Synthesis of some new compounds derived from ٤-hydroxy-٣-methoxybenzaldehyde with study of biological activity for some of them

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Abstract

The vanillin was converted to ethyl-٢-(٤-formyl-٢-methoxyphenoxy) acetate ($A_١$) by the reaction of vanillin with ethylchloroacetate in basic media in dry acetone.

The ٢-((٤-hydazonomethyl)-٢-methoxyphenoxy) acetohydrazide ($A_٢$) was synthesized by the reaction of ($A_١$) with hydrazine hydrate, ethanol absolute gave a hydrazide compound, from the hydrazide we synthesized series of compounds (Oxadiazole, Triazole, Aziridine, Schiff's bases and other derivative compounds).

These compounds were identified by T.L.C(thin layer chromatography)., M.P(melting point)., FT(fourier transform).IR, H-NMR and elemental analysis (C.H.N.S).

Key word Oxadiazole, Triazole, Aziridine, Schiff's bases and other derivative compounds.

Introduction

Hydrazide and thiosemicarbazide derivatives attracted a lot of attention because they are considered as intermediates to synthesized several compounds such as Oxadiazole, Triazole, Aziridine, Schiff's bases and other derivative compounds which all were reported to possess biological activities.

There are four isomeric types of Oxadiazole, the most thermally stable is ١,٣,٤- Oxadiazole, Oxadiazole derivatives is an important heterocyclic compounds present in variety biologically[١]

Oxadiazole was synthesized by the reaction of hydrazide derivative with carbon disulphide in basic media[٢].

The heterocyclic such as Oxadiazole are themselves important chemotherapeutic agents and exhibit antitubercular, bacteriostatic, hypoglycaemic, antiviral, antifungal, antithyroid, carcinostatic and stong herbicidal activities when properly substituted in ٢-and ٥-postions[٣].

The most important is symmetrical ١,٢,٤-Triazole, this primarily due to the large number of use, including drug synthesis, herbicide, photographic chemical and dyestuffs[٤].

Substituted triazoles have been associated with activities as plant regulars[٥]and as insecticidal agents[٦].

Compounds containing triazole moiety have been revealed to exhibit a wide variety of interesting biological properties such as anticancer, antifungal, antimicrobial, analgesic, anti-inflammatory, antibacterial, anticonvulsant and antitubercular[٧,٨]. Furthermore, they are used as a versatile reagent in the synthesis of heterocyclic compounds and/or as a raw material in drug synthesis. To expand and further explore the clinical significance of triazoles

Schiffs bases are widely utilized in both pharmaceutical and industrial fields[٩].Schiff bases derived from different heterocyclic compounds have been reported to possess cytotoxic [10], anticonvulsant[11], antiproliferative [12], antimicrobial [13], anticancer [14], and antifungal activities [15].

Aziridines are the dihydro derivatives of azirines. Aziridine is a three membered saturated heterocyclic ring containing two carbons and one nitrogen atom. Aziridines as a class are of interest as biological alkylating and anticancer agents[١٦].

Aziridines and its derivatives are potent pharmacological agent. The toxic effect of Aziridine itself causes irritation of eyes, skin and internal inflammation. Besides, the ability of Aziridines as an alkylating agent it is of important in industry and biology, and this property has resulted in a number of industrial applications of Aziridines. Certain antibiotics and anticancer agents possess the Aziridine ring [١٧].

Experimental

١-Thin layer chromatography(TLC)was carried out, and the plates were developed with iodine vapour.

٢-Melting point are recorded using hot stage gallen kamp melting point apparatus and they were uncorrected.

٣-Infrared spectra are recorded using fourier transform infrared SHMADZU(٨٣٠٠)(F.T.IR)infrared spectrophotometer, KBr disc, university of Baghdad.

٤-Analytical data (C.H.N.S.)were within±٠,٤٪ of the theoretical values.

٥-H NMR were recorded on fourier transform varian spectrometer operating at ٣٠٠MHz with(DMSO) BRUKER with TMS as an internal standard.

Synthesis of compound(A١)

A mixture of vanillin (٠,٠١mol.) and anhydrous potassium carbonate(٠,٠١mol.) was dissolved in dry acetone(٢٠ml). to this solution ethylchloroacetate (٠,٠١٥mol.) was added. The resulting mixture was heated under reflux for ٥hrs. then allowed at cool down to room temperature, the reaction was followed by (TLC), then filtered the product, after evaporating the

reaction content at (٥٠-٦٠)ºC under reduced pressure, an oily product was obtained.

Synthesis of compound(A٢)

A solution of the A١ compound(٠,٠١mol.) was refluxed with hydrazine hydrate(٠,٠٢mol.) for ٤hrs. after cooling it at room temperature, a yellow solid appeared. This was recrystallized from ethanol to afforded. The desired product, m.p=١٢٦-١٢٧ºC, Yield ٨٥٪.

Synthesis of compound(A٣)

To a round bottom flask was added compound A١ (٠,٠١mol), thiosemicarbazide(٠,٠٢mol.) in ethanol absolute(٢٥ml.) the resultant reaction mixture was refluxed for ٤h. after cooling it to room temperature, a yellow coloured solid separated out.it was filtered off , then dried and crystallized from ethanol, m.p=١٥٨ ºC, Yield ٧٣٪.

Synthesis of compound(A٤)

A mixture of A٢ (٠,٠١mol) and KOH (٠,٠٢mol.)in ethanol absolute (٢٥ml) ,CS_2 (٠,٠٢mol) was added slowly The reaction mixture was stirred for ٢٤hrs at room

Temperature the resulting precipitate was separated by filtration and recrystalized from ethanol, m.p=(١٩٤-١٩٥) ºC,yield ٧٧٪.

Synthesis of compound(A٥)

The corresponding compound A٤ (٠,٠١mol.) was added to a solution of ٢٠ml hydrazine hydrate and ٢ml H_2O,refluxed for ١,٥hrs. acidified with a solution of HCl,the precipitate was filtered and recrystallized from ethanol to afford the desired compound, m.p=٢٦٩-٢٧٠ ºC,yield ٨١٪

Synthesis of compound(A٦)

The corresponding compound A٢(٠,٠١mol.)and CS_2(٠,٠١mol.) were added to a solution of KOH (٠,٠١mol.) in ethanol absolute (٥٠ml.). The reaction mixture was refluxed for ٧hrs., after evaporating under reduced pressure, a solid was obtained, this was dissolved in ٣٠٠ml of H_2O and acidified with conc.HCl.The precipitate was filtered, washed with H_2O and recrystallized from ethanol to afford the desired compound, m.p=(١٩٨-٢٠٠) ºC, Yield ٧٨٪.

Synthesis of compound(A٧)

The corresponding compound A٢(٠,٠٢mol.) was dissolved in ١,٤-dioxan (٢٥ml.) refluxed for (٥-٧)hrs between (١٥٠-٢٥٠)ºC, after evaporating under reduced pressure, a precipitate was washed with ether to afford the desired compound, m.p=١٢٥ ºC, Yield ٦٢٪.

Synthesis of compound(A٨)

The corresponding compound A٦(٠,٠١mol.)and N,N-dimethylbenzaldehyde (٠,٠٣mol.) were added to ethanol absolute (٢٥ml.) in acidic condition(٣drops of acidic acid). The reaction mixture was refluxed in

water bath for (٤-٦)hrs., the precipitate was filtered and dried, recrystallized from ethanol to afford the desired compound, M.P.=١٨٥ ºC, Yield ٨٨٪.

Synthesis of compound(A٩)

The corresponding compound A٢(٠,٠١mol.) and phenyl iso thio cyanate (٠,٠٢mol.) in ١,٤-dioxane(٣٠ml) was refluxed for ٥ hrs.,after evaporation under reduced pressure, the precipitation was washed with ethanol to afford the desired compound. m.p=١٤٨ ºC,yield ٥٣٪.

Synthesis of compound(A١٠)

The corresponding compound A٢(٠,٠١mol.)and maleic anhydride(٠,٠٢mol.) were added to acetic acid(٢٥ml.). The reaction mixture was refluxed for (٥-٧)hrs. then dissolved in ٣٠٠ml of H٢O(ice), after evaporating under reduced pressure, washed with ether, a solid was obtained, m.p=٢٧٠-٢٧٢ ºC, Yield ٦٣٪.

Synthesis of compound(A١١)

The corresponding A٢ (٠,٠١mol.) and sodium azide (٠,٠٢mol.)with ammonium chloride(٠,٠١Mol) were added to THF(٢٥ml).the reaction mixture was refluxed in water bath for ١٠ hrs. . Then the mixture was filtered and the solvent was evaporated to give apurple crystal, m.p=٢٨٣ ºC yield ٧١٪ .

Results and discussion

Compound A١was obtained from the reaction of vanillin with ethylchloroacetate in basic media and their structure was confirmed using FT.IR spectral data and monitored by (T.L.C). The FT.IR spectrum showed disappearance of the wide absorption band in the region (٢٨٦٠-٣٢٥٠) cm^{-1} which belongs to the stretching vibration of (OH) group, appearance anew band in the ١٧٤٩cm^{-1} due to (C=O) ester with remain band at ١٦٧٨cm^{-1} due to(C=O) aldehyde and appearance band in the region (١٤٠٠-١٥٩١) cm^{-1} due to (C=C) aromatic, appearance band at ١٢٠٠cm^{-1} due to (C-O) of (O-CH_3) group.

Compound A٢was obtained from the reaction of easterA١ with hydrazine hydrate and their structure was confirmed using m.p and FT.IR spectral data. The FT.IR spectrum showed disappearance band at ٢٧٧٧ cm^{-1} due to (C-H) aldehyde with appearance two bands at (٣٢٥٥ and ٣٣٣٦) cm^{-1} due to NH_2 group and disappearance band at ١٧٤٩ cm^{-1} due to (C=O) ester with appearance band at ١٦٧٨cm^{-1} due to(C=O) amide, appearance band at١٦٢٠ cm^{-1} due to (C=N).

Compound A٣was obtained from the reaction of A١ with thiosemicarbazide in ethanol absolute and their structure was confirmed using m.p, FT.IR spectral data and C.H.N.S.analysis. The FT.IR spectrum showed appearance band at (٣١٧٨ and ٣٣١٧) cm^{-1} due to sym. and asym. of NH_2 group, disappearance band at (١٧٤٩,١٦٧٨) cm^{-1} due to (C=O) of ester and aldehyde respectively. with appearance two bands at ١٠٦٠ and ١٠٨٠ cm^{-1} due to(C=S), appearance band at (١٤١٩-١٥١٠) cm^{-1} due to (C=C) aromatic,appearacnce at (١٦١٦) cm^{-1} due

to(C=N)group,appearance band at (١٦٩٤) cm^{-1} due to(C=O) amide. The element analysis C, ٤٢,٤٨٪ ;H, ٣,٠٣٪ ;N,١٦,٤٢٪ ;S, ١٨,٨٣٪ .

Compound $A_٤$ was obtained from the reaction of $A_٢$with $CS_٢$ in basic media at room temperature and their structure was confirmed using m.p and F.T.IR spectral data. The F.T.IR spectrum showed disappearance band at (٣٢٥٥-٣٣٣٦) cm^{-1} due to sym. and asym of $NH_٢$ group with appearance band at ٣٣٠٠ cm^{-1} due to (N-H)aliphatic, also appearance band at ١٦٩٥ cm^{-1} due to(C=O) amide, appearance band at ١٦٢٠ cm^{-1} due to (C=N) and appearance band at ١٠٧٠ cm^{-1} due to (C=S)[١٨].

Compound $A_٥$ was obtained from the reaction of $A_٤$ with hydrazine hydrate and their structure was confirmed using m.p, FT.IR spectral data and C.H.N.S.analysis,H-NMR. The FT.IR spectrum showed appearance band at (٣٢٠١-٣٣٩٩) cm^{-1} due to sym and asym of $NH_٢$ group, appearance week band at ٢٥٦٠ cm^{-1} due to (S-H) group, also appearance band at ١٦٣١cm^{-1} due to(C=N) endocyclic of triazole ring with disappearance band at ١٦٩٥ cm^{-1} due to (C=O) amide group and disappearance band at ١٠٧٠ due to of (C=S), H-NMR of this compound shows the following characteristic chemical shifts (DMSO-d٦,PPM)the aromaric ring protons as multiplate at (٧,٨٨PPM),signal at (٩,٨١PPM,S) due to of proton in (SH)group, signal at (٣,٨٩PPM,S) due to of methoxy group, signal at(٤,٦٥PPM.S)due to of methylene group, and signal at(٥,٨٩PPM,S)due to of amino groups.

Compound $A_٦$ was obtained from the reaction of $A_٢$with $CS_٢$ in basic media and their structure was confirmed using m.p, FT.IR spectral data and C.H.N.S.analysis. The FT.IR spectrum showed disappearance band at (٣٢٥٥-٣٣٣٦) cm^{-1} due to sym and asym of $NH_٢$ group of hydrazide group with disappearance band at ١٦٩٥ cm^{-1} due to (C=O) amide and appearance band at (٢٧٠٠-٢٧٩٩) cm^{-1} due to(C-H) aliphatic, appearance band at (٢٨٠٠-٢٨٩٠) cm^{-1} due to (C-H) aromatic, appearance week band at ٢٧٠٠ cm^{-1} due to (S-H), also appearance band at ١٦٢٤,١٦٠٢ cm^{-1} due to (C=N) endocyclic of oxadiazole ring and (C=N) aliphatic. Moreover, appearance band at ٣٣٤٠ cm^{-1} due to(N-H) tautomer and appearance band at ١١٤١ cm^{-1} due to(C=S) tautomer. The element analysis C, ٤٢,٤٨٪ ;H, ٣,٠٣٪ ;N, ١٦,٤٢٪ ;S, ١٨,٨٣٪, H-NMR of this compound shows the following characteristic chemical shifts (DMSO-d٦,PPM)the aromaric ring protons as multiplate at (٨,٤٤PPM,M),signal at (٥,٦٤PPM,S) due to of proton in (SH)group, signal at (٣,٢٤PPM,S) due to of methoxy group, and signal at(٢,٤PPM,S)due to of methylene group[١٩].

Compound $A_٧$ was obtained from the reaction ٢mol. of $A_٢$ in ١,٤-dioxan and their structure was confirmed using m.p, FT.IR spectral data and C.H.N.S.analysis. The FT.IR spectrum showed disappearance band at ١٦٧٨ cm^{-1} due to (C=O) amide and appearance band at ١٦٢٤ cm^{-1} ,١٦٠٠ cm^{-1} due to(C=N)

exocyclic and endocyclic respectively,appearance band at (٣١٥٠ and ٣٣٧٨)due to of NH_2 group. The element analysis C, ٥٤,٢١٪ ;H, ٥,٢٥٪ ;N, ٢٥,٣١٪.

Compound A_8 was obtained from the reaction of A_7 with N,N-dimethylbenzaldehyde in absolute ethanol and their structure was confirmed using m.p, FT.IR spectral data and C.H.N.S.analysis. The FT.IR spectrum showed disappearance band at(٣١٥٠ and ٣٣٧٨) asym. and sym of NH_2 group and appearance multi band at (١٥٩٨-١٦٥١) cm^{-1} due to (C=N) exocyclic due to of five imine proups. The element analysis C, ٦٩,٦٤٪ ;H, ٥,٠٥٪ ;N,١٥,٨١٪.

Compound A_9 was obtained from the reaction of $A_2$with phenylisothiocyanate in ١,٤-dioxane and their structure was confirmed using m. and FT.IR spectral data. The FT.IR spectrum showed disappearance band at (٣٢٥٥-٣٣٣٦) cm^{-1} due to sym and asym of NH_2 group with appearance band at ٣٣٠٠ cm^{-1} due to (N-H)aliphatic, also appearance band at ١٦٥٠ cm^{-1} due to(C=O) amide, appearance band at ١٦٢٥ cm^{-1} due to (C=N), appearance band at (١٥٩٧-١٤٠٠) cm^{-1} due to (C=C) and appearance band at ١٠٨٢ cm^{-1} due to (C=S).

Compound A_{10} was obtained from the reaction of $A_7$with maleic anhydride in acidic media and their structure was confirmed using m.p and FT.IR spectral data. The FT.IR spectrum showed disappearance band at (٣٢٥٥-٣٣٣٦) cm^{-1} due to sym and asym of NH_2 group, disappearance band at ١٦٧٨cm^{-1} due to (C=O) hydrazide appearance band at (١٦٨١ and ١٦٤٣) cm^{-1} due to (C=O) exocyclic and endocyclic amide respectively , appearance band at ١٦٠٠cm^{-1} due to (C=C) for succinimide , appearance band at ٣٤٥١ cm^{-1} due to (N-H) stretching ,appearance band at ١٦١٨ due to of (C=N) group.

Compound A_{11} was obtained from the reaction of A_{10} with sodium azide in Tetrahydrofuran (THF) and their structure was confirmed using m.p, FT.IR spectral data and C.H.N.S.analysis. The FT.IR spectrum showed appearance band at ٣٣٦٩ cm^{-1} due to N-H of aziriden cyclic, appearance band at ١٦٨٣ cm^{-1} due to (C=O) exocyclic amide and appearance band at ١٦٤٧ cm^{-1} due to(C=O) endocyclic amide appearance band at ١٦١٨ due to of (C=N) group. The element analysis C, ٥٠,٢٤٪ ;H, ٣,٥٢ %;N,١٩,٣٠٪ .

Table (١) physical properties of compounds(A_1-A_{11}).

Comp. No.	Formula weight	Molecular weight	M.P. data °C
A_1	$C_{12}H_{14}O_5$	٢٣٨	Syrup
A_2	$C_{10}H_{14}N_4O_3$	٢٣٨	١٢٦-١٢٧
A_3	$C_{18}H_{14}N_4O_7$	٣٩٨	١٥٨-١٦٠
A_4	$C_{12}H_{16}N_6O_2S_2$	٣٥٦	١٩٤-١٩٥
A_5	$C_{12}H_{10}N_4O_4S_2$	٣٣٨	٢٦٩-٢٧٠
A_6	$C_{20}H_{24}N_8O_4$	٤٤٠	١٩٨-٢٠٠
A_7	$C_{24}H_{24}N_6O_2S_2$	٥٠٨	١٢٥-١٢٩ dec
A_8	$C_{12}H_{12}K_2N_4O_2S_4$	٤٦٧	١٨٥-١٨٨
A_9	$C_{18}H_{16}N_6O_7$	٤٢٨	١٤٨-١٥١

A١٠	$C_{١٢}H_{١٤}N_{٨}O_{٢}S_{٢}$	٣٦٦	٢٧٠-٢٧٢
A١١	$C_{٤١}H_{٣٦}N_{٨}O_{٤}$	٧٠٤	٢٨٣-٢٨٥

Biological Activity

A few pathogenic species are known to be almost sensitive to certain antimicrobial agents, although in some parts of the world the situation is changing. As strains of pathogenic organism differ from one to another within their species in their antibiotic sensitivity, sensitivity tests are required as a routine. Heterocyclic rings are considered an important class of compounds having a wide spectrum of biological activity, the heterocyclic compounds are well known for their antibacterial and antifungal activities .There are some types of bacteria: ***Bacillus aureous*** and ***Pseudomonas aureous***. The results of the preliminary screening tests are listed in

Table (٢) Antibacterial activities of some of the synthesized compounds.

Comp. No.	***Bacillus aureous***	***Pseudomonas aureous***
A٤	+	++
A٥	++	+++
A٦	+	++
A٧	++	+
A٩	-	+
A١٠	±	++
A١١	+	+

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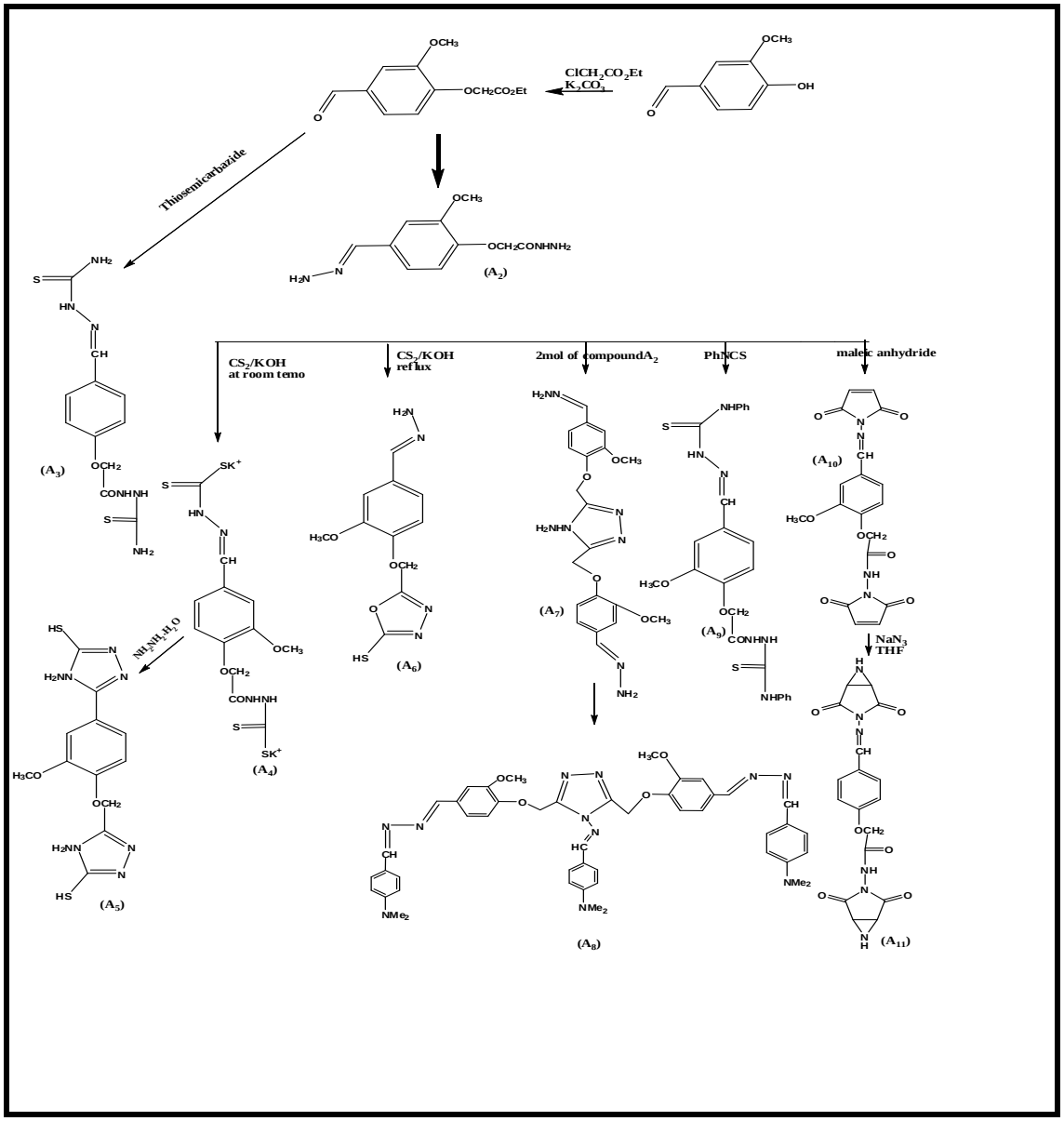

Scheme (١) show the structure of compounds A١-A١١

تحضـــــــير وتشخيـــــــص بعـض المركبـــــات الجديدة المشتقة من ٤-هيدروكسي-٣-ميـــثـــوكســـــي بنزالديهايد

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قسم الكيمياء

المقدمة

حول الفانلين الى اثيل-٢-(٤-فورميل-٢-ميثوكسي فينوكسي)أسيتايت بواسطة تفاعل الفانيلين مع اثيل كلورو اسيتيت في وسط قاعدي بوجود الاسيتون الجاف كمذيب.

تم تحضير ٢-(٤-(مثيل هايدرازون)-٢-ميثوكسي فينوكسي)اسيتو هايدرازايد بواسطة تفاعل ( )مع الهايدرازين هايدريت ٩٠% بوجود الايثانول ٩٩%, ومن الهايدرازايد حضرت سلسلة من المركبات (اوكساديازول, ترايازول, ازريدين, قواعد شف , وغيرها من المركبات المشتقة).

شخصت هذه المركبات بواسطة كروموتوكرافيا الطبقة الرقيقة, درجة الانصهار , الاشعة تحت الحمراء وتحليل العناصر.