HNUE JOURNAL OF SCIENCE DOI: 10.18173/2354-1059.2021-0037
Natural Sciences 2021, Volume 66, Issue 2, pp. 145-153
This paper is available online at http://stdb.hnue.edu.vn

STUDY ON SYNTHESIS AND STRUCTURE OF SOME HYDRAZONES FROM 3,4-DIMETHOXY-2-NITROBENZALDEHYDE

Truong Minh Luong[1] and Nguyen Thi My Hoa[2]
[1]*Faculty of Chemistry, Hanoi National University of Education*
[2]*Student of Faculty of Chemistry, Hanoi National University of Education*

Abstract. Three new hydrazones were synthesized by condensation reaction between 3,4-dimethoxy-2-nitrobenzaldehyde and aryl hydrazine hydrochlorides. 3,4-Dimethoxy-2-nitrobenzaldehyde needed for the Schiff base-imine condensation reaction was synthesized from vanillin through esterification, nitration, hydrolysis, and methylation reactions. All products were purified by re-crystallization in a suitable solvent. The structures of three new hydrazones were determined by ^{1}H NMR, ^{13}C NMR, and MS.

Keywords: vanillin, hydrazone, azomethine, 3,4-dimethoxy-2-nitrobenzaldehyde.

1. Introduction

Schiff bases are a class of compounds with unique biological [1], analytical and industrial properties [2]. A number of Schiff bases have been reported to possess antiglycation [3], antioxidant [4], antileishmanial [5], antifungal [6], anticancer [7], anticonvulsant [8], analgesic [9], and antituberculotic [10]. In addition, Schiff bases played an influencing role in the development of coordination chemistry and were involved as the key points in the development of inorganic biochemistry and optical materials [11]. Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions [12]. Some new Schiff base derivatives were synthesized in solvent-free processes, that is new environmental-friendly technology [13].

Vanillin (4-hydroxy-3-methoxybenzaldehyde), a dietary flavoring agent, is considered to be one of the most widely appreciated flavor compounds and has the unique characteristic that, even at high doses, the flavor is still pleasant [14]. Besides its flavor qualities, vanillin exhibits antimicrobial potential and has been used as a natural food preservative [15]. Some Schiff bases prepared from vanillin have good biological activity [16-18]. Some compounds such as Schiff bases, chalcones, heterocyclic compounds

Received June 11, 2021. Revised June 22, 2021. Accepted June 29, 2021.
Contact Truong Minh Luong, e-mail: luongtm@hnue.edu.vn

had been synthesized from vanillin by our group [19-23]. 3,4-Dimethoxy-2-nitrovanillin and their Schiff bases were synthesized from vanillin, which has been reported at [23]. In this paper, we are reporting some new hydrazones, which were synthesized from the 3,4-dimethoxy-2-nitrovanillin and aryl hydrazine hydrochlorides in the Parr reactor.

2. Content

2.1. Experiments

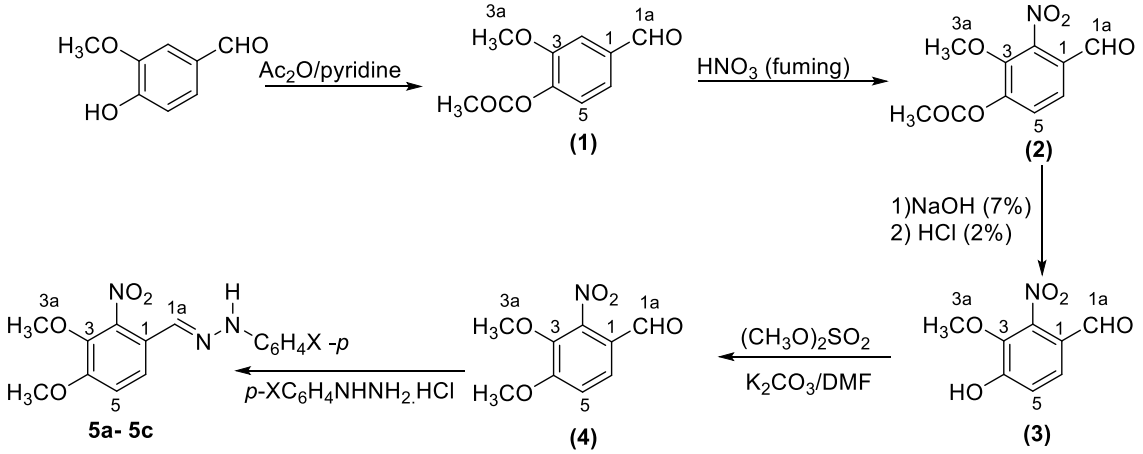
2.1.1. Materials and chemicals

All chemicals and reagents used in the current study were of analytical grade. Their chemicals were purchased from Sigma-Aldrich, Merck, and Aladdin.

The reactions were monitored by thin layer chromatography (TLC) on Merck pre-coated silica GF254 plates. ESI mass spectra were obtained on an LC-MSD-Trap-SL spectrometer, and ^{1}H NMR spectra were collected on a Bruker Avance 500 NMR spectrometer at room temperature with TMS and solvent signals allotted as internal standards. Chemical shifts are reported in ppm (δ). Some condensation reactions were conducted in the Parr reactor (model N.4544) under N_2 atmosphere and at 2.3 atm.

2.1.2. Synthetic procedure

The synthetic route to target compounds (**5a**, **5b,** and **3b**) is shown in scheme 1.



compound	5a	5b	5c
X	CH_3 -	O_2N -	Cl -

Scheme 1. Synthesis of the target compounds

**** Synthesis of 3,4-dimethoxy-2-nitrobenzaldehyde (4) [23]***

3,4-Dimethoxy-2-nitrobenzaldehyde (4) was synthesized from vanillin according to the ref. [23]. These products (**1**), (**2**), (**3**), and (**4**) were analyzed by TLC with standard chemicals.

**** Synthesis of Schiff bases***

General procedure:

A solution of 3,4-dimethoxy-2-nitrobenzaldehyde (0.032 g, 0.151 mmol, 211 g/mol) and aryl hydrazine hydrochloride (0.151 mmol) in absolute ethanol (5 mL) was added. The mixture was stirred and heated in the Parr reactor at 85 ^{o}C and 2.3 atm for 5 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion, the mixture was concentrated and then added water (20 mL). The precipitate was filtered and washed carefully with water and cold ethanol. Re-crystallization in ethanol gave the pure product.

*Synthesis of (E)-1-(3,4-dimethoxy-2-nitrobenzylidene)-2-(p-tolyl)hydrazine (**5a**)*

Using *3,4-dimethoxy-2-nitrobenzaldehyde (**4**)* (0.032 g, 0.151 mmol, 211 g/mol) and *p*-tolyl hydrazine hydrochloride (0.024 g, 0.151 mmol, 158 g/mol) gave **5a** as a deep yellow needle-shaped crystals (0.042 g, 88%, 315 g/mol): ESI-MS ($[M-1]^{+}$) ($C_{16}H_{16}N_3O_4$): Calcd: 314.3 and found: 314.0; MS ($[M+1]^{+}$) ($C_{16}H_{18}N_3O_4$): Calcd: 316.3 and found: 316.0; R_f = 0.62 (*n*-hexane/ethyl acetate = 2/1).

*Synthesis of (E)-1-(3,4-dimethoxy-2-nitrobenzylidene)-2-(4-nitrophenyl)hydrazine (**5b**)*

Using *3,4-dimethoxy-2-nitrobenzaldehyde (**4**)* (0.032 g, 0.151 mmol, 211 g/mol) and (4-nitrophenyl)hydrazine hydrochloride (0.029 g, 0.153 mmol, 189 g/mol) gave **5b** as a orange powder (0.045 g, 86 %, 346 g/mol). ESI-MS ($[M-1]^{+)}$ ($C_{15}H_{13}N_4O_6$): Calcd: 345.09 and found: 344.9; MS ($[M+1]^{+}$ ($C_{15}H_{15}N_4O_6$): Calcd: 347.09 and found: 346.9; R_f = 0.4 (*n*-hexane /ethyl acetate = 2/1).

*Synthesis of (E)-1-(4-chlorophenyl)-2-(3,4-dimethoxy-2-nitrobenzylidene)hydrazine (**5c**)*

Using *3,4-dimethoxy-2-nitrobenzaldehyde (**4**)* (0.032 g, 0.151 mmol, 211 g/mol) and (4-chlorophenyl)hydrazine hydrochloride (0.027 g, 0.151 mmol, 178 g/mol) gave **5c** as a light blue needle –shaped crystals (0.043 g, 85 %, 335 g/mol). MS ($[M-1]^{+)}$ ($C_{15}H_{13}ClN_3O_4$) : Calcd: 334.0 and found: 333.9; MS ($[M+1]^{+}$) ($C_{15}H_{15}ClN_3O_4$): Calcd: 336.0 and found: 335.9; R_f = 0.60 (*n*-hexane /ethyl acetate = 2/1).

2.2. Results and discussion

2.2.1. Synthesis hydrazones

The three hydrazone compounds were successfully synthesized as shown in scheme 1. These compounds were not found on Scifinder at the Leuven University (Belgium). 3,4-Dimethoxy-2-nitrobenzaldehyde (**4**) needed for the Schiff base-imine condensation reaction were not commercially available and therefore, it had to be synthesized. Vanillin was first esterified with Ac_2O in pyridine as a catalyst giving 4-formyl-2-methoxyphenyl acetate (**1**). In the second step, **1** was nitrated with HNO_3 (fuming) at -20^{o}C giving 4-formyl-2-methoxy-3-nitrophenyl acetate (**2**). In the third step, **2** was hydrolyzed with NaOH (7%), then treated with HCl (1M) giving 2-nitrovanillin (**3**). In the fourth step, **3** was methylated with $(CH_3O)_2SO_2$ giving 3,4-dimethoxy-2-nitrobenzaldehyde (**4).** It has been reported in [23]. These products **1**, **2**, **3,** and **4** were confirmed by TLC and compared with standard chemicals.

The synthesis of new hydrazones **5a**, **5b,** and **5c** was conducted through Schiff base-imine condensation reaction between 3,4-dimethoxy-2-nitobenzaldehyde (**4**) and aryl hydrazine hydrochloride compounds. In these reactions, aryl hydrazine chloride has two roles as a reactant and a catalyst, the reactions take place at high pressure (2.3 atm) and take place under N_2 atmosphere, so the condensation reactions occur more easily and form less byproducts. Synthesis of hydrazone compounds was carried out quite simply and in high yield as 5a (yield = 88%), 5b (yield = 86%), and 5c (yield = 85%). These products were easily purified by re-crystallization. The chemical structure of the prepared compounds **5a**, **5b,** and **5c** were confirmed by spectroscopic analysis.

2.2.2. Characterization of the structures of hydrazone compounds

**** MS spectra***

First of all, the negative mode-mass spectrum showed a base peak at *m/z* 344.9 au and the positive mode-mass spectrum showed a base peak at m/z 346.9 au that matched with the expected structure of compound **5b (**$C_{15}H_{14}N_4O_6$) (Figure 1).

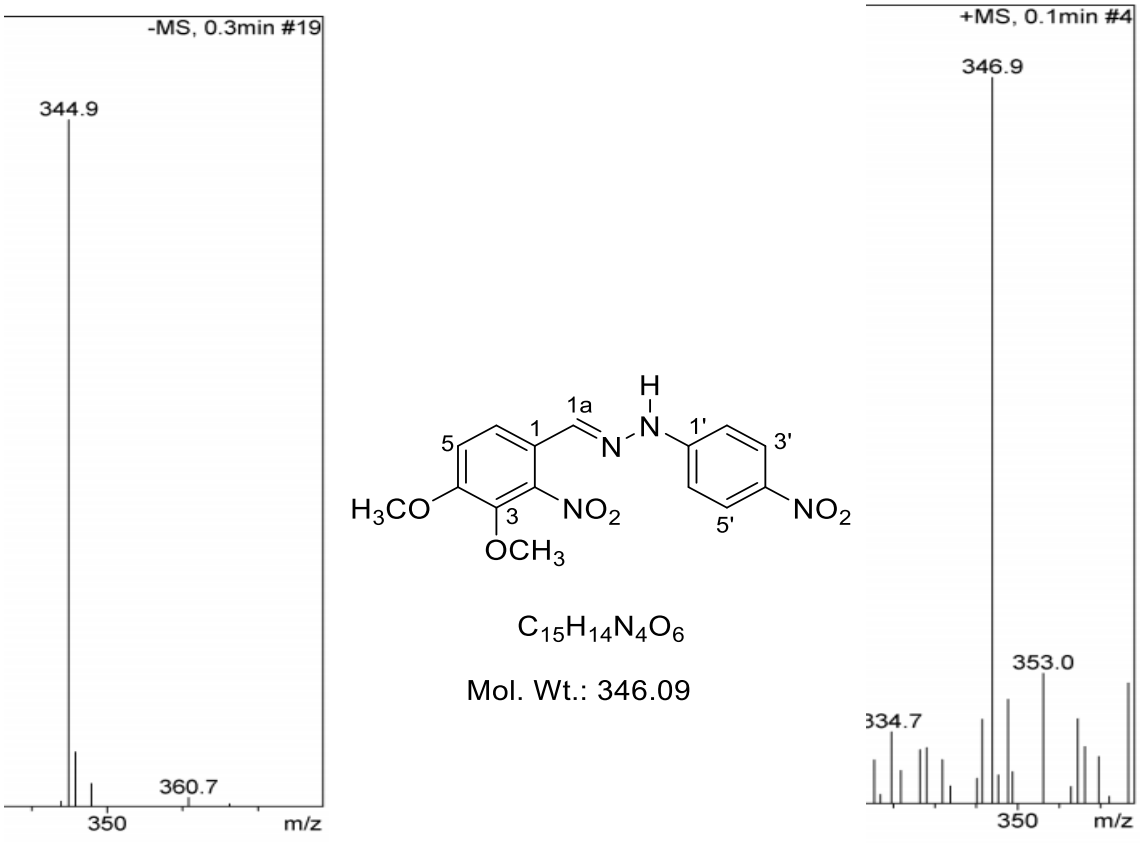


Figure 1. Part of MS spectra of compound 5b

Mass spectral analysis of other compounds **5b** and **5c** were shown in the experimental section. All of the results were consistent with the expected structure of products.

**** ^{1}H NMR spectrum***

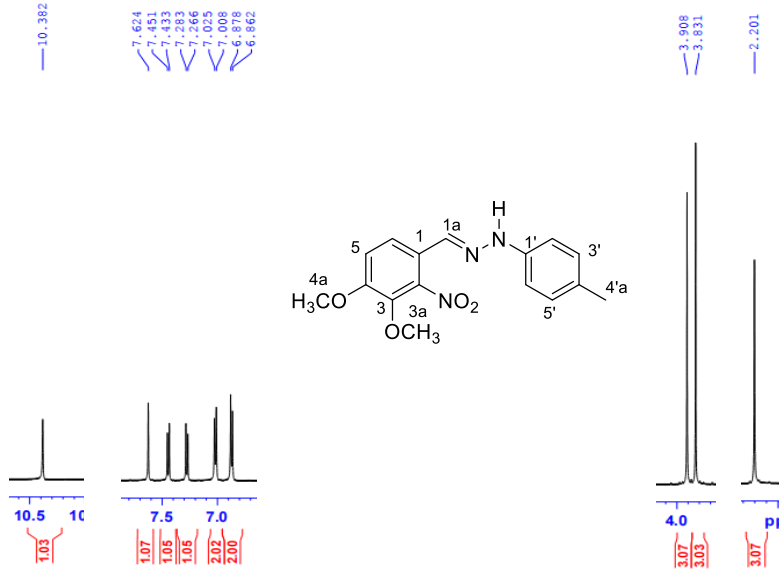
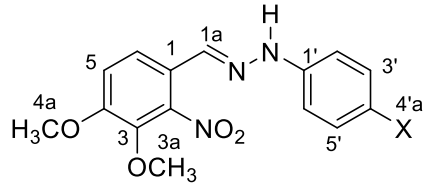


Figure 2. ^{1}H NMR spectrum of compound 5a

Table 1. ^{1}H NMR of hydrazones 5a, 5b, and 5c (DMSO-d_6, 500 MHz, δ (ppm), J (Hz))



Compound	5a	5b	5c
X-	CH_3-	O_2N-	Cl-
4a	3.83 (3H, s)	3.85 (3H, s)	3.84 (3H, s)
3a	3.91 (3H, s)	3.94 (3H, s)	3.93 (3H, s)
2', 6'	6.87 (2H, d, *J*= 8 Hz)	7.04 (2H, d, *J*=9 Hz)	6.95 (2H, d, *J*=9 Hz)
3', 5'	7.02 (2H, d, *J*= 8 Hz)	8.12 (2H, d, *J*=9 Hz)	7.25 (2H, d, *J*=8.5 Hz)
5	7.27 (1H, d, *J*=9 Hz)	7.34 (1H, d, *J*=9 Hz)	7.31 (1H, d, *J*=8.5 Hz)
6	7.44 (1H, d, *J*=9 Hz)	7.56 (1H, d, *J*=9 Hz)	
1a	7.62 (1H, s)	7.86 (1H, s)	7.68 (1H, s)
NH	10.38 (1H, s)	11.35 (1H, s)	10.61 (1H, s)
4'a	2.21 (3H, s)	-	-

^{1}H NMR spectrum of compound **5a** (Figure 2 and Table 1) indicated 17 protons including a broad proton signal at δ 10.38 ppm that was assigned for the proton of N-H group. One singlet signal at δ 7.62 ppm (s, 1H) was for H1a belonging to an imine group (-CH=N-). Three protons signal at δ 3.83 ppm (s, 3H) and 3 protons signal at δ 3.91 ppm (s, 3H) for H3a and H4a, 3 protons signal at 2.21 ppm (s, 1H) for H4'a. There were doublet peaks at δ 7.27 ppm (d, 1H, *J*= 9Hz) and 7.44 ppm (d, 1H, *J*= 9Hz) with a splitting constant of about 9 Hz which were for H5 or H6. Another two pairs of doublet were at δ*6.87* ppm (d, 2H, *J*= 8Hz) and 7.02 ppm (d, 2H, *J*= 8Hz) with a splitting constant of about 8Hz that must be for 2 protons at H2'+ H6' and 2 protons at H3' + H5'.

^{1}H NMR spectral analysis of other compounds **5b** and **5c** was shown in Table 1. All agreed with the expected products.

**** ^{13}C NMR spectrum***

^{13}C NMR spectrum of compounds **5a** (Figure 3 and Table 2) indicated 14 peaks associated with 16 carbon atoms. Certainly, a peak at δ 20.2 ppm was assigned for C4'a. Peaks at δ 56.5 ppm and δ 61.8 ppm were assigned for C3a and C4a respectively. Eleven peaks that appeared from 114.8 ppm to 152.0 ppm were assigned for carbons of aromatic and imine parts.

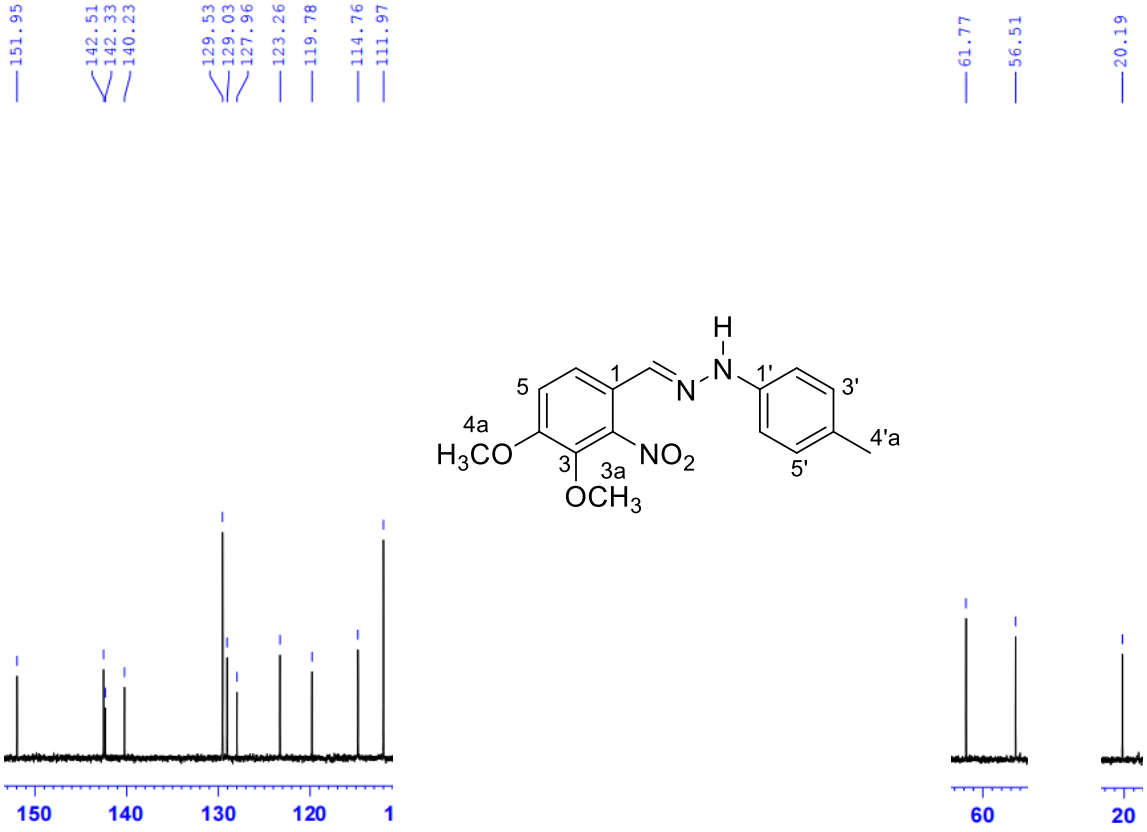
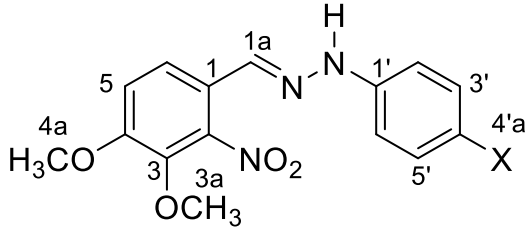


Figure 3. ^{13}C NMR spectrum of hydrazone 5a

^{13}C NMR spectral analysis of other compounds **5b** and **5c** was shown in Table 2. All the peaks were matched with the signals of the carbons in the expected structures.

Table 2. ^{13}C NMR spectrum of hydrazones 5a, 5b, and 5c

(DMSO-d_6, 125 MHz, δ (ppm))



Compound	**5a**	**5b**	**5c**	**Compound**	**5a**	**5b**	**5c**
X-	CH_3-	O_2N-	Cl-	X-	CH_3-	O_2N-	Cl-
3a	56.5	56.6	56.5	1a	142.5	150.1	143.7
4a	61.8	61.8	61.8	1’	129.0	138.9	130.8
1	119.8	118.3	119.2	2’, 6’	112.0	111.2	113.3
2	142.3	142.6	142.4	3’, 5,	129.5	126.0	128.9
3	140.2	140.3	140.2	4’	128.0	135.3	122.6
4	152.0	152.2	152.3	4’a	20.2	-	-
5	114.8	114.7	114.7				
6	123.3	124.7	123.7				

3. Conclusions

In summary, three new hydrazone derivatives **5a**, **5b,** and **5c** were synthesized by condensation reaction between 3,4-dimethoxy-2-nitrovanillin and aromatic hydrazine hydrochloride compounds. Structures of new hydrazone derivatives were determined with spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, and MS.

REFERENCES

[1] Khan, K.M. Shah, Z.; Ahmad, V.U.; Khan, M.; Taha, M.; Rahim, F.; Jahun, H.; Perveen, S.; Choudhary, M.I., 2011. Synthesis of 2,4,6-trichlorophenyl hydrazones and their inhibitory potential against glycation of protein. *Med. Chem., 7*, pp. 572-580.

[2] Musharraf, S.G.; Bibi, A.; Shahid, N.; Najam-ul-Haq, M.; Khan, M.; Taha, M.; Mughal, U.R.; Khan, K.M., 2012. Acylhydrazide and isatin Schiff bases as alternate UV-laser desorption ionization (LDI) matrices for low molecular weight (LMW) peptides analysis. *Am. J. Anal. Chem.*, 3, pp. 779-789.

[3] Taha, M.; Naz, H.; Rasheed, S.; Ismail, N.H.; Rahman, A.A.; Yousuf, S.; Choudhary, M.I., 2014. Synthesis of 4-methoxybenzoylhydrazones and evaluation of their antiglycation activity. *Molecules,* 19, pp. 1286-1301.

[4] Khan, K.M.; Taha, M.; Naz, F.; Ali, S.; Perveen, S.; Choudhary, M.I., 2012. Synthesis of acylhydrazide Schiff bases and their anti-oxidant activity. *Med. Chem.,* 8, pp. 705-710.

[5] Taha, M.; Baharudin, M.S.; Ismail, N.H.; Khan, K.M.; Jaafar, F.M.; Samreen; Siddiqui, S.; Choudhary, M.I., 2013. Synthesis of 2-methoxybenzoylhydrazone and evaluation of their antileishmanial activity. *Bioorg. Med. Chem. Lett.,* 23, pp. 3463-3466.

[6] Sundriyal, S.; Sharma, R.K.; Jain, R., 2006. Current advances in antifungal targets and drug development. *Curr. Med. Chem.,* 13, pp. 1321-1335.

[7] Popp, F.D.; Kirsch, W.J., 1961. Synthesis of potential anticancer agents. V. Schiff bases and related compounds. *J. Org. Chem.,* 26, pp. 3858-3860.

[8] Jain, J.S.; Srivastava, R.S.; Aggarwal, N.; Sinha, R., 2007. Synthesis and evaluation of Schiff bases for anticonvulsant and behavioural depressant properties. *Cent. Nerv. Syst. Agents Med. Chem.,* 7, pp. 200-204.

[9] Chinnasamy, R.P.; Sundararagan, R.; Govindaraj, S., 2010. Synthesis, characterization and analgesic activity of novel Schiff base isatin derivatives. *Soc. Pharm. Edu. Res.,* 1, pp. 342-347.

[10] Pandey, A.; Dewangan, D.; Verma, S.; Mishra, A.; Dubey, R.D., 2011. Synthesis of Schiff bases of 2-amino-5-aryl-1, 3,4-thiadiazole and its analgesic, anti-inflammatory, antibacterial and antitubercular activity. *Int. J. Chem. Tech. Res.,* 3, pp. 178-184.

[11] F. Tisato, F. Refosco, and G. Bandoli, 1994. Structural survey of technetium complexes. *Coordination Chemistry Reviews*, Vol. 135-136, pp. 325-397.

[12] A. Jarrahpour, D. Khalili, E. De Clercq, C. Salmi, and J. M. Brunel, 2007. Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. *Molecules*, Vol. 12, No. 8, pp. 1720-1730.

[13] A. Bhattacharya, V. C. Purohit, and F. Rinaldi, 2003. Environmentally friendly solvent-free processes: novel dual catalyst system in Henry reaction. *Organic Process Research and Development*, Vol. 7, No. 3, pp. 254-258.

[14] H. Korthou, R. Verpoorte, 2007. Vanilla. *Flavours and Fragrances*, Vol. 9, pp. 203-217.

[15] Patrica Cerrutti, Stela M. Alzamoza, Susana L. Vidales, 2006. Vanillin as an Antimicrobial for Producing Shelf-stable Strawberry Puree. *J. Food Science,* 62 (3), pp. 608-610.

[16] Juan Sun, Yong Yin, Gui-Hua Sheng, Zhi-Bo Yang, Hai-Liang Zhu, 2013. Synthesis, molecular modeling and structural characterization of vanillin derivatives as antimicrobial agents. *J. Molecular Structure*, 1039, pp. 214-218.

[17] Juan Sun, Ming-Hui Li, Xin-Yi Wang, Yang Zhang, Rong-Ju Yuan, Han-Yu Liu, Hai-Liang Zhu, 2014. Vanillin derivatives as the selective small molecule inhibitors of FtsZ. *Med. Chem. Res*., 23(6), pp. 2985-2994.

[18] Nguyen Kim Thu, Giang Thi Son, Tran Manh Binh, 1998. Study on synthesis some β-aminocketone derivatives of vanillin and preliminary exploration of biological activity. *Vietnam J. Pharm*., 12, pp. 10-13 (in Vietnamese).

[19] Truong Minh Luong, 2017. Synthesis, structure and biological evaluation of some azomethine and hydrozone derivatives from 2-nitrovanilline. *Vietnam J. Chem.*, 55 (5E34) (in Vietnamese).

[20] Truong Minh Luong, Nguyen Thi Huong Cam, Tran Thi Thai Ha, 2017. Study on synthesis, structure and biological activity of some azomethine, thiazolidine-4-one derivatives from 4,5-dimethoxy-2-nitrobenzaldehyde. *Vietnam J. Chem.*, 55 (5E34), pp. 78-83 (in Vietnamese).

[21] Truong Minh Luong, Nguyen Thi Hong Nhung, 2019. Study on synthesis, structure of some (E)-1-aryl-3-(4-hydroxy-3-methoxy-2-nitrophenyl)prop-2-en-1-one compounds from vanillin. *Vietnam J. Chem.*, 57 (4e34), pp. 35-39 (in Vietnamese).

[22] Truong Minh Luong and Ngo Thi Lien, 2019. Study on synthesis, structure and biological activity of two new thiazolidine-4-one derivatives from 2-nitrovanillin. *HNUE Journal of Science*, 64 (3), pp. 89-96 (in Vietnamese).

[23] Trương Minh Lương, Nguyen Thị My Hoa, Nguyen Thị Hong Nhung, 2019. Study on synthesis, structure and biological activity of some azomethine and hydrazone of 3,4-dimethoxy-2-nitrobenzaldehyde. *Vietnam J. Chem.*, 57 (e1,2), pp. 79-84 (in Vietnamese).