

Scientific and Research Writings



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Art of Writing

- **Writing is nature's way of letting you know how sloppy your thing is..**

Guindon, *San Francisco Chronicle*

Art of Scientific Writing

- **There is no form of prose more difficult to understand and more tedious to read than the average scientific paper.**

Francis Crick

Content

- Types of scientific writings
- Global view of publications in science and engineering
- What are high impact factor journals?
- Why it is important to publish in high impact factor journals?
- Which manuscripts are published in high impact journals?
- Attributes of a good manuscripts
- From good research to good reporting-Technical details of manuscript writing
- Ethics in scientific writings
- Examples and exercise (*Dr. Atia and Dr. Hina*)

Types of Scientific Writings

- Research Articles or Research Papers
- Review Articles
- Research Reports
- Research Projects for Funding
- Patents
- Dissertation or Thesis

Types of Scientific Writings-

Research Articles

- Ultimate Product of Intellectual Pursuit
- Report on research findings that are
- Sound (Valid)
- Previously unknown (Novel and original)
- Add new understanding, observation, proofs
- It has required structure and style IMRaD (Introduction, Material, Results and Discussion).

GLOBAL VIEW OF PUBLICATIONS IN SCIENCE

Global View of Publication in Science and Engineering

- Approximately 35,000 journals published regularly
- 22,000 of them are ISI or Scopus abstracted
- Total number of papers published annually exceeds 2.5 million
- Over 50% are never cited by any one

International Research Publications

Facts and Figures

- Articles published (1665-2012)= 53 million
- Free and paid abstracts available Scopus, ISI Web of Knowledge (WOK), PubMed Central, and Google Scholar
- PubMed Central holds over 2.2 million articles, has a collection of over 20 million citations
- SciVerse Scopus holds over 43 million records, it includes 18,000 peer-reviewed journals (including 1,800 open access journals), 700 trade publications, and 400 book series.

International Research Publications

Facts and Figures

- *ISI Web of Knowledge* claims to hold over 40 million items and 7387 science and engineering journals and 2257 social science journals.
- Google Scholar has almost taken over the world bibliometry.

Number of Journal Published

(Thomson Reuters-Web of Science –Master Journal List)

Field*	Number of Journals
Arts & Humanities Citation Index	1632
Biochemistry and Biophysics	473
Life Sciences	1408
Engineering, Computing & Technology	1329
Clinical Medicine	1519
Arts & Humanities	1338
Agriculture, Biology & Environmental Sciences	1261
Chemistry Citation Index	545
Biotechnology Citation Index	321
Biological Abstracts	4479

<http://science.thomsonreuters.com/mjl/>

* These are only selected fields

Number of Journal Published in the Major Fields of Science (Thomson Reuters-Web of Science–Master Journal List)

Science Citation Index® 3786

23,000 academic and science journals (Including Web of Science journal listings)

Field of Science*	Number of SCI Journals
Immunology	93
Geology	17
Mathematics	97
Biochemistry and molecular biology	206
Chemistry-multidiciplianary	90
Organic chemistry	43
Cell biology	135
Biology	48

<http://science.thomsonreuters.com/mjl/>

* These are only selected fields

Global View of Publications in Science- Hard Facts

- Over 50% of research papers receive no citation
- 90% readers glance through the content list only
- Only 5% open the journal to review through the titles
- Less than 2% scientists read the abstract and introduction
- Less than 1% read rest of the paper!!!!!!!!!!!!!!

What are High Impact Factor Journals?

What are High Impact Factor Journals?

- Impact factor of journal is the frequency of its citations.
- High impact factor journals are the ones which have high frequency of citations by others
- It is a superficial, but internationally accepted, measure of quality of journals
- A good high impact journal may publish a paper which have low to zero citations.

What is an Impact Factor of a Journal

- Reflecting the average number of citations of an article in a journal
- Appears in Journal Citation Reports - Science Citation Index
- Journals with high impact factors considered to be more scientifically important and more prestigious.

$$\text{Impact Factor} = \frac{\text{Citations in 2018 to articles published in 2017 and 2016}}{\text{Articles published in 2017 and 2016}}$$

Journal Impact Factor 2009

Journal	Impact Factor
<i>Nature</i>	34.480
<i>Science</i>	29.747
<i>LANCET</i>	30.758
<i>Angewandte-Chemie</i>	11.829
<i>Tetrahedron</i>	3.219
<i>Acta Crys. E</i>	0.453

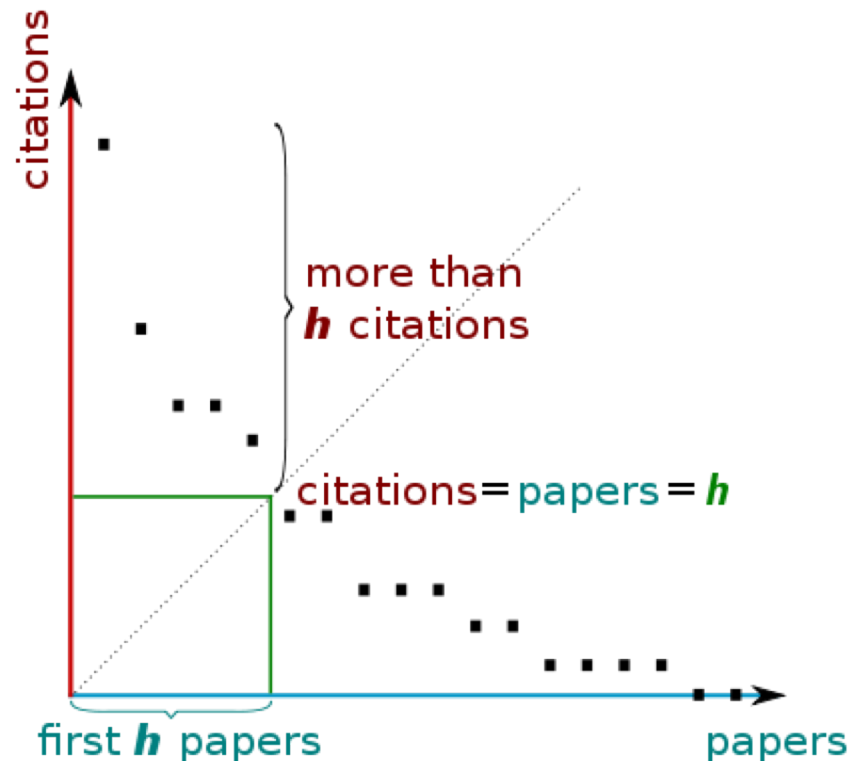


H-Index or Hirsch Index or Hirsch Number

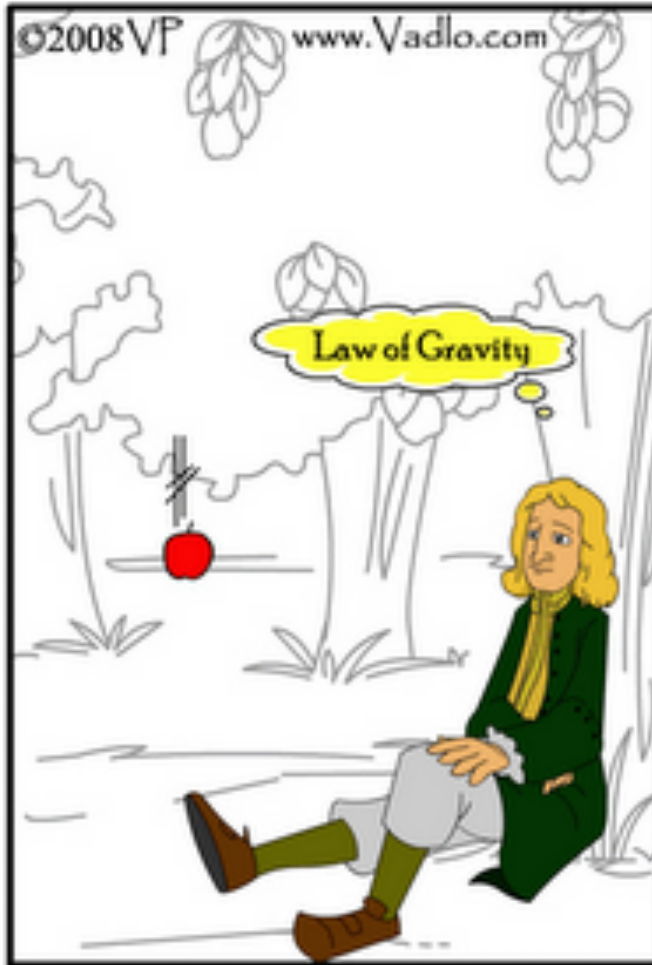
- It measure both the productivity and impact of the published work of a researcher.
- The index is based on the set of the scientist's most cited papers and the number of citations.
- The index can also be applied to the productivity and impact of a group of scientists, such as a department or university or country.

H-index or Hirsch index or Hirsch number

- The h-index is based on a list of publications ranked in descending order by the Times Cited. The value of h is equal to the number of papers (N) in the list that have N or more citations.



Publishing in High Impact Journals- It's the idea which matters



High Impact Paper



Low Impact Paper

E-Journals Vs Print Journal

E-Journals Vs Print Journal

E-Journals

Merits	Demerits
Easily accessible	Non-availability of full text (Sometime)
Online submission	Subscription only for a fixed duration
Online editing	Poor quality of Portable Document File
Time Savings	No perpetual access
On spot access	Can not read at your leisure
Can download any article with/without payment	Continuity of content is disturbed
	Problems in downloading

Print-Journals

Merits	Demerits
Easily accessible	Increased time spent in searching information
Personified copy	Non-availability of Indexes in some journals
Legibility	Expensive according to number of copies
No dependency on computer/electricity	Require more space
Can read at your leisure	
No need of link/continuity	
Can keep all printed versions to eyesight at a glance	

E-Journals Vs Print Journal

According to a survey conducted at H M Patel Centre for Medical Care and Education , India, following are the responses by professional about the usage of e-journal Vs Print journals

Category	E-copy	Print copy	Both	No response
Professor	02	13	01	-
Additional professor	02	06	-	01
Associate professor	03	13	-	02
Assistant professor	17	21	-	03
Tutor	05	01	01	03
MO/Resident	21	46	-	10
Total	56 (28.86%)	106 (54.63%)	02 (1.03%)	19 (9.79%)

Why it is Important to Publish in High Impact Factor Journals?

Why it is Important to Publish in High Impact Factor Journals

- *Publish or perish*
- Greater visibility of research findings
- Increase chances of citations
- Greater recognition among peers
- Associated benefits such as promotions, productivity allowances, etc

Which Manuscripts are Published in High Impact Factor Journals

Which Manuscript are Published in High Impact Factor Journals

- Work of established scientists
- Results of general interest
- Novelty of findings
- Concise and well written

Attributes of a Good Manuscript

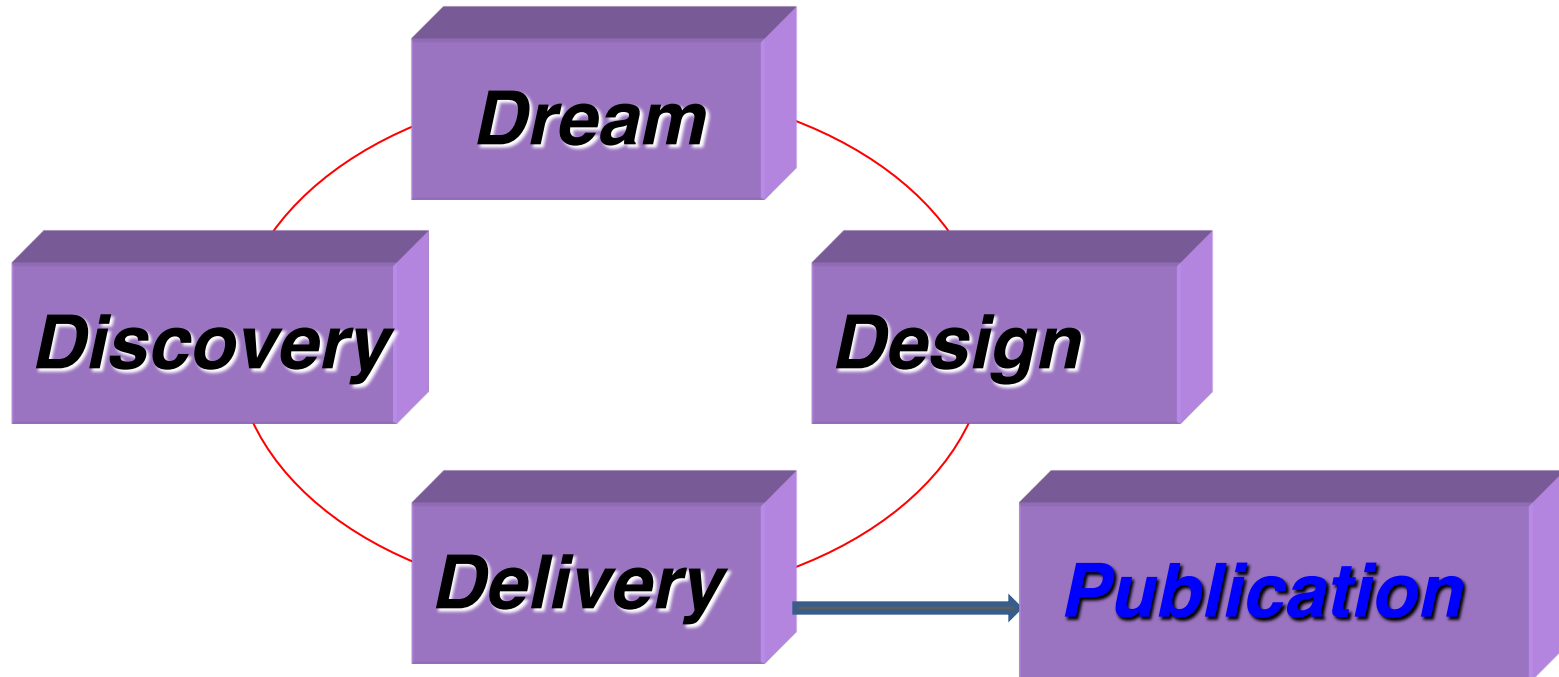
Attributes of a Good Manuscript

- Concise but powerful
- Story like
- To the point
- Free from grammatical and stylistic errors
- Recognizing contributions of others
- Technically correct

From Good Research to Good Writing

- Quality is state of mind
- Good science lead to great findings, and
- Great findings need to be reported in the best possible way to the world

Research Paradigm



“Creativity is fundamental attribute of science, which is driven by curiosity.”

Prof. Dr. M. Iqbal Choudhary, Dawn, Sunday December 6, 2009.

Why Publishing Research Articles is Important?

Ideally it is

- to communicate and share the new discoveries in science to improve the quality of life and for providing better healthcare.
- Make contributions to society

More often is

- to be advance in the field
- to get the research funding/grants
- to get the tenure
- to improve the scientific impact of institute/individual
- recognition by peers

When to Publish or Not to Publish?

- Quality of the scientific study
- Invention and innovation
- Depth of the study
- Interest of scientific community and layman
- Audience
- Message in the publication
- Time of publication

Deciding the Journal for Publishing

- **Aim high-** Go for first tier journals if you have time and temperament to write a good manuscript.
- Decide the target journal before writing or drafting the article.
- Prefer those journals which publish similar work or the journal articles you are citing for your work.
- If you think that your competitor is ahead of you, go for second tier rapid publication journal, because it is important to first

Points to be Considered before Publishing

- Targeted audience
- Prestige of journal and your own institution
- Access (open access/ subscribed)
 - availability free of charge on the World Wide Web
 - On payment
- Impact factor of the journal
- Probability of acceptance
- Publication time

How Important Citations are???



"I was published a couple of years ago in a crap journal and nobody is citing me"



"I was published a couple of years ago in a mid-tier journal. I've got slightly more citations than expected"



"I was published recently in a good journal. Citations are as expected."



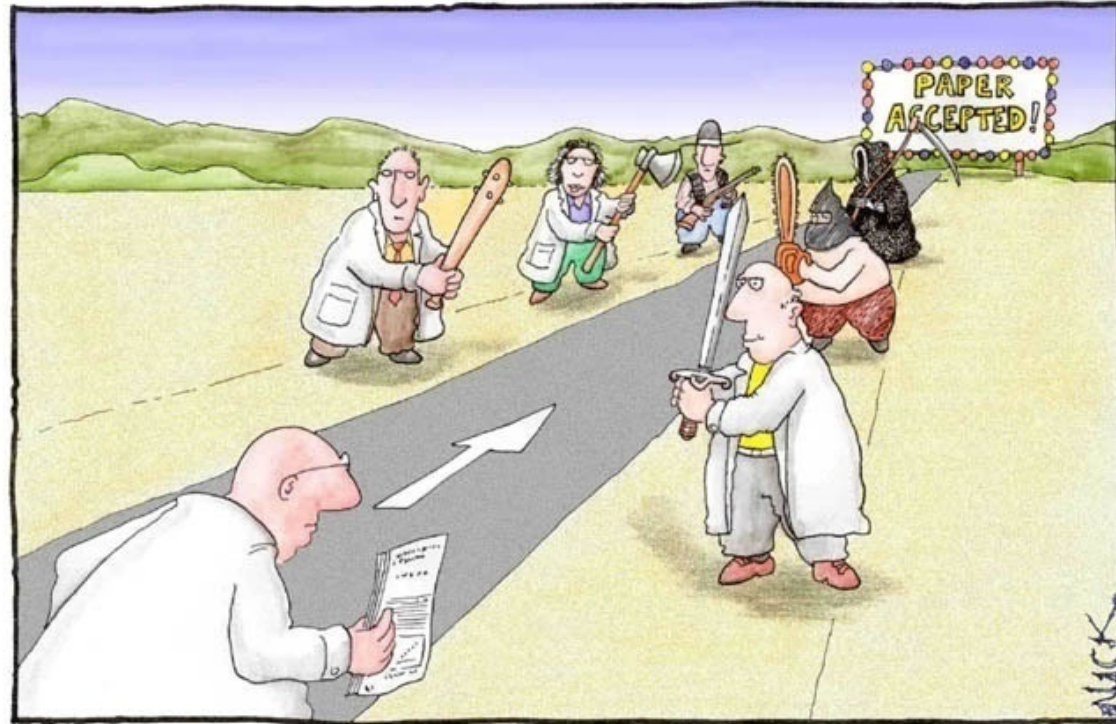
"I was published recently in a good journal and I'm getting lots of citations."

What is Peer Review Process?

- Exciting the reviewer's mind is far more important than exciting the reader's mind.

- It is likely that no one will ever read your paper more thoroughly than the reviewer.

- Suggest referees that appreciate your work
(political)



Most scientists regarded the new streamlined peer-review process as 'quite an improvement.'

www.weirdscience.ca

Kinds of the Research Articles

Letters

Articles

Communications

Research notes

Supplemental articles

Criteria of a Good Research Publication

- Novel idea (out of the box thinking)
- Quality science/research
- Good writing and attractive presentation
- Published in high impact journal

Remember a good article is the one that is read and cited!

Technical Details of Manuscript Writing

Writing is a critical step in science although scientists are not trained to write.

Even very creative experiments and novel results will have dull impact if the manuscript is not written well.

Key to Writing Skills

- The path to writing well is to read excellent writers and write.....and write...and write.
- “Free write” your thoughts. Don’t worry about structure initially.
- Use the best paper in your field as a template and try to convert your free write-up into a formate.
- Keep writing concise, dynamic and simple in construction.
- Convey enthusiasm in your writing so it attract the audience.

When to Write a Draft of Manuscript?

- **Best practice-** Prepare the figures and write the draft as the experiment is progressing
- **Second Best practice-** Write the first draft at a meeting where work is first presented. The experiment will be fresh in mind and free time in the evenings may be sufficient to write a draft.
- **Alternatively,** the script of a seminar can often be used as a starting draft.
- **The worst practice-** to write a paper after you have left the place (lab.) where the work was performed.

Divide and Conquer!!!!!!!

- Divide and work on.....

Eat an elephant bit by bit

- If you get stuck on a particular section, just skip to a different section that is easiest to write.
- *It means the easiest first and the most difficult latter.*

Four Questions of Manuscript Writing

What is the?

INTRODUCTION

What did you do?

METHODS

What did you find?

RESULTS

What does that mean?

DISCUSSION

Parts of a Manuscript

Title

Abstract

Introduction

Methods

Results

Discussion

Acknowledgements

References

Title, key words and abstracts are used for electronic searches

Title- The Backbone of an Article

It indicates content and main discoveries and attracts the readers attention.

It decides whether article is worth reading or will get attention of the readers.

Go for the Journal instruction in writing titles.

Examples:

Good Title: The Natural Product Cyclomarin Kills Mycobacterium Tuberculosis by Targeting the ClpC1 Subunit of the Caseinolytic Protease (online article in *Angewandte Chemie International*, 11 May 2011)

Bad Title: Anti-Tuberculosis agent Cyclomarin.

Attractive and Catchy Title –

makes reader going
through the
article for sure

Graphics plays an
important role in
catching the eyes of
readers.

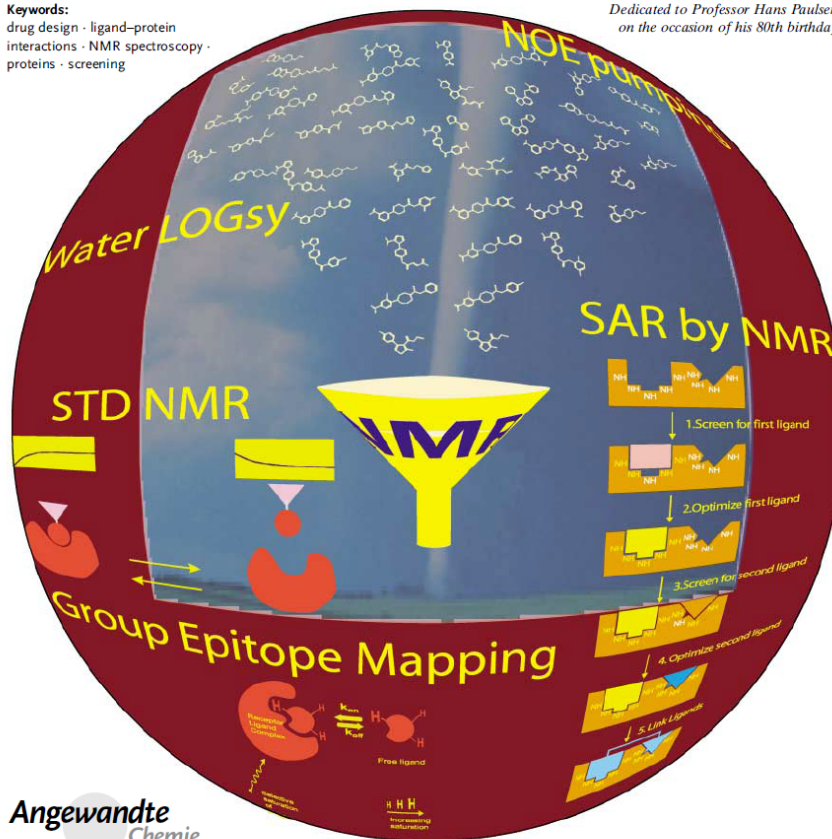
NMR Spectroscopy of Proteins

NMR Spectroscopy Techniques for Screening and Identifying Ligand Binding to Protein Receptors

Bernd Meyer* and Thomas Peters*

Keywords:
drug design · ligand–protein
interactions · NMR spectroscopy ·
proteins · screening

*Dedicated to Professor Hans Paulsen
on the occasion of his 80th birthday*



The Impact of Article Titles on Citation Hits

- Most published articles are not cited- the title play a vital role
- Construction of an article title has a significant impact on citation frequency.
- By a study conducted by Thomas S. Jacques and Neil J. Sebire* there was a strong association between increasing title length and citation rate.

The Impact of Article Titles on Citation Hits-Contd.

Reason:

- Electronic searches are now preferred over other means, which includes SciFinder, PubMed, Web of Science, Google Scholar, etc.
- These searches are based on the title or key word .
- Longer, comprehensive titles are more likely to contain given search terms.
- Therefore the title should provide clear description, finding of study

Nature's style -Manuscript Formatting Guide

Titles

- Titles do not exceed two lines in print.
- Titles do not normally include numbers, acronyms, abbreviations or punctuation.
- They should include sufficient detail for indexing purposes but be general enough for readers outside the field to appreciate what the paper is about.

Abstract- Most Critical Part of Paper

- Should be informative, indicative and reflects the main ‘story’ of the article.
- The only chance you have to get the reader’s attention.
- Should be crisp, concise and accurate.
- Gives the quick idea of the contents (**Stand alone**).
- What and how was done
- Provide a brief conclusions
- **I generally write abstract at the end**

The detailed information must be present in the body text, not in abstract.

Skeleton of an Article

- Structured
 - IMRaD formula (will discuss more on next slide)
- Unstructured
 - Paragraphs- few sentences summarizing each section

Skeleton of an Article-Continued

IMRaD structure- Writing a draft

Introduction--- **What is the?**

Materials and methods/experimental
procedures-- **What did you do?**

Results-- **What did you find?**

and

Discussion-- **What does it mean?**

Huth EJ. *Writing and Publishing in Medicine*, 3rd ed. Baltimore: Williams & Wilkins; 1999.

Scientific Writing: My Approach and Irreverent Opinions, Mark Yeager.

Introduction- *Setting the Scene*

- **< 2% readers actually cite your article**
 - And among these < 2% approximately 98% reader just read the introduction
- Brief background information of the current study
- Focused
- Integrated review of pertinent work
- Updated literature citation
- Should not be too long
- Importance of current study/advancement needed/summary of new findings



Introduction

- Ask question to yourself that why should anyone read your paper amongst the 1000' s appearing that month?

Create-A-Research-Space

- It should introduce the topic and relates to the existing research.
- significance of your research.
- Capture your audience. Why is your experiment important?

Avoid comprehensive review, self citations, etc

Material and Methods

- Write the methods section first because it is the easiest to write.
- Provide enough details for competent researchers to repeat the experiment (Who, What, When, Where, How, and Why?)
- Start writing when experiments still in progress
- Sufficient information must be provided for reproducibility
- Study design-new methods must be described in detail
- Supplies, manufacturer, country needs to be added
- Animal, human, protections details
- Measurements/ instruments
- Statistical analysis and data collection
- Descriptive subheadings— general experimental methods, animals, spectral data, etc

You are not expected to do it.....



<http://www.nature.com/scitable/ebooks/english-communication-for-scientists-14053993/writing-scientific-papers-14239285>

Results

- **Use descriptive headings that concisely state the results.**
- **Data representation-concise and accurate.**
- **Short and easy to understand**
- **Consistent with the abstract and introduction**
- **Give tables and figures where needed**
 - **With sufficient information so that minimum text is required.**
 - **Don' t repeat information in graphics and text.**

Results

- Appropriate numbering of figures and table mentioned in the text.
- Use significant figures where required.
- Avoid speculations and over discussion.
- Avoid using words such as **proves, confirmed, removed all doubts**, etc. Remember science is dynamic and ever changing.

Discussion

- Hardest section to write, but it is also the most important.
- Use descriptive headings that concisely summarize the interpretation of the results.
- Answer the question posed in introduction
- Correlation of your finding with the existing knowledge
- Discrepancies between new results and previously reported results.

Discussion

- **What is new without exaggerating.**
- **Conclusion/summary, perspectives, implications.**
- **Research limitations and need for future research.**
- **Theoretical implications and possible practical applications.**

Conclusion

- Identify key findings and application
- Should not be a summary of the work done- abstract is doing fine with that.
- Consistent with experimental and introduction

References

- Cite current and key pertinent references
- Reference citations must be accurate and complete
- Read the references
- Use correct style for journal

ACS Style References Citations

- Abstract:

Beharry, S.; Bragg, P.D. Properties of Bound Inorganic Phosphate on Bovine Mitochondrial F1F0-ATP Synthase. *J. Bioenerg. Biomembr.* **2001, 33, 35-42**

- Book:

Beall, H.; Trimbur, J. *A Short Guide to Writing about Chemistry*, 2nd ed.; Longman: New York, 2001; pp 17-32.

ACS Style References Citations

- Journals:

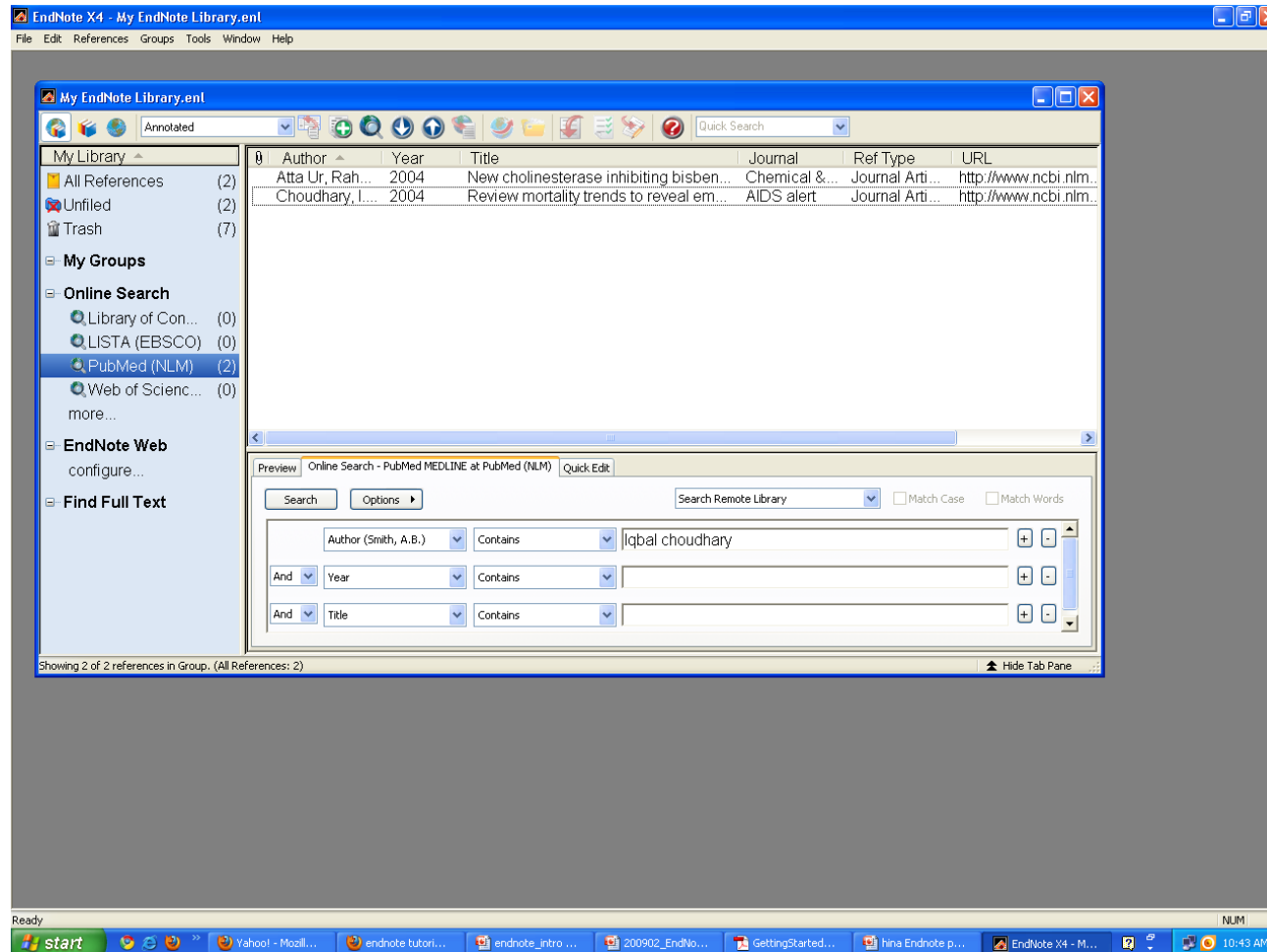
Labaree, D.C.; Reynolds, T.Y.; Hochberg, R.B. Estradiol-16 α -carboxylic Acid Esters as Locally Active Estrogens. *J. Med. Chem.* **2001**, *44*, **1802-1814**.

- Encyclopedias:

Diagnostic Reagents. *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed; VCH: Weinheim, Germany, 1985, p. 196

Modern electronic tools for writing manuscripts

Use **EndNote** for references
...Bibliographies Made Easy™



Acknowledgments

- Funding agencies
- Intellectual contributions
- Dedications
- Notes

Final Step is Revision and Proofreading



Revision, Revision, Revision

- After writing the first draft, at least a dozen revision are usually needed to improve to the text.
- Make sure that all authors read the first draft. Give them timeline...

Revision and Proofreading

Revision

- Effectiveness of the study
- Supporting information
- Order and flow of the article
- Must be leaving reader with a new question



Revision and Proofreading

- Proofreading **All authors should participate**
- Grammar and spelling errors
 - Consistent verb tense
 - Vocabulary
 - Tighten the sentences
 - spell-check
 - Punctuation
 - typos
- Technical terms
 - Scientific symbols
 - Reaction scheme
 - Chemical structures/names
 - references



PROOFREADING MARKS

Marks & Meanings

Examples



capitalize

They fished in lake tahoe.



make it
lowercase

Five \$tudents missed the \$us.

sp.

spelling mistake

The day was cloudy and cold.
sp.



add a period

Tomorrow is a holiday.



delete (remove)

Kim knew the the answer.



add a word

Six pups were in the litter.



add a comma

He ate peas, corn and squash.



reverse words or
letters

An otter swam in the bed kelp.



add an apostrophe

The child's bike was red.



add quotation
marks

Why can't I go? she cried.



make a space

He read two books.



close the space

Her favorite game is soft ball.



begin a new
paragraph

We had fun. Next we went to

To avoid

Jargon	Preferred use
a considerable amount of	much
on account of	because
a number of	several
Referred to as	called
In a number of cases	some
Has the capacity to	can
It is clear that	clearly
It is apparent that	apparently
Employ	use
Fabricate	make

Day, RA. "How to write and publish a scientific paper," 5th edition, Oryx Press, 1998.

Responsibilities of Authors from Preparation of Manuscript to Submission

- New and original research
- Manuscript have been checked by all the listed authors.
- Obtain copyright permission if figures/tables need to be reproduced
- Proper affiliation
- Acknowledgement

Criteria for Acceptance

- Originality
 - Novel or creative research methodology
 - New and important research findings
- Scientific Quality (It is impossible to write a good paper on the basis of lousy science!!!!)
- Experimental design and methodology
- Research data representation
- Depth of the investigation
- Thorough and logical discussion of results

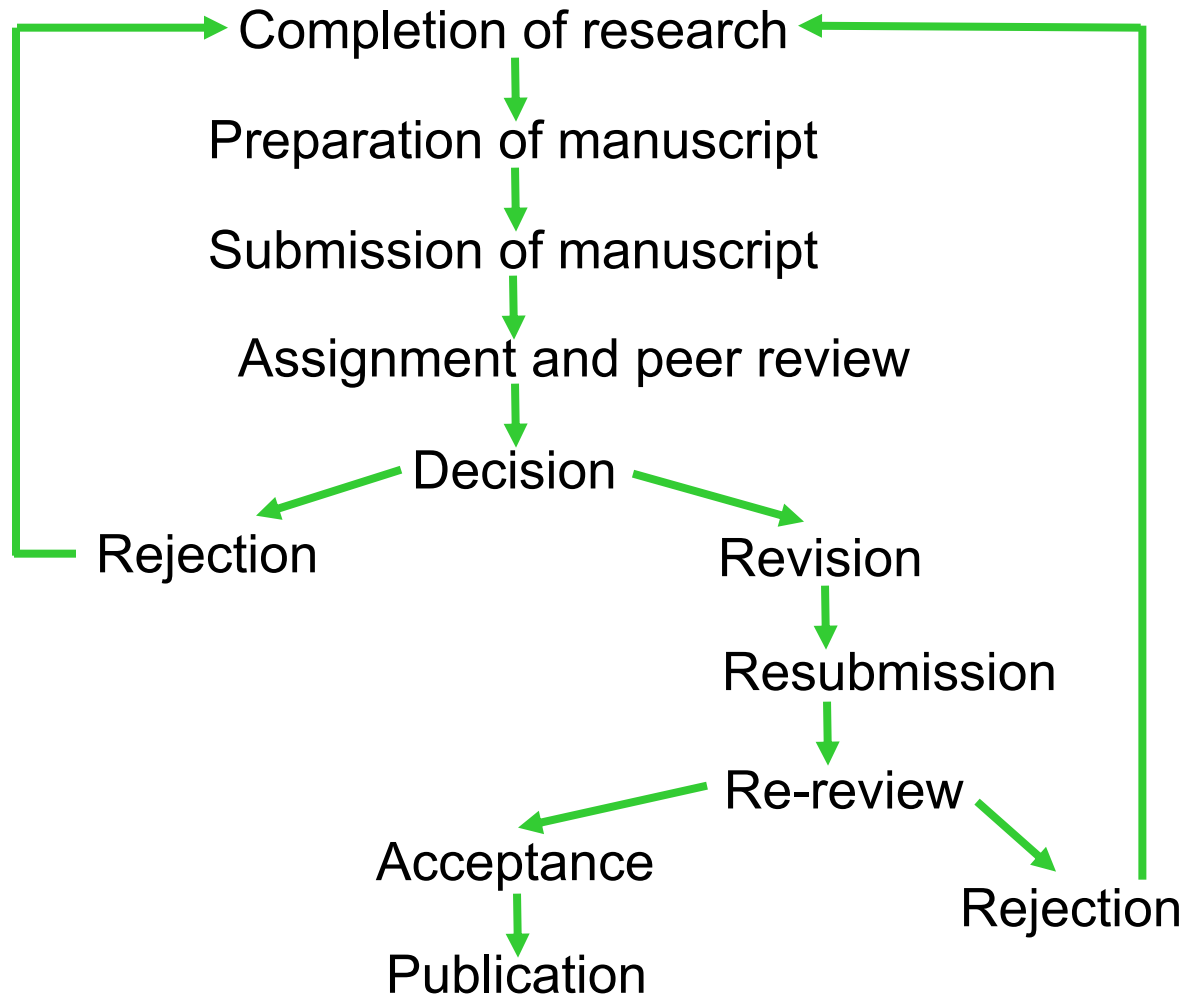
Criteria for Acceptance

- Clarity of Presentation
 - Organization/ presentation
 - Readability/ clarity of writing/ grammar
 - *Paper is much more likely to be rejected based on inadequate analysis than lack of originality*
- Importance in the scientific world

Major Reasons for Rejection

- The study is just confirmation of previous research
i.e. not novel
- Poor experimental design
- Targeted journal is not suitable
- Weakly written/presentation and language

Process of Research and its Publication



The most important factors that influence whether your manuscript will be considered/reviewed for publication are the title, abstract, cover letter, and your reputation based on your previous work.

Ethics in Scientific Writings

Do's and Don't in Scientific Writings

- Be factual
 - Be honourable
 - Be legal
 - Be truthful
 - Be objectives
 - Be accurate
-
- Don't deceive
 - Don't falsify
 - Don't plagiarize

Ethics in Scientific Writings

- Authorship issues
- Informed consent/ **institutional review board/ ethical review board** approval
- Acknowledging past and present contributions of others
- Registered Clinical Trials
- Acknowledge Grants/funding
- Avoid Fragmentary or duplicate publications

Ethics in Scientific Writings

1. Falsification and Data alteration

2. Plagiarism: Intentional use of another persons work with reference to your name without proper citation of the original source

1. www.turnitin.com and
2. www.plagiarism.com

1. Duplicate manuscripts

2. Unnecessary self citation

3. Redundant publication

4. Author conflicts of interest

5. Animal use concerns

6. Human use concerns



"Welcome to the co-author's party!
You're number twenty-one!"

Other Forms of Scientific Writing

Other Forms of Scientific Writing

- Thesis
- Patent
- Book
- Chapter (of a book)
- Technical/ Research progress reports
- Grant proposal/Research proposals

Example

1. Unstructured

Angewandte's most cited article of 2010

Type of Article:
CommunicationsTitle: Cross-Coupling Reactions
Iron-Catalyzed S-Arylation of Thiols with Aryl Iodides

Format: Unstructured

Cross-Coupling Reactions

Iron-Catalyzed S-Arylation of Thiols with Aryl Iodides**

Arkaitz Correa, Mónica Carril, and Carsten Bolm*

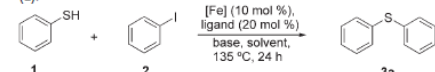
Transition-metal-catalyzed cross-coupling reactions of aryl halides with nitrogen, oxygen, and sulfur nucleophiles are powerful tools for the formation of C–N, C–O, and C–S bonds, respectively.^[1] Although several palladium, nickel, and copper catalysts have proven to be highly effective in such coupling processes,^[2] the development of new and cheap alternative catalysts for the aforementioned transformations is still desirable.

Among the various cross-coupling types, S-arylation is comparatively less studied.^[3] Two factors make this process difficult: First, thiols are prone to undergo oxidative S–S coupling reactions, which result in the undesired formation of disulfides, and second, organic sulfur compounds can be effective metal binders, which leads to catalyst modification (or deactivation).^[4] However, given the prevalence of C–S bonds in a wide range of pharmaceutically active compounds and polymeric materials,^[5] it is desirable to find novel catalytic procedures that provide efficient access to such highly useful organic products. In this regard we envisaged the application of readily available, inexpensive, and environmentally friendly iron salts.^[6] A particular challenge was seen in the required suppression of the known ability of iron to effect disulfide formation.^[7]

Iron-catalyzed C–C coupling reactions have recently emerged as appealing synthetic methods, since easy-to-handle catalysts can be applied.^[8] As part of our ongoing efforts devoted to the development of novel iron-catalyzed processes,^[9] we introduced ligand-assisted FeCl₃-catalyzed N- and O-arylation reactions.^[10,11] To our delight, we have now found that these iron-based catalysts can also be applied to arylations of sulfur nucleophiles. Thus, this novel and experimentally simple iron-catalyzed C–S bond-forming process provides ready access to valuable aryl sulfides.

Initially, the coupling of thiophenol (**1**) and phenyl iodide (**2**) was selected as a model system to optimize the reaction conditions. As shown in Table 1, the best conditions for the iron-catalyzed N-arylation^[10a] provided promising results, and afforded thioether **3a** in 61% yield (Table 1, entry 1).

Table 1: Fe-catalyzed S-arylation of thiophenol (**1**) with phenyl iodide (**2**).^[a]



Entry	Fe source	Ligand ^[b]	Base	Solvent	Yield of 3a [%] ^[c]
1	FeCl ₃	DMEDA	K ₃ PO ₄	toluene	61
2	FeCl ₃	TMHD	Cs ₂ CO ₃	DMF	28
3	FeCl ₃	DMEDA	Cs ₂ CO ₃	toluene	trace
4	FeCl ₃	DMEDA	NaOH	toluene	trace
5	FeCl ₃	DMEDA	K ₂ CO ₃	toluene	51
6	FeCl ₃	DMEDA	Na ₂ CO ₃	toluene	trace
7	FeCl ₃	DMEDA	NaOAc	toluene	trace
8	FeCl ₃	DMEDA	KOtBu	toluene	trace
9	FeCl ₃	DMEDA	NaOtBu	toluene	91
10	FeCl ₃	DMEDA	NaOtBu	toluene	75 ^[d]
11	Fe(ClO ₄) ₂	DMEDA	NaOtBu	toluene	trace
12	[Fe(acac) ₃]	DMEDA	NaOtBu	toluene	trace
13	Fe	DMEDA	NaOtBu	toluene	trace
14	FeCl ₃	DMEDA	NaOtBu	toluene	trace ^[e]
15	FeCl ₃	none	NaOtBu	toluene	0

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), [Fe] (0.1 equiv), ligand (0.2 equiv), base (2.0 equiv), solvent (1 mL mmol^{−1} of **1**), 135 °C, 24 h. [b] DMEDA = *N,N*-dimethylethylenediamine; TMHD = 2,2,6,6-tetramethyl-3,5-heptadione. [c] Yield of isolated product after flash chromatography. [d] Use of 5 mol % of FeCl₃ and 10 mol % of DMEDA. [e] Phenyl disulfide was used as the substrate instead of thiophenol (**1**). acac = acetylacetonate.

Conversely, the conditions for the iron-catalyzed O-arylation^[11] proved rather ineffective, and **3a** was obtained in very low yield (Table 1, entry 2). Moreover, the control experiment of the latter reaction in the absence of catalyst showed that under those conditions the product could also result from a classical aromatic nucleophilic substitution reaction.

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** We are grateful to the Fonds der Chemischen Industrie for financial support. A.C. thanks the Basque Government for support by "Programa de Perfeccionamiento de Doctores en el extranjero del Departamento de Educación, Universidades e Investigación", and M.C. thanks the Spanish Ministry of Education and Sciences (MEC) for a postdoctoral fellowship.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Abstract

Transition-metal-catalyzed cross-coupling reactions of aryl halides with nitrogen, oxygen, and sulfur nucleophiles are powerful tools for the formation of C–N, C–O, and C–S bonds, respectively.^[1] Although several palladium, nickel, and copper catalysts have proven to be highly effective in such coupling processes,^[2] the development of new and cheap alternative catalysts for the aforementioned transformations is still desirable.

Introduction

Among the various cross-coupling types, S-arylation is comparatively less studied.^[3] Two factors make this process difficult: First, thiols are prone to undergo oxidative S–S coupling reactions, which result in the undesired formation of disulfides, and second, organic sulfur compounds can be effective metal binders, which leads to catalyst modification (or deactivation).^[4] However, given the prevalence of C–S bonds in a wide range of pharmaceutically active compounds and polymeric materials,^[5] it is desirable to find novel catalytic procedures that provide efficient access to such highly useful organic products. In this regard we envisaged the application of readily available, inexpensive, and environmentally friendly iron salts.^[6] A particular challenge was seen in the required suppression of the known ability of iron to effect disulfide formation.^[7]

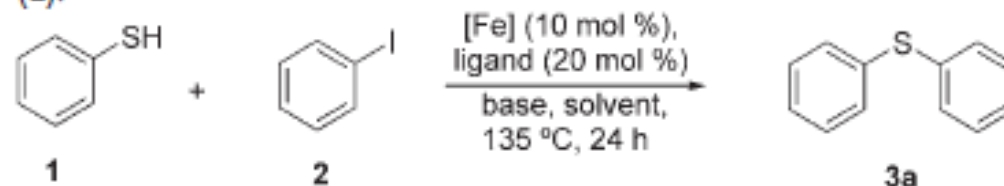
Introduction

Iron-catalyzed C–C coupling reactions have recently emerged as appealing synthetic methods, since easy-to-handle catalysts can be applied.^[8] As part of our ongoing efforts devoted to the development of novel iron-catalyzed processes,^[9] we introduced ligand-assisted FeCl₃-catalyzed N- and O-arylation reactions.^[10,11] To our delight, we have now found that these iron-based catalysts can also be applied to arylations of sulfur nucleophiles. Thus, this novel and experimentally simple iron-catalyzed C–S bond-forming process provides ready access to valuable aryl sulfides.

Initially, the coupling of thiophenol (**1**) and phenyl iodide (**2**) was selected as a model system to optimize the reaction conditions. As shown in Table 1, the best conditions for the iron-catalyzed N-arylation^[10a] provided promising results, and afforded thioether **3a** in 61% yield (Table 1, entry 1).

Model Study

Table 1: Fe-catalyzed S-arylation of thiophenol (**1**) with phenyl iodide (**2**).^[a]



Entry	Fe source	Ligand ^[b]	Base	Solvent	Yield of 3a [%] ^[c]
1	FeCl ₃	DMEDA	K ₃ PO ₄	toluene	61
2	FeCl ₃	TMHD	Cs ₂ CO ₃	DMF	28
3	FeCl ₃	DMEDA	Cs ₂ CO ₃	toluene	trace
4	FeCl ₃	DMEDA	NaOH	toluene	trace
5	FeCl ₃	DMEDA	K ₂ CO ₃	toluene	51
6	FeCl ₃	DMEDA	Na ₂ CO ₃	toluene	trace
7	FeCl ₃	DMEDA	NaOAc	toluene	trace
8	FeCl ₃	DMEDA	KOtBu	toluene	trace
9	FeCl₃	DMEDA	NaOtBu	toluene	91
10	FeCl ₃	DMEDA	NaOtBu	toluene	75 ^[d]
11	Fe(ClO ₄) ₂	DMEDA	NaOtBu	toluene	trace
12	[Fe(acac) ₂]	DMEDA	NaOtBu	toluene	trace
13	Fe	DMEDA	NaOtBu	toluene	trace
14	FeCl ₃	DMEDA	NaOtBu	toluene	trace ^[e]
15	FeCl ₃	none	NaOtBu	toluene	0

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), [Fe] (0.1 equiv), ligand (0.2 equiv), base (2.0 equiv), solvent (1 mLmmol⁻¹ of **1**), 135 °C, 24 h. [b] DMEDA = *N,N'*-dimethylethylenediamine; TMHD = 2,2,6,6-tetramethyl-3,5-heptadione. [c] Yield of isolated product after flash chromatography. [d] Use of 5 mol% of FeCl₃ and 10 mol% of DMEDA. [e] Phenyl disulfide was used as the substrate instead of thiophenol (**1**). acac = acetylacetonate.

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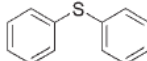
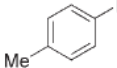
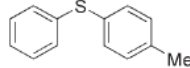
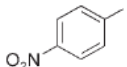
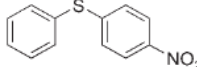
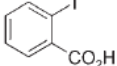
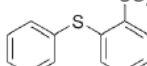
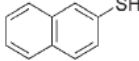
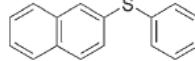
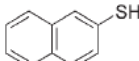
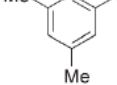
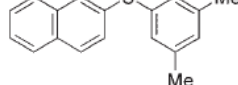
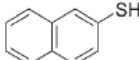
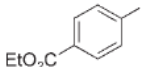
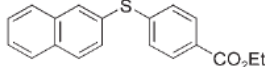
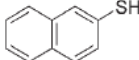
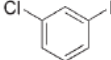
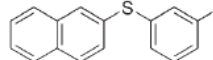
Further experiments revealed a significant dependence of the S-arylation of **1** with **2** on the nature of the base. Thus, whereas K₃PO₄, K₂CO₃, and NaOtBu provided the arylated compound in moderate to excellent yield (Table 1, entries 1, 5, and 9), other bases such as Na₂CO₃, Cs₂CO₃, NaOH, NaOAc, and KOtBu only gave trace amounts of **3a** (Table 1, entries 3, 4, and 6–8). It is noteworthy that in all the reactions the undesired phenyl disulfide, which arises from an iron-catalyzed oxidation reaction of **1**, was detected as a by-product. Unfortunately, the use of less-oxidizing iron species (Table 1, entries 11–13), degassed solvents, or other diamine-type ligands such as *N,N,N',N'*-tetramethylethylenediamine or *trans*-1,2-diaminocyclohexane did not prevent such competitive oxidation processes. To determine if **3a** was obtained by direct S-arylation of **1** or, alternatively, a two-step procedure involving oxidation of the thiophenol and subsequent aryla-

Results and Discussion

tion of the resulting corresponding disulfide, thiophenol (**1**) was replaced by diphenyl sulfide as the starting material. The absence of any arylated product in this reaction (Table 1, entry 14) ruled out the latter reaction path.

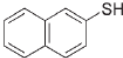
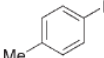
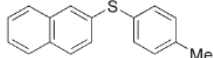
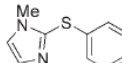
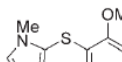
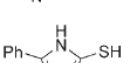
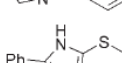
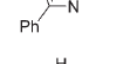
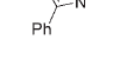
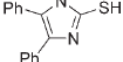
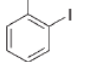
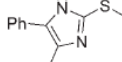
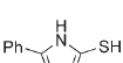
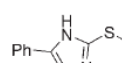
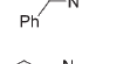
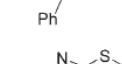
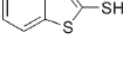
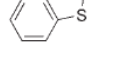
The importance of the ligand was revealed by a reaction carried out in its absence: In this case, the C–S coupling product was not observed at all, and diphenyl disulfide was the only product (Table 1, entry 15). Thus, the chemoselectivity of the iron-catalyzed S-arylation can be entirely controlled by the addition of a simple diamine ligand (Table 1, compare entries 9 and 15). The optimal reaction conditions for the S-arylation of thiophenol with phenyl iodide involved the use of 10 mol% of FeCl₃, 20 mol% of DMEDA, and 2 equivalents of NaOtBu in toluene at 135 °C.^[12] The use of 5 mol% of the iron source furnished **3a**, although in good but lower yield (Table 1, entry 10).

Table 2: Fe-catalyzed S-arylation of thiols with aryl halides.^[a]

R-SH + Ar-X 12 FeCl₃, DMEDA toluene, NaOtBu, 135 °C, 24 h R-S-Ar 3				
Entry	R-SH	Ar-X	Product	Yield [%] ^[b]
1		 X = I, Br, Cl		3 a X = I, 91 X = Br, 0 X = Cl, 0
2				3 b 98
3				3 c 88 ^[c]
4				3 d 90 ^[c]
5				3 e 85
6				3 f 84
7				3 g 81
8				3 h 85

Results and Discussion

Next, the scope of this novel transformation in coupling reactions of other thiols with differently substituted aryl halides was evaluated (Table 2). In general, all reactions were very clean, and the thioethers **3** were obtained in high yields under the previously optimized conditions. In a few cases, trace amounts of the undesired disulfide were detected, but those could be separated during the purification by column chromatography. The current iron-catalyst system efficiently coupled thiols with electron-rich, electron-neutral, and electron-deficient aryl iodides (32–98% yield, Table 2, entries 1–18). Furthermore, sterically demanding *ortho* substituents did not hamper the arylation reaction and the corresponding thioethers **3** were obtained in good yields (Table 2, entries 4, 11, 13, 16, and 17). Neither aryl bromides nor aryl chlorides were reactive under the standard conditions (Table 2, entry 1). Consequently, cross-coupling reactions with chloro-substituted aryl iodides proceeded exclusively at the iodo group

9				3 i	91
10				3 j	52 ^[d]
11				3 k	71 ^[d]
12				3 l	61
13				3 m	33 ^[e]
14				3 n	32
15				3 o	91
16				3 p	80
17				3 q	91

[a] Reaction conditions: R-SH (1.0 equiv), Ar-X (1.5 equiv), FeCl₃ (0.1 equiv), DMEDA (0.2 equiv), NaOtBu (2.0 equiv), toluene (1 mLmmol⁻¹ of R-SH), 135 °C, 24 h. [b] Yield of isolated product after flash chromatography. [c] Use of R-SH (1.6 equiv) and Ar-X (1.0 equiv). [d] Use of Cs₂CO₃ as base. [e] Use of K₃PO₄ as base.

(Table 2, entries 8 and 16). Importantly, the iron catalyst also proved efficient in coupling reactions of more challenging thiols bearing heterocycles such as benzisothiazole and imidazole, thus allowing access to heterocyclic sulfide derivatives which are present in numerous appealing compounds.^[13] Unfortunately, all attempts to couple aliphatic thiols (Table 2, entries 19 and 20) with aryl halides failed. The tolerance of potentially reactive functional groups such as carboxylic acids and esters to the described protocol is remarkable (Table 2, entries 4 and 7, res]

Summary

In summary, we have developed an efficient iron-catalyzed S-arylation protocol of aromatic and heteroaromatic thiol derivatives, which involves an inexpensive catalyst system formed by combining FeCl₃ and DMEDA. This method avoids the use of expensive and/or air-sensitive ligands and provides in most cases the desired sulfide in high yields. At the present stage, the success of the protocol is restricted to the use of aryl iodides as the electrophilic counterpart. This limitation is balanced by the fact that certain synthetically attractive heterocyclic thiols can be used as starting materials, which have not been utilized so far in these kinds of reactions. Overall the novel iron-catalyzed S-arylation reported here constitutes a promising C–S bond-forming process of potential industrial significance because of its operational simplicity and environmental and economic advantages. Its increased efficiency and enlargement of the substrate scope are currently under investigation by our research group.

Discussion

Experimental Section

General procedure for S-arylation of thiols: A sealable tube equipped with a magnetic stir bar was charged with thiophenol (**1**, 1.0 equiv), NaOtBu (2.0 equiv), and FeCl₃ (0.10 equiv). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. Phenyl iodide (**2**, 1.5 equiv), *N,N'*-dimethylethylenediamine (0.20 equiv), and toluene (1 mLmmol⁻¹ of **1**) were added by syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath at 135°C. After stirring the heterogeneous mixture at this temperature for 24 h, it was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica and concentrated to afford the product, which was purified by chromatography on silica gel to yield thioether **3**. The identity and purity of the known products was confirmed by ¹H and ¹³C NMR spectroscopic analysis, and the new products were fully characterized. See the Supporting Information for full details.

Received: December 11, 2007

Published online: March 3, 2008

Keywords: arylation · cross-coupling · heterogeneous catalysis · iron · thiols

Table 2: (Continued)

Entry	R-SH	Ar-X	Product	Yield [%] ^{b)}
18				3r 80
19				3s 0
20				3t 0

[a] Reaction conditions: R-SH (1.0 equiv), Ar-X (1.5 equiv), FeCl₃ (0.1 equiv), DMEDA (0.2 equiv), NaOtBu (2.0 equiv), toluene (1 mL mmol⁻¹ of R-SH), 135 °C, 24 h. [b] Yield of isolated product after flash chromatography. [c] Use of R-SH (1.6 equiv) and Ar-X (1.0 equiv). [d] Use of Cs₂CO₃ as base. [e] Use of K₃PO₄ as base.

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Structure–activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues

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Received 20 January 2005; revised 2 March 2005; accepted 2 March 2005

Available online 30 March 2005

Abstract—Here the tyrosinase inhibition studies of library of 2,5-disubstituted-1,3,4-oxadiazoles have been reported and their structure–activity relationship (SAR) also have been discussed. The library of the oxadiazoles was synthesized under the microwave irradiation and was structures of these were characterized by different spectral techniques. From this study it could be concluded that for a better inhibition of tyrosinase, electronegative substitution is essential as most probably the active site of the enzyme contain some hydrophobic site and position is also very important for the inhibition purposes due to the conformational space. The electronegativity of the compounds is somewhat proportional to the inhibitory activity. The compound 3e (30-[5-(40-bromophenyl)-1,3,4-oxadiazol-2-yl]pyridine) exhibited most potent ($IC_{50} = 2.18 \mu M$) inhibition against the enzyme tyrosinase which is more potent than the standard potent inhibitor L-mimosine ($IC_{50} = 3.68 \mu M$). This molecule can be the best candidate as a lead compound for further development of drug for the treatments of several skin disorders.

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Key words

- Tyrosinase inhibitor; 2,5-Disubstituted-1,3,4-oxadiazole library; Melanin; Vitiligo; Hyperpigmentation; Depigmentation.
- Gel Electrophoresis, Enzyme, Catalysis, ELISA reader, ????????????

Exercises

- Suggest few more suitable title for this article
- What should be the key words?
- How we can we improve the abstract?

Introduction

1. Introduction

Tyrosinase (E.C. 1.14.18.1), also known as polyphenol oxidase (PPO), is a multifunctional copper-containing enzyme, widely distributed in plants and animals. It catalyses the *o*-hydroxylation of monophenols and also the oxidation of *o*-diphenols to *o*-quinones. Tyrosinase is known to be a key enzyme for melanin biosynthesis in plants and animals. Therefore, tyrosinase inhibitors should be clinically useful for the treatment of some dermatological disorders associated with melanin hyperpigmentation and also important in cosmetics for whitening and depigmentation after sunburn. In addition, tyrosinase is known to be involved in the molting process of

insect and adhesion of marine organisms.¹ In insects, several functions of this enzyme have been reported in the generation of *o*-diphenols and quinones for pigmentation, wound healing, parasite encapsulation, and sclerotization and the enzyme is an alternative target site for the control of insect pests. In food industry, tyrosinase is responsible for the enzymatic browning reactions in damaged fruits during post-harvest handling and processing. Control of enzymatic browning during processing is important in fruit pulp manufacturing. In addition, tyrosinase inhibitors are becoming important constituents of cosmetic products that relate to hyperpigmentation. Therefore, there is a concerted effort to search for naturally occurring tyrosinase inhibitors from plant, because plants constitute a rich source of bioactive chemicals and many of them are largely free from harmful adverse effects.²

Introduction

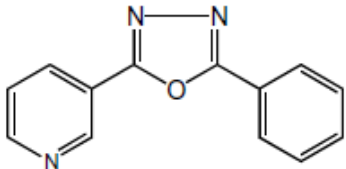
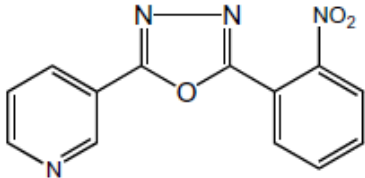
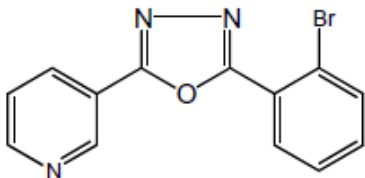
In recent years numbers of potent tyrosinase inhibitors have been reported from our and other groups. Very recently, we have reported two long chain esters, methyl 2 β (2*S*)-hydroxyl-7(*E*)-tritriacontenoate and methyl 2 β (2*S*)-*O*- β -D-galactopyranosyl-7(*E*)-tetratriacontenoate, showing strong to moderate inhibitory activities against tyrosinase.³ In another paper we have reported that, (+)-androst-4-ene-3,17-dione and its five metabolic analogues having steroidal skeletons, namely androsta-1,4-diene-3,17-dione, 17 β -hydroxyandrosta-1,4-dien-3-one, 11 α -hydroxyandrost-4-ene-3,17-dione, 11 α ,17 β -dihydroxyandrost-4-en-3-one and 15 α -hydroxyandrosta-1,4-dien-17-one, exhibited moderate inhibitory activities against the enzyme.⁴ Ahmad et al. in 2004 reported that, a new coumarinolignoid 8'-*epi*-cleomiscosin A together with the new glycoside 8-*O*- β -D-glucopyranosyl-6-hydroxy-2-methyl-4*H*-1-benzopyrane-4-one, exhibited strong inhibition against the enzyme tyrosinase, when compared to the standard tyrosinase inhibitors kojic acid and L-mimosine. The new coumarinolignoid exhib-

ited two times more potency than that of the standard potent inhibitor L-mimosine.⁵ Recently, Karbassi et al. reported the inhibition kinetics of two new synthetic bi-pyridine molecules, [1,4']bipiperidinyl-1'-yl-naphthan-2-yl-methanone (**I**) and [1,4']bipiperidinyl-1'-yl-4-methylphenyl-methane (**II**) of the catecholase activity of mushroom tyrosinase. The kinetics studies indicated that these are uncompetitive inhibitors and the values of the K_i are 5.87 and 1.31 μ M for **I** and **II**, respectively, which showed high potency. Fluorescent studies confirmed the uncompetitive type of inhibition for these two inhibitors. They also suggested that, the inhibition mechanism presumably coming from the presence of a particular hydrophobic site which can accommodate these inhibitors. This site could be formed due to a probable conformational change that was induced by binding of substrate with the enzyme.⁶

Here in this paper, we have discussed the tyrosinase inhibitory activities of a library of 26 analogues of 2,5-disubstituted-1,3,4-oxadiazoles, which were synthesized using microwave-assisted combinatorial synthetic approach and finally their structure-activity relationships (SAR) also have been discussed.

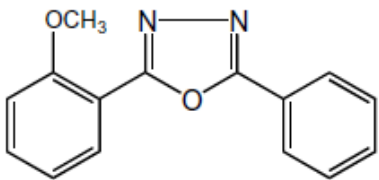
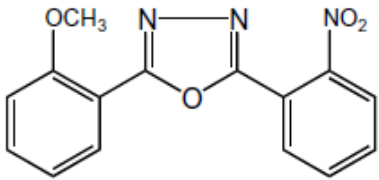
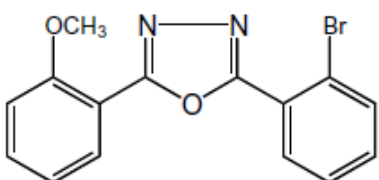
Results and Discussion

Table 1. Comparison between microwave-assisted and conventional method of synthesis of 2,5-disubstituted-1,3,4-oxadiazole 3 (a–m) in terms of time and yield

Sr.	R'	Structures	Microwave		Conventional	
			Time (min)	Yield (%)	Time (h)	Yield (%)
3a	C ₆ H ₅		12	92	6	81
3b	<i>o</i> -NO ₂ C ₆ H ₄		9	96	5	86
3c	<i>o</i> -BrC ₆ H ₄		12	92	6	76

Results and Discussion

Table 2. Comparison between microwave-assisted and conventional method of synthesis of 2,5-disubstituted-1,3,4-oxadiazole **4** (a–m) in terms of time and yield

Sr.	R'	Structures	Microwave		Conventional	
			Time (min)	Yield (%)	Time (h)	Yield (%)
4a	C ₆ H ₅		12	89	6	78
4b	<i>o</i> -NO ₂ C ₆ H ₄		9	95	5	80
4c	<i>o</i> -BrC ₆ H ₄		12	90	6	73

Results and Discussion

2.2. Tyrosinase inhibition studies

In the present studies, two types of 26 derivatives of the oxadiazole basic skeleton have been studied to explain their inhibition patterns and structure–activity relationships (SAR) against the enzyme tyrosinase, which is a multifunctional copper-containing enzyme, widely distributed in plants and animals and catalyses the *o*-hydroxylation of monophenols and also the oxidation of *o*-diphenols to *o*-quinones.¹

In one type of compounds, substitutions were changing at different positions of the phenyl ring at C-5 while keeping the pyridine ring constant at C-2. In another type of compounds, substitutions were changing at different positions of the phenyl ring while keeping the *o*-methoxy phenyl ring constant at C-2 position.

In a previous report it was found that 3-hydroxypyridine-4-ones is showing inhibition against tyrosinase.⁸ This was established that alkyl substitution at position 2 in the aromatic ring minimizes the interaction with tyrosinase. Several phenolic compounds have been reported to have potent tyrosinase inhibitory activity.^{9–11}

Compound **3a** exhibited potent tyrosinase inhibition and the IC_{50} value is $5.15\ \mu\text{M}$, where the IC_{50} value of reference tyrosinase inhibitor kojic acids (KA) is $16.67\ \mu\text{M}$. This compound was totally unsubstituted. When C-2'' position was substituted with $-\text{NO}_2$ group the resulting **3b** was showing highly potent ($IC_{50} = 3.18\ \mu\text{M}$) inhibition against tyrosinase, when compared with highly potent reference tyrosinase inhibitor L-mimosine (LM) ($IC_{50} = 3.68\ \mu\text{M}$). Due to the substitution of this $-\text{NO}_2$ group the resulting compound exhibited potent inhibition. But when the same phenyl ring was found to have bromine atom at C-2'' (**3c**, $IC_{50} = 5.23\ \mu\text{M}$) and C-3'' (**3d**, $IC_{50} = 6.04\ \mu\text{M}$)

Results and Discussion

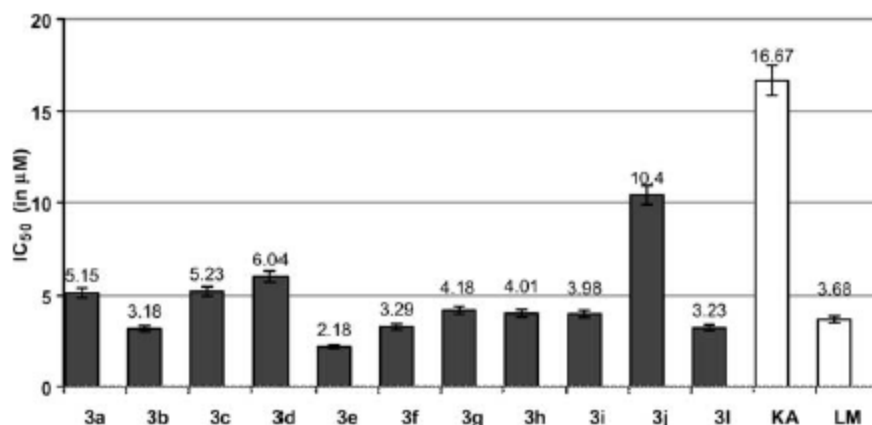


Figure 1. Graphical presentation of the comparative IC₅₀ values of the series 3 (a–m) against the enzyme tyrosinase.

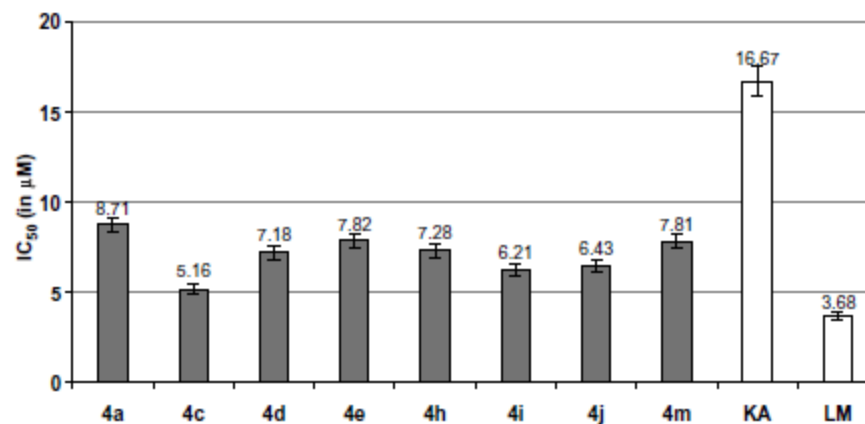


Figure 2. Graphical presentation of the comparative IC₅₀ values of the series 4 (a–m) against the enzyme tyrosinase.

Material and Methods

3. Materials and methods

3.1. General experimental

The ultraviolet spectra were measured in chloroform on a Lambda 5 UV/vis spectrophotometer (Perkin–Elmer). IR spectra (KBr discs or MeOH) were recorded on a Bruker FT-IR IFS48 spectrophotometer. EI mass spectra data were recorded with various MAT 711 (70 eV) spectrophotometers and data are tabulated as m/z . ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 and $\text{DMSO}-d_6$ using Bruker AC400 (500 and 400 MHz) spectrophotometer, respectively. Splitting patterns are as follows: s, singlet; d, doublet; dd, double doublets; t, triplet; m, multiplet. Chemical shifts are reported in δ (ppm) and coupling constants are given in hertz. The progress of all reactions was monitored by TLC, which was performed on 2.0×5.0 cm aluminum sheets precoated with silica gel 60F₂₅₄ to a thickness of 0.25 mm (Merck). The chromatograms were visualized under ultraviolet light (254–366 nm) or iodine vapours.

3.2. Tyrosinase inhibition assay

Tyrosinase inhibition assays were performed in 96-well microplate format using SpectraMax[®] 340 (Molecular Devices, CA, USA) microplate reader according to the developed method earlier described by Hearing.¹⁴

First the compounds were screened for the *o*-diphenolase inhibitory activity of tyrosinase using L-DOPA as substrate. All the active inhibitors from the preliminary screening were subjected for IC₅₀ studies. Briefly, all the compounds were dissolved in DMSO and finally the solvent mixture was 2.5%. Mushroom tyrosinase (30 units, 28 nM) was first preincubated with the compounds, in 50 nM Na-phosphate buffer (pH 6.8) for 10 min at 25 °C. Then the L-DOPA (0.5 mM) was added to the reaction mixture and the enzyme reaction was monitored by measuring the change in absorbance at 475 nm (at 37 °C) of the formation of the DOPA chrome for 10 min.

Spectral Data

3.3. Spectral data of the compounds

3.3.1. 3'-(5-Phenyl-1,3,4-oxadiazol-2-yl)pyridine (3a). Yield 92%; mp 112–114 °C; R_f = 0.34 (ethyl acetate–acetone, 9:1); UV (methanol): $\lambda_{\max}$ (log ϵ) 256 (2.32) nm⁻¹; IR (KBr) $\nu_{\max}$: 3073 (C–H), 1667 (C=N), 1557 (C=C), 1287 (C–O), 832, 659 (C–Br); ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.21 (d, 1H, J = 1.1 Hz, H-2'), 9.13 (dd, 1H, $J_{6',5'} = 4.9$ Hz, H-6'), 8.81 (br d, $J_{4',5'} = 8.3$ Hz, 1H, H-4'), 8.59 (dd, 1H, $J_{5',6'} = 4.9$, $J_{5',4'} = 8.3$ Hz, H-5'), 7.63 (dd, 2H, $J_{2'',3''/6'',5''} = 7.8$, $J_{2'',4''/6'',4''} = 2.3$ Hz, H-2''/H-6''), 7.50 (t, 1H, J = 7.8 Hz, H-4''), 7.38 (t, 2H, J = 7.8, H-3''/5''); EI MS (m/z): 223 (M^+ , 21), 145 (31), 106 (100), 77 (79), 78 (65), 68 (35), 51 (72). Anal. Calcd for C₁₃H₉N₃O: C, 9.95; H, 4.06; N, 18.82; O, 7.17. Found: C, 69.86; H, 3.97; N, 18.73; O, 7.08.

Acknowledgement and References

Acknowledgements

One of us (M.T.H.K.) gratefully acknowledges the travel support from Third World Academy of Sciences (TWAS), Italy, under the 'South-South Fellowship' scheme. He is also the recipient of the fellowships from the UNESCO-MCBN (Grant no. 1056); the CIB, Italy and the AVTL, Italy.

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