Pharmaceutical Chemistry of Antihypertensive Agents

Authors

György Szász, D.Sc.
Professor and Chairman
Institute of Pharmaceutical Chemistry
Semmelweis Medical University
Budapest, Hungary

Zsuzsanna Budvári-Bárány, M. Pharm.
Senior Lecturer
Institute of Pharmaceutical Chemistry
Semmelweis Medical University
Budapest, Hungary

CRC Press
Boca Raton Ann Arbor Boston

Library of Congress Cataloging-in-Publication Data

Szász, György.
Pharmaceutical chemistry of antihypertensive agents/authors, Görgy Szász, Zsuzsanna Budvári-Bárány.
p. cm.
Includes bibliographical references.
Includes index.
Contents: v. 1. Antihypertensive agents.
ISBN 0-8493-4724-6
1. Cardiovascular agents. 2. Hypotensive agents. 3. Pharmaceutical chemistry. I. Budvári-Bárány, Zsuzsanna. II. Title.
[DNLM: 1. Antihypertensive Agents. 2. Cardiovascular Agents. 3. Chemistry, Pharmaceutical. QV 150 S996p]
RS431.C25S93 1990
615'.71—dc20
DLC
for Library of Congress

90-2630
CIP

Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida 33431.

International Standard Book Number 0-8493-4724-6

Library of Congress Card Number 90-2630
Printed in the United States

Chapter 5

β-ADRENERGIC ANTAGONISTS (β-BLOCKERS)

I. INTRODUCTION

The β-adrenergic antagonists are commercially available as the water-soluble, absorbable salts of the nonsoluble or only slightly soluble bases. They behave as sympatholytics, i.e., they have the ability to interact with β-adrenergic receptors. The β-blocker compounds that are reasonably often used are to be found in the comprehensive Table 1; a few of them will be detailed in this chapter.

Unlike the agonists, the great majority of the β-blocker compounds may be regarded as 1,2-propanediol derivatives. Only sotalol has a skeleton resembling that of adrenergic agonists, including an ethanolamine moiety. On the basis of the elucidated relations, all those physical-chemical properties which are important in the *in vitro* and *in vivo* interactions of the β-blocker compounds can be deduced from the individual features of the main structural units of the molecules (Table 2).

II. PROPERTIES

The commercial salts of β-blocker agents (chloride, tartrate, maleate, etc.) are generally white or off-white odorless crystalline powders.

These salts are very soluble in water and alcohol. Depending upon their hydrophobicity, they may also be soluble in semi-polar solvents. Metoprolol tartrate (USP) is freely soluble in methylene chloride or chloroform, while propranolol hydrochloride (USP) is only slightly soluble, and timolol maleate (USP) sparingly soluble in chloroform. They are insoluble in ether or apolar solvents such as cyclohexane. Due to the poor water-solubility of their corresponding bases, their water-solubility, as expected, is pH-dependent. This may be illustrated by the data for pindolol:

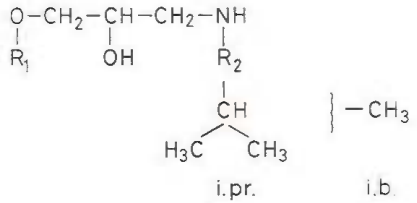
pH	1.5	5.2	7.5
parts of pindolol in 100 parts of water	2	0.03	0.001

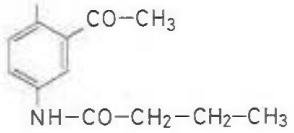
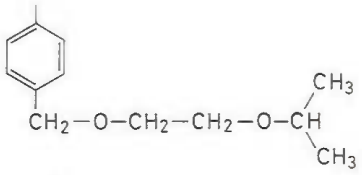
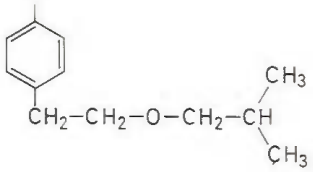
The octanol-water partition coefficients of the therapeutic β-blockers show a great variety,[1-3] there being a difference of several orders of magnitude between the values for the most hydrophobic and the most hydrophilic compounds (compare the P values of penbutalol, propranolol, and atenolol in Table 3). On this basis β-blockers may be grouped into three classes of lipophilicity.

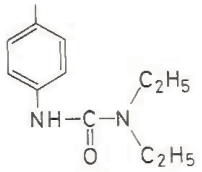
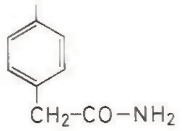
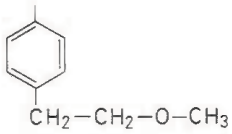
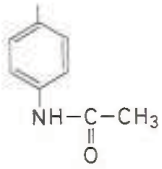
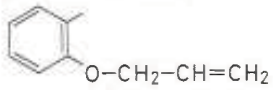
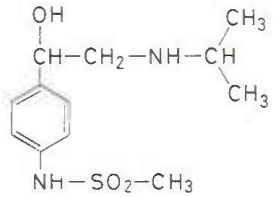
In spite of the often significant discrepancies between the values published for the same compounds by different authors, the octanol-water partition coefficient can be regarded as a good indicator of the predictable pharmacokinetic behavior of β-blocker molecules. The differences that may be encountered in the values for a given compound may stem from the different circumstances applied in the determination (pH of the aqueous phase, duration and temperature of equilibration, purity of the substance, etc.). However, the extremely different numerical values of the compounds in Table 3 arise from the different natures of the values. The data in column A are apparent partition coefficients, which relate to the partition of the protonated form of the compounds, while the much higher values in column B are true partition coefficients, which reflect the partition of the non-protonated (base) form.

A good correlation has been demonstrated between octanol-water partition coefficients

TABLE 1
β-Blockers in Therapeutic Use



Generic name	Chemical structure R_1	R_2	Proprietary name®	Therapeutic use	Doses
ctive β_1-receptor blocking agents					
cebutolol		i.pr.	IL-17803, Neptal, Prent, Sectral	Preferred in management of angina pectoris, hypertension, and cardiac arrhythmias. Reduces arterial pressure without reducing cardiac output. Exhibits intrinsic sympathomimetic activity (ISA), correlating with baseline plasma renin activity.	Maximum dose: 300—400 mg/day
isoprolol		i.pr.	Concor	Indicated in hypertension and angina pectoris. Does not exhibit any ISA properties.	Initial dose: 10 mg up to 20 mg once a day
etaxolol		i.pr.	Kerlone	Same as bisoprolol.	

eliprolol		i.b.	Selectol.	Has some ISA, β_2- and very slight α_2-receptor blocking effect. Indications similar to those of bisoprolol and betaxolol	Usual dose: 200—300 mg daily.
enolol		i.pr.	ICI 66082, Tenormin	Three times more potent than practolol. Used in management of hypertension alone or in combination with thiazide-type diuretics.	Initial dose: 50 mg/day (1 tablet) up to 100 mg/day.
letoprolol letoprolol artrate (USP)		i.pr.	Beloc, Betaloc, Lopressor, Selokeen	Has a preferential effect on β_1-adrenoreceptors, but inhibits β_2-receptors too, particularly in higher doses.	Initial dose: 100 mg/day (in single or divided doses) up to a maximum 450 mg/day.
actolol		i.pr.	Cordialine, Dabric, Eralex, Practol, Pralon, Teranol	Acts selectively on β_1-receptors of myocardium only. Therefore possesses fewer side effects than other β-blockers. Has some ISA.	Initial dose: 100 mg up to 400 mg/day.
-selective β-receptor (β_1 and β_2) blocking agents					
xprenolol		i.pr.	Coretal, Trasicor, Trazitensine	Intensity of β-blocking effect similar to that of propranolol. Indicated for all grades of hypertension. Does not cause orthostatic collapse, hypersensitivity, weakness, or fatigue. Cardioprotective. Combination with diuretics gives better hypotensive result and diminished side effects.	Usual dose: 2 × 80 mg/day
otalol			Beta-Cardone, Sotacor, Sotalex, Sotaper	Has screening effect against sympathomimetic stimulation, and weak negative inotropic and chronotropic effect. Indicated in therapy of hypertension, angina pectoris, and tachycardiac arrhythmia.	Usual dose: 300 mg/day

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.