

## BIBLIOGRAPHY

- Abordo, E.A., Bowden, K., Huntington, A.P. and Powell, S.L. 1998. "2-Formylphenyl esters of indomethacin, ketoprofen and ibuprofen and 6-substituted 2-formyl and 2-acylphenyl esters of aspirin", Il Farmaco. 53 (2), 95-101.
- Adson, A., Burton, P.S., Raub, T.J., Barsuhn, C.L., Audus, K.L. and Ho, N.F. 1995. "Passive diffusion of weak organic electrolytes across Caco-2 cell monolayers: uncoupling the contributions of hydrodynamic, transcellular, and paracellular barriers", J. Pharm. Sci. 84(1), 1197-1204.
- Allen, J., Brinkhuis, R., Wijnholds, J. and Schinkel, A. 1999. "The mouse Bcrp/Mxr/Abcp gene: amplification and overexpression in cell lines selected for resistance to topotecan, mitoxantrone, and doxorubicin ", Cancer Res. 59, 4237-4241.
- Anderle, P., Niederer, E., Rubas, W., Hilgendorf, C., Spahn-Langguth, H., Wunderli-Allenspach, H., Merkle, H.P. and Langguth, P. 1998. "P-Glycoprotein (P-gp) mediated efflux in Caco-2 cell monolayers: the influence of culturing conditions and drug exposure on P-gp expression levels", J. Pharm. Sci. 87(6), 757-62.
- Artursson, P. and Karlsson, J. 1991 "Correlation between oral drug absorption in humans and apparent permeability coefficients in human intestinal epithelial (Caco-2) cells", Biochem. Biophys. Res. Commun. 175(3), 880-885
- Artursson, P., Palm K., and Luthman, K. 2001. "Caco-2 monolayers in experimental and theoretical predictions of drug transport", Adv. Drug Del. Rev. 46, 27-43
- Artursson, P. 1990. "Epithelial transport of drugs in cell culture. I: A model for studying the passive diffusion of drugs over intestinal absorptive (Caco-2) cells",

J. Pharm. Sci. 79(6), 476-82.

Artursson, P. 1991. "Cell cultures as models for drug absorption across the intestinal mucosa", Crit. Rev. Ther. Drug Carrier. Syst. 8(4),305-330.

Artursson, P., Ungell, A.L. and Lofroth, J.E. 1993. "Selective paracellular permeability in two models of intestinal absorption: cultured monolayers of human intestinal epithelial cells and rat intestinal segments", Pharm.Res. 10 (8),1123-9.

Asgharnejad, M. 2000. "Improving oral drug transport via prodrugs", In Transport processes in pharmaceutical systems, pp 185-218. Amidon, G.L., et. al., eds. New York :Marcel Dekker.

Audus, K.L., Bartel, R.L., Hidalgo, I.J. and Borchardt, R.T. 1990. "The use of cultured epithelial and endothelial cells for drug transport and metabolism studies", Pharm. Res. 7(5), 433-451.

Augustijns, P., Anneart, P., Heylen, P., Van den Mooter, G. and Kinget, R. 1998. "Drug absorption studies of prodrug esters using Caco-2 model: evaluation of ester hydrolysis and transepithelial transport ", Int. J.Pharm. 166, 45-53.

Ayrton, A. and Morgan, P. 2001. "Role of transport proteins in drug absorption, distribution and excretion", Xenobiotica. 31(8-9), 469-97.

Bailey, C.A., Bryla, P. and Malick, A.W. 1996. "The use of intestinal epithelial cell culture model, Caco-2, in pharmaceutical development", Adv. Drug Del. Rev. 22 (1-2), 85-103.

- Bakos, E., Evers, R., Szakacs, G., Tusnady, G.E., Welker, E., Szabo, K., de Hass, M., van Deemter, L., Borst, P., Varadi, A. and Sarkadi, B. 1998. "Functional multidrug resistance protein (MRP1) lacking the N-terminal transmembrane domain", J. Biol. Chem. 273, 32167-32175.
- Balimane, P.V., Chong, S. and Morrison, R.A. 2000. "Current methodologies used for evaluation of intestinal permeability and absorption", J. Pharmacol. Toxicol. 44, 301-312.
- Barrand, M.A., Bagrij, T. and Neo, S.Y. 1997. "Multidrug resistance-associated protein: a protein distinct from P-glycoprotein involved in cytotoxic drug expulsion", Gen. Pharmacol. 28, 639-645.
- Bauer, B., Miller, D.S. and Fricker, G. 2003. "Compound profiling for P-glycoprotein at the blood-brain barrier using a microplate screening system", Pharm. Res. 20 (8), 1170-1176.
- Begley, D.J., Lechardeur, D., Chen, Z.D., Rollinson, C., Bardoul, M., Roux, F., Scherman, D. and Abbott, N.J. 1996. "Functional expression of P-glycoprotein in an immortalised cell line of rat brain endothelial cells RBE4", J. Neurochem. 67, 988-995.
- Bodo, A., Bakos, E., Szeri, F., Varadi, A. and Sarkadi, B. 2003. "The role of multidrug transporters in drug availability, metabolism and toxicity", Toxicol Lett. 140-141, 133-143.
- Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M.B., Hawkey, C.J., Hochberg, M.C., Kvien, T.K. and Schnitzer, T.J. 2000. "Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group", New Engl J. Med

343(21), 520-528.

- Borst, P., Evers, R., Kool, M. and Wijnholds, J. 1999. "The multidrug resistance protein family", Biochim. Biophys. Acta. 1461(2), 347-57.
- Bradford, M. 1976. "A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding", Anal. Biochem. 72, 248-254.
- Bruggeman, W.A., Van Der Steen, J., and Hutzinger, O. 1982. "Reversed-phase thin layer chromatography of polynuclear aromatic hydrocarbons and chlorinated biphenyls relationship with hydrophobicity as measured by aqueous solubility and octanol-water partition coefficient" J. Chromatogr. 238, 335-346.
- Burton, P.S., Conradi, R.A., Hilgers, A.R., Ho, N.F. and Maggiora, L.L. 1992. "The relationship between peptide structure and transport across epithelial cell monolayers", J. Control. Release. 19(1-3), 87-97.
- Burton, P.S., Goodwin, J.T., Conradi, R.A., Ho, N.F.H. and Hilgers, A.R. 1997. "In vitro permeability of peptidomimetic drugs: The role of polarized efflux pathways as additional barriers to absorption", Adv. Drug Del. Rev. 23(1-3), 143-156.
- Buur, A., Trier, L., Magnusson, C. and Artursson, P. 1996. "Permeability of 5-fluorouracil and prodrugs in Caco-2 cell monolayers", Int. J. Pharm. 129(1-2), 223-231.
- Camenisch, G., Folkers, G. and Van de Waterbeemd, H. 1998. "Comparison of passive drug transport through Caco-2 cells and artificial membranes", Int. J. Pharm. 147(1), 61-70.

- Chan, L.M., Lowes, S. and Hirst, B.H. 2004. "The ABCs of drug transport in intestine and liver: efflux proteins limiting drug absorption and bioavailability", Eur. J. Pharm. Sci. 21(1), 25-51.
- Chong, S., Dando, S.A., Soucek, K.M. and Morrison, R.A. 1996 "In vitro permeability through caco-2 cells is not quantitatively predictive of in vivo absorption for peptide-like drugs absorbed via the dipeptide transporter system", Pharm. Res. 13(1),120-3
- Cordon-Cardo, C., O'Brien, J.P., Casals, D., Bertino, J.R. and Melamed, M.R. 1990. "Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues", J. Histochem. Cytochem. 38, 1277–1287.
- Cordon-Cardo, C., O'Brien, J.P., Casals, D., Rittman-Grauer, L., Biedler, J.L., Melamed, M.R. and Bertino, J.R. 1989. "Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites", Proc. Natl. Acad. Sci. USA. 86, 695–698.
- Dantzig, A.H. and Bergin, L. 1990. "Uptake of the cephalosporin, cephalexin, by a dipeptide transport carrier in the human intestinal cell line, Caco-2", Biochim Biophys. Acta. 1027(3), 211-7.
- Dantzig, A.H., de Alwis, D.P. and Burgess, M. 2003. "Considerations in the design and development of transport inhibitors as adjuncts to drug therapy", Adv. Drug Deliv. Rev. 55(1),133-50.
- Daugherty, A.L. and Mrsny, R.J. 1999. "Transcellular uptake mechanisms of the intestinal epithelial barrier. Part I", Pharm Sci Technol Today. 2 (4), 144-151.

- Day, R., Quinn, D., Williams, K., Handel, M. and Brooks, P. 2000. "Connective tissue and bone diseases", In Clinical Pharmacology, pp 654-702. Carruthers, S.G., et. Al., eds. New York :McGraw-Hill.
- de Aizpurua, H.J. and Russell-Jones, G.J. 1988. "Oral vaccination. Identification of classes of proteins that provoke an immune response upon oral feeding", J. Exp. Med. 167(2), 440-51.
- De Caprariis, P., Palagiano, F., Bonina, F., Montenegro, L., D'Amico, M. and Rossi, F. 1994. "Synthesis and pharmacological evaluation of oligoethylene ester derivatives as indomethacin oral prodrugs", J. Pharm. Sci. 83(11),1578-81.
- Dennis, L.A., Houchins, J.O., Pratt, S.E., Horn, J., Xia X., Hanssen, B.R., Daniel, W.C., Dantzig, A.H. and Terry Lindstrom, T. 2002. "Characterization and application of a vinblastine-selected Caco-2 cell line for evaluation of P-glycoprotein", In Vitro Cell Dev. AN. 38 (7), 401–410.
- Dix, C.J., Hassan, I.F., Obray, H.Y., Shah, R. and Wilson, G. 1990. "The transport of vitamin B12 through polarized monolayers of Caco-2 cells", Gastroenterology. 98 (pt.1), 1272-1279.
- Donaldson, R.M. 1987. "Intrinsic factor and the transport of cobalamin" In Physiology of Gastrointestinal tract, pp. 959-973. Johnson, L.R. ed. 2nd ed. New York: Raven Press
- Draper, M.P., Martell, R.L. and Levy, S.B. 1997. "Indomethacin-mediated reversal of multidrug resistance and drug efflux in human and murine cell lines over-expressing MRP, but not P-glycoprotein", Br. J.Cancer 75 (6), 810-815.
- Drug Information Handbook, 12<sup>th</sup> edition. Charles F. Lacy, 2004 lexi-comp, Inc

Hudson, OH, U.S.A. 905-906.

- Duffy, C.P., Elliott, C.J., O'Connor, R.A., Heenan, M.M., Coyle, S., Cleary, I.M., Kavanagh, K., Verhaegen, S., O'Loughlin, C.M., NicAmhlaoibh, R. and Clynes, M. 1998. "Enhancement of chemotherapeutic drug toxicity to human tumour cells in vitro by a subset of non-steroidal anti-inflammatory drugs (NSAIDs)", Eur. J. Cancer. 34 (8),1250-9.
- Eneroth, A., Astrom, E., Hoogstraate, J., Schrenk, D., Conrad, S., Kauffmann, H.M. and Gjellan, K. 2001. "Evaluation of a vincristine resistant Caco-2 cell line for use in a calcein AM extrusion screening assay for P-glycoprotein interaction", Eur. J. Pharm. Sci. 12(3),205-214.
- Essodaigui, M., Broxterman, H.J. and Garnier-Suillerot, A. 1998. "Kinetic analysis of calcein and calcein-acetoxymethylester efflux mediated by the multidrug resistance protein and P-glycoprotein, *Biochemistry*. 37(8), 2243-50.
- Evers, R., de Haas, M., Kool, M., Sparidane, R., Beijnen, J., Wielinga, P.R., Lankelma, J. and Borst, P. 2000. "Vinblastine and sulfinpyrazone export by the multidrug resistance protein MRP2 is associated with glutathione transports" Br. J. Cancer 83, 374-383.
- Evers, R., Kool M., Smith, A.J., van Deemter, L., de Haas, M. and Borst, P. 2000. "Inhibitory effect of the reversal agents V-104, GF 120918 and Pluronic L61 on MDR1-Pgp, MRP1- and MRP2-mediated transport", Br. J. Cancer 83, 366-374.
- Evers, R., Zaman, G.J., van Deemter, L., Jansen, H., Calafat, J., Oomen, L.C., Oude Elferink, R.P., Borst, P., Schinkel, A.H. 1996. "Basolateral localization and export activity of the human multidrug resistance-associated protein in polarized pig kidney cells. ", J. Clin. Invest. 97(5), 1211-1218.

- Fagerholm, U. and Lennernas, H. 1995. "Experimental estimation of the effective unstirred water layer thickness in the human jejunum, and its importance in oral drug absorption", Eur. J. Pharm. Sci. 5, 247-253
- Fojo, A.T., Shen, D.W., Mickley, L.A., Pastan, I. and Gottesman, M.M. 1987a. "Intrinsic drug resistance in human kidney cancer is associated with expression of a human multidrug-resistance gene", J. Clin. Oncol. 5, 1922–1927.
- Fojo, A.T., Ueda, K., Slamon, D.J., Poplack, D.G., Gottesman, M.M. and Pastan, I. 1987b. "Expression of a multidrug-resistance gene in human tumors and tissues", Proc. Natl. Acad. Sci. U.S.A. 84, 265–269.
- Franks, N.P., Abraham, M.H. and Lieb, W.R. 1993. "Molecular organization of liquid n-octanol: an X-ray diffraction analysis", J. Pharm. Sci. 82(5), 466-70.
- Friedman, D.I. and Amidon, G.L. 1989. "Intestinal absorption mechanism of dipeptide angiotensin converting enzyme inhibitors of the lysyl-proline type: lisinopril and SQ 29,852", J. Pharm. Sci. 78(12),995-8.
- Fujita, T., Yamada, H., Fukuzumi, M., Nishimaki, A., Yamamoto, A. and Muranishi, S. 1997. "Calcein is excreted from the intestinal mucosal cell membrane by the active transport system", Life Sci. 60(4-5), 307-13.
- Galia, E., Nicolaidis, E., Horter, D., lobenberg, R., Reppas, C. and Dressman, J.B. 1998. "Evaluation of various dissolution media for predicting *in vivo* performance of class I and II drug", Pharm. Res. 15(5), 698-705.
- Gan, L.S., Yanni, S. and Thakker, D.R. 1998. "Modulation of the tight junctions of the Caco-2 cell monolayers by H<sub>2</sub>-antagonists", Pharm. Res. 15(1),53-7.



- Gatmaitan, Z.C. and Arias, I.M. 1993. "Structure and function of P-glyco- protein in normal liver and small intestine", Adv. Pharmacol. 24, 77-97.
- Gerk, P.M. and Vore, M. 2002. "Regulation of expression of the multidrug resistance-associated protein 2 (MRP2) and its role in drug disposition", J. Pharmacol. Exp. Ther. 302, 407-415.
- Goh, L.B., Spears, K.J., Yao, D., Ayrton, A., Morgan, P., Roland Wolf, C. and Friedberg, T. 2002. "Endogenous drug transporters in vitro and in vivo models for the prediction of drug disposition in man ", Biochem. Pharmacol. 64, 1569-1578.
- Grass, G.M. 1997 "Simulation models to predict oral drug absorption from in vitro data", Adv. Drug Del. Rev. 23(1-3), 199-219.
- Gutmann, H., Fricker, G., Torok, M., Michael, S., Beglinger, C. and Drewe, J. 1999. "Evidence for different ABC-transporters in Caco-2 cells modulating drug uptake", Pharm. Res. 16(3), 402-407.
- Hamilton, K.O., Backstrom, G., Yazdanian, M.A. and Audus, K.L. 2001. "P-glycoprotein efflux pump expression and activity in Calu-3 cells", J. Pharm. Sci. 90, 647-658.
- Herschman, H.R., Talley, J.J. and DuBois, R. 2003. "Cyclooxygenase 2 (COX-2) as a target for therapy and noninvasive imaging", Mol. Imageing. Biol. 5(5), 286-303.
- Hidalgo, I.J. and Li, J. 1996. "Carrier mediated transport and efflux mechanisms in Caco-2 cells", Adv. Drug Del. Rev. 22(1-2), 53-66.

- Hilgers, A.R., Conradi, R.A. and Burton, P.S. 1990. "Caco-2 cell monolayers as a model for drug transport across the intestinal mucosa", Pharm. Res. 7(9), 902-10.
- Hirohashi, T., Suzuki, H., Chu, X.Y., Tamai, I., Tsuji, A. and Sugiyama, Y. 2000. "Function and expression of multidrug resistance-associated protein family in human colon adenocarcinoma cells(Caco-2)", J. Pharmacol. Exp. Ther. 292(1), 265-70.
- Hogben, C.A., Tocco, D.J., Brodie, B.B. and Schanker, L.S. 1959. On the mechanism of intestinal absorption of drugs", J. Pharmacol. Exp. Ther. 125(4), 275-82.
- Hollo, Z., Homolya, L., Davis, C.W. and Sarkadi, B. 1994. "Calcein accumulation as a fluorometric functional assay of the multidrug transporter", Biochim. Biophys. Acta. 1191(2), 384-8.
- Hovgaard, L., Brondsted, H., Buur, A. and Bundgaard, H. 1995. "Drug delivery studies in Caco-2 monolayers. Synthesis, hydrolysis, and transport of O-cyclopropane carboxylic acid ester prodrugs of various beta-blocking agents", Pharm. Res. 12(3), 387-92.
- Hunter, J. and Hirst, B.H. 1997. "Intestinal secretion of drugs. The role of P-glycoprotein and related drug efflux systems in limiting oral drug absorption", Adv. Drug. Del. Rev. 25 (2-3),129-157.
- Hunter, J., Jepson, M.A., Tsuruo, T., Simmons, N.L. and Hirst, B.H. 1993. "Functional expression of P-glycoprotein in apical membranes of human intestinal Caco-2 cells. Kinetics of vinblastine secretion and interaction with modulators", J. Biol.Chem. 268(20), 14991-14997.

- Hunter, J., Hirst, B.H. and Simmons, N.L. 1993b. "Drug absorption limited by P-glycoprotein-mediated secretory drug transport in human intestinal epithelial Caco-2 cell layers", Pharm. Res. 10, 743–749.
- Inui, K., Yamamoto, M. and Saito, H. 1992. "Transepithelial transport of oral cephalosporins by monolayers of intestinal epithelial cell line Caco-2: specific transport systems in apical and basolateral membranes", J. Pharmacol. Exp. Ther. 261(1), 195-201.
- Jilani, J.A., Najib, N.M. and Ghariabeh, S.H. 1997. "Synthesis and evaluation of some acyloxyethyl mefenamates as possible prodrugs", Acta Pharm. Hung 67 (2-3), 99-104.
- Juliano, R.L. and Ling, V. 1976. "A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants", Biochim. Biophys. Acta 455,152–162.
- Kim, R.B., Fromm, M.F., Wandel, C., Leake, B., Wood, A.J, Roden, D.M. and Wilkinson, G.R. 1998. "The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors", J. Clin. Invest. 101 (2),289-294.
- Kondratov, R.V., Komarov, P.G., Becker, Y., Ewenson, A. and Gudkov, A.V. 2001. "Small molecules that dramatically alter multidrug resistance phenotype by modulating the substrate specificity of P-glycoprotein", Proc. Natl. Acad. Sci. USA. 98(24), 14078-14083.
- Kool, M., de Haas, M., Scheffer, G.L., Scheper, R.J., van Eijk, M.J., Juijn JA, Baas F, Borst P. 1997. "Analysis of expression of cMOAT (MRP2), MRP3, MRP4, and MRP5, homologues of the multidrug resistance-associated protein gene

(MRP1), in human cancer cell lines”, Cancer Res. 57(16), 3537-47.

Krämer, S.D. 1999. “Absorption prediction from physicochemical parameters”, Pharm Sci Technolo To. 2 (9), 373-380.

Kruh, G.D., Zeng, H., Rea, P.A., Liu, G., Chen, Z.S., Lee, K. and Belinsky, M.G. 2001. “MRP subfamily transporters and resistance to anticancer agents, J. Bioenerg. Biomembr. 33, 493–501.

Laloo, A.K., Feng, R.L., Guo, A., Paranjpe, P.V., Lee, S.H., Vyas, V., Rubin, E. and Sinko, P.J. 2004. “Membrane transport of camptothecin: facilitation by human P-glycoprotein (ABCB1) and multidrug resistance protein2 (ABCC2)”, BMC Medicine 2(16), 1-12.

Langman, M.J., Jensen, D.M., Watson, D.J., Harper, S.E., Zhao, P.L., Quan, H., Bolognese J.A. and Simon, T.J. 1999. “Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs”, J. Amer. Med. Assoc. 282, 1929-1933.

Larsen, A.K., Escargueil, A.E. and Skladanowski, A. 2000. “Resistance mechanisms associated with altered intracellular distribution of anticancer agents”, Pharmacol. Ther. 85, 217–229.

Lee, C., de Vruhe, R. and Smith, P.L. 1997. “Selection of development candidates based on in vitro permeability measurements”, Adv. Drug Del. Rev. 23 (1-3), 47-62.

Lee, G., Schlichter, L., Bendayan, M. and Bendayan, R. 2001. “Functional expression of P-glycoprotein in rat brain microglia”, J. Pharmacol. Exp. Ther. 299, 204–212.

- Lee, K. and Thakker, D.R. 1999. "Saturable transport of H<sub>2</sub>-antagonists ranitidine and famotidine across Caco-2 cell monolayers", J. Pharm. Sci. 88(7),680-7.
- Lee, K., Klein-Szanto, A.J. and Kruh, G.D. 2000. "Analysis of MRP4 drug resistance profile in transfected NIH3T3 cells", J Natl Cancer Inst 92,1934-1940.
- Lee, V.H. 2000. "Membrane transporters", Eur. J. Pharm. Sci. 11 (Suppl 2), S41-50.
- Lipinski, C.A., Lombardo, F., Dominy, B.W. and Feeney, P.J. 2001. "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings ", Adv Drug Del Rev. 46, 3-26.
- Litman, T., Brangi, M., Hudson, E., Fetsch, P., Abati, A., Ross, D.D., Miyake, K., Resau, J.H. and Bates, S.E. 2000. "The multidrug resistance phenotype associated with overexpression of the new ABC half-transporter, MXR (ABCG2)", J. Cell Sci. 113, 2011-2021.
- Litman, T., Druley, T.E., Stein, W.D. and Bates, S.E. 2001. "From MDR to MXR: new understanding of multidrug resistance systems, their properties and clinical significance ", Cell Mol Life Sci. 58(7), 931-959.
- Litman, T., Zeuthen, T., Skovsgaard, T. and Stein, W.D. 1997. "Structure-activity relationships of P-glycoprotein interacting drugs: kinetic characterization of their effects on ATPase activity ", Biochim. Biophys. Acta 1361, 159-168.
- Lown, K.S., Mayo, R.R., Leichtman, A.B., Hsiao, H.L., Turgeon, D.K., Schriedlin-Ren, P., Brown, M.B., Guo, W., Rossi, S.J., Benet, L.Z. and Watkins, P.B. 1997. "Role of intestinal P-glycoprotein (mdr1) in interpatient variation in the oral bioavailability of cyclosporine", Clin. Pharmacol. Ther. 62(3),248-260.

- Madara, J.L. 1988. "Loosening tight junctions. Lessons from the intestine", J. Clin. Invest. 82 (5),1516-24.
- Makhey, V.D., Guo, A., Norris, D.A., Hu, P., Yan, J. and Sinko, P.J. 1998. "Characterization of the regional intestinal kinetics of drug efflux in rat and human intestine and in Caco-2 cells", Pharm. Res. 15(8), 1160-1167.
- Maliapaard, M., Scheffer, G.L., Faneyte, I.F., van Gastelen, M.A., Pijnenborg, A.C., Schinkel, A.H., van De Vijver, M.J., Scheper, R.J. and Schellens, J.H. 2001. "Subcellular localization and distribution of the breast cancer resistance protein transporter in normal human tissues", Cancer Res. 61(8), 3458-3464.
- Marfouz, N.M., Omar, F.A., and Aboul-Fadl, T. 1999. "Cyclic amide derivatives as potential prodrugs II: *N*-hydroxymethylauccinimide-/isatin esters of some NSAIDs as prodrugs with improved therapeutic index", Eur. J. Med. Chem. 34 (7-8), 551-562.
- Martin, Y.C. 1981. "A Practitioner's perspective of the role of quantitative structure-activity analysis in medicinal chemistry", J Med Chem. 24(3), 229-237.
- Mentlein, R. and Heymann, E. 1984. "Hydrolysis of ester- and amide-type drugs by the purified isoenzymes of nonspecific carboxylesterase from rat liver", Biochem Pharmacol. 33, 1243-1248.
- Merkel, D.E., Fuqua, S.A.W., Tandom, A.K., Hill, S.M., Buzdar, A.U. and McGuire, W.L. 1989. "Electrophoretic analysis of 248 clinical breast cancer specimens for P-glycoprotein overexpression of gene amplification", J. Clin. Oncol. 7, 1129–1136.
- Meyer, S., Noisommit-Rizzi, N., Reuss, M. and Neubauer, P. 1999. "Optimized

analysis of intracellular adenosine and guanosine phosphates in *Escherichiacoli.*”, Anal. Biochem. 271(1), 43-52.

Morioka, N., Kumagai, K., Morita, K., Kitayama, S. and Dohi, T. 2004. “Nonsteroidal anti-inflammatory drugs potentiate 1-methyl-4-phenylpyridinium (MPP+)-induced cell death by promoting the intracellular accumulation of MPP+ in PC12 cell”, J. Pharmacol Exp. Ther. 311(2),476-484.

Muranishi, S. 1990. “Absorption enhancers”, Crit. Rev. Ther. Drug Carrier Syst. 7 (1), 1-33.

Narawane, L. and Lee, V.H. 1994. “Absorption barriers”, In Drug absorption enhancement: concepts, possibilities, limitation, and trends. pp 1-66. de Boer, A.G., ed. Singapore: Harwood Academic Publishers.

Naesens, L., Bischofberger, N., Augustijns, P., Annaert, P., Van den Mooter, G., Arimilli, M.N., Kim, C.U. and De Clercq, E. 1998. “Antiretroviral efficacy and pharmacokinetics of oral bis (isopropoxy carbonyloxymethyl)-9-(2-phosphonylmethoxypropyl) adenine in mice”, Antimicrob. Agents Chemother. 42 (7), 1568-1573.

Nellans, H.N. 1991. “Paracellular intestinal transport: modulation of absorption”, Adv. Drug Del. Rev. 7(3), 339-364.

Ogiso, T., Iwaki, M., Kinoshita, T., Tanino, T. and Paku, T. 1994. “Pharmacokinetics of indomethacin octyl ester (prodrug) and indomethacin produced from the prodrug”, J. Pharm. Sci. .83(1), 34-37.

Palm, K., Luthman, K., Ros, J., Grasjo, J. and Artursson, P. 1999. “Effect of molecular charge on intestinal epithelial drug transport: pH-dependent

- transport of cationic drugs”, J. Pharmacol. Exp. Ther. 291(2), 435-43.
- Palm, K., Luthman, K., Ungell, A.L., Strandlund, G. and Artursson, P. 1996. “Correlation of drug absorption with molecular surface properties”, J. Pharm. Sci. 85(1), 32-39.
- Pappenheimer, J.R. and Reiss, K.Z. 1987. “Contribution of solvent drag through intercellular junctions to absorption of nutrients by the small intestine of the rat”, J. Membr. Biol. 100(2), 123-36.
- Pearce, H.L., Winter, M.A. and Beck, W.T. 1990. “Structural characteristics of compounds that modulate P-glycoprotein-associated multidrug resistance”, Adv. Enzyme Regul. 30, 357-373.
- Peng, K.C., Cluzeaud, F., Bens, M., Van Huyen, J.P., Wioland, M.A., Lacave R. and Vandewalle, A. 1999. “Tissue and cell distribution of the multidrug resistance-associated protein (MRP) in mouse intestine and kidney”, J. Histochem.Cytochem. 47(6), 57-68.
- Polli, J.W., Jarrett, J.L., Studenberg, S.D., Humphreys, J.E., Dennis, S.W., Brouwer, K.R. and Woolley, J.L. 1999. “Role of P-glycoprotein on the CNS disposition of amprenavir (141W94), an HIV protease inhibitor”, Pharm.Res. 16(8), 1206-1212.
- Polli, J.W., Wring, S.A., Humphreys, J.E., Huang, L., Morgan, J.B., Webster, L.O. and Serabjit-Singh, C.S. 2001. “Rational Use of in vitro P-glycoprotein assays in drug discovery”, J. Pharmacol. Exp. Ther. 299 (2), 620-628.
- Prime-Chapman, H.M., Fearn, R.A., Cooper, A.E., Moore, V. and Hirst, B.H. 2004. “Differential Multidrug Resistance-Associated Protein 1 through 6 Isoform



Expression and Function in Human Intestinal Epithelial Caco-2 Cells”, J. Pharmacol. Exp. Ther. 311(2),476-484.

Purcell, P., Henry, D. and Melville, G. 1991. “Diclofenac hepatitis”, Gut 32(11), 1381-5.

Quaroni, A. and Hochman, J. 1996. “Development of intestinal cell culture models for drug transport and metabolism studies”, Adv. Drug Deliv. Rev. 22(1-2), 3-52.

Ramanujam, K.S., Seetharam, S., Ramasamy, M. and Seetharam, B. 1991. “Expression of cobalamin transport proteins and cobalamin transcytosis by colon adenocarcinoma cells”, Am. J. Physiol. 260(3 Pt 1), G416-22.

Rao, V.V., Dahlheimer, J.L., Bardgett, M.E., Snyder, A.Z., Finch, R.A., Sartorelli, A.C. and Piwnica-Worms, D. 1999. “Choroid plexus epithelial expression of MDR1 P-glycoprotein and multidrug resistance-associated protein contribute to the blood-cerebrospinal-fluid drug-permeability barrier”, Proc. Natl. Acad. Sci. U.S.A. 96, 3900–3905.

Raub, T.J., Barsuhn, C.L., Williams, L.R, Decker, D.E., Sawada, G.A. and Ho, N.F. 1993. “Use of a biophysical-kinetic model to understand the roles of protein binding and membrane partitioning on passive diffusion of highly lipophilic molecules across cellular barriers”, J. Drug Target. 1(4), 269-86.

Rebbeor, J.F., and Senior, A.E. 1998. “Effects of cardiovascular drugs on ATPase activity of P-glycoprotein in plasma membranes and in purified reconstituted form”, Biochim. Biophys. Acta. 1369 (1), 85-93.

Roller, A., Bahr, O.R., Streffer, J., Winter, S., Heneka, M., Deininger, M.,

- Meyermann, R., Naumann, U., Gulbins, E. and Weller, M. 1999. "Selective potentiation of drug cytotoxicity by NSAID in human glioma cells: the role of COX-1 and MRP", Biochem. Biophys. Res. Commun. 259(3), 600-605.
- Rubas, W., Cromwell, M.E.M. 1997. "The effect of chemical modification on octanol/water partition (logD) and permeabilities across Caco-2 monolayers", Adv. Drug Del. Rev. 23(1-3), 157-162.
- Safa, A.R. 1998. "Photoaffinity labels for characterizing drug interaction sites of P-glycoprotein", In Methods in Enzymology. ABC Transporters: Biochemical, Cellular, and Molecular Aspects. Vol. 292, pp 289-307. Ambudkar, S.T. and Gottesman, M.M. eds. London: Academic Press.
- Satoh, T., Hosokawa, M., Atsumi, R., Suzuki, W., Hakusui, H. and Nagai, E. 1994. "Metabolic activation of CPT-11, 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin, a novel antitumor agent, by carboxylesterase", Biol. Pharm. Bull. 17(5), 662-664.
- Scarborough, G.A. 1995. "Drug-stimulated ATPase activity of the human P-glycoprotein", J. Bioenerg. Biomembr. 27(1), 37-41.
- Schmid, D., Ecker, G., Kopp, S., Hitzler, M. and Chiba, P. 1999. "Structure-activity relationship studies of propafenone analogs based on P-glycoprotein ATPase activity measurements", Biochem. Pharmacol. 58(9), 1447-1456.
- Schinkel, A.H., Wagenaar, E., Mol, C.A. and van Deemter, L. 1996. "P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs", J. Clin. Invest. 97(11), 2517-24.
- Schmiedlin-Ren, P., Thummel, K.E., Fisher, J.M., Paine, M.F., Lown, K.S. and

- Watkins, P.B. 1997. "Expression of enzymatically active CYP3A4 by Caco-2 cells grown on extracellular matrix-coated permeable supports in the presence of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>", Mol. Pharmacol. 51(5), 741-754.
- Schwarz, U.I., Gramatte, T., Krappweis, J., Oertel, R. and Kirch, W. 2000. "P-glycoprotein inhibitor erythromycin increases oral bioavailability of talinolol in humans", Int. J. Clin. Pharmacol. Ther. 38(4), 161-167.
- Shanbhag V.R., Crider M.A., Gokhale R., Harpalani A., and Dick R.M. 1992. "Ester and amide prodrugs of ibuprofen and naproxen: Synthesis, anti-inflammatory activity, and gastrointestinal Toxicity", J. Pharm. Sci. 81(2), 149-154.
- Shapiro, A.B., Fox, K., Lam, P. and Ling, V. 1999. "Stimulation of P-glycoprotein-mediated drug transport by prazosin and progesterone: evidence for a third binding site", Eur. J. Biochem. 259, 841-850.
- Sharom, F.J., Yu, X., Lu, P., Liu, R., Chu, J.W., Szabo, K., Muller, M., Hose, C.D., Monks, A., Varadi, A., Seprodi, J. and Sarkadi, B. 1999. "Interaction of the P-glycoprotein multidrug transporter (MDR1) with high affinity peptide chemosensitizers in isolated membrane, reconstituted systems, and intact cells", Biol. Pharmacol. 58, 571-586.
- Shore, P.A., Brodie, B.B. and Hogben, C.A. 1957. "The gastric secretion of drugs: a pH partition hypothesis", J. Pharmacol. Exp. Ther. 119(3), 361-9.
- Silverstein, F.E., Faich, G., Goldstein, J.L., Simon, L.S., Pincus, T., Whelton, A., Makuch, R., Eisen, G., Agrawal, N.M., Stenson, W.F., Burr, A.M., Zhao, W.W., Kent, J.D., Lefkowitz, J.B., Verburg, K.M. and Geis, G. 2000. "Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A

randomized controlled trial. Celecoxib Long-term Arthritis Safety Study”, J. Amer. Med. Assoc. 284, 1247-1255.

Smith, D.A., Waterbeemd, H.V.D., and Walker, D.K. 2001. “Metabolic (hepatic) clearance”, In Pharmacokinetics and metabolism in drug design. pp 86-87. Mannhold, R., Kubinyi, H. and Timmerman, H., eds. Germany: Wiley-VCH.

Sparreboom, A., van Asperen, J., Mayer, U., Schinkel, A.H., Smith, J.W., Meijer, D.K., Borst, P., Nooijen, W.J., Beijnen, J.H. and van Tellingen, O. 1997. “Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine”, Proc. Natl. Acad. Sci. US A. 94 (5), 2031-2035.

Stenberg, P. 2001. “Computational Models for the Prediction of Intestinal membrane Permeability”, Doctor of Philosophy Dissertations Faculty of Pharmacy Uppsala University.

Stenberg, P., Luthman, K., Artursson, P. 2000. “Virtual screening of intestinal drug permeability”, J. Control. Release. 65(1-2), 231-43.

Stephens, R.H., O'Neill, C.A., Bennett, J., Humphrey, M., Henry, B., Rowland, M. and Warhurst, G. 2002. “Resolution of P-glycoprotein and non-P-glycoprotein effects on drug permeability using intestinal tissues from *mdr1a* (-/-) mice”, Br. J. Pharmacol. 135(8), 2038-46.

Taipalensuu, J., Tornblom, H., Lindberg, G., Einarsson, C., Sjoqvist, F., Melhus, H., Garberg, P., Sjostrom, B., Lundgren, B. and Artursson, P. 2001. “Correlation of gene expression of ten drug efflux proteins of the ATP-binding cassette transporter family in normal human jejunum and in human intestinal epithelial Caco-2 cell monolayers”, J. Pharmacol. Exp. Ther. 299(1), 164-70.

- Tamai, I., Nezu, J., Uchino, H., Sai, Y., Oku, A., Shimane, M. and Tsuji, A. 2000. "Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family", Biochem. Biophys. Res. Commun. 273(1),251-260.
- Tammara, V. K., Narurkar, M.M., Crider, A.M. and Khan, M.A. 1994. "Morpholinoalkyl ester prodrugs of diclofenac: synthesis, in vitro and in vivo evaluation", J. Pharm. Sci. 83(5), 644-648.
- Tantishaiyakul, V. and Wongpuwarak, W. 2005. "Prediction of Pgp-ATPase interaction and rhodamine 123 efflux inhibitory activities of propafenone analogs using PLS statistics ", J. Mol.Struc. (THEOCHEM) 718, 183-189.
- Taub, M.E., Kristensen, L. and Frokjaer, S. 2002. "Optimized conditions for MDCK permeability and turbidimetric solubility studies using compounds representative of BCS classes I-IV", Eur. J.Pharm.Sci. 15, 331–340.
- Taylor, M.D. 1996. "Improved passive oral drug delivery via prodrugs", Adv. Drug Deliv. Rev. 19,131-148.
- TenHoor, C.N., Bakatselou, V. and Dressman, J. 1991. "Solubility of mefenamic acid under simulated fed- and fasted state conditions ", Pharm. Res. 8(9), 1203-1205.
- Terao, T., Hisanaga, E., Sai, Y., Tamai, I. and Tsuji, A. 1996. "Active secretion of drugs from the small intestinal epithelium in rats by P-glycoprotein functioning as an absorption barrier", J. Pharm. Pharmacol. 48, 1083–1089.
- Thun, M.J., Henley, S.J. and Patrono, C. 2002. "Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues",

J. Nat. Cancer Inst. 94(4), 252-266.

Tozkoparan, B., Gokhan, N., Aktay, G., Yesilada, E. and Ertan, M. 2000. "6-Benzyl idenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones substituted with ibuprofen: synthesis, characterization and evaluation of anti-inflammatory activity", Eur. J. Med. Chem. 35 (7-8) , 743-750.

Topol, E.J. 2004. "Failing the Public Health---Rofecoxib, Merck, and the FDA", New. Engl. J. Med. 351 (17), 1707-1709.

Tsuji, A. and Tamai, I. 1996. "Carrier-mediated intestinal transport of drugs", Pharm. Res. 13(7), 963-77.

Tsuji, A., Terasaki, T., Takabatake, Y., Tenda, Y., Tamai, I., Yamashima, T., Moritani, S., Tsuruo, T. and Yamashita, J. 1992. "P-glycoprotein as the drug efflux pump in primary cultured bovine brain capillary endothelial cells", Life Sci. 51, 1427-1437.

Ungell, A.L., Nylander, S., Bergstrand, S., Sjoberg, A. and Lennernas, H. 1998. "Membrane transport of drugs in different regions of the intestinal tract of the rat", J. Pharm. Sci. 87(3), 360-6.

Ushigome, F., Takanaga, H., Matsuo, H., Yanai, S., Tsukimori, K., Nakano, H., Uchiumi, T., Nakamura, T., Kuwano, M., Ohtani, H. and Sawada, Y. 2000. "Human placental transport of vinblastine, vincristine, digoxin and progesterone: contribution of P-glycoprotein", Eur. J. Pharmacol. 408, 1-10.

Van Aobel, R.A., Smeets, P.H., Peters, J.G., Bindels, R.J. and Russels, F.G. 2002. "The MRP4/ABCC4 gene encodes a novel apical organic anion transporter in human kidney proximal tubules: putative efflux pump for urinary cAMP and cGMP", J. Am. Soc. Nephrol. 13, 595-603.

- Van Gelder, J., Shafiee, M., De Clercq, E., Penninckx, F., Van den Mooter, G., Kinget, R., Augustijns, P. 2000. "Species-dependent and site-specific intestinal metabolism of ester prodrugs", Int. J. Pharm. 205, 93-100.
- Varma, M.V.S., Ashokraj, Y., Dey, C.S. and Panchagnula, R. 2003. "P-glycoprotein inhibitors and their screening: a perspective from bioavailability enhancement", Pharmacol. Res. 48(4), 347-359.
- Vellonen, K.S., Honkakoski, P. and Urtti, A. 2004. "Substrates and inhibitors of efflux proteins interfere with the MTT assay in cells and may lead to underestimation of drug toxicity", Eur. J. Pharm. Sci. 23(2),181-8.
- Verschraagen, M., Koks, C.H., Schellens, J.H., Beijnen, J.H. 1999. "P-glycoprotein system as a determinant of drug interactions: the case of digoxin-verapamil", Pharmacol Res. 40(4), 301-306.
- Walgren, R.A., Karnaky Jr, K.J., Lindenmayer, G.E. and Walle, T. 2000. "Efflux of dietary flavonoid quercetin 4'-beta-glucoside across human intestinal Caco-2 cell monolayers by apical multidrug resistance-associated protein-2", J. Pharmacol.Exp.Ther. 294, 830-836.
- Warner, T.D., Giuliano, F., Vojnovic, I., Bukasa, A., Mitchell, J.A., and Vane, J.R. 1999. "Nonsteroidal drug selectivities for cyclooxygenase-1 rather than cyclooxygenase-2 are associated with human intestinal toxicity: A full in vitro analysis", Proc. Natl. Acad. Sci. USA. 96(13),7563-7568.
- Weber, J.P. 1984. "Epidemiology of adverse reactions to non-steroidal antiinflammatory drugs", In Advances in Inflammation Research, pp 1-7. Rainsford,

K.D. and Velo, G.P. eds. 6th ed. New York: Raven Press.

Wils, P., Warnery, A., Phung-Ba, V., Legrain, S. and Scherman, D. 1994. “High lipophilicity decreases drug transport across intestinal epithelial cells”, J. Pharmacol. Exp. Ther. 269(2), 654-8.

Winiwarter, S., Bonham, N.M., Ax, F., Hallberg, A., Lennernas, H. and Karlen, A. 1998. “Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach”, J. Med. Chem. 41, 4939-4949.

Wiwattanawongsa, K., Tantishiyakul, V., Lomlim, L., Rojanasakul, Y., Pinsuwan, S., and Keawnopparat, S. 2005. “Experimental and computational studies of epithelial transport of mefenamic acid ester prodrugs”, Pharm. Res. 22 (5), 721-727.

Wood, L.J., Mundo, F., Searle, J. and Powell, L.W. 1985. “Sulindac hepatotoxicity: effects of acute and chronic exposure”, Aust. N Z J. Med 15(4), 397-401.

Yazdanian, M., Glynn, S.L., Wright, J.L. and Hawi, A. 1998. “Correlating partitioning and Caco-2 cell permeability of structurally diverse small molecular weight compounds”, Pharm. Res. 15(9), 1490-4.

Yazdanian, M., Briggs, K., Jankovsky, C. and Hawi, A. 2004. “ The “high solubility” definition of the current FDA guidance on biopharmaceutical classification system may be too strict for acidic drugs”, Pharm. Res. 21(2), 293-299.

Yee, S. 1997. “In vitro Permeability across Caco-2 cells (colonic) can predict in vitro (small intestinal) absorption in man—Fact or Myth ”, Pharm. Res. 14 (6),



763-766.

Young, R.C., Mitchell, R.C., Brown, T.H., Ganellin, C.R., Griffiths, R., Jones, M., Rana, K.K., Saunders, D., Smith, I.R., Sore, N.E. and Wilks, T.J. 1988. "Development of a new physicochemical model for brain penetration and its application to the design of centrally acting H<sub>2</sub> receptor histamine antagonists", J. Med. Chem. 31(3), 656-71.

Zakaria, M. and Brown, P.R. 1981. "High Performance Liquid Chromatography of nucleotides", J. Chromatogr. 226,267-290.

Zelcer, N., Huisman, M.T., Reid, G., Wielinga, P., Breedveld, P., Kuil, A., Knipscheer, P., Schellens, J.H.M., Schinkel, A.H. and Borst, P. 2003 "Evidence for two interacting ligand binding sites in human multidrug resistance protein2 (ATP Binding Cassette C2) ", J. Biol. Chem. 278 (26), 23538-23544.

Zhang, Y., Bachmeier, C. and Miller, D.W. 2003. "In vitro and in vivo models for assessing drug efflux transporter activity", Adv. Drug Deliv. Rev. 55(1),31-51.

Zimmerman, H.J. 1981. "Effects of aspirin and acetaminophen on the liver", Arch. Intern. Med. 141(3 Spec No), 333-342.