

## 6-(*N*-IMIDOALKYL)AMINOALKYLBENZOTHIAZOLIN-2-ONES AS LIGANDS OF THE SEROTONINERGIC 5-HT<sub>1A</sub> RECEPTORS

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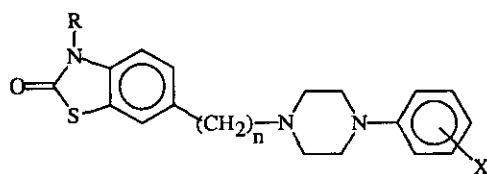
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**Abstract** - A synthesis of 6-(*N*-imidoalkyl)aminoalkylbenzothiazolin-2-ones, during which it was necessary to prepare the corresponding 3-methyl-6-(*n*-*N*-methylaminoalkyl)benzothiazolin-2-ones using as key intermediates the suitable trifluoromethylalkyl 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 serotonergic 5-HT<sub>1A</sub> receptors. These anxiolytic effects are expressed without anticonvulsant, 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.<sup>1</sup> 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;<sup>2</sup> it was therefore felt worthwhile to replace the polar pyrimidylpiperazine moiety by an alkylaminobenzothiazolinone system, which is more metabolically resistant.

Arylpiperazine derivatives are potent ligands at serotonergic receptors, especially for the 5-HT<sub>1A</sub> subtype.<sup>3</sup> However, most of them are devoided of selectivity as they reveal an important and undesirable affinity for the  $\alpha_1$ -adrenergic receptors.<sup>4</sup> Indeed, the arylpiperazino moiety is known as a good pharmacophore for the  $\alpha_1$ -receptors. In the peripheral system, this can lead to cardiovascular side-effects.<sup>5-7</sup> Some of us have previously prepared original 6-arylpiperazinoalkylbenzothiazolin-2-ones (A) which showed high affinity for the 5-HT<sub>1A</sub> receptors and particular psychotropic and analgesic activities<sup>8</sup> as a result of their potential double interaction with the central serotonergic 5-HT<sub>1A</sub> and dopaminergic D<sub>2</sub> receptors.<sup>9</sup> However, these products also possessed an important affinity for the  $\alpha_1$  adrenergic receptors. In order to decrease the 5-HT<sub>1A</sub> /  $\alpha_1$  ratio and in an effort to obtain highly potent and selective ligands for the 5HT<sub>1A</sub> 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<sub>1A</sub> receptors.<sup>10-14</sup> This has led to the design and the synthesis of the compounds of general structure B.

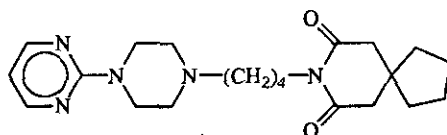


R = H or CH<sub>3</sub>

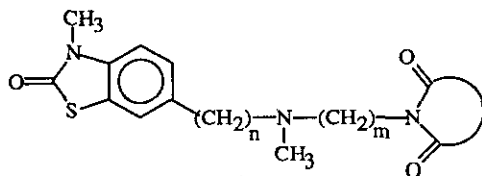
X = 3-CF<sub>3</sub> or 2-OCH<sub>3</sub>

n = 2 or 4

Structure A



Buspirone



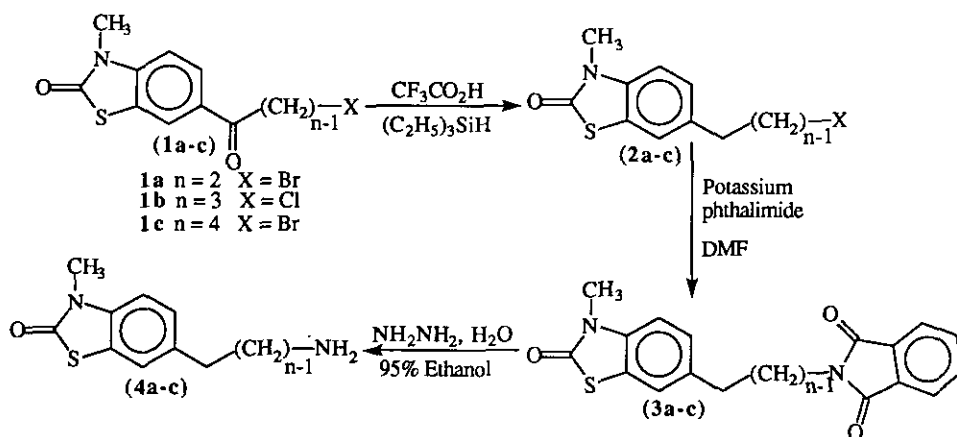
Structure B

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  $\omega$ -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*).<sup>15</sup>

*Scheme 1*



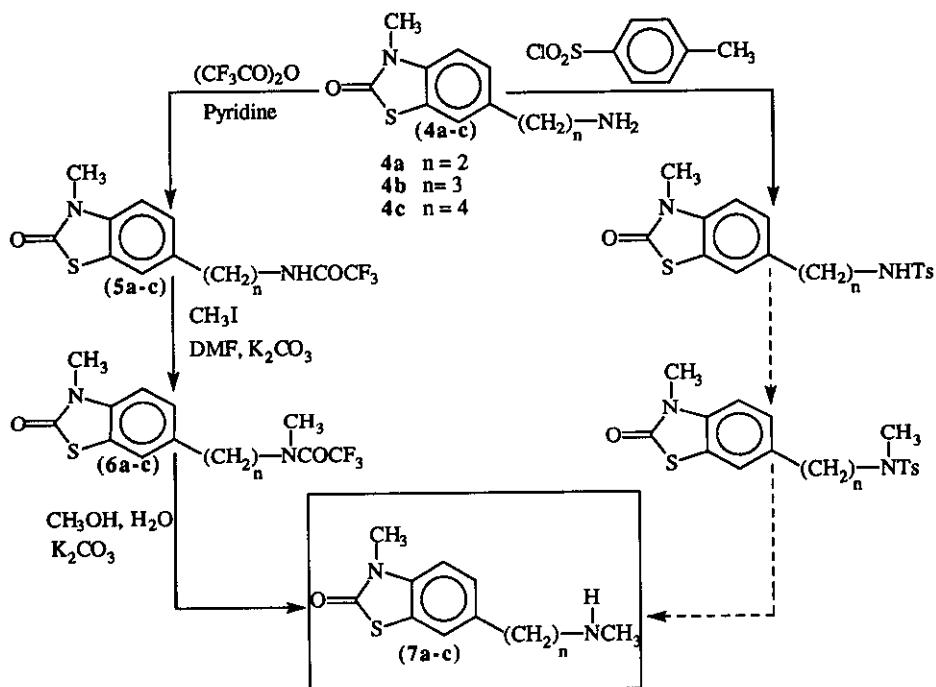
Compounds (**2a-c**) were obtained by reduction of the ketone carbonyl group of **1a-c** using the triethylsilane-trifluoroacetic acid reagent.<sup>16</sup> Synthesis of **4a-c** involved reaction of 3-methyl-6-(*n*-halogenoalkyl)benzothiazolin-2-ones (**2a-c**) with potassium phthalimide in anhydrous 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<sup>17</sup> 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<sup>18</sup> (*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  $\text{K}_2\text{CO}_3$  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).

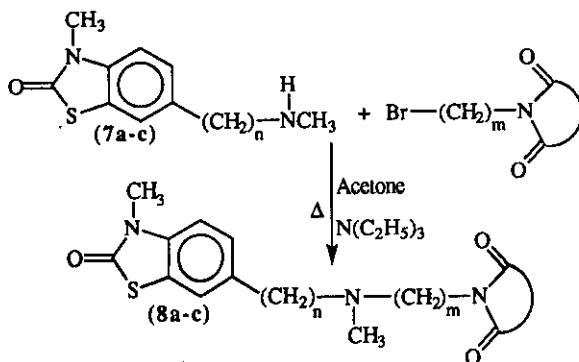
Scheme 2



### 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 serotonin (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>3</sub>) as well as dopamine (D<sub>2</sub>), adrenergic  $\alpha_1$ , and  $\sigma$  receptors. While these compounds were originally designed after buspirone as lead compounds for their potential anxiolytic properties, surprisingly enough, the final compounds were found relatively poor ligands at serotonin receptors (IC<sub>50</sub> 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<sub>1A</sub> affinity. However, the title compounds exhibit interesting affinity at  $\sigma$  receptors. In particular, compounds (8a), (8c) and (8d) had IC<sub>50</sub>'s of  $5 \times 10^{-8}$ ,  $5 \times 10^{-7}$  and  $5 \times 10^{-8}$  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 <sup>1</sup>H-nmr spectra. Ir spectra were recorded on a Perkin-Elmer 297 spectrophotometer, using KBr tablets; the wave numbers are expressed in cm<sup>-1</sup>. The <sup>1</sup>H-Nmr spectra were obtained on a Brücker WP 80 SY (80 MHz) apparatus, with Me<sub>4</sub>Si as the internal standard and with CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> as solvent; the chemical shifts are reported in ppm of Me<sub>4</sub>Si in  $\delta$  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  $\nu$ CO 1680, 1660 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-*d*<sub>6</sub>)  $\delta$  3.46 (s, 3H); 4.95 (s, 2H); 7.44 (d, *J* = 8.7 Hz, 1H); 8.07 (dd, *J*<sub>1</sub> = 8.7 Hz, *J*<sub>2</sub> = 1.7 Hz, 1H); 8.37 (d, *J* = 1.7 Hz, 1H). Anal. Calcd for C<sub>10</sub>H<sub>8</sub>NO<sub>2</sub>BrS: 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  $\nu$ CO 1660 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-*d*<sub>6</sub>)  $\delta$  3.48 (m, 2H); 3.51 (s, 3H); 3.90 (m, 2H); 7.77 (d, *J* = 8.4 Hz, 1H); 8.00 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.4 Hz, 1H); 8.10 (d, *J* = 1.4 Hz, 1H). Anal. Calcd for C<sub>11</sub>H<sub>10</sub>NO<sub>2</sub>ClS: 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  $\nu_{\text{CO}}$  1650, 1755  $\text{cm}^{-1}$ .  $^1\text{H-Nmr}$  (DMSO- $d_6$ )  $\delta$  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  $\text{C}_{12}\text{H}_{12}\text{NO}_2\text{BrS}$ : 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  $\text{CaCl}_2$  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)	<sup>1</sup> Hnmr (CDCl <sub>3</sub> ) δ	Molecular formula	Analysis (%)		
								Calcd	Found	
								C	H	N
2a	2	Br	86	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 <sub>10</sub> H <sub>10</sub> NOBrS	44.13	3.70	5.15
			Cyclohexane					44.36	3.60	5.36
2b	3	Cl	84	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 <sub>1</sub> =7.6 Hz, J <sub>2</sub> =5.7 Hz,2H).	C <sub>11</sub> H <sub>12</sub> NOCIS	54.64	5.00	5.79
			Cyclohexane					54.61	5.08	5.63
2c	4	Br	90	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 <sub>12</sub> H <sub>14</sub> NOBrS	47.99	4.70	4.66
			Cyclohexane					48.13	4.72	4.63

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

Compds	n	Yield (%) Solvent	mp (°C)	ir ν(C=O)	<sup>1</sup> Hnmr (CDCl <sub>3</sub> ) δ	Molecular formula	Analysis (%)		
							Calcd	Found	
							C	H	N
3a	2	60	>260	1775	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 <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S	63.90	4.17	8.28
		DMF		1710			63.90	4.24	7.88
3b	3	58 DMF	189	1760	7.20-7.80(m,7H); 3.40(s,3H); 2.60-2.80(m,4H); 1.70-1.80(m,2H).	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S	64.76	4.57	7.95
				1700			64.37	4.42	7.78
				1665					
3c	4	56 95% Ethanol	160	1770	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 <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S	65.56	4.95	7.64
				1720			65.95	4.95	7.76
				1670					

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

Compds	n	Yield (%) Solvent	mp (°C)	ir ν(C=O)	<sup>1</sup> Hnmr (DMSO-d <sub>6</sub> ) 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 <sub>10</sub> H <sub>13</sub> N <sub>2</sub> OCIS	49.07 49.17	5.35 5.38	11.45 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 <sub>11</sub> H <sub>15</sub> N <sub>2</sub> OCIS	50.14 50.52	5.88 6.11	10.63 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 <sub>12</sub> H <sub>17</sub> N <sub>2</sub> OCIS	52.83 52.90	6.28 6.46	10.27 10.23



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

Compds	n	Yield (%) Solvent	mp (°C)	ir		<sup>1</sup> Hnmr (CDCl <sub>3</sub> ) δ	Molecular formula	Analysis (%)		
				ν(C=O) NCOS	ν(C=O) NCOCF <sub>3</sub>			Calcd	Found	
								C	H	N
5a	2	97 Cyclohexane	157	1650	1720	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 <sub>12</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> F <sub>3</sub> S	47.37	3.64	9.21
					1560			47.34	3.51	9.08
5b	3	88 Cyclohexane	107	1660	1700	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 <sub>13</sub> H <sub>13</sub> N <sub>2</sub> O <sub>2</sub> F <sub>3</sub> S	49.00	4.32	8.80
					1550			49.34	4.16	8.39
5c	4	98 Cyclohexane	115	1660	1700	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 <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> F <sub>3</sub> S	50.60	4.55	8.43
					1560			50.78	4.60	8.28

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

Compds	n	Yield (%) Solvent	mp (°C)	ir $\nu(\text{C}=\text{O})$	<sup>1</sup> Hnmr (DMSO-d <sub>6</sub> ) $\delta$	Molecular formula	Analysis (%)		
							Calcd	Found	
							C	H	N
6a	2	91	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 <sub>13</sub> H <sub>13</sub> N <sub>2</sub> O <sub>2</sub> F <sub>3</sub> S	49.07	5.35	11.45
		Cyclohexane					49.17	5.38	11.38
6b	3	95	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 <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> F <sub>3</sub> S	50.14	5.88	10.63
		Cyclohexane					50.52	6.11	10.98
6c	4	82	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 <sub>15</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> F <sub>3</sub> S	52.83	6.28	10.27
		Cyclohexane					52.90	6.46	10.23

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

Compds	n	Yield (%) Solvent	mp (°C)	ir $\nu(\text{C}=\text{O})$	<sup>1</sup> Hnmr (DMSO-d <sub>6</sub> ) $\delta$	Molecular formula	Analysis (%)		
							Calcd	Found	
							C	H	N
7a	2	80	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 <sub>11</sub> H <sub>15</sub> N <sub>2</sub> OCIS	51.06	5.84	10.82
		Anhydrous acetone					50.68	6.03	10.69
7b	3	80	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 <sub>12</sub> H <sub>17</sub> N <sub>2</sub> OCIS	52.83	6.28	10.27
		Anhydrous acetone					52.44	6.19	10.12
7c	4	80	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 <sub>13</sub> H <sub>19</sub> N <sub>2</sub> OCIS	53.60	6.70	9.62
		Anhydrous acetone					53.47	6.78	9.43

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

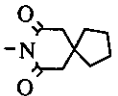
Comps	n	m	Bicyclic imide	Yield (%) Solvent	mp (°C)	ir v(C=O)	<sup>1</sup> Hnmr (δ)	Molecular formula	Analysis Calcd / Found C H N
	8a	2	4	32 Acetone/Ether (1/1)	174	1750 1680 1600	(CDCl <sub>3</sub> )  12.50(s,1H); 6.80-7.50(m,3H); 3.90 (m,2H); 3.50(m,3H); 3.00-3.40(m, 6H); 2.80(s,3H); 2.60(s,4H); 1.10- 1.30(m,12H).	C <sub>24</sub> H <sub>34</sub> N <sub>3</sub> O <sub>3</sub> ClS 1/2 H <sub>2</sub> O	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 <sub>6</sub> )  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 <sub>25</sub> H <sub>36</sub> N <sub>3</sub> O <sub>3</sub> ClS 5/2 H <sub>2</sub> O	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 <sub>3</sub> )  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 <sub>26</sub> H <sub>38</sub> N <sub>3</sub> O <sub>3</sub> ClS 3/2 H <sub>2</sub> O	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)	<sup>1</sup> Hnmr (DMSO-d <sub>6</sub> ) 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 <sub>22</sub> H <sub>24</sub> N <sub>3</sub> O <sub>3</sub> CIS 1 H <sub>2</sub> O	56.95 5.64 9.05 56.65 5.49 8.72
							8e		3
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 <sub>23</sub> H <sub>26</sub> N <sub>3</sub> O <sub>3</sub> CIS 3/2 H <sub>2</sub> O	56.72 6.11 8.63 56.77 5.78 8.63

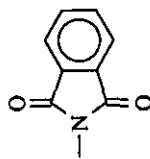
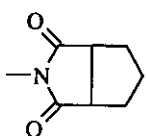


TABLE IX. Physical and spectral data of compounds (8)

Compds	n	m	Bicyclic imide	Yield (%) Solvent	mp (°C)	ir v (C=O)	<sup>1</sup> Hnmr (CDCl <sub>3</sub> ) δ	Molecular formula	Analysis		
									Calcd	Found	
									C	H	N
8g	2	4		44		1760	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 <sub>22</sub> H <sub>30</sub> N <sub>3</sub> O <sub>3</sub> ClS 1 H <sub>2</sub> O	56.21	6.43	8.94
				Acetone/Ether (1/1)	131	1700			56.00	6.60	8.96
8h	3	4		37	127	1760	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 <sub>23</sub> H <sub>32</sub> N <sub>3</sub> O <sub>3</sub> ClS 1 H <sub>2</sub> O	57.67	7.08	8.68
			Acetone/Ether (1/1)			1700			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  $\omega$ -(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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