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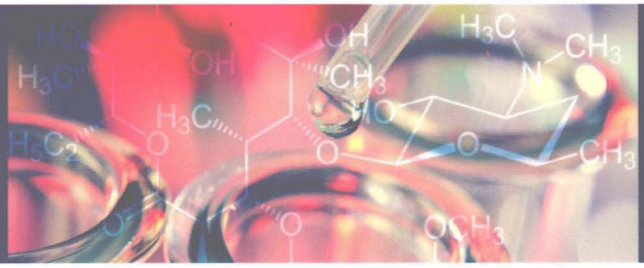
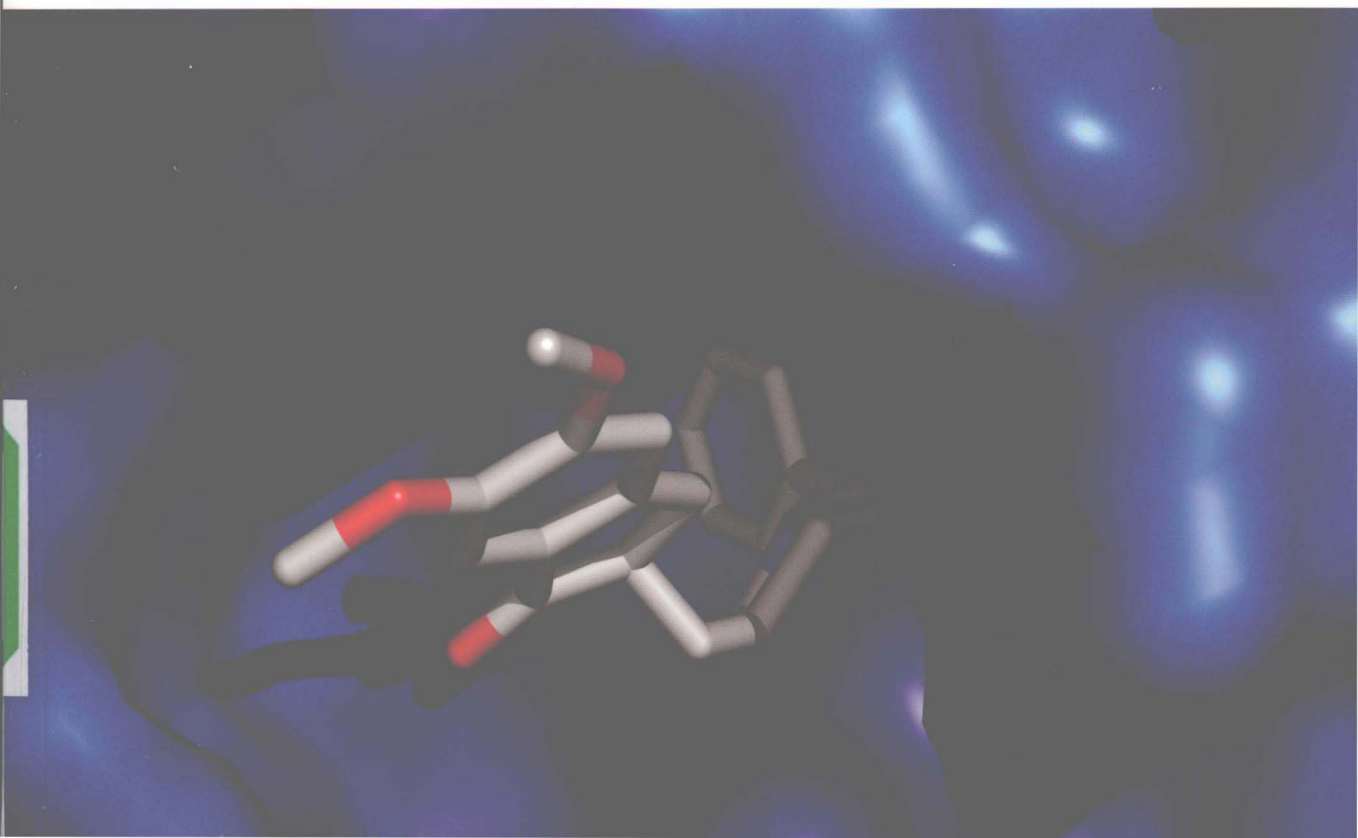
AN INTRODUCTION TO DRUG SYNTHESIS



GRAHAM L. PATRICK



An Introduction to

Drug Synthesis

Graham L. Patrick

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An Introduction to Drug Synthesis

Preface

This text is written for undergraduates and postgraduates who have a basic grounding in organic chemistry and are studying a module or degree in a chemistry-related field such as medicinal chemistry. It attempts to convey, in a readable and interesting style, an understanding about some of the issues and strategies relating to drug synthesis. In particular, the book aims to show the importance of organic synthesis to various aspects of the drug discovery process. For example, the kind of synthetic route chosen for a particular drug has an important bearing on what kind of analogues can be synthesized. These analogues can be used to study structure–activity relationships, as well as helping us to identify structures with improved activities and properties. Synthesis is also crucial to the economic and practical feasibility of manufacturing drugs on a commercial scale. Consequently, the book is of particular interest to students who might be considering a future career in research and development in the pharmaceutical industry.

The book is divided into three parts.

Part A contains six chapters that provide some general background on medicinal chemistry and organic synthesis. The first chapter gives an overview of the process involved in getting a drug to market and the impact that organic synthesis has at various stages of that journey. It also defines various medicinal chemistry terms that are used throughout the other chapters.

Chapter 2 identifies the different types of reactions that are involved in a drug synthesis, highlighting the importance of five general categories—coupling reactions, functional group transformations, functionalizations, functional group removals, and the use of protecting groups. Throughout the chapter, simple examples of drug syntheses are provided to illustrate these different reaction categories, and how the structure of a target compound has a crucial impact on the complexity of the overall synthesis.

Chapters 3–5 are overviews of retrosynthesis, cyclization reactions, and the synthesis of chiral compounds, where the emphasis is on explaining the key principles of these topics and relating them to the synthesis of important drug structures.

Finally, Chapter 6 describes the role of combinatorial and parallel synthesis in drug synthesis.

There are also three case studies. Two of these look at reactions that are particularly important in drug synthesis. Case study 1 considers the role of protecting groups and coupling agents in peptide synthesis, while case study 2 provides an overview of palladium-catalysed coupling reactions. Case study 3 provides an example of how retrosynthesis is used in designing a synthesis. In this case, the target structure is a natural product called huperzine A, which has interesting pharmacological properties.

Part B contains five chapters that describe how synthesis impacts on various stages of the drug design and development process. Chapter 7 focuses on the synthesis of novel structures as potential lead compounds in medicinal chemistry, whereas Chapter 8 looks at synthetic approaches to the analogues of known active compounds.

Chapter 9 covers synthetic and semi-synthetic approaches to the synthesis of medicinally important natural products and their analogues, and also describes how biosynthesis and genetic engineering has been used to generate such compounds.

Chapter 10 describes chemical and process development, and identifies many of the key issues that have to be considered in the synthesis of drugs on a commercial scale.

Finally, Chapter 11 describes the synthesis of isotopically labelled drugs, and the uses of such drugs in therapy, diagnosis, and scientific study.

A case study on gliotoxin provides an example of the use of radiolabelling studies to determine the biosynthesis of an important natural product.

Part C contains three chapters that focus on the design, synthesis, and activities of particular antibacterial agents. Chapters 12 and 13 describe tetracyclines and macrolides, respectively, while Chapter 14 describes different synthetic approaches to quinolones and fluoroquinolones.

In addition to the three main parts of the textbook, there are several appendices that summarize many of the most commonly used reactions in drug synthesis. Further information about these reactions is provided in the Online Resource Centre, as explained in the guide to the book that follows.

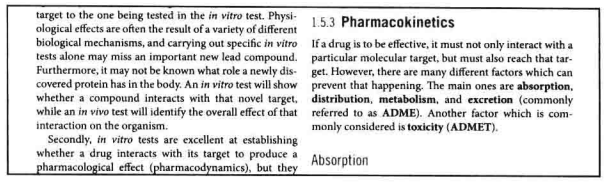
G. L. P.
June 2014

About the book

An Introduction to Drug Synthesis and its Online Resource Centre contain many learning features which will help you to understand this fascinating subject. This section explains how to get the most out of these features.

Emboldened key words

Terminology is emboldened within the main text and defined in a glossary at the end of the book, helping you to become familiar with the language of drug synthesis.



target to the one being tested in the *in vitro* test. Physiological effects are often the result of a variety of different biological mechanisms, and carrying out specific *in vitro* tests alone may miss an important new lead compound. Furthermore, it may not be known what role a newly discovered protein has in the body. An *in vitro* test will show whether a compound interacts with that novel target, while an *in vivo* test will identify the overall effect of that interaction on the organism.

Secondly, *in vitro* tests are excellent at establishing whether a drug interacts with its target to produce a pharmacological effect (pharmacodynamics), but they

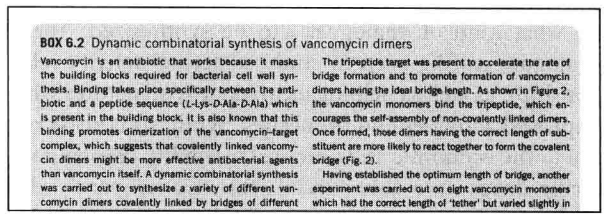
1.5.3 **Pharmacokinetics**

If a drug is to be effective, it must not only interact with a particular molecular target, but must also reach that target. However, there are many different factors which can prevent that happening. The main ones are **absorption, distribution, metabolism,** and **excretion** (commonly referred to as **ADME**). Another factor which is commonly considered is **toxicity (ADMET)**.

Absorption

Boxes

Boxes are used to present in-depth material and to explore how the concepts of drug synthesis are applied in practice.



BOX 6.2 Dynamic combinatorial synthesis of vancomycin dimers

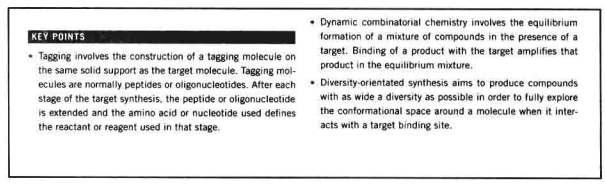
Vancomycin is an antibiotic that works because it masks the building blocks required for bacterial cell wall synthesis. Binding takes place specifically between the antibiotic and a peptide sequence (*L*-Lys-*D*-Ala-*D*-Ala) which is present in the building block. It is also known that this binding promotes dimerization of the vancomycin–target complex, which suggests that covalently linked vancomycin dimers might be more effective antibacterial agents than vancomycin itself. A dynamic combinatorial synthesis was carried out to synthesize a variety of different vancomycin dimers covalently linked by bridges of different

The tripeptide target was present to accelerate the rate of bridge formation and to promote formation of vancomycin dimers having the ideal bridge length. As shown in Figure 2, the vancomycin monomers bind the tripeptide, which encourages the self-assembly of non-covalently linked dimers. Once formed, those dimers having the correct length of substituent are more likely to react together to form the covalent bridge (Fig. 2).

Having established the optimum length of bridge, another experiment was carried out on eight vancomycin monomers which had the correct length of 'tether' but varied slightly in

Key points

Summaries at the end of major sections within chapters highlight and summarize key concepts, and provide a basis for revision.

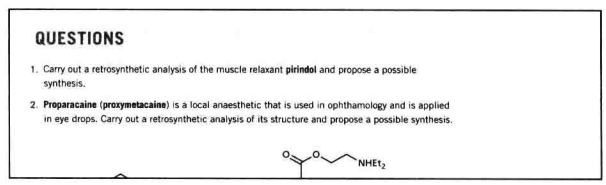


KEY POINTS

- Tagging involves the construction of a tagging molecule on the same solid support as the target molecule. Tagging molecules are normally peptides or oligonucleotides. After each stage of the target synthesis, the peptide or oligonucleotide is extended and the amino acid or nucleotide used defines the reactant or reagent used in that stage.
- Dynamic combinatorial chemistry involves the equilibrium formation of a mixture of compounds in the presence of a target. Binding of a product with the target amplifies that product in the equilibrium mixture.
- Diversity-orientated synthesis aims to produce compounds with as wide a diversity as possible in order to fully explore the conformational space around a molecule when it interacts with a target binding site.

Questions

End-of-chapter questions allow you to test your understanding and apply concepts presented in the chapter to solve the problems presented to you.

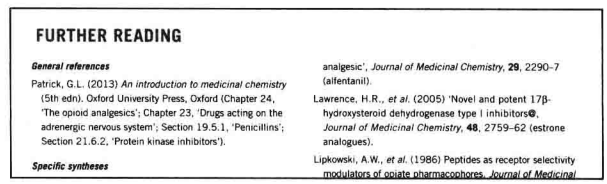


QUESTIONS

1. Carry out a retrosynthetic analysis of the muscle relaxant **pirindol** and propose a possible synthesis.
2. **Proparacaine (proxymetacaine)** is a local anaesthetic that is used in ophthamology and is applied in eye drops. Carry out a retrosynthetic analysis of its structure and propose a possible synthesis.

Further reading

Selected references allow you to easily research those topics that are of particular interest to you.



FURTHER READING

General references

Patrick, G.L. (2013) *An introduction to medicinal chemistry* (5th edn). Oxford University Press, Oxford (Chapter 24, 'The opioid analgesics'; Chapter 23, 'Drugs acting on the adrenergic nervous system'; Section 19.5.1, 'Penicillins'; Section 21.6.2, 'Protein kinase inhibitors').

Specific syntheses

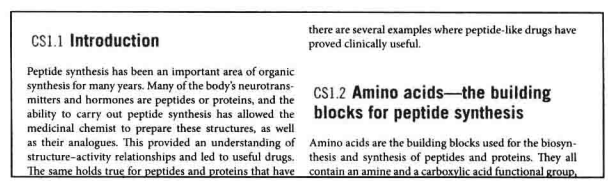
analgesic', *Journal of Medicinal Chemistry*, **29**, 2290–7 (alfentanil).

Lawrence, H.R., *et al.* (2005) 'Novel and potent 17β-hydroxysteroid dehydrogenase type I inhibitors', *Journal of Medicinal Chemistry*, **48**, 2759–62 (estrone analogues).

Lipkowski, A.W., *et al.* (1986) Peptides as receptor selectivity modulators of opiate pharmacophores. *Journal of Medicinal*

Case studies

Case studies within several chapters and at the end of Parts A and B demonstrate the practical application of drug synthesis by exploring the synthesis of a number of drugs in detail.



CS1.1 **Introduction**

Peptide synthesis has been an important area of organic synthesis for many years. Many of the body's neurotransmitters and hormones are peptides or proteins, and the ability to carry out peptide synthesis has allowed the medicinal chemist to prepare these structures, as well as their analogues. This provided an understanding of structure–activity relationships and led to useful drugs. The same holds true for peptides and proteins that have

there are several examples where peptide-like drugs have proved clinically useful.

CS1.2 **Amino acids—the building blocks for peptide synthesis**

Amino acids are the building blocks used for the biosynthesis and synthesis of peptides and proteins. They all contain an amine and a carboxylic acid functional group,

Appendix

There are seven appendices which summarize many of the most commonly used reactions in drug synthesis.

Appendix 1

Functional group transformations

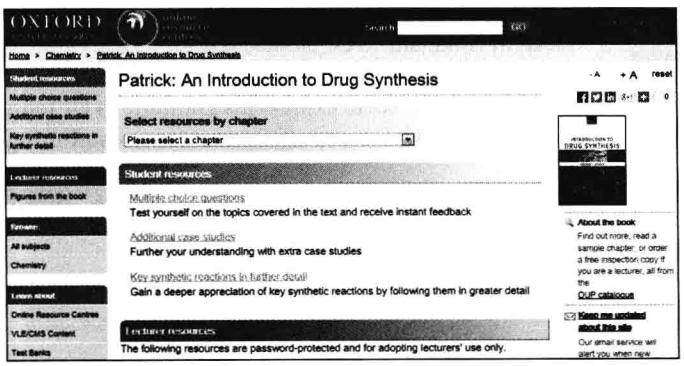
There are a large number of possible functional group transformations (FGTs) in organic synthesis. The following are examples of the most commonly used FGTs in

drug synthesis. Further details on each reaction are available in the book's Online Resource Centre.

About the Online Resource Centre

Online Resource Centres provide students and lecturers with ready-to-use teaching and learning resources to augment the printed book.

You will find the material to accompany *An Introduction to Drug Synthesis* at:
www.oxfordtextbooks.co.uk/orc/patrick_synth/



Student resources

Multiple-choice questions
Test yourself on the topics covered in the text and receive instant feedback.

Additional case studies
Further your understanding with extra case studies.

Key synthetic reactions in further detail
Gain a deeper appreciation of key synthetic reactions by following them in greater detail.

Lecturer resources

For registered adopters of the book

Figures from the book
All of the figures from the textbook are available to download electronically for use in lectures and handouts.

Acknowledgements

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Abbreviations and acronyms

aa	amino acid
Ac	acetyl
7-ACA	7-aminocephalosporinic acid
AcCl	acetyl chloride
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
Ac_2O	acetic anhydride
ACP	acyl carrier protein
AD	Alzheimer's disease
ADH	aldehyde dehydrogenase
ADHD	attention deficit hyperactivity disorder
ADME	absorption, distribution, metabolism, excretion
ADMET	absorption, distribution, metabolism, excretion, toxicity
ADP	adenosine 5′-diphosphate
AIDS	acquired immune deficiency syndrome
AMD	amorphadiene synthase
AMP	adenosine 5′-monophosphate
cAMP	cyclic adenosine 5′-monophosphate
amu	atomic mass unit
6-APA	6-aminopenicillanic acid
AT	acyltransferase
ATP	adenosine 5′-triphosphate
BBB	blood–brain barrier
BINAP	2,2′-bis(diphenylphosphino-1, 1′-binaphthyl)
BnBr	Benzyl bromide
Boc	*tert*-butyloxycarbonyl
Boc anhydride or $(Boc)_2O$	di-*t*-butyl dicarbonate
BOP	(benzotriazol-1-yloxy) tris(dimethylamino)phosphonium hexafluorophosphate
***n*-Bu**	*n*-butyl
***t*-Bu**	*tertiary*-butyl
cbz	benzyloxycarbonyl or carboxybenzyl
CDI	*N,N*′-carbonyldiimidazole
CHIRAPHOS	bis(diphenylphosphino)butane
Clog*P*	calculated logarithm of the partition coefficient
CNS	central nervous system
CoA	coenzyme A
COD	cyclooctadiene
COX	cyclooxygenase
cyclic AMP	cyclic adenosine 5′-monophosphate
CYP	cytochrome P450
DAGO or DAMGO	[D-Ala^2,MePhe^4,Glyol^5]enkephalin
DAST	diethylaminosulphur trifluoride
dba	dibenzylidene acetone
DBTA	dibenzoyl tartaric acid monohydrate
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexylurea
DEAD	diethyl azodicarboxylate
DEBS	6-deoxyerythronolide B synthase
DET	diethyl tartrate
DH	dehydratase
DIBAL or DIBAL-H	diisobutylaluminium hydride
DIC	*N,N*′- diisopropylcarbodiimide
DIOP	*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	ethane-1,2-diylbis[(2-methoxyphenyl) phenylphosphane]
DIPC	*N,N*′-diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DIU	diisopropylurea
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulphoxide
DNA	deoxyribonucleic acid
DOR	delta opioid receptor
DPDPE	tyr-c(D-Pen-Gly-Phe-D-Pen)
DPP-4	dipeptidyl peptidase-4
EC_{50}	concentration of drug required to produce 50% of the maximum possible effect
EDC or EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
EDU	1-ethyl-3-(3-dimethylaminopropyl)urea
ee	enantiomeric excess

EGF	epidermal growth factor
EGF-R	epidermal growth factor receptor
EMEA	European Agency for the Evaluation of Medicinal Products
ER	enoyl reductase
Et	ethyl
F-SPE	fluorous solid phase extraction
FDA	US Food and Drug Administration
^{18}F-FDG	[^{18}F]fluorodeoxyglucose
FG	functional group
FGI	functional group interconversion
FGT	functional group transformation
Fmoc	fluorenylmethyloxycarbonyl
Fmoc-Cl	fluorenylmethyloxycarbonyl chloride
FPP	farnesyl pyrophosphate
F-SPE	fluorous solid phase extraction
FT	farnesyl transferase
G-protein	guanine nucleotide binding protein
GABA	γ-aminobutyric acid
GABA-R	benzodiazepine receptor
GCP	Good Clinical Practice
GDP	guanosine 5′-diphosphate
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMP	guanosine 5′-monophosphate
GTP	guanosine 5′-triphosphate
H-R	histamine receptor
HATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HFC-134a	1,1,1,2-tetrafluoroethane
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
17β-HSD1	17β-dehydroxysteroid dehydrogenase type 1
HTS	high throughput screening
IC_{50}	concentration of drug required to inhibit a target by 50%
$^{d}Ipc_2BCl$	d-enantiomer of diisopinocampheylchloroborane
$^{l}Ipc_2BCl$	l-enantiomer of diisopinocampheylchloroborane
$IpcBH_2$	diisopinocampheylborane
K_d	binding affinity or dissociation binding constant
K_i	inhibition constant
KIE	kinetic isotope effect
$KN(TMS)_2$	potassium bis(trimethylsilyl)amide
KOR	kappa opioid receptor
KR	ketoreductase
KS	ketosynthase enzyme
LDA	lithium diisopropylamide
LDH	lactate dehydrogenase
LiHMDS or $LiN(TMS)_2$	lithium bis(trimethylsilyl)amide
Log*P*	logarithm of the partition coefficient
LUMO	lowest unoccupied molecular orbital
M-receptor	muscarinic receptor
MAA	Marketing Authorization Application
MAOS	microwave-assisted organic synthesis
mcpba	*meta*-chloroperbenzoic acid
Me	methyl
MIBK	methyl isobutyl ketone (4-methylpentan-2-one)
MOR	mu opioid receptor
mRNA	messenger RNA
Ms	mesyl
MsCl	methanesulphonyl chloride
MWt	molecular weight
N-Receptor	nicotinic receptor
NAD or NADH	nicotinamide adenine dinucleotide
NADP or NADPH	nicotinamide adenine dinucleotide phosphate
$NaN(TMS)_2$	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCE	new chemical entity
NDA	New Drug Application
$NH(TMS)_2$	bis(trimethylsilyl)amine
$Ni(cod)_2$	bis(cyclooctadiene)nickel(0)
$Ni(dppp)Cl_2$	dichloro(1,3-bis(diphenylphosphino) propane)nickel
NIS	*N*-iodosuccinimide
NME	new molecular entity
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance

NNRTI	non-nucleoside reverse transcriptase inhibitor
nor-BNI	norbinaltorphimine
NRPS	non-ribosomal peptide synthase
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVOC	nitroveratryloxycarbonyl
P	partition coefficient
PBS	phosphate-buffered saline
Pd/C	palladium charcoal catalyst
$Pd_2(dba)_3$	tris(dibenzylideneacetone) dipalladium(0)
PEG	polyethylene glycol
PET	positron emission tomography
Ph	phenyl
PI	protease inhibitor
PKS	polyketide synthase
PLP	pyridoxal phosphate
PMP	1,2,2,6,6-pentamethylpiperidine
PPA	polyphosphoric acid
PPE	polyphosphoric ethyl ester
PPI	proton pump inhibitor
PPts	pyridinium *para*-toluenesulphonate or pyridinium 4-toluenesulphonate
PTFE	polytetrafluoroethylene
$P(o\text{-}Tol)_3$	tri(*o*-tolyl)phosphine
ptsa	*para*-toluenesulphonic acid
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
PyBrOP	bromotripyrrolidinophosphonium hexafluorophosphate
Q-phos	pentaphenyl(di-*tert*-butylphosphino) ferrocene
R	symbol used to represent the rest of the molecule
Rapid	random peptide integrated discovery
RedAl or Red-Al	sodium bis(2-methoxyethoxy) aluminiumhydride
RNA	ribonucleic acid
rRNA	ribosomal RNA
SAR	structure–activity relationships
SCAL	safety catch acid-labile linker
SOP	standard operating procedure
SPA	scintillation proximity assay
SPE	solid phase extraction
SPECT	single photon emission computer tomography
SSRI	selective serotonin reuptake inhibitor
TBAF	tetrabutylammonium fluoride
TBDMS or TBS	*tert*-butyldimethylsilyl
TCA	tricyclic antidepressant
TFA	trifluoroacetic acid
TfOH	triflic acid or trifluorosulphonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMSCN	trimethylsilyl cyanide
$(TMS)_2NLi$	lithium bis(trimethylsilyl)amide
TMSOMe	methoxytrimethylsilane
T_2O	tritiated water
o-Tol	*ortho*-tolyl
Tris	tris(hydroxymethyl)aminomethane
Tris-HCl	tris hydrochloride
tRNA	transfer RNA
TsCN	*para*-toluenesulphonyl cyanide or 4-toluenesulphonyl cyanide
TsDAEN	*N*-[2-amino-1,2-bis(4-methoxyphenyl) ethyl]-4-methylbenzenesulphonamide
UTI	urinary tract infection
Vdw	van der Waals
Voc-Cl	vinyloxycarbonyl chloride
X	halogen or leaving group
Z	benzyloxycarbonyl

Brief contents

Detailed contents