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Analysis of biological potential of Aromatic Hydrazones as Novel Therapeutic Agents

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ABSTRACT

Aromatic hydrazones and their derivatives are being explored to develop new drugs against microorganisms, resistant to presently available anti-microbials. In the present study, 13 hydrazone derivatives were screened *in vitro* for their biological activity against microorganisms by employing agar well diffusion method. The microbes, *Escherichia coli, Staphylococcus aureus and Candida albicans* were cultured on agar plates. Wells in agar plates were loaded with 50 µl of 0.02 µg/ml and 0.04 µg/ml of hydrazone derivatives. Biological activity was examined by measuring the zone of growth inhibition. Compounds, 5, 6 and 11 exhibited none or negligible zone of inhibition against *S. aureus*. Compounds, 1, 4, 7, 8, 10 and 12, showed moderate zones of inhibition. Compound, 13, was found effective against *S. aureus*. Against *E. coli,* the compounds, 5 and 8, showed no zone of inhibition; the compounds, 1, 2, 3, 4, 6, 7, 12 and 13, showed little zone of inhibition, whereas the compound 9 and 11, reflected moderate zone of inhibition. Compound, 10, was found to be the most effective. When these compounds were investigated against *C. albicans*, the compounds, 1, 2, 3, 4, 5, 7 and 10, showed little zone of inhibition; the compounds, 6, 8, 9, 11 and 12 ,exhibited moderate activity. Compound, 13, was found to be the most effective against *C. albicans.* Overall, hydrazone derivatives are very effective against microorganisms and should be evaluated against other microbes to determine their anti-microbial potential.

Keywords: Hydrazones, Biological activity, Agar well diffusion method, *Escherichia coli, Staphylococcus aureus, Candida albicans*

INTRODUCTION

Hydrazones are biologically functional drug molecules which have appealed the scientists due to their broad spectrum pharmacological worth (Raj *et al*., 2016). Anti-microbials are one of the most effective weapons in fighting against bacterial diseases and have immensely contributed to the health-associated aspects of human body. Various antibiotics have either become ineffective or have significantly diminished effectiveness against infections (Kim *et al*., 2010; Kaplancikli *et al*., 2007). During the last decade, the number of fungal infections has alarmingly increased in humans. To overcome this problem, novel aromatic hydrazone derivatives are synthesized and screened against fungal pathogens (Özdemir *et al*., 2007). The anti-bacterial and anti-fungal behavior of hydrozones and their derivatives have been studied on large scale to explore new compounds as antimicrobial agents. Presently, the development of effective chemotherapeutic drugs is a challenging task and hydrazone derivatives are evaluated as effective compounds against bacterial infections (Deep *et al*., 2010).

The benzimidazole compounds are reported to be effective against both gram-positive and gram-negative bacterial strains because of their 5, 6 dinitro and thioalkyl or thioaryl groups

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(Kazimierczuk *et al*., 2002). Similarly, 2-(trifluoromethyl)-1H benzimidazole derivatives are highly effective *in vitro* as antiparasitic compounds against *T. vaginalis, E. histolytica, T. spiralis and G. intestinalis* (Hernández *et al*., 2015). Some derivative of hydrazones, such as trihalogen benzimidazole analogues, have displayed effective antibacterial activity against *S. aureus* (Tuncbilek *et al*., 2009). A newly synthesized phosphonoly hydrazone compound has shown efficiently superior activity against different bacteria (Ramin *et al*., 2013). Likewise, synthetic N-alkyl 2 Phenyl-1H Benzimidazole-5-carboximidines compound, is effective against *S. aureus* and other microbes (Göker *et al*., 2005). It is proposed that synthetic compounds of hydrazone are antibacterial agents against four gram-positive bacteria, *S.aureus*, *S. epidermidis*, *B. cereus* and *M. luteus*, and three gram-negative bacteria, *E.coli, P. aeruginosa and K. pneumoniae*. They are also effective against two fungi, namely *A. niger* and *A. fumigatus* (Suman *et al*., 2011).

The compound, 4-fluorobenzoic acid [(5-bromothiophen-2-yl) methylene] hydrazide, has displayed the most activity against *Candida albicans* with great inhibitory zone. Benzimidazole and their derivatives possess anti-fungal activity. Benomyl, thiabenzadole and thiophnate methyl are major examples of fungicide class as reported in the literature (Özkay *et al*., 2010). The derivative of hydrazones, azole and non-azole, are generally helpful in treating candida infections; however, regardless of the valuable anti-fungal activities noticed *in vitro*, candidemia has appeared as a fatal disease in animals (Schiaffella *et al*., 2005). The derivatives of hydrazones are not only effective against bacteria and fungi but these agents have shown potential against tumors. A new synthetic hydrazone compound, *N*-glycosyl-*N'*-(5-substituted phenyl-2-furoyl) hydrazide, is found to be effective against cancer and fungi (Zining *et al*., 2014).

In this context, the resistant infections to microbes induce deleterious impact on human health and economy of the country. The discovery of new antimicrobial agents is a major challenge for the investigators to treat the infections. In the present study, the potential of diverse novel hydrazones against fungi, and gram-positive and gram-negative bacteria was explored with the prime objective to develop these anti-microbial and anti-fungal agents for improving the quality of human life.

MATERIALS AND METHODS

Aromatic hydrazone and their derivatives (13 compounds) were collected and their biological activity was assessed by agar well diffusion method. Two different concentrations, 0.02 µg/ml and 0.04 µg/ml, of the compounds were prepared. In agar plates, the wells of 6mm diameter were made with sterile Pasteur pipette. The wells were sealed with 1-2 drops of molten media. *Escherichia coli, Staphylococcus aureus and Candida albicans* were grown on these agar plates. The wells were filled in with 50 µl of hydrazone compounds. The plates were turned upside down and placed at 37ºC (98.6ºF) in the incubator. Following 24 to 48 hours of incubation, development of the organisms was investigated and the width of zone of growth inhibition was measured with the help of the scale. The zone of inhibition indicated the area where the growth of the microorganisms was curbed by the action of hydrazone compounds. The antimicrobial activity of these compounds was investigated against gram-positive bacteria, such as *S. aureus*, gram-negative bacteria, such as *E. coli,* and fungi, such as *C. albicans* by well diffusion strategy.

RESULTS

Biological Activity of Hydrazones against *S. aureus*

Aromatic hydrazone and their derivatives (13 compounds) were screened against *S. aureus* by agar well diffusion method. Among the aromatic hydrazone derivatives, compounds 5, 6 and 11, exhibited none or negligible zone of inhibition. The compounds, 1, 4, 7, 8, 10 and 12, showed moderate zones of inhibition. The compound 13 was found to be the most effective against *S. aureus*. Zone of inhibition produced by hydrazone compounds against *S. aureus* are shown in Table I.

Table 1: Zone of inhibition exhibited by Hydrazone compounds against *S. aureus* strains

Sr. No.	Compound Name	Zone of Inhibition (mm) Concentration	
		0.02 µg/ml	**0.04 µg/ml**
1)	1-(4-bromobenzylidene)-2-(2,4-dinitrophenyl)hydrazine	8	10
2)	1-(4-bromobenzylidene)-2-(4-chlorophenyl)hydrazine	9	13
3)	1-(4-chlorophenyl)-2-(2,5-dimethoxybenzylidene) hydrazine	10	15
4)	3-nitro-4-((-2-(4nitrophenyl) hydrazono)methyl)phenol	9	11
5)	4-((2-(4-nitrophenyl) hydrazono)methyl)phenol	2	4
6)	1-(2,4-dinitrophenylphenyl)-2-(2,3,4-dimethoxybenzylidene) hydrazine	N.Z.	N.Z.
7)	4-((2-(4-chlorophenyl) hydrazono)methyl)phenol	7	10
8)	1-(4-chlorophenyl)-2-(diphenylmethylene) hydrazine	5	8
9)	1-(3,4-dimethoxybenzylidene) -2-(4-dinitrophenyl)hydrazine	10	14
10)	1-(2,4-dinitrophenyl)-2-(3,4,5-trimethoxybenzylidene) hydrazine	7	10
11)	1-(2,5-dimethoxybenzylidene) -2-(4-nitrophenyl)hydrazine	N.Z.	3
12)	2-methoxy-5-((2-(4-nitrophenyl)hydrazono)methyl)phenyl acetate	5	10
13)	5-((4-chlorophenyl)hydrazono)meth yl)-2-methoxyphenyl acetate	15	20

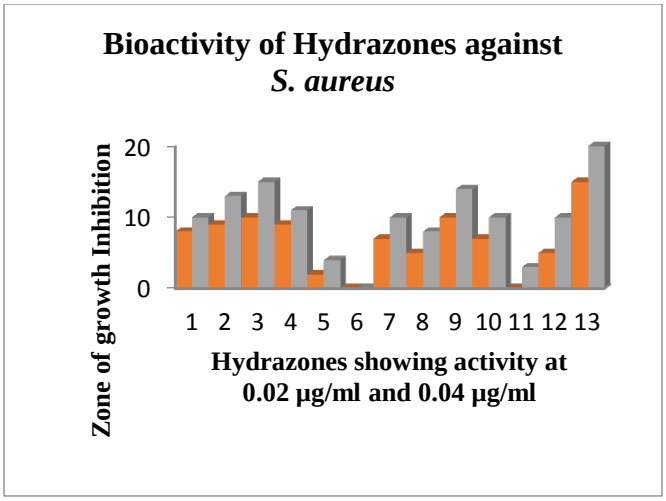

Fig. 1: Comparison of antibacterial activity of aromatic hydrazone compounds against *S. aureus* at 0.02 µg/ml and 0.04 µg/ml. The zone of growth inhibition at 0.02 µg/ml and 0.04 µg/ml are shown by brown and gray color bars respectively.

Biological activity of Hydrazones against *Escherichia coli*

Aromatic hydrazone compounds 5 and 8 showed no zone of inhibition; the compounds 1, 2, 3, 4, 6, 7, 12 and 13 showed little zone of inhibition whereas the compound 9 and 11 reflected moderate zone of inhibition. The compound 10 was found to be the most effective as shown in Table 2.

Table 2: Zone of inhibition exhibited by Hydrazone compounds against *E. coli*

Sr. No.	Compound Name	Zone of Inhibition (mm) Concentration	
		0.02 µg/ml	0.04 µg/ml
1)	1-(4-bromobenzylidene)-2-(2,4-dinitrophenyl)hydrazine	4	6
2)	1-(4-bromobenzylidene)-2-(4-chlorophenyl)hydrazine	6	7
3)	1-(4-chlorophenyl)-2-(2,5-dimethoxybenzylidene)hydrazine	7	8
4)	3-nitro-4-((-2-(4nitrophenyl)hydrazono) methyl)phenol	7	8
5)	4-((2-(4-nitrophenyl) hydrazono)methyl)phenol	N.Z	N.Z
6)	1-(2,4-dinitrophenylphenyl)-2-(2,3,4-dimethoxybenzylidene) hydrazine	6	7
7)	4-((2-(4-chlorophenyl)hydrazono) methyl)phenol	6	9
8)	1-(4-chlorophenyl)-2-(diphenylmethylene)hydrazine	N.Z	N.Z
9)	1-(3,4-dimethoxybenzylidene)-2-(4-dinitrophenyl)hydrazine	10	14
10)	1-(2,4-dinitrophenyl)-2-(3,4,5-trimethoxybenzylidene) hydrazine	17	19
11)	1-(2,5-dimethoxybenzylidene) -2-(4-nitrophenyl)hydrazine	10	15
12)	2-methoxy-5-((2-(4-nitrophenyl) hydrazono)methyl) phenyl acetate	5	8
13)	5-((4-chlorophenyl)hydrazono) methyl)-2-methoxyphenyl acetate	4	10

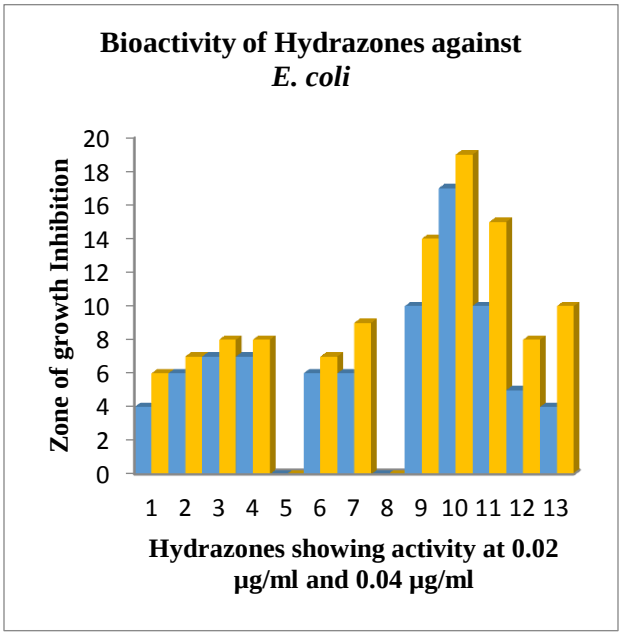

Fig. 2: Comparison of antibacterial activity of aromatic hydrazone compounds against *S. aureus* at 0.02 µg/ml and 0.04 µg/ml. The zone of growth inhibition at 0.02 µg/ml and 0.04 µg/ml are shown by blue and yellow color bars respectively.

Biological Activity of Hydrazones against *Candida albicans*

Aromatic hydrazone and their derivatives were evaluated against *C. albicans* as shown in table 3. The results revealed that the compounds 1, 2, 3, 4, 5, 7 and 10 showed little zone of inhibition, whereas the compounds 6, 8, 9, 11 and 12 exhibited moderate zone of inhibition. The compound 13 was found to be the most effective against *Candida albicans.*

Table 3: Evaluation of Hydrazone compounds against *C. albican* at 20µg and 40µg concentrations. **Zone of Inhibition (mm)**

Sr. No.	Compound Name	Concentration	
		0.02 µg/ml	0.04 µg/ml
1)	1-(4-bromobenzylidene)-2-(2,4-dinitrophenyl)hydrazine	5	6
2)	1-(4-bromobenzylidene) -2-(4-chlorophenyl)hydrazine	4	8
3)	1-(4-chlorophenyl)-2-(2,5-dimethoxybenzylidene) hydrazine	7	8
4)	3-nitro-4-((-2-(4nitrophenyl)hydrazono) methyl)phenol	9	8
5)	4-((2-(4-nitrophenyl)hydrazono) methyl)phenol	9	10
6)	1-(2,4-dinitrophenylphenyl)-2-(2,3,4-dimethoxybenzylidene) hydrazine	7	13
7)	4-((2-(4-chlorophenyl)hydrazono) methyl)phenol	4	11
8)	1-(4-chlorophenyl)-2-(diphenylmethylene)hydrazine	9	14
9)	1-(3,4-dimethoxybenzylidene)-2-(4-dinitrophenyl)hydrazine	9	13
10)	1-(2,4-dinitrophenyl)-2-(3,4,5-trimethoxybenzylidene) hydrazine	5	10
11)	1-(2,5-dimethoxybenzylidene)-2-(4-nitrophenyl)hydrazine	7	12
12)	2-methoxy-5-((2-(4-nitrophenyl)hydrazono) methyl)phenyl acetate	10	13
13)	5-((4-chlorophenyl) hydrazono) methyl)-2-methoxyphenyl acetate	10	16

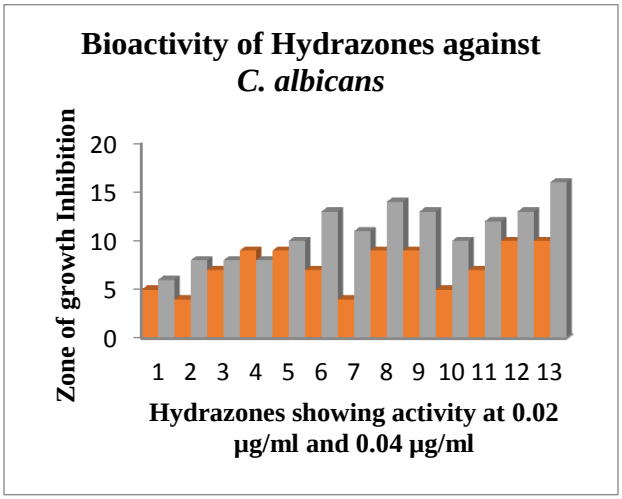

Fig. 3: Comparison of antifungal activity of hydrazone compounds against *C. albicans* at 0.02 µg/ml and 0.04 µg/ml. The zone of growth inhibition at 0.02 µg/ml and 0.04 µg/ml are shown by brown and gray color bars respectively.

DISCUSSION

Microbial infections are the main threat to health of humans and animals. Microbes are developing resistance against presently available antibiotics and treatment of infections is becoming more and more complicated. To explore new effective anti-microbial agents is a major field of interest for health care. In this context, hydrazones are analyzed on wide scale for their biological activity against different microbes. Hydrazone structure consists of two associated nitrogen atoms of different nature and a carbon-nitrogen (C-N) double bond that is linked with a lone electron pair of the terminal nitrogen atom. These structural factors are predominantly responsible for the biological characteristics of hydrazones (Kim *et al*., 2010; Brehme *et al*., 2007).

Results of the present study revealed that the derivatives, 5 and 8 respectively described as 4-((2-(4-nitrophenyl) hydrazono) methyl) phenol, and 1-(4-chlorophenyl)-2-(diphenylmethylene) hydrazine were inactive against *E. coli*, whereas the derivative 6, 1-(2,4-dinitrophenylphenyl) -2-(2,3,4-dimethoxy-benzylidene) hydrazine, was inactive against *S. aureus.* This insignificant activity is most likely due to the presence of nitrophenyle and chlorophenyle

groups. The present findings contradict with the results of Wankhede *et al*. (2016) who had shown that some of the hydrazones with metal complexes exhibited higher antibacterial activity. On the other hand, it has been reported that some hydrazone derivatives, such as 1, 2-benzisothiazolylhydrazides were inactive against *E.coli* and *S.aureus* (Vicini *et al*., 2002). The present study results are in line with the report of Kodisundaram *et al*. (2013) who described that few derivative of azabicyclomonane showed no activity against *S. aureus*.

Among the hydrazone derivatives, the compounds 1, 2, 3, 4, 6, 7, 12 and 13 were less active against *E.coli* and compounds 1, 5, 7, 11 and 12 showed insignificant activity against *S. aureus*. The present study findings are compatible with the report of Govindasami *et al*. (2011) that some of vanillin-related hydrazones showed poor activity against *S.aureus*. Similarly it was also reported by Özdemir *et al*. (2009) that some derivatives of hydrazone exhibited trivial activity against *E.coli*. Some derivatives of benzothiazole displayed poor activity against *E. coli* and *S. aureus* because of their substitution of chloro and nitro group at position 2 (Balram Soni *et al*., 2012).

Some compounds showed moderate zone of inhibition against *E. coli* and *S. aureus.* The present study results are compatible with those of Ioana *et al*. (2008) who described that some of the 2-hydroxybenzamide derivatives showed moderate activity against *E.coli* and *S.auerus*. It has also been reported that few hydrazones which were synthesized from cholesterol derivatives showed moderate activity against *E.coli* (Loncle *et al*., 2004). Similarly majority of the hydrazone derivatives of quinaxaline showed moderate activity against *E.coli* because of their choloro, bromo and fluoro substituent group at the position of 3 (Suroor *et al.,* 2009; Kumar *et al.,* 2009).

Hydrazone compounds 10 and 13 showed significant biological activity against *E.coli* and *S.aureus,* respectively. These findings are compatible with the report of Khalid *et al*. (2018) who documented that some of the hydrazone derivatives containing a core of pyrazole scaffold showed significant antimicrobial activity against *E.coli* and *S.aureus*. Likewise, hydrazone derivatives containing azometine and benzimidazole showed significant activity against *E.coli* and *S.aureus* (Narang *et al*., 2012; Ozdemir *et al*. 2007). The hydrazone compounds containing isoxazolyl group exhibited substantial activity against *E.coli* and *S.aureus* (Ramanpre et *et al*., 2011).

The hydrazone derivatives, 1, 2, 3, 4, 5, 7, 10, were less active against *C.albicans*. These findings are compatible with the report of Papakonstantinou *et al*. (2002) who revealed that cyclopentylidene hydrazide showed weak activity against *C. albicans*. Few compounds of sulfonyhydrazones and azabicyclomonan-9-one displayed less activity against *C. albicans* (Kodisundaram *et al*., 2013; Gündüzalp *et al*., 2014). Most of the compounds displayed moderate activity against *C.albicans* as reflected by the present study results. These findings are in line with the reports of Ajani *et al*. (2010) who documented that derivative of quinoxaline hydrazone showed moderate activity against *C. albicans*. The hydrazone compound 13 reflected significant activity against *C.albicans*. The hydrazone compounds synthesized from a variety of cholesterols were found significantly active against *C. albican* (Loncle *et al*., 2004). Similarly, benzothiazole derivatives showed significant activity against *C.albicans* because of substitution of 2,3 dimethoxy groups (Balram Soni *et al*,. 2012). Overall, hydrazone derivatives have anti-microbial potential which should be further explored against other microorganisms.

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