1
Introduction

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The cyclic nucleotide phosphodiesterases (PDEs) are a group of regulatory enzymes that affect intracellular signaling by inactivating the second messengers cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) to the corresponding nucleotides (Figure 1.1). The PDEs are critical in maintaining levels of these cyclic nucleotides within the narrow tolerances required for normal cell operation.

The superfamily of PDEs is encoded by 21 different genes that are grouped into 11 subfamilies according to primary sequence homology, composition of the N-terminal regulatory domain, and inhibitor sensitivity. The family has also been split into three sets based on their substrate preferences (Table 1.1). In addition, more than 60 splice variants have been reported.

Signal transduction cascades regulated by the PDEs are diverse and include a multitude of central and peripheral processes, such as cell proliferation and cell death, neuroplasticity, gene activation, insulin reaction, locomotion, neurotransmission, metabolism, vascular smooth muscle contraction and growth, and olfactory, taste, and visual responses. Pharmacological intervention of these signaling cascades through selective PDE inhibition is of great therapeutic interest for both central and peripheral targets.

The biological importance and druggability of these enzymes have led to market success with inhibitors for three of the PDE family members across multiple diseases (Table 1.2). The earliest examples include the PDE3 inhibitors amrinone and milrinone for cardiovascular indications, followed by PDE4 inhibitor roflumilast for severe chronic obstructive pulmonary disease. Unfortunately, both PDE3 and PDE4 inhibition result in highly undesirable side effects: sudden cardiac arrest and severe nausea, respectively. As a result, research into novel PDE inhibitors diminished in the late 1980s.

The commercial breakthrough for PDE inhibitors came from the discovery that the PDE5 inhibitor sildenafil was efficacious in the treatment of male erectile dysfunction. The approval of sildenafil under the brand name Viagra® was followed by the commercialization of closely related analogs, vardenafil (Levitra®/Staxyn®/Vivanza®) and tadalafil (Cialis®/Adcirca®). Two other sildenafil analogs (udenafil (Zydena®) and mirodenafil (Mvix®)) have been launched in some

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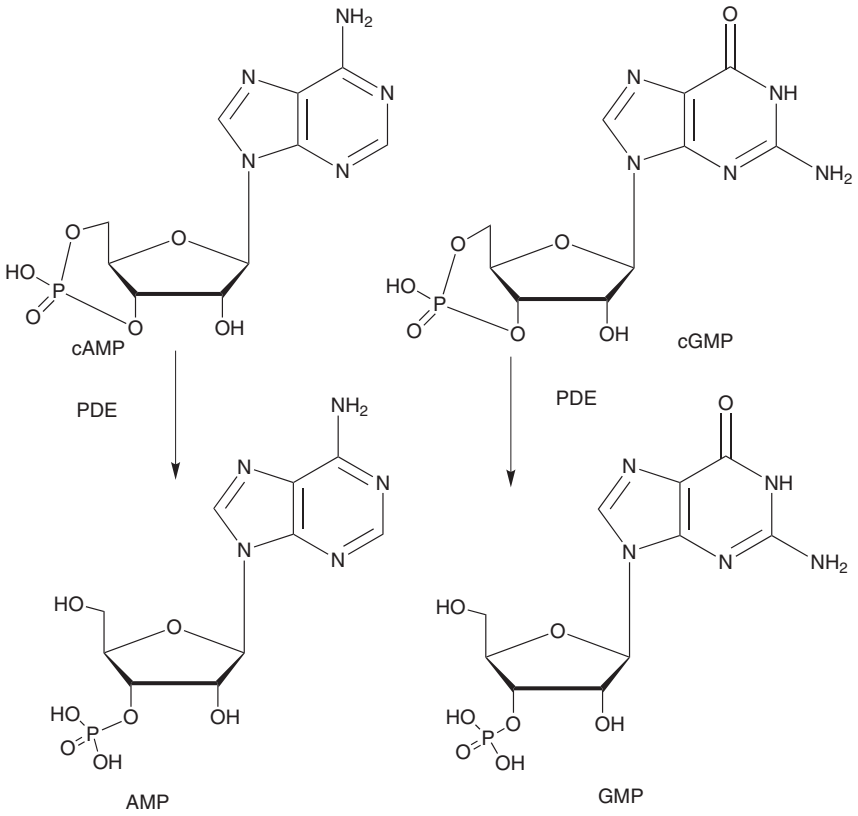


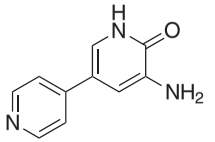
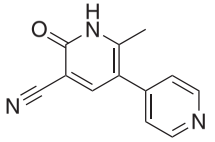
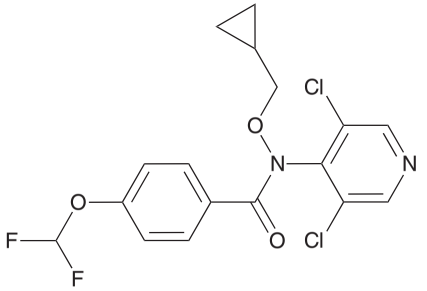
Figure 1.1 Hydrolysis of cyclic nucleotides by PDEs.

countries. A second generation of PDE5 inhibitors is still in development, with the most advanced example, avanafil (Stendra™), launched first in 2012. Sildenafil was also the first PDE5 inhibitor to be approved for the treatment of pulmonary hypertension (Revatio®), an indication closer to its original target, angina. Tadalafil is also approved for the treatment of pulmonary hypertension; in addition, it has been approved for benign prostatic hypertrophy.

Table 1.1 Substrate preferences of each class of PDE.

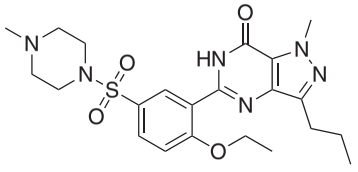
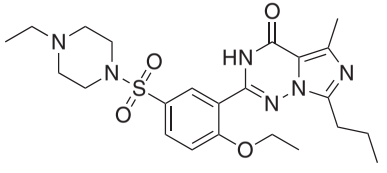
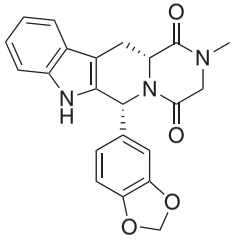
cAMP-specific	cGMP-specific	Mixed
PDE4	PDE5	PDE1
PDE7	PDE6	PDE2
PDE8	PDE9	PDE3
		PDE10
		PDE11

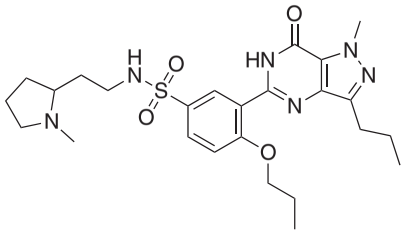
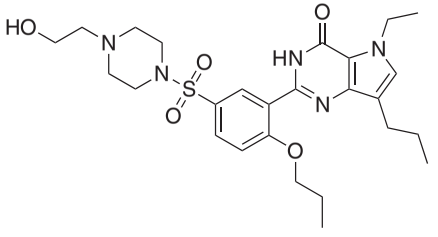
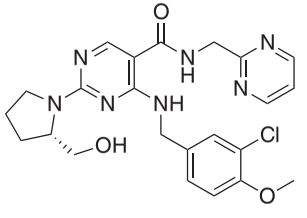
Table 1.2 Peak sales of PDE inhibitors, post-1997.

USAN	Structure	Launch date	Target	Indication	Peak sales ($, million)
Amrinone		1983	PDE3	Cardiotonic	20
Milrinone		1989	PDE3	Cardiotonic	228
Roflumilast		2010	PDE4	COPD	104

(*continued*)

Table 1.2 (*Continued*)

USAN	Structure	Launch date	Target	Indication	Peak sales ($, million)
Sildenafil		1998	PDE5	MED/PH	3119
Vardenafil		2003	PDE5	MED	517
Tadalafil		2003	PDE5	MED/PH/BPH	2222

Udenafil		2009	PDE5	MED	24
Mirodenafil		2009?	PDE5	MED	7.5
Avanafil		2012	PDE5	MED	2.4

Abbreviations: COPD: chronic obstructive pulmonary disease; MED: male erectile dysfunction; PH: pulmonary hypertension; BPH: benign prostatic hypertrophy.

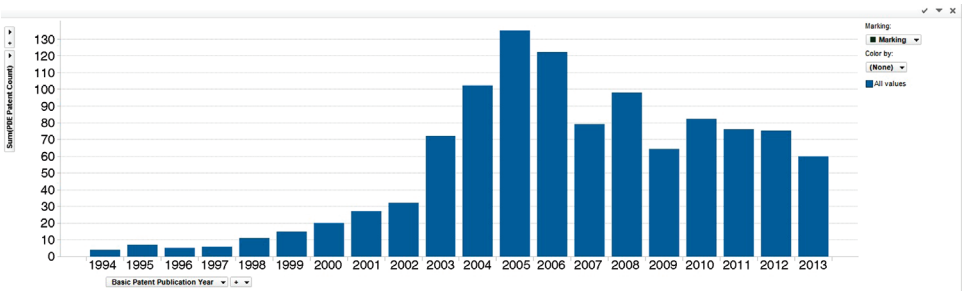


Figure 1.2 PDE inhibitor patent landscape 1994–2013 (*Data source*: Thomson_Reuters Integrity).

The discovery of clinical utility for PDE5 inhibitors triggered a renaissance in PDE research, leading to the identification of the last six subfamilies of PDEs. These included additional cGMP-hydrolyzing enzymes PDEs 6, 9, 10, and 11, which emerged as potential selectivity targets for the PDE5 inhibitors under development. PDE6 is located predominantly in the eye and remains undesirable off-target pharmacology, but the remainder are potential targets for alternative clinical indications. Pharmaceutical research in pursuit of selective PDE inhibitors for various conditions exploded in the 1990s and the field remains highly active today. In all, more than 1000 original patents for various PDEs have appeared in the literature since 1994. Patent activity peaked in 2004–2005 following the characterization and preclinical validation of targets including PDE10 (Chapter 4) and PDE9 (Chapter 7) and breakthroughs in structural biology and molecular modeling that enabled the generation of hypotheses that led to the discovery of selective PDE4 subtype inhibitors (Chapter 3). Since 2004 there has been a steady flow of more than 70 patents a year from major pharmaceutical companies, biotechnology firms, and academia (Figure 1.2). PDE4 and its subtypes, PDE10 and PDE5 (Chapter 2), have dominated patent activity for a broad spectrum of potential therapeutic indications, including schizophrenia, cognitive decline, vascular disease, and stroke, among others.

Although not yet resulting in clinical candidates that have advanced to proof-of-concept studies, several other PDEs have been explored by medicinal chemists in various companies. Recent advances in the field are summarized in separate chapters on PDE1 (Chapter 9), PDE2 (Chapter 5), PDE7 (Chapter 10), and PDE8 (Chapter 8). The only unexploited mammalian PDEs are PDE6 (due to known undesirable visual effects) and PDE11.

Although all of the approved agents target mammalian PDEs, there is evidence for the existence of PDE orthologs across the whole spectrum of eukaryotes including fungi and parasites. The PDEs from *Trypanosoma cruzi* and *Plasmodium falciparum*, the causative agents of Chagas disease and malaria, respectively, have received the most interest (Chapter 11).

All of the PDE inhibitors characterized to date have been shown to interact with the catalytic domain of their respective PDE. Despite there being only two substrates,

PDEs appear to be capable of tolerating a wide range of chemotypes as inhibitors, which in turn favors the identification of selective inhibitors, often through structure-aided drug design (Chapters 2 and 6). The first crystal structure reported of any PDE domain was that of the catalytic domain of PDE4B in 2000; this was the starting point for a host of structural studies in this important gene family. Crystal structures have been reported of the catalytic domains of PDE1, 2, 3, 4, 5, 7, 8, 9, and 10, by themselves or in complex with inhibitors, substrates, or products. Unfortunately, structural information on PDE regulatory domains is still lacking, and so far only PDE2 has a crystal structure with all its regulatory domains identified.

As a result of the large investment in the biology of PDEs, which occurred after the discovery and commercialization of sildenafil, today the clinical pipeline across the industry remains highly active. Currently, the clinical exploration of the therapeutic potential of numerous PDEs spans many disease areas, including psychiatry, neurology, inflammation, vascular disease, and respiratory diseases, among others. Some of the compounds that highlight the diversity of the current clinical pipeline include PDE4 inhibitors for inflammatory disorders (OCID-2987, Phase 2; GRC-4039, Phase 2). PDE4 inhibitors are also being evaluated for the treatment of cognitive disorders (HT-0712, Phase 2), as topical agents for atopic dermatitis (HT-0712, HT-0712, and AN-2898, all in Phase 2), and for the treatment of depression and anxiety (GSK-356278, Phase 1). The clinical pipeline is also populated with PDE10 inhibitors in various phases of clinical development for the treatment of schizophrenia and Huntington's disease (PF-2545920, Phase 2 for schizophrenia, Phase 1 for Huntington's disease; OMS-182410 and EVP-6308, both in Phase 1 for schizophrenia). PDE5 inhibitors are active in the clinical pipeline for many indications; worth highlighting is Pfizer's PF-00489791, currently in Phase 2 for renal disease. INDI-702 is a PDE3/5 inhibitor in Phase 3 clinical trials for the treatment of asthma, atherosclerosis, and intermittent claudication. Recently, PDE9, PDE2, and PDE1 inhibitors entered clinical trials for the treatment of cognitive disorders. Overall the diversity of this pipeline offers the promise of new drugs from this gene family.

The growth in PDE research had a profound impact on medicinal chemistry strategies and design principles, which the reader will appreciate in the subsequent chapters. Excellent application of structure-based drug design has been reported in the context of discovering the new generation of PDE inhibitors. Design principles for the use of conserved water have been developed; structural hypotheses for generating exquisitely selective agents have been explored and validated. Design principles that challenged legacy knowledge in terms of central nervous system penetration were developed, and new knowledge emerged that allowed medicinal chemists to expand design space for penetration and other tissue targeting.