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INHIBITORS OF HUMAN LEUKOCYTE ELASTASE. 2.[1] SYNTHESIS AND SAR OF BENZISOTHIAZOLINYLMETHYL ARYL ETHERS

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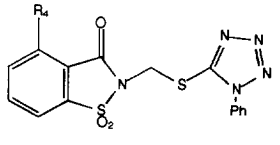
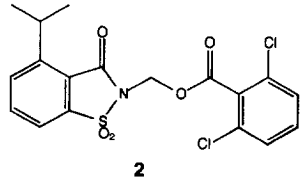
Abstract: A series of 4-isopropyl benzisothiazolinylmethyl aryl ethers were prepared and evaluated as inhibitors of human leukocyte elastase (HLE). Among the phenols attached as leaving groups onto N-methyl of the 4-isopropyl benzisothiazolone nucleus, the sulfonamido phenol **26** was found to be the best. Compound **7i** with K_i^* = 0.8 nM was the most potent inhibitor in this series.

Human leukocyte elastase (HLE) is a serine proteinase that has been invoked in the etiology of a number of pulmonary disorders such as emphysema[2], acute respiratory distress syndrome and chronic bronchitis[3]. A potential form of therapy is the inhibition of this enzyme in the lungs.[4] Recently, we reported that benzisothiazolones (**1**), are potent and selective inhibitors of HLE and that the potency was dependent on two important factors, namely the R4 substituent and the nature of the leaving group positioned on the nitrogen attached methylene of benzisothiazolone nucleus.[5] Structure-activity relationships studies led to the identification of the *i*-Pr group to be the optimal R4 substituent and when coupled with a disubstituted aryl carboxylate leaving group led to **2**, which is a very potent (K_i^* = 0.03 nM) inhibitor of HLE.[1] We now report that 4-isopropyl benzisothiazolones substituted with various N-methyl aryl ether leaving groups are potent inhibitors of HLE.



1

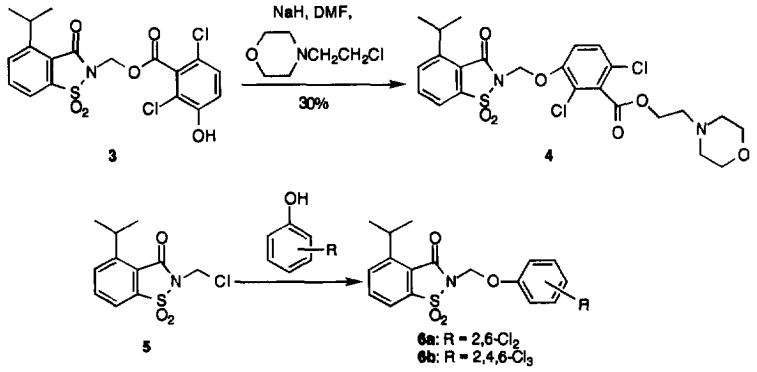


2

Our efforts in this area began with the serendipitous discovery that ether **4**,[6] a by product during the attempted alkylation of phenol **3**[7] with choroethylmorpholine (**Scheme I**) was a potent (K_i^* = 1.6 nM) inhibitor

of HLE. This was interesting because, our initial attempts to substitute the dichlorobenzoate portion of **2** with chlorosubstituted phenols (compounds **6a,b**) led to complete loss of HLE inhibitory activity. In order to better understand the structural features that are responsible for the observed activity of **4** and to improve the potency of this class of HLE inhibitors, we prepared a number of benzisothiazolinylmethyl aryl-ethers (compounds **7a-j**).

Scheme I



Chemistry: The synthesis of compounds reported in Table 1 is shown in Scheme II. Thus the readily available acids **8,9**[8] were converted to the corresponding amides **12,13** respectively by reaction with thionyl chloride followed by treatment of the intermediate acid chloride with N-methylpiperazine. The morpholino amides **14,15** were prepared from esters **10,11**[9] using the aluminum amide generated insitu from amine **16** and Me_3Al.[10] Alkylation of **8** with chloroethylmorpholine gave the ester **17**. Removal of the benzyl protecting group from **12-15** and **17** under hydrogenation conditions, provided the desired phenols **22a-e**. Synthesis of the sulfonamide substituted phenols **22f-g** was achieved from iodide **18** via a three step sequence. Thus protection of phenolic oxygen as the benzylether (BnBr, K_2CO_3, acetone, reflux), transmetallation of iodide with n-BuLi followed by treatment of the intermediate anion with SO_2 gave the corresponding lithiosulfinate which without isolation was reacted with sulfuryl chloride to give the sulfonyl chloride **19** in moderate (40% from **18**) yield.[11] Reaction of **19** with various amines provided the sulfonamides **20-21**, which after removal of the benzyl protecting group (H_2, Pd-C) gave phenols **22f-g**. Alkylation of **22a-g** with chloromethyl compound **5**[5] gave the desired targets **7a-g** in good yields.[12,13] Aryl ethers **7h-i** were prepared from the readily available[14] sulfonyl chlorides **23** and **24** via reaction with morpholine followed by alkylation of the intermediate sulfonamides **25** and **26** with chloride **5** in the presence of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD). In order to improve their aqueous solubility, ethers **7a-g** which have a basic amine functionality were converted to their hydrochloride salts by treatment with ethereal HCl. Compound **7j** was prepared from acid **27**[8] by 1) selective protection[15] of the acid (BnCl, NaOH, EtOH, reflux) to give ester **28** 2) alkylation of **28** with **5** and deprotection of the resulting benzylester **29** under hydrogenation conditions.

Scheme II

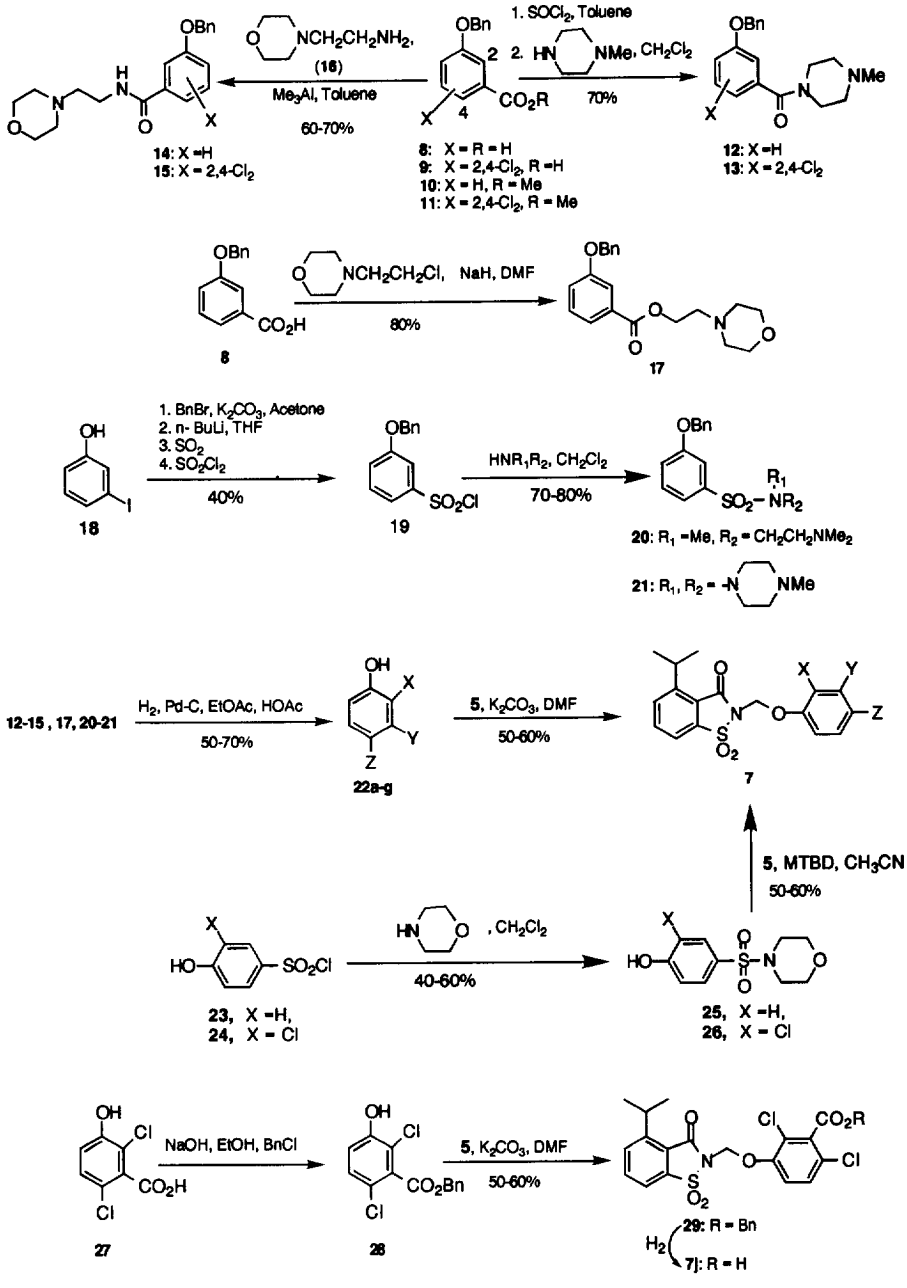
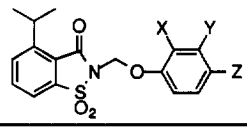
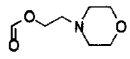
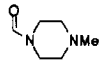
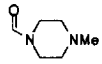
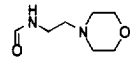
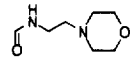
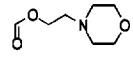
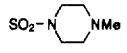
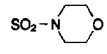
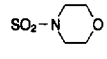

OBn
NCH2CH2NH2, (16)
Me3Al, Toluene
60-70%
1. SOCl2, Toluene
2. HN NMe, CH2Cl2
70%
14: X =H
15: X = 2,4-Cl2
8: X = R = H
9: X = 2,4-Cl2, R =H
10: X = H, R = Me
11: X = 2,4-Cl2, R = Me
12: X =H
13: X = 2,4-Cl2
NCH2CH2Cl, NaH, DMF
80%
8
17
1. BnBr, K2CO3, Acetone
2. n- BuLi, THF
3. SO2
4. SO2Cl2
40%
18
19
HNR1R2, CH2Cl2
70-80%
20: R1 =Me, R2 = CH2CH2NMe2
21: R1, R2 = -N NMe
12-15, 17, 20-21
H2, Pd-C, EtOAc, HOAc
50-70%
22a-g
5, K2CO3, DMF
50-60%
7
5, MTBD, CH3CN
50-60%
, CH2Cl2
40-60%
23, X =H,
24, X = Cl
25, X =H,
26, X = Cl
NaOH, EtOH, BnCl
27
28
5, K2CO3, DMF
50-60%
29: R = Bn
7]: R = H

Table 1: HLE inhibitory activity of benzisothiazolones **7a-j**:



Compound	X	Y	Z	HLE activity[a] $k_{inact.}$ (M^{-1} Sec^{-1})	K_i^* (nM)
4	Cl	Cl		25,000	1.6
6a	Cl	Cl	H	--	>100
7a	H		H	2,300	10.0
7b	Cl		Cl	6,000	4.0
7c	H		H	--	>100
7d	Cl		Cl	8,000	3.5
7e	H		H	--	>1000
7f	H	$SO_2N(Me)CH_2CH_2NMe_2$	H	460	51.6
7g	H		H	550	42.0
7h	H	H		1,900	13.6
7i	Cl	H		29,000	0.8
7j	Cl	CO_2H	Cl	750	34
L, 658,758	--	--	- -	3,700 (3800)[b]	2.2[c]
ICI-200,355	--	---	--	94,000 (87,000)[b]	0.4 (0.6)[b]

[a]HLE inhibitory activity was determined as described in ref.5. The potency of inhibition is expressed as an apparent binding constant, K_i^*, where $K_i^* = k_{react}/k_{inact}$. The rates and binding constants were reproducible to within ±10%. [b]The values in parenthesis are those reported in the literature (ref. 17, 18).[c]No literature K_i^* is available for this compound.

Biological results and discussion: Evaluation of inhibitors **7a-j** against HLE revealed these compounds to be potent mechanism-based inhibitors of the enzyme (**Table 1**). As is consistent with the proposed mechanism of HLE inhibition by this class of compounds,[1,16] the rate of inactivation ($k_{inact.}$) was the sole determinant factor that influences the potency amongst these HLE inhibitors. Compounds **4, 7b,d** with chlorosubstituted phenols as leaving groups were amongst the most potent in this series. Replacing the morpholinoester moiety in **4** with carboxamides (compounds **7b,d**) led to a 2-3 fold loss in activity while the corresponding carboxylic acid **7j** was 20 fold less active. The reason for this drop in activity is not very clear because molecular modeling studies indicated that the C-3 position of the phenolic group is oriented towards solvents and should tolerate hydrophilic substituents at this region. Compound **7a**, which lacks the chloro substituents was only two fold less active than the 2',4'-dichloro analog **7b**. This is interesting because, in the case of morpholinoester **4** and amide **7d**, removal of chlorines (compounds **7c,e**) resulted in > 100 fold loss in HLE inhibitory activity. The sulfonamides **7f-g** were more potent (> 2 fold), than the morpholino amide **7c** but were 5 fold less potent than the piperazine amide **7a**. Compound **7h**, wherein the sulfonamide group is moved to the C-4' position led to a 4 fold (vs **7g**) improvement in activity. The 2'-chloro analog **7i** with a K_i^* = 0.8 nM was the most potent inhibitor in this series. The Merck (**L-658,758**)[17] and Zeneca (**ICI-200,355**)[18] inhibitors are shown as reference compounds in Table **1**. Inspite of their good in vitro activity, the compounds reported here showed at best only marginal activity in an elastase induced pulmonary hemorrhage model in hamsters.[19] Compound **7d** with K_i^* = 3.5 nM showed 46% inhibition at 10 mg/kg, i.v. and was the most potent inhibitor in vivo.

In summary, we have extended the scope of the benzisothiazolone based inhibitors of HLE, with the synthesis of benzisothiazolinylmethyl aryl ethers. Compound **7i** with a K_i^* = 0.8 nM was the most potent inhibitor in this class. Studies are underway to structurally modify this class of compounds to improve their potency to the level observed with the benzisothiazolinylmethyl benzoate **2** and the results of these investigations will be the subject of future publications.

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References and Notes:

[¥]All future correspondence should be directed to the author at his present address: Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380-4245.

1. For the previous paper in this series, see:Subramanyam, C.; Bell, M.R.; Carabateas, P.; Court, J.J.; Dority, J.A. Jr.; Dunlap, R.P; Ferguson, E.; Franke, C.; Gordon, R.; Hlasta, D.J.; Kumar, V.; Mura, A.; Saindane, M. *J. Med. Chem.* **1994**, 37, 2623.
2. Powers, J.C. *Am. Rev. Respir. Dis.*, **1983**, *127*, S54.
3. For a recent review on HLE, see: Edwards, P.D.; Bernstein, P.R. *Med. Res. Rev.* **1994**, *14*, 127-194.
4. Snider, G.L. *Drug. Dev. Res.* **1987**, *10*, 235.

5. Hlasta, D.J.; Bell, M.R.; Boaz, N.W.; Court, J.J.; Desai, R.C.; Franke, C.A.; Mura, A.J.; Subramanyam, C.; Dunlap, R.P.*Bioorg. Med. Chem. Lett.* **1994**, *4*, 1801.
6. The structure of **4** was established by a combination of spectral data and an unequivocal synthesis starting from the benzylether **9**.
7. For the synthesis of phenol **3**, see U.S. Patent 5,128,339 [CA 117:69658n (1992)]
8. Studt, W.L.; Riley, R.L.; Douglas, G.H. *U.S. Patent* **448, 777,9** (July 1981)
9. Prepared in 90% yield from **8** by alkylation with dimethyl sulfate.
10. Nahm, S.; Wienreb, S.M. *Tetrahedron Lett.*. **1981**, *22*, 3815.
11. For a related procedure for the synthesis of sulfonamides, see: Hlasta, D.H.; Court, J.J.; Desai, R.D. *Tetrahedron Lett.* **1991**, *32*, 7179.
12. General proceudure for the alkylation of phenols **22a-g**: To a solution of phenol **22a-g** (1.1 eq.) and chloride **5** (1.0 eq) in DMF was added anhydrous K_2CO_3 (1.5 eq.). After stirring at room temperature for 12-16 h, the reaction mixture was evaporated to dryness in vacuo. The residue was taken up in EtOAc and filtered.The filtrate was washed with water, brine and dried. Removal of solvent under reduced pressure followed by chromatography yielded the ethers **7a-g** in good yields.
13. All new compounds gave satisfactory NMR (^1H and/or ^{13}C), IR, CIMS and/or elemental analysis data.
14. The sulfonylchlorides **23** and **24** were prepared from the corresponding phenols by reaction with $ClSO_3H$ according to the method of: Popoff, I.C.; Frank, J.R.; Whitaker, R.L.; Miller, H.J.; Demaree, K.D. *J. Agr. Food. Chem.* **1969**, *17*, 810
15. Cavallito, C.J.; Buck, J.S. *J. Am. Chem. Soc.* **1943**, *65*, 2140.
16. A mechanism similar to the one proposed by us (ref. 1, 5) was also proposed by Groutas, et al. for the inhibition of HLE by some saccharin derivatives. Groutas, W.C.; Houser-Archield,N.; Chong, L.S.; Venkataraman, R.; Epp, J.B.; Huang, H.; McClenahan, J.J. *J. Med. Chem.* **1993**, *36*, 3178.
17. Finke, P.E.; Shah, S.K.; Ashe, B.M.; Ball, R.G.; Blacklock, T.J.; Bonney, R.J.; Brause, K.A.; Chandler, G.O.; Cotton, M.; Davies, P.; Dellea, P.S.; Dorn, Jr., C.P.; Fletcher, D.S.; O'Grady, L.A.; Hagmann, W.K.; Hand, K.M.; Knight, W.B.; Maycock, A.L.; Mumford, R.A.; Osinga, D.G.; Sohar, P.; Thompson, K.R.; Weston, H.; Doherty, J.B. *J. Med. Chem.* **1992**, *35*, 3731.
18. Williams, J.C.; Falcone, R.C.; Knee, C.; Stein, R.L.; Strimpler, A.M.; Reaves, B.; Giles, R.E.; Krell. R.D. *Am. Rev. Respir. Dis.* **1991**, *144*, 875.
19. Gordon, R.J.; Ferguson, E.; Dunlap, R.P.; Franke, C.; Silver, P.J. *Annals of the New York Academy of Sciences.* **1991**, *624*, 331.

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