

CONTENTS

Preface.....	1
Introduction.....	3

FIRST PART AUTOMATED PHARMACOLOGICAL SCREENING

Chapter 1 - The pharmacological screening process: the small molecule, the biological target, the robot, the signal and the information	7
<i>Eric MARÉCHAL - Sylvaine ROY - Laurence LAFANECHÈRE</i>	
1.1. Introduction	7
1.2. The screening process: technological outline.....	8
1.2.1. Multi-well plates, robots and detectors	8
1.2.2. Consumables, copies of chemical libraries and storage	10
1.2.3. Test design, primary screening, hit-picking, secondary screening	10
1.3. The small molecule: overview of the different types of chemical library	12
1.3.1. The small molecule	12
1.3.2. DMSO, the solvent for chemical libraries.....	12
1.3.3. Collections of natural substances	12
1.3.4. Commercial and academic chemical libraries.....	14
1.4. The target, an ontology to be constructed	14
1.4.1. The definition of a target depends on that of a bioactivity.....	14
1.4.2. Duality of the target: molecular entity and biological function	15
1.4.3. An ontology to be constructed	16
1.5. Controls	17
1.6. A new discipline at the interface of biology, chemistry and informatics: chemogenomics	17
1.7. Conclusion.....	18
1.8. References	19

Chapter 2 - Collections of molecules for screening: example of the French National Chemical Library	23
<i>Marcel HIBERT</i>	
2.1. Introduction	23
2.2. Where are the molecules to be found?	25
2.3. State of progress with the European Chemical Library	27
2.4. Perspectives.....	28
2.5. References	28

Chapter 3 - The miniaturised biological assay: constraints and limitations	29
<i>Martine KNIBIEHLER</i>	
3.1. Introduction	29
3.2. General procedure for the design and validation of an assay	30
3.2.1. Choice of assay.....	31
3.2.2. Setting up the assay	33
3.2.3. Validation of the assay and automation	35
3.3. The classic detection methods.....	36
3.4. The results	36
3.4.1. The signal measured: increase or decrease?.....	36
3.4.2. The information from screening is managed on three levels	37
3.4.3. Pharmacological validation	40
3.5. Discussion and conclusion	40
3.6. References	41
Chapter 4 - The signal: statistical aspects, standardisation, elementary analysis	43
<i>Samuel WIECZOREK</i>	
4.1. Introduction	43
4.2. Normalisation of the signals based on controls.....	44
4.2.1. Normalisation by the percentage inhibition	44
4.2.2. Normalisation resolution	44
4.2.3. Aberrant values	46
4.3. Detection and correction of measurement errors	48
4.4. Automatic identification of potential artefacts.....	49
4.4.1. Singularities.....	49
4.4.2. Automatic detection of potential artefacts	50
4.5. Conclusion.....	52
4.6. References	52
Chapter 5 - Measuring bioactivity: Ki, IC50 and EC50	55
<i>Eric MARÉCHAL</i>	
5.1. Introduction	55
5.2. Prerequisite for assaying the possible bioactivity of a molecule: the target must be a limiting factor	55
5.3. Assaying the action of an inhibitor on an enzyme under Michaelian conditions: Ki	56
5.3.1. An enzyme is a biological catalyst.....	57
5.3.2. Enzymatic catalysis is reversible.....	57
5.3.3. The initial rate, a means to characterise a reaction.....	59
5.3.4. Michaelian conditions	59
5.3.5. The significance of Km and Vmax in qualifying the function of an enzyme ..	60
5.3.6. The inhibited enzyme: Ki	60
5.4. Assaying the action of a competitive inhibitor upon a receptor: IC50.....	62
5.5. Relationship between Ki and IC50: the CHENG-PRUSOFF equation.....	63
5.6. EC50: a generalisation for all molecules generating a biological effect (bioactivity)	64
5.7. Conclusion.....	64
5.8. References	65

Chapter 6 - Modelling the pharmacological screening: controlling the processes and the chemical, biological and experimental information.....	67
<i>Sylvaine ROY</i>	
6.1. Introduction	67
6.2. Needs analysis by modelling.....	68
6.3. Capture of the needs	69
6.4. Definition of the needs and necessity of a vocabulary common to biologists, chemists and informaticians	69
6.5. Specification of the needs	69
6.5.1. Use cases and their diagrams	70
6.5.2. Activity diagrams	72
6.5.3. Class diagrams and the domain model	73
6.6. Conclusion.....	78
6.7. References	78
Chapter 7 - Quality procedures in automated screening.....	79
<i>Caroline BARETTE</i>	
7.1. Introduction	79
7.2. The challenges of quality procedures.....	79
7.3. A reference guide: the ISO 9001 Standard.....	80
7.4. Quality procedures in five steps	82
7.4.1. Assessment	82
7.4.2. Action plan - planning	83
7.4.3. Preparation	83
7.4.4. Implementation.....	83
7.4.5. Monitoring.....	83
7.5. Conclusion.....	84
7.6. References	84

SECOND PART

HIGH-CONTENT SCREENING AND THE STRATEGIES FOR CHEMICAL GENETICS

Chapter 8 - Phenotypic screening of cells and the strategies for direct chemical genetics..	87
<i>Laurence LAFANECHÈRE</i>	
8.1. Introduction	87
8.2. The traditional genetics approach: from phenotype to gene and from gene to phenotype	88
8.2.1. Phenotype	88
8.2.2. Forward and reverse genetics	89
8.3. Chemical genetics	89
8.4. Chemical libraries for chemical genetics	90
8.4.1. Chemical library size.....	91
8.4.2. Concentration of molecules.....	91
8.4.3. Chemical structure diversity.....	91
8.4.4. Complexity of molecules	93

8.4.5. Accessibility of molecules to cellular compartments	93
8.4.6. The abundance of molecules	94
8.4.7. The possibility of functionalizing the molecules	94
8.5. Phenotypic tests with cells	94
8.6. Methods to identify the target	96
8.7. Conclusions	99
8.8. References	99

Chapter 9 - High information content screens for forward (phenotypic screening of organisms) and reverse (structural screening by NMR) chemical genetics 103

Benoît DÉPREZ

9.1. Introduction	103
9.2. Benefits of high-content screening.....	104
9.2.1. Summarised comparison of high-throughput screening and high-content screening	104
9.2.2. Advantages of high-content screening for the discovery of novel therapeutic targets	104
9.2.3. The nematode <i>Caenorhabditis elegans</i> : a model organism for high-content screening.....	105
9.2.4. Advantages of high-content screening for reverse chemical genetics and the discovery of novel bioactive molecules	108
9.3. Constraints linked to throughput and to the large numbers	110
9.3.1. Know-how	110
9.3.2. Miniaturisation, rate and robustness of the Assays	110
9.3.3. Number, concentration and physicochemical properties of small molecules .	111
9.4. Types of measurement for high-content screening	111
9.4.1. The critical information needed for screening	111
9.4.2. Raw, numerical results	111
9.4.3. Results arising from expert analyses	112
9.5. Conclusion.....	112
9.6. References	112

Chapter 10 - Some principles of Diversity-Oriented Synthesis..... 113

Yung-Sing WONG

10.1. Introduction	113
10.2. Portrait of the small molecule in DOS	114
10.3. Definition of the degree of diversity (DD).....	116
10.3.1. Degree of diversity of the building block	116
10.3.2. Degree of stereochemical diversity	118
10.3.3. Degree of regiochemical diversity	119
10.3.4. Degree of skeletal diversity.....	121
10.4. Divergent multi-step DOS by combining elements of diversity	124
10.5. Convergent DOS: condensation between distinct small molecules	127
10.6. Conclusion.....	130
10.7. References	130

THIRD PART**TOWARDS AN IN-SILICO EXPLORATION OF CHEMICAL AND BIOLOGICAL SPACE**

Chapter 11 - Molecular descriptors and similarity indices	143
<i>Samia ACI</i>	
11.1. Introduction	143
11.2. Chemical formulae and computational representation	144
11.2.1. The chemical formula: a representation in several dimensions	145
11.2.2. Molecular information content	145
11.2.3. Molecular graph and connectivity matrix	147
11.3. Molecular descriptors	148
11.3.1. 1D descriptors	149
11.3.2. 2D descriptors	149
11.3.3. 3D descriptors	152
11.3.4. 3D versus 2D descriptors?	154
11.4. Molecular similarity	155
11.4.1. A brief history	155
11.4.2. Properties of similarity coefficients and distance indices	155
11.4.3. A few similarity coefficients	156
11.5. Conclusion	156
11.6. References	158
Chapter 12 - Lipophilicity of molecules: a predominant descriptor for QSAR	161
<i>Gérard GRASSY - Alain CHAVANIEU</i>	
12.1. Introduction	161
12.2. History	161
12.3. Theoretical foundations and principles of the relationship between the structure of a small molecule and its bioactivity	162
12.3.1. QSAR, QPAR and QSPR	162
12.3.2. Basic equation of a QSAR study	163
12.4. Generalities about lipophilicity descriptors	163
12.4.1. Solubility in water and in lipid phases: conditions for bioavailability	163
12.4.2. Partition coefficients	164
12.4.3. The partition coefficient is linked to the chemical potential	164
12.4.4. Thermodynamic aspects of lipophilicity	165
12.5. Measurement and estimation of the octanol/water partition coefficient	166
12.5.1. Measurement methods	166
12.5.2. Prediction methods	168
12.5.3. Relationship between lipophilicity and solvation energy: LSER	171
12.5.4. Indirect estimation of partition coefficients from values correlated with molecular lipophilicity	171
12.5.5. Three-dimensional approach to lipophilicity	173
12.6. Solvent systems other than octanol/water	174
12.7. Electronic parameters	175
12.7.1. The HAMMETT parameter, σ	175
12.7.2. SWAIN and LUPTON parameters	176

12.8. Steric descriptors	177
12.9. Conclusion.....	177
12.10. References	177

Chapter 13 - The annotation and classification of chemical space in chemogenomics 179*Dragos HORVATH*

13.1. Introduction	179
13.2. From the medicinal chemist's intuition to a formal treatment of structural information	179
13.3. Mapping structural space: predictive models.....	182
13.3.1. Mapping structural space	182
13.3.2. Neighbourhood (similarity) models	183
13.3.3. Linear and non-linear empirical models	186
13.4. Empirical filtering of drug candidates.....	188
13.5. Conclusion.....	189
13.6. References	189

Chapter 14 - The annotation and classification of biological space in chemogenomics 193*Jordi MESTRES*

14.1. Introduction	193
14.2. Receptors.....	194
14.2.1. Definitions.....	194
14.2.2. Establishing the 'RC' nomenclature	195
14.2.3. Ion-channel receptors	196
14.2.4. G protein-coupled receptors	197
14.2.5. Enzyme receptors	198
14.2.6. Nuclear receptors	198
14.3. Enzymes	199
14.3.1. Definitions.....	199
14.3.2. The 'EC' nomenclature	200
14.3.3. Specialised nomenclature.....	201
14.4. Conclusion.....	201
14.5. References	202

Chapter 15 - Machine learning and screening data..... 205*Gilles BISSON*

15.1. Introduction	205
15.2. Machine learning and screening.....	207
15.3. Steps in the machine-learning process	210
15.3.1. Representation languages.....	211
15.3.2. Developing a training set	213
15.3.3. Model building	214
15.3.4. Validation and revision	215
15.4. Conclusion.....	217
15.5. References and internet sites	217

Chapter 16 - Virtual screening by molecular docking.....	221
<i>Didier ROGNAN</i>	
16.1. Introduction	221
16.2. The 3 steps in virtual screening.....	221
16.2.1. Preparation of a chemical library	221
16.2.2. Screening by high-throughput docking.....	224
16.2.3. Post-processing of the data.....	226
16.3. Some successes with virtual screening by docking.....	228
16.4. Conclusion.....	229
16.5. References	230

APPENDIX BRIDGING PAST AND FUTURE

Chapter 17 - Biodiversity as a source of small molecules for pharmacological screening: libraries of plant extracts.....	235
<i>Françoise GUERITTE, Thierry SEVENET, Marc LITAUDON, Vincent DUMONTET</i>	
17.1. Introduction	235
17.2. Plant biodiversity and North-South co-development.....	237
17.3. Plant collection: guidelines	238
17.4. Development of a natural-extract library	239
17.4.1. From the plant to the plate	239
17.4.2. Management of the extract library	239
17.5. Strategy for fractionation, evaluation and dereplication	241
17.5.1. Fractionation and dereplication process	241
17.5.2. Screening for bioactivities.....	243
17.5.3. Some results obtained with specific targets	244
17.5.4. Potential and limitations.....	247
17.6. Conclusion.....	248
17.7. References	248
Glossary	249
Authors	261