African Journal of Pharmaceutical Research & Development

Vol. 10 No.1; pp. 011-014 (2018)

LIMITATION OF DEREK IN ANALYSING NOVEL ASPIRIN ANALOGUES

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ABSTRACT

Derek Nexus software is the recommended system for the prediction of toxicity in compounds of known chemical structure, as it generates clear and scientifically robust predictions. Toxicity of compounds can be predicted without the need of animal studies. Thus, the Nexus Suite 2.1 Derek Nexus (Version 5.0.1) was used to predict the toxicity profile of each compound using its basic chemical structure. Aspirin, PN508 and PN517 were recognised as salicylates, positive for hepatotoxicity, mitochondrial dysfunction and nephrotoxicity. One of the shortcomings of this software however is that it can only work with chemical compounds already stored in its data bank. This led to it not recognising the chemical structure of some of the novel aspirin analogues (PN548, PN549, PN590, PN591 and PN592) synthesised and thus not providing a prediction for their toxicological profile.

KEYWORDS: Derek Nexus, *in silico*, aspirin analogues

INTRODUCTION

Traditionally, laboratory animals are used for toxicological studies on novel compounds. However, in the current economy, more, safer results and ethical methods are expected with less time and resources.

Assessment of the toxicological profile of compounds using a computer or through computer simulation, and not by using animals is termed *in silico* toxicology and different systems have been developed for this purpose [1]. The term *in silico* toxicology can be defined as 'the integration of modern computing and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals' [2]. This assessment is via predictions made according to alerts for toxic actions caused by certain functional groups in the compound's chemical structure and computational toxicology Models based on pharmacokinetics of such compounds [3,4]. In addition, this method could be used to assess the toxicological profile of a compound even before it is synthesized [5], thereby reducing a huge part of the expenses involved in drug development.

The recommended system for the prediction of toxicity in compounds of known chemical structure is the Derek Nexus software [6, 7] as it generates clear and scientifically robust predictions. This method uses structural alerts (SAs) and quantitative structure-activity relationship (QSAR) models [5]. This prediction is thus dependent on the basic chemical structure of the compound of interest.

Advantages of *in silico* toxicology include: i) It has the potential to reduce the use of animals in toxicological studies, ii) It is less expensive, iii) It is less time consuming, iv) Multiple toxicological

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endpoints of a compound can be determined at the same time [8].

The disadvantages of this method include:

(i). Absorption-Distribution-Metabolism-Excretion (ADME) features, and more importantly metabolism are not taken into account,

ii) Predictions on carcinogenicity does not work on all compounds,

iii) Transparency of the software program [8, 9].

Another disadvantage of Derek Nexus *in silico* was observed and is presented in this paper.

Aspirin and its analogues (PN548 [meta-aspirin], PN549 [para-aspirin], PN590 [ortho-thioaspirin], PN591 [meta-thioaspirin], PN592 [para-thioaspirin], PN508 [diaspirin], PN517 [fumaryldiaspirin]), which are novel compounds were analysed *in silico* for their toxicity profile. The toxicological endpoints assessed include hepatoxicity, nephrotoxicity, mitochondrial dysfunction and skin sensitisation in humans. The knowledge database used is the DEREK KB 2015 2.0, version 1.0, certified by Lhasa Limited, Leeds, Yorshire, UK. For this analysis, the compound's chemical structure was inputted into the software and the various endpoints of interest chosen.

MATERIALS AND METHODS

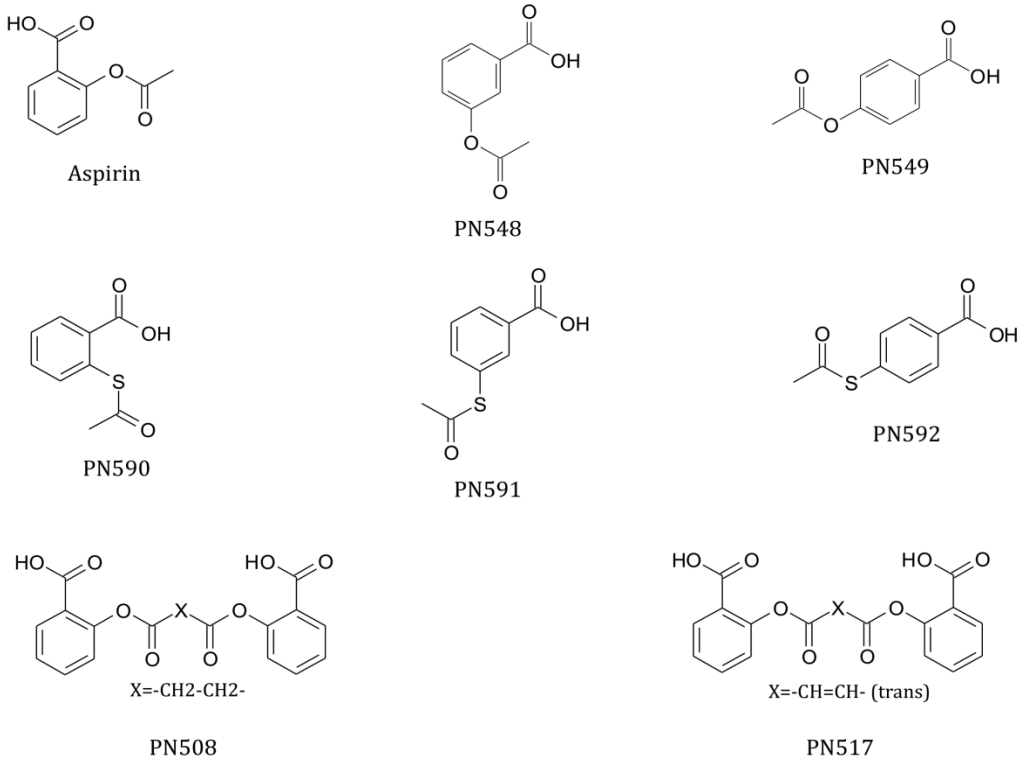

Figure 1: Chemical structure of aspirin and analogues used in this study

RESULTS

I analysed aspirin, PN548, PN549, PN590, PN591, PN592, PN508 and PN517 for their toxicological profile using DEREK analysis. The software recognised aspirin, PN508 and PN517 as salicylic acid, being positive to hepatotoxicity, mitochondrial dysfunction and nephrotoxicity. Skin sensitisation to these compounds is plausible. However, PN548, PN549, PN590, PN591 and PN592 were not recognised by the DEREK software and results were reported as 'The query structure does not match any structural alerts or examples in DEREK'.

Table 1: List of compounds, endpoints and results produced by *in silico* analysis using the DEREK software

Compound	Endpoint	Result
Aspirin (ortho-aspirin)	Hepatotoxicity	Positive
	Mitochondrial dysfunction	Positive
	Nephrotoxicity	Positive
	Skin sensitisation	Plausible
PN548 (meta-aspirin)	Hepatotoxicity	'The query structure does not match any structural alerts or examples in Derek'
	Mitochondrial dysfunction	
	Nephrotoxicity	
	Skin sensitisation	
PN549 (para-aspirin)	Hepatotoxicity	'The query structure does not match any structural alerts or examples in Derek'
	Mitochondrial dysfunction	
	Nephrotoxicity	
	Skin sensitisation	
PN590 (ortho-thioaspirin)	Hepatotoxicity	'The query structure does not match any structural alerts or examples in Derek'
	Mitochondrial dysfunction	
	Nephrotoxicity	
	Skin sensitisation	
PN591 (meta-thioaspirin)	Hepatotoxicity	'The query structure does not match any structural alerts or examples in Derek'
	Mitochondrial dysfunction	
	Nephrotoxicity	
	Skin sensitisation	
PN592 (para-thioaspirin)	Hepatotoxicity	'The query structure does not match any structural alerts or examples in Derek'
	Mitochondrial dysfunction	
	Nephrotoxicity	
	Skin sensitisation	
PN508 (diaspirin)	Hepatotoxicity	Positive
	Mitochondrial dysfunction	Positive
	Nephrotoxicity	Positive
	Skin sensitisation	Plausible
PN517 (fumaryldiaspirin)	Hepatotoxicity	Positive
	Mitochondrial dysfunction	Positive
	Nephrotoxicity	Positive
	Skin sensitisation	Plausible

DISCUSSION

A major setback in this analysis is that the software did not recognise the chemical structures of some of the compounds analysed and so did not produce any predictions for their toxicological profile. This indicates that the chemical structures of these novel compounds are not part of the DEREK software data bank. It is thus suggested that a provision should be made as part of the software for the submission of chemical structures for novel compounds, which could be useful for future analysis.

The aspirin analogues that the programme did recognise were identified as salicylates and thus produced predictions for their toxicological profile as that of salicylic acid. Salicylates have anti-inflammatory, analgesic and antipyretic effects and are known to cause liver injury that could lead to fatality in humans at doses that exceed 4 g orally

[10, 11, 12]. Mitochondrial dysfunction is also included in the toxicological profile of the salicylates [13]. Nephrotoxicity have also been reported to be caused by salicylates in the form of renal failure, nephrotic syndrome and interstitial nephritis [14].

ACKNOWLEDGEMENTS

I wish to thank Dr. C.J. Perry and Dr I. D. Nicholl for synthesizing and making the aspirin analogues available to me and also thanks to Dr. Jamilu Ya'u for his constructive criticisms.

COMPETING INTERESTS

Dr. C. J. Perry and Dr. I. D. Nicholl are named inventors for a patent for Fi-DiA (PN517) as an anti-colorectal cancer agent; US patent #9,351,980.

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