

**Title:** Preparation and Evaluation of Itraconazole-Cyclodextrin Complexes in Solid State

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**Source:** *Alex. J. Pharm. Sci.*, 21 (1), (2007)

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*Itraconazole (ITZ) solid complex was prepared using different types of cyclodextrins (CDs):  $\beta$ -cyclodextrin ( $\beta$ -CD), hydroxyethyl- $\beta$ -CD (HE- $\beta$ -CD) and hydroxypropyl- $\beta$ -CD (HP- $\beta$ -CD), and applying different techniques. The prepared complexes were evaluated by IR, DSC and X-ray diffractometry. The effects of the type and concentration of CDs, method of preparation and dissolution of ITZ-CD complexes were studied. The results of physicochemical characterization of ITZ-HP- $\beta$ -CD at 1:3 molar ratios, with or without polyvinylpyrrolidone (PVP), prepared by co-evaporation method, clearly indicated the formation of an amorphous powder. DSC, X-ray diffractometry and IR spectroscopy revealed the formation of inclusion complex of ITZ with CDs systems. ITZ-HP- $\beta$ -CD at 1:3 molar ratio with or without PVP showed the formation of a true complex (X-ray diffractometry and DSC analysis). In addition, ITZ-HP- $\beta$ -CD at 1:3 molar ratio with PVP, prepared by co-evaporation method, was superior in increasing dissolution rate of ITZ compared to the other systems under investigation.*

**Title:** Clinical Evaluation of Oral Insulin Formulation in Type-2 Diabetic Patients

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*The objective of this study was to assess the clinical efficacy of a single dose of insulin (100 IU) incorporated with a group of additives in enteric-coated, chitosan-coated capsules through its glucose lowering effect over a period of 12 hours. The capsules were administered orally to type-2 diabetic patients. The results were compared to those of oral administration of capsules of the same coating containing only insulin (100 IU) without additives, S.C. insulin injection (average dose 18 IU) and oral placebo. Ten patients with type-2 diabetes were enrolled in this blind, placebo-controlled, four-way crossover study. It was found that, capsules containing only insulin resulted in a slight decrease in the mean blood glucose levels of the 10 patients compared to control especially in the period from 6 to 12 hours following administration. On the other hand, capsules containing insulin with additives showed a remarkable lowering of the blood glucose levels. Their effect started 3 hours following administration and sustained to the end of the experiment (12 h). During the first 4 hours following administration was the reduction resulting from S.C. insulin was significantly*

*higher than that produced by capsules containing insulin with additives. In the period from 4-7 hours, the effect of the capsules was comparable to that of S.C. insulin (no significant difference). Beyond that (7-12 hours), there was a highly significant difference in favor of capsules. The relative bioavailability obtained by capsules containing only insulin was 3.43%, while that obtained by capsules containing insulin with additives was 18.54%.*

**Title:** Clinical Efficacy of Novel Unidirectional Buccoadhesive vs. Vaginoadhesive Bromocriptine Mesylate Discs for Treating Pathologic Hyperprolactinemia

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**Source:** *Fertility and Sterility*, (2007)

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**Objective:** *To test the clinical effectiveness of new bioadhesive unidirectional buccal and vaginal bromocriptine methylate discs in hyperprolactinemic patients.*

**Design:** *A preliminary randomized comparative study.*

**Setting:** *A pharmaceutical phase at the departments of Pharmaceutics, Faculties of pharmacy, Assiut and El-Minia Universities and a clinical phase at the Infertility Out-patient Clinic of Women's health University Center, Assiut University, Assiut, Egypt.*

**Patient(s):** *A total of 42 patients with pathologic hyperprolactinemia.*

**Intervention(s):** *Patients were randomly divided into groups, Group A comprised 21 patients who used uni-directional buccodhesive bromocriptine methylate discs once daily for 1 month. Group B included 21 patients who used vaginoadhesive bromocriptine methylate discs once daily for 1 month. Serum prolactin (PRL) was measured before and after therapy in all cases.*

**Main Outcome Measure(s):** Decline of serum PRL level after month of therapy.

**Result(s):** Pharmaceutically, tests for swelling, surface pH, in vitro and in vivo bioadhesion and in vitro release expressed satisfactory results. The in vitro release of vaginal bromocriptine from the discs is increased in pH 4.5 media. Both groups showed a highly statistically significant reduction of serum PRL levels after 1 month of therapy without any significant difference between both groups. The decline of serum PRL was not correlated with age, parity, or indication of entering into this study.

**Conclusion(s):** Both buccoadhesive and vaginoadhesive discs containing bromocriptine are of equal efficacy for treating pathologic hyperprolactinemia, Buccoadhesive discs have the advantages of being gender nonspecific (i.e., could be used by men), avoidance of manipulating the vagina, which is inconvenient to some patients like virgins, independence on cyclic estrogen (E) level, and could be easily used during menstruation.

**Title:** Development and Evaluation of Nefopam Hydrochloride Microcapsules

**Authors:** M. El-Mahdy

**Source:** *Bull. Pharm. Sci., Assiut University, 30 (2), 135-147 (2007)*

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*An attempt was performed to encapsulate Nefopam hydrochloride, a highly water soluble drug, by a modified emulsion solvent evaporation / extraction technique, using cellulose acetate butyrate (CAB) as a coating polymer. The influence of core/coat ratio (1:2, 1:1 and 2:1 ratio) on the yield, drug loading, size distribution as well as the release characteristics and surface topography of the prepared microcapsules was investigated. The obtained microcapsules exhibited higher encapsulation efficiency and a decreased release rate in simulated gastric fluid (S.G.F. pH 1.2) and simulated intestinal fluid (S.I.F. pH 7.4). On the other hand, the entrapment efficiencies increased (from 104.66 to 141.26, core coat ratio 1:1) and the release rate decreased with increasing microcapsule size (from 250 to 512.5  $\mu\text{m}$ ) and/or theoretical drug loading of microcapsules. Kinetic assessment of the release rate of microcapsules using different mathematical models has shown that the release rate followed Ritger-Peppas diffusion release kinetics.*

**Title:** Liposomal Gel of Diclofenac Sodium as Topical Delivery System

**Authors:** Mahmoud El-Badry

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*This study the preparation of diclofenac sodium in lecithin vesicles and loading in pluronic F-127 gel, the effect of sodium cholate on the diffusion of the drug through rat skin and the anti-inflammatory activity of the liposomal gel formulations. Lecithin vesicles were prepared in the presence or absence of sodium cholate by the dry film method and sonication. The size of liposomal vesicles ranged from 100-700 nm and the encapsulation efficiency of the diclofenac sodium was between 60-80%. The lecithin vesicles were loaded in pluronic F-127 gel. The highest cumulative of drug diffusion through rat skin was  $19.31 \pm 1.50$  ( $\mu\text{g}/\text{cm}^2$ ) for lecithin vesicles in the presence of sodium cholate (F4). Also the highest cumulative of drug diffusion through rat skin was  $12.20 \pm 0.50$  ( $\mu\text{g}/\text{cm}^2$ ) for liposomal gel (F8). The anti-inflammatory activity of the liposomal gel formulations was studied on carrageenan induced paw edema in rats. The results show that, F8 and F6 show superior anti-inflammatory activity in comparison with the other gel formulations. From the results, lecithin vesicles and liposomal gel of diclofenac sodium appear to be advantagesous for topical delivery of the drug.*

**Title:** Formulation and Characterization of Biodegradable Chitosan Films for Topical Application of Terbinafine HCl

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*Chitosan biodegradable films containing terbinafine HCl (Tr.HCl) were evaluated for their potential drug delivery at a controlled rate. Terbinafine HCl could be loaded at 1.8% w/w of polymer in films, which were translucent and flexible. The effect of drug loading and nature of plasticizers on the in-vitro release of Tr.HCl have been examined. Physicochemical characterization of Tr.HCl via thermal, spectroscopic, X-ray diffraction, and scanning electron microscopy techniques revealed information on the solid-state properties of Tr.HCl as well as chitosan in films. While chitosan was in an amorphous form, Tr.HCl seemed to be present in crystalline form in the films. It was found that the release rate of the drug was directly proportional to drug concentration. Also medicated chitosan films plasticized with water-soluble plasticizers as glycerol triacetate (GTA), propylene glycol (PG), and polyethylene glycol 400 (PEG 400), produced fast*

*release in comparison with water insoluble plasticizers as glycerol tributyrate (GTB), dimethyl phthalate (DMPH), and diethyl phthalate (DEPH). The characterizations of chitosan films conducted by IR, X-ray, and DSC, showed that no interaction occurred between Tr.HCl and chitosan polymer. The minimum inhibitory concentration (MIC) of the drug against candida albicans was investigated. Results showed that MIC of Tr.HCl was 1.4 µg/ml. The inhibition zone diameter of Tr.HCl chitosan films was higher than that of Tr.HCl normal dressing. Also antifungal activity of Tr.HCl was enhanced in plasticized chitosan films. The results were promising for topical formulation of Tr.HCl in biodegradable chitosan films and have the potential to be used as a novel drug delivery.*

**Title:** A New Steroid Glycoside and Furochromones from *Cyperus rotundus* L.

**Authors:** Hanaa M. Sayed<sup>1</sup>, Mahmoud H. Mohamed<sup>2</sup>, Salwa F. Farag<sup>1</sup>, Gamal A. Mohamed<sup>2</sup>, Peter Proksch<sup>3</sup>

**Source:** *Natural Product Research*, 21 (4), 343-350 (2007)

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*Further phytochemical investigation of the aerial parts of Cyperus rotundus L. afforded a new steroid glycoside named sitosteryl (6'-hentriacontanoyl)-β-D-galactopyranoside (4) in addition to three furochromones, khellin (2), visnagin (3) and ammiol (9). Furthermore, benzo-α-pyrone (coumarin) (1), salicylic acid (5), caffeic acid (6), protocatechuic acid (7), p-coumaric acid (8), triclin (10) and isorhamnetin (11) were isolated. The structures of these compounds were established by spectroscopic methods. The isolated furochromones were tested for insect antifeedant activity larvae Spodoptera littoralis when incorporated in artificial diet and offered to larvae in a chronic feeding bioassay. Also, visnagin, khellin and sitosteryl (6'-hentriacontanoyl)-β-D-galactopyranoside showed strong cytotoxic activity against L5178y mouse lymphoma cells and were also active in the brine shrimp lethality test.*

**Title:** Cesdiurins I-III, Steroidal Saponins from  
*Cestrum diurnum* L.

**Authors:** Mostafa A. Fouad<sup>1</sup>, Khaled M. Mohamed<sup>2</sup>,  
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**Source:** *J. Nat. Med.* (2007)

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*Phytochemical investigation of a methanolic extract of leaves of Cestrum diurnum L. (Solanaceae) resulted in isolation of several furostanol steroidal saponins, named cesdiurins I-III (1-3). Their structures of the isolated compounds were determined by spectroscopic analyses, including by use of 1D and 2D NMR spectroscopic techniques as well as by mass spectral analyses.*

**Title:** A New Norlignan Glycoside from *Cestrum diurnum* L.

**Authors:** Khaled M. Mohamed<sup>1</sup>, Mostafa A. Fouad<sup>2</sup>, Katsuyoshi Matsunami<sup>3</sup>, Mohamed s. Kamel<sup>2</sup>, Hideaki Otsuka<sup>3</sup>

**Source:** *Arkivoc*, (xiv), 63-70 (2007)

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*From the methanolic extract of Cestrum diurnum L. leaves, a new 9-norlignan glucoside (cestrumoside) (1) was isolated in addition to six known glycosides (2-7). The structures of the isolated compounds were determined on the bases of NMR spectral analysis (<sup>1</sup>H NMR, <sup>13</sup>C NMR, HSQC, HMBC, COSY) in addition to MS and CD to infer the stereochemistry of the compounds.*

**Title:**  $\delta$ -Pyrone Derivatives From *Crotalaria thebaica*

**Authors:** Zedan Z. Ibraheim and Amany S. Ahmed

**Source:** *Saudi Pharmaceutical Journal*, 15, Nos. 3-4, July-Oct. (2007)

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*From the aerial parts of Crotalaria thebaica (Del) DC (Fabaceae) three  $\delta$  pyrones (1-3) together with an isoflavone (tecreroginin) (4) were isolated. The structures of the isolated compounds were characterized by using different methods of spectral analysis including, IR, UV, NMR and MS.*

**Title:** Imidazole Alkaloids From the Indopacific Sponge *Pericharax heteroraphis*

**Authors:** A. A. Ali<sup>1</sup>, H. A. Hassanean<sup>1</sup>, Ehab S. Elkhayat<sup>2</sup>, Ru AnGelie Edrada<sup>3</sup>, Rainer Ebel<sup>3</sup>, Peter Proksch<sup>3</sup>

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*Chemical investigation of the sponge *Pericharax heteroraphis* (Polejeff) collected in Indonesia, has led to the isolation of three imidazole alkaloids, preclathridine-A (1), leucettamine-B (2) and leucettamine-A (3). The structures of the isolated compounds were unambiguously established by <sup>1</sup>D and <sup>2</sup>D NMR and mass data. This is the first report of this class of compounds from the *P. heteroraphis* sponge. Investigation of the antimicrobial activities of the isolated compounds showed that leucettamin-A (3) was active against the gram-positive bacteria *Staphylococcus aureus* and the fungus *Cladosporium herbarum*, while other compounds were inactive.*

**Title:** Synthesis and Three-dimensional Qualitative Structure Selectivity Relationship of 3,5-Disubstituted-2,4-Thiazolidinedione Derivatives as COX2 Inhibitors

**Authors:** Ahmed M. Ali<sup>1</sup>, Gamal E. Saber<sup>1</sup>, Nadia M. Mahfouz<sup>1</sup>, Mahmoud A. El-Gendy<sup>1</sup>, Awwad A. Radwan<sup>2</sup>, and Mohamed A. El-Hamid<sup>3</sup>

**Source:** *Arch. Pharm. Res.*, 30 (10), 1186-1204 (2007)

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*In our effort for synthesis of selective COX2 inhibitors, certain new 2,4-thiazolidinedione derivatives were synthesized. It necessitates preparation of potassium salt of 2,4-thiazolidinedione 2, which condensed with intermediate 4a. The resulting 3-[2-(4-methylphenyl)-2-oxo-1-phenylethyl]-2,4-thiazolidinedione 8 was condensed with appropriate aldehyde to afford compounds 10a, 10i-l, 10o and 10p. Compounds (9a-l, 10a-n, 10p, 11 and 12) were obtained through the preparation of 5-arylmethylidene-2,4-thiazolidinediones 6a-p and reaction of its potassium salt 7a-p with compounds 4a, 4b and 5. Some compounds displayed significant analgesic activity as compared to reference standards. The anti-inflammatory activity of the synthesized compounds revealed that intermediate 8 and compounds 9c, 10c and 10d showed good results. Compound 10c produced no*

significant mucosal injury. HipHop methodology of Catalyst program was used to build up hypothetical model of selective COX2 inhibitors followed by fitting the synthesized compounds to this model. Compounds **10c** and **10d** were suspected to be promising selective COX2 inhibitors. Also, compounds (**6c**, **8**, **9a,c,d,k**, **10a,c,d,k** and **12**) were docked into COX1 and COX2 X-ray structures, using DOCK6 program. Docking results suggested that several of these derivatives are active COX inhibitors with a significant preference for COX2.

**Title:** Design, Synthesis, and Docking Studies of New 1,3,4-thiadiazole-2-thione Derivatives with Carbonic Anhydrase Inhibitory Activity

**Authors:** Mohammed K. Abdel-Hamid<sup>1</sup>, Atef A. Abdel-Hafez<sup>1</sup>, Nawal A. El-Koussi<sup>1</sup>, Nadia M. Mahfouz<sup>1</sup>, Alessio Innocenti<sup>2</sup> and Claudiu T. Supuran<sup>2</sup>

**Source:** *Bioorganic & Medicinal Chemistry*, 15, 6975-6984 (2007)

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*A new series of 1,3,4-thiadiazole-2-thione derivatives have been prepared and assayed for the inhibition of three physiologically relevant carbonic anhydrase (CA, EC 4.2.1.1) isoenzymes, the cytosolic human isozymes I and II, and the transmembrane, tumor-associated hCA IX. Against hCA I the investigated thiones, showed inhibition constants in the range of 2.55-222  $\mu\text{M}$ , against hCA II in the range of 2.0-433  $\mu\text{M}$ , and against hCA IX in the range of 1.25-148  $\mu\text{M}$ . Compound 5c, 4-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)-1-(5-nitro-2-oxoindolin-3-ylidene)semicarbazide showed interesting inhibition of the tumor-associated hCA IX with  $K_i$  value of 1.25  $\mu\text{M}$ , being the first non-sulfonamide type inhibitor of such activity. This result is rather important taking into consideration the known antitumor activity of thiones. In addition, docking of the tested compounds into CA II active site was performed in order to predict the affinity and orientation of these compounds at the isozyme active site. The results showed similar orientation of the target compounds at CA II active site compared with reported sulfonamide type CAIs with the thione group acting as a zinc-binding moiety.*



**Title:** Microwave Assisted Synthesis Of  
Triazoloquinazolinones and Benzimidazoquinazolinones

**Authors:** Aboul-Fetouh E. Mourad<sup>1</sup>, Ashraf A. Aly<sup>1</sup>, Hassan H. Farag<sup>2</sup>, Eman A. Beshr<sup>3</sup>

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**Background:** *Benzimidazoquinazolinones and related quinazolines are classes of heterocycles that are of considerable interest because of the diverse range of their biological properties. Although numerous classes of quinazolines have been conventionally synthesized, their syntheses have been suffered due to the multiple steps that sometimes have described in their preparation and also their chemical transformations that have been taken hours or even days to be completed. However, microwave energy can offer numerous benefits for performing synthesis of organic compounds including reduced pollution, increased reaction rates, yield enhancements, and cleaner chemistries.*

**Results:** *Synthesis of a series of triazoloquinazolinones and benzimidazoquinazolinones has been achieved under microwave irradiation. The products were obtained in nearly quantitative yields within few minutes during the reaction of aromatic aldehydes with 5-amino-1 (H)-1,2,4-triazole (or 2-aminobenzimidazole)*

and dimedone in DMF.

**Conclusion:** Microwave irradiation can be used as a facile and general method for the construction of a wide variety of triazoloquinazolinones and benzimidazoquinazolinones. The reaction involves a three component condensation (with potential for combinatorial work) being carried out with almost productive yields by microwave irradiation and considerably shortened reaction time.

**Title:** Synthesis of New 1,3,8-Trisubstituted Purine-2,6-Diones and 1,3,6-Trisubstituted Thiazolo[2,3-f]Purine-2,4-Diones<sup>1</sup>

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*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 agents with potential biological activities. The final products were obtained by cyclization of carboxamide intermediates using 1,1,1,3,3,3-hexamethyldisilazane. This procedure gave higher yields, and was more convenient and easier in purification compared to other methods. We also found polyphosphoric acid to be the most efficient agent in the cyclization of 8-[2-(P-(un)substituted-phenyl)-2-oxoethylsulfanyl]-l,3-dipropyl-3,7-dihydro-purine-2,6-diones to 1,3-dipropyl-6-substituted)-IH- thiazolo [2,3-f]purine- 2,4-diones.*

**Title:** Design and Synthesis of New 1,8-Disubstituted-3,7-dihydro-purine-2,6-diones and 3,6-Disubstituted-1H-thiazolo[2,3-f]purine-2,4-diones as Potential Antinociceptive and Anti-inflammatory Agents

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*In this study, the design, synthesis and preliminary pharmacological investigation of novel 8-(2-oxo-2-p-(un)substituted phenyl)-1-substituted-3,7-dihydropurine-2,6-diones (11-20) and 3,6-disubstituted thiazolo(2,3-f]purine-2,4-diones (21-30) is described. 1,8Disubstitutedpurine-2,6-diones were prepared by the reaction of 3-substituted-8-thioxo3,7,8,9-tetrahydropurine-2,6-diones (4-5) with appropriate phenacyl bromides (6-10). Compounds (4-5) were in turn prepared by reaction of 3-substituted-5,6-diaminouracils (3a-b) with carbon disulfide. The derivatives (21-30) were obtained by cyclodehydration of compounds (11-20) in polyphosphoric acid (PPA). The effect of the new prepared derivatives as potential antinociceptive and anti-inflammatory agents was carried out on mice and rats. Aspirin and indomethacin were used as reference drugs. Some of the tested compounds have shown a pronounced analgesic and anti-inflammatory activity. The results here illustrate the newly synthesized derivatives are promising analgesic and anti-inflammatory activity.*



**Title:** Synthesis and Docking Study of Some Pyrazolo[3,4-d]pyrimidine-4(5H)-one Derivatives of Expected Phosphodiesterase-5 Inhibitor Activity

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**Source:** 6<sup>th</sup> AFMC International Medicinal Chemistry Symposium, July 8, 78 (2007)

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*In our effort for synthesis of phosphodiesterase-5 inhibitors, we had synthesized pyrazolo(3, 4-d] pyrimidine-4-one derivatives 13a-g, 14-17 and 24 in analogous with sildenafil and vardenafil structures. The oxygen group of alkoxy group is essential for hydrogen bonding with amidic NH proton of pyrimidine ring keeping the ring systems in co-planarity. The alkylpiperazinesulphonyl group was non essential for activity as there are many phosphodiesterases are devoid of this moiety. Also, the side of fusion of pyrazole ring with pyrimidinone ring is different between different classes of pde-5 inhibitors. In view of these findings we prepared pyrazolo(3,4-d] pyrimidine-4-one derivatives 13a-g, 14-17 and 24. Structure elucidation of the synthesized compounds was done using IR, <sup>1</sup>HNMR, mass spectroscopy and elemental analysis. Biological evaluation of the*

*synthesized compounds was done using rabbit isolated corpus cavernosum model. The synthesized compounds showed promising result in comparison with sildenafil. Docking study was done for these compounds into pde5 enzyme X-ray structures (complexed with vardenafil) using DOCK6 program. Docking results suggested that these derivatives are active pde5 inhibitors with docking score comparable with that of vardenafil. Also, these compounds explored binding mode as same as that of the vardenafil.*

**Title:** Synthesis of Some New Quinoline Derivatives of Potential Antiinflammatory and Analgesic Activities

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**Source:** 10<sup>th</sup> Ibn Sina International Conference on Pure and Applied Heterocyclic Chemistry, Luxor, Egypt, February 17-20, 191 (2007)

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*Quinoline derivatives are known to possess various kinds of biological activities such as antimalarial, antiamoebic,  $\beta$ -agonist, antidepressant, antitumor, gastric ATP-ase inhibitors, antimicrobial,  $\alpha_2$ -agonist, antiviral, platelet antiaggregating, antihypertensive, and anti-inflammatory activities. In this work new quinoline derivatives were synthesized through the reaction of the 7-substituted-2-chloroquinoline-3-carbaldehyde with the appropriate reagents. Some of the prepared compounds were tested for their analgesic and anti-inflammatory effects where most of these compounds showed significant results in comparison with indomethacin as a reference drug.*



**Title:** Pharmacophore Elucidation and Molecular Docking Studies on 5-Phenyl-1(3-Pyridyl)-1H-1,2,4-Triazole-3-Carboxylic Acid Derivatives as COX2 Inhibitors

**Authors:** Marc Lindner<sup>1</sup>, Wolfgang Sippl<sup>1</sup>, Awwad A. Radwan<sup>2</sup>

**Source:** 10<sup>th</sup> Ibn Sina International Conference on Pure and Applied Heterocyclic Chemistry, Luxor, Egypt, February 17-20, 192 (2007)

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*A set of 5-phenyl-1-(3-pyridyl)-1H-1,2,4-triazole-3-carboxylic acid derivatives (117) showing anti-inflammatory activity, were analyzed using a three-dimensional qualitative structure-selectivity relationship (3D QSSR) method. We used the CatalystHipHop approach to generate a pharmacophore model for COX2 inhibitors based on a training set of 14 active inhibitors (18-32). The degree of fitting of the test set compounds (1-17) to the generated hypothetical model revealed a qualitative measure of the more or less selective COX2 inhibition of these compounds. The results indicate that most derivatives (1,3, 5-9, 10 and 15-17) are able to effectively satisfy the proposed pharmacophore geometry using energy accessible conformers ( $E_{conf} < 20$  kcal/mol). In addition the triazole derivatives (1-17) were docked into COX1 and COX2 X-ray structures, using program GOLD. Based on the docking results it is suggested that several of these novel triazole derivatives are active COX inhibitors with a significant preference for COX2.*

**Title:** Synthesis and Quantitative Structure Activity Relationship (QSAR) Study of New 3-Allyl-5-Substituted-3,4,5,6-Tetrahydro-2H-1,3,5-Thiadiazine-2-Thiones of a Potential Antimicrobial Activity

**Authors:** Alaa M. Hayallah, and Awwad A. Radwan

**Source:** *Bull. Pharm. Sci., Assiut University, 30 (1), 39-50 (2007)*

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*Fifteen new 3-allyl-5-substituted-3,4,5,6-tetrahydro-2H-1,3,5-thiadiazine-2-thiones were synthesized by the reaction of allylamine with carbon disulfide and potassium hydroxide, followed by formaldehyde and appropriate primary amine such as alkyl, aralkylamines, glycine, L-alanine or ethyl glycine ester. The title compounds were tested, in vitro, for antimicrobial activity against gram-positive bacteria (*Bacillus cereus*, *Staphylococcus aureus*, *Micrococcus leuteus*), Gram-negative bacteria (*Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*), and some fungi (*Aspergillus flavus*, *Aspergillus niger*, *Candida albicans*, *Geotrichum candidum*, *Scopulariopsis brevicaulis* and *Trichophyton rubrum*), using agar disc method. Quantitative structure activity relationship study was performed using the log form of MIC against *Scopulariopsis brevicaulis* fungi and some physico-chemical descriptors ( $MR$ ,  $L$ , and  $Fr$ ) of substituents at N-5 position. The log MIC were found to be negatively linearly correlated with  $MR$  and  $L$  and positively linearly correlated with  $Fr$ .*

**Title:** Synthesis of New 4(3H)-Quinazolinone Derivatives of Potential Antimicrobial Activity

**Authors:** Awwad A. Radwan<sup>1</sup>, Salah G. Ali<sup>2</sup>

**Source:** *Bull. Pharm. Sci., Assiut University*, 30 (2), 181-192 (2007)

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*A new series of quinazolinone-4(3H)-one derivatives containing hydrazone, thiosemicarbazide, pyrazole moiety and 1,2,4-triazolo[4,3-a]quinazolin-5-(4H)-one derivatives, were prepared in order to study the effect of such combinations on the expected antimicrobial activity. Synthesis of target compounds (3-8) has been achieved through an interaction of the starting 2a or 2b with different alkyl or aryl isothiocyanate. Condensation of 2a or 2b with various aromatic aldehydes or ketones afforded the corresponding hydrazones 9-12. 1-(4-Pyridinyl)-1,2-dihydro-4-phenyl(allyl)-1,2,4-triazolo[4,3-a]quinazolin-5-(4H)-one derivatives 13, 14 have been synthesized through reflux of compound 9 or 10 in glacial acetic acid. On the other hand, 1-(3-substituted-3,4-dihydro-4-quinazolinon-2-yl)-3-(4-chlorophenyl) pyrazole-4-carbaldehyde 15 or 16 has also been synthesized through interaction of compounds 11 or 12 with Vilsmeier-Haack reagent<sup>1</sup>.*

*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. The tested compounds showed moderate antibacterial activity and weak or no antifungal activity.*



**Title:** Analysis of Cephalosporin Antibiotics

**Author:** Salwa R. El-Shaboury, Gamal A. Saleh, Fardous A. Mohamed and Azza H. Rageh

**Source:** *Journal of Pharmaceutical and Biomedical Analysis*, 45, 1-19 (2007)

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*A comprehensive review with 276 references for the analysis of members of an important class of drugs, cephalosporin antibiotics, is presented. The review covers most of the methods described for the analysis of these drugs in pure forms, in different pharmaceutical dosage forms and in biological fluids.*

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

**Author:** Hassan F. Askal<sup>1</sup>, Ibrahim H. Refaat<sup>2</sup>, Ibrahim A. Darwish<sup>1</sup>, Mostafa A. Marzouq<sup>2</sup>

**Source:** *Spectrochim. Acta, Part A, Mol. Biomol. Spectrosc.* (2007)

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*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  $\mu\text{g ml}^{-1}$ . The assay limits of detection and quantitation were 2.5 and 8.4  $\mu\text{g ml}^{-1}$ , respectively. The method was successfully applied to the analysis of bulk drug and laboratory-prepared tablets; the mean percentage recoveries were  $100.1\pm 0.33$  and  $101.24\pm 1.28\%$ , 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 fo 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:** Determination of Two Antibacterial Binary Mixtures by Chemometrics-Assisted Spectrophotometry

**Authors:** Abd El-Maaboud I. Mohamed<sup>1</sup>, Osama H. Abdelmageed<sup>2</sup>, Ibrahim H. Refaat<sup>1</sup>

**Source:** *Journal of AOAC International*, 90 (1), (2007)

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*Simple chemometrics-assisted spectrophotometric methods are described for determination of 2 antibacterial binary mixtures. The mixtures are composed of norfloxacin in combination with tinidazole and erythromycin (as ethylsuccinate ester or stearate salt) in combination with trimethoprim. The normal UV absorption spectra of each pair of drugs in the studied mixtures, in the range of 200-400 nm, showed a considerable degree of spectral overlapping: 77.5% for the norfloxacin-tinidazole mixture and 84.3% for the erythromycin-trimethoprim mixture. Resolution of the norfloxacin-tinidazole mixture and trimethoprim in the presence of erythromycin was accomplished successfully by using zero-crossing first derivative (<sup>1</sup>D), classical least-squares (CLS) regression analysis, and principal component regression (PCR) analysis methods. In addition, an alternative simple and accurate colorimetric method was developed for the determination of erythromycin in the presence of trimethoprim using 2,4-dinitrophenylhydrazine. All variables affecting the development of the colored*

chromogen were studied and optimized, and the product was measured at 526-529 and 538-542 nm for erythromycin stearate and erythromycin ethylsuccinate, respectively. For zero-crossing, first derivative technique Beer's law was obeyed in the general concentration range of 2-50  $\mu\text{g/mL}$  for norfloxacin, tinidazole, and trimethoprim with good correlation coefficients (0.9994-0.9996). Overall limits of detection (LOD) and quantification (LOQ) ranged from 0.59 to 2.81 and 1.96 to 9.33  $\mu\text{g/mL}$ , respectively. The obtained results from CLS and PCR were compared with those obtained from a 1D spectrophotometric method. With the exception of erythromycin, overall recoveries in the average range of 97.33-103.0% were obtained with a considerable degree of accuracy when the suggested methods were applied to analysis of synthetic binary mixtures, some commercial dosage forms such as tablets and oral suspension without interference from the commonly encountered excipients and additives. For the colorimetric method, Beer's law was obeyed in the general concentration range of 7.21-28.84  $\mu\text{g/mL}$ , erythromycin with good correlation coefficients (0.9980-0.9996). Overall LOD and LOQ ranged from 0.73 to 1.65 and 2.43-5.49  $\mu\text{g/mL}$ , respectively. Erythromycin derivatives were determined in the commercial dosage form, without interference from trimethoprim-encountered excipients and additives. The obtained results, with both chemometric and colorimetric methods, have been compared with those obtained from reported methods, and proper F- and t-values were observed, indicating no significant differences between the results of the suggested methods and reported method(s). The good percentage recoveries and proper statistical data obtained proved the efficiency of the proposed procedures for the determination of the studied drugs in their binary mixtures as well as in the commercial dosage forms with quite satisfactory precision.

**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, Ashraf M. Mahmoud, Nasr Y. Khalil

**Source:** *Journal of AOAC International* (2007)

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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  $\times$  3.9 mm i.d., 5  $\mu$ m 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:** Generic Simple Enzyme Immunoassay Approach to Avert Small Molecule Immobilization Problems on Solid Phases Application to the Determination of Tobramycin in Serum

**Authors:** Ibrahim A. Darwish, Ashraf M. Mahmoud, Abdel-Rahman A. Al-Majed

**Source:** *Talanta*, 72, 1322-1328 (2007)

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*Generic simple and sensitive universal enzyme immunoassay approach for the determination of small analytes has been developed to avert the problems associated with small molecule immobilization onto solid phases. The developed assay employed a heterogeneous non-competitive binding format. The assay used anti-analyte antibody coupled to polyacrylamide beads as a solid-phase and  $\beta$ -D-galactosidase enzyme-labeled analyte as a label. In this assay, the analyte in a sample was firstly incubated to react with an excess of the antibody-coupled beads, and then the unoccupied antibody binding sites were allowed to react with the enzyme-labeled analyte. Analyte bound to the antibody-coupled beads was separated by centrifugation, and the enzyme activity of the supernatant was measured spectrophotometrically at 420 nm, after reaction with 4-nitrophenyl- $\beta$ -D-galactopyranoside as a substrate for the enzyme. The signal was directly proportional to the concentration of analyte in the sample. The optimum conditions for the developed assay were established and applied to the*

*determination of tobramycin, as a representative example of the small analytes, in serum samples. The assay limit of detection was 10 ng mL<sup>-1</sup> and the effective working range at relative standard deviation of ≤ 10% was 40-800 ng mL<sup>-1</sup>. The assay precisions were acceptable; the relative standard deviations were 4.36-5.17 and 5.62-7.40% for intra- and inter-assay precision, respectively. Analytical recovery of tobramycin spiked in serum ranged from 95.89 ± 4.25 to 103.45 ± 4.60%. The assay results correlated well with those obtained by high-performance liquid chromatography (r= 0.992). The assay described herein has great practical value in determination of small analytes because it is sensitive, rapid, and easy to perform in any laboratory. Although the assay was validated for tobramycin, however, it is also anticipated that the same methodology could be used for essentially any analyte for which a selective antibody exists, and an appropriate enzyme conjugate can be made.*

**Title:** Sensitive Determination of Trimetazidine in Spiked Human Plasma by HPLC with Fluorescence Detection After pre-column Derivatization with 9-Fluorenylmethyl Chloroformate

**Authors:** Alaa Khedr<sup>1</sup>, Mahmoud M. Sheha<sup>2</sup>, Ibrahim A. Darwish<sup>3</sup>

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*A high-performance liquid chromatographic method for the determination of trimetazidine dihydrochloride (TMZ) in spiked human plasma is described. The method is based on the pre-column derivatization with 9-fluorenylmethyl chloroformate (FMOC-Cl) using the fluorimetric detection technique. Fluoxetine HCl (FLX) was used as internal standard. Both, TMZ and FLX were completely derivatized after heating at 50°C for 20 min in borate buffer pH 8.0. Samples were analyzed by high performance liquid chromatography (HPLC) using Zorbax-TMS column (250 mm x 4.6 mm, i.d., 51µm) and mobile phase consist of acetonitrile, methanol and 20 mM sodium acetate pH 4.7 (44:6:50; v/v/v). Fluorescence detector (FLD) was adjusted at excitation and emission wavelengths; 265 and 311 nm, respectively. The linearity of the method was in the range of 4.5-200 ng/ml. Limits of detection (LOD) and quantification (LOQ)*

were 1.5 and 4.5 ng/ml, respectively. Trimetazidine recovery was  $96.5 \pm 1.3\%$  ( $n=6$ ;  $RSD=2.1\%$ ).

**Title:** Evaluation of *N*-Bromosuccinimide as a New Analytical Reagent for the Spectrophotometric Determination of Fluoroquinolone Antibiotics

**Authors:** Hassan Askal<sup>1</sup>, Ibrahim Refaat<sup>1</sup>, Ibrahim Darwish<sup>1</sup>, Mostafa Marzouq<sup>2</sup>

**Source:** *Chem. Pharm. Bull.*, 55 (11), 1551-1556 (2007)

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*Analytical studies were carried out, for the first time, to evaluate the use of N-bromosuccinimide (NBS) as an analytical reagent for the spectrophotometric determination of eleven therapeutically important fluoroquinolone antibiotics (FQA). The procedures involved the reaction of the FQA with NBS and subsequent measurement of the excess NBS by its reaction with p-phenylenediamine (PDA) to give a violet colored product that was measured at 530 nm. Different variables affecting the reaction (concentration of NBS, concentration of PDA, pH of reaction medium, reaction time, and the diluting solvents) were carefully studied and optimized. The molar ratio and mechanism of the reaction between each of the studied FQA with NBS were proposed using UV-vis, IR, and NMR techniques. Under the optimum reaction conditions, the analytical method was developed and validated. Beer's law was obeyed in the general concentration range of 3-25 µg/ml. The assay limits of detection and quantitation were 0.33-1.29 and 1.10-4.31 µg/ml, respectively. The precision of*

*the method was satisfactory; the values of relative standard deviations did not exceed 2%. The proposed method was successfully applied to the analysis of the investigated FQA in their pure and pharmaceutical dosage forms without interference from the common excipients (label claim values were 99.85-100.17±0.13-0.59%). Interference from ascorbic acid, that is co-formulated as a stabilizer for the ampoule form, was avoided by its pre-oxidation with potassium bromate before applying the analytical procedure. The results obtained by the proposed method were comparable with those obtained by the official and reported methods.*

**Title:** Sensitive Indirect Spectrophotometric Method for Determination of  $H_2$  - Receptor Antagonists in Pharmaceutical Formulations

**Authors:** Ibrahim A. Darwish<sup>1</sup>, Samiha A. Hussein<sup>1</sup>, Ashraf M. Mahmoud<sup>1</sup>, Ahmed I. Hassan<sup>2</sup>

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*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-dimethylaminocinnamaldehyde to give a red colored product ( $\lambda_{max}$  at 464 nm). The decrease in the absorption intensity ( $\Delta A$ ) 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 the optimum conditions, linear relationships with good correlation coefficients (0.9985-0.9994) were found between  $\Delta A$  values and the concentrations of the drugs in a concentration range of 1-16  $\mu g ml^{-1}$ . The assay limits of detection and quantitation were 0.12-0.44 and 0.37-1.33  $\mu g ml^{-1}$ , 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 analysis of the investigated drugs in their pure and pharmaceutical dosage forms (recovery was  $98.8102.5 \pm 0.79-1.72\%$ ) without interference from the common excipients. The results obtained by the proposed method were comparable with those obtained by the official methods.*

**Title:** Determination of Vitamin K Homologues by High-Performance Liquid Chromatography with On-Line Photoreactor and Peroxyoxalate Chemiluminescence Detection

**Authors:** Sameh Ahmed<sup>1,2</sup>, Naoya Kishikawa<sup>1</sup>, Kenichiro Nakashima<sup>1</sup>, Naotaka Kuroda<sup>1</sup>

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*A sensitive and highly selective high-performance liquid chromatography (HPLC) method was developed for the determination of vitamin K homologues including phylloquinone (PK), menaquinone-4 (MK-4) and menaquinone-7 (MK-7) in human plasma using post-column peroxyoxalate chemiluminescence (PO-CL) detection following on-line ultraviolet irradiation. The method was based on ultraviolet irradiation (254 nm, 15 W) of vitamins K to produce hydrogen peroxide and a fluorescent product at the same time, which can be determined with PO-CL detection. The separation of vitamins K by HPLC was accomplished isocratically on an ODS column within 35 min. The method involves the use of 2-methyl-3-pentadecyl-1,4-naphthoquinone as an internal standard. The detection limits (signal-to-noise ratio = 3) were 32, 38 and 85 fmol for PK, MK-4 and MK-7, respectively. The recoveries of PK, MK-4 and MK-7 were greater than 82%*

*and the inter- and intra- assay RSD values were 1.9-5.4 %. The sensitivity and selectivity of this method were sufficient for clinical and nutritional applications.*