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Publication date	2017-04-01
Conference details	Pharacology 2016, London, United Kingdom, 13-15 December 2016
Publisher	British Pharmacological Society
Link to online version	http://www.pa2online.org/abstract/abstract.jsp?abid=33289
Item record/more information	http://hdl.handle.net/10197/12596

Structure-activity relationship of a novel family of cysteinyl leukotriene receptor antagonist quinoline compounds with anti-angiogenic activity.

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Introduction: Previously, we identified quininib (2-[(*E*)-2-(quinolin-2-yl)vinyl]phenol), a cysteinyl leukotriene receptor antagonist with anti-angiogenic and anti-permeable activity (1,2). Here, we report a structure activity relationship study to more comprehensively characterise features which confer anti-angiogenic activity.

Methods: 70 quininib analogues were synthesised or purchased (3). Anti-angiogenic activity was ranked based on ability of 10 µM compound to inhibit blood vessel formation in two *in vivo* developmental angiogenesis assays in Tg[*fli1*:EGFP] zebrafish (i) hyaloid/ocular vessel formation and (ii) intersegmental /tail vessel formation. Compounds were considered active where ≥40% inhibition was observed compared to control. Selected highly ranked compounds were tested in human endothelial cell lines (HMEC-1) for cytoxicity (MTT assay) and anti-angiogenic activity (in *vitro* tubule formation assay). Efficacy was also determined in mouse aortic ring assay (4). CYSLT receptor antagonism was quantified using reporter cell bioassays.

Results: 18 analogues showed ≥40% inhibition in formation of hyaloid vessels and fourteen showed ≥40% inhibition in formation of intersegmental vessels. These compounds comprised those with "triene" bond and benzene ring modifications. Six compounds were selected for further testing (Q8: (*E*)-2-(2-Quinolin-2-yl-vinyl)benzene-1,4-diol HCl; Q 14: 3-(2-Quinolin-2-yl-ethyl)-phenol HCl; Q 18: 2-[(*Z*)-2-(Quinolin-2-yl)vinyl]phenol HCl; Q 20: (*E*)-2-(2-Quinolin-2-yl-propenyl)-phenol HCl; Q 22: 2-Quinolin-2-yl-ylethynyl-phenol HCl and Q 54: 2-(2-(2-Methoxyphenyl)vinyl)quinoline). No compound showed an effect on cell viability. Three compounds (Q 8, Q 18, Q 22) showed ≥40% reduction in in *vitro* tubule length and Q 18 showed ≥40% reduction in sprout formation in the aortic ring assay. Cell bioassays showed all six compounds inhibited LTD_4 induced activation of $CYSLT_1$ (IC_{50}: 1.7 - 6.7 µM) and at 30 µM, four compounds (Q 14, Q 18, Q 20, Q 22) showed ≥50% inhibition of LTC_4 induced activation of $CYSLT_2$.

Conclusions: More than 10 compounds showed robust anti-angiogenic activity in both assays. Three quinoline compounds demonstrated anti-angiogenic activity in human cell lines and mouse aortic ring. This study is the first step in identifying a quinoline pharmacophore for antagonism of the CYSLT pathway as a therapeutic target for inhibiting the aberrant pathological angiogenesis occurring in blindness, cancer and arthritis.

References

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