Riluzole Series. Synthesis and in Vivo "Antiglutamate" Activity of 6-Substituted-2-benzothiazolamines and 3-Substituted-2-imino-benzothiazolines

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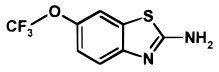
Two series of analogues of riluzole, a blocker of excitatory amino acid mediated neurotransmission, have been synthesized: monosubstituted 2-benzothiazolamines and 3-substituted derivatives. Of all the compounds prepared in the first series, only 2-benzothiazolamines bearing alkyl, polyfluoroalkyl, or polyfluoroalkoxy substituents in the 6-position showed potent anticonvulsant activity against administration of glutamic acid in rats. The most active compounds displaying in vivo "antiglutamate" activity were the 6-OCF_3 (riluzole), 6-OCF_2CF_3, 6-CF_3, and 6-CF_2CF_3 substituted derivatives with ED_{50} values between 2.5 and 3.2 mg/kg i.p. Among the second series of variously substituted benzothiazolines, compounds as active as riluzole or up to 3 times more potent were identified in two series: benzothiazolines bearing a β-dialkylaminoethyl moiety and compounds with an alkylthioalkyl chain and their corresponding sulfoxides and sulfones. The most potent derivatives were 2-imino-3-(2-methylthio)- and 2-imino-3-(2-methylsulfinyl)-ethyl-6-trifluoromethoxybenzothiazolines (**61** and **64**, $ED_{50} = 1.0$ and 1.1 mg/kg i.p., respectively). In addition, intraperitoneal administration of some of the best benzothiazolines protected mice from mortality produced by hypobaric hypoxia.

Introduction

In the 1950s, a number of 2-benzothiazolamines were intensively studied as central muscle relaxants. The major work concerned with this field is that of Domino et al. [1] Since then medicinal chemists have not taken an active interest in this chemical family. Biologists' attention was drawn to this series when the pharmacological profile of riluzole was discovered. Riluzole (**1**, 6-(trifluoromethoxy)-2-benzothiazolamine, PK 26124, RP 54274, Rilutek) was found to interfere with glutamate neurotransmission in biochemical, electrophysiological, and behavioral experiments.



Riluzole 1

In biochemical models riluzole antagonized the release of acetylcholine induced by *N*-methyl-D-aspartate (NMDA) in vitro and blocked the increase in cyclic guanosine monophosphate levels in the cerebellar cortex induced by glutamate in vitro and in vivo.[2] Riluzole was also found to be a potent antagonist of glutamate-stimulated release of D-aspartate in rodent cerebellar cells,[3,4] and it decreased the glutamate-induced release of dopamine (DA) in the "push−pull" model in the cat striatum.[5]

In addition, electrophysiological studies have shown riluzole to be active against responses evoked by microiontophoretically applied excitatory amino acids in motoneurons of the facial nucleus.[6] Thus riluzole seems to interfere with glutamatergic transmission at both the pre- and postsynaptic level. However, riluzole did not act as a competitive antagonist at NMDA type receptors,[7] and it had negligible activity on 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid binding, a selective NMDA antagonist.[8] Furthermore, it did not interact, at least at submillimolar concentrations, with kainate (KA) and quisqualate (QUIS) sensitive subtypes of excitatory amino acid receptor.[9] Finally it has also been demonstrated that riluzole is a highly specific blocker of inactivated Na channels,[10] which in turn inhibit glutamate release.

In pharmacological experiments, riluzole possessed anticonvulsant properties in different models including maximal electroshock in mice, convulsions induced by glutamic acid decarboxylase inhibitors in mice and rats, sound-induced convulsions in DBA/2 mice, and photosensitive epilepsy in baboons. However, unlike benzodiazepines, valproic acid, or barbiturates, riluzole was ineffective against seizures induced by pentylenetetrazole, bicuculline, or picrotoxin[11] and did not induce phencyclidine-like behavioral activity in pigeons, rats, or monkeys.[12] Riluzole has been shown to have interesting neuroprotective effects in vitro, protecting primary cultures of rat cortical neurones against anoxic stress[13] and against an excitotoxic factor present in cerebrospinal fluid from ALS patients.[14] Furthermore, rat motoneurons were protected by riluzole from the excitotoxic effects of glutamic acid uptake inhibitors.[15] These stud-

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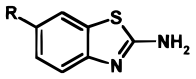
Table 1. Physical Properties and "Antiglutamate" Activity of 6-Substituted-2-benzothiazolamines



no.	R	method	formula[a]	mp,°C	cryst. solvent	ClogP[34]	protection against glutamic acid evoked convulsions ED_{50}, mg/kg i.p.[v]
1	OCF_3	A	$C_8H_5F_3N_2OS$	119[s]	EtOH-H_2O	3.41	3.2
2	H	E[w]	$C_7H_6N_2S$			2.00	>10
3	F	A	$C_7H_5FN_2S$	184[b]	EtOH	2.15	>10
4	Cl	E	$C_7H_5ClN_2S$	209[c]	*e*	2.72	>10
5	Br	A	$C_7H_5BrN_2S$				>10
6	I	B	$C_7H_5IN_2S$	214[e]	acetone		>10
7	NH_2		$C_7H_7N_3S$	208[f]	MeCN		>10
8	CN	A	$C_8H_5N_3S$	207[g]	*d*		>10
9	CO_2Et	A	$C_{10}H_{10}N_2O_2S$	243[h]	EtOH−H_2O		>10
10	NO_2	E	$C_7H_5N_3O_2S$				10
11	SO_2Me	B	$C_8H_8N_2O_2S_2$	224[i]	PrOH		>10
12	OMe	B	$C_8H_8N_2OS$	147[j]	EtOH−H_2O		>10
13	O-*t*-C_4H_9	A	$C_{11}H_{14}N_2OS$	183	$CHCl_3$−hexane		>10
14	$SiMe_3$	D	$C_{10}H_{14}N_2SSi$	140	*d*	4.58	5
15	C_6H_{11}	A	$C_{13}H_{16}N_2S$	217[k]	MeCN		>10
16	Ph	A	$C_{13}H_{10}N_2S$	248[l]	$CHCl_3$−EtOAc−EtOH		>10
17	Me	A	$C_8H_8N_2S$	137[m]	*d*	2.50	>10
18	Et	A	$C_9H_{10}N_2S$	115[n]	cyclohexane	3.03	7
19	*n*-Pr	A	$C_{10}H_{12}N_2S$	119[o]	cyclohexane	3.56	6
20	*i*-Pr	A	$C_{10}H_{12}N_2S$	125[p]	cyclohexane	3.43	>10
21	*n*-Bu	A	$C_{11}H_{14}N_2S$	114[q]	EtOAc−cyclohexane	4.09	4
22	*t*-Bu	A	$C_{11}H_{14}N_2S$	146	cyclohexane	3.83	4
23	*n*-Pen	A	$C_{12}H_{16}N_2S$	122	cyclohexane	4.62	7.5
24	*t*-Pen	A	$C_{12}H_{16}N_2S$	134	*d*		>10
25	CH_2CMe_3	A	$C_{12}H_{16}N_2S$	196	*d*	4.36	>10
26	*n*-Hex	A	$C_{13}H_{18}N_2S$	121	cyclohexane	5.14	7
27	*n*-Hep	A	$C_{14}H_{20}N_2S$	109	cyclohexane	5.67	>10
28	CH_2CF_3	A	$C_9H_7F_3N_2S$	186	*d*		8
29	$COCF_3$	A	$C_9H_5F_3N_2OS$	249	EtOAc		>10
30	SCF_3	A	$C_8H_5F_3N_2S_2$	155[r]	*i*-Pr_2O/cyclohexane	4.03	8
31	$OCHF_2$	A	$C_8H_6F_2N_2OS$	118[t]	toluene	2.74	7.5
32	OCH_2CF_3	A	$C_9H_7F_3N_2OS$[r]	134	*d*	6.50	6.5
33	$OCH_2C_2F_5$	A	$C_{10}H_7F_5N_2OS$	147	toluene		7.5
34	OCF_2CHF_2	A	$C_9H_6F_4N_2OS$	161	toluene	4.16	8.5
35	OC_2F_5	A	$C_9H_5F_5N_2OS$	156	cyclohexane	5.15	2.5
36	C_2F_5	A	$C_9H_5F_5N_2S$,HCl	191	EtOH−acetone	3.26	2.5
37	CF_3	A	$C_8H_5F_5F_3S$	122[u]	cyclohexane	2.96	2.5
(±) MK-801							2.2

[a] Microanalysis results on new compounds were within ±0.4% of theoretical values unless otherwise indicated. [b] Lit.[39] mp 182 °C. [c] Lit.[40] mp 210 °C. [d] Purified on a silica gel column and triturated in 40/60 petroleum ether. [e] Lit.[41] mp 217 °C. [f] Lit.[42] mp 207 °C. [g] Lit.[19] mp 198 °C. [h] Lit.[43] mp 242 °C. [i] Lit.[44] mp 224−6 °C. [j] Lit.[43] mp 147 °C. [k] Lit.[52] mp 219−21 °C. [l] Lit.[45] mp 227−8 °C. [m] Lit.[19] mp 136 °C. [n] Lit.[41] mp 116 °C. [o] Lit.[46] mp not indicated. [p] Lit.[47] mp 123−6 °C. [q] Lit.[48] mp not indicated. [r] Lit.[49] mp 153−4 °C. [s] Lit.[50] mp 117−9 °C. [t] Lit.[51] mp 116 °C. [u] N: calcd, 11.29; found, 10.8. [v] The variability in the glutamic acid-induced convulsion test is between 15 and 25%. [w] Method E: commercially available product (Aldrich).

ies suggest that riluzole may have neuroprotective effects in whole animals, and this has indeed been demonstrated in animal models of cerebral ischemia.[16,17] Clinical studies have also demonstrated that riluzole slows disease progression in amyotrophic lateral sclerosis.[18]

In this paper, we describe the synthesis of many close analogues of riluzole, thus showing the crucial importance of the 6-substituent of these benzothiazoles, and the preparation of 3-substituted derivatives of riluzole and their in vivo "antiglutamate" activity. All the compounds were evaluated, together with reference drugs, for their ability to protect against seizures induced by intracerebroventricular administration of glutamic acid in rats.

Chemistry

6-Substituted-2-benzothiazolamines. 2-Benzothiazolamines **1**−**37** bearing various substituents in the 6-position are listed in Table 1. Scheme 1 shows the classical synthetic route[19] used for the preparation of most of them: **1, 3, 5, 8, 9, 13, 15**−**37**. One-pot reaction of the appropriate aniline with thiocyanogen generated from bromine and alkaline thiocyanate in acetic acid medium led to formation of the desired products in good to moderate yields (method A). The starting anilines have been described in the literature, except 4-(2,2,2-trifluoroethyl)aniline which was prepared by reduction of the corresponding nitro compound. Another classical way[20] previously used for the preparation of 2-benzothiazolamines is cyclization of phenylthioureas with bromine in chloroform (Scheme 2, method B): compounds **6, 11,** and **12** were thus prepared.

Scheme 1

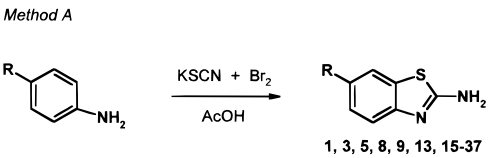
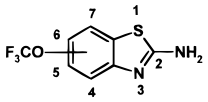


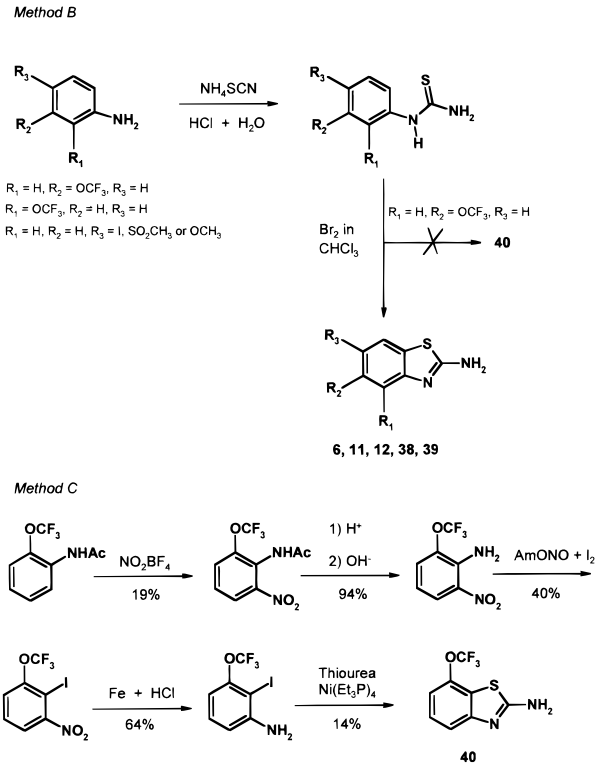
Table 2. Physical Properties and "Antiglutamate" Activity of Trifluoromethoxy-2-benzothiazolamines



no	OCF_3 position	method	formula[a]	mp,°C	cryst. solvent	protection against glutamic acid-evoked convulsions ED_{50}, mg/kg i.p.[c]
1	6	A	$C_8H_5F_3N_2OS$	119	$EtOH-H_2O$	3.2
38	4	B	$C_8H_5F_3N_2OS$	132	CCl_4	>10
39	5	B	$C_8H_5F_3N_2OS$,HCl	158	*d*	>10
40	7	C	$C_8H_5F_3N_2OS$ [b]	108	*e*	>10

[a] Microanalysis results were within ±0.4% of theoretical values unless otherwise indicated. [b] Determined for C, H, N. [c] The variability in the glutamic acid-induced convulsion test is between 15 and 25%. [d] Washed with acetone. [e] Purified on a silica gel column.

Scheme 2



Compounds **2, 4**, and **10** are commercially available and **7** was obtained through reduction of the corresponding nitro compound **10**. Positional isomers of riluzole were synthesized as outlined in Scheme 2 according to method B and are listed in Table 2. Two isomers, **38** and **39**, with the trifluoromethoxy group at the 4- or 5-position were obtained from the corresponding ortho or meta thioureas. Cyclization of this last thiourea did not give the 7-trifluoromethoxylated isomer **40**; it only gave the 5-trifluoromethoxylated isomer **39**. Synthesis of **40** was achieved via a five-step procedure (Scheme 2, method C): Nitration of 2-trifluoromethoxyacetanilide with nitronium tetrafluoroborate afforded a mixture of mononitrated products which, after separation and hydrolysis, yielded the 2-nitroaniline isomer; this compound was treated with amyl nitrite and iodine to give the corresponding 2-iodonitro derivative. After reduction, the resulting 2-iodoaniline was finally cyclized into **40** by using thiourea and $Ni(Et_3P)_4$[21] generated in situ from bis(triethylphosphine)nickel(II) chloride and sodium cyanoborohydride as a reducing agent. The trimethylsilyl derivative, **14**, was prepared as

Scheme 3

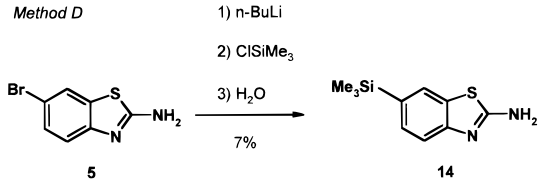
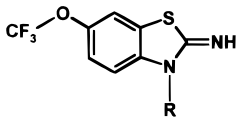


Table 3.
3-Substituted-2-imino-6-trifluoromethoxy-benzothiazolines



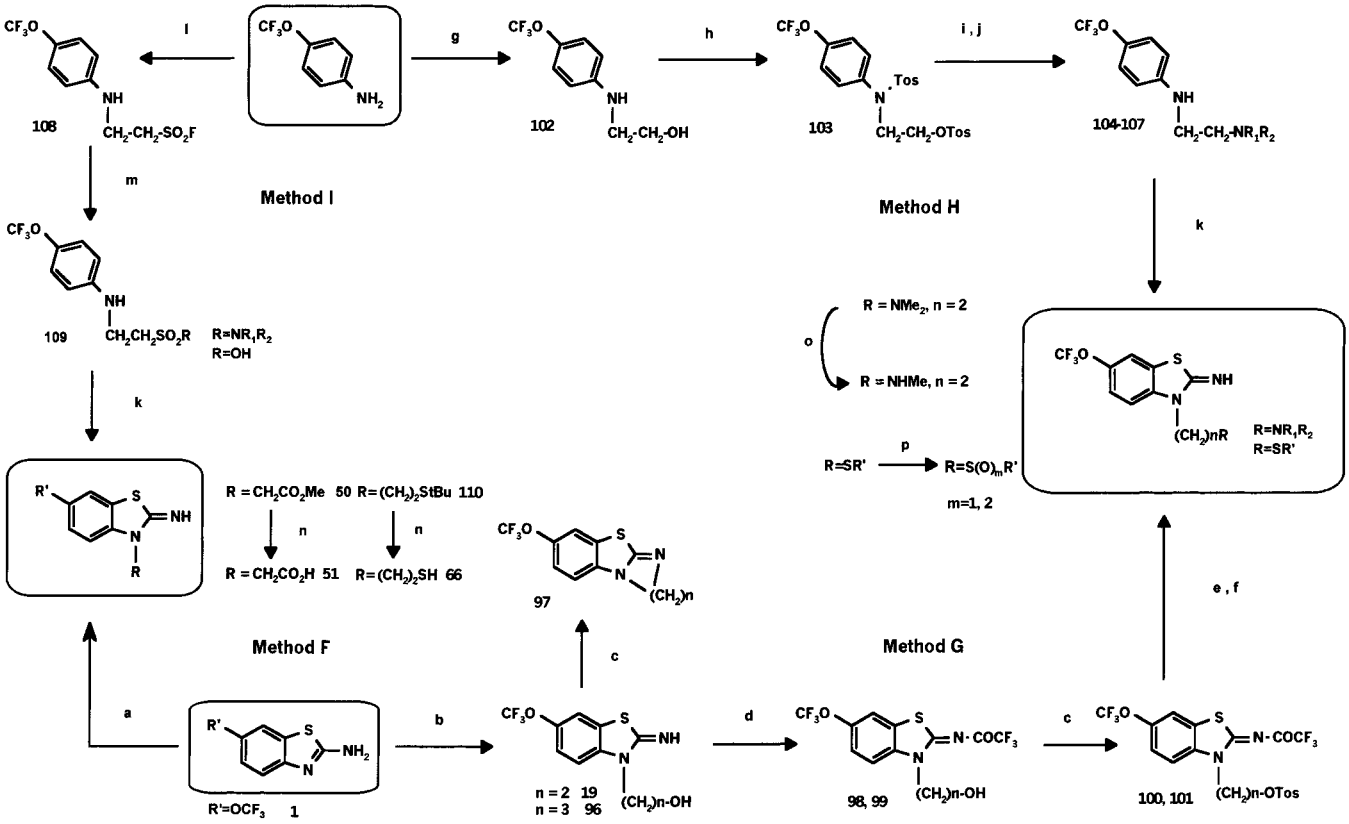
no	R	method	protection against glutamic acid-evoked convulsions ED_{50}, mg/kg i.p.[a]
1	H (riluzole)		3.2
41	methyl	F	5.0
42	ethyl	F	5.0
43	*n*-propyl	F	4.5
44	*n*-butyl	F	10
45	allyl	F	7.0
46	propargyl	F	4.0
47	CH_2CN	F	3.5
48	CH_2Ph	F	>10
49	$(CH_2)_2Ph$	F	>10
50	CH_2CO_2Me	F	>10
51	CH_2CO_2H		>10
52	CH_2CONH_2	F	7.0
53	CH_2CONEt_2	F	9.0
54	$(CH_2)_2SO_2NH_2$	I	6.0
55	$(CH_2)_2SO_2NHMe$	I	4.0
56	$(CH_2)_2SO_2NMe_2$	I	>10
57	$(CH_2)_2SO_3H$	I	>10
58	$(CH_2)_2OH$	F	8.0

[a] The variability in the glutamic acid-induced convulsion test is between 15 and 25%.

shown in Scheme 3 (method D). The bromo compound **5** was treated with *n*-butyllithium and chlorotrimethylsilane to give after hydrolyses the desired product, **14**, in a low but not optimized yield.

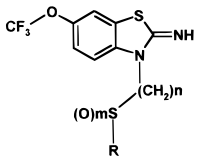
3-Substituted-2-imino-benzothiazolines. Compounds listed in Tables 3−6 were synthesized by the routes outlined in Scheme 4. Alkylation of 6-trifluoromethoxy-2-benzothiazolamine **1** occurred exclusively on the endocyclic nitrogen, at the 3-position. [22] The reaction was carried out very easily by mixing **1** and the alkylating agent R−X in an alcohol, methylethyl ketone, or dimethylformamide and refluxing the mixture for several hours (method F). In many experiments, salts of the expected products precipitated. The simplic-

Scheme 4[a]



[a] Reagents: (a) RX, EtOH or MEK or DMF, reflux; (b) $Br(CH_2)_nOH$, EtOH, reflux; (c) TosCl, pyridine, 0 °C−rt, (d) CF_3CO_2Et, Et_3N, EtOH, rt; (e) $R_1R_2NH_2$, $NaHCO_3$, DMF, 80 °C or R′SNa, DMF; (f) aqueous K_2CO_3, MeOH, rt; (g) $Br(CH_2)_2OH$, 160 °C; (h) TosCl, Et_3N, CH_2Cl_2, 0 °C−rt; (i) R_1R_2NH, $NaHCO_3$, DMF, 80 °C; (j) HCl, aqueous AcOH, reflux; (k) Br_2, KSCN, AcOH, rt; (l) $CH_2{=}CHSO_2F$, DMF, rt; (m) R_1R_2NH, acetone, reflux or AcOH, reflux; (n) aqueous HCl or HBr, reflux; (o) VOC-Cl, DBU, CH_2Cl_2, rt, then aqueous HCl, MeOH, reflux; (p) 1 equiv mCPBA, EtOH, −35 °C (m = 1) or 2 equiv mCPBA, CH_2Cl_2, rt (m = 2).

Table 4. Sulfur-Containing 3-Substituted Benzothiazolines



no.	$S(O)_m$−R: R	m	n	method	protection against glutamic acid-evoked convulsions ED_{50}, mg/kg i.p.[a]
59	Me	0	1	F	3.0
60	Me	1	1		2.3
61	Me	0	2	F	**1.0**
62	Et	0	2	F	2.2
63	Pr	0	2	F	2.4
64	Me	1	2		**1.1**
65	Me	2	2		1.8
66	H	0	2		2.0
67	Ph	0	2	F	4.5
68	Ph	1	2		4.2
69	Me	0	3	G	4.2
70	Me	1	3		2.3
71	Me	2	3		5.0

[a] The variability in the glutamic acid-induced convulsion test is between 15 and 25%.

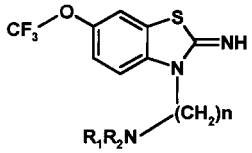
ity of this reaction and the availability of many potential alkylating reagents allowed a rapid synthesis of a large number of compounds: **41**−**50, 52, 53, 58, 59, 61**−**63, 67, 73**−**75.** Yields were moderate or low, except for molecules containing a thioether group on the side chain, due to β-halosulfide reagent activation via an electrophilic episulfonium.[23] In some cases, especially when the required alkylating agents R−X were not commercially available, alternative methods were used.

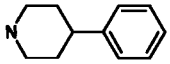
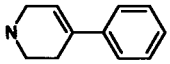
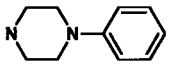
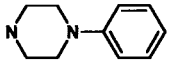
According to method G, riluzole reacted with an appropriate hydroxyalkyl bromide to give **58** or **96**.[24] When treated by *p*-toluenesulfonyl chloride, the alcohol **58** did not give the corresponding tosylate since, predictably, intramolecular nucleophilic attack of the imino group occurred, leading to the tricyclic derivative **97**. This cyclization also occurred spontaneously with acetyl, trityl, or *t*-Boc-imino protected compounds.[25] To overcome this difficulty, imine nitrogen nucleophilicity was decreased by imine acylation with an electron-withdrawing group such as trifluoroacetyl (compounds **98** and **99**); thus the tosylates **100** and **101** were isolated with a good yield and reacted with appropriate thiolate R′SNa or amines R_1R_2NH to give the expected compounds **69, 80**, and **81.** However, yields were still low (10−30%), except for **69** (83%).

Method H avoided cyclization side reactions by reacting 2-bromoethanol with 4-trifluoromethoxy aniline.[26] The resulting compound **102** was tosylated to give the ditosylate **103,** which was then condensed with an appropriate amine R_1R_2NH to give **104**−**107** after acid hydrolyses. Ring closure to the benzothiazoline derivatives **76**−**79** was effected by thiocyanogen generated in situ from bromine and potassium thiocyanate in acetic acid medium.[27] Overall yield remained low due to the nonoptimized thiazole ring formation step.

Sulfonamides **54, 55, 56** and sulfonic acid **57** were synthesized according to method I. Michael addition of

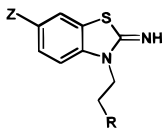
Table 5. Nitrogen-Containing 3-Substituted Benzothiazolines



no.	NR_1R_2	n	Method	Protection against glutamic acid-evoked convulsions ED_{50} mg/kg i.p.[a]
72	NHMe	2		>10
73	NMe_2	2	F	**2.3**
74		2	F	**2.0**
75	NMe_2	3	F	9.0
76	$N(Me)CH_2Ph$	2	H	7.0
77	$N(Me)(CH_2)_2Ph$	2	H	5.0
78		2	H	**3.0**
79		2	H	**2.2**
80		2	G	**3.5**
81		3	G	10.0

[a] The variability in the glutamic acid-induced convulsion test is between 15 and 25%.

Table 6. Simultaneous Modifications in Positions 3 and 6



no.	R	Z	protection against glutamic acid-evoked convulsions ED_{50}, mg/kg i.p.[a]
82	NMe_2	H	>10
73	NMe_2	OCF_3	2.3
83	NMe_2	*t*-Bu	>10
84	S(O)Et	*t*-Bu	>10
85	S(O)Et	*n*-Bu	>10
86	S(O)Et	OCF_3	1.2
87	S(O)Et	CF_3	1.7
88	$S(O)_2Et$	C_2F_5	2.1
89	$S(O)_2Et$	OC_2F_5	2.6

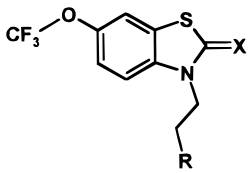
[a] The variability in the glutamic acid-induced convulsion test is between 15 and 25%.

4-trifluoromethoxyaniline to ethenesulfonyl fluoride easily gave **108**,[28] which was converted into either the expected benzothiazoline sulfonamides by reaction with appropriate amines or the sulfonic acid by hydrolysis in aqueous acetic acid, followed by the usual thiazole ring closure.

Compounds **51** ($R = CH_2CO_2H$) and **66** ($R = (CH_2)_2$-SH) could not be obtained directly from riluzole by reaction with the functionalized reagent; they were thus prepared in a two-step process after acidic hydrolyses of their benzothiazoline precursors **50** ($R = CH_2CO_2$-Me) and **110** ($R = (CH_2)_2S$*t*Bu), respectively. Vinylchloroformate (VOC-Cl) monodemethylation of the dimethylamino derivative **73** ($R = (CH_2)_2N(CH_3)_2$ gave **72**.[29] Sulfoxides (compounds **60, 64, 68,** and **70)** and sulfones (compounds **65** and **71)** were prepared from their respective parent thioethers by oxidation with *m*-chloroperbenzoic acid (mCPBA). Use of 1 equiv of mCPBA in ethanol at −35 °C afforded sulfoxides, whereas 2 equiv of mCPBA in dichloromethane at room temperature gave sulfones.

The 6-substituted analogues of the most active benzothiazolines bearing amino- and sulfur-containing side chains are listed in Table 6; they were obtained following the same synthetic pathway (method F) as the trifluoromethoxylated compounds, a pathway starting from the corresponding benzothiazoles. The importance of the imino group of the thioether-containing compounds **61** and **62** was demonstrated by the synthesis of imino-modified benzothiazolines (Table 7, Schemes 5 and 6). Imino alkylated benzothiazolines **90** and **91** were obtained by direct alkylation of the N-2-alkylated benzothiazoles **113** and **114** with chloroethyl-methyl-(or ethyl)-sulfide (Scheme 5). Acetylation of **61** provided **94**. Reaction of the tricyclic key intermediate **116** with hydroxylamine and methoxylamine led, after alkylation of the free thiol, to oximes **92** and **93,** respectively, whereas ring opening with sodium methoxide gave directly the 2-benzothiazolone **95** (Scheme 6).[30] The

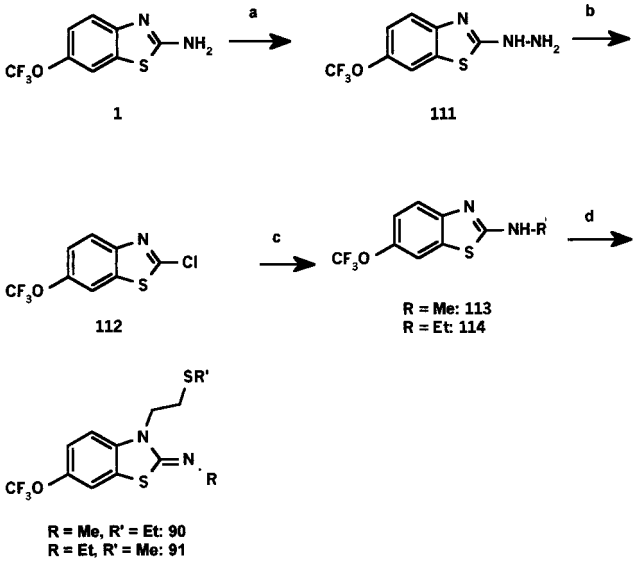
Table 7. Simultaneous Modifications in Positions 2 and 3



no.	R	X	protection against glutamic acid-evoked convulsions ED_{50}, mg/kg i.p.[a]
62	SMe	NH	2.2
90	SEt	NMe	3.7
91	SMe	NEt	8.5
92	SEt	NOMe	>10
93	SEt	NOH	>10
94	SMe	NCOMe	>10
95	SMe	O	>10

[a] The variability in the glutamic acid-induced convulsion test is between 15 and 25%.

Scheme 5[a]



[a] Reagents: (a) NH_2NH_2, (b) $SOCl_2$, (c) aqueous RNH_2, (d) $Cl(CH_2)_2SR'$, MEK, reflux.

same reaction performed with sodium methyl sulfide did not lead to 2-benzothiazolethione, but unexpectedly stopped at a stable tricyclic benzothiazole derivative **119** (inactive in our tests), which contains a rarely observed four-heteroatom-substituted carbon atom.

Results and Discussion

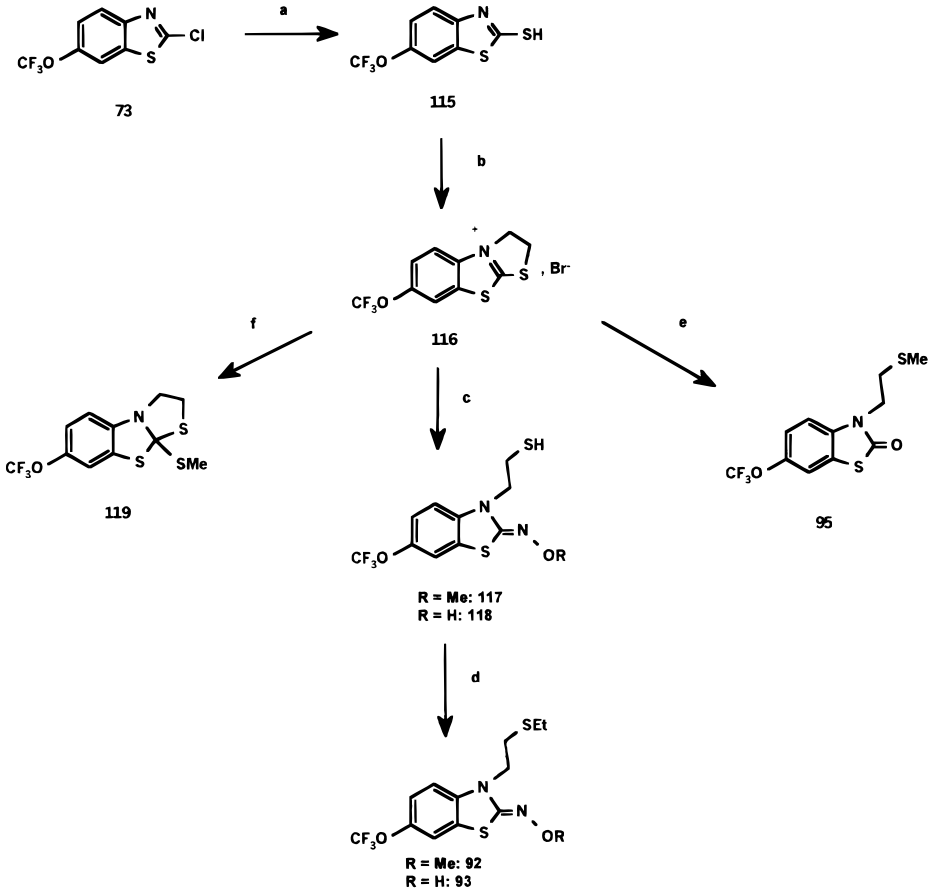
Compounds **1**−**95** were evaluated for their ability to protect against seizures induced by intracerebroventricular administration of glutamic acid in rats[31] (see Experimental Section). The in vivo "antiglutamate" activity of the studied compounds is listed in Tables 1−7. In this test, the noncompetitive NMDA receptor antagonist dizocilpine ((±)MK-801, see Table 1) was found to be active with an ED_{50} of 2.2 mg/kg i.p. (administered 10 min before challenge).

6-Substituted-2-benzothiazolamines. In this test, riluzole **1** had an ED_{50} of 3.2 mg/kg i.p., whereas the unsubstituted 2-benzothiazolamine **2** was much less active. Many 6-substituted-2-benzothiazolamines such as compounds **7** (R = NH_2), **8** (R = CN), **9** (R = $CO_2C_2H_5$), **10** (R = NO_2), **11** (R = SO_2CH_3), **12** (R = OCH_3), **13** (R = O-*t*-C_4H_9), **16** (R = C_6H_5), and **29** (R = $COCF_3$) displayed very weak activity ($ED_{50} \geq 10$ mg/kg i.p.). Thus electronic factors seem to be relatively unimportant, since substitution with electron-donating groups as well as electron-withdrawing groups at the 6-position did not increase the activity of the parent compound **2**. Additional evidence for this trend comes from comparison of the activity for the 6-trifluoromethoxy derivative **1** with the 6-chloro derivative **4** (ED_{50} = 3.2 mg/kg i.p. vs ED_{50} > 10 mg/kg i.p., respectively). It is known that the trifluoromethoxy group deactivates the benzene ring by inductive electron withdrawal and donates electrons by resonance exactly as does chlorine.[32] Replacement of chlorine by such a "pseudohalogen" in compounds of medicinal interest has frequently resulted in active compounds; for example the 7-chloro substituent in diazepam was replaced by a trifluoromethoxy group with retention of activity.[33] Thus it appears that riluzole's in vivo activity depends essentially on nonelectronic factors such as lipophilicity.

Examination of the structure of the most potent compounds in the series gave support to this hypothesis: all the significantly active compounds fell into two sets: (1) compounds bearing a rather large alkyl substituent and (2) compounds bearing a polyfluoroalkyl or a polyfluoroalkoxy substituent. (1) On varying the size of the alkyl moiety it appeared that there was an optimal size for activity. Among the linear alkyl substituted derivatives (compounds **17**−**19, 21, 23, 26, 27**), the most potent is **21** (R = C_4H_9). Lengthening or shortening the chain decreased the potency (C_4H_9 > C_3H_7 ~ C_2H_5 > CH_3 and C_4H_9 > C_5H_{11} ~ C_6H_{13} > C_7H_{15}). Changing the butyl group (compound **21**) to a *tert*-butyl group (compound **22**) or a trimethylsilyl group (compound **14**) did not affect the activity; on the other hand, decreasing the size of branched substituents (compound **20**, R = isopropyl) or increasing the size (compounds **24**, R = *t*-C_5H_{11}, **25**, R = CH_2-*t*-C_4H_9) led to compounds with weak activity (ED_{50} > 10 mg/kg i.p.). (2) Compounds closely related to riluzole **1,** 6-pentafluoroethoxy-2-benzothiazolamine **35** and perfluoroalkyl derivatives **36** and **37** displayed strong "antiglutamate" activities with ED_{50} values of 2.5 mg/kg i.p. Replacement of one or more fluorine atoms by hydrogens always decreased the activity (**28** (R = CH_2CF_3) < **36** (R = C_2F_5); **31** (R = $OCHF_2$) < **1** (R = OCF_3); **34** (R = OCF_2-CHF_2) < **35** (R = OC_2F_5)). All these results are consistent with lipophilicity of the substituent at the 6-position as a major contributing factor for "antiglutamate" activity. Calculated ClogP[34] of compounds listed in Table 1 showed that values around 4.0 are the most favorable in the alkyl series, whereas a wider range is observed in the fluorinated series: 2.96 (compound **37**)−5.15 (compound **35**). Thus, in this latter series no clear-cut correlation can be made between ClogP and biological activity since in vivo testing involves not only drug−receptor interactions but also additional parameters such as bioavailability, metabolism, and brain penetration. In addition, the trifluoromethoxy group position on the aromatic ring was of crucial importance, since all positional isomers of riluzole (compounds **38**−**40**) have ED_{50} values of >10 mg/kg i.p. (Table 2).

From the in vivo data obtained in this study we can only speculate that the moiety in the 6-position in

Scheme 6[a]



[a] Reagents: (a) thiourea, 1 N H_2SO_4, 60 °C; (b) 1,2-dibromoethane, DMF; (c) NH_2OR, 1 N NaOH, refulx; (d) EtONa, EtOH, EtBr, rt; (e) MeONa, MeOH, reflux; (f) MeSNa, EtOH, rt.

riluzole or in its active analogues is an essential anchorage point allowing lipophilic interactions at a binding site, but influence of other parameters such as bioavailability and/or other mechanisms of action cannot be ruled out. Study of this series of compounds in relevant in vitro tests would be required to corroborate this hypothesis and thereby to allow quantitative structure−activity relationship (QSAR) analysis of substituent effects. QSAR analysis of a set of substituted benzothiazoles has already been done using sodium flux measurements in rat cortical membranes as an in vitro test.[35] Our conclusions are similar to those reached by Hays et al.: need for a small liphophilic substituent and emphasis on other probable mechanisms of action limiting QSAR interpretation and responsible for in vivo effects.

3-Substituted-2-imino-benzothiazolines. In contrast with the 2-methylamino-6-trifluoromethoxy-benzothiazole **113** which was inactive at 10 mg/kg i.p. (data not shown), the 3-methyl derivative **41** displayed a good anticonvulsant activity (ED_{50} = 5 mg/kg i.p.). This encouraging result prompted us to study systematically the substituent influence at the 3-position (Table 3). Replacement of the methyl group by another aliphatic chain such as an ethyl, propyl, allyl, or propargyl group (compounds **42, 43, 45,** and **46,** respectively) did not substantially affect the activity, whereas introduction of larger alkyl substituents (e.g., butyl, compound **44**) or aromatic substituents (compounds **48** and **49**) reduced the potency dramatically. At this stage, we prepared some functionalized benzothiazolines: ester (**50**), amides (**52** and **53**), sulfonamides (**54**−**56**), carboxylic acid (**51**), sulfonic acid (**57**), and alcohol (**58**) did not display more potency than riluzole, and no clear-cut correlation between structure and activity can be deduced.

A significantly enhanced "antiglutamate" activity was obtained by introduction of nitrogen- or sulfur-containing 3-substituents. Concerning the sulfur-containing series, results showed that the methylthioethyl derivative **61** was one of the most potent benzothiazolines with an ED_{50} of 1 mg/kg i.p. (Table 4). Surprisingly, the corresponding sulfoxide **64** and sulfone **65** were as active as their parent thioether. This might suggest that the active molecule in vivo is in fact a common metabolite.[36] Lengthening or shortening the alkyl chain by one carbon atom (compounds **59, 60**, and **69**−**71**), as well as the replacement of the methylthio group by a thiol or larger and/or aromatic substituents (compounds **62, 63, 67,** and **68**), resulted in a loss of anticonvulsant effect; however, all compounds diplayed a reasonable level of activity ($ED_{50} \leq 5$ mg/kg i.p.). Looking at the amino-containing series, in contrast to the monomethylated compound **72**, the dimethylaminoethyl-substituted benzothiazoline **73** and the cyclic analogue **74** demonstrated good anticonvulsant potency with an ED_{50} value of about 2 mg/kg i.p. (Table 5). Homologation of **73** to the aminopropyl derivative **75** resulted in a reduced protective effect, thus indicating the β-position of the amino group to be preferable. Replacement in **73** of the

Table 8. Neuroprotective Activities of Selected Benzothiazolines

	ED_{50} (mg/kg i.p.)	
no.	Glu[a]	H.H.[b]
61	1.0	14.0
64	1.1	5.5
65	1.8	2.5−10
73	2.3	4.0
74	2.0	<5
78	3.0	2.5−10
79	2.2	2.5−10
80	3.5	5.5
81	10.0	>10
riluzole	3.2	4.0

[a] Protection against glutamic acid-evoked convulsions in rats. The variability in this test is between 15 and 25%. [b] Protective effect against mortality induced by hypobaric hypoxia in mice. The variability in this test is 20%.

dimethylamino group by a group containing an aromatic moiety such as *N*-methyl-*N*-benzylamino group (**76**) or *N*-methyl-*N*-phenethylamino group (**77**) gave compounds with reduced potency. Unexpectedly however, the 4-phenyl-piperidinyl derivative **78** as well as the 4-phenyl-1,2,3,6-tetrahydropyridyl and 4-phenyl-piperazinyl analogues (compounds **79** and **80**, respectively) displayed a high level of activity in the same range (ED_{50} = 2−3 mg/kg i.p.). In this series, as for the aminated aliphatic one, lengthening of the alkyl chain (compound **81**) decreased "antiglutamate" activity.

To study simultaneous modifications at the 3- and 6-positions, the 6-trifluoromethoxy groups of three of the most active benzothiazolines were replaced by other substituents which had been shown previously to be the most efficient in the benzothiazole series, i.e., polyfluoroalkoxy, polyfluoroalkyl, and alkyl groups (Table 6). Surprisingly, from these three series of derivatives, only the 6-polyfluoroalkyl- (compounds **87** and **88**) and 6-polyfluoroalkoxy- (compounds **73**, **86**, and **89**) substituted compounds displayed high and comparable potencies, suggesting that the presence of an electron-withdrawing group containing fluorine atoms is of crucial importance.

Furthermore, the importance of the 2-imino group in the thioalkyl series was illustrated by the slight (compound **90**) or more dramatic (compound **91**) decrease of activity observed with the 2-N-alkylated-iminobenzothiazolines. A decrease was also seen with the 2-N-hydroxylated and 2-N-acylated derivatives (compounds **92**−**94**), as well as with the keto analogue **95** (Table 7).

Neuroprotective Activities of Selected Compounds. Some of the most active and representative benzothiazolines have been evaluated for their protective effects against mortality induced by hypobaric hypoxia.[37] As shown in Table 8, all compounds studied display high protective activities following i.p. administration. Activities in the hypobaric hypoxia model are very similar to that of riluzole, except for the thioether **61** which, surprisingly, is about 3 times less effective. ED_{50} values for the other compounds range between 2.5 and 10 mg/kg, thus showing the potential neuroprotective activity of riluzole derivatives.

Conclusions

A series of 6-substituted-2-benzothiazolamines was first evaluated against seizures induced by intracerebroventricular administration of glutamic acid in rats. Two sets of products were shown to be active in this model: compounds bearing a large but not too large alkyl substituent, and compounds bearing a polyfluoroalkyl or a polyfluoroalkoxy substituent. These biological data suggest that the 6-substituted-2-benzothiazolamine series possesses excitatory amino acid antagonist activity. This may endow members of this series with interesting anticonvulsive and neuroprotective properties. Indeed, riluzole, a lead in this series, has been shown to be neuroprotective in curative treatment in animal models of focal and global ischaemia[17] and had been selected for clinical trials in amyotrophic lateral sclerosis where it showed efficacy in slowing disease progression.

As a second step, 3-substituted-2-imino-benzothiazolines were evaluated in the same test. It was shown that a wide variety of modifications in the 3-position of riluzole were possible. Of all the analogues, compounds as active as riluzole or up to 3 times more potent were found among benzothiazolines bearing heteroatoms in the β-position of the alkyl substituent; the dialkylaminoethyl- and unchanged or oxidized alkylthioethyl-benzothiazolines are strong "antiglutamate" compounds in vivo, twice as active as the noncompetitive NMDA antagonist dizocilpine. The most potent glutamic acid antagonists in vivo protected mice against mortality induced by hypobaric hypoxia, a simple pharmacological test capable of predicting neuroprotective potential for these compounds. Anti-ischemic activities of RP 66055 (3-{2-[1-(4-fluorophenyl-piperazinyl)]ethyl}-2-imino-6-trifluoromethoxybenzothiazoline), a fluorinated derivative of the benzothiazoline **80**, were recently reported.[38]

Experimental Section

Melting points were determined on a Köfler apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP 200 (200 MHz), a Bruker WM 250 (250 MHz), or a Bruker AM 400 (400 MHz). IR spectra were taken on a FT-IR Nicolet 60 SX-R, a Perkin-Elmer 580 B, or a Perkin-Elmer 983 G. Mass spectra were recorded on a Finnigan 3300 spectrometer (EI at 70 eV) or on a Nermag R10-10B (DCl, NH_3). NMR data are reported in ppm downfield relative to external TMS (0 ppm) as standard. Elemental analyses are indicated by the symbol of the elements, and the results were within ± 0.4% (for C, H, Br, Cl, F, N, S) of the theoretical values unless otherwise noted. Medium-pressure chromatographic separations were performed on silica gel (0.04−0.063 mm supplied by Merck). All organic solutions were dried over magnesium sulfate. Yields are not optimized. Compounds **1, 3, 5**−**9, 11, 12, 15**−**21, 30,** and **37** were prepared according to literature procedures.[19,39−52]

Method A. 6-Pentyl-2-benzothiazolamine (23). 4-Pentylaniline (4.9 g; 0.03 mol), AcOH (45 mL), and potassium thiocyanate (11.6 g; 0.12 mol) were stirred at 19 °C for 10 min, and then a solution of bromine (1.5 mL; 0.03 mol) in AcOH (20 mL) was added over 20 min; during the addition, the temperature rose to 35 °C. The reaction mixture was stirred for 21 h at room temperature, then poured into cold water (600 mL), made alkaline with 28% aqueous NH_4OH (∼90 mL), and extracted with EtOAc (250 + 150 mL). The organic phase was washed with water (150 mL), dried, filtered, and evaporated. A crude yellow product was obtained which was chromatographed on silica gel (500 g) eluted with 5:5 cyclohexane−EtOAc and crystallized from cyclohexane (55 mL) to yield **23** as white pearly crystals (4.3 g; 71%): mp 122 °C; NMR (DMSO, 200 MHz) δ 0.82 (t, 3H, CH_3), 1.36 (m, 4H, 2 CH_2), 1.55 (quint, 2H, CH_2), 2.55 (t, 2H, CH_2Ar), 6.97 (dd, 1H, H5), 7.22 (d, 1H, H4), 7.32 (bs, 2H, NH_2), 7.92 (d, 1H, H7); IR (KBr) 820, 865,

1055, 1105, 1285, 1300, 1465, 1530, 1560, 1625, 2850, 2865, 2920, 2950, 3100, 3275, 3430 cm^{-1}; MS *m/z* 220 (M^+), 163 ($M^+ - (CH_2)_3CH_3$). Anal. ($C_{12}H_{16}N_2S$) C, H, N, S.

Fourteen other new compounds were synthesized according to method A: **13** (28%), Anal. ($C_{11}H_{14}N_2OS$) C, H, N, S; **22** (68%), Anal. ($C_{11}H_{14}N_2S$) C, H, N, S; **24** (65%), Anal. ($C_{12}H_{16}N_2S$) C, H, N, S; **25** (54%), Anal. ($C_{22}H_{16}N_2S$) C, H, N, S; **26** (41%), Anal. ($C_{13}H_{18}N_2S$) C, H, N, S; **27** (65%), Anal. ($C_{14}H_{20}N_2S$) C, H, N, S; **28** (29%), Anal. ($C_9H_7F_3N_2S$) C, H, F, N, S; **29** (11%), Anal. ($C_9H_5F_3N_2OS$) C, H, F, N, S; **31** (52%), Anal. ($C_8H_6F_2N_2OS$) C, H, F, N, S; **32** (43%), Anal. ($C_9H_7F_3N_2OS$) C, H; **33** (39%), Anal. ($C_{10}H_7F_5N_2OS$) C, H, F, N, S; **34** (50%), Anal. ($C_9H_6F_4N_2OS$) C, H, F, N, S; **35** (55%), Anal. ($C_9H_5F_5N_2OS$) C, H, F, N, S. Base **36** was converted to the hydrochloride and crystallized as noted in Table 1: **36** (18%), Anal. ($C_9H_6F_3NS\cdot HCl$) C, H, Cl, F, N.

4-(2,2,2-Trifluoroethyl)aniline. The starting material for **24** was prepared as follows: To a stirred solution of 4-(2,2,2-trifluoroethyl)nitrobenzene[53] (3.8 g; 0.0185 mol) in EtOH (20 mL) was added 5% Pd/C (0.17 g), and then a solution of hydrazine hydrate (1.8 mL; 0.036 mol) in EtOH (10 mL) was added dropwise over 20 min; during the addition the reaction temperature rose to 44 °C. After addition, the mixture was refluxed for 15 min and cooled to room temperature. The catalyst was filtered off, and the filtrate was concentrated, then diluted with water, and extracted with EtOAc (200 mL). The organic phase was dried and the solvent evaporated under reduced pressure to yield a yellow oil (2.7 g; 83%) which was purified by chromatography on silica gel. Elution with 7:3 cyclohexane−EtOAc gave 4-(2,2,2-trifluoroethyl)aniline as an oil (2.3 g; 71%): NMR ($CDCl_3$, 200 MHz) δ 3.25 (q, $J = 10$ Hz, 2 H, CH_2CF_3), 3.60 (mf, 2H, NH_2), 6.66 (dd, 2H, H3, H5), 7.10 (bd, 2H, H2, H6); MS *m/z* 175 (M^+), 106 ($M^+ - CF_3$).

Method B. 4-(Trifluoromethoxy)-2-benzothiazolamine (38). Step 1. *N*-[2-(Trifluoromethoxy)phenyl]thiourea. A stirred solution of 2-(trifluoromethoxy)aniline[54] (17.7 g; 0.1 mol), ammonium thiocyanate (8 g; 0.105 mol), sodium hydrogen sulfite (0.7 g), and 20% hydrochloric acid (18.2 mL) was heated at 90 °C for 14 h. The cooled mixture was filtered, washed with water to neutrality, triturated with isopropyl ether, filtered, and dried to give the desired product as a white solid (16 g; 68%): mp 157 °C; NMR ($CDCl_3$, 200 MHz) δ 6.25 (mf, 2H, NH_2), 7.30−7.60 (rnt, 5H, Ar), 7.87 (mf, 1H, NH); IR (KBr) 725, 775, 1065, 1155, 1175, 1220, 1265, 1310, 1450, 1490, 1520, 1590, 1615, 1625, 3030, 3075, 3150, 3250, 3425 cm^{-1}; MS *m/z* 236 (M^+), 219 ($M^+ - NH_3$), 151 ($M^+ - OCF_3$). Anal. ($C_8H_7F_3N_2OS$) C, H, F, N, S.

In a similar way, starting from 3-(trifluoromethoxy)aniline (4 g; 0.024 mol), *N*-[3-(trifluoromethoxy)phenyl]thiourea was obtained as a white solid (1.7 g; 30%): mp 86 °C; MS *m/z* 236 (M^+), 203 ($M^+ - SH$).

Step 2. 4-(Trifluoromethoxy)-2-benzothiazolamine (38). To a stirred suspension of *N*-[2-(trifluoromethoxy)phenyl]-thiourea (16 g; 0.068 mol) in $CHCl_3$ (130 mL) was added dropwise a solution of bromine (7 mL; 0. 136 mol) in $CHCl_3$ (15 mL). The reaction mixture was refluxed for 2.5 h and allowed to stand at room temperature overnight. The mixture was evaporated to dryness in vacuo, and the orange residue was treated with diluted NH_4OH and extracted with CH_2Cl_2 (2 × l50 mL), dried, filtered, and evaporated. A yellowish solid (14 g) was obtained which was crystallized twice from CCl_4 to yield **38** as white crystals (6.5 g; 41%): mp 132 °C; NMR ($CDCl_3$, 200 MHz) δ 7.08 (t, $J = 9$ Hz, 1H, H6), 7.17 (mf, 2H, NH_2), 7.21 (mt, 1H, H5), 7.5 (dd, 1H, H7); IR (KBr) 710, 785, 1055, 1175, 1250, 1285, 1430, 1470, 1540, 1575, 1605, 1640, 1645, 3100, 3250, 3295, 3495 cm^{-1}; MS *m/z* 234 (M^+), 214 ($M^+ - HF$), 165 ($M^+ - CF_3$). Anal. ($C_8H_5F_3N_2OS$) C, H, F, N, S.

By the same method, starting from *N*-[3-(trifluoromethoxy)-phenyl]thiourea (12.8 g; 0.054 mol), 5-(trifluoromethoxy)-2-benzothiazolamine (3 g) was obtained after chromatography on silica gel, eluting with 8:1:1 toluene−MeOH−diethylamine. The base was converted to the hydrochloride and washed with acetone to give **39** (3.2 g; 22%): mp 158 °C; NMR (base) (DMSO, 200 MHz) δ 7.00 (bd, $J = 8.0$ Hz, 1H, H6), 7.27 (mf, 1H, H4), 7.75 (mf + d, 3H, NH_2, H7); IR (KBr) 800, 865, 1175, 1215, 1250, 1485, 1550, 1600, 1610, 1650, 3050, 3150, 3280, 3400 cm^{-1}; MS *m/z* 234 (M^+), 207 ($M^+ - HCN$), 165 ($M^+ - CF_3$). Anal. ($C_8H_5F_3N_2OS\cdot HCl$) C, H, Cl, N, S.

Method C. 7-(Trifluoromethoxy)-2-benzothiazolamine (40). Step 1. 2-Nitro-6-(trifluoromethoxy)acetanilide. Nitronium tetrafluoroborate (20 g; 0.15 mol) was added in small portions over 40 min to a stirred solution of 2-(trifluoromethoxy) acetanilide[53] (21.9 g; 0.1 mol) in CH_3CN (200 mL) cooled at −30 °C. The reaction mixture was allowed to stand at −5 °C for 30 min and was poured into cold water. The solid thus obtained was filtered off, washed with water, and then crystallized in toluene (200 mL) to give 2-nitro-6-(trifluoromethoxy)acetanilide (3.6 g). The filtrate was concentrated under reduced pressure and chromatographed on alumina (700 g) containing water (3% w/w), eluting with toluene then CH_2Cl_2 to afford another crop (1.5 g). Total yield was 19%: mp 160 °C; NMR ($CDCl_3$, 200 MHz) δ 2.25 (s, 3H, $COCH_3$), 7.41 (t, $J = 9$ Hz, 1H, H4), 7.6 (d, $J = 9$ Hz, 1H, H5), 7.88 (mf, 1H, NH), 7.95 (dd, 1H, H3); IR (KBr) 675, 695, 735, 815, 805, 1080, 1175, 1210, 1260−1275, 1365, 1450, 1475, 1510, 1450, 1595, 1610, 1675, 3270 cm^{-1}; MS *m/z* 264 (M^+), 221 ($M^+ - COCH_3$).

Step 2. 2-Nitro-6-(trifluoromethoxy)aniline. A mixture of 2-nitro-6-(trifluoromethoxy) acetanilide (12.5 g; 0.0473 mol), EtOH (125 mL), and concentrated HCl (125 mL) was refluxed for 3.5 h, then concentrated under reduced pressure, poured onto ice−water (800 mL), made alkaline with 28% aqueous NH_4OH (95 mL), and extracted with EtOAc (4 × 250 mL). The organic layer was dried and evaporated to yield 2-nitro-6-(trifluoromethoxy)aniline as a yellow oil (9.9 g; 94%): NMR ($CDCl_3$, 200 MHz) δ 6.35 (mf, 2H, NH_2), 6.72 (dd, 1H, H4), 7.42 (bdd, 1H, H3), 8.10 (dd, 1H, H5); IR (CC14) 730, 1080, 1185, 1220, 1250, 1365, 1460, 1530, 1580, 1630, 3400, 3525 cm^{-1}; MS *m/z* 222 (M^+), 192 ($M^+ - NO$), 153 ($M^+ - CF_3$).

Step 3. 2-Iodo-3-(trifluoromethoxy)nitrobenzene. Iodine (65.8 g; 0.26 mol) followed by isoamylnitrite (10 mL; 0.075 mol) was added to a stirred solution of 2-nitro-6-(trifluoromethoxy)aniline (11 g; 0.05 mol) in $CHCl_3$ (200 mL). The reaction mixture was refluxed for 4 h and allowed to stand at room temperature overnight. The liquid phase was taken off and concentrated to give a purple oil (18 g) which was chromatographed on silica gel (700 g), eluting with 8:2 cyclohexane−EtOAc. 2-Iodo-3-(trifluoromethoxy)nitrobenzene was thus obtained as a red oil (6.7 g; 40%) suitable for use in the following step.

Step 4. 2-Iodo-3-(trifluoromethoxy)aniline. A mixture of 2-iodo-3-(trifluoromethoxy)-nitrobenzene (7 g; 0.021 mol), EtOH (65 mL), H_2O (65 mL), Fe (powder) (9.5 g), and concentrated HCl (2.2 mL) was refluxed for 4.5 h. The cooled mixture was poured into ice−water (500 mL), made alkaline with 28% aqueous NH_4OH (10 mL), and extracted with EtOAc (5 × 200 mL). The organic phase was dried, evaporated, and chromatographed on silica gel (400 g), eluting with 8:2 cyclohexane−AcOEt to give 2-iodo-3-(trifluoromethoxy)aniline as a light brown oil (4.1 g; 64%): NMR (DMSO, 300 MHz) δ 6.55 (d, $J = 9$ Hz, 1H, H4), 6.74 (dd, 1H, H6), 7.15 (t, $J = 9$ Hz, 1H, H5); IR (CCl_4) 715, 1025, 1080, 1170, 1215, 1265, 1460, 1470, 1570, 1615, 3070, 3375, 3475 cm^{-1}; MS *m/z* 303 (M^+), 175 ($M^+ - HI$).

Step 5. 7-(Trifluoromethoxy)-2-benzothiazolamine (40). A mixture of 2-iodo-3-(trifluoromethoxy)aniline (3.7 g; 0.012 mol), DMF (120 mL), thiourea (3.7 g), bis(triethylphosphine)-Ni^{II} (1.8 g), and sodium cyanoborohydride (1.5 g) was heated at 85 °C with stirring for 16 h. Additional bis(triethylphosphine)Ni^{II} (1 g) and $NaBH_3CN$ (0.7 g) were added, and heating was kept at 85 °C for 6 h. The reaction mixture was poured into water (600 mL) and extracted with EtOAc (5 × l00 mL). The organic layer was dried, evaporated, and chromatographed on silica gel (600 g), eluting with 2:1 cyclohexane−EtOAc to yield **40** (0.4 g; 14%). After a second chromatography (the same eluting mixture), an analytical sample melted at 108 °C: NMR ($CDCl_3$, 200 MHz) δ 5.35 (mf, 2H, NH_2), 7.05 (bd, 1H, H6), 7.33 (t, 1H, H5), 7.60 (dd, 1H, H4). IR (KBr) 710, 775, 1060, 1110, 1120, 1160, 1220, 1260, 1290, 1435, 1480, 1530, 1550,

1570, 1610, 1630, 3120, 3280, 3360 cm^{-1}; MS *m/z* (234 M^+), 207 ($M^+ - HCN$), 165 ($M^+ - CF_3$). Anal. ($C_8H_5F_3N_2OS$) C, H, N, S.

Method D. 6-(Trimethylsilyl)-2-benzothiazolamine (14). A 1.6 M solution of *n*-BuLi in hexane (46 mL) was added with stirring under Ar to a −70 °C cooled solution of **5** (6.8 g; 0.03 mol) in dry THF (100 mL), followed by a solution of chlorotrimethylsilane (9.3 mL; 0.04 mol) in dry THF (10 mL) at 0 °C. After the temperature was allowed to rise to 20 °C, the reaction mixture was refluxed for 1.5 h and then cooled to −10 °C before additional *n*-BuLi solution (19 mL) was added. The temperature was allowed to rise to 0 °C, and to the light red solution thus obtained was added a solution of chlorotrimethylsilane (4.7 mL; 0.037 mol) in dry THF (10 mL). During the addition, the temperature rose to 17 °C, and then the reaction mixture was refluxed for 4.5 h. The cooled mixture was poured into water (100 mL), alkalized with 28% aqueous NH_4OH, and extracted with CH_2Cl_2 (4 × 200 mL). The lower layer was dried, filtered, and evaporated in vacuo. The orange oil (10.1 g) thus obtained was chromatographed twice on silica gel using a 6:4 mixture of EtOAc−cyclohexane to yield a white solid (0.55 g). This material was triturated with 40/65 petroleum ether, filtered, and dried to yield **14** (0.45 g; 7%): mp 140 °C; NMR (DMSO, 200 MHz) δ 0.25 (mf, 9H, $(CH_3)_3Si$), 7.34 (s, 2H, H4, H5), 7.53 (mf, 2H, NH_2), 7.78 (s, 1H, H7); IR (KBr) 840, 900, 1050, 1105, 1150, 1245, 1260, 1300, 1380, 1445, 1455, 1520, 1545, 1585, 1632, 2895, 2950, 3090, 3280, 3425 cm^{-1}; MS *m/z* 222 (M^+), 207 ($M^+ - CH_3$). Anal. ($C_{10}H_{14}N_2SSi$) C, H, N, S.

General Procedures for 3-N-Alkylation of 6-Substituted-2-benzothiazolamine (Methods F−I). Method F. 3-(2-Methylthio-ethyl)-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (61). A stirred suspension of 6-trifluoromethoxy-2-benzothiazolamine **1** (10 g, 0.0427 mol) and 2-methylthioethyl chloride (5 mL, 0.050 mol) in 20 mL of methyl ethyl ketone (MEK) was heated under reflux for 24 h. After cooling to room temperature, the resulting precipitate was filtered and washed twice with 20 mL of MEK to give **61** (11.5 g, 78%) as a colorless solid: mp 208 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.17 (s, 3H, SCH_3), 2.9 (t, 2H, J = 7 Hz, CH_2S), 4.6 (t, 2H, J = 7 Hz, NCH_2), 7.58 (bd, 1H, 5-H), 7.8 (d, 1H, J = 9 Hz, 4-H), 8.19 (bs, 1H, 7-H), 10.0−1 1.7 (m, 2H, =NH·HCl); MS *m/e* 308 (M^+), 234 (100). Anal. ($C_{11}H_{11}F_3N_2OS_2$·HCl) C, H, Cl, F, N, S.

Compounds **41−50, 52, 53, 59, 62, 63, 67, 73−75** were prepared from **1** in the same way as **61** using the appropriate alkylating reagents. Compounds **82** and **83** were prepared from **22** and **2**, respectively.

2-Imino-3-methyl-6-trifluoromethoxy-benzothiazoline (41): mp 60−62 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.41 (s, 3H, NCH_3), 7.2 (d, 1H, J = 9 Hz, 4-H), 7.31 (bd, 1H, 5-H), 7.7 (bs, 1H, 7-H); MS *m/e* 248 (M^+), 220 (100). Anal. ($C_9H_7F_3N_2OS$) C, H, F: calcd, 22.96; found, 22.08; N, S.

3-Ethyl-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (42): mp 234 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 0.8 (t, 3H, J = 7 Hz, NCH_2CH_3), 4.42 (q, 2H, J = 7 Hz, NCH_2CH_3), 7.6(bd, 1H, 5-H), 7.85 (d, 1H, J = 9 Hz, 4-H), 8.2 (bs, 1H, 7-H), 11.3−12.7 (m, 2H, NH·HCl); MS *m/e* 262 (M^+), 234 (80),165 (100). Anal. ($C_{10}H_9F_3N_2OS$·HCl) C, H, Cl, F, N, S.

2-Imino-3-propyl-6-trifluoromethoxy-benzothiazoline Hydrochloride (43): mp 231 °C dec; ^{1}H NMR (base) δ (200 MHz, DMSO-d_6) 0.91 (t, 3H, J = 7.5 Hz, $NCH_2CH_2CH_3$), 1.62 (m, 2H, $NCH_2CH_2CH_3$), 3.86 (t, 2H, J = 7.5 Hz, $NCH_2CH_2CH_3$), 7.1 (d, 1H, J = 9 Hz, 4-H), 7.2 (bd, 1H, 5-H), 7.58 (bs, 1H, 7-H), 8.4 (bs, 1H, NH); MS *m/e* 276 (M^+), 234 (100), 165 (80). Anal. ($C_{11}H_{11}F_3N_2OS$·HCl) C, H, Cl, N, S.

3-Butyl-2-imino-6-trifluoromethoxy-benzothiazoline Hydrobromide (44): mp 243 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 0.9 (t, 3H, J = 7.5 Hz, $NCH_2CH_2CH_2CH_3$), 1.38 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.63 (m, 2H, $NCH_2CH_2CH_2CH_3$), 4.29 (t, 2H, J = 7.5 Hz, $NCH_2CH_2CH_2CH_3$), 7.6 (bd, 1H, 5-H), 7.86 (d, 1H, J = 9 Hz, 4-H), 8.21 (bs, 1H, 7-H), 10.0−10.8 (m, 2H, =NH·HBr); MS *m/e* 290 (M^+), 234 (100), 165 (85). Anal. ($C_{12}H_{13}F_3N_2OS$·HBr) C, H, Br, F, N, S.

3-Allyl-2-imino-6-trifluoromethoxy-benzothiazoline Hydrobromide (45): mp 225 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 5.0 (d, 2H, J = 4.5 Hz, NCH_2), 5.22 and 5.29 (d, J = 16 Hz, and d, J = 10 Hz, $NCH_2CH{=}CH_2$), 5.95 (m, 1H, $NCH_2CH{=}CH_2$), 7.59 (bd, 1H, 5-H), 7.76 (d, 1H, J = 9 Hz, 4-H), 8.22 (bs, 1H, 7-H), 10.0−11.0 (m, 2H, =NH·HBr); MS *m/e* 274 (M^+), 259 (80). Anal. ($C_{11}H_9F_3N_2OS$·HBr) C, H, Br, F, N, S.

2-Imino-3-(2-propynyl)-6-trifluoromethoxy-benzothiazoline Hydrobromide (46): mp 210 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.69 (bs, 1H, $NCH_2C{\equiv}CH$), 5.32 (bs, 2H, $NCH_2C{\equiv}CH$), 7.63 (bs, 1H, 5-H), 7.87 (d, 1H, J = 9 Hz, 4-H), 8.27 (bs, 1H, 7-H), 10.4−11.1 (m, 2H, =NH·HBr); MS *m/e* 272 (M^+), 271 (85). Anal. ($C_{11}H_7F_3N_2OS$·HBr) C, H, Br, F, N, S.

3-(2-Cyanoethyl)-2-imino-6-trifluoromethoxy-benzothiazoline Oxalate (47): mp 180 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.00 (t, 2H, J = 7 Hz, CH_2CN), 4.42 (t, 2H, J = 7 Hz, NCH_2), 5.00−5.80 (bb, 3H, =NH·$(COOH)_2$), 7.42 (bd, 1H, J = 8 Hz, 5-H), 7.63 (d, J = 8 Hz, 1H, 4-H), 7.87 (bs, 1H, 7-H); MS *m/e* 286 ($M - 1^+$), 233 (100); (CI^+) 288 ($M + 1^+$). Anal. ($C_{11}H_8F_3N_3OSC_2H_2O_4$) C, H, F, N, S.

3-Benzyl-2-imino-6-trifluoromethoxy-benzothiazoline Hydrobromide (48): mp 200 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 5.65 (m, 2H, NCH_2), 7.25−7.50 (m, 5H, ArH), 7.55 (bd, 1H, 5-H), 7.68 (d, 1H, J = 9 Hz, 4-H), 8.25 (bs, 1H, 7-H), 10.3−11.0 (m, 2H, =NH·HBr); MS *m/e* 324 (M^+), 91 (100). Anal. ($C_{15}H_{11}F_3N_2OS$·HBr·H_2O) C, H, Br, F, N, S.

2-Imino-3-phenethyl-6-trifluoromethoxy-benzothiazoline Hydrobromide (49): mp 210 °C (sublimes); ^{1}H NMR δ (250 MHz, DMSO-d_6) 3.03 (t, 2H, J = 7.5 Hz, NCH_2CH_2Ar), 4.57 (t, 2H, J = 7.5 Hz, NCH_2CH_2Ar), 7.15−7.4 (m, 5H, ArH), 7.5 (bd, 1H, 5-H), 7.71 (d, 1H, J = 9 Hz, 4-H), 8.2 (bs, IH, 7-H), 10.2−10.7 (m, 2H, =NH·HBr); MS *m/e* 338 (M^+), 234 (100). Anal. ($C_{16}H_{13}F_3N_2OS$·HBr) C, H, Br, F, N, S.

2-Imino-3-methoxycarbonylmethyl-6-trifluoromethoxy-benzothiazoline Hydrobromide (50): mp 246 °C dec; ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.77 (s, 3H, CO_2CH_3), 5.37 (s, 2H, NCH_2CO_2), 7.6 (bd, 1H, 5-H), 7.84 (d, 1H, J = 9 Hz, 4-H), 8.24 (bs, 1H, 7-H), 10.2−11.2 (m, 2H, =NH·HBr); MS *m/e* 306 (M^+), 247 (100), 220 (95). Anal. ($C_{11}H_9F_3N_2O_3S$·HBr) C, H, Br, F, N, S.

3-Aminocarbonylmethyl-2-imino-6-trifluoromethoxy-benzothiazoline (52): mp 228 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 4.53 (bb, 2H, NCH_2CO), 6.96 (d, 1H, J = 8.5 Hz, 4-H), 7.20 (bd, 1H, J = 8.5 Hz, 5-H), 7.25 and 7.65 (two bb, 1H each, $CONH_2$), 7.60 (bs, 1H, 7-H), 8.45 (bb, 1H, =NH); MS *m/e* 291 (M^+), 220 (100). Anal. ($C_{10}H_8F_3N_3O_2S$) C, H, F, N, S.

3-Diethylaminocarbonylmethyl-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (53): mp 223 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.05 and 1.32 (t, 1H each, J = 7 Hz, $CON(CH_2CH_3)_2$, 3.31 and 3.49 (q, 2H each, J = 7 Hz, $CON(CH_2CH_3)_2$), 5.55 (s, 2H, NCH_2CO), 7.57 (bd, 1H, 5-H), 7.62 (d, 1H, J = 9 Hz, 4-H), 8.19 (bs, 1H, 7-H), 10.6−11.6 (m, 2H, =NH·HCl); MS *m/e* 347 (M^+), 113 (100). Anal. ($C_{14}H_{16}F_3N_3O_2S$·lHCl) C, H, Cl, F: calcd, 14.85; found, 14.30; N, S.

3-Methylthiomethyl-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (59): mp 170 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.2 (s, 3H, SCH_3), 5.76 (s, 2H, NCH_2S), 7.6 (bd, 1H, 5-H), 7.91 (d, 1H, J = 9 Hz, 4-H), 8.2 (bs, 1H, 7-H), 10.85−11.4 (m, 2H, =NH·HCl); MS *m/e* 294 (M^+), 247 (100). Anal. ($C_{10}H_9F_3N_2OS_2$·HCl) C, H, Cl, F, N, S.

3-(2-Ethylthio-ethyl)-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (62): mp 160 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.12 (t, 3H, J = 7.5 Hz, SCH_2CH_3), 2.65 (q, 2H, J = 7.5 Hz, SCH_2CH_3), 2.93 (t, 2H, J = 7 Hz, CH_2S), 4.61 (t, 2H, J = 7 Hz, NCH_2), 7.58 (bd, 1H, 5-H), 7.8 (d, 1H, J = 9 Hz, 4-H), 8.2 (bs, 1H, 7-H), 10.2−11.4 (m, 2H, =NH·HCl); MS *m/e* 322 (M^+), 234 (100). Anal. ($C_{12}H_{13}F_3N_2OS_2$·HCl) C, H, Cl, F, N, S.

2-Imino-3-(2-propylthio-ethyl)-6-trifluoromethoxy-benzothiazoline Hydrochloride (63): mp 187 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 0.87 (t, 3H, J = 7.5 Hz, $SCH_2CH_2CH_3$), 1.47 (m, 2H, $SCH_2CH_2CH_3$), 2.56 (t, 2H, J = 7 Hz, $SCH_2CH_2CH_3$), 2.91 (bt, 2H, J = 7 Hz, NCH_2CH_2S), 4.56 (t, 2H, J = 7

Hz, NCH_2CH$_2$S), 7.6 (bd, 1H, 5-H), 7.8 (d, IH, J = 9 Hz, 4-H), 8.16 (bs, 1H, 7-H), 10.5−11.5 (m, 2H, ═NH·HCl); MS *m/e* 336 (M^+), 234 (100). Anal. ($C_{13}H_{15}F_3N_2OS_2$−HCl) C, H, Cl, F, N, S.

2-Imino-3-(2-phenylthio-ethyl)-6-trifluoromethoxy-benzothiazoline Hydrochloride (67): mp 174 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.5 (t, 2H, J = 6.5 Hz, NCH$_2$CH_2S), 4.65 (t, 2H, J = 6.5 Hz, NCH_2CH$_2$S), 7.15 (m, 5H, ArH), 7.49 (bd, 1H, 5-H), 7.6 (d, 1H, J = 9 Hz, 4-H), 8.02 (bs, 1H, 7-H), 10.5−11.5 (m, 2H, ═NH·HCl); MS *m/e* 371 (M^+), 234 (90), 136 (100). Anal. ($C_{16}H_{13}F_3N_2OS_2$·HCl) C, H, Cl, F, N, S.

3-(2-Dimethylamino-ethyl)-2-imino-6-trifluoromethoxy-benzothiazoline Dihydrochloride (73): mp 200 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.92 (s, 6H, N(CH$_3$)$_2$), 3.5 (t, 2H, J = 6 Hz, NCH$_2$CH_2NMe$_2$), 4.85 (t, 2H, J = 6 Hz, NCH_2CH$_2$NMe$_2$), 7.51 (bd, 1H, 5-H), 8.18 (d, 1H, J = 9 Hz, 4-H), 8.2 (bs, 1H, 7-H), 10.7−11.7 (m, 3H, ═NH·HCl and NR$_3$·HCl); MS *m/e* (CI$^+$) 306 (M + 1$^+$). Anal. ($C_{12}H_{14}F_3N_3OS$·2HCl) C: calcd, 38.11; found, 38.70; H, Cl, F, N, S.

2-Imino-3-(2-piperidino-ethyl)-6-trifluoromethoxy-benzothiazoline Dihydrochloride (74): mp 200 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.3−2.0 (m, 6H, H-piperidine), 3.15 and 3.47 (m, 2H and 4H, N(piperidine)-CH$_2$), 4.88 (t, 2H, J = 6.5 Hz, NCH_2CH$_2$N(piperidine, 7.6 (bd, 1H, 5-H), 8.07 (bs, 1H, 7-H), 8.24 (d, 1H, J = 9 Hz, 4-H), 10.5−11.5 (m, 3H, ═NH·HCl and NR$_3$·HCl); MS *m/e* 346 (M^+), 111 (70), 98 (100); Anal. ($C_{15}H_{18}F_3N_3OS$·2HCl) C, H, Cl, F, N, S.

3-(3-Dimethylamino-propyl)-2-imino-6-trifluoromethoxy-benzothiazoline Oxalate (75): mp 218 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.05 (m, 2H, NCH$_2$CH_2CH$_2$-NMe$_2$), 2.76 (s, 6H, N(CH$_3$)$_2$), 3.14 (t, 2H, J = 6 Hz, CH_2NMe$_2$), 4.12 (t, 2H, J = 6 Hz, NCH_2CH$_2$CH$_2$NMe$_2$), 7.38 (bd, 1H, 5-H), 7.48 (d, 1H, J = 9 Hz, 4-H), 7.81 (bs, 1H, 7-H); MS *m/e* 319 (M^+), 248 (100); Anal. ($C_{13}H_{16}F_3N_3OS$·1.6$C_2H_2O_4$) C, H, F: calcd, 12.54; found, 11.90; N, S.

3-(2-Dimethylaminoethyl)-2-imino-benzothiazoline Dihydrochloride (82): mp 200 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.90 (s, 6H, N(CH$_3$)$_2$), 3.50 (CH_2NMe$_2$, this signal is overlapped by DOH signal of (CD$_3$)$_2$SO), 4.82 (bt, 2H, J = 7.5 Hz, NCH$_2$), 7.42 and 7.58 (2t, 1H each, J = 8 Hz, 5-H and 6-H), 8.00 and 8.05 (2d, 1H each, J = 8 Hz, 4-H and 7-H), 10.50−11.60 (very bb, 3H, ═NH·HCl and NR$_3$·HCl); MS *m/e* 221 (M^+), 71 (100). Anal. ($C_{11}H_{15}N_3S$·2.0HCl) C, H, Cl, N, S.

6-*tert*-Butyl-3-(2-dimethylaminoethyl)-2-imino-benzothiazoline Dihydrochloride (83): mp 200 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.32 (s, 9H, C(CH$_3$)$_3$), 2.92 (s, 6H, N(CH$_3$)$_2$), 3.50 (bb, 2H, NCH$_2$CH_2NMe$_2$), 4.87 (bb, 2H, NCH_2CH$_2$NMe$_2$), 7.60 (bd, 1H, J = 8.5 Hz, 5-H), 8.05 (bd, 1H, J = 8 Hz, 4-H), 8.10 (bs, 1H, 7-H), 11.25 (bb, 2H, ═NH·HCl); MS *m/e* 277 (M^+), 71 (100). Anal. ($C_{15}H_{23}N_3S$·2.0HCl) C: calcd, 51.42; found, 50.7; H, Cl, N, S.

Method G. 2-Imino-3-[2-(4-phenyl-1-piperazinyl)-ethyl]-6-trifluoromethoxy-benzothiazoline Hydrochloride (80). Ethyl trifluoroacetate (17 g, 0.12 mol) was added slowly to a stirred suspension of 3-(2-hydroxy-ethyl)-2-imino-6-trifluoromethoxy-benzothiazoline **58**[24] (27.8 g, 0.1 mol) and triethylamine (1 6 mL, 0.11 mol) in 200 mL of absolute ethanol at room temperature. The reaction mixture was stirred overnight at room temperature. The solvent was then removed, and the solid residue dissolved in boiling ethanol/water (1:1); the solution was cooled, and the white precipitate was collected and washed with the same solvent to provide the trifluoroacetylated compound 59 (32 g, 85%): mp 141 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.85 (bq, 2H, J = 5 Hz, NCH$_2$CH_2OH), 4.60 (bt, 2H, J = 5 Hz, NCH_2CH$_2$OH), 5.00 (bt, 1H, NCH$_2$-CH$_2$OH), 7.66 (bd, 1H, J = 8.5 Hz, 4-H), 8.03 (d, 1H, J = 8.5 Hz, 4-H), 8.25 (bs, 1H, 7-H); MS *m/e* 374 (M^+), 45 (100).

The imino-protected alcohol **98** (53 g, 0.14 mol) was added slowly to an ice-cooled solution of *p*-toluenesulfonyl chloride in 120 mL of dry pyridine. The reaction mixture was stirred overnight at room temperature. The solution was then poured onto ice and acidified to pH 4 with concentrated HCl. The resulting solid was collected and washed several times with water to give **100** (68 g, 90%), mp 145 °C, then solidified to melt at 220 °C (mp of tosylate of **97**). **100:** ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.37 (s, 3H, ArCH$_3$), 4.57 (t, 1H, J = 5 Hz, CH$_2$OTos), 4.80 (t, 1H, J = 5 Hz, NCH$_2$, 7.16 and 7.32 (2d, 2H each, J = 8 Hz, ArH), 7.68 (bd, 1H, J = 8.5 Hz, 5-H), 7.98 (d, 1H, J = 8.5 Hz, 4-H), 8.25 (bs, 1H, 7-H); MS *m/e* 528 (M^+), 91 (100).

To a stirred solution of **100** (6.9 g, 13 mmol) in 100 mL of dimethylfonnamide were added NaHCO$_3$ (1.1 g, 13 mmol) and *N*-phenylpiperazine (2.4 g, 14 mmol). The mixture was heated to 80 °C overnight. After cooling, the reaction mixture was concentrated to dryness in vacuo, and water was added to the yellow residue. Extraction of the organic phase with ethyl acetate gave the pure trifluoroacetylated precursor of **80** after purification by flash chromatography using 80:20 EtOAc/cyclohexane as eluent (2.4 g, 36%): mp 88 °C; ^{1}H NMR δ (400 MHz, DMSO-d_6) 3.00−4.00 (m, 10H, N(piperazine)-CH$_2$), 5.00 (m, 2H, NCH$_2$CH$_2$N(piperazine)), 6.90 (t, 1H, J = 7.5 Hz, 4′-ArH), 7.00 (d, 2H, J = 7.5 Hz, 2′-ArH), 7.33 (t, 2H, J = 7.5 Hz, 3′-ArH), 7.74 (bd, 1H, J = 8.5 Hz, 5-H), 8.22 (d, 1H, J = 8.5 Hz, 4-H), 8.30 (bs, 1H, 7-H), 11.00 (bs, 1H, NR$_3$·HCl); MS *m/e* 518 (M^+), 132 (100).

A solution of the protected compound prepared above (1.06 g, 1.9 mmol) in a mixture of saturated aqueous K$_2$CO$_3$ (12 mL) and methanol (50 mL) was stirred at room temperature for 5 h. Methanol was then removed under reduced pressure and the organic phase extracted with EtOAc. EtOAc was evaporated and the crude product transformed into HCl salt to give **80** (0.78 g, 89%): mp 230 °C; ^{1}H NMR δ (400 MHz, DMSO-d_6) 3.0−3.5 (m, 10H, N(piperazine)-CH$_2$), 4.67 (m, 2H, NCH$_2$-CH$_2$N(piperazine)), 6.83 (t, 1H, J = 7.5 Hz, ArH), 6.99 (d, 2H, J = 7.5 Hz, ArH), 7.25 (t, 2H, J = 7.5 Hz, ArH), 7.56 (bd, 1H, 5-H), 7.96 (d, 1H, J = 9 Hz, 4-H), 8.1 (bs, 1H, 7-H), 10.0−11.5 (m, 2H, ═NH·HCl); MS *m/e* 422 (M^+), 188 (95), 132 (100); (FAB$^+$) 423 (M + 1$^+$); Anal. ($C_{20}H_{21}F_3N_4OS$·1HCl) C, H, Cl, F, N, S.

Compounds **69** and **81** were prepared from **96** following an analogous synthetic pathway.

3-(3-Methylthio-propyl)-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (69): mp 181 °C; ^{1}H NMR δ (400 MHz, DMSO-d_6) 1.98 (m, 2H, NCH$_2$CH_2CH$_2$SMe), 2.06 (s, 3H, SCH$_3$), 2−64 (t, 2H, J = 7 Hz, NCH$_2$CH$_2$CH_2SMe), 4.42 (t, 2H, J = 7 Hz, NCH_2CH$_2$CH$_2$SMe), 7.6 (bd, 1H, 5-H), 7.83 (d, 1H, J = 9 Hz, 4-H), 8.17 (bs, 1H, 7-H), 10.5−11.2 (m, 2H, ═NH·HCl); MS *m/e* 321 (M^+), 248 (100), 220 (90). Anal. ($C_{12}H_{13}F_3N_2OS_2$·HCl) C, H, Cl, F, N.

2-Imino-3-(3-(4-phenyl-1-piperazinyl)propyl)-6-trifluoromethoxy-benzothiazoline Dihydrochloride (81): mp 260 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.25 (m, 2H, NCH$_2$CH_2CH$_2$N(piperazine)), 3.1−3.95 (m, 10H, N(piperazine)-CH$_2$, 4.52 (t, 2H, J = 7 Hz, NCH_2CH$_2$CH$_2$N(piperazine)), 6.88 (t, 1H, J = 7.5 Hz, ArH), 7.01 (d, 2H, J = 7.5 Hz, ArH), 7.28 (t, 2H, J = 7.5 Hz, ArH), 7.63 (bd, 1H, 5-H), 7.99 (d, 1H, J = 9 Hz, 4-H), 8.19 (bs, 1H, 7-H), 10.8−11.3 (m, 3H, ═NH·HCl and NR$_3$·HCl); MS *m/e* 304 (70), 248 (80), 201 (65), 173 (100), 132 (95), 106 (90); (CI$^+$) 437 (M + 1$^+$); Anal. ($C_{21}H_{23}F_3N_4OS$·2HCl) C: calcd, 49.51; found, 48.7; H, Cl, F, N, S.

3-(3-Hydroxypropyl)-2-imino-6-trifluoromethoxy-benzothiazoline Hydrobromide (96). Compound **96** was prepared from 6-trifluoromethoxy-2-benzothiazolamine, following method F: mp 181 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.90 (m, 2H, NCH_2CH$_2$CH$_2$OH), 3.50 (t, J = 6 Hz, 2H, NCH$_2$-CH$_2$CH_2OH), 4.35 (t, 2H, J = 6 Hz, N−CH_2CH$_2$CH$_2$OH), 7.60 (bd, 1H, J = 8 Hz, 5-H), 7.82 (bd, 1H, J = 8 Hz, 4-H), 8.22 (bs, 1H, 7-H), 10.0−10.3 (bb, 2H, ═NH·HBr); Anal. ($C_{11}H_{11}F_3N_2O_2S$·HBr) C, H, Br, F, N, S.

Method H. 3-[2-(4-phenyl-1-piperidinyl)-ethyl]-6-trifluoromethoxy-2-imino-benzothiazoline (39). 4-Trifluoromethoxy-aniline (88.5 g, 0.5 mol) and 2-bromo-ethanol (31.2 g, 0.25 mol) were heated at 160 °C for 1.5 h. After cooling, the mixture was suspended in 200 mL of CH$_2$Cl$_2$, and the resulting solid was collected to provide the hydrobromide of the starting material (44.1 g). The filtrate was evaporated in vacuo to give 74 g of an oily residue which was purified by flash chroma-

tography (EtOAc/cyclohexane 40:60) to give the alcohol **102** (26.8 g, 49%) as a yellow oil.

To an ice-cooled and stirred solution of the alcohol **102** (20.9 g, 0.095 mol) and Et_3N (26.7 mL, 0.19 mol) in 200 mL of CH_2Cl_2 was added dropwise *p*-toluenesulfonyl chloride (36.2 g, 0.19 mol). The mixture was stirred for 1.5 h at 0 °C and then allowed to reach ambient temperature. After dilution with 200 mL of CH_2Cl_2, the organic phase was washed with water, dried ($MgSO_4$), and evaporated to give 48.4 g of an oily residue which was crystallized in absolute ethanol. This gave the ditosylate **103** (27.6 g, 55%) as a white solid, mp 88 °C.

A stirred solution of the ditosylate **103** (7.2 g, 13.6 mmol), $NaHCO_3$ (2.4 g, 28.6 inmol), and 4-phenylpiperidine (4.85 g, 28.6 mmol) in 50 mL of DMF was heated at 80 °C overnight (ca. 18 h). The solvent was evaporated in vacuo and the residue washed twice with water. The crude product was added to a solution of concentrated HCl (30 mL), acetic acid (30 mL), and water (20 mL), and the mixture was heated at 110 °C for 3 h. After cooling, the reaction mixture was poured into 100 mL of water and treated by aqueous K_2CO_3. The resulting solid was collected and recrystallized in 2-propanol to give **106** (6.2 g, 85%) as the *p*-toluenesulfonate salt, mp 176 °C.

To a suspension of the substituted aniline **106** (2.96 g, 8.12 mmol), obtained by treatment of the *p*-toluenesulfonate salt with 1 N NaOH, and KSCN (3.17 g, 32.5 mmol) in acetic acid (15 mL), a solution of bromine (1.29 g, 8.12 mmol) in acetic acid (15 mL) was added dropwise. The reaction was allowed to continue overnight at room temperature. The mixture was poured into 100 mL of water, neutralized by 30% NaOH solution, and then extracted twice with EtOAc (200 mL). The extracts were dried and concentrated in vacuo to give 3.0 g of crude product. The dark oily residue was purified by flash chromatography using EtOAc as eluent to afford **78** (2.06 g, 60%) transformed into diHCl salt in Et_2O: mp 220 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.95−2.25(m, 4H, piperidine-CH_2), 2.9 (m, 1H, piperidine-CH), 3.27 (m, 2H, piperidine-axial NCH_2), 3.55 (bt, 2H, J = 7 Hz, NCH_2CH_2-piperidine), 3.68 (bd, 2H, J = 12.5 Hz, piperidine-equatorial NCH_2), 4.91 (bt, 2H, J = 7 Hz, NCH_2CH_2piperidine), 7.15−7.4 (m, 5H, ArH), 7.55 (bd, 1H, 5-H), 8.1 (bs, 1H, 7-H), 8.2(d, 1H, J = 9 Hz, 4-H), 11.35 (m, 2H, =NH·HCl); MS *m/e* 421 (M^+), 187 (100), 174 (80). Anal.($C_{21}H_{22}F_3N_3OS$·2HCl) C, H, Cl, F, N, S.

Compounds **76**, **77**, and **79** were prepared following an analogous synthetic pathway.

3-[2-(*N*-benzyl-*N*-methyl-amino)ethyl]-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (76): mp 180 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.55 (s, 3H, NCH_3), 3.05 (m, 2H, CH_2N(Me)benzyl), 3.96 (bs, 2H, NCH_2Ph), 4.63 (m, 2H, NCH_2CH_2N(Me)benzyl), 7.27 (m, 5H, ArH), 6.8−7.5 (m, 2H, =NH·HCl), 7.44 (bd, 1H, 5-H), 7.74 (d, 1H, J = 9 Hz, 4-H), 8.07 (bs, 1H, 7-H); MS *m/e* (CI^+) 382 (M + 1^+). Anal. ($C_{18}H_{18}F_3N_3OS$·1HCl) C: calcd, 51.74; found, 51.0; H, Cl, F, N, S.

2-Imino-3-[2-(*N*-methyl-*N*-phenethyl-amino)ethyl]-6-trifluoromethoxy-benzothiazoline Dihydrochloride (77): mp 216 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.02 (s, 3H, N + CH_3), 3.0−3.55 (m, 4H, N + (Me)CH_2CH_2Ph), 3.61 (t, 2H, J = 6 Hz, NCH_2CH_2N + (Me) $(CH_2)_2$Ph), 4.94 (t, 2H, J = 6 Hz, NCH_2CH_2N + (Me)CH_2CH_2Ph), 7.34 (m, 5H, ArH), 7.2−7.5 (m, 1H, NR_3·HCl), 7.64 (bd, 1H, 5-H), 8.2 (bs, 1H, 7-H), 8.23 (d, 1H, J = 9 Hz, 4-H), 10.9−11.9 (m, 2H, =NH·HCl); MS *m/e* (CI^+) 396 (M + 1^+). Anal. ($C_{19}9H_{20}F_3N_3OS$·2HCl) C, H, Cl, F, N, S.

2-Imino-3-[2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)-ethyl]-6-trifluoromethoxy-benzothiazoline Dihydrochloride (79): mp 256 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 2.9 (m, 2H, 3-pyridyl-CH_2), 3.65 (m, 4H, NCH_2CH_2N + pyridyl and 2-pyridyl-CH_2), 4.12 (m, 2H, 6-pyridyl-CH_2), 4.95 (t, 2H, NCH_2-CH_2N + pyridyl), 6.27 (bs, 1H, CH_2CH·C(Ph), 7.3−7.6 (m, 5H, ArH), 7.0−7.9 (m, 1H, NR_3·HCl), 7.6 (bd, 1H, 5-H), 8.19 (bs, 1H, 7-H), 8.25 (d, 1H, J = 9 Hz, 4-H), 10.9−11.9 (m, 2H, = NH·HCl); MS *m/e* 419 (M^+), 185 (100). Anal. ($C_{21}H_{20}F_3N_3OS$·2HCl) C, H, Cl, F, N, S.

Method I. 3-[2-(Aminosulfonyl)ethyl]-2-imino-6-trifluoromethoxy-benzothiazoline Hydrochloride (54). A solution of ethenesulfonyl fluoride[28] (11.9 g, 0.108 mol) in DMF (10 mL) was added dropwise to a solution of 4-trifluoromethoxy-aniline (19.14 g, 0.108 mol) in 20 mL of DMF. The mixture was stirred at room temperature for 2 h, and the solution was poured into water (300 mL). The mixture was extracted with Et_2O (3 × 100 mL), and the combined extracts were washed with water (2 × 100 mL) and then dried ($MgSO_4$) and evaporated to lead to the sulfonyl fluoride **108** as an orange oil (25.8 g, 75%): ^{1}H NMR δ (400 MHz, $CDCl_3$) 3.57 (m, 2H, CH_2SO_2F), 3.77 (t, 2H, J = 6.5 Hz, NCH_2), 4.05 (very bb, 1H, NH), 6.56 (d, 2H, J = 8.5 Hz, 3,5-ArH), 7.08 (d, 2H, J = 8.5 Hz, 2,6-ArH).

This sulfonyl fluoride (8.6 g, 0.03 mol) was dissolved in acetone (20 mL) and added dropwise to a refluxing mixture of 8 N NH_4OH solution (30 mL, 8 molar equiv) and acetone (30 mL). After 1 h at the same temperature, the acetone was removed in vacuo and the mixture extracted with EtOAc (2 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue obtained was purified by flash chromatography on silica gel, using 50% EtOAc/cyclohexane as eluent, to give the sulfonamide **109** (R = NH_2) as a colorless oil (5.45 g, 64%): ^{1}H NMR δ (200 MHz, $CDCl_3$) 3.37 (t, 2H, J = 6.5 Hz, $CH_2SO_2NH_2$), 3.63 (bm, 2H, NCH_2), 4.39 (bb, 1H, NH), 5.16 (bb, 2H, SO_2NH_2), 6.58 (d, 2H, J = 8.5 Hz, 3,5-ArH), 7.05 (bd, 2H, J = 8.5 Hz, 2,6-ArH).

This sulfonamide (4.12 g, 0.0144 mol) was dissolved in acetic acid (20 mL) at room temperature. KSCN (5.6 g, 0.0577 mol) was added all at once, and then a solution of bromine (2.3 g, 0.0144 mol) in acetic acid (10 mL) was added dropwise (15 min). The reaction mixture was stirred overnight at room temperature, then diluted with water (30 mL), and treated with 30% NaOH. The orange precipitate was filtered and then washed with methanol. The methanolic solution was concentrated to dryness and the solid residue solubilized in EtOH/Et_2O and treated with HCl in Et_2O (3.6 mL of 4.2 N solution) to give the expected sulfonamide **54** as a colorless solid (2.9 g, 53%): mp 225 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 3.61 (bt, 2H, J = 6 Hz, $CH_2SO_2NH_2$), 4.81 (bt, 2H, J = 6 Hz, NCH_2), 7.39 (bb, 2H, NH_2), 7.63 (bd, 1H, J = 8.5 Hz, 5-H), 7.81 (d, 1H, J = 8.5 Hz, 4-H), 8.21 (bs, 1H, 7-H), 11.00 (2bb, 2H, =NH·HCl); MS *m/e* 341 (M^+), 234 (100). Anal. ($C_{10}H_{10}F_3N_3O_3S_2$.HCl) C: calcd, 31.79; found, 31.30; H, Cl, F, N, S.

Compounds **55** and **56** were prepared from **108** as described for **54**, using the appropriate amine.

2-Imino-3-[2-(methylaminosulfonyl)ethyl]-6-trifluoromethoxy-benzothiazoline Hydrochloride (55): mp 242 °C; ^{1}H NMR δ (400 MHz, DMSO-d_6) 2.64 (d, 3H, J = 5 Hz, SO_2NHCH_3), 3.62 (t, 2H, J = 6.5 Hz, CH_2SO_2, 4.74 (t, 2H, J = 6.5 Hz, NCH_2), 7.53 (q, 1H, J = 5 HZ, SO_2NHCH_3), 7.63 (bd, 1H, J = 8.5 Hz, 5-H), 7.75 (d, 1H, J = 8.5 Hz, 4-H), 8.17 (bs, 1H, 7-H); MS *m/e* 355 (M^+), 234 (100). Anal. ($C_{11}H_{12}F_3N_3O_3S_2$·HCl) C, H, Cl, F, N, S.

3-[2-(Dimethylaminosulfonyl)ethyl]-2-imino-6-trifluoromethoxy-benzothiazoline (56): mp 140 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.81 (s, 6H, $SO_2N(CH_3)_2$), 3.43 (t, 2H, J = 7 Hz, $CH_2SO_2NMe_2$), 4.28 (t, 2H, J = 7 Hz, NCH_2), 7. 11 (d, 1H, J = 8.5 Hz, 4-H), 7.27 (bd, 1H, J = 8.5 Hz, 5-H), 7.61 (bs, 1H, 7-H), 8.61 (s, 1H, =NH); MS *m/e* 369 (M^+), 234 (100). Anal. ($C_{12}H_{14}F_3N_3O_3S_2$) C, H, F, N, S.

2-(2-Imino-6-trifluoromethoxy-3-benzothiazolinyl)-ethanesulfonic Acid (57), The sulfonyl fluoride **108** (7.0 g, 0.024 mol) was dissolved in glacial acetic acid (30 mL) and heated under reflux for 40 h. After the mixture cooled, the colorless needles were filtered, washed with water, and dried to give the expected sulfonic acid **109** (R = OH) (2.0 g, 29%): mp 220 °C; ^{1}H NMR δ (400 MHz, DMSO-d_6) 2.85 (t, 2H, CH_2-SO_3), 3.50 (t, 2H, CH_2N), 7.3 (d, 2H, J = 8 Hz, ArH), 7.4 (d, 2H, J = 8 Hz, ArH), 9.3 (bs, $NH + SO_3H + H_2O$); MS *m/e* 285 (M^+), 190 (100).

This sulfonic acid (1.8 g, 0.0063 mol) was dissolved in glacial acetic acid (20 mL). KSCN (2.46 g, 0.025 mol) was added all at once to this solution, followed by a dropwise addition of a

solution of bromine (1.0 g, 0.0063 mol) in acetic acid (10 mL). The mixture was then stirred overnight at room temperature, then diluted with water (30 mL) and treated with 30% NaOH. After acidification with 1 N HCl, the precipitate was filtered, washed with water, and dried. Recrystallization in methanol gave the expected benzothiazoline sulfonic acid **57** as a yellow powder (1.05 g, 49%): mp >260 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.97 (bt, 2H, J = 6 Hz, NCH$_2$CH_2SO$_3$H), 4.51 (bt, 2H, J = 6 Hz, NCH_2CH$_2$SO$_3$H), 7.61 (bd, 1H, J = 8.5 Hz, 5-H), 7.80 (d, 1H, J = 8.5 Hz, 4-H), 8.11 (bs, 1H, 7-H), 10.20 (bb, 2H, =NH·HCl); MS *m/e* (CI$^+$) 360 (M + NH$_4^+$), 343 (M + 1$^+$). Anal. ($C_{10}H_9F_3N_2O_4S_2$) C: calcd, 35.09; found, 34.5; H, F, N, S.

(2-Imino-6-trifluoromethoxy-3-benzothiazolinyl)acetic Acid (51). A stirred solution of 2-imino-3-methoxycarbonylmethyl-6-trifluoromethoxy-benzothiazoline **50** (10.19 g, 0.026 mol) in 6 N HCl (40 mL) was heated to reflux for 20 h. The reaction mixture was cooled to room temperature and the precipitate filtered and washed with water. Treatment of this solid with 1 N NaOH (60 mL), followed by recrystallization in water (25 mL), yielded the sodium salt of the expected compound **51** as a colorless solid (3.12 g, 28%): mp >260 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 4.30 (bs, 2H, NCH$_2$CO$_2$Na), 6.83 (dd, 1H, J = 8.5 Hz, J'= 2 Hz, 4-H), 7.18 (bd, 1H, J = 8.5 Hz, 5-H), 7.54 (bs, 1H, 7-H); MS *m/e* 234 (M − CH$_2$CO$_2$Na + 1$^+$), 219 (100). Anal. ($C_{10}H_6F_3N_2NaO_3S$) C, H, F, N, S.

2-Imino-3-(2-mercaptoethyl)-6-trifluoromethoxy-benzothiazoline Hydrobromide (66). The intermediate 2-imino-3-(2-*tert*-butylthioethyl)-6-trifluoromethoxy-benzothiazoline **110** (prepared following method F) was converted to **66** by a method similar to that described for **51** (using 48% HBr instead of 6 N HCl): yield 0.85 g (53%); mp 180 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 2.85 (dd, 2H, J = 8 Hz, J' = 7 Hz, NCH$_2$CH_2SH), 3.07 (t, 1H, J = 8 Hz, NCH$_2$CH$_2$SH), 4.45(t, 2H, J = 7 Hz, NCH_2CH$_2$SH), 7.60 (bd, 1H, J = 8.5 Hz, 5-H), 7.96 (d, 1H, J = 8.5 Hz, 4-H), 8.20(bs, 1H, 7-H), 10.45 (bb, 2H, =NH·HBr); MS *m/e* 294 (M$^+$), 234 (100). Anal. ($C_{10}H_9F_3N_2OS_2$·HBr) C, H, Br, F, N, S.

2-Imino-3-(2-methylaminoethyl)-6-trifluoromethoxy-benzothiazoline Dihydrochloride (72). To a stirred solution of 2-imino-3-(2-dimethylaminoethyl)-6-trifluoromethoxy-benzothiazoline **73** (2.7 g, 0.0088 mol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (1.35 g, 0.0088 mol) in CH_2Cl_2 at room temperature was added dropwise vinyl chloroformate (2.17 g, 0.020 mol), and the reaction mixture was allowed to stand overnight at the same temperature. The precipitate was then filtered and washed with CH_2Cl_2, and the filtrate was concentrated to dryness. The residue was purified by rapid filtration on silica gel leading to a yellow oil of the intermediate dicarbamate (1.1 g, 29%).

After refluxing this compound with 37% HCl (2 mL) in methanol (10 mL) for 24 h, the reaction mixture was concentrated to dryness and the residue recrystallized in ethanol to give the dihydrochloride of the expected compound **72** as colorless crystals (0.31 g, 33%): mp 152 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6), 2.62 (s, 3H, NCH$_3$), 3.4 (t, 2H, J = 5 Hz, NCH$_2$CH_2NHMe), 4.78 (t, 2H, J = 5 Hz, NCH_2CH$_2$NHMe), 7.6 (bd, 1H, 5-H), 8.08 (d, 1H, J = 9 Hz, 4-H), 8.19 (bs, 1H, 7-H), 9.49 (m, 2H, NHR$_2$·HCl), 10.7−11.7 (m, 2H, =NH·HCl); MS *m/e* (CI$^+$) 292 (M + 1$^+$). Anal. ($C_{11}H_{12}F_3N_3OS$·2HCl) C, H, Cl, F, N, S.

(*RS*)-2-Imino-3-(2-methylsulfinylethyl)-6-trifluoromethoxy-2-benzothiazoline (64): *m*-Chloroperbenzoic acid (60.5 g, 0.263 mol) was added progressively to a stirred solution of 3-(2-methylthioethyl)-6-trifluoromethoxy-2-benzothiazolimine **61** (81.3 g, 0.263 mol) in 900 mL of absolute ethanol at −35 °C. The reaction mixture was stirred for 30 min after the addition was completed and then poured into 3 L of Et$_2$O. To this cold stirred solution, 65 mL of a 4 N Et$_2$O·HCl solution was added dropwise. The resulting white precipitate was filtered and purified by acid−base treatment to give **64** as hydrochloride (72.5 g, 70%): mp 186 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 2.67 (s, 3H, S(O)CH$_3$), 3.19 and 3.38 (two dt, 1H each, J = 14 and 6.5 Hz, CH$_2$S(O)Me), 4.76 (t, 2H, J = 6.5 Hz, NCH$_2$CH$_2$S(O)Me), 7.59 (bd, 1H, 5-H), 7.8 (d, 1H, J = 9 Hz, 4-H), 8.13 (bs, 1H, 7H); MS *m/e* 324 (M$^+$), 259 (100), 234 (95); Anal. ($C_{11}H_{11}F_3N_2O_2S_2$-1.0HCl·0.79H$_2$O) C, H, Cl, F, N, S: calcd, 17.77; found, 17.2.

Compounds **60, 68, 70,** and **84**−**87** could be obtained from the corresponding thioether following the same synthetic pathway.

(*RS*)-2-Imino-3-methylsulfinylmethyl)-6-trifluoromethoxy-2-benzothiazoline Hydrochloride (60): mp 150 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6), 2.93 (s, 3H, S(O)CH$_3$), 5.9 (m, 2H, NCH$_2$S(O)Me), 7.63 (bd, 1H, 5-H), 7.98 (d, 1H, J = 9 Hz, 4-H), 8.18 (bs, 1H, 7-H), 11.35 (m, 2H, = NH·HCl); MS *m/e* 310 (M$^+$), 247 (80); Anal. ($C_{10}H_9F_3N_2O_2S_2$· 1.0HCl) C, H, Cl, F, N, S.

(*RS*)-2-Imino-3-(2-phenylsulfinylethyl)-6-trifluoromethoxy-2-benzothiazoline Hydrochloride (68): mp 210 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 3.30 and 3.57 (two dt, 1H each, J = 14 and 7.5 Hz, CH_2S(O)Ph), 4.7 (t, 2H, J = 7.5 Hz, NCH_2CH$_2$S(O)Ph), 7.4−7.8 (m, 7H, ArH, 4-H and 5-H), 8.12 (bs, 1H, 7-H), 10.5−11.5 (m, 2H, =NH·HCl); MS *m/e* 386 (M$^+$), 261 (100); Anal. ($C_{16}H_{13}F_3N_2O_2S_2$·1.0HCl·0.48H$_2$O) C, H, Cl, F, N, S.

(*RS*)-2-Imino-3-(3-methylsulfinylpropyl)-6-trifluoromethoxy-2-benzothiazoline (70): mp 114 °C; ^{1}H NMR δ (200 MHz, CDCl$_3$), 2.27 (m, 2H, NCH$_2$CH_2CH$_2$S(O)Me), 2.6 (s, 3H, S(O)CH$_3$), 2.83 (m, 2H, CH_2S (O)Me), 4.07 and 4.20 (two dt, 1H each, J = 11 and 6 Hz, NCH_2CH$_2$CH$_2$S(O)Me), 6.92 (d, 1H, J = 9 Hz, 4-H), 7.11 (bd, 1H, 5-H), 7.17 (bs, 1H, 7-H); MS *m/e* 338 (M$^+$), 234 (90), 220 (100); Anal. ($C_{12}H_{13}F_3N_2O_2S_2$) C, H, F, N, S.

(*RS*)-2-Imino-3-(2-ethylsulfinylethyl)-6-*tert*-butyl-2-benzothiazoline (84). The corresponding thioether was obtained by reacting the 6-*tert*-butyl-2-benzothiazolamine **22** with 2-chloroethyl-ethyl-sulfide, following method F: mp 100 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 1.20 (t, 3H, J = 6.5 Hz, SCH$_2$CH_3), 1.30 (s, 9H, C(CH$_3$)$_3$), 2.60−3.30 (m, 4H, CH_2-SOCH_2CH$_3$), 4.25 (t, 2H, J = 7 Hz, NCH_2CH$_2$SOEt), 7.05 (d, 1H, J = 8.5 Hz, 4-H), 7.27 (dd, 1H, J = 8.5 Hz, J'= 1 Hz, 5-H), 7.50 (d, 1H, J = 1 Hz, 7-H), 8.18 (bb, 1H, =NH); MS *m/e* 311 (M + 1$^+$), 231 (100). Anal. ($C_{12}H_{13}F_3N_2O_2S_2$) C, H, F, N, S.

(*RS*)-2-Imino-3-(2-ethylsulfinylethyl)-6-*n*-butyl-2-benzothiazoline Hydrochloride (86). The corresponding thioether was obtained by reacting the 6-*n*-butyl-2-benzothiazolamine **21** with 2-chloroethyl-ethyl-sulfide, following method F: mp 174 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 0.90 (t, 3H, J = 7 Hz, butyl-CH$_3$), 1.20 (t, 3H, J = 7.5 Hz, SCH$_2$CH_3), 1.32 (m, 2H, butyl-CH_2CH$_3$), 1.58 (m, 2H, butyl-CH_2CH$_2$CH$_3$), 2.68 (t, 2H, J = 7 Hz, butyl-CH_2CH$_2$CH$_2$CH$_3$), 2.70−3.05 (m, 2H, SOCH_2CH$_3$), 3.15 and 3.35 (two dt, 1H each, J = 14 and 6.5 Hz, NCH$_2$CH_2SOEt), 4.75 (t, 2H, J = 6.5 Hz, NCH_2CH$_2$SOEt), 7.40 (bd, 1H, J = 8.5 Hz, 5-H), 7.60 (d, 1H, J = 8.5 Hz, 4-H), 7.82 (bs, 1H, 7-H), 10.88 (bb, 2H, =NH·HCl); MS *m/e* 310 (M$^+$), 231 (100). Anal. ($C_{15}H_{22}N_2OS_2$·1.0HCl) C, H, Cl, N, O, S.

(*RS*)-2-Imino-3-(2-ethylsulfinylethyl)-6-trifluoromethoxy-2-benzothiazoline Hydrochloride (86). The starting thioether was obtained by reacting 6-trifluoromethoxy-2-benzothiazolamine with 2-chloroethyl-ethyl-sulfide, following method F: mp 174 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 1.20 (t, 3H, J = 7.5 Hz, SCH$_2$CH_3), 2.60−3.05 (m, 2H, SOCH_2CH$_3$), 3.15 and 3.35 (two dt, 2H, J = 14 and 6.5 Hz, NCH$_2$CH_2SOEt), 4.80 (t, 2H, J = 6.5 Hz, NCH_2CH$_2$SOEt), 7.62 (bd, 1H, J = 8.5 Hz, 5-H), 7.80 (d, 1H, J = 8.5 Hz, 4-H), 8.20 (bs, 1H, 7-H), 10.5−11.80 (two very bb, 2H, =NH·HCl); MS *m/e* 338 (M$^+$), 234 (100). Anal. ($C_{12}H_{13}F_3N_2O_2S_2$·1.0HCl·0.8H$_2$O) C, H, Cl, F, N, S.

(*RS*)-2-Imino-3-(2-ethylsulfinylethyl)-6-trifluoromethyl-2-benzothiazoline Hydrochloride (87). The starting thioether was obtained by reacting the 6-trifluoromethyl-2-benzothiazolamine **37** with 2-chloroethyl-ethyl-sulfide, following method F: mp 150 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 1.17 (t, 3H, J = 7.5 Hz, SCH$_2$CH_3), 2.65−3.00 (m, 2H, SOCH_2CH$_3$), 3.15 and 3.35 (two dt, 2H, J = 14 and 6.5 Hz, NCH$_2$CH_2SOEt), 4.82 (t, 2H, J = 6.5 Hz, NCH_2CH$_2$SOEt), 7.94 (limit AB, 2H, J = 8.5 Hz, 4-H and 5-H), 8.50 (bs, 1H, 7-H), 11.20 (very bb,

2H, =NH·HCl); MS *m/e* 322 (M^+), 218 (100). Anal. ($C_{12}H_{13}F_3N_2OS_2$·1.0HCl) C, H, Cl, F, N, S.

2-Imino-3-(2-methylsulfonylethyl)-6-trifluoromethoxybenzothiazoline Hydrochloride (65). *m*-Chloroperbenzoic acid (26.9 g, 0.117 mol) was added to a stirred solution of 2-imino-3-(2-methylthioethyl)-6-trifluoromethoxy-benzothiazoline **61** (17.8 g, 0.0577 mol) in 400 mL of CH_2Cl_2 at room temperature. The reaction was allowed to continue overnight at room temperature, and then the mixture was poured into 200 mL of Et_2O. The hydrochloride was precipitated by addition of 4 N Et_2O·HCl and the resulting solid recrystallized in water to give **65** (17.4 g, 80%): mp >260 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 3.21 (s, 3H, SO_2CH_3), 3.75 (t, 2H, J = 6.5 Hz, $NCH_2CH_2SO_2Me$), 4.83 (t, 2H, J = 6.5 Hz, $NCH_2CH_2SO_2Me$), 7.65 (bd, 1H, 5-H), 7.76 (d, 1H, J = 9 Hz, 4-H), 8.2 (bs, 1H, 7-H), 10.5−11.5 (m, 2H, =NH·HCl); MS *m/e* 340 (M^+), 234 (100), 165 (30); Anal. ($C_{11}H_{11}F_3N_2O_3S_2$·1.0HCl) C, H, Cl, F, N, S.

Compounds **71, 88,** and **89,** starting from the corresponding thioether **69, 120,** and **121**, respectively, were prepared following the same synthetic pathway.

2-Imino-3-(3-methylsulfonylpropyl)-6-trifluoromethoxybenzothiazoline Oxalate (71): mp 180 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 2.1 (m, 2H, $NCH_2CH_2CH_2SO_2Me$), 3.0 (s, 3H, SO_2CH_3), 3.28 (m, 2H, $NCH_2CH_2CH_2SO_2Me$), 4.21 (t, 2H, J = 7 Hz, $NCH_2CH_2CH_2SO_2Me$), 7.46 (bd, 1H, 5-H), 7.56 (d, 1H, J = 9 Hz, 4-H), 7.9 (bs, 1H, 7-H); MS *m/e* 354 (M^+), 275 (100), 248 (60), 234 (100),165 (40); Anal. ($C_{12}H_{13}F_3N_2O_3S_2$, $C_2H_2O_4$) C, H, F, N, S.

3-(2-Ethylsulfonylethyl)-2-imino-6-pentafluoroethylbenzothiazoline (88): mp 125 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$), 1.40 (t, 3H, J = 7 Hz, $SO_2CH_2CH_3$), 3.03 (q, 2H, J = 7 Hz, $SO_2CH_2CH_3$), 3.45 (t, 2H, J = 7.5 Hz, $NCH_2CH_2SO_2Et$), 4.43 (t, 2H, J = 7.5 Hz, $NCH_2CH_2SO_2Et$), 7.15 (d, 1H, J = 8 Hz, 4-H), 7.46 (s, 1H, 7-H), 7.48 (d, 1H, J = 8 Hz, 5-H); MS *m/e* 388 (M^+), 199 (100). Anal. ($C_{13}H_{13}F_5N_2O_2S_2$) C, H, F, N, S.

The starting 3-(2-ethylthioethyl)-2-imino-6-pentafluoroethylbenzothiazoline (**120**) was prepared following method F starting from the 6-pentafluoroethyl-2-benzothiazolamine **36**: mp < 50 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 1.30 (t, 3H, J = 7.5 Hz, SCH_2CH_3), 2.65 (q, 2H, J = 7.5 Hz, SCH_2CH_3), 2.90 (dd, 2H, J = 7 Hz, NCH_2CH_2S), 4.17 (dd, 2H, J = 7 Hz, NCH_2CH_2S), 7.00 (d, 1H, J = 8 Hz, 4-H), 7.20 (bb, 1H, =NH), 7.46 (bd + s, 2H, 5-H + 7-H).

3-(2-Ethylsulfonylethyl)-2-imino-6-pentafluoroethoxybenzothiazoline Hydrochloride (89): mp 230 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 1.24 (t, 3H, J = 7.5 Hz, $SO_2CH_2CH_3$), 3.30 (q, 2H, J = 7.5 Hz, $SO_2CH_2CH_3$), 3.72 (t, 2H, J = 7 Hz, $NCH_2CH_2SO_2Et$), 4.78 (t, 2H, J = 7 Hz, $NCH_2CH_2SO_2Et$), 7.62 (bd, 1H, J = 8.5 Hz, 5-H), 7.74 (d, 1H, J = 8.5 Hz, 4-H), 8.16 (bs, 1H, 7-H), 11.90 (very bb, 2H, =NH·HCl); MS *m/e* 404 (M^+), 165 (100). Anal. ($C_{13}H_{13}F_5N_2O_3S_2$·1.0HCl) C, H, Cl, F, N, S.

The starting 3-(2-ethylthioethyl)-2-imino-6-pentafluoroethoxy-benzothiazoline hydrochloride (**121**) was prepared following method F starting from the 6-pentafluoroethoxy-2-benzothiazolamine **35**: mp 115 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.14 (t, J = 7.5 Hz, 3H, SCH_2CH_3), 2.64 (q, J = 7.5 Hz, 2H, SCH_2CH_3), 2.94 (bt, J = 7 Hz, 2H, NCH_2CH_2S), 4.58 (bt, J = 7 Hz, 2H, NCH_2CH_2S), 7.57 (bd, 9 Hz, 1H, 5-H), 7.83 (d, J = 9 Hz, 1H, 4-H), 8.17 (bs, 1H, 7-H), 1 1.0 (bb, 2H, $=NH_2 + Cl^-$).

3-(2-Ethylthioethyl)-2-methylimino-6-trifluoromethoxybenzothiazoline Hydrochloride (90). (a) 2-Chloro-6-trifluoromethoxy-benzothiazole[55] (22.05 g, 0.087 mol) and a 40% aqueous solution of methylamine were shaken at 110 °C in a sealed pressure flask. After 24 h the mixture was poured into distilled water (300 mL), and the precipitate was collected by filtration, washed with water, and dried to give 2-methylamino-6-trifluoromethoxy-benzothiazole **113** as a white solid (19.52 g, 90.4%): mp 168 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.96 (dt, 3H, $NHCH_3$), 7.20 (dd, 1H, J = 9 and 2 Hz, 5-H), 7.45 (d, 1H, J = 9 Hz, 4-H), 7.80 (m, 1H, 7-H), 8.1 (bq, 0.7H, J = 5 Hz, N*H*Me); Anal. ($C_9H_7F_3N_2OS$) C, H, F, N, S.

(b) This compound (7.05 g, 0.0284 mol) and 2-chloroethyl-ethyl-sulfide were dissolved in 2-butanone and heated under reflux for 48 h. The reaction mixture was then cooled to room temperature, and the precipitate was collected by filtration, washed with the same solvent, and recrystallized from 2-propanol to give **90** as a colorless powder (5.33 g, 50.3%): mp 150 °C (sublimes); ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.14 (t, 3H, J = 7.5 Hz, SCH_2CH_3), 2.65 (q, 2H, J = 7.5 Hz, SCH_2CH_3), 2.93 (t, 2H, J = 7 Hz, NCH_2CH_2SEt), 3.14 (s, 3H, $=NCH_3$), 4.67 (t, 2H, J = 7 Hz, NCH_2CH_2SEt), 7.63 (bd, 1H, J = 8.5 Hz, 5-H), 7.82 (d, 1H, J = 8.5 Hz, 4-H), 8.28 (bs, 1H, 7-H), 9.00−11.50 (very bb, 1H, =NMe·HCl); MS *m/e* 336 (M^+), 248 (100). Anal. ($C_{13}H_{15}F_3N_2OS_2$·l.0HCl) C, H, Cl, F, N, S.

2-Ethylimino-3-(2-methylthioethyl)-6-trifluoromethoxybenzothiazoline Hydrochloride (91). Compound **91** was preprared in the same way as described for **90** using ethylamine in the first step to obtain the 2-(ethylamino)-benzothiazole **114** and 2-chloroethyl-methyl-sulfide in the second step: mp 208 °C (sublimes); ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.35 (t, 3H, J = 7.5 Hz, $=NCH_2CH_3$), 2.18 (s, 3H, SCH_3), 2.90 (t, 2H, J = 7 Hz, NCH_2CH_2SMe), 3.55 (q, 2H, J = 7.5 Hz, $=NCH_2CH_3$), 4.75 (t, 2H, J = 7 Hz, NCH_2CH_2SEt), 7.60 (bd, 1H, J = 8.5 Hz, 5-H), 7.83 (d, 1H, J = 8.5 Hz, 4-H), 8.28 (bs, 1H, 7-H), 11.65 (bb, 1H, =NEt·HCl); MS *m/e* 336 (M^+), 262 (100). Anal. ($C_{13}H_{15}F_3N_2OS_2$·1.0HCl) C, H, Cl, F, N, S.

3-(2-Ethylthioethyl)-2-methoxyimino-6-trifluoromethoxy-benzothiazoline (92): (a) To a solution of thiourea (12 g, 0.157 mol) in 1 N sulfuric acid (200 mL) was added the 2-chloro derivative **112** (25.4 g, 0.1 mol), and the yellow suspension was heated to 60 °C. After 25 h the mixture was cooled to room temperature, and the precipitate was collected by filtration, washed with water and petroleum ether, and dried to give the thiol **115** as a colorless solid (22.7 g, 90.3%): mp 228 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 7.35 and 7.42 (limit AB, 1H each, J = 8.5 Hz, 4-H and 5-H, respectively), 7.87 (bs, 1H, 7-H), 13.5−14.3 (very bb, 1H, N=C−SH); MS *m/e* 251 (M^+), 69 (100).

(b) This thiol (22.4 g, 0.089 mol) was dissolved in DMF (90 mL) and added to a stirred and hot (100 °C) solution of 1,2-dibromoethane (163 g, 0.86 mol) in DMF (90 mL). After 19 h at the same temperature the mixture was cooled to 0 °C, and the white precipitate was collected and recrystallized from a 95% aqueous solution of EtOH (450 mL) to give the tricyclic thiazolium salt **116** (18.37 g, 57.6%): mp >260 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 4.28 (t, 2H, J = 7.5 Hz, $=N^+CH_2CH_2S$), 5.02 (t, 2H, J = 7.5 Hz, $=N^+CH_2CH_2S$), 7.83 and 8.18 (two bd, 1H each, J = 8.5 Hz, 4-H and 5-H), 8.50 (bs, 1H, 7-H); MS *m/e* 356 ($M - 1^+$), 278 (100). Anal. ($C_{10}H_7BrF_3NOS_2$·0.5H_2O) C, H, Br, F, N, S.

(c) This salt (3.6 g, 0.01 mol) was added to an aqueous solution (5 mL) of methoxylamine hydrochloride (2.5 g, 0.03 mol). This mixture was treated with 1 N NaOH (10 mL), heated under reflux for 20 min, and then cooled, filtered, and concentrated. The residue was added to water and extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated to give the thiol oxime **117** as a colorless solid (1.23 g, 37.9%): mp 70 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6), 2.66 (t, 1H, J = 8 Hz, SH), 2.80 (dd, 2H, J = 8 and 7 Hz, NCH_2CH_2SH), 3.80 (s, 3H, $=NOCH_3$), 4.03 (t, 2H, J = 7 Hz, NCH_2CH_2SH), 7.28 and 7.35 (limit AB, 2H, J = 8.5 Hz, 5-H and 4-H, respectively), 7.72 (bs, 1H, 7-H); MS *m/e* 324 (M^+), 233 (100).

(d) To a solution of **117** (1.15 g, 0.0035 mol) in EtOH (5 mL) under an atmosphere of nitrogen was added sodium ethylate (prepared from 0.081 g of Na in 5 mL of EtOH) followed by ethyl bromide (0.77 g, 0.0071 mol). The resulting mixture was stirred at room temperature overnight then evaporated to dryness under vacuum, and the solid residue was washed with water and recrystallized from EtOH to give **92** as a colorless solid (0.56 g, 45.5%): mp 68 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.20 (t, 3H, J = 7.5 Hz, SCH_2CH_3), 2.60 (q, 2H, J = 7.5 Hz, SCH_2CH_3), 2.85 (t, 2H, J = 7 Hz, NCH_2CH_2SEt), 3.78 (s, 3H, $=NOCH_3$), 4.02 (t, 2H, J = 7 Hz, NCH_2CH_2SEt), 7.25 (limit

AB, 2H, 5-H and 4-H), 7.72 (bs, 1H, 7-H); MS *m/e* 352 (M^+), 89 (100). Anal. ($C_{13}H_{15}F_3N_2O_2S_2$) C, H, F, N, S.

3-(2-Ethylthioethyl)-2-hydroxyimino-6-trifluoromethoxy-benzothiazoline (93). Compound **93** was prepared, as described above for **92**, using hydroxylamine: mp 136 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 1.22 (t, 3H, J = 7.5 Hz, SCH_2CH_3), 2.62 (q, 2H, J = 7.5 Hz, SCH_2CH_3), 2.85 (t, 2H, J = 7 Hz, NCH_2CH_2SEt), 4.05 (t, 2H, J = 7 Hz, NCH_2CH_2SH), 7.22 (limit AB, 2H, J = 8.5 Hz, 5-H and 4-H), 7.70 (bs, 1H, 7-H); MS *m/e* 338 (M^+), 89 (100). Anal. ($C_{12}H_{13}F_3N_2O_2S_2$) C, H, F, N, S.

2-Acetylimino-3-(2-methylthioethyl)-6-trifluoromethoxy-benzothiazoline (94). Acetyl chloride (0.46 g, 0.0058 mol) was added dropwise to a stirred solution of **61** (1.34 g, 0.0039 mol) and triethylamine (0.79 g, 0.0078 mol) in acetone (15 mL), and the mixture was left at room temperature overnight. Water was then added, and the white precipitate was collected by filtration and recrystalized from refluxing methanol to give **94:** mp 110 °C; ^{1}H NMR δ (200 MHz, $CDCl_3$) 2.25 (s, 3H, SCH_3), 2.35 (s, 3H, $=NCOCH_3$), 2.95 (t, 2H, J = 7.5 Hz, NCH_2CH_2SMe), 4.55 (t, 2H, J = 7.5 Hz, NCH_2CH_2-SMe), 7.32 (AB, 2H, 5-H and 4-H), 7.55 (bs, 1H, 7-H); MS *m/e* 350 (M^+), 234 (100). Anal. ($C_{13}H_{13}F_3N_2O_2S_2$) C, H, F, N, S.

3-(2-Methylthioethyl)-6-trifluoromethoxy-2-benzothiazolone (95). The tricyclic thiazolium **116** (4.35 g, 0.012 mol) was added to a stirred methanolic solution (100 mL) of sodium methylate (prepared from 0.279 g of sodium) under an atmosphere of nitrogen. After refluxing for 23 h, the reaction mixture was evaporated to dryness under vacuum, and the residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water, dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with 20% EtOAc in cyclohexane to give **95** as a yellow oil (1.13 g, 30.2%): ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.13 (s, 3H, SCH_3), 2.84 (t, 2H, J = 6.5 Hz, NCH_2CH_2SMe), 4.15 (t, 2H, J = 6.5 Hz, NCH_2CH_2SMe), 7.40 (bd, 1H, J = 8.5 Hz, 5-H), 7.55 (d, IH, J = 8.5 Hz, 4-H), 7.89 (bs, 1H, 7-H); MS *m/e* 309 (M^+), 74 (100). Anal. ($C_{11}H_{10}F_3NO_2S_2$) C, H, F, N, S.

2,3-Dihydro-9*a*-methylthio-7-trifluoromethoxy-thiazolo-[2,3-*b*]benzothiazole (119). The tricyclic thiazolium **116** (4.35 g, 0.012 mol) was added to a stirred ethanolic solution (45 mL) of sodium methanethiolate (0.9 g, 0.012 mol). After 0.5 h at room temperature, the precipitate was removed and the filtrate evaporated to dryness. Recrystallization from ethanol gave **119** as a colorless solid (1.8 g, 46.1%): mp 86 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 2.20 (s, 3H, SCH_3), 2.90 and 3.20 (two m, 1H each, NCH_2CH_2S), 3.60 and 4.61 (two m, 1H each, NCH_2CH_2S), 7.13 (limit AB, 2H, J = 8.5 Hz, 5-H and 4-H, respectively), 7.43 (bs, 1H, 7-H); MS *m/e* 325 (M^+), 278 (100). Anal. ($C_{11}H_{10}F_3NOS_3$) C, H, F, N, S.

Glutamic Acid-Induced Seizures.[31] Groups of seven male Sprague−Dawley rats per dose weighing 200 ± 20 g were used. Drugs were injected i.p. at at least 3 concentrations (normally 1, 3, and 10 mg/kg) plus vehicle alone 30 min prior to intracerebroventricular (icv) administration of 10 μL/rat of a 12.5 μmol/kg solution of L-glutamic acid in saline according to a free hand technique. After this treatment, the rats were observed for 30 min; L-glutamic acid alone provoked seizures immediately after injection: animals ran wildly, jumped violently, and exhibited clonic seizures. ED_{50} for studied compounds was defined as the dose of drug (mg/kg) which totally protected 50% of the rats from clonic convulsions. In this test, riluzole (**1**) displayed an ED_{50} of 3.2 ± 0.6 mg/kg (19% variability). A similar variability was observed with the other evaluated compounds. The majority of compounds were tested once only.

Mortality Induced by Hypobaric Hypoxia.[37] Each mouse was enclosed in a 1 L decompression container. The animal was brought to a simulated altitude of 12 000 m at a speed of 70 m/s (maximum hypobaric pressure = 200 hPa). The pressure was controlled by a numeric captor (Enertec/Schlumberger CA4300/0/1). After the simulated altitude was reached, the survival time for each mouse was measured. With this material and protocol, two groups of six mice can be observed simultaneously. Under these conditions, the mean survival time for control mice was 230.4 ± 4.0 s. Each compound to be tested was given to six mice per dose (2.5 mL/100 g body weight) by intraperitoneal route (i.p.) 30 min before the challenge. In this test, riluzole (**1**) displayed an ED_{50} of 4.0 ± 0.8 mg/kg (20% variability). The same variability was observed with the other compounds evaluated, unless otherwise stated in Table 8 for compounds **65, 78**, and **79.**

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