

## Instructions for Contributors Preparing Camera-ready Typescripts

These instructions are designed to assist contributors and their typists in preparing camera-ready typescripts in a form and style that will facilitate the production process. Please read them very carefully and follow the specifications they contain.

### 1 Submission of Typescripts

The final typescript and a photocopy should be sent to the Editor. Authors are advised to retain a copy of the complete chapter. Please do not staple, fold, or crease the pages of the original.

### 2 Preparation of Typescripts

A word processing package should be used in conjunction with a laser or inkjet printer. Document settings should follow the guidelines given below; the typeface is *Times New Roman 12 point*.

Alternatively, a simple template document has been created in order to assist authors in the preparation of typescripts. Settings within the template have already been fixed in accordance with the specifications given here so that the correct layout and style of material is produced. Further details are given in the instructions that follow. NB: it is important that **all** instructions are read in conjunction with whichever method of preparation is chosen.

**Typing Paper, Margins and Spacing**<sup>†</sup> – The typescript should be prepared on the specially formatted paper whenever possible. Set the margins to the following measures: top 3.5 cm; bottom 1.8 cm; left 3.5 cm; right 2.0 cm. These yield suitable margins for printing on the formatted paper; do not leave extra margins inside the blue outlines. The text should be *justified* and occupy the whole page area; it should also, as far as possible, be parallel, to the top and bottom blue margins. Single spacing between lines should be used.

Do not leave pages short of the bottom margin. If there is insufficient space for a Figure or Table at the bottom of the page, complete the page with subsequent text and place the Figure or Table at the top of the next page.

The typescript may also be prepared on plain paper, as long as the margins and spacing are set, as above, to correspond to the print area of 154 × 240 mm, as on the blue lined paper.

**Chapter or Paper Title** – The title and the names and addresses of each author should be typed on the first page where shown on the special paper. The text should then begin on line 18. Subsequent pages begin on line 1.

**Headings** – Over-organisation of the text should be avoided, as should putting headings as the last entry on a page. Headings and

sub-headings of the same value should be typed in the same manner throughout the typescript according to the following style.

#### 1 MAIN HEADING

Main headings are *indented 5 spaces*, numbered with arabic numerals followed by *2 spaces*, and typed in *capitals*. There should be two lines of space above the heading and one space below it. The first line of text following the main heading is typed flush left.

#### 1.1 First-value Sub-heading

First-value sub-headings are typed *flush left with initial capitals* for all principal words, compound numbered, *i.e.* 1.1, 1.2, *etc.*, and bold. There should be one line space above and one line space below.

*1.1.1 Second-value Sub-heading.* Second-value sub-headings are typed as part of the succeeding paragraph with initial capitals for all principal words, compound numbered, and *italic*. They are *indented 5 spaces* and followed by a full stop before running on to the text. No line space should be left above the heading.

**Paragraphing** – The first line of each paragraph should be indented except when following a main heading. A line should not be left between paragraphs.

**Numbering the Typescript Pages** – The pages should be arranged in the desired sequence and numbered consecutively in blue crayon or pencil in the bottom right-hand corner outside the blue outline of the paper.

### 3 Presentation of Material

**Figures and Structural Formulae** – Artwork should if possible be original, top copy drawings. Good photocopies may be used if necessary but will usually not reproduce so well. Please bear in mind the final page size. The typescript will be reduced to 80% in the reproduction operation and the maximum final width for a Figure after reduction is 120 mm. Detailed Figures designed to fill a whole page may have unacceptably small lettering when reduced to fit the book page; use lettering of 9–10pt to obtain adequate clarity following reproduction (capital letters about 2–2.5 mm in height).

Modern laser or inkjet printers can produce very good looking grey-shaded illustrations. Such illustrations are, however, very difficult to reproduce satisfactorily. Fine degrees of shading in particular are likely to become indistinguishable. Please therefore use such illustrations only if necessary, and do not use

<sup>†</sup> The general settings are designed for use with the specially formatted A4 paper. For US authors using the American Quarto paper size (8.5 × 11 in), set the margins to: top 0.8 in; bottom 0.75 in; left 1.44 in; right 1.0 in. This gives a print area equivalent to that set for the A4 page (6.06 × 9.45 in).

photocopies as they will certainly give poor results. Hatching will almost always give better results than shading.

Take care to ensure that adequate space is allowed in the text for structural formulae and figures to be inserted. These should, if possible, be positioned on the same page as the text in which they are discussed or on the following page. Figures are best positioned at the top or bottom of the page, while formulae may appear at convenient points within the page or be gathered together to fill an entire page. These pages should then be interleaved with the relevant text pages. Mounting of all material may, if preferred, be left to the editorial staff, but the appropriate spaces must be left.

Whenever possible, photographs should be supplied as transparencies or prints. They should be sharp and of good contrast as a little quality is inevitably lost on reproduction. Dimension bars should be added to photomicrographs rather than stating magnifications in the captions. Black and white prints should be supplied if possible since colour prints often do not reproduce well in black and white. Photographs cut from printed publications are also seldom satisfactory. Photographs should not be mounted in the typescript; suitable spaces should be left and the photographs, clearly identified, supplied separately.

However, with increasing frequency nowadays, authors submit typescripts in which the artwork is embedded electronically within the text. Please note that the considerations which apply to hard copy illustrations and photographic material also apply to embedded artwork with regard to their presentation and quality of reproduction. If using electronic artwork files, please use an adequate resolution – minimum 300 dpi, but ideally 600 dpi.

Line drawings and photographs should be numbered with arabic numerals in a single sequence within each chapter. All illustrations should be cited within the text.

Each Figure must have a descriptive caption, beginning **Figure 1**, **Figure 2**, etc. The caption should be typed in italics to the width of the Figure and placed below the illustration. Do not incorporate a caption into the artwork. If text follows an illustration, leave a line of space between the caption and the text. Large Figures that need to be placed sideways must have their captions typed sideways to the length of the page and no other text should appear on that page.

All formulae, including, where necessary, structures in complex reaction schemes, should be numbered consecutively **1**, **2**, etc. Reaction schemes should be numbered **Scheme 1**, **Scheme 2**, etc. These numbers should be typed centrally below the formulae or reaction schemes.

Equations should be indented 5 spaces and displayed on a separate line so that there is a line of space above and a line of space below them. The equations should be numbered in a single sequence throughout each chapter using arabic numerals in parentheses placed at the right-hand edge of the type area.

**Tables** – These should be placed at the top or bottom of a page and be centred on the page width. Column headings should be brief, and the units of all numerical values should be clearly stated in each Table. The Tables should be numbered consecutively in arabic numerals within each chapter and should be provided with a brief title above the body of the Table, beginning **Table 1**, **Table 2**, etc. The caption should be typed to the width of the Table and in italics.

**Bibliographic References and Footnotes** – You are responsible for the accuracy of the references. All names, dates, and volume and page numbers should be double-checked before the typescript is submitted.

References should be indicated in the text by superior numerals, which must be cited in numerical sequence and appear after any punctuation.

The abbreviations to be used for journal titles should follow the Chemical Abstracts Service Source Index; a list of these for most journals of chemical relevance is available from the editorial office.

The references should be collected at the end of each chapter and should immediately follow the end of the text, *i.e.* the reference list should not start on a new page unless there is insufficient space on the last page of text for the heading and at least one reference.

The references should be listed in numerical order and should be arranged as shown in the following examples.

#### *Journal reference*

Number of reference, name(s) of author(s) with initials preceding the surname(s), short title of periodical (italic), year of publication, volume number (bold), first page number, *e.g.*

1 R. Cobban, D. Gregson and P. Phillips, *Chem. Br.*, 1998, **34**, 40.

#### *Book reference*

Number of reference, name(s) of author(s), title of book in italics, edition number (if any), name(s) of editor(s) (if any), name of publisher, place of publication, year of publication, volume number (if any), chapter number, page number, *e.g.*

2 A.G. Clarke and A.S. Tomlin, in *Understanding Our Environment*, 3rd Edn., ed. R.M. Harrison, Royal Society of Chemistry, Cambridge, 1999, ch. 1, p. 66.

In references to reports or bulletins as much information as possible should be given and abbreviations should not be used.

**Nomenclature, Units, and Symbols** – The use of standard IUPAC nomenclature is encouraged, and a list of IUPAC nomenclature publications is available at <http://www.rsc.org/pdf/general/append.pdf>. As far as possible authors should use SI units and symbols. A space should always be left between a numerical value and its unit, *e.g.* 5 mm.

## **4 Specimen Typescript**

The following pages illustrate most of the points made in the preceding sections. Note especially the need to use the whole text area as specified by the blue lines.

## **5 Template Document**

Pc- and Mac-compatible copies of the template (for Word and WordPerfect; for UK and US paper sizes) are available from the Editor and the Cambridge editorial office. A further document is also provided with the template: it contains simple user guidelines and a specimen chapter along the lines of the example given in the following pages.

OCTOBER 2000

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1 DISCOVERY OF A SMALL, NON-PEPTIDYL MIMIC OF GRANULOCYTE  
2 COLONY-STIMULATING FACTOR

Authors

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Addresses

10 <sup>1</sup> Department of Chemistry, The University, Cambridge CB4 0BN, UK  
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12 Cambridge CB4 0WF, UK

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18 1 INTRODUCTION

20 Granulocyte colony-stimulating factor (G-CSF) is a 21 kDa hematopoietic cytokine  
21 secreted by bone marrow stroma cells, macrophages, fibroblasts and endothelial cells.  
22 Recombinant human G-CSF, available in both glycosylated and non-glycosylated forms,  
23 has become an important therapeutic agent for the treatment of a variety of human  
24 neutropenias, including those resulting from chemotherapy, congenital defects and bone  
25 marrow transplantation.<sup>1</sup> Genetically engineered G-CSF, like any other recombinant  
26 growth factors, must be administered either subcutaneously or intravenously. Although  
27 other agents have been shown to activate cytokine receptors by oligomerization,<sup>2</sup> no small-  
28 molecule cytokine mimics with potential for oral delivery have yet been reported.

31 2 METHOD AND RESULTS

33 **2.1 Identification of a Suitable G-CSF Mimic**

35 An assay was designed to identify non-peptidyl compounds that activate the G-CSF receptor  
36 based on activation of STATs, which are known to play a central role in the G-  
37 CSF-mediated responses. From the drug resistant clones responsive to G-CSF, a single clone,  
38 which exhibited 20-fold induction of luciferase activity by G-CSF and the same pattern of  
39 JAK and STAT activation as the parental cells, was selected to screen a library  
40 of synthetic organic compounds. For the screen, the cells were incubated for 2.5 hours with  
41 individual compounds at a concentration of 10  $\mu$ M in a 96 well plate format. Compound  
42 SB-247464 (Figure 1) was identified as a hit in the assay and showed a dose-response  
43 effect with a maximum efficacy of 30% that of G-CSF at 1  $\mu$ M.

44 As expected, SB-247464 induced activation of G-CSF signal transduction pathways, the  
45 efficacy being *ca.* 25–50% that of G-CSF, consistent with data from the luciferase assay.

47 **2.2 Assessment of Activity of SB-247464**

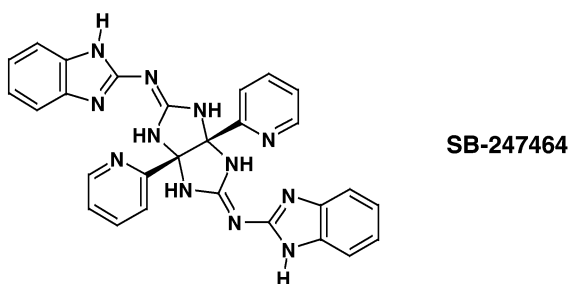
49 To assess SB-247464 in supporting the proliferation and differentiation of cells of the  
50 granulocytic lineage, colony-forming unit-granulocyte (CFU-G) assays from murine bone

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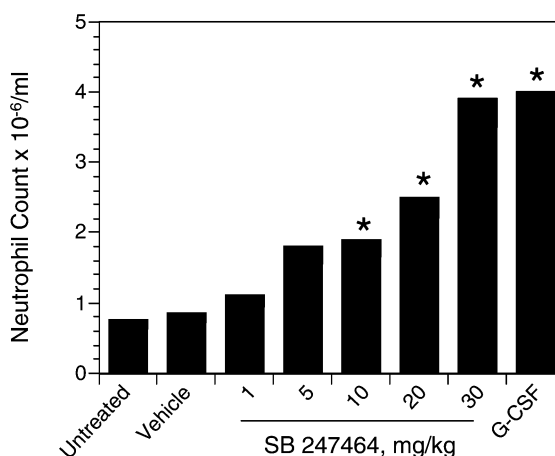
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**Figure 1** Structure of SB-247464

marrow were performed. SB-247464 stimulated the production of granulocytic colonies, with an efficacy 20–80% of that of G-CSF at 0.3–3  $\mu$ M; the colonies appeared uniformly smaller than those promoted by G-CSF, but were consistently larger than 30 cells. Likewise, SB-247464 was able to mimic the activity of G-CSF *in vivo* (Figure 2): subcutaneous administration twice a day to normal mice caused a dose-dependent increase in peripheral blood neutrophils after 4 days. Efficacy at 30 mg/kg was comparable to that of 50  $\mu$ g/kg of G-CSF, elevating the neutrophil counts to *ca.* 400% over baseline. The magnitude of the increase was equivalent to that effected by administration of 5–30  $\mu$ g/kg/day of G-CSF to normal or neutropenic humans.



**Figure 2** Granulopoietic activity *in vivo*; \* indicate neutrophil counts > those of control

### 3 CONCLUSION

The identification of SB-247464 as a G-CSF mimetic provides proof of principle for drug discovery using JAK/STAT-based assays, and shows for the first time that a small non-peptidyl molecule can trigger the selective activation of a cytokine receptor. These findings may lead to the development of orally available G-CSF mimics for use in the treatment of neutropenia associated with cancer chemotherapies.

### References

- 1 K. Welte, J. Gabrilove, M.H. Bronchud, E. Platzer and G. Morstyn, *Blood*, 1996, **88**, 1907.
- 2 M. Fourcin, S. Chevalier, C. Guillet, O. Robledo, J. Froger, A. Pouplard-Barthelaix and H. Gascan, *J. Biol. Chem.*, 1996, **271**, 11756.

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