Biochemical Pharmacology 98 (2015) 541–555

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

New paradigms in GPCR drug discovery

Kenneth A. Jacobson*

Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bldg. 8A, Rm. B1A-19, Bethesda, Maryland 20892, USA

ARTICLE INFO

Article history:
Received 12 June 2015
Accepted 5 August 2015
Available online 8 August 2015

Keywords:
Drug discovery
GPCR
X-ray crystallography
structure-based design
Signaling
Inhibitors

ABSTRACT

G protein-coupled receptors (GPCRs) remain a major domain of pharmaceutical discovery. The identification of GPCR lead compounds and their optimization are now structure-based, thanks to advances in X-ray crystallography, molecular modeling, protein engineering and biophysical techniques. In silico screening provides useful hit molecules. New pharmacological approaches to tuning the pleotropic action of GPCRs include: allosteric modulators, biased ligands, GPCR heterodimer-targeted compounds, manipulation of polypharmacology, receptor antibodies and tailoring of drug molecules to fit GPCR pharmacogenomics. Measurements of kinetics and drug efficacy are factors influencing clinical success. With the exception of inhibitors of GPCR kinases, targeting of intracellular GPCR signaling or receptor cycling for therapeutic purposes remains a futuristic concept. New assay approaches are more efficient and multidimensional: cell-based, label-free, fluorescence-based assays, and biosensors. Tailoring GPCR drugs to a patient's genetic background is now being considered. Chemoinformatic tools can predict ADME-tox properties. New imaging technology visualizes drug action in vivo. Thus, there is reason to be optimistic that new technology for GPCR ligand discovery will help reverse the current narrowing of the pharmaceutical pipeline.

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1. Introduction

G protein (heterotrimeric guanine nucleotide-binding protein)-coupled receptors (GPCRs), also known as 7 transmembrane helical (7TM) receptors, remain a major source of new pharmaceuticals and the focus of extensive research efforts in academia, government and pharma. Recent reviews cover the structural features of the receptors [1,2,17] and the chemical aspects of orthosteric [16,18] and allosteric [88] ligands.

Among the 19 approved drug products with the greatest sales revenues at their peak year in the period up to 2013, 7 are directed toward GPCRs (Table 1) [3]. That is equal to the number of biologic drugs (non-GPCR directed) in the same category of top earners. One of those GPCR drugs, the antithrombotic drug Plavix **1** (Fig. 1) and the highest in revenues during that period, serves as a prodrug that must be activated in the liver [4]. Other GPCR-related drugs in the blockbuster category, such as selective serotonin reuptake inhibitors (SSRIs), increase the synaptic availability of natural neurotransmitters that act at GPCRs. Since 2013, 15 GPCR-related drugs were approved as new chemical entities (NCEs) in 31 months, with exclusions as specified in Table 2. Among these NCEs, naloxegol **12** is a derivative of a known opioid receptor (OR) antagonist that is covalently linked to a short polyethylene glycol (PEG) chain to prevent its intestinal absorption; thus, it selectively blocks opiate receptors in the gut to prevent side effects of systemic opiates [5]. Several of these new drugs treat sleep

Abbreviations: cAMP, 3′,5′-cyclic adenosine monophosphate; ADP, adenosine 5′-diphosphate; GPCR, G protein-coupled receptor; TM, transmembrane helix; ERK, extracellular signal-regulated kinase; T4L, T-4 lysozyme; BRIL, thermostabilized apocytochrome b_{562}; StaRs, stabilized receptors; GRK, GPCR kinase; DREADD, designer receptor exclusively activated by designer drugs; NMR, nuclear magnetic resonance; RGS, regulator of G protein signaling; 5HT, 5-hydroxytrypamine (serotonin); PAM, positive allosteric modulator; NAM, negative allosteric modulator; GIP, glucose-dependent insulinotropic peptide; GLP, glucagon like peptide; GLP-R, glucagon-like peptide receptor; CRF-R, corticotropin-releasing factor receptor; DPP IV, dipeptidyl peptidase-4; GABA-R, γ-aminobutyric acid receptor; mGluR, metabotropic glutamate receptor; HF, heart failure; IL, intracellular loop; AT_1R, angiotensin receptor type 1; CCR2, chemokine receptor type 2; SKR, PEG; PET, positron emission tomography; PNA, peptide nucleic acid; SKR, structure-kinetics relationship; SSRI, selective serotonin reuptake inhibitor; NIH, National Institutes of Health (United States); OR, opioid receptor; BRET, bioluminescence resonance energy transfer; ADME, absorption; Tox, toxicology; CYP450, cytochrome-P450; SAR, structure activity relationship; SNP, single-nucleotide polymorphism; SPR, Surface Plasmon Resonance.

* Fax: +301 480 8422.
E-mail address: kajacobs@helix.nih.gov (K.A. Jacobson).

http://dx.doi.org/10.1016/j.bcp.2015.08.085
0006-2952/Published by Elsevier Inc.

Table 1
Top selling pharmaceuticals that act, directly or indirectly, via GPCRs (Peak Sales Year, as of 2013).[a]

Drug[b] (structure class)	Action	Treatment of:	Peak year sales (~billion $)
Clopidogrel 1 (thienopyridine)	$P2Y_{12}R$ antagonist (prodrug)	Thrombosis	9
Salmeterol 2 (phenylethanolamine)	b_2 adrenergic-R agonist	Asthma	8
Aripiprazole 3a (phenylpiperazine)	D_2 dopamine-R partial agonist	Psychosis	7
Quetiapine 4 (dibenzothiazepine-piperazine)	Antagonist, biogenic amine Rs	Psychosis	6
Valsartan 5 (tetrazolyl-biphenyl)	AT_1R antagonist	High blood pressure, congestive heart failure	6
Montelukast 6 (phenylvinyl-quinoline)	$CysLT_2R$ antagonist	Asthma, allergies	6
Olanzapine 7 (piperazinyl-benzodiazepine)	$5HT_2$ serotonin-R and D_2 dopamine-R antagonist	Psychosis	5

[a] Source of sales information: http://pharmamkting.blogspot.com/2013/01/lipitor-plavix-last-of-small-molecule.html.
[b] Structures shown in Fig. 1.

conditions: suvorexant **10** blocks two subtypes of the orexin receptor, which is a first drug in that category [6]. Approval of a melatonin receptor agonist, tasimelteon **13** followed several other approved drugs acting at the same GPCR [7].

The GPCR field is advancing rapidly, and new paradigms for GPCR drug discovery must be considered in the larger context of drug discovery. Drug discovery for GPCR targets has encountered many of the limitations associated with a changing paradigm for drug discovery in general, and there are many commentaries on why the pharmaceutical pipeline has narrowed [84]. Classical approaches to drug discovery have waning productivity; the linear, stepwise and iterative process through which new compounds

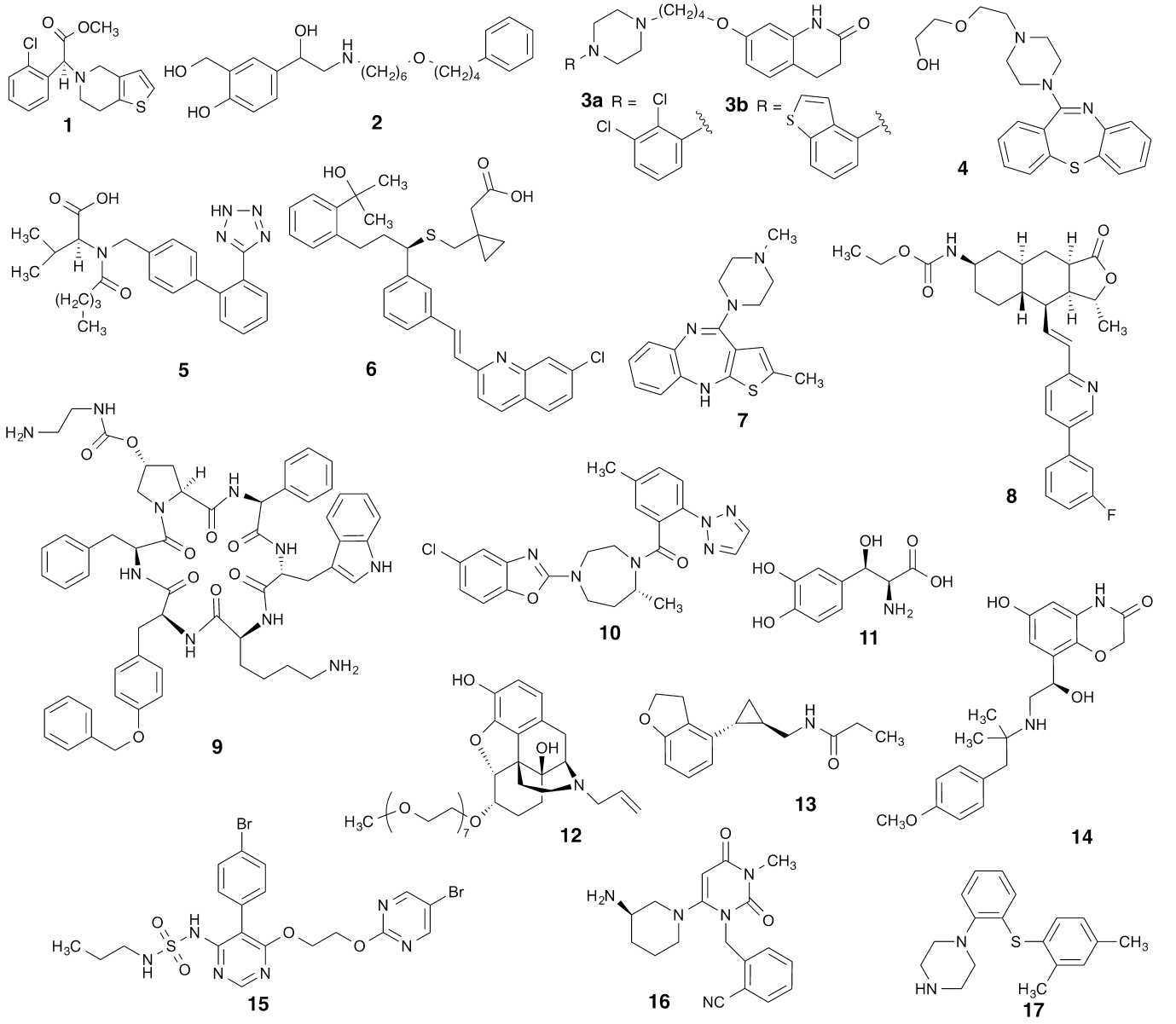

Fig. 1. The most successful small molecular GPCR ligands (**1**–**7**) as of 2013 and the small molecular GPCR ligands that have been approved since 2013 (**3b, 8**–**17**).