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Nota di contenuto	Antitargets; Contents; List of Contributors; Preface; I General Aspects; 1 Why Drugs Fail - A Study on Side Effects in New Chemical Entities; 1.1 Introduction; 1.2 Drugs Withdrawn from the Market between 1992 and 2006 Listed Alphabetically; 1.2.1 Amineptine; 1.2.2 Aminophenazone (Aminopyrine); 1.2.3 Astemizole; 1.2.4 Bromfenac Sodium; 1.2.5 Cerivastatin; 1.2.6 Chlormezanone; 1.2.7 Fenfluramine and Dexfenfluramine; 1.2.8 Flosequinan; 1.2.9 Glafenine; 1.2.10 Grepafloxacin; 1.2.11 Levacetylmethadol; 1.2.12 Mibefradil; 1.2.13 Rapacuronium Bromide; 1.2.14 Rofecoxib; 1.2.15 Temafloxacin 1.2.16 Troglitazone1.2.17 Ximelagatran; 1.3 Borderline Cases; 1.4 Investigational Drugs That Failed in Clinical Phases from 1992 to 2002; 1.4.1 A Case Study: Fialuridine; 1.4.2 A Recent Case Study: Torcetrapib; 1.4.3 General Reasons for Project Failing in Clinical Phases I-III; 1.5 Strategies for Avoiding Failure; 1.6 An Unusual Case: The Revival of

Thalidomide; References; 2 Use of Broad Biological Profiling as a Relevant Descriptor to Describe and Differentiate Compounds: Structure-In Vitro (Pharmacology-ADME)-In Vivo (Safety) Relationships; 2.1 Introduction
2.1.1 Biological Profiling/Fingerprints and Drug Discovery Applications2.1.2 Polypharmacology of Drugs; 2.2 The BioPrint(®) Approach; 2.2.1 BioPrint(®) - General; 2.2.2 BioPrint(®) Assay Selection and Profile Description; 2.2.3 Compounds in BioPrint(®); 2.2.4 BioPrint (®) In Vivo Data sets; 2.2.4.1 Compound Details; 2.2.4.2 ADR Data; 2.2.4.3 Pharmacokinetics; 2.2.4.4 Toxicity Data; 2.3 Structure-In Vitro Relationships; 2.3.1 Similarity, Chemotypes - What Is a Biologically Relevant Descriptor?; 2.3.2 Using Biological Fingerprints as a Meaningful Descriptor for Drug Leads and Candidates
2.3.2.1 Differentiation of Leads2.3.2.2 Analysis of Attrited Compounds; 2.3.3 Structural versus Experimental Differentiation - Dependence on Structure-Derived Descriptor Used; 2.3.4 Predictive Models from Pharmacological Data; 2.3.5 Predictive Models from ADME Data - BioPrint(®) Learnings; 2.4 Chemogenomic Analysis - Target-Target Relationships; 2.5 In Vitro-In Vivo Relationships - Placing Drug Candidates in the Context of BioPrint(®); 2.5.1 Analyzing Potential ADR Liabilities Based on Individual Hits; 2.5.2 Analyzing Potential ADR Liabilities Based on Profile Similarity
2.6 A Perspective for the FutureReferences; II Antitargets: Ion Channels and GPCRs; 3 Pharmacological and Regulatory Aspects of QT Prolongation; 3.1 Introduction; 3.2 hERG: Target Versus Antitarget; 3.3 Pharmacology of QT Prolongation; 3.3.1 Multiple Mechanisms Leading to QT Prolongation; 3.3.2 hERG as the Key Mechanism for the Drug-Induced Long QT Syndrome; 3.3.3 Pharmacogenetic Aspects; 3.4 Significance of Drug-Induced QT Prolongation; 3.4.1 Prolonged QT/QTc and Occurrence of TdP; 3.4.2 Dose-Response Relationship for QT Prolongation; 3.5 Regulatory Aspects of QT Prolongation
3.5.1 Regulatory Guidance Documents

Sommario/riassunto

This practice-oriented handbook surveys current knowledge on the prediction and prevention of adverse drug reactions related to off-target activity of small molecule drugs. It is unique in collating the current approaches into a single source, and includes several highly instructive case studies that may be used as guidelines on how to improve drug development projects.With its large section on ADME-related effects, this is key knowledge for every drug developer.