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SHORT COMMUNICATION

Synthesis and Spectral Characterization of 4-Hydroxy-3-Methoxybenzaldehyde Derivatives

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ABSTRACT

Vanillin plays an important role in flavouring and as aroma agent. Vanillin has been used as a chemical intermediate in pharmaceutical and chemical syntheses. Schiff base products have been proved to poses beneficial biological effect towards health. Fourteen vanillin derivatives were synthesized *via* Schiff base reaction using p-vanillin as the starting material reacted with 2-aminobenzenethiol, furan-2-carbohydrazide, 2-hydrazinylpyridine, 4-hydroxybenzohydrazide, acetohydrazide, benzohydrazide, (diphenylmethylidene) hydrazine, pyridine-4-carbohydrazide, benzene-1,2-diamine, phenylhydrazine, 2-hydroxybenzohydrazide, 1,3-benzothiazol-2-amine, 1-cyclohexylthiourea respectively. All of the compounds were characterized by elemental analysis, FTIR and ^{1}H NMR.

Keywords: Vanillin, Schiff bases, Amines

Para-vanillin is an organic compound which can be found synthetically or naturally in vanilla plant and one of the most widely used as flavouring agents (Chobpattana *et al*., 2000; Fitzgerald *et al*., 2005; Walton *et al*., 2003). The chemical structure of p-vanillin is shown in Figure 1.

Many researchers used 4-hydroxy-3-methoxybenzaldehyde (vanillin) as a starting material for Schiff bases reaction. Schiff bases are compounds of containing C=N group. These compounds are often synthesized from amine and aldehyde and possess diverse biological activities (Li *et al*., 2003). Schiff base derivatives are widely used in chemical and pharmaceutical application such as the combination of thiazolyl and benzothiazolyl rings with vanillin type moiety for their anti-inflammatory activity (Litina & Geronikaki, 2003), antimicrobial (Pandeya *et al*., 1999a), antifungal (Pandeya *et al*., 1999b, 1999c; Popp, 1964), anti-HIV (Hodnett & Dunn, 1970; Samadhiya & Halve, 2001), anti-tumor activities and as herbicides (Latif *et al*, 1983). In this work, we report the reaction of *p*-vanillin with various types of amine compounds. The general synthesis rote of the Schiff bases is shown in Scheme 1. They have been characterized by elemental analysis (CHN), FTIR and ^{1}H NMR.

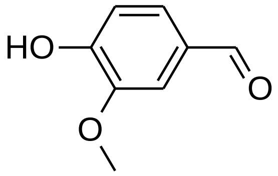

Figure 1. Structure of *p*-vanillin.

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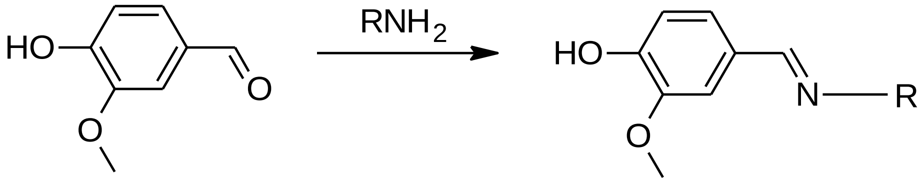
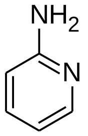


R = primary amine

Scheme 1. The general synthesis route of the Schiff bases.

R=



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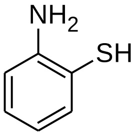

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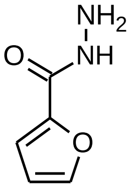

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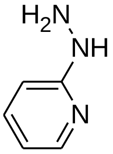

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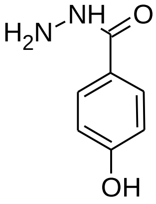

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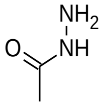

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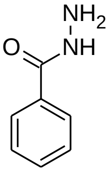

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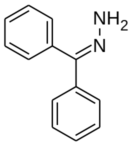

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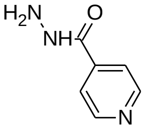

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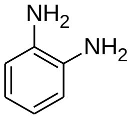

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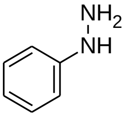

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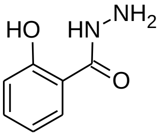

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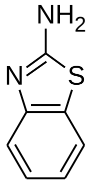

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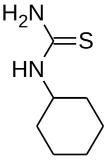

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EXPERIMENTAL

General procedures

Reagents and chemicals were purchased from Fluka (Switzeland), Aldrich (Steinheim, Germany), Merck (Hohenbrunn, Germany) and Acros (Geel, Belgium) were used without further purification. All solvents were purified according to the standard procedures (Armarego & Perrin, 1996). The melting point was measured using open capillary in Stuart MP3. The FTIR spectra were obtained on KBr disc using a Perkin Elmer Spectrum GX Fourier-Transform Spectrometer (4000–370 cm^{-1}). ^1H NMR spectra were recorded in DMSO-d_6, Acetone-d_6, $CDCl_3$ or MeOH-d_3 solution on a JEOL 500 MHz NMR spectrophotometer. Chemical shifts were reported downfield in part per million (ppm) from a tetramethylsilane (TMS) reference and coupling constants (*J*) were measured in Hz. Finally the synthesized compounds were characterized using Flesh EA 1112 for the elemental (CHN) analysis to determine the elemental percentage of carbon, hydrogen and nitrogen in each synthesized compounds.

Synthesis of 2-methoxy-4-[(*E*)-(pyridin-2-ylimino)methyl]phenol (1)

Pyridine-2-amine (0.94 g, 10 mmol) was dissolved in 20 mL of absolute ethanol before mixing it with 20 mL of ethanolic solution of *p*-vanillin (1.52 g, 10 mmol). The mixture was heated under reflux for 5 h as shown in Scheme 2. The solution was allowed to cool to room temperature for 30 minutes. The compound was filtered off and washed using absolute ethanol. The compound was purified by crystallization from hot ethanol and dried *in vacuo* over silica gel. Yield 80%, orange powder, mp 108-112°C. FTIR (KBr, cm^{-1}) υ_{max} : 3450 (O-H), 1608 (C=N), 1077 (C-O), 733 (pyridine in plane); ^{1}H NMR (DMSO-d_6) δ: 8.47 (s, 1H), 8.54 (m, 1H), 7.93 (m, 1H), 7.46 (m, 1H), 7.36 (m, 2H), 7.17 (m, 1H), 6.93 (m, 1H), 3.83 (s, 3H) ppm. Calc. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%. Found: C, 68.06; H, 5.13; N, 12.05%.

The other compounds were synthesized using a similar procedure using appropriate fourteen amine compounds, respectively: 2-aminobenzenethiol, furan-2-carbohydrazide, 2-hydrazinylpyridine, 4-hydroxybenzohydrazide, acetohydrazide, benzohydrazide, (diphenylmethylidene)hydrazine, pyridine-4-carbohydrazide, benzene-1,2-diamine, phenylhydrazine, 2-hydroxybenzohydrazide, 1,3-benzothiazol-2-amine, 1-cyclohexylthiourea. Figure 2 shows the compounds of Schiff bases (2-14).

Synthesis of 2-methoxy-4-{(*E*)-[(2-sulfanylphenyl)imino]methyl}phenol (2)

Yield 85%, orange crystal, mp 149-150°C. IR (KBr, cm^{-1}) υ_{max} : 3450 (O-H), 3051 (N-H), 2500-2700 (S-H), 1613 (C=N), 1081 (C-O); ^{1}H NMR (DMSO-d_6) δ: 9.00 (s, 1H), 7.57 (m, 1H), 7.50 (m, 1H), 7.36 (m, 1H), 7.30 (m, 2H), 7.18 (m, 1H), 6.96 (m, 1H), 3.86 (s, 3H) ppm; Calc. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40%. Found: C, 63.64; H, 4.45; N, 5.65%.

Synthesis of *N*'-[(*E*)-(4-hydroxy-3-methoxyphenyl)methylidene]furan-2-carbohydrazide (3)

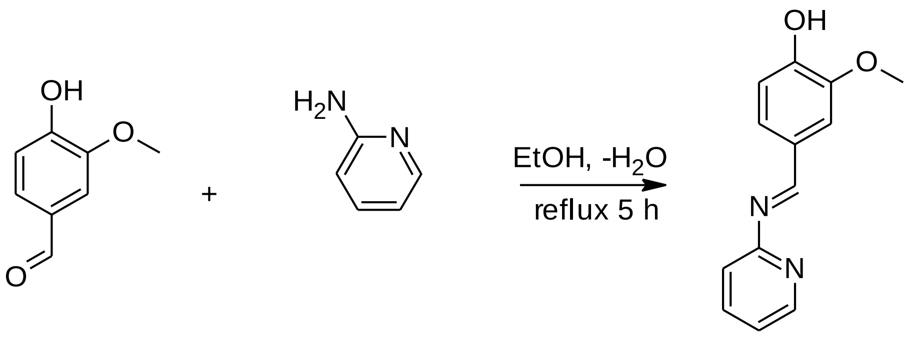
Yield 80%, yellow crystal, mp 155-159°C. IR (KBr, cm^{-1}) υ_{max} : 3583 (O-H), 3133 (N-H), 1609 (C=N), 1656 (C=O-NH), 1079 (C-O), 966 (N-N); ^{1}H NMR (Acetone-d_6) δ: 8.64 (s, 1H), 7.78 (s, 1H), 7.02 (s, 1H), 7.03 (m, 2H), 6.87 (m, 1H), 6.67 (m, 1H), 3.85 (s, 3H) ppm; Calc. for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.76%. Found: C, 56.0; H, 4.90; N, 10.55%.

Synthesis of 2-methoxy-4-{(*E*)-[2-(pyridin-2-yl)hydrazinylidene]methyl}phenol (4)

Yield 75%, white crystal, mp 203-206°C. IR (KBr, cm^{-1}) υ_{max}: 3445 (O-H), 3192 (N-H), 1603 (C=N), 1093 (C-O), 991 (N-H), 729 (pyridine in plane); ^{1}H NMR (Acetone-d_6) δ: 8.32 (s, 1H), 8.16 (d, J=3.8 Hz, 1H), 7.69 (m, 1H), 7.08 (m, 2H), 7.05 (m, 1H), 6.86 (m, 2H), 3.89 (s, 3H) ppm. Calc. for $C_{13}H_{13}N_3O_2$: C, 64.29; H, 5.39; N, 17.27%. Found: C, 63.94; H, 5.63; N, 18.32%.

Synthesis of 4-hydroxy-*N*'-[(*E*)-(4-hydroxy-3-methoxyphenyl) methylidene] benzohydrazide (5)

Yield 85%, yellow crystal, mp 205-206°C. IR (KBr, cm^{-1}) υ_{max}: 3450 (O-H), 3217 (N-H), 1610 (C=N), 1647 (C=O-NH), 1079 (C-O), 969 (N-H); ^{1}H NMR (DMSO-d_6) δ: 8.63 (s, 1H), 7.88 (d, j=8.4 Hz, 2H), 7.11 (d, j=7.65 Hz, 1H), 6.98 (d, j=7.65 Hz, 1H), 6.92 (d, j=8.4 Hz, 2H), 6.84 (m, 1H), 3.79 (s, 3H) ppm. Calc. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79%. Found: C, 62.38; H, 4.79; N, 9.77%.



Vanillin pyridine -2-amine (**1**)

Scheme 2. Synthesis pathway of compound 1.

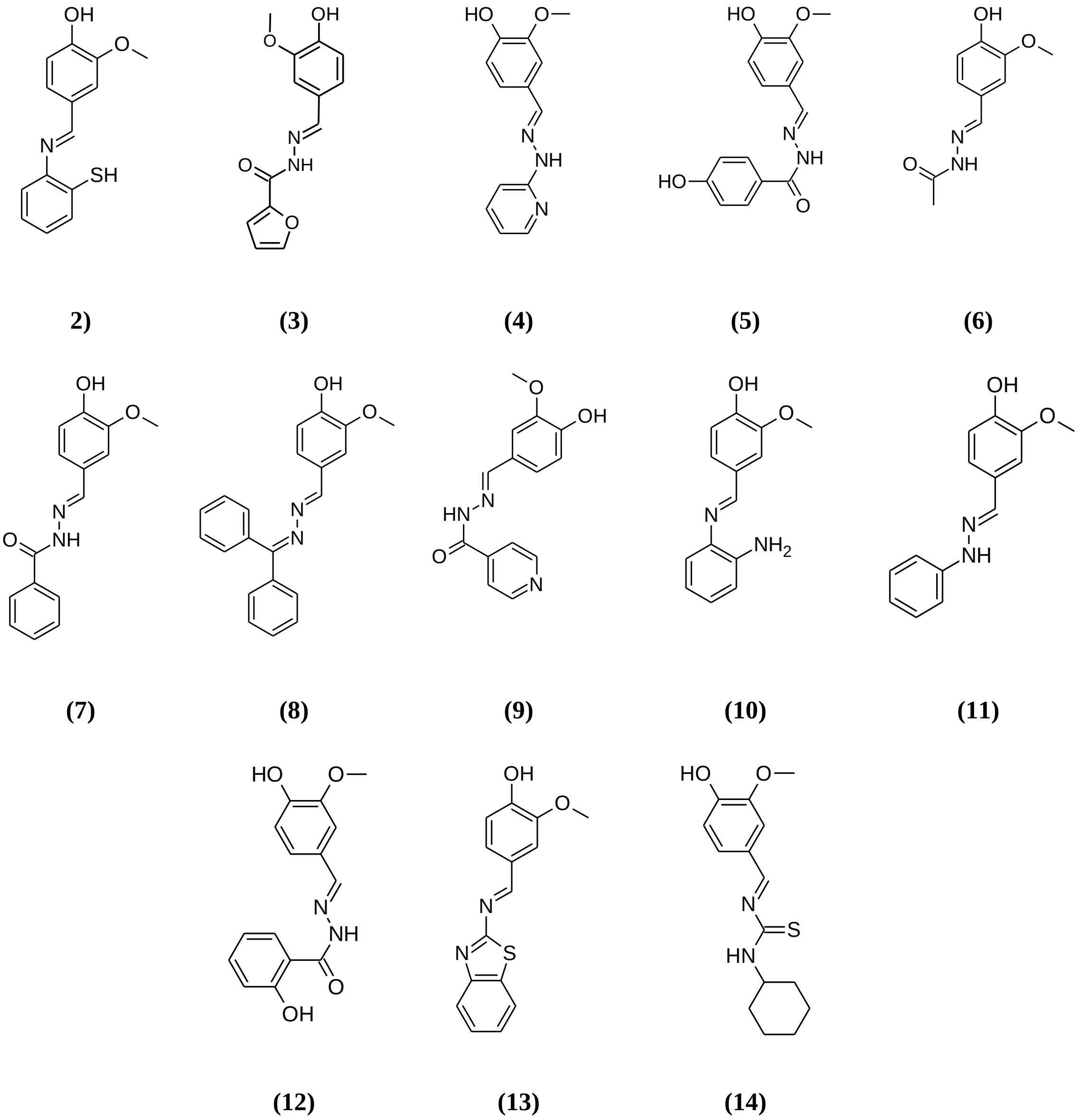


Figure 2. Structures of synthesized vanillin derivatives.

Synthesis of *N*'-[(*E*)-(4-hydroxy-3-methoxyphenyl)methylidene]acetohydrazide (6)

Yield 80%, white crystal, mp 216-218°C. IR (KBr, cm^{-1}) υ_{max}: 3468 (O-H), 3188 (N-H), 1577 (C=N), 1678 (C=O-NH), 1078 (C-O), 973 (N-H); ^1H NMR (DMSO-d_6) δ: 8.32 (s, 1H), 7.22 (dd, *j*=7.65, 7.65 Hz, 1H), 7.00 (m, 1H), 6.84 (m, 1H), 3.49 (s, 3H), 1.05 (s, 3H) ppm. Calc. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45%. Found: C, 57.83; H, 5.82; N, 13.76%.

Synthesis of *N*'-[(*E*)-(4-hydroxy-3-methoxyphenyl)methylidene]benzohydrazide (7)

Yield 85%, yellow crystal, mp 203-205°C. IR (KBr, cm^{-1}) υ_{max}: 3569 (O-H), 3205 (N-H), 1606 (C=N), 1654 (C=O-NH), 1077 (C-O), 965 (N-H); ^1H NMR (DMSO-d_6) δ: 8.65 (s, 1H), 7.94 (d, *j*=7.65 Hz, 2H), 7.62 (m, 3H), 7.15 (d, *j*=7.65 Hz, 1H), 7.04 (d, *j*=8.4 Hz, 1H), 6.88 (m, 1H), 3.81 (s, 3H) ppm. Calc. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36%. Found: C, 64.83; H, 5.22; N, 10.21%.

Synthesis of 4-{(*E*)-[(diphenylmethylidene)hydrazinylidene]methyl}-2-methoxyphenol (8)

Yield 85%, yellow crystal, mp 96-98°C. IR (KBr, cm^{-1}) υ_{max}: 3450 (O-H), 1610 (C=N), 1079 (C-O) 966 (N-N); ^{1}H NMR (DMSO-d_6) δ: 8.78 (s, 1H), 7.73 (m, 2H), 7.47 (m, 4H), 7.39 (m, 2H), 7.29 (m, 2H), 6.94 (m, 1H), 6.90 (m, 1H), 6.84 (m, 1H), 3.82 (s, 3H) ppm. Calc. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48%. Found: C, 76.00; H, 5.28; N, 8.52%.

Synthesis of *N*'-[(*E*)-(4-hydroxy-3-methoxyphenyl)methylidene]pyridine-4-carbohydrazide (9)

Yield 85%, yellow crystal, mp 236-239°C. IR (KBr, cm^{-1}) υ_{max}: 3459 (O-H), 3202 (N-H), 1602 (C=N), 1690 (C=O-NH), 1080 (C-O), 973 (N-N), 740 (pyridine in plane); ^{1}H NMR (DMSO-d_6) δ: 8.79 (s, 2H), 8.69 (s, 1H), 7.84 (d, *j*=4.55 Hz, 2H), 7.20 (d, *j*=7.65 Hz, 1H), 7.05 (d, *j*=7.6 Hz, 1H), 3.81 (s, 3H) ppm. Calc. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49%. Found: C, 61.71; H, 4.79; N, 15.20%.

Synthesis of 4-{(*E*)-[(2-aminophenyl)imino]methyl}-2-methoxyphenol (10)

Yield 80%, orange crystal, mp 96-98°C. IR (KBr, cm^{-1}) υ_{max}: 3465 (O-H), 3370 (N-H), 1625 (C=N), 1078 (C-O); ^{1}H NMR (DMSO-d_6) δ: 8.84 (s, 1H), 7.26 (d, *j*=7.65 Hz, 1H), 7.14 (m, 2H), 7.03 (m, 1H), 6.92 (m, 1H), 6.79 (d, *j*=7.65 Hz, 1H), 6.64 (m, 1H), 5.07 (s, 2H), 3.82 (s, 3H) ppm. Calc. for $C_{13}H_{13}N_2O_2$: C, 69.40; H, 5.82; N, 11.56%. Found: C, 68.55; H, 5.97; N, 11.61%.

Synthesis of 2-methoxy-4-[(*E*)-(2-phenylhydrazinylidene)methyl]phenol (11)

Yield 90%, yellow crystal, mp110-111°C. IR (KBr, cm^{-1}) υ_{max}: 3592 (O-H), 3295 (N-H), 1604 (C=N), 1094 (C-O), 974 (N-N); ^{1}H NMR (CDCl$_3$) δ: 7.83 (s, 1H), 7.27 (m, 2H), 6.97 (m, 2H), 7.00 (m, 4H), 3.90 (s, 3H) ppm. Calc. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56%. Found: C, 69.40; H, 5.77; N, 11.78%.

Synthesis of 2-hydroxy-*N*'-[(*E*)-(4-hydroxy-3-methoxyphenyl) methylidene] benzohydrazide (12)

Yield 80%, yellow crystal, mp 258-259°C. IR (KBr, cm^{-1}) υ_{max}: 3440 (O-H), 3231 (N-H), 1607 (C=N), 1700 (C=O-NH), 1079 (C-O), 952 (N-N); ^{1}H NMR (DMSO-d_6) δ: 8.69 (s, 1H), 7.90 (d, *j*=8.4 Hz, 1H), 7.47 (m, 1H), 7.18 (m, 1H), 7.06 (m, 4H), 3.82 (s, 3H) ppm. Calc. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79%. Found: C, 63.22; H, 4.36; N, 10.19%.

Synthesis of 4-[(*E*)-(1, 3-benzothiazol-2-ylimino)methyl]-2-methoxyphenol (13)

Yield 80%, orange crystal, mp 183-187°C. IR (KBr, cm^{-1}) υ_{max}: 3440 (O-H), 1607 (C=N), 1079 (C-O); ^{1}H NMR (CDCl$_3$) δ: 8.23 (s, 1H), 7.95 (d, *j*=8.4 Hz, 1H), 7.82 (d, *j*=7.65 Hz, 1H), 7.48 (m, 1H), 7.36 (m, 1H), 7.11 (d, *j*=7.65 Hz, 1H), 7.04 (d, *j*=7.65 Hz, 1H), 6.92 (m, 1H), 3.91 (s, 3H) ppm. Calc. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85%. Found: C, 63.94; H, 5.18; N, 9.71%.

Synthesis of 1-cyclohexyl-3-[(*E*)-(4-hydroxy-3 methoxyphenyl) methylidene]thiourea (14)

Yield 80%, white crystal, IR (KBr, cm^{-1}) υ_{max}: 3442 (O-H), 3358 (N-H), 2930, 2852 (cyclohexyl), 1639 (C=N), 1259 (C-O), 947 (N-N), 1326, 838 (C=S); 11.79 (OH), 9.63 (N3-H), 8.82 (N2-H), ^{1}H NMR (CDCl$_3$) δ: 8.33 (s, 1H, CyC1-H), 7.93-7.19 (m, 3H, phenyl ring), 2.91 (s, 3H, OCH$_3$), 2.50-2.12(m, 10H, CyC-H). Calc. for $C_{15}H_{20}N_2O_2S$: C, 61.51; H, 7.27; N, 9.54%. Found: C, 61.90; H, 6.63; N, 10.10%.

p-Vanillin derivatives (1-14) were synthesized by the condensation with the mole ratio of vanillin to primary amines, 1:1 at reaction temperature of 50-60°C for about five hours reaction time. The compounds are air-stable both in the solid-state and in nitrogen atmosphere and soluble in common organic solvents. The vanillin derivatives possess structurally divers with high yield of more than 80%. From Infrared spectroscopic analysis, several characteristics band were observed in the synthesized *p*-vanillin derivatives at 3295-3583 cm^{-1} which assign to υ (O-H), 3051-3370 to υ (N-H), 947-991 to υ (N-N), 1577-1639 to υ (C=N), 1647-1700 to υ (C=O) and 729-740 to υ (pyridine in plane). All Schiff bases compounds shows stretch absorption of O-H bond of phenol. The band stretch absorption of C=N shows the condensation part of *p*-vanillin and the amines, respectively indicating the conjugation has occurred. The bands corresponding to C=O-NH are present in compounds 3, 5, 6, 7, 9 and 12. Compounds 1, 4 and 9 possess pyridine ring which shows absorption band at 729-740 cm^{-1}. In the ^{1}H NMR spectra of *p*-vanillin, the HC=O group resonance signal is observed as a singlet at 9.76 ppm (data not shown). This signal is not seen in the synthesized compounds but a signal of an azomethine (HC=N) proton appears in the spectra 7.83-9.00 ppm, of the respective compounds. Thus, the appearance of the azomethine proton signal and the disappearance of the HC=O group resonance signal both suggest the condensation of the proposed synthesized compounds. These results of analyses confirmed the structure of aim compounds.

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