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Synthesis, spectroscopic, structural and conformational study of some tri-substituted ureas derived from *N*-methylpiperazine containing phenyl and *N*-heterocyclic substituents

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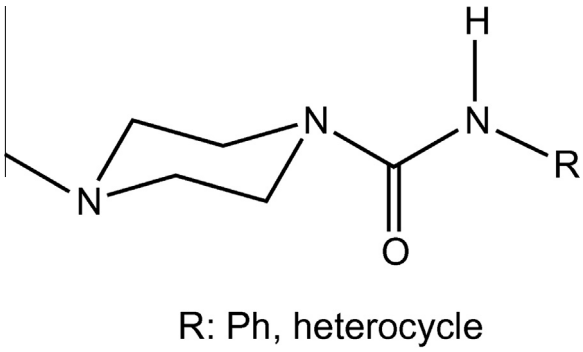
GRAPHICAL ABSTRACT



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ABSTRACT

A series of tri-substituted ureas containing an *N*-methylpiperazine moiety as well as phenyl and *N*-heterocyclic substituents were synthesized and studied by ^{1}H, ^{13}C NMR and IR spectroscopies. From ^{1}H and ^{13}C NMR data, in $CDCl_3$ solution at room temperature, a fast inter-conversion of the piperazine ring with the *N*-CH_3 group in equatorial position can be proposed. Amino–imino tautomerism is observed for both thiazole and benzothiazole derivatives. Moreover, with the exception of the imino form of the thiazole derivative, the aryl substituted *N*-carbamoyl group rotates freely. IR data show that the compounds adopt a planar *trans* conformation of the —CO—NH— moiety.

1. Introduction

Substituted piperazines are common motifs in a large number of compounds with biological activity. Specifically, *N*-urea and *N*,*N*′-bis-urea piperazine derivatives have interesting therapeutic indications [1–3]. Furthermore, thiazole and benzothiazole derivatives are widely used in the synthesis of medicinal compounds [4].

As a result of a continuing effort to develop novel heterocyclic compounds with potential therapeutic activity, we have designed and prepared a series of tri-substituted ureas using 4-methyl-1-piperazine carbonyl chloride and the aromatic compounds aniline, aminopyridines, 2-aminobenzothiazole and 2-aminothiazole.

The biological effect of organic compounds is very often associated with their conformational state. In order to gain deeper insight into the structure–activity relationships, the conformational isomerism at the urea group and the amino–imino tautomerism in the benzothiazole and thiazole derivatives were studied using IR and NMR spectroscopies.

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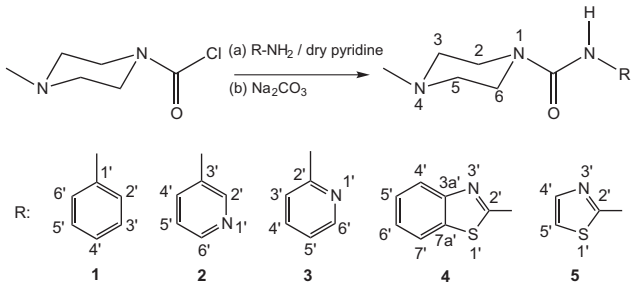


Scheme 1. Synthesis of ureas **1**–**5**.

2. Experimental

2.1. General procedure for preparing the ureas *1*–*5*

4-Methyl-1-piperazine carbonyl chloride, aniline and *N*-heterocyclic amines were purchased from Aldrich and they were used without further purification. Pyridine was distilled over sodium hydroxide pellets.

For the synthesis of the ureas **1**–**5**, we started with the 4-methyl-1-piperazine carbonyl chloride (Scheme 1). By reaction of this compound with the corresponding amine in dry pyridine as solvent, at room temperature, the urea derivative crystallized as hydrochloride. The hydrochloride was dissolved in water, basified with aqueous Na_2CO_3 (10%) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was removed to afford a residue, which was purified by chromatography column to obtain the corresponding ureas **1**–**5**.

2.2. NMR spectra

The NMR spectra of compounds **1**–**5** were recorded on a Varian UNITY-300 spectrometer.

The ^1H NMR spectra of $CDCl_3$ solutions (about 4% w/v) were obtained at 300 MHz using spectral width of 4000 Hz in 24 K memory and acquisition time of 3.0 s over 64 transients. Resolution enhancement (LB = −0.80, GF = 0.60 and GFS = 0.20) was followed by zero filling into 32 K memory prior to Fourier transformations.

The ^{13}C NMR spectra were obtained in $CDCl_3$ solutions (20% w/v) at 75.429 MHz with a spectral width of 16501 Hz in 64 K memory, acquisition time of 1 s and relaxation delay of 1 s.

2.3. IR spectra

The IR spectra of compounds **1**–**5** were recorded on a Perkin–Elmer FTIR 1725X spectrophotometer, assisted by a computer, in the solid state (KBr) in the 4000–400 cm^{-1} and in $CDCl_3$ solution (≈0.15 M) in the 4000–900 cm^{-1} region using 0.2 mm NaCl cells. Spectra for very dilute CCl_4 solutions were taken in the 4000–2500 cm^{-1} region with 4 cm quartz cells. The reported wavenumbers are estimated to be accurate to within ±3 cm^{-1}.

3. Results and discussion

3.1. Chemistry

The carbamoyl chloride derived from 4-methylpiperazine with aniline affords the expected urea **1**.

Primary *N*-heterocyclic aromatic amines react as a nucleophile with either of its nitrogen atoms, the exocyclic or the endocyclic sp^2 nitrogen, depending upon the electrophilic centre and the experimental conditions. Usually, with acyl halides the exocyclic nitrogen is the main nucleophile [5]. Consequently, the aminopyridines, the 2-aminobenzothiazole and the 2-aminothiazole were acylated on the exocyclic nitrogen atom obtaining the urea derivatives **2**–**5**. Products of the *N*-ring acylation have not been isolated.

Compounds **4**–**5** can undergo tautomerization to give amino (**a**) and imino (**b**) isomers (Scheme 2).

3.2. NMR spectra

3.2.1. Spectral analysis and assignments

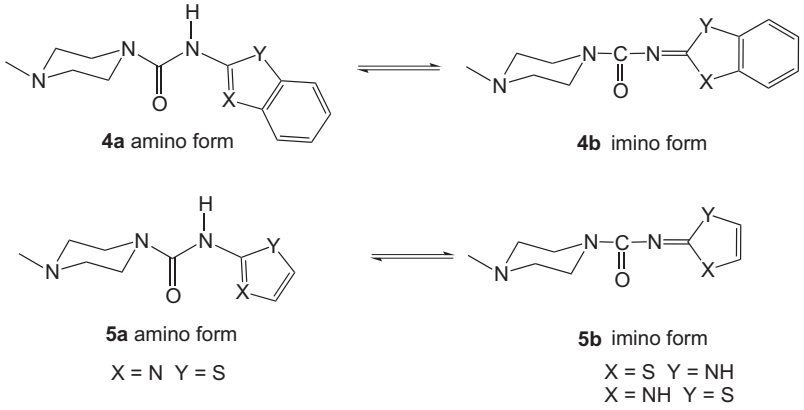
The values of the ^1H NMR chemical shifts with the signal assignments are listed in Table 1.

At 300 MHz in $CDCl_3$ solution the signals corresponding to the piperazine moiety for compounds **1**–**4** and **5a** appeared as a singlet at 2.21–2.31 ppm and two multiplets at 2.31–2.43 ppm and 3.45–3.56 ppm. However, for compound **5b** a singlet at 2.26 ppm and four multiplets at 2.40, 2.30, 3.55 and 3.25 ppm were observed. The aromatic protons appeared well differentiated in all cases.

The singlet at 2.21–2.31 ppm for compounds **1**–**4** and **5a** has been assigned to the *N*-CH_3 protons according to results in related compounds [6]. For the assignment of the signals corresponding to C2, C6, C3 and C5 protons, the electronic, anisotropic and the steric effects exerted by the urea group have been taken into account. The signal at 3.45–3.56 ppm has been assigned to H2ax(H2eq), H6ax(H6eq) and the signal at 2.31–2.43 ppm to H3ax(H3eq), H5ax(H5eq).

Concerning compound **5b,** the singlet at 2.26 ppm corresponds to the *N*-CH_3 protons. The signals corresponding to the C2, C6, C3 and C5 protons have been assigned according to the reported values for related compounds [6].

It can be noted that the spectra of the compounds studied showed only a signal for H2ax and H2eq, H6ax and H6eq, H3ax



Scheme 2. Tautomers for benzothiazole (**4**) and thiazole (**5**) derivatives.

Table 1
^{1}H NMR chemical shifts (δ, ppm) for compounds **1**–**5** in $CDCl_3$.

	1	**2**	**3**	**4**	**5**	
					Amino (5a)	**Imino (5b)**
H2ax(H2eq) (m)	3.50	3.49	3.45	3.56	3.55	3.55
H6ax(H6eq) (m)	3.50	3.49	3.45	3.56	3.55	3.25
H3ax(H3eq) (m)	2.43	2.37	2.31	2.34	2.39	2.30
H5ax(H5eq) (m)	2.43	2.37	2.31	2.34	2.39	2.40
N—CH_3 (s)	2.31	2.31	2.21	2.24	2.28	2.26
NH (brs)	6.35	7.74	7.81	11	nd	nd
H2′	7.31 (dd)	8.38 (d)	–	–	–	–
H3′	7.26 (m)	–	7.92 (d)	–	–	–
H4′	7.01 (tt)	7.89 (ddd)	7.54 (dd)	7.72 (d)	7.28 (d)	6.87 (d)
H5′	7.26 (m)	7.14 (dd)	6.83 (dd)	7.34 (t)	6.81 (d)	6.41 (d)
H6′	7.31 (dd)	8.14 (dd)	8.07 (d)	7.22 (t)	–	–
H7′	–	–	–	7.53 (d)	–	–

Abbreviations: brs, broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; m, multiplet; nd, not determined; s, singlet; t, triplet; tt, triplet of triplets.

Table 2
^{13}C chemical shifts (δ, ppm) for compounds **1**–**5** in $CDCl_3$.

	1	**2**	**3**	**4**	**5**	
					Amino (5a)	**Imino (5b)**
C5	54.68	54.54	54.48	54.44	54.99	55.47
C3	54.68	54.54	54.48	54.44	54.99	54.77
C6	44.07	43.95	43.85	43.95	44.63	46.88
C2	44.07	43.95	43.85	43.95	44.63	42.80
N—CH_3	46.17	45.99	45.92	45.89	46.18	46.36
C=O	154.71	154.88	153.90	163.68	166.00	170.05
C1′	138.72	–	–	–	–	–
C2′	119.75	143.20	152.62	155.14	161.16	150.70
C3′	128.77	136.39	113.28	–	–	–
C3a′	–	–	–	145.63	–	–
C4′	123.02	127.58	137.81	118.07	138.33	136.00
C5′	128.77	123.39	118.02	125.99	112.55	112.70
C6′	119.75	141.09	146.97	123.20	–	–
C7′	–	–	–	121.43	–	–
C7a′	–	–	–	130.91	–	–

and H3eq and H5ax and H5eq, suggesting a conformational dynamics of the piperazine ring, which is fast enough on the NMR time-scale to give one average signal.

The aromatic protons have been assigned in agreement with the data of the literature [7,8].

For the assignment of ^{13}C NMR chemical shifts (Table 2), substituent, electronic effects and the values for related compounds [6] have been taken into consideration.

3.2.2. Conformational study

As said above, from the ^{1}H and ^{13}C NMR data in $CDCl_3$ solution at room temperature a fast inter-conversion of the piperazine chair ring with an equatorial position of the *N*-CH_3 group can be proposed. This is evidenced by the ^{1}H NMR spectra where the *N*-CH_3 ^{1}H chemical shifts of compounds **1**–**4**, **5a** and **5b** of 2.21–2.31 ppm have the same values as those found in equatorial *N*-CH_3 substituted piperazines. Besides, the *N*-CH_3 ^{13}C chemical shifts of 45.89–46.368 ppm are in agreement with previously reported values in related compounds with an equatorial disposition of this group [6].

For compounds **1**–**4** and **5a** in $CDCl_3$ solution the existence of free rotation of the carbamoyl group around the N1—CO bond is deduced. This conclusion is based on the equivalence of the H2ax and H6ax, the H2eq and H6eq, the H3ax and H5ax and the H3eq and H5eq and also on the equivalence of C2 and C6, and of C3 and C5. On the contrary, for compound **5b** a restricted rotation around the N1—CO bond is proposed due to the non-equivalence of the mentioned carbons and protons of the piperazine ring.

3.2.3. Amino–imino tautomerism

Amino derivatives of *N*-heterocyclic compounds can exist in the amino or imino form. Previously published data of the literature [9,10] confirm the importance of the heterocyclic moiety and of the medium on the tautomeric ratio of this type of compounds. Pyridine derivatives (e.g. compound **2** and **3**) do not exhibit any imino form even when strong electron-withdrawing groups are bonded to the exocyclic nitrogen. On the contrary, the N-heterocyclic five-membered ring (e.g. compounds **4** and **5**) is more prone to transform itself in a non-aromatic form than the six-membered one. This fact may be related to the relative stabilization by the resonance energy, which is higher for six- than for five-membered heterocycles [9].

Taking into account the above considerations we have investigated, by means of IR and NMR spectroscopies, the amino/imino equilibria for 2-aminothiazole derivative **5** and its benzo analog **4** (Scheme 2).

With respect to the prototopic tautomerism in aminobenzothiazoles, some authors reported that the displacement to lower values of ^{13}C chemical shifts for C4 (C4′ in compound **4**) upon passing from the amino to the imino tautomer, enables the detection and relative quantification of the imino tautomers of the heterocycles [11,12].

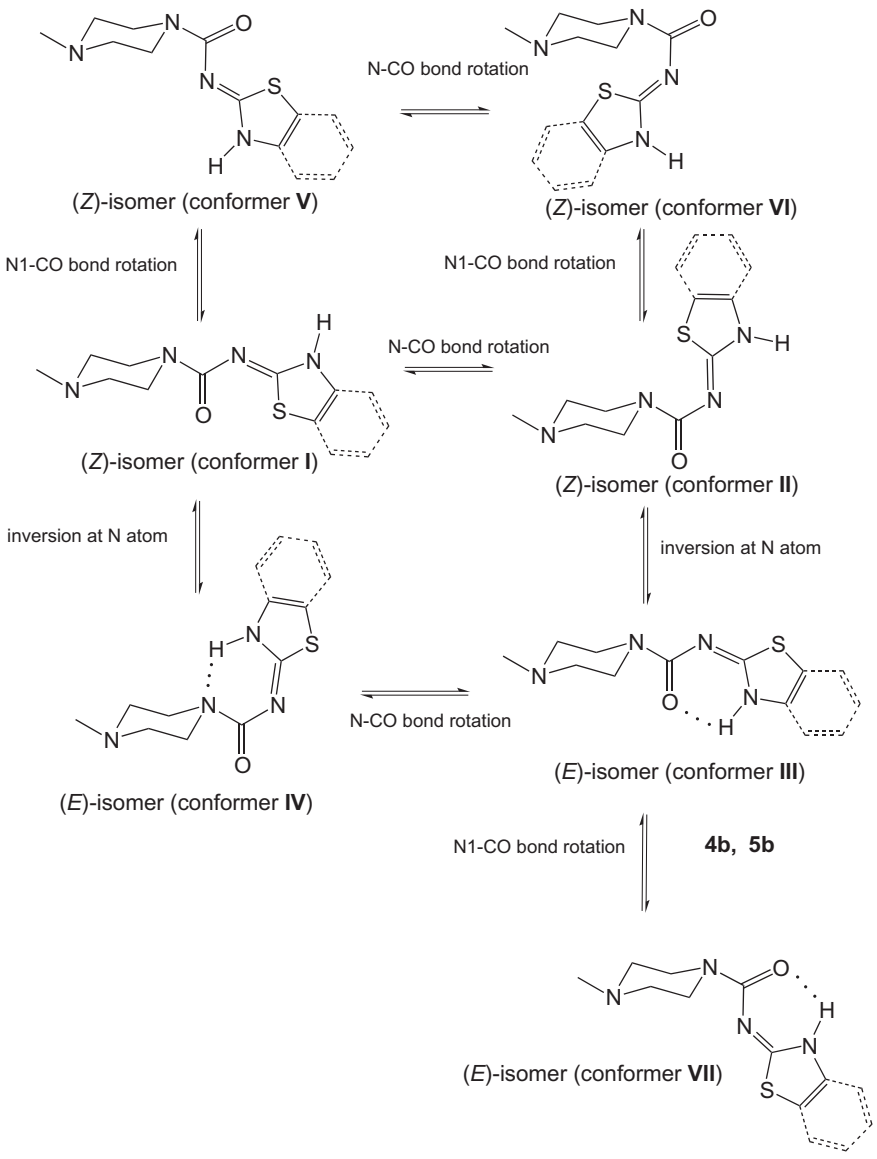
Furthermore, for 2-aminobenzothiazole derivatives the C3a (C3a′ in compound **4**) chemical shift of 151–153 ppm is characteristic of a carbon atom vicinal to an sp^2 nitrogen bearing a lone pair (amino form). On the contrary, values of 137–138 ppm are typical for a C3a (C3a′ in compound **4**) bound to an N—H group (imine form) [13].

With respect to the tautomeric process, compounds **4** and **5** can be represented by imidol type, amino and imino tautomers.

Two configurations *Z* and *E* can be proposed for the imidol type tautomer and each configuration may have four preferred conformers. In the case of the amino tautomer, four preferred conformers for each *trans* and *cis* conformation of the —CO—NH— structure are possible.

For the imino tautomer two configurations *Z* and *E* are expected, which can exchange by isomerization at the exocyclic nitrogen of the amino thiazole moiety. At the same time, each configuration may have several conformers obtained by rotation around the N1—CO and the CN—CO single bonds. Four preferred conformers (**I**, **II**, **V** and **VI**) for the (*Z*)-isomer and three preferred conformers (**III**, **IV** and **VII**) for the (*E*)-isomer are shown in Scheme 3.

Examination of conformers and isomers for the imino form of compounds **4** and **5** suggests that the (*E*)-isomer is the most stable due to the formation of an intra-molecular hydrogen bond (**III**, **IV** and **VII**).



Scheme 3. Conformers and isomers for imino forms of compounds **4** and **5**.

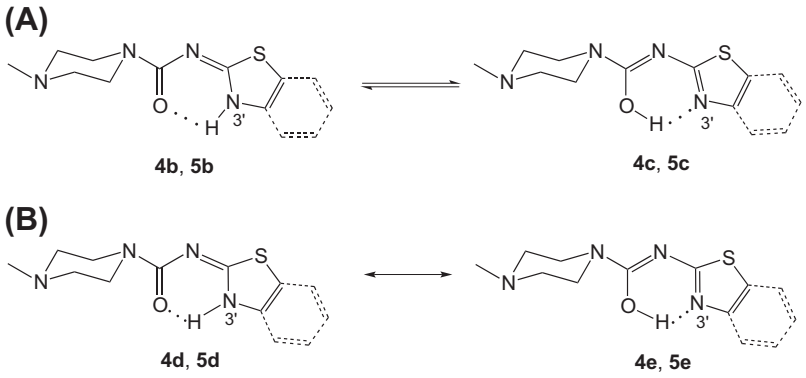
3.2.3.1. Compound 4. Regarding the identification of the preferred amino–imino tautomers in $CDCl_3$ solution for 2-aminobenzothiazole derivative **4**, the ^{13}C NMR analysis could give evidence by closely looking at C3a′ and C4′ chemical shifts. This compound presented for C3a′ a chemical shift value of 145.63 ppm, which is in between the characteristic values for the amino and the imino forms (see above), in agreement with a fast inter-conversion between the amino and imino forms. Besides, the chemical shift value of C4′(118.07 ppm) is lower than the value found in related compounds (*ca.* 120 ppm), in which the amino tautomer dominates over the imino form [14,15]. The decrease in the δ value indicates the presence of the imino tautomer.

Furthermore, the proton migration from the urea group to the nitrogen atom in position 3′ of the thiazole fragment in compound **4**, as a result of amino–imino tautomerism, was also confirmed in the ^1H NMR spectrum by the presence of resonance from the N3′ proton of the thiazole moiety at high chemical shift (δ = 11 ppm). According to the data of the literature [16–18], the high value of this signal and the results in the ν N—H infrared region in very diluted CCl_4 solution (see below) suggest the formation of an intramolecular hydrogen bond (Scheme 3). These results confirm that the *E* configuration is the preferred for the imino tautomer in solution.

The chemical shift values of the ^{13}C and ^1H signals for the piperazine moiety in compound **4** are similar in magnitude to those of the compounds **1**–**3** (Tables 1 and 2). The values are characteristic of a piperazine ring where the nitrogen atom does not take part in a hydrogen bond [6]; therefore, the conformers **III** and **VII** are predominant.

The amino–imino tautomerization is also observed by the broadening of the ^1H and ^{13}C NMR signals as this exchange process lead to average signals at room temperature [19]. Moreover, the broadening and chemical shifts also indicate a fast interconversion between the amino and imino forms.

3.2.3.2. Compound 5. For compound **5** only one form could be isolated by chromatography column which is characterized as the amino tautomer (**5a**), mainly because the H4′ resonates at 7.28 ppm and H5′ resonates at 6.81 ppm, with a coupling constant of 3.2 Hz (the vicinal coupling constants of 2-aminothiazoles are generally in the range 3.1–3.8 Hz [7]). The spectrum in $CDCl_3$ obtained after several days, presented new signals along with those



Scheme 4. Proton exchange between the N3′ atom and the carbonyl oxygen in compounds **4b** and **5b**. (A) Tautomerism and (B) single bond-no bond resonance.

of the amino form. Two of the new signals appear at 6.81 ppm and at 6.41 ppm with a coupling constant of 5 Hz, which are assigned to H4′ and H5′, respectively. Given that the vicinal coupling constants of 2-aminothiazolidines (imino forms) are in the range 5.4–5.0 Hz [7], the presence of the imino form (**5b**) is deduced. The N—H proton signal was not clearly visible but the results in the ν N—H infrared region (see below) indicate the formation of an intramolecular hydrogen bond as in compound **4** (Scheme 3). The ^{1}H NMR results in $CDCl_3$ solution show that the exchange tautomerism process in compound **5** is slow.

3.2.3.3. Proton exchange between nitrogen atom N3′ and the carbonyl oxygen. Another prototropy can also be considered for the imino forms of compounds **4** and **5** (**4b** and **5b,** conformers **III** and **VII**). If the N—H bond is shorter than the O···H (Scheme 4A), two tautomers can be proposed by intramolecular exchange of the hydrogen between N3′ and the carbonyl oxygen. On the other hand, if the proton of the O···H—N intramolecular bond would be situated just in the middle, the system would show single bond-no bond resonance with two mesomeric forms [17,20] (Scheme 4B). In our working conditions, IR spectra do not present OH bands. Therefore, the imidol type tautomers (**4c**, **5c**) and mesomeric forms (**4d**, **5d**, **4e**, **5e**) can be excluded.

3.3. IR spectra

In the ν(N—H) region, the infrared spectrum of the phenyl derivative **1** in $CDCl_3$ and in very dilute CCl_4 solution showed a main sharp band at 3462 and 3470 cm^{-1}, respectively, which is assigned to a planar *trans* conformation of the —CO—NH— structure, according to literature data for tri-substituted ureas [21]. Moreover, a very weak band in CCl_4 at 3410 cm^{-1} is tentatively assigned to a small proportion of the *cis* conformation. In the pyridyl derivatives **2** and **3** the corresponding ν(N—H) band appeared at 3455 and 3462 in $CDCl_3$ and 3448 and 3452 in CCl_4, respectively.

Compounds **1**–**3** presented in $CDCl_3$ in the double bond region a strong band at 1655–1660 cm^{-1} attributed to the urea ν(C=O) vibration, and a second band at 1627–1522 cm^{-1} assigned to the Amide II band.

Moreover, results for compound **1** in the ν(N—H) region presented in $CDCl_3$ solution a broad weak band at *ca.* 3355 cm^{-1} which decreased on dilution and is assigned to intermolecular NH···O bonding, as the ν(C=O) band was shifted from 1635 cm^{-1} in the solid (KBr) to 1658 cm^{-1} in $CDCl_3$.

The spectrum of the oily compound **2** showed a broad band at 3284 cm^{-1}, which shifted to 3313 cm^{-1} in $CDCl_3$, decreasing with dilution and disappearing in very dilute CCl_4 solution. This band is attributed to the presence of intermolecular hydrogen bonding, probably NH···N since the ν(C=O) at 1650 cm^{-1} in the solid (KBr) did not practically change in $CDCl_3$ solution (1655 cm^{-1}). In the case of compound **3** results in the ν(C=O) region also suggest the presence of NH···N intermolecular hydrogen bonding in the solid state.

Compounds **4** and **5**, besides the ν(N—H) of the urea amide group in the amino tautomer at 3431–3438 cm^{-1} and 3447–3452 cm^{-1} in $CDCl_3$ and CCl_4, respectively, presented a complex and broad absorption centered at ca. 3172 cm^{-1} in $CDCl_3$ and at 3164–3171 cm^{-1} in CCl_4. In agreement with the literature data [8,22,23] the low frequency absorption is attributable to the intramolecularly bonded NH group of the imino tautomer (see Scheme 3). In both cases the proportion of the imino tautomer, as revealed by the intensity ratio of the amino/imino ν(N—H) absorptions, is greater in the more polar $CDCl_3$ solvent than in CCl_4. In compound **5** in CCl_4 an increase of the imino tautomer with the corresponding decreasing of the amino tautomer was observed with time (3 days). Moreover, the proportion of the imino tautomer is also greater in the aminothiazole **5** than in the aminobenzobenzothiazole derivative **4**, in the solid and in CCl_4 and $CDCl_3$ solutions.

The ν(C=O) band of compounds **4** and **5** appeared, in $CDCl_3$ solution, in the expected region at 1665–1660 cm^{-1} and the band amide II at ca. 1535 cm^{-1}.

In compound **4**, the three characteristic bands of the benzothiazole ring in the 1600–1500 cm^{-1} region (“thiazole I”, aromatic ν(C=C) and “thiazole II” [8,23]) appeared at 1599 (m), 1560 (sh) and ca. 1535 cm^{-1} (overlapped by the Amide II band).

According to the results in the ν(N—H) region, a medium band at 1620 cm^{-1} in $CDCl_3$ solution in compound **4** is tentatively assigned to the coupled O=C—N=C system of the imino structure **4b** [9]. In compound **5** the band at ca. 1590 cm^{-1} may have the same origin whereas the shoulder at ca. 1550 cm^{-1} is assigned to ν(C4′=C5′) of the imino structure.

4. Conclusions

Reaction of 4-methyl-1-piperazine carbonyl chloride with aniline gives the urea **1**. The reaction with primary *N*-heterocyclic amines yields the ureas **2–5** where the acylation takes place at the exocyclic nitrogen.

Amino–imino tautomerism is observed by means of NMR and IR spectroscopies for both benzothiazole and thiazole derivatives (**4** and **5**). NMR results reveal that the tautomeric equilibrium in compound **5** is slower than in compound **4**. Moreover, the IR spectra in our working conditions show that the proportion of the imino tautomer is greater in the more polar $CDCl_3$ solvent than in CCl_4 and also greater in the solid and in CCl_4 and $CDCl_3$ solution for the aminothiazole **5** with respect to the benzoaminothiazole derivative **4**.

^{1}H and ^{13}C NMR data for compounds **1**–**4**, **5a** and **5b** show that, in $CDCl_3$ solution at room temperature, a fast inter-conversion of the piperazine ring with the *N*-CH_3 group in equatorial position can be proposed.

In compounds **1**–**4** and **5a** in $CDCl_3$ solution the carbamoyl group rotates freely around the N1—CO bond.

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