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# Synthesis and NMR spectroscopic assignment of chlorinated benzimidazole-2-thione derivatives

Matic Proj, Izidor Sosič, Stanislav Gobec *

*University of Ljubljana, Faculty of Pharmacy, Chair of Pharmaceutical Chemistry, Aškerčeva 7, 1000 Ljubljana, Slovenia*

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ABSTRACT

The benzimidazole-2-thione scaffold is present in many drugs encompassing various therapeutic areas. Due to the broad spectrum of bioactivities it also represents an important starting point in drug discovery campaigns, especially those based on fragment-based design. Despite simple structures the tautomerism and regioisomerism of substituted benzimidazole-2-thiones makes unambiguous structural analysis difficult. Tautomeric duplicates are present in commercial libraries resulting in two tautomers being sold as different products. To showcase an example of appropriate structural determination, we synthesized and characterized a set of benzimidazole-2-thiones with different positions of a chlorine atom on the ring. Using NOESY and $^{13}$C NMR spectroscopy, we determined that the thione tautomer predominates in the thione-thiol equilibrium. Furthermore, NOESY and HMBC experiments confirmed the position of the substituents on the benzimidazole-2-thione ring.



## Introduction

Benzimidazole-2-thione (commonly known as 2-mercaptobenzimidazole) is an important fragment, present in various compounds with biological activity. It has been found in progesterone receptor antagonists [1], luteinizing hormone-releasing hormone antagonists [2,3], antiviral [4,5], antiprotozoal [6,7], antimicrobial [8–10], analgesic [11], anti-inflammatory [11], anticonvulsant [12], and antidiabetic [12] compounds. Furthermore, an even wider range of biological activities has been reported for compounds with the benzimidazole core, including clinically approved drugs [13–15].

Tautomerism is a phenomenon involving the dynamic equilibrium between interconvertible structural isomers. The most widespread form of tautomerism is relocation of a proton, called prototropy. A subtype of prototropy, typical for heterocyclic aromatic compounds, such as benzimidazoles, is annular tautomerism, where a proton migrates between cyclic nitrogen or carbon atoms while retaining aromaticity [16]. Benzimidazole tautomerism has also been the subject of various studies [16–20]. An example of tautomeric equilibria is given for compounds **1**, **2** and **3** (Fig. 1). Benzimidazole-2-thiones are sulfur analogs of benzimidazolones that exhibit thione-thiol (i.e. thioamide-iminothiol) prototropy, which is analogous to the keto-enol type of tautomerism. Furthermore, compounds with hydrogen at positions 1 and 3 exhibit annular tautomerism, resulting in two thiol forms (**1b** and **1c**). When a larger substituent is attached at position 1, annular tautomerism is prevented and two distinct, isomeric compounds exist (**2** and **3**, in this case).

A recent study evaluated tautomerism overlap in commercial databases and it was shown that the presence of tautomeric duplicates is not rare, meaning that the same chemicals are sold as different products [21]. In the case of compound **4** (Fig. 2), two tautomers were sold under different supplier IDs for different prices, despite having the same CAS number [22,23]. Furthermore, nomenclature for this type of compounds is not well established and different vendors use different tautomers (thiole or thione) when naming compounds. Sometimes, the rule for assigning the lowest substituent number is also neglected. According to IUPAC, the numbering of benzimidazoles starts from the nitrogen atom of the NH (or the *N*-methyl) in the direction of other heteroatoms so that the substituents have the lowest possible numbers [24]. In general practice, compounds for which the tautomerism is well studied, are named by the tautomer that predominates at equilibrium. Therefore, the actual name for 2-mercaptobenzimidazole is 1,3-dihydro-2*H*-benzo[*d*]imidazole-2-thione.

*Abbreviations:* NOESY, nuclear overhauser effect spectroscopy; HSQC, heteronuclear single-quantum correlation spectroscopy; HMBC, heteronuclear multiple-bond correlation spectroscopy.

* Corresponding author.
*E-mail address:* stanislav.gobec@ffa.uni-lj.si (S. Gobec).

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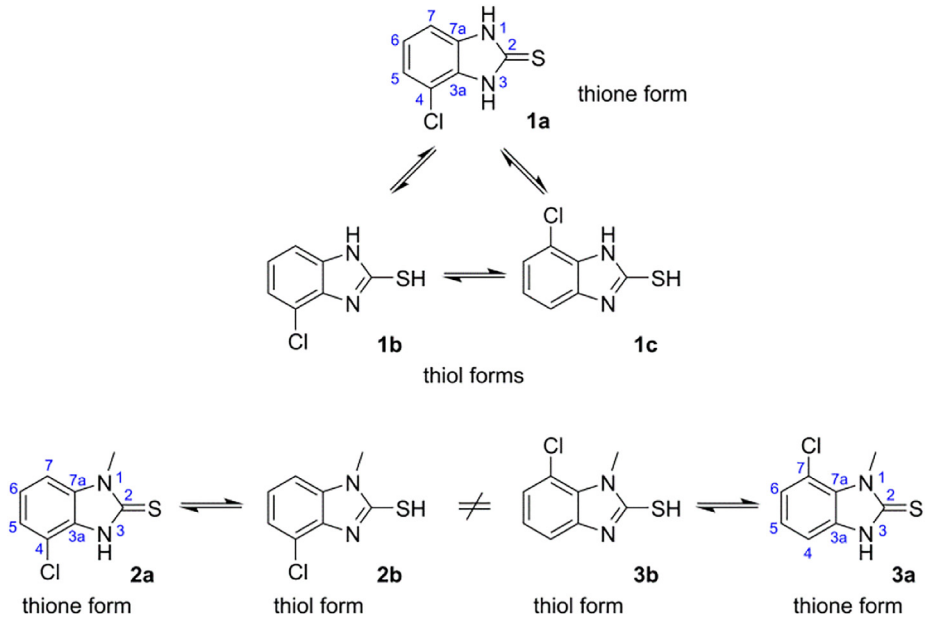



**Fig. 1.** Tautomeric equilibria for benzimidazole-2-thione derivatives. Only compounds with hydrogen at position 1 exhibit annular tautomerism and have two thiol forms. When N1 is methylated, two isomeric compounds, i.e. **2** and **3** exist.

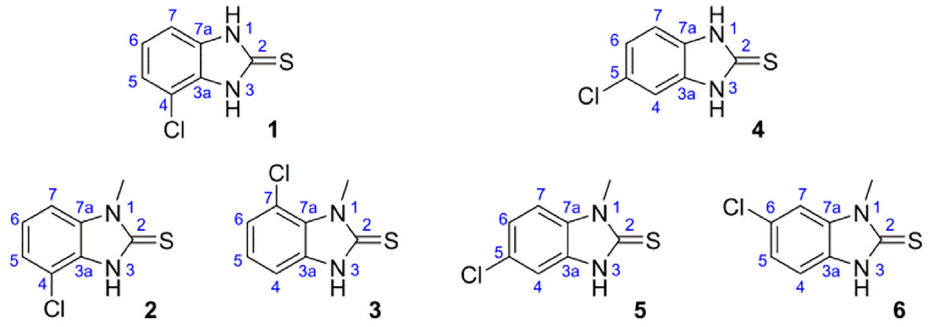


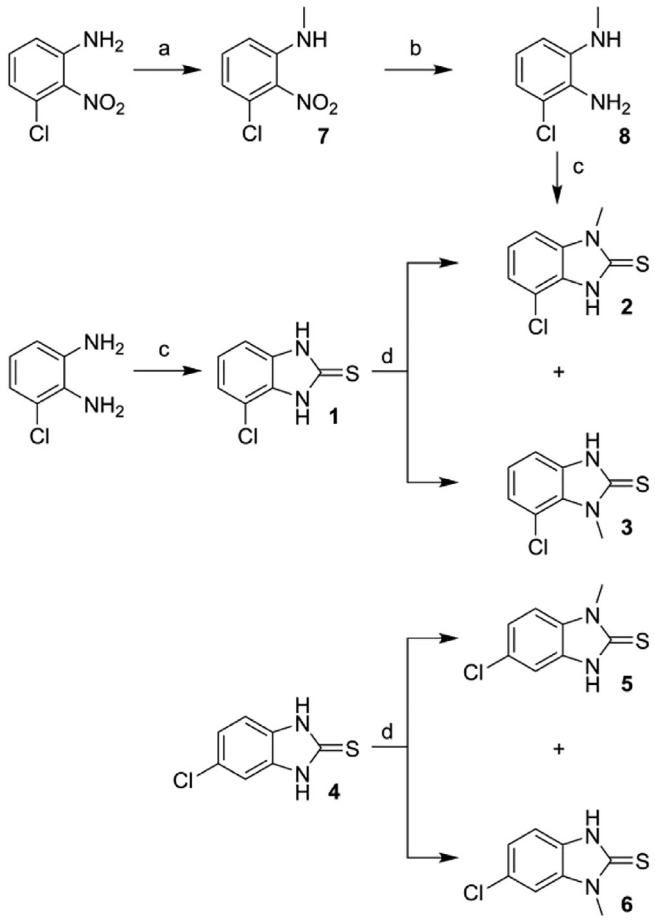

**Fig. 2.** The six examined chlorobenzimidazole-2-thiones with the correct ring numbering, so that the substituents have the lowest possible numbers.

The most effective tool to study tautomerism is NMR spectroscopy. Interconversion of benzimidazole tautomers occurs either through intermolecular transfer of a proton from one molecule to another or through interaction with a protic solvent. The interconversion has a low energy barrier which can result in NMR spectra presenting average signals. To slow down the prototropic rate in solution, either the temperature must be lowered or the solvent (hexamethylphosphoramide-*d18*, for example) must prevent formation of hydrogen bonds. Dynamic NMR studies have further explored thermodynamic and kinetic aspects of the equilibrium [17–19]. $^{15}$N NMR spectroscopy is a powerful tool for determining the tautomerism of nitrogen containing heteroaromatic compounds, because of the wide range of chemical shifts and high sensitivity to structural and environmental changes [16]. Solid state NMR experiments enable the study of tautomerism in solid samples, as an alternative to X-ray crystallography [17]. Based on crystallographic data available in the Cambridge Structural Database for benzimidazole-2-thiones, an exocyclic C—S distance indicates that the thione form is the predominant tautomer in the solid state [25–28]. Furthermore, a $^{15}$N NMR study reported that the thione form is also predominant in deuterated DMSO for benzimidazole-2-thione and 1-methylbenzimidazole-2-thione [29]. Therefore, we decided to name and represent the compounds only in the thione form in this manuscript.

Herein, we report the synthesis and straightforward NMR assignment of benzimidazole-2-thiones with varying positions of the chlorine atom (Fig. 2). Such sets of compounds are useful as starting points in fragment-based drug discovery campaigns to explore the space around the binding site and determine the direction for further fragment evolution [30]. Due to the fact that benzimidazole-2-thione is present as a hit in fragment-based drug design campaigns, we believe that it is important to unambiguously demonstrate the position of substituents on the ring before interpreting any biochemical results [31].

## Results and discussion

4-Chloro-1,3-dihydro-2*H*-benzo[*d*]imidazole-2-thione (**1**) was prepared from the corresponding *o*-phenylenediamine and potassium ethyl xanthate (Scheme 1). In the next step, trityl chloride was used as a thiol protective group to enable the selective methylation of nitrogen. Due to annular tautomerism of thiol-protected **1**, two positional isomers 4-chloro (**2**) and 7-chloro (**3**) were formed after the methylation procedure. Both products were successfully isolated using column chromatography. In the same manner, positional isomers 5-chloro (**5**) and 6-chloro (**6**) were prepared from commercially available 5-chloro-1,3-dihydro-2*H*-benzo[*d*]



**Scheme 1.** Synthesis of chlorinated benzimidazole-2-thione derivatives. Reagents and conditions: (a) MeI, NaH, DMF, 0 °C, 1 h, 47% yield; (b) Fe, HCl (37%), EtOH, 80 °C, 6 h, 76% yield; (c) potassium ethyl xanthate, EtOH (96%), $H_2O$, 80 °C, overnight, 27% yield for **1**, 16% yield for **2**; (d) i) TrCl, TEA, anhydrous THF, Ar, rt, overnight; ii) MeI, KOH, acetone, rt, 2–5 h; iii) 5% AcOH in MeOH, 65 °C, 30 min, 58% yield for **2** and **3**, 73% yield for **5** and **6**.

imidazole-2-thione (**4**) (Scheme 1). Compound **2** was also prepared using an alternative procedure where the nitrogen atom was methylated prior to cyclization. To increase the selectivity of monomethylation *vs.* dimethylation for the aniline derivative in step *a*, the ratio between the reagents was adjusted, the reaction was carried out in an ice bath, and methyl iodide was diluted in DMF before adding it dropwise to the reaction mixture. In step *b*, the nitro group was reduced to the amine group in the presence of iron metal and HCl. Finally, the benzimidazole-2-thione core was formed using the same procedure as for compound **1**; this time leading to a single regioisomer **2**. By this alternative synthetic procedure, we could unambiguously confirm the position of the methyl group relative to the chlorine atom (Scheme 1). For full synthetic procedures, see the ESI. Three benzimidazole-2-thione derivatives were also commercially available: **3** (Innovapharm Ltd.), **4** (Fluorochem Ltd.) and **6** (Innovapharm Ltd.). Compounds **3** and **4** were used without further purification, while **6** was recrystallized from EtOH. Notably, the analytical data for purchased compounds **3** and **6** was the same as for the synthesized compounds (compound **4** was not synthesized).

The appropriate deuterated solvents for NMR spectroscopy, i.e. pyridine-$d_5$ and/or acetone-$d_6$, were selected based on the solubility and peak separation for all analyzed compounds. An example of peak separation for **3** in various solvents (acetone-$d_6$, pyridine-$d_5$, DMSO-$d_6$, TFA-*d* and $CD_3OD$) is presented in the ESI (Fig. S1). The complete assignment of $^1H$ and $^{13}C$ chemical shifts was straightforward following these steps: i) splitting pattern and coupling constants of the trisubstituted benzene ring distinguished the 5- and 6-chloro derivatives from the 4- and 7-chloro derivatives; ii) NOESY experiments further distinguished between the 5- and 6-chloro, and between the 4- and 7-chloro analogs; iii) HSQC experiments determined which hydrogens are connected to which carbons; iv) HMBC experiments and/or; v) comparison between different isomers enabled the identification of the remaining carbons. It is important to state that with HMBC spectroscopy only correlations through three covalent bonds (*meta*) were observed for compounds **1**–**6**. Tables 1 and 2 contain chemical shift data in pyridine-$d_5$ and acetone-$d_6$. For graphical representations and assigned spectra in other solvents see the ESI (Figs. S2–5).

For example, in the $^1H$ NMR spectrum of compound **2** two doublets of doublets and one triplet were present in the aromatic region, which means that only 4-chloro or 7-chloro substitutions were possible. NOESY experiment showed coupling between the C<u>H</u>$_3$ protons and the doublets of doublets of C7-<u>H</u> (Fig. 3a). Therefore, compound **2** was determined to be 4-chloro substituted. The first step in assigning the $^{13}C$ NMR spectrum was to determine which hydrogens are connected to which carbons using HSQC experiments. The remaining signals were identified by observing

**Table 1**
$^1H$ NMR chemical shifts in pyridine-$d_5$ and acetone-$d_6$ (δ in ppm) of benzimidazole-2-thiones **1**–**6**. Splitting patterns and *ortho*, *meta* and *para* coupling constants are given in parentheses. See ESI (Figs. S2–3) for graphical representations.

| Compound | Solvent | N<u>H</u> | C4-<u>H</u> | C5-<u>H</u> | C6-<u>H</u> | C7-<u>H</u> | C<u>H</u>$_3$ |
|---|---|---|---|---|---|---|---|
| **1** | Pyridine-$d_5$ | 14.88 (bs, 1H), 14.59 (bs, 1H) | – | 7.22 (1H) or 7.20 (1H)[a] | 7.10 (t, *J* = 8.0 Hz, 1H) | 7.22 (1H) or 7.20 (1H)[a] | – |
| | Acetone-$d_6$ | 11.77 (bs, 1H), 11.59 (bs, 1H) | – | | 7.22–7.14 (multiplet, 3H) | | – |
| **2** | Pyridine-$d_5$ | 14.95 (bs, 1H) | – | 7.21 (1H)[a] | 7.10 (t, *J* = 8.0 Hz, 1H) | 7.02 (dd, *J* = 8.0, 0.9 Hz, 1H) | 3.70 (s, 3H) |
| | Acetone-$d_6$ | 11.88 (bs, 1H) | – | | 7.32–7.20 (multiplet, 3H) | | 3.71 (s, 3H) |
| **3** | Pyridine-$d_5$ | 14.73 (bs, 1H) | 7.19 (dd, *J* = 7.7, 1.1 Hz, 1H) | 7.06 (t, *J* = 7.9 Hz, 1H) | 7.13 (dd, *J* = 8.0, 1.1 Hz, 1H) | – | 4.06 (s, 3H) |
| | Acetone-$d_6$ | 11.75 (bs, 1H) | 7.22 (dd, *J* = 7.1, 2.0 Hz, 1H) | 7.21–7.15 (multiplet, 2H) | | – | 4.05 (s, 3H) |
| **4** | Pyridine-$d_5$ | 14.54 (bs, 1H), 14.50 (bs, 1H) | 7.47 (dd, *J* = 1.7, 0.6 Hz, 1H) | – | 7.24 (dd, *J* = 8.4, 1.8 Hz, 1H) | 7.28 (dd, *J* = 8.4, 0.6 Hz, 1H) | – |
| | Acetone-$d_6$ | 11.46 (bs, 2H) | 7.25 (d, *J* = 1.9 Hz, 1H) | – | 7.17 (dd, *J* = 8.5, 1.9 Hz, 1H) | 7.23 (d, *J* = 8.5 Hz, 1H) | – |
| **5** | Pyridine-$d_5$ | 14.65 (bs, 1H) | 7.44 (d, *J* = 1.8 Hz, 1H) | – | 7.25 (dd, *J* = 8.5, 2.0 Hz, 2H) | 7.06 (d, *J* = 8.5 Hz, 1H) | 3.68 (s, 3H) |
| | Acetone-$d_6$ | 11.59 (bs, 1H) | 7.26 (dd, *J* = 1.9, 0.4 Hz, 1H) | – | 7.22 (dd, *J* = 8.5, 2.0 Hz, 1H) | 7.31 (d, *J* = 8.5 Hz, 1H) | 3.70 (s, 3H) |
| **6** | Pyridine-$d_5$ | 14.60 (bs, 1H) | 7.23 (1H)[a] | 7.26 (dd, *J* = 8.4, 1.7 Hz, 1H) | – | 7.32 (dd, *J* = 1.6, 0.5 Hz, 1H) | 3.73 (s, 3H) |
| | Acetone-$d_6$ | 11.58 (bs, 1H) | 7.25 (d, *J* = 8.1 Hz, 1H) | 7.20 (dd, *J* = 8.4, 1.9 Hz, 1H) | – | 7.41 (d, *J* = 1.3 Hz, 1H) | 3.71 (s, 3H) |

[a] Signal overlaps with the solvent peak.

**Table 2**
$^{13}$C NMR chemical shifts in pyridine-$d_5$ and acetone-$d_6$ (δ in ppm) of benzimidazole-2-thiones **1**–**6**. See ESI (Figs. S4–5) for graphical representations.

| Compound | Solvent | C2 | C3a | C4 | C5 | C6 | C7 | C7a | $\underline{C}H_3$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | Acetone-$d_6$ | 171.78 | 131.24 | 114.78 | 123.15 or 109.01[b] | 124.46 | 123.15 or 109.01[b] | 134.63 | – |
| | Pyridine-$d_5$ | 172.46 | 132.25 | 114.79 | 122.65 or 108.76[b] | 123.77 | 122.65 or 108.76[b] | 135.40 | – |
| **2** | Acetone-$d_6$ | 171.85 | 129.57 | 114.88 | 124.23 and 123.45[a] | | 108.79 | 135.80 | 30.92 |
| | Pyridine-$d_5$ | 172.01 | 130.30 | 114.92 | 123.10 | 123.62 | 108.25 | 135.74 | 30.98 |
| **3** | Acetone-$d_6$ | 172.16 | 133.83 | 109.39 | 124.67 and 124.63[a] | | 115.87 | 130.33 | 33.36 |
| | Pyridine-$d_5$ | 172.25 | 134.24 | 109.12 | 124.12[a] | | 115.75 | 130.29 | 33.35 |
| **4** | Acetone-$d_6$ | 171.80 | 134.37 or 128.49[b] | 110.24 | 134.37 or 128.49[b] | 123.33 | 111.24 | 132.35 | – |
| **5** | Acetone-$d_6$ | 171.78 | 128.80 | 110.21 | 132.58 | 123.09 | 110.96 | 133.46 | 30.63 |
| **6** | Acetone-$d_6$ | 172.00 | 130.64 | 111.21 | 123.59 | 128.47 | 110.23 | 135.54 | 30.68 |

[a] Unambiguous assignment is not possible, because the signals are too close.
[b] Carbons show the same correlation with protons in the HMBC spectrum.

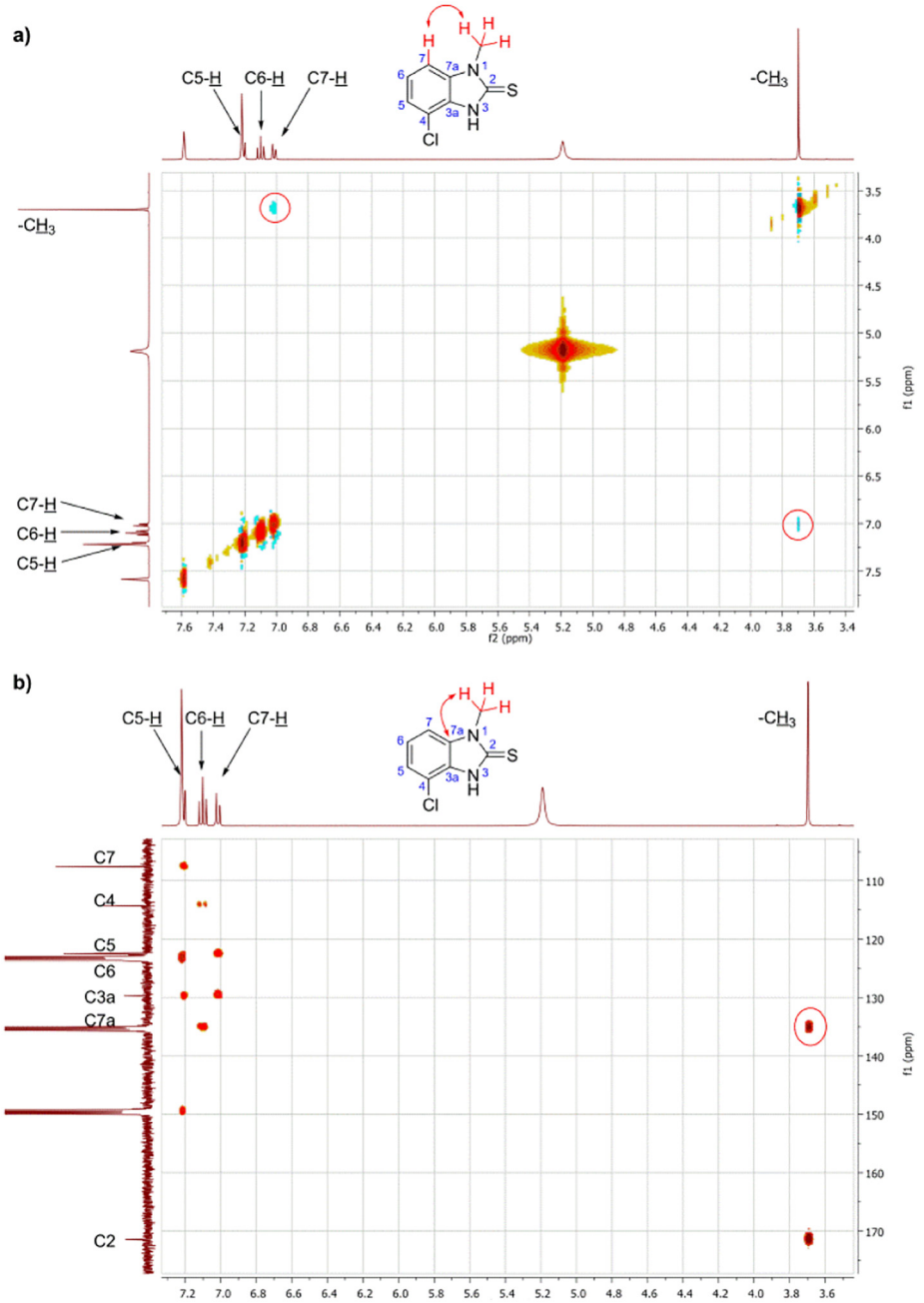



**Fig. 3.** 2D NMR spectra for compound **2**. a) NOESY experiment, pyridine-$d_5$. Circled cross-peaks indicate coupling between $C\underline{H}_3$ and C7-$\underline{H}$. Solvent and residual water peaks are unassigned. b) HMBC experiment, pyridine-$d_5$. Circled peak indicates coupling between $C\underline{H}_3$ and $\underline{C}$7a (overlapping with solvent peak). Only the cross peaks that correlate protons and carbons, which are connected through three covalent bonds, are visible. Solvent and residual water peaks are unassigned.

*meta* correlations using HMBC experiments. Furthermore, correlations between $CH_3$ and C2, C7a were confirmed using HMBC experiments (Fig. 3b). Overall, both NOESY and HMBC experiments confirmed the 4-chloro substitution for compound **2**. NOESY and HMBC spectra for all compounds are available in the ESI (Figs. S6–17). The assignments and substitutions were determined following the same steps as for the compound **2**. However, some missing signals in the $^{13}C$ NMR were assigned only after comparing different isomers.

In our experiments, all compounds (**1**–**6**) exhibited $^{13}C$ NMR chemical shifts for C2 above 170 ppm (C2 = S), while in the literature C2 was reported at around 150 ppm for compounds with an alkylated sulfur atom, such as 2-(methylthio)-1*H*-benzo[*d*]imidazole (C2-SMe) [33]. Thus, we can assume that the thione form predominates at equilibrium [34]. Additionally, our NOESY experiments confirmed this assumption. For compound **4**, couplings between protons N1-H and C7-H, as well as between N3-H and C4-H were observed (Fig. S12); for compounds **3**, **5**, **6**, couplings between NH and C4-H were observed (Figs. S11, S14 and S16). Using NOESY and $^{13}C$ NMR spectroscopy, we confirmed that instead of observing average signals due to rapid tautomerization, only signals from a single thione tautomer, which predominates in solution, were observed. Nonetheless, the importance of tautomerism was evident to us when conducting synthetic procedures on benzimidazole-2-thiones (see above). In some reactions, they behaved as though they were in the thione form (methylation), while in other reactions they behaved as thiols (trityl protection). This observation is analogous to the reactivity of benzimidazolones [32] and confirms that the tautomeric equilibrium can be shifted during the reaction from major to the minor tautomeric form.

## Conclusion

In summary, benzimidazole-2-thione is an important fragment in biologically active compounds. The tautomerism and regioisomerism of azoles and related heterocycles make the structural assignment of such compounds difficult in some cases. In this work we synthesized a set of benzimidazole-2-thiones with varying positions of the chlorine atom and performed complete $^{1}H$ and $^{13}C$ chemical shift assignment. Methylation of benzimidazole-2-thione chloro derivatives (**1** and **4**) afforded a mixture of regioisomers, since both nitrogen atoms (N1 and N3) can be methylated. Both NOESY and HMBC experiments confirmed the position of the substituents. Using NOESY and $^{13}C$ NMR spectroscopy, we determined that the thione tautomer predominates in the thione-thiol equilibrium. We demonstrated that 2D NMR spectroscopy is a sufficient method to determine the substituent position and the tautomeric form of benzimidazole-2-thiones. Such experiments should be performed in cases when similar chemical structures are discovered as hits in fragment-based drug discovery campaigns.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

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## Appendix A. Supplementary data

Supplementary data (full experimental section, synthetic procedures, $^{1}H$ and $^{13}C$ NMR spectroscopy data, 2D NMR spectra and HPLC chromatograms) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151078.

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