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Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	2014_IJBcRR_15784
Title of the Manuscript:	Kinetics For The Inhibition of Serum Acetylthiocholin Esterase Activity by Some New Phenobarbital Derivatives.
Type of the 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 manuscript is scientifically robust and technically sound.

To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

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PART 1: Review Comments

	Reviewer's comment	Author's comment <i>(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)</i>



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<u>Compulsory</u> REVISION comments	Authors should clearly define the aspect of their paper: - medical, oriented to phenobarbital derivatives itself and their action, including enzymes - or (and in my opinion they have done this kind of research) toxicological, where they have biomarker of the “detoxification engagement of the body ” (in this case only indirectly connected with investigated drug and its metabolites) and they are looking for the quantitative relation between the chemical structure of medicine and the enzyme activity, while – in fact – they investigate the side effect of four phenobarbital derivatives. Paradoxically phenobarbitals (Diazepam) are applied to patients intoxicated by cholinesterase inhibitors (pesticides or some heavy metals) as “sedative drugs” and this kind of treatment increases survival and reduces brain damage (e.g. Leikin et al. 2002. A review of nerve agent exposure for the critical care physician. Critical Care Medicine 30 (10): 2346-2354)). First of all, authors did not explain why they have chosen serum esterase, because it is not a target point for phenobarbital as well as its derivatives, because phenobarbitals act, as medicines via GABA receptors, and are detoxified via cytochrome P-450 system. They cited the review paper of Colovic et al., 2013 about cholinesterase inhibitors, but did not comment that in this paper phenobarbitals are absent. If experiments were planned differently, e.g. using animals, authors should include into their research some aspects of the cytochrome P-450 activity (as main detoxification way of phenobarbital compounds) and – having this background – to investigate inhibitory effect of four phenobarbital derivatives. The accessory weak point of this paper is a source of an enzyme. One health subject is not enough for the serious study, because we do not know if there are some interrupting or “masking” factors which seriously affected the interaction between phenobarbital	I wish to study toxicology and pharmacology and I shall try to read about these field thanks to orient me in these way. I am a chemists try to study the enzyme and its action by a series of studies some of it was published and some of it under study kinetic and thermodynamic of AChE in presence and absence of inhibitors. I can not have the full text of this paper. Sure all these are true but there were many study about the effect of phenobarbital as sedative drug on AChE for this reason I tend to test the prepared derivatives on enzyme. I had more one study on curoplasmin oxidase, paraoxonase , glutathione reductase, lactate dehydrogenase in addition to AChE . Serum is only sample that can use it
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	derivatives and the investigated enzyme. The much better source of the AChE is the standardized version from bovine serum – in this case we have pure biochemical experiment instead of the described in the reviewed paper, where we have living blood donator (I hope still alive though procedure) and the fresh blood. Unfortunately, the presented version does not give opportunity to re-define experiments and their description, so to rescue the work (the described inhibitory effect itself is quite interesting and, regarding all restrictions, seems to be well documented) I suggest the presented below changes. Introduction Authors should describe what kind of biological activity of the four examined derivatives they expect, regarding their chemical structure (of course in general). Authors should present some information about biomarker role of cholinesterase, using e.g. Lionetto M.G., Caricato R., Calisi A., Giordano M.E., Schettino T. Acetylcholinesterase as a Biomarker in Environmental and Occupational Medicine: New Insights and Future Perspectives. BioMed Research International, vol. 2013, Article ID 321213, 8 pages, 2013. doi:10.1155/2013/321213. Authors should add at least one aim of their study – why they performed this kind of experiment. Materials & Methods Supplementary information about four derivatives, presented in Table 1 is necessary, especially results for databases searching that proves the described derivatives are not matched, so are really new (be very inquiring, because the barbituric acid is commercialized by Bayer in 1912, so there is a lot of known	until now under bad environment and laboratory in my place. With my pressure. I add it with it references. I use it , thanks a lot for these references . The present work aims to study the effect of prepared phenobarbital derivatives on AChE as biomarker in relation to the current and future as in environmental and occupational of human health monitoring. All these question can answer by reference 17.
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	derivatives, e.g. Toxnet has 2578 matches to phenobarbital, and the lack of compound name e.g. in Chemicalize.org is not a proof of having new compound.). Results & Discussion Authors should bring the concentrations used by them in “<i>ex situ</i>” experiments to real pharmacokinetics and pharmacodynamics. They correctly use molar concentration 10^{-10} to 10^{-4}, but in the supplementary paragraph they should compare these concentrations with available toxicological and pharmacological data, e.g. Dreisbach R.H. and Robertson W.O. (1987) in their Handbook of Poisoning give lethal dose of barbituric compounds, which varies from 1 to 2 g per individual what reflects about 30 mg/dm^3 of blood in very hard intoxication. Assuming that examined compounds have molecular weight about 600, the concentration 10^{-4} means that we have 60 mg/dm^3, so practically the lethal dose. Which concentrations from the used range are possible regarding the typical pharmacological doses of barbituric acid derivatives and how strong is the inhibitory effect regarding this real conditions? Authors should also give a hypothesis why C compound differ from the others, regarding its inhibitory properties.	In future work there is a study of toxic effect of these new tested derivatives this is not documented. Because I am sure it was not completely dissolve.
Minor REVISION comments	Literature chapter is bad formatted and there is lack of some titles. As I know the requested by the IJBRR form is for published paper: 1. Hilly M, Adams ML, Nelson SC. A study of digit fusion in the	I change all what you pointed to it .



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	mouse embryo. Clin Exp Allergy. 2002;32(4):489-98. Note: List the first six authors followed by et al. Note: Use of DOI number for the full-text article is encouraged. (if available). Note: Authors are also encouraged to add other database's unique identifier (like PUBMED ID). See more at the guide for authors: http://www.sciencedomain.org/page.php?id=general-guideline-for-authors While in the literature chapter we have: 11. SUNNY J., ANIL J. , AVNEET G. , HEMRA J.: SYNTHESIS, BIOLOGICAL ACTIVITIES AND CHEMISTRY OF THIADIAZOLE DERIVATIVES AND SCHIFF BASES . Asian Jou. of Pharm. and Clini. Rese.2012;Vol. 5, Issue 3. 12. Mithun R. andBiplabV.: Chemistry and Biological Importance of heterocyclic Schiff's Bases.Intern.Res.Jou. of Pure &Appl. Chem.2010;3(1):1-5. 13. Behl, P., Lantieri, K. L., Streiner, D. L. and Black, S. E.: The effect of cholinesterase inhibitors on decline in multiple functional domains in Alzheimer's disease: a two-year observational study in the Sunnybrook dementia cohort. International Psychogeriatrics, 2008; 20, 1141–1159. 14. Ellman G.L. Courtney K.P., Andres V. and Feather Stone R.M., Biochem. Pharmacol. , 1961; 23: 161-171. 15. O.R. Gantum and P.J. Carlson, molecules, 2012; 17(12): 1811-1821. There are also some spelling and syntax errors, e.g. authors write: "The enzyme activity is determined with and without the <u>inhibitions</u> using the lineweaver –Burk equation..." why instead of inhibitions they should use "inhibitors" . I resigned to correct these kind of errors because I suggested a major revision and, as a consequence, the text should be rewritten.	I formatted and check it and change some of it . Ok, that's right I change it .
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<u>Optional/General</u> comments	The presented study gives simply answers to simply questions using the <i>ex vivo</i> protocol but, unfortunately for authors, this approach is too simple, because did not fulfil nor the preclinical trials requirements nor the toxicological characteristics of new compounds. Regarding my experience, this paper is similar to protocols prepared by Msc students as a documentation of the master exercises and projects, including all typical mistakes. Before the authors start improve their paper, I suggest them to read the online course: Agency for Toxic Substances and Disease Registry. Case Studies in Environmental Medicine. Cholinesterase Inhibitors: Including Pesticides and Chemical Warfare Nerve Agents available at http://www.atsdr.cdc.gov/csem/cholinesterase/docs/cholinesterase.pdf.	Until now I have not these vision in these field medicin, pharmacology ,toxiology. I am a biochemists and I wish to read and learn more about these fields and how can use it to explain the results and findings of each work that I tend to do it.