6-(*N*-IMIDOALKYL)AMINOALKYLBENZOTHIAZOLIN-2-ONES AS LIGANDS OF THE SEROTONINERGIC 5-HT$_{1A}$ RECEPTORS

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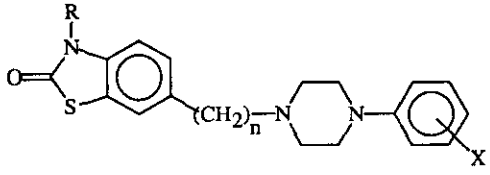
Abstract - A synthesis of 6-(*N*-imidoalkyl)aminoalkylbenzothiazolin-2-ones, during which it was necessary to prepare the corresponding 3-methyl-6-(n-*N*-methylaminoalkyl)benzothiazolin-2-ones using as key intermediates the suitable trifluoromethylalkyl derivatives, is described. This approach allowed access to monomethylated secondary amines which were then reacted with the bromoalkylimides to give the title compounds. All these compounds possess a common alkylimido linking group which was flanked by a 3-methylaminoalkylbenzothiazolin-2-one moiety. The variation of the number of methylene groups linking the central basic nitrogen to the benzothiazolin-2-one and to the imido group as well as the nature of the imido group were studied to delineate the structure-affinity relationships of this series.

Buspirone is an anxiolytic agent which exerts its antianxiety effects *via* the central serotoninergic 5-HT$_{1A}$ receptors. These anxiolytic effects are expressed without anticonvulsivant, sedative or muscle relaxant effects associated classically with benzodiazepines. Structure-affinity relationships of buspirone analogs have been described and it was shown that these anxiolytic effects are dependent on the existence of two substructural pharmacophores: the azaspirodecanedione imide and the pyrimidylpiperazine moiety.[1] With regard to buspirone, the following rationale was put forward to design the synthesized compounds: buspirone is subjected to an important hepatic first pass effect, which dramatically decreases its central

bioavailability;[2] it was therefore felt worthwile to replace the polar pyrimidylpiperazine moiety by an alkylaminobenzothiazolinone system, which is more metabolically resistant.

Arylpiperazine derivatives are potent ligands at serotoninergic receptors, especially for the 5-HT_{1A} subtype.[3] However, most of them are devoided of selectivity as they reveal an important and undesirable affinity for the α_1-adrenergic receptors.[4] Indeed, the arylpiperazino moiety is known as a good pharmacophore for the α_1-receptors. In the peripheral system, this can lead to cardiovascular side-effects.[5-7] Some of us have previously prepared original 6-arylpiperazinoalkylbenzothiazolin-2-ones (A) which showed high affinity for the 5-HT_{1A} receptors and particular psychotropic and analgesic activities [8] as a result of their potential double interaction with the central serotoninergic 5-HT_{1A} and dopaminergic D_2 receptors.[9] However, these products also possessed an important affinity for the α_1 adrenergic receptors. In order to decrease the 5-HT_{1A} / α_1 ratio and in an effort to obtain highly potent and selective ligands for the $5HT_{1A}$ receptors, we have replaced the non-selective arylpiperazino pharmacophore moiety with a *bicyclic imide present in the structure of many specific ligands* for the 5-HT_{1A} receptors.[10-14] This has led to the design and the synthesis of the compounds of general structure B.

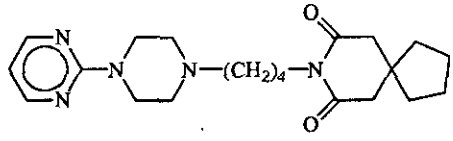


R = H or CH_3

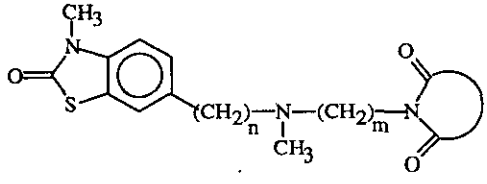
X = 3-CF_3 or 2-OCH_3

n = 2 or 4

Structure A



Buspirone



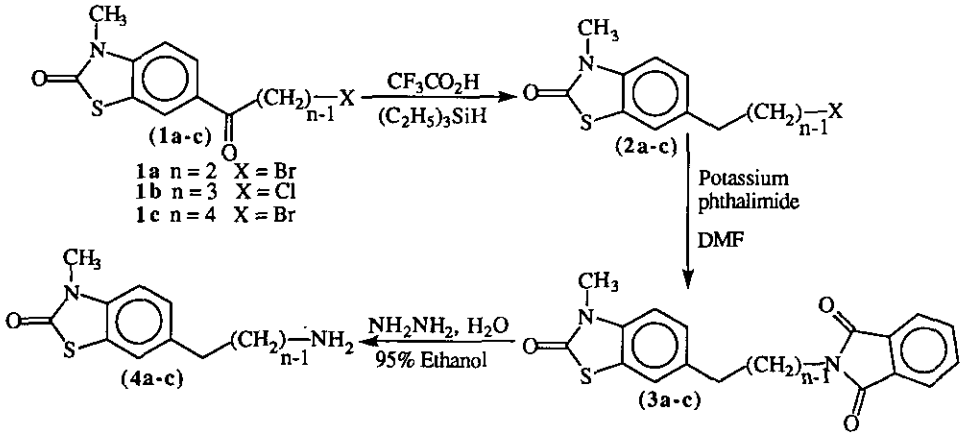
Structure B

The present work investigates several methods to provide access to such compounds. In this connection,we synthesized the 3-methyl-6-(n-aminoalkyl)benzothiazolin-2-one derivatives **(4a-c)** which were then selectively monomethylated and condensed with suitable ω-bromoalkylimides to give the desired compounds of general structure **(B)**.

3-Methyl-6-(n-aminoalkyl)benzothiazolin-2-ones (4a-c)

Compounds **(4a-c)** were prepared by application of the well-known Gabriel procedure for primary amines *(Scheme 1)*.[15]

Scheme 1



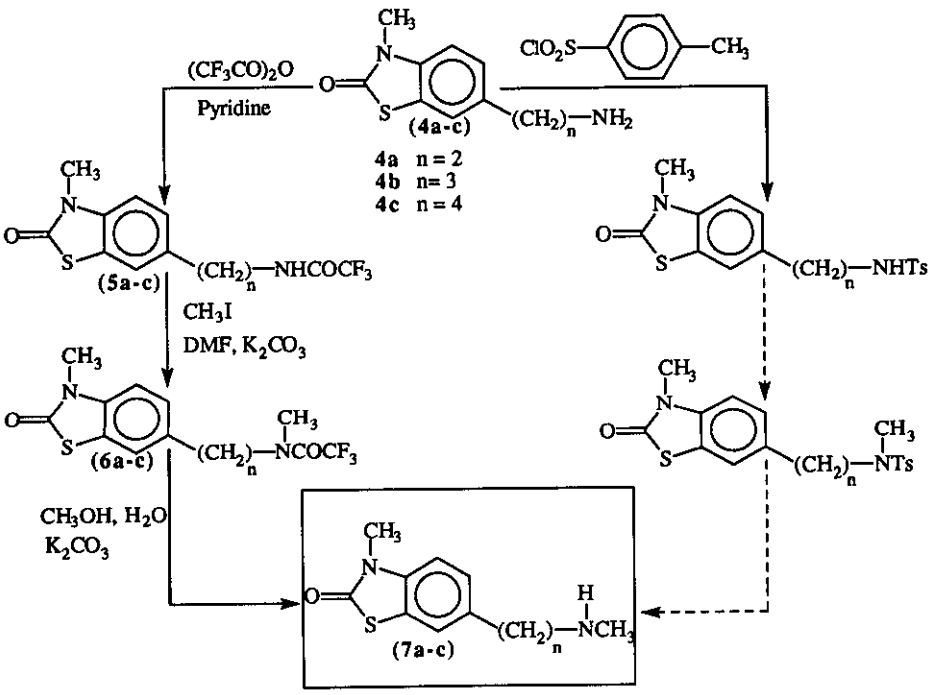
Compounds **(2a-c)** were obtained by reduction of the ketone carbonyl group of **1a-c** using the triethylsilane-trifluoroacetic acid reagent.[16] Synthesis of **4a-c** involved reaction of 3-methyl-6-(n-halogenoalkyl)benzothiazolin-2-ones **(2a-c)** with potassium phthalimide in anhydrous dimethylformamide. Compounds **(3a-c)** so obtained led to the corresponding primary amines **(4a-c)** after reaction with hydrazine monohydrate in 95% ethanol.

3-Methyl-6-(n-methylaminoalkyl)benzothiazolin-2-ones (7a-c)

To obtain the monomethylated amines **(7a-c)**, we initially tried a previously described method [17] using the sulfonamides as key intermediates *(Scheme 2)*. This approach was found unsuccessful since no complete methylation occurred leading to difficulties in separating the residual primary amine from the formed secondary amine. The second method [18] *(Scheme 2)* used the 3-methyl-6-(n-*N*-methyltrifluoroacetamidoalkyl) benzothiazolin- 2-ones **(6a-c)** as intermediates before hydrolysis to the desired secondary amines **(7a-c)** with good yields (80 %). Compounds **(5a-c)** are obtained by reacting primary amines **(4a-c)** with trifluoroacetic anhydride. Treatment of the resulting **(5a-c)** with iodomethane in anhydrous dimethylformamide in the presence of K_2CO_3 led to the tertiary trifluoroacetamides **(6a-c)**.

Cleavage of the trifluoroacetyl group occurred in aqueous methanol in the presence of K_2CO_3 leading to compounds (**7a-c**).

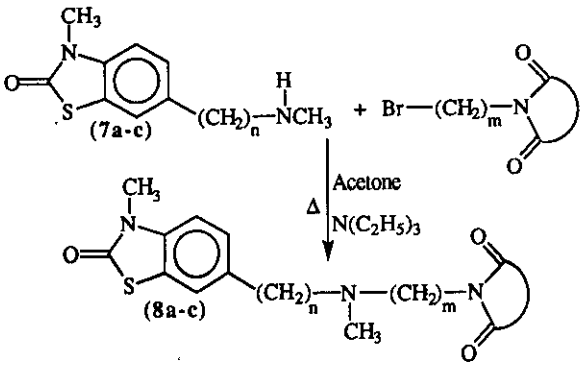
Scheme 2



3-Methyl-6-(*N*-imidoalkyl)aminoalkylbenzothiazolin-2-ones (8a-h)

The desired 3-methyl-6-(*N*-imidoalkyl)aminoalkylbenzothiazolin-2-ones (**8a-h**) were obtained by reacting the secondary amines (**7a-c**) with suitable *N*-(ω-bromoalkyl)imides. This reaction takes place in anhydrous acetone in the presence of triethylamine *(Scheme 3)*. Values of n and m and nature of the bicyclic imido moiety for compounds (**8a-h**) are reported in Tables VII to IX.

Scheme 3



CONCLUSION

This paper reports the synthesis of original 6-(*N*-imidoalkyl)aminoalkylbenzothiazolin-2-ones which were tested *in vitro* for their affinity at serotonine (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C},5-HT_{1D}, 5-HT_{2A}, and 5-HT_3) as well as dopamine (D_2), adrenergic α_1, and σ receptors. While these compounds were originally designed after buspirone as lead compounds for their potential anxiolytic properties, surprizingly enough, the final compounds were found relatively poor ligands at serotonine receptors (IC_{50} in the micromolar range). This result is presumably due to the absence of an arylpiperazine pharmacophore which is considered as mandatory for high 5-HT_{1A} affinity. However, the title compounds exhibit interesting affinity at σ receptors. In particular, compounds **(8a)**, **(8c)** and **(8d)** had IC50's of 5 X 10^{-8}, 5 X 10^{-7} and 5 X 10^{-8} M, respectively. A complete report of the pharmacology of these compounds will be published elsewhere.

EXPERIMENTAL PART

Each compound was characterized by elemental analysis, ir spectra and ^{1}H-nmr spectra. Ir spectra were recorded on a Perkin-Elmer 297 spectrophotometer, using KBr tablets; the wave numbers are expressed in cm^{-1}. The ^{1}H-Nmr spectra were obtained on a Brücker WP 80 SY (80 MHz) apparatus, with Me_4Si as the internal standard and with $CDCl_3$ or DMSO-d_6 as solvent; the chemical shifts are reported in ppm of Me_4Si in δ units; coupling constants are expressed in Hz. Melting points were determined using a Büchi SMP-20 apparatus and are uncorrected. Elemental analyses were determined by the CNRS center of analysis in Vernaison (France).

3-Methyl-6-bromoacetylbenzothiazolin-2-one (1a)

Aluminium chloride (210 g, 1.60 mol) and 3-methylbenzothiazolin-2-one (33 g, 0.20 mol) in anhydrous dimethylformamide (43 ml) were heated at 70°C under stirring. Bromoacetyl chloride (19.8 ml, 0.24 mol) was added dropwise and the reaction was continued for 1 h. After cooling, the mixture was poured onto ice and the resulting precipitate was filtered, washed with water, dried and recrystallized from 95% ethanol (37.80 g, 66 %). mp 164-165°C. Ir νCO 1680, 1660 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ 3.46 (s, 3H); 4.95 (s, 2H); 7.44 (d, J = 8.7 Hz, 1H); 8.07 (dd, J_1 = 8.7 Hz, J_2 = 1.7 Hz, 1H); 8.37 (d, J = 1.7 Hz, 1H). Anal. Calcd for $C_{10}H_8NO_2BrS$: C, 41.97; H, 2.82; N, 4.89. Found; C, 42.26; H, 2.70; N, 4.72.

3-Methyl-6-(3-chloropropionyl)benzothiazolin-2-one (1b)

1b was prepared by treatment of 3-methylbenzothiazolin-2-one (33 g, 0.20 mol) with 3-chloropropionyl chloride (22.9 ml, 0.24 mol) in the presence of aluminium chloride (210 g, 1.60 mol) in dimethylformamide (43 ml) as described for compound **(1a)** (30.60 g, 60 %). mp 174-177°C. Ir νCO 1660 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ 3.48 (m, 2H); 3.51 (s, 3H); 3.90 (m, 2H); 7.77 (d, J = 8.4 Hz, 1H); 8.00 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H); 8.10 (d, J = 1.4 Hz, 1H). Anal. Calcd for $C_{11}H_{10}NO_2ClS$: C, 51.66; H, 3.94; N, 5.47. Found; C, 51.67; H, 3.83; N, 5.83.

3-Methyl-6-(4-bromobutyryl)benzothiazolin-2-one (1c)

3-Methylbenzothiazolin-2-one (16.52 g, 0.1 mol) and polyphosphoric acid (200 g) were heated at 60°C and to the stirred mixture was added dropwise 4-chlorobutyryl chloride (14.1 ml, 0.125 mol). The mixture was heated at 120°C for 3 h and after cooling, was poured onto ice. The solid precipitate corresponding to the 3-methyl-6-(4-hydroxybutyryl)benzothiazolin-2-one was filtered, washed with water, dried and recrystallized from toluene. The resulting pure product was redissolved in anhydrous acetone (100 ml). HBr was bubbled into the solution and the mixture was stirred at room temperature for 1 h. The solvent was evaporated *in vacuo* and the residue was recrystallized from 95% alcohol (19.60 g, 62 %). mp 96-98°C. Ir νCO 1650, 1755 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ 2.29 (m, 2H); 3.18 (t, J = 5.82 Hz, 2H); 3.53 (m, 3H); 7.11 (d, J = 8.9 Hz, 1H); 8.00 (m, 2H). Anal. Calcd for $C_{12}H_{12}NO_2BrS$: C, 45.86; H, 3.84; N, 4.45. Found; C, 45.72; H, 3.80; N, 4.38.

General procedure for the synthesis of the 3-methyl-6-(n-halogenoalkyl)-benzothiazolin-2-one derivatives (2a-c)

Compounds **(1a-c)** (0.1 mol) were dissolved in trifluoroacetic acid (70 ml). The solution was stirred at room temperature and triethylsilane (39.90 ml, 0.25 mol) was added dropwise. After 20 h, the mixture was poured onto ice. The resulting precipitate was filtered, washed with water, dried and recrystallized from an appropriate solvent (Table I).

General procedure for the synthesis of the 3-methyl-6-(n-phthalimidoalkyl)-benzothiazolin-2-one derivatives (3a-c)

A mixture of potassium phthalimide (1.85 g, 0.01 mol) in dimethylformamide (20 ml) was stirred and heated under reflux. A solution of **2a-c** (0.01 mol) in dimethylformamide (5 ml) was then added dropwise. After 1 h, the mixture was cooled and poured onto ice. The resulting precipitate was filtered, dried and recrystallized from an appropriate solvent (Table II).

General procedure for the synthesis of the 3-methyl-6-(n-aminoalkyl)-benzothiazolin-2-one derivatives (4a-c)

A mixture of **3a-c** (0.01 mol) in 95 % ethanol (100 ml) was refluxed. Hydrazine hydrate (4.85 ml, 0.10 mol) was added and the reaction was continued for 3 h. After elimination of the solvent under reduced pressure, the resulting residue was dissolved in water and extracted with chloroform. The organic layer was dried over $CaCl_2$ and evaporated under reduced pressure. The resulting residue was dissolved in 50 ml of absolute ethanol and HCl was bubbled into the solution. The precipitate was filtered and recrystallized from an appropriate solvent (Table III).

General procedure for the synthesis of the 3-methyl-6-{n-(trifluoromethyl-acetamido)alkyl}benzothiazolin-2-one derivatives (5a-c)

Compounds **(4a-c)** (0.01 mol) were dissolved in anhydrous pyridine (50 ml) and trifluoroacetic anhydride (1.70 ml, 0.012 mol) was added dropwise at 0°C. After stirring for 1 h, the mixture was poured

Table I. Physical and spectral data of compounds (2)

Compds	n	X	Yield (%) Solvent	mp (°C)	ir ν(C=O)	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) Calcd / Found C	H	N
2a	2	Br	86 Cyclohexane	98	1660	6.75-7.30(m,3H); 3.50-3.80(m,2H); 3.40(s,3H); 3.19(t,J=5.51 Hz, 2H).	$C_{10}H_{10}NOBrS$	44.13 / 44.36	3.70 / 3.60	5.15 / 5.36
2b	3	Cl	84 Cyclohexane	42	1665	7.20-7.30(m,3H); 3.50 (t,J=5.71 Hz,2H); 3.40 (s,3H); 2.80(t,J=7.6 Hz, 2H); 2.10(q,J_1=7.6 Hz, J_2=5.7 Hz,2H).	$C_{11}H_{12}NOClS$	54.64 / 54.61	5.00 / 5.08	5.79 / 5.63
2c	4	Br	90 Cyclohexane	66	1670	7.15-7.35(m,3H); 3.40-3.50(m,5H); 2.70(t,J= 5.52 Hz,2H); 1.80-2.00 (m,4H).	$C_{12}H_{14}NOBrS$	47.99 / 48.13	4.70 / 4.72	4.66 / 4.63

Table II. Physical and spectral data of compounds (3)

Compds	n	Yield (%) Solvent	mp (°C)	ir ν(C=O)	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) Calcd / Found C	H	N
3a	2	60 DMF	>260	1775 1710	7.80(m,4H); 7.00-7.20 (m,3H); 3.70(t,J=6.15 Hz 2H); 3.30(s,3H); 3.00(t, J=6.15 Hz,2H).	$C_{18}H_{14}N_2O_3S$	63.90 / 63.90	4.17 / 4.24	8.28 / 7.88
3b	3	58 DMF	189	1760 1700 1665	7.20-7.80(m,7H); 3.40 (s,3H); 2.60-2.80(m,4H); 1.70-1.80(m,2H).	$C_{19}H_{16}N_2O_3S$	64.76 / 64.37	4.57 / 4.42	7.95 / 7.78
3c	4	56 95% Ethanol	160	1770 1720 1670	7.80-7.95(m,4H); 7.20-7.40(m,3H); 3.50(s,3H); 2.50-2.60(m,4H); 1.60-1.80(m,4H).	$C_{20}H_{18}N_2O_3S$	65.56 / 65.95	4.95 / 4.95	7.64 / 7.76

Table III. Physical and spectral data of compounds (4)

Compds	n	Yield (%) Solvent	mp (°C)	ir ν(C=O)	^{1}Hnmr (DMSO-d_6) δ	Molecular formula	Analysis (%) Calcd / Found C H N
4a	2	72 Absolute ethanol	230	1680	8.17(s,3H); 7.55(s,1H); 7.28(m,2H); 3.30(s,3H); 3.00(m,4H); 1.50-2.10 (m,2H).	$C_{10}H_{13}N_2OClS$	49.07 5.35 11.45 49.17 5.38 11.38
4b	3	75 Absolute ethanol	220	1660	8.30(s,3H); 7.20-7.60(m, 3H); 3.40(s,3H); 2.60-3.00 (m,4H).	$C_{11}H_{15}N_2OClS$	50.14 5.88 10.63 50.52 6.11 10.98
4c	4	82 Absolute ethanol	215	1660	7.95(s,3H); 7.20-7.50 (m,3H); 3.30(s,3H); 2.50-2.90(m,4H); 1.50-1.80(m,4H).	$C_{12}H_{17}N_2OClS$	52.83 6.28 10.27 52.90 6.46 10.23

Table IV. Physical and spectral data of compounds (5)

Compds	n	Yield (%) Solvent	mp (°C)	ir ν(C=O) NCOS	ir ν(C=O) $NCOCF_3$	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) Calcd / Found C	H	N
5a	2	97 Cyclohexane	157	1650	1720 1560	7.00-7.40(m,3H); 6.60 (s,1H); 3.50-3.90(q,J=8.00 Hz,2H); 3.40(s,3H); 2.90 (t,J=8.00 Hz,2H).	$C_{12}H_{11}N_2O_2F_3S$	47.37 47.34	3.64 3.51	9.21 9.08
5b	3	88 Cyclohexane	107	1660	1700 1550	7.00-7.40(m,3H); 6.40 (s,1H); 3.40(s,3H); 2.60-2.80(m,4H); 1.70-2.10(m,2H).	$C_{13}H_{13}N_2O_2F_3S$	49.00 49.34	4.32 4.16	8.80 8.39
5c	4	98 Cyclohexane	115	1660	1700 1560	7.00-7.20(m,3H); 6.50 (s,1H); 3.300-3.50(m,5H); 2.60-2.80(m,2H); 1.50-1.80(m,4H).	$C_{14}H_{15}N_2O_2F_3S$	50.60 50.78	4.55 4.60	8.43 8.28

Table V. Physical and spectral data of compounds (6)

Compds	n	Yield (%) Solvent	mp (°C)	ir ν(C=O)	^{1}Hnmr (DMSO-d_6) δ	Molecular formula	Analysis (%) Calcd / Found C H N
6a	2	91 Cyclohexane	123	1650	6.90-7.20(m,3H); 3.60-3.80(m,2H); 3.40(s,3H); 2.80-3.10(m,5H).	$C_{13}H_{13}N_2O_2F_3S$	49.07 5.35 11.45 49.17 5.38 11.38
6b	3	95 Cyclohexane	80	1670	6.80-7.20(m,3H); 3.40 (m,3H); 2.70-3.20(m,7H); 1.80-2.20(m,2H).	$C_{14}H_{15}N_2O_2F_3S$	50.14 5.88 10.63 50.52 6.11 10.98
6c	4	82 Cyclohexane	64	1670	6.80-7.20(m,3H); 3.30-3.50(m,5H); 3.00-3;20 (m,3H); 2.60-2.80(m,2H); 1.50-1.80(m,4H).	$C_{15}H_{17}N_2O_2F_3S$	52.83 6.28 10.27 52.90 6.46 10.23

Table VI. Physical and spectral data of compounds (7)

Compds	n	Yield (%) Solvent	mp (°C)	ir ν(C=O)	^{1}Hnmr (DMSO-d_6) δ	Molecular formula	Analysis (%) Calcd / Found C H N
7a	2	80 Anhydrous acetone	204	1670	9.00-9.20(s,2H); 7.60 (m,1H); 7.10-7.30(m,2H); 3.40(s,3H); 3.10-3.20(m, 4H); 2.50(s,3H).	$C_{11}H_{15}N_2OClS$	51.06 5.84 10.82 50.68 6.03 10.69
7b	3	80 Anhydrous acetone	165	1660	9.60(s,2H); 6.80-7.40(m, 3H); 3.40(s,3H); 2.60-3.10 (m,7H); 1.60-1.80(m,2H).	$C_{12}H_{17}N_2OClS$	52.83 6.28 10.27 52.44 6.19 10.12
7c	4	80 Anhydrous acetone	131	1660	8.90(s,2H); 7.60(s,1H); 7.20-7.30(m,2H); 3.40 (s,3H); 2.60-2.80(m,7H); 1.50- 1.70(m,4H).	$C_{13}H_{19}N_2OClS$	53.60 6.70 9.62 53.47 6.78 9.43

Table VII. Physical and spectral data of compounds (8).

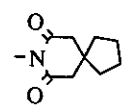
Compds	n	m	Bicyclic imide	Yield (%) Solvent	mp (°C)	ir ν(C=O)	^{1}Hnmr (δ)	Molecular formula	Analysis Calcd / Found C H N
8a	2	4		32 Acetone/Ether (1/1)	174	1750 1680 1600	(CDCl$_3$) 12.50(s,1H); 6.80-7.50(m,3H); 3.90 (m,2H); 3.50(m,3H); 3.00-3.40(m, 6H); 2.80(s,3H);2.60(s,4H); 1.10-1.30(m,12H).	$C_{24}H_{34}N_3O_3ClS$ 1/2 H_2O	58.93 7.21 8.50 58.78 7.02 8.46
8b	3	4		43 Acetone/Ether (1/1)	147	1720 1680 1660	(DMSO-d$_6$) 10.30(s,1H); 7.00-7.50(m,3H); 3.60 (m,2H); 3.40(s,3H); 2.80-3.10(m, 2H); 2.60-2.70(m,11H); 1.50-2.00 (m,14H).	$C_{25}H_{36}N_3O_3ClS$ 5/2 H_2O	55.69 7.71 7.70 55.68 7.14 7.74
8c	4	4		32 Acetone/Ether (1/1)	122	1450 1700 1650	(CDCl$_3$) 12.00(s,1H); 7.00-7.20(m,3H); 3.60-4.00(m,2H); 3.40(s,3H); 2.80-3.00(m, 2H); 2.50-2.70(m,11H); 1.50-2.00 (m,16H).	$C_{26}H_{38}N_3O_3ClS$ 3/2 H_2O	58.55 7.76 8.12 58.68 7.72 7.85

Table VIII. Physical and spectral data *of compounds* (8).

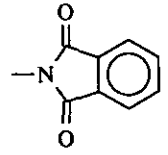
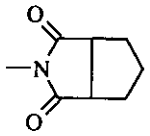
Compds	n	m	Bicyclic imide	Yield (%) Solvent	mp (°C)	ir ν(C=O)	^{1}Hnmr (DMSO-d_6) δ	Molecular formula	Analysis Calcd / Found C H N
8d	2	3		62 Absolute ethanol	251	1750 1680	10.30(s,1H); 7.90(s,4H); 7.50(s,1H); 7.20-7.30(m,2H); 3.60-3.80(m,2H); 3.40(s,3H); 3.10-3.30(m,6H); 2.80(s,3H); 2.00-2.30(m,2H).	$C_{22}H_{24}N_3O_3ClS$ 1 H_2O	56.95 5.64 9.05 56.65 5.49 8.72
8e	3	2		54 Acetone/Ether (1/1)	236	1770 1710 1680	10.50(s,1H); 7.90(s,4H); 7.20-7.40(m,3H); 3.90-4.00(m,2H); 3.40(s,3H); 3.20-3.30(m,6H); 2.60-2.80(s,3H); 1.80-1.90(m,2H).	$C_{22}H_{24}N_3O_3ClS$ 1/2 H_2O	58.07 5.12 9.42 57.88 5.27 9.23
8f	3	3		60 Acetone/Ether (1/1)	174	1750 1720 1680	10.90(s,1H); 7.80(s,4H); 7.20-7.50(m,3H); 3.80-3.90(m,2H); 3.30-3.60(m,7H); 3.00-3.20(m,2H); 2.60-2.80(s,3H); 1.80-2.10(m,4H).	$C_{23}H_{26}N_3O_3ClS$ 3/2 H_2O	56.72 6.11 8.63 56.77 5.78 8.63

TABLE IX. Physical and spectral data of compounds (8)

Compds	n	m	Bicyclic imide	Yield (%) Solvent	mp (°C)	ir ν (C=O)	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis Calcd / Found C H N
8g	2	4		44 Acetone/Ether (1/1)	131	1760 1700 1600	12.50(s,1H); 6.90-7.80(m,3H); 3.40-3.70(m,5H); 3.00-3.30(m,8H); 2.80(s,3H); 1.40-1.90(m,10H).	$C_{22}H_{30}N_3O_3ClS$ 1 H_2O	56.21 6.43 8.94 56.00 6.60 8.96
8h	3	4		37 Acetone/Ether (1/1)	127	1760 1700 1660	12.50(s,1H); 6.90-7.40(m,3H); 3.30-3.50(m,5H); 2.60-3.10(m,11H); 1.40-1.90(m,12H).	$C_{23}H_{32}N_3O_3ClS$ 1 H_2O	57.67 7.08 8.68 57.76 6.94 8.49

onto ice. The resulting precipitate was filtered, washed with water, dried and recrystallized from an appropriate solvent (Table IV).

General procedure for the synthesis of the 3-methyl-6-(n-*N*-methyltrifluoromethyl-acetamidoalkyl)benzothiazolin-2-one derivatives (6a-c)

The mixture of **5a-c** (0.01 mol) and K_2CO_3 (5.52 g, 0.04 mol) in anhydrous dimethylformamide (50 ml) was heated under reflux for 1 h. After cooling to 40°C, iodomethane (1.25 ml, 0.02 mol) was added dropwise and the reaction was continued for 2 h. After cooling, the mixture was poured onto ice. The resulting precipitate was filtered, washed with water, dried and recrystallized from an appropriate solvent (Table V).

General procedure for the synthesis of the 3-methyl-6-(n-*N*-methylamino-alkyl)benzothiazolin-2-one derivatives (7a-c)

Compounds **(6a-c)** (0.01 mol) were dissolved in a mixture of methanol (60 ml) and water (10 ml). K_2CO_3 (5.52 g, 0.04 mol) was added and the mixture was heated under reflux for 1 h. Methanol was evaporated *in vacuo*, water (50 ml) was added and the solution was extracted with ethyl acetate. The organic layer was dried over K_2CO_3 and evaporated. The resulting residue was dissolved in anhydrous acetone (50 ml) and HCl was bubbled into the solution. The resulting precipitate was filtered, dried and recrystallized from an appropriate solvent (Table VI).

General procedure for the synthesis of the 3-methyl-6-(n-imidoalkyl)aminoalkyl benzothiazolin-2-ones (8a-h)

A mixture of **7a-c** (0.01 mol), triethylamine (3.10 ml, 0.022 mol) and anhydrous acetone (50 ml) was refluxed. The appropriate ω-(bromoalkyl)imide (0.01 mol) previously dissolved in anhydrous acetone (20 ml) was added dropwise. The reaction mixture was stirred for 24 h. After cooling, the formed triethylamine hydrobromide was filtered. The solvent was evaporated and the residue was dissolved in an aqueous solution of 3N HCl (50 ml) and extracted with toluene. The aqueous layer was made basic with a 10 % aqueous solution of sodium hydroxide and extracted with chloroform. The chloroform organic layer was washed with a 3 % aqueous solution of acetic acid to remove any secondary amine and then with a 10 % aqueous solution of Na_2CO_3. The chloroform solution was dried over $CaCl_2$ and evaporated. The residue was dissolved in anhydrous acetone and a saturated solution of HCl in diethylether was added dropwise. The resulting precipitate was filtered, dried and recrystallized from an appropriate solvent (Tables VII, VIII and IX).

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Received, 6th January, 1995