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# Potent Inhibitors of Subgenomic Hepatitis C Virus RNA Replication through Optimization of Indole- N -Acetamide Allosteric Inhibitors of the Viral NS5B Polymerase

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## 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.

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# 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 clinical 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 Articles*.

**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](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 *Miniperspectives*.

**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 abbreviations are mp, bp, °C, K, min, h, mL,  $\mu$ L, g, mg,  $\mu$ g, cm, mm, nm, mol, mmol,  $\mu$ mol, 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/jmcmr/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/jmcmr/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/jmcmr/submission/jmcmr\\_mfstrings.html](http://pubs.acs.org/page/jmcmr/submission/jmcmr_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,  $\mu$ mol/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  $^1\text{H}$  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  $\geq 95\%$  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  $^1\text{H}$  or  $^{13}\text{C}$  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,  $^1\text{H}$  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:  $[\alpha]^{20}_{\text{D}} 25$  ( $c$  1.9,  $\text{CHCl}_3$ ), where the concentration  $c$  is in g/100 mL and the path length  $l$  is in decimeters. The units of the specific rotation,  $(\text{deg}\cdot\text{mL})/(\text{g}\cdot\text{dm})$ , 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 ( $^1H$  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](mailto: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

Manuscripts must be submitted via the ACS Paragon Plus Environment (<http://paragonplus.acs.org/login>). Complete instructions and an overview of the electronic online (Web) submission process are available through the secure ACS Paragon Plus Web site. Authors will view the PDF version of their manuscripts prior to formal submission to the Editor. In order to use Web submission, authors must be able to provide electronic versions of text and graphics. Supporting information should also be submitted electronically via the Web site (as a separate document). Instructions on [supported platforms and word processing packages](#) are available at the submission site.

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[Authors](#) on the Web prior to submission of a manuscript. Close attention to all the required details discussed in Guidelines for Authors will expedite review and reduce the time to publication.

### 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."

### 3.4 Journal Publishing Agreement

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During manuscript submission, the submitting author must provide contact information (full name, email address, institutional affiliation and mailing address) for all of the co-authors. Because all of the author names are automatically imported into the electronic Journal Publishing Agreement, the names must be entered into ACS Paragon Plus in the same sequence as they appear on the first page of the manuscript. (Note that co-authors are not required to register in ACS Paragon Plus.) The author who submits the manuscript for publication accepts the responsibility of notifying all co-authors that the manuscript is being submitted. Deletion of an author after the manuscript has been submitted requires a confirming letter to the assigned editor from the author whose name is being deleted. For more information on ethical responsibilities of authors, see the [Ethical Guidelines to Publication of Chemical Research](#).

### 3.6 Funding Sources

When submitting a manuscript to the Journal via ACS Paragon Plus, the submitting author is asked to identify the funding sources for the work presented in the manuscript. Identifying funding sources is optional during submission of an original manuscript. Funding source information is required when a revised manuscript is submitted.

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### 3.8 Revision

*Articles*, *Brief Articles*, *Perspectives*, and *Drug Annotations* revisions must be submitted within 30 days of a minor revision request and 60 days of a major revision request.

### 3.9 Proofs

The corresponding author of an accepted manuscript will receive e-mail notification and complete instructions when page proofs are available for review via a secure Web site. Authors will access the secure site through ACS ChemWorx and will need an ACS ID. To obtain an ACS ID or to reset your password, go to [www.acschemworx.org](http://www.acschemworx.org).

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Correspondence regarding accepted papers, proofs, and reprints should be directed to Journal Publications, American Chemical Society, 2540 Olentangy River Road, P.O. Box 3330, Columbus, OH 43210; 614-447-3665; fax, 614-447-3745; [acsproof@acs.org](mailto:acsproof@acs.org).

Accepted manuscripts will be published on the “Articles ASAP” page on the Journal Web site as soon as page proofs are corrected and all author concerns are resolved. Publication on the Web usually occurs within 4 working days of receipt of page proof corrections, and this can be anywhere from 3 to 6 weeks in advance of the cover date of the issue. Manuscripts assigned to a special issue often remain published ASAP for several months. Unless the paper has already been published as a *Just Accepted* manuscript, authors should take this schedule into account when planning intellectual and patent activities related to a manuscript. The first date on which an accepted paper is published on the Web (be it *Just Accepted*, ASAP, or issue) is recorded in the Web version of the manuscript and on the first page of the PDF version.

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Articles may be retracted for scientific or ethical reasons. Articles that contain seriously flawed or erroneous data such that their findings and conclusions cannot be relied upon may be retracted in order to correct the scientific record. Retractions may be requested by the article author(s) or by the journal Editor(s) but are ultimately published at the discretion of the Editor. When an article is retracted, a notice of Retraction will be published containing information about the original article title, author list, and the reason for the Retraction. Retracted articles will be accompanied by the related Retraction notice and will be marked as “Retracted”. The originally published article will remain on the Web except in extraordinary circumstances (e.g., where deemed legally necessary, or if the availability of the published content poses public health risks). The American Chemical Society follows guidance from the Committee on Publication Ethics (COPE) when considering retractions; for more information see <http://publicationethics.org/>.

## 4. Standard Abbreviations and Acronyms

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

b.i.d.	twice a day	Ci	curie
B3LYP	3-parameter hybrid Becke exchange/ Lee–Yang–Parr correlation functional	CI	chemical ionization; configuration interaction
BACE	beta-site amyloid precursor protein cleaving enzyme	CIDNP	chemically induced dynamic nuclear polarization
BACE-1	beta-secretase	CIF	crystallographic information file
BBB	blood-brain barrier	CKD	chronic kidney disease
BChE; BuChE	butyrylcholinesterase	cLopP	calculated logP
Bcl-xL	B-cell lymphoma-extra large	cm	centimeter(s)
BMI	body mass index	cm <sup>-1</sup>	wavenumber(s)
Bn	benzyl	CML	chronic myelogenous leukemia
BOC, boc	<i>tert</i> -butoxycarbonyl	CMV	cytomegalovirus
bp	boiling point; base pair	CNS	central nervous system
BPH	Benign Prostatic Hypertrophy	CoA	coenzyme A
BRCA1	breast cancer gene 1	cod	1,5-cyclooctadiene
BSA	bovine serum albumin	CoMFA	comparative molecular field analysis
Bu, <i>n</i> -Bu	normal (primary) butyl	compd	compound
BUN	blood urea nitrogen	CoMSIA	computational molecular similarity index analysis
Bz	benzoyl (not benzyl)	concd	concentrated
ca.	circa, about [used before an approximate date or figure (ca. 1960)]	conc; concn	concentration
CADD	computer-assisted drug design	COPD	chronic obstructive pulmonary disease
calcd	calculated	CoQ	coenzyme Q10
cAMP	3',5'-cyclic adenosine monophosphate	COSY	correlation spectroscopy
CAN	ceric ammonium nitrate	COX	cyclooxygenase
CASPT2	complete active space with second-order perturbation theory	Cp	cyclopentadienyl
CASSCF	complete active space self-consistent field	CRH	corticotrophin-releasing hormone
cat	catalytic	CRP	C-reactive protein
CB	cannabinoid	CSF	cerebrospinal fluid
CBC	complete blood count	CV	cyclic voltammetry
CBZ, Cbz	benzyloxycarbonyl (preferred over the abbreviation Z)	Cy	cyclohexyl
CC	coupled cluster	CYP	cytochrome P
CCK	cholecystokinin	d	day(s); doublet (spectral); deci
CD	circular dichroism	<i>d</i>	density
CDC	center for disease control	DA	dopamine
CDER	Center for Drug Evaluation and Research, FDA	DABCO	1,4-diazabicyclo[2.2.2]octane
CDK	cyclin-dependent kinase	DART	developmental and reproductive toxicology
cDNA	complementary deoxyribonucleic acid	DAT	dopamine transporter
CETP	cholesteryl ester transfer protein	DBN	1,5-diazabicyclo[4.3.0]non-5-ene
cGLP	current good laboratory practices	DBP	diastolic blood pressure
cGMP	current good manufacturing practice; 3,5'-cyclic guanosine monophosphate	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
CGRP	calcitonin gene-related peptide	DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
CHF	congestive heart failure	DCE	1,2-dichloroethane
CHK1	checkpoint kinase 1	DCM	dichloromethane
CHK2	checkpoint kinase 2	DDI	drug-drug interaction
CHMP	Committee for Medicinal Products for Human Use	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	FGF	fibroblast growth factor
DIBALH	diisobutylaluminum hydride	FID	flame ionization detector; free induction decay
DIO	diet induced obesity	Fmoc	9-fluorenylmethoxycarbonyl
DLT	dose limiting toxicity	FRET	Förster resonance energy transfer
DMA	dimethylacetamide	FSH	follicle-stimulating hormone
DMAP	4-( <i>N,N</i> -dimethylamino)pyridine	FT	Fourier transform
DMDO	dimethyldioxirane		
DME	1,2-dimethoxyethane	g	gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g. gCOSY, gHMQC)
DMF	dimethylformamide		
DMPK	drug metabolism and pharmacokinetics	GABA	$\gamma$ -aminobutyric acid
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i> )-pyrimidinone	GC	gas chromatography
DMSO	dimethyl sulfoxide	GDP	guanosine 5'-diphosphate
DMT	4,4'-dimethoxytrityl (4,4'-dimethoxyltriphenylmethyl)	GERD	gastroesophageal reflux disease
DNA	deoxyribonucleic acid	GFP	green fluorescent protein
Dopa	3-(3,4-dihydroxyphenyl)alanine (also DOPA)	GFR	glomerular filtration rate
DTT	dithiothreitol	GI	gastrointestinal
		GLP-1	glucagon like peptide-1
		GlyR	glycine receptor
e.g.	for example (exempli gratia)	GMP	guanosine 5'-monophosphate; guanosine 5'-phosphate
E1	unimolecular elimination	GnRH	gonadotropin-releasing hormone
E2	bimolecular elimination	GPCR	G-protein coupled receptor
EC <sub>50</sub>	half maximal effective concentration	GFR	growth factor receptor
ECG	electrocardiogram	GST	glutathione S-transferase
ED <sub>50</sub>	dose effective in 50% of test subjects	GTP	guanosine 5'-triphosphate
EDTA	ethylenediaminetetraacetic acid	h	hour(s); human
ee	enantiomeric excess	HBA	hydrogen bond acceptors
EEG	electroencephalogram	HBD	hydrogen bond donors
EGF	epidermal growth factor	HBV	hepatitis B virus
EGFR	epidermal growth factor receptor	HCS	high-content screening
EI	electron impact	HCV	hepatitis C virus
EKG	electrocardiogram	HDAC	histone deacetylase
ELISA	enzyme-linked immunosorbent assay	hERG	human Ether-a-go-go-Related Gene
EPR	electron paramagnetic resonance	HDL-C	high-density lipoprotein cholesterol
eq	equation	HEK	human embryonic kidney
equiv	equivalent	HF	Hartree–Fock
er	enantiomer ratio	HGH	human growth hormone
ERK	extracellular regulated kinase	HIV	human immunodeficiency virus
ESI	electrospray ionization	HMBC	heteronuclear multiple bond correlation
ESR	electron spin resonance	HMPA	hexamethylphosphoric triamide (hexamethylphosphoramide)
Et	ethyl	HMQC	heteronuclear multiple quantum correlation
et al.	and others	HOMO	highest occupied molecular orbital
etc.	and so forth	HPLC	high-performance liquid chromatography; high-pressure liquid chromatography
F%	% oral bioavailability	HPV	human papilloma virus
FAAH	fatty acid amide hydrolase	HR	heart rate
FAB	fast atom bombardment	HRMS	high-resolution mass spectrometry
FAD	flavin adenine dinucleotide	HRT	hormone replacement therapy
FaSSIF	fasted state simulated intestinal fluid	HSA	human serum albumin
FBDD	fragment-based drug discovery	HSP	heat shock protein
FD	field desorption	HSQC	heteronuclear single quantum correlation
FDA	Food and Drug Administration		
FeSSIF	fed state simulated intestinal fluid		



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

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

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

VEGFR	vascular endothelial growth factor receptor	WT wt	wild type 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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