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Synthesis and Structural Characterization of 6-(*N*-Methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic Acid Methyl Ester Isomers

(Sintesis dan Pencirian Struktur Isomer 6-(*N*-Metil-piridina-2-ylkarbamoil)-piridina-2-karboksilik Asid Metil Ester)

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ABSTRACT

A series of monoamide isomers have been successfully synthesised and characterised using combination of common spectroscopic techniques such Fourier Transform Infrared (FT-IR), ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) and Ultraviolet-visible (UV-vis). The monoamide compounds namely 6-(3-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L1), 6-(4-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L2), 6-(5-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L3) and 6-(6-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L4) were prepared from reaction between 6-(methoxycarbonyl) pyridine-2-carboxylic acid with 2-amino-N-methylpyridine (where N = 3, 4, 5 and 6) by using acyl chloride reaction. In this present studies, the synthesis and characterization of these compounds are discussed along with the inductive effects contributed by methyl substituted groups at the pyridine ring.

Keywords: Acyl chloride; inductive; isomers; monoamide; pyridine

ABSTRAK

Suatu siri isomer baru monoamida telah berjaya disintesis dan dicirikan menggunakan gabungan beberapa teknik spektroskopi seperti Fourier Penukar Inframerah (FTIR), ^{1}H dan ^{13}C Resonans Magnet Nukleus (RMN) dan Ultra-lembayung boleh nampak (UV-vis). Sebatian yang dinamakan sebagai 6-(3-metil-piridin-2-ilkarbamoil)-piridina-2-karboksilik asid metil ester (L1), 6-(4-metil-piridin-2-ilkarbamoil)-piridina-2-karboksilik asid metil ester (L2), 6-(5-metil-piridin-2-ilkarbamoil)-piridina-2-karboksilik asid metil ester (L3) dan 6-(6-metil-piridin-2-ilkarbamoil)-piridina-2-karboksilik asid metil ester (L4) dihasilkan daripada tindak balas antara 6-(metoksikarbonil)piridin-2-karboksilik asid dengan 2-amino-N-metilpiridin (dengan N = 3, 4, 5 dan 6) menggunakan kaedah asil klorida. Dalam kajian ini, kaedah sintesis dan pencirian struktur sebatian berikut akan dibincangkan bersama kesan induktif yang disumbangkan oleh kumpulan penukarganti metil pada gegelang piridin.

Kata kunci: Asil klorida; induktif; isomer; monoamida; piridina

INTRODUCTION

The development in the synthesis of new amide compounds has progressed rapidly due to their increasing demand in several applications such as bioconjugates, bioactive macrocylic drugs, nanostructures and organic linker in supramolecular architectures (Ardona & Tovar 2015; Dunetz et al. 2016; Leggio et al. 2015; Lenstra et al. 2015; Pattabiraman & Bode 2011; Zivec et al. 2009). Among of many reported amides, little attention has been paid on the synthesis of amides containing pyridine (aminopyridyl in particular), even though their application as organic linker in the construction of coordination polymers has nowadays become a great attention. According to Zhang (2009), the study was limited by the synthesis and purification of aminopyridyl's procedure that are tedious and problematic. This is because, aminopyridyl molecules has labile functionalities that requires activation for substitution reaction to be occurred (Devi et al. 2015; Janeta et al. 2014; Zhang et al. 2009). To overcome this problem, an acyl chloride was used as precursor to activate the amine sites and promote nucleophilic substitution reaction. Although the acyl chloride method is tedious; the interest in using acyl chloride reaction is still relevant for aminopyridyl preparation as this method is low-cost, environmental friendly and produce high yield of products (Zaragoza 2015). Therefore, we have used acyl chloride reactions to produce several aminopyridyl compounds which derived from pyridine dicarboxylic acid (Abdul-Kadir et al. 2011; Kadir et al. 2014). By using similar approach, again via this study, we have prepared a series of new isomers aminopyridyl compounds with substituted methyl group at the pyridine pendant arms. This study will discuss the preparation and chemistry of 6-(*N*-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester isomers along with their spectroscopic data.

According to literature, the substituted methyl at pyridine is described as α , β and γ, not ortho, meta and para as in other aromatic rings (Figure 1). Meanwhile,

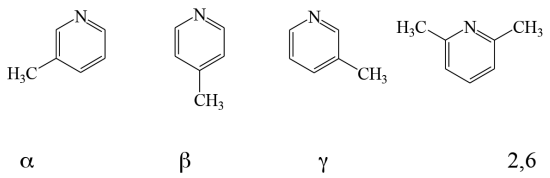


FIGURE 1. Description of methyl substituted position at pyridine ring

structure 4 is described as (2,6) with regards to the position of methyl at that respective positions (Boon et al. 1986). The structure of four new compounds prepared in this study is shown in Figure 2.

MATERIALS AND METHODS

All chemicals or reagents used were purchased from standard supplier (Merck and Sigma Aldrich) and used as received without further purification. The infrared (IR) spectra were recorded on a Fourier Transform-Infrared Spectrometer, Perkin Elmer Spectrum 100 in the range of 4000-400 cm^{-1} using potassium bromide (KBr) pellets. For UV-Vis analysis, all compounds were recorded by using Spectrophotometer Shimadzu UV-1601PC in 1 cm^3 cuvette in methanolic solution for absorbance analysis. NMR spectra of ^1H and ^{13}C NMR were recorded using Bruker Advance III 400 spectrometer with deuterated chloroform ($CDCl_3$) the solvents and chemical shift values were given in parts per million (ppm) relative to solvent resonances as internal standard. Melting points were measured using Melting Point Stuart SMP3 while CHNS elemental analyses were recorded by CHNS Flashes 1112 series.

SYNTHESES OF MONOAMIDE COMPOUNDS

A suspension of 6-(methoxycarbonyl)pyridine-2-carboxylic acid (0.5 g, 2.0 mol) was heated at reflux in dichloromethane in the presence of thionyl chloride (0.5 mL) and a little amount of dried DMF (1 µL) as catalyst under nitrogen. After an hour, the dichloromethane was removed using rotary evaporator and leave in vacuum desiccator for another one hour to remove all the solvent. The acyl chloride (1.67 g, 3.5 mol) was redissolved in dichloromethane (40 mL), before 2-amino-3-methyl pyridine (1.567 g, 3.5 mol) and distilled triethylamine (1.7 mL, 3.5 mol) were added. The mixture was heated at reflux for another 24 h. After the reaction was completed, the solvent was removed using rotary evaporator. Then the residue was redissolved with dichloromethane, washed with sodium hydrogen bicarbonate to remove unreacted starting material. Dichloromethane was dried over magnesium sulfate and the solvent removed using rotary evaporator under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with 8:2 ethyl acetate: dichloromethane. The product was obtained as powder from column as pale yellow precipitate. The rest of the compounds (L2-L4) were prepared using similar methods described for L1, by replacing 2-amino-3-methyl pyridine with 2-amino-4-methyl pyridine, 2-amino-5-methyl pyridine and 2-amino-6-methyl pyridine, respectively. All compounds were obtained in moderate to good yields, approximately 70-88%.

RESULTS AND DISCUSSION

Compounds 6-(3-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L1), 6-(4-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L2), 6-(5-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L3) and 6-(6-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L4) were prepared from acyl chloride reactions, which involve continuous steps of combination between 6-(methoxycarbonyl)pyridine-2-carboxylic acid (6-mpcd), thionyl chloride and aminopyridine in inert condition (Scheme 1). In the synthesis of the compound, acyl chloride was prepared as precursor before being reacted with amine. In the reaction, the activated amine from aminopyridyl will attack the acyl carbonyl and forming the isomers (Scheme 2).

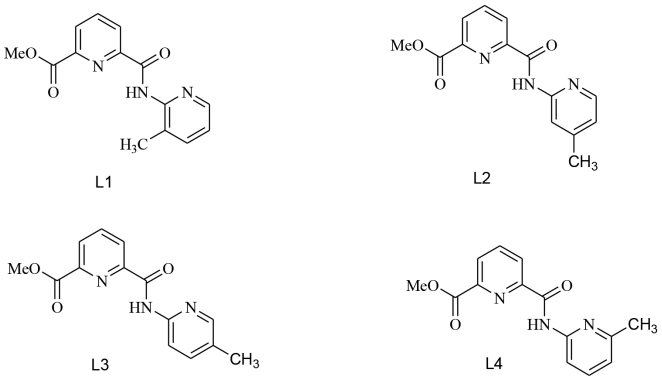
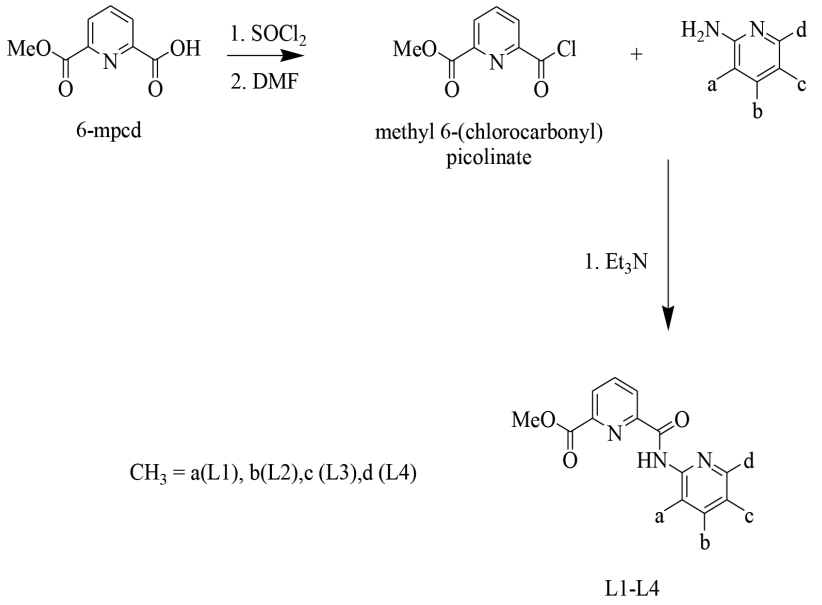
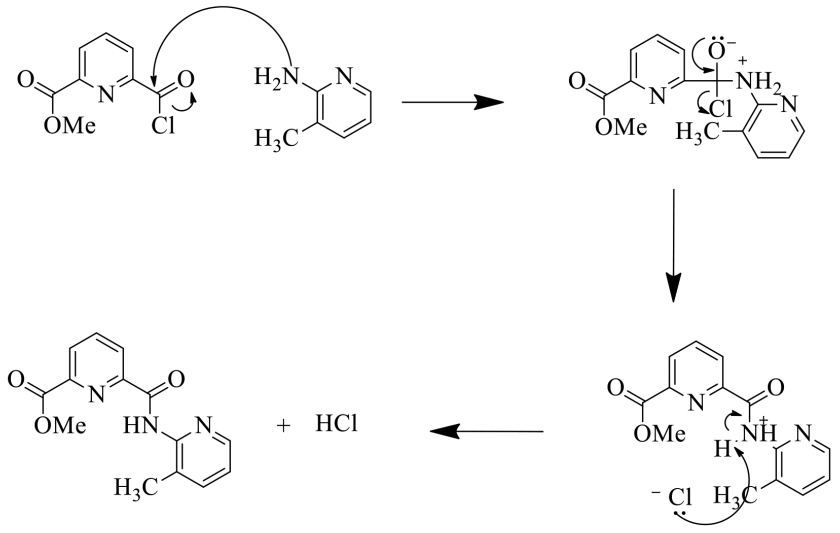


FIGURE 2. Molecular structure of L1, L2, L3 and L4



SCHEME 1. General synthetic reaction for the synthesis of L1-L4



SCHEME 2. Proposed mechanism for the formation of L1

In the FTIR spectra of L1-L4, several distinctive peaks for N-H stretching, N-H bending and C=O stretching were indicated at range 3339-3358, 1525-1535 and 1699-1742 cm^{-1}, respectively (Figure 3). From the IR spectra, it was observed that compound L4 has the highest frequency of NH stretching found at 3358 cm^{-1}. This might be due to the position of methyl substituted that is far from amino (NH) and experienced less steric effect compared to L1-L3. The shift might also attribute by intramolecular hydrogen bonding that shifts the N-H stretching to higher frequency as reported by Sharma et al. (2011). In contrast to N-H stretching, the peaks for methyl group shows insignificant different and were found at range 2920-2962 and 1320-1324 cm^{-1}, respectively. It is obvious from this study that the methyl groups for these four compounds were indicated at lower frequency which is below than 3000 cm^{-1} due to the behaviour of CH_3 that formed sp^3 hybridization (Lanigan et al. 2013). The CH bending for mono substituted phenyl ring was also observed at the range 682-685 cm^{-1}, in similar to the spectroscopic data reported by Yalcin et al. (2015). As shown in Figure 2, compounds L1-L4 are differed in methyl position at the pyridine pendant arms. Methyl, which is an electron donating group (EDG), pulls the electron density away from the hydrogen towards carbon. This resulted to inductive effects which led to the increment of electron density at carbon atoms.This explains why the compound with methyl at γ position experienced more electron donating effects compared to β, therefore

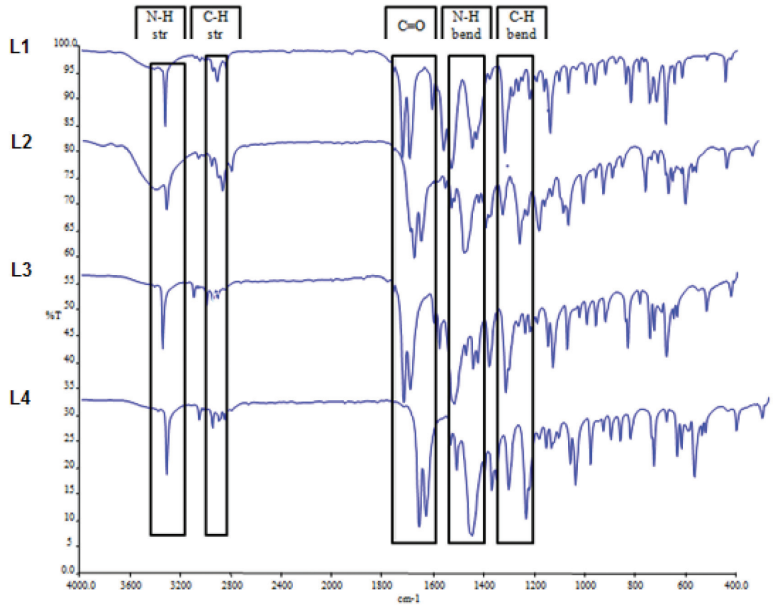


FIGURE 3. The FTIR spectra for L1, L2, L3 and L4

the frequency of C=O and N-H at γ position was found at higher region compared to the compound with methyl at α and β positions. This was also related to the shortening of the bond lengths between methyl, C=O and N-H due to this inductive phenomenon (Diaz-Alejo et al. 2013). The comparison between the functional groups obtained from the IR spectra is shown in Tables 1 and 2.

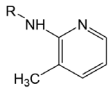
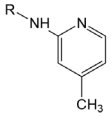
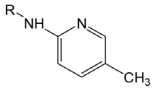
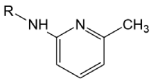
In the ^{1}H NMR spectra for L1-L4, the resonances for two methyl group (CH_3) are indicated at range 2.36-2.53 ppm and 4.0-4.06 ppm, respectively. According to the data showed in Table 3, the resonance for C-H methyl that attached to pyridyl appeared further downfield (2.53 ppm) compared to the other isomers, due to the position of the methyl substituted that is near to the nitrogen atom of the pyridine. Compound L3, which has methyl substituted at γ position that has a less steric effect towards amino shows NH resonance at further downfield (10.41 ppm). In the ^{13}C NMR spectrum, the resonances of two δ (CH_3) were observed at 17.93-53.05 ppm. The resonance signals for pyridine, δ (C-aromatic pyridine) were indicated at 111.13-157.28 ppm while (C=O) peaks were found further downfield around 161.27-164.99 ppm. The methyl that attached to oxygen atoms shifts to the downfield region due to the electronegativity of the oxygen (Jakob et al. 2015; Lanigan et al. 2013; Wilson et al. 2012). In this case, the pyridine ring protons are deshielded by the diamagnetic anisotropy of the ring and give the benzene ring protons a large chemical shift to 6.96-8.48 ppm (Park et al. 2013; Yalcin et al. 2015). The ^{1}H NMR and ^{13}C NMR spectra for L1 are shown in Figures 4 and 5, respectively.

The UV-Vis spectrum shows that compounds L1-L4 displayed two absorption peaks which corresponded to carbonyl (C=O) and pyridine (Figure 6). The absorbance at λ_{max} 273-293 nm represents overlapping of C=O group and pyridine group. The λ_{max} for L1 and L2 is lower than L3 and L4 and shift to longer wavelength. This is caused by molecule modification which is called as bathochromic effect. In this experiment, the molar absorptivity for C=O and pyridine groups were determined as 2.73×10^{7} - 2.93×10^{7} L mol^{-1} cm^{-1} which led to n → π* transition and π → π* transition, respectively. Yalcin et al. (2015) had stated that, amide and benzoyl carbonyl group had n → π* transition and phenyl ring had π → π* transition. The data obtained is summarized in Table 3.

TABLE 1. Data comparison of IR spectra for L1-L4

Vibrational modes	L1 (cm^{-1})	L2 (cm^{-1})	L3 (cm^{-1})	L4 (cm^{-1})
ν (CH_3)	2925	2923	2962	2920
ν (N-H str)	3339	3357	3350	3358
ν (C=O)	1732, 1702	1742, 1727	1731, 1702	1725, 1699
ν (N-H bend)	1567, 1535	1533	1533	1525
ν (CH_3 bend)	1324	1321	1322	1320

TABLE 2. The selected data for the functional group (N-H and C-H) in the FTIR and NMR spectra of L1-L4

Compounds	^{1}H NMR		FTIR		Structure
	δ(N-H)	δ(C-H)	ν(N-H) str	ν(N-H) bend	
L1	10.28	2.39	3339	1535	
L2	10.28	2.45	3357	1533	
L3	10.41	2.36	3350	1533	
L4	10.36	2.53	3358	1520	

R= $C_9H_6NO_3$

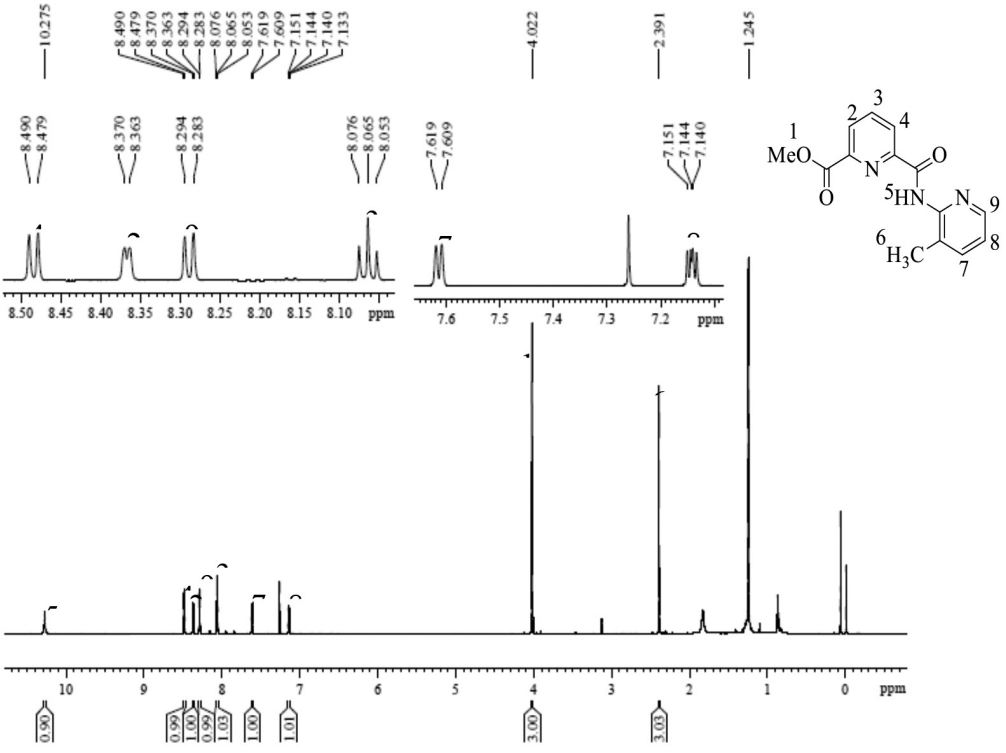


FIGURE 4. ^{1}H NMR spectrum of monoamide ligand, L1

Several approaches have been attempted to crystallise these compounds, however no crystals were obtained. This might due to the high polarity of the compounds that prohibits them to crystallise in any solvents, where the product precipitate after each of crystallization was attempted. However, the combination of spectroscopic studies particularly NMR has proved that the studied molecules are successfully obtained as expected.

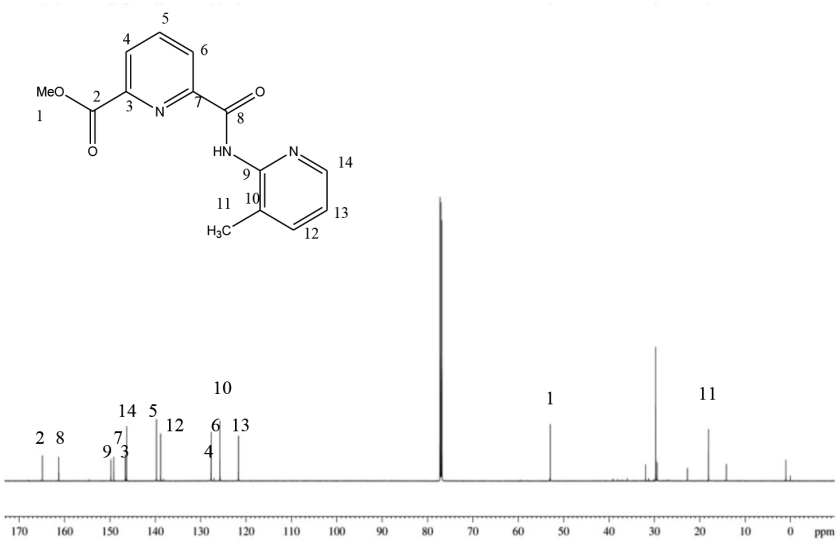


FIGURE 5. ^{13}C NMR spectrum of monoamide ligand, L1

TABLE 3. The UV-Vis data for L1-L4

	Chromophores	Transition	λ_{max}(nm)	ε, L mol^{-1} cm^{-1}
L1	Pyridine, C=O	n → π*, π → π*	273	2.73×10^7
L2	Pyridine, C=O	n → π*, π → π*	273	2.73×10^7
L3	Pyridine, C=O	n → π*, π → π*	293	2.93×10^7
L4	Pyridine, C=O	n → π*, π → π*	291	2.91×10^7

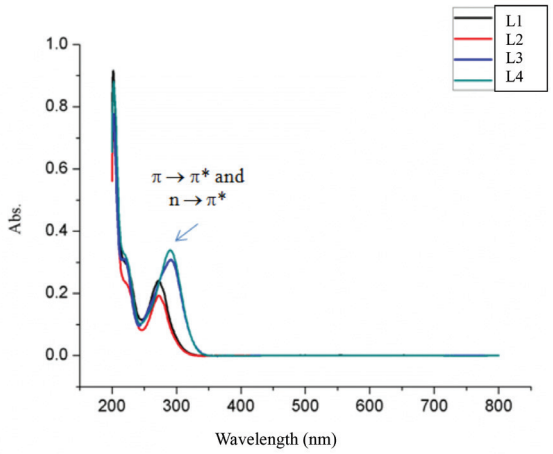


FIGURE 6. UV-Vis spectra for L1-L4

CONCLUSION

In conclusion, a series of monoamide compounds namely 6-(3-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L1), 6-(4-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L2), 6-(5-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L3) and 6-(6-methyl-pyridin-2-ylcarbamoyl)-pyridine-2-carboxylic acid methyl ester (L4) have been successfully synthesized by using acyl chloride methods. The different position of methyl substituents position has significant impacts towards the spectroscopic data, due to several factors such as inductive and steric effects. Compound L4 which has methyl nearby the nitrogen pyridine shows the highest frequency of N-H stretching. Meanwhile, compound L3 and L4 that experienced less steric effects compared to the other isomers displays N-H resonance at further downfield.

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