

# Synthesis and Antifungal Activity of Hydrazone Derivatives of Some Carbonyl Compounds

## Abstract

Ten hydrazones derivatives of carbonyl compounds were obtained and purified to investigate antifungal activity. Minimum inhibitory concentration (MIC) and sensitivity test were used to express the effectiveness of the compound as antifungal agent. MIC values of the compounds were determined by tube dilution techniques. Sensitivity testing was done to determine the compound under specified conditions. It has been done by disk diffusion method. Most of the compounds showed more activity than standard drug ketonazole.

The presence of chloro and bromo group in the phenyl ring enhanced the antifungal activity.

**Keyword:** Synthesis, Hydrazones, Antifungal Activity.

## Introduction

Hydrazones have been demonstrated to possess, among other, antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular and antitumoral activities. For example, isonicotinoyl hydrazones are antitubercular; 4-hydrobenzoic acid [(5-nitro-2-furyl)methylene]-hydrazide (nifuroxazide) is an intestinal antiseptic; 4-fluorobenzoic acid [(nitro-2-furyl)methylene]-hydrazide [1] and 2,3,4-pentanetrione-3-[4-[(5-nitro-2-furyl)methylene]hydrazino]carbonyl]phenyl-hydrazone [2], which were synthesized in our department, have antibacterial activity against both *Staphylococcus aureus* ATCC 29213 and *Mycobacterium tuberculosis* H37Rv at a concentration of 3.13 µg/mL. N<sup>1</sup>-(4-methoxybenzamido)benzoyl]-N<sup>2</sup>-[5-nitro-3-furyl)methylene]hydrazine, which was also synthesized in our department [3], demonstrated antibacterial activity. In addition, some of the new hydrazine-hydrazones that we have recently synthesized were active against the same strain of *M. tuberculosis* H37Rv between the concentration of 0.78-6.25 µg/mL [4].

Isonicotinic acid hydrazide (isoniazid, INH) have very high in vivo inhibitory activity towards *M. tuberculosis* H37Rv. Sah and Peoples synthesized INH hydrazide-hydrazones 1 by reacting INH with various aldehydes and ketones. These compounds were reported to have inhibitory activity in mice infected with various strains of *M. tuberculosis* [5]. They also showed less toxicity in these mice than INH [5,6] Buu-Hoi et al. synthesized some hydrazide-hydrazones that were reported to have lower toxicity than hydrazides because of the blockage of -NH<sub>2</sub> group. These findings further support the growing importance of the synthesis of hydrazide-hydrazones compounds [7].

## Materials and Methods

The melting points of the compounds were determined in open capillary tubes on a Thomas Hooker melting point apparatus (Perfit) and are uncorrected. IR spectra were recorded in KBr pellets and JASCO FTIR-5300 infrared spectrophotometer (Japan) <sup>1</sup>H-NMR spectra were determined at 300.40 MHz JEOL-AL 300 (Fourier Transform, Japan) (300.40 MHz) JEOL FX 90Q (90 MHz) (Japan) and Mercury Plus Varian (400 MHz) spectrometers with tetramethylsilane as internal standard.

## Experimental

### Synthesis of Acetophenone hydrazone (HD1)

#### Procedure

Acetophenone (10 mL, .007 mol) was taken in a round bottom borosil flask and 10 ml hydrazine hydrate was added and 10 ml ethanol solution with 10 ml glacial acetic acid and heated in a distillation unit, then synthesized compound was dried and collected.

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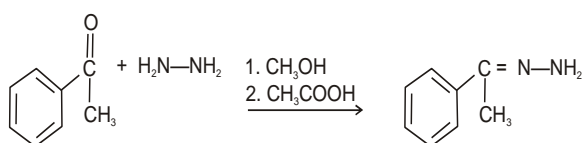
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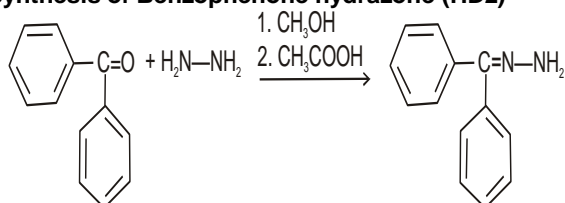
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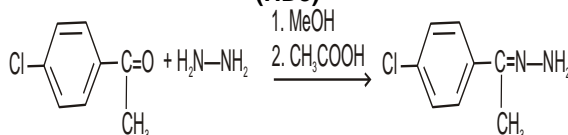
**Synthesis of Benzophenone hydrazone (HD2)**



**Procedure**

The (0.005 mol) of benzophenone and 10 ml a round bottom flask of 500 ml and make alkali the solution by adding 10 ml methanol and then neutralized by adding 10 ml glacial acetic acid and heated in a distillation unit upto 1.5 h-2.5 h and synthesized compound was dried and collected.

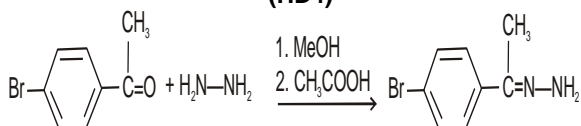
**Synthesis of p-chloroacetophenone hydrazone (HD3)**



**Procedure**

The 10 ml (.006 mol) p-chloroacetophenone solution and 10 ml of hydrazine hydrate were taken in a RBF of 500 ml and make solution alkali by adding 10 ml of methanol and the neutralizing of glacial acetic acid and heating in a distillation unit, synthesized compound were dried and collected.

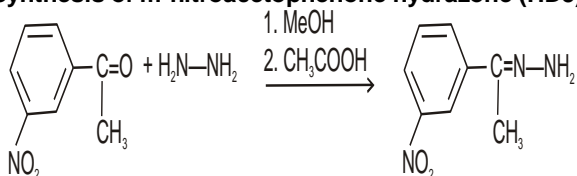
**Synthesis of p-Bromoacetophenone hydrazone (HD4)**



**Procedure**

The 10 ml (0.004 mol) of p-bromo acetophenone solution and 10 ml of hydrazine hydrate solution was taken in a RBF (500 ml) and 10 ml methanol was then added 40 ml glacial acetic acid and heating in a distillation unit, synthesized compound were dried and collected.

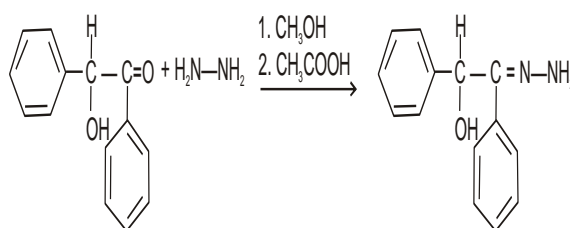
**Synthesis of m-nitroacetophenone hydrazone (HD5)**



**Procedure**

The 10 ml (0.005 mol) of m-nitroacetophenone solution and have been taken in a RBF (500 ml) and add 10 ml methanol then 10 ml glacial acetic acid and heating in distillation unit, synthesized compound were dried and collected .

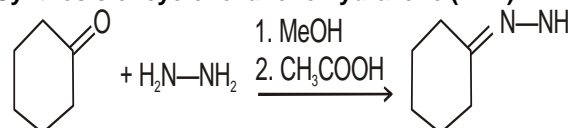
**Synthesis of Benzoin hydrazone (HD6)**



**Procedure**

The 10 ml (0.004 mol) of benzoin and 10 ml hydrazine hydrate solution was taken in a RBF (500 ml) and 10 ml methanol and 10 ml glacial acetic acid were added in it. The mixture distilled in a distillation unit and synthesized compound were dried and collected.

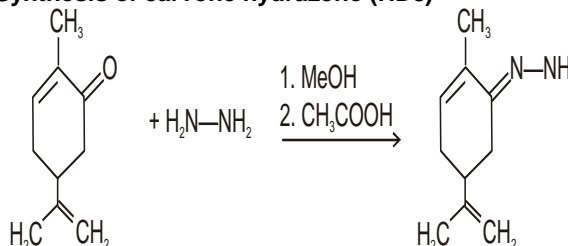
**Synthesis of cyclohexanone hydrazone (HD7)**



**Procedure**

1 gm cyclohexanone and 10 ml (0.01 mol) of hydrazine hydrate solution was taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid was added and mixture was distilled in distillation unit and synthesized compound dried and collected.

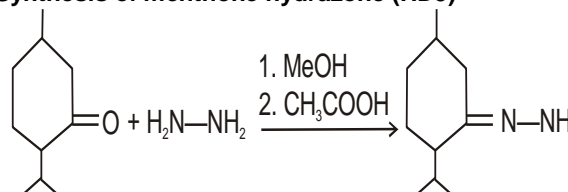
**Synthesis of carvone hydrazone (HD8)**



**Procedure**

1 gm carvone and 10 ml (0.006 mol) of hydrazine hydrate were taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid were added and mixture was heated in a distillation unit and synthesized compound dried and collected.

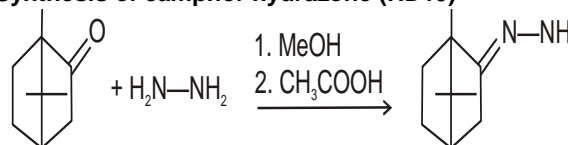
**Synthesis of menthone hydrazone (HD9)**



**Procedure**

1 gm menthone (0.005 mol) and 10 ml of hydrazine hydrate were taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid was added mixture was heated in a distillation unit and synthesized compound dried and collected.

**Synthesis of camphor hydrazone (HD10)**



**Procedure**

1 gm camphor (0.006 mol) and 10 ml of hydrazine hydrate were taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid was added. The mixture was heated in a distillation unit and the synthesized compound dried and collected.

**Antifungal activity**

Antifungal activity of hydrazones were screened against *C. albicans*, *A. niger*, *S. cervisiae*. All the compounds exhibited antifungal activity against these fungi. Compound HD3, HD4 and HD5 were most potent compound against *A. niger* and *C. albicans* compound HD1, HD6 and HD8 was equipotent against *A. niger* at 50 mg/mL. The compound HD1, HD6, HD8 and HD10 was equipotent against *A. niger* at 100 mg/mL. Compound HD3, HD4 and HD5 were most active against *C. albicans* and *A. niger*.

The compound HD1, HD2, HD6, HD9 and HD10 were least potent against *C. albicans* at 50 mg/mL dose.

**Results and Discussion**

The hydrazone derivatives were screened at 100 mg/kg interperitoneally in mice for anticonvulsant activity using procedure described previously.

In the first series of the experiments the compounds were administered by i.p. route and the MES and ScSTY testes were performed for each compound and the evaluation of hydrazones in mice i.p. MES, ScSTY and NT screens are summarized in table 3 along with the literature data on phenytoin.

**Mes Test**

At doses tested (100 mg/kg) compounds (HD<sub>3</sub>, HD<sub>4</sub>, HD<sub>5</sub> and HD<sub>6</sub>) possessed anti MES activity. Compound HD<sub>3</sub> and HD<sub>4</sub> was further tested for anti MES activity in rats p.o. it possessed 100% activity in 0.5 and in till 24 h at the dose of 100 mg/kg which is better than standard drug phenytoin.

**Scsty Test**

Compound HD<sub>3</sub> HD<sub>4</sub> HD<sub>5</sub> and HD<sub>9</sub> are active in the ScSTY test. Compound HD<sub>9</sub> is potent in ScSTY test at 4 h at the dose of 100 mg/kg and compound HD<sub>3</sub>

HD<sub>4</sub> active at 0.5h at the doses of 100 mg/kg and shows 100% protection. HD<sub>9</sub> is active at 4h at the dose of 100 mg/kg compounds are most active taken phenytoin at the dose of 100 mg/kg.

**Neurotoxic screen**

Mice were unable to grasps rotored after administration of the all compounds. HD<sub>1</sub> (300, 5h, 4h), HD<sub>2</sub> (300, 5h, 4h), HD<sub>3</sub> (100, 5h, 4h) etc.

**References**

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**Physical Data of Hydrazones**

Comp. code	Molecular formula	Molecular weight	melting point	C H N					
				Calculated			Found		
				C	H	N	C	H	N
HD1	C <sub>8</sub> H <sub>10</sub> N <sub>2</sub>	135	250	71.64	7.46	20.89	71.45	7.02	20.38
HD2	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub>	196	238	79.59	6.12	14.28	79.49	6.32	14.48
HD3	C <sub>8</sub> H <sub>9</sub> N <sub>2</sub> Cl	168.5	231	56.97	5.34	16.61	56.99	5.44	16.67
HD4	C <sub>8</sub> H <sub>9</sub> N <sub>2</sub> Br	213	230	45.07	4.22	13.14	45.27	4.24	13.34
HD5	C <sub>8</sub> H <sub>9</sub> N <sub>3</sub> O <sub>2</sub>	179	228	53.63	5.02	23.46	53.65	5.12	23.56
HD6	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O	226	245	74.43	6.19	12.38	74.48	6.29	12.48
HD7	C <sub>6</sub> H <sub>7</sub> N <sub>2</sub>	93	148	74.41	7.52	30.10	74.44	7.56	30.14
HD8	C <sub>10</sub> H <sub>13</sub> N <sub>2</sub>	161	191	74.53	8.07	17.39	74.43	8.27	17.49
HD9	C <sub>10</sub> H <sub>20</sub> N <sub>2</sub>	168	146	71.42	11.90	16.66	72.15	11.94	16.56
HD10	C <sub>10</sub> H <sub>18</sub> N <sub>2</sub>	166	177	72.28	10.84	16.86	72.38	10.74	16.96

**Table-2: The Physical and Spectral Data of the Hydrazones Derivatives**

S. No.	Compound Name	Compound Code	IR KBr V cm <sup>-1</sup>	HNMR (d <sub>6</sub> -DMSO) δ ppm
1.	Acetophenone hydrazone	HD1	3470 (NH) 2998 (CH) 1610 (C=N)	6.1 (S, 2H, NH <sub>2</sub> ), 0.9 (S, 3H, CH <sub>3</sub> ), 7.3-7.8 (m, 10H, Ar-H)
2.	Benzophenone hydrazone	HD2	3480 (NH) 3010(CH) 1640 (C=N)	6.0 (S, 2H, NH <sub>2</sub> ), 7.4-7.7 (m, 10H, Ar-H) 7.4-7.7 (m, 10H, Ar-H)
3.	p-Chloroacetophenone hydrazone	HD3	3472 (NH) 3020 (CH) 1630 (C=N)	6.3 (S, 2H, NH <sub>2</sub> ), 0.9 (S, 3H, CH <sub>3</sub> ) 4.3(S, 8H,CH <sub>2</sub> ), 7.4-7.8 (m, 4H, Ar-H)
4.	p-Bromoacetophenone hydrazone	HD4	3470 (NH) 3010 (CH) 1624 (C=N)	6.2 (S, 2H, NH <sub>2</sub> ), 0.8 (S, 3H, CH <sub>3</sub> ) 4.6(S, 8H,CH <sub>2</sub> ), 7.3-7.9 (m, 4H, Ar-H)
5.	M-nitroacetophenone hydrazone	HD5	3458 (NH) 2990 (CH) 1626 (C=N)	6.0 (S, 2H, NH <sub>2</sub> ), 0.9 (S, 3H, CH <sub>3</sub> ) 6.9(S, 4H,CH <sub>2</sub> ), 5.8(S, 4H, CH <sub>3</sub> ), 6.9-7.4 (m, 4H, Ar-H)
6.	Benoin hydrazone	HD6	3460 (NH) 3300(OH) 2992 (CH) 1628 (C=N)	4.0 (S, 1H, OH), 6.1 (S, 2H, NH <sub>2</sub> ) 7.3-7.8 (m, 10H, Ar-H)
7.	Cyclohexanone hydrazone	HD7	3475 (NH) 2980 (CH) 1630 (C=N)	1.3 (m, 10H, 5CH <sub>2</sub> ), 5.8 (S, 2H, NH <sub>2</sub> )
8.	Carvone hydrazone	HD8	3476 (NH) 2996 (CH) 1710 (C=N)	5.9 (S, 2H, NH <sub>2</sub> ), 0.9 (S, 6H, 2CH <sub>3</sub> ), 2.9 (m, 6H, 2CH <sub>3</sub> )
9.	Menthone hdyrazone	HD9	3470 (NH) 3020 (CH) 1726(C=N)	5.8 (S, 2H, NH <sub>2</sub> ), 0.8 (S, 6H, 2CH <sub>3</sub> ) 3.0(m, 4H, 2CH <sub>2</sub> ), 3.9(S, 6H, CH), 2.1 (S, 2H, =CH <sub>2</sub> )
10.	Camphour hydrazone	HD10	3480 (NH) 3033 (CH) 1720 (C=N)	6.2 (S, 2H, NH <sub>2</sub> ), 0.9 (S, 6H, 2CH <sub>3</sub> ) 2.8(m, 6H, 3CH <sub>2</sub> ), 3.1 (S, 6H, CH <sub>3</sub> )

**Table-3: Antifungal Activity of Hydrazones**

Compound code	Zone inhibition in mm and dose µg/ml			
	A. niger		C. albicans	
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
HD1	15	20	8	12
HD2	12	14	8	12
HD3	20	25	18	20
HD4	22	24	20	22
HD5	21	20	25	24
HD6	16	20	10	12
HD7	10	12	12	15
HD8	16	20	10	12
HD9	12	14	7	8
HD10	13	15	08	07
Standard drug	15	17	14	17