SHORT COMMUNICATION

Synthesis and biological evaluation of n-butylphthalide derivatives as anti-platelet aggregation agents

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ABSTRACT

New analogues of n-butylphthalide (NBP) bearing various lengths of alkyl and different substitution at the two-position of phthalide were designed and synthesised. Preliminary evaluation and prediction of ACD LogP software indicate that the derivatives display significant improvement in water solubility than NBP does. Further biological analysis showed that NBP analogues specifically inhibit platelet aggregation induced by arachidonic acid but have no effect on that induced by adenosine 5-diphosphate. Especially compounds 1 and 3 were stronger than classical anti-platelet drug, aspirin, and equal potent with NBP, respectively. These findings provide an alternative approach to the development of NBP analogues with anti-platelet aggregation activity with good water solubility for the intervention of ischemic stroke.

1. Introduction

Ischemic stroke is the leading cause of disability worldwide, the second most common cause of dementia and the third leading cause of death (Deb et al. 2010). n-Butylphthalide (NBP),...
has been well established to benefit patients with ischemic stroke (Peng & Cui 2013; Diao et al. 2014) and has also been proved to be safe in patients with acute ischemic stroke (Feng et al. 2012). However, the clinical application of NBP is limited due to its poor water solubility thus contributing to dissolution-limited absorption and unsatisfying effects.

It is reported that phthalide including NBP has the anti-platelet activity (Yang et al. 2007; Jasamai et al. 2015). Structure modification indicated that modifications of NBP with different substituents at the three-position could reserve the anti-platelet aggregation activity (Li et al. 2011) and replacement of the oxygen atom at the two-position with sulphur showed stronger anti-platelet aggregation and antithrombotic activities (Wu et al. 2012).

Nevertheless, synthesis of NBP analogues with better water solubility and potent anti-platelet activity, to the best of our knowledge, has not been reported. Given that installation of an amino moiety in the structure was considered as a means of increasing solubility, we therefore designed and synthesised two series of compounds (N, N- and N, O-acetal analogues of NBP), by bioisosteric substitution of the oxygen atom with nitrogen at the two-position of phthalide, the scaffold of NBP, and meanwhile, introduction of various lengths of alkyl. It is anticipated that these novel compounds could have good water solubility and potent anti-platelet aggregation.

2. Results and discussion

Compound 1–3 was synthesised as outlined in Scheme S1 and compound 4–6 were synthesised as outlined in Scheme S2.
The lipophilicities of the compounds were approximated by ClogP values, calculated by ACD Log P/Log D prediction software as previously described (version 4.55, Advanced Chemistry Development Inc., Toronto, Canada) (Tran et al. 2013). N, N- or N, O-acetal analogues of NBP generally resulted in lower lipophilicities, in comparison with NBP (Table 1). Water solubility was determined in simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 6.8 (Tran et al. 2013). As is shown in Table 1, compound 5 exhibited the best solubility (nearly 200 folds over NBP), consistent to lipophilicity evaluation.

Compounds were screened for inhibition of platelet aggregation in human whole blood in response to arachidonic acid (0.5 mmol) and adenosine diphosphate (6.5 μM) using Born’s turbidimetric method (Li et al. 2011; Son et al. 2014). For the AA-induced platelet aggregation, two out of six compounds exhibited significant inhibitory effects, which were superior to aspirin (ASP), a classical antiplatelet drug, and equipotent to NBP at the same dosage. As shown in Table 2, the inhibitory rate of 1 and 3 (100%, 100%) on the AA-induced platelet aggregation was stronger than those of ASP (90%) (Table 2). However, only compounds 3 and 4 exerted inhibition towards ADP-induced platelet aggregation.

Analysis of structure and antiplatelet aggregation activities relationship revealed that replacement of the oxygen at the two-position of phthalide appeared to significantly affect the antiplatelet aggregation effects. For the inhibition of AA-induced platelet aggregation, compounds 1–3 with various alkyl groups showed equal potent activity to NBP (100%), while compound 4–6 substituted with nitrogen (70%, 90%, 10%) displayed poorer activity.

3. Conclusion

In summary, our results indicated that the NBP analogues, considering their good water solubility, significant anti-platelet aggregation activity, are worth to be further studied and developed into novel promising anti-platelet aggregation drugs in the future.

Disclosure statement

No potential conflict of interest was reported by the authors.

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