Response to Reviewers

TO: Prof. Dr. Dejan Opsenica

Editor

Journal of the Serbian Chemical Society

Dear Prof. Dejan Opsenica

Please find enclosed the revised manuscript entitled "Synthetic route towards potential bivalent ligands possessing opioid and D2/D3 pharmacophores ".

We would like to acknowledge Reviewers for dedicated work on our manuscript and for useful advices. In the following lines we offer detailed response to Reviewer’s comments; accordingly, changes have been made in the main text of the manuscript, the experimental section and the supporting information.

 All those revised documents/files (including corrected schemes) will be uploaded together with this response to the decision letter.

 We hope that the manuscript in present form will be suitable for publishing in *Journal of the Serbian Chemical Society*

 Sincerely,

 Dr Slađana Kostić-Rajačić

The List of responses to the comments:

**Reviewer #1**:

Recommendation: Minor Revision

Comments:

“This paper describes the synthetic pathway towards potential bivalent receptor ligands. Novel synthesized compounds contain two different pharmacophores, opioid and D2/D3, and have the potential to be used for various pharmacological tests. These results would be useful for understanding of the interaction between dopaminergic and opioid signal pathways as well as related phenomena. All new compounds were completely characterized by NMR and IR spectroscopy, and MS spectrometry. I recommend that presented manuscript can be accepted for publication after minor revisions.

In my opinion, this manuscript should: be published after minor revision without additional review.

If manuscript is suitable for publishing, referees recommendation: Original scientific paper.ˮ

1) “Line 10: Correct optimised into optimized”

2) “Line 10: instead structures write compounds.”

3) “Line 12: instead in nearly 35% write in 33%, 35% and 39%.”

4) “Line 16: instead both opioid and D2/D3 pharmacophores with two pharmacophores, opioid and D2/D3ˮ

5) “Line 27: Correct the pharmacophores into these pharmacophoresˮ

6) “Line 52-54: In this place write something about the main goal of researchˮ

7) “Line 72: provide the type of spectrometer for NMR measuringsˮ

8) “Line 81: provide the type of spectrometer that you used for recording of IR spectraˮ

9) “Line 91: delete on SiO2 platesˮ

10) “Line 92: How much of 10% HBr was addedˮ

**Authors responds to the comments 1-10:** We appreciate these observations from the Reviewer. Changes are made as suggested and these parts of the manuscript are highlighted green.

11) “Line 98: instead 14a-c write 13a-cˮ

12) “Line 99: instead 13a-c write 2a-cˮ

13) “Line 108: instead 15a-c write 14a-cˮ

14) “Line 108: instead 15a-c write 14a-cˮ

15) “Line 109: instead 14a-c write 13a-cˮ

16) “Line 116: instead 17a-c write 16a-cˮ

17) “Line 117: instead 15a-c write 14a-cˮ

18) “Line 126: instead 18a-c write 1a-cˮ

19) “Line 127: instead 17a-c write 16a-cˮ

**Authors responds to the comments 11-19:** We appreciate these observations from the Reviewer. However, numbers of the compounds changed after we performed corrections recommended by Reviewer #1, namely comments 20) and 22), so the new numbers are in accordance with the changes that we made, and these parts of the manuscript and in the schemes are highlighted green.

20) “Line 139-141: It would be appropriate to write retrosynthetic route for developed synthetic pathwayˮ

21) “Line 144: Correct pierazines into piperazinesˮ

22) “Line 144-145 and line 159: From Scheme 2 remove part A.ˮ

23) “Line 148: Delete text: since we had it more in stockˮ

24) “Line 149-153 and line 159 (Scheme 2): On Scheme 2 describes only the synthesis of 8b and 8c, and discusses these results in the textˮ

25) “Line 167: On Scheme 3 provide yields for compound 14a-c and 16a-cˮ

**Authors responds to the comments 20-25:** We appreciate these observations from the Reviewer. Changes are made as suggested and these parts of the manuscript are highlighted green.

26)“Line 174-178: It would be appropriate to add more details for comparison between compounds 5 and 9ˮ

**Authors responds to the comment 26:** We appreciate this observation from the Reviewer. We considered the issue, and decided to remove the paragraph, since it was not relevant any more, because the part of the Scheme 2 where compound **5** was mentioned, was deleted according to the Reviewersʼ recommendation (comment 22). Changes are made as suggested and this part of the manuscript is highlighted green.

27) “Line 229: instead strukture write jedinjenjaˮ

28) “Line 234: instead obe farmakofore write dve farmakoforeˮ

29) “According to corrected Scheme 2 remove spectral data for compounds 8a and 8dˮ

30) “Line 76 and 77: Carbon NMR shifts should be reported to the nearest 0.1 ppm

except when greater precision is needed to distinguish closely spaced peaksˮ

**Authors responds to the comments 27-30:** We appreciate these observations from the Reviewer. Changes are made as suggested and these parts of the manuscript and supporting information are highlighted green.

**Reviewer #2**:

Recommendation: Minor Revision

Comments:

“ The manuscript entitled "Synthetic route towards potential bivalent ligands possessing opioid and D2/D3 pharmacophores" by Ivana I. Jevtic and co-authors represents the synthesis of bivalent ligands in an efficient manner. The piperidine derived compounds were synthesized from commercially available compounds in a four step reaction sequence. Some of the synthetic

steps were reported before and the present procedure is cost-effective and have significant improvement. The authors reported the alternative route for the synthesis of key intermediates when the reaction gave cyclic amines with dihalo alkanes (8). The design and presentation strategy is good, even though there are some typos and errors, these need to be fixed. The present

work is interesting and attract the readers of this journal. Overall, this work holds the conceptual advance and novel to be published on the Journal of the Serbian Chemical Society after making the minor correction as noted below.

In my opinion, this manuscript should: be published after language correction by the author(s)

If manuscript is suitable for publishing, referees recommendation: Original scientific paper ˮ

1) “Line 90: Check the spelling of “steer” and this is repeated severaltimes in the manuscript (Line: 101, 102, 108, 110, 111, 119, 129 etc.).ˮ

2) “Line 93: “2x 20 ml” should be “2 x 20 mL”ˮ

3) “Line 100: “4-chloro-butyrilchlorid” should be “and 4-chloro-butyrilchloride”

**Authors responds to the comments 1-3:** We appreciate these observations from the Reviewer. Changes are made as suggested and these parts of the manuscript are highlighted cyan.

4) “Line 103: “MeOH (10 ml)” should be “MeOH (10 mL)” similarly several places in the entire manuscript. “dry-column flash chromatography” may be “column flash chromatography”

**Authors responds to the comment 4:** We appreciate these observation from the Reviewer. However the used chromatography method for purification of the compounds, is called “dry-column flash chromatography” according to the references given in the manuscript and here. The column flash chromatogaphy is a diferrent chromatography method.

1. L. M. Harwood, *Aldrichimica Acta*, **18** (1985) 25
2. B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, *Vogel's textbook of practical organic chemistry, 5th ed*. John Wiley & Sons, New York, 1989
3. A. J. Shusterman, P. G. McDougal, A. Glasfeld, *J. Chem. Educ.,* **74** (1997) 1222

5) “Line 111: “8h” change it to “8 h”; similarly several places in the manuscript includes ChemDraw also. Change it to standard format (0 h).ˮ

6) “Line 122: “50 mL of CH2Cl2 was added and the mixture was extracted with 2 x 25 mL of brine.” Change this sentence to “50 mL of CH2Cl2 was added, the layers were separated and the organic phase was washed with 2 x 25 mL of brine.”

**Authors responds to the comments 5 and 6:** We appreciate these observations from the Reviewer. Changes are made as suggested and these parts of the manuscript are highlighted cyan.

7) “Line 147: “For the starting material in the first alkylation step we selected norfentanyl 4, since we had it more in stock.” This sentence is not so appropriate to say based on the compound you have, modify this sentence to give a meaning that started form this compound.ˮ

**Authors responds to the comment 7:** We appreciate this observation from the Reviewer. Changes are made as suggested and this part of the manuscript is highlighted cyan.

8) “Authors should include these references in the introduction section: Chemical Science, 2018, 9, 1782-1788; Organic Letters 2016, 18, 5620–5623; Journal of Natural Products 2017, 80, 2561–2565.ˮ

**Authors responds to the comment 8:** We have consider this suggestion of the Reviewer, however introducing these references would lead to a conceptual changes of the introduction section, therefore we decided not to add them. We will have in mind these references for another manuscript in the future.

9) “In ChemDraw also yields should be accurate numbers may not be decimal value and hours format in a uniform all over the paper.ˮ

**Authors responds to the comment 9:** We appreciate these observation from the Reviewer. Changes are made as suggested and these parts of the schemes are highlighted green.

10) “Did authors test these compounds for the proposed biological evaluation?ˮ

**Authors responds to the comment 10:** We appreciate this interest from the Reviewer. Pharmacological evaluation of novel compounds presented in our manuscript is a part of our future work.