

# A Review: Microwave Assisted Synthesis and Characterization of Some novel 3, 5-diaryl-2-pyrazolin-1-Carboxaldehyde Hydrazones.

Dr. Gunwanti Malhotra

Associate Professor, Chemistry Department  
M. P. Govt. PG College, Chittorgarh(312001)

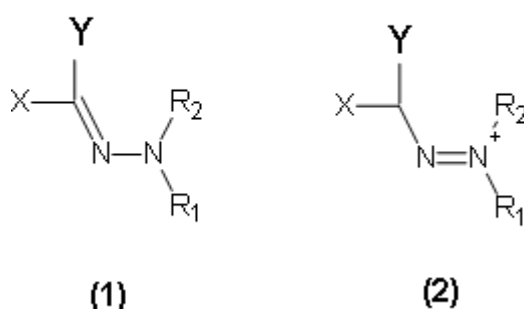
**Abstract:** Hydrazones and their derivatives are very important compounds in medicinal chemistry<sup>1</sup> due to their reported biological activity for the treatment of several diseases, like Alzheimer's, cancer, inflammation, and leishmaniasis. However, most of the investigations on hydrazones available in literature today are directed to the synthesis of these molecules with little discussion available on their biological activities. With the purpose of bringing lights into this issue, we performed a revision of the literature and wrote this review based on some of the most current research reports of hydrazones and derivatives, making it clear that the synthesis of these molecules can lead to new drug prototypes. Our goal is to encourage more studies focused on the synthesis and evaluation of new hydrazones, as a contribution to the development of potential new drugs for the treatment of various diseases. The development of novel compounds, hydrazones has shown that they possess a wide variety of biological activities viz. antimicrobial, anticonvulsant, antidepressant, anti-inflammatory<sup>2</sup>, analgesic, antiplatelet, antimalarial, anticancer<sup>3</sup>, antifungal, antitubercular, antiviral, cardio protective etc., Hydrazones/azomethines/imines possess  $\text{NHN}=\text{CH}-$  and constitute an important class of compounds for new drug development. A number of researchers have synthesized and evaluated the biological activities<sup>4</sup> of hydrazones. This review aims at highlighting the diverse biological activities of hydrazones.

**Keywords:** Alzheimer's; Hydrazones; biologic activity; cancer; guanylhyaazones; Azomethine.

## INTRODUCTION

There has been considerable interest in the development of novel compounds with pharmacological activities. Azomethines or hydrazines are one of the interesting class of compound in pharmacological chemistry. They are the derivatives of carbonyl compounds possessing an azomethine  $-\text{NH}-\text{N}=\text{CH}$  proton. They constitute an important class of compounds for new drug development. Hydrazone with X and Y carbon functionalities as COOR, CN etc are extremely important compounds in dye industry<sup>5</sup>. First hydrazones were osazones and were landmark achievement in development of sugar chemistry. They were prepared by the reaction of phenyl hydrazine with sugars. Introduction of nicotinic acid hydrazide, an important anti tubercular drug, paved new interesting hetero aryl hydrazides and hydrazones.

The nitrogen lone pair resonance in hydrazones renders hydrazone carbon atom electron rich (1) & (2) and the nucleophilicity of this carbon atom although has been noted in the literature<sup>4</sup> has now been recognized and utilized extensively in organic synthesis.



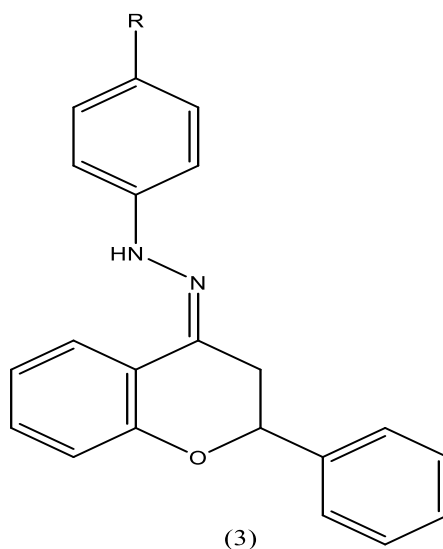
Due to wide spectrum of pharmacological activities of hydrazones, many researchers have prepared these compounds as target structure for evaluation of their biological activities. A number of biological activities such as antibacterial, anticonvulsant, analgesic, anti-inflammatory, antitubercular and antitumor activities are prominently reported to be possessed by hydrazones and their derivatives.

### Microwave Induced Synthesis of Hydrazones:-

Microwave induced synthesis of various chemical compounds has gained popularity recently. The use of microwave heating results in shorter reaction time compared to conveniently heating, easy work up, decrease in usual thermal degradation and better selectivity<sup>6</sup>. Microwave ovens provide a cleaner and cheap alternative to the conveniently heating method. The popularity of microwave heating for carrying out organic synthesis has increased to the extent that it now forms the basis of a number of commercial systems and has even made its way into undergraduate laboratory courses.

The combination of solvent free protocol; and microwave heating can be easily used to carry out a wide range of organic reactions.<sup>7,8</sup> Within short reaction time, higher conversion rate and selectivity. This approach is efficient, easy to perform, economic and ecofriendly and forms a part of e-chemistry.

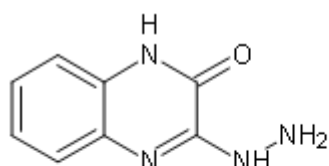
An environmentally benign aqueous protocol for the synthesis of cyclic, bicyclic and heterocyclic hydrazones (3) using polystyrene sulfonic acid (PSSA) as a catalyst has been developed. The reaction efficiently proceed in aqueous media in absence of any organic solvent under microwave irradiation<sup>9</sup>.



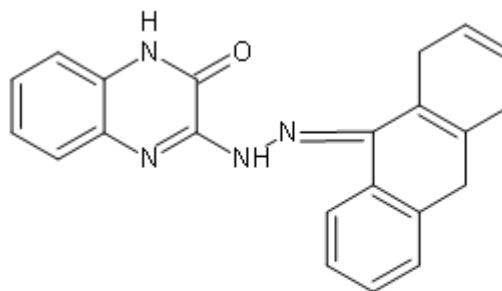
A convenient method for the preparation by hydrazone derivatives from condensation reaction of [3-phenoxy methyl-4-phenyl-1, 2, 4-triazol-5-yl-thia]-acetyl hydrazine with various substituted benzaldehydes under microwave irradiation has been developed by Wei et al<sup>10</sup>.

Several (un) substituted benzaldehyde (5-aryl-1, 3, 4-thiadiazol-2-yl)-hydrazones were efficiently synthesized by reaction of substituted benzaldehyde thio carbohydrazones with aromatic carboxylic acids using silica supported dichloro phosphate as a recoverable dehydrant under microwave irradiation. Microwave induced synthesis of hydrazones and Wleft-Kishner redction of carbonyl compounds has been reported by Gadhwal .

A simple and convenient method has been developed for the synthesis of various quinoxalin-3-hydrazone derivatives<sup>11</sup> (4& 5) using microwave irradiation protocol.

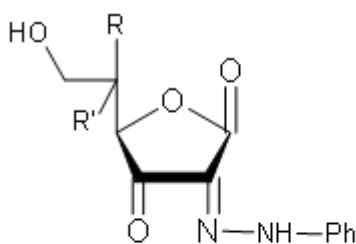


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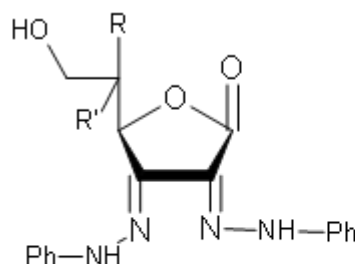


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Microwave assisted organic synthesis and organic reaction enhancement for the conversion of L-ascorbic acid and D-iso ascorbic acid to various heterocyclic compound via their monophenyl hydrazones (6) and bis (phenyl hydrazones) (7) have been achieved by El-Ashry .

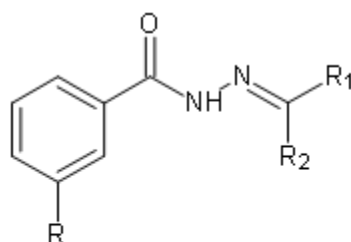


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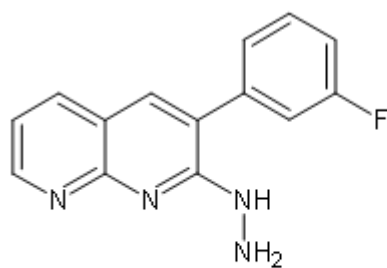
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Several 2-[(4-methyl-2-oxo-2H-chromen-7-yl) oxy]-acetohydrazide have been synthesized . A variety of N-acyl hydrazones (8) were synthesized under microwave irradiation, starting from benzo, salicylo and isonicotinic hydrazides.

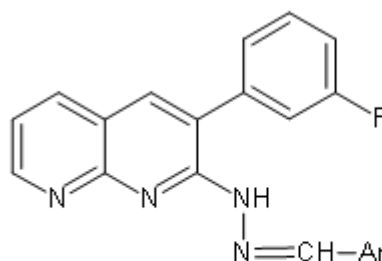


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Microwave assisted synthesis of some arylaldehyde-3-(3-fluoro phenyl)-1, 8-naphthyridin-2-yl-hydrazones (10) has been achieved by condensation of 2-hydrazino-3-(3-fluoro phenyl)-1, 8-naphthyridine (9).



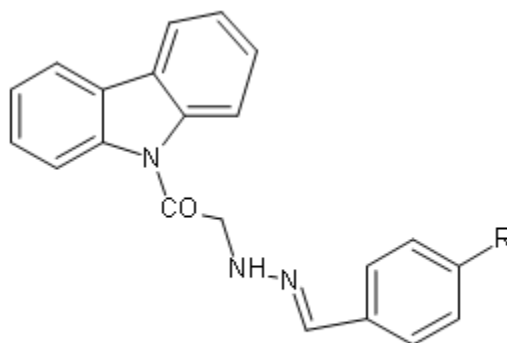
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A novel protocol for catalyst free reaction under solvent free microwave assisted condition for synthesis of heterocyclic hydrazones below the melting points of neat reactants has been reported by Jeselnik.

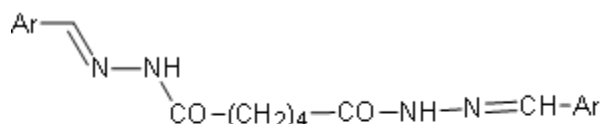
Several N-[( $\alpha$ -substituted benzylidene hydrazine)-acetyl]-1, 2, 3, 4-tetra hydrocarbazoles (11) have been synthesized using microwave assisted protocol.



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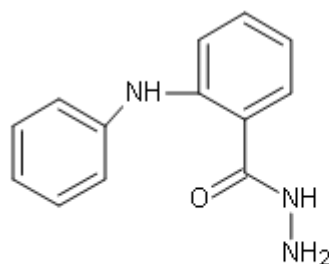
A series of some phenyl hydrazones has been prepared by the reaction of aromatic diazonium salts and active methylene compounds. These hydrazones have been screened for their biological activities. Synthesis of some new 1-(3-oxo-1, 4-benzoxazin-6-yl)-ethanol-(4-aryl-1, 3-thiazol-2-yl)-hydrazones under microwave irradiation has been achieved by Jagath Reddy<sup>12</sup>.

A simple efficient and ecofriendly method for the synthesis of bis(acylhydrazones) (12) from hexane dihydrazide and aldehydes under microwave irradiation without use of solvent and catalyst is reported by Li<sup>13</sup>.



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Some novel N-aryl hydrazone derivatives (13) of phenyl anthranilic acid were synthesized by use of microwave irradiation.

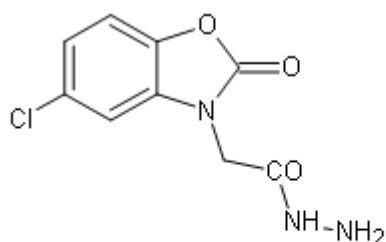


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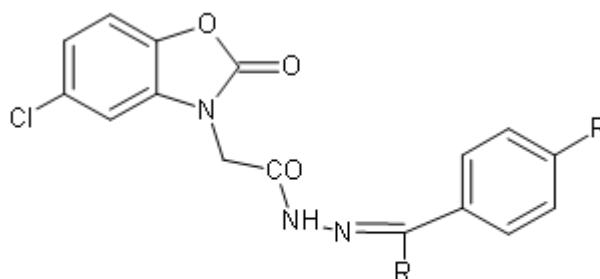
Microwave assisted synthesis of a series of N'-[5-R'-phenyl)-furan-2-yl)-methylene]-2-R-4H-furo-[3, 2,b]-pyrrole-5-carboxy hydrazides has been reported by Gasparova<sup>14</sup>.

The synthesis of hydrazone derivatives containing thiazole unit was achieved with condensation of thiosemicarbazidene and ω-bromoacetophenone at room temperature.

Synthesis pathway for 5-chloro-2-(3H)-benzoxazoline-3-acetyl-(2-p-substituted benzyl)-hydrazone (14) and 5-chloro-2(3H)-benzoxazoline-3-acetyl-2(p-substituted) aceto phenone hydrazone (15) derivatives has been reported using microwave irradiation<sup>15</sup>.



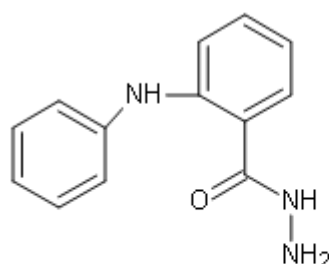
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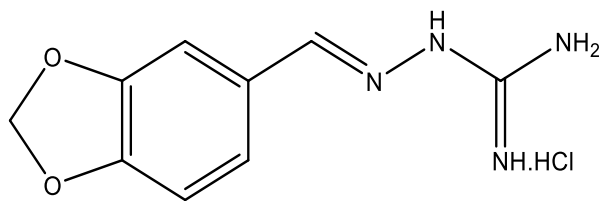
A series of some phenyl hydrazones has been prepared by the reaction of aromatic diazonium salts and active methylene compounds. These hydrazones have been screened for their biological activities.

Some novel N-aryl hydrazone derivatives (16) of phenyl anthranilic acid were synthesized by use of microwave irradiation.



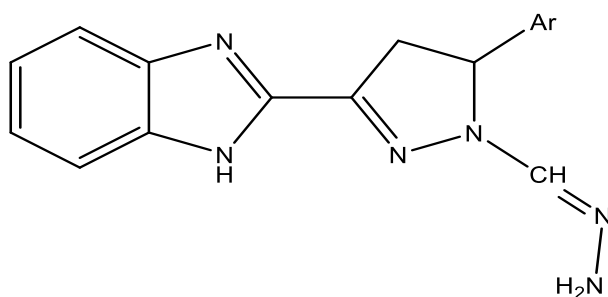
(16)

A rapid efficient and ecofriendly method for the preparation of new aryl-1, 4-bisoxacyacetyl hydrazone molecular tweezers has been reported. The reaction is accelerated by microwave irradiation under solvent free condition in presence of solid Al<sub>2</sub>O<sub>3</sub>. Microwave assisted synthesis of guanyl hydrazone (17) by the reaction of aromatic aldehydes and ketones with amino guanidine hydrochloride has been achieved by Martin .



(17)

Ecofriendly microwave assisted synthesis of some 3-benzimidazolyl-5-aryl-2-pyrazolin-1-carboxaldehyde hydrazones (18) as potent antimicrobial agent has been reported by Rajora et al<sup>16</sup>.



(18)

Several hydrazone derivatives have been prepared under microwave irradiation by Romanova. Microwave assisted synthesis of using Gabriel approach as a route to new pyrazolyl hydrazoneazole has been achieved by Al-Mousawi.

## PRESENT WORK

Since past decade the need for a cleaner chemical processes including monitoring, analysis, synthetic procedure catalyst and reaction condition was continuously felt in order to reduce the environmental impact of pollution. Green chemistry is being developed in order to achieve this goal. It is based on non conventional and innovative synthetic procedures. In recent years<sup>17</sup>, the use of microwave irradiation for the synthesis of various class of organic compounds has been successfully carried out. The use of such nonconventional reaction condition reveals several advantages such as operational simplicity, easy work up, cleaner reaction procedures, shorter reaction time with enhanced yield as compared to the conventional heating method. The microwave heating process has proved particularly beneficial for the reaction in solvent less condition or dry media.<sup>18,19</sup> The use of domestic microwave oven in this regard in a well known established procedure in MORE chemistry.<sup>20</sup>

Pyrazoline nucleus has always attracted the attention of researcher as these derivatives have played an important role in the development of theory in heterocyclic chemistry. These derivatives have been extensively used in organic synthesis. Due to their ready accessibility, diverse chemical reactivity and a variety of industrial application pyrazoline derivatives have been studied extensively. A broad spectrum of biological activities is associated with them. Pyrazoline derivatives have been reported to possess anti-inflammatory, antidiabetic, anesthetic, analgesic and antimicrobial activities.

Keeping in view the significant biological activities of pyrazolines, usefulness of hydrazones as important pharmacophores as well as their chelating behavior and advantages of microwave heating, in the present investigation we have carried out synthesis of variously substituted 3-(2'-hydroxy phenyl)-5-(substituted phenyl)-2-pyrazolin-2-yl-1-carboxaldehyde hydrazones by both conventional and microwave induced methods.

The structure of newly prepared compounds has been finally confirmed by their elemental analysis and spectral data.

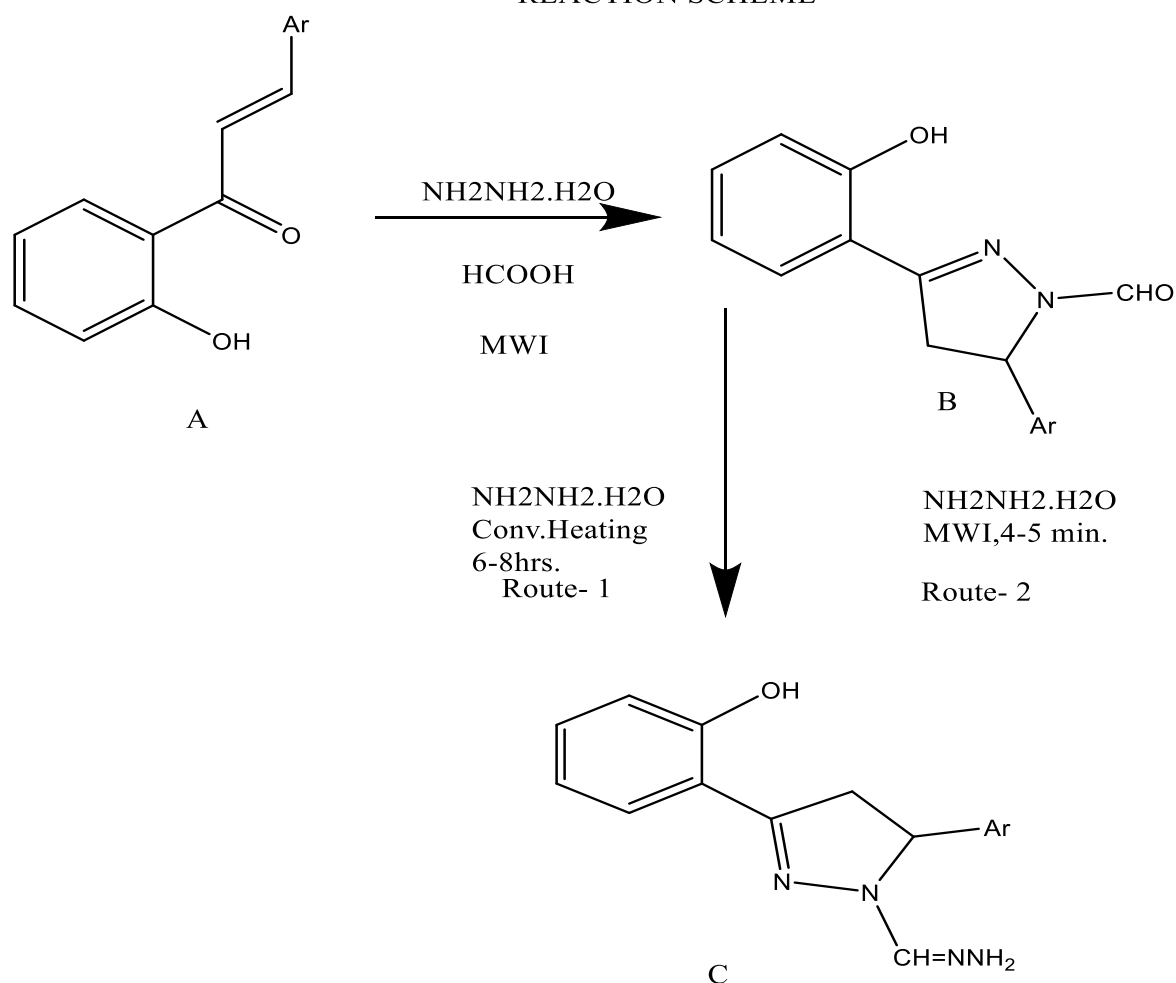
### 1. Conventional Method

A mixture of 3-(2'-hydroxy phenyl)-5-aryl-2-pyrazolin-1-carboxaldehyde and hydrazine hydrate was refluxed for 7-8 hours using ethanol as solvent. After completion of the reaction, the reaction mixture was left at room temperature. The separated solid was filtered crystallized and identified as the desired product in 60-68% yield.

### 2. Microwave Induced Method

3-(2-Hydroxy phenyl)-5-aryl-2-pyrazoline-1-carboxaldehyde and hydrazine hydrate were mixed thoroughly to form a homogeneous slurry. It was then subjected to microwave irradiations for 4-5 minutes and mixer cooled at room temperature. The residue obtained was extracted with ethanol which on standing gave desired product in 80-85% yield.

#### REACTION SCHEME



## RESULT AND DISSCUSSION

New 3, 5-Diaryl-2-pyrazolin-1-carboxaldehyde hydrazones were synthesized by both conventional and microwave induced methods. The structure of these compounds was established on the basis of their elemental analysis and spectral data. The identify of the compounds obtained by different method has been confirmed by m.p., CO-TLC and super imposable IR spectra.

The comparison of above synthetic methods clearly indicates that reaction can be conveniently carried out under solvent less condition using microwave irradiation. In comparison to conventional heating method the microwave induced method provides the product in better yield with high purity and work up of the product in quite easy. The reaction under microwave irradiation can be conveniently carried out with reduction in reaction time from hours to minutes.

The identify of newly prepared hydrazone was established on the basis of their analytical and spectral data. The IR (KBr) spectra of these compounds gave prominent absorption bands at  $3320\text{--}3300\text{ cm}^{-1}$  a weak intensity band for OH stretching,  $3198\text{--}3115\text{ cm}^{-1}$  sharp band with medium intensity for  $\text{NH}_2$  of hydrazone and a broad band at  $1495\text{--}1433\text{ cm}^{-1}$  for coupled vibration of C=N and N-N groupings.

The PMR spectra ( $\text{CDCl}_3$ ) of these hydrazones gave the signals at  $\delta$  3.32-3.37 (double doublet for  $\text{H}_A$ ),  $\delta$  3.86-3.96 (double doublet for  $\text{H}_B$ ) and  $\delta$  5.49-5.54 (double doublet for  $\text{H}_X$ ) indicating the presence of typical ABX pattern of pyrazoline ring system. The proton of OH group gave a sharp singlet at  $\delta$  10.1 whereas the  $\text{NH}_2$  proton were observed as singlet at  $\delta$  8.93. The methine proton of azomethine group ( $-\text{CH}=\text{N}-\text{NH}_2$ ) gave a singlet at  $\delta$  1.61 whereas the aromatic protons were observed a multiplet at  $\delta$  6.90-7.39.

The mass spectra (FAB) of these compounds gave molecular ion peaks. Corresponding to their molecular masses. The mass spectra were recorded using m-nitro benzyl alcohol as matrix. The matrix peaks were observed at  $m/z$  156, 154, 286 and 307.

## CONCLUSION

From this review it can be stated that hydrazone and their derivatives have a great importance in chemical fields like medicinal chemistry, research industry, coordination chemistry, in analytical chemistry as a reagents and other uses.

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