TRƯỜNG ĐẠI HỌC SƯ PHẠM TP HỒ CHÍ MINH
TẠP CHÍ KHOA HỌC
KHOA HỌC TỰ NHIÊN VÀ CÔNG NGHỆ
ISSN: 1859-3100 Tập 14, Số 9 (2017): 76-84
HO CHI MINH CITY UNIVERSITY OF EDUCATION
JOURNAL OF SCIENCE
NATURAL SCIENCES AND TECHNOLOGY
Vol. 14, No. 9 (2017): 76-84
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PREPARATION OF SOME NEW SCHIFF BASES FROM 5-NITROVANILLIN

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Received: 03/5/2017; Revised: 02/6/2017; Accepted: 23/9/2017

ABSTRACT

*A series of Schiff bases were synthesized successfully based on the condensation reaction between 5-nitrovanillin and aromatic amines in moderate and high yields. The condensation underwent better in DCM solvent, acetic acid catalyst and anhydrous $MgSO_4$ as a drying agent and increased the yield up to 100 %.These new Schiff bases were determined with ^1H, ^{13}C NMR spectral analysis and compound **3a** was studied further HSQC, HMBC, NOSY and MS spectra. The C=N bond exists in E conformation.*

Keywords: antibacterial activity, nitrovanillin, Schiff base, vanillin.

TÓM TẮT

Tổng hợp của một số bazơ ship mới từ 5-nitrovanillin

*Một dãy các bazơ Schiff mới được tổng hợp bằng phản ứng ngưng tụ giữa 5-nitrovanillin và amin thơm. Dung môi dichlorometan có axit axetic làm xúc tác và chất hút ẩm $MgSO_4$ khan. Phương pháp này làm tăng hiệu suất của phản ứng từ 60-100%. Cấu trúc của những bazơ Schiff được nghiên cứu bằng phương pháp phổ cộng hưởng từ hạt nhân. Riêng cấu trúc của hợp chất **3a** được nghiên cứu trên cơ sở phân tích phổ cộng hưởng từ hạt nhân hai chiều HSQC, HMBC, NOSY và phổ khối lượng MS. Liên kết C=N được chứng minh tồn tại ở dạng cấu dạng E.*

Từ khóa: bazơ Schiff, kháng khuẩn, nitrovanillin, vanillin.

1. Introduction

Schiff bases are characterized by the -N=CH- (imine) group which imports in elucidating the mechanism of transamination and racemization reaction in biological system [1, 2]. Schiff bases are active against a wide range of organisms for example; *Candida Albicans, Escherichia coli Staphylococcus aureus, Bacillus polymxa, Trychophyton gypseum, Mycobacteria, Erysiphe graminis and Plasmopora viticola.* To increase the bioactive properties, Schiff bases worked as ligands in complexes with metals showing the remarkably bioactive activities [3]. Metal-imine complexes have been widelyinvestigated due to antitumor and herbicidal use. They can work asmodels for

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biologically important species [4]. Exploration and development of more effective antifungal agents is necessary, and the individual Schiff bases areconsidered to be promising antifungal medicines [5], [6].

Nitro aromatic compounds have been considered recently. For example, pyrrolnitrin and chaloramphenicol are antibiotics; 1-nitroaknadine and aristolochic acid are natural products that are metabolites. Nitrofen is a pesticide while the 3-nitrotyrosine works as a signaling molecule [6].

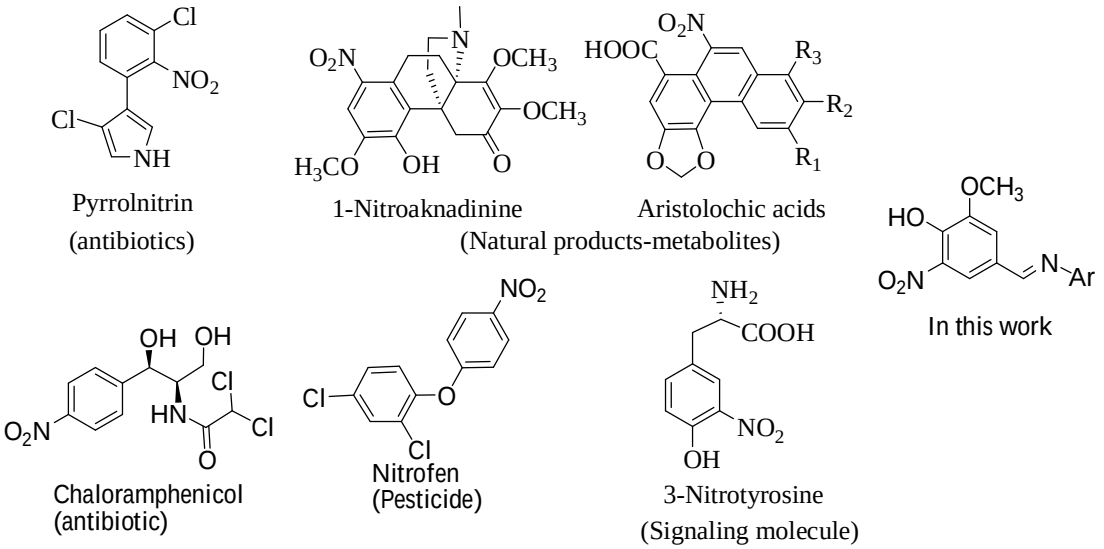


Figure 1. *Some examples of nitro aromatic compounds*

B. R. Thorat *et al.*[7] reported a series of Schiff bases of 5-nitrovanillin but did not test any their bioactivities. In Vietnam, Schiff bases of 5-nitrovanillin were investigated in 1999 [8], and showed considerable biological activities; however, some Schiff bases of 5-nitrovanillin have not been test yet. In this paper, taking advantages of Schiff bases and nitroaromatic compounds, the combination of imine group and nitroaromatic compounds is not only hope to increase their bioactive propertiesbut also provide good sources for synthesis of secondary amines, oxazolidine and others, Figure 1.

2. Content

2.1. Experimental section

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck were used as received, unless indicated. The ^{1}H NMR and ^{13}C NMR spectra were recorded on the Bruker Avance 500 NMR spectrometer in deuterated solvents. Chemical-shift data for each signal was reported in ppm units. Mass spectra were obtained from Mass Spectrometry

Facility of The Vietnam Academy of Science and Technology on LC-MSD-Trap-SL spectrometer. Ethanol was redistilled after drying.

2.2. Synthetic procedure

*Synthesis of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (**2**)[7,9]*

Concentrated HNO_3 (2 mL) was carefully added to a cooled (5 °C) solution of vanillin (5 g, 33 mmol) and acetic acid (50 mL) over a period of 30 min. The gold colored precipitate that formed was filtered, washed with water, and allowed to dry (5.21 g, 80%): mp. 171 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz)δ (ppm): 9.87 (s, 1H), 8.1 (d, J =2.0 Hz, 1H), 7.6 (d, J = 2.0 Hz, 1H), 3.96 (s, 3H). R_f = 0.2 (n-hexan /ethyl acetate = 2/1).

2.2.2. Synthesis of Schiff bases

General procedure:

Method 1: To a solution of 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and amine (2.5 mmol) in absolute ethanol (10 mL) was added 2-3 drops of glacial acetic acid. The mixture was refluxed for 5- 20 h. The progress of reaction was monitored with thin layer chromatography (TLC). After reaction completion, the mixture was concentrated and then added water (20 mL). The precipitate was filtered and washed well with water and cold ethanol. Re-crystallization in ethanol gave pure enough product for next reaction.

Method 2: To a solution of 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol), anhydrous magnesium sulfate (10 mmol, 1.2 g) and amine (2.5 mmol) in DCM (10 mL) was added 2-3 drops of glacial acetic acid. The mixture was refluxed for 2 h. Then filtration was used to get rid of $MgSO_4$. The mother liquid was washed with 3% HCl (5 mL x 3), dried over with Na_2SO_4 and then concentrated *in vacuo*. The title products were purified with flash column chromatography in eluent *n*-hexan and ethyl acetate (1/1).

*Synthesis of 2-methoxy-4-[(E)-(naphthalen-1-ylimino)methyl]-6-nitrophenol(**3a**)*

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol)and 1-naphthylamine (2.5 mmol, 0.36 g, 143 g/mol) gave **3a** as a redish brown powder (0.53 g, 82 %, 322 g/mol): m.p = 182 °C ; R_f = 0.73 (*n*-hexan /ethyl acetate = 2/1).

*Synthesis of 2-methoxy-4-[(E)-(naphthalen-2-ylimino)methyl]-6-nitrophenol (**3b**)*

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 2-naphthylamine (2.5 mmol, 0.36 g, 143 g/mol) gave **3b** as a reddish brown powder (0.49 g, 76 %, 322 g/mol): m.p = 185 °C;^{1}H NMR ($CDCl_3$, 500 MHz)δ (ppm):11.07 (s, br, 1H), 8.42 (s, 1H), 8.28 (m, 1H), 8.04 (d, J = 1.5 Hz, 1H), 8.00 (d, J = 1.0 Hz, 1 H), 7.85 (m, 1 H), 7.73 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 9.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 4.06 (s, 3H);^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm):157.3, 150.6, 149.0, 148.3, 134.0, 133.6, 128.6, 128.1, 127.7, 126.5, 126.3, 126.1, 125.9, 123.6, 118.6, 114.5, 112.8, 56.9. R_f = 0.75 (*n*-hexan/ethyl acetate = 2/1).

*Synthesis of 2-methoxy-6-nitro-4-[(E)-(4-hydroxyphenylimino)methyl]phenol(**3c**)*

Following the general procedureof method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 4-hydroxyanilline(2.5 mmol, 272 mg, 109 g/mol) gave **3c** as a dark yellow powder(0.35 g, 78 %, 228 g/mol): m.p =190 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz)δ (ppm): 9.60 (s, 1H), 8.59 (s, 1H), 8.05 (s, 1H), 7.66 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.90 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm): 157.4, 150.6, 149.0, 148.2, 134.3, 133.2, 125.3, 119.8, 117.5, 116.5, 114.3, 56.8. R_f = 0.8 (n-hexan /ethyl acetate = 2/1).

*Synthesis of 4-[(E)-(2-hydroxyphenylimino)methyl]-2-methoxy-6-nitrophenol (**3d**)*

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 2-hydroxyaniline (2.5 mmol, 0.3 g, 123 g/mol) gave**3d** as adark yellow powder (0.37 g, 62 %, 302 g/mol): m.p= 168 °C;^{1}H-NMR (DMSO, 500 MHz)δ (ppm): 8.62 (d, *J* = 1.5 Hz, 1H), 8.06 (d, *J* = 1.5 Hz, 1H), 7.69 (s, 1H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H), 3.78 (s, 3H).^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm): 158.7, 154.9, 152.8, 150.5, 148.7, 143.8, 139.9, 133.6, 128.3, 122.2, 118.2, 116.4, 114.8, 114.5, 114.2, 56.9, 55.7, 55.5. R_f = 0.8 (n-hexan /ethyl acetate = 2/1).

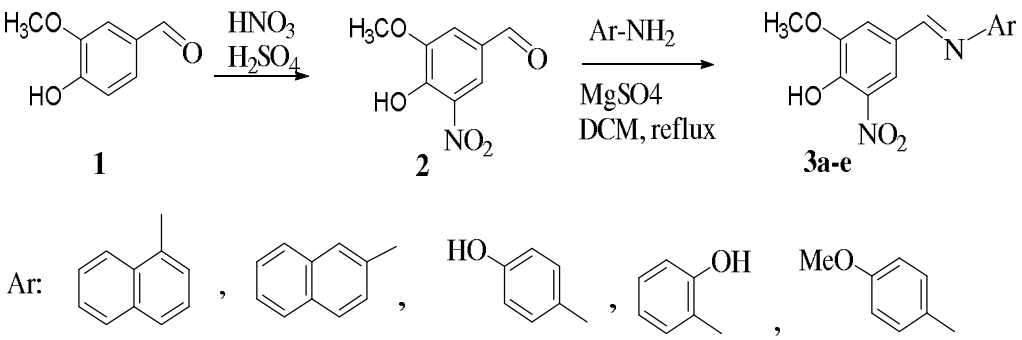
*Synthesis of 4-[(E)-(4-methoxyphenylimino)methyl]-2-methoxy-6-nitrophenol(**3e**)*

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 4-methoxyaniline (2.5 mmol, 0.27 g, 109 g/mol) gave**3e** as a dark yellow powder (0.38 g, 67 %, 288 g/mol): m.p = 172 °C;^{1}H-NMR ($CDCl_3$, 500 MHz)δ (ppm): 8.60 (s, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.22 (td, *J* = 8.0, 1.5 Hz, 1H), 7.03 (br, 1H), 7.03 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.92 (td, *J* = 8.5, 1.0 Hz, 1H), 4.05 (s, 3H).^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm): 154.4, 152.1, 150.7, 149.1, 134.9, 133.7, 129.5, 127.5, 120.3, 118.6, 116.4, 115.3, 114.2, 56.9; R_f = 0.7 (n-hexan /ethyl acetate = 2/1).

3. Results and Discussion

3.1. Synthesis

The five Schiff bases were synthesized successfully shown in the Scheme 1. These compounds were checked on Scifinder in the Leuven University (Belgium).



Scheme 1. *Synthesis of the target compounds*

First of all, vanillin (**1**) was nitrated in cold condition and mixture reagent of HNO_3 and H_2SO_4 giving 5-nitro vanillin in 80 %. This compound was checked with ^1H NMR spectrum. Then, 5-nitro vanillin was condensed with aromatic amine gave Schiff bases **3a**, **3b**, **3c**, **3d** and **3e** in moderate and good yield. Since they have long conjugation system, they are darkish yellow. The traditional method (method 1) gave yield lower than 50%. We also tried condition including $MgSO_4$ in DCM without acetic acid gave low yield too. Method 2 using $MgSO_4$ (5 eq.) and 1 drop of acetic acid was the best in our cases. In aniline case, the yield was about 100%, other cases their yields were 60 ÷ 85 %. The un-reacted amine was washed with 3% HCl. Therefore, after work up the crude products can be used for next step without further purification.

3.2. Structure determination

To understand the structures of these Schiff bases, compound **3a**, one of the most complicated compounds, was chosen to study ^1H NMR, ^{13}C NMR, HMBC and MS spectra. First of all, the negative mass spectrum showed a base pick at *m/z* 321 au and the positive mass spectrum showed a peak at *m/z* 323 au. That indicated the molecular weight of compound **3a** must be 322 g/mol matching with the designed product, expectedly, Figure 2.

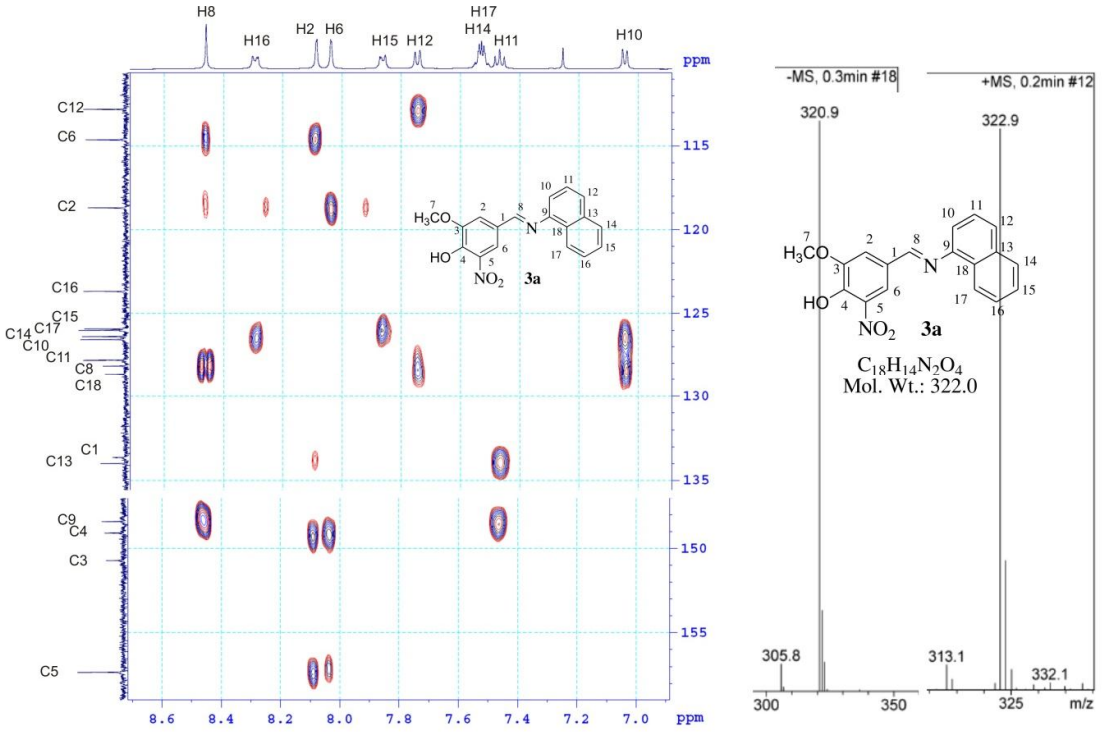
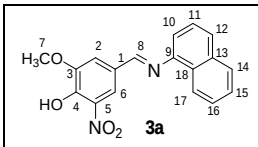


Figure 2. *Part of HMBC and MS spectra of compound* ***3a***

Secondly, retention factor of compound **3a** was much bigger than that of 5-nitrovanillin (**2**) (see experimental section). In addition, melting points of all Schiff bases were higher than that of 5-nitrovanillin due to molecular mass increased. Thirdly, ^{1}H NMR spectrum of compound **3a**indicated 14 protons including a broaden proton at δ 11.08 ppm was for H (OH), at δ 8.48 ppm for H8 and 3 protons at δ 4.09 ppm for H7. There were two doublet of doublet peaks at δ 8.29 and 7.86 ppm for either H16 or H15. There were doublet peaks at δ8.08 and 8.03 ppm with splitting constant about 1.0 ÷ 2.0 Hz which were for H2 or H6. Another pair of doublets was at δ 7.74 ppm and δ 7.04 ppm with splitting constant about 8.5 Hz that must be for H10 or H12. A unique triplet at δ 7.46 ppm was H11 due to their ortho position of both H10 and H12. Unfortunately, H14 and H17 overlapped each other giving a multiplet although each was a doublet of doublet peak. ^{13}C NMR spectrum of compounds **3a** indicated 18 peaks associated with 18 carbon atoms. Certainly, peak at δ 56.9 ppm was assigned for C7. Others carbons were not identified on the ^{13}C NMR spectrum. The HSQC cross peaks show the carbons bearing protons that combined with the HBMC cross peaks; therefore, all carbons and protons were assigned as shown in Table 1 and Figure 2. For instance, H7 had a cross peak with C3 that had a weak cross peak with H2 indicating the assignment of H2 from H6. Another example is that H10 and H12 were the doublet but H10 had a cross peak with C8 that bound the proton at δ8.45 ppm.

Table 1. *NMR spectral analysis of compound* ***3a*** *(ppm, Hz)*



3a

^{1}H NMR		^{13}C NMR		HSQC	HMBC
-	-	C1	133.6	-	C1xH2
H2	8.08 (d, *J* = 1.5 Hz, 1H)	C2	118.6	H2xC2	H2xC6, C4, C5, C3
-	-	C3	150.7	-	C3x H7
-	-	C4	149.0	-	C4xH2, H6
-	-	C5	157.3	-	C5xH2, H6
H6	8.03 (d, *J* = 1.0 Hz, 1H)	C6	114.6	H6xC6	H6xC2, C4, C5 C6xH8, H2
H7	4.09 (s, 3H)	C7	56.9	H7xC7	H7xC3 C7x -
H8	8.45 (s, 1H)	C8	128.1	H8xC8	H8xC6, C2, C9, C8x-
-	-	C9	148.4	-	C9x H8, H11
H10	7.04 (d, *J* = 8.5 Hz, 1H)	C10	126.5	H10xC10	H10xC12, C18 C10xH12
H11	7.46 (t, *J* = 8.0 Hz, 1H)	C11	127.7	H11xC11	H11x C13, C9 C11x-
H12	7.74 (d, *J* = 7.5 Hz, 1H)	C12	112.8	H12xC12	H12 xC14, C18 C12xH10
-		C13	134.0	-	C13xH11
H14	7.52 (m, 1H)	C14	126.3	H14xC14	H14x- C14xH16
H15	7.86 (dd, *J* = 7.0, 2.0 Hz, 1H)	C15	125.9	H15xC15	H15xC17 C15x-
H16	8.29 (dd, *J* = 7.0, 2.5 Hz, 1H)	C16	123.6	H16xC16	H16xC14 C16x-
H17	7.52 (m, 1H)	C17	126.0	H17xC17	H17x- C17xH15
-	-	C18	128.6		C18xH10, H12
H(O)	11.08 (br, s, 1H),	-	-	-	-

NMR spectral analysis of other compounds**3b**, **3c**, **3d** and **3e** was shown in the experimental section. All agreed with the expected products. Interestingly, compound **3d** was observed the tautomerization around the imine bond in $CDCl_3$; consequently, ^{13}C NMR spectrum was more complicated. Changing to DMSO solvent reduced that observation as shown.

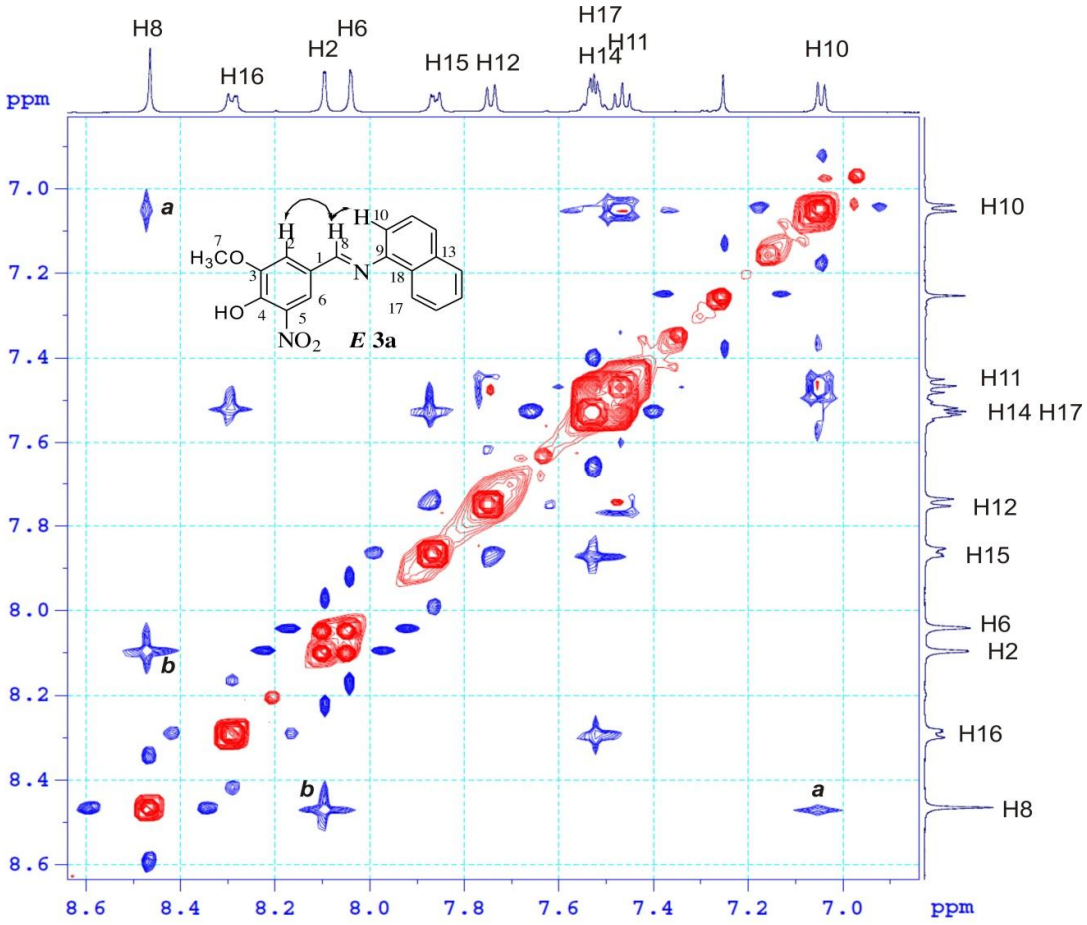


Figure 3. *A part of NOSY NMR spectrum of compound* ***3a***

In order to confirm E-conformation of the Schiff bases, NOSY spectrum of compound **3a** was studied, Figure 3 and Figure 4. It was found that the conformation of **3a** must be the ***E*-3a**. Because the cross peak ***a*** showed the H8 and H10 that were close to each other. In addition, the cross peak ***b*** improved that distance between H8 and H2 in space are short enough (see ***E*-3a**, in Figure 4). Interestingly, there were no data to see the naphthyl group flipped over to have a cross peak of H17 and H8 in the case of ***E*-3a'** in the NOSY spectrum.

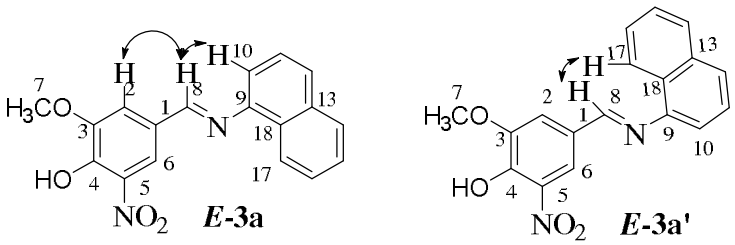


Figure 4. *Some examples of E and Z conformations around C=N bond*

4. Conclusion

Five new Schiff bases were synthesized by condensation reaction between 5-nitrovanillin and aromatic amines. The modification method of condensation reaction including drying reagent anhydrous $MgSO_4$, catalysis acetic acid in dry DCM was used to give high yield. Structures of Schiff bases were determined with spectroscopy methods such as NMR and MS. E conformation of C=N bond was determined with NOSY NMR spectrum.

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