

1. Record Nr.	UNINA9910141339303321
Titolo	Polypharmacology in drug discovery // edited by Jens-Uwe Peters
Pubbl/distr/stampa	Hoboken, N.J., : Wiley, c2012
ISBN	1-280-58932-9 9786613619150 1-118-09813-7 1-118-09814-5 1-118-09812-9
Edizione	[1st ed.]
Descrizione fisica	1 online resource (544 p.)
Altri autori (Persone)	PetersJens-Uwe
Disciplina	615.19
Soggetti	Drugs - Design Polypharmacy
Lingua di pubblicazione	Inglese
Formato	Materiale a stampa
Livello bibliografico	Monografia
Note generali	Description based upon print version of record.
Nota di bibliografia	Includes bibliographical references and index.
Nota di contenuto	Machine generated contents note: List of contributors. Preface. Introduction: the case for polypharmacology Andrew L. Hopkins Part A: Polypharmacology - a safety concern in drug discovery. 1 The relevance of off-target polypharmacology Bruce D. Car 2 Screening for safety-relevant off-target activities Laszlo Urban, Steven Whitebread, Jacques Hamon, Dmitri Mikhailov and Kamal Azzaoui 2.1 Introduction. 2.2 General aspects. 2.3 Selection of off-targets. 2.4 In silico approaches to off-target profiling .2.5 Summary and conclusions. 3 Pharmacological promiscuity and molecular propertiesJens-Uwe Peters 3.1 Introduction: pharmacological promiscuity in the history of drug discovery. 3.2 Lipophilicity. 3.3 Molecular weight. 3.4 Ionisation state. 3.5 Other molecular descriptors and structural motifs. 3.6 Implications for drug discovery. 4 Kinases as antitargets in genotoxicity Stephan Kirchner 4.1 Protein Kinases and inhibitor-binding sites. 4.2 Cyclin-Dependent Kinases (CDKs) controlling unregulated cell proliferation. 4.3 Mitotic kinases as guardians protecting cells from aberrant chromosome segregation. 5 Activity at cardiovascular ion channels: a key issue for drug discoverylan M. Bell, Mark T. Bilodeau and Armando A. Lagrutta 5.1 Introduction. 5.2 Screening methods. 5.3 Structural insights into

the interaction between drugs and CV ion channels. 5.4 Medicinal Chemistry approaches. 5.5 Conclusion. 6 Prediction of side effects based on fingerprint profiling and data mining Jacques Migeon 6.1 Introduction to BioPrint. 6.2 The pharmacological fingerprint. 6.3 Antidepressant example. 6.4 Profile similarity at non-therapeutic targets. 6.5 Interpreting the polypharmacology profile. 6.6 Methods. 6.7 Patterns of activity. 6.8 Integrating function profile data with traditional pharmacological binding data. 6.9 Analysis of the antifungal tioconazole. 6.10 Conclusions. Part B: Polypharmacology - an opportunity for drug discovery. 7 Polypharmacological drugs - "magic shotguns" for psychiatric diseases Wesley K. Kroeze and Bryan L. Roth 7.1 Introduction. 7.2 Definition. 7.3 The discovery and extent of promiscuity among psychiatric drugs. 7.4 Why are so many psychiatric drugs promiscuous? 7.5 Conclusions. 8 Polypharmacological kinase inhibitors: new hopes for the therapy of cancer Annalisa Petrelli 8.1 Targeted therapies: a new era in the treatment of cancer. 8.2 The single-targeted therapy. 8.3 From single to multi-targeted drugs in cancer therapy. 8.4 Polypharmacology kinase inhibitors in clinical practice and under development. 8.5 Concluding remarks. 9 Polypharmacology as an emerging trend in antibacterial discovery Lynn L. Silver 9.1 Introduction. 9.2 Classical antibacterial polypharmacology. 9.3 New approaches to multi-targeted single pharmacophores. 9.4 Synthetic lethals. 9.5 Hybrid molecules. 9.6 Conclusions. 10 A "magic shotgun" perspective on anticonvulsant mechanisms Matt T. Bianchi and Kathy Chuang 10.1 Introduction. 10.2 Anticonvulsant mechanism. 10.3 Defining promiscuity. 10.4 Promiscuity: lessons from endogenous signaling. 10.5 Promiscuity: lessons from anticonvulsant electrophysiology. 10.6 Use of anticonvulsants in disorders other than epilepsy. 10.7 Experimental and theoretical support for a "Magic Shotgun" approach. 10.8 Current multi-target strategies. 10.9 Practical considerations. 10.10 Conclusion. 11 Selective Optimization of Side Activities (SOSA): a promising way for drug discovery Thierry Langer and Camille-Georges Wermuth 11.1 Introduction. 11.2 Definition and principle. 11.3 Rationale of SOSA. 11.4 Establishing the SOSA approach. 11.5 A successful example of the SOSA approach. 11.6 Other examples of SOSA switches. 11.7 Discussion. 11.8 Computer-assisted design using pharmacophores. 11.9 Conclusions. Part C: Selected approaches to polypharmacological drug discovery 12 Selective multi-targeted drugs Richard Morphy 12.1 Introduction. 12.2 Lead Generation. 12.3 Lead optimization. 12.4 Case studies. 12.5 Summary. 13 Computational multitarget drug discovery Jeremy A. Horst, Adrian Laurenzi, Brady Bernard and Ram Samudrala 13.1 Introduction. 13.2 The pharmacologic hunt of yester year. 13.3. Established technological advancements. 13.4. Computational drug discovery. 13.5. Recent technical improvements. 13.6. Emerging concepts. 13.7 Summary. 14 Behavior-based screening as an approach to polypharmacological ligands Dani Brunner, Vadim Alexandrov, Barbara Caldarone, Taleen Hanania, David Lowe, Jeff Schneider and Jayaraman Chandrasekhar 14.1 The Challenges of CNS Drug Discovery. 14.2 In vivo high throughput screening. 14.3 Screening libraries of compounds. 14.4 Relationship between molecular properties and in vivo CNS activity. 14.5 Following screening hits in secondary assays. 14.6 Potential therapeutic value of dual adenosine compounds. 14.7 Summary. 15 Multicomponent Therapeutics Alexis A. Borisy, Grant R. Zimmermann and Joseph Lehar 15.1 Introduction. 15.2 Drug synergies are statistically more context dependent. 15.3 How a synergistic mechanism can lead to therapeutic selectivity. 15.4 Discussion. Part D: Case studies 16 The discovery of sunitinib as a multitarget treatment of cancer Catherine Delbaldo,

Camelia Colichi, Marie-Paule Sablin, Chantal Dreyer, Bertrand Billefont, Sandrine Faivre and Eric Raymond 16.1 A brief introduction to tumor angiogenesis. 16.2 The discovery of sunitinib: from drug design to first evidences of clinical activity. 16.3 Pharmacology of sunitinib. 16.4 Safety of sunitinib. 16.5 Activity of Sunitinib. 16.6 Surrogate imaging techniques to capture vascular changes. 16.7 Surrogate biomarkers. 16.8 Conclusion. 17 Antipsychotics Claus Riemer 17.1 Definition and diagnosis of schizophrenia. 17.2 Etiology and pathophysiology of schizophrenia. 17.3 Epidemiology. 17.4 Medical practice and treatment options. 17.5 Case studies. 17.6 CATIE. 17.7 Conclusions. 18 Triple Uptake Inhibitors ("Broad Spectrum" Antidepressants) Phil Skolnick 18.1 Introduction. 18.2 What is the rationale for developing triple uptake inhibitors as antidepressants? 18.3 Preclinical data. 18.4 Clinical data. 18.5 Concluding remarks. 19 Therapeutic potential of small molecules modulating the cyclooxygenase and 5-lipoxygenase pathway Stefan Laufer and Wolfgang Albrecht 19.1 Targets of the eicosanoid pathway. 19.2 Rationale for development of dual inhibitors of the cyclooxygenase and 5-lipoxygenase pathway. 19.3 Dual inhibitors of the cyclooxygenase and 5-lipoxygenase pathway. 19.4 Development of Licofelone. 19.5 Conclusions. 20 Drug research leading to imatinib and beyond to nilotinib Paul W. Manley and Jurg Zimmermann 20.1 Introduction. 20.2 Historical background. 20.3 BCR-ABL1 as the molecular target for CML therapy. 21 Towards antimalarial hybrid drugs Bernard Meunier 22 Multitarget drugs for the treatment of Alzheimer's disease Andrea Cavalli and Maria Laura Bolognesi 22.1 Introduction. 22.2 Case studies. 22.3 Conclusions and perspectives. 23 Carbonic anhydrases: off-targets, add-on activities, or emerging novel targets? Claudiu Supuran 23.1 Introduction. 23.2 Carbonic anhydrase inhibition. 23.3 Topiramate and zonisamide, antiepileptics with potent antiobesity action. 23.4 Sulfonamide coxibs with antitumor activity due to CA IX/XII inhibition. 23.5 Sulfamates with steroid sulfatase and carbonic anhydrase inhibitory action as anticancer agents in clinical development. 23.6 Lacosamide, an antiepileptic with a strange binding mode to Cas. 23.7 The protein tyrosine kinase inhibitors imatinib and nilotinib strongly inhibit several mammalian CA isoforms. 23.8 Conclusions.

Sommario/riassunto

"Covers the two-sided nature of polypharmacology--its contribution to adverse drug reactions and its benefit in certain therapeutic drug classes. Addresses the important topic of polypharmacology in drug discovery, a subject that has not been thoroughly covered outside of scattered journal articles Overviews state-of-the-art approaches and developments to help readers understand concepts and issues related to polypharmacology"--Provided by publisher.
