PEER-REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-18-00626
Title: Multitarget therapeutic strategies for neurodegenerative diseases
Reviewer's Name: Paulina Carriba
Reviewer's country: UK
Date sent for review: 2018-09-07
Date reviewed: 2018-09-21
Review time: 14 Days

1. Do you consider this paper is hotspots or important areas in the research field related to neural regeneration?
The manuscript focus in the multitarget-directed ligands (MTDLs) as a potential and powerful tools against neurodegenerative diseases.
2. Which area do you think this paper falls into? Neurorepair, neuroprotection, neuroregeneration or neuroplasticity.
Neurorepair and neuroregeneration.
3. Is the manuscript technically sound, and do the data support the conclusions?
Considering that it is a review manuscript, yes, it is.
4. Has the statistical analysis been performed appropriately and rigorously?
Question not applicable in a review manuscript.
5. Is the manuscript presented in an intelligible fashion and written in Standard English?
In mi opinion some changes has to be made in order that it will be really intelligible.
6. Your peer review comments will be published as an open peer review report. Do you agree to have your name included with the published article?
Yes

Manuscript Rating Question(s):	Scale	Rating
The subject addressed in this article is worthy of investigation. (3 as the best score)	[1-3]	3
The information presented was new. (5 as the best score)	[1-5]	3

COMMENTS TO AUTHORS

The etiology of neurodegenerative diseases involves multifactorial causes. Therefore the authors argue that an interesting approach to halt or even cure neurodegenerative diseases is by using multitarget-directed ligands (MTDLs). In this regard, the authors in this manuscript review these MTDLs.

The topic is really interesting, but in my opinion the text has to be reorganised and rewritten to be more comprehensible. For example, they describe in the third paragraph monoamine oxidase (MAO) that is one of the targets in the MTDLs described in iron chelators drugs in the second paragraph. Then, I suggest that after presenting neurodegenerative illnesses as multifactorial causes, the first group of MTDL described would be "Dual functional cholinesterase and MAO inhibitors" and then "Multitarget brain permeable iron chelator drugs". Another point related to how text is presented is the lack of connections

between sentences, sometimes it seems ideas are exposed without any link or order, it would be really useful that the authors guide the reader considering the intrinsic MTDL complexity.

It is necessary to include the refs for:

- "For example, neuronal death in AD animal models was detected in the early amyloid aggregation phase in the presence of the oligomeric species."
- "literature reveals the key role of iron in promoting Aβ neuro-toxicity in AD by delaying the formation of well-ordered aggregates of Aβ."
- "In 2018, a novel propargylamine-modified pyrimidinylthiourea derivative was developed as a potential mutlitarget agent as it demonstrated a high affinity for the inhibition of both AChE and MAO-B in mouse brain and the ability to alleviate scopolamine-induced cognitive impairment in AD in mice."
- "It was reported that the homo and hetero dimers of tacrine can improve its efficiency, potency and reduce its undesired side effects."
- "Inhibition of NAD(P)H quinone dehydrogenase 1 (NQO1) by the curcumin derivatives is postulated to contribute to their neuroprotective effect by counteracting oxidative stress in neurological disorders."

Imprecisions, mistakes in the text, please revise these sentences:

- "The progression of many neurodegenerative diseases such as Alzheimer's (AD), Huntington's (HD) and Parkinson's diseases (PD) is directly correlated to the deposition of amyloid-β peptides…". This is true for AD, but not for HD and PD.
- "Taking into consideration the multifaceted nature of neurodegenerative diseases, development of multitarget-directed ligands (MTDLs) has evolved as an attractive strategy to target multiple proteins …" however, strictly not all the targets are proteins.
- "In 2018, a novel propargylamine-modified pyrimidinylthiourea derivative was developed as a potential mutlitarget "
- "The superior therapeutic profiles of MTDLs to single-target small molecules are attributed to the ability of MTDLs to target multiple major pathological cascades of neurodegenerative diseases, for example, tau and amyloid cascades." However I think none of the MTDLs presented here target these two factors.