Chiral Resolution of (1,2-benzothiazin-4-yl)Acetic Acid Enantiomers as Aldose Reductase Inhibitors

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ABSTRACT: Two novel (1,2-benzothiazin-4-yl)acetic acid enantiomers were prepared by chiral resolution, and their enantiomeric purity was tested by chiral HPLC. The biological evaluation of the racemate and the single enantiomers showed that the isomer (R)-(-)-**4** was the most active with an IC_{50} value of 0.120 μM, which was 35 times more active than the other isomer (S)-(+)-**4**, indicating an important effect of C4 position on both the activity and selectivity.
KEYWORD: Aldose reductase inhibitor; Chiral resolution; 1,2-Benzothiazine 1,1,-dioxide; Absolute configuration determination

1 INTRODUCTION

In our recent studies, acetic acid derivatives of benzothiazine 1,1-dioxide (Fig. 1) have been developed as potent inhibitors of aldose reductase (EC 1.1.1.21,ALR2),[1] which is a drug target for the therapy of long-term diabetic complications. Our results suggest that the C4 position, a chiral atom, might play an important role for binding affinity with the active site of the enzyme, but the mixture of enantiomers remains resolved. Here, we describe the chiral separation of 2-[2-(2,4,5-trifluorbenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazin-4-yl]acetic acid ((±)-**4**), the most potent inhibitor in the series, and relationships of stereostructure-activity.

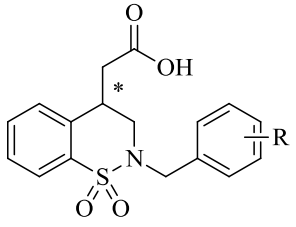


Figure 1. Structure of acetic acid derivatives of benzothiazine 1,1-dioxide

2 RESULTS AND DISCUSSION

2.1 *Chemistry*

According to the previous work,[1] α,β-unsaturated ester 2 was prepared from the N-substituted ketone 1 via Wittig reaction,[4] then Pd/C-catalyzed H_2 gave enantiomeric mixture of the ester 3,[5] which was converted to the acid mixture (±)-4 by hydrolysis with sodium hydroxide.

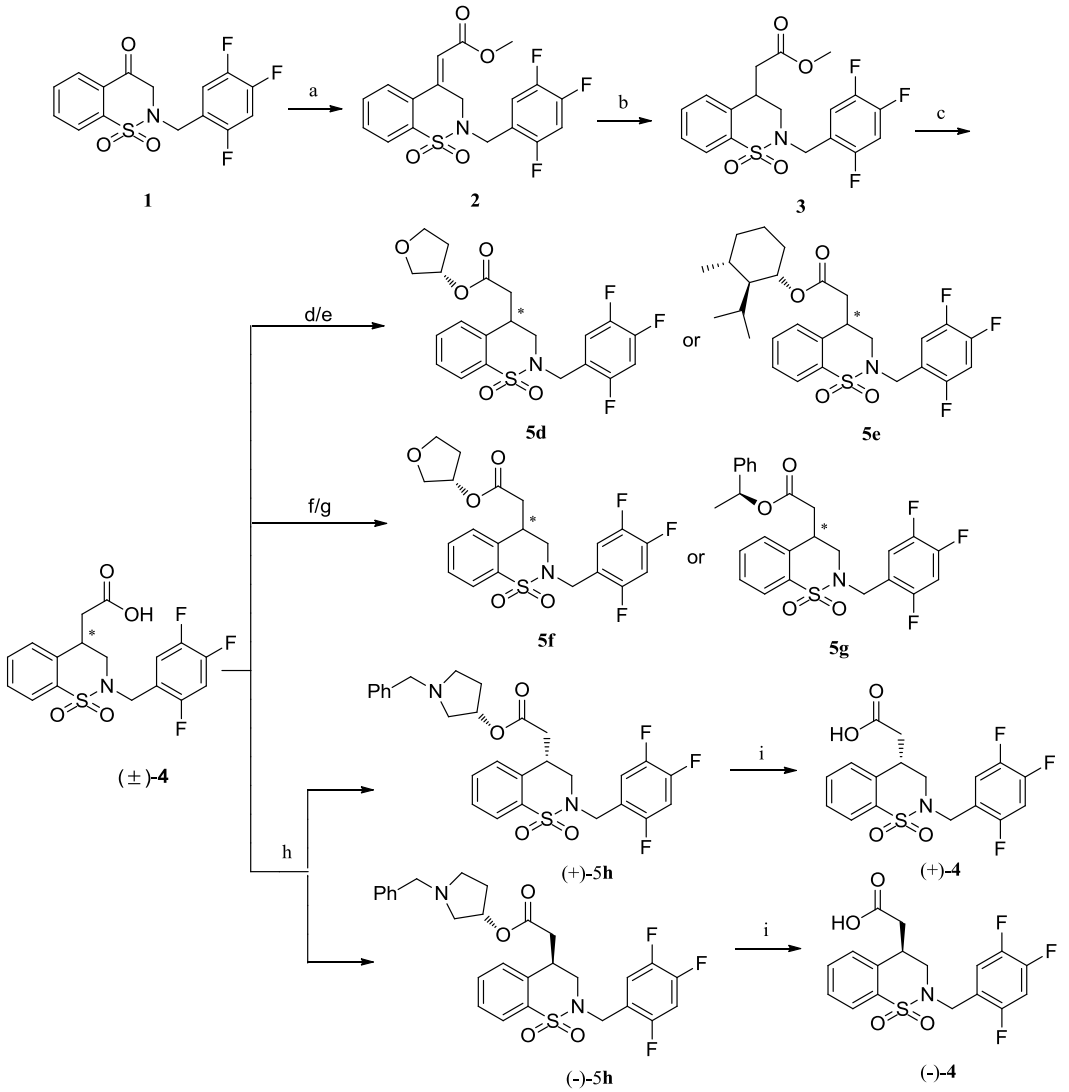
In order to resolve the mixture (±)-**4**, we tried the approach of preparing a diastereomeric ester with some chiral alcohol, and then regenerating the target acid via hydrolysis. After a series of attempts, (±)-**4** could be resolved by forming the ester 5h although the yield was low (5%) while the other ester pathways were failed (Scheme 1).

The acid isomers (+)-**4** and (-)-**4** were analyzed for their enantiomeric purity using chiral HPLC, and the enantiomeric excesses were 95.2% and 97.9%, respectively. This indicates a successful preparation of diastereomeric compounds **5h**.

2.2 *Aldose reductase inhibition and SAR studies*

The two newly prepared acids were tested for their potential inhibition effect on ALR2 isolated from rat lenses. In order to evaluate their selectivity for the ALR2 inhibition, these acids were also subjected to test for their inhibitoty activity against ALR1 isolated from rat kidneys. The IC_{50} values were determined by linear regression analysis of log of the concentration-response curve.[1]

Their effectiveness was evaluated with respect to epalrestat, the only marketed ALR2 inhibitor, as listed in Table 1. (R)-(-)-**4** was the most active having an IC_{50} value of 0.120 μM comparable to that of epalrestat, and showed a significantly lower activity in the ALR1 inhibition, indicating an excellent selectivity for the isomer.



Scheme 1.Reagents and conditions: (a) Ph_3P=$CHCOOCH_3$, $PhCH_3$, reflux; (b) 10% Pd/C, MeOH, H_2, EtOAc; (c) NaOH, 1,4-dioxane; (d) (S)-tetrahydrofuran-3-ol, Ph_3P, DEAD;[2] (e) (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol, Ph_3P, DEAD;[2] (f) (S)-tetrahydrofuran-3-ol, EDCI, DMAP, CH_2Cl_2;[3] (g) (R)-1-phenylethanol, EDCI, DMAP, CH_2Cl_2.[3] (h) EDCI, DMAP, CH_2Cl_2, (1S)-3-benzylcyclopentanol,;[3] (i) 1,4-dioxane, HCl, reflu

Table 1.Biological activity data for 1,2-benzothiazine 1,1-dioxide acetic acid derivatives.

Compd	ALR2 IC_{50}* (μM)	ALR1 (% of inhibition)**
(rac)-(±)-**4**	0.676(0.589-0.763)	14.7
(R)-(-)-**4**	0.120(0.084-0.156)	7.5
(S)-(+)-**4**	4.174(3.692-4.656)	11.8
Epalrestat	0.086(0.059-0.112)	73.6

* IC_{50}(95% CL) values represent the concentration required to produce 50% enzyme inhibition

** The inhibitory effect was estimated at a concentration of 10 μM

The results suggest that the acetic acid head at the C4 position not only plays a key role for the binding with ALR2 but also has an important function in discriminating and excluding homologous enzymes.

3 CONCLUSION

The enantiomers of 2-[2-(2,4,5-trifluorbenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazin-4-yl]acetic acid were successfully prepared, and results showed that (R)-(-)-**4** was approximately 35 times more active than (S)-(+)-**4** and had much better selectivity. Thus, the C4 position has a significant impact on both the activity and selectivity in the ALR2 inhibition.

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