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SYNTHESIS, STRUCTURE OF SOME NOVEL DERIVATIVES CONTAINING BENZOXAZOLE RING FROM *p*-HYDROXYBENZALDEHYDE

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Abstract. Six derivatives containing benzoxazole were synthesized from *p*-hydroxybenzaldehyde via four step-route in high yields. The benzoxazole cyclization step was promoted with microwave irradiation for 10 to 30 min. Free *o*-aminophenol derivative **A3** reacted with aldehydes to form benzoxazole **A4a-f**, but **A3.HCl** couldn't due to the presence of iron (II). Their structures were elucidated with spectroscopic methods: IR, 1D, 2D NMR, and MS.

Keywords: domestic microwave oven, benzothiazole, benzoxazole, *p*-hydroxybenzaldehyde.

1. Introduction

Benzoxazole plays an essential role in the skeleton of drug design. The scaffold is found as a constituent of many natural products. For example, calcimycin (known as A23187) is not only well-known as an antibiotic against (+) Gram and fungi but also as a cation ionophore which owns significant selectivity of manganese (II) cation [1, 2].

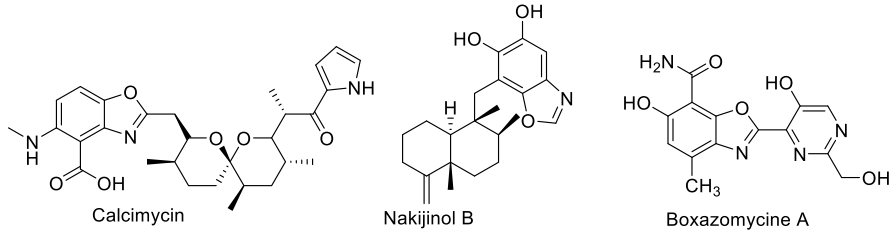

Figure 1 Some benzoxazole containing natural products

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Another benzothiazole-based natural product is nakijinol B which shows anti-proliferative activity against several human cancer cell lines in the micromolar range [3]. In addition, boxazomycine also acts as an antibiotic drug [4], Figure 1.

Apart from benzoxazole containing natural products, many series of benzoxazole derivatives have been synthesized. Compound **1** acts as an anti *P. vulgaris* at MIC = 6.3 $mg.mL^{-1}$ [5]; compound **2** exhibits antimicrobial activity as standards: penicillin, streptomycin and amphotericin [6]; compound **3** and its family show anti-HIV at about 1.6 $mmol.L^{-1}$ [7], Figure 2. The heterocyclic class of benzoxazole scaffold could bind to the host protein energetically. Kelly *et al.* reported three reasons. First, oxygen and nitrogen atoms of the benzoxazole ring can form hydrogen bonding as acceptors; second, both pi-pi stacking and pi-cation interactions can be possible by its aromatic planar nature; finally, because of its lipophilic character, hydrophobic moiety can interact with its host protein. X-ray crystal structure of compound **4** with homotetrameric WT-TTR (wild type- transthyretin) shows that benzoxazole ring preferred binding to LeuA17, Lys A17, AlaA108, ThrA129, Figure 2 [8].

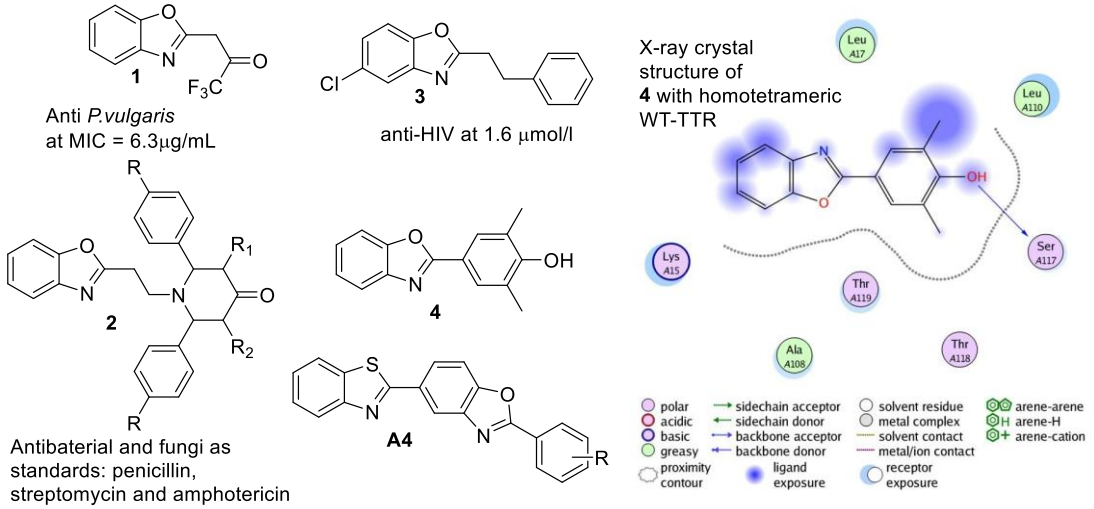


Figure 2. Some synthetic benzoxazole derivatives and their bioactivities

In order to polish our tune in our previous paper [9], we applied the possibility to carry out the synthesis of some novel derivatives containing benzoxazole ring **A4** under microwave irradiation, Figure 2.

2. Content

2.1. Experimental

2.1.1. Chemicals and equipment

4-Hydroxybenzaldehyde and other aldehydes and *o*-aminothiophenol were bought from Aladdin.com. The 1D and 2D NMRs spectra were recorded on the Bruker Avance 500 NMR spectrometer in DMSO-d6. The chemical shifts were reported in ppm and the coupling constants were in Hz. Agilent LC-MSD-Trap-SL series 1100 were used to record MS spectra. IR spectra were recorded on an IMPACK-410 NICOLET

spectrometer in KBr disks. Goldsun MWO-G2051, 1200W Microwave Power, made in China in 2017, was used to irradiate reactions.

2.1.2. Synthetic procedure

*4-hydroxy-3-nitrobenzaldehyde (**A1**), 4-(benzo[d]thiazol-2-yl)-2-nitrophenol (**A2**)*

A1 and **A2** were prepared following the procedure shown in our paper [10, 11].

*2-amino-4-(benzo[d]thiazol-2-yl) phenol (**A3**)*

$Na_2S_2O_4$ (2.1 g, 12 mmol) was added slowly into a refluxed solution of **A2** (0.54 g, 2 mmol) in ethanol (20 mL) for 30 min. The progress of the reaction was observed with the disappearance of the yellow color or TLC in eluent *n*-hexane/ethyl acetate (1:1). The mother liquid was collected. The ethanol was removed up to two third of the volume. The residue was added to cold water to form a pale yellow solid, **A3**, in 85 %. IR (ν, cm^{-1}): 3263, 3056, 1537, 1500, 1452, 1424, 1255, 1180, 1073; ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm), *J* (Hz): 8.04 (dd, *J* = 0.5; 7.5, 1H; H2); 7.37 (td, *J* = 1.5; 7.5, 1H; H3); 7.56 (t, *J* = 1.5; 7.5, 1H; H4); 7.94 (d, *J* = 8.0, 1H; H5); 7.39 (d, *J* = 7.5, 1H; H9); 6.77 (d; *J* = 8.0; 1H; H10); 7.18 (dd, *J*=2.0; 8.0, 1H; H13); 10.10 (br., 1H; OH); 4.84 (br., 2H; NH_2); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 134.0 (C1); 121.9 (C2); 124.6 (C3); 126.2 (C4); 122.0 (C5); 153.7 (C6); 168.3 (C7); 124.5 (C8); 116.4 (C9); 114.4 (C10); 147.3 (C11); 137.3 (C12); 112.3 (C13); ESI-MS: $[M+H]^+$, m/z (au)/relative intensity (%): 242.9/ 100 %; $[M+H]^-$: 240.8/ 100 %.

Synthesis of derivatives containing both benzothiazole and benzoxazole rings (***A4a-f***) [9]

General procedure: To a mixture of **A3** (0.242 g, 1.0 mmol) and an aldehyde (0.75 mmol) in a 100mL beaker was added acetic acid (1 mL) and irradiated for 10 to 30 min. The progress of the reaction was monitored with the TLC method in eluent of *n*-hexane/ethyl acetate (1:1). The reaction mixture was cooled down at rt. and iced to maximize the solid amount. The solid was filtered and washed with ethanol and recrystallized in ethanol/ water = 4/1 (v/v) to yield **A4a-f** in moderate yield.

*4-(5-(benzo[d]thiazol–2-yl)-benzo[d]oxazol–2-yl)phenol (**A4-a**)*

The synthesis was followed by the general procedure: **A3** (0.242 g, 1.0 mmol), 4-hydroxybenzaldehyde (0.1 g, 0.75 mmol), and acetic acid (1 mL) gave a gray powder of **A4-a** (0.18 g, 80%, mp. 301 ^{o}C) after recrystallization in ethanol: H_2O = 4:1. ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm, *J* (Hz): 8.1 (d, *J* = 7.5, 1H; H2); 7.4 (t, *J* = 7.5, 1H; H3); 7.5 (t, *J* = 7.5, 1H; H4); 8.09 (d, *J* = 7.5, 1H; H5); 8.13 (dd, *J* = 8.5, 1.5, 1H; H9); 7.9 (d, *J* = 8.0, 1H; H10); 8.39 (d, *J* = 1.5, 1H; H13); 8.09 (d, *J* = 8.5, 1H; H16); 7.00 (d, *J* = 8.5, 1H; H17); 7.00 (d, *J* = 8.5, 1H; H19); 8.09 (d, *J* = 8.5, 1H; H20); 10.37 (s,1H; OH); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 134.6 (C1); 122.3 (C2); 125.5 (C3); 126.7 (C4); 122.8 (C5); 153.6 (C6); 167.1 (C7); 129.8 (C8); 124.3 (C9); 111.5 (C10); 152.0 (C11); 142.7 (C12); 117.8 (C13); 164.3 (C14); 116.6 (C15); 129.6 (C16); 116.2 (C17); 161.3 (C18); 116.2 (C19); 129.6 (C20); ESI-MS: $[M+H]^+$, m/z (au)/relative intensity (%): 344.8/ 100 %; $[M+H]^-$: 342.8/ 100 %.

*4-(5-(benzo[d]thiazol–2-yl)-benzo[d]oxazol-2-yl)–2-methoxyphenol (**A4-b**)*

The synthesis was followed by the general procedure: **A3** (0.242 g, 1.0 mmol), vanillin (0.12 g; 0.75 mmol), and acetic acid (1mL) gave **A4-b** (0.18 g, 80%, mp. 181 ^{o}C) as a dark brown solid after recrystallization in ethanol: H_2O = 4:1. IR (ν, cm^{-1}): 3427, 1612, 1590, 1500, 1466, 1428; 1368; 1265; 1194; 1156; 1068; 1026; ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm), *J* (Hz): 8.16 (d, *J* = 7.5, 1H; H2); 7.47 (t, *J* = 7.5, 1H; H3); 7.56 (t, *J* = 7.5, 1H; H4); 8.13 (d, *J* = 8.5, 1H; H5); 8.09 (d, *J* = 8.0, 1H; H9); 7.92 (d, *J* = 7.5, 1H; H10); 8.40 (s, 1H; H13); 7.71 (s, 1H; H16); 7.02 (d, *J* = 8.0, 1H; H19); 7.72 (d, *J* = 8.0, 1H; H20); 3.92 (s, 3H, H21); 10.04 (s,1H; OH); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 134.5 (C1); 122.2 (C2); 125.4 (C3); 126.6 (C4); 122.7 (C5); 153.5 (C6); 167.0 (C7); 129.8 (C8); 124.3 (C9); 111.4 (C10); 151.9 (C11); 142.6 (C12); 117.7 (C13); 164.2 (C14); 116.7 (C15); 121.5 (C16); 148.0 (C17); 150.9 (C18); 116.0 (C19); 110.7 (C20); 55.7 (C21); ESI-MS: $[M+H]^+$, m/z (au)/relative intensity (%): 374.9/ 100 %; $[M+H]^-$: 372.8/ 100%.

*5-(benzo[d]thiazol–2-yl)–2-phenylbenzo [d]oxazole (**A4-c**)*

The synthesis was followed by the general procedure: **A3** (0.242 g, 1.0 mmol), benzaldehyde (0.08 g; 0.75 mmol), and acetic acid (1 mL) gave **A4-c** (0.23 gam; 87%; mp. 250 ^{o}C) as a gray solid after recrystallization in ethanol: H_2O = 4:1. ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm), *J* (Hz): 8.2 (d, *J* = 8.5, 1H; H2); 7.47 (t, *J* = 7.5, 1H; H3); 7.56 (t, *J* = 7.5, 1H; H4); 8.18 (d, *J* = 7.5, 1H; H5); 8.09 (dd, *J* = 8.0, 1H; H9); 7.99 (d, *J* = 8.0, 1H; H10); 8.47 (s, 1H; H13); 8.25 (d, *J* = 7.5, 1H; H16); 7.65 (t, *J* = 7.5, 1H; H17); 7.66 (d, *J* =8.5; 1H, H18); 7,65 (t, *J* = 7.5, 1H; H19); 8.25 (d, *J* = 7.5, 1H; H20); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 134.6 (C1); 122.2 (C2); 125.4 (C3); 126.6 (C4); 122.8 (C5); 153.5 (C6); 166.8 (C7); 132.3 (C8); 125.9 (C9); 111.5 (C10); 152.0 (C11); 142.2 (C12); 117.8 (C13); 163.7 (C14); 125.9; (C15); 127.4 (C16); 129.3 (C17); 125.0 (C18); 130.0 (C19); 129.3 (C20); ESI-MS: $[M+H]^+$, m/z (au)/relative intensity (%): 328.9/ 100 %.

*5-(benzo[d]thiazol–2-yl)-2-(4-methylphenyl)benzo[d]oxazole (**A4-d**).*

The synthesis was followed by the general procedure: **A3** (0.242 g, 1.0 mmol), 4-methylbenzandehyde (0.096 g, 0.8 mmol), and acetic acid (0.8 mL) gave **A4-d** (0.246 g; 89% mp. 257 ^{o}C) as a milky white solid after recrystallization in ethanol: H_2O = 4:1. ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm), *J* (Hz): 8.17 (d, *J* = 1.5; 7.0; 1H; H2); 7.49 (t, *J* = 8.0; 1H; H3); 7.58 (t, *J* = 1.0, 8.0, 1H; H4); 8.17 (td, *J* = 1.5, 7.0, 1H; H5); 8.09 (dd, *J* = 8.0, 1H; H9); 7.99 (d, *J* = 8.5, 1H; H10); 8.44 (d, *J* = 1.0, 1H; H13); 8.13 (d, *J* = 8.0, 1H; H16); 7.45 (d, *J* = 8.0, 1H; H17); 7.45 (d, *J* = 8.0, 1H; H19); 8.13 (d, *J* = 8.0, 1H; H20); 2.43 (s, 3H, H21); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 134.5 (C1); 122.2 (C2); 124.8 (C3); 126.6 (C4); 122.8 (C5); 153.5 (C6); 166.9 (C7); 130.0 (C8); 125.5 (C9); 111.5 (C10); 152.0 (C11); 142.6 (C12); 118.2 (C13); 163.9 (C14); 123.1 (C15); 129.9 (C16); 127.4 (C17); 142.3 (C18); 127.4 (C19); 129.9 (C20); 21.1 (C21); ESI-MS: $[M+H]^+$, m/z (au)/relative intensity (%): 342.6/ 100 %.

*5-(benzo[d]thiazol–2-yl)-2-(4-methoxy phenyl)benzo[d]oxazole (**A4-e**).*

The synthesis was followed by the general procedure: **A3** (0.242 g, 1.0 mmol), 4-methoxybenzandehyde (0.109 g, 0.8 mmol), and acetic acid (1 mL) gave **A4-e** (0.258 g, 87%; mp. 265 ^{o}C) as a dark brown solid after recrystallization in ethanol: H_2O = 4:1. ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm), *J* (Hz): 8.15 (d, *J* = 8.0; 1H; H2); 7.45 (t, *J* = 7.0; 1H; H3); 7.54 (t, *J* = 7.0, 1H; H4); 8.15 (d, *J* = 8.0, 1H; H5); 8.07 (d, *J* = 7.5, 1H; H9); 7.90 (d, *J* = 8.0, 1H; H10); 8.13 (s, 1H; H13); 8.13 (d, *J* = 9.0, 1H; H16); 7.15 (d, *J* = 8.0, 1H; H17); 7.15 (d, *J* = 8.0, 1H; H19); 8.13 (d, *J* = 9.0, 1H; H20); 3.86 (s, 3H, H21); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 134.6 (C1); 122.2 (C2); 125.4 (C3); 126.6 (C4); 122.8 (C5); 153.5 (C6); 166.9 (C7); 129.9 (C8); 124.5 (C9); 111.5 (C10); 151.9 (C11); 142.5 (C12); 118.2 (C13); 163.8 (C14); 117.9 (C15); 129.4 (C16); 114.8 (C17); 162.5 (C18); 114.8 (C19); 129.4 (C20); 55.5 (C21); ESI-MS: $[M+H]^+$, m/z (au)/relative intensity (%): 359.0/ 100 %.

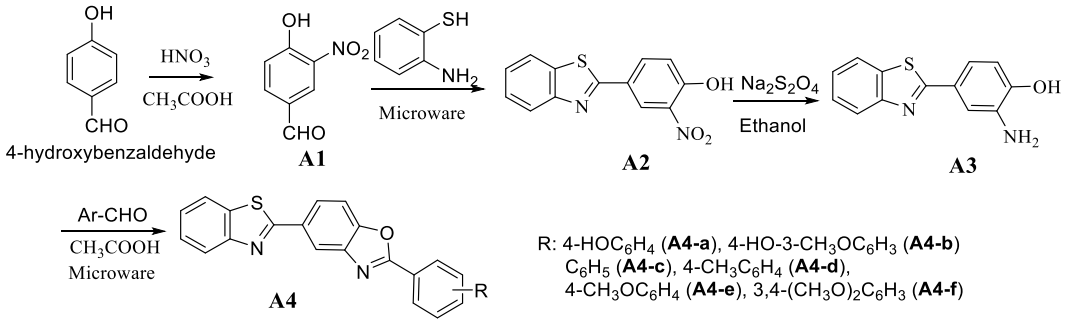
*5-(benzo[d]thiazol-2-yl)-2-(3,4-dimethoxyphenyl)benzo[d]oxazole (**A4-f**)*

The synthesis was followed by the general procedure: **A3** (0.242 g, 1.0 mmol), 3,4-dimethoxybenzaldehyde (0.13 g, 0.75 mmol), and acetic acid (1mL) gave **A4-f** (0.262 g; 85%; mp. 276 ^{o}C) as a gray solid after recrystallization in ethanol : DMF = 5 :1. IR (ν, cm^{-1}): 3069, 2933, 2835, 1599, 1558, 1512, 1462, 1434, 1281, 1261, 1230, 1138, 1173, 1024; ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm), *J* (Hz): 8.16 (d, *J* = 7.5, 1H, H2); 7.47 (t, *J* = 7.5, 1H, H3); 7.56 (t, *J* = 7.5, 1H, H4); 8.15 (d, *J* = 8.0, 1H, H5); 8.15 (d, *J* = 8.0, 1H, H9); 7.94 (d, *J* = 7.5, 1H, H10); 8.4 (s, 1H, H13); 7.70 (s, 1H, H16); 7.20 (d, *J* = 8.0, 1H, H19); 7.84 (d, *J* = 8.0, 1H, H20); 3.87 (s, 3H, H21); 3.91 (s, 3H, H22); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 134.8 (C1); 122.2 (C2); 125.4 (C3); 126.6 (C4); 122.8 (C5); 153.5 (C6); 166.9 (C7); 129.9 (C8); 125.4 (C9); 111.6 (C10); 152.0 (C11); 142.5 (C12); 117.8 (C13); 163.9 (C14); 118.1 (C15); 109.0 (C16); 149.0 (C17); 152.3 (C18); 111.9 (C19); 121.2 (C20); 55.6 (C21); 55.7(C22).

2.2. Results and discussion

2.2.1. Synthesis

The synthesis of benzoxazole derivatives was expressed in Scheme 1. Nitration of 4-hydroxybenzaldehyde and benzoxazole cyclization were followed as described in our previous papers [10, 11]. Reduction of **A2** was finished by Fe/HCl as reported in our paper [9], however, the product was the salt of **A3** with HCl acid was not converted to **A4** when it was treated with aldehydes in presence of acetic acid under irradiation [9], and the black mixture with many spots on TLC was formed instead of. It seems that the Fe^{2+} ion might incorporate with *o*-aminophenol forming a complex, Figure 3. Many attempts to produce crystals of Fe[**A3**]$_2$ were unsuccessful. In situ, the iron (II) cation was oxidized to the iron (III) cation by oxygen in the air that oxidized **A3** to make a type of aniline black to give rise to a decrease the yield of benzoxazole cyclization. To overcome this issue, the conversion of the nitro group to the amino group was modified by using sodium dithionite ($Na_2S_2O_4$) in ethanol [12]. This application was convenient to make **A3** as a free *o*-amino phenol derivative due to its simple work up and good visualization as its color changes.



Scheme 1. Synthesis of benzoxazole derivatives

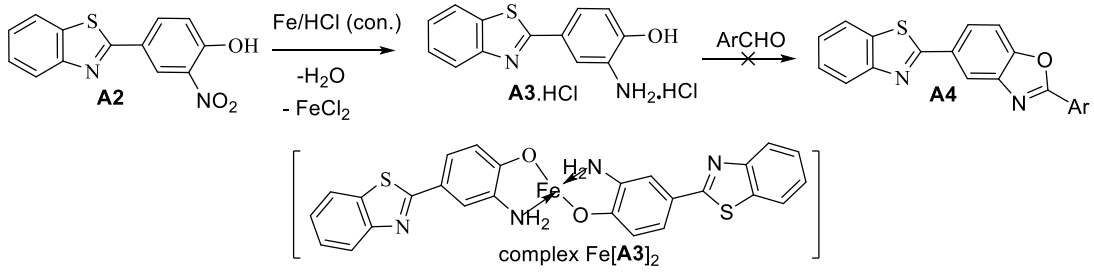


Figure 3. Proposal of the complex Fe[A3]$_2$

2.2.2. Structural determination

Novel benzoxazole derivatives **A4-a,b,c,d,e,f** were determined with IR, HSQC, HMBC, and MS spectral analysis. The infrared absorption frequencies of the N-H bond disappeared on the IR spectrum of **A4-f** compared with the stretching vibration of N-H at 3263 cm^{-1} which confirms that benzoxazole cyclization was set. Moreover, ESI-MS also gives further information to highly agree with the molecular weight of all derivatives. For example, MS of **A4-a** indicates pseudo molecular weight $[M+H]^+$ ion at *m/z* 344.8/ 100% that is compatible with $C_{20}H_{12}N_2O_2S$ and molecular weight 344 g/mol. HSQC and HMBC spectra of compound **A4-f** were performed in Figure 4. Spectral analysis of the other compounds was indicated in the experimental section.

Compound **A4-f** owns three parts: benzothiazole; benzoxazole; aryl moieties. In the first part, benzothiazole was far from the reactive centers: hydroxyl group and amino group, therefore, protons and carbons were ascribed based on our previous papers [9,10] and then were screened again on its spectra. Consequently, H2, H3, H4, H5 were identified at δ 8.16 (d, J = 7.5, 1H), 7.47 (t, J = 7.5, 1H), 7.56 (t, J = 7.5, 1H), 8.15 (d, J = 8.0, 1H) ppm, respectively. Similarly, C1, C2, C3, C4, C5, C6 and C7 were also assigned at δ 134.8, 122.2, 125.4, 126.6, 122.8, 153.5, and 166.9 ppm, respectively. The chemical shift of C7 at δ 166.9 ppm allowed us to confirm H13 as a singlet at δ 8.4 ppm (s, 1H) of the middle moiety of compound **A4-f**. In addition, HSQC's correlation peak is used to indicate C13 at δ 117.8 ppm. C9 at δ 125.4; C11 at δ 152.0 ppm and δ 8.15 (d, J = 8.0, 1H) were agreed with two correlation peaks on HMBC and HSQC spectra. In the veratraldehyde moiety, two sharp methyl singlets at δ 3.87 (s, 3H, H21), 3.91 (s, 3H,

H22) ppm are possibly assignable as the methyl protons of the two OCH_3 group which has two correlation peaks on HSQC with δ 55.6; 55.7 ppm respectively. C18 at δ 152.3 and C17 at δ 149.0 were got through correlation peaks that lead to assign H16 at δ 7.70 (s, 1H); H20 at δ 7.84 (d, J = 8.0, 1H) and H19 at δ 7.20 (d, J = 8.0, 1H). These resonances let us assign C20 at δ121.2, C14 at δ 163.9; C15 at δ 118.1; C16 at δ 109.0 and C19 at δ 111.9ppm. The last doublet at δ 7.94 (d, J = 7.5, 1H) was for H10 which was split by H9; then C10 was also indicated at δ 111.6 ppm. Two quaternary carbons C8 and C12 did not correlate with any protons, nevertheless, C12 should be in the weaker field than C8 due to bonding with the N atom. Therefore, C12 was assignable at δ 142.5 ppm and C8 at δ 129.9 ppm, Figure 4.

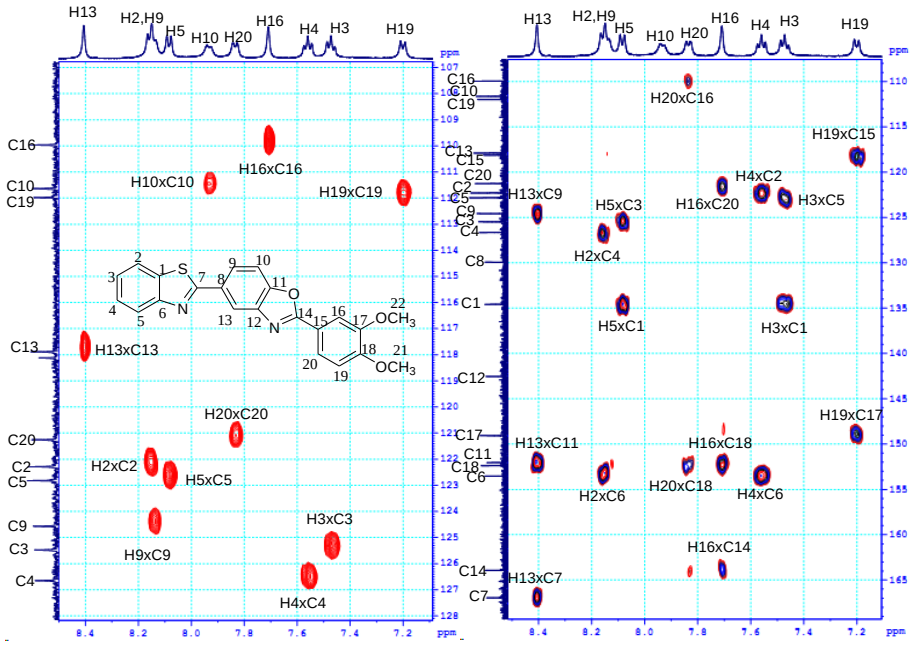


Figure 4. Partial HSQC and HMBC spectra of A4-f

3. Conclusions

Six novel benzoxazole derivatives were synthesized in moderate yield from 4-hydroxybenzaldehyde in four steps in about 28 % overall yield. Free *o*-aminophenol derivative **A3** was synthesized which helped benzoxazole cyclization be more convenient. The spectral analysis of IR, 1D, 2D NMRs, and MS confirmed the structures of expected compounds.

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