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# Synthesis and Characterization of Novel Schiff Bases, N-Acyl and Diazetines Derived from 3-((5-hydrazinyl-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-1H-indole

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**ABSTRACT**

This work involves synthesis of some new heterocyclic compounds including 1,3-diazetine. The new Schiff bases[VI]$_{a-d}$ derived from 3-((5-hydrazinyl-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-1H-indole [V] which was synthesized by refluxing 5-((1H-indol-3-yl)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol[IV] with hydrazine hydrate in absolute ethanol and this amino compound[V] condensation with different aromatic aldehydes in absolute ethanol to yielded a new Schiff bases[VI]$_{a-d}$. N-acyl compounds[VII]$_{a-d}$ were synthesized by addition reaction of acetyl chloride to imine group of Schiff bases in dry benzene. The new diazetine derivatives [VIII]$_{a-d}$ synthesized by the reaction of N-acyl compounds[VII]$_{a-d}$ with sodium azide in dimethylformamid at (55-60) $^0$C. All the synthesized compounds have been characterized by melting points , FTIR and $^1$HMNR spectroscopy (of some of theme).

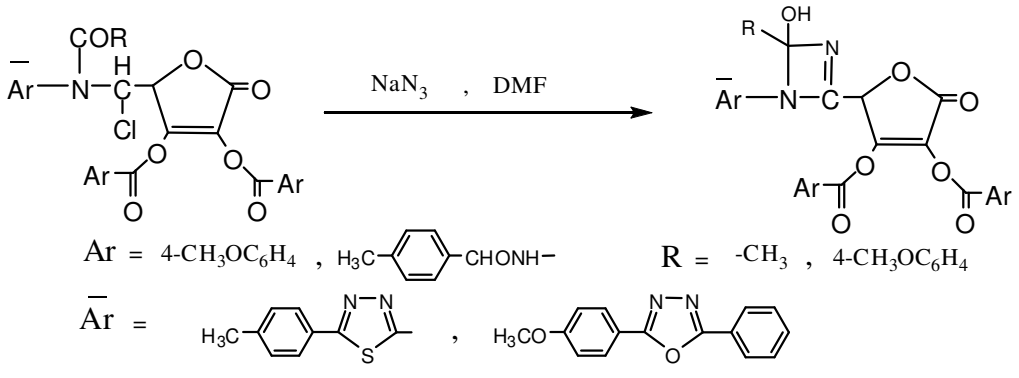
**Key words :** Schiff bases, N-Acyl, Indole, Diazetine.

## INTRODUCTION

Indole is an electron-rich N-aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five membered nitrogen containing pyrrole ring through the 2- and 3-positions of the pyrrole nucleus. Indole is called as benzopyrrole. The indole skeleton is one of the most important heterocyclic ring systems which is found in many natural products and biologically active molecules, pharmaceutical agents and polymer[1-3]. Indole derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds because of their varied biological properties. Most of the Indole derivatives are biologically active chemicals present in microorganisms, plants and animals representing an important class of therapeutic agent in medicinal chemistry [4-8].

In the last few decades, the chemistry of 1,2,4-triazoles and their heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance[9,10].

Recently 1,3-diazetine compounds were synthesized by the reaction of N-acyl with sodium azide in dimethylformamid [11]




Depending on the above finding , we decided to synthesize novel indole derivatives containing triazole with imine group, N-acyl or Diazetine ring, respectively (scheme 1).

## EXPERIMENTAL

MATERIALS : All chemicals were supplied from Merck , GCC and Aldrich Chemicals Co. and used as received .

TECHNIQUES : FTIR spectra were recorded using potassium bromide discs on a Shimadzo (Ir prestige-21) FTIR spectrophotometer . $^{1}$HNMR spectra were carried out by company : Bruker , model: ultra shield 300 MHz , origin : Switzerland and are reported in ppm(δ), DMSO was used as a solvent with TMS as an internal standard . Measurements were made at chemistry department, Al-albyat university in Jordan , Uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus.

## MATERIALS AND METHODS

**methyl (1H-indol-3-carboxylate) [I]**:

This compound was prepared according to the let.[12] , yield 94%, m.p. oily.

**1H-indol-3-acetohydrazide [II]:**

This compound was prepared according to the let. [13] , yield 97%, m.p. 110-112$^{0}$C.

**[(phenyl thiosemicarbazide)methylene-3-yl]-1H-indole [III]**:

This compound was prepared according to the let. [14], yield 89%, m.p. 174-176$^{0}$C.

**5-((1H-indol-3-yl)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol[IV]:**

This compound was prepared according to the let. [14], yield 93%, m.p. 264-266$^{0}$C.

**3-((5-hydrazinyl-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-1H-indole [V]:**

To 5-((1H-indol-3-yl)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (IV) (1.5 g,0.01 mol) was dissolved in ethanol, hydrazine hydrate (5 mL,0.02 mol) was added dropwise with stirring and the mixture was then refluxed for (6hrs), then the excess solvent was distilled off. Filtered the resulting solid which was separated out on cooling and recrystalized from ethanol to give the desired product, yield 82%, m.p. 251$^{0}$C dec.

**Synthesis of Schiff bases [VI]$_{a-d}$**

A mixture of new hydrazine compound [V] (0.01 mol) , aromatic aldehydes(4-N,N-dimethyl, 4-nitro, 3-nitro, benzaldehyde (0.01 mol), absolute ethanol (15 mL) and 2 drops of glacial acetic acid was refluxed for (6hrs). The solvent was evaporated under vacuum and the residue crystallized from chloroform.

**Synthesis of N-acyl derivatives [VII]a-d**

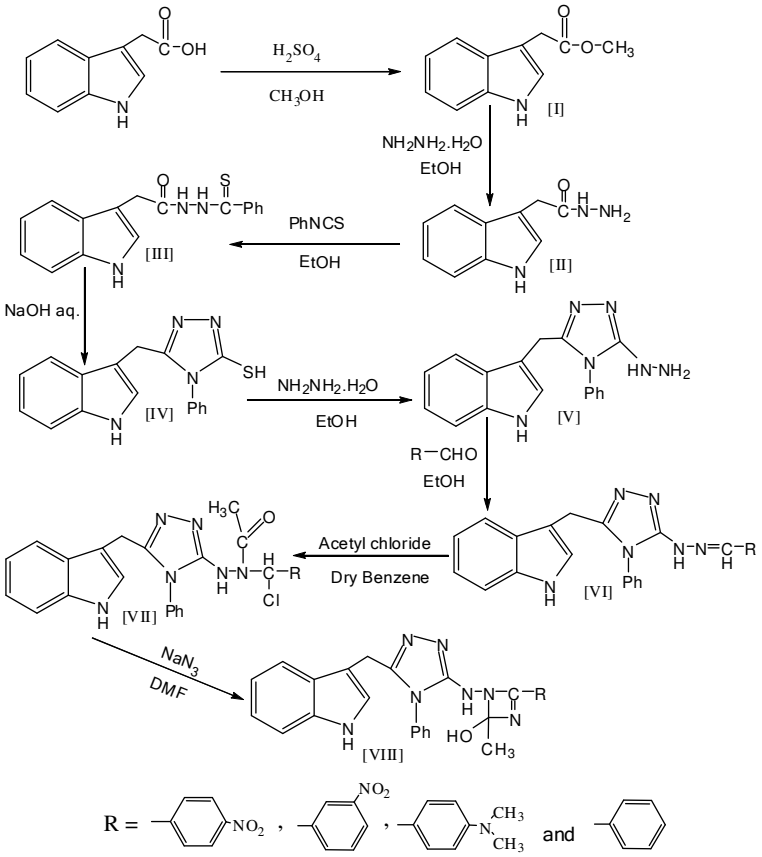
To a stirred solution of Schiff bases[VI]$_{a-d}$ (0.01mol) in 10 mL dry benzene was added dropwise acetyl chloride (0.012mol) after cooling , the reaction mixture was refluxed for 1 hour. The solvent was evaporated and the residue was filtered and washed with water for many times and recrystalized from ethanol.

**Synthesis of 1,3-diazetine derivatives [VIII]a-d**

To a stirring solution of N-acyl derivatives [VII]$_{a-d}$ (0.01mol) in 10 mL of dimethylformamid, sodium azide (0.65gm,0.01mol) was added. After the addition, the mixture was heated for 2 hrs at(55-60) $^{0}$C with stirring, then cooled at room temperature and the precipitate was filtered , washed with cold water. Recrystalized from petroleum ether (40-55) $^{0}$C to give compounds [VIII]$_{a-d}$.

Physical data of Schiff bases[VI]$_{a-d}$, N-acyl[VII]$_{a-d}$ compounds and 1,3-diazetine derivatives [VIII] $_{a-d}$ were listed in Table (1) .




Scheme 1

## RESULTS AND DISCUSSION

Methyl (1H-indol-3-carboxylate) [I] was obtained by esterification of indole-3-acetic acid with absolute methanol in conc.$H_2SO_4$ as a catalyst, following the procedure described by Vogel[12]. this structure was identified by FTIR spectroscopy. The FTIR absorption spectrum showed the disappearance of absorption stretching bands of O─H and C═O (carboxylic moiety) groups of indole-3-acetic acid together with the appearance of a stretching bands at 1732cm$^{-1}$ which is assigned to C═O of ester moiety.

Condensation ester [I] with hydrazine hydrate to get the 1H-indol-3-acetohydrazide [II], which is characterized by higher melting point and the FTIR spectrum revealed stretching vibration in the region (3113-3287)cm$^{-1}$ which are assigned to (N─H, $NH_2$) groups as well as stretching absorption at 1649 cm$^{-1}$ due to C═O (amid) group and disappearance of absorption stretching band due to C═O of ester moiety.

The reaction of acid hydrazide [II] with phenyl isothiocyanate leads to the formation of thiosemicarbazide derivative[III] by neucleophilic addition reaction. The structure of this compound was identified by melting point , FTIR spectroscopy. FTIR indicated to disappearance of two bands which could be attributed to asymmetric and symmetric stretching vibration of $NH_2$ group with show absorption bands in the range 3134 - 3221cm$^{-1}$ assigned for three N─H groups, bands at 1681 cm$^{-1}$ and 1296 cm$^{-1}$ that could be assigned to (C=O amide) and C=S groups, respectively[15].

Cyclization of thiosemicarbazide derivative [III] is carried out in aqueous sodium hydroxide solution followed by acidification with hydrochloric acid yielded 1,2,4-triazole derivative[IV], this Compound show absorption band around 2600 cm$^{-1}$ that are attributed to the S─H stretching frequency. The FTIR spectra show also the disappearance of the band of the (C=O amide) group, which are observed in the starting materials[III].

The novel compound[V] was synthesized by neucleophilic substitution of 1,2,4-triazole-5-thiol derivative[IV] with hydrazine hydrate in absolute ethanol as solvent. The structure of this compound[V] was studied by melting point , FTIR and $^1$HNMR spectroscopy. FTIR absorption spectra showed the disappearance of absorption bands due to (S─H) and (C═S) groups of the compound [IV] together with appearance of new absorption band in the region (3188-3314)cm$^{-1}$ which is assigned to (N-H, $NH_2$) groups .

$^1$HNMR spectrum of compound [V], in DMSO as a solvent exhibited a singlet signal at δ 3.96 ppm for two protons of $CH_2$ group and many signals in the region δ 6.93-7.47 ppm that could be attributed to

aromatic protons and one proton of NH-het group, besides to these a singlet signal appear at δ 6.65 ppm due to one proton at C-2 of indole ring which is interference with a broad signal for $NH_2$ protons at δ (6.3-6.7)ppm.

New Schiff bases$[VI]_{a-d}$ were synthesized in the usual way by condensation of compound[V] with different aromatic aldehydes. These Schiff bases$[VI]_{a-d}$ were identified by their melting points, FTIR and $^1$HNMR spectroscopy. FTIR absorption spectra showed the disappearance of absorption bands due to $NH_2$ and C═O groups of the starting materials together with appearance of new absorption band in the region (1608-1635) $cm^{-1}$ which is assigned to C═N stretching.

$^1$HNMR spectrum of Schiff bases $[VI]_a$ , showed singlet signal at δ 3.95 ppm due to two protons of $CH_2$, the sharp signal at δ 8.36 may be assigned to imine (CH=N) proton, and the singlet band at δ 13.65ppm can be attributed to one proton of NH group, many signals in the region δ 6.92-7.48 ppm that could be attributed to the thirteen aromatic protons and one proton at (C-2) of indole ring appear as singlet signal at δ 6.65 ppm, finally singlet signal at δ 10.80 ppm due to proton of NH indole ring.

N-acyl compounds $[VII]_{a-d}$ were synthesized by refluxing acetyl chloride with Schiff bases$[VI]_{a-d}$ in dry benzene. The reaction is initiated by attack of the azomethine nitrogen at the carbonyl group of acetyl chloride.

These compounds identified by their melting points, FTIR and $^1$HNMR spectroscopy. FTIR absorption spectra showed the disappearance of absorption bands due to C═N stretching of Schiff bases with appearance of new absorption band in the rang(1647-1701) $cm^{-1}$ which is assigned to C═O (amide) stretching, a new band in the region at (710-746)$cm^{-1}$ can be attributed to C-Cl absorption band.

The $^1$HNMR spectrum of compound $[VII]_c$ (in DMSO as a solvent) showed a signals as multiplet in the region δ (6.65-7.48)ppm that could be attributed to the fourteen aromatic protons, a singlet signal at δ 3.95 ppm for two protons of $CH_2$ group. This spectrum also showed a singlet signal at δ 6.01 ppm that could be attributed to proton of (CH-Cl) group, the singlet signal at δ 10.81 ppm for NH indole ring. Finally two singlet signal at δ (1.991-1.98) ppm may be attributed to six protons of two $CH_3$ groups.

The 1,3-diazetine derivatives$[VIII]_{a-d}$ were obtained by addition reaction of compound$[VII]_{a-d}$ with sodium azide in dimethylformamid as a solvent. These compounds were identified by their melting points, FTIR and $^1$HNMR spectroscopy. The FTIR absorption spectra showed the disappearance of absorption bands due to C-Cl and C═O (amide) with appearance of new absorption stretching band in the rang (1658-1670)$cm^{-1}$ for C═N (endocyclic) of diazetine and a broad peak in the region (3200-3280) $cm^{-1}$ assigned for O─H group[11].

The $^1$HNMR spectrum of compound $[VII]_b$ ,(in DMSO as a solvent) showed a sharp signal at δ 1.3 ppm due to the three protons of $CH_3$ group and showed a sharp signal at δ 3.95 ppm for two protons of $CH_2$ group also showed many signals(due to fourteen aromatic protons) appeared in the region δ 6.65-8.34 ppm and singlet sharp signal at δ 8.91 ppm can be attributed to one proton of O-H group and two signals at δ 10.79 ppm and δ 13.72 ppm for two NH groups of indole and (NH-het.), respectively.

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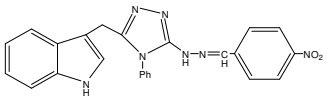
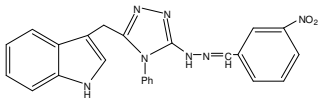
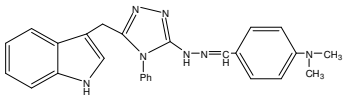
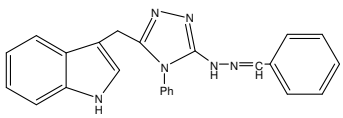
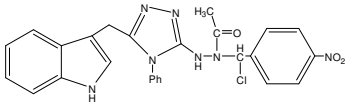
**Table-1: Physical properties of synthesized compounds [VI]a-d - [VIII]a-d**

| Com p.No. | Nomenclature | Structural formula | Molecular formula | M.P ◦C | Yiel d% | Color |
|---|---|---|---|---|---|---|
| $[VI]_a$ | 3-((5-(2-(4-nitrobenzylidene) hydrazinyl) -4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-1H-indole |  | $C_{24}H_{19}N_7O_2$ | 248-250 | 86 | Yellow |
| $[VI]_b$ | 3-((5-(2-(3-nitrobenzylidene) hydrazinyl)-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-1H indole |  | $C_{24}H_{19}N_7O_2$ | 242-244 | 92 | gray |
| $[VI]_c$ | 4-((2-(5-((1H-indol-3-yl) methyl)-4-phenyl-4H-1,2,4-triazol-3-yl) hydrazono) methyl) -N,N-dimethyl aniline |  | $C_{26}H_{25}N_7$ | 176-178 | 84 | Dark yellow |
| $[VI]_d$ | 3-((5-(2-benzylidenehydrazinyl)-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-1H-indole |  | $C_{24}H_{20}N_6$ | 258-260 | 76 | Pale yellow |
| $[VII]_a$ | N'-(5-((1H-indol-3-yl)methyl) -4-phenyl-4H-1,2,4-triazol-3-yl)-N-(α-chloro(4-nitrophenyl )methyl) acetohydrazide |  | $C_{26}H_{22}ClN_7O_3$ | 164-166 | 77 | Pale yellow |

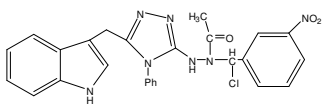
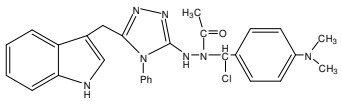
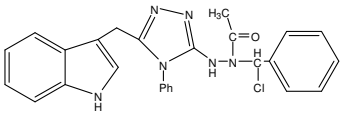
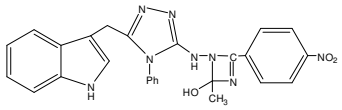
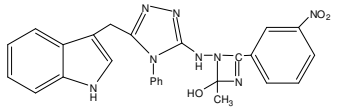
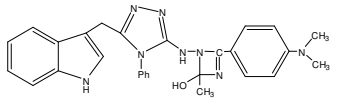
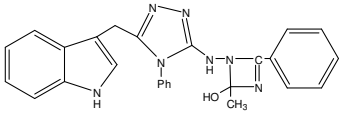
| | | | | | | |
|---|---|---|---|---|---|---|
| $[VII]_b$ | N'-(5-((1H-indol-3-yl) methyl )-4-phenyl-4H-1,2,4-triazol-3 -yl)-N-(α-chloro(3-nitrophenyl) methyl) acetohydrazide |  | $C_{26}H_{22}ClN_7O_3$ | 156-158 | 67 | Yellow |
| $[VII]_c$ | N'-(5-((1H-indol-3-yl) methyl)-4-phenyl-4H-1,2,4-triazol-3-yl) -N-( α-chloro(4-(dimethyl amino) phenyl) methyl) acetohydrazide |  | $C_{28}H_{28}ClN_7O$ | 222-224 | 65 | Red |
| $[VII]_d$ | N'-(5-((1H-indol-3-yl) methyl )-4-phenyl-4H-1,2,4-triazol-3-yl)-N-(α-chloro (phenyl) methyl)acetohydrazide |  | $C_{26}H_{23}ClN_6O$ | I61-163 | 87 | Off white |
| [VIII] a | 1-(5-((1H-indol-3-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylamino) -2-methyl-4-(4-nitrophenyl)-1,2-dihydro-1,3-diazet-2-ol |  | $C_{26}H_{22}N_8O_3$ | 290-292 | 50 | Pale yellow |
| [VIII] b | 1-(5-((1H-indol-3-yl)methyl)-4 phenyl-4H-1,2,4-triazol-3-yl- amino)-2-methyl-4-(3-nitrophenyl)-1,2-dihydro-1,3-diazet-2-ol |  | $C_{26}H_{22}N_8O_3$ | 178-180 | 60 | Yellow |
| [VIII] c | 1-(5-((1H-indol-3-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylamino)-4-(4-(dimethyl amino) phenyl)-2-methyl-1,2-dihydro-1,3-diazet-2-ol |  | $C_{28}H_{28}N_8O$ | 192-194 | 65 | Dark yellow |
| [VIII] d | 1-(5-((1H-indol-3-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylamino)-2-methyl-4-phenyl-1,2-dihydro-1,3-diazet-2-ol |  | $C_{26}H_{23}N_7O$ | 202-204 | 67 | Yellow |

Table-2: Characteristic FTIR absorption bands($cm^{-1}$) of synthesized compounds

| Comp.No. | νO-H | νN-H | νC-H arom. | νC-H alipha. | νC=O amide | νC=N endocyc. | νC=N exocyc. | νC=C arom. | Other |
|---|---|---|---|---|---|---|---|---|---|
| $[VI]_a$ | ___ | 3346 | 3045 | 2937-2845 | ___ | ___ | 1629 | 1597 | p-$NO_2$ :1519,1346 |
| $[VI]_b$ | ___ | 3344 | 3043 | 2937-2850 | ___ | ___ | 1626 | 1597 | m-$NO_2$ :1525,1354 |
| $[VI]_c$ | ___ | 3346 | 3043 | 2937-2854 | ___ | ___ | 1608 | 1590 | νC-N-C 1168,813,1365 |
| $[VI]_d$ | ___ | 3346 | 3045 | 2937-2852 | ___ | ___ | 1635 | 1590 | ___ |
| $[VII]_a$ | ___ | 3385 | 3061 | 2978-2848 | 1681 | ___ | ___ | 1591 | p-$NO_2$ :1518,1340 C-Cl: 723 |
| $[VII]_b$ | ___ | 3331 | 3055 | 2926-2854 | 1701 | ___ | ___ | 1595 | m-$NO_2$ :1529,1365 C-Cl: 710 |
| $[VII]_c$ | ___ | 3346 | 3043 | 2920-2854 | 1647 | ___ | ___ | 1601 | νC-N-C:1172,817,1375 C-Cl: interference with746 |
| $[VII]_d$ | ___ | 3333 | 3051 | 2931-2850 | 1695 | ___ | ___ | 1591 | C-Cl:715 |
| [VIII]a | 3270 | 3346 | 3045 | 2926-2854 | ___ | 1658 | ___ | 1597 | p-$NO_2$ :1525,1338 |
| [VIII]b | 3280 | 3346 | 3051 | 2924-2854 | ___ | 1670 | ___ | 1595 | m-$NO_2$:1529, 1354 |
| [VIII]c | 3205 | 3288 | 3045 | 2920-2852 | ___ | 1658 | ___ | 1573 | νC-N-C 1168,815,1365 |
| [VIII]d | 3200 | 3346 | 3045 | 2937-2854 | ___ | 1662 | ___ | 1597 | ____ |