Arabian Journal of Chemistry (2021) **14**, 103037

King Saud University

Arabian Journal of Chemistry

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REVIEW ARTICLE

Recent developments of synthesis and biological activity of sultone scaffolds in medicinal chemistry

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Received 2 December 2020; accepted 17 January 2021
Available online 2 February 2021

KEYWORDS

Sultone;
Sultonyl drug;
Anti-carbonic anhydrase activity;
Anti-HIV activity;
Cholinesterase activity;
Structure–activity relationship

Abstract Sulfonyl drugs are widely used to treat various types of diseases, in which sultones have several desirable properties that have led to their increased use, including improving its simple and effective synthetic methods and/or potentially enhancing potency of drugs. This review focuses on the recent progress in typical synthesis of sultones and the latest developments in various therapeutic applications, including carbonic anhydrase inhibitory activity, HIV-I and HIV-II inhibitory activity, human cytomegalovirus inhibitory activity, and cholinesterase inhibitory activity and their structure–activity relationship. We hope that this review will encourage medicinal chemists to consider the potential benefits to incorporating sultone scaffold into future drug discovery.

Contents

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.arabjc.2021.103037
1878-5352

1. Introduction

Sultone moieties (Fig. 1), the internal esters of sulfonic acids introduced by Erdmann in 1888, have emerged as significantly valuable heterocycles that has been widely used as a general building block in the field of medicinal chemistry (Erdmann, 1988; Pustenko and Žalubovskis, 2017). Novel sultone-functionalized heterocyclic compounds will be particularly useful and desirable in the fields of diversity-oriented chemistry, medicinal chemistry, chemical biology, drug discovery and pharmaceutical industry (Fang et al., 2019; Revathi et al., 2018; Zhang et al., 2018). The early synthesis methods involved carbanion-mediated sulfonate intermolecular or intramolecular coupling reaction (CSIC reaction) (Postel et al., 2003) or sulfonation of olefins with dioxane-sulfur trioxide (Tin and Durst, 1970). Mondal (Mondal, 2012) and Pustenko (Pustenko and Žalubovskis, 2017) further summarized the synthesis methods of sultones in 2012 and 2017, including cycloaddition reaction (Ghandi et al., 2012; Tian et al., 2003), intramolecular Diels-Alder reaction (Bovenschulte et al., 1989; Chan et al., 1997; Doye et al., 1997; Ghandi et al., 2013; Metz et al., 1992; Metz et al., 1994; Metz et al., 1996; Moghaddam et al., 2013; Plietker et al., 2000), ring closure translocation (Karsch et al., 2004; Le-Flohic et al., 2003), Pd-catalyzed reaction (Tamaru et al., 1990), Rh-catalyzed C-H insertion (Wolckenhauer et al., 2007), Heck reaction (Wolckenhauer et al., 2008). Currently, the simple and effective synthesis method of sultones have received an increasing attention to synthetic organic chemists and biologists.

Besides their synthetic application, Molecules containing sultone scaffolds are widely used to treat various types of diseases, for example, phenolsulfonphthalein (**F1**) (Fig. 2) is a non-toxic compound that has been approved for human

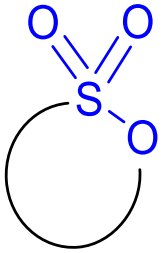


Fig. 1 Structure of sultone.

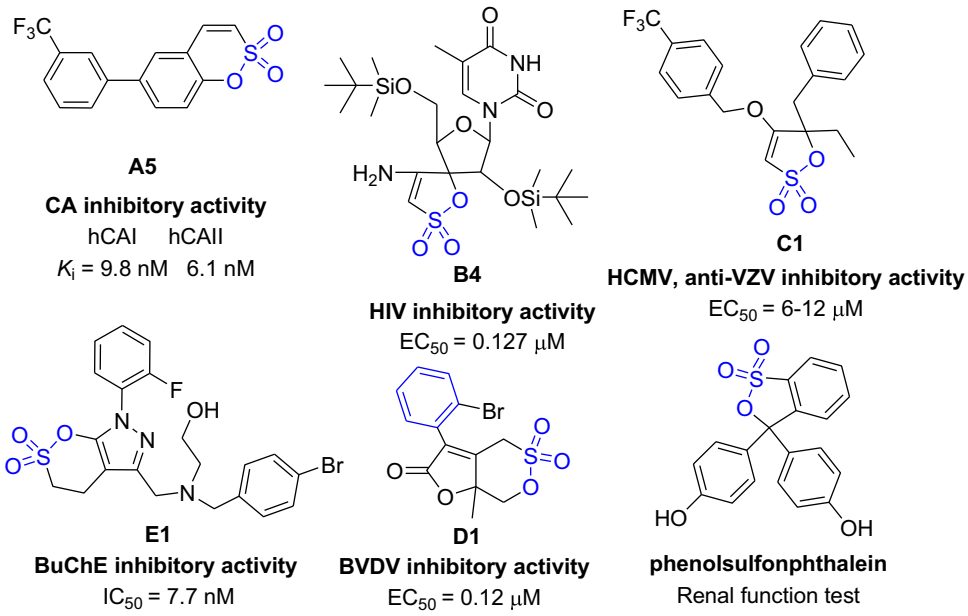
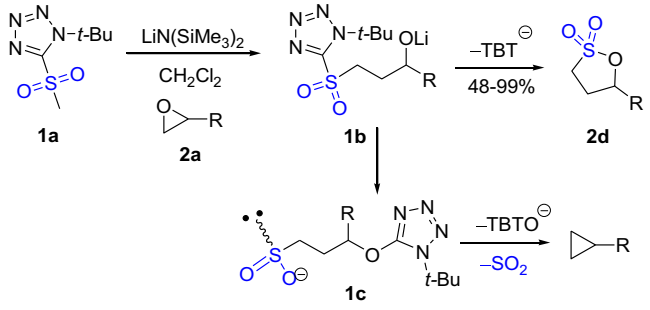
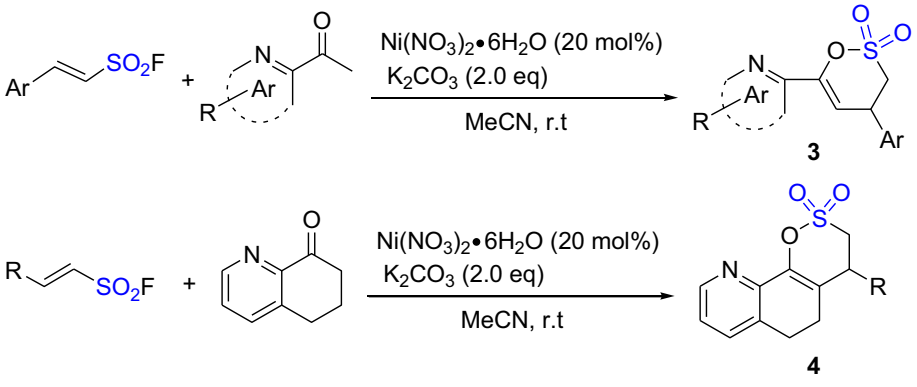


Fig. 2 The structures of some active compounds.

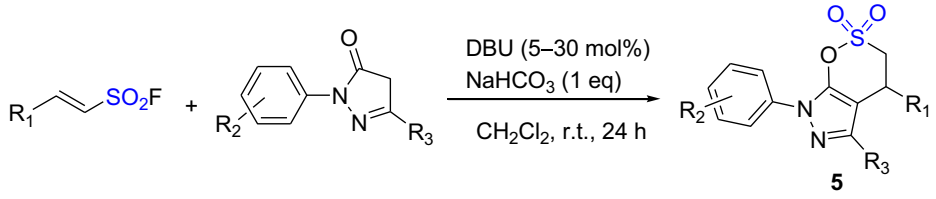


Scheme 1 The synthesis of γ-sultones by Julia–Kocienski reaction.

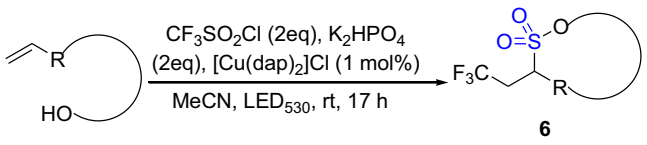
kidney function testing (Itagaki et al., 2018; Russel et al., 1987). In previous reports, sultones were found to have diverse biological activities, such as skin sensitization (Bolt and Golka, 2004; Meschkat et al., 2001; Ritz et al., 1975), anti-tumor activity, anti-virus (human immunodeficiency virus (HIV-I, II), human cytomegalovirus (HCMV) inhibitory activity, and varicella virus (VZV)) inhibitory activity (Balzarini et al., 1992; Bonache et al., 2005; Bonache et al., 2008; Bonache et al., 2011; Camarasa et al., 1992; Camarasa et al., 2004; Camarasa et al., 2005; Camarasa et al., 2006a; Camarasa et al., 2006b; Das et al., 2011; De-Castro et al., 2003; De-Castro et al., 2005; De-Castro et al., 2006a; De-Castro et al., 2006b; De-Castro et al., 2007; De-Castro et al., 2008; De-Castro et al., 2009; De-Castro et al., 2011; De-Castro and Camarasa, 2018; Lobatón et al., 2002; Perez-Perez et al., 1992; Rodríguez-Barrios et al., 2001; Velazquez et al., 1992; Velázquez et al., 2004; Sluis-Cremer et al., 2006), carbonic anhydrase (CA) inhibitory activity (Grandane et al., 2014; Grandane et al., 2015a; Grandane et al., 2015b; Nakai et al., 2018; Nocentini et al., 2018; Pustenko et al., 2017; Tanc et al., 2013; Tanc et al., 2015; Tars et al., 2012), selective butyrylcholinesterase (BuChE) inhibitory activity (Xu et al., 2019), and so on. This review mainly summarizes the advances



Scheme 2 The synthesis of δ-sultones by Ni-catalyzed SuFEx reaction.



Scheme 3 The synthesis of δ-sultones by DBU-catalyzed SuFEx reaction.



Scheme 4 The synthesis of δ-sultones by photocatalytic redox reaction.

in the recent synthesis and pharmacology, and discusses the structure–activity relationship (SAR) of active compounds.

2. Synthesis of sultones

Recently, many powerful methods for sultones synthesis were discovered, such as Julia–Kocienski reaction, Diels-Alder reaction, closed-loop metathesis, Rh-catalyzed C-H insertion, Rh-catalyzed carbene cycloaddition cascade, or other metal catalysts reactions using palladium, rhodium, gold, copper, ruthenium.

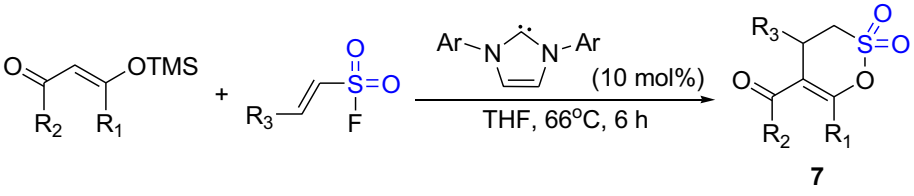
2.1. Julia–Kocienski reaction

Smith et al. prepared firstly γ-sultones in a stereocontrolled method through the epoxide and the homologous Julia-Kocienski reaction (Scheme 1). In the early experiment, it was expected that alkoxysulfones **1b** gave sulfinates **1c** through Smiles rearrangement, subsequently **1c** lose SO_2 and cyclized to produce cyclopropane. But compound **1a** and (*R*)-propylene oxides **2a** (R = Me) under the basic conditions of $LiN(SiMe_3)_2$ at room temperature gave γ-sultones **2d** (R = Me). Both the yield and the ee values were > 99%, and no cyclopropane was observed. The yield of γ-sultones obtained from compound **1a** with a terminal alkyl-substituted epoxide was excellent. Protected alcohols, amines, ketones, halogen-substituted epoxides, diepoxides, and alkyl-substituted terminal epoxides can all give the corresponding substituent γ-sultones. However, when the substrate is a *bis*-epoxide, only a *mono*-sulfonylation product can be obtained, because the formation of the first internal sulphur ring may slow down the formation of the second sultone ring. The disubstituted epoxide reaction may involve a single inversion of stereochemistry (*cis*-1,2-butene oxide produces only *trans*-sultone, while *trans*-1,2-butene oxide produces only *cis*-sulfonate lactone) (Smith et al., 2015). This pathway provides access to γ-sultones using a one-pot method in a stereo-controlled manner.

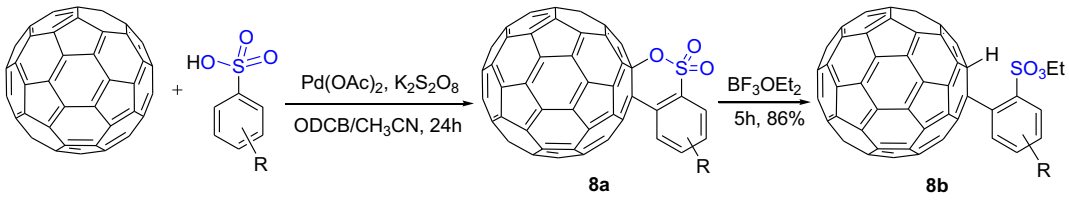
2.2. Sulfur fluoride exchange (SuFEx) click reaction

2.2.1. Nickel-catalyzed SuFEx reaction

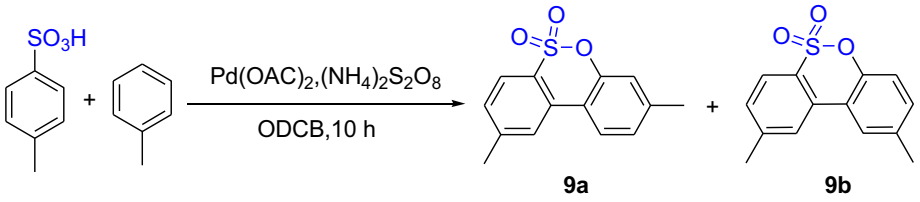
Chen et al. have developed a mild and efficient nickel-catalyzed cyclization method by using sulfur (VI) fluoride exchange (SuFEx) click reaction for the synthesis of sultone-functionalized pyridines (Scheme 2). The sultones **3** were obtained by Ni-catalyzed cyclization reaction from substrate (*E*)-2-phenylethanesulfonyl fluoride (1 eq) and 2-acetylpyridine (2 eq) in acetonitrile. The (hetero)aralkylsulfonyl fluorides with *p*- or *m*-substituted groups have moderate to excellent yield. In which, the reaction time for the *o*-substituted one is longer, but the yield is higher (> 90%); the halide group (F, Cl and Br) have better tolerance to the catalytic conditions; the yield of the *p*-substituted one with stronger electron-withdrawing ester group is reduced (44%); the 2-aralkylsulfonyl fluoride with a disubstituted aromatic ring has a good to excellent yield (73–89%). This method is also applicable to 2-arylsulfonyl fluoride, thiophene, dibenzothienyl, and indole with complex and heterocyclic aromatic substrates (including naphthyl). 2-Phenylethenesulfonyl fluorine can react with substituted 2-acetylpyridine to form sultones in moderate to good yields. However, when the substituent group is adjacent to the N atom of pyridine, the yield becomes low. When 6,7-dihydroquinoline-8(5*H*)-one was reacted with various 2-substituted ethenesulfonyl fluorides, a novel class of fused-sultones **4** were obtained in a yield of 37–99%. Besides, this method is practical so that sultone-functionalized pyridines can be prepared on a reasonable scale (Chen et al., 2018). An efficient Ni-catalyzed annulative process for the synthesis of sultones were developed using SuFEx chemistry. This method features a wide scope to serve as an irreplaceable asset for medicinal chemistry and medicinal discovery.



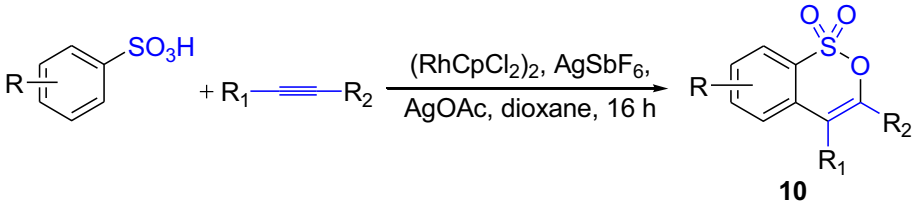
Scheme 5 The synthesis of δ-sultones by carbene-catalyzed (3 + 3) annulation.



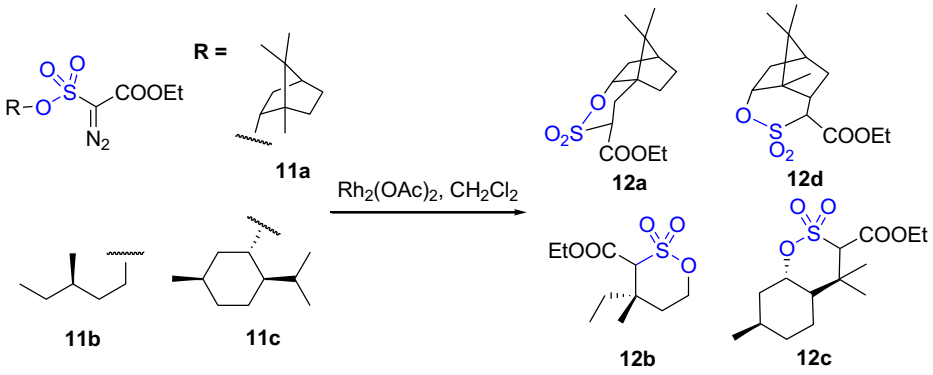
Scheme 6 The synthesis of C_{60}-fused sultones by Pd-catalyzed C-H activation reaction.



Scheme 7 The synthesis of aromatic sultones by Pd-catalyzed C-H activation.



Scheme 8 The synthesis of δ-sultones by Rh-catalyzed C-H activation reaction.



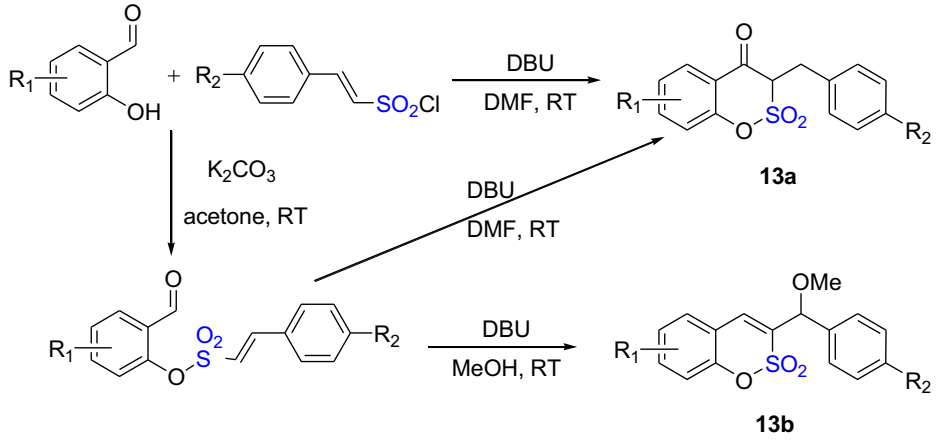
Scheme 9 The synthesis of δ-sultones by Rh-catalyzed C-H insertion reaction.

2.2.2. DBU-catalyzed SuFEx click reaction

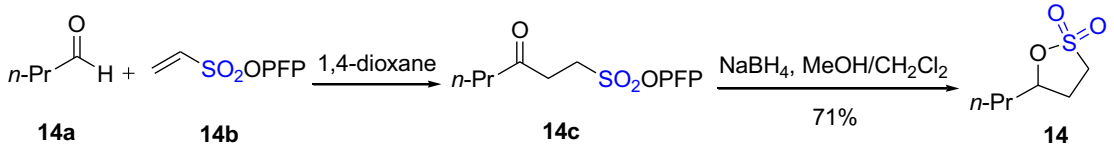
Chen et al. synthesized a new class of δ-sultones through direct cyclization of ethenesulfonyl fluoride (ESF) and pyrazolone or 1,3-dicarbonyl compounds catalyzed by 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 3). The δ-sultones **5** were obtained from pyrazolones or 1,3-dicarbonyl compounds (1.0 eq) with (*E*)-2-(hetero)arylethenesulfonyl fluoride (1.0 eq), DBU (5–30 mol%) and $NaHCO_3$ (1.0 eq) in CH_2Cl_2 at room temperature for 3–24 h in excellent yields (> 90%) (Dong et al., 2014). It is a simple and effective synthesis method.

2.3. Photocatalytic redox reaction

The γ- and δ-sultones **6** were synthesized from different α,ω-enol and trifluoromethylsulfonyl chloride by one-step synthesis under $(Cu(dap)_2)Cl$ photo-redox catalysis (Scheme 4). Focusing on fluorinated sultones, a wide range of substrates can be cleanly converted to the title compounds. The fluorinated sultones are attractive as structural motifs in drug synthesis with being demonstrated with the synthesis of a trifluoroethyl-substituted analogue of a benzoxathiin that has high anti-arrhythmic activity (Rawner et al., 2016). This method uses



Scheme 10 The synthesis of δ-sultones by Baylis-Hillman reaction.



Scheme 11 The synthesis of sultones by hydroacylation–elimination.

an inexpensive low load copper catalyst to obtain the corresponding sultones with moderate to excellent yields.

2.4. N-Heterocyclic carbine-catalyzed (3 + 3) annulation

As shown in Scheme 5, a series of unsaturated δ-sultones were obtained from (3 + 3) annulation of α,β-unsaturated sulfonyl azolium intermediates with trimethylsilyl enol ethers of various 1,3-dicarbonyl compounds in modest yields (40–88%). The δ-sultones **7** were synthesized from different trimethylsilyl (TMS) enol ethers, α,β-unsaturated sulfonyl fluoride and Imes (10 mol %) in tetrahydrofuran (THF) for 17 h. The electron-deficient sulfonyl fluorides have more efficient conversion than the electron-rich ones. The yields of 2-Furyl-substituted sultone and ESF-derived sultone are moderate. The TMS enol ether derived from 1,3-cyclohexadione and the acyclic TMS enol ether of acetylacetone gave the δ-sultones in acceptable yields. TMS enol ethers derived from unsymmetric diketones gave the expected δ-sultones in good yields and modest regioselectivity. In contrast, TMS enol ethers derived from β-ketoesters gave the methyl- and isopropyl-substituted δ-sultones in good yields (Ungureanu et al., 2015).

2.5. C-H activation reaction

2.5.1. Pd-catalyzed C-H activation reaction

Li et al. firstly reported the functionalization with the sulfonic acid group as the directing group in a C–H activation reaction. (60)Fullerene-fused sultones has been employed in the unprecedented Pd-catalyzed C–H activation reaction of arylsulfonic acids to afford (60)fullerene-fused sultones. As shown in Scheme 6, C60-fused sultones **8a** were obtained from arylsulfonic acids and C_{60} in 18–30% yields. C_{60}-fused sultones were treated in *o*-dichlorbenzene (ODCB) with excess $BF_3{\cdot}OEt_2$ at 150 °C to give arylsulfonate-substituted fullerenes **8b** in good yields (Li et al., 2012b).

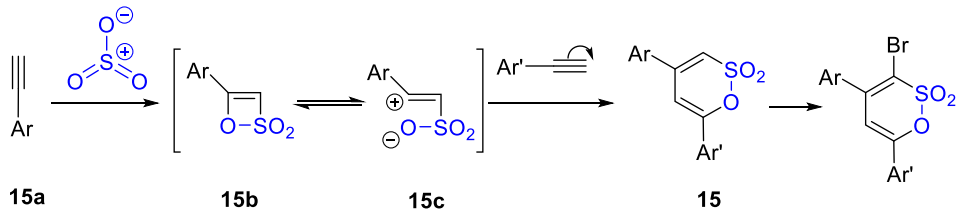
Li et al. disclosed a Pd-catalyzed cyclization of arylsulfonic acids with simple arenes to give aromatic sultones through sulfonic acid group-directed multiple C-H activation and C-C/C-O formation. As shown in Scheme 7, one isomer aryl sulfonyl lactone **9** can be obtained by reacting aryl sulfonic acid with aromatics (20 eq), $Pd(OAc)_2$ (10 mol%) and $(NH_4)_2S_2O_8$ (3 eq) in ODCB solution at 90 °C for 10 h. except the reaction between toluene and 4-methylbenzenesulfonic acid produced an inseparable regioisomers **9a** and **9b** at a ratio of 2:1 (Li et al., 2012a).

2.5.2. Rh-catalyzed C-H activation reaction

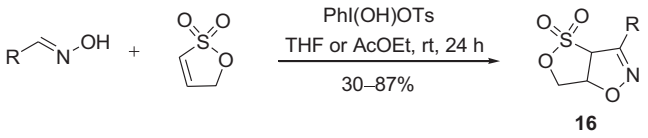
Qi et al. described a new Rh-catalyzed synthesis of sultones *via* the oxidative coupling of sulfonic acids with internal alkynes. The sultones **10** were obtained from different arylsulfonic acids *via* aryl C–H activation assisted by a sulfonic acid group in Scheme 8, for example, alkynes with electron-donating groups had good yields, *para*-alkynes or diarylalkynes with *o*-OMe had lower yields, asymmetric alkynes showed moderate yields but higher regioselectivity, 1-naphthalenesulfonic acid and diphenylacetylene exhibited moderate reactivity (Qi et al., 2014). A broad scope of substrates has been examined and good functional group compatibility has been realized. This approach provides a new access to sultones.

2.6. C-H insertion reaction

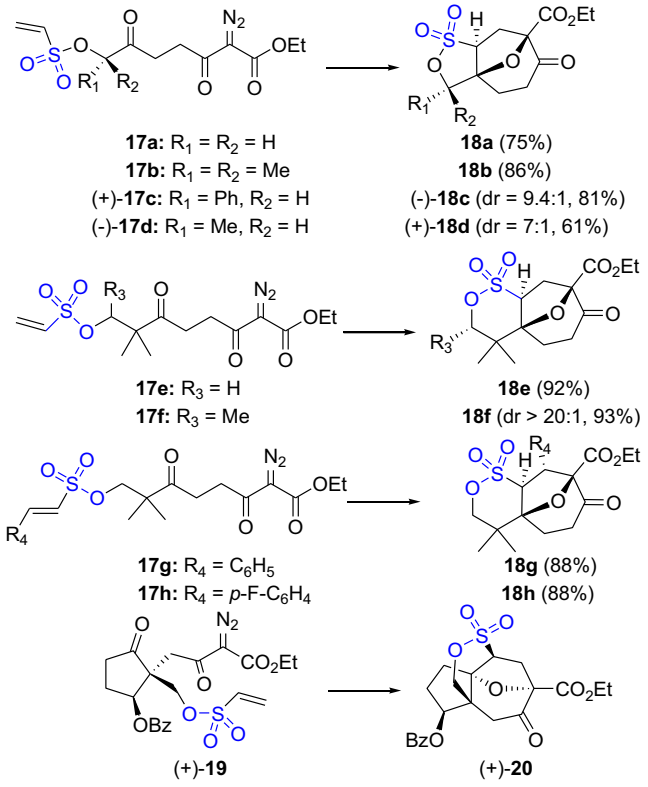
Liyanage et al. reported that key intermediates can be prepared through intramolecular C-H insertion on diazosulfonate substrates. The δ-sultones **12a–d** were synthesized from the



Scheme 12 One-step synthesis of 1,3-dienic δ-sultones in the presence of SO_3.



Scheme 13 The synthesis of sultones by iodine-catalyzed cycloaddition.



Scheme 14 The synthesis of sultones by Rh-catalyzed cycloaddition.

diazosulfonate substrates of borneol (**11a**), 3-methylpentan-1-ol (**11b**), and isomenthol (**11c**) in high yields in Scheme 9. This C-H insertion reaction was used to prepare a series of stereoselective sultones from easily available materials (Liyanage et al., 2015). By using C–H insertion on sulfonyl substrates, a series of useful intermediates were prepared from inexpensive and easily available starting materials.

2.7. Baylis-Hillman (BH) reaction

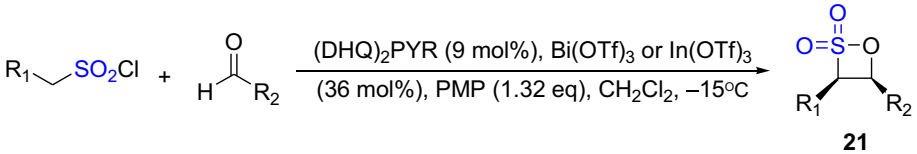
A solvent-dependent method was used to synthesize β-keto-benzo-δ-sultone scaffolds. As shown in Scheme 10, the sultones **13a** were obtained in high yields in DMF using a one-pot, DBU-catalyzed condensation of 2-hydroxybenzaldehydes and (*E*)-2-phenylethenesulfonyl chlorides, on the other hand, the initially prepared 2-formylphenyl-(*E*)-2-phenylethenesulfonate derivatives underwent DBU-catalyzed reactions to sultones **13b** in moderate to good yields. These reactions presumably proceed *via* DBU-catalyzed *o*-sulfonylation/intramolecular Baylis–Hillman/1,3-H shift or dehydration tandem sequences, respectively (Ghandi et al., 2011). These broaden the benzo-δ-scaffolds that are accessible through intramolecular BH reactions, and many of them may represent interesting pharmacophores.

2.8. Asymmetric hydrogenation

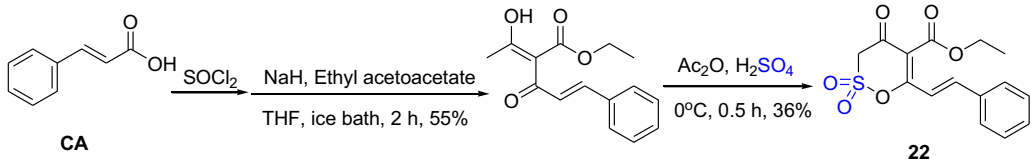
Chudasama et al. reported the use of aerobically initiated, metal-free hydroacylation of various C = C and N = N acceptor molecules with a wide range of aldehydes, for example, the hydroacylation of vinyl sulfonate **14b** with *n*-butyraldehyde **14a** in 1,4-dioxane gave the pentafluorophenyl (PFP) γ-keto-sulfonate **14c**. The sultone **14** could be achieved by reducing the ketone moiety of γ-keto-PFP-sulfonate and subsequently eliminating pentafluorophenol in good yield (Scheme 11) (Chudasama et al., 2013).

2.9. Heterocyclization of arylalkynes

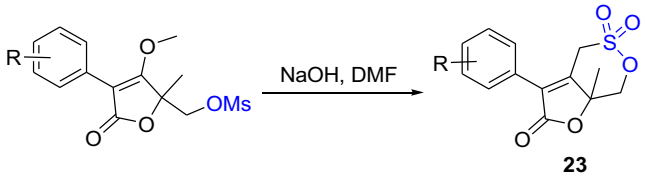
Gaitzsch et al. reported the synthesis of 1,3-dienic δ-sultones **15** *via* a one-step reaction of arylalkynes with sulfotrioxide in dioxane (Scheme 12). It is presumed that alkynes **15a** were first sulfonated with SO_3 to afford a highly reactive β-sultones existing in the cyclic **15b** and zwitterionic **15c** form. Subsequent



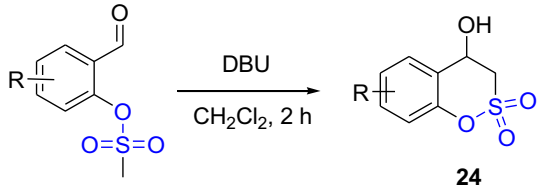
Scheme 15 The synthesis of β-sultones by (2 + 2) cycloaddition.



Scheme 16 The synthesis of δ-sultone by acid-catalyzed cyclization.



Scheme 17 The synthesis of δ-sultones by base-catalyzed cyclization.



Scheme 18 The synthesis of δ-sultones by DBU-catalyzed aldol cyclization.

electrophilic addition of alkyne to this β-sultones then gives the stable δ-sultones **15**. Thus, a range of monosubstituted arylalkynes were investigated in a heterocyclization with SO_3 to give δ-sultones. The resulting sultones were regioselectively brominated with Br_2 or NBS (Gaitzsch et al., 2011).

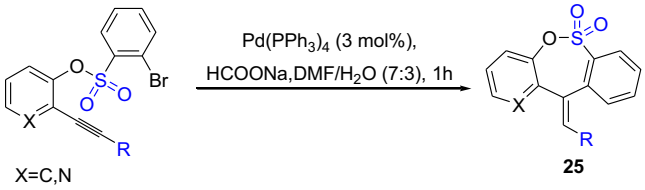
2.10. Cycloaddition reaction

2.10.1. Iodine-catalyzed oxidative heterocyclic reaction

Yoshimura et al. has developed an efficient cycloaddition of heterocyclic alkenes with nitrile oxides generated *in situ* from the corresponding aldoximes using Koser's reagent. The oxidative cyclization of various aldoximes with 1-propene-1,3-sultone affords the respective isoxazoline-ring-fused heterobicyclic products **16** in moderate to good yields (Scheme 13). Furthermore, under similar conditions, the reaction of aldoxime with a cyclic phospholene-oxide produces the corresponding heterobicyclic phospholene oxides in moderate yields. The structures of bicyclic phospholene oxide and two sultones were established by X-ray crystallography (Yoshimura et al., 2017). This reaction generally afforded the corresponding heterobicyclic products in moderate to good yields.

2.10.2. Rh-catalyzed carbene cyclization cycloaddition reaction

Carbene cyclization cycloaddition cascade (CCCC) is a powerful and atomically economical reaction that produces stereogenic oxapolycyclic adducts. Shi et al. reported that vinylsulfonates are excellent dipolarophiles for carbonyl ylides derived from diazoketones in Rh-catalyzed intramolecular



Scheme 19 The synthesis of sultones by Heck cyclization.

cycloadditions (Scheme 14). The cycloaddition of diazoketones **17a–d** and **17e–h** under the catalysis of 3 mol% $Rh_2(oct)_4$ in CH_2Cl_2 occurred smoothly to give the γ-sultones **18a–d** and δ-sultones **18e–h**, respectively, in high yields and excellent stereoselectivities. The CCCC reaction of vinyl sulfonate (+)-**19** gave sultone-bridged hydroazulene (+)-**20** with the only diastereomer under the catalysis of $Rh_2(OAc)_4$ in 90% yield (Shi et al., 2009). The multifunctional substrate forms polycyclic sultones with high yield and very good diastereoselectivity under mild reaction conditions.

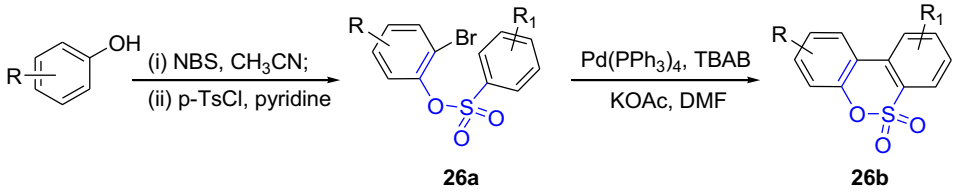
2.10.3. (2 + 2) cycloaddition reaction

Koch et al. reported the catalytic asymmetric synthesis of β-sultones, which has enabled a rapid access to a number of highly enantioenriched biologically interesting sulfonyl and sulfinyl compounds, either two vicinal stereocenters, such as in β-hydroxy-sulfonamides, -sulfonates, -sulfones, -sulfonic acids, -sulfinic acids, γ-sultines, and γ-sultones or a single stereocenter, such as in α-branched alkyl or allyl sulfonic acids (Scheme 15). The inherent ring strain of the four-membered heterocycles **21** was used to produce the sulfene intermediates in asymmetric catalysis. The reactivity of a sulfene as an electrophile could be reverted by the formation of a nucleophilic zwitterionic sulfene-amine adduct. The cooperative catalysis achieves a combination of high enantioselectivity and reactivity (Koch and Peters, 2011). The catalytic asymmetric synthesis of β-sultones have firstly been developed. This methodology enables a rapid access to a number of highly enantioenriched sulfonyl and sulfinyl compounds.

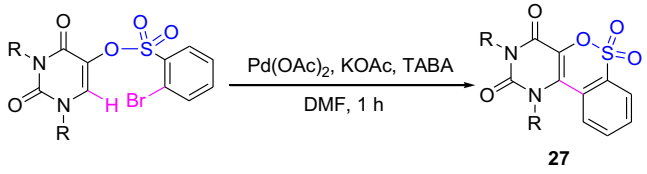
2.11. Closed-ring reaction

2.11.1. Acid-catalyzed cyclization

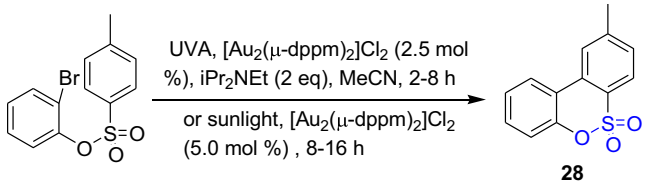
To facilitate more detailed studies of sultones, a new method was used to synthesize the sulfonic acid lactones and finish its ring-closing reaction. A new sultone, (*E*)-ethyl 4-oxo-6-styryl-3,4-dihydro-1,2-oxathiine-5-carboxylate 2,2-dioxide (S-CA), was synthesized and identified. Its synthesis extended the method of ring-closing reaction of sulfonic acid lactones. Li et al. synthesized the sultone **22** by a fast ring-closing reaction (Scheme 16). The reaction of cinnamoyl chloride with



Scheme 20 The synthesis of sultones by Pd-catalyzed intramolecular cyclization.



Scheme 21 The synthesis of sultones by Pd-catalyzed intramolecular cyclization.



Scheme 22 The synthesis of δ-sultones by gold-catalyzed cyclization.

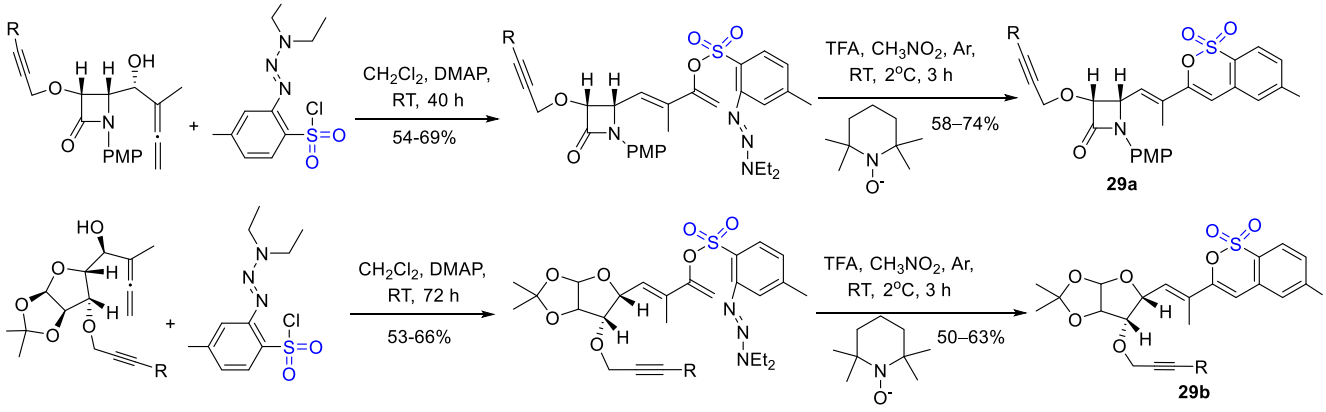
ethyl acetoacetate under NaH condition gives ethyl 2-cinnamoyl-3-ketobutyrate, subsequently transfers to sultone **22** by ring-closing reaction under Ac_2O and H_2SO_4. Compound **22** selectively suppress small angiogenesis in chorioallantoic membrane, without influencing middle or large angiogenesis (Li et al., 2015).

2.11.2. Base-catalyzed cyclization

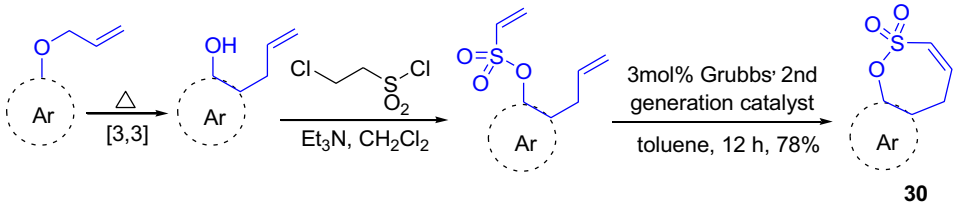
Xu et al. (Xu et al., 2014) reported the synthesis of a novel series of bicycle δ-sultones containing γ-lactones and their activity against bovine viral diarrhea virus (BVDV). The alkylsulfonate intramolecular cyclization reaction (CSIC reaction) gave the δ-sultones **23** in 32–70% yields (Scheme 17).

2.11.3. DBU-catalyzed intramolecular aldol cyclization

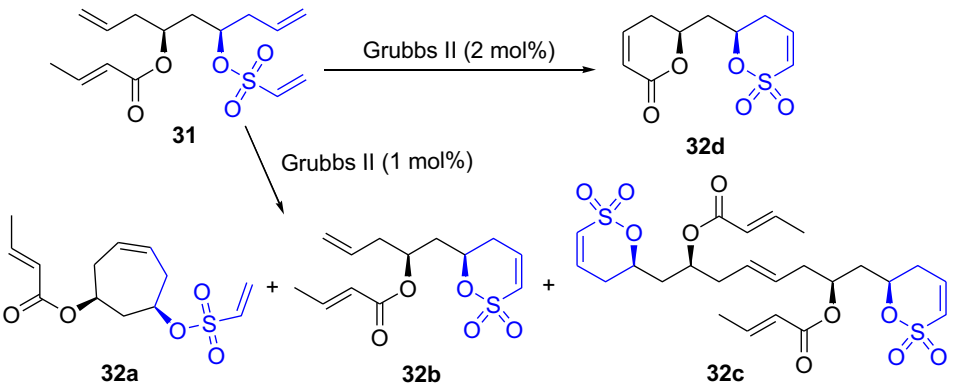
Grandane et al. reported a synthetic method of benzo-δ-sultones as bioisosteres of coumarin through the intramolecular aldol cyclization of mesylsalicyl aldehydes in the presence of DBU (Scheme 18). The benzo-δ-sultones **24** were obtained from mesyl derivatives by cyclization reaction in CH_2Cl_2 under a catalytic of DBU in good yields (Grandane et al., 2012). This



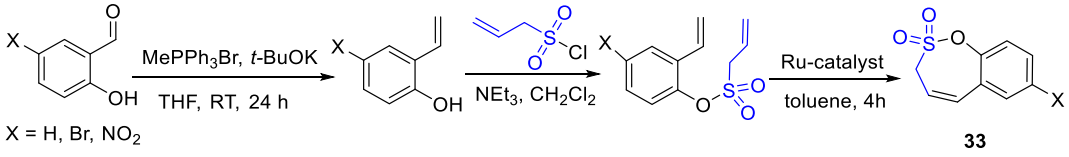
Scheme 23 The synthesis of enantiopure polycyclic-fused sultones.



Scheme 24 The synthesis of seven-membered sultones by Grubbs-catalyzed RCM.



Scheme 25 The synthesis of sultone by Grubbs-catalyzed RCM.



Scheme 26 The synthesis of sultones by Ru-catalyzed olefin metathesis.

method is reproducible and applicable for a broad scope of substrates with electron-withdrawing and -donating substituents.

2.11.4. Pd-catalyzed Heck cyclization

Mondal et al. reported an effective method for the synthesis of seven-membered fused-sultones by intramolecular Heck cyclization catalyzed by $Pd(PPh_3)_4$ (Scheme 19). The seven-membered fused-sultones **25** were obtained in excellent yield and regio- and stereo-selectivity from the mixture of raw materials (1.5 eq), 3 mol% $Pd(PPh_3)_4$ and HCOONa in DMF-H_2O at 100 °C for 1 h. Heck-type cyclization is regio- and stereo-selective, which the stereochemistry of exocyclic double bond in the dibenzo-fused sultone is opposite to that of the benzopyridin-fused sulfonate (Mondal et al., 2015a). The method offers the regio- and stereo-selective synthesis of highly functionalized benzopyrido-fused or dibenzo-fused sultone derivatives in high yield under mild conditions.

2.11.5. Pd-catalysed intramolecular cyclization

A Pd-catalyzed intramolecular arylation of 2-bromobenzene-sulfonates was reported (Scheme 20). The arylation was affected by the substituents on phenol moiety, for example, electron-donating ones favor the reaction while electron-withdrawing ones are unfavorable. The clization of the intermediate phenyl 2-bromobenzenesulfonates **26a** gave sultones **26b** in good yields, which effective method generates tricyclic and tetracyclic sultones (Bheeter et al., 2012; Majumdar et al., 2009).

This Pd-catalyzed intramolecular arylation can be used to synthesize the regioselective uracil-, coumarin- and quinolone-fused benzosultams and benzosultones (Scheme 21). Pd-catalyzed cyclization of uracil 2-bromobenzenesulfonates gave uracil-fused benzosultones **27** in high yields (Mondal et al., 2015b).

2.11.6. Dimer gold-catalyzed cyclization

Similarly, a dimeric phosphine-gold complex as a photocatalyst can catalyze the photoreductive radical reaction of an aryl bromide to give the biaryl compound **28** (Scheme 22). Sultone **28** was formed in the presence of the dimerized phosphine-gold complexes $(Au_2(\mu\text{-dppm})_2)Cl_2$ (2.5 mol%) under ultraviolet radiation A (UVA) or sunlight $(Au_2(\mu\text{-dppm})_2)Cl_2$ (5.0 mol %) in MeCN in good yields (Revol et al., 2013). This photoredox process has uniqueness and high synthesis potential.

2.11.7. Direct cyclization/desaturation radical cascade reaction

A sulfonylation/rearrangement sequence of allyl ether containing β-lactam or glucofuranoside with 2-(3,3-diethyltriazine-1-enyl)-4-methylbenzene-1-sulfonyl chloride gave the functionalized 1,3-diene-2-yl arenesulfonates, which suffered a direct cyclization/desaturation radical cascade to give title δ-sultones **29a-b** in moderate yields (Scheme 23). Experiments and density functional theory (DFT) calculations demonstrated stereoselective cyclization of the readily formed core through intramolecular Diels-Alder reaction. This metal-free C-C cyclization reaction is feasible and universal (Alcaide et al., 2016).

2.11.8. Grubbs-catalyzed ring-closing metathesis

Mondal et al. reported the synthesis of seven-membered sultones fused with different carbo- and heterocycles through ring-closing metathesis (RCM) in good yields (Scheme 24). Sulfonylation reaction of *o*-allylphenol derivatives with 2-chloroethylsulfonyl chloride gave the vinyl-sulfonates with yields of 81–95%, which were transferred to the sultones **30** under catalysis of Grubbs' 2nd generation (3 mol %) with yields of 70–80% (Mondal and Debnath, 2014).

Walleser et al. reported a twofold ring-closing metathesis under forcing conditions provided unsaturated lactone/unsaturated sultone (Scheme 25). Ethanesulfonate **31** with different

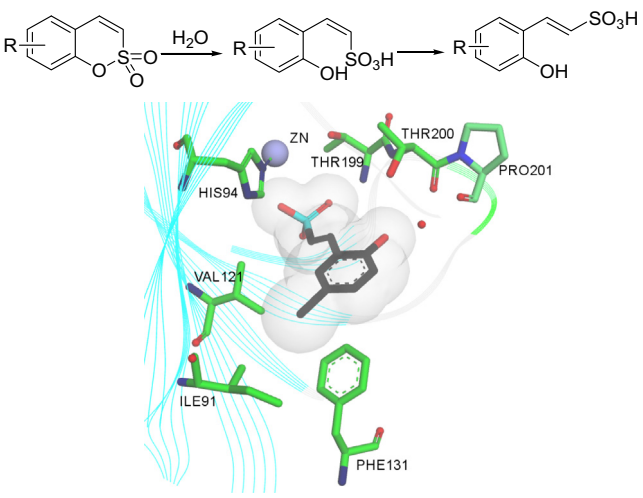


Fig. 3 Active site CA-mediated hydrolysis of *trans*-vinylsulfonic acid. Binding of *trans*-vinylsulfonic acid within the active site of the CA II/IX mimic (PDB: 4BCW). The Zn (II) ion (larger sphere), His ligand (His94), water molecule (small sphere) coordinated to the zinc are shown by X-ray crystallography (Tars et al., 2012). Discovery Studio Client v18.1.0 was used to present a 3D image.

functional groups gave monometathesis products **32a** (18%), **32b** (52%) and cross metathesis products **32c** (9%) mixtures under catalysis of 1 mol% Grubbs II, while only sultone **32d** was obtained under catalysis of 2 mol% Grubbs II catalyst in 75% yield (Walleser and Brückner, 2014).

2.11.9. Ru-catalyzed olefin metathesis

Pustenko et al. reported the synthesis of sultones using Ru-catalyzed olefin metathesis. The seven-membered fused-sultones **33** were obtained from the reaction of 4-substituted 2-ethenylprop-2-ene-1-sulfonate with Ru-catalyst (tricyclohexyl phosphine(1,3-bis(2,4,6-trimethyl-phenyl)imidazol-2-yli dene)(3-phenyl-1H-inden-1-ylidene)ruthenium(II) dichloride) (0.05 eq) in dry toluene (10 mL/0.2 g) at 70 °C for 4 h in yields of 84–96% (Scheme 26) (Pustenko et al., 2017).

Although we reviewed the various synthetic methods of the sultone scaffolds, there is an urgent need to develop more effective and mild synthetic methods to obtain plenty of sultone compounds with new scaffolds to enrich sultone compound libraries. In addition, there are few reports on synthesis of sultones based on rational drug design. We hope that researchers can optimize the methods of batch synthesis of sultones to find the potential sultone inhibitors by high-throughput screening.

3. Biological activities of sultones

Sulfonyl compounds are widely used as basic structural frameworks in pharmaceutical chemistry (Zhao et al., 2018; Zhao et al., 2019). Phenolsulfonphthalein (**F1**) is a synthetic small molecular as various medical diagnostic agents for many years, for example, phenolsulfonphthalein has been used clinically as a diagnostic marker to detect renal function by estimating urinary excretion rate after intravenous injection, in addition to improving the accuracy of gastric secretion studies and oviduct patency assessments (Itagaki et al., 2005; Horhota and Fung, 1978). It was also found that sultone has a variety of biological activities, including antiviral (HIV-1, HIV-II, HCMV and VZV) activity, anticarbonic anhydrase (CA) activity, selective antibutyrylcholine (BuChE) activity (Fig. 2).

3.1. Carbonic anhydrase inhibitors

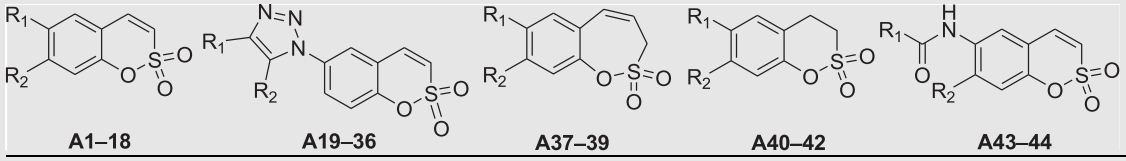
Carbonic anhydrases (CAs, EC 4.2.1.1) are ubiquitous Zn^{2+} metallo-enzymes, and 16 isozymes have been identified. The α-CAs are present in vertebrates, protozoa, algae and cytoplasm of green plants and in some bacteria, the β-CAs are predominantly found in bacteria, algae and chloroplasts of both mono- as well as dicotyledons, but also in many fungi and some archaea. The γ-CAs were found in archaea and some bacteria, whereas the δ- and ζ-CAs seem to be present only in marine diatoms. Among those identified, there are eight cytosolic proteins (CA I, CA II, CA III, CA VII, CA VIII, CA X, CA XI, CA XIII), two mitochondrialmatrix proteins (CA VA, CA VB), one secreted protein (CA VI), two glycosylphosphatidylinositol (GPI)-anchored proteins (CA IV and CA XV), and three transmembrane proteins (CA IX, CA XII, CA XIV). Indeed, 16 such isozymes were described in non-primates, CAs I-XV with two V-type isoforms, CA VA and CA VB, and 15 isoforms are known in primates, as CA XV is not expressed in these mammals (Fisher et al., 2012; Lee et al., 2009; McKenna and Supuran, 2014; Savile and Lalonde, 2011; Vullo et al., 2013).

CAs catalyze the hydration of CO_2 and the dehydration of bicarbonate, which play an important role in regulating the intracellular and extracellular pH in various physiological processes. Abnormal levels or activities of these enzymes are often associated with different diseases (Alterio et al., 2012; Krishnamurthy et al., 2008). CA II is associated with glaucoma, edema, epilepsy, altitude sickness, et al. Inhibiting CA II can reduce bone loss in osteoporosis. CA IV is a drug target for several pathologies including glaucoma (along with CA II and XII), pigmented retinitis and stroke. CA VA and VB are targets of anti-obesity drugs, while CA IX and XII are targets of anticancer drugs (Alterio et al., 2012; Krishnamurthy et al., 2008). CA IX is a marker of the progression of many types of hypoxic tumors, such as primary tumors and metastatic tumors (Alterio et al., 2012). CA XII over-expression is found in meningiomas, hemangioblastomas, gliomas, brain tumors, and so on. In breast cancer, CA XII expression levels indicate a potential attack of the disease (Alterio et al., 2012; Baig et al., 2019; Ilie et al., 2011; Parkkila et al., 2000). Because CAs with multiple isoforms exist in a variety of tissues and organs, it is important to design selective CA inhibitors.

3.1.1. Mechanism of sulfocoumarin as CA inhibitors

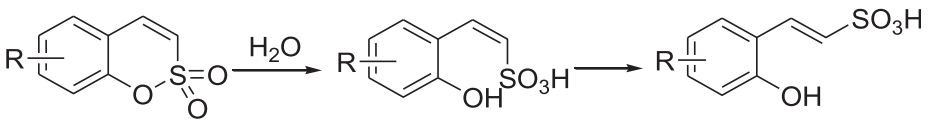
The sulfocoumarin is converted into 2-hydroxyphenyl-vinylsulfonic acid by hydrolysis of the intramolecular sulfonic acid ester mediated by esterase CA, and then isomerized to obtain *trans*-vinylsulfonic acid. For (E)-2-(5-bromo-2-hydroxyphenyl) ethene-1-sulfonic acid (Fig. 3), the OH moiety in ortho to the ethenylsufonate group participates in a bifurcated hydrogen bond with the hydroxyl of Thr200 and through a bridging water molecule, with the carbonyl oxygen of Pro201. hCA IX and XII have larger active sites than hCA I and II, which may lead to the selective inhibition of CA isoforms by sulfocoumarin (Alterio et al., 2012; Nocentini et al., 2018; Supuran, 2016).

Table 1 Chemical structures of compounds **A1-A44** and their inhibitory activities against hCA.



Compd	R^1	R^2	K_i (nM)					Ref.
			hCA I	hCA II	hCA VA	hCA IX	hCA XII	
A1	4-F-phenyl	H	*nd*	*nd*	_	95.3	4.6	(Grandane et al., 2015b)
A2	3-F-phenyl	H	*nd*	*nd*	_	10.3	9.4	
A3	4-tBu-phenyl	H	*nd*	*nd*	_	9.1	6.8	
A4	4-CF_3-phenyl	H	*nd*	*nd*	_	29.7	3.7	
A5	3-CF_3-phenyl	H	*nd*	*nd*	_	9.8	6.1	
A6	4-CH_3OOC-phenyl	H	*nd*	*nd*	_	9.0	9.1	
A7	–NO_2	H	*nd*	*nd*	_	3770	3160	(Tars et al., 2012 Nocentini et al., 2018)
A8	–NH_2	H	6780	8890	_	46	23	
A9	Cl	H	*nd*	*nd*	_	136.3	89.5	(Nocentini et al., 2018)
A10	H	–NO_2	*nd*	*nd*	_	37.0	81.7	
A11	H	–NH_2	*nd*	*nd*	_	33.5	38.4	
A12	H	-Cl	*nd*	*nd*	_	33.7	60.9	
A13	–OCH_2CH_2OH	H	*nd*	*nd*	60	26.8	10.4	(Tanc et al., 2015)
A14	-OMe	H	*nd*	*nd*	*nd*	42.1	10.9	(Grandane et al., 2015a)
A15	–CN	H	*nd*	*nd*	*nd*	33.8	26.6	
A16	H	BnO	*nd*	2.5	835	*nd*	*nd*	(Tanc et al., 2013)
A17	H	4-Cl-phenylacetyloxyl	*nd*	2.6	3910	*nd*	*nd*	
A18	H	2-Br-phenylacetyloxyl	*nd*	1.9	7060	*nd*	*nd*	
A19	cyclopropyl	H	*nd*	*nd*	_	60.6	5.9	(Grandane et al., 2014)
A20	3-Cl-phenyl	H	*nd*	*nd*	_	93.1	7.6	
A21	4-Cl-phenyl	H	*nd*	*nd*	_	7.8	17.7	
A22	2-NH_2-phenyl	H	*nd*	*nd*	_	7.9	6.3	
A23	3-NH_2-phenyl	H	*nd*	*nd*	_	875	9.2	
A24	4-CF_3-phenyl	H	*nd*	*nd*	_	136	5.5	
A25	4-F-phenyl	H	*nd*	*nd*	_	531	6.7	
A26	Ph	H	6860	7760	_	29	32	(Tars et al., 2012)
A27	Et_2NCH_2-	H	8110	9370	_	25	7	
A28	4-CF_3O-phenyl	H	8430	9640	_	74	14	
A29	H	2-NH_2-phenyl	*nd*	*nd*	_	9.5	9.2	(Grandane et al., 2014)
A30	H	3-MeO-phenyl	*nd*	*nd*	_	9.1	7.6	
A31	H	4-MeO-phenyl	*nd*	*nd*	_	8.3	44.0	
A32	H	3-CF_3-phenyl	*nd*	*nd*	_	9.6	8.9	
A33	H	4-CF_3-phenyl	*nd*	*nd*	_	7.2	30.1	
A34	H	4-F-phenyl	*nd*	*nd*	_	8.3	7.8	
A35	H	3-Cl-phenyl	*nd*	*nd*	_	8.8	9.4	
A36	H	4-Cl-phenyl	*nd*	*nd*	_	9.2	31.2	
A37	4-(4-CF_3O-phenyl) −1,2,3-triazole	H	*nd*	5770	_	340	1720	(Grandane et al., 2015b)
A38	4-(2- NH_2-phenyl) −1,2,3-triazole	H	*nd*	*nd*	_	460	2320	
A39	–NO_2	H	*nd*	*nd*	_	27	640	
A40	H	–OCH_3	*nd*	2.4	91	*nd*	*nd*	(Tanc et al., 2013)
A41	H	4-Cl-phenylacetyloxyl	*nd*	2.2	206	*nd*	*nd*	
A42	H	2-Br-phenylacetyloxyl	*nd*	3.4	141	*nd*	*nd*	
A43	Bn	H	*nd*	*nd*	_	81.3	4.0	(Grandane et al., 2015a)
A44	2-furyl	H	*nd*	*nd*	_	33.0	6.2	

"*nd*" represents the activity to be measured and the activity is poor (K_i > 10 μM).
"-" represents the inhibitor activity has not been measured.



3.1.2. SAR analysis

Table 1 shows the structure and activity of inhibitors containing sultone scaffold, and discuss their structure–activity relationship as shown in Fig. 4.

6-Substituted sultones:

(i) 6-Arylsultones are potent and selective inhibitors of tumor-associated hCA IX and XII. The size and position of substituted phenyl significantly affect the inhibitory activity, slightly larger groups may enhance the hCA IX inhibitory activity (*t*-Bu in **A3**, COOMe in **A6**), *m*-substituted phenyl is more active than the *p*-substituted (**A5** > **A4**, **A2** > **A1**). Compounds with 6-aryl are highly effective hCA XII inhibitors (Grandane et al., 2015b).

(ii) Compounds with 1,2,3-triazole scaffold are effective hCA IX and hCA XII inhibitors. 5-Substituted 1,2,3-triazole is better hCA IX inhibitor than 4-substituted one (**A33** > **A24**, **A34** > **A25**, **A35** > **A20**), in which, most substitution patterns, both aliphatic and aromatic R groups, lead to highly effective hCA XII inhibitors (Grandane et al., 2014).

(iii) 6-carboxamido-substituted sultones are selective and effective inhibitor of hCA IX and XII. The introduction of carbon unit spacers or heterocyclic five-membered rings (**A43**, **A44**) reduced hCA IX inhibitory effect (K_i = 81.3, 33.0 nM). All 6-amide-substituted sultones exhibited high affinity for hCA XII (K_i = 2.1–8.7 nM), which was higher than that of 6-methoxy (**A14**) and 6-cyano (**A15**) sultones (K_i = 10.9, 26.6 nM) (Grandane et al., 2015a).

(iv) Some of 4-substituted 1,2,3-triazoles have moderate hCA I and hCA II inhibition, effective hCA IX inhibition, and low nanomolar hCA XII inhibition (**A26-A28**) (Tars et al., 2012).

(v) 6-Hydroxyethoxylsultone (**A13**) is a potent inhibitor of hCA VA (K_i = 60 nM), and excellent inhibitory activity on tumor-associated enzymes hCA IX and XII (K_i = 26.8, 10.4 nM) (Grandane et al., 2012; Tanc et al., 2015).

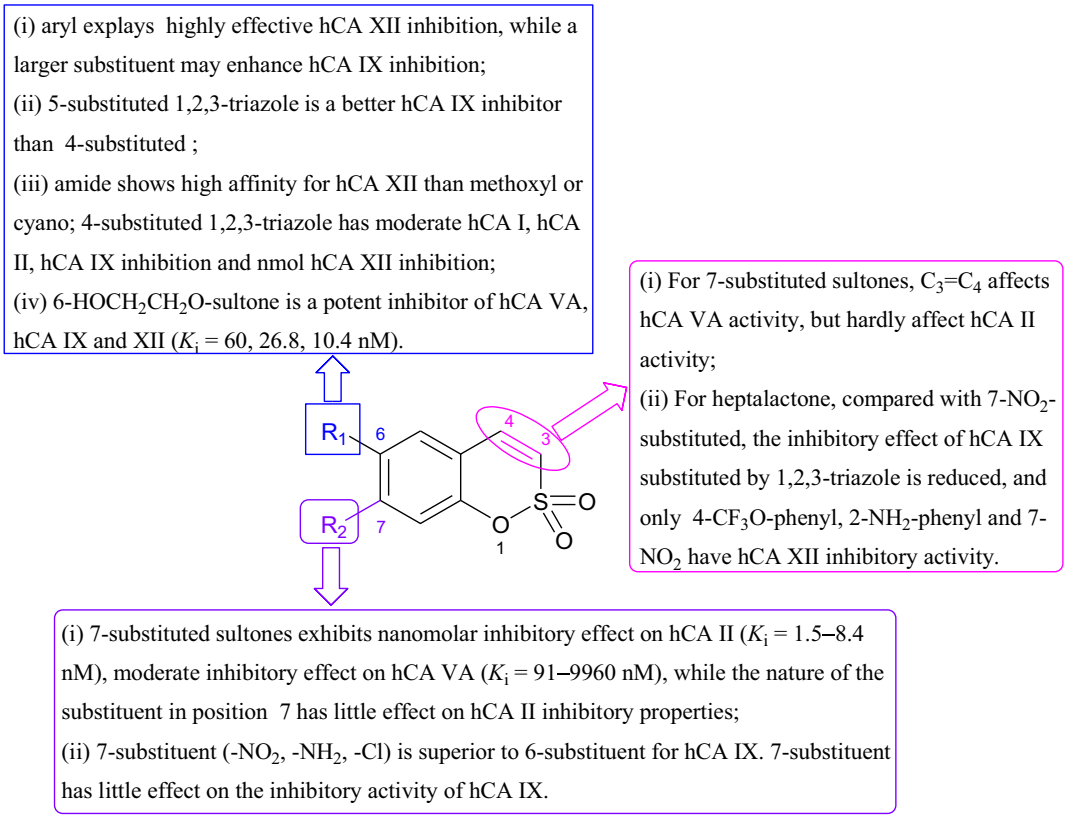


Fig. 4 SARs of the sultone-based hCA inhibitors.

7-Substituted sultones:

(i) 7-substituted sultones and 3,4-dihydrosultones showed low nanomolar inhibitory effect on hCA II (K_i = 1.5–8.4 nM), moderate inhibitory effect on hCA VA (K_i = 91–9960 nM). The changes of substituents and the C3 = C4 bond have no significant effect on the inhibition of hCA II (**A41** ≈ **A42** ≈ **A17** ≈ **A18**). Compounds with methoxyl (**A40**), 4-chlorophenylacetyloxyl (**A41**) and 2-bromophenylacetyloxyl (**A42**) for 3,4-dihydrosulfocoumarin skeleton have good hCA VA inhibitory activity (K_i = 91–206 nM) (Tanc et al., 2013).
(ii) For heptasultones: only **A37** is a moderate hCA II inhibitor (K_i = 5.77 μM). **A39** (7-NO_2) has the best hCA IX inhibitory activity (K_i = 27 nM), and the 7-substituted 1,2,3-triazole does not increase hCA IX inhibitory activity (**A39** > **A37** > **A38**). 7-NO_2 (**A39**), 1,2,3-triazole with 4-trifluoromethoxyphenyl (**A37**) and 2-aminophenyl (**A38**) have hCA XII inhibitory activity (K_i = 0.64–2.32 μM) (Pustenko et al., 2017).
(iii) 7-Substituent (–NO_2, –NH_2, -Cl) is superior to 6-substituent for hCA IX (**A10** > **A7**, **A11** > **A8**, **A12** > **A9**). This 7-substituent has little effect on the inhibitory activity of hCA IX (**A10** ≈ **A11** ≈ **A12**) (Nocentini et al., 2018).

3.2. Anti-HIV activity

HIV is the causative agent of acquired immunodeficiency syndrome (AIDS), which has caused significant damage worldwide over the past 40 years. Side effects and resistance to long-term chemotherapy may be the most important factor in the failure of treating and eradicating HIV infection (Barre-Sinoussi et al., 1983; Nanfack et al., 2017; Trivedi et al., 2020). To date, 20 drugs have been approved for the treatment of AIDS. However, viral rebound during therapy, the emergence of drug-resistant and the need for long-term treatment modalities are the main causes for the failure of current antiretroviral therapy. There is still a need for the development of new drugs with less toxic, active against growing drug-resistant or novel targets in the viral life cycle. Eleven of anti-HIV drugs target the reverse transcriptase (RT). The non-nucleoside RT inhibitors (NNRTIs), (2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl)-3′-spiro-5′'-(4′'-amino-1′',2′'-oxathiole-2′',2′'-dioxide) nucleosides (TSAO) derivatives, are an unusual class of compounds that exert their unique selectivity for HIV-1 through a specific interaction with the p51 subunit of HIV-1 RT (Camarasa et al., 2005).

TSAO compounds are the only NNRTIs for which amino acids at both HIV-1 RT subunits (p66 and p51) are needed for optimal interaction with the enzyme. In fact, it has been demonstrated that the heterodimeric enzyme shows a reduced DNA binding ability in the presence of the 5-fold molar excess of TSAO-T. TSAO-e^{3}T can induce the dissociation of RT into inactive monomers under certain conditions (Velazquez et al., 1992). SAR in Fig. 5 showed that the 3′-spironucleosides with *S* stereospecificity (**B1**-**B3**) didn't have anti-HIV-1 activity, while those with *R* configuration (**B4**-**B6**) and *tert*-butyldimethylsilyl (TBDMS) at C-5′ and C-2′ had significant anti-HIV-1 activity. The replacement of 2′-TBDMS group led to reduce twice to 20-fold anti-HIV-1 activity while that of the 5′-position showed inactivity. The base part of TSAO molecule is structurally less stringent, which plays a modulatory role in its activity/cytoxicity (Camarasa et al., 1992; Perez-Perez et al., 1992; Rodríguez-Barrios et al., 2001).

As first small non-peptide molecule, TSAO compounds interfere with the HIV-1 RT dimerization process (Bonache et al., 2011; De-Castro et al., 2011; De-Castro and Camarasa, 2018). As shown in Fig. 6, crystal analysis of TSAO-T into HIV-1 RT showed that TSAO-T binding morphology is similar to the "dragon" configuration, in which the thymine base, ribose ring and helix are similar to the head, body and tail, respectively. The "head" thymidine is between the aromatic side chains of Tyr188 and Phe227. One sulfonyloxy group of the sultone group forms a hydrogen bond with Lys103, and the other S = O group interacts with RT through water. As two wings of dragon NNRTI of 2′ and 5′ two TBDMS moieties, 5′-TBDMS (I wing) part interacts with Trp229, Pro95, Tyr183 and Leu100, while 2′-TBDMS (II wing) part interacts with Tyr318 (Das et al., 2011).

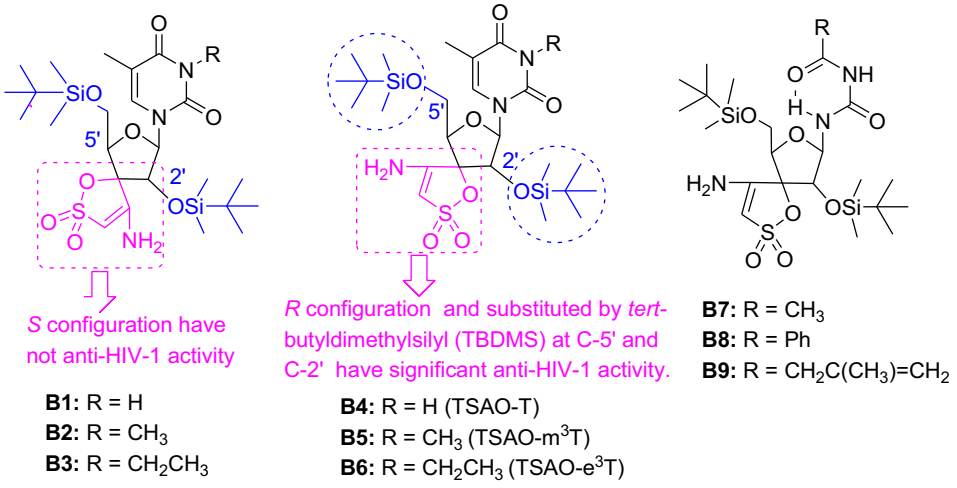


Fig. 5 SARs of base-modified TSAO compounds.

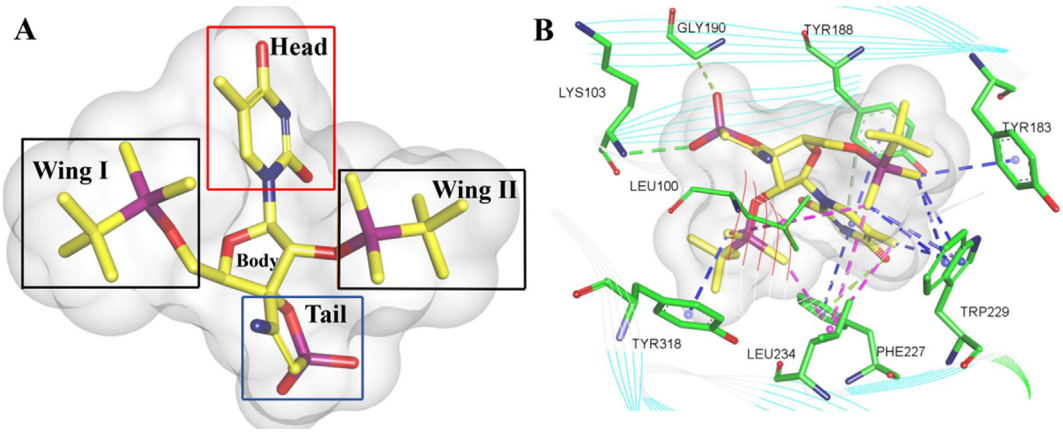


Fig. 6 3D conformations of compound **B4** (**A**) (TSAO-T) docked in HIV-1 RT (PDB: 3QO9) (Das et al., 2011). Discovery Studio Client v18.1.0 were used to present a 3D images.

Replacement of the thymine base of TSAO-T by other pyrimidines, purines or 1,2,4-substituted triazoles didn't significantly influence the activity or toxicity, for example, the abasic TSAO analogue **B9** showed only moderate loss of activity, which may be due to the energy penalty involved in breaking the intramolecular H-bond in order to adopt a suitable conformation for binding into the enzyme (Camarasa et al., 2005).

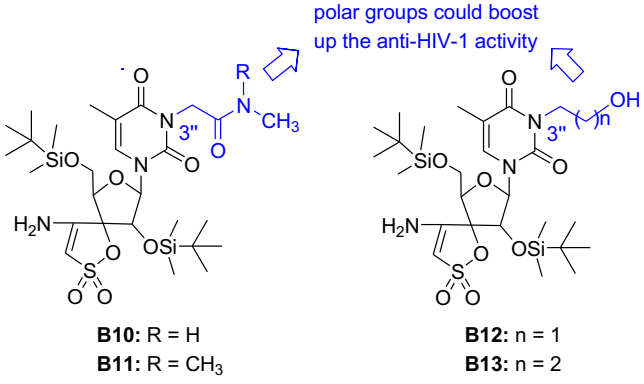


Fig. 7 Structures of TSAO with polar groups at the N-3 position of thymine.

Further modifications at the N-3 position of thymine (introducing alkyl, alkenyl and alkynyl; polar groups such as acids, amides, alcohols and amines; lipophilic groups; aromatic groups; amino acids and others) led to interesting results. As shown in Fig. 7, some compounds exhibited attenuated cytotoxicity and higher selectivity indices (SI = CC_{50}/EC_{50}), such as the SIs of compounds **B10** and **B11** increased two orders of magnitude (200 and 12500, respectively), that of compound **B13** increased twice to 6-fold. Moreover, several compounds with polar groups exhibited more effective in inhibiting/disrupting dimerization of HIV-1 RT than TSAO-T (Bonache et al., 2005; Bonache et al., 2008; Camarasa et al., 2004; Sluis-Cremer et al., 2006).

The 4′′-amino group at the spiro moiety was substituted by different carbonyl functionalities (including keto, carboxylic acid, ester, amide and urea groups), which may interfere with hydrogen bond formation of the residue Lys138 in TSAO-resistant HIV-1 strains (De-Castro et al., 2005). Surprisingly, some compounds in Fig. 8 were firstly observed activity against HCMV replication at sub-toxic concentrations. In particular, compound **B21** represents the first TSAO derivative with dual anti-HIV-1 and HCMV activity, which is important because HCMV infection is common for AID patients. Moreover, compounds **B17-B19** only gained anti-HCMV activity,

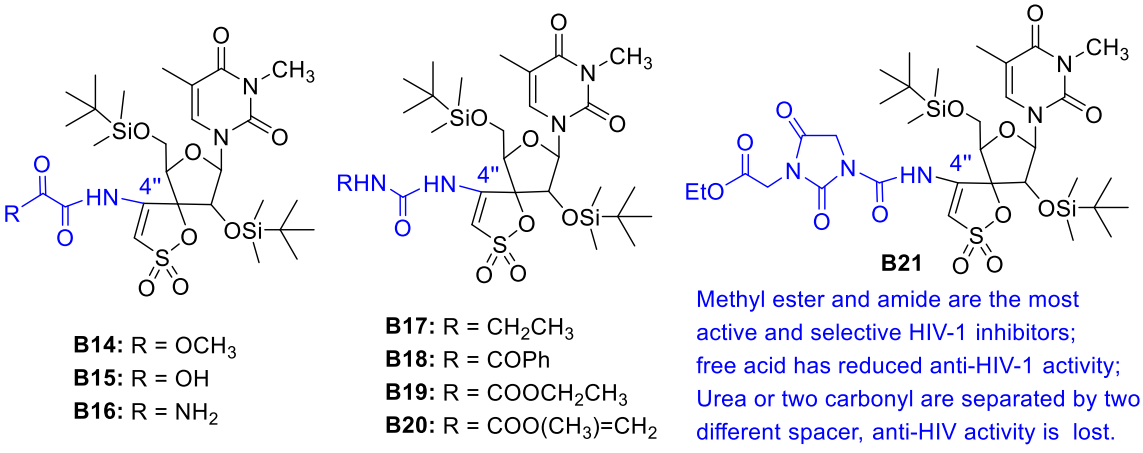


Fig. 8 Potent anti-HIV-1 and HCMV activity of TSAO derivatives **B14-B21.**

resulting in the first TSAO molecules specific for HCMV replication.

The 3′′-postion of spiro moiety was substituted by different functional groups (halogen, alkenyl, alkynyl, allyl, aromatic and heteroaromatic groups), which may give additional interactions with residues adjacent to Glu138 of p51 subunit (Lobatón et al., 2002). Amongst them, the 4′′-amino group of the sultone was maintained to allow the crucial interaction of TSAO derivatives with residue Glu138 of HIV-1 RT p51 subunit. As shown in Fig. 9, the brief SAR of compounds **B22-B27** on HIV-1 and HIV-2 replication activities was discussed, and the inhibitory activity of B10-B27 against HIV is shown in Table 2.

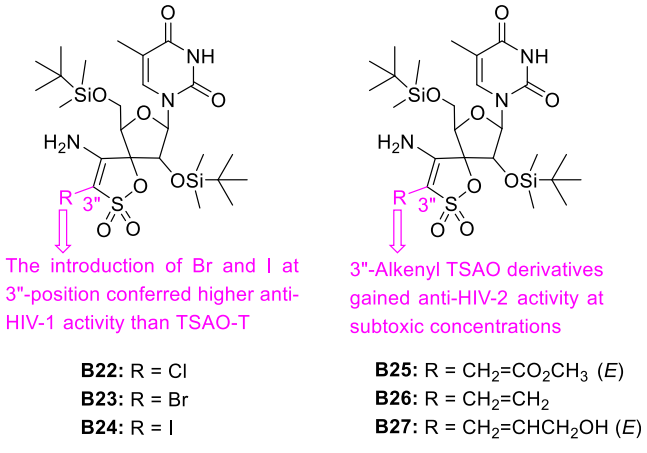


Fig. 9 Potent anti-HIV-1 and anti-HIV-2 activity of TSAO derivatives **B22-B27**.

Among the human immunodeficiency virus (HIV) reverse transcriptase (RT) inhibitors, the so called nonnucleoside RT inhibitors (NNRTIs) have gained a definitive place in the treatment of HIV infections in combination with nucleoside analogue RT inhibitors (NRTIs) and HIV protease inhibitors (PIs). The virus can be markedly suppressed for a relatively long period of time when exposed to multiple drug combination therapy (highly active antiretroviral therapy, HAART). TSAO derivatives are a peculiar group of highly functionalized nucleosides that belong to the so-called NNRTIs. They exert their unique selectivity for HIV-1 through a specific interaction with the p51 subunit of HIV-1 RT. They are the first small molecules that seem to interfere with the dimerization process of the enzyme. This review covers the work carried out with this unique class of specific inhibitors of HIV-1 reverse transcriptase, including SAR studies, its mechanism of action, resistance studies, model of interaction with the enzyme, etc.

Emergence of drug-resistant viral strains is one of the major milestones and the main cause for the failure of antiretroviral therapy. Combination of different anti-HIV agents has become the standard clinical practice to prevent emergence of virus-drug resistance. The Glu138Lys RT mutant virus had the most marked resistance to TSAOs, followed by the Glu138Gln, Glu138Phe, Glu138Gly, Glu138Tyr, and Glu138Ala virus mutants. In the mutant Glu138Lys RT HIV-1 strains, virus replication can be completely inhibited by NNRTIs (i.e., TIBO, BHAP, nevirapine). TSAO derivatives have been used in several double and triple drug combination studies with both NNRTIs. Individually used 3TC, TSAO-m^3T and the thiocarboxanilide UC10 rapidly led to the emergence of drug-resistant HIV-1 mutants (Glu138Lys for TSAO-m^3T, Met184Val for 3TC, and Lys103Thr/Asn for UC10). When

Table 2 Chemical structures of compounds **B10-B27** and their anti-HIV activities.

Compd	EC_{50} (μM)				SI	IC_{50} (μM)	EC_{50} (μM)		Ref.
	MT-4		CEM		CEM		HCMV (AD-169)	HCMV (Davis)	
	HIV-1	HIV-2	HIV-1	HIV-2		HIV-1 RT	-	-	-
B10	0.03	>250	0.02	>50	>12500	3.1	–	–	(Bonache et al., 2005)
B11	0.04	>250	0.02	>250	12,250	3.5	–	–	
B12	0.06	>10	0.04	>10	282	3.1	–	–	
B13	0.03	>2	0.01	>2	386	3.0	–	–	
B14	0.08	> 4	0.06	>4	–	–	253	179	(De-Castro et al., 2005)
B15	1.30	> 10	0.2	>50	–	–	>80	36	
B16	0.0057	> 2	0.7	>10	–	–	6.5	6.5	
B17	>2	>2	>2	> 2	–	–	1.8	2.0	
B18	>2	>10	>2	>2	–	–	1.2	0.8	
B19	>2	>2	>2	>2	–	–	2.3	1.8	
B20	>0.8	>0.8	>0.8	>0.8	–	–	>20	>4	
B21	0.88	>2	0.24	>2	–	–	0.29	0.32	
B22	> 10	>10	> 10	> 10	–	–	–	–	(Lobatón et al., 2002)
B23	0.93	>10	0.85	>10	–	–	–	–	
B24	0.12	>2	0.06	>2	–	–	–	–	
B25	3.7	9.9	3.0	7.3	–	–	–	–	
B26	3.2	3.3	4.0	4.0	–	–	–	–	
B27	6.6	5.4	> 2	1.2	–	–	–	–	
TSAO-T	0.06	>20	0.06	>20	200	–	–	–	(Bonache et al., 2005)
TSAO-m^3T	0.06	>50	0.04	>250	2875	3.1	–	–	

"-" represents the inhibitor activity has not been measured.

3TC was combined with either TSAO-m^{3}T, UC10 or UC42, emergence of drug-resistant virus was markedly delayed or even fully suppressed (Balzarini et al., 1993; Balzarini et al., 1995; Balzarini et al., 1996; Perez-Perez et al., 1992).

3.3. Anti-HCMV and anti-VZV activity

Human cytomegalovirus (HCMV) belongs to a widely distributed member of the herpesvirus family that generally remains unnoticed in the human body, but can be severely pathogenic in immunocompromised patients (Kenneson and Cannon, 2007; Lilleri and Gerna, 2016; Plotkin and Boppana, 2019). HCMV is found to lead to a variety of serious diseases (mainly pneumonia and gastroenteritis) that can severely cause to death (Boppana and Britt, 1995; Perotti and Perez, 2019; Sandhu and Buchkovich, 2020), and is the main viral cause of congenital diseases affecting children by causing deafness, learning disabilities, and mental retardation (Gupta et al., 2014). In despite of tremendous efforts in vaccine and treatment, HCMV infections still threaten the lives of individuals with poor immune function and newborns, but currently available compounds for HCMV have poor drug-like properties such as oral bioavailability, toxicity, and so on. Therefore, it is needed for anti-HCMV compounds with effective safety and novel mechanisms of action. 4′′-Benzoylurea-TSAO derivatives showed pronounced antiviral activity against replication of HCMV at micromolar concentrations (0.29–2.0 μM) that is below the toxicity threshold. In particular, compound **C1** showed the highest anti-HCMV activity. The brief SAR was discussed in Fig. 10 (De-Castro et al., 2007; De-Castro et al., 2008).

Herpesvirus infections are the most frequent causes of viral infections in immunocompetent as well as in immunocompromised patients. Several 4-benzyloxy-γ-sultone derivatives were found to have a selective inhibitory activity against HCMV and Varicella zoster virus (VZV) replication *in vitro*. These novel compounds don't show cross-resistance against mutant drug-resistant HCMV strains, pointing to a novel antiviral mechanism. The brief SAR was discussed in Fig. 11 (De-Castro et al., 2009).

3.4. Anti-BVDV activity

Hepatitis C virus (HCV) is a major health problem worldwide. The most common complications are fibrosis (20–30%) and cirrhosis (10–20%), in which 1–4% has developed hepatocellular carcinoma and 350,000 people each year die from HCV-related advanced liver disease (Alkharsah et al., 2020; Darweesh et al., 2015; Lapa et al., 2019; Rau et al., 2013). There is an urgent need for efficient and selective HCV replication inhibitors. HCV and BVDV belong to the Flavivirus genus with similar genomic structure and replication pathways. BVDV infection is able to affect most of the organ system, which acute infection may lead to peripheral blood lymphocyte reduction, apoptosis and immunosuppression. Antiviral agents targeting BVDV replication may inhibit HCV replication. As shown in Fig. 12, novel δ-sultones containing γ-lactone may be developed as antiviral agents against HCV infection (Lanyon et al., 2014; Liu et al., 2018; Tabarrini et al., 2006; Villalba et al., 2016; Xu et al., 2014).

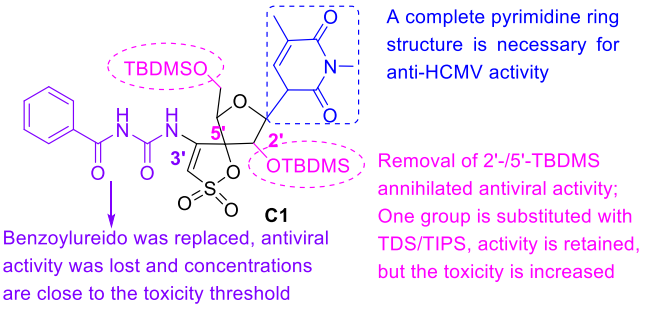


Fig. 10 Anti-HCMV activity of 4′′-benzoylurea-TSAO derivatives.

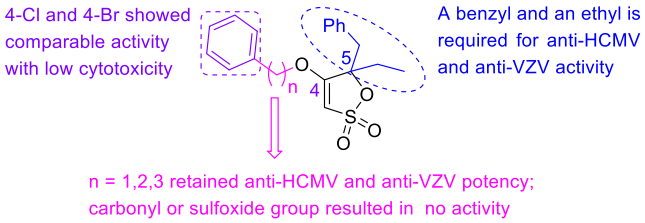


Fig. 11 Anti-HCMV and anti-VZV activity of 4-benzyloxy-γ-sultone derivatives.

3.5. Selective BuChE inhibitors

Alzheimer's disease (AD) is a chronic neurodegenerative disease. The most effective strategy of improving the symptoms of AD is to use cholinesterase (ChE), acetylcholinesterase (AChE) and butyrylcholine (BuChE), inhibitors to restore acetylcholine (ACh) levels (Kumar et al., 2018; Liu et al., 2017; Zhou et al., 2016). Clinical studies have shown that BuChE inhibition in cerebrospinal fluid is correlated with cognitive function in AD patients. Selective BuChE inhibitors infused into the cerebral cortex of rats can increase extracellular ACh levels by 15 times, and no choline-like adverse reactions have been found. In advanced AD patients, BuChE took over the role of AChE, reaching almost 80% of the overall ChE activity (Contestabile, 2011). Therefore, selective BuChE inhibitors have great potential to develop drug candidates.

Recent, a class of novel δ-sultone-fused pyrazole scaffold was discovered as highly selective sub-micromolar BuChE inhibitors, which is an effective selective BuChE inhibitor and has non-toxic, lipophilic and significant neuroprotective activity. Moreover, this scaffold showed reversible, mixed-type BuChE inhibitory activity, which may be used to improve disease symptoms in progressive AD. Further research found

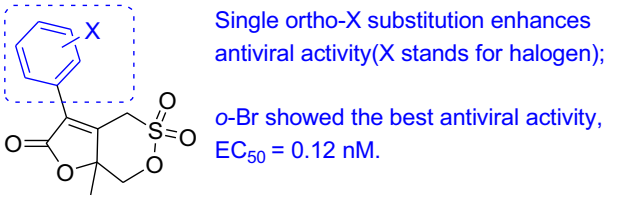


Fig. 12 Anti-BVDV activity of δ-sultone.

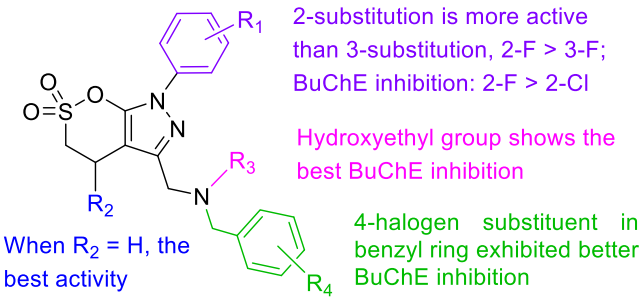


Fig. 13 SARs of *δ*-sultones as BuChE inhibitors.

that there are two flexible amino acids (Leu286 and Val288) in the acyl pocket of hBuChE compared to hAChE, which allows binding of bulkier ligands. Simultaneously, a ChE inhibitor (reversible or pseudo-irreversible) contains a basic nitrogen atom crucial for the interaction with the ChE binding site. Therefore, the structure-based optimization of *δ*-sultone-fused pyrazoles was conducted to further improve the potency and selectivity of BuChE inhibitor (Zhang et al., 2020). Fig. 13 showed SAR of *δ*-sultone-fused pyrazoles as BuChE inhibitors.

The amino acid sequence of AChE and BuChE is 65% homologous, and its protein structure contains a catalytic active site (CAS), a deep canyon and a peripheral anion site (PAS). The two aromatic residues of hAChE burst into the canyon to occupy the valley space, while the replacement of hBuChE with smaller residues provided a wider space, allowing larger substrates to bind and be hydrolyzed (Brus et al., 2014; Cavallaro et al., 2018; Chen et al., 2018). The different structural characteristics of the two enzymes lead to substrate specificity: AChE is more selective for small acetylcholine molecules, and BuChE has greater affinity for various neuroactive peptides (Chierrito et al., 2018; Košak et al., 2018; Panek et al., 2018). Molecular docking (Fig. 14) showed that compound **E1** is nicely bound into hBuChE *via* a strong hydrogen bond interaction between the hydroxyl unit with Asn68, *p*–π interaction between the benzyl ring with Leu286, Val288 and Phe329 in the acyl sub-pocket, and a π–anion interaction between the S atom of sultone ring with His438 in the hydrolysis sub-pocket (Zhang et al., 2020).

3.6. *β-Receptor antagonists*

As shown in Figs. 15, 8-(3-amino-2-hydroxypropoxy)benzoxa thiin was developed as an ideal remedy for cardiovescular disorders such as arrhythmie, angina pectoris, hypertension, and so on. Compounds with *N*-alkyl or an aralkyl substitution showed clearly its effect as a *β*-blocker which may be applied to angina pectoris and hypertension in addition to arrhythmia, wherein R^1 represents hydrogen atom or a lower alkyl group, and R^2 represents a lower alkyl group or an aralkyl group. Among them, N-t-Bu substitution substitution showed excellent anti-arrhythmic effect with 96.3% of rat brain synaptosome membrane β-receptor inhibitory effect and 0.03 mg/kg (ED50) activity at 1 μM, while toxicity and side-effects are very low (Hori, 1985).

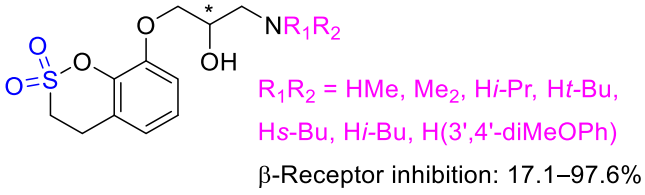


Fig. 15 *δ*-Sultones as *β*-receptor inhibitors.

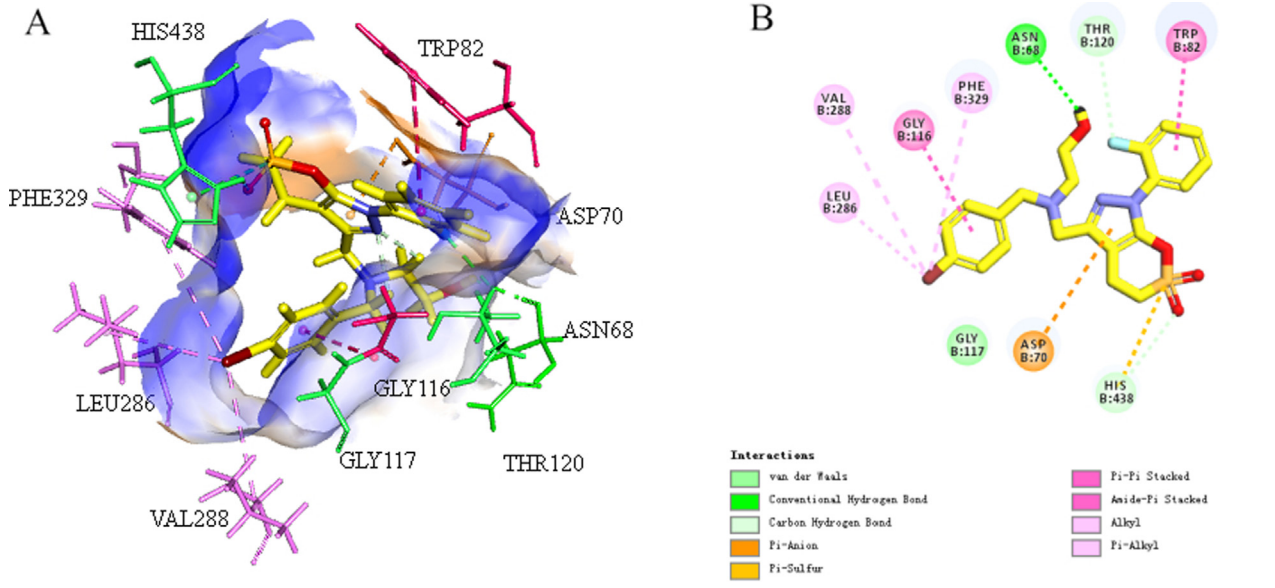


Fig. 14 (**A**) 3D mode of the pocket surface of compound **E1** with receptor hBuChE (PDB ID: 5LKR), (**B**) 2D mode of the interaction of active compound with receptor hBuChE (conventional H bond and C–H bond, halogen, π–anion, alkyl, and π–alkyl are represented by green, light green, brown, pink and light pink lines, respectively). Discovery Studio Client v18.1.0 were used to present images.

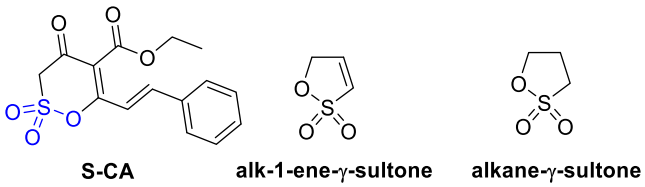


Fig. 16 The anti-angiogenesis and skin sensitization, carcinogenic effects of δ-sultone.

3.7. Anti-angiogenic effect and skin sensitization, carcinogenic effect

The angiogenesis activity of S-CA was evaluated by the chick chorioallantoic membrane (CAM) model. As shown in Fig. 16, In vivo a murine sarcoma S180 model, reduction of the tumor weight and tumor HE staining regions demonstrated that S-CA (iv, 10 mg/kg) had potent inhibition effects (44.7% inhibitory rate in S180 mice) and low acute toxicity (LD50: 25.6 mg/kg) (Li et al., 2015). Alk-1-ene-γ-sultone has been proven to be a particularly strong skin sensitizer, while alkane-γ-sulfolactone has been found to be a medium sensitizer (Fig. 16). In rats of either weekly or a single intravenous injecting 1,3-propanelactone, tumors were observed at various tissues including the brain and nervous system. Skin exposure to 1,3-propane sultone can cause tumors in the skin and lymph reticulum of bisexual mice, while subcutaneous injection can cause lung cancer (regenerative adenocarcinoma) in male rats (Meschkat et al., 2001).

Sultone stents show a wide range of pharmacological activities, but reports on preclinical trials of sultone are rarely a matter to be solved. Future medicinal chemists should increase the relevance of sultone pharmacokinetic studies to provide a theoretical basis for the subsequent application of sultone structured drugs as clinical candidate compounds. CA inhibitors are used to treat different diseases. Based on the difference of CA isoforms, rational drug design can be used to improve selectivity and activity of CA inhibitors. SARs of TSAO as anti-HIV agents can be used to optimize the base part of TSAO, which plays a modulatory role in its activity/cytoxicity. In the future, these compounds with benign activity and a clear mechanism of action can be regarded as valuable candidate prototypes for the design and development of candidate drugs. It is interesting to explore the role of sultones in the field of medicine by studying the SAR, the toxicity level of active compounds and their mechanism of action, as well as discussing those binding conformations in the active site.

4. Conclusion

This review aims to provide a wide range of information on sultone scaffolds, the unique sultone scaffold has multiple pharmacological activities in medicinal chemistry. In this review, we discuss in detail various strategies for the simple and effective synthesis of sultone derivatives from readily available raw materials. In addition, sultone-based drugs have great potential therapeutic value for a variety of drug targets, such as anti-CA, anti-viral, anti-tumor, et al. We have disclosed present role of diverse sultone in the field of medicinal chemistry by discussing insights of the SAR studies, their mechanism action and binding conformation of these heterocycles with various targets. Additionally, we hope that SARs can be further used for structural optimization. Target-based sultone synthesis should be designed to obtain novel compounds with target selectivity. Synthetic chemists can develop the methods of batch synthesis of sultones to build up sultone compound libraries find potent lead compounds containing sultone in the future.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgments

Financial support was provided by the Natural Science Foundation of Anhui Province (2008085MH272) and Natural Science Fundation of Anhui Provincial Department of Education (KJ2019ZD21) and Anhui Provincial Training Programs of Innovation and Entrepreneurship for Undergraduates (20810366046).

Notes.

The authors declare no competing financial interest.

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