

6 Literaturverzeichnis

- [1] IARCdatabase: www-dep.iarc.fr/globocan
- [2] World Health Report 1997 (WHO, Geneva)
- [3] Blume-Jensen, P.; Hunter, T.: *Oncogenic kinase Signaling*, Nature, **411**, 355-365, (2001)
- [4] Hong, W. K.; Ullrich, A.: *The role of EGFR in tumor growth*, Oncol. Biother., **1/1**, 2-6, (2000)
- [5] Ullrich, A.; Coussens, L.; Hayflick, J. S.; Dull, T.J.; Gray, A.; Tam, A.; Lee, J.; Yarden, Y.; Lebermann, T.; Schlessinger, J.; Downyard, J.; Bye, J.; Whittle, N.; Waterfield, M.; Seeburg, P.: *Human epidermal growth factor receptor cDNA sequenz and aberrant expression of the amplified gene in A431 epidermoid carcinoma cells*, Nature, **309**, 418-425, (1984)
- [6] Downyard, J.; Yarden, Y.; Mayes, E.; Scrace, G.; Totty, N.; Stockwell, P.; Ullrich, A.; Schlessinger, J.; Waterfield, M. D.: *Close similarity of epidermal growth factor receptor and v-erbB oncogene protein sequenzen*, Nature, **307**, 521-527, (1984)
- [7] Salomon, D.; Gullick, W.: *The erbB family of receptors and their ligands: multiple targets for therapy*, Signal, **2/3**, 4-11, (2001)
- [8] Pederson, M. W.; Poulson, H. S.: *Epidermal Growth Factor Receptor in Cancer Therapy*, Science & Medicine, 32-43, 2002
- [9] Yarden, Y.; Ullrich, A.: *Growth Factor Receptor Tyrosine Kinases*, Ann. Rev. Biochem., **57**, 443-478, (1988)
- [10] Harris, A. L.: *EGFR Signal Transduction 2001*, Signal, **2/3**, Poster-Beilage, (2001)
- [11] Schlessinger, J.; Ullrich, A.: *Growth Factor Signaling by Receptor Tyrosine Kinases*, Neuron, **9**, 383-391, (1992)
- [12] Riese II., D.J.; Stern, D. F.: *Specifity within the EGF family/ErbB receptor family signaling network*, BioEssays, **20**, 41-48, (1998)
- [13] Duschl, A.: *Rezeptortyrosinkinassen*, www.natur.sbg.ac.at/arnulf/biochem/%signal/VL%20Signal%203.pdf
- [14] McInnes, C.; Sykes, B. D.: *Growth factor receptors: Structure, mechanism, and drug discovery*, Biopolymers, **43/3**, 339-366, (1997)

-
- [15] Prenzel, N.; Fischer, O. M.; Streit, S.; Hart, S.; Ullrich, A.: *The epidermal growth factor receptor family as a central element for cellular signal transduction and diversification*, *Endocrine-Related Cancer*, **8**, 11-31, (2001)
- [16] Pschyrembel-Klinisches Wörterbuch, 258., neu bearb. Auflage, Walter-de-Gruyter-Verlag, Berlin-New York, , 766, (1998)
- [17] Löffler, G.; Petrides, P. E.: *Physiologische Chemie*, 4. Aufl., S. 666, (1988)
- [18] Jones, J. T.; Akita, R. W.; Sliwskowski, M. X.: *Binding specificities and affinities of egf domains for ErbB receptors*, *FEBS Lett.*, **447**, 227-231, (1999)
- [19] Cunningham, B. C.; Ultsch, M.; Devos, A. M.; Mulkerrin, M. G.; Clauser, K. R.; Wells, J. A.: *Dimerization of the extracellular domain of the human growth hormone receptor by a single hormone molecule*, *Science*, **254**, 821-825, (1991)
- [20] Van Zoelen, E. J.; Stortelers, C.; Lenferink, A. E.; Van de Poll, M. L.: *The EGF domain: requirements for binding to receptors of the ErbB family*, *Vitam. Horm.*, **59**, 99-131, (2000)
- [21] Ullrich, A.; Schlessinger, J.: *Signal Transduction by Receptors with Tyrosine Kinase Activity*, *Cell*, **61**, 203-212, (1990)
- [22] Raymond, E.; Faivre, S.; Armand, J. P.: *Epidermal Growth Factor Receptor Tyrosine Kinase as a Target for Anticancer Therapy*, *Drugs*, **60/1**, 15-23, (2000)
- [23] Margolis, B.; Li, N.; Koch, A.; Mohammadi, M; Hurwitz, D. R.; Zilberstein, A.; Ullrich, A.; Pawson, T.; Schlessinger, J.: *The tyrosine phosphorylated carboxy terminus of the EGF receptor is binding site for GAP and PLC- γ* , *EMBO J.*, **9**, 4375-4380, (1990)
- [24] Honegger, A.; Dull, T. J.; Bellot, F.; Van Obberghen, E.; Szapary, D.; Schmidt, A.; Ullrich, A.; Schlessinger, U.: *Biological activities of EGF-receptor mutants with individually altered autophosphorylation sites*, *EMBO J.*, **7**, 3045-3052, (1988)
- [25] Ceresa, B. P.; Schmid, S. L.: *Regulation of signal transduction by endocytosis*, *Curr. Op. Cell Biol.*, **12**, 204-210, (2000)
- [26] Lenferink, A. E.; Pinkas-Kramarski, R.; Van de Poll, M. L.; Van Vugt, M. J.; Klapper, L. N.; Tzahar, E.; Waterman, H.; Sela, M.; Van Zoelen, E. J.; Yarden, Y.: *Differential endocytic routing of homo- and hetero-dimeric ErbB tyrosine kinases confers signaling*, *EMBO J.*, **17**, 3385-3397, (1998)

-
- [27] Waterman, H.; Sabanai, I.; Geiger, B.; Yarden, Y.: *Alternative intracellular routine of ErbB receptors may determine signalling potency*, J. Biol. Chem., **273**, 13819-13827, (1998)
- [28] www.cellsignal.com
- [29] Bonni, A.; Brunet, A.; West, A. E.; Datta, S. R.; Takasu, M. A.; Greenberg, M. E.: *Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms*, Science, **286**, 1358-1362, (1999)
- [30] Datta, S. R.; Brunet, A.; Greenberg, M. E.: *Cellular survival: a play in three Acts*, Genes Dev., **13/22**, 2905-2927, (1999)
- [31] Gross, A.; McDonnell, J. M.; Korsmeyer, S. J.: *Bcl-2 family members and the mitochondria in apoptosis*, Genes Dev., **13/15**, 1899-1911, (1999)
- [32] Cobb, M. H.: *MAP kinase pathways*, Prog. Biophys. Mol. Biol., **71/3-4**, 479-500, (1999)
- [33] Lewis, T. S.; Shapiro, P. S.; Ahn, N. G.: *Signal transduction through MAP kinase cascades*, Adv. Cancer Res., **74**, 49-139, (1998)
- [34] Stokoe, D.; Macdonald, S. G.; Cadwallader, K.; Symons, M.; Hancock, J. F.: *Activation of Raf as a result of recruitment to the plasma membrane*, Science, **264**, 1463-1467, (1994)
- [35] Leever, S. J.; Paterson, H. F.; Marshall, C. J.: *Requirement for Ras in Raf activation is overcome by targeting Raf to the plasma membrane*, Nature, **369**, 411-414, (1994)
- [36] Adjei, A. A.: *Blocking Oncogenic Ras Signaling for Cancer Therapy*, J. Nat. Cancer Inst., **93/14**, 1062-1074, (2001)
- [37] Burgering, B. T.; Coffey, P. J.: *Protein kinase B (c-Akt) in Phosphatidylinositol-3-OH-kinase signal transduction*, Nature, **376**, 599-602, (1995)
- [38] Franke, T. F.; Yang, S.-I.; Chan, T. O.; Datta, K.; Kazlaukas, A.; Morrison, D. K.; Kaplan, D. R.; Tschlis, P. N.: *The protein kinase encoded by the Akt protooncogene is a target of the platelet-derived growth factor (PDGF)-activated phosphatidylinositol 3-kinase (PI3-kinase)*, Cell, **81**, 727-736, (1995)
- [39] Van der Geer, P.; Hunter, T.; Lindberg, R. A.: *Receptor Protein-Tyrosine Kinases and their Signal Transduction Pathways*, Annu. Rev. Cell Biol., **10**, 251-337, (1994)
- [40] Schultz, C.; Dinkel, C.: *Phosphatidylinositol: Informationsträger der anderen Art*, Nachrichten aus der Chemie, **50/5**, 590-595, (2002)
- [41] Schulte, U.: *Die Kontrolle des Zellzyklus*, DAZ, **141/43**, 75-76, (2001)

-
- [42] Hohmann, C.: „*Stop and go*“ *im Zellzyklus*, PZ, **146/42**, 63-64, (2001)
- [43] Funk, J. O.; Kind, P.: *Zellzykluskontrolle, genetische Instabilität und Krebs*, Hautarzt, **48**, 157-165, (1997)
- [44] Frödin, M.; Gammeltoft, S.: *Role and regulation of 90kDa ribosomal S6 kinase (RSK) in signal transduction*, Mol. Cell. Endocrinol., **151**, 65-77, (1999)
- [45] Deak, K. M.; Clifton, A. D.; Lucocq, L. M.; Alessi, D. R.: *Mitogen- and stress-activated protein kinase-1 (MSK-1) is directly activated by MAPK and SAPK2/p38, and may mediate reactivation of CREB*, EMBO J., **17/15**, 4426-4441, (1998)
- [46] Kaiser, A.: *Transkriptionsfaktoren*, DAZ, **139/13**, 47-51, (1999)
- [47] Jefferies, M. B. J.; Fumagalli, S.; Dennis, P. B.; Reinhard, C.; Pearson, R. B.; Thomas, G.: *Rapamycin suppresses 5' TOP mRNA translation through inhibition of p70SK6*, EMBO J., **16**, 3693-3704, (1997)
- [48] Ashkenazi, A.; Dixit, V. M.: *Apoptosis control by death and decoy receptors*, Curr. Opin. Cell Biol., **11/2**, 255-260, (1999)
- [49] Wang, X.: *The expanding role of mitochondria in apoptosis*, Genes Dev., **15/22**, 2922-2933, (2001)
- [50] Budihardjo, I.; Oliver, H.; Lutter, M.; Luo, X.; Wang, X.: *Biochemical pathways of caspase activation during apoptosis*, Annu. Rev. Cell Dev. Biol., **15**, 269-290, (1999)
- [51] Ruchaud, S.; Korfali, N.; Villa, P.; Kottke, T. J.; Dingwall, C.; Kaufmann, S. M.; Earnshaw, W. C.: *Caspase-6 gene disruption reveals a requirement for lamin A cleavage in apoptotic chromatin condensation*, EMBO J., **21/8**, 1967-1977, (2002)
- [52] Franke, T. F.; Cantley, L. C.: *A Bad kinase makes good*, Nature, **390**, 116-117, (1997)
- [53] Burridge, K.; Fath, K.; Kelly, T.; Nuckolls, G.; Turner, C.: *Focal Adhesions: Transmembrane Junction Between the Extracellular Matrix and the Cytoskeleton*, Annu. Rev. Cell Biol., **4**, 487, (1988)
- [54] Craig, S. W.; Johnson, R. P.: *Assembly of focal adhesions: progress, paradigms and portents*, Curr. Opin. Cell Biol., **8/1**, 74, (1996)
- [55] www.nature.com/nrm/journal/v3/n4/clideshow/nrm779_F3.html
- [56] Lauffenburger, D. A.; Horwitz, A. F.: *Cell Migration: A Physically Integrated Molecular Process*, Cell, **84/3**, 359-369, (1996)
- [57] Glading, A.; Chang, P.; Lauffenburger, D. A.; Wells, A.: *Epidermal Growth Factor Receptor Activation of Calpain Is Required for Fibroblast Motility and occurs via an ERK/MAP Kinase Signaling Pathway*, J. Biol. Chem., **275/4**, 2390-2398, (2000)

-
- [58] Haley, J.; Whittle, N.; Bennet, P.; Kinchington, D.; Ullrich, A.; Waterfield, M.: *The human EGF receptor gene: structure of the 110kb locus and identification of sequences regulating its transcription*, *Oncogene Res.*, **1**, 375-396, (1987)
- [59] Yamamoto, T.; Nishida, T.; Miyajima, N.; Kawai, S.; Ooi, T.; Toyoshima, K.: *The v-erbB gene of Avian erythroblastosis virus is a member of the src gene family*, *Cell*, **35**, 71-78, (1983)
- [60] Hayman, M. J.; Enrietto, P. J.: *Cell transformation by growth factor receptor and v-erbB*, *Cancer Cell*, **8**, 302-307, (1991)
- [61] Coussens, L.; Yang-Feng, T. L.; Liao, Y. C.; Chen, E.; Gray, A.; McGrath, J.; Seeburg, P. H.; Libermann, T. A.; Schlessinger, J.; Francke, U.; Levinson, A.; Ullrich, A.: *Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene*, *Science*, **230**, 1132-1139, (1986)
- [62] Yamamoto, T.; Ikawa, S.; Akiyama, T.; Semba, K.; Nomura, N.; Miyajima, N.; Saito, T.; Toyoshima, K.: *Similarity of protein encoded by the human c-erbB-2 gene to epidermal growth factor*, *Nature*, **319**, 230-234, (1986)
- [63] www.uni-kl.de
- [64] Wells, A.: *Tumor invasion: role of growth factor-induced cell motility*, *Adv. Cancer Res.*, **78**, 31-101, (2000)
- [65] Hazan, R. B.; Norton, L.: *The EGFR modulates the interaction of E-Cadherin with the actin-skeleton*, *J. Biol. Chem.*, **273**, 9078-9084, (1998)
- [66] Damstrup, L.; Rude Voldborg, B.; Spang-Thomsen, M.; Brunner, N.; Poulsen, H. S.: *In vitro invasion of small-cell lung cancer cell lines correlates with expression of epidermal growth factor receptor*, *Br. J. Cancer*, **78**, 631-640, (1998)
- [67] Giordano, A.; Rustum, Y. M.; Wenner, C. E.: *Molecular Targets for Diagnosis and Therapy: Tumor Suppressor Genes and Cell Cycle Progression in Cancer*, *J. Cell Biochem.*, **70**, 1-7, (1998)
- [68] Gibson, S.; Tu, S.; Oyer, R.; Anderson, S. M.; Johnson, G. L.: *Epidermal Growth Factor Protects Epithelial Cells against Fas-induced Apoptosis*, *J. Biol. Chem.*, **274**, 17612-17618, (1999)
- [69] De Jong, J. S.; van Diest, P. J.; van der Valk, P.; Baak, J. P. A.: *Expression of growth factors, growth-inhibiting factors, and their receptors in invasive breast cancer. II: Correlations with proliferation and angiogenesis*, *J. Pathol.*, **184/1**, 53-57, (1998)

-
- [70] Salomon, D. S.; Brandt, R.; Ciardello, F.; Normanno, N.: *Epidermal growth factor-related peptides and their receptors in human malignancies*, Crit. Rev. Oncol. Hematol., **19/3**, 183-232, (1995)
- [71] Buchdunger, E.; O'Reilly, T.; Woods-Cock, K. Furet, P.; Traxler, P.: *PKI166 modulates proliferation, apoptosis and tumor growth of erbB1/2 overexpressing cells*, Proc. Am. Assoc. Cancer Res., **41**, 481 Abs. 3070, (2000)
- [72] Dullea, R. G.; Barbacci, E. G.; Miller, P. E.; Moyer, J. D.: *Induction of apoptosis by CP 358,774, an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase, in combination with cisplatin (CDDP)*, Proc. Am. Assoc. Cancer Res., **41**, 401 Abs. 2550, (2000)
- [73] Normanno, N.; Kim, N.; Wen, D.; Smith, K.; Harris, A. L.; Plowman, G.; Colletta, G.; Ciardiello, F.; Salomon, D. S.: *Expression of messenger RNA for Amphiregulin, Heregulin, and cripto-1, the three new members of the epidermal growth factor family, in human breast cancer*, Breast Cancer Res. Treat., **35**, 293-297, (1995)
- [74] Rusch, V.; Klimstra, D.; Venkatraman, E.; Pisters, P.; Langenfeld, J.; Dmitrovsky, E.: *Overexpression of EGFR and its ligand TGF- α , is frequent in resectable non-small lung cancer, but does not predict tumor progression*, Clin. Cancer Res., **3**, 512-522, (1997)
- [75] Wang, X. Y.; Blahnik, A.; James, C. D.: *A C-958 truncation mutant EGF Receptor expressed in human glioblastomas utilizes differential substrates for signal transduction and enhances tumor growth*, Proc. Am. Assoc. Cancer Res., **41**, 357 Abs. 2265, (2000)
- [76] Fan, Z.; Masui, M.; Atlas, I. et al.: *Blockade of epidermal growth factor by bivalent and monovalent fragments of 225 anti-epidermal growth factor receptor monoclonal antibody*, Cancer Res., **53**, 4322-4328, (1993)
- [77] Fan, Z.; Lu, Y.; Wu, X. et al.: *Antibody-induced epidermal growth factor receptor dimerization mediates inhibition of autocrine proliferation of A431 squamous carcinoma cells*, J. Biol. Chem., **269**, 27595-27602, (1994)
- [78] Merck KGaA: *Innovative Biotherapeutika gegen Krebserkrankungen*, (2001)
- [79] Pivot, X.; Guardiola, E.; Stein, U.: *Epidermal growth factor receptor as a target for anticancer therapy*, CancerFutures, **1**, 90-93, (2002)
- [80] Baselga, J.; Pfister, D.; Cooper, M. R.; Cohen, R.; Burtness, B.; Bos, M.; D'Andrea, G.; Seidman, A.; Norton, L.; Gunnet, K.; Falcey, J.; Anderson, V.; Waksal, H.;

- Mendelsohn, J.: *Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin*, J. Clin. Oncol., **18**, 904-914, (2000)
- [81] Cao, Y.; Lam, L.: *Applications of bispecific antibodies in therapeutics*, Drugs of the Future, **27/1**, 33-41, (2002)
- [82] Curnow, R. T.: *Clinical experience with CD64-directed immunotherapy. An Overview*, Cancer Immunol Immunother, **45/3-4**, 210-215, (1997)
- [83] Chatal, F.; Faivre-Chauvet, A.; Bardies, M.; Peltier, P.; Gautherot, E.; Barbei, J.: *Bifunctional antibodies for radio-immunotherapy*, Hybridomas, **14**, 125-128, (1995)
- [84] Fitzgerald, D.: *Why toxins!*, Cancer Biol., **7**, 87-95, (1996)
- [85] www.ih.org/pages/egf-genistein.html
- [86] Uckun, F. M.; Narla, R. K.; Jun, X.; Zeren, T.; Venkatachalam, T.; Waddick, K. G.; Rostostev, A.; Myers, D. E.: *Cytotoxic Activity of Epidermal Growth Factor-Genistein against Breast Cancer Cells*, Clin. Cancer. Res., **4**, 901-912, (1998)
- [87] www.usalchemistry.com
- [88] Onoda, T.; Iinuma, H.; Sasaki, Y.; Hamade, M.; Isshiki, K.; Naganawa, H.; Takeuchi, T.: *Isolation of a Novel Tyrosine Kinase Inhibitor, Lavendustin A, from Streptomyces griseolavendus*, J. Nat. Prod., **42/6**, 1252-1257, (1989)
- [89] Nussbaumer, P.; Winiski, A. P.; Cammisuli, S.; Hiestand, P.; Weckbecker, G.; Stütz, A.: *Novel Antiproliferative Agents Derived from Lavendustin A*, J. Med. Chem., **37**, 4079-4084, (1994)
- [90] Artaega, C. L.: *The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia*, J. Clin. Oncol., **19/15**, 32S-40S, (2001)
- [91] Ciardiello, F.; Caputo, R.; Bianco, R.; Vincenzo, D.; Pomatico, G.; De Placido, S.; Bianco, R. A.; Tortora, G.: *Antitumor Effect and Potentiation of Cytotoxic Drugs Activity in human Cancer Cells by ZD-1839 (Iressa), an Epidermal Growth Factor Receptor-selective Tyrosine Kinase Inhibitor*, Clin. Cancer Res., **6**, 2053-2063, (2000)
- [92] Pollack, V.; Savage, D. M.; Baker, D. A. Et al.: *Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP 358,774 dynamics of receptor inhibition in situ and antitumour effects in athmic mice*, J. Pharmacol. Exp. Ther., **291/2**, 739-748, (1999)

-
- [93] Morin, M. J.: *From oncogene to drug: development of small molecule tyrosine kinase inhibitors as anti-tumor and anti-angiogenic agents*, *Oncogene*, **19**, 6574-6583, (2000)
- [94] Flanagan, W. M.: *Antisense comes of age*, *Cancer and Metastasis Rev.*, **17**, 169-176, (1998)
- [95] www.uni-muenchen.de
- [96] [www:online-media.uni-marburg.de](http://www.online-media.uni-marburg.de)
- [97] Henderson, L. et al.: *Improving Treatments for Breast Cancer, Non-Hodgkin Lymphoma, Diabetes, and Congestive Heart Failure*, *Btech Investor Reports*, 1-17, (2002)
- [98] Karp, J. E.; Lancet, J. E.; Kaufmann, S. M.; End, D. W.; Wright, J. J.; Bol, K.; Hovak, I.; Tidwell, M. L.; Liesveld, J.; Kottke, T. J. Et al.: *Clinical and biologic activity of the farnesyl transferase inhibitor R115777 in adults with refractory and relapsed acute leukemias: a phase I clinical-laboratory correlative trial*, *Blood*, **97/11**, 3361-3369, (2001)
- [99] Adjei, A. A. et al.: *A Phase I Trial of the Farnesyltransferase Inhibitor R115777, in Combination with Gemcitabine and Cisplatin in Patients with Advanced Cancer*, *Proceedings of ASCO*, **20**, Nr. 320, (2001)
- [100] Piccart-Gebhart, M. J. et al.: *A Phase I, Clinical and Pharmacokinetic (PK) Trial of the Farnesyl Transferase Inhibitor (FTI) R115777 + Docetaxel: a Promising Combination in Patients (PTS) with Solid Tumors*, *Proceedings of ASCO*, **20**, Nr. 318, (2001)
- [101] Lee, J. S.; Cho, Y. S.; Park, E. J. Et al.: *Phospholipase C γ inhibitor principles from the sarcotestas of *Ginkgo biloba**, *J. Nat. Prod.*, **61**, 867-872, (1998)
- [102] Ryu, S. Y.; Choisu, S. K. Et al.: *In vitro antitumour activity of flavonoids from *Sophora Flavescens**, *Phytother Res.*, **11**, 51-53, (1997)
- [103] Oh, W. K.; Lee, H. S.; Kim, B. Y. et al.: *Inhibition of phospholipase C activity by ariculatin and 8-prenylluteone isolated from *Erythrina senegalensis**, *Phytother Res.*, **12**, 9-12, (1998)
- [104] Klupp, J.; Langrehr, J. M.; Junge, G.; Neuhaus, P.: *Inhibition of mammalian target of rapamycin*, *Drugs of the Future*, **26/12**, 1179-1189, (2001)
- [105] Wells, A.: *Tumor invasion: Role of growth factor-induced cell motility*, *Adv. Cancer Res.*, **78**, 31-101, (2000)

-
- [106] Khazaie, K.; Schirmacher, V.; Lichtner, R. B.: *EGF Receptor in Neoplasia and Metastasis*, *Cancer Met. Rev.*, **12**, 255-274, (1993)
- [107] Baselga, J.: *New technologies in epidermal growth factor receptor-targeted cancer therapy*, *Signal*, **1/1**, 12-21, (2000)
- [108] Lynch, T.: *ASCO meeting highlights the potential of EGFR-targeted therapy*, *Signal*, **2/3**, 17-22, (2001)
- [109] Witzel, S.: *Synthesen und Pharmakologie neuer Chromanol-, Isoflavon- und Indolderivate*, Dissertation, Freie Universität Berlin, (1999)
- [110] Lubczyk, V.; Bachmann, H.; Gust, R.: *Investigations on Estrogen Receptor Binding. The Estrogenic, Antiestrogenic, and Cytotoxic Properties of C2-Alkyl-Substituted 1,1-Bis(4-hydroxyphenyl)-2-phenylethenes*, *J. Med. Chem.*, **45/24**, 5358-5364, (2002)
- [111] Horwitz, K. B.; McGuire, W. L.: *Nuclear mechanism of estrogen action: effects of estradiol and antiestrogen on cytoplasmic and nuclear estrogen receptors and nuclear receptor processing*, *J. Biol. Chem.*, **253**, 8185-8191, (1978)
- [112] Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E.: *Synthesis and Evaluation of Stilbene and Dihydrostilbene Derivatives as Potential Anticancer Agents That Inhibit Tubulin Polymerization*, *J. Med. Chem.*, **34/8**, 2579-2588, (1991)
- [113] Mahboobi, S.; Pongratz, H.; Hufski, H.; Hockemeyer, J.; Frieser, M.; Lyssenko, A.; Paper, D. H.; Bürgermeister, J.; Böhmer, F.-D.; Fiebig, H.-H.; Burger, A. M.; Baasner, S.; Becker, T.: *Synthetic 2-Aroylindole Derivatives as a New Class of Potent Tubulin-Inhibitory, Antimitotic Agents*, *J. Med. Chem.*; **44/26**, 4535-4553, (2001)
- [114] Bradlow, H. L.; Sepkovic, D. W.; Telang, N. T. et al.: *Multifunctional aspect of the action of indole-3-carbinol as antitumor agent*, *Ann. NY Acad. Sci.*, **889**, 204-213, (1999)
- [115] Michnovic, J. J.; Adlercreutz, H.; Bradlow, H. L.: *Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans*, *J. Nat. Cancer Inst.*, **89**, 718-723, (1997)
- [116] Traxler, P.; Green, J.; Mett, H.; Séquin, U.; Furet, P.: *Use of a pharmacophore Model for the design of EGFR Tyrosine Kinase Inhibitors: Isoflavones and 3-Phenyl-4-(1H)-quinolones*, *J Med Chem*, **42/6**, 1018-1026, (1999)

-
- [117] Vlattas, I.: *Imidazobenzodiazepine, Verfahren zu ihrer Herstellung, pharmazeutische Präparate enthaltend diese Verbindungen sowie ihre therapeutische Verwendung*, Europäisches Patentamt, Pat.-Nr.: 0081461 A2, 22-23, (1982)
- [118] Okauchi, T.; Honaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H.: *A General Method for Acylation of Indoles at 3-Position with Acyl Chlorides in the Presence of Dialkylaluminiumchloride*, *Org. Lett.*, **2/10**, 1485-1487, (2000)
- [119] Inega, K.: *Acyindole derivatives and their use in pharmaceutical compositions*, United States Patent, Nr. 4,708,901, (1987)
- [120] Zaharevitz, D. W. et al.: *Discovery and initial characterization of the paullones, a novel class of small-molecule inhibitors of cyclin-dependent kinases*, *Cancer Res.*, **59**, (1999), 2566-2569
- [121] Sielecki, T. M.; Boylan, J. F.; Benfield, P. A.; Trainor, G. L.: *Cyclin-Dependent Kinase Inhibitors: Useful Targets in Cell Cycle Regulation*, *J. Med. Chem.*, **43/1**, 1-17, (2000)
- [122] Pavletich, N. P.: *Mechanism of cyclin-dependent kinases: engines, clocks, and microprocessors*, *Annu. Rev. Cell Dev. Biol.*, **13**, 261-291, (1997)
- [123] Schultz, C. et al.: *Paullones, a series of cyclin-dependent kinase inhibitors: synthesis, evaluation of CDK₁/cyclinB inhibition and in vitro antitumor activity*, *J. Med. Chem.*, **42**, 2909-2919, (1999)
- [124] Onoda, T.; Isshi, K.; Takeuchi, T.; Tatsuta, K.; Umezawa, K.: *Inhibition of tyrosine kinase and epidermal growth factor receptor internalization by lavendustin A methylester in cultured A431 cells*, *Drugs Exp. Clin. Res.*, **16/6**, 249-253, (1990)
- [125] Nussbaumer, P.; Winiski, A. P.; Cammisuli, S.; Hiestand, D.; Weckbecker, G.; Stütz, A.: *Novel Antiproliferative Agents Derived from Lavendustin A*, *J. Med. Chem.*, **37**, 4079-4084, (1994)
- [126] Chen, H.; Boiziau, J.; Parker, F.; Mailliet, P.; Commercon, A.; Toque, B.; Le Peca, J. B.; Roques, B. -P.; Garbay, C.: *Structure-Activity-Relationships in a Series of 5-[(2,5-Dihydroxybenzyl)-amino]-salicylate Inhibitors of EGF-Receptor-Associated Tyrosine Kinase: Importance of Additional Hydrophobic Aromatic Interactions*, *J. Med. Chem.*; **37/6**, 845-859, (1994)
- [127] Hsu, C. -Y. J.; Persons, P. E.; Spada, A. P.; Bednar, R. A.; Levitzki, A.; Zilberstein, A.: *Kinetic Analysis of the Inhibition of the Epidermal Growth Factor Receptor*

- Tyrosine Kinase by Lavendustin-A and its Analogues*, J. Biol. Chem., **266/31**, 21105-21112, (1991)
- [128] Billmann, J. H.; McDowell, J. W.: *Reduction of Schiff Bases. III. Reduction with Dimethylamine Borane*, J. Org. Chem., **26**, 1437-1440, (1961)
- [129] Bechgaard, H.; Lund-Jensen, C.: *Antituberculous Agents. Structure-Activity Relationships of Substituted 4-Aminosalicylates as Potential Transport Forms of 4-Aminosalicylic Acid (PAS)*, Eur. J. Med. Chem., **10/2**, 103-111, (1975)
- [130] Banerjea, P. R.; Drain, D. J.; Overton, H. K.; Seymor, D. E.: *4-Aminosalicylic Acid and its Derivatives. Part III.*, J. Chem. Soc.; S. 3863-3864, (1952)
- [131] Allen, C. F. H.; VanAllan, J.: *Salicyl-o-Toluidine (o-Salicylotoluidine)*, Org. Synth. Coll., **3**, sec. Ed., 765-767, (1960)
- [132] Lardon, A.; Reichstein, T.: *49.Synthese von freiem 11-Epi-corticosteron über 11 α -Trifluoracetate*, Helv. Chim. Act., **37/49**, 388-393, (1954)
- [133] Hodge, C. N.; Pierce, J. A.: *A diazine heterocycle replaces a six-membered hydrogen-bonded array in the active site of scytalone dehydratase*, Bioorg. Med. Chem. Lett., **3**, 1605-1608, (1993)
- [134] Ward, W. H. J.; Cook, P. N.; Slater, A. M.; Davies, H.; Holdgate, G. A.; Green, L. R.: *Epidermal growth factor receptor tyrosine kinase. Investigation of catalytic mechanism, structure-based searching and discovery of a potent inhibitor*, Biochem. Pharmacol., **48**, 659, (1994)
- [135] Fry, D. W.; Kraker, A. J.; McMichael, A.; Ambroso, L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J.: *A specific inhibitor of the epidermal growth factor receptor tyrosine kinase*, Science, **265**, 1093-1095, (1994)
- [136] Palmer, B. D.; Trumpp-Kallmeyer, S.; Fry, D. W.; Nelson, J. M.; Showalter, H. D. H.; Denny, W. A.: *Tyrosine Kinase Inhibitors 11. Soluble Analogues of Pyrrolo- and Pyrazoloquinazolines as Epidermal Growth Factor Receptor Inhibitors: Synthesis, Evaluation and Modelling of the Mode of Binding*, J. Med. Chem., **40/10**, 1519-1529, (1997)
- [137] Rewcastle, G. W.; Denny, W. A.; Bridges, A. J.; Zhou, H.; Cody, D. R.; McMichael, A.; Fry, D. W.: *Tyrosine Kinase Inhibitors 5. Synthesis and Structure-Relationships for 4-[(Phenylmethyl)-amino]- and 4-(Phenylamino)-quinazolines as Potent Adenosine 5'-Triphosphate Binding Site Inhibitors of the Tyrosin Kinase Domain of Epidermal Growth Factor Receptor*, J. Med. Chem., **38/18**, 3482-3487, (1995)

-
- [138] Bridges, A. J.; Zhou, H.; Cody, D.; Rewcastle, G. W.; McMichael, A.; Showalter, H. D. H.; Fry, D. W.; Kraker, A. J.; Denny, W. A.: *Tyrosine Kinase Inhibitors 8. An unusually steep structure activity relationship for analogues of 4-(3-bromoanilino)-6,7-dimethoxyquinazline (PD153035), a potent inhibitor of the epidermal growth factor receptor*, J. Med. Chem., **39/1**, 267-276, (1996)
- [139] N. N.: *IressaTM*, Drugs of the Future, **27/4**, 339-345, (2002)
- [140] N. N.: *Erlotinib Hydrochloride*, Drugs of the Future, **27/10**, 923-934, (2002)
- [141] Woodburn, J. R.: *The epidermal growth factor receptor and its inhibition in cancer therapy*, Pharmacological Therapy, **82**, 241-250, (1999)
- [142] Rusnack, D. W.; Affleck, K.; Cockerill, S. G.; Stubberfield, C.; Harris, R.; Page, M.; Smith, K. J.; Guntrip, S. B.; Carter, M. C.; Shaw, R. J.; Jowett, A.; Stables, J.; Topley, P.; Wood, E. R.; Brignola, P. S.; Kadwell, S. H.; Reep, B. R.; Mullin, R. J.; Alligood, K. J.; Keith, B. R.; Crosby, R. M.; Murray, D. M.; Knight, W. B.; Gilmer, T. M.; Lackey, K.: *The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: Potential therapy for cancer*, Cancer Research, **61**, 7196-7203, (2001)
- [143] Christensen, J. G.; Schreck, R. E.; Chan, E. et al.: *High levels of HER-2 expression alter the ability of epidermal growth factor receptor (EGFR) family tyrosine kinase inhibitors to inhibit EGFR phosphorylation in vivo*, Clinical Cancer Research, **7**, 4230-4238, (2001)
- [144] Moyer, J. D.; Barbacci, E. G.; Iwata, K. K. et al.: *Induction of apoptosis and cell cycle arrest by CP 358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase*, Cancer Research, **42**, 4838-4848, (1997)
- [145] Tsou, H.-R.; Mamuya, N.; Johnson, B. D.; Reihc, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn, F. E.; Greenberger, L. M.; Wang, Y.-F.; Wissner, A.: *6-Substituted-4-(3-bromophenylamino)quinazolines as Putative Irreversible Inhibitors of the Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor (HER-2) Tyrosine Kinases with Enhanced Antitumor Activity*, J. Med. Chem.; **44/3**, 2719-2734, (2001)
- [146] Ignar-Teowbridge, D.M.; Nelson, K. G.; Bidwell, M. C.; Curtis, S. W.; Washburn, T. F.; McLachlan, J. A.; Korach, K. S.: *Coupling of dual signalling pathways: Epidermal growth factor action involves the estrogen receptor*, Proc. Natl. Acad. Sci., **89**, 4658-4662, (1992)

-
- [147] Nicholson, R. I.; Gee, J. M. W.; Barrow, D.; McClelland, R. A.: *Endocrine resistance in breast cancer can involve a switch towards EGFR signaling pathway and a gain of sensitivity to an EGFR-selective tyrosine kinase inhibitor, ZD1839*, Clin. Cancer Res., **5** (Abstr. 740), (1999)
- [148] Fry, D. W.; Bridges, A. J.; Denny, W. A.; Doherty, A.; Greis, K.; Hicks, J. L.; Hook, K. E.; Keller, P. R.; Leopold, W. R.; Loo, J.; McNamara, D. J.; Nelson, J. M.; Sherwood, V.; Smaill, J. B.; Trumpp-Kallmeyer, S.; Dobrusin, E. M.: *Specific irreversible inactivation of the epidermal growth factor receptor and erbB2, by a unique class of tyrosine kinase inhibitor*, Proceedings of the National Academy of Sciences, USA, **95**, 12022, (1998)
- [149] Bridges, A. J.; Denny, W. A.; Dobrusin, E. M.; Doherty, A. M.; Fry, D. W.; McNamara, D. J.; Showalter, H. D. H.; Smaill, J. B.; Zhou, H.: *Irreversible inhibitors of tyrosine kinases*, World patent application, WO 9738983, (1997)
- [150] Bridges, A. J.: *Irreversible inhibitor of tyrosine kinases*, World patent application, WO 9906378, (1999)
- [151] Smaill, J. B.; Palmer, B. D.; Rewcastle, G. W.; Denny, W. A.; McNamara, D. J.; Dobrusin, E. M.; Bridges, A. J.; Zhou, H.; Showalter, H. D. H.; Winters, R. T.; Leopold, W. R.; Fry, D. W.; Nelson, J. M.; Slintak, V.; Elliot, W. L.; Roberts, B. J.; Vincent, P. W.; Patmore, S. J.: *Tyrosine kinase inhibitors 15. 4-(Phenylamino)chinazoline- and 4-(Phenylamino)pyrido[2,3-d]pyrimidine-6-acrylamides as irreversible inhibitors of the ATP binding site of the epidermal growth factor receptor*, J. Med. Chem., **42/10**, 1803-1815, (1999)
- [152] Smaill, J. B.; Rewcastle, G. W.; Loo, J. A.; Chan, O. H.; Reyner, E. L.; Lipka, E.; Showalter, H. D. H.; Fry, D. W.; Sherwood, V.; Nelson, J. M.; Denny, W. A.: *Tyrosine kinase inhibitors 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[2,3-d]pyrimidine-6-acrylamides bearing additional solubilizing functions*. J. Med. Chem., **43/7**, 1380-1397, (2000)
- [153] Tsou, H.-R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn, F. E.; Greenberger, L. M.; Wang, Y.-F.; Wissner, A.: *6-Substituted-4-(3-bromophenylamino)-chinazolines as Putative Irreversible Inhibitors of the Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor*

- (*Her-2*) Tyrosine Kinase with Enhanced Antitumor Activity, *J. Med. Chem.*, **44/17**, 2719-2734, (2001)
- [154] Fry, D. W.: *Site-directed irreversible inhibitors of the erbB family of receptor tyrosine kinases as novel chemotherapeutic agents for cancer*, *Anti-Cancer Drug Design*, **15**, 3-16, (2000)
- [155] Bridges, A. J.: *Chemical Inhibitors of Protein Kinases*, *Chem. Rev.*, **101**, 2541-2571, (2001)
- [156] Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B., Jr.; Greenberger, L. M.; Gruber, B. C.; Johnson, B. D.; Mamuya, N.; Nilakantan, R.; Reich, M. F.; Shen, R.; Tsou, H.-R.; Upeslakis, E.; Wang, Y.-F.; Wu, B.; Ye, F.; Zhang, N.: *4-Anilino-6,7-dialkoxychinolin-3-carbonitrile Inhibitors of Epidermal Growth Factor Receptor (EGFR) Kinase and Their Bioisosteric Relationship to the 4-Anilino-6,7-dialkoxychinazoline Inhibitors*. *J. Med. Chem.*, **43/17**, 3244-3256, (2000)
- [157] Smaill, J. B.; Hollis-Showalter, H. D.; Zhou, H.; Bridges, A. J.; McNamara, D. J.; Fry, D. W.; Nelson, J. M.; Sherwood, V.; Vincent, P. W.; Roberts, B. J.; Elliot, W. L.; Denny, W. A.: *Tyrosine kinase Inhibitors 18. 6-Substituted 4-Anilinoquinazolines and 4-Anilinopyrido[3,4-d]pyrimidines as Soluble, Irreversible Inhibitors of the Epidermal Growth Factor Receptor*, *J. Med. Chem.*, **44/3**, 429-440, (2001)
- [158] Sirotnak, F. M.; Zakowski, M. F.; Miller, V. A.; Scher, H. I.; Kris, M.: *Efficacy of Cytotoxic Agents against Human Tumor Xenografts Is Markedly Enhanced By Coadministration of ZD1839 (Iressa), an Inhibitor of EGFR Tyrosine Kinase*, *Clin. Canc. Res.*, **6**, 4885-4892, (2000)
- [159] Rao, G. S.; Murray, S.; Ethier, S. P.: *Radiosensitization of human breast cancer cells by a novel ErbB family receptor tyrosine kinase inhibitor*, *Int. J. Radiat. Oncol. Biol. Phys.*, **48/5**, 1519-1522, (2000)
- [160] Braude, E. A.; Jackman, L. M.; Linstead, R. P.: *Hydrogen Transfer. Part II. The Dehydrogenation of 1:4-Dihydronaphthalene by Quinones. Kinetic and Mechanism*, *J. Chem. Soc.*, 3548-3563, (1954)
- [161] Braude, E. A.; Jackman, L. M.; Linstead, R. P.: *Hydrogen Transfer. Part XII. Dehydrogenation of "Blocked" Hydroaromatic Compounds by Quinones*, *J. Chem. Soc.*, 3123-3132, (1960)
- [162] Rocek, J.; Müller, P.: *Oxidations of Hydroaromatic Systems. II. 2,3-Dichloro-5,6-dicyanobenzoquinone*, *J. Amer. Chem. Soc.*, **94**, 2716-2719, (1972)

-
- [163] Probst, R.: *5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-1,2- und 1,4-Anthrachinonderivate als potente 5-Lipoxygenase-Inhibitoren*, Dissertation, Freie Universität Berlin, (1999)
- [164] Smith, B. M.; March, J.: *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, John Wiley & Sons Inc., New York, 5.Ed., 242, (2001)
- [165] Sustmann, R.; Korth, H.-G.: *The Captodative Effect*, Adv. Phys. Org. Chem., **26**, 131-178, (1990)
- [166] Viehe, H. G.; Janousek, Z.; Merenyi, R.; Stella, L.: *The Captodative Effect*, Acc. Chem. Res., **18**, 148-154, (1985)
- [167] Schlosser, M. J.; Shurina, R. D.; Kalf, G. F.: *Prostaglandin H Synthase Catalyzed Oxidation of Hydrochinone to a Sulfhydryl-Binding and DANN-Damaging Metabolite*, Chem. Res. Toxicol., **3**, 333-339, (1990)
- [168] Testa, B.: *The Metabolism of drugs and other xenobiotics*, Acad. Press, London, Chapter 10: Reactions catalysed by peroxidases, 346-375, (1995)
- [169] Pfeifer, S.; Pflugel, P.; Borchert, H. -H.: *Grundlagen der Biopharmazie, Pharmakokinetik, Bioverfügbarkeit, Biotransformation*, Verlag Chemie, Weinheim, 220, 224-225, (1984)
- [170] Günther, G.: *NMR-Spektroskopie*, Georg Thieme Verlag, Stuttgart, 192-198, (1992)
- [171] S. Bergemann, persönliche Mitteilung
- [172] Schmidt, K.: *Struktur-Wirkungs-Studien an estrogen wirksamen 1,2-Diarylethanderivaten sowie an antitumoraktiven Acetylenhexacarbonyl-dikobaltkomplexen*, Dissertation, Freie Universität Berlin, (2000)
- [173] Geissler, J. F.; Traxler, P.; Regenass, U.; Murray, B. J.; Roesel, J. L.; Meyer, T.; McGlynn, E.; Storni, A.; Lydon, N. B.: *Thiazolidine-diones: Biochemical and biological activity of a novel class of tyrosine protein kinase inhibitors*, J. Biol. Chem., **265**, 22255-22261, (1990)
- [174] Wedegartner, P. S.; Gill, G. N.: *Activation of the purified protein tyrosine kinase domain of the epidermal growth factor receptor*, J. Biol. Chem., **264**, 11346-11353, (1989)
- [175] Yaish, P.; Gazit, A.; Golin, C.; Levitzki, A.: *Blocking of EGF-dependent cell proliferation by EGF receptor tyrosine kinase inhibitors*, Science, **242**, 933-935, (1988)
- [176] Lin, A. (MDS Pharma Services, Taiwan R.O.C.), Mitteilung