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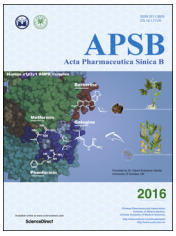

ORIGINAL ARTICLE

Structural optimization and biological evaluation of 1,5-disubstituted pyrazole-3-carboxamines as potent inhibitors of human 5-lipoxygenase

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KEY WORDS

5-Lipoxygenase;
5-LOX inhibitors;
Pyrazole derivatives;
Leukotrienes-related diseases;
In vivo;
Benzo-fused heterocycle;
Ischemic incults;
Brain inflammation

Abstract Human 5-lipoxygenase (5-LOX) is a well-validated drug target and its inhibitors are potential drugs for treating leukotriene-related disorders. Our previous work on structural optimization of the hit compound **2** from our in-house collection identified two lead compounds, **3a** and **3b,** exhibiting a potent inhibitory profile against 5-LOX with IC_{50} values less than 1 μmol/L in cell-based assays. Here, we further optimized these compounds to prepare a class of novel pyrazole derivatives by opening the fused-ring system. Several new compounds exhibited more potent inhibitory activity than the lead compounds against 5-LOX. In particular, compound **4e** not only suppressed lipopolysaccharide-induced inflammation in brain inflammatory cells and protected neurons from oxidative toxicity, but also significantly decreased infarct damage in a mouse model of cerebral ischemia. Molecular docking analysis further confirmed the consistency of our theoretical results and experimental data. In conclusion, the excellent *in vitro* and

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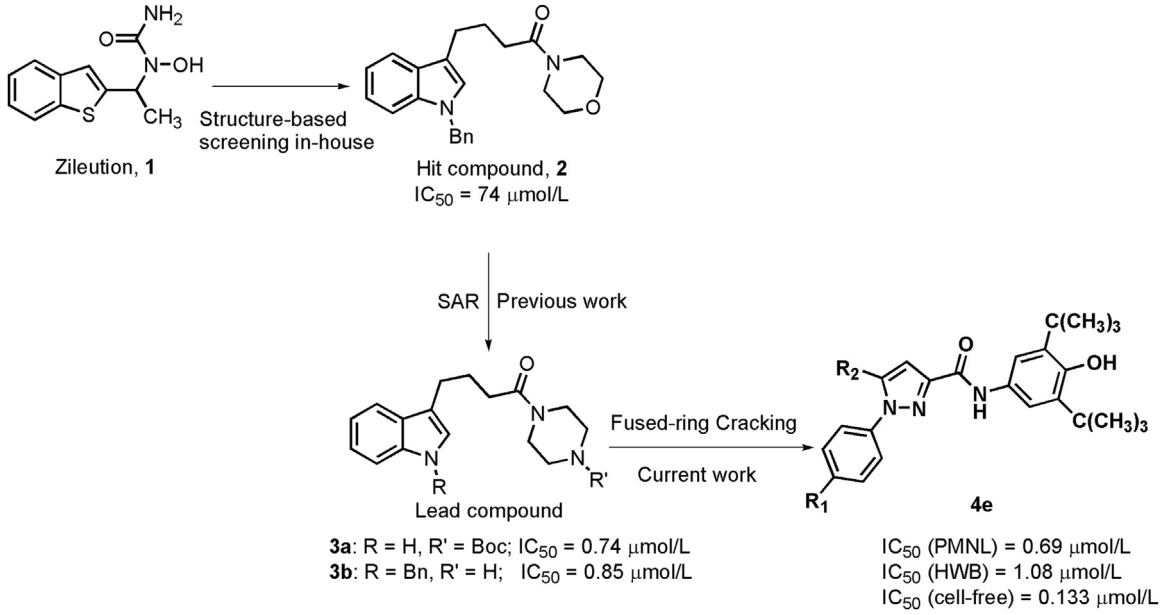
in vivo inhibitory activities of these compounds against 5-LOX suggested that these novel chemical structures have a promising therapeutic potential to treat leukotriene-related disorders.

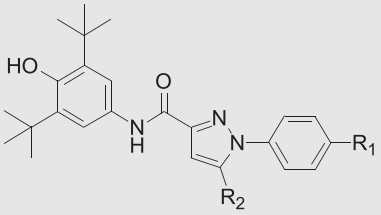
1. Introduction

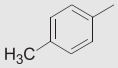
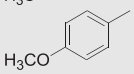
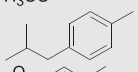
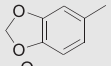
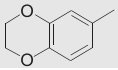
5-Lipoxygenase (5-LOX) is the key enzyme that metabolizes arachidonic acid (AA) into the bioactive leukotrienes (LTs), which are considered to be potent mediators of inflammatory responses[1,2]. Accumulated evidence suggested that LTs play important roles in the development of allergic diseases such as asthma[3–5], various inflammatory disorders such as rheumatoid arthritis and cardiovascular



Scheme 1 Design of novel 1,5-disubstituted pyrazole-3-carboxamines by fused-ring cracking.

Table 1 Structures and inhibitory activity against 5-LOX in rat peritoneal polymorphonuclear leukocytes (PMNLs).



Compd.	R_1	R_2	Inhibition at 5 μmol/L (%)[a]
4a	SO_2NH_2		55.7
4b	SO_2NH_2		65.7
4c	SO_2NH_2		74.9
4d	SO_2NH_2		59.0
4e	SO_2NH_2		90.1
4f	SO_2NH_2		50.7