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Preparation of novel imidazo[1,2-*a*]pyrimidine derived schiff bases at conventional and microwave heating conditions

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Abstract

In this study, novel imidazo[1,2-a]pyrimidine derived schiff bases were synthesized via imine formation reaction and characterized with various spectral analysis such as FT-IR, ^{1}H NMR, ^{13}C NMR and MS. In addition to conventional heating reactions, microwave-assisted synthesis was applied to the C=N bond formation step. The reactions were carried out at reflux temperature in toluene and magnesium sulfate as drying agent. While final products were obtained at 10-36 h reaction times with moderate to good yields at conventional heating conditions, synthesized at 45-120 min reaction times with good yields at microwave heating conditions. Results showed that microwave-assisted synthesis which is a well-known green process for the synthesizing organic molecules provides to obtain shorter reaction times and higher yields in our study.

Keywords: *Schiff base, imidazo[1,2-a]pyrimidine, microwave synthesis, conventional heating.*

Geleneksel ve mikrodalga ısıtma koşullarında yeni imidazo[1,2-*a*]pirimidin türevi schiff bazlarının hazırlanması

Öz

Bu çalışmada yeni imidazo[1,2-a]pirimidin türevli schiff bazları, imin oluşum reaksiyonu ile sentezlenmiş ve FT-IR, ^{1}H NMR, ^{13}C NMR, MS gibi çeşitli spektral analizler ile yapıları aydınlatılmıştır. Geleneksel ısıtma ile gerçekleştirilen reaksiyonlara ek olarak C=N oluşum basamağına mikrodalga-destekli sentez de uygulanmıştır. Reaksiyonlar, magnezyum sülfatın kurutucu olarak kullanıldığı, toluen

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içerisinde kaynama sıcaklığı koşullarında yürütülmüştür. Son ürünler, geleneksel ısıtma koşullarında 10-36 sa reaksiyon sürelerinde orta-iyi verimlerle elde edilirken, mikrodalga ısıtma koşullarında 45-120 dk reaksiyon sürelerinde iyi verimlerle sentezlenmiştir. Sonuçlar göstermiştir ki, organik moleküllerin sentezinde, iyi bir yeşil proses olarak bilinen mikrodalga-destekli sentez, bizim çalışmamızda daha kısa reaksiyon süreleri ve yüksek verimler elde edilebilmesini sağlamıştır.

Anahtar kelimeler: *Schiff bazı, imidazo[1,2-a]pirimidin, mikrodalga sentez, geleneksel ısıtma.*

1. Introduction

Nitrogen containing heterocycles are significant inputs of the drug industry since commonly found in synthetic and natural drugs. Among them, the fused heterocyclic cores with pyrimidine ring have a central place due to their exclusive medicinal applications [1]. The synthesis, biological and pharmacological studies on imidazo[1,2-*a*]pyrimidines which forms the fusion of imidazole and pyrimidine moieties have speeded up in recent days because of their superior medical properties such as anticancer, cardiovascular, antibacterial, antimicrobial, antifungal, antiviral, anti-inflammatory, HIV inhibitor, local anesthetic, kinase inhibitors and their photophysical applications such as biomarkers and photochemical sensors due to their fluorophore properties [2-5]. Fasiplon, taniplon and divaplon are known as anxiolytic and anticonvulsant drugs in the market from the imidazo[1,2-*a*]pyrimidine drug family [3].

Schiff bases are obtained as a result of the condensation reaction with aldehyde/ketone and aromatic amines. Schiff bases are known as imine compounds containing C=N bond and synthesized the first time in 1869 by German chemist, Hugo Schiff. These compounds are an interesting class because of be stable, easily synthesized and their broad range applications such as biological including anticancer, antioxidant, antimicrobial, antitubercular, antifungal, analgesic, antiinflammatory and material science such as optical computer, photodetector, photostabilizer, solar filter, opto-electronic, electrode, organic battery, electrochromic device and corrosion areas [6-10].

Microwave energy has been using to synthesize various molecules by different type of reactions as an efficient eco-friendly technique since 1980s [11-14]. Microwave-assisted organic synthesis (MAOS) has many advantages over the conventional heating methods such as reduction in the reaction times, improvement in the yields, decreasement the decomposition of reactants and products, enhancement the product purities and selectivity in an environmentally friendly reaction medium [12-14]. However, there are not many examples on the microwave-assisted synthesis of imines in the literature [11, 15-17].

We report herein the conventional and green microwave-asssisted synthesis of a variety of imidazo[1,2-*a*]pyrimidine derived schiff bases. These compounds may be used for potential biological application in future drug research.

2. Material and method

2.1. General Information

All chemicals were supplied from commercial sources and used directly in reactions. Microwave synthesis experiments were conducted by using CEM SP Discover Microwave Synthesis Reactor with dynamic mode option. The melting points were determined with X-4 Melting-point Apparatus. Analytical thin-layer chromatography was performed on precoated Kieselgel 60GF254 plates. The spots were visualized by UV light (254 nm) and $KMnO_4$ stain. Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Perkin Elmer Spectrum 100 FTIR spectrophotometer was used for Infrared spectra by applying ATR techniques. ^{1}H and ^{13}C NMR spectras were obtained by Jeol 400 MHz NMR spectrometer using TMS as internal standard and DMSO-d6 as solvent. The molecular weights of products were determined at Shimadzu LC-MS/MS 8040 Liquid Chromatograph Mass Spectrometer using an ESI source.

2.2. Synthesis and Characterization of S1-S5

General Procedure for Conventional Heating Reactions

The mixture of imidazo[1,2-*a*]pyrimidine-2-carbaldehyde (1.0 equiv.) and aromatic amines (aniline, 4-chloroaniline, 4-aminophenol, 1-naphthylamine and 3,5-difluoroaniline) (1.0 equiv.) were dissolved in appropriate volume of toluene. Magnesium sulfate (1.0 equiv.) was added to the reaction medium and the resulting mixture was refluxed for various reaction times (10-36 h). After completion of the reaction detected by TLC (EtOAc), toluene was evaporated to dryness. DCM was added to the residue, $MgSO_4$ was filtered and washed with DCM. The solvent was concentrated in vacuo. The crude product was purified by using crystallization or column chromatography techniques.

General Procedure for Microwave Irradiation Reactions

Aldehyde (1.0 equiv.) and aromatic amines (1.0 equiv.) were dissolved in toluene at a 10 mL microwave reaction vessel. $MgSO_4$ (1.0 equiv.) was added and stirred at room temperature for 3 min. The mixture was heated at 120 °C under dynamic mode of microwave irradiation for 45-120 min. After completion of the reaction, the mixture was warmed to room temperature. Same work-up and purification procedures mentioned above were applied.

***N*-(Phenyl)-1-(imidazo[1,2-*a*]pyrimidin-2-yl)methanimine (S1).** The reaction was performed under general procedure conditions as described above, using aldehyde derivative and aniline with 10 h and 60 min reaction times for conventional and microwave heating conditions, respectively. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:12) to give compound **S1**. Yellow solid; 82 and 80% yield (conventional and microwave reactions, respectively); m.p. 172-174°C; IR (ATR) ϑ 3112, 3089, 3060, 3003, 2990, 2949, 2923, 2907, 2869, 2851, 1620, 1607, 1520, 1471, 1404, 1342, 1283, 1277, 1224, 1162, 1140, 1080, 969, 886, 860, 801, 781, 761, 704 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (dd, J=6.82 and 2.09 Hz, 1H), 8.89 (s, 1H), 8.76 (dd, J=4.18 and 2.07 Hz, 1H), 8.39 (s, 1H), 7.44-7.39 (m, 2H), 7.38-7.32 (m, 3H), 7.23 (tt, J=7.28 and 1.19 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.21, 151.65, 150.97, 149.96, 144.03, 137.24, 129.84, 126.53, 121.64, 121.29, 111.50; LC/MS (ESI) m/z: ($C_{13}H_{10}N_4$) 223.0 $[M+H]^+$.

***N*-(4-Chlorophenyl)-1-(imidazo[1,2-*a*]pyrimidin-2-yl)methanimine (S2).** The reaction was performed under general procedure conditions as described above, using aldehyde derivative and 4-chloroaniline with 24 h and 60 min reaction times for conventional and microwave heating conditions, respectively. The crude product was purified by column chromatography on silica gel (ethyl acetate) to give compound **S2**. Light yellow solid; 46 and 79% yield (conventional and microwave reactions, respectively); m.p. 211-214°C; IR (ATR) ϑ 3100, 3091, 3061, 2948, 2923, 2852, 1619, 1607, 1489, 1479, 1414, 1337, 1284, 1229, 1157, 1085, 1009, 959, 869, 832, 793, 775, 761, 712, 682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (dd, J= 6.85 and 2.06 Hz, 1H), 8.89 (s, 1H), 8.76 (dd, J= 2.06 Hz, 1H), 8.39 (s, 1H), 7.46 (m, 2H), 7.36 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.35, 151.10, 150.53, 150.43, 144.41, 137.34, 130.68, 129.76, 123.46, 121.21, 111.58; LC/MS (ESI) m/z: ($C_{13}H_9ClN_4$) 257.0 $[M+H]^+$.

***N*-(4-Hydroxyphenyl)-1-(imidazo[1,2-*a*]pyrimidin-2-yl)methanimine (S3).** The reaction was performed under general procedure conditions as described above, using aldehyde derivative and 4-aminophenol with 18 h and 45 min reaction times for conventional and microwave heating conditions, respectively. The crude product was purified by crystallization with methanol/acetonitrile mixture to give compound **S3**. Light brown solid; 74 and 68% yield (conventional and microwave reactions, respectively); m.p. 273-275°C (dec.); IR (ATR) ϑ 3106, 3025, 2951, 2899, 1624, 1607, 1504, 1453, 1406, 1342, 1265, 1240, 1165, 1101, 879, 840, 804, 772, 722 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (dd, J= 6.85 and 2.07 Hz, 1H), 9.49 (s, 1H), 8.86 (s, 1H), 8.72 (dd, J= 2.07 Hz, 1H), 8.30 (s, 1H), 7.32 (dd, J= 4.22 and 2.63 Hz, 1H), 7.26 (dt, J= 8.75 and 2.62 Hz, 2H), 6.79 (dt, J= 8.75 and 2.62 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.78, 152.75, 150.66, 146.75, 142.92, 142.88, 137.08, 122.91, 121.50, 116.32, 111.23; LC/MS (ESI) m/z: ($C_{13}H_{10}N_4O$) 237.0 $[M-H]^-$.

***N*-(Naphthalen-1-yl)-1-(imidazo[1,2-*a*]pyrimidin-2-yl)methanimine (S4).** The reaction was performed under general procedure conditions as described above, using aldehyde derivative and 1-naphthylamine with 24 h and 100 min reaction times for conventional and microwave heating conditions, respectively. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:12) to give compound **S4**. Yellow solid; 65 and 72% yield (conventional and microwave reactions, respectively); m.p. 212-214°C; IR (ATR) ϑ 3100, 3082, 3046, 3004, 2955, 2923, 2853, 1617, 1604, 1567, 1514, 1480, 1417, 1369, 1350, 1284, 1235, 1158, 1145, 1085, 1040, 963, 901, 831, 795, 768, 661 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (dd, J= 6.82 and 2.06 Hz, 1H), 8.96 (s, 1H), 8.81 (dd, J= 2.06 Hz, 1H), 8.47 (s, 1H), 8.38 (m, 1H), 7.93 (m, 1H), 7.79 (d, J= 8.29 Hz, 1H), 7.56-7.53 (m, 3H), 7.46 (dd, J= 4.2 and 2.63 Hz, 1H), 7.27 (dd, J= 7.35 and 1.03 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.37, 151.10, 150.37, 149.02, 144.48, 137.20, 134.16, 128.93, 128.26, 127.04, 126.92, 126.58, 126.21, 124.07, 121.72, 113.61, 111.82; LC/MS (ESI) m/z: ($C_{17}H_{12}N_4$) 274.0 $[M+H]^+$.

***N*-(3,5-Difluorophenyl)-1-(imidazo[1,2-*a*]pyrimidin-2-yl)methanimine (S5).** The reaction was performed under general procedure conditions as described above, using aldehyde derivative and 3,5-difluoroaniline with 36 h and 120 min reaction times for conventional and microwave heating conditions, respectively. The crude product was purified by washing with plenty of diethylether to give compound **S5**. Gold yellow crystal; 79 and 84% yield (conventional and microwave reactions, respectively); m.p. 238-240°C (dec.); IR (ATR) ϑ 3104, 3082, 3062, 3033, 3017, 2956, 1610, 1584, 1520,

1455, 1412, 1345, 1287, 1235, 1163, 1125, 1113, 986, 965, 855, 793, 776, 686, 675 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.99 (dd, J= 6.85 and 1.95 Hz, 1H), 8.93 (s, 1H), 8.78 (dd, J= 2.06 Hz, 1H), 8.41 (s, 1H), 7.37 (dd, J= 4.26 and 2.54 Hz, 1H), 7.11 (m, 2H), 7.06 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.69, 164.54, 162.25, 162.10, 154.67, 154.56, 154.44, 153.68, 152.13, 151.37, 145.15, 137.51, 120.94, 111.74, 105.50, 105.24, 101.73, 101.47, 101.27; LC/MS (ESI) m/z: ($C_{13}H_8F_2N_4$) 259.0 $[M+H]^+$.

3. Result and discussion

Two-step synthesis of the imidazo[1,2-*a*]pyrimidine-2-carbaldehyde was performed as described in the literature [18] and was confirmed by comparison of their spectral data reported in the literature [18, 19]. To sum up, the first step is a condensation reaction with 2-aminopyrimidine and 1,1,3-trichloroacetone in THF to produce HCl salt of fused biheterocycle and the following step is a hydrolysis reaction of the intermediate with sodium acetate in water to obtain aldehyde derivative (Figure 1). Then, target imine compounds were synthesized from imidazo[1,2-*a*]pyrimidine-2-carbaldehyde and readily available aromatic amines via imine formation reaction (Figure 1). Aniline and 1-naphthylamine as non-substituted, 4-chloroaniline and 3,5-difluoroaniline as electron-withdrawing, 4-hydroxyaniline as electron-donating aniline derivatives were used in the last step. The compounds **S1-S5** were fully characterized by their melting point, FT-IR, ^1H NMR, ^{13}C NMR and MS spectras. For the schiff base formation step, microwave and ultrasound techniques were used as alternative methods to the conventional method and the parameters such as reaction time, yield and by-product formation were compared in three methods.

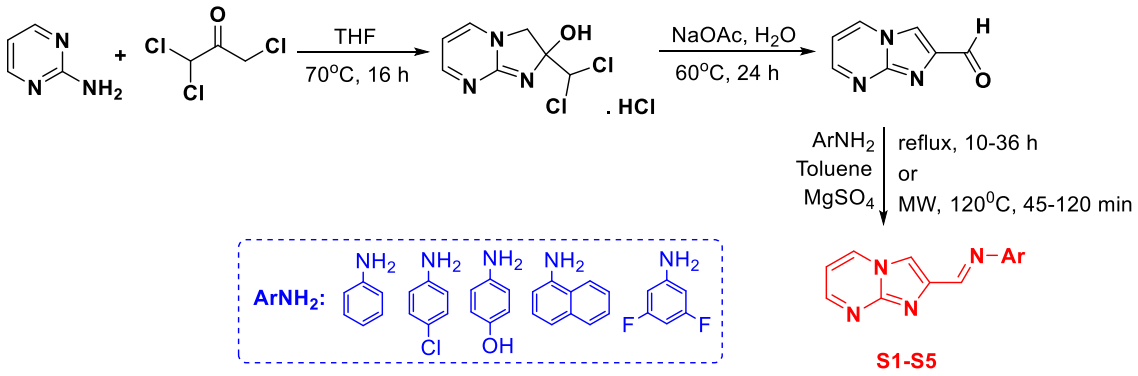

Figure 1. Synthesis route of imidazo[1,2-*a*]pyrimidine derivatives **(S1-S5)**.

At the outset, we investigated the imine formation reaction of **S1** from aldehyde derivative and aniline as a model reaction. The optimization of the solvent, temperature, and reaction time by using conventional heating and microwave irradiation was performed as illustrated in Table 1. Two solvent, ethyl alcohol and toluene were tried as solvent choice and reflux temperature of solvents were applied in two methods at the synthesis of **S1**. Although the reaction times of toluene conditions were longer, the yields were found higher compared to ethyl alcohol conditions in two methods. So, toluene was selected as an ideal solvent for the next reactions. The second optimization were done on the selection of methods, conventional heating or microwave irradiation. It was observed that the reaction times of **S1** decreased to 60 min at microwave-assisted reaction from 10 h at conventional heating reaction whereas the yields were at similar

level (82 and 80%) in two methods (Table 1). In addition, to synthesis of **S1**, ultrasound-assisted reaction conditions were applied as the alternative third method. According to TLC tracking, although the product formation was observed, the reaction was completed at 40% level even in 2 h at the conditions in ethyl alcohol and 80 °C in an ultrasonic bath. Ultrasound technique was not applied to the other compounds because of the disadvantageous longer reaction times compared to microwave technique. The optimized reaction conditions for imine formation step were determined as toluene, reflux temperature for conventional heating reactions and toluene, 120°C for microwave irradiation reactions. When all the experimental data were evaluated, it can be concluded that the microwave-assisted synthesis technique is better, preferable option for the synthesis of **S1-S5** because of the shorter reaction times, less by-products and higher yields (Table 1).

Table 1. The comparison of reaction conditions for **S1-S5**.

Entry	Compound	Method	Solvent	Temperature (°C)	Time	Yield (%)[a]
1	**S1**	Conventional H.	EtOH	reflux	6 h	71
2			Toluene	reflux	10 h	82
3		Microwave I.	EtOH	80 °C	40 min	75
4			Toluene	120°C	60 min	80
5	**S2**	Conventional H.	Toluene	reflux	24 h	46
6		Microwave I.		120°C	60 min	79
7	**S3**	Conventional H.		reflux	18 h	74
8		Microwave I.		120°C	45 min	68
9	**S4**	Conventional H.		reflux	24 h	65
10		Microwave I.		120°C	100 min	72
11	**S5**	Conventional H.		reflux	36 h	79
12		Microwave I.		120°C	120 min	84

[a] Isolated yield.

Compounds **S1-S5** were characterized by melting point, FT-IR, ^{1}H NMR, ^{13}C NMR and MS analyses. The characteristic C=N stretching band of imine was identified in the range of 1607-1584 cm^{-1} depends on the effects of different substituents in the aromatic rings adjacent to the azomethine group in the IR spectra. Also, aromatic C=C stretching and imidazo[1,2-*a*]pyrimidine C=N stretching peaks were observed at the similar region of the spectra. Aromatic C-H stretching peaks and aliphatic C-H stretching of azomethine were observed in the range of 3112-3003 and 2990-2851 cm^{-1}, respectively. All other peaks at FT-IR spectras confirm the structures of target compounds.

Sample ^{1}H and ^{13}C NMR spectrums of a selected compound (*N*-(4-hydroxyphenyl)-1-(imidazo[1,2-*a*]pyrimidin-2-yl)methanimine, **S3**) were given in detail in Figure 2. The ^{1}H NMR spectrum of compound **S3** showed the following characteristic chemical shifts of imidazo[1,2-*a*]pyrimidine skeleton: three doublet of doublets signals at 10.05, 8.72 and 7.32 ppm for the three hydrogen of pyrimidine ring (H_h, H_e and H_c) and the singlet

peak at 8.30 ppm for one hydrogen of imidazole ring (H_d), respectively. The characteristic proton of azometine group (H_f) was observed as a singlet peak at 8.86 ppm. In addition to these signals, two triplet of doublets aromatic hydrogens with symmetrical 2H integration at 7.26 and 6.79 ppm for phenyl ring (H_b and H_a) and singlet peak at 9.49 ppm for hydroxy proton at para position (H_g) were also identified. Eleven different carbon signals were observed in the range of 156.78-111.23 ppm at ^{13}C NMR spectra (Figure 2). The stronger peaks at 116.32 and 122.91 ppm belong to the two symmetrical carbons at phenyl ring. The spectral values of the compounds **S1-S5** are given in Figure 2-4.

Finally, the molecular weights of products were confirmed by using the negative or positive quick scan modes of LC/MS spectra.

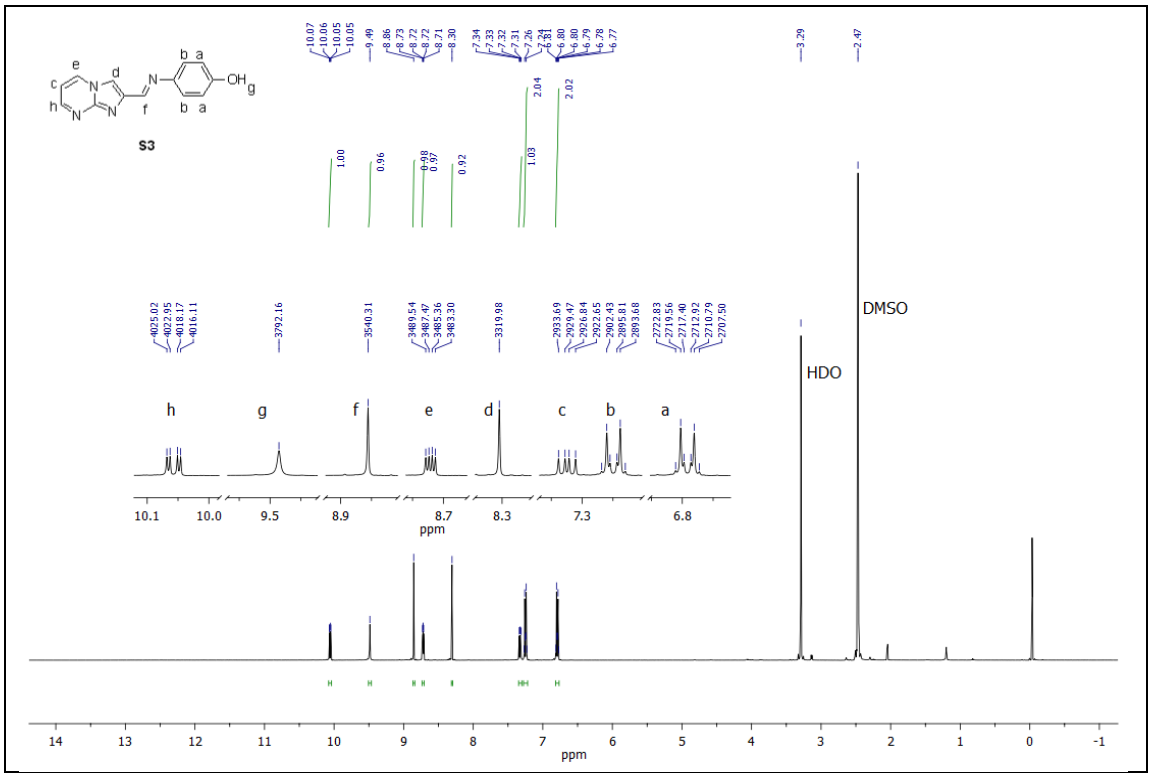

Figure 2. ^{1}H NMR and ^{13}C NMR spectras of **S3**.

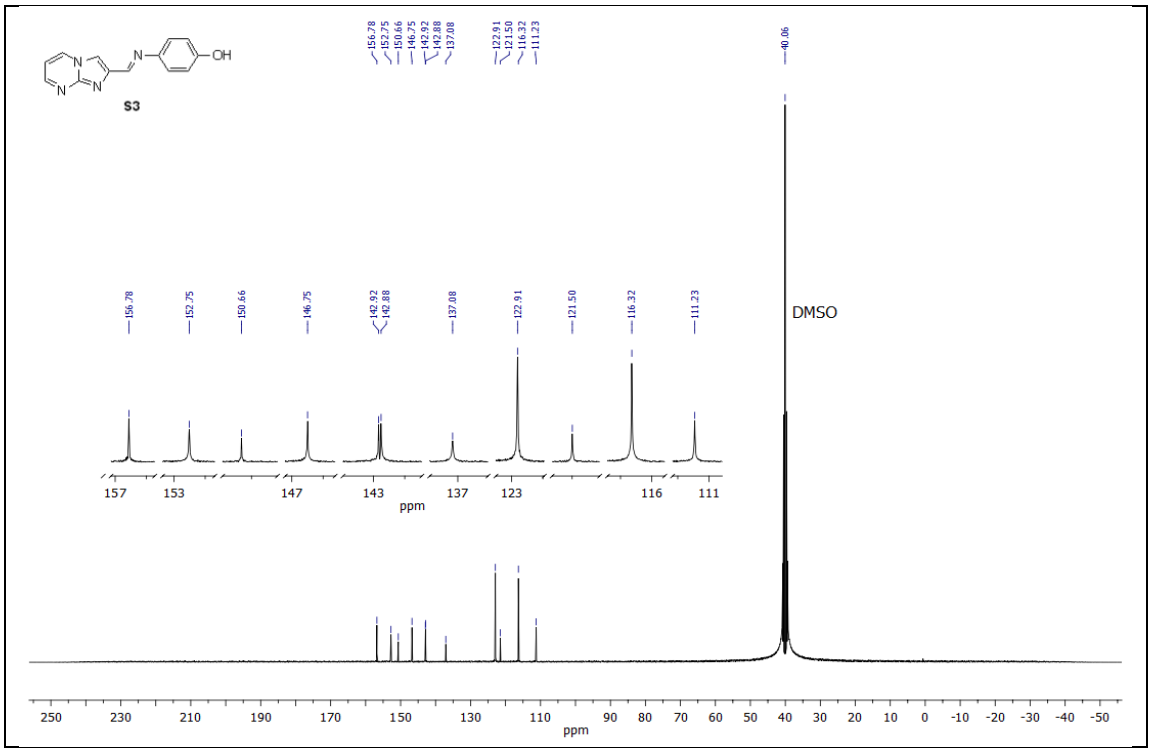

Figure 2. (Continued).

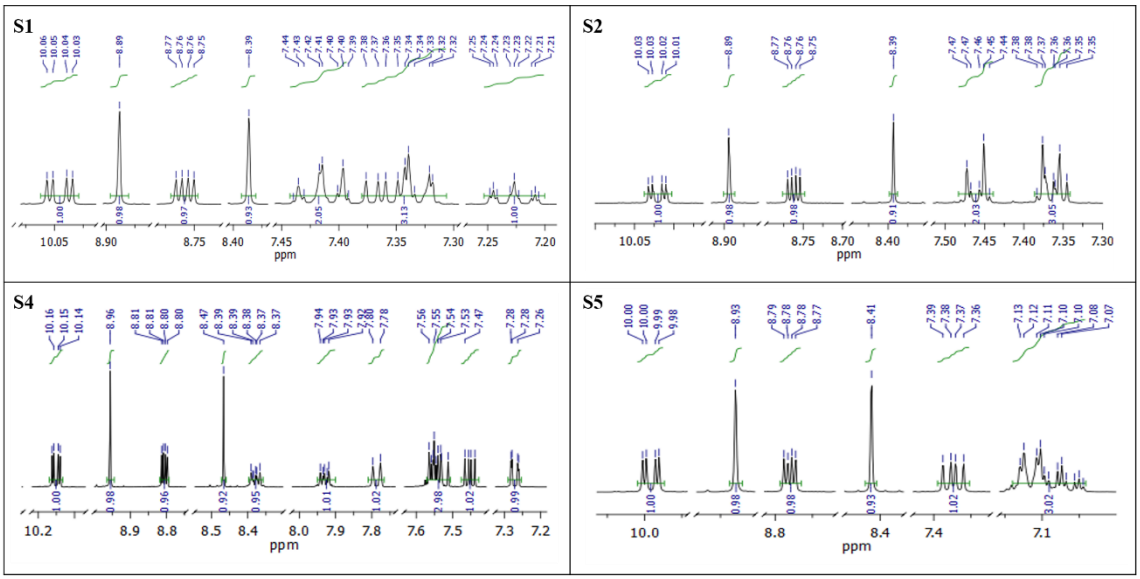

Figure 3. ^{1}H NMR spectras of **S1-S2** and **S4-S5**.

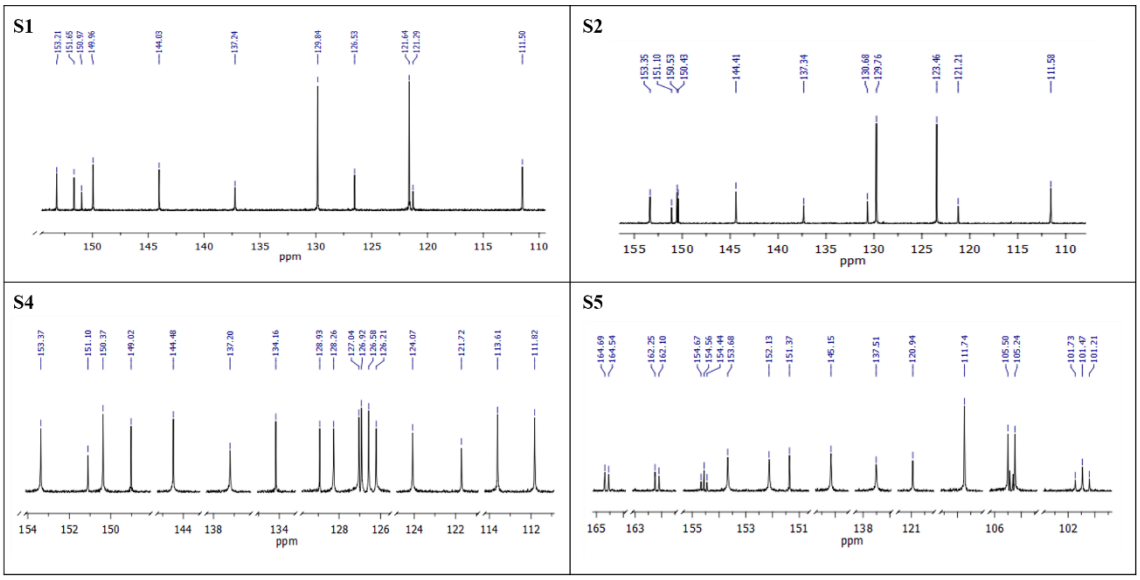

Figure 4. ^{13}C NMR spectras of **S1-S2** and **S4-S5**.

4. Conclusion

We have reported efficient conventional heating and microwave-assisted methods for the synthesis of novel imidazo[1,2-*a*]pyrimidine derived schiff bases. The structures of novel products **S1-S5** were confirmed with FT-IR, ^{1}H NMR, ^{13}C NMR and MS analyses. While imine formation reaction took 10-36 h and resulted in moderate to good yields (46-82%) at optimized conventional heating conditions, took only 45-120 min and resulted in good yields (68-84%) under optimized microwave reaction conditions. Our microwave-assisted process used for schiff base formation reactions provides an energy-efficient green method which can be has a potential to be scale-up industrial uses due to its mild conditions, shorter reaction times and higher yields. The biological studies of compounds **S1-S5** are ongoing.

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