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New Imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole Derivatives: Synthesis, Antimicrobial and Antifungal Activity

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Abstract

A series of new derivatives of imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole were synthesised, which they are substituted at position 2. Then, the new prepared imidazo thiazole derivatives were reacted with N,N-dimethyl formamide (DMF) and $POCl_3$ to obtain new aldehyde derivatives at position 3. The new aldehyde derivatives underwent condensation reaction with the hydrazine afforded new hydrazone derivatives. The new compounds were characterized by spectra [IR, ^{1}HNMR, ^{13}CNMR, 2D NMR (hsqc spectra)]. The synthesised compounds were examined the antimicrobial and antifungal activities, their antimicrobial activities against *Escherichia coli*, *Streptococcus faecalis*, *Aeromonas hydrophila* and *Staphylococcus aureus were examined*. Most of these compounds demonstrated antimicrobial activity. Interestingly, most of hydrazone derivatives showed antifungal activity towards spore germe and hyphae growth.

Keywords: Imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole, hydrazones, antimicrobial, antifungal.

تحضير مشتقات جديدة من [2,1-b] نفثا [2,1-d] [1,3] ثايزول، اختبار الفعالية الميكروبية والمضادات الفطرية

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الخلاصة

تم تحضير سلسلة من مشتقات جديدة من الاميدازونفثا [2,1-b] [2,1-d] [1,3] ثايزول المعوضة في الموقع 2 وبعدها تم معاملة المشتقات الجديدة المحضرة مع DMF و $POCl_3$ للحصول على الديهايد في الموقع 3 . تم مفاعلة مشتقات الالديهايدات الجديدة مع الهيدرازين للحصول على مشتقات الهيدرازون. تم تشخيص المركبات المحضرة بواسطة اطياف [IR, ^{1}H-NMR, ^{13}C-NMR, 2D NMR (hsqc)].تم اختبار الفعالية الميكروبية, والفطريات للمركبات المحضرة، اختبرت الفعالية المايكروبية لها مع *Escherichia coli*, *Streptococcus faecalis, Aeromonas hydrophila* and *Staphylococcus aureus* . وقد اظهرت اغلب المركبات المحضرة فعالية مضادة للبكتريا . وبشكل ملفت اظهرت اغلب مشتقات الهايدروزون فعالية مضادة للفطريات ضد الابواغ الجرثومية والنمو الخيطي.

1. Introduction:

Recently much interest has been focused on the synthetic routes of Imidazo [2,1-b]thiazole derivatives and their biological activity. Since the imidazo[2,1-b]thiazole derivatives have been reported in the literature as antibacterial [1], antifungal [2], antihelmintic [3,4] and antitumour agents.[5-9].

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The formation of an imidazo[2,1-b]thiazole from a preformed thiazole usually is accomplished by treatment of a 2-aminothiazole derivative with any α-haloketone. Such reactions give 2-alkyl and 2-aryl derivatives [10]. The imidazo[2,1-b]thiazole system is a main precursor of the well known antithelminitic and immunomodulatory agent levamisole, which is 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole. Andreani [11] and co-workers studied and tested a several of imidazo[2,1-b]thiazole guanyl hydrazones, which were active against various cancer cell lines. In view of these observations, this contribution was planned the synthesis of novel imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole hydrazones to evaluate their primary cytotoxicity and to explore the antifungal activity of them.

2. Experimental:

^{1}H-NMR spectra were measured on a Bruker Avance 500 MHz spectrometer or a Bruker Avance DPX 400 NMR spectrometer at Cardiff University. ^{13}C-NMR spectra were measured on a Bruker Avance 500 MHz spectrometer and are reported as chemical shift downfield from tetramethylsilane. IR spectra were recorded on Perkin ELMER 1600 series FTIR spectrometer, and samples were prepared as thin films of neat liquid on NaCl discs for oils and as KBr disks for solids. The purity of purified compounds was judged to be > 95% by TLC and/or GC analyses and NMR spectroscopic analyses. TLC analyses were performed on plates pre-coated with 250 µM layers of either silica gel 60 F254. TLC visualisations were performed with 5% phosphomolybdic acid, CAM (ceric-ammonium-molybdate), $KMnO_4$, I_2 vapor, or UV light. Melting points were recorded with a melting apparatus and are quoted uncorrected.

* Most of this work and characterisation have been done at Cardiff University-Wales-UK

2.1 General procedure for the synthesis of 9-(4-phenyl, 4-bromophenyl, 4-chlorophenyl)imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole 2, 3, 4:

2-Amino naphtha thiazole, 0.005 mole was heated under reflux with mixture of (0.05 g, 0.005 mole) of the appropriate aromatic α-halo ketones in 30 ml ethanol (95%) and sodium bicarbonate (0.01) mole for 14-22 h. After that, the mixture was filtered of and added 5% of sodium hydroxide to filtrate until reach to pH 10. The precipitate obtained was purified by washing with hot ethanol; all physical properties are listed in Table-1.

2.2 General procedure for the synthesis of aldehydes 5, 6, 7:

$POCl_3$ (0.05 mole) was added to a cooled mixture of DMF (0.05 g, 0.05 mole) in $CHCl_3$ (75 ml). Then,9-(4-phenyl, 4-bromophenyl, 4-chlorophenyl)imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole **2, 3, 4** (0.05 mole) were added cautiously to mixture of DMF-$POCl_3$. After addition was completed, the reaction mixture was heated under reflux for 2-3 h. The solvent was removed by evaporation in vacuo and the residue was poured into ice in H_2O. The resulting solid was filtered off, washed well with H_2O, and purified; all physical properties are listed in Table-1.

2.3 General procedure for the synthesis of hydrazones 8, 9, 10:

Aldehydes **5**, **6**, **7** (3 mL, 0.1 mole) were added to a refluxing solution of 95% NH_2NH_2 (0.15 mole) in ethanol (70 ml). The mixture was heated for 3 h then cooled until a solid separated. This solid was filtered off and dried, all physical properties in Table-1.

3. Results and discussion:

The preparation of substituted imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole **2**, **3**, **4** (Figure-1) was achieved by the condensation of 2-amino naphthothiazole **1** with the following α-halo ketons (phenacyl bromide, 4-bromophenacyl bromide and 4-chlorophenacyl bromide) using sodium bicarbonate as a base in aqueous alcohol. The susceptibility of this π-excessive system in imidazo thiazole to electrophilic attack permitted the preparation of a variety of 3-substituted imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole, therefore, the Vilsmeier reaction was used to give the aldehydes **5**, **6**, **7** at position 3. Those aldehydes are readily formed hydrazone derivatives by condensation reaction of aldehydes **5**, **6**, **7** with hydrazine.

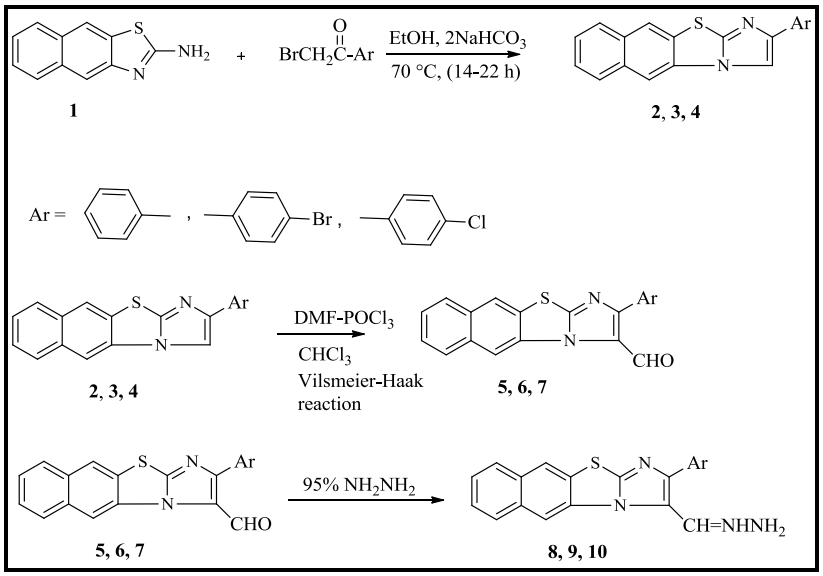
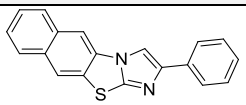
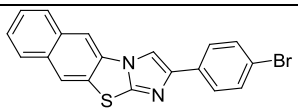
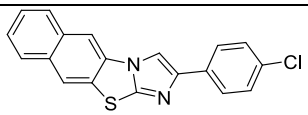
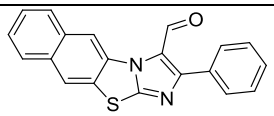
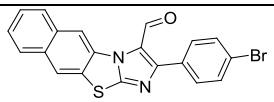
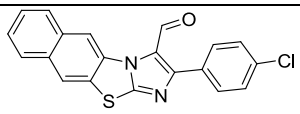
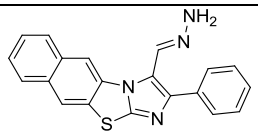
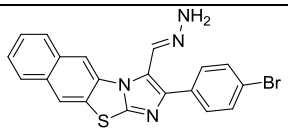
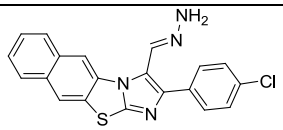


Figure 1- General synthesis of imidazo[2,1-b]naphtha[2,1-d][1,3]thiazoles **2**, **3**, **4, 5, 6,7, 8, 9** and **10**

The general mechanism of ring closure reaction was involved nucleophilic displacement of halogen of α-haloketone from nitrogen of imidazo thiazole ring to generate quaternary salt as intermediate (Figure-2), following the ring closure to give substituted imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole **2**, **3**, **4** with using sodium bicarbonate to get red off the two molecules of HBr and H_2O as shown in Figure-2.

Table 1- Physical properties of compounds 2, 3, 4, 5, 6, 7, 8, 9, 10

Comp. No.	Structure	Yield%	Mp, °C	Recrystn. solvent
2	 2-phenylImidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	76	192-193	Ethanol
3	 2-(4-bromophenyl)Imidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	69	212-213	Ethanol
4	 2-(4-chlorophenyl)Imidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	78	185-187	Ethanol
5	 2-phenyl-3-formylImidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	65	210-211	MeOH
6	 2-(4-bromophenyl)-3-formylImidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	77	180-182	MeOH
7	 2-(4-chlorophenyl)-3-formylImidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	62	119-122	MeOH
8	 2-phenyl-3-hydrazonomethylImidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	75	155-157	*i*-PrOH
9	 2-(4-bromophenyl)-3-hydrazonomethylImidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	65	177-178	*i*-PrOH
10	 2-(4-chlorophenyl)-3-hydrazonomethylImidazo[2,1-b]naphtho[3,2-d][1,3]thiazole	55	165-167	*i*-PrOH

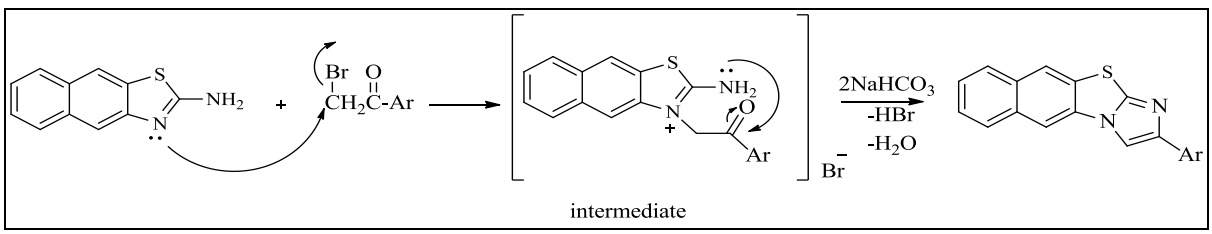


Figure 2-General mechanism of formation of imidazo[2,1-b]naphtha[2,1-d][1,3]thiazoles **2**, **3**, **4**

The Vilsmeier reaction is the chemical reaction of a substituted amide (DMF) with phosphorus oxychloride ($POCl_3$) and an electron-rich arene like imidazo thiazole ring. The reaction of the amide with phosphororus oxycholride produces an electrophilic iminium cation (Figure-3). The subsequent electrophilic aromatic substitution gives an iminium ion intermediate, which is hydrolysed to yield desired aryl aldehyde.

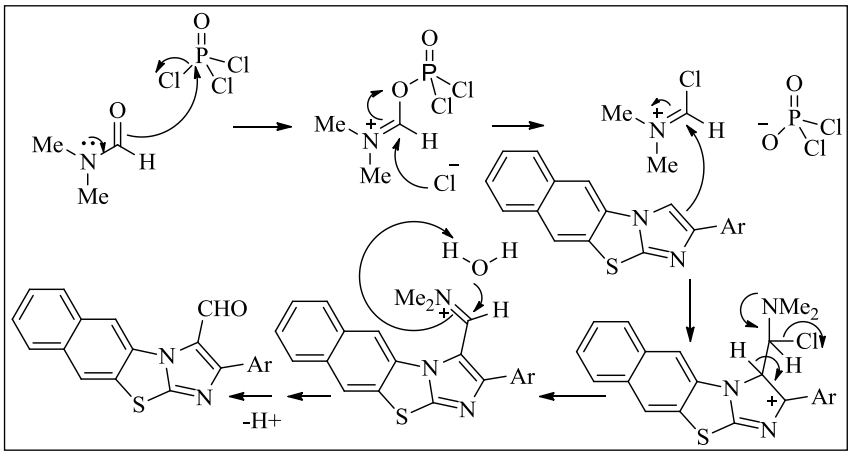
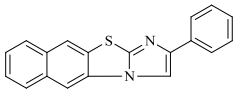
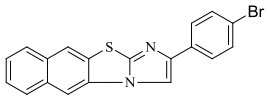
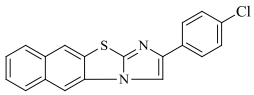
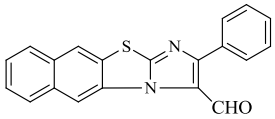
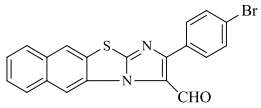
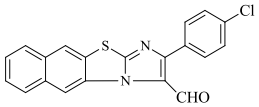
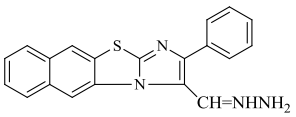
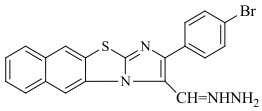
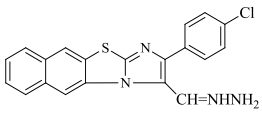


Figure 3-Mechanism of Vilsmeier reaction of substituted of imidazo[2,1-b]naphtha[2,1-d][1,3]thiazoles.

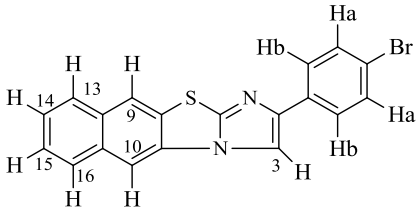
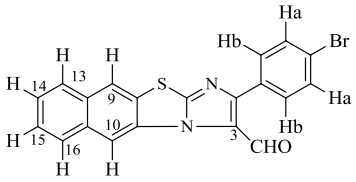
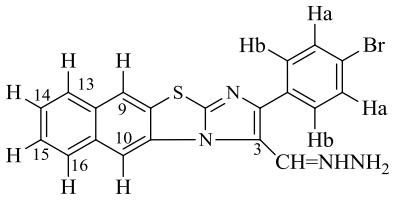
Structures of all prepared compounds in this research were confirmed using FT-IR, in the IR spectra, the asymmetrical NH stretch and symmetrical NH stretch, CO and CN bands were observed in the 3400-3330 and 3330-3250 cm^{-1}, 1688-1660 cm^{-1} and 1618-1598 cm^{-1} region, respectively. These bands and other FT-IR absorption bands are listed in Table-2. ^{1}H-NMR spectra of compound (**3**, **6**, **9**) showed characteristics signals belongs to these compounds as shown in Table-3. All signals in proton nmr spectra of compound **3** shifted to upfield in aromatic region (Figure 4), due to desheilding effect of aromaticity system of imidazo thiazole system. While ^{13}C-NMR spectrum of compound **3** displayed characteristic signals at 107, 127, 130, 135, 145 ppm belong to C̲H imidazol ring at position 3, C=C aromatic, C̲-Br, C̲=N, C̲=S (Figure-5). 2D-NMR, HSQC (Heteronuclear single-quantum correlation) spectra (Figure-6) showed correlation peak between the signal at 7.6 ppm (ArH^{a}) in ^{1}HNMR as first dimension and the C-Br at 130 ppm in ^{13}CNMR as a second dimension.

Table 2-FT-IR data of prepared compounds 2, 3, 4, 5, 6, 7, 8, 9, 10 cm^{-1}

Comp. No.	Structure	ν C-H aromatic	ν C=C aromatic	ν C-N	ν C=N	ν C-S	δ C-H aromatic out of plane	Other bands
2		3100	1490 1450	1070 1030	1630	760	755	-
3		3070	1470 1400	1060 1020	1620	763	830	C-Br 1037
4		3080	1590 1500	1150 1020	1630	760	840	C-Cl 1030
5		3070	1470 1400	1060 1050	1600	770	850	1690 ν C=O aldehyde
6		3100	1450 1400	1050 1040	1618	720	800	1695 ν C=O aldehyde
7		3080	1490 1400	1120 1060	1620	780	840	1690 ν C=O aldehyde
8		3100	1450 1400	1150 1020	1630	770	820	ν NH asym. 3400- 3300 sym. 3330- 3250
9		3100	1470 1400	1150 1060	1618	760	830	ν NH asym. 3400- 3300 sym. 3330- 3250
10		3080	1490 1400	1120 1070	1630	750	820	ν NH asym. 3400- 3300 sym. 3330- 3250

The NMR spectra of compound **3** showed characteristic signal at 7.1 ppm owing to proton on C-3. This signal was disappeared in nmr spectra of compounds **6** and **9**, due to occupy the position 3 with aldehyde and hydrazone groups (Figure-7 and 8). Therefore, these results confirmed the structure of compound **3**. New signals appeared in nmr spectra of compounds **6** and **9** at δ 9.9 ppm and 9.1 ppm owing to aldehyde proton C<u>H</u>O and NH proton in hydrazone group CH=N<u>H</u> respectively, as well as abroad signal appeared at δ 1.3 ppm belong to protons of NH_2 group (Figure-7) and (Figure-8).

Table 3-The ^{1}H-NMR chemical shifts of some prepared imidazothiazoles derivatives

Comp. No.	Structure	Chemical shifts in ppm	Fig. No.
3		δ 7.1 (s, H^{3}, CH) δ 7.2 (s, H^{9}, HAr) δ 7.3 (s, H^{10}, HAr). δ 7.4 (m, H^{14}, H^{15}, HAr) δ 7.5 (m, H^{b}, H^{b}, HAr) δ 7.6 (m, H^{a}, H^{a}, HAr) δ 7.8 (d, H^{13}, H^{16}, HAr)	**2**
6		δ 7.2 (s, H^{9}, HAr) δ 7.3 (s, H^{10}, HAr). δ 7.4 (m, H^{14}, H^{15}, HAr) δ 7.5 (m, H^{b}, H^{b}, HAr) δ 7.6 (m, H^{a}, H^{a}, HAr) δ 7.8 (d, H^{13}, H^{16}, HAr) δ 9.9 (s, H, CHO)	**5**
9		δ 1.3 (s abroad, NH_2) δ 7.2 (s, H^{9}, HAr) δ 7.3 (s, H^{10}, HAr). δ 7.4 (m, H^{14}, H^{15}, HAr) δ 7.5 (m, H^{b}, H^{b}, HAr) δ 7.6 (m, H^{a}, H^{a}, HAr) δ 7.8 (d, H^{13}, H^{16}, HAr) δ 9.0 (s, H, CH=N<u>H</u>)	**6**

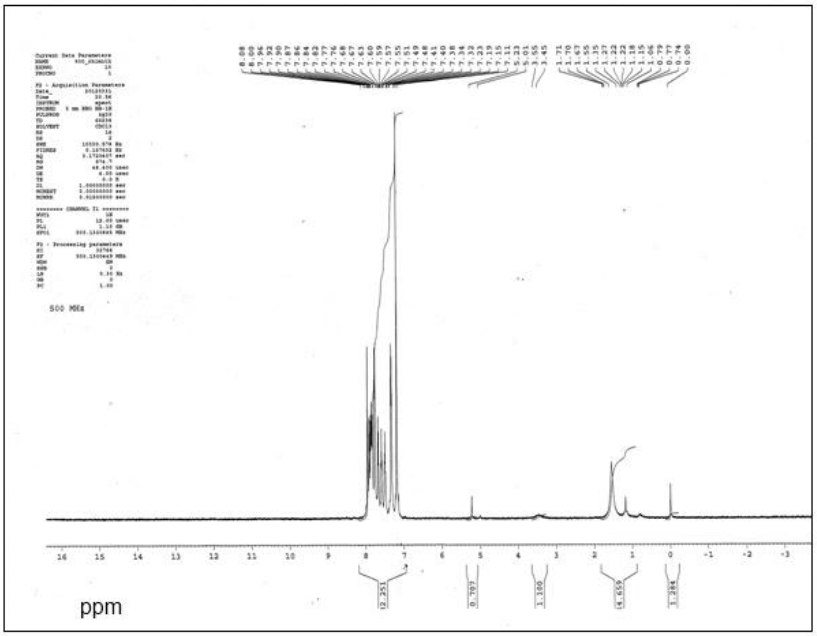


Figure 4- ^{1}HNMR spectrum of compound **3**

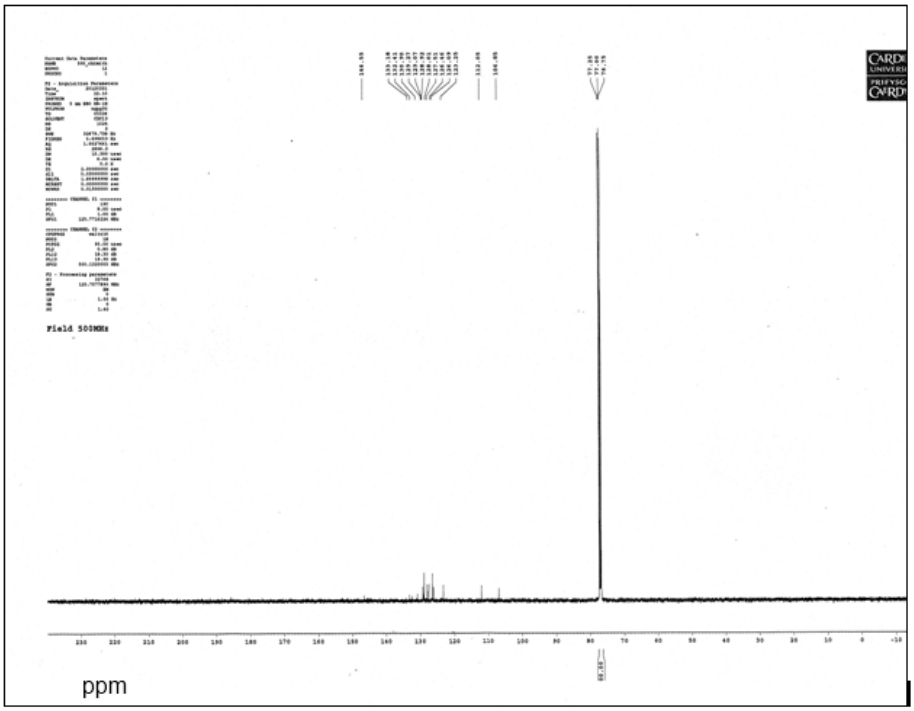


Figure 5- ^{13}CNMR spectrum of compound **3**

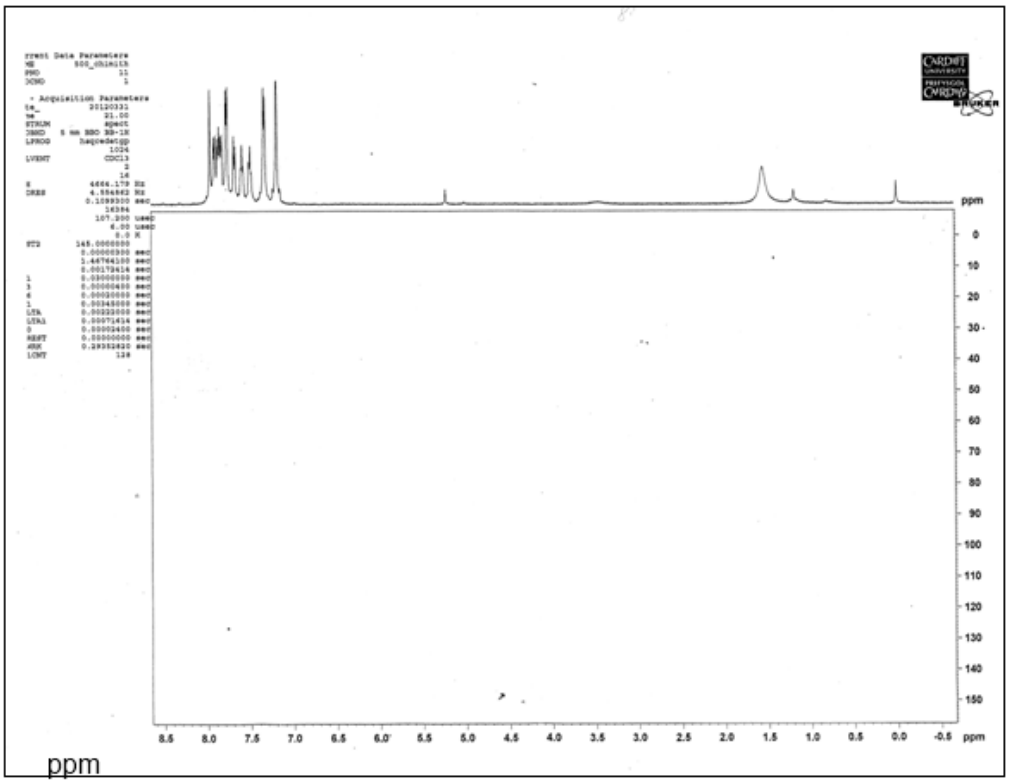


Figure 6- HSQC nmr (2D) of compound **3**

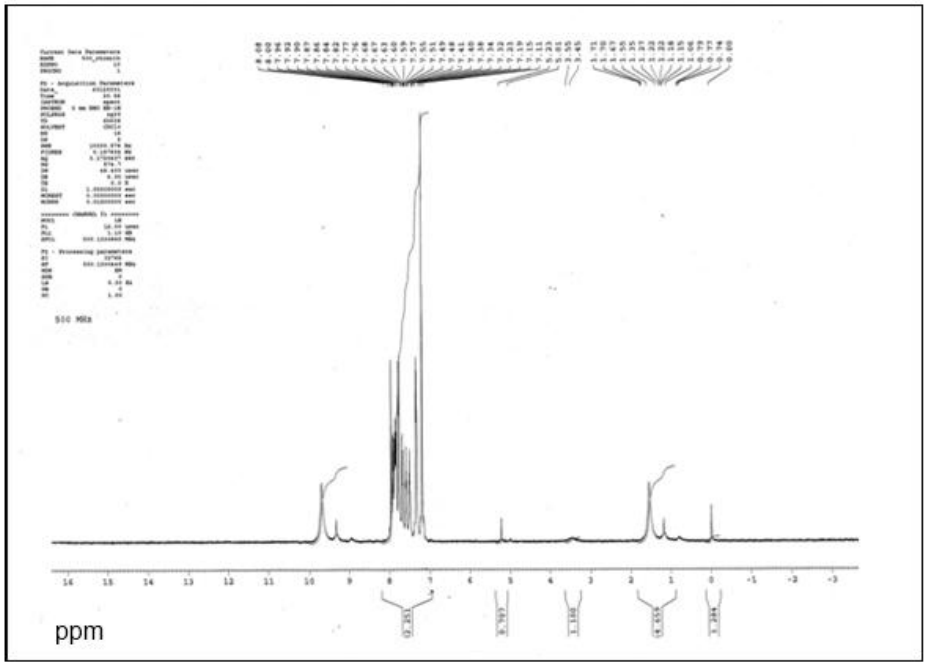


Figure 7- ^{1}HNMR spectrum of compound **6**

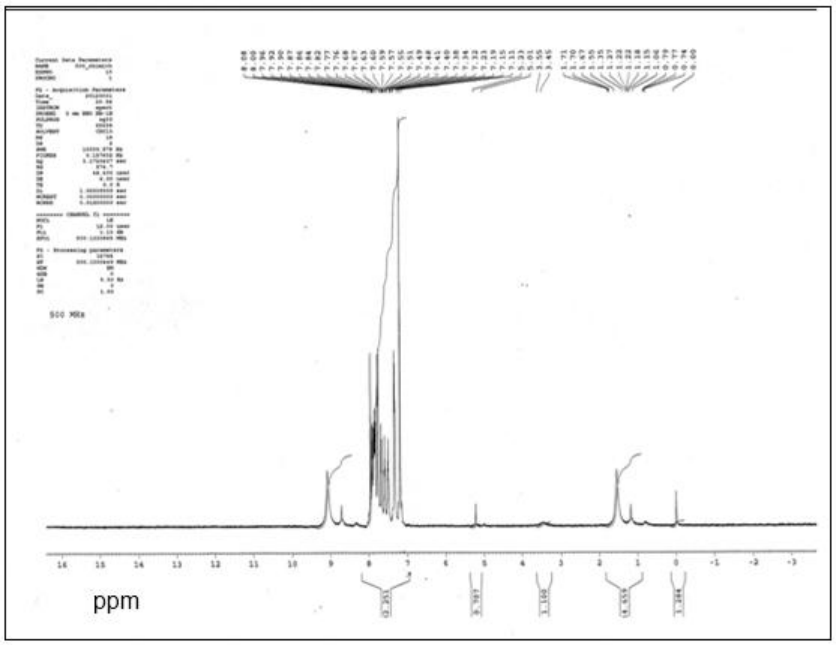


Figure 8- ^{1}HNMR spectrum of compound **9**

1. Antimicrobial activity:

Antimicrobial activities of compounds **5**, **6,** **7**, **8** , **9**, **10** were tested using microbroth dilution** method [12,13]. Tested microorganism strains were: *Escherichia coli*, *Streptococcus faecalis, Aeromonas hydrophila* and *Staphylococcus aureus*. Chlorophenicol and flucanazol were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs are given in Table 4. Microdilution broth susceptibility assay was used for the antibacterial evaluation of the compounds. [12] Chloramphenicol was used as standard antibacterial agent. Most of these compounds demonstrated modest antibacterial activity towards *Escherichia coli*, *Streptococcus faecalis*, *Aeromonas hydrophila* and *Staphylococcus aureus*.

Table 4 - MIC*** values (µg/mL) of compounds 5-10

Comp. No.	*Escherichia coli*	*Streptococcus faecalis*	*Aeromonas hydrophila*	*Staphylococcus aureus.*
5	250	15.6	62.5	31.2
6	250	125	125	62.5
7	125	125	62.5	250
8	125	125	125	62.5
9	250	250	125	65.5
10	250	250	250	250
Chloramphenicol (standard antibacterial)	-	-	-	250

Broth microdilution:** is a method used to test the susceptibility of bacteria to antibiotic.
MIC*:** In microbiology, minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial that will inhibit the visible growth of microorganism after overnight incubation.

4. Antifungal activity of compounds 2-10:

Since the imidazo[2,1-b]thiazole derivatives have been reported in the literature as antifungal [2,14] activity, imidazo[2,1-b]thiazole derivatives were examined to inhibit fungal spore germination and hyphal growth in this contribution. Aliquots of solutions of eight purified compounds **3-10** along with compound **2** were arrayed on silica TLC plates (Figure 9) and either visualized with a vanillin-H_2SO_4 developing reagent (left panel) or subjected to a fungal overlay bioassay (right). Antifungal activity was evident as white zones reflecting an inhibition of spore germination and hyphal growth. Somewhat surprising, only compound **2** and the two 3-hydrazone 9-(4-bromophenyl, 4-chlorophenyl)imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole (**8**, **9)** exhibited significant anti-fungal activity while no such activity was observed with either of the aldehydes and other derivatives of imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole (**5-7)** and **3**,**4.** The minimum inhibitor concentration (MIC) observed for compound **2** was 3 ng/spt, 10-fold below that required for compounds **8** and **9** (30 ng/ spot), indicating the importance of hydrazone function at position 3 for full antifungal activity. However, the lack of antifungal activity with compounds **5-7** suggests that aldehyde at position 3 is not sufficient for activity.

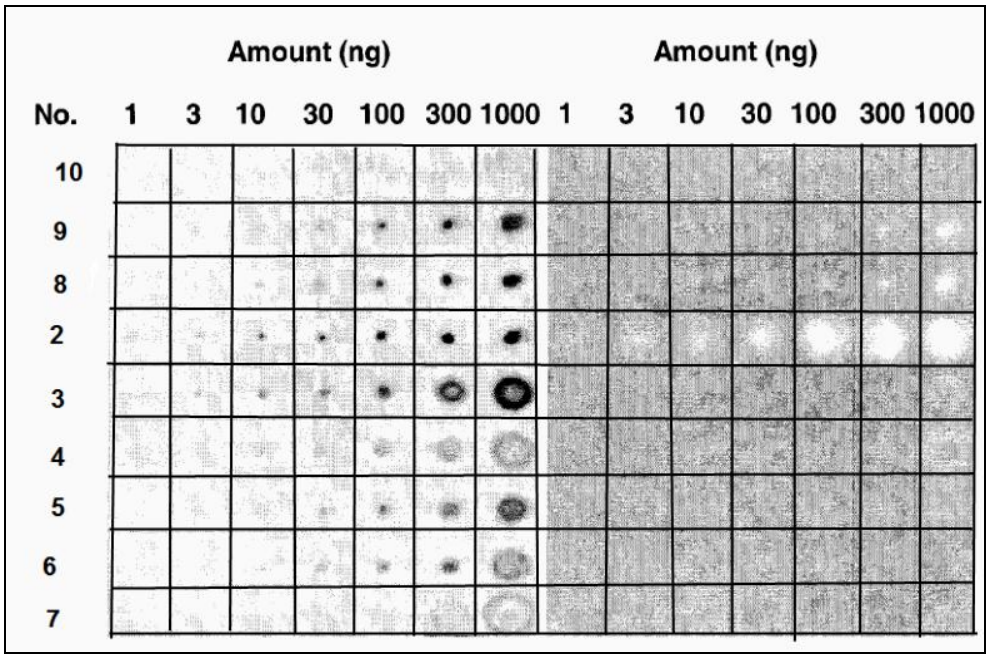


Figure 9- Antifungal activity assay of compounds **2-10**

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