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Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	2014_IJBcRR_9721
Title of the Manuscript:	(1H-pyrrolo [2,3-b] pyridine) 7-Azaindole as Cholinesterase/ Glycation inhibitors
Type of the Article	Original Research Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the



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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments DISCUSS	The article titled "(1H-pyrrolo [2,3-b] pyridine) 7-Azaindole as Cholinesterase/Glycation inhibitors" describes new azaindole derivatives with anti-cholinesterase and antiglycation properties. However, the manuscript needs to be checked by the native speaker as some of the sentences do not make sence. -The introduction is confused. Try to rewrite it into one rational complex, not running from one point to another. -There is no data available that 7-Azaindole derivatives can be used as cholinesterase inhibitors. Authors should at least mention why they decided to investigate the anti-cholinesterase activity in the introduction.	The manuscript has been checked by the native speaker The introduction has been written into one rational complex, now it is not running from one point to another. 7-Azaindole were used as inhibitors of p38 MAP kinase. 7-Azaindole were reported for analgesic, blood pressure lowering and anti-inflammatory activities. and is an effective drug against nervous central system and shown affinity for serotonin receptor. Sulfonamide, derivatives of 7-azaindole also exhibit antinociceptive activity Enlightened by these findings and as a continuation of our interest in this area, we extended our investigation to the synthesis of other related 7-Azaindole derivatives.



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	-There are several awkward expressions that need to be carefully checked by the native speaker (e.g. "Alzheimer's disease is age related neurodegenerative disease and is due to progressive memory failure and extra cognitive mutilations." should better read as "Alzheimer's disease is age related neurodegenerative disease connected with memory failure and cognitive decline") The procedure of "modified" Ellman's protocol is not well defined even though, there is reference to literature (Please specify concentrations of cholinesterase, ATCh and inhibitor used in the assay). I am not sure about the right analytical recordings of compounds (e.g. "J" interacting constant must be rounded to one decimal). In experimental protocol, there is no mention about using 2D NMR spectra (estimating according to precise matching of hydrogens).	The target compounds were also designed to comprise the 7-Azaindole nucleus in order to explore further their acetylcholinesterase, butyrylcholinesterase activity. The sentence "Alzheimer's disease is age related neurodegenerative disease and is due to progressive memory failure and extra cognitive mutilations." Now has been written as "Alzheimer's disease is age related neurodegenerative disease connected with memory failure and cognitive decline" The procedure of "modified" Ellman's protocol is now well defined. Concentrations of cholinesterase, ATCh and inhibitor used in the assay has been included. The assay procedure has been previously described. Khalid A, Zaheer ul H, Ghayur N, Feroz F, Atta ur R, Gilani AH, Choudhary MI. J Steroid Biochem Mol Biol 2004; 92:477. "J" interacting constant has been rounded to one decimal (that was the
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	-Figure placed on the line 280 must be drawn using convenient chemical software (e.g. ChemDraw or ChemSketch, based on the journal's requirements) using ACS style for the whole subset of the reported compounds. Do not forget to introduce positive charge into the structure. I did not find also any link to the figures in the text. The same must be applied for structures in the lines 298 and following figures. - Authors should also consider remaking "results and discussion" as there are several awkward statements and sentences. Authors should unify the table in order to round all the values to valid decimals (i.e. 0.98 ± 0.0518 is not the same as 8.5 ± 0.02). The structure of physostigmine is not correct.	typographical mistake). In experimental protocol, now there is mention about using 2D NMR spectra (HMQC estimating according to precise matching of hydrogens). Figure placed on the line 280 has been drawn using convenient chemical software (e.g. ChemDraw or ChemSketch, based on the journal's requirements) using ACS style for the whole subset of the reported compounds. positive charge into the structure. has been introduced. link to the figures in the text has been done. The same has been applied for structures in the lines 298 and following figures. Remaking of results and discussion" has been done. The table has been unified in order to round all the values to valid decimals (i.e. 0.98 ± 0.05 is now the same as 8.51 ± 0.02). The structure of physostigmine has been corrected that was typographical
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	- The statement that “Azaindole derivatives are closely related to physostigmine and can be compared for their use in the treatment of Alzheimer’s disease.” is not correct. I recommend authors to read more about physostigmine effect towards cholinesterase as it is well known carbamate acting as pseudoirreversible inhibitor of cholinesterases forming covalent bond with Ser residue in the active site. I can see there only marginal similarity based on the structural features. Based on the aforementioned note, physostigmine cannot be compared by methods of molecular modelling studies. All the part considering docking studies must be rewritten for the reversible inhibitors. Moreover, I also recommend studying the kinetics of the enzyme inhibition for at least AChE. References must be written uniformly according to the journal recommendations.	mistake. Azaindole derivatives are closely related to physostigmine and could be compared for their use in the treatment of AD. Physostigmine was one of the clinically tested AChE inhibitor . There was no data available that 7-Azaindole derivatives can be used as cholinesterase inhibitors. So we decided to do their cholinesterase activity. By doing so we get very promising results. Due to the completion of the project it is not possible to do the kinetics of the enzyme inhibition for AChE. References has been written uniformly according to the journal recommendations.
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Minor REVISION comments	-kindly check all the gaps are correctly used (e.g. IC₅₀ values 120.6±0.2 μM should be correctly used as follows: IC₅₀ values 120.6 ± 0.2 μM) -“withdrawing affect” should be replace by “withdrawing effect” -there are similar repeating words in one sentence e.g. “showed potent antiglycation potential...” as this should by replace by “showed potent antiglycation properties...”; the same can be applied for introduction (working on its own synthesis and synthesizing its different analogues...) -the sentence “we now wish...” should begin with big letter (We now wish) - The sentence “Augments β amyloid -(Aβ) formation, [22] and tau hyper phosphorylation [23] calcium entry through the L-subtype of high voltage activated calcium channels causes both calcium in excess and mitochondrial disruption, which activate the apoptotic cascade and cell death” does not make sense at all. I would recommend its shortening/separation to several integral parts. -When you used abbreviated words once (e.g. Alzheimer’s disease – AD), apply it for the whole manuscript total awkward statement: “In U.S.A alone, Alzheimer’s disease related expenses surpassed \$100 billion every year per patient [26]” \$100 billion expenses every year are probably the expenses for the treatment of all patients having AD in U.S.	All the gaps now correctly used (e.g. IC₅₀ values 120.6±0.2 μM should be correctly used as follows: IC₅₀ values 120.6 ± 0.2 μM) -“withdrawing affect” has been replaced by “withdrawing effect” -there were similar repeating words in one sentence e.g. “showed potent antiglycation potential...” as this has been replaced by “showed potent antiglycation properties...”; the same has been applied for introduction (working on its own synthesis and synthesizing its different analogues...) -the sentence “we now wish...” begins with big letter (We now wish) - The sentence Augments β amyloid -(Aβ) formation, and tau hyper phosphorylation calcium entry through the L-sub type of high voltage, activated calcium channels causing both calcium in excess and mitochondrial disruption. This activated the apoptotic cascade and cell death does make sense now. Abbreviated word (e.g. Alzheimer’s disease – AD), now has been applied for the whole manuscript Now the sentence has been written as In U.S.A alone, AD related expenses surpassed \$100 billion every year [32].
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	- revise the sentence: "Its two feature abnormalities are plaques deposits of a protein fragment called beta amyloids and tangle, twisted strands of another protein tau [28]. the enzyme code for BChE is 3.1.1.8 use abbreviation for acetylcholine (ACh), acetylcholinesterase (AChE), Alzheimer's disease (AD) - Another awkward sentence: "For the treatment of late diabetic complications antiglycation agents is an important approach." The correct statement should be for instance: "Antiglycation agents are used for the treatment of the diabetic complications." or "The development of novel antiglycation agents represents an interesting strategy for management late diabetic complications" - There is a verb missing: "Aminoguanidine, an inhibitor of advanced glycation end products formation [45]. consider rewriting: "It has demonstrated that polyamines, spermidine and spermine have potent antiglycation effects, comparable to those of aminoguanidine and carnosine [47]. Focused on "general method of preparation of compounds", the first sentence here is meant that you obtain a mixture of several compounds that form, in my opinion, inseparable mixture. Rewrite the following sentence to clear form: "To a stirred equimolar, quantity of 7-azaindole in acetone (20-25 ml) was added successively and 2-bromo-2-acetonaphthone, 1-adamantile-bromo ethyl-ketone, 2-bromo-3-nitro acetophenone, 2-bromo-4-nitro-acetophenone were dissolved separately in 20-25 ml of acetone."	The sentence "Its two feature abnormalities are plaques deposits of a protein fragment called beta amyloids and tangle, twisted strands of another protein tau has been eliminated from the manuscript.. the enzyme code for BChE is 3.1.1.8 The abbreviations has been used for acetylcholine (ACh), acetylcholinesterase (AChE), Alzheimer's disease (AD) respectively. The sentence has been changed to "The development of novel antiglycation agents represents an interesting strategy for management late diabetic complications" The sentence has been changed to "It has demonstrated that polyamines, spermidine and spermine have potent antiglycation effects, comparable to those of aminoguanidine and carnosine [47]. The Sentence has been changed to 7-azaindole (0.01 mol) and substituted phenacyl halide (0.01 mol) were dissolved separately in acetone (20 mL) and then mixed together in a round-bottommed flask (Scheme-1).
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	thin layer chromatography as well as the advanced glycation end product (AGE) should be abbreviated firstly galanthamine is written as galanthamine not "Galanthamine" (the same for physostigmine, indole)	thin layer chromatography as well as the advanced glycation end product (AGE) has been abbreviated firstly galanthamine has been written as galanthamine not "Galanthamine" (the same for Physostigmine, Indole)
<u>Optional/General</u> comments	- revision by the native speaker is necessary - introduction should be written more clearly - results and discussion part must be rewritten according to aforementioned notes	As desired by the reviewer revision has been done by the native speaker - introduction has been written more clearly - results and discussion part has been rewritten according to aforementioned notes