Synthesis and characterization of some New Mannich bases and their thione derivatives .

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Abstract:

N,N'-methylenebis(N-phenylacetamide), N-((2,3-dioxoindolin-1-yl)methyl)-N-phenylacetamide, 2-amino-3-(1-((N-phenylacetamido)methyl)-1H-indol-3-yl) propanoic acid, 2-amino-3-(1-((N-phenylacetamido)methyl)-1H-imidazol-5-yl)propanoic acid, and N-((1,3-dioxoisoindolin-2-yl)methyl)-N-phenylacetamide were prepared by the condensation of acetanilide with paraformaldehyde and secondary amines, and were found to react with phosphours penta sulphide to give N,N'-methylenebis(N-phenylethanethioamide), N-((2,3-lethan -1-yl)methyl)-N-phenylethanethioamide, 2-amino-3-(1-((N-pheny dithioxoindolin ethioamido)methyl)-1H-indol-3-yl)propanoic acid, 2-amino-3-(1-((N-phenylethan)-1H-imidazol-5-yl) propanoic acid and N-((1,3-dithioxoisoindolin-2-) methyl ethioamido yl)methyl)-N-phenyl ethane thioamide respectively.

The structures of the prepared compounds (1-10) are characterized by C.H.N.S analysis and FT-IR,^{1}H-NMR (for some of them) spectroscopy ,the melting points are reported and the purity of compounds are checked by T.LC.technique.

تحضير وتشخيص بعض قواعد مانخ الجديدة ومشتقات الثايون لها.

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مفتاح البحث: قواعد مانخ، مركبات الثايون

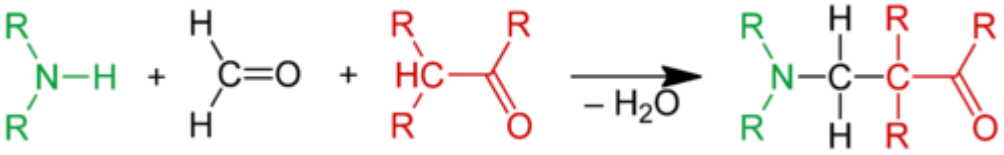
الخلاصة:

تم تحضير عدد من مشتقات الاستنالايد الجديدة (قواعد مانخ) N',N مثلين بس(N-فنيل استيدامايد,N-((3,2-ثنائي اوكسواندولين -1- يل)مثيل)—N-فنيل استيدامايد, 2-امينو-3-(1-((N-فنيل استيداميدو)مثيل)-H1-اندول-3-يل)حامض بروبانويك , 2-امينو-3-(1-((N-فنيل استيداميدو)مثيل)-H1-اندول-5-يل)حامض بروبانويك , N-((1,3-داي اوكسوزواندولين -2-يل)مثيل)-N-فنيل استيدامايد, من مفاعلته مع البارافورمالديهايد وعدد من الأمينات الثانوية .فوعلت

قواعد مانخ مع خامس كبريتيد الفسفور فأعطت مشتقات الاستنالايد N',N مثلين بس(N-فنيل ايثان ثايوامايد, N-((3,2-ثنائ اوكسواندولين -1- يل)مثيل)—N-فنيل ايثان ثايومايد, 2-امينو-3-(1-((N-فنيل ايثان ثايوامايد)مثيل)-H1-اندول-3-يل)حامض بروبانويك , 2-امينو-3-(1-((N-فنيل ايثان ثايوامايد)مثيل)-H1-اندول-5-يل)حامض بروبانويك , N-((1,3-ثنائي اوكسوزواندولين -2-يل)مثيل)-N-فنيل ايثان $_2$ ثايوامايد ثايون.

Introduction:

Mannich reaction is an organic reaction which consists of an **amino alkylation** of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound also known as a Mannich base.[1] Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich[2,3].



Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which introduced in the second step in electrophilic addition with a compound containing an acidic proton(which is, or had become an enol). The Mannich reaction is also considered a condensation reaction.

In the Mannich reaction, ammonia or primary or secondary amines are employed for the activation of formaldehyde. Tertiary amines lack an N-H proton to form the intermediate imine. α-CH-acidic compounds (nucleophiles) include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. It is also possible to use activated phenyl groups and electron-rich heterocycles such as furan, pyrrole, and thiophene. Indole is a particularly active substrate; the reaction provides gramine derivatives[4,5].

Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. tropinone). Other applications are in agro chemicals such as plant growth regulators,[6] paint- and polymer chemistry, catalysts and crosslinking.

Mannich reaction is also used in the synthesis of medicinal compounds e.g. rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant), tramadol, and tolmetin (anti-inflammatory drug) [3].

A new 5-alkyl and 3-(2,4-dimethylphenyl) substituted 1,3,4-oxadiazole-2-thione derivatives were synthesized by the ring closure reaction of various acyl hydrazide with carbon

disulfide. Mannich bases for some of these compounds were also synthesized by condensation with benzaldehyde and primary amines[7].

F.Dawood[8] has synthesized some new Mannich bases starting from hydrazide derivatives and he found that these compounds have biological activity.

Techniques :

1. Melting points were recorded with Stuart Melting point apparatus and were uncorrected.
2. Infra red spectra (FT-IR) were recorded on Shimadzu FT-IR-8300 spectrophotometer in Ibn Sina State Company (ISSC).
3. Uv/vis spectra were recorded on Uv/vis varian Uv-Cary-100 spectrophotometer in (ISSC).
4. ^{1}H-NMR spectra were recorded on a BRUKER-400 MHz operating at 300 MHZ with tetra methyl silane as internal standard in $CDCl_3$ and DMSO-d_6 as a solvent, measurements were made at Chemistry Department, AL-Baath University-Syria.
5. Elemental Analysis (C.H.N.S.) was carried out with: Euroea Elemental Analyzer Italia by Chemical Department College of Science, Babylon University.

Table (1): C.H.N.S analysis of prepared compounds.

Comp. No.	M. F.	C%	H%	N%	O%	S%
1	$C_{19}N_2O_2H_{18}$	Calc.74.53	5.87	9.14	10.44	-
		Found.74.40	5.79	8.89	10.04	-
2	$C_{18}N_2O_3H_{21}$	Calc. 69.03	6.70	8.94	15.31	-
		Found 68.90	5.90	8.01	15.11	-
3	$C_{14}N_4O_3H_{18}$	Calc.57.95	6.20	19.30	16.53	-
		Found. 57.20	6.01	19.11	16.32	-
4	$C_{17}N_2O_3H_{14}$	Calc.69.41	4.75	9.52	16.30	-
		Found. 69.10	4.03	9.20	15.91	-
5	$C_{17}N_2O_3H_{14}$	Calc.69.41	4.75	9.52	16.30	-
		Found. 68.71	4.49	9.21	15.91	-
6	$C_{19}N_2S_2H_{18}$	Calc. 67.44	5.32	8.27	-	18.95

		Found .67.80	4.80	7.80	-	18.20
7	$C_{18}N_2S_3H_{21}$	Calc.59.82	5.81	7.74	-	26.61
		Found 59.01	4.91	7.01	-	26.20
8	$C_{14}N_4S_3H_{18}$	Calc.49.69	5.32	16.55	-	28.42
		Found 49.91	4.90	15.90	-	27.91
9	$C_{17}N_2S_3H_{14}$	Calc.59.63	4.08	8.17	-	28.94
		Found 60.02	3.81	8.01	-	28.10
10	$C_{17}N_2S_3H_{14}$	Calc.59.63	4.08	8.17	-	28.94
		Found 59.90	4.00	7.80	-	28.10

Methods:

I) Preparation of compounds (1-5).

Acetanilde (0.005mol) in(25ml) absolute ethanol was added to secondary amines (0.005mol) with paraformaldehyde (0.006mol) and refluxed for four hours, then (100ml) of ice distilled water was added,the precipitate was filtered , dried and re crystallized from ethanol and water (50%50).

II) Preparation of thione compounds (6-10).

A mixture of compounds (1-5) of acetanilide Mannich bases (0.002mol) in dry dioxane (50ml) was stirred and phosphorous pentasulfide (P_2S_5) (0.004mol) was added at once . The reaction mixture was heated under reflux temperature with stirring for one hour ,the reaction mixture was then allowed to cool to room temperature, the precipitate was filtered , dried and re crystallized from petroleum ether b.p [40-60] ^{0}C to give yellow crystals[6,9].

Table (2): Physical properties of the prepared compounds.

Comp. No	Comp. name	Molecular formula	colour	M.P	Yelid %
s	Acetanilide	$C_8N_1O_1H_9$	white	117-120	-
1	N,N'-methylenebis(N-(phenylacetamide	$C_{19}N_2O_2H_{18}$	white	98-100	85

2	N-((2,3-dioxoindolin-1-yl)methyl)-N-phenylacetamide	$C_{18}N_2O_3H_{21}$	white	138-140	80
3	amino-3-(1-((N-phenylacetamido -2)methyl)-1H-indol-3-yl)propanoic acid	$C_{14}N_4O_3H_{18}$	yellow	116-118	90
4	2-amino-3-(1-((N-phenylacetamido)methyl)-1H-imidazol-5-yl)propanoic acid	$C_{17}N_2O_3H_{14}$	Pale yellow	218-220	76
5	N-((1,3-dioxoisoindolin-2-yl)methyl)-N-phenylacetamide	$C_{17}N_2O_3H_{14}$	Orange	178-180	83
6	N,N'-methylenebis(N-phenylethanethioamide)	$C_{19}N_2S_2H_{18}$	Pale yellow	129-131	77
7	N-((2,3-dithioxoindolin-1-yl)methyl)-N-phenylethanethioamide	$C_{18}N_2S_3H_{21}$	Pale yellow	210-212	73
8	amino-3-(1-((N-phenylethan -2 ethioamido)methyl)-1H-indol-3-yl)propanoic acid	$C_{14}N_4S_3H_{18}$	yellow	228-230	86
9	amino-3-(1-((N--2 phenylethanethioamido)methyl)-1H-imidazol-5-yl)propanoic acid	$C_{17}N_2S_3H_{14}$	yellow	167-169	70
10	N-((1,3-dithioxoisoindolin-2-yl)methyl)-N-phenylethanethioamide	$C_{17}N_2S_3H_{14}$	Pale Orange	183-185	79

S= starting material.

Results and Discussion:

FT-IR spectrum of compound [3] as example, confirmed the appearance of carbonyl group band at (1662 cm^{-1}) also, (C-H) aromatic band appeared at (3062 cm^{-1}) and (C-H) aliphatic band at (2800 cm^{-1}) Fig. (1). All the spectral data for other compounds are listed in table (3).

^{1}H-NMR spectrum of compound [3], Fig. (2), shows the following characteristic chemical shifts, (DMSO-d_6) ppm. (N-H) proton appeared at (δ 3.4), NH_2 protons appeared at (δ 4.4), (CH=CH) (olefinic protons) appeared at (δ 6.5), and five aromatic ring protons appeared at the range (δ 7.3-7.8). Furthermore, the signal at (δ 10.3) due to (O-H) proton.

FT-IR spectrum of compound [8], Fig. (3), shows the appearance of absorption band at (1275cm^{-1})attributed to (C=S) thione group, besides the disappearance of band of carbonyl group. Also, the band at (1595cm^{-1}) due to υ (C=C) group, and at (1650cm^{-1}) assigned to (C=N) of ring, besides the presence of C=O of carboxylic acid.

The Uv/vis., spectrum of compound [3], Fig. (4) shows the absorption peak at (215 nm) due to (n → π*) or (π → π*) transitions.

Table (3) : FT-IR spectral data of compounds (1-5).

Comp. No.	υ(C-H) Aliphatic. cm^{-1}	υ(C-H) aromatic cm^{-1}	υ(C=O) cm^{-1}	Ar υ(C=C) cm^{-1}	Other bands cm^{-1}
S actenalide	2858, 2927	3074	1666	1600, 1554, 1435	υ(N-H) 3294, 3259 (C-N) 1260
1	2927, 2858	3062	1666	1600, 1554, 1435	υ(C-N) 1267
2	2800, 2858	3020, 3062	1662	1600, 1554, 1435	(N-H) 3298, 3259 (C-N) 1280
3	2800	3020, 3062	1662	1600, 1550, 1433	(O-H) 3402 (N-H) 3294 3194 , (C-N) 1260
4	2897	3062	1747,1666(C=O)amide	1600, 1554, 1438	(C-N) 1260
5	2885, 2815	3059	1728,1662(C=O) amide	1616, 1558, 1462	υ(C-N) 1145, 1261

Table(4) : FT-IR spectral data of compounds (6-10).

Comp. No.	**υ(C-H) Aliphatic. cm^{-1}**	**υ(C-H) aromatic cm^{-1}**	**υ(C=S) cm^{-1}**	**υ(C=C)$_{Ar}$ cm^{-1}**	**Other bands cm^{-1}**
S actenalide	2852, 2930	3065	1270	1590, 1544	(N-H) 3291, 3259 (C-N) 1276
6	2920, 2857	3069	1265	1590, 1550	υ(C-N) 1275
7	2855, 2878	3045, 3062	1271	1602, 1555	(N-H) 3298, 3258 (C-N) 1267
8	2890	3020, 3069	1275	1595, 1560	(O-H) 3397 (N-H) 3294 3196 (C-N) 1265
9	2899	3055	1274	1556, 1567	(C-N) 1283
10	2886, 2850	3065	1268	1611, 1558	υ(C-N) 1280

Table (5) : H^1-NMR spectral data of compound 3.

Comp. No.	**Comp. name**	**data**
3	amino-3-(1-((N--2 phenylacetamido)methyl)-1H-indol-3-yl)propanoic acid	δ = 4.4ppm NH_2,δ 3.4ppm NH, 6.5 ppm CH=CH Olefin, aromatic ring proton δ =(7.3-7.8)ppm, the single δ =10.3ppm O-H protone

Biological screening. Antibacterial activity test

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds ([1], [4], [6], [9] and [10]) were assayed for their antimicrobial activity *in vitro* against three strains of Gram negative bacteria (***Escherichia Coli, Klebsiella Pneumonia*** and ***Proteus Vulgaris***). Prepared agar and Petri dishes were sterilized by autoclaving for 15min. at 121 ºC. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 0.1 ml of the prepared compounds (10mg of the compound dissolved in 1ml of DMSO solvent), DMSO was used as a solvent. These plates were incubated at 37 ºC for 24hr for bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in Table (6).

Table (6): Results of antibacterial activity of thetested compounds.

compound No.	*Escherichia Coli*	*Klebsiella Pneumonia*	*Proteus Vulgaris*
[1]	+	+	-
[4]	-	-	+
[6]	++	+	-
[9]	-	++	-
[10]	++	++	+

Note:

- = No inhibition = inactive

\+ = (5-10) mm = slightly active

++ = (11-20) mm = moderately active

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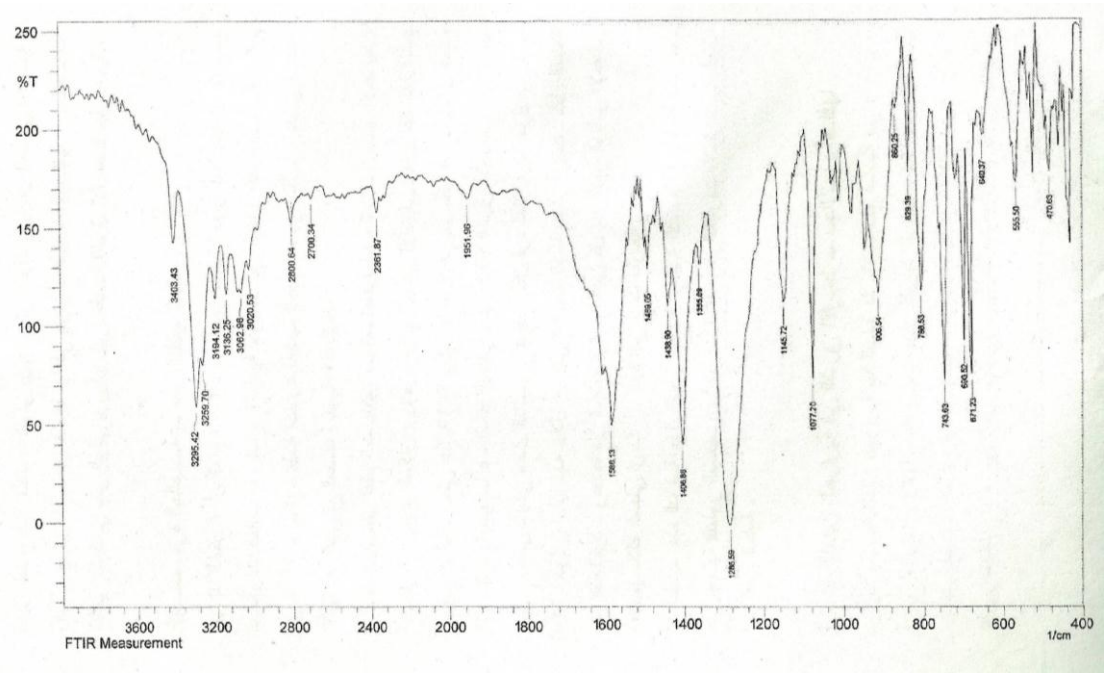


Fig. (1): FT-IR spectrum of compound 3.

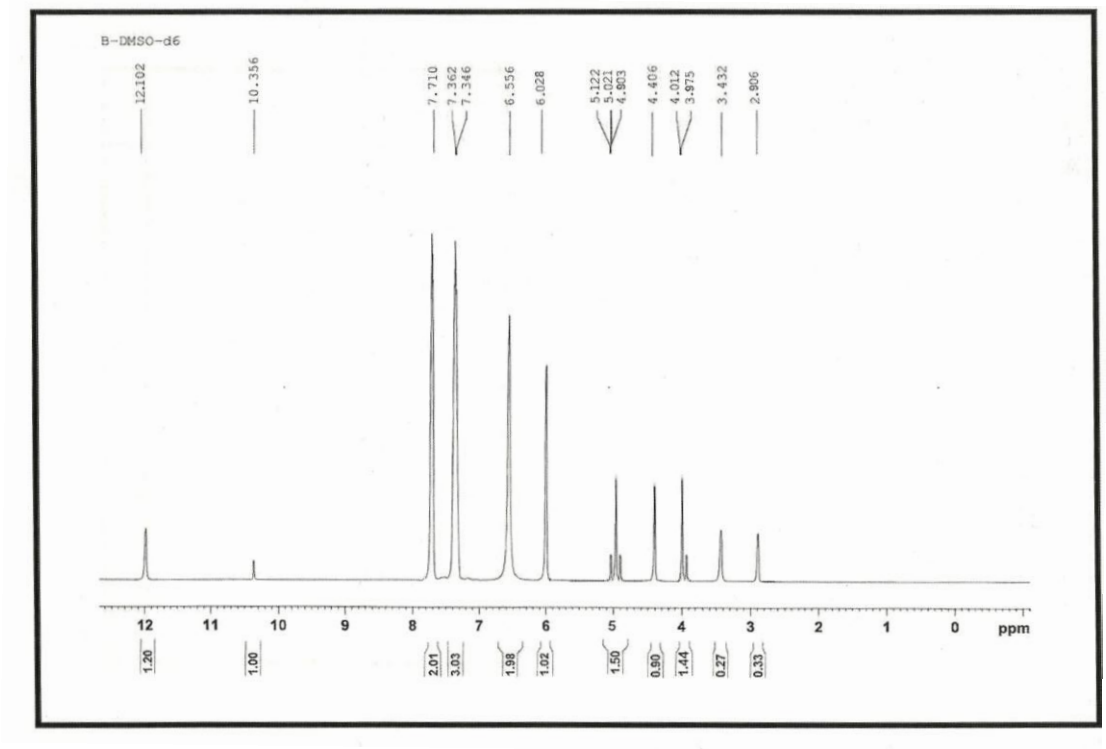


Fig (2):[1] H-NMR spectrum of compound 3.

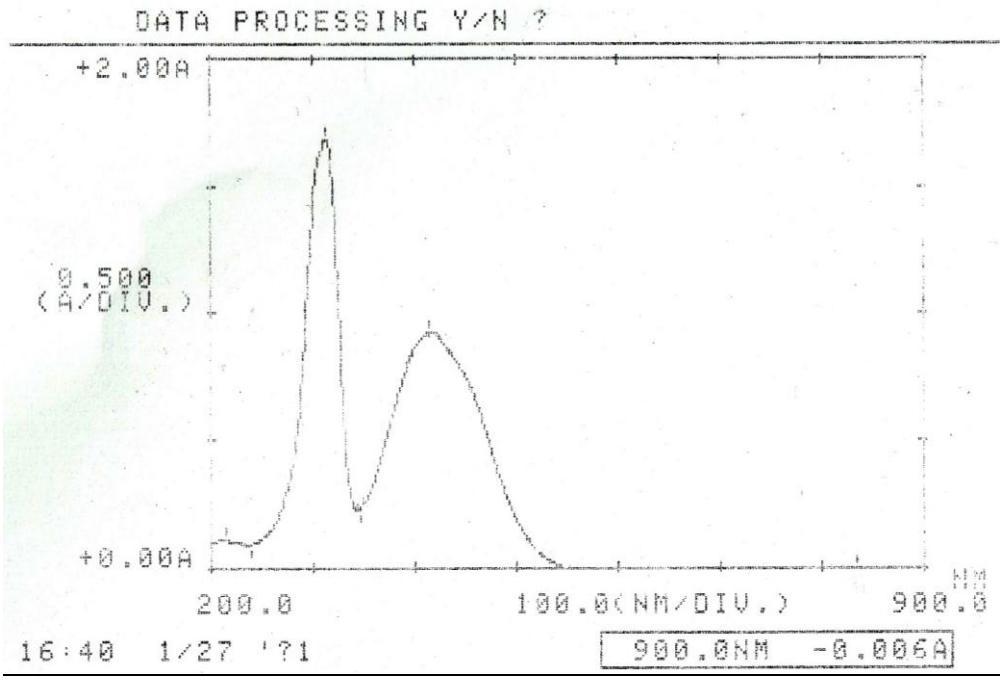
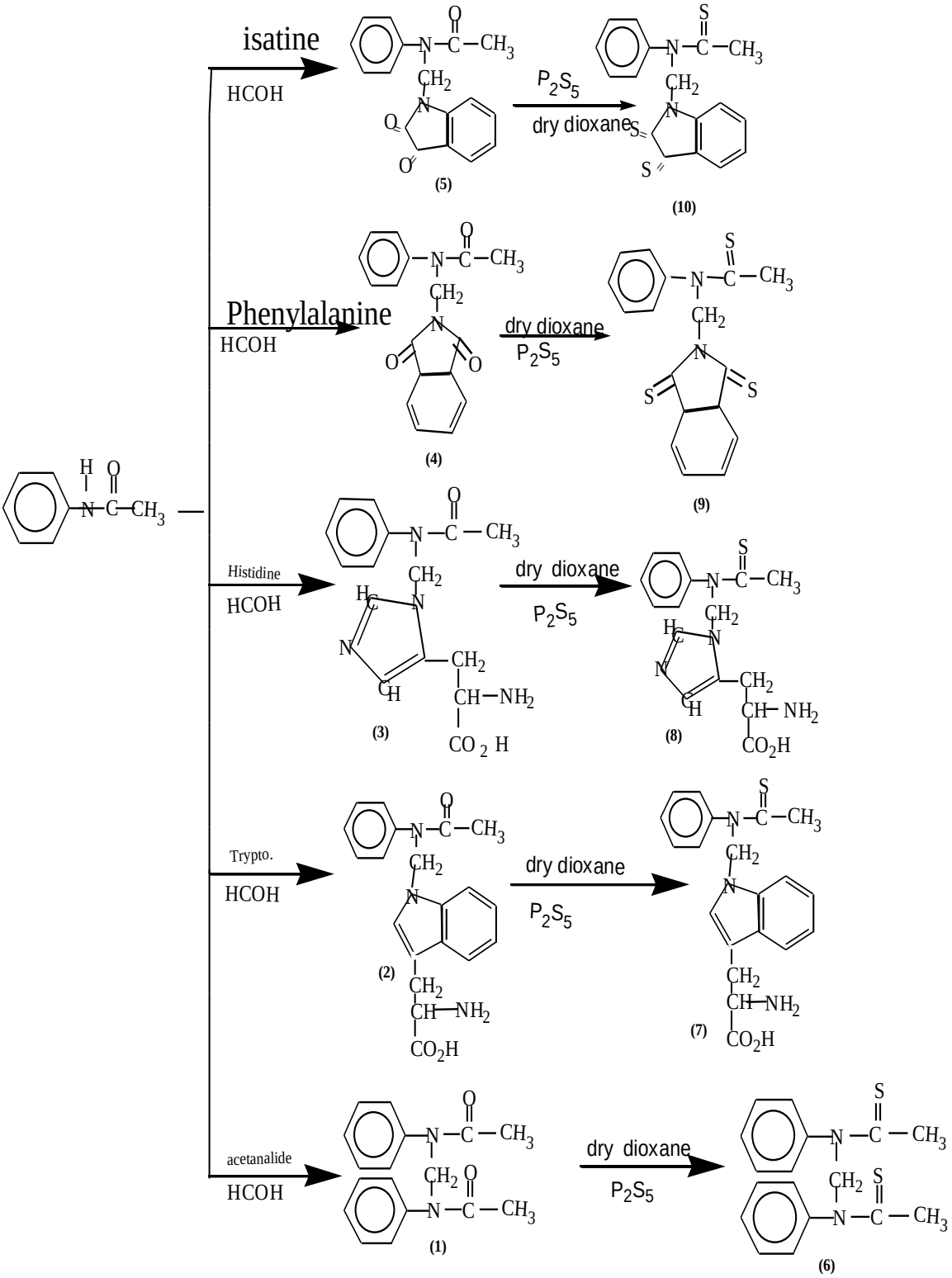


Fig (3): Uv/vis spectrum of compound 3.



Scheme (1) : The prepared compounds (1-10).