MEDICINAL CHEMISTRY

Manuscript Evaluation Form

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PAPER TITLE	Gram-scale preparation of C-terminal modified enkephalin analogues by typical liquid-phase peptide synthesis
AUTHOR(S) NAME	Yeon Sun Lee

Sec. A: REFEREE'S ASSESSMENT *(cross as appropriate)*

Criterion	Excellent	Good	Fair	Poor
Originality of the topic	x			
Technical Quality		x		
Importance in its Field	x			
Style & Overall Representation		x		
Readily Understandable	x			
Suitability for the Journal	x			
Adequate Illustrations or Drawings	x			
English language		x		

Description	Yes	No	Comments/ Suggestions
Does the title represent manuscript's contents?	x		
Is the Abstract accurate and concise?	x		
Are the approach/ methods properly described?	x		
Are the conclusions and interpretations sound?	x		A short Conclusion can be added after Discussion
Are the references properly cited?	x		
Is this a new/ original/ contribution?	x		
Is it within the scope of the journal?	x		

Overall the Paper is Rated: **(Excellent -8---------- Poor)**
10 9 **8** 7 6 5 4 3 2 1

Sec. B: REFEREE'S RECOMMENDATIONS

		OTHER SPECIFIC CRITICISMS	
Accept with minor changes	x	Imperfect style	x
Accept with major changes		Too long	
Reject in current form, but may be resubmitted		References incorrectly presented	
Reject, with no resubmission		Typographical and Grammatical errors	x

PAPER TYPE: **Research article** ☐ **Review article** ☐ **Letter article** ☐

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Confidential Comments to the Editor (not for Transmission to Authors):

The article is within the scope of the journal and suitable for publication after some revision that I send in comments for the authors.

Some conclusions and key features of a robotic liquid-phase peptide synthesis for large scale, step simple and cost effective production of peptides are given within the Discussion section, as well as in the Abstract.
A short conclusion can be added also at the end of the manuscript.

It should be stated that the obtained C-terminal modified encephalin analogues, by lipophilic moiety substitution, enabled synergistic effects with mixed opioid receptor activities, had improved and optimized metabolic stability and blood brain barrier penetration. Lead compounds showed high analgesic efficacy in nerve injured animal models with strong binding affinity at mu and delta opioid receptors. Preparation of large quantities of high-purity analogues was done by the cost effective liquid phase peptide synthesis established for long period in the laboratory.

Comments for the Authors *(continue on another sheet, if necessary)*:

Review of the article entitled
Gram-scale preparation of C-terminal modified enkephalin analogues by typical liquid-phase peptide synthesis, by Yeon Sun Lee

This article describes the gram-scale, liquid-phase peptide synthesis protocol of C-terminal modified encephalin analogues that enable synergistic effects with mixed opioid receptor activities, have improved and optimized metabolic properties and analgesic efficacy.

The article is within the scope of the journal and suitable for publication after some revision.

The English language, spelling and grammar have to be improved.
For example, use the correct spelling in the entire manuscript, such as encephalin, Buchner funnel, Erlenmeyer, Separation funnel, Stir bars, with the first capital letters in the paragraph Apparatus and equipment, as well as material, rotary evaporator, unsterile, purification, etc.
On page 3, in the Abbreviations, replace comma after TLC instead of point.
In the Abstract, replace
The preparation of large quantity of analogues was done by liquid phase peptide synthesis
instead of
The preparation of large quantity of analogues were done by liquid phase peptide synthesis
In the Introduction, replace
encephalins are still limited as a clinically viable drug because of: low bioavailability, low blood-brain barrier penetration and low metabolic stability [2-9].
instead of

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enkephalins are still limited as a clinically viable drug because of low bioavailability: low blood-brain barrier penetration and low metabolic stability. [2-9]
Use italic *in vivo*
Use the abbreviation equiv., instead of equiv, as well as min, instead of mins in the entire manuscript.

The entire manuscript should be formatted according to the style of the journal.
Put the names of compounds in the same row wherever it is possible.
For example, on page 3, in the Abbreviations, 1-hydroxybenzotriazole
On page 4, in the Abstract, *N*-phenyl-*N*-(piperidin-4-yl)-propionamide
Put the numbers of references before, instead of after the sign of punctuation.
Put the point after the legends of Figures 1 and 2 and Scheme 1.
Put the number beside the unit of measure in the same row, for example: on page 8, 50 mL, in Table 3, 10 mm x 250 mm, in the legend of Scheme 1, 1.1 equiv.

The quality of Figures 2, 3 and 4 can be improved, resolution or font of letters and numbers increased.
Font of letters and numbers can also be increased in Tables.

Some conclusions and key features of a robotic liquid-phase peptide synthesis for large scale, step simple and cost-effective production of peptides are given within the Discussion section, as well as in the Abstract.
A short conclusion can be added also at the end of the manuscript.
It should be stated that the obtained C-terminal modified encephalin analogues, by lipophilic moiety substitution, enabled synergistic effects with mixed opioid receptor activities, had improved and optimized metabolic stability and blood brain barrier penetration. Lead compounds showed high analgesic efficacy in nerve injured animal models with strong binding affinity at mu and delta opioid receptors. Preparation of large quantities of high-purity analogues was done by the cost effective liquid phase peptide synthesis established for long period in the laboratory.

FIELD OF EXPERTISE OF REFEREE: Materials and chemical technologies, nanotechnologies, biomedical engineering, chemistry**,** medicinal chemistry

Name & Affiliation of referee: Tamara Jovanovic, Department of Biomedical Engineering, Faculty of Mechanical Engineering, University of Belgrade, Kraljice Marije 16, 11120 Belgrade, Serbia

Dr Tamara Jovanovic / January 16, 2019
SIGNATURE OF REFEREE / DATE