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Research Article

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Hydrazones: Synthesis, biological activity and their spectral characterization

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ABSTRACT

As hydrazones have key role in synthetic chemistry & are available in many synthetic compounds, in the research work a series of some sulfonyl hydrazone derivatives were obtained from the reaction between aryl aldehydes & hydrazide in extremely good yield.

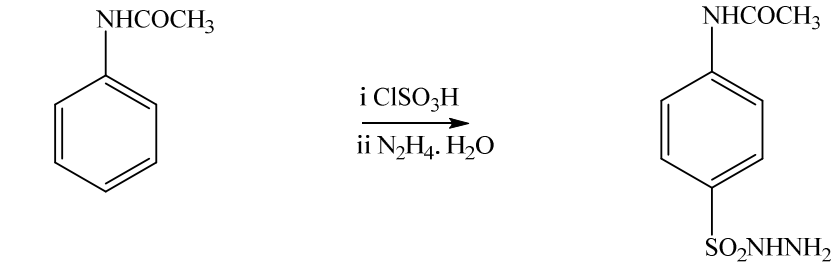
Keywords: Hydrazone, Spectral studies, Antibacterial, Antifungal.

INTRODUCTION

Hydrazones possess an important class of biologically active drug molecules [1]. It has been synthesized as drugs in order to cure diseases with less toxicity and high effects. Hydrazones are studied as reaction intermediates since they can further undergo various ring closure reactions [2,3]. Hydrazones[4,5] having an azometine -NHN=CH- proton are synthesized by heating the appropriate substituted hydrazides with aldehydes in solvent. Hydrazone compounds are not only intermediates but also very effective organic compounds. Hydrazones are very well-known compounds because of their interesting chemical properties. Hydrazones have enough various biological [6-8], physical [9] or industrial [10] applications. Hydrazone derivatives with anti-inflammatory[11], analgesic, anticonvulsant, anti-HIV, antimicrobial [12-14], antibacterial [15,16], and antitumor properties [17], were already reported. Hydrazone derivatives undergoes formation of their transition metals complexes were already used in the treatment of tuberculosis[18-20]. Characteristic properties of hydrazones are imprinted by the presence of the >C=N-N< structural unit, which contains two nitrogen atoms with nucleophilic character and a carbon atom which may act as either electrophile or nucleophile according to the reaction environment.

EXPERIMENTAL SECTION

All compounds were characterized by ^{1}H NMR, IR. Melting points were taken in open capillaries. Progress of reaction as well as purity of compounds was monitored by silica gel Gcoated TLC plates. The spot was visualized by exposing dry plate to iodine vapor chamber. The IR spectra were recorded on SHIMADZU FTIR 8400S spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on BRUKER AVANCE II 400 NMR spectrometer using DMSO as solvent with TMS as an internal standard, chemical shifts (δ) are reported in parts per million.



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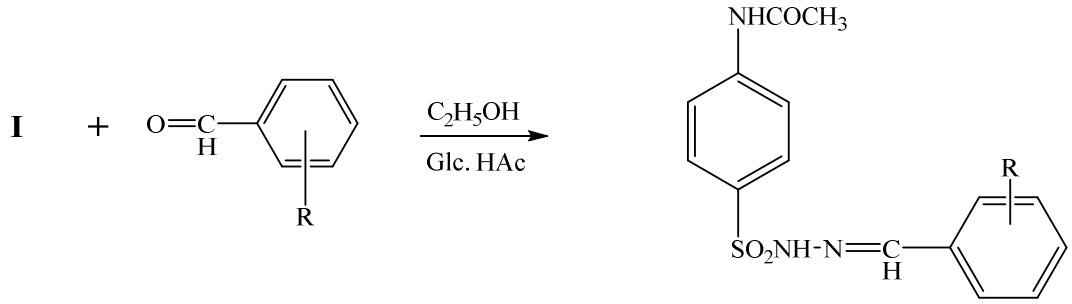

IIa-i

2a: R = H ; 2b: R = 4-Cl ; 2c: R = 4-OH ; 2d: R = 2-OH ; 2e: R = 4-OCH_3

2f: R = 3,4-OCH_3 ; 2g: R = 2-Cl ; 2h: R = 3-NO_2 ; 2i: R = 4-$N(CH_3)_2$

N-(4-(hydrazinylsulfonyl)phenyl)acetamide (I)

In an ice bath place the round bottom flask containing 1.0 gm N-phenylacetamide. Take 2.5ml chlorosulfonic acid in dropping funnel & place it in the hood. Chlorosulfonicacid was added drop wise with continuous stirring and keeping temperature at 0˚C. After completion of addition the mixture was heated on water bath at 60˚-70˚C for 1hr. The oily mass was poured over crushed ice carefully with stirring in the hood. The resulted precipitate was filtered, washed with cold water. Collect the product by suction filtration & then press down the solid carefully to squeeze out the water. Then transfer the solid into a clean flask.

Now to the moist 4-acetamidobenzenesulfonyl chloride add mixture of 1.2ml of hydrazine hydrate in 5ml butanol with constant stirring & keeping temperature 15-20˚ C. The resulted mixture was allowed to heat for 3hours& then cooled to room temp before pouring on ice water. The resulting residue was filtered, washed with water & dried. Crystalized in ethanol. M.P. = 186˚C.IR (cm-1):1369 cm^{-1}& 1152 cm^{-1}(S=O), 1686 cm^{-1} (C=O), 3240 cm^{-1} (N-H), 1593 cm^{-1}& 1494 cm^{-1} (C=C).

General procedure for N-(4-((2- substituted benzylidenehydrazinyl)sulfonyl)phenyl)acetamide (IIa-i)

A mixture of N-(4-(hydrazinylsulfonyl)phenyl)acetamide (I) (0.01mole), various aromatic aldehyde (0.01mole) and (2-3) drops of glacial acetic acid in absolute ethanol (15 ml) was refluxed for 3 hrs. The progress of the reaction was monitored by TLC using hexane: ethyl acetate (8:2) as eluent. The residue was poured into cold water. The obtained precipitate was filtered, dried and recrystallized from suitable solvent.

N-(4-((2-benzylidenehydrazinyl)sulfonyl)phenyl)acetamide(IIa)
The compound obtained with yield77%. M.P. =169-170˚C.IR (cm-1):1693 cm^{-1} (HC=N), 1365 cm^{-1}& 1166 cm^{-1}(S=O), 1674 cm^{-1}(C=O), 3269 cm^{-1}(N-H), 1627 cm^{-1}& 1500 cm^{-1}(C=C), 3078 cm^{-1}(C-H). ^{1}H NMRδ (ppm): 2.07 (3H, s, -CH_3); 7.55, 7.89, 7.81, 7.76 (9H, m, Ar C-H); 8.79 (1H, s, -CH=N-); 10.30 (1H, s, -NH- of $NHCOCH_3$); 11.34 (1H, s, -NH- of -SO_2NH-).

N-(4-((2-(4-chlorobenzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IIb)
The compound obtained with yield 78%. M.P. =202˚C. IR (cm-1):1690 cm^{-1}(HC=N), 1361 cm^{-1}& 1165 cm^{-1}(S=O), 1678 cm^{-1}(C=O), 3271 cm^{-1}(N-H), 1593 cm^{-1}& 1512 cm^{-1}(C=C), 3097 cm^{-1}(C-H),725 cm^{-1}(C-Cl). ^{1}H NMRδ (ppm): 2.07 (3H, s, -CH_3); 7.41, 7.75, 7.80, 7.75 (8H, m, Ar C-H); 8.72 (1H, s, -CH=N-); 10.28 (1H, s, -NH- of $NHCOCH_3$); 11.43 (1H, s, -NH- of-SO_2NH-).

N-(4-((2-(4-hydroxybenzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IIc)
The compound obtained with yield 76%. M.P. =170˚C. IR (cm-1):1687 cm^{-1}(HC=N), 1336 cm^{-1}& 1157 cm^{-1} (S=O), 1673 cm^{-1}(C=O), 3279 cm^{-1} (N-H), 1592 cm^{-1}& 1513 cm^{-1}(C=C), 3074 cm^{-1}(C-H),3348 cm^{-1} (O-H)& 1226 cm^{-1} (C-O). ^{1}H NMRδ (ppm) = 2.07 (3H, s, -CH_3); 6.88, 7.70, 7.82, 7.72 (8H, m, Ar C-H); 8.77 (1H, s, -CH=N-);10.31 (1H, s, -NH- of $NHCOCH_3$); 11.37 (1H, s, -NH- of -SO_2NH-); 9.72 (1H, s, OH).

N-(4-((2-(2-hydroxybenzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IId)
The compound obtained with yield 82%. M.P. =217˚C. IR (cm-1):1685 cm^{-1} (HC=N), 1345 cm^{-1}& 1162 cm^{-1} (S=O), 1659 cm^{-1} (C=O), 3268 cm^{-1} (N-H), 1608 cm^{-1}& 1489 cm^{-1} (C=C), 3064 cm^{-1} (C-H), 3357 cm^{-1}(O-H)& 1234 cm^{-1}(C-O). ^{1}H NMRδ (ppm) = 2.07 (3H, s, -CH_3); 6.98, 7.41, 6.72, 7.64, 7.83, 7.78 (8H, m, Ar C-H); 8.80 (1H, s, -CH=N-); 10.27 (1H, s, -NH- of $NHCOCH_3$); 11.33 (1H, s, -NH- of -SO_2NH-); 11.10 (1H, s, OH).

N-(4-((2-(4-methoxybenzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IIe)
The compound obtained with yield 81%. M.P. =181-182˚C. IR (cm-1):1680 cm^{-1}(HC=N), 1351 cm^{-1}& 1157 cm^{-1} (S=O), 1677 cm^{-1} (C=O), 3275 cm^{-1} (N-H), 1597 cm^{-1}& 1493 cm^{-1} (C=C), 3086 cm^{-1} (C-H), 1039 cm^{-1}& 1257 cm^{-1}(C-O-C). ^{1}H NMRδ (ppm) = 2.07 (3H, s, -CH_3); 7.22, 7.97, 7.81, 7.70 (8H, m, Ar C-H); 8.73 (1H, s, -CH=N-); 10.30 (1H, s, -NH- of $NHCOCH_3$); 11.41 (1H, s, -NH- of -SO_2NH-); 3.93 (3H, s, OCH_3).

N-(4-((2-(3,4-dimethoxybenzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IIf)
The compound obtained with yield 91%. M.P. =194˚C. IR (cm-1):1691 cm^{-1}(HC=N), 1339 cm^{-1}& 1171 cm^{-1} (S=O), 1668 cm^{-1} (C=O), 3272 cm^{-1} (N-H), 1615 cm^{-1}& 1511 cm^{-1} (C=C), 3077 cm^{-1} (C-H), 1044 cm^{-1}& 1268 cm^{-1}(C-O-C). ^{1}H NMRδ (ppm) = 2.07 (3H, s, -CH_3); 7.10, 7.33, 7.68, 7.82, 7.71 (7H, m, Ar C-H); 8.73(1H, s, - CH=N-); 10.33 (1H, s, -NH- of $NHCOCH_3$); 11.36 (1H, s, -NH- of -SO_2NH-); 3.98 (6H, s, OCH_3).

N-(4-((2-(2-chlorobenzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IIg)
The compound obtained with yield 92%. M.P. =207-208˚C. IR (cm-1):1689 cm^{-1}(HC=N), 1358 cm^{-1}& 1174 cm^{-1} (S=O), 1671 cm^{-1} (C=O), 3266 cm^{-1} (N-H), 1592 cm^{-1}& 1506 cm^{-1} (C=C), 3091 cm^{-1} (C-H),752 cm^{-1}(C-Cl). ^{1}H NMRδ (ppm) = 2.07 (3H, s, -CH_3); 7.44, 7.61, 7.86, 7.82, 7.76 (8H, m, Ar C-H); 8.74 (1H, s, -CH=N-); 10.26 (1H, s, -NH- of $NHCOCH_3$); 11.45 (1H, s, -NH- of -SO_2NH-).

N-(4-((2-(3-nitrobenzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IIh)
The compound obtained with yield 87%. M.P. =213-214˚C. IR (cm-1):1692 cm^{-1}(HC=N), 1343 cm^{-1}& 1169 cm^{-1} (S=O), 1665 cm^{-1} (C=O), 3270 cm^{-1} (N-H), 1598 cm^{-1}& 1484 cm^{-1} (C=C), 3270 cm^{-1} (C-H), 1522 cm^{-1} (N=O). ^{1}H NMRδ (ppm) = 2.07 (3H, s, -CH_3); 7.77, 8.12, 8.18, 8.51, 7.83, 7.75 (8H, m, Ar C-H); 8.72 (1H, s, -CH=N-); 10.31 (1H, s, -NH- of $NHCOCH_3$); 11.44 (1H, s, -NH- of -SO_2NH-).

N-(4-((2-(4-(dimethylamino)benzylidene)hydrazinyl)sulfonyl)phenyl)acetamide (IIi)
The compound obtained with yield 90%. M.P. =210˚C. IR (cm-1):1688 cm^{-1}(HC=N), 1332 cm^{-1}& 1161 cm^{-1} (S=O), 1657 cm^{-1} (C=O), 3267 cm^{-1} (N-H), 1621 cm^{-1}& 1510 cm^{-1} (C=C), 3053 cm^{-1} (C-H), 1336 cm^{-1} (C-N). ^{1}H NMRδ (ppm) = 2.07 (3H, s, -CH_3); 6.94, 7.63, 7.84, 7.69 (8H, m, Ar C-H); 8.76 (1H, s, -CH=N-); 10.29 (1H, s, -NH- of $NHCOCH_3$); 11.35 (1H, s, -NH- of -SO_2NH-); 3.13 (6H, s, $N(CH_3)_2$).

Table-1: Analytical data

Compd. No.	R	Molecular Formula	% Analysis Calculated (Found)		
			%C	%H	%N
IIa	H	$C_{15}H_{15}N_3O_3S$	56.77 (56.88)	4.76 (4.84)	13.24 (13.40)
IIb	4-Cl	$C_{15}H_{15}ClN_3O_3S$	51.21 (51.32)	4.01 (4.13)	11.94 (11.98)
IIc	4-OH	$C_{15}H_{15}N_3O_4S$	54.04 (54.11)	4.54 (4.65)	12.16 (12.25)
IId	2-OH	$C_{15}H_{15}N_3O_4S$	54.04 (54.19)	4.54 (4.62)	12.61 (12.66)
IIe	4-OCH_3	$C_{16}H_{17}N_3O_4S$	55.32 (55.42)	4.93 (5.02)	12.10 (12.21)
IIf	3,4-OCH_3	$C_{17}H_{19}N_3O_5S$	54.10 (54.15)	5.07 (5.14)	11.13 (11.22)
IIg	2-Cl	$C_{15}H_{15}ClN_3O_3S$	51.21(51.34)	4.01 (4.14)	11.94 (12.04)
IIh	3-NO_2	$C_{15}H_{15}N_4O_5S$	49.72 (49.79)	3.89 (3.930	15.46 (15.59)
IIi	4-$N(CH_3)_2$	$C_{17}H_{20}N_4O_3S$	56.65 (56.76)	5.59 (5.70)	15.54 (15.67)

RESULTS AND DISCUSSION

The newly synthesized hydrazones arestable at room temperature. Hydrazones are soluble in common organic solvents, such as ethanol, methanol. Hydrazones were relatively well soluble in DMF and DMSO. The antimicrobial activity of all the synthesized compounds (2a -i) were examined against different Gram-positive (*Staphylococcus aureus & Bacillus subtilis)* and Gram-negative (*Escherichia coli & Klebsiella pneumoniae*) and fugal strains (*Candida albicans &Saccharomyces cerevisiae*) organisms by measuring zone of inhibition. The antimicrobial activity was performed by Kirby-Bauer method as recommended by *NCCLS* [10]. All the synthesized Schiff bases have shown good activity against the tested microbes. The antibacterial activity of the most of the compounds exhibited moderate to good antibacterial activity. Results were compared with the activity of the standard antibiotic Ciprofloxacin. The results are summarized in Table-2 below.

Table-2:*In vitro* antibacterial and antifungal activity of the synthesized compounds IIa-i

Compound No.	Zone diameter in millimeter (mm) at 50 µg/ml					
	Antibacterial activity				Antifungal activity	
	Gram Negative		Gram Positive			
	Escherichia coli	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Bacillus subtilis*	*Candida albicans*	*saccharomyces cerevisiae*
IIa	26	9	19	6	24	23
IIb	22	8	R	8	20	R
IIc	20	R	17	8	24	21
IId	R	7	18	R	19	20
IIe	23	5	16	6	23	20
IIf	21	6	R	9	R	16
IIg	24	R	18	5	22	22
IIh	R	8	17	R	18	15
IIi	20	6	R	7	R	R
Ciprofloxacin*	**30**	**10**	**21**	**10**	**-**	**-**
Fluconazole*	**-**	**-**	**-**	**-**	**25**	**25**

*Where, R=Resistant, *=Standard*

CONCLUSION

All the synthesized compounds were purified by successive recrystallization using ethanol. The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their IR and ^{1}HNMR data. Most of the compounds have shown good activity against all the tested bacteria and fungi. It leads to the further synthesis of highly bioactive compound such as β-lactam & metal complex.

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