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Copper-Catalyzed Asymmetric Synthesis and Comparative Aldose Reductase Inhibition Activity of (+)/(−)-1,2-Benzothiazine-1,1-dioxide Acetic Acid Derivatives

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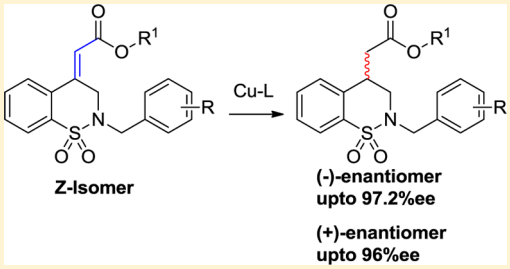
Supporting Information

ABSTRACT: A copper catalyst system for the asymmetric 1,4-hydrosilylation of the α,β-unsaturated carboxylate class was developed by which synthesis of (+)- and (−)-enantiomers of 1,2-benzothiazine-1,1-dioxide acetates has been achieved with a good yield and an excellent level of enantioselectivity. A comparative structure−activity relationship study yielded the following order of aldose reductase inhibition activity: (−)-enantiomers > racemic > (+)-enantiomers. Further, a molecular docking study suggested that the (−)-enantiomer had significant binding affinity and thus increased inhibition activity.



INTRODUCTION

Aldose reductase (ALR2) is a cytosol enzyme, present in several tissues of the human body. It plays a pivotal role in the etiology of long-term diabetic complications such as neuropathy, nephropathy, and retinopathy.[1] It initializes the polyol pathway under hyperglycemic conditions and, in the first rate-limiting step, reduces glucose to sorbitol in the presence of NADPH, leading to excessive osmotic and oxidative stress that damages cells.[2,3] Aldose reductase inhibitors have been scrutinized as potential remedies for various diabetic complications, and continuous efforts dedicated to its development afforded two main chemical classes, carboxylic acid derivatives (e.g., tolrestat[4] and epalrestat[5]) and spirohydantoins (e.g., fidarestat[6] and sorbinil[7]). However, many ARIs have failed to reach various clinical trial and have been withdrawn either because of their cross reactivity with other analogous enzymes or because of their adverse side effects and inefficacy.[8] Therefore, the development of novel chemotypes with weaker side effects and a rich pharmacokinetic profile is very challenging.

Recently, we have designed a series of effective ARIs based on the scaffolds of 1,2,4-benzothiadiazine-1,1-dioxide,[9] pyrido[2,3-*e*][1,2,4]thiadiazine-1,1-dioxide,[10,11] and 1,2-benzothiazine-1,1-dioxide.[12] 1,2-Benzothiazine-1,1-dioxide-based ARIs contained a chiral center at position C4, to which the acetate side chain is attached. The C4 carboxylate plays a key role for this class of ARIs in binding within the active site of the enzyme commonly known as the anion binding pocket, which is the most important region for ligand binding.[12] It is suggested that the direction or orientation of the carboxylate head might have a large impact on the inhibitory activity of ARIs, and studies of this topic may then provide insight into the interaction mechanism of inhibitors bound to the enzyme. Therefore, enantiomers of the 1,2-benzothiazine-1,1-dioxide-based class provide valuable probes for justifying the configuration role of the carboxylate head in enzyme inhibition.

The demand for the enantiomerically pure compounds has grown rapidly in recent years. It has become increasingly clear that enantiomerically pure drugs have many advantages over racemic drug mixtures because of fewer side effects and greater potency in many cases.[13] The catalytically asymmetric reduction of α,β-unsaturated carbonyl compounds offers an efficient and convenient method for the construction of tertiary stereogenic centers in organic synthesis. Over the past few decades, tremendous effort has been spent to achieve this transformation with a substantial emphases on the use of catalysts derived from various transition metals. Copper hydride complexes with chiral ligands have emerged as powerful reagents[14,15] for the effective asymmetric reduction of a series of α,β-unsaturated carbonyl compounds such as enones,[16−19] α,β-unsaturated esters,[20−24] α,β-unsaturated lactones and lactams,[25,26] nitroalkene,[27,28] α,β-unsaturated sulfones,[29] α,β-unsaturated nitriles,[30,31] and 2-alkenylheteroarenes.[32] However, it failed to convert members of the 1,2-benzothiazine-1,1-dioxide-based α,β-unsaturated carboxylate class into their corresponding acetates by using the reported catalytic methods in our preliminary work, presumably because of the distinctive substrate structures in which the α,β-double bond is attached to the fused ring system.

This study focuses on the stereocontrolled synthesis of C4 of 1,2-benzothiazine-1,1-dioxide acetates by catalytic asymmetric

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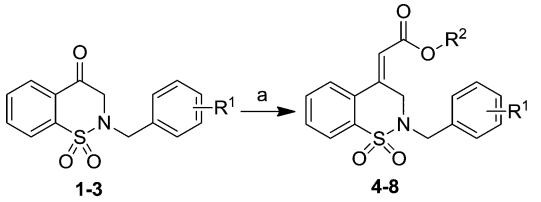
1,4-hydrosilylation of their respective α,β-unsaturated Z-esters and the effect of the obtained (−)- and (+)-acid enantiomers on the ALR2 inhibition to explore the structure−activity relationship.

RESULTS AND DISCUSSION

Initially, we prepared the α,β-unsaturated (*Z*)-esters as the precursor of targeted C4 enantiomers. As shown in Scheme 1,

Scheme 1. Synthesis of (*Z*)-Olifinic Isomers of 1,2-Benzothiazine-1,1-dioxide Carboxylate[a]



1 R^1 = 2,4,5-F_3
2 R^1 = 4-CF_3
3 R^1 = 4-F

4(Z) R^1 = 2,4,5-F3 R^2 = Me
5(Z) R^1 = 2,4,5-F3 R^2 = iPr
6(Z) R^1 = 2,4,5-F3 R^2 = t-Bu
7(Z) R^1 = 4-CF3 R^2 = iPr
8(Z) R^1 = 4-F R^2 = iPr

[a]Ph_3P=CHCOOR (R = Me, iPr, or tBu), $PhCH_3$, 40 °C.

ketones **1**−**3** were prepared according to the method reported previously,[12] and then coupling of **1**−**3** with alkyl bromoacetate by the Wittig olefination reaction resulted in target substrates **4**−**8**.[33]

To achieve further synthesis of C4 enantiomers, catalytically asymmetric 1,4-hydrosilylation of the (*Z*)-isomer of α,β-unsaturated 1,2-benzothiazine 1,1-dioxide carboxylate was investigated. The chiral synthesis was started with ester **4** as the substrate. The combinations of copper salts and diphosphine ligands (Figure 1) were examined for the establishment of a catalyst system in the reaction (Table 1).

Initially, the reported procedure[21] that included the catalyst complex of S-BINAP (**L1**) and $Cu(OAc)_2·H_2O$, the hydrogen source of PMHS (polymethylhydrosiloxane), and tBuOH in toluene was employed (entry 1, Table 1), but no reaction was observed after 24 h at room temperature.

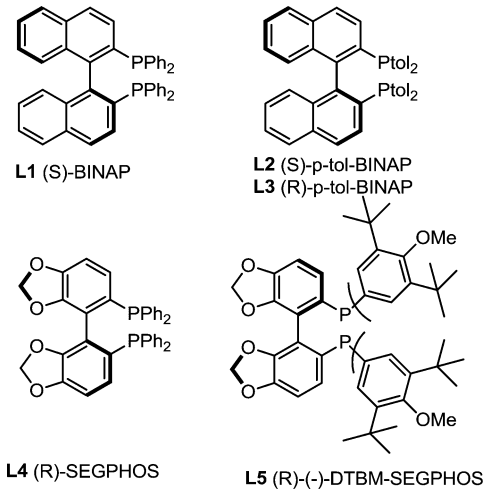


Figure 1. Chiral diphosphine ligands evaluated in the asymmetric 1,4-reduction.

Fortunately, it was found that the reaction proceeded in 24 h when NaOtBu was used as an additive instead of tBuOH, producing the product in 10% yield and 36.4% ee (entry 2, Table 1). Encouraged by this result, we conducted a systematic exploration of different reaction conditions to optimize the enantioselectivity of the reaction. A brief survey of the efficiency of ligands for this process showed that *p*-tol-BINAP ligands **L2** (*S*) and **L3** (*R*) afforded high enantioslectivities for the reaction, and opposite stereochemistry for the two products (entries 3 and 4). However, this enantioselective reaction gave only low yields, while the reaction using (*R*)-SEGPHOS (**L4**) and (*R*)-DTBM-SEGPHOS (**L5**) failed to reduce the substrate **4** (entries 5 and 6). Then screening of copper salts (entries 7−10) showed that the reaction could be improved significantly in both yield and enantioselectivity with anhydrous $Cu(OAc)_2$ as the Cu precursor (entry 8). Further efforts aimed at improvements include the screening of the hydrogen source and the optimization of other reaction conditions. The effect of silane reagents (entries 8 and 11−13) revealed that Ph_2SiH_2 offered best enantioselectivity and a moderate yield while $PhSiH_3$ could increase the yield but gave an obviously lower enantioselectivity in comparison with those of other silane reagents. By a solvent screening (entries 12 and 14−18), THF was identified as being optimal. The reaction proceeded at a higher rate in THF than in other solvents, and the reaction conversion could be accomplished even at lower temperatures (0−20 °C) and in a shorter time (18 h), presumably because of the good solubility of the copper precatalyst. As a result, the optimization of the solvent and temperature coefficient provided a better yield and greater enantioselectivity for the reaction (entry 14). These efforts eventually resulted in the establishment of the catalyst system and reaction conditions for 1,4-hydrosilylation of **4**.

We then investigated the influence of the substrate on the catalytic 1,4-hydrosilyaltion of α,β-unsaturated benzothiazine-1,1-dioxide ester derivatives **5**−**8** to further scrutinize the efficiency of the catalyst system, although a moderate yield and an excellent ee were achieved using methyl ester **4** (entry 1, Table 2). Fortunately, both the reactivity and enantioselectivity were significantly increased by using the isopropyl ester **5** in place of the methyl ester **4**, while the *tert*-butyl ester **6** was found to be less selective, although it gave good yields (entries 1, 2, and 4, Table 2). In particular, compound **5** was found to enhance greatly the reaction rate, and it subsequently provided an excellent yield much higher than those seen with **4** and **6**. In addition, excellent yields and enantioselectivities were also obtained from the hydrogenation of different isopropyl esters **7** and **8** (entries 5 and 7, Table 2). The positive substrate effect was further confirmed by the reaction using this series of isopropyl esters combined with the oppositely configured ligand (*S*)-*p*-tol-BINAP **L2** (entries 3, 6, and 8, Table 2). Therefore, it indicated that bulkier ester groups were preferred for the asymmetric 1,4-hydrosilylation over the methyl ester group to achieve both a high yield and a high enantioselectivity.

Consequently, our studies resulted in a successful catalyst system that is highly efficient for the asymmetric reduction of α,β-unsaturated benzothiazine ester derivatives. In comparison with conventional Cu-diphosphine catalyst systems,[20,21] the catalyst system presented here is more effective with respect to reaction rate and enantioselectivity. The absolute configurations of products were proposed by the sign of their optical rotation compared with that of a reference compound.[34]

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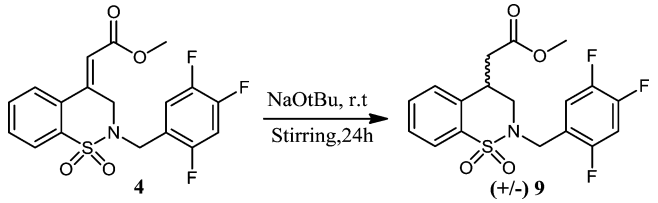
Table 1. Asymmetric 1,4-Reduction of (*Z*)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-2*H*-1,2-benzothiazin-4(3*H*)-ylidene]acetic Acid Methyl Ester (4)[a]



entry	ligand	copper salt	hydrogen source	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	$Cu(OAc)_2·H_2O$/*t*-BuOH	PMHS	toluene	–	–
2	**L1**	$Cu(OAc)_2·H_2O$	PMHS	toluene	10	36
3	**L2**	$Cu(OAc)_2·H_2O$	PMHS	toluene	28	86
4	**L3**	$Cu(OAc)_2·H_2O$	PMHS	toluene	30	86
5	**L4**	$Cu(OAc)_2·H_2O$	PMHS	toluene	–	–
6	**L5**	$Cu(OAc)_2·H_2O$	PMHS	toluene	–	–
7	**L3**	CuCl	PMHS	toluene	25	80
8	**L3**	$Cu(OAc)_2$	PMHS	toluene	43	91
9	**L3**	$[(Ph_3P)CuH]_6$	PMHS	toluene	29	85
10	**L3**	$Cu(Otf)_2$	PMHS	toluene	39	89
11	**L3**	$Cu(OAc)_2$	TMDS	toluene	42	91
12	**L3**	$Cu(OAc)_2$	Ph_2SiH_2	toluene	45	92
13	**L3**	$Cu(OAc)_2$	$PhSiH_3$	toluene	51	77
14	**L3**	$Cu(OAc)_2$	Ph_2SiH_2	THF	57	90/94(+)[d]
15	**L3**	$Cu(OAc)_2$	Ph_2SiH_2	CH_2Cl_2	30	86
16	**L3**	$Cu(OAc)_2$	Ph_2SiH_2	$(C_2H_5)_2O$	15	73
17	**L3**	$Cu(OAc)_2$	Ph_2SiH_2	1,4-dioxane	21	91
18	**L3**	$Cu(OAc)_2$	Ph_2SiH_2	DMF	–	–

[a]Substrate **4** (0.5 mmol), 0.1 equiv of chiral phosphine ligand (**L**), 0.05 equiv of Cu precursor, 0.1 equiv of NaOtBu, and 4 equiv of silane at room temperature in 6 mL of solvent for 24 h. [b]Isolated yields. [c]Enantiomeric excesses were determined by chiral HPLC. [d]Reaction conducted over the temperature range of 0−20 °C for 18 h.

The enantiomers obtained from the asymmetric 1,4-hydrosilylation were then converted into their respective acids, and the inhibitory activity of aldose reductase was tested for all the synthesized carboxylic acid enantiomers of 1,2-benzothiazine-1,1-dioxide (Table 3).

The stereostructure−activity relationship study showed a significant enhancement of ALR2 inhibition activity for the (−)-**14** enantiomer versus that of its corresponding (+)-**14** enantiomer. Similar behavior was found in the case of **15**. Therefore, only the (−)-enantiomer of **16** was then synthesized, and a significant increase in activity was found for (−)-**16** with respect to that of racemic (±)-**16** (Table 3). It was also observed that (−)-**14** was the most active against aldose reductase with an IC_{50} value of 0.5 μM among this series of compounds, whereas (−)-**16** was the least active.

Molecular docking was performed on human ALR2 (PDB entry 1US0) complexed with $NADP^+$ and ligand IDD 594 {[2-(4-bromo-2-fluorobenzylthiocarbamoyl)-5-fluorophenoxy]-acetic acid} to investigate the mechanism responsible for the activity of the (−)-enantiomer being higher than that of the (+)-enantiomer. The docking protocol was validated by the ligand IDD 594, and it resulted in a MolDock score of −148.133 kcal/mol. Then, the (−)- and (+)-enantiomers were docked into the active site of ALR2, and it was determined that the energy score for (−)-**14** (MolDock score of −151.601 kcal/mol) was better than those of (+)-**14** (MolDock score of −147.96 kcal/mol) and IDD 594.

It is also obvious from the docking results when comparing the lowest-energy poses of the (−)- and (+)-enantiomers that the carboxylic acid head of (+)-**14** was not placed in the anion binding pocket of the enzyme while the oxygen of the thionyl group formed one hydrogen bond with Trp111 (3.24 Å) of the pocket as shown in Figure 2A. By contrast, the carboxylate head of (−)-**14** was found to enter exactly into the anion pocket, forming three strong hydrogen binding interactions with NE1 of the indole ring of Trp111 (2.89 Å), NE2 of the imidazole ring of His110 (2.76 Å), and the OH of Tyr48 (2.68 Å) (Figure 2B). The *N*-benzyl ring of both enantiomers showed π-stacking interaction with the indole ring of Trp111 (Figure 2A,C). The protein surface presentation revealed that the carboxylic acid head of (+)-**14** (Figure 2B) resides away from the anion binding pocket, while in the case of (−)-**14** (Figure 2D), the carboxylic acid head is deeply imbedded in the anion binding pocket. Similar behavior was shown by the docking study of the remaining enantiomers of this series. This made evident the fact that the (−)-enantiomer had inhibitory activity against ALR2 higher than that of the (+)-enantiomer.

In summary, these studies developed an efficient copper catalytic system for asymmetric 1,4-hydrosilylation of α,β-unsaturated 1,2-benzothiazine-1,1-dioxide carboxylate ester derivatives that led to the asymmetric synthesis of acetic acid derivatives in good yield and excellent enantioselectivity. The work also disclosed that isopropyl esters were the best substrates for this catalytic system while substituents on the N2-benzyl ring have no significant impact on selectivity. Further, the SAR study suggested that the orientation of the C4 acetic acid group with levorotation or the (−)-configuration played a vital role in the inhibition of ALR2, whereas dextrorotation or the (+)-configuration led to a drastic loss of inhibitory activity. It was also supported by molecular docking

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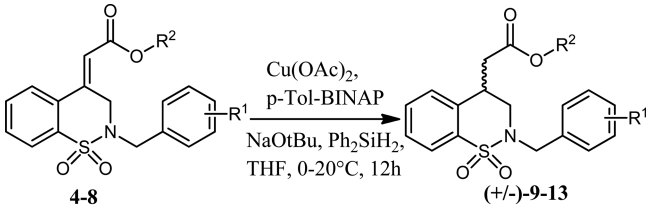
Table 2. Cu-Catalyzed Asymmetric 1,4-Reduction of (Z)-N-Substituted Benzothiazine 1,1-Dioxide α,β-Unsaturated Ester Derivatives (4−8)[a]



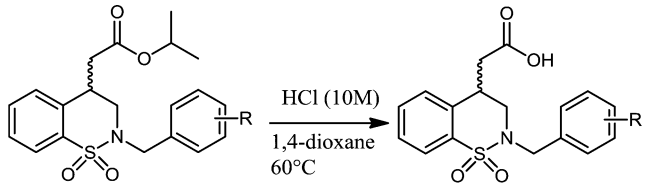
4-8 (+/-)-9-13

9 R1= 2,4,5-F3, R2= Me
10 R1= 2,4,5-F3, R2= iPr
11 R1= 2,4,5-F3, R2= tBu
12 R1= 4-CF_3, R2= iPr
13 R1= 4-F, R2= iPr

entry	substrate; R^1; R^2	ligand	yield (%)[b]	ee (%)[c]/configuration[d]
1	**4**; 2,4,5-F3; Me	**L3**	57	94 (+)[e]
2	**5**; 2,4,5-F3; iPr	**L3**	85	96 (+)/*S*
3	**5**; 2,4,5-F3; iPr	**L2**	89	97 (−)/*R*
4	**6**; 2,4,5-F3; *t*-Bu	**L2**	61	93 (−)
5	**7**; 4-CF_3; iPr	**L3**	84	91 (+)
6	**7**; 4-CF_3; iPr	**L2**	86	96 (−)
7	**8**; 4-F; iPr	**L3**	87	96 (+)
8	**8**; 4-F; iPr	**L2**	85	95 (−)

[a]Substrates **4**−**8** (0.5 mmol), 0.1 equiv of chiral phosphine ligand (**L**), 0.05 equiv of Cu precursor, 0.1 equiv of NaOtBu, and 4 equiv of silane at room temperature in 6 mL of solvent for 12 h. [b]Isolated yields in parentheses. [c]Determined by chiral HPLC. [d]Absolute configuration determined by the sign of the specific rotation vs that of a reference compound.[34] [e]Entry 14 of Table 1.

Table 3. Synthesis of (±)-N-Subsituted Benzothiazine-1,1-dioxide Acetic Acid Derivatives and Biological Activity Data



(+/-)10,12-13
10 R= 2,4,5-F3
12 R= 4-CF_3
13 R= 4-F

(+/-) 14-16
14 R= 2,4,5-F3
15 R= 4-CF_3
16 R= 4-F

product	yield (%)[a]	ee (%)[b]/configuration[c]	ALR2 IC_{50} (μM)[d]
(±)-**14**	–	–	0.74 (0.678−0.78)
(+)-**14**	89	96 (+)/*S*	4.15 (3.69−4.9)
(−)-**14**	85	97 (−)/*R*	0.50 (0.38−0.62)
(±)-**15**	–	–	23.9 (22.27−25.3)
(+)-**15**	90	93 (+)/*S*	31.4 (27.2−35.5)
(−)-**15**	80	96 (−)/*R*	20.9 (18.1−23.6)
(±)-**16**	–	–	85.7 (84.96−86.5)
(−)-**16**	87	95 (−)/*R*	55.9 (55.15−56.58)
epalrestat			0.12 (0.05−0.19)

[a]Isolated yield. [b]Determined by HPLC. [c]Absolute configuration determined by comparing the sign of optical rotaion with that of a reference compound.[34] [d]IC_{50} (95% CL) values represent the concentration required to produce 50% enzyme inhibition.

results in which the (−)-enantiomer is tightly anchored in the active site with its C4 acetic acid moiety deeply trapped in the anion binding pocket while the (+)-enantiomer exhibited some reverse behavior.

EXPERIMENTAL SECTION

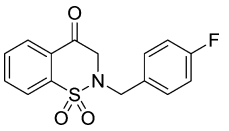
General Methods. All the solvents were dried and purified according to standard procedures. All manipulations involving air sensitive materials were conducted in a vacuum glovebox under an atmosphere of argon unless stated otherwise. Yield refers to isolated yields of >95% pure compounds as determined by NMR and HPLC. Melting points were recorded and are uncorrected. Thin layer chromatography (TLC) was performed on silica gel Merck $60F_{254}$. NMR spectra were recorded using a spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) in DMSO-d_6 and $CDCl_3$ using TMS as an internal reference. ^{1}H NMR data are reported as follows: chemical shifts (δ), multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad), integration, and coupling constants. Data for ^{13}CNMR are reported in terms of chemical shifts (δ). Individual resonances were assigned on the basis of their chemical shifts, signal intensities, multiplicities of resonances ,and coupling constants. HPLC was conducted on an HPLC system equipped with a Chiralpak ID column. MS and HRMS were performed by the ESI and ESI-TOF methods, respectively. Optical rotations were measured at the indicated concentration of grams per 100 mL.

The sodium saccharin, methyl bromoacetate, isopropyl bromoacetate, *tert*-butyl bromoacetate, 2,4,5-trifluorobenzyl bromide, 4-fluorobenzyl bromide, and 4-(trifluoromethyl)benzyl bromide used for the preparation of **1**−**3** according to reference methods and copper salts, hydrosilane, ligands, and Nao*t*-Bu/*t*-BuOH used for the copper-catalyzed asymmetric reduction are commercially available.

Racemic products analogous to the enantiomerically pure compounds described below were synthesized by reduction of the olefin substrates catalyzed by Pd/C under a hydrogen atmosphere. The HPLC retention times of enantiomerically enriched products were the same as those of the racemic products.

General Synthetic Procedure for 1−3. Compounds **1**−**3** were prepared according to the synthetic pathway depicted in Scheme 1.[12]

*2-[4-(Fluoromethyl)benzyl]-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (**3**).* Yield: 77% (3.9 g). Pale yellow powder. mp: 107−110



°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95−7.87 (m, 2H), 7.84−7.76 (m, 2H), 7.28 (t, 2H, *J* = 6.0 Hz), 7.01−7.06 (m, 2H, *J* = 8.9, 2.3 Hz), 4.51 (d, 2H, *J* = 2.2 Hz), 4.46 (d, 2H, *J* = 1.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.5, 135.5, 133.4, 131.3, 131.1, 127.6, 123.9, 115.3, 115.1, 57.2, 53.0, 40., 39.8, 39.5, 39.3, 39.1, 38.9. MS (ESI): *m*/*z* 328.2 $[M + Na]^+$.

General Synthetic Procedure for 4−8. To a stirred solution of triphenylphosphine (26.2 g, 0.1 mol) in benzene (300 mL) was added dropwise a solution with the appropriate amount of alkyl bromoacetate (1.5 equiv) in benzene (100 mL) over 1 h. The solid was filtered and washed with hexane to provide a white solid phosphonium product. The crude product was dissolved in water (800 mL), and the mixture was made alkaline via the dropwise addition of Et_3N until the solution became sufficiently basic. The solution was stirred for 1 h, and the precipitates thus obtained were filtered and washed with water to afford the product. Methyl 2-(triphenylphosphoranylidene) acetate, isopropyl 2-(triphenylphosphoranylidene) acetate, and *tert*-butyl 2-(triphenylphosphoranylidene) acetate were recrystallized from methanol.

A solution containing the appropriate choice of **1**−**3** (6 mmol) and the appropriate amount of alkyl (triphenylphosphoranylidene) acetate (9 mmol) in toluene (30 mL) was heated at 40 °C for 12 h. After evaporation of the solvent, the residue was purified by column

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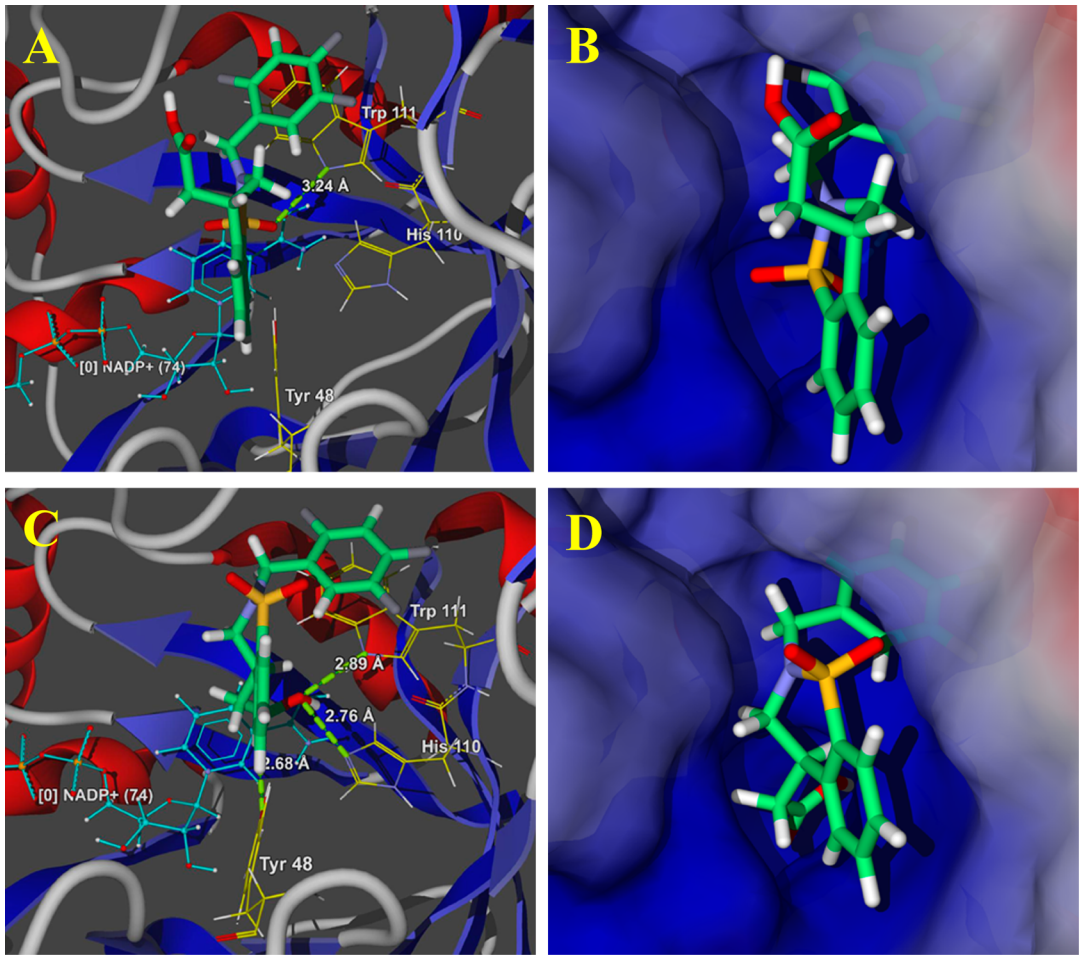
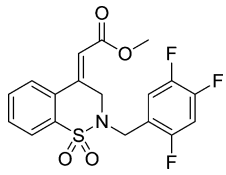


Figure 2. Molecular docking of (+)- and (−)-enantiomers of inhibitor **14**. Docking of (A and B) (+)-**14** and (C and D) (−)-**14** in cartoon diagrams of protein backbones with selected and labeled protein residues presented in wireframe in medium yellow (C) and in surface presentation with docked poses colored spring green (C), red (O), blue (N), dark yellow (S), and gray (F). Hydrogen bond interactions are shown as lime dotted lines, while the $NADP^+$ molecule is colored sky blue.

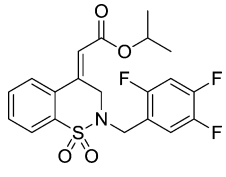
chromatography (1:15 to 1:20 ethyl acetate:petroleum ether) to afford pure product.

*(Z)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-2H-1,2-benzothiazin-4(3H)-ylidene]acetic Acid Methyl Ester (**4**).*[33] Yield: 66% (1.57 g).



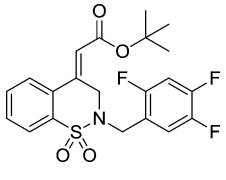
White crystalline solid. mp: 132−136 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07−7.98 (m, 1H), 7.92−7.82 (m, 1H), 7.71 (dd, 2H, J = 6.3, 2.7 Hz), 7.48 (m, 2H), 6.75 (s, 1H), 4.93 (d, 2H, J = 11.4 Hz), 4.19 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2, 142.6, 134.8, 133.3, 132.1, 131.3, 128.8, 126.6, 124.4, 121.6, 119.2, 118.3, 106.7, 106.4, 106.1, 105.9, 51.6, 49.4, 46.0, 39.9, 39.7, 39.5, 39.3, 39.1. MS (ESI): m/z 398.1 $[M + H]^+$.

*(Z)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-2H-1,2-benzothiazin-4(3H)-ylidene]acetic Acid Isopropyl Ester (**5**).* Yield: 68% (1.7 g).



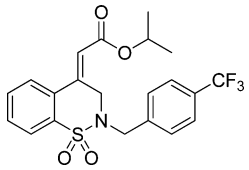
White crystalline solid. mp: 172−176 °C. ^{1}H NMR (400 MHz, DMSO): δ 8.09−8.03 (m, 1H), 7.89−7.85 (m, 1H), 7.73−7.68 (m, 2H), 7.51 (dd, 1H, J = 13.6, 6.8 Hz), 7.48−7.42 (m, 1H), 6.71 (s, 1H), 5.00−4.95 (m, 1H), 4.91 (s, 2H), 4.19 (s, 2H), 1.24 (dd, 6H, J = 6.3, 1.7 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 142.2, 134.8, 133.3, 132.1, 131.2, 126.6, 124.4, 119.0, 67.9, 49.3, 46.0, 39.9, 39.7, 39.5, 39.3, 39.1, 21.5. MS (ESI): m/z 424 $[M - H]^-$. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{19}F_3NO_4S$, 426.0981; found, 426.0984.

*(Z)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-2H-1,2-benzothiazin-4(3H)-ylidene]acetic Acid tert-Butyl Ester (**6**).* Yield: 72% (1.9 g).



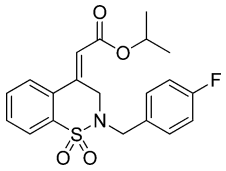
White crystalline solid. mp: 88−90 °C. ^{1}H NMR (400 MHz, DMSO): δ 8.06−8.02 (m, 1H), 7.90−7.82 (m, 1H), 7.71−7.68 (m, 2H), 7.56−7.43 (m, 2H), 6.63 (s, 1H), 4.87 (s, 2H), 4.18 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 141.2, 134.8, 134.7, 133.3, 132.2, 131.1, 126.5, 124.4, 120.4, 119.2, 106.3, 81.0, 49.1, 46.0, 40.0, 39.7, 39.5, 39.3, 39.1, 38.9, 27.7. MS (ESI): m/z 438 $[M - H]^-$. HRMS (ESI-TOF): m/z $[M + NH_4]^+$ calcd for $C_{21}H_{20}F_3NO_4SNH_4$, 457.1403; found, 457.1414.

dx.doi.org/10.1021/jo500338c | J. Org. Chem. 2014, 79, 4963−4972



*(Z)-2-[2-(4-Trifluoromethylbenzyl)-1,1-dioxido-2H-1,2-benzothiazin-4(3H)-ylidene]acetic Acid Isopropyl Butyl Ester (**7**).* Yield: 61.5% (1.6 g). White solid. mp: 116−119 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09−8.05 (m, 1H), 7.91−7.87 (m, 1H), 7.73 (dd, 2H, J = 5.8, 2.1 Hz), 7.71 (d, 2H, J = 6.9 Hz), 7.53 (d, 2H, J = 7.7 Hz), 6.70 (s, 1H), 4.90 (t, 1H, J = 6.3 Hz), 4.85 (s, 2H), 4.24 (s, 2H), 1.25−1.13 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 142.2, 134.8, 133.3, 132.3, 131.3, 129.0, 126.8, 125.4, 124.3, 119.2, 67.8, 52.0, 49.5, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 21.5. MS (ESI): m/z 438 [M − H]$^-$. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{21}H_{21}F_3NO_4S$, 440.1138; found, 440.1150

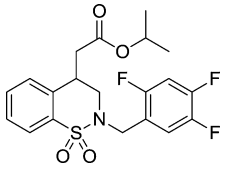
*(Z)-2-[2-(4-Fluorobenzyl)-1,1-dioxido-2H-1,2-benzothiazin-4(3H)-ylidene]acetic Acid Isopropyl Ester (**8**).* Yield: 65.2% (1.5 g). White



crystalline solid. mp: 109−112 °C. ^{1}H NMR (400 MHz, DMSO): δ 8.05 (dd, 1H, J = 6.0, 3.1 Hz), 7.88 (dd, 1H, J = 6.0, 2.9 Hz), 7.75−7.69 (m, 2H), 7.31 (dd, 2H, J = 7.2, 4.3 Hz), 7.15 (dd, 2H, J = 8.8, 5.8 Hz), 6.68 (s, 1H), 4.93 (dd, 1H, J = 7.7, 4.8 Hz), 4.81 (s, 2H), 4.12 (s, 2H), 1.22−1.18 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9, 147.7, 138.6, 137.6, 136.6, 135.9, 135.9, 132.1, 129.6, 124.4, 120.8, 120.6, 73.2, 57.0, 54.3, 45.5, 45.3, 45.1, 44.9, 44.7, 44.5, 26.9. MS (ESI): m/z 388 [M − H]$^-$. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{21}FNO_4S$, 390.1170; found, 390.1162.

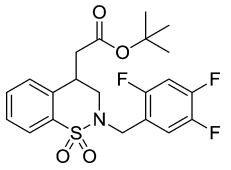
General Method for Olefin Reduction. A solution of the appropriate α,β-unsaturated ester of **4**−**8** (0.5 mmol) in EtOAc (5 mL) was added to a suspension of 10% palladium on carbon (0.16 g) in methanol (5 mL). The mixture was allowed to stir at room temperature for 12 h under a hydrogen atmosphere. The product obtained was filtered through a Celite pad, and the filtrate was concentrated over vacuum. Flash chromatography (SiO_2, 3:1 EtOAc:petroleum ether) was performed to obtain pure product (**9**−**13**).[12]

*2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(±)-**10**].* Yield: 67%



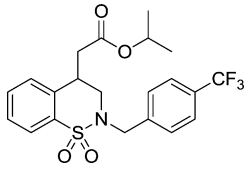
(0.144 g). White crystalline solid. mp: 69−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1H, J = 7.8 Hz), 7.52−7.50 (m, 1H), 7.44 (t, 1H, J = 7.5 Hz), 7.35 (dd, 1H, J = 12.9, 5.7 Hz), 7.31 (d, 1H, J = 7.9 Hz), 6.98−6.92 (m, 1H), 4.99−4.93 (m, 1H), 4.55 (d, 1H, J = 15.0 Hz), 4.20 (d, 1H, J = 14.9 Hz), 3.82−3.77 (m, 1H), 3.70 (d, 1H, J = 7.7 Hz), 3.56 (d, 1H, J = 6.1 Hz), 2.64 (s, 2H), 1.19 (d, 3H, J = 1.3 Hz), 1.17 (d, 3H, J = 1.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 137.8, 136.7, 135.7, 132.7, 128.7, 128.1, 126.9, 124.7, 118.9, 118.7, 106.0, 105.7, 77.5, 77.0, 76.8, 68.8, 49.7, 43.7, 39.4, 32.1, 21.8. MS (ESI): m/z 426 [M − H]$^-$. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{21}F_3NO_4S$, 428.1138; found, 428.1141.

*2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid tert-Butyl Ester [(±)-**11**].* Yield: 67.7% (0.15 g). Colorless oil. ^{1}H NMR (400 MHz, DMSO): δ 7.79 (d, 1H, J = 7.9 Hz), 7.64−7.59 (m, 2H), 7.57 (dd, 1H, J = 9.6, 2.1 Hz), 7.50



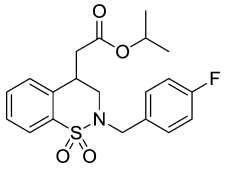
(dd, 2H, J = 17.6, 8.2 Hz), 4.51 (d, 1H, J = 14.6 Hz), 4.15 (d, 1H, J = 14.6 Hz), 3.72−3.64 (m, 2H), 3.61 (d, 1H, J = 6.3 Hz), 2.69−2.62 (m, 2H), 1.28 (d, 9H, J = 2.1 Hz). MS (ESI): m/z 440.1 [M − H]$^-$. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{21}H_{23}F_3NO_4S$, 442.1294; found, 442.1301.

*2-[2-(4-Trifluoromethylbenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(±)-**12**].* Yield: 71.5%



(0.158 g). White crystalline solid. mp: 98−100 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.82 (d, 1H, J = 7.9 Hz), 7.76 (d, 2H, J = 8.2 Hz), 7.64 (d, 2H, J = 5.8 Hz), 7.61 (s, 1H), 7.54−7.49 (m, 2H), 4.78−4.73 (m, 1H), 4.58 (d, 1H, J = 15.0 Hz), 4.27 (d, 1H, J = 15.1 Hz), 3.75−3.65 (m, 2H), 3.62 (d, 1H, J = 3.3 Hz), 2.77−2.64 (m, 2H), 1.04−1.01 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 170.1, 141.1, 138.0, 137.9, 136.1, 135.6, 132.6, 129.0, 129.0, 127.7, 127.0, 125.4, 124.0, 123.9, 67.5, 49.3, 49.0, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 37.3, 30.5, 21.3, 21.2. MS (ESI): m/z 440.1 [M − H]$^-$. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{21}H_{23}F_3NO_4S$, 442.1294; found, 442.1295.

*2-[2-(4-Fluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(±)-**13**].* Yield: 81.6% (0.16 g).



White powder. mp: 94−96 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.81 (d, 1H, J = 7.7 Hz), 7.60 (d, 1H, J = 7.1 Hz), 7.52−7.48 (m, 2H), 7.44−7.41 (m, 2H), 7.19 (d, 2H, J = 8.8 Hz), 4.79−4.73 (m, 1H), 4.48 (d, 1H, J = 14.3 Hz), 4.07 (s, 1H), 3.64−3.59 (m, 2H), 3.56 (d, 1H, J = 3.3 Hz), 2.65 (dd, 2H, J = 23.2, 6.2 Hz), 1.05 (d, J = 1.5 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 138.3, 138.2, 137.0, 136.3, 132.6, 130.7, 130.6, 129.0, 127.7, 123.8, 115.5, 115.3, 67.6, 48.9, 48.4, 40.2, 40.0, 39.8, 39.5, 39.3, 39.1, 38.9, 37.5, 30.6, 21.4. MS (ESI): m/z 390 [M − H]$^-$. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{23}FNO_4S$, 392.1254; found, 392.1328.

General Method for Asymmetric 1,4-Reduction. In a flame-dried Schlenk tube, the appropriate chiral ligand (0.05 mmol), NaOtBu (0.05 mmol), and the appropriate Cu precusor (0.025 mmol) were added sequentially under an argon-filled glovebox. The tube was removed from the glovebox and degassed by briefly being subjected to the vacuum and back-filled with argon (the degassing procedure was repeated three times), and then solvent (6 mL) was added under argon and the reaction mixture stirred for 1 h at 0−20 °C unless otherwise stated. Hydrosilane (2 mmol) was then added followed by the appropriate α,β-unsaturated ester of **4**−**8** (0.5 mmol), and the reaction mixture was allowed to stir over the same temperature range for 12−24 h. Ethanol was added dropwise to the reaction mixture after the reaction had reached completion. The resulting solution was diluted with petroleum ether, washed with water (5 mL) and brine (5 mL), and back-extracted with petroleum ether. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica column chromatography (15:1 to 20:1 petroleum ether:EtOAc).

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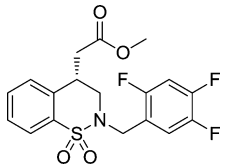
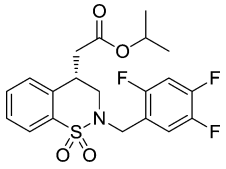


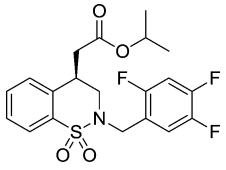
*(+)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Methyl Ester [(+)-**9**].* Yield: 57% (0.114 g). Colorless sticky oil in 93.7% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(minor) = 16.63 min, t_R(major) = 20.49 min]. $[\alpha]_D^{31}$ = +5.7 (*c* 1.47, C_2H_5OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1H, *J* = 7.8 Hz), 7.53 (t, 1H, *J* = 8.1 Hz), 7.44 (d, 1H, *J* = 7.4 Hz), 7.33 (d, 1H, *J* = 9.0 Hz), 7.29 (s, 1H), 6.99−6.91 (m, 1H), 4.57 (s, 1H), 4.14 (s, 1H), 3.83 (d, 1H, *J* = 9.5 Hz), 3.63 (s, 3H), 3.54 (d, 2H, *J* = 5.4 Hz), 2.65 (d, 2H, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 137.7, 134.8, 132.8, 132.0, 128.7, 128.2, 124.7, 119.1, 109.8, 105.8, 77.4, 77.1, 76.8, 52.0, 49.5, 43.3, 38.8, 32.5. MS (ESI): *m*/*z* 398 $[M - H]^-$.

*(+)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(+)-**10**)].* Yield: 85%



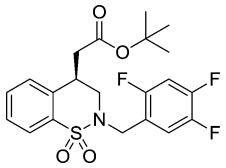
(0.181 g). Colorless sticky oil in 96% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(minor) = 12.65 min, t_R(major) = 16.32 min]. $[\alpha]_D^{31}$ = +7.97 (*c* 1.505, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 1H, *J* = 7.8 Hz), 7.53 (t, 1H, *J* = 7.1 Hz), 7.43 (d, 1H, *J* = 7.5 Hz), 7.34 (d, 1H, *J* = 2.5 Hz), 7.32−7.27 (m, 1H), 6.98−6.91 (m, 1H), 4.99−4.92 (m, 1H), 4.55 (d, 1H, *J* = 15.0 Hz), 4.20 (d, 1H, *J* = 14.9 Hz), 3.82−3.76 (m, 1H), 3.70 (dd, 1H, *J* = 14.5, 6.8 Hz), 3.60−3.53 (m, 1H), 2.64 (t, 2H, *J* = 7.3 Hz), 1.19 (d, 3H, *J* = 1.7 Hz), 1.18 (d, 3H, *J* = 1.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 137.8, 136.7, 132.8, 128.7, 128.1, 124.7, 119.5, 119.4, 118.9, 118.7, 106.0, 105.8, 105.8, 105.5, 77.5, 77.2, 76.9, 68.8, 49.8, 43.7, 39.4, 32.1, 21.8. MS (ESI): *m*/*z* 450.3 $[M + Na]^+$.

*(−)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(−)-**10**].* Yield: 89%



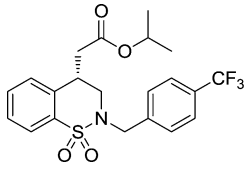
(0.189 g). Colorless sticky oil in 97.2% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(major) = 12.67 min, t_R(minor) = 16.33 min]. $[\alpha]_D^{31}$ = −6.53 (*c* 1.5, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, 1H, *J* = 9.0 Hz), 7.43 (t, 1H, *J* = 7.4 Hz), 7.35 (d, 1H, *J* = 7.9 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.23 (dd, 1H, *J* = 15.6, 7.7 Hz), 6.98−6.91 (m, 1H), 4.99−4.93 (m, 1H), 4.54 (d, 1H, *J* = 15.0 Hz), 4.19 (d, 1H, *J* = 14.9 Hz), 3.82−3.76 (m, 1H), 3.70 (dd, 1H, *J* = 14.5, 6.8 Hz), 3.60−3.52 (m, 1H), 2.66−2.61 (m, 2H), 1.19 (d, 3H, *J* = 2.3 Hz), 1.17 (d, 3H, *J* = 2.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 137.8, 136.7, 134.4, 132.7, 128.7, 128.0, 124.6, 119.5, 118.9, 118.7, 106.0, 105.8, 105.7, 105.5, 77.5, 77.2, 76.7, 68.8, 49.8, 43.7, 39.3, 32.1, 21.7. MS (ESI): *m*/*z* 450.3 $[M + Na]^+$.

*(−)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid tert-Butyl Ester [(−)-**11**].* Yield: 61% (0.135 g). Colorless sticky oil in 93.3% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(major) = 12.77 min, t_R(minor) = 18.52 min]. $[\alpha]_D^{31}$ = −6.67 (*c* 0.33, C_2H_5OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d, 1H, *J* = 7.9 Hz), 7.62 (d, 1H, *J* = 6.2 Hz), 7.60−7.55 (m, 2H), 7.50 (dd, 2H, *J* = 16.5, 8.1 Hz), 4.51 (d, 1H, *J* = 14.6 Hz), 4.15 (d, 1H, *J* = 14.6 Hz), 3.75−3.68 (m, 1H), 3.66 (d,



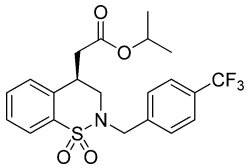
1H, *J* = 5.0 Hz), 3.62−3.58 (m, 1H), 2.69−2.64 (m, 1H), 2.62−2.56 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.0, 137.9, 132.5, 129.0, 127.7, 123.9, 119.1, 101.1, 80.4, 49.0, 43.5, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 38.2, 30.5, 27.5. MS (ESI): *m*/*z* 440.1 $[M - H]^-$.

*(+)-2-[2-(4-Trifluoromethylbenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(+)-**12**].* Yield: 84%



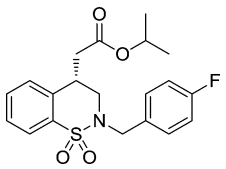
(0.185 g). Colorless sticky oil in 91.2% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(minor) = 5.91 min, t_R(major) = 6.76 min]. $[\alpha]_D^{27}$ = +24.18 (*c* 0.43, C_2H_5OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (dd, 1H, *J* = 7.8, 1.1 Hz), 7.76 (d, 2H, *J* = 8.2 Hz), 7.63 (s, 2H), 7.61 (s, 1H), 7.55−7.48 (m, 2H), 4.78−4.72 (m, 1H), 4.58 (d, 1H, *J* = 15.0 Hz), 4.26 (d, 1H, *J* = 15.1 Hz), 3.76−3.64 (m, 2H), 3.62 (s, 1H), 2.74 (dd, 1H, *J* = 16.7, 4.2 Hz), 2.67 (dd, 1H, *J* = 16.6, 8.0 Hz), 1.02 (dd, 6H, *J* = 7.1, 6.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 141.1, 138.0, 136.1, 132.6, 129.1, 128.9, 127.7, 127.6, 125.4, 123.9, 119.1, 109.2, 67.6, 49.4, 49.1, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 37.4, 30.5, 21.3, 21.2. MS (ESI): *m*/*z* 440.3 $[M - H]^-$.

*(−)-2-[2-(4-Trifluoromethylbenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(−)-**12**].* Yield: 86%



(0.189 g). Colorless sticky oil in 95.96% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(major) = 5.91 min, t_R(minor) = 6.76 min]. $[\alpha]_D^{27}$ = −21.78 (*c* 0.589, C_2H_5OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (d, 1H, *J* = 7.9 Hz), 7.75 (d, 2H, *J* = 8.2 Hz), 7.65−7.61 (m, 2H), 7.61−7.58 (m, 1H), 7.51 (dd, 2H, *J* = 12.8, 7.5 Hz), 4.78−4.72 (m, 1H), 4.57 (d, 1H, *J* = 15.0 Hz), 4.26 (d, 1H, *J* = 15.1 Hz), 3.71 (dd, 1H, *J* = 15.1, 9.1 Hz), 3.64 (d, 1H, *J* = 4.9 Hz), 3.59 (d, 1H, *J* = 15.3 Hz), 2.74 (dd, 1H, *J* = 16.7, 4.1 Hz), 2.66 (dd, 1H, *J* = 16.7, 8.0 Hz), 1.06−0.97 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 141.1, 138.0, 136.1, 132.6, 129.1, 128.9, 127.7, 125.5, 125.5, 125.4, 123.9, 118.8, 109.6, 67.5, 49.4, 49.1, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 37.4, 30.5, 21.3, 21.3. MS (ESI): *m*/*z* 440.3 $[M - H]^-$.

*(+)-2-[2-(4-Fluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(+)-**13**].* Yield: 87% (0.170 g).

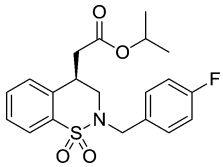


Colorless sticky oil in 95.75% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(minor) = 7.31 min, t_R(major) = 8.78 min]. $[\alpha]_D^{31}$ = +37.57 (*c* 0.33, C_2H_5OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (d, 1H, *J* = 7.9 Hz), 7.63−7.58 (m, 1H), 7.49 (t,

dx.doi.org/10.1021/jo500338c | J. Org. Chem. 2014, 79, 4963−4972

2H, J = 8.2 Hz), 7.42 (dd, 2H, J = 8.5, 5.6 Hz), 7.20 (t, 2H, J = 8.8 Hz), 4.79−4.73 (m, 1H), 4.48 (d, 1H, J = 14.3 Hz), 4.08 (d, 1H, J = 14.3 Hz), 3.65−3.59 (m, 2H), 3.56 (d, 1H, J = 3.4 Hz), 2.65 (dd, 2H, J = 22.7, 6.2 Hz), 1.05 (dd, 6H, J = 8.1, 6.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 138.0, 136.3, 132.5, 132.1, 130.7, 130.6, 129.0, 127.7, 127.0, 123.8, 115.5, 115.3, 109.3, 67.6, 48.8, 48.4, 40.2, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 37.5, 30.6, 21.7. MS (ESI): m/z 414.2 [M + Na]$^+$.

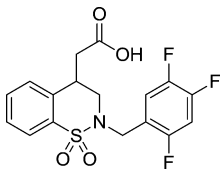
*(−)-2-[2-(4-Fluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid Isopropyl Ester [(−)-**13**].* Yield: 85%



(0.165 g). Colorless solid in 95.44% ee [Chiralpak ID, 10:90 ethanol:*n*-hexane, 1.0 mL/min, 220 nm, t_R(major) = 7.37 min, t_R(minor) = 8.91 min]. mp: 57−59 °C. $[\alpha]_D^{27}$ = −35.4 (c 0.53, C_2H_5OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (d, 1H, J = 7.9 Hz), 7.61 (dd, 1H, J = 10.9, 4.3 Hz), 7.55−7.47 (m, 2H), 7.42 (dd, 2H, J = 8.5, 5.6 Hz), 7.21 (t, 2H, J = 8.8 Hz), 4.78−4.71 (m, 1H, J = 12.5, 6.2 Hz), 4.48 (d, 1H, J = 14.3 Hz), 4.09 (d, 1H, J = 14.3 Hz), 3.69−3.58 (m, 2H), 3.57−3.52 (m, 1H), 2.70 (dd, 1H, J = 16.7, 3.9 Hz), 2.61 (dd, 1H, J = 16.7, 8.4 Hz), 1.05 (dd, 6H, J = 8.1, 6.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 138.0, 136.2, 132.5, 132.1, 130.7, 130.6, 129.0, 127.7, 123.8, 115.5, 115.3, 109.2, 67.6, 48.8, 48.4, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 37.4, 30.1, 21.3. MS (ESI): m/z 414.2 [M + Na]$^+$.

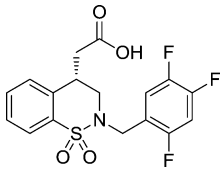
General Method for Acid Hydrolysis. A mixture of the appropriate ester of **10**, **12**, or **13** (0.5 mmol), 1,4-dioxane (5 mL), and 10 M HCl (8 mL) was stirred at room temperature for 12 h unless otherwise stated. After the reaction had reached completion, ice-cold water (5 mL) was added to the reaction mixture and extracted 3-fold with ethyl acetate (3 × 30 mL). The combined organic layers were dried and concentrated under reduced pressure, and the crude product was purified by silica gel chromatography (100:1 CH_2Cl_2:MeOH).

*2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid [(±)-**14**].*[12] Yield: 79% (0.168 g). White



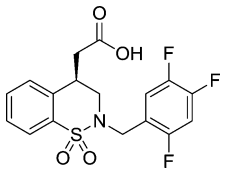
crystalline solid. mp: 69−71 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.36 (s, 1H), 7.79 (dd, 1H, J = 7.9, 1.2 Hz), 7.65−7.61 (m, 1H), 7.59 (dd, 1H, J = 4.6, 2.0 Hz), 7.56 (t, 1H, J = 3.8 Hz), 7.54−7.47 (m, 2H), 4.51 (d, 1H, J = 14.5 Hz), 4.15 (d, 1H, J = 14.5 Hz), 3.68−3.65 (m, 1H), 3.57 (d, 1H, J = 9.2 Hz), 3.17 (s, 1H), 2.72 (dd, 1H, J = 16.9, 4.1 Hz), 2.58−2.52 (m, 1H). MS (ESI): m/z 384 [M − H]$^-$.

*(+)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid [(+)-**14**].* Yield: 89% (0.190 g). Colorless



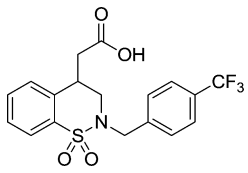
sticky oil in 96% ee [Chiralpak ID, 8:92:0.1 ethanol:*n*-hexane:TFA, 1.0 mL/min, 250 nm, t_R(minor) = 12.20 min, t_R(major) = 13.73 min]. $[\alpha]_D^{31}$ = +7.55 (c 1.325, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.37 (s, 1H), 7.78 (d, 1H, J = 7.1 Hz), 7.61 (s, 1H), 7.58 (d, 1H, J = 4.3 Hz), 7.53 (d, 2H, J = 7.7 Hz), 7.48 (d, 1H, J = 7.3 Hz), 4.51 (d, 1H, J = 14.4 Hz), 4.14 (d, 1H, J = 14.5 Hz), 3.66 (d, 1H, J = 2.0 Hz), 3.58−3.53 (m, 1H), 3.16 (s, 1H), 2.72 (dd, 1H, J = 17.0, 4.1 Hz), 2.57−2.51 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.4, 138.2, 136.0, 132.6, 132.1, 128.9, 127.7, 123.8, 119.4, 106.6, 106.3, 49.0, 43.5, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 37.3, 30.6, 20.6, 14.0. MS (ESI): m/z 384 [M − H]$^-$.

*(−)-2-[2-(2,4,5-Trifluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid [(−)-**14**].* Yield: 85% (0.181 g). Colorless



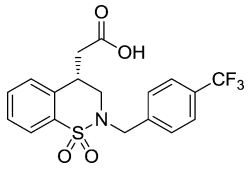
sticky oil in 97.2% ee [Chiralpak ID, 8:92:0.1 ethanol:*n*-hexane:TFA, 1.0 mL/min, 250 nm, t_R(major) = 12.25 min, t_R(minor) = 13.93 min]. $[\alpha]_D^{31}$ = −9 (c 1.4, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, 1H, J = 8.5 Hz), 7.55 (t, 1H, J = 7.0 Hz), 7.46 (t, 1H, J = 7.4 Hz), 7.36−7.31 (m, 1H), 7.28 (d, 1H, J = 10.8 Hz), 6.97−6.97 (m, 1H), 4.61 (d, 1H, J = 14.6 Hz), 4.15 (d, 1H, J = 14.6 Hz), 3.84 (d, 1H, J = 9.5 Hz), 3.64 (dd, 1H, J = 14.4, 6.1 Hz), 3.53 (d, 1H, J = 5.9 Hz), 3.49 (s, 1H), 2.72−2.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 137.4, 132.9, 128.6, 128.3, 124.7, 119.2, 119.0, 109.7, 105.9, 99.2, 77.5, 77.1, 76.8, 49.3, 49.3, 44.1, 43.4, 38.4, 32.3, 14.4. MS (ESI): m/z 384 [M − H]$^-$.

*2-{2-[4-(Trifluoromethyl)benzyl]-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl}acetic Acid [(±)-**15**].*[12] Yield: 83% (0.183 g). White



powder. mp: 155−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 7.9 Hz), 7.53 (d, 2H, J = 6.5 Hz), 7.49−7.45 (m, 2H), 7.27 (d, 2H, J = 4.3 Hz), 4.79 (d, 1H, J = 14.5 Hz), 4.02 (d, 1H, J = 13.9 Hz), 3.79−3.73 (m, 1H), 3.55 (dd, 1H, J = 10.6, 4.2 Hz), 3.49 (s, 2H), 2.64 (d, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.4, 141.2, 138.3, 136.1, 132.6, 129.0, 128.8, 127.6, 125.4, 123.8, 56.0, 49.7, 49.4, 39.7, 39.5, 39.3, 37.5, 30.4. MS (ESI): m/z 398 [M − H]$^-$.

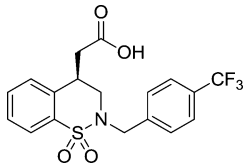
*(+)-2-{2-[4-(Trifluoromethyl)benzyl]-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl}acetic Acid [(+)-**15**].* Yield: 90% (0.199 g). White



solid in 93.35% ee [Chiralpak ID, 8:92:0.1 ethanol:*n*-hexane:TFA, 1.0 mL/min, 250 nm, t_R(minor) = 12.03 min, t_R(major) = 13.04 min]. mp: 117−119 °C. $[\alpha]_D^{31}$ = +27.6 (c 0.55, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1H, J = 7.8 Hz), 7.62 (d, 2H, J = 8.0 Hz), 7.53 (d, 2H, J = 4.5 Hz), 7.51 (s, 1H), 7.45 (d, 1H, J = 7.6 Hz), 7.29 (d, 1H, J = 7.6 Hz), 4.77 (d, 1H, J = 14.3 Hz), 4.05 (d, 1H, J = 14.4 Hz), 3.78−3.77 (m, 1H), 3.65 (d, 1H, J = 5.0 Hz), 3.49 (s, 2H), 2.64−2.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 137.8, 136.8, 132.9, 132.9, 131.2, 129.4, 129.4, 128.7, 128.2, 128.2, 125.9, 124.7, 116.8, 112.7, 109.8, 77.5, 77.2, 76.9, 50.9, 50.0, 48.9, 38.4, 32.3. MS (ESI): m/z 398.2 [M − H]$^-$.

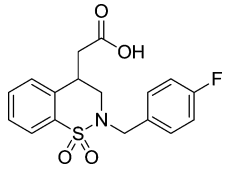
*(−)-2-{2-[4-(Trifluoromethyl)benzyl]-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl}acetic Acid [(−)-**15**].* Yield: 80% (0.176 g). Colorless sticky oil in 95.93% ee [Chiralpak ID, 8:92:0.1 ethanol:*n*-hexane:TFA, 1.0 mL/min, 250 nm, t_R(major) = 12.27 min, t_R(minor) = 13.31 min]. $[\alpha]_D^{31}$ = −29.3 (c 0.375, EtOAc). ^{1}H NMR (400 MHz,

dx.doi.org/10.1021/jo500338c | J. Org. Chem. 2014, 79, 4963−4972



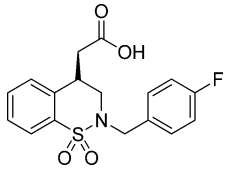
$CDCl_3$): δ 7.94 (d, 1H, J = 7.5 Hz), 7.62 (d, 2H, J = 8.1 Hz), 7.53 (d, 2H, J = 7.0 Hz), 7.47 (dd, 1H, J = 10.2, 4.7 Hz), 7.28 (d, 2H, J = 7.9 Hz), 4.79 (d, 1H, J = 14.3 Hz), 4.03 (d, 1H, J = 14.2 Hz), 3.73 (t, 1H, J = 5.9 Hz), 3.57−3.52 (m, 1H), 3.49−3.45 (m, 1H), 2.65 (d, 2H, J = 6.8 Hz). ^{13}C NMR (100 MHz, DMSO): δ 172.4, 141.2, 138.4, 136.2, 132.6, 129.0, 128.8, 127.7, 125.4, 123.9, 49.7, 49.4, 39.9, 39.7, 39.5, 39.3, 39.1, 37.5, 30.4. MS (ESI): m/z 398.2 $[M - H]^-$.

2-[2-(4-Fluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid [(±)-16]. Yield: 80% (0.156 g). Colorless sticky



oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.46 (d, 1H, J = 7.6 Hz), 7.36−7.33 (m, 2H), 7.27 (d, 1H, J = 1.2 Hz), 7.02 (d, 2H, J = 8.5 Hz), 4.72 (d, 1H, J = 13.8 Hz), 3.92 (d, 1H, J = 13.9 Hz), 3.75−3.70 (m, 1H), 3.56−3.54 (m, 1H), 3.49 (s, 2H), 2.62 (d, 1H, J = 6.1 Hz). MS (ESI): m/z 348 $[M - H]^-$. HRMS (ESI-TOF): m/z $[M - H]^-$ calcd for $C_{17}H_{15}FNO_4S$, 348.0711; found, 348.0710.

(−)-2-[2-(4-Fluorobenzyl)-1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazinyl]acetic Acid [(−)-16]. Yield: 87% (0.170 g). Colorless sticky



oil in 95.44% ee [Chiralpak ID, 8:92:0.1 ethanol:*n*-hexane:TFA, 1.0 mL/min, 250 nm, t_R(major) = 24.92 min, t_R(minor) = 28.57 min]. $[\alpha]_D^{31}$ = −34.6 (c 0.3, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 1H, J = 7.8 Hz), 7.52 (t, 1H, J = 7.6 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.38−7.32 (m, 2H), 7.28 (d, 1H, J = 7.8 Hz), 7.02 (t, 2H, J = 8.6 Hz), 4.70 (d, 1H, J = 13.9 Hz), 3.94 (d, 1H, J = 13.9 Hz), 3.74−3.69 (m, 1H), 3.57−3.51 (m, 1H), 3.46−3.45 (m, 2H), 2.60 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.4, 138.4, 136.3, 132.6, 132.1, 128.9, 127.7, 123.8, 115.5, 115.3, 49.1, 48.7, 40.0, 39.7, 39.5, 39.3, 39.1, 37.6, 30.6. MS (ESI): m/z 348 $[M - H]^-$.

Enzymetic Assay. A partially purified ALR2 was obtained from Wistar rats (200−250 g) supplied by Vital River (Beijing, China). NADPH, D,L-glyceraldehyde, and all chemicals of reagent grade were from Sigma-Aldrich.

ALR2 of rat lens was prepared by following the method of Hayman and Kinoshita[35] and La Motta et al.[36] Freshly removed rat lenses were ground in a glass potter and homogenized in 3 volumes of deionized cold water and then centrifuged for 30 min at 12000 rpm and 0−4 °C. The supernatant was skimmed off and precipitated using $(NH_4)_2SO_4$ at 40, 50, and 75% saturation. The precipitates obtained from the 75% saturation fraction (possessing ALR2 activity) were dissolved in a 0.05 M NaCl solution, dialyzed overnight, stored at −20 °C, and then further used for the enzymetic assay.

Enzyme inhibition activity was asssayed by measuring the decrease in absorption of NADPH at 340 nm (λ), which escorts the oxidation of NADPH catalyzed by ALR2. ALR2 activity was determined in a reaction mixture containing 0.25 mL of 0.1 M sodium phosphate buffer (pH 6.2), 0.15 mL of deionized water, 0.25 mL of 0.10 mM NADPH, 0.1 mL of enzyme extract, and 0.25 mL of 10 mM D,L-glyceraldehyde as a substrate in a final volume of 1 mL at 32 °C. The reaction mixture excluding D,L-glyceraldehyde was incubated for 10 min, and then the substrate was added to start the reaction, which was monitored for 4 min.

The inhibitory activity against ALR2 of the newly synthesized compounds was assayed by adding 5 μL of the inhibitor, solution in DMSO, to the reaction mixture described above. The inhibitory effect was routinely estimated at a concentration of the compound in the reaction mixture between 10^{-4} and 10^{-8} M. At least four concentrations of the compound with three replicates at each concentration with inhibitory activity between 20 and 80% was used to generate each dose−response curve. The 95% confidence limits (95% CL) were calculated from t values for $n - 2$, where n is the total number of determinations.

Molecular Docking. Docking studies were executed using Molegro Virtual Docker, version 5.0. The crystal structure of human aldose reductase with bound inhibitor IDD 594 (PDB entry 1US0) was used for docking, which was retrieved from the Protein Data Bank.

For the docking procedure, all solvent molecules within the protein structure were removed, and to identify the potential binding site in the protein, five possible binding cavities were detected. The cavity around the anion binding site (volume of ∼124 Å^3) was chosen for docking calculations using the grid-based MolDock score (GRID) function with a grid resolution of 0.30 Å, and each docking process lasted between 4 and 6 min. The lowest-energy ligand poses were chosen on the basis of the MolDock score and ReRank score. All structural parameters of ligands such as bond orders, explicit hydrogen atoms, hybridization, and charges were assigned when necessary in Molegro Virtual Docker.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, and NOE spectra and chiral HPLC chromatograms of all chiral and racemic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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