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

Authors: Fawzia S. Habib[1], Ehub A. Fouad[1], Mohamed S. Abdel-Rhaman[2], Dina Fathalla[1]

Source: *Acta Ophthalmologica, Accepted in 8/2009*

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Purpose: *To study the clinical effect of topical controlled-release ophthalmic fluconazole liposomal formulation and to compare its effect with fluconazole solution in a reproducible model of Candida keratitis in rabbits.*

Methods: *Forty adult rabbits were included in this study. Right eyes were inoculated with freshly prepared Candida albicans strain no. 4925 and showed signs of infected keratitis. The rabbits were divided randomly into two groups: in the first group (18 rabbits) the right eyes received fluconazole solution, while in the second group (22 rabbits) the right eyes received fluconazole-loaded liposomes. The rabbits' eyes were examined daily over a 21-day period and results were recorded.*

Results: *Rabbits infected with C. albicans responded better and showed more improvement in terms of size of ulcer and hypopyon using fluconazole-loaded liposomal formulae than using fluconazole solution. In the first group (solution), nine rabbits' cornea showed complete healing (50%) at the end of third week, while in group 2 (liposome), 19 rabbits' cornea showed complete healing (86.4%) at equal duration. These results were statistically significant.*

Conclusion: *Therapy with topical liposomal fluconazole (2 mg/ml) was successful in eliminating experimental C. albicans infection of the rabbit cornea and was superior to fluconazole solution.*

Title: Improvement of Solubility and Dissolution Rate of Indomethacin by Solid Dispersions in Gelucire 50/13 and PEG4000

Authors: Mahmoud El-Badry[1], Gihan Fetih[2], Mohamed Fathy[2]

Source: *Journal of the Saudi Pharmaceutical Society, 17, 219-229 (2009)*

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The aim of this study was to prepare and characterize solid dispersions of water insoluble non-steroidal anti-inflammatory drug, indomethacin (IND), with polyethylene glycol 4000 (PEG4000) and Gelucire 50/13 (Gelu.) for enhancing the dissolution rate of the drug. The solid dispersions (SDs) were prepared by hot melting method at 1:1, 1:2 and 1:4 drug to polymer ratios. 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 dissolution rate of the drug in its different systems were explored. The data from the XRD showed that the drug was still detectable in its solid state in all SDs of IND–Gelu. and disappeared in case of higher ratio of IND–PEG4000. DSC thermograms showed the significant change in melting peak of the IND when prepared as SDs suggesting the change in crystallinity of IND. The highest ratio of the polymer (1:4) enhanced the drug solubility about 4-folds or 3.5- folds in case of SDs of IND–PEG or IND–Gelu.,

respectively. An increased dissolution rate of IND at pH 1.2 and 7.4 was observed when the drug was dispersed in these carriers in form of physical mixtures (PMs) or SDs. IND released faster from the SDs than from the pure crystalline drug or the PMs. The dissolution rate of IND from its PMs or SDs increased with an increasing amount of polymer.

Title: Preparation of Hydrocortisone Nanosuspension Through a Bottom-up Nanoprecipitation Technique using Microfluidic Reactors

Authors: Hany S.M. Ali[1,2], Peter York[1], Nicholas Blagden[1]

Source: *International Journal of Pharmaceutics, 375, 107-113 (2009)*

Address: [1]Institute of Pharmaceutical Innovation, School of Pharmacy, University of Bradford, Richmond Road, Bradford BD7 1DP, United Kingdom, [2]Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Egypt

In this work, the possibility of bottom-up creation of a relatively stable aqueous hydrocortisone nanosuspension using microfluidic reactors was examined. The first part of the work involved a study of the parameters of the microfluidic precipitation process that affect the size of generated drug particles. These parameters included flow rates of drug solution and antisolvent, microfluidic channel diameters, microreactors inlet angles and drug concentrations. The experimental results revealed that hydrocortisone nano-sized dispersions in the range of 80–450 nm were obtained and the mean particle size could be changed by modifying the experimental parameters and design of microreactors. The second part of the work studied the possibility of preparing a hydrocortisone nanosuspension using microfluidic reactors. The nano-sized particles generated from a microreactor were rapidly introduced into an aqueous solution of stabilizers stirred at high speed with a propeller mixer. A tangential flow filtration system was then used to concentrate the prepared nanosuspension. The nanosuspension produced was then characterized using photon correlation

spectroscopy (PCS), Zeta potential measurement, transmission electron microscopy (TEM), differential scanning calorimetry (DSC) and X-ray analysis. Results showed that a narrow sized nanosuspension composed of amorphous spherical particles with a mean particle size of 500 ± 64 nm, a polydispersity index of 0.21 ± 0.026 and a zeta potential of −18 ± 2.84 mV was obtained. Physical stability studies showed that the hydrocortisone nanosuspension remained homogeneous with slight increase in mean particle size and polydispersity index over a 3-month period.

Title: Artificial Neural Networks Modelling the Prednisolone Nanoprecipitation in Microfluidic Reactors

Authors: Hany S.M. Ali[1,2], Nicholas Blagden[1], Peter York[1], Amir Amani[1,3], Toni Brook[1]

Source: *European Journal of Pharmaceutical Sciences, 37, 514-522 (2009)*

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This study employs artificial neural networks (ANNs) to create a model to identify relationships between variables affecting drug nanoprecipitation using microfluidic reactors. The input variables examined were saturation levels of prednisolone, solvent and antisolvent flow rates, microreactor inlet angles and internal diameters, while particle size was the single output. ANNs software was used to analyse a set of data obtained by random selection of the variables. The developed model was then assessed using a separate set of validation data and provided good agreement with the observed results. The antisolvent flow rate was found to have the dominant role on determining final particle size.

Title: Novel Lipidated Sorbitol-Based Molecular Transporters for Non-Viral Gene Delivery

Authors: Tomoko Higashi, Ikramy A. Khalil, Kaustabh K. Maiti, Woo Sirl Lee, Hidetaka Akita, Hideyoshi Harashima, Sung-Kee Chung

Source: *Journal of Controlled Release, 136, 140-147 (2009)*

Title: Enhanced Gene Expression by a Novel Stearylated INF7 Peptide Derivative Through Fusion Independent Endosomal Escape

Authors: Ayman El-Sayed, Tomoya Masuda, Ikramy A. Khalil, Hidetaka Akita, Hideyoshi Harashima

Source: *Journal of Controlled Release, 138, 160-167 (2009)*

Title: Multi-Layered Nanoparticles for Penetrating the Endosome and Nuclear Membrane via a Step-Wise Membrane Fusion Process

Authors: Hidetaka Akita, Asako Kudo, Arisa Minoura, Masaya Yamaguti, Ikramy A. Khalil, Rumiko Moriguchi, Tomoya Masuda, Radostin Danev, Kuniaki Nagayama, Kentaro Kogure, Hideyoshi Harashima

Source: *Biomaterials, 30, 2940-2949 (2009)*

Title: Delivery of Nucleic Acids Through the Controlled Disassembly of Multifunctional Nanocomplexes

Authors: Mahmoud Elsabahy, Nada Wazen, Núria Bayó-Puxan, Glen Deleavey, Marc Servant, Masad J. Damha, Jean-Christophe Leroux

Source: *Advanced Functional Materials, 19, 3862-3867 (2009)*

Title: Preparation, *In-vitro* Release and Anti-Inflammatory Activity of Meloxicam in Different Gel Formulations

Authors: Mahmoud El-Badry

Source: *Bull. Pharm. Sci., Assiut University, 32 (1), 213-224 (2009)*

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

This study was designed to evaluate different polymers to their suitability for formulation as vehicles for topical delivery system. Meloxicam (MX) was incorporated into the gel vehicles in a concentration of 1.0% w/w. It is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class of compounds.

Polymers used in this study are methylcellulose (MC), tylose (Ty), polyvinyl alcohol (PVA), poloxamer 407 (polo), polyethylene glycol (PEG), carbopol 974P (Carb. and eudispert mv. (Eud). They are used in a suitable concentration for gel formation.

In-vitro release characteristics of the drug from different gels were carried out using dialysis membrane in phosphate buffer pH 6.8. The release data were treated with various kinetic principles to assess the relevant parameters.

The general rank order of MX release was MC > Ty > polo > PVA > other gel forms. The results also showed that, the release of drug from the prepared gels obeyed the diffusion model (Higuchi's equation).

The influence of some formulation and processing variables (initial drug concentration of 0.5, 1.0 and 2.0% w/w, poloxamer 407 concentration of 20, 25, 30% w/v in the aqueous gel formulation) on the release patterns have been

studied. The results revealed an inverse correlation between the drug release rate and the poloxamer 407 concentration and direct correlation between the drug release rate and the initial drug concentration.

The anti-inflammatory activity of the drug in different gel formulations was studied using carrageenan induced rat paw edema method. The results obtained show an excellent anti-inflammatory activity on rat paw edema.

Title: Formulation of Ketorolac Tromethamine in Semi-Solid Dosage Forms

Authors: Fawzia Habib, Maha Abdel Azeem, Amal El Sayeh Fadl, Raafat El Sayed

Source: *Bull. Pharm. Sci., Assiut University, 32 (2), 257-271 (2009)*

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Ketorolac tromethamine (KT) is one of NSAIDs that has GIT, renal and hepatic disorder if taken orally. The study aimed at avoiding the adverse effects of KT by formulating it in different topical dosage form such as gel (Sodium algnate, NaCMC, HPMC, Carbopol 934 and Pluronic F127), emulgel (O/W), microemulsion and cream (O/W and W/O). The interactions between KT, polymers and other ingredients used were studied using differential scanning calorimeter (DSC) and Infra red (IR) spectroscopy. The physical properties of these formulations appearance, homogeneity, pH and viscosity were studied. The in-vitro release of KT from these formulations through cellophane membrane was carried out. The kinetic study of KT release from these formulations was also studied. In-vitro study of KT permeation in diffusion cell using rat skin from the selected formulations was carried out.

Physical investigation of KT and polymers indicated that no interaction between KT and polymers. Among the polymers used in gel formulations, HPMC and NaCMC gave the highest release rate of KT in-vitro, while pluronic F127 gave promising sustained release. In case of emulgel formulations, O/W emulgel base gave higher release than microemulsion base. Also in case of emulsion

ointment base formulations, the release of KT from O/W base was higher than W/O type which gave the lowest release.

In-vitro study of KT through the diffusion cell using rat skin as biological membrane, higher permeation was obtained in case of carbopol 934 gel and O/W emulgel comparison with pluronic F127 gel which gave the lowest permeation of KT.

Title: Enhancement of Solubility and Dissolution of Nimesulide Using Solubilization, Solid Dispersion and Complexation Techniques

Authors: S. Ismail, M. El-Mahdy, S. S. Al-Kubati

Source: *Bull. Pharm. Sci., Assiut University, 32 (2), 321-338 (2009)*

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Nimesulide is a preferential COX-2 inhibitor. It has high anti-inflammatory, antipyretic and analgesic activities. It has poor aqueous solubility (0.01mg/ml). Solubility of nimesulide was studied using different cosolvent mixtures and various classes of nonionic surfactants. Dimethylacetamide (DMA); at 10% v/v exhibited the highest solubilizing effect (10-fold) towards nimesulide as compared with other cosolvents. Among the tested nonionic surfactants at 10% w/v, brij 58 which exhibited the highest solubilization effect (39-fold). The dissolution of nimesulide from solid dispersions was also studied. Solid inclusion complexes of nimesulide with β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HP β-CD) were prepared at a molar ratio of 1:1. Eutectic mixtures were obtained at weight ratio of 1:9 binary systems as confirmed by DSC studies. The dissolution studies indicated that the highest relative amounts dissolved were obtained from solid dispersions as compared with physical mixtures or pure nimesulide. Also higher relative amounts dissolved were obtained with polyvinylpyrrolidones (PVPs) at weight ratio of nimesulide/PVP 40000 1:7. Physicochemical characterization of pure drug, PVP 40000, nimesulide/PVP 40000 solid dispersion and the physical mixture at this ratio were conducted by DSC, FTIR,

X-RPD and SEM. The DSC thermograms and X-RPD patterns demonstrated that nimesulide existed in an amorphous form and there is an intermolecular hydrogen bond between the drug and the carrier as shown from FTIR analysis. SEM images confirmed the absence of the crystalline structure of nimesulide in the solid dispersion.

Title: Oral Protein Delivery: A Patent Review of Academic and Industrial Approaches

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

Source: *Recent Pat. Drug Deliv. Formul., 3, 94-104 (2009)*

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

Protein therapeutics are used in the treatment of a broad variety of diseases, however, usually they are not available as peroral formulations. Oral delivery systems of proteins including insulin, glucagon like peptide, calcitonin or parathyroid hormone are highly demanded by patients suffering from chronic diseases such as diabetes or osteoporosis. The need for oral protein formulations has been recognized by researchers of various scientific disciplines and a number of patents have been filed that deal with technologies capable of facilitating oral protein delivery. Within the current review, patents based on approaches such as particulate delivery systems, multifunctional polymers, enzyme inhibitors, permeation enhancers and ligand-specific binding and uptake are discussed. In addition, the technology platforms of several innovative drug delivery companies are highlighted.

Title: pH-Sensitive Nanospheres for Colon-Specific Drug Delivery in Experimentally-Induced Colitis Rat Model

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

Source: *Eur. J. Pharm. Biopharm., 72, 1-8 (2009)*

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

Novel pH-sensitive nanospheres designed for colon-specific delivery were prepared using polymeric mixtures of poly (lactic-co-glycolic) acid (PLGA) and methacrylate copolymers. Budesonide (BSD), a topically active corticosteroid, was entrapped as a model drug. The therapeutic efficacy of the prepared nanospheres was assessed using the trinitrobenzenesulfonic acid (TNBS) colitis rat model, in comparison with conventional enteric microparticles. In addition, the colon targeting properties, systemic bioavailability, and specific uptake by the inflamed colon mucosa were evaluated using coumarin-6 (C-6) loaded nanospheres. The prepared nanospheres showed strongly pH-dependent drug release properties in acidic and neutral pH media followed by a sustained release phase at pH 7.4. Animal experiments revealed the superior therapeutic efficiency of BSD nanospheres in alleviating the conditions of TNBS-induced colitis model. The in-vivo studies using C-6-loaded nanospheres displayed higher colon levels and lower systemic availability of the fluorescent marker when compared with simple enteric coating. Moreover, quantitative analysis of the fluorescent marker and confocal

laser scanning studies showed strong and specific adhesion of the nanospheres to the ulcerated and inflamed mucosal tissue of the rat colon. In conclusion, the proposed nanosphere system combined the properties of pH-sensitivity, controlled release, and particulate targeting that could be useful for colon-specific delivery in inflammatory bowel disease.

Title: New Isoflavone Glycosides from *Iris spuria* L. (Calizona) Cultivated in Egypt

Authors: Salwa F. Farag[1], Yuka Kimura[2], Hideyuki Ito[2], Junko Takayasu[3], Harukuni Tokuda[3], Tsutomu Hatano[2]

Source: *Journal of Natural Medicines, 63 (1), 91-95 (2009)*

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*Two new isoflavone glycosides, tectorigenin 7-O-β-D-glucopyranoside-4′-O-[β-D-glucopyranosyl-(1‴→6″)-β-D-glucopyranoside] (**1**) and iristectorigenin B 4′-O-[β-D-glucopyranosyl-(1‴→6″)-β-D-glucopyranoside] (**2**), together with 11 known compounds, including six isoflavones, tectorigenin 7-O-β-D-glucopyranoside-4′-O-β-D-glucopyranoside (**3**), tectorigenin 4′-O-[β-D-glucopyranosyl-(1‴→6′)-β-D-glucopyranoside] (**4**), tectorigenin 7-O-β-D-glucopyranoside (**5**), genistein 7-O-β-D-glucopyranoside (**6**), tectorigenin 4′-O-β-D-glucopyranoside (**7**), and tectorigenin (**8**); two phenolic acid glycosides, vanillic acid 4-O-β-D-glucopyranoside (**9**) and glucosyringic acid (**10**); a phenylpropanoid glycoside, E-coniferin (**11**); an auronol derivative, maesopsin 6-O-β-D-glucopyranoside (**12**); and a pyrrole derivative, 4-(2-formyl-5-hydroxymethylpyrrol-1-yl) butyric acid (**13**), were isolated from fresh Iris spuria (Calizona) rhizomes. The structures of these compounds were established on the*

basis of spectroscopic and chemical evidence. Inhibitory effect on the activation of Epstein–Barr virus early antigen was examined for compounds **1–8** *and* **12**.

Title: Stilbene Glucosides from the Bulbs of *Iris tingitana*

Authors: Salwa F. Farag[1], Yoshiaki Takaya[2], Masatake Niwa[3]

Source: *Phytochemistry Letters, 2 (4), 148-151 (2009)*

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*Two new dimeric stilbene glucosides, tingitanol A (**1**) and tingitanol B (**2**) together with trans-resveratrol 3-O-glucopyranoside (**3**) in addition to three known isoflavones, 5-O-methylgenistein (**4**), 5-Omethylgenistein 7-O-β-D-glucopyranoside (**5**) and betavulgarin (**6**) have been isolated for the first time from the fresh bulbs of Iris tingitana Boiss. & Reut. Their structures were established on the basis of the spectral data and direct comparison with values from previously identified analogues. Additionally, the isolated compounds (**1–6**) were evaluated for the free radical scavenging activity.*

Title: Iridoids from *Spathodea campanulata* P. Beauvais Leaves

Authors: Yaser G. Gouda

Source: *Natural Product Communications, 4, 753-756 (2009)*

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*Three new and four known iridoids have been isolated from the leaves of Spathodea campanulata, the structures of the new compounds were determined as 6-O-trans-caffeoyl-decinnamoyl globularimin, 6-O-trans-caffeoyl-asystasioside E and 6-O-trans-caffeoyl-5,7-bisdeoxycynanchoside and provisionally named as spatheosides A **1**, B **2** and C **3** respectively. The known iridoids were identified as verminoside **4**, 6'-O-trans-caffeoyl-loganic acid **5**, catalpol **6** and ajugol **7**. The structures of the isolated compounds were characterized by different spectroscopic methods.*

Title: Iotrochotamides I and II New Ceramides from the Indonesian Sponge *Iotrochota purpurea*

Authors: Sabrin R.M. Ibrahim[1], Gamal A. Mohamed[2], Mostafa A. Fouad[3], Ehab S. El-Khayat[2], Peter Proksch[4]

Source: *Natural Product Research, 23 (1), 86-92 (2009)*

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*Our search for biologically active marine natural products led to the isolation of two new ceramides iotrochotamide I (**1**) and iotrochotamide II (**2**), together with three known 6-bromoindole alkaloids (6-bromo-1H-indole-3-carbaldehyde (**3**), 6-bromo-1H-indole-3-carboxylic acid methyl ester (**4**), and 6-bromo-1H-indole-3-carboxylic acid ethyl ester (**5**)) from the sponge Iotrochota purpurea collected in Indonesia. The structure elucidation of these compounds was secured by spectroscopic methods (^{1}H, ^{13}C, DEPT, COSY, HMQC and HMBC), accurate mass measurements (ESI, EI and GS-MS) as well as comparison to known compounds.*

Title: Chemical Composition of the Stem Bark and Leaves of *Ficus pandurata* Hance

Authors: M.A. Ramadan[1,2], A.S. Ahmad[2], A.M. Nafady[3], A.I. Mansour[3]

Source: *Natural Product Research, 23 (13), 1218-1230 (2009)*

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*A new compound; 3-O-α-L-arabinopyranosyl-4-hydroxybenzoic acid (**13**) in addition to 16 first reported compounds α-amyrin acetate (**1**), β-amyrone (**2**), 3β-acetoxy-20-taraxasten-22-one (**3**), α-amyrin (**4**), ceryl alcohol (**5**), stigmasterol (**6**), β-sitosterol (**7**), 2α,3α-dihydroxy-lup-20(29)-en-28-oate (**8**), ursolic acid (**9**), β-sitosterol-3-O-glucosoide (**10**), protocatechuic acid (**11**), betulinic acid (**12**), quercetin (**14**), quercetin-3-O-β-D-glucoside (**15**), kampferol-3-O-β-neohesperidoside (**16**) and rutin (**17**) were isolated from the stem bark and leaves of Ficus pandurata (Hance) cultivated in Egypt. Identification of these compounds has been established by physical, chemical and spectral data (UV, IR, MS, ^{1}H- and ^{13}C-NMR) as well as comparison with authentic samples.*

Title: Chemical Composition and Hepato-protective Activity of *Imperata cylindrica Beauv*

Authors: Gamal A. Mohamed[1], Ahmed Abdel-Lateff[2], Mostafa A. Fouad[2], Sabrin R. M. Ibrahim[3], Ehab S. Elkhayat[1], Tatsufumi Okino[4]

Source: *Pharmacognosy Magazine, 4 (17), 28-36 (2009)*

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Fractionation and purification of the methanolic extract of the aerial parts of Imperata cylindrica Beauv. (Graminae), growing in Egypt yielded four methoxylated flavonoids ***1-4****,* β*-sitosterol 3-O-*β*-D-glucopyranosyl-6´-tetradecanoate* ***5****, 3-hydroxy-4-methoxy-benzaldehyde* ***6****, together with β-sitosterol-3-O-*β*-D-glucopyranoside, β-sitosterol and α-amyrin* ***7-9****. A significant hepato-protective activity had been observed when the methanolic extracts of I. cylindrica co-administration with CCl_4 in addition to cytotoxic activity using brine shrimp lethality test. The structures of the isolated compounds were determined by interpretation of their spectroscopic data; 1D (^1H and ^{13}C), 2D (HSQC and HMBC) NMR; MS; UV and IR.*

Title: Iron-Mediated Cleavage of C-C Bonds in Vicinal Tricarbonyl Compounds in Water

Authors: Mecinović J., Hamed R. B., Schofield C. J.

Source: *Angew. Chem. Int. Ed., 48, 2796-2800 (2009)*

Address: ---

Title: Evidence that Thienamycin Biosynthesis Proceeds via C-5 epimerization: ThnE Catalyzes the Formation of (2S,5S)-trans-Carboxymethylproline

Authors: Hamed R. B., Batchelar E. T., Mecinović J., Claridge T. D. W., Schofield C. J.

Source: *ChemBioChem., 10, 246-250 (2009)*

Address: ---

Title: Synthesis of Regio- and Stereoselectively Deuterium-Labelled Derivatives of L-Glutamate Semialdehyde for Studies on Carbapenem Biosynthesis

Authors: Ducho C., Hamed R. B., Batchelar E. T., Sorensen J. L., Odell B., Schofield C. J.

Source: *Org. Biomol. Chem., 7, 2770-2779 (2009)*

Address: ---

Title: Macro- and Micromorphology of *Grindelia camporum* Var. *Camporum Greene*. Family Asteraceae, Cultivated in Egypt: Leaf, Stem and Root

Authors: A. M. El-Moghazy[1], F. M. Darwish[1], E. S. El-Khayat[2], M. O. Mohamed[2]

Source: *Bull. Pharm. Sci., Assiut University, 32 (1), 23-43 (2009)*

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The detailed macro-and micromorphological characters of the stems, leaves and roots of Grindelia camporum varity camporum Greene (syn. Grindelia Robusta) 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: Macro- and Micromorphological Study of the Leaf, Stem and Inflorescence of *Eranthemum nervosum* T. Anders (Fam. Acanthaceae), Cultivated in Egypt

Authors: Mahmoud H. Assaf[1], Yaser G. Gouda[1], Ehab S. El-Khayat[2], Reda A. Abd El-Hamid[2]

Source: *Bull. Pharm. Sci., Assiut University, 32 (1), 85-109 (2009)*

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Many ornamental plants belonging to the family Acanthaceae, showed interesting medicinal activities in treating: cough, chronic bronchitis, rheumatism, jaundice, ear troubles and fever. In addition to treatment of some skin diseases. In the present work, the detailed macro- and micromorphological characters of the leaf, stem and inflorescence of Eranthemum nervosum T. Anders family Acanthaceae, 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: Macro- and Micromorphology of the Leaf and Stem of *Ruellia brittoniana* Leonard Cultivated in Egypt

Authors: D. W. Bishay, A. M. Abdel-Baky, S. A. M. El-Moghazy, L. G. Gobraeil

Source: *Bull. Pharm. Sci., Assiut University, 32 (2), 279-300 (2009)*

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

The genus Ruellia L. is sometimes called Dipteracanthus, it comprises about 150 species native to tropical and temperate North and South America. Ruellia brittoniana Leonard is known as Britton's wild petunia, wild petunia, Mexican bluebell and Ruellia tweediana Grisebach. Some species of genus Ruellia are used medicinally to cure gonorrhoea, syphilis, eye sores and in renal infections.

Title: Flavonoids and Phenylpropanoids from *Spathodea campanulata* P. Beauvais Leaves

Authors: Yaser G. Gouda

Source: *Bull. Pharm. Sci., Assiut University, 32 (2), 301-309 (2009)*

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*Fractionation and purification of the methanolic extract of the leaves of Spathodea campanulata P. Beauvais cultivated in Egypt afforded six compounds identified as: 1-O-caffeoyl-β-D-glucopyranoside (**1**), kaempferol 3-O-(2-O-β-D-xylopyranosyl)-β-D-galacto-pyranoside (**2**), kaempferol 3-O-(6-O-α-L-rhamnopyranosyl)-β-D-galactopyranoside (**3**), acteoside (**4**), kaempferol 3-O-(6-O-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**5**) and quercetin 3-O-(2-O-β-D-xylopyranosyl)-β-D-galactopyranoside (**6**). The structures of the isolated compounds were determined by physical, chemical and spectroscopic methods. All these compounds have been isolated for the first time from the genus spathodea.*

Title: Phenolic Constituents of Cucurbita pepo L. CV `Eskandrani` (Summer Squash) Flowers

Authors: G. A. Mohamed[1], S. R. M. Ibrahim[2], H. M. Sayed[2]

Source: *Bull. Pharm. Sci., Assiut University, 32 (2), 311-319 (2009)*

Address: [1]Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt, [2]Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut, Egypt

*One new flavonoid named 5,7-dihydroxy-3,6,3`-trimethoxyflavone (**1**), together with eight known phenolic compounds; 3,4-dihydroxy methyl benzoate (**2**), 3,4-dihydroxybenzoic acid (**3**), isorhamnetin (**4**), quercetin (**5**), myricetin (**6**), isorhamnetin-4`-O-β-D-glucopyranoside (**7**), quercetin-4`-O-β-D-glucopyranoside (**8**) and quercetin-3,4`-O-β-D-diglucopyranoside (**9**) were isolated from the flowers of Cucurbita pepo L. for the first time except **3** which was previously isolated from the plant. Their structures have been established on the basis of physical, chemical and spectroscopic methods in addition to comparison with literature data and/or authentic samples. The methanolic and ethyl acetate extracts were evaluated for their antimicrobial activity.*

Title: Chlorzoxazone Esters of some Non-Steroidal Anti-Inflammatory (NSAI) Carboxylic Acids as Mutual Prodrugs: Design, Synthesis, Pharmacological Investigations and Docking Studies

Authors: Ahmed Z. Abdel-Azeern, Atef A. Abdel-Hafez, Gamal S. El-Kararnany, Hassan H. Farag

Source: *Bioorganic & Medicinal Chemistry, 17, 3665-3670 (2009)*

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

*The discovery of the inducible isoform of cyclooxygenase enzyme (COX-2) spurred the search for anti-inflammatory agents devoid of the undesirable effects associated with classical NSAIDs. New chlorzoxazone ester prodrugs (**6-8**) of some acidic NSAIDs (**1-3**) were designed, synthesized and evaluated as mutual prodrugs with the aim of improving the therapeutic potency and retard the adverse effects of gastrointestinal origin. The structure of the synthesized mutual ester prodrugs (**6-8**) were confirmed by IR, ^1H NMR, mass spectroscopy (MS) and their purity was ascertained by TLC and elemental analyses. In vitro chemical stability revealed that the synthesized ester prodrugs (**6-8**) are chemically stable in hydrochloric acid buffer pH 1.2 as a non-enzymatic simulated gastric fluid (SGF) and in phosphate buffer pH 7.4 as non-enzymatic simulated intestinal fluid (SIF), in 80% human plasma, the mutual prodrugs were found to be susceptible to enzymatic hydrolysis at relatively faster rate ($t_{½} \approx 37$ and 34 min for prodrugs **6** and **7**, respectively). Mutual ester prodrugs (**6-8**) were evaluated for their anti-inflammatory and muscle relaxation activities. Scanning electromicrographs of the*

*stomach showed that the ester prodrugs induced very little irritancy in the gastric mucosa of rats after oral administration for 4 days. In addition, docking of the mutual ester prodrugs (**6-8**) into COX-2 active site was conducted in order to predict the affinity and orientation of these prodrugs at the enzyme active site.*

Title: Quantitative Structure-Activity Relationship (QSAR) Studies on a Series of 1,3,4-thiadiazole-2-thione Derivatives as Tumor-Associated Carbonic Anhydrase IX Inhibitors

Authors: Mohammed K. Abdel-Hamid, Atef A. Abdel-Hafez, Nawal A. El-Koussi, Nadia M. Mahfouz

Source: *Journal of Enzyme Inhibition and Medicinal Chemistry, 24 (3), 722-729 (2009)*

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A linear quantitative structure-activity relationship (QSAR) study that encodes various aspects of physicochemical, topological and electronic descriptors has been developed for a series of 1,3,4-thiadiazole-2-thione derivatives (la-r and 2a-c). The carbonic anhydrase IX inhibitory activity of the candidates under study (la-r and 2a-c) were correlated to the selected parameters using stepwise linear regression analyses to achieve the best QSAR model. Promising results were obtained with the employed tetra-parametric model indicating that the information approach used in the present investigation is quite useful for modeling carbonic anhydrase IX inhibitors.

Title: Small-Sized Human Immunodeficiency Virus Type-1 Protease Inhibitors Containing Allophenylnorstatine to Explore the S2' Pocket

Authors: Koushi Hidaka[1], Tooru Kimura[1], Hamdy M. Abdel-Rahman[1], Jeffrey-Tri Nguyen[1], Keith F. McDaniel[2], William E. Kohlbrenner[2], Akhteruzzaman Molla[2], Motoyasu Adachi[3], Taro Tamada[3], Ryota Kuroki[3], Noriko Katsuki[3], Yoshiaki Tanaka[1], Hikaru Matsumoto[1], Jun Wang[1], Yoshio Hayashi[1], Dale J. Kempf[2], Yoshiaki Kiso[1]

Source: *Journal of Medicinal Chemistry, ASAP (2009), DOI: 10.1021/jm9005115*

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A series of HIV protease inhibitor based on the allophenylnorstatine structure with various P20 moieties were synthesized. Among these analogues, we discovered that a small allyl group would maintain potent enzyme inhibitory activity compared to the o-methylbenzyl moiety in clinical candidate 1 (KNI-764, also known as JE-2147, AG-1776, or SM-319777). Introduction of an anilinic amino group to 2 (KNI-727) improved water-solubility and anti-HIV-1 activity. X-ray crystallographic analysis of 13k (KNI-1689) with a β-methallyl group at

P20 position revealed hydrophobic interactions with Ala28, Ile84, and Ile500 similar to that of 1. The presence of an additional methyl group on the allyl group in compound 13k significantly increased anti-HIV activity over 1 while providing a rational drug design for structural minimization and improving membrane permeability.

Title: Synthesis of Some Pyrazolylbenzenesulfonamide Derivatives as Anti-Inflammatory Antimicrobial Agents

Authors: Adnan A. Bekhit[1], Hayam M.A. Ashour[1], Alaa El-Din A. Bekhit[2], Hamdy M. Abdel-Rahman[3], Salma A. Bekhit[4]

Source: *J. Enzyme Inhibition and Medicinal Chemistry, 24, 296-309 (2009)*

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Four series of pyrazolylbenzenesulfonamide derivatives were synthesized and evaluated for their anti-inflammatory activity using cotton pellet induced granuloma and carrageenan-induced rat paw edema bioassays. Moreover, COX-1 and COX-2 inhibitory activity, ulcerogenic effect and acute toxicity were also determined. Furthermore, the target compounds were screened for their in-vitro antimicrobial activity against Eischerichia coli, Staphylococcus aureus and Candida albicans. Compounds 4-(3-Phenyl-4-cyano-1H-pyrazol-1-yl)benzenesulfonamide ***9a*** *and 4-(3-Tolyl-4-cyano-1H-pyrazol-1-yl)benzenesulfonamide* ***9b*** *were not only found to be the most active dual anti-inflammatory antimicrobial*

agents in the present study with good safety margin and minimal ulcerogenic effect but also exhibited good selective inhibitory activity towards COX-2. A docking pose for ***9a*** *and* ***9b*** *separately in the active site of the human COX-2 enzyme was also obtained. Therefore, these compounds would represent a fruitful matrix for the development of dual anti-inflammatory antimicrobial candidates with remarkable COX-2 selectivity.*

Title: Fluorinated 1,2,4-Triazolo[1,5-a]Pyrimidine-6-Carboxylic Acid Derivatives as Antimycobacterial Agents

Authors: Hamdy M. Abdel-Rahman, Nawal A. El-Koussi, Hoda Y. Hassan

Source: *Arch. Pharm. Chem. Life Sci., 339, 378-387 (2009)*

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A series of fluorinated 1,2,4-triazolo[1,5-a]pyrimidine-6-carboxylic acid derivatives was designed and synthesized as fluoroquinolone analogues. The synthesized compounds were screened against Mycobacterium tuberculosis H37Rv strain at 6.25 µg/ml concentration. Compound **4**, *the 7-Oxo-2-(trifluoromethyl)-4,7-dihydro-1,2,4-triazolo[5,1-a]pyrimidine-6-carboxylic acid was found to be a very potent inhibitor, being able to inhibit 92% growth of M. tuberculosis H37Rv at 6.25 µg/ml concentration and in the same time nontoxic to mammalian cells (IC50 > 62.5 µg/ml in VERO cells).*

Title: Design, Synthesis and Molecular Modeling Study of Acylated 1,2,4-Triazole-3-Acetates with Potential Anti-Inflammatory Activity

Authors: Ashraf M. Abdel-Megeed, Hamdy M. Abdel-Rahman, Gamal-Eldien S. Alkaramany, Mahmoud A. El-Gendy

Source: *European Journal of Medicinal Chemistry, 44, 117-123 (2009)*

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The present investigation is concerned with synthesis of different acylated 1,2,4-triazole-3-acetates with the objective of discovering novel and potent anti-inflammatory agents. Structures of the synthesized compounds were elucidated by spectral and elemental analyses. The obtained compounds were evaluated for their anti-inflammatory activity as well as gastric ulcerogenic effects and acute toxicity. Results showed that the 1-acylated-5-amino-1,2,4-triazole-3-acetates ***3a-e*** *showed higher anti-inflammatory activity than the corresponding 5-acylamino derivatives* ***4a-e*** *in carageenan-induced rat paw edema test with low gastric ulcerogenicity compared with indomethacin. Furthermore, molecular modeling studies were performed in order to rationalize the obtained biological results.*

Title: Synthesis and Investigation of Anti-Inflammatory Activity and Gastric Ulcerogenicity of Novel Nitric Oxide-Donating Pyrazoline Derivatives

Authors: Mai E. Shoman[1], Mohamed Abdel-Aziz[1], Omar M. Aly[1], Hassan H. Farag[2], Mohamed A. Morsy[3]

Source: *European Journal of Medicinal Chemistry, 44, 3068-3076 (2009)*

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A group of 3,5-diaryl-2-pyrazoline derivatives were prepared via the reaction of various chalcones with hydrazine hydrate in ethanol. A group of NO-donating-2-pyrazoline derivatives were synthesized by carrying a nitrate ester group or an oxime group onto the prepared pyrazoline derivatives through different spacers. The prepared compounds were evaluated for their anti-inflammatory activity using carrageenan-induced rat paw edema and compared to a well-known NSAID. indomethacin as a reference drug. The ability of the prepared compounds to induce gastric toxicity was also evaluated. Most of the prepared compounds showed significant anti-inflammatory activity at the injected dose (100 mg/kg) but they were safer than indomethacin in regard to gastric toxicity. The incorporation of the NO-donating group into the parent pyrazoline derivatives caused a non-significant reduction in the anti-inflammatory activity while a

marked decrease in gastric ulcerations induced by their parent pyrazolines was observed.

Title: 1-Malonyl-1,4-dihydropyridine as a Novel Carrier for Specific Delivery of Drugs to the Brain

Authors: Heba A. Hassan[1], Mohamed Abdel-Aziz[1], Gamal El-Din A. A. Abuo-Rahma[1], Hassan H. Farag[2]

Source: *Bioorganic & Medicinal Chemistry, 17, 1681-1692 (2009)*

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A group of 1-malonyl-1,4-dihydropyridine derivatives were synthesized as novel carrier systems for site-specific and sustained drug delivery to the brain. Such carriers are expected to be stable against air oxidation due to the presence of the carbonyl group close to nitrogen of the dihydropyridine. These carrier systems were attached to a group or different aldehydes to afford novel quaternary pyridinium derivatives ***9a-e, 11a-d, 13*** *and* ***18a-b****. Reduction of the prepared quaternary pyridinium derivatives with sodium dithionite afforded a novel group of 1-malonyl-1,4-dihydropyridine chemical delivery systems (CDSs)* ***10a-e, 12a-d, 14*** *and* ***19a-b****. The synthesized 1-malonyl-1,4-dihydropyridine CDSs were subjected to various chemical and biological investigations to evaluate their ability to cross the blood-brain barrier, and to be oxidized biologically into their corresponding quaternary derivatives. The in vitro oxidation studies showed that most of the 1-malonyl-1,4-dihydropyridine CDSs could be oxidized into their corresponding quaternary derivatives at an adequate rate. The in vivo studies*

showed that compounds **10c** *and* **14** *were able to cross the blood-brain barrier at detectable concentrations. Moreover, the pyridinium quaternary intermediates* **9a, 9c, 13, 18a** *and their corresponding dihydro derivatives* **10a, 10c, 14** *and* **19a** *were screened for their antidepressant activity using tail suspension behavioral despair test compared to imipramine as a reference at a dose level of 10 mg/kg, The results indicated that compounds* **13, 14** *and* **19a** *induced remarkable antidepressant activity comparable to imipramine. Compounds* **10a, 10c** *and* **18a** *exhibited good antidepressant activity, their activities nearly equal to 92.8%, 86.7% and 90.20% of the activity of imipramine, respectively. The other derivatives* **9a** *and* **9c** *exhibited moderate antidepressant activity compared with imipramine.*

Title: Design, Synthesis and Biological Investigation of Certain Pyrazole-3-carboxylic Acid Derivatives as Novel Carriers for Nitric Oxide

Authors: El-Shimaa M. N. Abdel-Hafez[1], Gamal El-Din A. A. Abuo-Rahma[1], Mohamed Abdel-Aziz[1], Mohamed F. Radwan[1], Hassan H. Farag[2]

Source: *Bioorganic & Medicinal Chemistry, 17, 3829-3837 (2009)*

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*Some novel pyrazole-NO hybrid molecules **5a-e**, **6**, **8** and **10** were prepared through binding of the pyrazole-3-carboxylic acid derivatives with nitric oxide donor moiety like oxime or nitrate ester. The prepared compounds were evaluated for nitric oxide release, antibacterial and anti-inflammatory activities. The organic nitrate **10** exhibited the highest percentage of NO release using Griess diazotization method. Some of the prepared compounds exhibited remarkable antibacterial activity against Escherichia coli C-600, Pseudomonas aeruginosa, Bacillus subitilis and Staphylococcus aureus NCTC 6571 compared to ciprofloxacin. Most of the tested compounds showed significant anti-inflammatory activity compared to indomethacine using carrageenan induced paw edema method. In general, structural modification of compound **2** either to nitrate ester or oxime hybrids showed better anti-inflammatory with less ulcerogenic liability than their corresponding starting intermediates.*

Title: Biotransformation Studies of Prednisone Using Human Intestinal Bacteria. Part II: Anaerobic Incubation and Docking Studies

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

Source: *Journal of Enzyme Inhibition and Medicinal Chemistry, 24, 1211-1219 (2009)*

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*Anaerobic incubation of prednisone **1** with human intestinal bacteria (HIB) afforded nine metabolites: 5β-androst-1-ene-3,11,17-trione **3**, 3α-hydroxy-5α-androstane-11,17-dione **4**, 3β,17α,20-trihydroxy-5α-pregnan-11-one **5**, 3α,17α-dihdyroxy-5α-pregnane-11,20-dione **6**, 3α,17α-dihydroxy-5β-pregnane-11,20-dione **7**, 3β,17β-dihydroxy-5α-androstan-11-one **8β**, 3β,17α-dihydroxy-5α-androstan-11-one **8α**, 3α,17β-dihydroxy-5α-androstan-11-one **9β**, 3α,17α-dihydroxy-5α-androstan-11-one **9α**. The structures of these metabolites (**3-9**) were elucidated using several spectroscopic techniques. Computer-aided prediction of potential biological activities of the isolated prednisone metabolites (**3-9**) revealed potential inhibition of prostaglandin E2 9-ketoreductase (PGE2 9-KR). Docking studies applied to PGE2 9-KR allowed recommendation of the metabolites **4, 8β**, and **8α** for further pharmacological study as PGE2 9-KR inhibitors.*

Title: Design, Synthesis and Molecular Modeling Study of 1,2,4-Triazole Carbohydrazide Derivatives with Potential Antimicrobial and Anti-Inflammatory Activities

Authors: Nawal A. El-Koussi

Source: *Bull. Pharm. Sci., Assiut University, 32 (1), 225-240 (2009)*

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The present investigation is concerned with the synthesis of 1,2,4-triazole carbohydrazide derivatives ***(6a-l)*** *with the objective of discovering novel and potent antimicrobial and anti-inflammatory agents.*

The chemical structures of the target compounds were elucidated by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The antimicrobial activity of the target compounds were evaluated and compared with ampicillin trihydrate and clotrimazole as references compounds. The results showed that compound ***6i*** *revealed a similiar level of activity as ampicillin against Staphylococcus aureus, while compounds* ***6j*** *and* ***6l*** *exhibited comparable activity against Escherichia coli. All compounds were less active against Candida albicans when compared with clotrimazole. The results of anti-inflammatory showed that compounds* ***6d, 6l*** *possessed higher anti-inflammatory activity than celecoxib in carageenan-induced rat paw edema test with low gastric ulcerogenicity compared with indomethacin. Molecular modeling studies were performed in order to rationalize the obtained biological results.*

Title: Synthesis and Potential Biological Activities of Certain New Substituted Thiazoline-Quinoline Derivatives

Authors: Mostafa A. Hussein, Abdel-Hamid N. Kafafy, Samia G. Abdel-Moty, Ola Mohamed F. Abou-Ghadir

Source: *Journal of Acta Pharmaceutica, 59, 365-382 (2009)*

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*5-Acyl-8-hydroxyquinoline-2-(3'-substituted-4'-aryl-2,3-dihydrothiazol-2'-ylide- ne)hydrazones, (**5-9;a-e** and **10a-c**) were prepared by acylation of the appropriate 5-acyl-8-hydroxyquinoline-4-substituted thiosemicarbazones (**3a-e**) and phenacyl bromides (**4a-e**) in the presence of anhydrous sodium acetate in absolute ethanol. Structures of the new compounds (**5-9;a-e** and **10a-c**) were verified on the basis of spectral and elemental methods of analyses. Twenty-eight new compounds (**5-9;a-e** and **10a-c**) were tested for their possible antimicrobial activities. Most of the test compounds showed weak to moderate antibacterial activity against most of the used bacterial strains in comparison to gatifloxacin as a reference drug. The test compounds showed weak to moderate antifungal activity against tested fungi in comparison to ketoconazole as a reference drug. On the other hand, the newly synthesized compounds were tested for their anti-inflammatory effects and most of them showed good to excellent anti-inflammatory activity in comparison to indomethacin. Moreover, the ulcerogenicity and the median lethal dose (LD_{50}) of the most active anti-*

*inflammatory compounds (**6b** and **9e**) were determined in mice; they were non-toxic at doses up to 400 mg/Kg (i.p.).*

Title: Slit2–Robo4 Signalling Promotes Vascular Stability by Blocking Arf6 Activity

Authors: Christopher A. Jones[1,2], Naoyuki Nishiya[3,10], Nyall R. London[1,2], Weiquan Zhu[1,2], Lise K. Sorensen[2], Aubrey C. Chan[1,2], Chinten J. Lim[3], Haoyu Chen[4,11], Qisheng Zhang[5], Peter G. Schultz[6], Alaa M. Hayallah[7,12], Kirk R. Thomas[2,8], Michael Famulok[7], Kang Zhang[4,13], Mark H. Ginsberg[3], and Dean Y. Li[1,2,9]

Source: *Nature Cell Biology, 1325-1333 (2009)*

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Slit–Roundabout (Robo) signalling has a well-understood role in axon guidance1–5. Unlike in the nervous system, however, Slit-dependent activation of an endothelialspecific Robo, Robo4, does not initiate a guidance program. Instead, Robo4 maintains the barrier function of the mature vascular network by inhibiting neovascular tuft formation and endothelial hyperpermeability induced by pro-angiogenic factors6. In this study, we used cell biological and biochemical techniques to elucidate the molecular mechanism underlying the maintenance of vascular stability by Robo4. Here, we demonstrate that Robo4 mediates Slit2-dependent suppression of cellular protrusive activity through direct interaction with the intracellular adaptor protein paxillin and its paralogue, Hic-5. Formation of a Robo4–paxillin complex at the cell surface blocks activation of the small GTPase Arf6 and, consequently, Rac by recruitment of Arf-GAPs (ADP-ribosylation factor- directed GTPase-activating proteins) such as GIT1. Consistent with these in vitro studies, inhibition of Arf6 activity in vivo phenocopies Robo4 activation by reducing pathologic angiogenesis in choroidal and retinal vascular disease and VEGF- 165 (vascular endothelial growth factor-165)-induced retinal hyperpermeability. These data reveal that a Slit2–Robo4–paxillin–GIT1 network inhibits the cellular protrusive activity

underlying neovascularization and vascular leak, and identify a new therapeutic target for ameliorating diseases involving the vascular system.

Title: Synthesis of New 1,2,4-Triazole Derivatives of Nalidixic Acid as Potential Antibacterial and Antifungal Agents

Authors: Samia G. Abdelmoty[1], Helal F. Heta[2]

Source: *Bull. Pharm. Sci., Assiut University, 32 (1), 125-140 (2009)*

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Triazole and triazole fused heterocyclic ring systems possess diverse applications in the fields of medicine, agriculture and industry. A new series of nalidixic acid derivatives having 1,2,4-triazole moiety at position 3 were synthesised to achieve enhanced biological activity and wide spectrum of activity. Nalidixic acid was first converted into its methyl ester which upon hydrazinolysis afforded nalidixic acid hydrazide. Condensation of the hydrazide with CS_2/KOH furnished the potassium dithiocarbazate salt, which cyclized to the 3-[4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]-1-ethyl-7-methyl-1H-[1,8] naphthyridin-4-one, **(4)**, *on refluxing with hydrazine hydrate. Condensation of the key intermediate* **4** *with aryl aldehydes afforded Schiff's bases* **5a-f**, *while its reaction with alkyl or aralkyl halides gave compounds* **6a-e**. *Furthermore, compounds* **5a,e** *were reacted with benzyl chloride to afford* **7a,b**. *The chemical structure of the target compounds was confirmed by IR, ^{1}H-NMR, FAB-MS, EI-MS spectra and elemental analyses. The title compounds and the starting Nalidixic acid; were tested for their in-vitro antibacterial and antifungal*

activities. Most of the tested compounds showed comparable antibacterial activity with those of Nalidixic acid and higher activity than ampicillin. The tested compounds and Nalidixic acid showed non or moderate antifungal activity in comparison to clotrimazole as a reference drug.

Title: Synthesis, Anti-Bronchoconstrictive, and Antibacterial Activities of Some New 8-Substituted-1,3-Dimethylxanthine Derivatives

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

Source: *Bull. Pharm. Sci., Assiut University, 32 (1), 153-187 (2009)*

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Methylxanthines especially theophylline have been recognized as potent bronchodilators for the relief of acute asthma for over 50 years. Recently, it was found that bacterial infection has a role in asthma pathogenesis. Accordingly, the present work involves the synthesis of different series of 8-substituted (aryl, aralkyl, cycloalkyl, and heteroaryl)-1,3-dimethylxanthines. The chemical structures of these compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, elemental analyses, and high resolution EI-MS or FAB-MS for some compounds. The bronchodilator activity was evaluated using acetylcholine induced bronchospasm in guinea pigs, and most of the compounds showed significant anti-bronchoconstrictive activity in comparison with aminophylline as a standard. Also, the antibacterial activity of all the target compounds was investigated in-vitro against Gram-positive and Gram-negative bacteria using ampicillin as a reference drug. Results showed that some of the tested compounds have potent antibacterial activity. A pharmacophore model was computed to get useful insight on the essential structural features of bronchodilator activity.

Title: New Sensitive Kinetic Spectrophotometric Methods for Determination of Omeprazole in Dosage Forms

Authors: Ashraf M. Mahmoud

Source: *Intl. J. Anal Chem. (2009) (Published online, Vol. 2009, Article ID 307045, 11 pages, doi: doi:10.1155/2009/307045)*

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New rapid, sensitive, and accurate kinetic spectrophotometric methods were developed, for the first time, to determine omeprazole (OMZ) in its dosage forms. The methods were based on the formation of charge-transfer complexes with both iodine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The variables that affected the reactions were carefully studied and optimized. The formed complexes and the site of interaction were examined by UV/VIS, IR, and ^{1}H-NMR techniques, and computational molecular modeling. Under optimum conditions, the stoichiometry of the reactions between OMZ and the acceptors was found to be 1:1. The order of the reactions and the specific rate constants were determined. The thermodynamics of the complexes were computed and the mechanism of the reactions was postulated. The initial rate and fixed time methods were utilized for the determination of OMZ concentrations. The linear ranges for proposed methods were 0.10-3.00 and 0.50-25.00 μg ml^{-1} with the lowest LOD of 0.03 and 0.14 μg ml^{-1} for iodine and DDQ, respectively. Analytical performance of the methods was statistically validated; RSD was < 1.25% for the precision and < 1.95% for the accuracy. The proposed methods were successfully applied to the analysis of OMZ in its dosage forms. The recovery values were 98.91–100.32% ±

0.94-1.84, and these values were found to be comparable with those of reference method.

Title: New Non-Extractive and Highly Sensitive HPLC Method for Determination of Paroxetine in Plasma after Offline Pre-Column Derivatization with 7-Chloro-4-Nitrobenzo-2-Oxa-1,3-Diazole

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Source: *J. AOAC Int., 92 (5), 1-8 (2009)*

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New non extractive and simple pre-column derivatization procedures have been proposed, for the first time, for the trace determination of paroxetine (PXT) in human plasma by HPLC with fluorescence detection. Trimetazidine (TMZ) was used as an internal standard. Plasma samples were treated with acetonitrile for protein precipitation and then derivatized with 7-chloro-4-nitrobenzo-2-oxa-1,3-diazole in borate buffer of pH 8 at 70°C for 30 min. Separations of the derivatized PXT and TMZ were performed on Nucleosil CN column 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 = 0.9998, n = 7) was found between the peak area ratio and PXT concentrations in the range of 5-600 ng/mL. The limit of detection and

limit of quantitation were 1.37 and 4.20 ng/mL, respectively. The intra and inter-assay precisions were satisfactory; the relative standard deviations did not exceed 4.2%. The accuracy of the method was proved; the recovery of PXT from the spiked human plasma were 97.28 – 104.38 ± 0.41-3.62%. The proposed method had high throughput as the analysis involved simple sample pre-treatment procedure and short run-time (<10 min). The results demonstrated that the method would have a great value when it is applied in both the bioavailability and pharmacokinetic studies for PXT.

Title: Selective Spectrophotometric and Spectrofluorometric Methods for the Determination of Amantadine Hydrochloride in Capsules and Plasma via Derivatization with 1,2-Naphthoquinone-4-Sulphonate

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

Source: *Intl. J. Anal Chem. (2009) (Published online, Vol. 2009, Article ID 810104, 8 pages, doi: 10.1155/2009/810104)*

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New selective and sensitive spectrophotometric and spectrofluorometric methods have been developed and validated for the determination of amantadine hydrochloride (AMD) in capsules and plasma. The proposed methods were based on the condensation of AMD with 1,2-naphthoquinone-4-sulphonate (NQS) in an alkaline medium to form an orange-colored product. The spectrophotometric method involved the measurement of the colored product at 460 nm. The spectrofluorometric method involved the reduction of the colored product with potassium borohydride and the subsequent measurement of the formed green fluorescent reduced AMD-NQS product at 382 nm after excitation at 293 nm. The variables that affected the reaction between AMD and NQS were carefully studied and optimized. Under the optimum conditions, linear relationships with

good correlation coefficients (0.9974 and 0.9972) and low LOD (1.39 and 0.013 µg ml^{-1}) were obtained in the ranges of 5-80 and 0.05-10 µg ml^{-1} for the spectrophotometric and spectrofluorometric methods, respectively. The precisions of the methods were ≤ 2.04%. Both methods were successfully applied to the determination of AMD in capsules. As its higher sensitivity, the spectrofluorometric method was applied to the determination of AMD in plasma; the recovery percentages ranged from 96.3-101.2 ± 0.57-4.2%. The results obtained by the proposed methods were comparable with those obtained by the official method.

Title: A Highly Sensitive Enzyme Immunoassay for Evaluation of 2'-Deoxy-Cytidine Plasma Level as a Prognostic Marker for Breast Cancer Chemotherapy

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A highly sensitive competitive enzyme immunoassay (EIA) has been developed and validated for the determination of the plasma level of 2`-deoxycytidine (dCyd), the potential prognostic marker for breast cancer chemotherapy. This assay employed a monoclonal antibody that recognizes dCyd with a high specificity, and 5'-succinyl-dCyd (5'sdCyd) conjugate of bovine serum albumin (5'sdCyd-BSA) immobilized onto microplate wells as a solid phase. The assay involved a competitive binding reaction between dCyd, in plasma sample, and the immobilized 5`sdCyd-BSA for the binding sites of the anti-dCyd antibody. The bound antibody was quantified with horseradish peroxidase-labeled anti-immunoglobulin second antibody and 3,3`,5,5`-tetramethylbenzidine as a peroxidase substrate. The concentration of dCyd in the sample was quantified by its ability to inhibit the binding of the antibody to the immobilized 5`sdCyd-BSA and subsequently the color formation in the assay. The assay limit of detection

was 8 nM and the effective working range at relative standard deviations (RSD) of ≤ 10% was 20-800 nM. No cross reactivity from the structurally related nucleobases, nucleosides, and nucleotides was observed in the proposed assay. Mean analytical recovery of added dCyd was 98–100 ± 3.2–8.2%. The precision of the assay was satisfactory; RSD was 3.4-4.2 and 4.3-8.9% for intra- and inter-assay precision, respectively. The proposed EIA compared favorably with HPLC method in its ability to accurately measure dCyd spiked into plasma samples. The analytical procedure is convenient, and one can analyze 200 samples per working day, facilitating the processing of large-number batch of samples. The proposed EIA is expected to contribute in further evaluation of dCyd as a prognostic marker for breast cancer chemotherapy and elucidation of the role of dCyd in various biological and biochemical systems.

Title: Kinetic Spectrophotometric Determination of Certain Cephalosporins Using Oxidized Quercetin Reagent

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A simple, precise and accurate kinetic spectrophotometric method for determination of cefoperazone sodium, cefazolin sodium and ceftriaxone sodium in bulk and in pharmaceutical formulations has been developed. The method is based upon a kinetic investigation of the reaction of the drug with oxidized quercetin reagent at room temperature for a fixed time of 30 min. The decrease in absorbance after the addition of the drug was measured at 510 nm. The absorbance concentration plot was rectilinear over the range 80-400 gmL^{-1} for all studied drugs. The concentration of the studied drugs was calculated using the corresponding calibration equation for the fixed time method. The determination of the studied drugs by initial rate, variable time and rate-constant methods was feasible with the calibration equations obtained but the fixed time method has been found to be more applicable. The analytical performance of the method, in terms of accuracy and precision, was statistically validated; the results were satisfactory. The method has been successfully applied to the determination of the studied drugs in commercial pharmaceutical formulations. Statistical comparison

of the results with a well established reported method showed excellent agreement and proved that there is no significant difference in the accuracy and precision.

Title: Analytical and Environmental Aspects of the Flame Retardant Tetrabromobisphenol-A and its Derivatives

Authors: Adrian Covaci[1], Stefan Voorspoels[2], Mohamed Abou-Elwafa Abdallah[3,5], Tinne Geens[1], Stuart Harrad[3], Robin J. Law[4]

Source: *Journal of Chromatography A, 1216, 346–363 (2009)*

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The present article reviews the available literature on the analytical and environmental aspects of tetrabromobisphenol-A (TBBP-A), a currently intensively used brominated flame retardant (BFR). Analytical methods, including sample preparation, chromatographic separation, detection techniques,

and quality control are discussed. An important recent development in the analysis of TBBP-A is the growing tendency for liquid chromatographic techniques. At the detection stage, mass-spectrometry is a well-established and reliable technology in the identification and quantification of TBBP-A. Although interlaboratory exercises for BFRs have grown in popularity in the last 10 years, only a few participating laboratories report concentrations for TBBP-A. Environmental levels of TBBP-A in abiotic and biotic matrices are low, probably due to the major use of TBBP-A as reactive FR. As a consequence, the expected human exposure is low. This is in agreement with the EU risk assessment that concluded that there is no risk for humans concerning TBBP-A exposure. Much less analytical and environmental information exists for the various groups of TBBP-A derivatives which are largely used as additive flame retardants.

Title: An Ultrasensitive and Highly Selective Determination Method for Quinones by High-Performance Liquid Chromatography with Photochemically Initiated Luminol Chemiluminescence

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Quinones are a class of compounds of substantial toxicological and pharmacological interest. An ultrasensitive and highly selective chemiluminescence (CL) method was newly developed for the determination of quinones based on the utility of photochemically initiated luminol CL. The method involves ultraviolet (UV) irradiation of quinones to generate ROS through the unique photosensitization reaction accompanied with the photolytical generation of 3,6-dihydroxyphthalic acid (DHPA) from quinones.

The photoproducts were detected by luminol CL reaction. Interestingly, it was noticed that DHPA had enhancement effect for the luminol CL. The generation of the enhancer (DHPA) in association with the oxidant (ROS) in the photochemical reaction greatly increases the sensitivity and selectivity of the proposed luminol CL method. In order to elucidate the type of ROS produced by the photosensitizaion reaction in relation to the proposed CL reaction, we investigated the quenching effect of selective ROS scavengers in the luminol CL. Although several ROS were generated, superoxide anion was the most effective ROS for the generated CL. Moreover, the enhancement mechanism of DHPA for luminol CL was confirmed. The enhancement was found to be through the formation of stabilized semiquinone anion radical that provided long-lived CL. The generation of the semiquinone radical was confirmed by electron spin resonance technique. Furthermore, we developed an HPLC method with on-line photochemical reaction followed by the proposed CL detection for the determination of four quinones. A luminol analogue, L-012, was used for its high sensitivity. The detection limits for quinones obtained with the proposed method (S/N=3) were in the range 1.5- 24 fmol that were 10-1000 times more sensitive compared with the previous methods. Finally, the developed HPLC-CL system was successfully applied for the determination of quinones in airborne particulate samples collected at Nagasaki city.

Title: Selective Determination of Doxorubicin and Doxorubicinol by HPLC with Photosensitization Reaction Followed by Chemiluminescence Detection

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A highly sensitive and selective high-performance liquid chromatography (HPLC) method was developed for the determination of doxorubicin (DXR) and its metabolite doxorubicinol (DXR-ol) in rat plasma. The method was based on photosensitization reaction followed by peroxyoxalate chemiluminescence detection (PO-CL). DXR and DXR-ol that were fluorescent quinones, served as a photosensitizer in presence of a hydrogen atom donor such as ethanol under aerobic conditions to produce hydrogen peroxide. Then the generated hydrogen peroxide and DXR or DXR-ol were monitored through PO-CL reaction by mixing with aryloxalate as a single post-column reagent that enabled highly selective and sensitive determination of DXR and DXR-ol. The separation of DXR and DXR-ol by HPLC was accomplished isocratically on an ODS column within 15 min. The method involves a simple one step protein precipitation by methanol and a

sample size of 50-□L was sufficient. Besides, it can detect accurately the low plasma concentrations. The detection limits (signal-to-noise ratio = 3) were 4.5 and 3.8 fmol for DXR and DXR-ol, respectively. The percentage recovery was found to be 90.7-102.4% and the inter- and intra-assay RSD values in rat plasma were 2.5-8.9%. The method has been successfully used to study pharmacokinetic profiles of DXR and DXR-ol in rats after a single dose of DXR.

Title: Simultaneous Separation and Determination of Lamivudine and Zidovudine in Pharmaceutical Formulations Using the HPTLC Method

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A high-performance thin-layer chromatographic method (HPTLC) for the simultaneous determination of lamivudine and zidovudine in a binary mixture has been developed. The method developed was based on HPTLC separation of the two drugs followed by densitometric measurements of spots at 276 and 271 nm for lamivudine and zidovudine, respectively. Separation was carried out on Merck HPTLC silica-gel 60F254 plates, using toluene/chloroform/methanol (1:6:3 v:v) as the mobile phase. Validation of the method was performed based on The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines in terms of linearity, accuracy, precision, limit of detection, limit of quantification, and robustness. Second-order polynomial equations were obtained for the regression line in the ranges of 250–1400 and 250–1700 ng/spot for lamivudine and zidovudine respectively. Correlation coefficient (r) values were 0.9998 for both

analytes. The method provides sufficient accuracy as indicated by recovery percentages given for lamivudine and zidovudine. For system precision study, the low coefficient of variation values (<2%) for both lamivudine and zidovudine ensured reproducible performance of the instrument. In the method precision study, coefficients of variation <2% were obtained, which showed that the proposed method provides acceptable intraday and interday variation. The detection and quantification limits and were 3.06 and 9.28 ng/spot for lamivudine and 3.34 and 10.13 ng/spot for zidovudine, respectively. Parameters such as mobile-phase composition, volume of mobile phase, time from spotting to development, and time from development to scanning were employed while testing for robustness of the method, and the standard deviation of peak areas was calculated for each parameter. The low coefficient of variation values indicated the robustness of the method. Statistical manipulation did not show any significant effect of one parameter over the others on the robustness of the method.

Title: Causes of Variability in Concentrations and Diastereomer Patterns of Hexabromocyclododecanes in indoor dust

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The temporal evolution of concentrations of α-, β-, and γ-hexabromocyclododecanes (HBCDs), and pentabromocyclododecenes (PBCDs — degradation products of HBCDs) was studied in separate aliquots of a well-homogenized indoor dust sample. These were: (a) exposed to natural light, and (b) kept in the dark. Results revealed a rapid photolytically-mediated shift from γ-HBCD to α-HBCD that was complete after 1 week of exposure, and a slower degradative loss of HBCDs via elimination of HBr. Under the specific conditions studied in this experiment, calculated half-lives ($t_{1/2}$) showed the decay in ΣHBCDs concentration was faster in light-exposed samples ($t_{1/2}$=12 weeks), than in light-shielded dust ($t_{1/2}$=26 weeks). Within room spatial and temporal variability in concentrations and diastereomer patterns were studied in six and three rooms respectively. While in some rooms, little variability was detected, in

others it was substantial. In one room, concentrations of ΣHBCDs and the relative abundance of γ-HBCD declined dramatically with increasing distance from a TV. The same TV appears to have influenced strongly the temporal variation in that room; with higher concentrations observed in its presence and when the TV was moved closer to the area sampled. Significant negative correlation was observed in one room between concentrations of ΣHBCDs and dust loading (g dust m^{-2} floor), implying "dilution" occurs at higher dust loadings.

Title: Personal Exposure to HBCDs and its Degradation Products via Ingestion of Indoor Dust

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Personal exposures via ingestion of indoor dust to α-, β-, and γ-hexabromocyclododecanes (HBCDs) and the degradation products (pentabromocyclododecenes (PBCDs) and tetrabromocyclododecadienes (TBCDs)) were estimated for 21 UK adults. Under an average dust ingestion scenario, personal exposures ranged from 4.5 to 1851 ng ΣHBCDs day^{-1}; while the range under a high dust ingestion scenario was 11 to 4630 ng ΣHBCDs day^{-1}. On average, personal exposure to ΣHBCDs via dust ingestion in this study was 35% α-, 11% β-, and 54% γ-HBCD. However, while exposure to β-HBCD (4-18% of ΣHBCDs) was relatively consistent with that expected from HBCD commercial formulations, exposures to α- and γ-isomers showed substantial variability within the studied group (11-58% and 29-82% of ΣHBCDs respectively). Personal exposures to ΣTBCDs (median = 0.2 ng day^{-1} under an average dust ingestion scenario) and ΣPBCDs (1.4 ng day^{-1}) were significantly lower ($p<0.05$) than for ΣHBCDs (48 ng day^{-1}). Despite this, the exposure of one participant to ΣPBCDs

exceeded the exposure to ΣHBCDs received by 85% of the other participants. On average, house dust provided the major contribution to personal exposure via dust ingestion to all target compounds due to the large time fraction spent in houses. In contrast, although participants spent less time in cars than in offices, car dust makes a higher average contribution (17%) to ΣHBCDs exposure than office dust (13%).

Title: Identifying Transfer Mechanisms and Sources of Decabromodiphenyl Ether (BDE 209) in Indoor Environments Using Environmental Forensic Microscopy

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Source: *Environmental Science and Technology, 43, 3067–3072 (2009)*

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Although the presence of polybrominated diphenyl ethers (PBDEs) in house dust has been linked to consumer products, the mechanism of transfer remains poorly understood. We conjecture that volatilized PBDEs will be associated with dust particles containing organic matter and will be homogeneously distributed in house dust. In contrast, PBDEs arising from weathering or abrasion of polymers should remain bound to particles of the original polymer matrix and will be heterogeneously distributed within the dust. We used scanning electron microscopy and other tools of environmental forensic microscopy to investigate PBDEs in dust, examining U.S. and U.K. dust samples with extremely high levels of BDE 209 (260-2600 μg/g), a nonvolatile compound at room temperature. We found that the bromine in these samples was concentrated in widely scattered, highly contaminated particles. In the house dust samples from Boston (U.S.), bromine was associated with a polymer/organic matrix. These results suggest that the BDE 209 was transferred to dust via physical processes such as abrasion or weathering. In conjunction with more traditional tools of environmental chemistry, such as gas chromatography/mass spectrometry (GC/MS), environmental forensic microscopy provides novel insights into the origins of BDE 209 in dust and their mechanisms of transfer from products.

Title: Factors Influencing Concentrations of Polybrominated Diphenyl Ethers (PBDEs) in Students from Antwerp, Belgium

Authors: Laurence Roosens[1], Mohamed Abou-Elwafa Abdallah[2,3], Stuart Harrad[2], Hugo Neels[1], Adrian Covaci[1,4]

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Human exposure to polybrominated diphenyl ethers (PBDEs) through food and indoor dust ingestion was assessed for 19 Belgian adults. The intake of PBDEs (Σtri-hepta BDEs and BDE 209) in the studied population is influenced mainly by diet. Dietary intakes of Σtri-hepta BDEs (BDEs 28, 47, 99, 100, 153, 154, and 183) were 5.9-22.0 ng/day (median 10.3), while those via dust ingestion were 0.1-1.4 ng/day (median 0.25) or 0.3-3.5 ng/day (average 0.6), assuming dust

ingestion rates of 20 and 50 mg/day, respectively. Dietary intakes of BDE 209 were50-238 ng/day (median 95),whereasthose via dust ingestion were 0.4-11 ng/day (median 1.8) or 1.0-29 ng/day (median 4.6) for dust ingestion rates of 20 and 50 mg/day, respectively. It is important to acknowledge the uncertainty associated with the dust ingestion rates. Concentrations of Σtri-hepta BDEs measured in blood serum were 0.9-7.2 ng/g lipid weight (lw) (median 1.9). This is similar to other European populations, but lower than for non occupationally exposed Americans (average of 19 ng/g lw). When compared with estimates of exposure via both dietary and indoor dust ingestion for Americans, the exposures reported here are consistent with the hypothesis that the difference between European and American body burdens of PBDEs is attributable primarily to greater exposure via dust ingestion for Americans. The total intake of PBDEs through food and dust for each participant could not be correlated with the corresponding serum concentration. Instead, it is hypothesized that past and episodic current higher intakes of PBDEs are more important determinants of body burden than continuous background exposures at the low levels measured in this study.

Title: Exposure to Hexabromocyclododecanes (HBCDs) via Dust Ingestion, but Not Diet, Correlates with Concentrations in Human Serum: Preliminary Results

Authors: Laurence Roosens[1], Mohamed Abou-Elwafa Abdallah[2,3], Stuart Harrad[2], Hugo Neels[1], Adrian Covaci[1,4]

Source: *Environmental Health Perspectives, 117, 1707–1712 (2009)*

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Background: *Hexabromocyclododecane (HBCD) is a high-production-volume chemical used as flame retardant in polystyrene insulation and textiles. Because it is not chemically bound to the polymer, HBCD can migrate into the environment, contaminating indoor dust and foodstuff.*

Objectives: *We examined for the first time the relationship between combined exposure to three HBCD isomers (ΣHBCDs) via ingestion of food (duplicate diets) and indoor dust and HBCD concentrations in serum for 16 Belgian adults (20–25 years of age). We also determined the chiral signatures of HBCDs to*

advance understanding of source-to-human enantioselective degradation and/or metabolism.

Methods: *Concentrations and chiral signatures of α-, β-, and γ-HBCD in duplicate diets, dust, and serum were measured by liquid chromatography/tandem mass spectrometry.*

Results: *Dietary intakes of ΣHBCDs were 1.2–20 ng/day (average, 7.2 ng/day), whereas those estimated under average (20 mg dust/day) and high (50 mg dust/day) dust ingestion scenarios were 1.1–15 ng/day (average intake, 3.2 ng/day) and 2.8–38 ng/day (average intake, 8.0 ng/day), respectively. Concentrations of ΣHBCDs measured in blood serum were<0.5 to 11 ng/g lipid weight (lw) (average, 2.9 ng/g lw). γ-HBCD dominated in food, whereas α-HBCD dominated in dust and was the sole isomer in serum. Although exposure via dust ingestion correlated significantly ($p<0.01$) with concentrations in serum, no such correlation was evident with dietary exposure ($p>0.1$). Although no enantioselective enrichment was detected in either dust or diet, substantial enrichment of (–)-α-HBCD was observed in serum.*

Conclusions: *Serum concentrations of HBCDs were correlated with the exposure via dust, but not via dietary ingestion. The enrichment of the (–)-α-HBCD enantiomer in humans appears to be due to in vivo enantioselective metabolism/excretion rather than ingestion of dust or diet.*

Title: Current-Use Brominated Flame Retardants in Water, Sediment, and Fish from English Lakes

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Source: *Environmental Science and Technology, 43, 9077–9083 (2009)*

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Concentrations are reported of hexabromocyclododecanes (HBCDs) and tetrabromobisphenol-A (TBBP-A) in water (n = 27), sediment (n=9), and fish samples (n=30) from nine English lakes. Seasonal variation in concentrations in water is minimal. Concentrations of TBBP-A range from 140 to 3200 pg L^{-1} (water), 330 to 3800 pg g^{-1} dry weight (sediment), and <0.29 to 1.7 ng g^{-1} lipid weight (fish). Those of ΣHBCDs range between 80 and 270 pg L^{-1} (water), 880 and 4800 pg g^{-1} dry weight (sediment), and 14 and 290 ng g^{-1} lipid weight (fish). Aqueous concentrations of ΣHBCDs and TBBP-A are significantly positively correlated, indicating a common source. Average ± σ_n "freely-dissolved" phase proportions are 47 ± 4.7% (ΣHBCDs) and 61 ± 2.9% (TBBP-A). Average field-derived bioaccumulation factors are 5900, 1300, 810, and 2100 for α-, β-, γ-, *and*

ΣHBCDs, respectively. Tetrabromocyclododecadienes are detected in all sediments, with pentabromocyclododecenes present in some. This suggests HBCD degrades via sequential loss of HBr. The δ-HBCD meso form was quantified in 43% of fish samples (1.0-11% ΣHBCDs). Its absence from temporally and spatially consistent water and sediment samples suggests it is formed via bioisomerization. While HBCD chiral signatures are racemic in water and sediment, our data reveal enantiomeric enrichment of (-)-α-HBCD and (+)-γ-HBCD in fish.

Title: Isotope Dilution Method for Determination of Polybrominated Diphenyl Ethers Using Liquid Chromatography Coupled to Negative Ionisation Atmospheric Pressure Photoionization Tandem Mass Spectrometry: Validation and Application to House Dust

Authors: Mohamed Abou-Elwafa Abdallah[1,2], Stuart Harrad[1], Adrian Covaci[3]

Source: *Analytical Chemistry, 81, 7460–7467 (2009)*

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Fourteen tetra- to deca- PBDE congeners were separated on a C_{18} reversed phase liquid chromatographic column. PBDEs 47, 85, 99, 100, 153, 154, 183, 196, 197, 203, 206, 207, 208 and 209 were eluted using a gradient methanol: water: toluene mobile phase system at a flow rate of 0.5 ml min.$^{-1}$. ^{13}C-BDE-47, ^{13}C-BDE-99, ^{13}C-BDE-153, BDE-128 and ^{13}C-BDE-209 were used as internal standards, while ^{13}C-BDE-100 was used as a syringe standard. Separated analytes were ionized using an atmospheric pressure photoionization (APPI) source equipped with a 10 eV krypton lamp and operated in negative ion mode. $[M-Br+O]^-$ ions were monitored as precursor ions for all studied PBDEs, except for BDE-208 and BDE-209 which produced higher intensity at the $[C_6Br_5O]^-$

ion cluster. $[Br]^-$ ions were monitored as fragment ions for all target compounds. Method detection limits ranged from 12 to 30 pg. The method was applied to determination of PBDEs in standard reference material (SRM 2585) and favourable results obtained. Unlike GC methods, no thermal degradation was encountered in the analysis of higher brominated PBDEs. This rendered the method useful for quantification of BDE-209 debromination products. The method also allows the use of ^{13}C-labeled internal standards which compensate for instrumental fluctuations and matrix-related ion suppression or enhancement.

Title: Determination of Lamivudine and Stavudine in Pharmaceutical Preparations Using Chemometrics-Assisted Spectrophotometry

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A simple chemometrics-assisted spectrophotometric method for the simultaneous determination of lamivudine and stavudine in pharmaceutical tablets is described. The UV absorption spectra of the studied drugs, in the range of 200–310 nm, showed a considerable degree of spectral overlapping ($[D_i]^{0.5}$= 94.9%). Resolution of the mixture has been accomplished by using classical least-squares regression analysis (CLS) and principle components regression analysis methods (PCR). Beer's law was obeyed for both drugs in the general concentration ranges of 2–12 and 3–15 μg ml-1 for lamivudine and stavudine, respectively. The proposed methods were successfully applied for the determination of the two drugs in laboratory prepared mixtures. The overall recoveries percent were found 98.58±1.53 – 101.30 ±1.35 (CLS) and 98.62±1.65 – 101.13±1.04 (PCR) for lamivudine and 98.43±1.62 – 99.42±1.55 (CLS) and 98.23±1.97 – 101.20±1.79 (PCR) for stavudine, respectively. The commercial tablets percentage content was

found 98.10±2.5 – 102.47±2.94 (CLS) and 99.12±1.71 – 100.92 ±1.54 (PCR) for lamivudine and 96.0±2.94 – 98.17± 1.72 (CLS) and 97.40±1.55 – 97.80±1.92 (PCR) for stavudine, respectively. Good percentage recoveries and proper statistical data obtained with both the laboratory prepared mixtures and the commercial tablets proved the suitability and efficiency of the proposed procedures for routine analysis and quality control purposes with quite satisfactory precision. A comparison of the obtained results from CLS and PCR were also performed with those obtained from reported method. The obtained F- and t-values obtained indicating no significant differences between the results of the proposed and reported methods.

Title: Analysis of Paracetamol and Ascorbic Acid in Pharmaceutical Binary Mixture

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Two simple and sensitive spectrophotometric methods were developed for the determination of paracetamol (I) and ascorbic acid (II) in pharmaceutical binary mixture. The first method depends on the use of the first-derivative spectrophotometric technique for the simultaneous determination of components of the mixture. The second method depends on the reaction of the studied drugs with 5-diazo-1, 2, 4-triazol-3-carboxylic acid (DTCA) reagent to give colored products measured at 480 nm and 380 nm for (I) and (II), respectively. All variables affecting reaction conditions were optimized. The proposed methods were successfully applied for the analysis of the studied drugs in their pure and commercial dosage forms and are 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. Molar ratios of the drugs with the colorimetric reagent (DTCA) were determined and the reaction mechanisms were suggested.