# Synthesis and Benzodiazepine Receptor Affinity of Pyrazolo[1,5- a ]pyrimidine Derivatives. 3. New 6-(3-Thienyl) Series as α1 Selective Ligands

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Journal of Medicinal Chemistry

# Guidelines for Authors

Revised May 2015

## Major Changes for 2015

- Section 2.1.9 Interference Compounds added.
- Section 2.3.2 Purity of Tested Compounds addition of qHNMR protocol as evidence of purity.

## Contents (click on the topic)

# 1 Scope and Editorial Policy

## 1.1 Scope of the Journal

The *Journal of Medicinal Chemistry* (Journal) invites original research contributions dealing with chemical-biological relationships. The primary objective of the Journal is to publish studies that contribute to an understanding of the relationship between molecular structure and biological activity or mode of action.

Some specific areas that are appropriate include the following.

- Design, synthesis, and biological evaluation of novel biologically active compounds, diagnostic agents, or labeled ligands employed as pharmacological tools.
- Molecular modifications of reported series that lead to a significantly improved understanding of their structure-activity relationships (SAR). Routine extensions of existing series that do not utilize novel chemical or biological approaches or do not add significantly to a basic understanding of the SAR of the series will normally not be considered for publication.
- Structural biological studies (X-ray, NMR, etc.) of relevant ligands and targets with the aim of investigating molecular recognition processes in the action of biologically active compounds.
- Molecular biological studies (e.g., site-directed mutagenesis) of macromolecular targets that lead to an improved understanding of molecular recognition.
- Computational studies that analyze the SAR of compound series of general interest and lead to experimental studies or analysis of other available chemical and/or biological data that substantially advance medicinal chemistry knowledge.
- Substantially novel computational chemistry methods with demonstrated utility for the identification, optimization, or target interaction analysis of bioactive molecules.
- Effect of molecular structure on the distribution, pharmacokinetics, and metabolic transformation of biologically active compounds. This may include design, synthesis, and evaluation of novel types of prodrugs.
- Novel methodology with *broad* application to medicinal chemistry, but only if the methods have been tested on relevant molecules.

## 1.2 Manuscript Categories

Manuscripts can be submitted as *Articles*, *Brief Articles*, *Perspectives*, or *Drug Annotations*.

**1.2.1** *Articles* are definitive, full accounts of significant studies.

**1.2.2** *Brief Articles* are definitive reports whose scope is more limited than the scope of *Articles*, but whose format is identical except for length. They are subject to the same editorial appraisal as *Articles* and should be of similar scientific quality.

**1.2.3** *Perspectives* are interpretive accounts on subjects of current interest to medicinal chemists. This series is intended to be a forum for experts to present their perspectives on emerging or active areas of research that affect the practice of medicinal chemistry. Manuscripts are usually submitted at the invitation of the Perspectives Editor. However, experts are welcome to contact the Perspective Editor to ensure that a topic is suitable. Approval is recommended prior to submission.

**1.2.4** *Drug Annotations* are reports of drug candidates in phase I, II, and III clinical trials, as well as new drugs in the market. *Drug Annotations* manuscripts focus on a single drug and should provide a description of a candidate molecule (including structure), target(s), mechanism of action, and rationale for bringing the candidate to clincial trial (for example, first in class or improvement over previous compounds). Reports on original research are also acceptable. Manuscripts are usually submitted after an invitation from the *Drug Annotations* Editors. However, authors are welcome to contact the *Drug Annotations* Editors to ensure that a topic is suitable. Approval is recommended prior to submission.

**1.2.5** *Viewpoint* manuscripts are invited by the Editors. *Viewpoint* manuscripts are typically accompanied commentaries to *Featured Article*s.

**1.2.6** *Featured Articles* are selected by the Editors from accepted *Articles*, *Brief Articles*, and *Drug Annotations.*

## 1.3 Prior Publication

Authors should submit only original work that has not been previously published and is not under consideration for publication elsewhere.

Academic theses, including those on the Web or at a college Web site, are not considered to be prior publication.

## 1.4 Patents and Intellectual Property

Authors need to resolve all patent and intellectual property issues. Acceptance and publication will not be delayed for pending or unresolved issues of this type. Note that *Just Accepted* manuscripts (section 3.11) and ASAP manuscripts (section 3.12) are published documents.

## 1.5 Professional Ethics

Editors, reviewers, and authors are expected to adhere to the American Chemical Society's Ethical Guidelines to Publication of Chemical Research. The guidelines are available at http://pubs.acs.org/page/jmcmar/submission/index.html.

**1.5.1** ***Author Consent.*** Submitting authors are reminded that consent of all coauthors must be obtained prior to submission of manuscripts. If an author is removed after submission, the submitting author must have the removed author consent to the change by e-mail or faxed letter to the assigned Editor.

**1.5.2.** ***Plagiarism.*** Manuscripts must be original with respect to concept, content, and writing. It is not appropriate for an author to reuse wording from other publications, including one's own previous publications, whether or not that publication is cited. Suspected plagiarism should be reported immediately to the editorial office. Report should *specifically* indicate the plagiarized material within the manuscripts.

**1.5.3.** ***Use of Human or Animal Subjects.*** Manuscripts must comply with the ACS Ethical Guidelines to Publication of Chemical Research: *Research involving animals must be performed in accordance with institutional guidelines as defined by Institutional Animal Care and Use Committee for U.S. institutions or an equivalent regulatory committee in other countries. Research studies involving humans must have institutional review board approval. Authors are requested to identify the institutional or licensing committee that has approved the experiments. For research involving animals or humans, Editors reserve the right to request additional information from authors.*

### 1.6 Issue Frequency

The Journal publishes 24 issues per year on the second and fourth Thursdays of each month.

# 2 Preparing the Manuscript

## 2.1 General Considerations

Manuscripts should be kept to a minimum length. Authors should write in clear, concise English, employing an editing service if necessary. For convenience, ACS has compiled a list of language-editing companies (http://pubs.acs.org/page/4authors/tools/language_editing.html). The responsibility for all aspects of manuscript preparation rests with the authors. Extensive changes or rewriting of the manuscript will not be undertaken by the Editors. Information on a standard list of abbreviations for ACS Journals is in *The ACS Style Guide* (2006), available from Oxford University Press, Order Department, 2001 Evans Road, Cary, NC 27513.

Authors are strongly encouraged to use the templates available on the Journal Web site.

It is best to use the fonts "Times" and "Symbol." Other fonts, particularly those that do not come bundled with the system software, may not translate properly. Ensure that all special characters (e.g., Greek characters, math symbols) are present in the body of the text as characters and not as graphic representations. Be sure that all characters are correctly represented throughout the manuscript—e.g., 1 (one) and l (letter l), 0 (zero) and O (letter o).

All text (including the title page, abstract, all sections of the body of the paper, figure captions, scheme or chart titles, and footnotes and references) and tables should be in *one* file. Graphics may be included with the text or uploaded as separate files.

Manuscripts that do not adhere to the guidelines may be returned to authors for correction.

**2.1.1** ***Articles***. *Articles* must be double-spaced including text, references, tables, and legends. Vertically orient all pages. Use page size 8.5 x 11 inches. This applies to figures, schemes, and tables as well as text. Manuscripts do not have page limitations but should be kept to a minimum length. The experimental procedures for all of the steps in the synthesis of target compounds must be included in the experimental section of the manuscript.

**2.1.2** ***Brief Articles.*** Manuscripts must not exceed 7 pages of the double-column template including title page, abstract, text with experimental section, references, tables, illustrations, and table of contents graphic. The abstract is limited to 75 words. If manuscripts exceed 7 journal pages at the galley stage, authors will be asked to reduce the length of their manuscripts. To remain within the page limit, some material may be included in supporting information. However, the experimental procedures for all of the steps in the synthesis of target compounds must be included in the experimental section of the manuscript.

**2.1.3** ***Perspectives.*** *Perspectives* manuscripts do not have the same headings as other manuscript types. Author(s) biographies of less than 125 words each should be placed immediately before the references. Generally, *Perspectives* are no more than 25 journal pages (100 double-spaced manuscript pages) and should not contain more than 180 references. *Miniperspectives* are no more than 8 journal pages (32 double-spaced manuscript pages) and should not contain more than 70 references. Page limits for Award Perspectives are flexible, but they should conform to other requirements stated for *Perspectives* or *Miniperspectvies*.

**2.1.4** ***Drug Annotations.*** Manuscripts should be double-spaced including text, references, tables and legends. Vertically orient all pages. Use page size 8.5 x 11 inches. This applies to figures, schemes, and tables as well as text. Limit manuscripts to approximately 40 double-spaced pages

(10 journal pages), including title page, abstract of 150 words or less, up to 50 references, and tables, charts, schemes, and figures. In general, manuscripts should include design and chemistry, known biological targets, in vitro and in vivo biological activity, pharmacological properties, available toxicity information, and clinical data.

**2.1.5** ***Viewpoint.*** Manuscripts are limited to 8 double-spaced pages (2 journal pages), including title page, abstract, references, tables, and illustrations.

**2.1.6 Nomenclature.** It is the responsibility of the authors to provide correct nomenclature. Nomenclature should conform to current American usage. It is acceptable to use semisynthetic or generic names for certain specialized classes of compounds, such as steroids, peptides, carbohydrates, etc. In such a case, the name should conform to the generally accepted nomenclature conventions for the compound class. Chemical names for drugs are preferred. If these are not practical, generic names, or names approved by the U.S. Adopted Names Council or by the World Health Organization, may be used. Authors may find the following sources useful for recommended nomenclature:

- *The ACS Style Guide*; Coghill, A. M., Garson, L. R., Eds.; American Chemical Society: Washington DC, 2006.
- *Enzyme Nomenclature*; Webb, E. C., Ed.; Academic Press: Orlando, 1992.
- IUPHAR database of receptors and ion channels (http://www.iuphar-db.org/index.jsp).

**2.1.7 Compound Code Numbers.** Code numbers assigned to a compound may be used as follows:

- Once in the manuscript title, when placed in parentheses AFTER the chemical or descriptive name.
- Once in the abstract.
- Once in the text (includes legends) and once to label a structure. Code numbers in the text must correspond to structures or, if used only once, the chemical name must be provided before the parenthesized code number, e.g., "chemical name (JEM-398)." If appearing a second time in the text, a bold Arabic number must be assigned on *first* usage, followed by the parenthesized code number, e.g., "**1** (JEM-398)." Subsequently, only the bold Arabic number may be used. All code numbers in the text must have a citation to a publication or a patent on first appearance.

Compounds *widely* employed as research tools and recognized primarily by code numbers may be designated in the manuscript by code numbers without the above restrictions. Their chemical name or structure should be provided as above. Editors have the discretion of determining which code numbers are considered widely employed.

**2.1.8 Trademark Names.** Trademark names for reagents or drugs must be used only in the experimental section. *Perspectives* may use trademark names once in the manuscript. Do not use trademark or service mark symbols.

**2.1.9. Interference Compounds.** Active compounds from any source must be examined for known classes of assay interference compounds and this analysis must be provided in the General Experimental section. Compounds shown to display misleading assay readouts by a variety of mechanisms include, but are not limited to, aggregation, redox activity, fluorescence, protein reactivity, singlet-oxygen quenching, the presence of impurities, membrane disruption, and their decomposition in assay buffer to form reactive compounds. Many of these compounds

have been classified as Pan Assay Interference Compounds (PAINS; see Baell & Holloway, *J. Med. Chem.* **2010**, *53*, 2719-2740). Provide firm experimental evidence in at least two different assays that reported compounds with potential PAINS liability are specifically active and their apparent activity is not an artifact.

## 2.2 Manuscript Organization

**2.2.1 Title Page.** *Title*: The title of the manuscript should reflect the purposes and findings of the work in order to provide maximum information in a computerized title search. Minimal use of nonfunctional words is encouraged. Only commonly employed abbreviations (e.g., DNA, RNA, ATP) are acceptable. Code numbers for compounds may be used in a manuscript title when placed in parentheses AFTER the chemical or descriptive name.

*Authors' Names and Affiliations*: The authors' full first names, middle initials, last names, and affiliations with addresses at time of work completion should be listed below the title. The name of the corresponding author should be marked with an asterisk (*).

**2.2.2 Abstract.** *Articles*, *Brief Articles*, *Perspectives*, and *Viewpoints* must have an abstract following the title page. *Brief Articles* have a strict 75 word limit; for *Articles* and *Perspectives*, 150 words are usually adequate; for *Viewpoints*, 1–3 sentences are adequate. Abstracts should be presented in a findings-oriented format in which the most important results and conclusions are summarized. Code numbers may be used once in the abstract.

**2.2.3 Introduction.** The rationale and objectives of the research should be discussed in this section. The background material should be brief and relevant to the research described.

**2.2.4 Results.** This section could include synthetic schemes and tables of biological data. The discussion of the chemistry and biology should be descriptive.

**2.2.5 Discussion and Conclusions.** Authors should discuss the analysis of the data together with the significance of results and conclusions, if an optional conclusions section is not employed.

**2.2.6 Experimental Section.** Authors should be as concise as possible in experimental descriptions. General reaction conditions should be given only once. The title of an experiment should include the chemical name and a bold Arabic identifier number; subsequently, only the bold Arabic number should be used. Experiments should be listed in numerical order. Molar equivalents of all reactants and percentage yields of products should be included.

A general introductory section should include general procedures, standard techniques, and instruments employed (e.g., determination of purity, chromatography, NMR spectra, mass spectra, names of equipment) in the synthesis and characterization of compounds described subsequently in this section. Special attention should be called to hazardous reactions or toxic compounds. Provide analysis for known classes of assay interference compounds.

*Abbreviations.* Standard abbreviations should be used throughout the experimental section (see 4. Standard Abbreviations and Acronyms). Please note that these are used in ACS Journals without periods. The preferred forms for some of the more commonly used abbrevations are mp, bp, ºC, K, min, h, mL, μL, g, mg, μg, cm, mm, nm, mol, mmol, μmol, ppm, TLC, GC, NMR, UV, and IR. Units are abbreviated in table column heads and when used with numbers, not otherwise. For further information, refer to *The ACS Style Guide* (see 2.1 General Considerations).

**2.2.7 Ancillary Information.** Include pertinent information in the order listed immediately before the references.

*Supporting Information Availability.* If supporting information has been submitted, include a statement of the availability using the following format:

> **Supporting Information.** Brief statement in nonsentence format listing the contents of the material supplied as Supporting Information.

*PDB ID Codes*: Include the PDB ID codes.

*Corresponding Author Information:* Provide telephone numbers and email addresses for each of the designated corresponding authors.

*Present/Current Author Addresses:* Provide information for authors whose affiliations or addresses have changed.

*Author Contributions:* Include statement such as "These authors contributed equally."

*Acknowledgment***:** Authors may acknowledge people, organizations, and financial supporters in this section.

*Abbreviations Used:* Provide a list of nonstandard abbreviations and acronyms used in the paper, e.g., YFP, yellow fluorescent protein. Do not include compound code numbers in this footnote. It is not necessary to include abbreviations and acronyms from the Standard Abbreviations and Acronyms list (http://pubs.acs.org/page/jmcmar/submission/authors.html).

**2.2.8 References and Notes.** Number literature references and notes in one *consecutive* series by order of mention in the text. Numbers in the text are non-parenthesized superscripts. The accuracy of the references is the responsibility of the author. List all authors; do not use et al. Provide inclusive page numbers. Titles may have capitalization of first word only (excluding, for example, acronyms and trade names) or standard capitalization as shown below. The chosen style should be used consistently throughout the references. Double-space the references using the following format.

- For journals: Rich, D. H.; Green, J.; Toth, M. V.; Marshall, G. R.; Kent, S. B. H. Hydroxyethylamine Analogues of the p17/p24 Substrate Cleavage Site Are Tight-Binding Inhibitors of HIV Protease. *J. Med. Chem.* **1990**, *33*, 1285-1288.
- For online early access: Rubner, G.; Bensdorf, K.; Wellner, A.; Kircher, B.; Bergemann, S.; Ott, I.; Gust, R. Synthesis and Biological Activities of Transition Metal Complexes Based on Acetylsalicylic Acid as Neo-Anticancer Agents. *J. Med. Chem.* [Online early access]. DOI: 10.1021/jm101019j. Published Online: September 21, 2010.
- For periodicals published in electronic format only: Author 1; Author 2; Author 3; etc. Title of Article. *Journal Abbreviation* [Online] **Year**, *Volume*, Article Number or other identifying information.
- For monographs: Casy, A. F.; Parfitt, R. T. *Opioid Analgesics*; Plenum: New York, 1986.
- For edited books: Rall, T. W.; Schleifer, L. S. Drugs Effective in the Therapy of the Epilepsies. In *The Pharmacological Basis of Therapeutics*, 7th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F., Eds.; Macmillan: New York, 1985; pp 446-472.

List submitted manuscripts as “in press” only if formally accepted for publication. Manuscripts available on the Web with a DOI number are considered published. For manuscripts not accepted, use “unpublished results” after the names of authors. Incorporate notes in the correct numerical sequence with the references. Footnotes are not used.

**2.2.9 Tables.** Tabulation of experimental results is encouraged when this leads to more effective presentation or to more economical use of space. Tables should be numbered consecutively in order of citation in the text with Arabic numerals. Footnotes in tables should be given italic lowercase letter designations and cited in the tables as superscripts. The sequence of letters should proceed by row rather than by column. If a reference is cited in both table and text, insert a lettered footnote in the table to refer to the numbered reference in the text. Each table must be provided with a descriptive title that, together with column headings, should make the table self-explanatory.

Titles and footnotes should be on the same page as the table. Tables may be created using a word processor's text mode or table format feature. The table format feature is preferred. Ensure each data entry is in its own table cell. If the text mode is used, separate columns with a single tab and use a return at the end of each row. Tables may be inserted in the text where first mentioned or may be grouped after the references.

**2.2.10 Figures, Schemes/Structures, and Charts.** The use of illustrations to convey or clarify information is encouraged. Structures should be produced with the use of a drawing program such as ChemDraw. Authors using other drawing packages should, in as far as possible, modify their program's parameters so that they conform to ChemDraw preferences. Remove all color from illustrations, except for those you would like published in color. Illustrations may be inserted into the text where mentioned or may be consolidated at the end of the manuscript. If consolidated, legends should be grouped on a separate page(s). Include as part of the manuscript file.

To facilitate the publication process, please submit manuscript graphics using the following guidelines:

1. The preferred submission procedure is to embed graphic files in a Word document. It may help to print the manuscript on a laser printer to ensure all artwork is clear and legible.
2. Additional acceptable file formats are: TIFF, PDF, EPS (vector artwork) or CDX (ChemDraw file). If submitting individual graphic files in addition to them being embedded in a Word document, ensure the files are named based on graphic function (i.e. Scheme 1, Figure 2, Chart 3), not the scientific name. Labeling of all figure parts should be present and the parts should be assembled into a single graphic.

   EPS files: Ensure that all fonts are converted to outlines or embedded in the graphic file. The document settings should be in RGB mode. **NOTE:** *While EPS files are accepted, the vector-based graphics will be rasterized for production.* Please see below for TIFF file production resolutions.
3. TIFF files (either embedded in a Word doc or submitted as individual files) should have the following resolution requirements:
   - Black & White line art: 1200 dpi
   - Grayscale art (a monochromatic image containing shades of gray): 600 dpi
   - Color art (RGB color mode): 300 dpi
   - The RGB and resolution requirements are essential for producing high-quality graphics within the published manuscript. Graphics submitted in CMYK or at lower resolutions may be used; however, the colors may not be consistent and graphics of poor quality may not be able to be improved.

- Most graphic programs provide an option for changing the resolution when you are saving the image. Best practice is to save the graphic file at the final resolution and size using the program used to create the graphic.

4. Graphics should be sized at the final production size when possible. Single column graphics are preferred and can be sized up to 240 points wide (3.33 in.). Double column graphics must be sized between 300 and 504 points (4.167 in. and 7 in.). All graphics have a maximum depth of 660 points (9.167 in.) including the caption (please allow 12 points for each line of caption text).

   Consistently sizing letters and labels in graphics throughout your manuscript will help ensure consistent graphic presentation for publication.

For more information, please visit http://pubs.acs.org/page/jmcmar/submission/authors.html and http://pubs.acs.org/page/4authors/submission/index.html.

**2.2.11 Image Manipulation.** According to *ACS Ethical Guidelines*, images should be free from misleading manipulation. Images included in an account of research performed or in the data collection as part of the research require an accurate description of how the images were generated and produced. Apply digital processing uniformly to images, with both samples and controls. Cropping must be reported in the figure legend. For gels and blots, use of positive and negative controls is highly recommended. Avoid high contrast settings to avoid overexposure of gels and blots. For microscopy, apply color adjustment to entire image and note in the legend. When necessary, authors should include a section on equipment and settings in supporting information to describe all image acquisition tools, techniques and settings, and software used. All final images must have resolutions of 300 dpi or higher. Authors should retain unprocessed data in the event that the Editors request them. Unprocessed data can also be part of the supporting information.

**2.2.12 Table of Contents Graphic.** A graphic entry for the table of contents (TOC) must be supplied as the last page of the manuscript and labeled "Table of Contents graphic." This *small* graphic should capture the reader's attention and, in conjunction with the manuscript title, should give the reader an idea of the key target compounds or series discussed in the paper. The TOC graphic will also appear in the abstract of the published PDF file.

• A chemical structure should be clearly depicted.

• The TOC graphic should be entirely original work created by one of the coauthors and should not be a duplicate of a graphic appearing elsewhere in the manuscript.

• The TOC graphic should be no wider than 21 cm and no taller than 5.5 cm.

• Code numbers should not be used in the TOC graphic.

For additional information see the *ACS Publications Guidelines for Table of Contents/Abstract Graphics*. For resolution/quality requirements see *Figures, Schemes/Structures, and Charts.*

**2.2.13 Supporting Information.** Authors are encouraged to make use of this resource when manuscripts contain extensive tabulations of data that are of interest only to those readers who may need more complete data.

The first page of the supporting information file should contain the title of the manuscript, the names of all authors, and a table of contents; label this page "Supporting Information". The pages must be consecutively numbered S1 (the title page), S2, etc. Figure captions, titles to tables, and other identifying captions should appear on the same page as the figures or tables. Supporting information may be single-spaced. Generally, if one has difficulty reading the

material as submitted, it is unacceptable. Refer to *The ACS Style Guide* (see 2.1 General Considerations) for more specific information.

Supporting information must be submitted at the same time as the manuscript and uploaded separately to the ACS Paragon Plus Environment. A list of acceptable file types is available on the Web. All supporting information files of the same type should be prepared as a single file (rather than submitting a series of files containing individual images or structures). For example, all supporting information available as PDF files should be contained in one PDF file. Author-created file names will be automatically replaced with standardized file names generated at the time of publication.

**DO NOT UPLOAD FIGURES AND TABLES THAT ARE TO BE PUBLISHED IN THE MANUSCRIPT INTO THE SUPPORTING INFORMATION FILE.**

**2.2.14 Molecular Formula Strings.** Authors are encouraged to submit SMILES string computer-readable identifiers of molecules discussed in the manuscript along with the associated biochemical and biological data. Submission of molecular formula strings and associated data enables enhanced quality control at review and can increase an article's discoverability and citability. Complete submission instructions are available at http://pubs.acs.org/page/jmcmar/submission/jmcmar_mfstrings.html.

## 2.3 Specialized Data

**2.3.1 Biological Data.** Quantitative biological data are required for all tested compounds. Biological test methods must be referenced or described in sufficient detail to permit the experiments to be repeated by others. Detailed descriptions of biological methods should be placed in the experimental section. Standard compounds or established drugs should be tested in the same system for comparison. Data may be presented as numerical expressions or in graphical form; biological data for extensive series of compounds should be presented in tabular form. Tables consisting primarily of negative data will not usually be accepted; however, for purposes of documentation they may be submitted as supporting information.

Active compounds obtained from combinatorial syntheses should be resynthesized and retested to verify that the biology conforms to the initial observation.

Statistical limits (statistical significance) for the biological data are usually required. If statistical limits cannot be provided, the number of determinations and some indication of the variability and reliability of the results should be given. References to statistical methods of calculation should be included. Doses and concentrations should be expressed as molar quantities (e.g., mol/kg, μmol/kg, M, mM). The routes of administration of test compounds and vehicles used should be indicated, and any salt forms used (hydrochlorides, sulfates, etc.) should be noted. The physical state of the compound dosed (crystalline, amorphous; solution, suspension) and the formulation for dosing (micronized, jet-milled, nanoparticles) should be indicated. For those compounds found to be inactive, the highest concentration (in vitro) or dose level (in vivo) tested should be indicated. See section on *Statistical Criteria* for more detailed requirements.

Cytotoxicity mean graphs from the National Cancer Institute (NCI) should appear in Supporting Information and not in the main body of the manuscript. Numerical data derived from a limited number of cell lines may be tabulated in the text of the manuscript.

**2.3.2 Purity of Tested Compounds.**

*Methods:* All scientifically established methods (e.g., HPLC, combustion analysis, absolute quantitative $^{1}$H NMR (qHNMR) following the established Journal protocol or equivalent

qHNMR methods) of establishing purity are acceptable. If the target compounds are solvated, the quantity of solvent should be included in the compound formulas. No documentation is required with the exception of qHNMR (see Purity by Absolute qNMR instructions).

*Purity Percentage:* All tested compounds, whether synthesized or purchased, should possess a purity of at least 95%. Target compounds must have a purity of at least 95%. In exceptional cases, authors can request a waiver when compounds are less than 95% pure. For solids, the melting point or melting point range should be reported as an indicator of purity.

*Statements:* Include the specific analytical method used to determine purity in the general part of the experimental section together with a statement confirming ≥95% purity. If the purity of a particular compound is less than 95%, specify the percentage of purity at the end of the description of its synthesis in the experimental section. For qHNMR experiments, additional documentation is required.

*Cover Letter:* Specify the method employed for establishing purity and percentage of purity in the cover letter. Waivers for compounds of less than 95% purity should be requested in the cover letter.

**2.3.3 Confirmation of Structure.** Adequate evidence to establish structural identity must accompany all new compounds that appear in the experimental section of *Articles* and *Brief Articles*. Sufficient spectral data should be presented in the experimental section to allow for the identification of the same compound by comparison. Generally, a listing of $^{1}H$ or $^{13}C$ NMR peaks is sufficient. However, when the NMR data are used as a basis of structural identification, the peaks must be assigned. See *NMR Guidelines for ACS Journals*.

List only infrared absorptions that are diagnostic for key functional groups. If a series contains very closely related compounds, it may be appropriate merely to list the spectral data for a single representative member when they share a common major structural component that has identical or very similar spectral features. HRMS data may be supplied as an additional criterion of compound identity. For the first member of a new class of oligomers containing up to 10 residues, $^{1}H$ NMR (300-500 MHz) and HRMS are a requirement.

Specific optical rotations should be reported for isolated natural products, enantiopure compounds, and enantioenriched isomer mixtures when sufficient sample is available. Specific rotations based on the equation $[\alpha] = (100\alpha)/(lc)$ should be reported as unitless numbers as in the following example: $[\alpha]^{20}_{D}$ 25 (*c* 1.9, $CHCl_3$), where the concentration *c* is in g/l00 mL and the path length *l* is in decimeters. The units of the specific rotation, (deg*mL)/(g*dm), are implicit and are not included with the reported value.

**2.3.4 Combinatorial Chemistry.** When combinatorial chemistry has been employed to generate molecules which become prototypes for a subsequent focused SAR investigation, the lead compounds and any other compounds that are key to the analysis and interpretation of the SAR of the focused series must conform to the appropriate criteria for purity and structural identity required by this Journal. However, the combinatorial chemistry methodology, screening data, and *preliminary* SAR which led to the generation of the lead molecule(s) may be reported as supporting information without confirmation of structure or demonstration of purity. These data may be briefly summarized in the main manuscript when they clarify the SAR discussion of the focused series.

**2.3.5 Computational Chemistry.**

2.3.5.1 Manuscript Categories. When computational chemistry is a major component of a study, manuscripts must fall into one or more of the following categories:

*(A) Practical applications of existing computational methods combined with original experimental data. Manuscripts that report prospective computational design, synthesis, and experimental evaluation of new chemical entities are highly encouraged.*

Applications of existing computational methods are not considered without original experimental data that assess the computational predictions. QSAR modeling is acceptable only if a significant number of new compounds is predicted, prepared, and tested. Avoid overinterpretation of computational predictions and conclusions drawn from molecular models as if they represent experimental data.

*(B) Substantially novel methods along with evidence for utility in medicinal chemistry with significant potential for advancing the field.*

Clearly describe computational methods manuscripts to be accessible to a general medicinal chemistry audience and clarify the relevance of the new method to medicinal chemistry. Present sufficient information to allow the method to be reproduced and tested in other laboratories.

*(C) Statistical analysis or data mining of publicly available databases or data sets that provide unexpected or provocative insights into the advancement of topical medicinal chemistry problems.*

Such investigations must be based upon large data sets. Small series of compounds whose properties are reinvestigated using computational methods do not qualify for this category.

2.3.5.2 Proprietary Data. Normally, the use of proprietary data for computational modeling or analysis is not acceptable because it is inconsistent with the ACS Ethical Guidelines. All experimental data and molecular structures used to generate and/or validate computational models must be reported in the paper, reported as supporting information, or readily available without infringements or restrictions. The Editors may choose to waive the data deposition requirement for proprietary data in a rare case where studies based on very large corporate data sets provide compelling insight unobtainable otherwise.

2.3.5.3 Virtual Screening Studies. In order to validate virtual screening hits obtained from any source, provide proof of dose-response behavior, confirmation of $IC_{50}$ or $K_i$ values, and controls for nonspecific or artificial inhibition (i.e., proof of reversibility, detergent controls). Submit structure confirmation ($^1$H NMR and MS; see section 2.3.3) for active compounds.

For virtual screens that produce compound rankings, provide as supporting information the total number of compounds that were screened and the ranks of identified hits before application of any further manual or other subjective selection steps.

Complex virtual screening protocols are not validated per se by identifying a few active compounds. Evidence must be provided that much simpler approaches would not have yielded comparable results (e.g., 2D similarity or substructure searching). Experimental findings must be significant. For example, identifying weakly potent ATP-site directed protein kinase inhibitors through virtual screening is no longer considered a significant advance due to the availability of many known potent inhibitors acting by this mechanism.

2.3.5.4 Retrospective Use of Computational Methods. Manuscripts that contain experimental studies with a retrospective computational component will be considered only under the following conditions:

(a) Computational work must lead to a clearly stated message, either an improved understanding of the experimental work or a well-defined experimentally testable hypothesis.

(b) Clearly distinguish models and hypothetical statements from experimental observations both

in the text and in figure captions.

(c) Describe computational methods in sufficient detail for the reader to reproduce the results.

(d) Computational methods must be thoughtfully selected. Explain why the applied method is an appropriate choice and was chosen over similar existing methods. Calculation results, in particular those of automated modeling software, must be critically examined.

(e) Draw conclusions from modeling with an appropriate amount of caution in light of assumptions made and within the accuracy limitations of the applied computational methods. The overall amount of space (text and figures) devoted to retrospective computational work must be proportionate to its significance.

2.3.5.5 Predicted Compound Binding Modes. The prediction of compound binding modes by docking is a frequent computational application submitted to the Journal in combination with experimental data. Models derived by minor modifications of known X-ray structures are often reliable, whereas binding modes suggested on the basis of a protein homology model are usually speculative. To be considered for publication in the Journal, all binding mode predictions must be well founded. In the absence of supporting structural information, demonstrate that putative binding modes are consistent with structure–activity relationships for a series of analogues.

QSAR, pseudo-receptor, or machine learning models that are occasionally applied retrospectively to analyze biological activities observed in the context of experimental SAR studies are acceptable only when used in a predictive fashion or used to illustrate a point of central relevance for a manuscript.

2.3.5.6 Computational Data Analysis. The Journal encourages the submission of manuscripts presenting analyses of publicly available databases or data sets that provide unexpected or provocative insights into topical problems and advance medicinal chemistry knowledge. Investigations must be based upon large data sets rather than small series of compounds. Benchmark investigations, such as comparisons of virtual screening algorithms, are considered only if they provide particularly clear and generally relevant conclusions that set new standards in the field. General relevance must be clearly stated and put into scientific context.

**2.3.6 QSAR/QSPR and Proprietary Data.** The following are general requirements for manuscripts reporting work done in this area:

(1) Authors should explicitly state in the abstract, introduction, and/or results sections of the paper what is novel about the quantitative structure–activity relationships/quantitative structure–property relationships (QSAR/QSPR) study being reported. In this respect, "novel" must be presented with respect to methodology/theory and/or the findings from the system(s) studied.

(2) If a new method/theory is being reported, it should be compared and “validated” against at least one other common data set of reasonable size for which a published study exists using at least one other method/approach and preferably a method/approach that has been widely used in the field.

(3) All data and molecular structures used to carry out a QSAR/QSPR study are to be reported in the paper and/or in its supporting information or should be readily available without infringements or restrictions. The use of proprietary data is generally not acceptable.

(4) Standard QSAR/QSPR studies are considered only if the predictions are experimentally tested and if the experimental data are novel and significant. Only QSAR/QSPR analyses that provide new insights into the activity are encouraged.

Some guidelines to assist prospective Journal authors of manuscripts in the field of QSAR/QSPR that report novel methods are as follows:

(i) 3D-QSAR studies that overlap with, and enhance, structure-based design (SBD) methods are encouraged. QSAR models that lead to subsequently validated experimental findings are encouraged.

(ii) Papers reporting new QSAR/QSPR methods and approaches for facilitating a mechanistic understanding of ADMET properties, and/or for reliable ADMET screening, are welcomed.

(iii) New QSAR/ QSPR methods that interface with chem- and bio-informatics methods and/or with data-mining techniques are encouraged.

(iv) QSAR/QSPR approaches for virtual screening must demonstrate distinct advantages or advances over current virtual screening schemes. For methods falling into categories (1)-(3), the same acceptance criteria apply as for any manuscript describing new computational methods according to 2.3.5.

Specifically discouraged are (a) QSAR and QSPR modeling for data sets that have already been extensively modeled, (b) model development featuring high ratios of descriptors to data points, and (c) reports of new descriptors without clear evidence for their superiority in QSAR/QSPR modeling to existing, commonly used alternatives.

**2.3.7 Statistical Criteria.** Appropriate statistical assessment is equally important for experimental and computational studies in medicinal chemistry. Reported results generally require statistical validation. Statistical analyses of compound data are also frequently presented, which must adhere to acceptable statistical and scientific standards. Specifically:

(1) A clear and comprehensive description of experimental data or computed data underlying the analysis is required.

(2) Statistical methods used must be clearly identified. Non-standard statistical methods should be described in sufficient detail or precisely referenced.

(3) Underlying assumptions of statistical methods should be specified. For example, many statistical tests assume the presence of normal data distributions, which is often an approximation in practice.

(4) Depending on the type of experiments reported, either confidence limits must be provided or a statistical significance analysis performed. For example, assay curves must contain errors bars derived from multiple measurements.

(5) For regression curves, their uncertainty must be assessed by plotting the original data along the curve or by establishing experimental or calculation confidence limits.

(6) If average values are reported from computational analysis, their variance must be documented. This can be accomplished by providing the number of times calculations have been repeated, mean values, and standard deviations (or standard errors). Alternatively, median values and percentile ranges can be provided. Data might also be summarized in scatter plots or box plots.

(7) Reporting averages of data assigned to pre-defined value ranges and ‘averages of average values’ must be avoided.

**2.3.8 Software.** Software used as a part of computer-aided drug design (e.g., molecular modeling or QSAR) should be readily available from reliable sources, and the authors should specify where the software can be obtained. When conformational calculations are included in such

papers, the parameters employed for the relevant potential functions should be given. All details needed to reproduce the numbers in the manuscript should be indicated in the paper or as supporting information. This includes coordinates of hypothetical computer-generated receptor models. Authors should refer to *J. Med. Chem.* **1988**, *31*, 2230–2234 for publication guidelines.

**2.3.9 Structural Data.** For papers describing structures of biological macromolecules, the atomic coordinates and the related experimental data (structure factor amplitudes/intensities and/or NMR restraints) must be deposited at a member site of the Worldwide Protein Data Bank (http://www.wwpdb.org): RCSB PDB (http://www.pdb.org), Protein Databank in Europe (PDBe) (http://www.ebi.ac.uk/pdbe/docs/References.html), PDBj (http://www.pdbj.org), or BMRB (http://www.bmrb.wisc.edu). The PDB ID must appear before the references (see section 2.2.7). Authors must agree to release the atomic coordinates and experimental data when the associated article is published. Questions related to deposits should be sent to info@wwpdb.org. Papers that utilize coordinates of molecules already in the database should specify the PDB ID as a reference.

For X-ray diffraction of structures of small molecules with anisotropically refined atoms, a figure displaying the thermal ellipsoids should ordinarily be presented; a spherical-atom representation may be substituted if necessary for clarity. If a spherical atom view is chosen for the manuscript, a thermal ellipsoid figure should be included in the supporting information. In cases where intermolecular interactions are relevant to the discussion, a view of the unit cell may be included. Articles should list for each structure the formula, formula weight, crystal system, space group, unit cell parameters, temperature of data collection, and values of *Z*, *R*, and GOF in the experimental section. Tables of atom coordinates and thermal parameters will not be printed. CIF files must be deposited with Cambridge Crystallographic Data Centre (CCDC).

**2.3.10 Compound Characterization Checklist.** When manuscripts report the synthesis of compounds, submission of a completed Compound Characterization Checklist (CCC) is recommended *but not required*. The CCC form (accessed via http://pubs.acs.org/page/jmcmar/submission/authors.html) can be completed on-screen and saved for uploading with the submission of the manuscript (Supporting Information for Review Only). The CCC will be provided to reviewers to help them assess the overall thoroughness of the characterization of synthesized compounds.

# 3 Submitting the Manuscript

## 3.1 Paragon Plus Web Site

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## 3.2 Cover Letter

The cover letter should include the manuscript type and corresponding author's name, e-mail address, and telephone and fax numbers. Include special instructions (e.g., publish back-to-back with companion paper). Specify the method employed in determining purity (see 2.3.2 Purity of Tested Compounds) and that the purity requirements have been met.

## 3.3 Conflict of Interest Disclosure

A statement describing any financial conflicts of interest or lack thereof is published with each manuscript. During the submission process, the corresponding author must provide this statement on behalf of all authors of the manuscript. The statement should describe all potential sources of bias, including affiliations, funding sources, and financial or management relationships, that may constitute conflicts of interest (please see the ACS Ethical Guidelines). The statement will be published in the final article. If no conflict of interest is declared, the following statement will be published in the article: "The authors declare no competing financial interest."

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## 4. Standard Abbreviations and Acronyms

| | |
|---|---|
| α | observed optical rotation in degrees |
| [α] | specific rotation [expressed without units; the units, (deg·mL)/(g·dm), are understood] |
| δ | chemical shift in parts per million downfield from tetramethylsilane |
| μ | micro |
| Å | angstrom(s) |
| °C | degrees Celsius |
| 2-D | two-dimensional (also 2D) |
| 3-D | three-dimensional (also 3D) |
| 5HT | 5-hydroxytryptamine (serotonin) |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN–H | 9-borabicyclo[3.3.1]nonane |
| Aβ | amyloid β-protein |
| aa | amino acid |
| AA | arachidonic acid |
| Ac | acetyl |
| Acac | acetylacetonate |
| AcCh; ACh | acetylcholine |
| AcChE; AChE | acetylcholine esterase |
| ACE | angiotensin-converting enzyme |
| ACP | acyl carrier protein |
| ACTH | adrenocorticotropic hormone |
| AD | Alzheimer's disease |
| ADH | antidiuretic hormone |
| ADME | absorption, distribution, metabolism and excretion |
| ADMET | absorption, distribution, metabolism, excretion, and toxicity |
| ADP | adenosine 5'-diphosphate |
| ADR | adverse drug reaction |
| AE | adverse event |
| AIBN | 2,2'-azobisisobutyronitrile |
| AIDS | acquired immune deficiency syndrome |
| ALK | anaplastic lymphoma kinase |
| ALS | amyotrophic lateral sclerosis |
| AM1 | Austin model 1 |
| AMI | acute myocardial infarction |
| AML | acute myelogenous leukemia |
| AMP | adenosine 5'-monophosphate; adenosine 5'-phosphate |
| AMPA | 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid |
| Anal. | combustion elemental analysis |
| anhyd; anh | anhydrous |
| ANP | atrial natriuretic peptide |
| antilog | antilogarithm |
| AO | atomic orbital |
| API | active pharmaceutical ingredient |
| ApoB | Apolipoprotein B |
| ApoE | Apolipoprotein E |
| APP | amyloid-β precursor protein |
| aq | aqueous |
| Ar | aryl |
| ARB | angiotensin receptor blocker |
| ARDS | adult respiratory distress syndrome |
| atm | atmosphere(s) |
| ASO | antisense oligonucleotide |
| ATP | adenosine 5'-triphosphate |
| ATPase | adenosine triphosphatase |
| AUC | area under the curve |

| | |
|---|---|
| b.i.d. | twice a day |
| B3LYP | 3-parameter hybrid Becke exchange/ Lee–Yang–Parr correlation functional |
| BACE | beta-site amyloid precursor protein cleaving enzyme |
| BACE-1 | beta-secretase |
| BBB | blood-brain barrier |
| BChE; BuChE | butyrylcholinesterase |
| Bcl-xL | B-cell lymphoma-extra large |
| BMI | body mass index |
| Bn | benzyl |
| BOC, boc | *tert*-butoxycarbonyl |
| bp | boiling point; base pair |
| BPH | Benign Prostatic Hypertrophy |
| BRCA1 | breast cancer gene 1 |
| BSA | bovine serum albumin |
| Bu, *n*-Bu | normal (primary) butyl |
| BUN | blood urea nitrogen |
| Bz | benzoyl (not benzyl) |
| ca. | circa, about [used before an approximate date or figure (ca. 1960)] |
| CADD | computer-assisted drug design |
| calcd | calculated |
| cAMP | 3',5'-cyclic adenosine monophosphate |
| CAN | ceric ammonium nitrate |
| CASPT2 | complete active space with second-order perturbation theory |
| CASSCF | complete active space self-consistent field |
| cat | catalytic |
| CB | cannabinoid |
| CBC | complete blood count |
| CBZ, Cbz | benzyloxycarbonyl (preferred over the abbreviation Z) |
| CC | coupled cluster |
| CCK | cholecystokinin |
| CD | circular dichroism |
| CDC | center for disease control |
| CDER | Center for Drug Evaluation and Research, FDA |
| CDK | cyclin-dependent kinase |
| cDNA | complementary deoxyribonucleic acid |
| CETP | cholesteryl ester transfer protein |
| cGLP | current good laboratory practices |
| cGMP | current good manufacturing practice; 3,5'-cyclic guanosine monophosphate |
| CGRP | calcitonin gene-related peptide |
| CHF | congestive heart failure |
| CHK1 | checkpoint kinase 1 |
| CHK2 | checkpoint kinase 2 |
| CHMP | Committee for Medicinal Products for Human Use |
| Ci | curie |
| CI | chemical ionization; configuration interaction |
| CIDNP | chemically induced dynamic nuclear polarization |
| CIF | crystallographic information file |
| CKD | chronic kidney disease |
| cLopP | calculated logP |
| cm | centimeter(s) |
| $cm^{-1}$ | wavenumber(s) |
| CML | chronic myelogenous leukemia |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CoA | coenzyme A |
| cod | 1,5-cyclooctadiene |
| CoMFA | comparative molecular field analysis |
| compd | compound |
| CoMSIA | computational molecular similarity index analysis |
| concd | concentrated |
| conc; concn | concentration |
| COPD | chronic obstructive pulmonary disease |
| CoQ | coenzyme Q10 |
| COSY | correlation spectroscopy |
| COX | cyclooxygenase |
| Cp | cyclopentadienyl |
| CRH | corticotrophin-releasing hormone |
| CRP | C-reactive protein |
| CSF | cerebrospinal fluid |
| CV | cyclic voltammetry |
| Cy | cyclohexyl |
| CYP | cytochrome P |
| d | day(s); doublet (spectral); deci |
| *d* | density |
| DA | dopamine |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DART | developmental and reproductive toxicology |
| DAT | dopamine transporter |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBP | diastolic blood pressure |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N*,*N'*-dicyclohexylcarbodiimide |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DDI | drug-drug interaction |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DDT | 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane |
| de | diastereomeric excess |
| DEAD | diethyl azodicarboxylate |
| dec | decomposition |
| DEPT | distortionless enhancement by polarization transfer |

| | |
|---|---|
| DFT | density functional theory |
| DIBALH | diisobutylaluminum hydride |
| DIO | diet induced obesity |
| DLT | dose limiting toxicity |
| DMA | dimethylacetamide |
| DMAP | 4-(*N*,*N*-dimethylamino)pyridine |
| DMDO | dimethyldioxirane |
| DME | 1,2-dimethoxyethane |
| DMF | dimethylformamide |
| DMPK | drug metabolism and pharmacokinetics |
| DMPU | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone |
| DMSO | dimethyl sulfoxide |
| DMT | 4,4'-dimethoxytrityl (4,4'-dimethoxyltriphenylmethyl) |
| DNA | deoxyribonucleic acid |
| Dopa | 3-(3,4-dihydroxyphenyl)alanine (also DOPA) |
| DTT | dithiothreitol |
| e.g. | for example (exempli gratia) |
| E1 | unimolecular elimination |
| E2 | bimolecular elimination |
| $EC_{50}$ | half maximal effective concentration |
| ECG | electrocardiogram |
| $ED_{50}$ | dose effective in 50% of test subjects |
| EDTA | ethylenediaminetetraacetic acid |
| ee | enantiomeric excess |
| EEG | electroencephalogram |
| EGF | epidermal growth factor |
| EGFR | epidermal growth factor receptor |
| EI | electron impact |
| EKG | electrocardiogram |
| ELISA | enzyme-linked immunosorbent assay |
| EPR | electron paramagnetic resonance |
| eq | equation |
| equiv | equivalent |
| er | enantiomer ratio |
| ERK | extracellular regulated kinase |
| ESI | electrospray ionization |
| ESR | electron spin resonance |
| Et | ethyl |
| et al. | and others |
| etc. | and so forth |
| F% | % oral bioavailability |
| FAAH | fatty acid amide hydrolase |
| FAB | fast atom bombardment |
| FAD | flavin adenine dinuleotide |
| FaSSIF | fasted state simulated intestinal fluid |
| FBDD | fragment-based drug discovery |
| FD | field desorption |
| FDA | Food and Drug Administration |
| FeSSIF | fed state simulated intestinal fluid |
| FGF | fibroblast growth factor |
| FID | flame ionization detector; free induction decay |
| Fmoc | 9-fluorenylmethoxycarbonyl |
| FRET | Förster resonance energy transfer |
| FSH | follicle-stimulating hormone |
| FT | Fourier transform |
| g | gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g. gCOSY, gHMQC) |
| GABA | γ-aminobutyric acid |
| GC | gas chromatography |
| GDP | guanosine 5'-diphosphate |
| GERD | gastroesophogeal reflux disease |
| GFP | green fluorescent protein |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| GLP-1 | glucagon like peptide-1 |
| GlyR | glycine receptor |
| GMP | guanosine 5'-monophosphate; guanosine 5'-phosphate |
| GnRH | gonadotropin-releasing hormone |
| GPCR | G-protein coupled receptor |
| GFR | growth factor receptor |
| GST | glutathione S-transferase |
| GTP | guanosine 5'-triphosphate |
| h | hour(s); human |
| HBA | hydrogen bond acceptors |
| HBD | hydrogen bond donors |
| HBV | hepatitis B virus |
| HCS | high-content screening |
| HCV | hepatitis C virus |
| HDAC | histone deacetylase |
| hERG | human Ether-a-go-go-Related Gene |
| HDL-C | high-density lipoprotein cholesterol |
| HEK | human embryonic kidney |
| HF | Hartree–Fock |
| HGH | human growth hormone |
| HIV | human immunodeficiency virus |
| HMBC | heteronuclear multiple bond correlation |
| HMPA | hexamethylphosphoric triamide (hexamethylphosphoramide) |
| HMQC | heteronuclear multiple quantum correlation |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography; high-pressure liquid chromatography |
| HPV | human papilloma virus |
| HR | heart rate |
| HRMS | high-resolution mass spectrometry |
| HRT | hormone replacement therapy |
| HSA | human serum albumin |
| HSP | heat shock protein |
| HSQC | heteronuclear single quantum correlation |

| | |
|---|---|
| HSV | herpes simplex virus |
| HTS | high throughput screening |
| Hz | hertz |
| i-NOS | inducible nitric oxide synthase |
| *i*-Pr | isopropyl |
| $IC_{50}$ | half-maximum inhibitory concentration |
| IBD | inflammatory bowel disease |
| IBS | irritable bowel syndrome |
| ICR | ion cyclotron resonance |
| icv | intracerebroventricular (dosing) |
| Ig | immunoglobulin |
| iGluR | ionotropic glutamate receptor |
| IHC | immunohistochemistry |
| IM | intramuscularly |
| INDO | intermediate neglect of differential overlap |
| ip | intraperitoneally |
| IP | ionization potential |
| IR | infrared |
| it | intrathecal |
| iv | intravenous |
| IVUS | intravascular ultrasound |
| *J* | coupling constant (in NMR spectrometry) |
| K | kelvin(s) (absolute temperature) |
| k | kilo |
| $K_i$ | inhibition constant |
| Km | Michaelis constant |
| L | liter(s) |
| LAH | lithium aluminum hydride |
| LBD | ligand binding domain |
| LC | liquid chromatography |
| LC-MS | liquid chromatography-mass spectrometry |
| LCAO | linear combination of atomic orbitals |
| $LD_{50}$ | dose that is lethal in 50% of test subjects |
| LDA | lithium diisopropylamide; local density approximation |
| LDL-C | low-density lipoprotein cholesterol |
| LE | ligand efficiency |
| LFER | linear free energy relationship |
| LFT | liver function test |
| LH | luteinizing hormone |
| LHMDS | lithium hexamethyldisilazane; lithium bis(trimethylsilyl)amide |
| LHRH | luteinizing hormone releasing hormone |
| lit. | literature value (abbreviation used with period) |
| LogP | logarithm of partition coefficient |
| LPS | lipopolysaccharide |
| LTMP | lithium 2,2,6,6-tetramethylpiperidide |
| LTP | long-term potentiation |
| LUMO | lowest unoccupied molecular orbital |
| M | molar (moles per liter); mega |
| m | multiplet (spectral); meter(s); milli; isotopic mass; magnetic quantum number (ESR and NMR spectroscopy); meta; molal (mol kg-1) |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| *m/z* | mass-to-charge ratio (not *m/e*) |
| $M^+$ | parent molecular ion |
| mAcChR | muscarinic ACh receptor |
| MALDI | matrix-assisted laser desorption ionization |
| MAP | mean arterial pressure |
| MAPK | mitogen-activated protein kinase |
| max | maximum |
| MCD | magnetic circular dichroism |
| MCR | multicomponent reaction |
| MCSCF | multi-configuration self-consistent field |
| MD | molecular dynamics |
| MDR | multidrug resistance |
| Me | methyl |
| MED | medium effective dose/minimum efficacious dose |
| MEM | (2-methoxyethoxy)methyl |
| Mes | 2,4,6-trimethylphenyl (mesityl) [not methylsulfonyl (mesyl)] |
| mGluR | metabotropic glutamate receptor |
| MHC | major histocompatibility complex |
| MHz | megahertz |
| MIC | minimal inhibitory concentration |
| min | minute(s); minimum |
| mL | milliliter |
| mM | millimolar (millimoles per liter) |
| MMP | matrix metalloproteinase |
| MO | molecular orbital |
| MOA | mechanism of action |
| mol | mole(s); molecular (as in mol wt) |
| MOM | methoxymethyl |
| mp | melting point |
| MP | Møller–Plesset perturbation theory |
| MRCI | multi-reference configuration interaction |
| MRSA | methicillin-resistant Staphylococcus aureus |
| MRI | magnetic resonance imaging |
| mRNA | messenger RNA |
| mRNA | messenger ribonucleic acid |
| MRSA | methicillin-resistant Staphylococcus aureus |
| MS | mass spectrometry |
| Ms | methylsulfonyl (mesyl) |

| | |
|---|---|
| MTBE | methyl *tert*-butyl ether |
| MTD | maximum tolerated dose |
| MW, mol wt | molecular weight |
| nAcChR | nicotinic ACh receptor |
| $NAD^+$ | nicotinamide adenine dinucleotide |
| NADH | reduced nicotinamide adenine dinucleotide |
| NADP | nicotinamide adenine dinucleotide phosphate |
| NADPH | reduced nicotinamide adenine dinucleotide phosphate |
| NAM | negative allosteric modulator |
| NBO | natural bond orbital |
| NBS | *N*-bromosuccinimide |
| NCE | new chemical entity |
| NCI | National Cancer Institute |
| NCS | *N*-chlorosuccinimide |
| NDA | new drug application |
| NE | norepinephrine |
| NF-kB | nuclear factor k B |
| NICS | nucleus-independent chemical shift |
| NIH | National Institutes of Health |
| nm | nanometer(s) |
| NMDA | *N*-methyl-D-aspartic acid |
| NME | new molecular entity |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMP | *N*-methylpyrrolidone |
| NMR | nuclear magnetic resonance |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NO | nitric oxide |
| NOAEL | no adverse effect level |
| NOE | nuclear Overhauser effect |
| NOEL | no-effect level |
| NOESY | nuclear Overhauser effect spectroscopy |
| NOS | nitric oxide synthase |
| NPY | neuropeptide Y |
| NRT | natural resonance theory |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NSAID | non-steroidal anti-inflammatory drug |
| NSCLC | non-small cell lung cancer |
| Nu | nucleophile |
| o | ortho |
| obsd | observed |
| OCT | organic cation transporter |
| OD | optical density |
| ORD | optical rotary dispersion |
| p | para |
| PAF | platelet activating factor |
| PAGE | polyacrylamide gel electrophoresis |
| PAM | positive allosteric modulator |
| PAMPA | parallel artificial membrane permeability assay |
| PAS | peripheral anionic site |
| PBO | placebo |
| PBS | phosphate buffered saline |
| PCA | principle component analysis |
| PCC | pyridinium chlorochromate |
| PCR | polymerase chain reaction |
| PD | pharmacodynamics; Parkinson's disease |
| PDB | Protein Data Bank |
| PDC | pyridinium dichromate |
| PDE | phosphodiesterase |
| PEG | polyethylene glycol |
| PES | photoelectron spectroscopy |
| PET | positron emission tomography |
| P-gp | P-glycoprotein |
| Ph | phenyl |
| PI3K | phosphoinositide 3-kinase |
| PIPES | 1,4-piperazinediethanesulfonic acid; piperazine-N,N'-bis(2-ethanesulfonic acid) |
| PK | pharmacokinetics |
| PKA | protein kinase A |
| PKB | protein kinase B |
| PKC | protein kinase C |
| PLS | partial least squares |
| pm | picometer(s) |
| PM3 | parametric method 3 |
| PMB | *p*-methoxybenzyl |
| PNS | peripheral nervous system |
| po | oral administration |
| PPA | poly(phosphoric acid) |
| PPAR | peroxisome proliferator-activated receptor |
| PPB | plasma protein binding |
| ppm | part(s) per million |
| PPTS | pyridinium *para*-toluenesulfonate |
| Pr | propyl |
| PRH | prolactin releasing hormone |
| PSA | polar surface area |
| psi | pounds per square inch |
| PT | perturbation theory; prothrombin time |
| PTT | partial thromboplastin time |
| PTC | phase-transfer catalysis |
| PTH | parathyroid hormone |
| PXR | pregnane X receptor |
| py | pyridine |
| q | quartet (spectral) |
| q.d. | once daily ("quaque die") |
| q.i.d. | four times a day (dosing) ("quater in die") |
| QSAR | quantitative structure–activity relationship |
| QSPR | quantitative structure-property relationship |

| | |
|---|---|
| QW | once a week (dosing) |
| RAS | renin-angiotensin system |
| RBC | red blood cell |
| RCM | ring-closure metathesis |
| redox | reduction–oxidation |
| $R_f$ | retention factor (in chromatography) |
| RHF | restricted Hartree–Fock |
| RIA | radioimmunoassay |
| rmsd | root mean square deviation |
| RNA | ribonucleic acid |
| RO5 | rule of five (Lipinski) |
| ROESY | rotating frame Overhauser effect spectroscopy |
| ROMP | ring-opening metathesis polymerization |
| ROS | reactive oxygen species |
| rpm | revolutions per minute |
| rRNA | ribosomal ribonucleic acid |
| rt | room temperature |
| s | singlet (spectral); second(s) |
| *s*-Bu | *sec*-butyl |
| SAHA | suberoylanilide hydroxamic acid |
| SAR | structure–activity relationship |
| SARM | selective androgen receptor modulator |
| SBDD | structure-based drug discovery |
| SBP | systolic blood pressure |
| sc | subcutaneous |
| SCF | self-consistent field |
| SDS | sodium dodecyl sulfate |
| SEM | scanning electron microscopy |
| SERM | selective estrogen-receptor modulator |
| SERT | serotonin transporter |
| SET | single electron transfer |
| SFC | supercritical fluid chromatography |
| SIRT1 | silent mating type information regulation 2 homolog 1 |
| $S_N'$ | nucleophilic substitution with allylic rearrangement |
| $S_N1$ | unimolecular nucleophilic substitution |
| $S_N2$ | bimolecular nucleophilic substitution |
| SNP | single nucleotide polymorphism |
| SOMO | single-occupied molecular orbital |
| SPECT | single-photon emission computed tomography |
| PR | surface plasmon resonance; stroboscopic pulse radiolysis |
| SSRI | selective serotonin reuptake inhibitor |
| *T* | absolute temperature in units of kelvins (K) |
| *t* | time; temperature in units of degrees Celsius (°C) |
| t | triplet (spectral) |
| *t*-Bu | *tert*-butyl |
| $t_{1/2}$ | half-time |
| t.i.d. | three times daily ("ter in die") |
| T2DM | type 2 diabetes mellitus |
| TAE | tris-acetate-EDTA |
| TB | tuberculosis |
| TBAB | tetrabutylammonium bromide |
| TBAC | tetrabutylammonium chloride |
| TBAF | tetrabutylammonium fluoride |
| TBHP | *tert*-butyl hydroperoxide |
| TBS | *tert*-butyldimethylsilyl |
| TCA | trichloroacetic acid |
| TCA | tricyclic antidepressant |
| TCNE | tetracyanoethylene |
| TDDFT | time-dependent density functional theory |
| TEAB | tetraethylammonium bromide |
| temp | temperature |
| Tf | trifluoromethanesulfonyl (triflyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyran-2-yl |
| TIPS | triisopropylsilyl |
| TK | toxicokinetics |
| TLC | thin-layer chromatography |
| TLR | toll-like receptor |
| TMAI | tetramethylammonium iodide |
| TMEDA | *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine |
| TMS | trimethylsilyl; tetramethylsilane |
| TNF | tumor necrosis factor |
| TNF-alpha | tumor necrosis factor-alpha |
| TOF | time of flight |
| TON | turn over number (in catalysis) |
| $^tR$ | retention time (in chromatography) |
| Tr | triphenylmethyl (trityl) |
| Tris | tris(hydroxymethyl)aminomethane |
| tRNA | transfer ribonucleic acid |
| Ts | para-toluenesulfonyl (tosyl) |
| TS | transition state |
| TSH | thyroid stimulating hormone |
| TT | thrombin time |
| UDP | uridine 5'-diphosphate |
| UHF | unrestricted Hartree–Fock |
| UHPLC | ultra-high pressure liquid chromatography |
| UV | ultraviolet |
| v.i. | see below (vide infra) |
| v.s. | see above (vide supra) |
| v/v | volume per unit volume (volume-to-volume ratio) |
| VCD | vibrational circular dichroism |

| | | | |
|---|---|---|---|
| VEGFR | vascular endothelial growth factor receptor | WT | wild type |
| | | wt | weight |
| vis | visible | | |
| viz. | namely | XAFS | X-ray absorption fine structure spectroscopy |
| VLDL | very low density lipoprotein | | |
| vol | volume | | |
| VRE | vancomycin resistant enterococci | ZINDO | Zerner parameterization of intermediate neglect of differential overlap |
| WBA | whole body autoradiography | | |
| w/w | weight per unit weight (weight-to-weight ratio) | | |

STANDARD AMINO ACID ABBREVIATIONS:

•The three-letter code or name may be used in the text.

•With a single amino acid, use the three-letter code (e.g., Met246).

•If more than one amino acid is specified, as in mutants or substitutions, use one-letter code (S238H).

•When two or more amino acids are used in a string, use either the three-letter code or single letter (e.g., His-Ile-Thr-Ser or HITS).

•For use of D amino acids, use the 3 letter abbreviation only (e.g., DAla)

| | | | | | |
|---|---|---|---|---|---|
| alanine | Ala | A | leucine | Leu | L |
| arginine | Arg | R | lysine | Lys | K |
| asparagine | Asn | N | methionine | Met | M |
| aspartic acid | Asp | D | phenylalanine | Phe | F |
| cysteine | Cys | C | proline | Pro | P |
| glutamic acid | Glu | E | serine | Ser | S |
| glutamine | Gln | Q | threonine | Thr | T |
| glycine | Gly | G | tryptophan | Trp | W |
| histidine | His | H | tyrosine | Tyr | Y |
| isoleucine | Ile | I | valine | Val | V |

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