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Synthesis and Structure Determination of Alicycle-fused Thiazolo- and Thiazino[2,3-b]quinazolones and Cycloalkylimino-3(N)-thiazolinylthiazolidines

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Dedicated to Professor Gábor Fodor on the occasion of his 75th birthday.

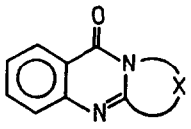
Key Words: alicyclic ethyl 2-aminocarboxylates; haloalkyl isothiocyanates; thiazolo- and thiazino[2,3-*b*]quinazolones; cycloalkylimino-3(*N*)-thiazolinylthiazolidines.

Abstract: Starting from various stereoisomeric, alicyclic ethyl 2-aminocarboxylates (1-6, 23, 24) and 2-chloroethyl, 3-chloropropyl or 3-bromopropyl isothiocyanate, ring-closure reactions were performed under mild conditions. Thus, partially saturated thiazolo- and thiazino[2,3-b]quinazolinone derivatives (7-18) and asymmetric 2-[2'-(ethoxycarbonyl-cycloalkyl and -cycloalkenyl)-imino]-3-(2''-thiazolin-2''-yl)-thiazolidine diadducts (19-22) were formed. The structures of the new compounds were proved via their IR, ^{1}H and ^{13}C NMR spectra, use also being made of DR, DNOE, DEPT and 2D-HSC measurements.

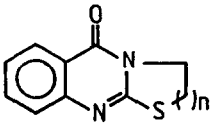
INTRODUCTION

A number of quinazoline derivatives are used as drugs, among them *methaqualone* as a sedative-hypnotic; *bunazosine*, *ketanserine* and *prazosine* as antihypertensives; and *quinethazone* as a diuretic.[2] Since the isolation of certain pharmacologically promising pyracridone alkaloids, the tricyclic, condensed-skeleton quinazoline derivatives [**A**, X=$(CH_2)_n$] have received much more attention.[3-5] Heterocondensed derivatives containing nitrogen (**A**, X=N),[6,7] oxygen (**A**, X=O)[8-11] or sulphur (**A**, X=S)[12,13] in the third ring have also been prepared.

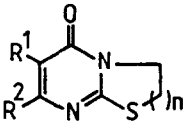
Although many publications relate to the thiazolo[2,3-*b*]quinazolin-5-ones (**B**, n=1)[14-19] and variously substituted analogous bicyclic thiazolo[3,2-*a*]pyrimidin-5-ones (**C**, n=1) or pyrimido[2,1-*b*]thiazin-6-ones (**C**, n=2)[20-23] with valuable pharmacological effects,[15,17,20,21] we have found no data on the synthesis of derivatives containing a flexible cycloalkyl moiety instead of the aromatic ring in similar quinazolines.



A



B



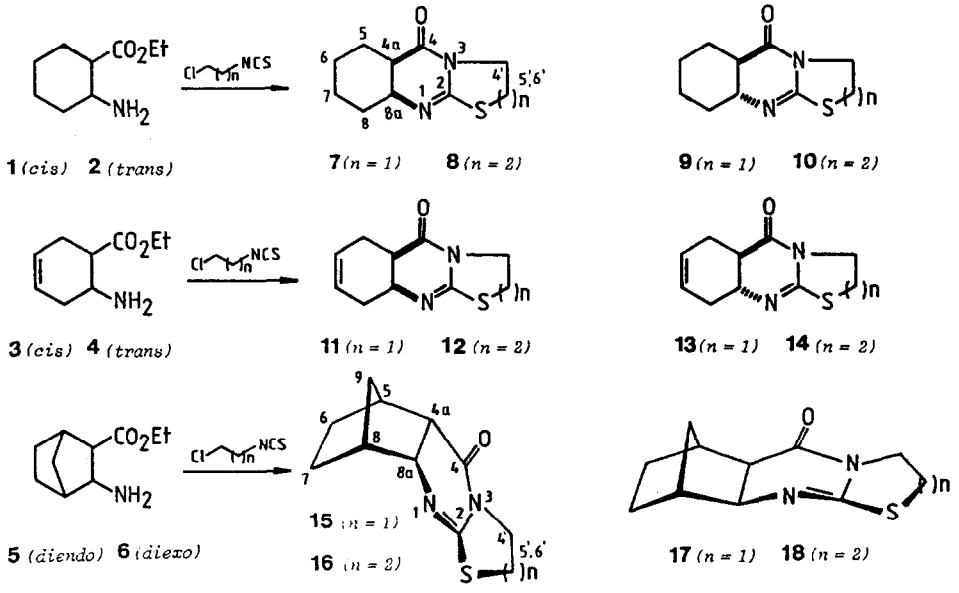
C

Here, we report on the synthesis and structure determination of derivatives of type **B** in which there is a fully or partially saturated cycloalkyl moiety instead of the aromatic ring.

SYNTHESIS

We have found only two examples in the literature for the preparation of thiazolo- and thiazino-[2,3-*b*]quinazolinones (**B**, n=1,2) starting from haloalkyl isothiocyanates. One of them[14] reports on the reaction of 2-chloroethyl isothiocyanate with anthranilamide in acetonitrile. The tricyclic product, 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**B**, n=1), was obtained in 77% yield after refluxing of the solution for 48 h. In the other paper,[19] methyl anthranilate was reacted with both 2-chloroethyl and 3-chloropropyl isothiocyanates. After the ethanol solution had been boiled for 20 h, the above compound (**B**, n=1) was obtained in 68%, and the homologous thiazine (**B**, n=2) in 72% yield.

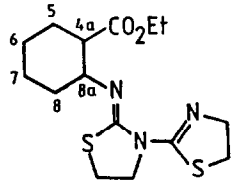
The present paper describes the reactions of haloalkyl isothiocyanates with different alicyclic, stereoisomeric ethyl 2-aminocarboxylates[23-26] (**1-6, 23** and **24**; Scheme). In our early experiments, one equivalent of 2-chloroethyl isothiocyanate[27] was reacted with ethyl *cis*-2-aminocyclohexanecarboxylate (**1**).



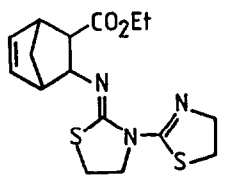
Scheme. *For the norbornene analogues **23** and **24** of **5** and **6**, see ref. 23.

The ethanol solution was allowed to stand overnight at RT, in the presence of TEA. The work-up procedure resulted in a crude oily product. This was dissolved in ether, from which the expected tricyclic product **7** crystallized in 30% yield. The mother liquor was treated with ethanolic HCl, to afford the hydrochloride salt of the diadduct **19**.

Under identical conditions, ethyl *trans*-2-aminocyclohexanecarboxylate (**2**) yielded a mixture of the corresponding *trans* tricyclic product **9** and the *trans* diadduct **20**.



19 *(cis)* **20** *(trans)*



21 *(diendo)* **22** *(diexo)*

We set out to find reaction conditions under which the tricyclic products (Scheme) and diadducts can be obtained selectively. Changing the solvent to benzene, ethyl acetate, diethyl ether, hexane or diisopropyl ether did not lead to satisfactory results. However, the slow addition of one equivalent of 2-chloroethyl isothiocyanate through a dropping funnel to an ethanolic solution of the corresponding ethyl 2-aminocarboxylate (**1-6**) under ice cooling resulted in the formation of the desired tricycles **7-18** (Scheme). The diadducts (**19-22**) could also be synthesized selectively by using two equivalents of the isothiocyanate in ethanol at RT.

It is noteworthy that all attempts to prepare the homologous thiazino diadducts failed to give the expected products. With 3-chloro- or 3-bromopropyl isothiocyanate, **1** and **2** afforded only the thiazino[2,3-*b*]quinazolin-6-one tricycles (**8, 10**), even if two or more equivalents of isothiocyanate was added.

In this reaction, the first step is the addition of the NCS moiety to the amino group. We assume that the reason for the difference between the reactions of 2-chloroethyl and 3-chloropropyl isothiocyanate is to be found in the following two ring-closure steps. In the case of thiazoline ring formation, the elimination of HCl may be far more rapid than the formation of the pyrimidine ring. On the other hand, the latter ring-closure is the faster with 3-chloropropyl isothiocyanate.

We earlier reported[23] the first synthesis of the parent pyrimido[2,1-*b*]thiazine by a retro Diels-Alder reaction. The norbornene-fused thiazolo- and thiazino[2,3-*b*]quinazoline derivatives described in that paper underwent retrodiene decomposition at 140 °C. The five-membered homologue product and its 7-oxo isomer were prepared previously.[22]

STRUCTURE DETERMINATION BY SPECTROSCOPY

The structures of the new compounds **7-22** were established by means of IR, ^{1}H and ^{13}C NMR spectroscopy. The spectral data given in Tables 1 and 2 are self-explanatory and only the following comments are necessary.

A comparison of the ^{1}H NMR data on the *cis-trans* pairs **7-9, 8-10, 11-13** and **12-14** permits the postulation of a fast inversion of the condensed six-membered rings for the *cis* isomers. If a conformationally homogeneous system is assumed, significantly different half-bandwidths of the H-4a and H-8a signals and a marked difference in the shifts of these signals as compared to the values measured for the *trans* counterparts would be expected. However, both the signal widths and the shift differences are of practically the same magnitude. This means that the two relatively stable conformers containing the cyclohexane ring in chair form and the carbonyl and imine nitrogen in the *axial* and *equatorial* position, respectively, or *vice versa,* take part

in roughly equal proportions in the conformational equilibrium. If only one of these conformers were present, one of the H-4a or H-8a signals would have a similar ^{1}H NMR shift and width to those of the corresponding signal of the *trans* counterpart (the *axial* one), and the other would be sharper and shifted downfield due to its *equatorial* position. The flexibility of these compounds is a consequence of the strained skeleton containing four sp^2 atoms in the heteroring, lowering the energy barrier of conformational motion.

Table 1. Characteristic ^{1}H NMR Chemical Shifts (δ_{TMS}=0 ppm) for Compounds **7-22**

Compound	H-4a *m*(1H)[b]	H-8a *m*(1H)[c]	SCH_2 *m*(2H)[d]	NCH_2 *m*(2H)[e]	CH_2(5-9), CH(5,8) 1-4 *m*(8/4H)[f]
7	2.55	3.73	3.21	4.11	1.4-1.8[g] ~1.9[h]
8	2.62	3.68	3.06	3.85	1.4-1.7[g] 1.88[h]
9	~1.9[i]	~3.2[j]	~3.2[j]	3.92 4.40	1.2-1.5[k] 1.8-2.0[i,l] 2.2-2.4[l]
10	~2.0[i,m]	~3.05	~3.05	3.45 4.25	1.1-1.5[k] 1.8[l] 1.9-2.4[i,l,m]
11	2.74	3.96	3.23	~4.15	2.0-2.7[k]
12	2.80	~3.9[j]	3.06	~3.9[j]	2.0-2.6[k,m]
13	2.25[i]	3.55	~3.2	3.90 4.40	2.25[i,l] 2.65[l]
14	2.40	~3.5[j]	3.07	~3.5[j] 4.25	~2.2[l,m] 2.62[l]
15	2.66[i]	4.15[j]	3.20	4.15[j]	~1.2[h] ~1.4[n] 2.66[i,o] 2.76[p]
16	2.76[i]	4.05	3.07	3.88	1.25[n] ~1.45[h] 2.68[o] 2.76[i,p]
17	2.60	3.77	3.12	4.07	1.1-1.8[q] 2.45[o] 2.65[p]
18	2.58[i]	~3.8[j]	3.03	~3.8[j]	1.1-1.7[q] 2.50[o] 2.62[i,p]
19	2.12	3.77	3.13 3.22	3.93 4.15	1.2-1.9[g] 2.50[h]
20	3.58	~3.25[i]	3.10 ~3.25[i]	3.95 ~4.15[j]	1.2-1.6[k] ~1.8[r] 2.0[h]
21	3.18	~4.0	3.07 ~3.26	~4.0[j]	1.38[s] 1.50[s] 3.0[h] 3.1[h]
22	2.53	3.44	3.13[i] 3.27	4.1 4.25	13.6[s] 2.33[s] 2.67[h] 3.1[h,i]

[a]Further signals, CCH_2C (heteroring): 2.1-2.2 (**8**, **10**, **12**, **14**, **16** and **18**); CH_3 *t* (3H, *J*: 7.1 Hz): 1.20 (**19**, **20**), 1.13 (**21**) and 1.17 (**22**); OCH_2 *qa* (2H): 4.10 (**19**), ~4.15[j] (**20**), ~4.0[j] (**21**) and 3.92 (**22**); Olefinic CH(6,7): 5.67 *s* or *m* (2H) for **11-14**, 6.15 and 6.50 (**21**), 6.12 and 6.25 (**22**), 2x*dd* (*J*: 5.6 and 2.9 Hz). Measuring frequency was 80 MHz for **17** and **18**. Assignments were proved by double resonance (for **9**, **11**), two-dimensional heteronuclear shift correlation (**11**, **14**, **15**) and differential nuclear Overhauser effect measurements (for **15**). [b]Quartet-like signal for **11**, **12**, *d* for **17** (*J*: ~8 Hz) and **22** (*J*: 7.6 Hz). [c]Quartet-like signal for **7**, **8**, **11** and **19**, *d* for **17** (*J*: ~8 Hz), **22** (*J*: 7.6 Hz). [d]Triplet for **7**, **17** (*J*: 6.8 Hz) and **8**, **12**, **14**, **16** and **18** (*J*: 6.3 Hz), 2x*t* for **19**, **22** (*J*: 8.1 and 7.0 Hz). [e]Triplet for **9** (*J*: 6.8 Hz), *dt* for **17** and 2x*dt* for **9** (*J*: ~6.5 and ~3 Hz), 2x*m* for **9**, **10**, **13**, **14**, **19-22**. [f]CH(5,8) in case of **15-18**, **21** and **22**, 1-4 *m*'s of total intensity 8H (**7-10**, **15-18**, **19** and **20**), 4H (**11-14**, **21**, **22**). [g,h,i,l,n,o,r]Intensity: 7H/1H/4H/2H/5H/6H/3H. [i,j]Overlapping signals. [m]In overlap with the CCH_2C signal of the heteroring. [o]H-8. [p]H-5. [s]Doublet, one of the two *d*'s of an *AB*-type spectrum arising from the 9-methylene group (*J*: 8.7 Hz).

Compounds **19** and **20**, containing non-fused cyclohexane rings, are stereohomogeneous. In the *trans* isomer (**20**) the alicycle takes the chair form, of course, and both substituents are *equatorial*. The *cis* counterpart **19** is also homogeneous conformationally, with the carbethoxy group in the *equatorial* and the substituted imino group in the *axial* position. This is clear from the double triplet of "H-4a" (following the numbering of the tricycles **7-18** in Tables 1 and 2) at 2.50 ppm with a split of 12 Hz (due to the *diaxial* H-4a,H-5 interaction) and from the unaltered shift value relative to that of the corresponding signal of the *trans* isomer **20**.

In contrast, the "H-8a" signal is significantly narrower (ca. 8 Hz) than that for **20** and downfield shifted by ca. 0.5 ppm, in accordance with the *equatorial* position of this hydrogen in **19**.

Table 2. ^{13}C NMR Chemical Shifts (δ_{TMS}=0 ppm) for Compounds **7-22**

Compound	C-2	C-4	C-4a	C-8a	NCH_2	CH_2(5-9, 5', 6')
7	156.1	170.0	40.1	56.8	46.1	22.7 23.2 23.6 26.3[b] 29.6[c]
8	150.6	171.0	40.3	54.1	41.0	22.5 23.1 23.5 23.8 27.7[b] 29.1[c]
9	156.9	169.8	42.6	60.3	46.2	24.9[d] 25.0 26.6 34.3[c]
10	151.6	171.2	43.2	57.3	40.5	23.6 24.7[d] 25.2 27.5[b] 34.0[c]
11	156.9	169.7	37.2	54.1	46.2	22.4[b] 26.5[e] 28.6[c] 124.4[g] 124.8[g]
12[f]	151.6	170.7	38.0	51.2	40.4	22.5[b] 23.6 27.6[c] 28.0[c] 124.2[g] 124.8[g]
13	156.8	169.7	38.9	57.0	46.4	25.9[b] 26.5[c] 33.9[e] 125.1[g] 125.5[g]
14[f]	151.4	170.9	39.5	53.7	40.7	23.6 26.0[b] 27.6[c] 33.4[c] 124.9[g] 125.3[g]
15[f]	153.3	168.6	41.1	62.9	46.3	21.2[h] 24.8[d] 37.0[j] 42.1[b] 43.6[c]
16[f]	147.1	169.1	42.7[i]	59.5	40.2	21.3[h] 24.2 24.8 28.2[e] 36.5[j] 42.8[i] 43.9[i]
17	153.5	168.2	46.8[i]	66.4	46.6[i]	24.6 26.0 29.7[j] 34.4[e] 43.0[b] 45.6[c]
18[f]	147.3	168.4	48.4	63.3	40.6	21.4 25.8 28.2 29.6[j] 34.4[e] 43.5[b] 48.8[c]
19	150.7[l] 158.7[k]	173.8	47.7	63.0	50.6[l] 57.1[k]	20.9 23.6 25.5 26.6 32.5[c] 33.8[e,k]
20	151.8[l] 158.4[k]	174.9	50.6[i]	65.2	50.4[d,l] 57.0[k]	24.2 24.7 26.5 28.2 31.6 33.4[e,k]
21[f]	152.2[l] 158.7[k]	171.8	48.5	69.6	50.5[l] 56.8[k]	26.6[e] 33.7[e,k] 44.8[b] 46.4[j] 51.2[c] 134.1[g] 136.0[g]
22[f]	152.3[l] 159.1[k]	172.9	49.0	68.7	50.5[l] 5 6.2[k]	26.6[c] 33.4[e,k] 44.0[b] 45.8[j] 50.1[c] 135.9[g] 139.3[g]

[a]Measuring frequency 20.14 MHz for **11**. Further signals, CH_3: 14.2 (**19-22**); OCH_2: 60.6 (**19**), 59.9 (**20-22**). [b]C-5. [c]C-8. [d]Two overlapping lines. [e]SCH_2 group. [f]Assignments were proved *via* DEPT measurements. [g]C-6 and 7. [h]C-7. [i]Interchangeable assignments. [j]C-9. [k]Thiazoline ring. [l]Thiazolidine ring.

The unaltered *diexo* annelation of the pyrimidone ring to the norbornane skeleton in **17** is proved by the doublet split of the H-4a and H-8a signals (by ca. 8 Hz) due to the H-4a,H-8a interaction. For *diendo* isomers, a further split of these signals is characteristic,[28] arising from the H-4a,H-5 and the H-8,H-8a interactions. This split is not significant for *diexo* compounds because of the corresponding dihedral angle of ca. 90° (this is ca. 30° for the *diendo* annelated isomers). The multiplicity of the H-4a and H-8a signals is not identifiable for **15, 16** and **18**, but the ^{13}C NMR chemical shift of the C-9 line (37.0 and 36.5 ppm for **15** and **16**, and 29.7 and 29.6 ppm for **17** and **18**) is enough for a firm decision concerning the unaltered annelation of the starting compounds in the products. A further characteristic difference between the *diendo* (**15, 16**) and *diexo* annelated compounds (**17, 18**) is the ^1H NMR chemical shift of H-8a, which is downfield shifted by ca. 0.3 ppm for the former, in accordance with literature data.[29] In the case of **22**, the *diexo* position of the substituents to the norbornene skeleton follows from the doublet split of the "H-4a" and "H-8a" signals by 7.6 Hz, while the *diendo* structure of **21** is quite definite from the downfield shift of the "H-8a" signal by ca. 0.55 ppm as compared to that for **22**. The C-2 shifts in the ^{13}C NMR spectra are significantly different for thiazoles and thiazines: they are downfield shifted for the former by 5.4 (**7-14**) and 6.2 ppm (**15-18**).

The asymmetric structure of compounds **19-22** containing two different thiazole rings is perfectly obvious because of the doubling of all the ^1H and ^{13}C signals of these moieties. In the originally expected symmetric *N,N*-bis(2-thiazolinyl) diadducts, the two heterorings are equivalent and consequently all their corresponding H and C pairs would give common (coincident) signals.

EXPERIMENTAL

Mp.s. were determined on a Boetius micro melting point apparatus and are uncorrected.

The IR spectra were measured in KBr pellets on an Aspect 2000 computer-controlled Bruker IFS-113v vacuum optic FT spectrometer.

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT on a Bruker WM-250 FT spectrometer at 250.13 (^1H) and 62.89 MHz (^{13}C), respectively, using the ^2H signal of the solvent as the lock and TMS as internal standard. Conventional CW irradiation of approximately 0.15 W was used for the double resonance (DR) experiments. NOE difference (DNOE) and two-dimensional heteronuclear shift correlation (2D-HSC) measurements were carried out using the standard software written for the Aspect 2000 computer of the spectrometer. DEPT spectra were run in a standard way, using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively.

Procedure for the preparative separation of compounds 7 and 9, and of 19 and 20, respectively, from their mixtures. The hydrochlorides of **1** and **2** (10 mmol) were dissolved in EtOH (15 ml). A solution of isothiocyanate (10 mmol) and TEA (3.5 ml) in EtOH (15 ml) was added at once, and the mixture was allowed to stand overnight at RT. The solvent was next distilled off under diminished pressure, and the residue was partitioned between H_2O and EtOAc. The organic phase was dried (Na_2SO_4) and evaporated. The oily residue was dissolved in Et_2O to afford fine crystals, which were filtered. Products **7** and **9** were prepared in approximately 30% yield.

The mother liquor was evaporated and the residue was treated with 22% EtOH/HCl (2 ml). This was dissolved in EtOH and diluted with Et_2O. The diadducts **19** and **20** were filtered off after standing overnight at RT (yield ~30%).

General procedure for preparation of tricycles 7-18. The hydrochlorides of ethyl 2-aminocarboxylates **1-6** (10 mmol) and TEA (3.5 ml) were dissolved in EtOH (20 ml). To the stirred mixture, a solution of the appropriate alkyl isothiocyanate (10 mmol) was added dropwise over a period of one h, at 0 °C. After this, the reaction mixture was allowed to stand for 48 h at RT. The solvent was removed, and the residue was partitioned between H_2O and $CHCl_3$. The organic phase was dried (Na_2SO_4) and evaporated. The oily residue was treated with 22% EtOH/HCl (2 ml) and dissolved in EtOH/Et_2O. The crystalline products were filtered off after standing overnight (Table 3).

General procedure for preparation of diadducts 19-22. The hydrochlorides of ethyl *cis*-2-aminocyclohexanecarboxylate (**1**), ethyl *trans*-2-aminocyclohexanecarboxylate (**2**), ethyl *endo*-aminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate[23] (**23**) and ethyl *exo*-aminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate[23] (**24**) (10 mmol) were dissolved in EtOH (20 ml). A solution of $ClCH_2CH_2NCS$ (20 mmol) and TEA (5.6 ml) in EtOH (20 ml) was added at once. The mixture was allowed to stand at RT for 10 h, and then evaporated. The residue was

washed with EtOAc (2x50 ml), and the solution was dried (Na_2SO_4). After evaporation, the residue was dissolved in hot EtOAc. After standing overnight, the crystals of compounds **19-22** were filtered off (Table 3).

Table 3. Characteristic IR Bands,[a] Physical and Analytical Data on Compounds Prepared

Compound	$\nu_{C=O}$ [cm^{-1}]	$\nu_{C=N}$ [cm^{-1}]	M.p.[b] [°C]	Yield [%]	Found C H N	Formula	Calculated C H N
7	1691	1634	192-193	54	49.0 6.0 11.5	$C_{10}H_{15}ClN_2OS$	48.7 6.1 11.4
8	1693	1608	198-199	53	50.2 6.5 10.4	$C_{11}H_{17}ClN_2OS$	50.7 6.4 10.7
9	1694	1624	172-173	55	48.3 6.0 11.1	$C_{10}H_{15}ClN_2OS$	48.7 6.1 11.4
10	1694	1600	231-232	57	50.3 6.2 10.8	$C_{11}H_{17}ClN_2OS$	50.7 6.4 10.7
11	1693	1638	228-229	56	49.4 5.3 11.6	$C_{10}H_{13}ClN_2OS$	49.1 5.4 11.5
12	1691	1600	234-235	52	49.7 5.6 10.7	$C_{11}H_{15}ClN_2OS$	51.1 5.8 10.8
13	1691	1641	219-220	53	49.6 5.6 11.7	$C_{10}H_{13}ClN_2OS$	49.1 5.4 11.5
14	1727	1593	221-222	58	51.2 6.0 11.0	$C_{11}H_{15}ClN_2OS$	51.1 5.8 10.8
15	1675	1655	232-233	51	48.9 6.4 11.5	$C_{10}H_{15}ClN_2OS$	48.7 6.1 11.4
16	1685	1622	223-224	53	50.7 6.7 10.9	$C_{11}H_{17}ClN_2OS$	50.7 6.6 10.7
17	1655[c]		233-234	52	48.5 6.0 11.5	$C_{10}H_{15}ClN_2OS$	48.7 6.1 11.4
18	1678	1633	226-227	54	50.4 6.3 10.8	$C_{11}H_{17}ClN_2OS$	50.7 6.6 10.7
19	1692	1605	186-187	90	47.2 6.2 11.2	$C_{15}H_{24}ClN_3O_2S_2$	47.7 6.4 11.1
20	1735	1655 1591	187-188	87	48.1 6.5 11.0	$C_{15}H_{24}ClN_3O_2S_2$	47.7 6.4 11.1
21	1722	1645 1591	201-202	87	50.0 5.5 10.6	$C_{16}H_{22}ClN_3O_2S_2$	49.5 5.7 10.8
22	1732	1644 1594	181-182	88	49.1 5.8 10.6	$C_{16}H_{22}ClN_3O_2S_2$	49.5 5.7 10.8

[a]From the spectra of the corresponding bases. [b]HCl salt. [c]Overlapping signals.

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