



SDI FINAL EVALUATION FORM 1.1

PART 1:

Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	MS: 2013_IJBcRR_3268
Title of the Manuscript:	Structural Mapping of Inhibitor Binding Sites on P-glycoprotein: Mechanism of Inhibition of P-glycoprotein by Herbal Isoflavones.

PART 2:

FINAL EVALUATOR'S comments on revised paper (if any)	Authors' response to final evaluator's comments
The manuscript (IJBRR_3268) has been significantly improved in its presentation. There remains few scores: - line 26: MRP1 is ABCC1, so shift the bracket - ln 33: fluorescent - ln 43-49: I don't see ref 30 - ln 59, 98 and 158: transporter, not receptor - ln 131, 143 and 229: cavity, not channel - ln 173 and 175, and Tab1: kcal - ln 208: of (of) - ln 224: exotransport - ln 226: og/of However, the main question that is opened by this manuscript is : how is it possible that so subtle differences in the chemical structures of the tested isoflavones can induce a "shift" in their binding between Site 1 and Site 2 (see Table 1) ? This shows the importance to assess the validity of the presented dockings. Indeed, the 3 basic points quoted in the previous review are still not fully addressed, although they are worth being: 1- For each ligand with different poses obtained after clustering the calculated docking positions (see ln 179 and 190), does the second (and/or the third) one fit to the same Site (1 or 2) that the first one that is shown ? Or alternatively, does it "shift" to the other Site ? In other words, do these two Sites actually reflect perfectly selective binding, or possibly are they two alternative binding modes for all the tested ligands that can be obtained when considering the few relevant docking positions of rather comparable energies ? 2- The docking calculations show that the glycosides isoflavones have systematically better binding scores than the aglycones counterparts, but do they indeed display better affinities in experimentally collected data reported in the literature ? If this was the case, even for few examples of isoflavones (or even related molecules), this would be a fair validation of the presented in silico data. 3- Even if sequence similarity level between the murine and the human isoforms is rather high, it is not total, and a single residue difference could make a sensitive difference in binding modes for a given ligand. Actually, there are few examples in literature showing species specificities for P-gp handling of drugs or dyes. So, docking data performed on a murine structural model can hardly be taken for (human) therapeutical perspectives with good confidence, and this requires, at least,	



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very carefull statements.

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