A Novel Class of Cyclic β-Dicarbonyl Leaving Groups and Their Use in the Design of Benzisothiazolone Human Leukocyte Elastase Inhibitors

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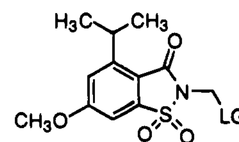
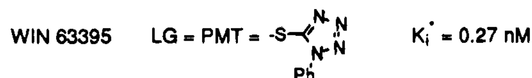
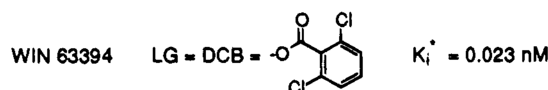
Human leukocyte elastase (HLE) has been proposed to be a primary mediator of pulmonary emphysema, and inhibitors of this enzyme should be effective in the treatment of emphysema and other pulmonary diseases. We have discovered a novel class of alicyclic and heterocyclic leaving groups which share one common structural feature, a cyclic β-dicarbonyl. This design concept for leaving groups has not been previously reported. A structure–activity relationship has been developed and the concept extended to several types of alicyclic and heterocyclic β-dicarbonyl systems. This work led to the identification of a potent (K_i^* of 0.066 nM) and tissue stable (*in vitro*: blood $t_{1/2}$ = 160 min, liver $t_{1/2}$ > 240 min) benzisothiazolone HLE inhibitor, WIN 65936 (**13b**).

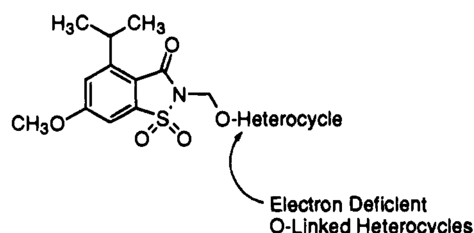
Human leukocyte elastase (HLE) has been proposed to be a primary mediator of pulmonary emphysema.[1] In emphysematous patients neutrophils at the inflammation sites release a mixture of proteases, including HLE, cathepsin G, and collagenase. The endogenous regulatory proteins, e.g., α_1-protease inhibitor, normally inactivate free HLE that may be present in the lung. An imbalance between HLE and the endogenous regulatory protein is postulated to occur in emphysema, where the deficiency of the α_1-protease inhibitor leads to elastin connective tissue destruction in the lung by HLE. HLE inhibitors are expected to be efficacious in emphysema and other pulmonary inflammatory disease where HLE is thought to play a role, such as cystic fibrosis, chronic bronchitis, and adult respiratory distress syndrome.

We have identified orally bioavailable inhibitors of human leukocyte elastase (HLE) from the benzisothiazolone class of mechanism-based inactivators. In our early SAR studies the phenylmercaptotetrazole (PMT) leaving group was used; however, we later found that inhibitors with the 2,6-dichlorobenzoate (DCB) leaving group were more potent inhibitors while exhibiting *in vitro* metabolic stability similar to the PMT leaving group inhibitors.[2-4] WIN 63395 and WIN 63394 are the most potent and tissue stable HLE inhibitors in the PMT and DCB classes of inhibitors. Although the DCB inhibitors WIN 64733 and 63759 had oral bioavailability in the range of 46%–67%,[5] these compounds are extensively metabolized, predominantly to the unsubstituted benzisothiazolone **1** and the DCB leaving group. For example, in dogs that were administered 30 mg/kg p.o. of WIN 63759, a maximum concentration in plasma (C_{max}) of 2.6 μg/mL for the parent WIN 63759 was observed, while a C_{max} of 27 μg/mL of the benzisothiazolone **1** was observed.[6] Our goal was to determine what other novel leaving groups could be used to retain inhibitor potency, while compounds with even better *in vitro* metabolic stability and improved *in vivo* properties were found, i.e., improved oral bioavailability or lower clearance. Our approach was to prepare compounds with leaving groups that were electron deficient heterocycles and that were oxygen-linked to the *N*-methyl of the benzisothiazolone. An initial lead was the 3-hydroxy-4-pyrone compound **6a** that had an apparent binding constant (K_i^*) of 100 nM. It occurred to us that if the oxygen was linked to a pyrone at the β-position, then the leaving group ability of the heterocycle would increase dramatically, since the leaving group would be a stabilized β-dicarbonyl. Indeed, the next analog prepared and tested was the 4-hydroxy-2-pyrone **6b** that was O-linked at the β-position to the benzisothiazolone. Analog **6b** (K_i^* = 0.25 nM) was *400 times more potent*









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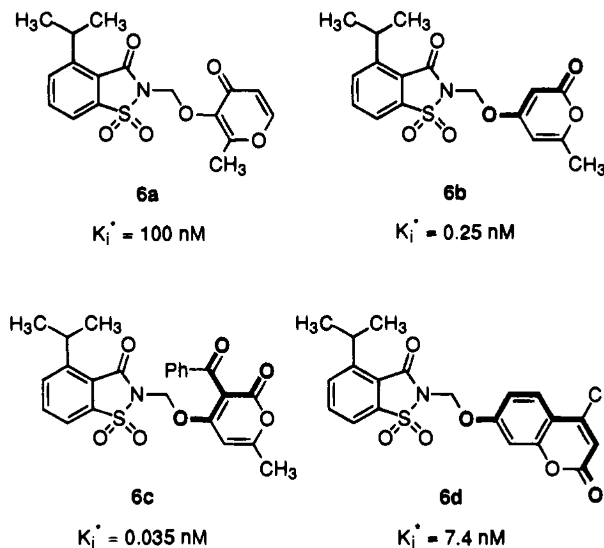


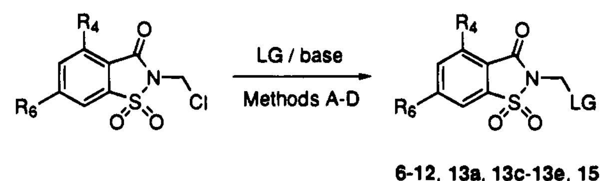
Table 1. Method of Synthesis, Yields, and Physical Properties

compd	% yield (method)[a]	mp, °C	recrystn solvent[b]	formula[c]
6a	48 (A)[d]	136.5−138	EA−C	$C_{17}H_{17}NO_6S$
6b	58 (A)[d]	188−189.5	EA−H	$C_{17}H_{17}NO_6S$
6c	13 (A)[d]	204−207	Et	$C_{24}H_{21}NO_7S$
6d	35 (A)[d]	213−215	Et	$C_{21}H_{19}NO_6S$
7a	84 (A)	172.5−174	EA	$C_{18}H_{19}NO_7S$
7b	18 (C)[e]	182.5−183.5	E−H	$C_{21}H_{19}ClNO_7S$
7c	19 (A)	175−177	Et	$C_{25}H_{23}NO_8S$
7d	62 (A)	168−170	EA	$C_{21}H_{19}NO_6S$
8a	50 (A)	259.5−260.5	EA	$C_{21}H_{19}NO_7S$
8b	29 (A)	227−228	M	$C_{21}H_{19}NO_6S_2$
8c	28 (A)	198−200	Et−W	$C_{22}H_{22}N_2O_6S$
9a	35 (A)	195−196.5	EA	$C_{16}H_{17}NO_7S$
9b	29 (A)	149.5−150.5	CT	$C_{16}H_{16}ClNO_7S\cdot 1/4H_2O$
9c	20 (B)	180−182	EA−E	$C_{22}H_{21}N_2O_7S$
9d	47 (A)	126.5−128.5	EA−C	$C_{23}H_{23}NO_7S$
9e	58 (B)	141−142.5	EA−H	$C_{18}H_{21}NO_7S$
9f	34 (D)	189−193	B−C	$C_{24}H_{25}NO_7S$
9g	48 (A)	136.5−137.5	CT	$C_{25}H_{27}NO_7S$
10	33 (D)	176.5−178	B−C	$C_{23}H_{24}N_2O_6S$
11a	25 (A)	129−132	EA−C	$C_{16}H_{17}NO_6S$
11b	32 (A)	115−117	CT	$C_{18}H_{21}NO_6S$
11c	36 (A)	122.5−124	B−C	$C_{24}H_{25}NO_6S$
11d	13 (A)	129−131	EA−C	$C_{19}H_{23}NO_6S$
12	13 (A)	193−203	B−C	$C_{21}H_{19}NO_6S$
13a	38 (B)	173−176	M	$C_{20}H_{19}N_3O_6S$
13b	59 (C)	227−229	EA	$C_{20}H_{18}ClN_3O_6S$
13c	10 (C)[e]	217−218	EA	$C_{20}H_{18}BrN_3O_6S$
13d	42 (A)	165.5−167.5	EA	$C_{21}H_{21}N_3O_6S$
13e	47 (B)	204−206	DE−EA	$C_{27}H_{25}N_3O_6S$
14	54[f]	183.5−185.5	EA−H	$C_{20}H_{23}N_3O_6S$
15a	63 (D)[g]	276−281	DS−W	$C_{16}H_{10}ClN_3O_5S$
15b	73 (C)[d]	208.5−210	EA	$C_{19}H_{16}ClN_3O_5S$
15c	59 (D)[g]	211−212	EA	$C_{20}H_{18}ClN_3O_5S$

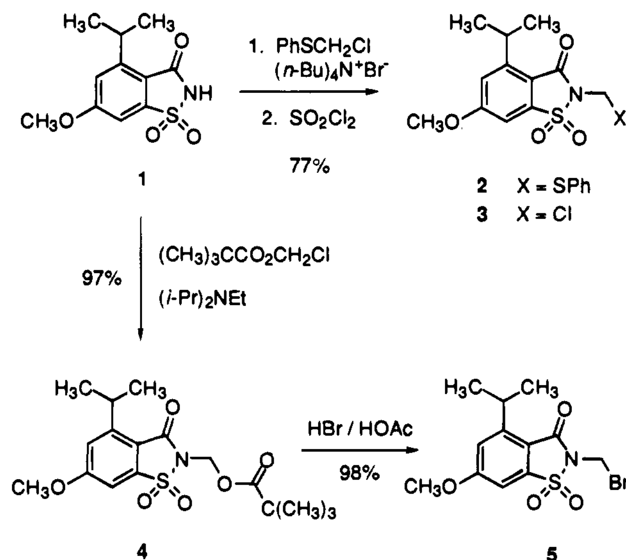
[a] Method A = NaH/DMF, B = $CsCO_3$/DMF, C = $(i\text{-PrN})_2NEt$/DMF, D = MTBD/CH_3CN. [b] B = benzene, C = cyclohexane, CT = carbon tetrachloride, DE = 1,2-dichloroethane, DS = dimethyl sulfoxide, E = ether, Et = ethanol, EA = ethyl acetate, H = hexanes, M = methanol, W = water. [c] Carbon, hydrogen, and nitrogen analysis were within ±0.4% of the theoretical values. [d] The preparation of the *N*-(chloromethyl)benzisothiazolone starting material is described in ref 2. [e] Used K_2CO_3 as the base. [f] See experimental section. [g] Used DMF as reaction solvent.

than **6a**. This paper describes the development of the structure−activity relationship (SAR) and how this design concept has been extended to several types of alicyclic and heterocyclic β-dicarbonyl systems. This work led to the identification of inhibitors that have similar potency to the DCB inhibitors but improved *in vitro* tissue stability. The oral bioavailability of these inhibitors could not be determined due to poor solubility properties. These classes of cyclic β-dicarbonyl leaving groups are novel, and to the best of our knowledge, we are the first to described their use as leaving groups in any context.

Scheme 1



Scheme 2



Chemistry

The benzisothiazolone inhibitors **6−12**, **13a**, **13c−13e**, and **15** were prepared by coupling an *N*-(chloromethyl)benzisothiazolone with a leaving group in the presence of base (Scheme 1). In the case of **13b**, *N*-(bromomethyl)benzisothiazolone **5** was reacted with 3-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (CPD) to afford **13b** in 59% yield. Hydrogenation of **13a** over palladium gave tetrahydropyridopyrimidinone **14**. The physical properties, synthetic methods, and isolated yields for the inhibitors **6−15** are listed in Table 1.

The *N*-(halomethyl)benzisothiazolones **3** and **5** were prepared as shown in Scheme 2. We have recently reported on the generality of the improved two-step procedure described for the preparation of **5**.[7] The syntheses of 2-(chloromethyl)-4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide[2] and 2-(chloromethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide[8] have been reported. The synthetic methods used to prepare **3** were followed in the preparation 2-(chloromethyl)-4-(1-methylpropyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide, which was used in the synthesis of **15c**.

Results and Discussion

The inhibitory potency of **6b** was improved further by the addition of an electron-withdrawing group onto the pyrone ring. Thus, in compound **6c** the inhibitory potency was improved 7-fold over that of **6b**. However, the doubly vinylogous β-dicarbonyl system **6d** was considerably less potent. Although the pyrones **6b** and **6c** were potent, both compounds were unstable in human blood when incubated at 37 °C with half-lives of less than 15 min. We have reported that the addition

of a 6-methoxy group on the benzisothiazolone ring improves the stability of the DCB and PMT inhibitors;[4] therefore, we extended this finding to this series. Also, due to our initial success at identifying the potent inhibitors **6b** and **6c**, we searched for commercially available compounds that were alicyclic or heterocyclic β-dicarbonyl systems to use as leaving groups. The search yielded a variety of potential leaving groups to be linked to the 4-isopropyl-6-methoxybenzisothiazolone system. Numerous structurally divergent β-dicarbonyl systems were prepared and all were potent inhibitors. The first group of compounds prepared and tested were the hydroxypyrones **7a** and **7c**, the hydroxycoumarin **8a**, the hydroxyquinolone **8c**, the tetronic acid **9c**, and the 2-hydroxypyrido[1,2-*a*]pyrimidin-4-one **13d** (Table 2). All of these compounds had interesting properties that warranted expanding the SAR to include each of these systems and led to the preparation of other β-dicarbonyl systems such as the tetramic acid **10**, the cycloalkane-1,3-diones **11**, and the 1,3-indandione **12**.

The pyrones **7a** and **7c**, which are the 6-methoxybenzisothiazolone analogs of **6b** and **6c**, were very potent inhibitors and like **6b** and **6c** were unstable in human blood. The 3-chloro analog **7b** gave similar results, but the pyridone **7d** was less potent. The coumarin **8a** was potent and stable, while the 1-thio and 1-aza analogs **8b** and **8c** were less potent. The coumarin SAR was not pursued further since the 4-hydroxycoumarin leaving group has anticoagulant activity and is structurally related to the anticoagulant warfarin.[9]

Expansion of the SAR of the tetronic acids **9** was productive, since all of these derivatives had bindings constants less than 100 pM. The 3-hydrogen and 3-chloro compounds **9a** and **9b** were very potent inhibitors, but unstable. However, the 3-phenyl and 3-benzyl compounds **9c** and **9d** were very potent inhibitors with moderate stability. Increasing the lipophilicity of these compounds by introducing 5,5-dimethyl groups retained inhibitory potency and also further improved the blood stability. The 5,5-dimethyltetronates **9f** and **9g** were equipotent to the tetronates **9c** and **9d**, but were 3−5 times more blood stable. Compared to the DCB inhibitor WIN 63394, tetronate **9f** was an equipotent inhibitor and had similar stability in blood and liver S9 homogenate incubations (see Table 5). The tetronates **9d** and **9g** were equipotent inhibitors, but were less stable than **9f**.

The SAR of the tetronic acids was expanded to the analogous nitrogen and carbon systems. The tetramic acid **10** was less potent than the tetronic acids, and the carbon analogs, the cycloalkane-1,3-diones **11**, were potent inhibitors but did not offer any advantage over the tetronic acids in terms of potency or stability. The 2-benzyl-1,3-cyclopentanedione analog **11c** was a potent inhibitor but had properties that were similar to the analogous tetronate **9d**. The benzo-fused carbon analog indandione **12** was potent, but unstable.

A search of our compound files revealed the known 2-hydroxypyrido[1,2-*a*]pyrimidin-4-one system, which structurally is an even more unique system. In contrast to the tetronates **9** and the cycloalkanediones **11**, the unsubstituted 3-hydrogen analog **13a** was potent and blood stable ($t_{1/2}$ = 107 min). The potent and blood stable 3-hydrogen and 3-chloro analogs **13a** and **13b** were shown to have significant *in vitro* liver S9 homogenate stability compared to the DCB inhibitor (see Table 5). In particular, the 3-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (CPD) **13b** was greater than 3 times more stable in liver S9 homogenate than the DCB analog. Tetrahydropyrido[1,2-*a*]pyrimidin-4-one **14** was less potent and less blood stable than the CPD **13b** and **13a**. The transition-state mimetic trifluoromethyl ketone ICI 200,355[10] and the mechanism-based inhibitor L-658,758 [11] are listed in Table 2 as literature reference compounds.

On the basis of the above discussion, one can see that our approach was a simple empirical approach, since a clear SAR for the effect of the leaving group on HLE inhibition and blood stability does not exist. The only trend that exists for improved blood stability is that the more stable compounds tend to be the more lipophilic compounds that bear a phenyl or benzyl substituent or a fused benzo ring. Also, the acidity of the inhibitor leaving group (pK_a value) does not correlate with HLE inhibitory potency (K_i^*). Increasing the acidity of the leaving group in **7a** by introducing an electron withdrawing group such as in **7b** and **7c** did increase potency; however, introducing a benzyl group into **9a** led to **9d**, which is 4 times more potent, while the leaving groups of **9a** and **9d** have very similar pK_a values. In addition, introduction of a benzyl group into **13a** to give **13e** led to the opposite effect on potency noted in **9a** and **9d**: the potency decreased 12-fold. The data suggests that a threshold pK_a value for the leaving group of <8 is necessary but not sufficient for potent HLE inhibition. Other factors appear to affect HLE inhibitory activity such as favorable or unfavorable interactions of the leaving group portion of the inhibitor and its substituents with the surface of the enzyme.[12]

The derivative **13b** with the CPD leaving group was the most potent and tissue stable inhibitor in this new class of cyclic β-dicarbonyl systems. The SAR of the CPD group was examined for comparison to our previously reported SAR study with the PMT and DCB leaving groups. The same SAR result was obtained and is shown in Table 3. The inhibitory potency and human blood stability SAR was the same for all three leaving groups. The most potent and stable benzisothiazolone was confirmed to be the 4-isopropyl-6-methoxybenzisothiazolone. The similarity of the HLE inhibition SAR is clearly demonstrated in Table 4, where the rank order for potency is 4-*i*-Pr-6-OMe > 4-*i*-Pr > 4-*s*-Bu > 4-H for all three leaving groups. The DCB leaving group is more potent than PMT in all four examples. When the activity of CPD is compared with that of PMT, only the 4-isopropyl-6-methoxybenzisothiazolone CPD example **13b** was more potent than the PMT inhibitor.

In summary, a novel class of cyclic β-dicarbonyl leaving groups has been discovered and applied to the design of mechanism-based inhibitors of HLE. The SAR development led to the identification of a potent and tissue stable HLE inhibitor, WIN 65936 (**13b**), which bears the 3-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (CPD) leaving group. WIN 65936 has similar or better inhibitory potency and a better tissue stability profile than the analogous compounds which bear the DCB and PMT leaving groups, WIN 63394 and WIN 63395, respectively. Additionally, the β-dicarbonyl leaving groups should be useful in other protease inhibitors; in fact, our colleagues have extended the use of β-dicarbonyl leaving groups to ICE cysteine protease inhibitors.[13]

Experimental Section

The leaving groups (LGs) for the preparation of compounds **6a**, **6b**, **6d**, **7a**, **8a**, **8c**, **9a**−**9d**, **11a**, **11b**, **11d**, and **12** are

Table 2. Leaving Group Effects on HLE Inhibition and Stability

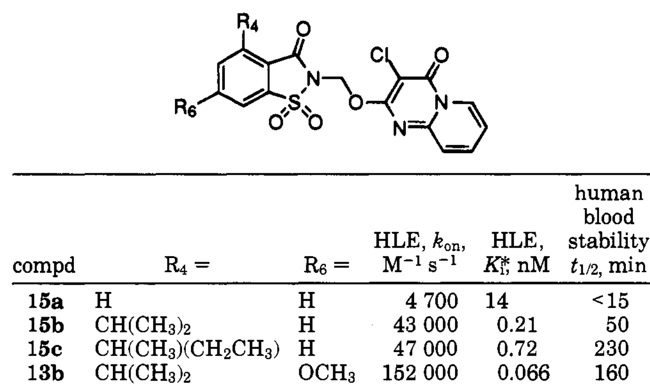
LG =	Cmpd	Substitution		HLE,[a] K_i^*, nM	human blood stability[b] $t_{1/2}$, min
	7a	X = O	R = H	0.05	<15
	7b	O	Cl	0.025	<15
	7c	O	COPh	0.027	<15
	7d	NCH_3	H	0.85	
	8a	X = O		0.09	360
	8b	S		0.22	
	8c	NCH_3		0.50	
	9a	R = H	R' = H	0.052	< 15
	9b	Cl	H	0.030	< 15
	9c	Ph	H	0.025	29
	9d	CH_2Ph	H	0.013	58
	9e	H	CH_3	0.093	< 15
	9f	Ph	CH_3	0.021	154
	9g	CH_2Ph	CH_3	0.016	169
	10			0.14	14
	11a	n = 0	R = H	0.033	< 15
	11b	1	CH_3	0.06	< 15
	11c	1	CH_2Ph	0.034	55
	11d	2	CH_3	0.18	16
	12			0.083	< 15
	13a		R = H	0.078	107
	13b		Cl	0.066	160
	13c		Br	0.058	124
	13d		CH_3	0.25	350
	13e		CH_2Ph	0.90	
	14			0.110	51
--	ICI 200,355			0.40	
--	L-658,758			2.2	< 15
PMT	WIN 63395			0.27	260
DCB	WIN 63394			0.023	140

[a] The potency of inhibition is expressed as an apparent binding constant, defined as $K_i^* = k_{off}/k_{on}$. The binding constants are reproducible to within ±10%. Methods are described in ref 2. [b] Incubations were at 37 °C and disappearance of parent was monitored by HPLC. The blood half-lives were reproducible to within ±25%. Methods are described in ref 5.

commercially available. The leaving groups for compounds **6c**,[14] **7c**,[14] **7d**,[15] **8b**,[16] **9e**,[17] **9f**,[18] **9g**,[18] **10**,[19] **11c**,[20] **13a**,[21] **13b**,[22] **13d**,[21] and **13e**[23] were prepared by literature methods. The new leaving groups for compounds **7b** and **13b** are described below. The leaving group for **13c** was prepared by replacing NCS with bromine in the method described for 3-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

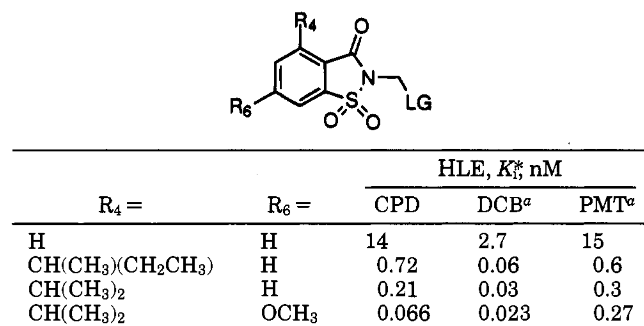
3-Chloro-4-hydroxy-6-methyl-2-pyrone. A stream of chlorine was passed into an ice-bath cooled suspension of 10.0 g (80 mmol) of 4-hydroxy-6-methyl-2-pyrone in 60 mL of acetic

Table 3. Phenyl Substituent Effects on HLE Inhibition and Stability



compd	R_4 =	R_6 =	HLE, k_{on}, $M^{-1}s^{-1}$	HLE, K_i^*, nM	human blood stability $t_{1/2}$, min
15a	H	H	4 700	14	<15
15b	$CH(CH_3)_2$	H	43 000	0.21	50
15c	$CH(CH_3)(CH_2CH_3)$	H	47 000	0.72	230
13b	$CH(CH_3)_2$	OCH_3	152 000	0.066	160

Table 4. SAR Comparision of the CPD Leaving Group Inhibitory Potency with those of the DCB and PMT Leaving Groups



R_4 =	R_6 =	HLE, K_i^*, nM		
		CPD	DCB[a]	PMT[a]
H	H	14	2.7	15
$CH(CH_3)(CH_2CH_3)$	H	0.72	0.06	0.6
$CH(CH_3)_2$	H	0.21	0.03	0.3
$CH(CH_3)_2$	OCH_3	0.066	0.023	0.27

[a] Data taken from ref 3 and 4.

Table 5. Comparison of HLE Inhibition and Tissue Stability by Leaving Group

compd	HLE, K_i^*, nM	$t_{1/2}$, min	
		human blood stability	human liver S9 stability[a]
9d	0.013	58	75
9f	0.021	154	82
9g	0.016	169	35
13a	0.078	107	102
13b	0.066	160	>240[b]
13d	0.25	350	103
WIN 63395 PMT	0.27	260	17 ± 3
WIN 63394 DCB	0.023	140	73 ± 10

[a] Mean ± standard deviations of triplicate determinations are given. All other values are expressed as the mean of duplicate determinations with less than 15% variation. Methods are given in ref 5. [b] Less than 5% metabolism occurred within the incubation period. An accurate half-life can not be determined.

acid until 6.0 g (85 mmol) of chlorine had been absorbed. The mixture was stirred for 5 min, diluted with 60 mL of carbon tetrachloride, and filtered. The crude white solid was recrystallized from ethyl acetate and then from acetic acid to afford 1.5 g (12%) of the pyrone as off-white blades: mp 242–243 °C. Anal. Calcd for $C_6H_5ClO_3$: C, 44.87; H, 3.14; Cl, 22.09. Found: C, 45.00; H, 3.14; Cl, 22.00.

3-Chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one. To a mixture of 3.24 g (200 mmol) of 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[21] and 27.6 g (203 mmol) of *N*-chlorosuccinimide in 180 mL of acetic acid was added 20 mL of TFA. After a mild exotherm, the reaction was stirred at room temperature for 72 h, poured over ice–water, and diluted to 600 mL with water. The solids were filtered, washed with water, and dried to give 26 g (67%) of 3-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[22] as a colorless solid: mp 290 °C dec; IR (KBr) 1709, 1530 (broad) cm^{-1}; NMR (DMSO) δ 7.34–7.40 (m, 2H), 8.10 (t, J = 7.4 Hz, 1H), 8.91 (d, J = 6.6 Hz, 1H). Anal. Calcd for $C_8H_5ClN_2O_2$: C, 48.88; H, 2.56; N, 14.25. Found: C, 48.75; H, 2.49; N, 14.21.

6-Methoxy-4-(1-methylethyl)-2-[(phenylthio)methyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (2). A mixture of 51.0 g (0.20 mol) of 6-methoxy-4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide[24] (1), 39.6 g (0.25 mol) of chloromethyl phenyl sulfide, and 6.4 g (0.02 mol) of tetrabutylammonium bromide in 280 mL of toluene was refluxed for 45 h, cooled, and concentrated. The residue was column chromatographed on silica gel (630 g) eluted with a gradient of hexanes to 15% hexanes in methylene chloride, which gave 65.7 g (87%) of the phenyl sulfide **2** as a white solid: mp 76–78 °C.

2-(Chloromethyl)-6-methoxy-4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (3). To a solution of 65.7 g (0.174 mol) of the phenyl sulfide **2** in 300 mL of methylene chloride was added dropwise 45 mL (0.56 mol) of sulfuryl chloride. The mixture was stirred at room temperature for 16 h and then concentrated. The residue was triturated with hexanes, and the solid was collected and recrystallized from benzene–cyclohexane to give 46.43 g (88%) of the *N*-(chloromethyl)benzisothiazolone **3** as a white solid: mp 155–157 °C; NMR ($CDCl_3$) δ 1.38 (d, J = 7.0 Hz, 6H), 3.97 (s, 3H), 4.19 (m, 1H), 5.56 (s, 2H), 7.22 (m, 2H); MS 304 (MH^+), 268 (MH^+ – Cl). Anal. Calcd for $C_{12}H_{14}ClNO_4S$: C, 47.45; H, 4.65; N, 4.61. Found: C, 47.48; H, 4.55; N, 4.50.

[6-Methoxy-4-(1-methyethyl)-3-oxo-1,2-benzisothiazol-2(3*H*)-yl]methyl 2,2-dimethylpropanoate *S*,*S*-Dioxide (4). A mixture of 5.1 g (20 mmol) of 6-methoxy-4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide[24] (1) and 4.2 mL (24 mmol) of *N*,*N*-diisopropylethylamine in 50 mL of acetonitrile was stirred at room temperature for 5 min, and then 3.2 mL (22 mmol) of chloromethyl pivalate was added in one portion. The reaction mixture was refluxed for 16 h, cooled, and concentrated, and the solid crystalline residue was triturated with water. The material was filtered, washed with water, and dried under vacuum to afford 7.16 g (97%) of **4** as a tan crystalline solid: mp 177–179 °C; IR (KBr) 1732 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 9H) 1.29 (d, J = 6.9 Hz, 6H), 3.95 (s, 3H), 4.20 (m, 1H), 5.81 (s, 2H), 7.20 (m, 2H). Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79. Found: C, 55.15; H, 6.34; N, 3.79.

2-(Bromomethyl)-6-methoxy-4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (5). A suspension of 7.0 g (19 mmol) of the pivalate **4** and 5 mL of 45% anhydrous HBr in acetic acid in 45 mL of glacial acetic acid was heated gently on a steam bath for 30 min. The homogeneous reaction mixture, after cooling to room temperature, was slowly poured onto 350 mL of ice–water. A solid formed and was filtered, washed with water, and dried under vacuum to give 6.51 g (98%) of **5** as a white solid: mp 157–159 °C; IR (KBr) 1736 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (d, J = 7.0 Hz, 6H), 3.96 (s, 3H), 4.19 (m, 1H), 5.50 (s, 2H), 7.21 (m, 2H). Anal. Calcd for $C_{12}H_{14}BrNO_4S$: C, 41.39; H, 4.05; N, 4.02. Found: C, 41.67; H, 4.02; N, 3.95.

Method A. To a stirred suspension of 100 mg (2.5 mmol) of 60% sodium hydride in mineral oil in 8 mL of DMF at 0 °C and under nitrogen was added 480 mg (2.2 mmol) of α-benzyl-δ,δ-dimethyltetronic acid[18] as a solid. After stirring at room temperature for 30 min, a solution of 607 mg (2.0 mmol) of the *N*-(chloromethyl)benzisothiazolone **3** in 8 mL of DMF was added dropwise. The reaction mixture was stirred at room temperature for 144 h and then poured onto water. A solid separated and filtration afforded 670 mg of an off-white solid. Column chromatography on silica gel eluted with a gradient from 14% to 25% EtOAc/cyclohexanes gave 470 mg (48%) of **9g** as a white solid: mp 136.5–137.5 °C (CCl_4); IR (KBr) 1736, 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (d, J = 7 Hz, 6H), 1.49 (s, 6H), 3.89 (s, 2H), 3.97 (s, 3H), 4.13 (cm, 1H), 5.70 (s, 2H), 7.16–7.41 (cm, 7H); MS 486 (MH^+). Anal. Calcd for $C_{25}H_{27}NO_7S$: C, 61.84; H, 5.60; N, 2.88. Found: C, 61.47; H, 5.48; N, 2.80.

Method B. The cesium salt was preformed by dissolving 0.5 g (2.0mmol) of 2-hydroxy-3-(phenylmethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[23] in 15 mL of methanol. Addition of 0.36 g (1.1mmol) of cesium carbonate to the mixture, stirring at room temperature for 2 h, and then removal of the solvent at reduced pressure gave the cesium salt as a white solid. A

mixture of the salt and 0.64g (2.0 mmol) of the *N*-(chloromethyl)benzisothiazolone **3** in 15 mL of DMF was stirred at room temperature for 48 h. The mixture was poured over ice–water, and the solids were collected and dried. The solids were purified by flash chromotography (SiO_2, 1:1 ethyl acetate-hexanes) to give 0.48 g (47%) of **13e** as a colorless glass. Crystallization from CH_2Cl_2–ethyl acetate afforded 0.44 g of **13e** as colorless needles: mp 204–206 °C; IR (KBr) 1732, 1676 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (d, J = 6.9 Hz, 6H), 3.94 (s, 3H), 3.96 (s, 2H), 4.18 (m,1H), 6.21 (s, 2H), 7.01–7.18 (m, 6H), 7.41 (d, J = 7.1 Hz, 2H), 7.57 (d, J = 8.7 Hz, 1H) 7.70 (dt, J = 1.2 Hz, J = 6.8 Hz, 1H), 9.04 (d, J = 7.1 Hz, 1H); MS 519 (M^+), 268 (M^+ – 251). Anal. Calcd for $C_{27}H_{25}N_3O_6S$: C, 62.43; H, 4.85; N, 8.09. Found: C, 62.40; H, 4.79; N, 8.04.

Method C. To a solution of 0.324 g (1.65mmol) of 3-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and 0.37 mL (2.15mmol) of *N,N*-diisopropylethylamine in 13 mL of DMF was added 0.522 g (1.50 mmol) of the *N*-(bromomethyl)-benzisothiazolone **5**.[25] The mixture was stirred at room temperature for 18 h and then poured over ice and diluted to 150 mL with water. The precipitated solids were collected and dried to give 0.75 g of a pale yellow solid that was crystallized from ethyl acetate to give 0.413 g (59%) of **13b** as a colorless crystalline solid: mp 227–229 °C; IR (KBr) 1731, 1705, 1691 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (d, J = 6.8 Hz, 6H), 3.94 (s, 3H), 4.21 (m, 1H), 6.26 (s, 2H), 7.18 (s, 2H), 7.22 (m, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.83 (t, J = 7.0 Hz, 1H), 9.08 (d, J = 7.3 Hz, 1H); MS 464 (MH+), 268(M+ – 195). Anal. Calcd for $C_{20}H_{18}ClN_3O_6S$: C, 51.78; H, 3.91; N, 9.06. Found: C, 51.81; H, 3.85; N, 8.96.

Method D. A mixture of 160 mg (0.78 mmol) of δ,δ-dimethyl-α-phenyltetronic acid[18] and 120 mg (0.78 mmol) of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) in 10 mL of acetonitrile was stirred until a solution formed (~30 min), then 237 mg (0.78 mmol) of the *N*-(chloromethyl)benzisothiazolone **3** was added. The solution was stirred for 5 h at room temperature and then poured onto water and extracted with chloroform. The organic extract was dried over sodium sulfate, filtered, and concentrated to give 380 mg of a pale yellow oil. Column chromatography on silica gel eluted with 12% EtOAc in cyclohexanes gave 125 mg (34%) of **9f** as a white solid: mp 189–193 °C (C_6H_6–cyclohexane); IR (KBr) 1741, 1734, 1672, 1608 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, J = 6.9 Hz, 6H), 1.57 (s, 6H), 3.96 (s, 3H), 4.13 (m, 1H), 5.46 (s, 2H), 7.17 (s, 2H) 7.46 (m, 5H); MS 472 (MH^+). Anal. Calcd for $C_{24}H_{25}NO_7S$: C, 61.13; H, 5.34; N, 2.97. Found: C, 61.25; H, 5.28; N, 2.93.

Tetrahydro 14. A mixture of 0.304 g (0.708 mmol) of **13a** and 0.30 g of 10% palladium on carbon in 14 mL of ethyl acetate was shaken on a Parr apparatus under 50 psi of hydrogen gas for 7 h. The reaction mixture was filtered through Celite, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromotography (SiO_2, 70% ethyl acetate–hexanes) to give 0.165 g (54%) of **14** as a colorless glass. Crystallization from ethyl acetate–hexanes afforded a crystalline solid: mp 183.5–185.5 °C; IR-(KBr) 1735, 1677cm^{-1}; NMR ($CDCl_3$) δ 1.29 (d, J = 6.7 Hz, 6H), 1.96 (m, 4H), 2.96 (t, J = 6.5 Hz, 2H), 3.93 (t, J = 6.0 Hz,2H), 3.96 (s, 3H), 5.73(s, 1H), 4.20 (m, 1H), 6.02 (s, 2H) 7.19 (s, 2H); MS 434 (MH^+), 268(M^+ – 165). Anal. Calcd for $C_{20}H_{23}N_3O_6S$: C, 55.42; H, 5.35; N, 9.69. Found: C, 55.46; H, 5.26; N, 9.59.

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