MOLECULAR PHARMACOLOGY AN INTERNATIONAL JOURNAL

VOLUME 44 NUMBER 2 AUGUST 1993

FOUNDED BY AVRAM GOLDSTEIN-1965



A PUBLICATION OF THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS



Published by Williams & Wilkins

INFORMATION FOR SUBSCRIBERS

MOLECULAR PHARMACOLOGY (MOL/ISSN 0026-895X) is an official publication of The American Society for Pharmacology and Experimental Therapeutics and is published by Williams & Wilkins, 428 E. Preston St., Baltimore, MD 21202-3993. Second class postage paid at Baltimore, MD and at additional mailing offices. POSTMASTER: Send address changes to MOLECULAR PHARMACOLOGY, 428 E. Preston St., Baltimore, MD 21202-3993.

Frequency: Monthly: Two volumes a year beginning in January and July. Printed on acid-free paper.

Correspondence concerning business matters should be addressed to: Customer Service, Subscriptions, Williams & Wilkins, 428 E. Preston Street, Baltimore, MD 21202-3993. Telephone 1-800-638-6423 from anywhere in the U.S. and Canada. From other countries, call 410-528-8555. Fax: 410-528-8596.

Correspondence regarding editorial matters should be addressed to the Editor: Dr. T. Kendall Harden, Molecular Pharmacology, CB #7368, Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7368. Telephone: 919-966-3744. Fax: 919-966-4854.

For information on Society membership, contact: The American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814. Telephone: 301-530-7060. Fax: 301-530-7061.

Instructions to Authors appears in every issue.

Annual Subscription Rates: U.S.: Personal \$105; Institutional \$230; Single copy \$19. Outside the U.S., except Japan: Personal \$135; Institutional \$260; Single copy \$23.

Institutional (multiple reader) rate applies to libraries, schools, hospitals, clinics, group practices, and federal, commercial and private institutions and organizations.

For Japanese rates, please contact: Igaku-Shoin MYW Ltd., 3-23-14 Hongo, Bunkyo-Ku, Tokyo 113, JAPAN. Telephone: 03-5689-5400 or 5401. Fax: 03-5689-5402.

PRICES ARE SUBJECT TO CHANGE.

The GST number for Canadian subscribers is 123394371. Country of origin USA.

New subscriptions received before May 1st of each year will begin with the first issue of the year. Subscriptions received between May 1st and October 31st will start with the midyear issue (July). Subscriptions received after October 31st will start with the first issue of the following year. Subscriptions may start with any current volume's issue upon request.

Renewals should be done *promptly* to avoid a break in journal delivery. The publisher cannot guarantee to supply back issues on late renewals.

Change of address: The publisher must be notified 60 days in advance. Journals undeliverable because of incorrect address will be destroyed. Duplicate copies may be obtained, if available, from the publisher at the regular price of a single issue. Send address changes to MOLECULAR PHARMACOLOGY, 428 East Preston Street, Baltimore, MD 21202-3993. If a member, please contact the Society with your change.

Reprints of individual articles are available only from the authors.

Reprints in large quantities for commercial or academic use may be purchased from the publisher. For information and prices call 410-528-5580.

Microfilm and Microfiche: Prices are available upon request. Microfilm editions may be ordered from Williams & Wilkins.

The Journal subscription list is available for rental on a controlled basis from Williams & Wilkins. All promotional literature must be approved in advance.

Disclaimer: The statements and opinions contained in the articles of MOLECULAR PHARMACOLOGY are solely those of the individual authors and contributors and not of The American Society for Pharmacology and Experimental Therapeutics or Williams & Wilkins. The appearance of advertisements in the Journal is not a warranty, endorsement or approval of the products or safety. The American Society for Pharmacology and Experimental Therapeutics and the publisher disclaim responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

Volume indexes appear in the June and December issues.

Indexing/Abstracting Services: The Journal is currently included by the following services in print and/or electronic format: Index Medicus, Current Contents (Life Sciences), Excerpta Medica, Current Awareness in Biological Sciences, and Reference Update/Research Information Systems.

Copyright Information: MOLECULAR PHARMACOL-OGY is copyrighted by the American Society for Pharmacology and Experimental Therapeutics. No portion(s) of the work(s) may be reproduced without written consent from Williams & Wilkins. Permission to reproduce copies of articles for non-commercial use may be obtained from the Copyright Clearance Center, 27 Congress Street, Salem, MA 01970, with a fee of \$3.00 per copy.

Copyright © 1993 by The American Society for Pharmacology and Experimental Therapeutics.

INSTRUCTIONS TO AUTHORS

Molecular Pharmacology will publish the results of investigations that contribute significant new information on drug action or selective toxicity at the molecular level. The term "drug" is defined broadly to include chemicals that selectively modify biological function.

Suitable papers are those that describe applications of the methods of biochemistry, biophysics, genetics, and molecular biology to problems in pharmacology or toxicology. Also suitable are reports of fundamental investigations which, although not concerned directly with drugs, nevertheless provide an immediate basis for further study of the molecular mechanism of drug action. Observations of phenomena that shed no light upon underlying molecular interactions are not appropriate for publication. Comparative studies, such as those involving drug-receptor or drug-enzyme interactions that already have been well characterized in other types of cells or tissues, also are inappropriate for publication unless they contribute significant new insight into mechanisms.

Molecular Pharmacology has adopted a uniform policy for evaluation of manuscripts utilizing molecular modeling. Key aspects of content that determine suitability and eventual acceptance include: use of modeling technology to generate predictions concerning new molecules, modeling studies that offer significant new insights into the mechanism of actions of drugs, and inclusion of experimental data that support the predictions of molecular modeling. It is not necessary that each aspect be reflected in every manuscript; however, manuscripts that are purely theoretical in nature or that simply generate structural predictions without correlating these to drug action or new biological data will be returned as unsuitable for publication.

Specific areas of interest include: identification and characterization of receptors for hormones, growth factors, neurotransmitters, toxins, and other drugs; analysis of receptor response pathways; drug effects on metabolic pathways, biosynthesis and degradation of macromolecules, and cellular regulatory mechanisms; analysis of drug-receptor and drug-enzyme interactions; effects of drugs on structure and properties of macromolecules and membranes; relationships between drug structure and activity; molecular mechanisms of drug metabolism; distribution and transport between biological compartments; molecular mechanisms of chemical mutagenesis, carcinogenesis, and teratogenesis; and molecular mechanisms of selective toxicity, drug allergy, and pharmacogenetics.

Page charges. Authors will be billed at the rate of \$40.00 per page after the paper has been published. It is expected that the page charge will be paid if funds are available for that purpose from the author's institution or from the sponsor of this research. Payment of the charge is not a condition for publication. In case of personal financial hardship, page charges will be waived. Neither the editors nor the reviewers will have knowledge as to who has paid the charge, and this payment always will be considered entirely voluntary.

Submission of manuscript. Manuscripts are published in English only and should be sent to Dr. T. Kendall Harden, Editor, Molecular Pharmacology, CB 7368, Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27599-7368, U. S. A.

The expenses associated with the review of manuscripts submitted to Molecular Pharmacology and other ASPET-sponsored journals that are devoted to publishing original research articles have escalated dramatically in recent years because of ever-increasing costs of postage, supplies, and other office expenses, and the growing number of manuscripts submitted for publication. Thus, it has become necessary for ASPET to follow the example of several other scientific societies which have instituted uniform manuscript handling fees. Therefore, all manuscripts must be accompanied either by a check for \$40 (in U. S. funds drawn on a U. S. bank payable to ASPET) or by a validated purchase order from the authors' institution. The review process for submitted manuscripts will be delayed until the manuscript handling fee or purchase order is received in the Editor's office. If submission of the manuscript handling fee entails a personal financial hardship to the author(s), the fee will be waived. In that event, the author(s) should submit a request for waiver of the fee when the manuscript is submitted.

Manuscripts should be typewritten double-spaced with ample margins on one side of the paper, $8\frac{1}{2} \times 11$ inches (ca. 215×280 mm). Submit four complete copies of the manuscript and four copies of each figure, plus one original drawing or photograph of each figure. Each half-tone figure requires four original drawings or photographs. All pages should be numbered consecutively beginning

with the title page. References must be limited to a maximum number of 40.

The Summary should be no more than 250 words.

Under usual circumstances reviewers will be instructed to return only their comments to the editorial office and to destroy manuscripts after a final decision on their acceptability has been made. Original drawings and single copies of manuscripts not accepted for publication will be returned to the authors upon request.

It is understood that the manuscripts and the results they contain will not have been published previously and are not being submitted elsewhere. If the submitted manuscript utilizes or makes bibliographic reference to articles in press, copies should be included with the manuscript. Manuscripts are accepted for review with the understanding that all persons listed as authors have given their approval for the submission of the paper; further, that any person cited as a source of personal communications has approved such citation. Written authorization may be required at the Editor's discretion. Articles and any other material published in *Molecular Pharmacology* represent the opinions of the author(s) and should not be construed to reflect the opinions of the Editor(s) and the Publisher. If and when a manuscript is published, it will become the sole property of the Journal.

Authors submitting a manuscript do so on the understanding that if it is accepted for publication, copyright in the article, including the right to reproduce the article in all forms and media, shall be assigned exclusively to the Society for Pharmacology and Experimental Therapeutics. No reasonable request by the author for permission to reproduce any of his or her contributions to the journal will be refused.

Authors are encouraged to submit electronic diskettes of the final version of their manuscripts along with the typed REVISED manuscript. Diskettes produced on IBM or IBM-compatible computers are preferred, but those produced on most Apple/MacIntosh or Wang computers can also be converted. The following word processing programs are preferred: XyWrite III Plus, Word Perfect 4.2, 5.0, or 5.1 (IBM or Macintosh), Microsoft Word (IBM or Macin-

tosh), Wang OIS (WPS), and Wordstar (IBM). Among other word processing systems that we can convert are CPT 8000, MacWrite 2.2 or 4.5, Display Write 3 or 4, Multimate, PC Write, Volkswriter, and Write Now. Authors preparing diskettes on MacIntosh computers should not use the Fast Save option. Files in ASCII can also be used, but are not preferred. Identify the diskette by providing journal name, manuscript number, senior author's name, manuscript title, name of computer file, type of hardware, operating system and version number, and software program and version number.

The journal does not assume responsibility for errors in conversion of customized software, newly released software, and special characters. Mathematics and tabular material will be processed in the traditional manner.

Accelerated Communications. In order to provide a mechanism for rapid publication of novel experimental findings of unusual and timely significance, manuscripts will be accepted for consideration as Accelerated Communications. Accelerated Communications are not intended for publication of preliminary results. Manuscripts submitted under this category should present novel results that are clearly documented and should make a conceptual advance in their field. They will be reviewed by the same criteria applied to regular papers in Molecular Pharmacology. The manuscript should be accompanied by a transmittal letter briefly outlining the significance of the work and providing a list of at least three scientists who would be appropriate reviewers.

Accelerated Communications will be reviewed as rapidly as possible with the aim of reaching an editorial decision within four weeks of receipt of the manuscript. It is expected that Accelerated Communications which are accepted will be published in essentially the form submitted. Manuscripts accepted without revision will be published within four to five months of initial receipt. Manuscripts accepted with a requirement for minor revisions will be published two or three months following receipt of a suitably revised version.

All manuscripts that require major revisions or that do not fit the criteria for Accelerated Communications will be returned to authors for revision and further consideration as a regular paper. Such manuscripts will retain the original submission date if revised versions are received in a timely manner.

Accelerated Communications may be submitted in the same style as regular manuscripts. Results and Discussion may be combined at the discretion of the authors. Manuscripts must not exceed five printed pages in the journal. This corresponds approximately to 25 double-spaced typewritten pages (1-inch margins) including all components of the manuscript and counting each figure as a page of typewritten text. Manuscripts that are judged to be too long will be considered as regular papers.

Organization and style of manuscripts. The policy of the Journal is to allow authors maximum freedom in organizing and presenting their material, and in expressing their ideas, provided only that clarity and conciseness are achieved. For most manuscripts, the most suitable format is: (1) Summary, (2) Introduction, (3) Materials and Methods, (4) Results, and (5) Discussion.

Certain conventions must be observed. Chemical and mathematical formulas and abbreviations should follow the *Instructions to Authors of the Journal of Biological Chemistry* (Vol. 261, pp. 1-11, January 10, 1986). Drugs must be referred to by their generic or chemical names throughout the text, but may be identified by trade name in parentheses or a footnote. The systematic name and number given by the Commission on Enzymes of the International Union of Biochemistry should be included for each enzyme of importance in a paper, at the point in the Summary or Introduction where the enzyme is first mentioned. The use of abbreviations should be minimized and abbreviations avoided in the Summary.

All essential abbreviations should be defined in a single footnote when first introduced. Abbreviations of journal names should conform to the style of *Biological Abstracts*. References to papers that have been accepted for publication, but have not appeared, should be cited like other references with the abbreviated name of the journal followed by the words "in press." Three copies of such papers should be sent whenever the findings described in them have a direct bearing on the paper being submitted for publication. "Personal Communications" and "Unpublished Observations" should be cited in footnotes to the text and should not be included in the reference list.

A manuscript should include the following, in the order listed: (1) Title. Numbered footnotes to the title should be avoided; acknowledgment of financial support should be given in an unnumbered footnote to the title. (2) Names of authors, their laboratory and institution. (3) A running title, not exceeding 60 characters and spaces. (4) Summary. (5) Text. Footnotes should be referred to by superscript numbers and references by numbers in parentheses. (6) References, numbered according to order of citation in the text, including title and complete pagination. Examples: 1. Goren, J. H., L. G. Bauce, and W. Vale. Forces and structural limitations of binding of thyrotropin-releasing receptor: the pyroglutamic acid moiety. Mol. Pharmacol. 13:606-614 (1977). 2. Chernow, B., and J. T. O'Brian. Overview of catecholamines in selected endocrine systems, in Norepinephrine (M. G. Ziegler and C. R. Lake, eds.). Williams and Wilkins, Baltimore, 439-449 (1984). 3. Snedecor, G. W., and W. G. Cochran. Statistical Methods. Iowa State University Press, Ames (1967). (7). Footnotes, numbered according to order of appearance in the text. (8) Tables. (9) Figures. (10) Legends to figures. (11) Name and address of person to receive galley proof.

Tables. These should be numbered with arabic numerals and designed to fit the single-column width of the full-page width. Every table should have an explanatory title and sufficient experimental detail in a paragraph following the title to be intelligible without references to the text (unless the procedure is given in the Methods section, or under another table or figure). Footnotes to tables should appear beneath the tables themselves and should be designated by lower-case italic superscript letters, a, b, c, etc.

Figures. These should be numbered with arabic numerals. Each of the four manuscript copies should contain all of the figures. Only the original set need be of quality suitable for reproduction except in the case of half-tones, which require four sets of photographs or original drawings. These should be unmounted glossy photographs (or original India-ink drawings). Usually figures will be reduced to one column width (85 mm) and all numbers after such reduction should be at least 1.5 mm high. The figures must be ready, in all respects, for direct reproduction: no lettering or other art work will be done by the publisher. If symbols are not explained on the face of the figure, only standard characters, of which the printer has type, may be used $(\times, \bigcirc, \bigcirc, \square, \triangle, \triangle, \bigcirc)$. The back of each photograph should bear its number, and the legend TOP at the appropriate edge. The list of legends for the figures should give captions and sufficient experimental detail, as required for tables.

Page proof. Authors will be billed for substantial changes in page proof. The Editors are very much interested in having accepted contributions appear in the earliest possible issue of the Journal, and therefore request that galley proof be returned within 24 hours after its receipt. In exceptional cases, a "Note added in proof" may be attached and will be published if the Editor approves.

Reprints and page charges. An order form for reprints as well as information on the estimation of page charges will be mailed with galley proof. Please direct questions on reprints, page charges, or other business matters to Kay Croker, Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Md. 20814. Telephone (301)530-7060.

Leading Pharmacology Journals

Publications of the American Society for Pharmacology and Experimental Therapeutics, Inc.

The Journal of Pharmacology and Experimental Therapeutics

Editor: John A. Harvey, Ph.D.

JPET is respected the world over as one of the leading research journals in the field of pharmacology. Readers find broad coverage of all aspects of the interactions of chemicals with biological systems, including autonomic, behavioral, cardiovascular, cellular, clinical, developmental, gastrointestinal, immuno-, neuro-, pulmonary, and renal pharmacology, as well as analgesics, drug abuse, metabolism and disposition, chemotherapy, and toxicology. *Monthly*

Drug Metabolism and Disposition: the biological fate of chemicals

Editor: Vincent G. Zannoni, Ph.D.

Drug Metabolism and Disposition publishes in vitro and in vivo experimental results that bring readers significant and original information on xenobiotic metabolism and disposition, including metabolism of all pharmacologic agents or drugs and environmental chemicals, reactants and preservatives. The areas covered are: pharmacokinetics, pharmacodynamics and mechanisms, genetic, nutritional, or hormonal factors affecting the biological fate of chemicals, toxicological consequences of xenobiotic metabolism. *Bimonthly*

Pharmacological Reviews

Editor: Robert E. Stitzel, Ph.D.

Pharmacological Reviews is a showcase for important review articles in your field, featuring longer papers on topics of high current interest. The areas covered in review papers have included biochemical and cellular pharmacology, drug metabolism and disposition, renal pharmacology, neuropharmacology, behavioral pharmacology, clinical pharmacology, and toxicology. No library serving the pharmacologic community should be without a subscription. *Quarterly*

Discounts available to members on all ASPET publications.

SAVE 10% when ordering two

SAVE 15% when ordering three

SAVE 20% when ordering all four

Molecular Pharmacology

Editor: T. Kendall Harden, Ph.D.

The papers published in **Molecular Pharmacology** are on the cutting edge of research on drug action and selective toxicity at the molecular level. Original applications of biochemistry, biophysics, genetics, and molecular biology are juxtaposed with innovative pharmacologic research to elucidate basic problems in pharmacology and toxicology, including such areas as molecular mechanisms involved in drug receptor-effector coupling, xenobiotic metabolism, and antibiotic and anticancer drug action. *Monthly*

citing action. Monthly
Yes! Enter my subscription(s) to the following: The Journal of Pharmacology and Experimental Therapeutics (monthly) Individual \$190/yr Institutional \$340/yr (Please add \$65/yr outside the US; in Canada, also add 7% GST.) New Subscription Renewal 3 yrs 2 yrs 1 yr
Drug Metabolism and Disposition (bimonthly) ☐ Individual \$85/yr ☐ Institutional \$140/yr (Please add \$20/yr outside the US; in Canada, also add 7% GST.)
Molecular Pharmacology (monthly) Individual \$105/yr
Pharmacological Reviews (quarterly) ☐ Individual \$60/yr ☐ Institutional \$107/yr ☐ In-training* \$45/yr (Please add \$15/yr outside the US; in Canada, also add 7% GST.) ☐ New Subscription ☐ Renewal ☐ 3 yrs ☐ 2 yrs ☐ 1 yr
Payment options: Check enclosed (payable to Williams & Wilkins) Hill me VISA MasterCard American Express
Card #Exp. date
MD and PA subscribers must add appropriate state sales tax. Subscriptions outside the US must be prepaid in US dollars only. Rates valid until October 31, 1993. Please allow 10 weeks for delivery of first issue. Surface mail delivery to countries outside US may take 16 weeks. Airmail rates available upon request. *Specify institution and training status.
Name
Address
City/State/Zip
Return coupon to: Williams & Wilkins Mail in this coupon or call
P.O. Box 23291 toll-free 1-800-638-6423

Baltimore, MD 21203-9990

(from anywhere in US or Canada)