Letter - spectral assignment

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# $^{1}H$ and $^{13}C$ assignments of three series bioactive imidazo[2,1-*b*]thiazole derivatives

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## Introduction

Imidazo[2,1-*b*]thiazoles make an interesting group of heterocyclic molecules. The compounds containing imidazo[2,1-*b*]thiazole moiety show interesting pharmacological activities as well as properties useful from the technological and agricultural point of view.[1–3] Their antitumor,[4–6] antiallergic,[7] anesthetic,[8] anticancer,[9–12] antiviral,[13] antimicrobial[14] and antioxidant[15] activities have been widely investigated. In spite of the information on the wide range of imidazo[2,1-*b*]thiazoles applications and extensive studies on their chemistry, no systematic studies on their NMR properties have been published. Therefore, 13 compounds with typical substitute group from these three series were selected to carry out a detailed NMR investigation using 1D and 2D NMR experiments including $^{1}H$ NMR, $^{13}C$ NMR, HMQC and HMBC. Here, we present the detailed $^{1}H$ and $^{13}C$ NMR assignments of these compounds and further analyze and compare the NMR data of these compounds.

## Experimental

### Synthesis

Typical procedure for synthesis of imidazo[2,1-b]thiazole.[16–18]

A mixture of corresponding 2-aminothiazole (20 mmol) and 2-bromo-1-arylethanone (20 mmol) was dissolved in acetone (20 ml). The reaction mixture was stirred for 24 h. The resulting precipitate was collected, suspended in water (100 ml) and heated under reflux for 6 h. The warm solution basified with 20% $NH_4OH$ yielded the expected imidazo[2,1-b]thiazole after cooling up to room temperature. The residue crystallized from *N,N*-dimethylformamide.

Physical and elemental analysis data for the imidazo[2,1-b] thiazoles (**1a–g**, **2a–b**, **3a–d**) are presented in Table 1.

### NMR measurements

All experiments were performed on a Bruker Avance™ 600 spectrometer operating at 600.22 and 150.93 MHz for $^{1}H$ and $^{13}C$ respectively at room temperature in dimethyl sulfoxide (DMSO) – $d_6$. $^{1}H$ and $^{13}C$ chemical shifts are reported in parts per million downfield from TMS; for $^{1}H$ NMR spectra, residual signal of DMSO-$d_6$ was used as reference (2.50 ppm). In $^{13}C$ NMR measurements, the signal of DMSO-$d_6$ was used as reference (35.9 ppm). The $^{1}H$ NMR spectra were recorded with a spectral width of 7.1 KHz, data point of 64 K, digital resolution of 0.22 Hz, relaxation delay of 1.0 s and 30° pulse width of 2.8 μs, whereas the $^{13}C$ with a spectral width of 39.06 KHz, data points of 64 K, relaxation delay of 2.0 s and 30° pulse width of 5.6 μs. The HMQC spectra were collected as a 128 × 1024 matrix with one transient per t1 increment and processed as a 1024 × 1024 matrix, and the one bond heteronuclear coupling value was set to 145 Hz. The HMBC spectra were collected as a 128 × 4096 matrix with one transient per t1 increment and processed as a 2048 × 1024 matrix, and the long-range coupling value was set to 10 Hz.

## Result and Discussion

The structures and numbering of representative compounds of each series are presented in Fig. 1. 1D and 2D NMR experiments were used for the complete $^{1}H$ and $^{13}C$ chemical shift assignments of these compounds. Protonated carbons were assigned unequivocally from HMQC spectra. The remaining quaternary carbons were assigned mainly based on HMBC spectra. The $^{1}H$ and $^{13}C$ NMR data of compounds **1–3** are summarized in Tables 2–4.

The $^{1}H$ NMR spectra of all the described compounds were well resolved, and unambiguous proton chemical shift assignments were based on the multiplicity pattern of proton resonances and confirmed by two-dimensional experiments. Some typical proton and carbon resonances can be found in the NMR spectra imidazo[2,1-b]thiazoles **1**, namely the singlet at $\delta$ 2.41–2.45 ppm as a result of the 3-$CH_3$ proton resonance (Fig. 1 and Table 2), its carbon resonance at $\delta$ 13.3 ppm and in the NMR spectra imidazo[2,1-b]thiazoles **3**, namely the multiplets at $\delta$ 1.93–1.79 ppm and $\delta$ 2.73–2.69 ppm as a result of the 6,7 and 5,8 proton resonance (Fig. 1 and Table 4), its carbon resonance at $\delta$ 21.6–22.6 ppm and $\delta$ 23.1–24.2 ppm.

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**Table 1.** Physical and elemental analysis data for imidazo[2,1-b]thiazole derivatives

| Compound | Melting point (°C/mmHg) | Molecular formula | Formula weight | | Analysis (%) C | H | N |
|---|---|---|---|---|---|---|---|
| **1a** | 112–113 | $C_{12}H_{10}N_2S$ | 214.3 | Calc. | 67.26 | 4.70 | 13.07 |
| | | | | Found | 67.31 | 4.76 | 13.12 |
| **1b** | 121–122 | $C_{13}H_{12}N_2S$ | 228.3 | Calc. | 68.39 | 5.30 | 12.27 |
| | | | | Found | 68.45 | 5.35 | 12.33 |
| **1c** | 132–135 | $C_{13}H_{12}N_2S_2$ | 260.4 | Calc. | 59.97 | 4.65 | 10.76 |
| | | | | Found | 60.06 | 4.71 | 10.81 |
| **1d** | 122–123 | $C_{12}H_9ClN_2S$ | 248.7 | Calc. | 57.95 | 3.65 | 11.26 |
| | | | | Found | 58.02 | 4.73 | 11.31 |
| **1e** | 131–132 | $C_{12}H_9BrN_2S$ | 293.2 | Calc. | 49.16 | 3.09 | 9.55 |
| | | | | Found | 49.24 | 3.14 | 9.60 |
| **1f** | 221–222 | $C_{12}H_9N_3O_2S$ | 259.3 | Calc. | 55.59 | 3.50 | 16.21 |
| | | | | Found | 55.67 | 3.56 | 16.27 |
| **1g** | 235–237 | $C_{10}H_8N_2S$ | 220.3 | Calc. | 54.52 | 3.66 | 12.72 |
| | | | | Found | 54.61 | 3.72 | 12.79 |
| **2a** | 161–162 | $C_{16}H_{12}N_2S$ | 264.3 | Calc. | 72.70 | 4.58 | 10.60 |
| | | | | Found | 72.77 | 4.64 | 10.66 |
| **2b** | >260 | $C_{15}H_9N_3O_2S$ | 295.3 | Calc. | 61.01 | 3.07 | 14.23 |
| | | | | Found | 61.11 | 3.14 | 14.29 |
| **3a** | 167–168 | $C_{15}H_{14}N_2S$ | 254.4 | Calc. | 70.83 | 5.55 | 11.01 |
| | | | | Found | 70.92 | 5.61 | 11.11 |
| **3b** | 191–192 | $C_{16}H_{16}N_2S$ | 268.4 | Calc. | 71.61 | 6.01 | 10.44 |
| | | | | Found | 71.72 | 6.09 | 10.49 |
| **3c** | 162–163 | $C_{15}H_{13}ClN_2S$ | 288.8 | Calc. | 62.38 | 4.54 | 9.70 |
| | | | | Found | 62.45 | 4.60 | 9.77 |
| **3d** | 163–164 | $C_{15}H_{13}BrN_2S$ | 333.3 | Calc. | 54.06 | 3.93 | 8.41 |
| | | | | Found | 54.13 | 4.02 | 8.47 |

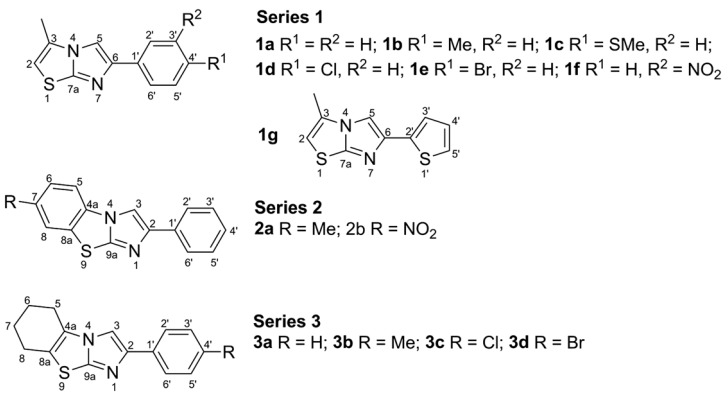


**Figure 1.** Sctructures and numbering of compounds **1–3** series.

The aromatic region of the $^1$H NMR spectra is slightly different among the described compounds because of the substitution pattern. In the case of compounds **1a–g** and taking 6-(4-bromophenyl)-3-methylimidazo[2,1-b]thiazole **1e** as an example, one can identify two singlets at $\delta$ 6.89 and 8.29 ppm corresponding to H-2 and H-5. The aromatic substitution pattern in phenyl ring of the reported compounds causes some characteristic signals in the $^1$H NMR spectra. The most common is the presence of a pair of doublets at $\delta$ 7.75–7.86 and $\delta$ 7.20–7.58 ppm (Table 2) corresponding, respectively, to the resonances of H-2′,6′ and H-3′,5′. The coupling constants are characteristic of an *ortho*-coupling in a *para*-substituted aromatic ring. In the case of compound series **2–3,** one can identify one singlet at $\delta$ 8.11–8.91 ppm (Tables 3 and 4) corresponding to H-3 annulation imidazole ring.

The $^1$H NMR spectra of compounds **2a–2b** show two doublets and one singlet corresponding to the proton resonances of the annelated benzene ring. In addition, the pair of doublets corresponding to the resonances of H-5 and H-6 protons at, respectively, $\delta$ 7.84–8.47 and $\delta$ 7.84–8.47 ppm, with a typical *ortho*-coupling constants $^3J$ 8.2 Hz (an example of the case of **2a**).

The analysis of the $^{13}$C spectra of imidazo[2,1-*b*]thiazole derivatives **1–3** with the aid of the 2D heteronuclear correlation experiments (HMQC, $^1$H, $^{13}$C) allowed the assignments of all protonated carbon resonances. For instance, the carbon resonance of the 3-methyl group can be easily assigned at $\delta$ 2.41–2.45 ppm, as well as the aromatic carbon resonances of the protonated carbons (Tables 2–4).

To confirm the assignments made from HMQC and assigned, the signals corresponding to quaternary carbons HMBC spectra

**Table 2.** $^{1}H$ and $^{13}C$ NMR chemical shifts (ppm), H multiplicities, and constant coupling (Hz), $^{1}H$–$^{13}C$ correlations in heteronuclear multiple bond correlation spectra for imidazo[2,1-b]thiazole derivatives (series 1)

| No. | **1a** | | | **1b** | | | **1c** | | | **1d** | | | **1e** | | | **1f** | | | **1g** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | δH | δC | HMBC | δH | δC | HMBC | δH | δC | HMBC | δH | δC | HMBC | δH | δC | HMBC | δH | δC | HMBC | δH | δC | HMBC |
| 2 | 6.89 s | 107.5 | C-3, 7a | 6.87 s | 107.3 | C-3, 7a | 6.88 s | 107.5 | C-3, 7a | 6.89 s | 107.8 | C-3, 7a | 6.89 s | 107.8 | C-3s, 7a | 6.95 s | 108.4 | C-3, 7a | 6.89 s | 107.7 | C-3, 7a |
| 3 | — | 128.6 | — | — | 128.6 | | — | 128.6 | — | — | 128.6 | — | — | 128.6 | — | — | 128.7 | — | — | 128.6 | — |
| 3-$CH_3$ | 2.43 s | 13.3 | C-2, 3 | 2.41 s | 13.3 | C-2, 3 | 2.42 s | 13.3 | C-2, 3 | 2.41 s | 13.3 | C-2, 3 | 2.42 s | 13.3 | C-2, 3 | 2.45 s | 13.3 | C-2, 3 | 2.41 s | 13.3 | C-2, 3 |
| 5 | 8.27 s | 108.4 | C-6, 7a | 8.19 s | 107.9 | C-6, 7a | 8.24 s | 108.2 | C-6, 7a | 8.28 s | 108.8 | C-6, 7a, 1′ | 8.29 s | 108.9 | C-6, 7a, 1′ | 8.54 s | 110.2 | C-6, 7a, 1′ | 8.12 s | 107.6 | C-6, 7a, 2′ |
| 6 | — | 146.7 | — | — | 146.8 | — | — | 146.3 | — | — | 145.5 | — | — | 145.5 | — | — | 144.4 | — | — | 141.9 | — |
| 7a | — | 149.0 | — | — | 148.8 | — | — | 149.0 | — | — | 149.2 | — | — | 149.1 | — | — | 149.6 | — | — | 148.8 | — |
| 1′ | — | 134.8 | — | — | 136.6 | — | — | 137.0 | — | — | 133.7 | — | — | 134.1 | — | — | 136.6 | — | — | — | — |
| 2′ | 7.86 (d, 7.6) | 125.1 | C-6, 4′ | 7.75 (d, 8.0) | 125.1 | C-6, 1′, 3′, 5′ | 7.80 (d, 8.4) | 125.6 | C-6, 1′ | 7.86 (d, 8.6) | 126.7 | C-6, 4′ | 7.81 (d, 8.5) | 127.1 | C-6, 3′, 4′, 5′ | 8.65 s | 119.3 | C-6, 3′, 4′ | — | 138.5 | — |
| 3′ | 7.40 (t, 7.6) | 129.1 | C-1′ | 7.20 (d, 8.0) | 129.6 | C-4′ | 7.29 (d, 8.4) | 126.7 | C-6, 4′ | 7.44 (d, 8.6) | 129.1 | C-1′, 4, 6′ | 7.58 (d, 8.5) | 132.0 | C-6, 1′, 4′ | — | 148.9 | — | 7.42 (d, 5.0) | 124.7 | C-6, 2′, 4′, 5′ |
| 4′ | 7.25 (t, 7.3) | 127.4 | C-2′, 3′, 5′, 6′ | — | 132.1 | — | — | 131.6 | — | — | 131.7 | — | — | 120.2 | — | 8.09 (d, 7.8) | 131.2 | C-2, 3′ | 7.39 (d, 3.5) | 122.6 | C-6, 3′, 4′, 5′ |
| 4′-$CH_3$ | — | — | — | 2.31 s | 21.3 | C-1′, 3′, 5′ | 2.50 s | 15.2 | C-1′ | — | — | — | — | — | — | — | — | — | — | — | — |
| 5′ | 7.40 (t, 7.6) | 129.1 | C-1′ | 7.20 (d, 8.0) | 129.6 | C-4′ | 7.29 (d, 8.4) | 126.7 | C-6, 4′ | 7.44 (d, 8.6) | 129.1 | C-1′, 4, 6′ | 7.58 (d, 8.5) | 132.0 | C-6, 1′, 4′ | 7.69 (t, 8.0) | 130.7 | C-1′, 4′, 4′, 6′ | 7.10–7.07 m | 128.3 | C-6, 2′, 3′, 4′ |
| 6′ | 7.86 (d, 7.6) | 125.1 | C-6, 4′ | 7.75 (d, 8.0) | 125.1 | C-6, 1′, 3′, 5′ | 7.80 (d, 8.4) | 125.6 | C-6, 1′ | 7.86 (d, 8.6) | 126.7 | C-6, 4′ | 7.81 (d, 8.5) | 127.1 | C-6, 3′, 4′, 5′ | 8.28 (d, 7.8) | 121.9 | C-6, 2′, 3′ | — | — | — |




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**Table 3.** $^{1}H$ and $^{13}C$ NMR chemical shifts (ppm), H multiplicities, and constant coupling (Hz), $^{1}H$–$^{13}C$ correlations in heteronuclear multiple bond correlation spectra for imidazo[2,1-b]thiazole derivatives (series 2)

| No. | **2a** | | | **2b** | | |
|---|---|---|---|---|---|---|
| | δH | δC | HMBC | δH | δC | HMBC |
| 2 | — | 146.5 | — | — | 147.8 | — |
| 3 | 8.72 s | 109.5 | C-2, 9a | 8.91 s | 110.2 | C-2, 9a |
| 4a | — | 129.6 | — | — | 131.1 | — |
| 5 | 7.84 (d, 8.2) | 113.4 | C-4a, 6, 7 | 8.47 (d, 8.8) | 114.0 | C-4a, 6, 7 |
| 6 | 7.35 (d, 8.2) | 127.9 | C-4a, 8, 7-$CH_3$ | 8.19 (d, 8.8) | 123.2 | C-4a, 8, |
| 7 | — | 135.3 | — | — | 144.6 | — |
| 7-$CH_3$ | 2.41 s | 21.6 | C-5, 6, 7, 8 | — | — | C-5, 6, 7, 8 |
| 8 | 7.79 s | 125.3 | C-6, 7-$CH_3$, 8a | 9.13 s | 122.1 | C-6, 8a |
| 8a | — | 130.2 | — | — | 133.8 | — |
| 9a | — | 147.2 | — | — | 149.4 | — |
| 1′ | — | 134.4 | — | — | 136.5 | — |
| 2′ | 7.86 (d, 7.3) | 125.1 | C-2, 3′, 5′ | 7.88 (d, 7.2) | 125.3 | C-2, 3′, 5′ |
| 3′ | 7.43 (t, 7.6) | 129.2 | C-2, 1′, 2′, 6′ | 7.46 (t, 7.6) | 129.3 | C-2, 1′, 2′, 6′ |
| 4′ | 7.28 (t, 7.3) | 127.6 | C-2′, 3′, 5′, 6′ | 7.33 (t, 7.3) | 128.2 | C-2′, 3′, 5′, 6′ |
| 5′ | 7.43 (t, 7.6) | 129.2 | C-2, 1′, 2′, 6′ | 7.46 (t, 7.6) | 129.3 | C-2, 1′, 2′, 6′ |
| 6′ | 7.86 (d, 7.3) | 125.1 | C-2, 3′, 5′ | 7.88 (d, v 7.2) | 125.3 | C-2, 3′, 5′ |

**Table 4.** $^{1}H$ and $^{13}C$ NMR chemical shifts (ppm), H multiplicities, and constant coupling (Hz), $^{1}H$–$^{13}C$ correlations in heteronuclear multiple bond correlation spectra for imidazo[2,1-b]thiazole derivatives (series 3)

| No. | **3a** | | | **3b** | | | **3c** | | | **3d** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | δH | δC | HMBC | δH | δC | HMBC | δH | δC | HMBC | δH | δC | HMBC |
| 2 | — | 145.6 | — | — | 145.7 | — | — | 144.4 | — | — | 144.4 | — |
| 3 | 8.15 s | 108.0 | C-2, 9a | 8.11 s | 107.5 | C-2, 9a | 8.21 s | 108.4 | C-2, 9a | 8.24 s | 108.5 | C-2, 9a |
| 4a | — | 126.7 | — | — | 126.8 | — | — | 126.6 | — | — | 126.8 | — |
| 5 | 2.69–2.62 m | 24.2 | C-4a, 6, 7, 8a | 2.73–2.62 m | 24.2 | C-4a, 6, 7, 8a | 2.68–2.63 m | 24.2 | C-4a, 6, 7, 8a | 2.70–2.65 m | 24.2 | C-4a, 6, 7, 8a |
| 6 | 1.90–1.81 m | 21.6 | C-4a, 8a | 1.93–1.79 m | 21.6 | C-4a, 8a | 1.91–1.81 m | 21.6 | C-4a, 5, 8, 8a | 1.91–1.82 m | 21.6 | C-4a, 5, 8, 8a |
| 7 | 1.90–1.81 m | 22.6 | C-4a, 8a | 1.93–1.79 m | 22.6 | C-4a, 8a | 1.91–1.81 m | 22.6 | C-4a, 5, 8, 8a | 1.91–1.82 m | 21.6 | C-4a, 5, 8, 8a |
| 8 | 2.69–2.62 m | 23.1 | C-4a, 6, 7, 8a | 2.73–2.62 m | 23.1 | C-4a, 6, 7, 8a | 2.68–2.63 m | 23.1 | C-4a, 6, 7, 8a | 2.70–2.65 m | 23.1 | C-4a, 6, 7, 8a |
| 8a | — | 121.1 | — | — | 120.9 | — | — | 121.4 | — | — | 121.4 | — |
| 9a | — | 147.1 | — | — | 146.9 | — | — | 147.3 | — | — | 147.3 | — |
| 1′ | — | 134.9 | — | — | 132.2 | — | — | 133.8 | — | — | 134.2 | — |
| 2′ | 7.84 (d, 7.7) | 125.0 | C-2, 4′, | 7.72 (d, 6.7) | 124.9 | C-2, 4′ | 7.84 (d, 8.4) | 126.6 | C-2, 1′, 4′ | 7.78 (d, 8.5) | 126.9 | C-2, 3′, 4′, 5′ |
| 3′ | 7.38 (t, 7.6) | 129.0 | C-1′, 2′, 6′ | 7.19 (d, 6.9) | 129.6 | C-1′ | 7.43 (d, 8.5) | 129.1 | C-1′, 4′ | 7.57 (d, 8.5) | 132.0 | C-1′, 4′ |
| 4′ | 7.23 (t. 7.3) | 127.2 | C-2′, 3′, 5′, 6′ | — | 136.4 | — | — | 131.5 | — | — | 120.0 | — |
| 4′-$CH_3$ | — | — | — | 2.31 s | 21.27 | C-3′, 4′, 5′ | — | — | — | — | — | — |
| 5′ | 7.38 (t, 7.6) | 129.0 | C-1′, 2′, 6′ | 7.19 (d, 6.9) | 129.6 | C-1′ | 7.43 (d, 8.5) | 129.1 | C-1′, 4′ | 7.57 (d, 8.5) | 132.0 | C-1′, 4′ |
| 6′ | 7.84 (d, 7.7) | 125.0 | C-2, 4′, | 7.72 (d, 6.7) | 124.9 | C-2, 4′ | 7.84 (d, 8.4) | 126.6 | C-2, 1′, 4′ | 7.78 (d, 8.5) | 126.9 | C-2, 3′, 4′, 5′ |

were recorded. The correlation of H-5 with C-6 ($^2J_{CH}$), C-7a ($^3J_{CH}$) (series **1**) and H-3 with C-2 ($^2J_{CH}$), C-9a ($^3J_{CH}$) (series **2–3**) in the HMBC spectrum were used to attribute the chemical shift of C-6 with at $\delta$ 141.9–146.8, C-7a with at $\delta$ 148.8–149.6, C-2 at $\delta$ 144.4–147.8, C-9a with at $\delta$ 146.9–149.4 (Tables 2–4).

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