-429 was confirmed to significantly inhibit Ab production in vivo. However, acidic moieties at the P4 and P10 positions of KMI-compounds were thought to be unfavorable for membrane permeability across the blood–brain barrier. Herein, we replaced acidic moieties at the P4 position with other hydrogen bond acceptor groups, and these inhibitors exhibited improved BACE1

inhibitory activities in cultured cells. In this study, we replaced the acidic moieties at the P10 position with non-acidic and low molecular sized moieties.

Medicinal Chemistry

Title: Design, Synthesis and Antitubercular Evaluation of Small Schiff Base Combinatorial Library

Authors: Wesam S. Abdel Aal, Hoda Youssef, *Tarek Aboul-Fadl, M.O. Khalid, Adel F. Youssef

Source: *The 7th International Saudi Pharmaceutical Conference, March (2008)*

Address: Department of Medicinal Chemistry, Faculty of Pharmacy, Assiut University, Egypt and *College of Pharmacy, King Saud University

Objectives: Design, synthesis and antitubercular evaluation of small Schiff base combinatorial library. Methods: A mixture-based combinatorial library composed of five hydrazides and five carbonyl derivatives to formally generate 25 hydrazones has been designed. All reactions took place in solution phase. In order to deduce the most active member of the library, it was prepared as 10 sublibraries in which one of the reacting components was fixed and the other reactants were used as an equimolar ratios. The product 10 mixtures were screened against four Mycobacterium strains (M. intercelulari, M. xenopi, M. cheleneoi and M. smegmatis). The matrix in the table (1) describes the starting materials of the reactions carried out, all the compounds synthesized and all ten of the mixtures produced. Results: The intersection of the columns and rows corresponding to the mixture that show antitubercular activity corresponds to the active compound figure (1). Four mixtures are active and from the interpretation of antitubercular activity matrix six individual hydrazones are under biological investigation. Table of results and illusterative figures will be presented. Conclusion: To prove the

validity of the technique and the predictions made from AntiTB data of mixtures, the 25 individual hydrazones were synthesized and are under biological investigation.

Title: Synthesis of 2-Trifluoromethyl-4,7-Dihydro-7-oxo-(1,2,4)Triazolo[1,5-a]pyrimidine-6-carboxylic Acid Derivatives as Potential Antimyco-Bacterial and Antimicrobial Agents

Authors: Nawal A. El-Koussi

Source: *Bull. Pharm. Sci., Assiut University, 31 (1), 109-121 (2008)*

Address: Department of Medicinal Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt

Syntheses of the target compounds were achieved by reaction of 3-amino-5-trifluoromethyl-1,2,4-triazole ***1*** *and diethyl-ethoxymethylenemalonate (DEEM) in glacial acetic acid to afford ethyl 2-(trifluoromethyl)-4,7-dihydro-7-oxo[1,2,4]-triazolo[1,5-a]pyrimidine-6-carboxylate* ***2.*** *Reaction of compound* ***2*** *with hydroxylamine hydrochloride gave hydroxamic acid* ***3****, while reaction with hydrazine hydrate in methanol gave the corresponding carbohydrazide* ***4****. Schiff bases of compound* ***4*** *with appropriate aldehyde yielded series* ***5a-g****. Refluxing of hydrazide* ***4*** *with appropriate isothiocyanate gave thiosemicarbazides* ***6a-f.*** *The antimycobacterial evaluation was determined against Mycobacterium tuberculosis $H_{37}Rv$(ATCC 27294). Compound* ***5e*** *and* ***5b*** *showed activity with IC90(6.672, 7.362 µg/ml respectively) and IC50 (4.627, 6.382 µg/ml respectively). In vitro antibacterial screening for the prepared compounds were determined against certain strains of gram positive and gram negative bacteria. The results showed that compounds* ***3, 5a, 6b*** *possessed higher activity than ampicillin against all strains, also the activity range from half to sixth activity of nalidixic acid against E. coli. Compounds* ***3, 5a, 5b, 5c, 5f, 6b*** *exhibited activity against P. aeruginosa,*

while nalidixic acid possessed no activity. Compounds ***3, 5a, 5b*** *and* ***6b*** *possessed antifungal activity.*

Title: Biotransformation Studies Of Prednisone Using Human Intestinal Bacteria; Part I: Aerobic Incubation

Authors: Mohammed M. Al-Sanea, Atef A. Abdel-Hafez, Farghaly A. Omar, Adel F. Youssef

Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 215-228 (2008)*

Address: Department of Medicinal Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt

Several corticosteroids are commonly used for treatment of conditions associated with inflammatory disorders and as immune modulators. Specifically in cases of ulcerative colitis and the related inflammatory bowel syndromes, these therapeutic agents are administered rectally and are subjected to several intestinal micro floras. The present study aimed to investigate the effect of human intestinal bacterial (HIB) aerobic incubation on prednisone **1** *as a model for corticosteroids. Within 96 hours,* **1** *was mostly transformed by HIB in vitro to various metabolites, which could be separated by column chromatography into two fractions. The first eluted fraction A was found to contain the major metabolite adrenosterone, (androst-4-ene-3,11,17-trione)* m_1*, whereas fraction B contains metabolite* m_2*, which was identified by chiral HPLC as a mixture of androst-1,4-diene-3,11,17-trione diastereomers. The structures of metabolites* m_1 *and* m_2 *were identified and characterized by spectroscopic techniques, including 2D-NMR and mass spectrometry. Time course of biotransformation of* **1** *by HIB was also studied.*

Title: Adenosine Receptor Subtype-Selective Antagonists in Inflammation and Hyperalgesia

Authors: Andras Bilkei-Gorzo[1], Osama M. Abo-Salem[2], Alaa M. Hayallah[3], Kerstin Michel[1], Christa E. Müller[4], Andreas Zimmer[1]

Source: *Naunyn-Schmiedeberg's Arch Pharmacol., 377, 65-76 (2008)*

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In this study, we examined the effects of systemic and local administration of the subtype-selective adenosine receptor antagonists PSB-36, PSB-1115, MSX-3, and PSB-10 on inflammation and inflammatory hyperalgesia. Pharmacological blockade of adenosine receptor subtypes after systemic application of antagonists generally led to a decreased edema formation after formalin injection and, with the exception of A_3 receptor antagonism, also after the carrageenan injection. The selective A_{2B} receptor antagonist PSB-1115 showed a biphasic, dose-dependent effect in the carrageenan test, increasing edema formation at lower doses and reducing it at a high dose. A_1 and A_{2B} antagonists diminished pain-related behaviors in the first phase of the formalin test, while the second, inflammatory phase was attenuated by A_{2B} and A_3 antagonists. The A_{2B} antagonist was particularly potent in reducing inflammatory, pain dose-dependently reaching the

maximum effect at a low dose of 3 mg/kg. Inflammatory hyperalgesia was totally eliminated by the A_{2A} antagonist MSX-3 at a dose of 10 mg/kg. In contrast to the A_1 antagonist, the selective antagonist of A_{2A}, A_{2B}, and A_3 receptors were also active upon local administration. Our results demonstrate that the blockade of adenosine receptor subtypes can decrease the magnitude of inflammatory responses. Selective A_{2A} antagonists may be useful for the treatment of inflammatory hyperalgesia, while A_{2B} antagonists have potential as analgesic drugs fort the treatment of inflammatory pain.

Title: Selenium Containing Heterocycles: Synthesis and Anti-inflammatory, Analgesic and Ulcerogenic Activities of Some New 3-Cyano-4-ethylquinoline-2(1)-Selenone Derivatives

Authors: Shams H. Abdel-Hafez[1], Mostafa A. Hussein[2]

Source: *Archiv. Pharm. Pharm. Med. Chem., 341, 4, 240-246 (2008)*

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*Several seleno[2,3-b]quinolines, pyrimido [4',5':4,5]seleno [2,3-b] quinolines were prepared by annulations of sodium hydrogenselenide with 2-chloro-3-cyano-4-methylquinoline (**1**). Elemental analysis, IR, ^1H NMR and mass spectral data confirmed the structure of the newly synthesized compounds. Some of the selected compounds **5a, 7b, 7c, 8c-e, 9a, 11b** and **11d** investigated for their antibacterial, antifungal, anti-inflammatory and analgesic activities. Compounds **7c, 9a, 11b, 11d** which showed activity comparable to the standard drug Indomethacin were screened for their analgesic activity. The same tested compounds were screened for their antimicrobial activity, where there is no effect of the synthesized compounds has a considerable antimicrobial activity against fungi species except for where compounds **7c** and **9a** showed very strong fungicidal effect against some various tested fungi strains.*

Title: Affinity-Based Labeling of Cytohesins with a Bifunctional SecinH3 Photoaffinity Probe

Authors: Xihe Bi[1], Anton Schmitz[1], Alaa M. Hayallah[1,2], Jin-Na Song[1], Michael Famulok[1]

Source: *Angew. Chem. Int. Ed., 47, 9565-9568 (2008)*

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Herein we report the design, synthesis, and application of SecinH3 photoaffinity probes. By applying them to a wide range of GEFs and their small GTPase substrates, we demonstrate that Secin derivatives, which enable the direct detection of the covalent linkage between the photoaffinity probe and the cytohesin Sec7 domain, exhibit high specificity for cytohesins. Preliminary structure–activity-relationship (SAR) studies of SecinH3 showed that the terminal thiophenyl group is critical for inhibitory activity. The deletion of this residue in XH1009 resulted in a dramatic loss of inhibition of Sec7-catalyzed guanine-nucleotide exchange on [D17] Arf1. In contrast, modification of the phenyl ring had little effect on the inhibitory activity, or was even beneficial. To convert SecinH3 into a photoaffinity probe, we took advantage of this finding by substituting a photolabile benzophenone (Bp) group for the terminal phenyl ring, as in SecinPP. The advantages of Bp as the photophore are its chemical stability, specificity of insertion sites during photoactivation, and ability to be excited

repeatedly by UV light without loss of reactivity. The attachment of the biotin group with the aminoethoxyethanol spacer in Bio-SecinPP was based on preliminary SAR studies, according to which the methoxy group at the 3-position of the triazole ring can be extended without significant loss of inhibitory activity. The application of this probe to a variety of GEFs and GTPases provided cogent evidence for the specific binding of SecinH3 to the Sec7 domain of the members of the cytohesin family.

Title: Synthesis of New 3-Substituted-5-(2-hydroxy-ethyl)-3,4,5,6-tetrahydro-2H-1,3,5-thiadiazine-2-thione Derivatives with Potential Antimicrobial Activity

Authors: Mostafa A. Hussein[1], Mohammed Hashem[2]

Source: *Arch. Pharm. Chem. Life Sci., 341, 370-376 (2008)*

Address: [1]Department of Pharm. Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut, Egypt and [2]Department of Botany, Faculty of Science, Assiut University, Assiut, Egypt

The purpose of this study is based upon design and synthesis of a new series of flexible molecules of 3,4,5,6-tetrahydro-2H-1,3,5-thiadiazine-2-thione (THTT) derivatives depending upon in corporation of 2-aminoethanol as a part of the polar moiety in this nucleus. Thirteen derivatives of 3-substituted-5-(2-hydroxyethyl)-3,4,5,6-tetrahydro-2H-1,3,5-thiadiazine-2-thione were synthesized by reaction of the appropriate alkyl, cycloalkyl, aralkyl amine, or glycine with carbon disulphide, formaldehyde, and 2-aminoethanol. The structures of the target compounds were elucidated using spectral methods as well as elemental analyses. A mass-spectrometry study was carried out on representatives of the synthesized derivatives. The title compounds were tested for their antibacterial activity in vitro against some gram positive and gram negative bacteria. The in-vitro antifungal activity was tested against dermatophytic, saprophytic, phytopathogenic, and antagonistic fungi. In most cases, the newly synthesized compounds ***4-16*** *exhibited a considerable inhibitory effect on the growth of some of the tested organisms in comparison to that of ampicillin or muconazole as reference drugs.*

Moreover, the results indicated that the polar hydroxyethyl group at the N5- and the lipophilic one at the N3-positions are essential for the antimicrobial activity of the tested compounds.

Title: Synthesis and Antimicrobial Activity of Certain New 1,2,4-Triazolo[1,5-a]pyrimidine Derivatives

Authors: Yaser A.-H. Mostafa, Mostafa A. Hussein, Awwad A. Radwan, Abd EI-Hamid N. Kfafy

Source: *Arch. Pharm. Res., Feb. (2008)*

Address: Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut-71526, Egypt

Certain new derivatives of 1 ,2,4-triazolo[1,5-a]pyrimidines were synthesized through the reaction of 1,2,4-triazolo[1,5-a]pyrimidine-7-ol with ethyl bromoacetate to afford the ethyl acetate ester, which upon hydrazinolysis gives the corresponding hydrazide. The hydrazide is the key intermediate which was used for the synthesis of the target compounds. The structures of the new compounds were assigned by spectral and elemental methods of analyses. The synthesized compounds were tested for their in vitro antibacterial and antifungal activities. Most of the tested compounds showed comparable results with those of ampicillin and fluconazole reference drugs.

Title: Synthesis of Some Novel 1, 3, 5-Trisubstituted [1,2,4]Triazole Derivatives as Potential Antibacterial Agents

Authors: Alaa M. Hayallah[1], Helal F. Heta[2]

Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 375-390 (2008)*

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In the present work, some new 1,3,5-trisubstituted[1,2,4]-triazole derivatives and their Schiff's bases were synthesized. The chemical structure of the target compounds was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, FAB-MS, EI-HRMS spectra and elemental analyses. The title compounds were tested for their in vitro antibacterial activity against Gram-positive and Gram-negative ones using ampicillin and nalidixic acid as reference drugs. Some of them showed antibacterial activity more significant than the reference drugs.

Title: Antitumor Activity of Some New 1,3,8-Trisubstituted Purine-2,6-Diones and 1,3,6-Trisubstituted Thiazolo[2,3-F]Purine-2,4-Diones

Authors: Alaa M. Hayallah[1], Georgi Momekov[2], Michael Famulok[3]

Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 391-399 (2008)*

Address: [1]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt, [2]Department of Pharmacology and Toxicology Faculty of Pharmacy, MU-Sofia 2 Dunav Str., 1000 Sofia, Bulgaria and [3]LIMES Institute, Program Unit Chemical Biology & Medicinal Chemistry, c/o Kekulé Institut für Organische Chemie, Gerhard-Domagk-Str.1, 53121 Bonn, Germany

New 1,3,8-trisubstituted purine-2,6-diones and 1,3,6-trisubstituted thiazolo[2,3-f]purine-2,4-diones were designed and synthesized as potential antitumor agents. The cytotoxic effects of the tested compounds were assessed against two human malignant cell lines: T-cell leukemia derived SKW-3 and breast cancer – derived MDA-MB-231 using the methyl thiazolyl tetrazolium (MTT-dye) reduction assay, after 72 h exposure. The data were fitted to sigmoidal concentration response curves and the corresponding IC_{50} values were calculated using commercially available software (GraphPad Prizm). Compound ***AH-206*** *was the most potent cytotoxic agent among the newly synthesized compounds, with IC_{50} value of 17.3 μM. Prominent activity was also encountered with*

compounds ***AH-201, AH-205, AH-208, AH-214*** *and* ***AH-217****, all having* IC_{50} *values below 100 μM.*

Title: Stability-Indicating Thin-Layer Chromatographic Method for Quantitative Determination of Ribavirin

Authors: Ibrahim A. Darwish[1], Hassan F. Askal[1], Alaa S. Khedr[1], Ramadan M. Mahmoud[2]

Source: *Journal of Chromatographic Science, 46, 4-9, January (2008)*

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A simple and accurate stability-indicating thin-layer chromatographic (TLC) method is developed and validated for the quantitative determination of ribavirin (RBV) in its bulk and capsule forms. The method employs TLC aluminum plates precoated with silica gel 60F-254 as a stationary phase. The solvent system used for development consists of chloroform-methanol-acetic acid (60:15:15, v/v/v). The separated spots are visualized as bluish green spots after being sprayed with anisaldehyde reagent. RBV is subjected to different accelerated stress conditions. The drug is found to undergo degradation under all stress conditions, and the degradation products are well resolved from the pure drug with significantly different R_f values. The optical densities of the separated spots are found to be linear with the amount of RBV in the range of 5-40 µg/spot with a good correlation coefficient (r= 0.9980). The limit of detection and limit of quantitation values are 1.40 and 4.67 µg/Spot, respectively. Statistical analysis proves that the method is repeatable and accurate for the determination of RBV

in the presence of its degradation products. The method meets the International Conference on Harmonisation/Food and Drug Administration regulatory requirements. The proposed TLC method is successfully applied for the determination of RBV, pure and in capsules, with good accuracy and precision; the label claim percentages are 98.8% ± 1.5%. The results obtained by the proposed TLC method are comparable with those obtained by the official method.

Title: Spectrophotometric Determination of H_2-Receptor Antagonists via their Oxidation with Cerium(IV)

Authors: Ibrahim A. Darwish[1], Samiha A. Hussein[1], Ashraf M. Mahmoud[1], Ahmed I. Hassan[2]

Source: *Spectrochimica Acta, Part A, 69, 33-40 (2008)*

Address: [1]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt [2]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, AI-Azhar University, Assiut 71524, Egypt

A simple, accurate and sensitive spectrophotometric method has been developed and validated for determination of H_2-receptor antagonists: cimetidine, famotidine, nizatidine and ranitidine hydrochloride. The method was based on the oxidation of these drugs with cerium (IV) in presence of perchloric acid and subsequent measurement of the excess Ce(IV) by its reaction with p-dimethylaminobenzaldehyde to give a red colored product (λ_{max} at 464 nm). The decrease in the absorption intensity of the colored product (ΔA), due to the presence of the drug was correlated with its concentration in the sample solution. Different variables affecting the reaction were carefully studied and optimized. Under the optimum conditions, linear relationships with good correlation coefficients (0.9990-0.9994) were found between ΔA values and the concentrations of the drugs in a concentration range of 1-20 $\mu g\ ml^{-1}$. The assay limits of detection and quantitation were 0.18-0.60 and 0.54-1.53 $\mu g\ ml^{-1}$, respectively. The method was validated, in terms of accuracy, precision,

ruggedness and robustness; the results were satisfactory. The proposed method was successfully applied to the determination of the investigated drugs in pure and pharmaceutical dosage forms (recovery was 98.3-102.6 ± 0.57-1.90%) without interference from the common excipients. The results obtained by the proposed method were comparable with those obtained by the official methods.

Title: A Selective Spectrophotometric Method for Determination of Rosoxacin Antibiotic Using Sodium Nitroprusside as a Chromogenic Reagent

Authors: Hassan F. Askal[1], Ibrahim H. Refaat[1], Ibrahim A. Darwish[1], Mostafa A. Marzouq[2]

Source: *Spectrochimica Acta, Part A, 69, 1287-1291 (2008)*

Address: [1]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy; Assiut University, Assiut, Egypt, [2]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt

A selective spectrophotometric method for the determination of rosoxacin (ROS), a 4-quinolone antimicrobial agent, has been developed and validated. The method was based on the reaction of ROS with alkaline sodium nitroprusside (SNP) reagent at room temperature forming a red colored chromogen measured at 455 nm. The conditions affecting the reaction (SNP concentration, pH, color-developing time, temperature, diluting solvent and chromogen stability time) were optimized. Under the optimum conditions, good linear relationship (r= 0.9987) was obtained between the absorbance and the concentration of ROS in the range of 20-50 /µg ml-1. The assay limits of detection and quantitation were 2.5 and 8.4/µg ml-1, respectively. The method was successfully applied to the analysis of bulk drug and laboratory-prepared tablets; the mean percentage recoveries were 100.1 ± 0.33 and 101.24 ± 1.28%, respectively. The results were compared favourably with those obtained by the reported method; no significant difference

in the accuracy and precision as revealed by the accepted values of t- and F-tests, respectively. The robustness and ruggedness of the method was checked and satisfactory results were obtained. The proposed method was found to be highly selective for ROS among the fluoroquinolone antibiotics. The reaction mechanism was proposed and it proceeded in two steps; the formation of nitroferrocyanide by the action of sodium hydroxide alkalinity on SNP and the subsequent formation of the colored nitrosyl-ROS derivative by the attack at position 6 of ROS.

Title: Quantitative Thin-Layer Chromatographic Method for Determination of Amantadine Hydrochloride

Authors: Hassan F. Askal[1], Alaa S. Khedr[1], Ibrahim A. Darwish[1], Ramadan M. Mahmoud[2]

Source: *Int. J. Biomed. Sci., 4 (2), 155-160, June (2008)*

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A simple and accurate thin-layer chromatographic (TLC) method for quantitative determination of amantadine hydrochloride (AMD) was developed and validated. The method employed TLC aluminum plates pre-coated with silica ge1 60F-254 as a stationary phase. The solvent system used for development consisted of n-hexane-methanol-diethylamine (80: 40: 5, v/v/v). The separated spots were visualized as brown spots after spraying with modified Dragendorff's reagent solution. Amantadine hydrochloride was subjected to accelerated stress conditions: boiling, acid and alkaline hydrolysis, oxidation, and irradiation with ultraviolet light. The drug was found to be stable under all the investigated stress conditions. The method was validated for linearity, limits of detection (LOD) and quantitation (LOQ), precision, robustness, selectivity and accuracy. The optical densities of the separated spots were found to be linear with the amount of AMD in the range of 5-40 µg/spot with good correlation coefficient (r= 0.9994). The

LOD and LOQ values were 0.72 and 2.38 µg/spot, respectively. Statistical analysis proved that the method is repeatable and accurate for the determination of AMD. The method, in terms of its sensitivity, accuracy, precision, and robustness met the International Conference of Harmonization/Federal Drug Administration regulatory requirements. The proposed TLC method was successfully applied for the determination of AMD in bulk and capsules with good accuracy and precision; the label claim percentages were 99.0 ± 1.0%. The results obtained by the proposed TLC method were comparable with those obtained by the official method. The proposed method is more advantageous than the previously published chromatographic methods as it involved the most simple chromatographic technique; TLC. In addition, method relies on the use of inexpensive equipment, a scanner and software, and not critical derivatizing reagent, thus maximizing the ability of laboratories worldwide to analyze samples of AMD.

Title: A Sensitive Spectrophotometric Method for the Determination of H_2-Receptor Antagonists by Means of N-Bromosuccinimide and p-Amino-phenol

Authors: Ibrahim A. Darwish[1] Samiha A. Hussein[1], Ashraf M. Mahmoud[1], Ahmed I. Hassan[2]

Source: *Acta Pharm., 58, 87-97 (2008)*

Address: [1]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt [2]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Al-Azhar University Assiut, 71524, Egypt

A simple, accurate and sensitive spectrophotometric method for determination of H_2-receptor antagonists: cimetidine (CIM), famotidine (FAM), nizatidine (NIZ), and ranitidine hydrochloride (RAN) has been fully developed and validated. The method was based on the reaction of these drugs with NBS and subsequent measurement of the excess N-bromosuccinimide by its reaction with p-aminophenol to give a violet colored product (λ_{max} at 552 nm). Decrease in the absorption intensity (ΔA) of the colored product, due to the presence of the drug, was correlated with its concentration in the sample solution. Different variables affecting the reaction were carefully studied and optimized. Under optimal conditions, linear relationships with good correlation coefficients (0.9988-.09998) were found between ΔA values and the corresponding concentrations of the drugs in a concentration range of 8-30, 6-22, 6-25, and 4-20 $\mu g\ mL^{-1}$ for CIM,

FAM, NIZ, and RAN, respectively. Limits of detection were 1.22, 1.01, 1.08 and 0.74 µg mL^{-1} for CIM, FAM, NIZ, and RAN, respectively. The method was validated in terms of accuracy, precision, ruggedness, and robustness; the results were satisfactory. The proposed method was successfully applied to the analysis of the above mentioned drugs in bulk substance and in pharmaceutical dosage forms; percent recoveries ranged from 98.5 ± 0.9 to 102.4 ± 0.8% without interference from the common excipients. The results obtained by the proposed method were comparable with those obtained by the official methods.

Title: Non-Extractive Procedure and Pre-Column Derivatization with 7-Chloro-4-Nitrobenzo-2-Oxa-1,3-Diazole for Trace Determination of Trimetazidine in Plasma by HPLC with Fluorescence Detection

Authors: Ibrahim A. Darwish[1], Ashraf M. Mahmoud[1,2], Nasr Y. Khalil[1]

Source: *J. AOAC Int., 91 (5), 1037-1044 (2008)*

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A highly sensitive high-performance liquid chromatographic method with fluorescence detection has been developed and validated in a single-laboratory for the trace determination of trimetazidine (TMZ) in human plasma. Fluoxetine (FLX) was used as internal standard. TMZ and FLX were isolated from plasma by protein precipitation with acetonitrile and derivatized by heating with 7-chloro-4-nitrobenzo-2-oxa-1,3-diazole in borate buffer of pH 8 at 70°C for 30 min. Separations were performed in isocratic mode on Nucleosil CN column (250 mm length × 3.9 mm i.d., 5 µm particle diameter) using a mobile phase consisting of acetonitrile:10 mM sodium acetate buffer (pH 3.5): methanol (47:47:6, v/v) at a flow rate of 1.0 mL/min. The derivatized samples were excited at 470 nm and monitored at an emission wavelength of 530 nm. Under the optimum chromatographic conditions, a linear relationship with good correlation coefficient

(r = 0.9997, n = 5) was found between the peak area ratio of TMZ to FLX and TMZ concentration in the range of 1–120 ng/mL. The proposed method has the lowest limit of detection (LOD) and limit of quantification (LOQ) reported to date for determination of TMZ in plasma as the LOD and LOQ were 0.3 and 0.95 ng/mL, respectively. The intra and inter-assay precisions were satisfactory; the relative standard deviations did not exceed 4.39%. The accuracy of the method was proved; the recovery of TMZ from spiked human plasma were 98.13 – 102.82 ± 1.42-3.73%. The method had higher throughput as it involved simple sample preparation procedure and short run-time (<10 min). The results demonstrated that the proposed method would have a great value when it is applied in the pharmacokinetic studies for TMZ.

Title: Reconstructed Epidermis and Full-Thickness Skin for Absorption Testing: Influence of the Vehicles Used on Steroid Permeation

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Source: *ATLA, 36, 441-452 (2008)*

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A protocol for percutaneous absorption studies has been validated, based on the use of reconstructed human epidermis (RHE) and aqueous solutions of test substances. However, it is often the case that it is more complex formulations of drugs or chemicals which will make contact with the skin surface. To investigate whether RHE and the reconstructed full-thickness skin model (FT-model) can be used to predict uptake from formulations, we compared the permeation of hydrocortisone and testosterone when applied in emulsion form and as a solution containing the permeation enhancer, ethanol. Human and pig skin and non-cornified alveolar model served as references. The results were compared with steroid release from the formulations. The permeation rates of the steroids were ranked as: alveolar model >> RHE > FT-model, pig skin > human skin. In accordance with the rapid hydrocortisone release from the formulations the permeation rates of this steroid exceeded those of testosterone. Only minor differences were observed when comparing the testosterone formulations, in terms

of release and permeation. However, the ranking of the permeation of the hydrocortisone formulations was: solution > w/o emulsion > o/w emulsion, which permitted the elucidation of permeation enhancing effects, which is not possible with drug release studies. Differences in penetration were more obvious with native skin and reconstructed tissues, which exhibited a well-developed penetration barrier. In conclusion, RHE and skin preparations may be useful in the development of topical dermatics, and in the framework of hazard analysis of toxic compounds and their various formulations.

Title: Validated Spectrofluorometric Methods for Determination of Amlodipine Besylate in Tablets

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Source: *Spectrochimica Acta, Part A, 70, 564-570 (2008)*

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Two simple and sensitive spectrofluorometric methods have been developed and validated for determination of amlodipine besylate (AML) in tablets. The first method was based on the condensation reaction of AML with ninhydrin and phenylacetaldehyde in buffered medium (pH 7.0) resulting in formation of a green fluorescent product, which exhibits excitation and emission maxima at 375 and 480 nm, respectively. The second method was based on the reaction of AML with 7-chloro-4-nitro-2,1,3-benzoxadiazole (NBD-CI) in a buffered medium (pH 8.6) resulting in formation of a highly fluorescent product, which was measured fluorometrically at 535 nm (λ, 480 nm). The factors affecting the reactions were studied and optimized. Under the optimum reaction conditions, linear relationships with good correlation coefficients (0.9949-0.9997) were found between the fluorescence intensity and the concentrations of AML in the concentration range of 0.35-1.8 and 0.55-3.0 μg ml^{-1} for ninhydrin and NBD-CI methods, respectively. The limits of assay detection were 0.09 and 0.16 μg ml^{-1} for the first and second method, respectively. The precision of the methods were satisfactory; the relative standard deviations were ranged from 1.69 to 1.98%.

The proposed methods were successfully applied to the analysis of AML in pure and pharmaceutical dosage forms with good accuracy; the recovery percentages ranged from 100.4-100.8 ± 1.70-2.32%. The results were compared favorably with those of the reported method.

Title: Selective Densitometric Analysis of Cephalosporins Using Dragendorff's Reagent

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Source: *Chromatographia, 68, 365-374 (2008)*

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A simple, selective, precise, and stability-indicating thin-layer chromatographic method has been developed and validated for analysis of the cephalosporins cefpodoxime proxetil, ceftriaxone sodium, ceftazidime pentahydrate, cefotaxime sodium, cefoperazone sodium, cefazolin sodium, and cefixime in the bulk drug and in pharmaceutical formulations. TLC was performed on aluminium sheets precoated with silica gel G 60F254 as stationary phase. The mobile phases chosen for development gave compact spots for all the drugs (RF values 0.43–0.60). The separated compounds were visualized as orange spots by spraying with Dragendorff's reagent. Linear regression analysis data for the calibration plots revealed good linear relationships between response and amounts of the drugs with correlation coefficients ranging from 0.9977 to 0.9998 and determination coefficients ranging from 0.9954 to 0.9996 over the concentration ranges 5–25 lg per spot for cefpodoxime proxetil, ceftriaxone sodium, and ceftazidime pentahydrate and 10–50 lg per spot for cefotaxime sodium, cefoperazone sodium, cefazolin sodium, and cefixime. The method was validated for precision, recovery, and robustness. Limits of detection and

quantitation for the drugs ranged from 0.35 to 2.48 and from 1.07 to 7.50 lg per spot, respectively. The method was successfully applied to analysis of the drugs in their pharmaceutical dosage forms with good precision and accuracy. The method can also be used as a stability-indicating assay.

Title: Hexabromocyclododecanes in Indoor Dust From Canada, the United Kingdom, and the United States

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Source: *Environmental Science and Technology, 42, 459-464 (2008)*

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α-, β-, and γ-hexabromocyclododecane diastereomers (HBCDs) were measured in house dust from Birmingham, UK (n=31, median concentration = 730 ng ΣHBCDs g^{-1}); Amarillo/Austin, USA (n=13, 390 ng g^{-1}); and Toronto, Canada (n=8, 640 ng g^{-1}). Concentrations in dust (n= 6, 650 ng g^{-1}) from UK offices were within the range for UK homes. Concentrations from each country were statistically indistinguishable. In one UK house dust sample, 110,000 ng g^{-1} was recorded - the highest recorded in indoor dust to date. While upper bound average UK dietary exposure for adults and toddlers respectively is 413 and 240 ng ΣHBCDs day^{-1}, UK adults and toddlers daily ingesting respectively 50 and

200 mg dust contaminated at the 95th percentile concentration, are exposed respectively to 1100 and 4400 ng ΣHBCDs day^{-1}. Normalised to body weight, this high-end exposure scenario estimate for toddlers is within the range reported elsewhere for occupationally-exposed adults. While in commercial formulations γ-HBCD predominates (>80%), α-HBCD in dust constitutes 14-67% of ΣHBCDs (average 32%). Hence the predominance of the α-diastereomer in humans may arise partly from dust ingestion, and not solely to in vivo metabolism (when α-HBCD is formed from bioisomerisation of other diastereomers), or dietary exposure (where α-HBCD predominates in most foodstuffs).

Title: Comparative Evaluation of Liquid Chromatography–Mass Spectrometry Versus Gas Chromatography–Mass Spectrometry for the Determination of Hexabromocyclo-dodecanes and Their Degradation Products in Indoor Dust

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Source: *Journal of Chromatography A, 1190, 333-341 (2008)*

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Domestic and office dust samples (n=37) were analyzed for HBCDs using gas chromatography-electron capture negative ionization mass spectrometry (GC-ECNI/MS) and liquid chromatography-electrospray tandem mass spectrometry (LC-ESI/MS/MS). To determine the best method to quantify HBCDs using GC-ECNI/MS, BDE 128 was used as internal standard (IS) in all samples, while ^{13}C-labeled α-HBCD was used as IS in some samples. Total HBCD concentrations (sum of α-, β-, and γ-HBCD diastereomers) were calculated using response factors (RFs) for α- and γ-HBCD as individual diastereomers and using

an average RF for both diastereomers. Statistical comparison showed that concentrations obtained via GC-ECNI/MS were statistically indistinguishable ($p>0.05$) from those obtained using LC-ESI/MS/MS. The closest match between the two techniques was obtained using ^{13}C-α-HBCD as IS and the average RF for α- and γ-HBCDs. Excellent linear correlations (Pearson coefficient values $r>0.9$) were obtained between the GC-ECNI/MS and LC-ESI/MS/MS results, with slopes ranging from 0.76 to 1.36. Pentabromocyclododecenes (4 isomers) and tetrabromocyclododecadienes (2 isomers) were detected in the studied samples and were identified as degradation products of HBCDs after separation from the parent compound on the basis of both retention time and mass spectrum. This finding suggests that the elimination of HBr is the major degradation pathway for HBCDs in dust.

Title: Calibration of Two Passive Air Sampler Configurations for Monitoring Concentrations of Hexabromocyclododecanes in Indoor Air

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Source: *Journal of Environmental Monitoring, 10, 527-531 (2008)*

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While Poly Urethane Foam (PUF) disk passive air samplers are employed increasingly to monitor persistent organic pollutants in indoor air, they essentially sample only the vapour phase. As a previous report of the vapour:particle phase partitioning of hexabromocyclododecanes HBCDs in (outdoor) air, reported them to be present largely in the particulate phase, we monitored in three offices using active air samplers. In each, ~65% of HBCDs were present in the vapour phase, suggesting PUF disk passive samplers are suitable for monitoring HBCDs in indoor air. Concentrations in the three offices (239 - 359 pg ΣHBCD m^{-3}) exceed substantially those reported in outdoor air from the United States (2.1-11 pg ΣHBCD m^{-3}), but are in line with outdoor air from Stockholm. The relative abundance of the three principal diastereomers in office air was closer to that found in technical HBCD formulations (i.e. predominantly γ-HBCD) than in most US outdoor air samples. Time integrated air concentrations of α-, β-, and γ-HBCD were obtained for an office using a low volume sampler operated over a 50

d period alongside PUF disk samplers. This yielded the following passive air sampling rates for both a fully- and part-sheltered PUF disk sampler design: for α-, β-, and γ-HBCD, 0.87, 0.89, and 0.91 m^3 d^{-1} respectively (fully-sheltered) and 1.38, 1.54, and 1.55 m^3 d^{-1} respectively (part-sheltered). Deployment of the part-sheltered configuration, yielded concentrations ~35% lower than those obtained using a high volume sampler, consistent with PUF disk samplers measuring primarily the vapour phase.

Title: Hexabromocyclododecanes and Tetrabromobisphenol-A in Indoor Air and Dust in Birmingham, UK: Implications for Human Exposure

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Source: *Environmental Science and Technology, 42, 6855-6861 (2008)*

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Hexabromocyclododecanes (α-, β- and γ-HBCDs) and tetrabromobisphenol-A (TBBP-A) were determined in indoor air from homes (n=33; median concentrations ΣHBCDs=180 pg m^{-3}; TBBP-A=15 pg m^{-3}), offices (n=25; 170; 11), public microenvironments (n=4; 900; 27) and outdoor air (n=5; 37; 1). HBCDs and TBBP-A were also determined in dust from homes (n=45; median concentrations ΣHBCDs=1300 ng g^{-1}; TBBP-A=62 ng g^{-1}), offices (n=28; 760; 36), cars (n=20; 13000; 2) and public microenvironments (n=4; 2700; 230). While ΣHBCDs in car dust exceeded significantly ($p<0.05$) those in homes and offices, TBBP-A in car dust was significantly lower ($p<0.05$) than in homes and offices. No significant differences were observed between ΣHBCDs and TBBP-A in air or dust from homes and offices. Compared to dietary and inhalation exposures,

dust ingestion constitutes an important pathway of exposure to HBCDs and TBBP-A for the UK population. Specifically, using average dust ingestion rates and concentrations in dust, dust ingestion constitutes for adults, 34% (TBBP-A) and 24% (HBCDs) of overall exposure, and 90% (TBBP-A) and 63% (HBCDs) for toddlers. Inhalation appears a minor exposure pathway to both HBCDs and TBBP-A. On average, dust is 33% α -, 11% β- and 56% γ -HBCD, while air is 22% α -, 11% β- and 65% γ -HBCD.

Title: Concentrations of Brominated Flame Retardants in Dust from United Kingdom Cars, Homes, and Offices: Causes of Variability and Implications for Human Exposure

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Source: *Environment International, 34, 1170–1175 (2008)*

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Average concentrations of polybrominated diphenyl ethers (PBDEs) in dust in 30 homes, 18 offices, and 20 cars were 260,000, 31,000, and 340,000 ng ΣPBDEs g^{-1} respectively. Concentrations of BDEs 47, 99, 100, and 154 in cars exceeded significantly ($p<0.05$) those in homes and offices. Average concentrations of 1,2-bis(2,4,6-tribromophenoxy)ethane (TBE) and decabromodiphenyl ethane (DBDPE) in homes, offices, and cars respectively were lower at 120, 7.2, and 7.7 ng g^{-1} (TBE) and 270, 170, and 400 ng g^{-1} (DBDPE). BDE-209 concentrations in three samples are the highest to date at 2,600,000, 2,200,000, and 1,400,000 ng g^{-1}. UK toddlers daily consuming 200 mg dust

contaminated at the 95th percentile concentration, ingest 180 ng Σtri-hexa-BDEs and 310 μg BDE-209 day^{-1}. For TBE, exposure was lower than for PBDEs and hexabromocyclododecanes (HBCDs), while that for DBDPE was similar in magnitude to Σtri-hexa-BDEs, but less than for BDE-209 and HBCDs. BDE-209 concentrations recorded in ten samples taken at monthly intervals in one room varied 400-fold, implying caution when using single measurements of dust contamination for exposure assessment. Significant negative correlation was observed in one room between concentrations of BDE-47, 99, and 153 and dust loading (g dust m^{-2} floor), suggesting "dilution" occurs at higher dust loadings.

Title: Spectrofluorimetric Method for Determination of Some Oxicams Using Potassium Bromate

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Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 169-181 (2008)*

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A sensitive and selective spectrofluorimetric method has been developed for the determination of some non-steroidal anti-inflammatory oxicams derivatives namely: tenoxicam (Tx), piroxicam (Px) and lornoxicam (Lx) after their complete oxidative acidic hydrolysis to 2-aminopyridine. The hydrolytic product 2-aminopyridine exhibits fluorescence emission at 365 nm (excitation at 305 nm). The optimal conditions of the reaction were investigated. The method was found to be linear in the ranges of (0.015-0.500 µg/ml) for Tx (0.006-0.300 µg/ml) for Px and (0.060-0.200 µg/ml) for Lx. The suggested method was successively applied for the determination of the studied drugs in different dosage forms with a recovery percentages ranged 96.82-102.79 ± 0.614-2.578. The method was also applied for the determination of the drugs in spiked urine with a recovery percentages ranged 80.51-105.35 ± 1.067-5.338. The validity of the method was assessed according to USP guidelines. Statistical analysis of the results reveled high accuracy and good precision.

Title: Utility of Certain Spectrofluorimetric Methods for Analysis of Two Pharmaceutical Binary Mixtures

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Source: *Bull. Pharm. Sci., Assiut University, 31 (2), 183-195 (2008)*

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Simple and very sensitive spectrofluorimetric methods were developed for determination of adrenaline (I)–procaine hydrochloride (II) mixture and salbutamol sulfate (III) – guaifenesin (IV) mixture. Adrenaline (I) in the first mixture was determined by coupling with 5-diazo-1,2,4-triazolo-3-carboxylic acid (DTCA) reagent in alkaline medium forming fluorigenic product which can be measured at 340 nm (λex. 245 nm), while procaine hydrochloride (II) gave no fluorescence. Salbutamol sulfate (III) was analyzed by reaction with ethyl acetoacetate (EAA) forming coumarin derivative, which can be measured at 320 nm (λex. 280 nm). Guaifenesin (IV), the second drug in mixture has a considerable native fluorescence in methanol was measured at 310 nm (λex. 230 nm). All variables affecting reaction conditions were optimized. Linear correlations were obtained over the range of 19-100, 37-400 and 22-150 ng/ml for (I), (III) and (IV), respectively. The proposed methods were successfully applied for the analysis of the studied drugs in their pure and commercial dosage forms and the obtained results were in good agreement with those obtained from the

reported methods; no significant difference in the accuracy and precision as revealed by the accepted values of t- and F-tests, respectively.