Synthesis and Structural Studies of O-vanillin Indomethacin Hydrazone and P-vanillin Indomethacin Hydrazone

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Abstract

Three steps of two novel ligands of Indomethacin hydrazide based Schiff bases ligands were synthesized. For our targeted ligands, first we synthesized Indomethacin Ethyl Ester ($RCOOC_2H_5$), This ester was further reacted with hydrazine hydrate to produce Indomethacin acid hydrazide ($RCONHNH_2$). Finally, this hydrazide condensed with ***o*-Vanillin and *p*-Vanillin** to get targeted compounds. Structure confirmation was characterized based on IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Keywords: NSIADs, Indomethacin, *o*-Vanillin, *p*-Vanillin, acid hydrazide, Hydrazone, transition metal complexes, Hydrazide Base Schiff Bases.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSIADs) are among the most common classes of drugs that have analgesic, anti-inflammatory and antipyretic properties [1]. Indomethacin (Hind, Fig. 1) or 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1h-indole-3-acetic acid, is a powerful human anti-inflammatory drug that used in the treatment of a variety of severe inflammatory conditions; by reducing the synthesis of prostaglandins from arachidonic acid through the inhibition of the cyclooxygenase enzymes, COX-1 and COX-2, but it has been noticed that the inhibition of COX-1 produced some toxic effects particularly in the gastrointestinal tract. Therefore, many studies have been done to make these drugs more selective toward the inhibition of COX-2 so it would be safer and more effective [2-3]. The coordination of drug molecules to metal ions has considerable potential to increase the arsenal for treating a variety of diseases by improving the pharmacological activity and reducing the side effects in comparison with the parent drug. Over the past few years many organometallic compounds or metal-based drugs have been synthesized and characterized and their biochemical properties investigated [4-9].

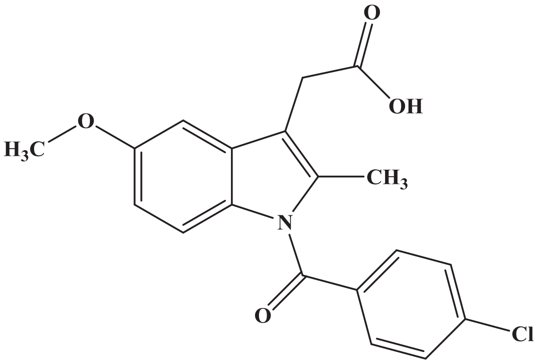


Figure 1. Structural formula of Indomethacin.

One of largely used families of organic compounds includes "Schiff bases" or imines ($^{-}$N=C<). They are used as artificial intermediates and also in coordination chemistry as chelating ligands [10] which play an important role in inorganic chemistry as they easily form stable complexes with most transition metal ions. The coordination chemistry of transition metals with ligands from the hydrazide family has been of interest due to different bonding modes shown by these ligands with both electron rich and electron poor metals. The remarkable biological activity of acid hydrazides ($RCONHNH_2$) [11], a class of Schiff base, their corresponding hydrazones (RCONHN=C<) and the dependence of their mode of chelation [12-13] with transition metals ions present in the living system have been of significant interest [11].

Vanillin is an inexpensive, human benign and readily available flavor, which has been widely used in food, beverage, and pharmaceutical industry. As a corrosion inhibitor [14], but there were only a few reports about its ability of combined with metal ions [15]. The structural formula of *o*-Vanillin is shown Fig. 2a and *p*-Vanillin is shown Fig. 2b.

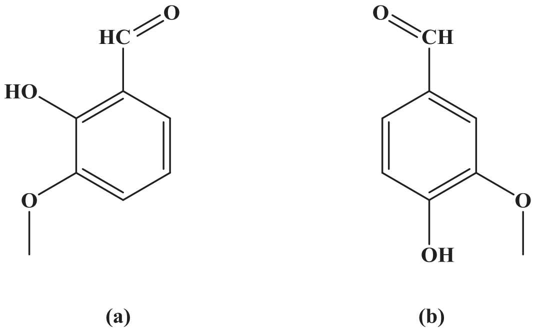


Figure 2. a) Structural formula of *o*-Vanillin, and **2. b)** Structural formula of *p*-Vanillin

In this paper, we report the synthesis and characterizing studies of the ligands *o*-Vanillin Indomethacin Hydrazone and *p*-Vanillin Indomethacin Hydrazone.

2. Experimental:

2.1. Materials, Reagents and Solutions:

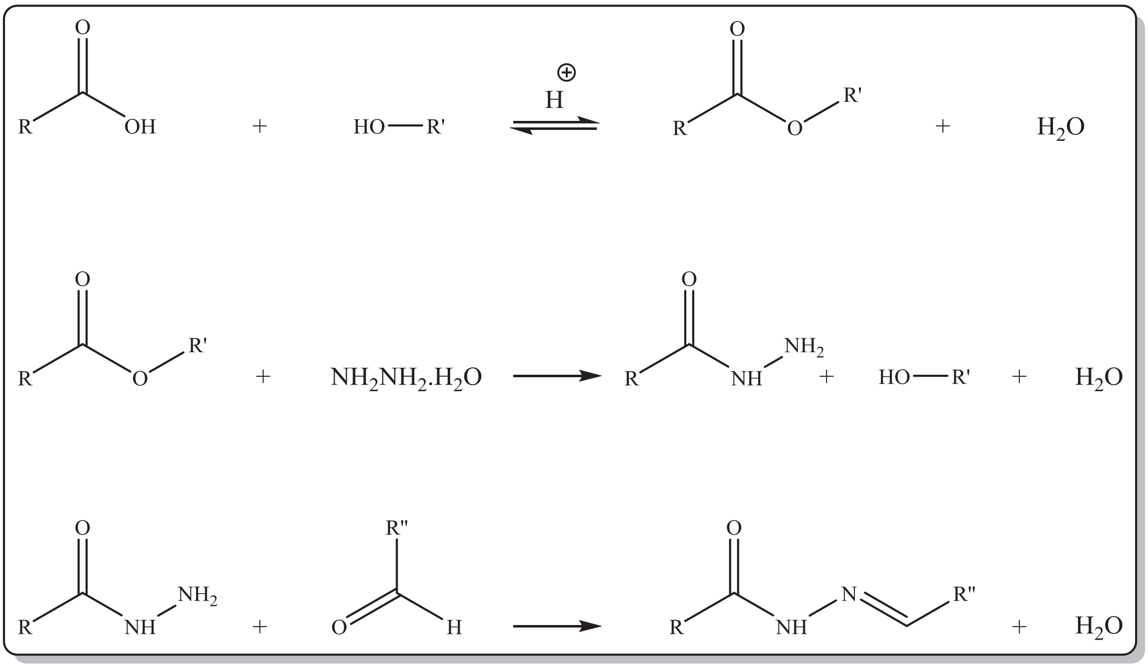
Indomethacin (99%), *o*-vanillin (99%), *p*-vanillin (98%), Amberlyst® 15 hydrogen form and Hydrazine Hydrate (60%) were purchased from SIGMA-ALDRICH. Ethanol absolute (99.9%) were purchased from CHEMLAB. all materials were used without further purification. Thin layer chromatographic of aluminum coated by Silica Gel 60F_{254} measuring 20×20 from the German company MERCK.

2.2. Instrumentation and Physio-Chemical Measurements:

Melting points were determined in an Electrothermal Melting Point Apparatus. The Infrared spectra FT-IR were recorded in the range (400-4000 cm^{-1}) by KBr pellet from the Japanese company Jasco spectrophotometer. The Proton nuclear magnetic resonance ^{1}H-NMR and the Carbon-13 nuclear magnetic resonance ^{13}C-NMR device 400 MHz model by Switzerland company.

2.3. General synthesis of the Ligands:

General outline to synthesize hydrazide base Schiff bases is shown in Scheme No. 1.



Scheme 1. General Scheme for synthesis of hydrazide base Schiff bases.

2.3.1. *Synthesis of the Ligands*:

The ligands, *o*-Vanillin Indomethacin Hydrazone (OVIH) and *p*-Vanillin Indomethacin (PVIH) was synthesized in three steps.

2.3.1.1. *Synthesis of Indomethacin Ethyl Ester (IEE)*:

Indomethacin (0.001 mol, 1.07 gr) and absolute ethanol (0.03 mol, 5 ml) in the presence of amberlyst-15 (0.101 gr) were refluxed for 6 hours at the temperature (78.3 ºC). The mixture was cooled at room temperature then, the excess of ethanol was evaporated and the resulted solid was resolved in 20 ml ethyl acetate and extracted 3 to 4 times with saturated sodium hydrogen carbonate solution in a separatory funnel to get rid of the remaining acid. The organic layer was separated and evaporated. The resulting solid as lime yellow powder was left to dry, m.p. 94 ºC, yield 92%.

2.3.1.2. *Synthesis of Indomethacin Acid Hydrazide (IAH)*:

IEE (0.01 mol, 0.5 gr) and hydrazine hydrate (0.2 mol, 4.2 ml) were refluxed in hydrazine hydrate as solvent (b.p. 118 ºC) for 3 to 4 hours. The mixture was cooled at room temperature and left overnight. The solid thus separated filtered off as white crystals, washed with cold distilled water then dried and crystallized from hot ethanol, m.p. 170 ºC, yield 65%.

2.3.1.3. *Synthesis of o- and p-Vanillin Indomethacin Hydrazone (OVIH) and (PVIH)*:

IAH (0.0003 mol, 0.1 gr) was dissolved in hot ethanol then an ethanolic solution of vanillin (0.0003 mol, 0.04 gr) were added slowly to it. After mixing these two solutions, the mixture was refluxed for 3 to 4 hours, then cooled at room temperature. The solid filtered off, washed 2-3 times with ethanol and left to dry. The color, meting points and yields of *o*- and *p*-Vanillin Indomethacin Hydrazone are shown in Table. 1.

Table 1. shows some physical properties and yields of *o*- and *p*-Vanillin Indomethacin Hydrazone.

Hydazone	Color	Melting point	Yield
OVIH	Yellow powder	208 ºC	88 %
PVIH	Wight powder	197 ºC	84 %

3. Results and Discussions:

3.1. Infrared Spectra of IEE and IHA:

Spectrum of **Hind** displays a very broad, intense O-H stretching absorption of the carboxylic acid in the region of 3300-3500 cm^{-1} with weaker and much sharper C-H stretches superimposed. Meanwhile, **IEE** shows disappearance of the O-H absorption bands which confirm the formation of the targeted ester. **IHA** shows very intense NH and NH_2 stretching bands in the region 3200-3030 cm-1 beside the appearance of amid-I and amid-II groups at 1632-1656 cm^{-1} confirm the formation of the hydrazide acid.

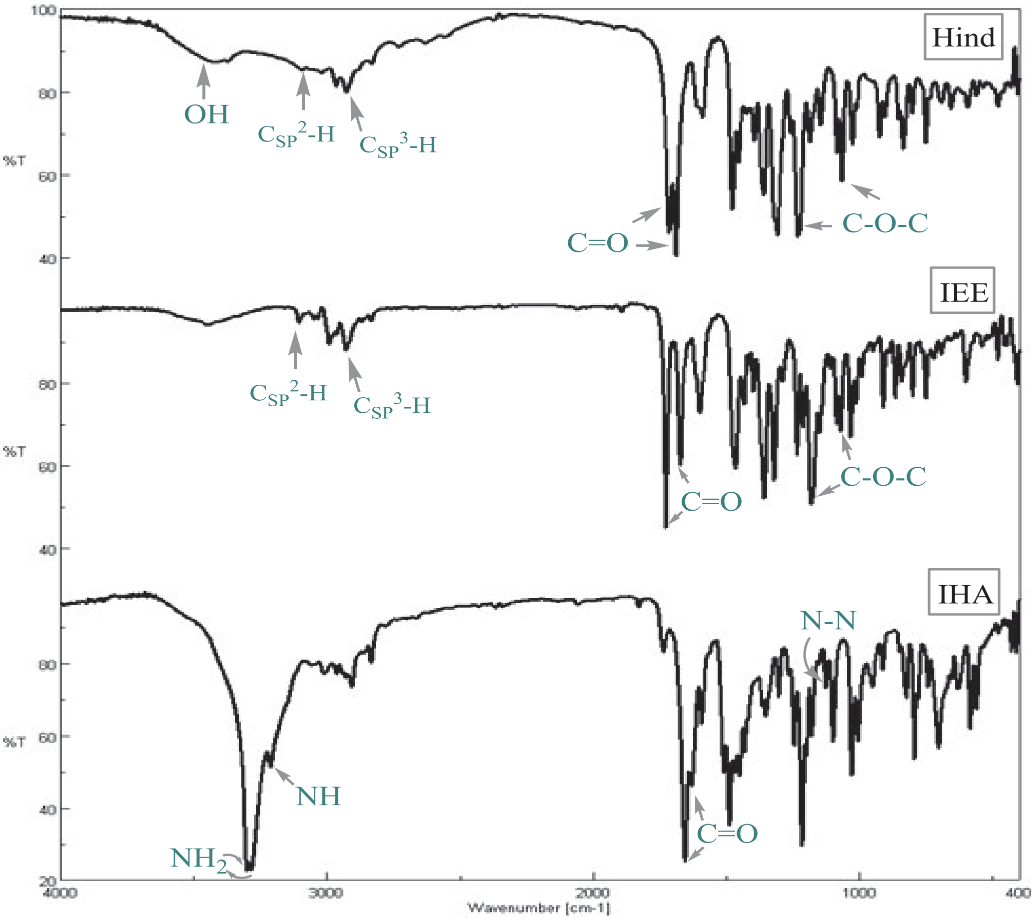


Figure 3. IR spectra of Hind, IEE and IHA.

Hind-IR Spectrum (ν, cm^{-1}): ν(-OH) 3422, ν(C_{SP}^{2}-H) 3099, ν(C_{SP}^{3}-H) 2927, ν(C=O) 1716-1691, ν(C-O-C) 1233-1067.
IEE-IR Spectrum (ν, cm^{-1}): ν(C_{SP}^{2}-H) 3105, ν(C_{SP}^{3}-H) 2928, ν(C=O) 1727-1675, ν(C-O-C) 1183-1072.
IHA-IR Spectrum (ν, cm^{-1}): ν(-NH_2) 3301-3283, ν(-NH-) 3212, ν(C_{SP}^{2}-H) 3010, ν(C_{SP}^{3}-H) 2908, ν(C=O) 1656-1632, ν(C_{SP}^{2}-O) 1216, ν(C-N) 1353, ν(N-N) 1128.

3.2. Characterization of OVIH:

3.2.1. Infrared Spectra:

Infrared spectra of the ligand OVIH, has prominent bands at 3457 and 3392 cm^{-1} due to ν(-OH) + ν(-NH-) stretching mode respectively, the ν(-NH_2) stretching band has disappeared, a new sharp band appears at 1550 cm^{-1} belongs to ν(C=N) stretching band which confirm the formation of the targeted hydrazone.

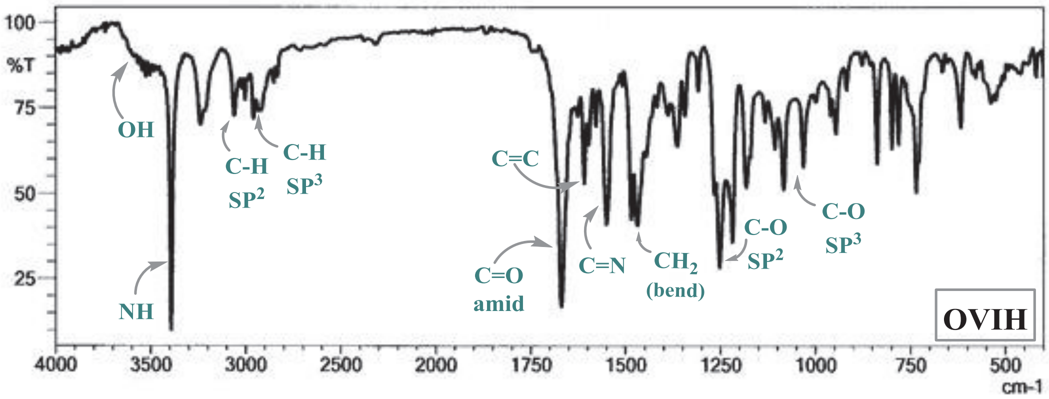


Figure 4. IR spectra of OVIH.

Table 2. Characteristic infrared absorption frequencies (cm^{-1}) of OVIH.

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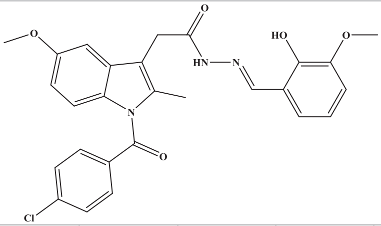
<tr><td colspan="11">
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<tr><th>Functional Group</th><th>OH</th><th>NH</th><th>C_{SP}^{2}-H</th><th>C_{SP}^{3}-H</th><th>C=O amid</th><th>C=C</th><th>C=N</th><th>CH_2 bend</th><th>C_{SP}^{2}-O</th><th>C_{SP}^{3}-O</th></tr>
<tr><th>Wavenumer (cm^{-1})</th><td>3457</td><td>3392</td><td>3018</td><td>2957</td><td>1668</td><td>1594</td><td>1550</td><td>1485</td><td>1251</td><td>1083</td></tr>
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3.2.2. ^{13}C-NMR Spectra:

o-Vanillin Indomethacin Hydrazone was confirmed by ^{13}C-NMR spectroscopy in the solvent DMSO-6d. We observed twenty-five signals refer to the twenty-seven carbon atoms that existed in the compound.

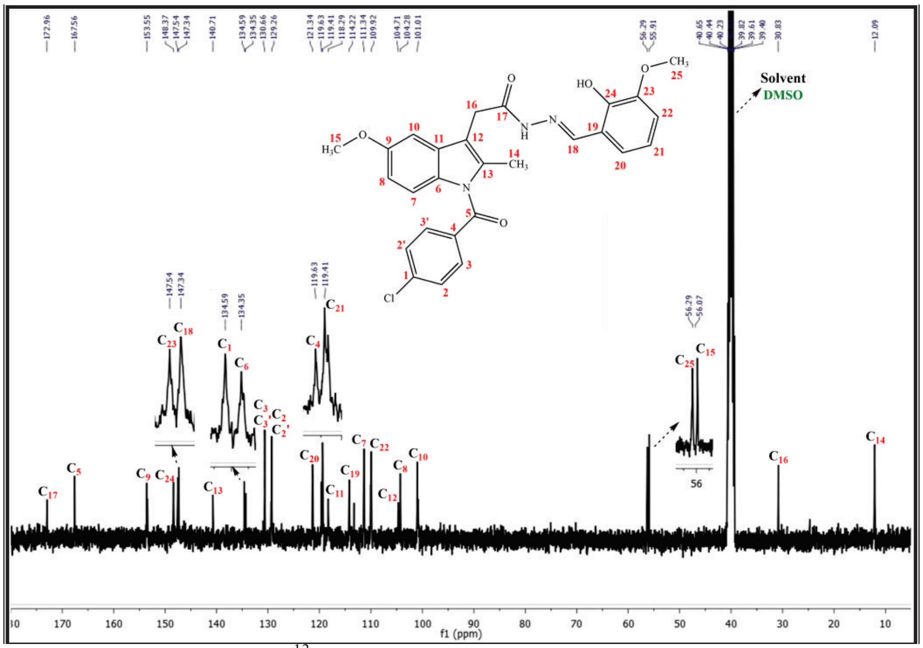
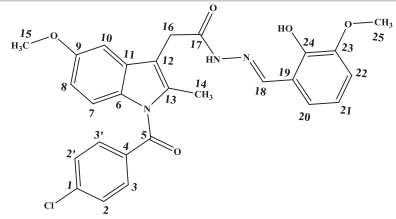


Figure 5. ^{13}C-NMR spectra of OVIH in DMSO-6d.

Table 3. ^{13}C-NMR chemical shifts of OVIH.



Carbon Atom number	Chemical Shift (ppm)	Carbon Atom number	Chemical Shift (ppm)
1	134.59	**14**	12.09
2, 2'	129.25	**15**	55.91
3, 3'	130.66	**16**	30.83
4	119.63	**17**	172.96
5	167.56	**18 (C=N)**	147.34
6	134.26		
7	111.34	**19**	114.22
8	104.28	**20**	121.34
9	153.55	**21**	119.41
10	101.01	**22**	109.92
11	118.29	**23**	147.54
12	104.71	**24**	148.87
13	140.71	**25**	56.29

3.2.3. H-NMR Spectra:

o-Vanillin Indomethacin Hydrazone was confirmed by H-NMR spectroscopy in the solvent DMSO-6d. We observed the presence of -CH=N- proton signal at (δ = 9.55 ppm), -NH- proton signal at (δ = 10.82 ppm) and -OH proton signal at (δ = 11.39 ppm).

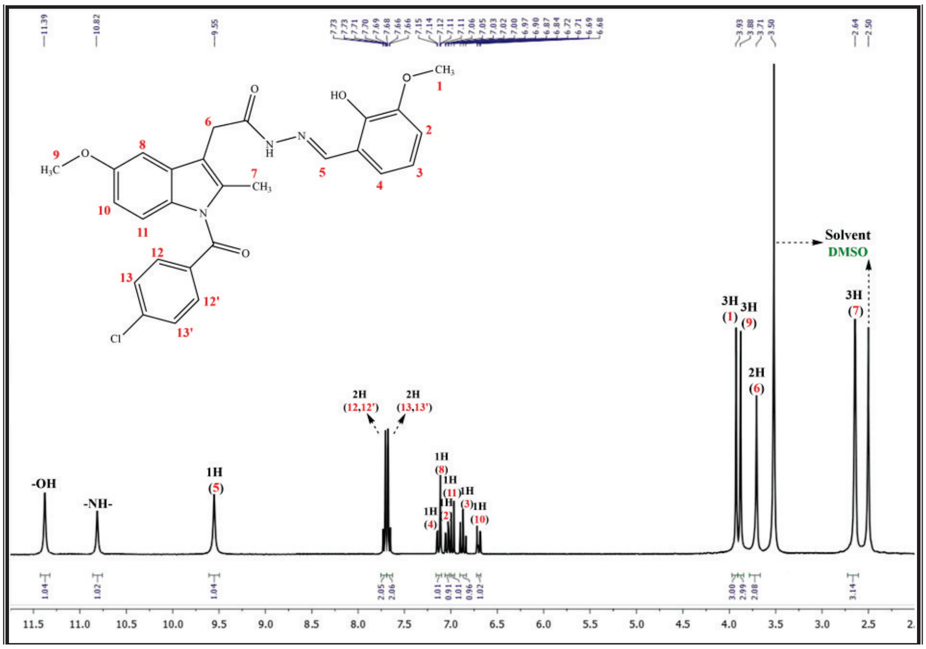


Figure 6. H-NMR spectra of OVIH in DMSO-6d.

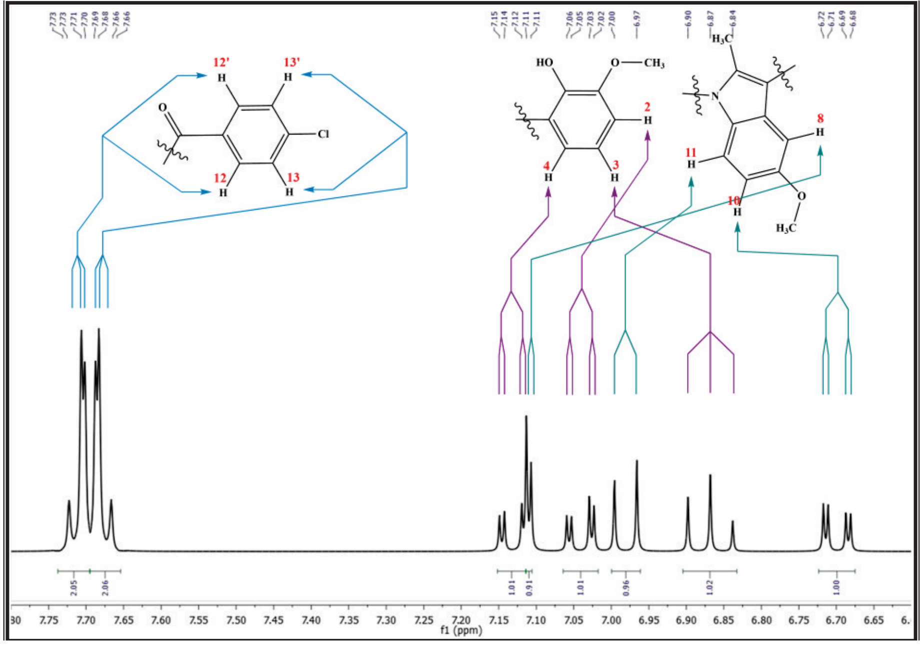
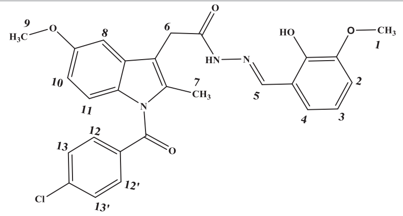


Figure 7. Expand of the aromatic area from 6.60 ppm to 7.80 ppm.

Table 4. H-NMR chemical shifts of OVIH.



Hydrogen Type & Number	Chemical Shift (ppm) & Constance de Couplage J (Hz)	Hydrogen Type & Number	Chemical Shift (ppm) & Constance de Couplage J (Hz)
1 (Aliphatic)	3.93 (s, 3H)	**7 (Aliphatic)**	2.64 (s, 3H)
2 (Aromatic)	7.06-7.02 (dd, 1H) J=14.9, 3.1	**8 (Aromatic)**	7.11-7.10 (d, 1H) J=3.2
3 (Aromatic)	6.91-6.89 (t, 1H) J=14.9	**9 (Aliphatic)**	3.88 (s, 3H)
4 (Aromatic)	7.14-7.11 (dd, 1H) J=14.8, 3.2	**10 (Aromatic)**	6.72-6.68 (dd, 1H) J=15.0, 3.1
5 (Azomethine)	9.55 (s, 1H)	**11 (Aromatic)**	7.00-6.97 (d, 1H) J=14.9
		12, 12' (Aromatic)	7.73-7.70 (m, 2H)
6 (Aliphatic)	3.71 (s, 2H)	**13, 13' (Aromatic)**	7.69-7.66 (m, 2H)
-NH-	10.82 (s, 1H)	**-OH**	11.39 (s, 1H)

3.3. Characterization of PVIH:

3.3.1. Infrared Spectra:

Infrared spectra of the ligand PVIH, has prominent bands at 3457 and 3294 cm^{-1} due to ν(-OH) + ν(-NH-) stretching mode respectively, the ν(-NH$_2$) stretching band has disappeared, a new sharp band appears at 1512 cm^{-1} belongs to ν(C=N) stretching band which confirm the formation of the targeted hydrazone.

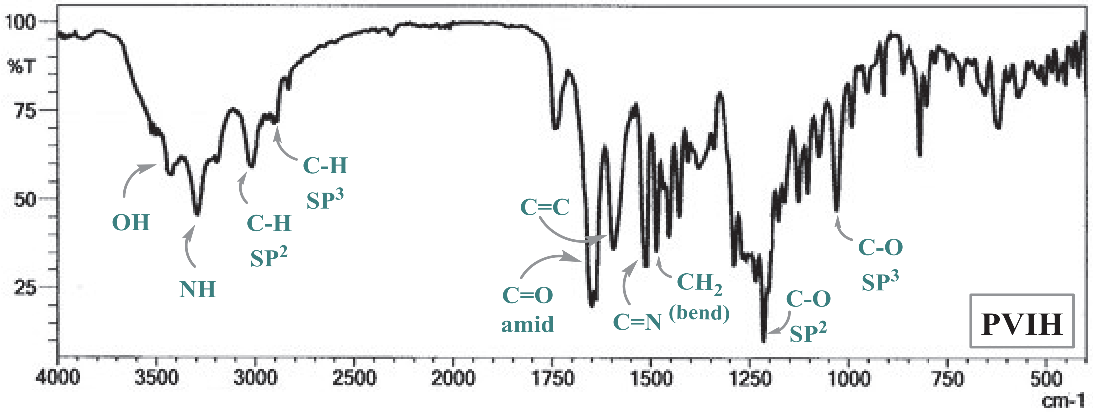
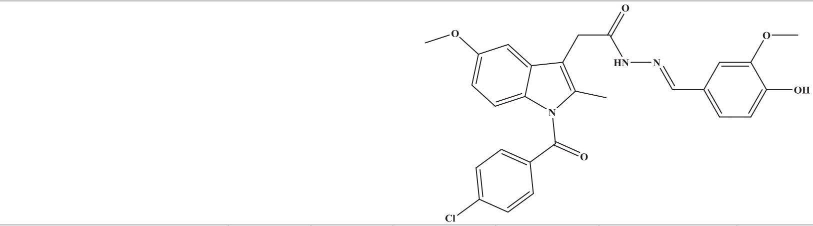


Figure 8. IR spectra of PVIH.

Table 5. Characteristic infrared absorption frequencies (cm^{-1}) of PVIH.

										
Functional Group	**OH**	**NH**	**$C_{SP}{}^{2}$-H**	**$C_{SP}{}^{3}$-H**	**C=O amid**	**C=C**	**C=N**	**CH_2 bend**	**$C_{SP}{}^{2}$-O**	**$C_{SP}{}^{3}$-O**
Wavenumer (cm^{-1})	3457	3294	3018	2910	1665	1597	1512	1487	1215	1029

3.3.2. ^{13}C-NMR Spectra:

p-Vanillin Indomethacin Hydrazone was confirmed by ^{13}C-NMR spectroscopy in the solvent DMSO-6d. We observed twenty-five signals refer to the twenty-seven carbon atoms that existed in the compound.

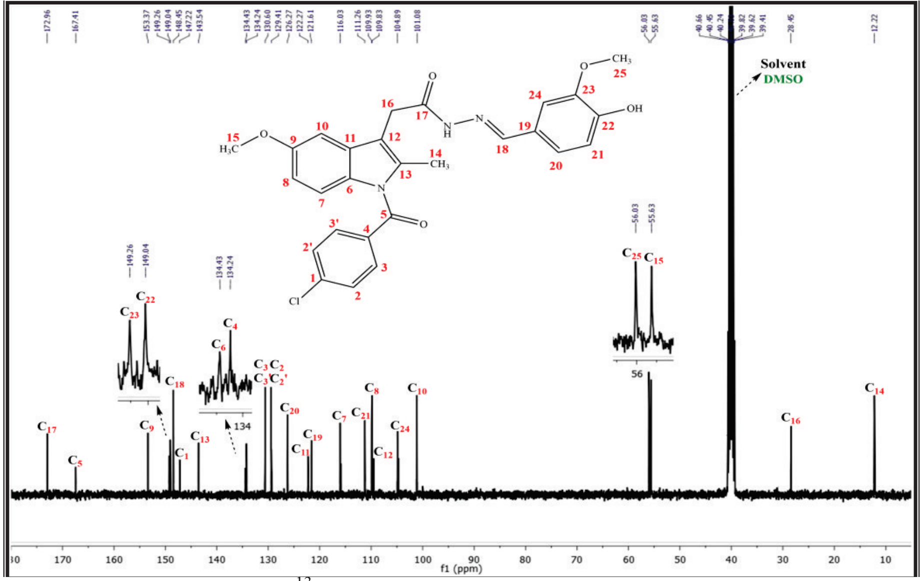
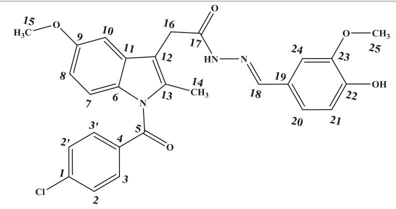


Figure 9. ^{13}C-NMR spectra of PVIH in DMSO-6d.

Table 6. ^{13}C-NMR chemical shifts of PVIH.

			
Carbon Atom number	**Chemical Shift (ppm)**	**Carbon Atom number**	**Chemical Shift (ppm)**
1	147.22	**14**	12.22
2, 2'	129.41	**15**	55.63
3, 3'	130.60	**16**	28.45
4	134.24	**17**	172.96
5	167.41	**18 (C=N)**	148.45
6	134.43		
7	116.03	**19**	
8	109.83	**20**	126.27
9	153.37	**21**	111.26
10	101.08	**22**	149.04
11	122.29	**23**	149.26
12	109.93	**24**	104.89
13	143.54	**25**	56.03

3.3.3. H-NMR Spectra:

p-Vanillin Indomethacin Hydrazone was confirmed by H-NMR spectroscopy in the solvent DMSO-6d. We observed the presence of -CH=N- proton signal at (δ = 9.59 ppm), -NH- proton signal at (δ = 10.71 ppm) and -OH proton signal at (δ = 11.19 ppm).

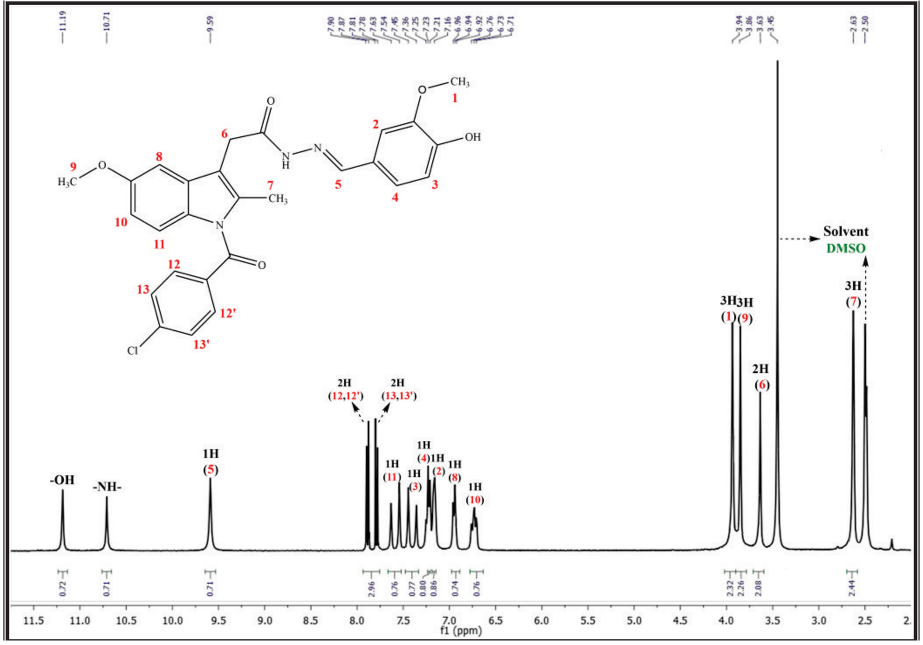


Figure 10. H-NMR spectra of PVIH in DMSO-6d.

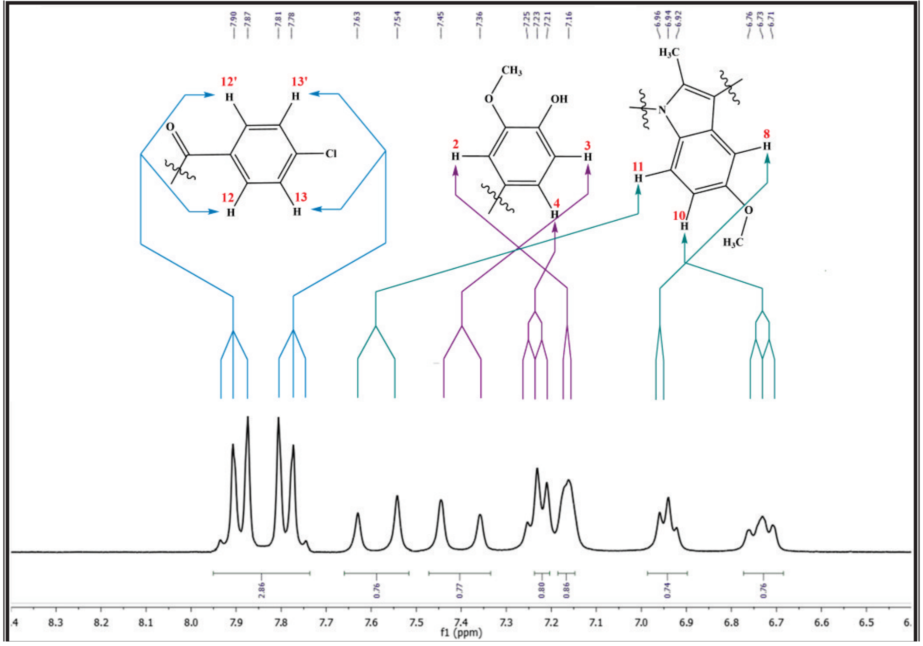
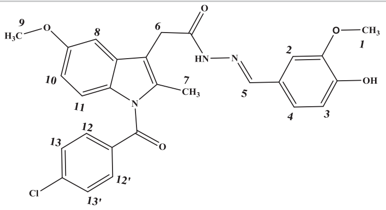


Figure 11. Expand of the aromatic area from 6.40 ppm to 8.40 ppm.

Table 7. H-NMR chemical shifts of PVIH.



Hydrogen Type & Number	Chemical Shift (ppm) & Constance de Couplage *J* (Hz)	Hydrogen Type & Number	Chemical Shift (ppm) & Constance de Couplage *J* (Hz)
1 (Aliphatic)	3.94 (s, 3H)	**7 (Aliphatic)**	2.63 (s, 3H)
2 (Aromatic)	7.18-7.16 (d, 1H) *J*=6.5	**8 (Aromatic)**	6.94-6.92 (d, 1H) *J*=7.6
3 (Aromatic)	7.45-7.36 (d, 1H) *J*=34.7	**9 (Aliphatic)**	3.86 (s, 3H)
4 (Aromatic)	7.25-7.21 (dd, 1H) *J*=18.1, 8.6	**10 (Aromatic)**	6.76-6.71 (dd, 1H) *J*=17.3, 4.5
5 (Azomethine)	9.59 (s, 1H)	**11 (Aromatic)**	7.63-7.54 (d, 1H) *J*=39.2
		12, 12' (Aromatic)	7.92-7.87 (m, 2H)
6 (Aliphatic)	3.63 (s, 2H)	**13, 13' (Aromatic)**	7.81-7.76 (m, 2H)
-NH-	10.71 (s, 1H)	**-OH**	11.19 (s, 1H)

4. Conclusions

In this paper, two novel Hydrazide Base Schiff Bases ligands (OVIH & PVIH) were successfully synthesized in three steps with yields 88% and 84% constantly. The structures of these ligands were confirmed by the obtained analytical IR and NMR spectral data. These two compounds can be further reacted with several transition metallic salts and form their corresponding complexes and it is expected that they might have an important biological activity.

5. Acknowledgement

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6. References

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