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SYNTHESIS AND *IN-VITRO* ANTIMICROBIAL STUDIES OF SOME 2-{2-HYDROXY-5-[PHENYLDI AZENYL]BENZYLIDENE}-N-PHENYLHYDRAZINECARBOTHIOAMIDES AND TEREPHTHALOYL-BIS[4-(4'-SUBSTITUTED-PHENYL)THIOSEMICARBAZIDES OF BIOLOGICAL INTEREST

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Abstract: Present communication reports the synthesis and antimicrobial activity of a new series of 2-{2-hydroxy-5-[phenyldiazenyl]benzylidene}-N-phenylhydrazinecarbothioamides and Terephthaloyl-bis[4-(4'-substituted-phenyl)-thiosemicarbazides. Structural characterization was done by elemental analysis and spectroscopic data. The synthesized compounds were screened *in-vitro* against fungal pathogens viz. *C. albicanes A. fumigatus C. neoformans A. niger* and *P. ittalecum* and bacterial pathogens i.e. *S. aureus, E. coli, B. anthrasis S. flaxinerri* and *K. pneumoniae* using disc diffusion assay. The endeavour shows assuring results.

Keywords: Thiosemicarbazones, Thiosemicarbazide, Antimicrobial assay/ Biological activity.

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INTRODUCTION

Extensive use of antibiotics has led to the emergence of multi-drug resistant microbial pathogens. This highlights the incessant need for the development of new class of antimicrobial agents and alterations of known drugs in such a way that would allow them to retain their physiological action along with combating resistively by the pathogens. The design of the proposed chemotherapeutic agents is particularly beneficial due to their distinctive mode of action which can avoid cross resistance to known drugs.

Thiosemicarbazides are valuable building blocks for the synthesis of 5-membered heterocycles (Kappel 2004). Biologically active thiosemicarbazide derivatives include 1,3,4-thiadiazoles as antibacterial (Halve 2010) and antifungal (Jalilian 2000) agents and 1,3,4-thiadiazolium-2-amidines as anticonvulsant (Chapleo 1998), antimicrobial (Da Silva 2002) and antitumour agents (Grynberg 1997). Certain thiosemicarbazones showed a selective inhibition of herpes simplex virus (Blumenkopf 1992) (HSV) infection *in-vitro* and also thiosemicarbazones were active inhibitors of *in- vivo* HSV genital infection (Sidwell 1990). The effect of thiosemicarbazones on the HIV structural protein synthesis (Teitz 1994) has also been reported against human immunodeficiency virus (HIV). Thiosemicarbazones are of considerable interest because of their chemistry and potentially beneficial biological activities such as antitumour, antibacterial, antiviral and antimalarial activities (Da Silva 2001; Jouad 2001).

The pharmacological action of the thiosemicarbazons has been enhanced due to presence of co-ordination metal ions (Rosu 2010; Chandra 2005). It is well authenticated that a N, S bi-dentate systems are present in most of the thiosemicarbazones having carcinostatic potency and possessing substantial *in-vitro* activity against various human tumour cell lines (Ferraz 2009; Saha 2003). The thiosemicarbazone derivatives of Pd(II) have proven to be more effective as anticancer or antimicrobial agents than the ligand by itself, probably due to the increased lipophilicity of the complexes as compared to the free ligands alone (West 1994). Furthermore, interest in the chemistry, synthesis and biology of these pharmacophores continues to be fuelled by their wide range of biological properties *viz.* antifungal, anticancer, antibacterial, antiviral, anti-amoebic, antiproliferative, antitubercular, antitumour, anticonvulsant, antimalarial and trypanocidal activities (Chen 2002; Quiroga 2004; Casas 2002; Blanco 2002, Perez Rebolledo 2005; Karatas 2006; Kumar 2003; Hu 2006; Kolocouris 2002; Terzioglu 2006; Chohan 2005; Sharma 2005; Singh 2006; Patole 2005; Shriram 2005; Easman 2001; Seebacher 2004; Yogeeswari 2002; Du 2002 and Aguirre 2004).

Looking to the pronounced activity of Schiff bases (Halve 2009) and 1,3-diketoamino (Halve 2005), thiosemicarbazones (Halve 2008) and their cyclic (Halve 2007) analogues synthesized earlier, it was thought of interest to combine some bio labile moiety, such as -Cl, -F, -OCH_3 and -

CH_3, together in a molecular framework of thiosemicarbazone and thiosemicarbazide, in order to enhance their biological interest.

Keeping this in mind the present effort is directed towards developing new antimicrobial agents with maximum efficacy in minimum concentrations. For this purpose we have synthesized two series of 2- hydroxy- 5 (2- chlorophenyl- azo) benzaldehyde- N- 4- (4- substituted phenyl) thiosemicarbazone and 2- hydroxy- 5 (2- methyl- phenyl- azo) benzaldehydes- N- 4- (4- substitutedphenyl) thiosemicarbazone and another series of terephthaloyl bis- 4 (4'- substituted phenyl) thiosemicarbazide. Moreover in order to assess the efficacy of the synthesized compound, microbial sensitivity tests were performed against the selected fungal and bacterial pathogens and results were compared with reference drugs.

MATERIALS AND METHODS

All the melting points were determined in open glass capillaries and are uncorrected. The progress of the reaction was monitored on TLC silica gel plates. Spot were visualized by iodine vapours and the purity of these compounds was ascertained by column chromatography. IR spectra were recorded in KBr on a Perkin-Elmer 398 spectrophotometer. The NMR spectra were recorded in DMSO-d_6 on a Bruker DRX-300 FT-NMR spectrometer. The chemical shifts were reported as ppm (δ ppm) in tetra-methylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Carlo Erba 1108 analyzer. All chemicals and reagents were of AR grade and used after further purification.

(i) General procedure for the synthesis of 2-hydroxy-5-[phenyldiazenyl]benzaldehyde (1);

Aniline (3.72mL) was dissolved in aqueous hydrochloric acid (28mL, 6N) and mechanically stirred at 0-5^{o}C. A cold solution of sodium nitrite (5gm/10mL water) was added drop wise to the constantly stirred reaction mixture. The diazotized solution was immediately added in small portions to salicylaldehyde (5mL dissolved in 40mL 6N NaOH), with constant stirring at 0-5^{o}C. The stirring was continued for 4h. The solid obtained was filtered under suction washed with cold water and re-crystallized from glacial acetic acid.

(ii) General procedure for the synthesis of N-phenyl hydrazine carbothioamide (2);

Carbon disulphide (12mL) was added drop wise to a mixture of an ethanolic (20mL) solution of aniline (10 mL) and liquor ammonia (15mL) and stirred at 10-15°C for 2h. The reaction mixture was transferred to another flask containing lead nitrate (75gm in 200mL distilled water) and stirred further until the precipitation of lead sulphide was complete. The reaction mixture was steam distilled and isothiocyanatobenzene was collected, dissolved in ethanol (10mL) and

refluxed with an ethanolic solution of hydrazine hydrate (25%, 0.6mL in 10mL ethanol) for 5h. The product obtained was collected by filtration, washed with cold water and re-crystallized from ethanol.

(iii) General procedure for the synthesis of N-phenyl-2-{3-phenyl-diazenyl-benzylidene}hydrazinecarbothioamide (3 and 4);

A mixture of the appropriate, 2-hydroxy-5-[phenyldiazenyl]benzaldehyde (1) (2.5 gm) and the N-phenyl hydrazinecarbothioamide (2) (1.5 gm) were refluxed for 8h in DMF (30 mL). The mixture was then cooled in an ice bath and the product separated was repeatedly washed with water followed by ethanol and re-crystallized from diethyl ether.

(iv) General procedure for the synthesis of Terephthaloyl bis 4-(4'-substitutedphenyl)thiosemicarbazide (5);

0.5 M of terephthalic acid and 1 M of phosphoruous pentachloride was taken in dry benzene. The flask was fitted with a calcium chloride guard tube and connected to a gas absorption device. Then it was refluxed till the vigorous evolution of hydrogen chloride has almost ceased. The flask was then attached with a condenser and phosphorous oxychloride has been removed at an ordinary pressure. It was allowed to cool and residual liquid was finally distilled and poured into water, by which white crystals of terephthaloyl chloride were obtained. Terephthaloyl chloride (0.5M) was refluxed with ethanol (500 mL) till the clear solution obtained. Excess of ethanol has been removed by distillation under reduced pressure. The solid, separated on cooling was washed with a saturated solution of sodium bicarbonate, followed by water, dried and recrystallised from ethanol. White shining needle shape crystal of the product has been obtained. Diethyl terephthalate (0.005M) was reflux for 8 hr with 4-(4'-methyl phenyl) thiosemicarbazide (0.01M) in DMF. The reaction mixture was cooled to room temperature, when product terephthaloyl-bis[4(4'-methylphenyl)thiosemicarbazide] separated as a light yellow solid, by addition of requisite amount of water. It was repeatedly washed with water followed by ethanol.

Table 1 Physical characterization data of synthesized compounds.

S.No.	Comp.No.	R	R'	m.p.°C	Yield %	Molecular Formula	Nitrogen	
							Found	Calculated
1	3a	CH_3	H	173	62	$C_{21}H_{19}N_5OS$	17.89	17.98
2	3b	CH_3	F	149	63	$C_{21}H_{18}N_5OSF$	17.09	17.19
3	3c	CH_3	Cl	154	65	$C_{21}H_{18}N_5OSCl$	16.45	16.52
4	3d	CH_3	OCH_3	187	60	$C_{22}H_{21}N_5O_2S$	16.60	16.69
5	3e	CH_3	CH_3	195	70	$C_{22}H_{21}N_5OS$	17.30	17.36
6	4a	Cl	H	185	71	$C_{20}H_{16}N_5OSCl$	16.98	17.09
7	4b	Cl	F	199	67	$C_{20}H_{15}N_5OSClF$	16.30	16.37
8	4c	Cl	Cl	152	57	$C_{20}H_{15}N_5OSCl_2$	15.65	15.76
9	4d	Cl	OCH_3	168	60	$C_{21}H_{18}N_5O_2SCl$	15.85	15.92
10	4e	Cl	CH_3	197	73	$C_{21}H_{18}N_5OSCl$	16.46	16.52
11	5a	H	NA	141	68	$C_{22}H_{20}N_6O_2S_2$	18.00	18.09
12	5b	F	NA	226	54	$C_{22}H_{18}O_2N_6S_2F_2$	16.68	16.79
13	5c	Cl	NA	245	57	$C_{22}H_{18}O_2N_6S_2Cl_2$	15.65	15.75
14	5d	OCH_3	NA	191	65	$C_{24}H_{24}O_4N_6S_2$	15.94	16.02
15	5e	CH_3	NA	210	70	$C_{24}H_{24}O_2N_6S_2$	16.95	17.06

(i) Analytical data of compound (1a); m.p. 128°C, Yield 65%, IR KBr (ν cm^{-1}) λ_{max} 3431(OH), 3009(C-H), 2850 and 2780 (C-H of CHO), 1666 (C=O), 1600 (-N=N-), 1595-1466 (-C=C-), 720 (-C-Cl); NMR DMSO-d_6 (δ ppm) 7.4-7.8 m (8H) Ar-H, ; MS (FAB MS) M^+ 260m/z & m+2 262m/z; Elemental analysis, found (cacld) %, C 59.90(59.81), H 3.48(3.38), N 10.75(10.63).

(ii) Analytical data of compound (2a); m.p. 140°C, Yield 65%, IR KBr (ν cm^{-1}) λ_{max} 3254(-N-H), 3090 (-C-H), 1601-1452 (-C=C), 1312 (Ar-N), 1277 (C=S); NMR DMSO-d_6 (δ ppm) 7.38-7.49 m(4H) Ar-H, 8.15 s(2H) $-NH_2$, 9.03 s(1H) Ar-NH, 10.05 s(1H) $-NH-NH_2$; MS (FAB MS) M^+ 167m/z; Elemental analysis, found (cacld) %, C 50.27 (50.17), H 5.42 (5.30), N 21.13 (21.04).

(iii) Analytical data of compound (3a); m.p. 185°C, Yield 71 %, IR KBr (ν cm^{-1}) λ_{max} 3445-3245 (-O-H & -N-H), 3049 (C-H), 1665 (C=C), 1620 (C=N), 1595 (N=N), 1330 (Ar-N), 1255 (C=S), 750 (Ar-Cl); NMR DMSO-d_6 (δ ppm) 6.5 s(1H)(-OH), 6.9-7.5 m(12H)(Ar-H), 8.9 s(1H)(Ar-NH), 9.8

s(1H)(CH=N), 10.32 s(1H)(N-NH); MS (FAB MS) M^+ 409m/z & m+2 411m/z; Elemental analysis, found (cacld) %, C 58.60(58.55), H 3.65(3.57), N 17.09(17.01).

(iv) Analytical data of compound (4a); m.p. 173°C, Yield 62 %, IR KBr (ν cm^{-1}) λ_{max} 3450-3240 (-O-H & -N-H), 3050 (C-H), 2950 & 2890 (C-H, CH_3), 1675 (C=C), 1625 (C=N), 1590 (N=N), 1330 (Ar-N), 1250 (C=S); NMR DMSO-d_6 (δ ppm) 2.49 s (3H)(CH_3), 6.5 s(1H)(-OH), 6.8-7.7 m(12H)(Ar-H), 8.9 s(1H) (Ar-NH), 9.7 s(1H)(CH=N), 10.30 s(1H)(N-NH); MS (FAB MS) M^+ 389m/z; Elemental analysis, found (cacld) %, C 64.76(64.65), H 4.92(4.87), N 17.98(17.90).

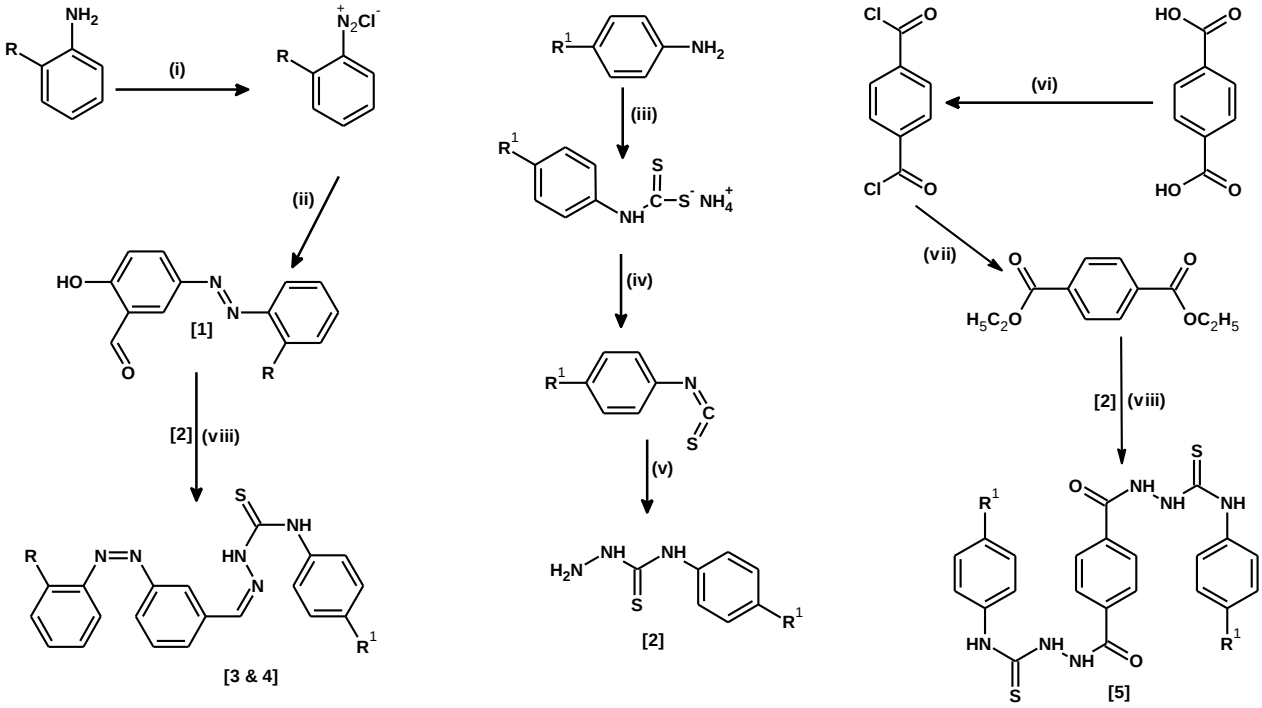
(v) Analytical data of compound (5a); m.p. 141°C, Yield 68 %, IR KBr (ν cm^{-1}) λ_{max} 3379-3339 (-N-H), 3058 (C-H), 1704 (C=O), 1559-1432 (C=C), 1272 (C=S), 1310 (Ar-N); NMR DMSO-d_6 (δ ppm) 7.0-7.74 m (12H)(Ar-H), 8.08 s (1H)(-NH-C=S), 9.38 s (1H)(Ar-NH), 9.68 s (1H)(-NH-C=O); MS (FAB MS) M^+ 492m/z; Elemental analysis, found (cacld) %, C 56.88(56.79), H 4.34(4.28), N 18.09 (17.94).

Antimicrobial activity screening

In disc-diffusion assay, few colonies of organisms were inoculated in 2-5 mL nutrient broth (for bacterial strains) and Sabourauds broth (for fungal strains) grown for 2.5 h. The agar plates were dried and inoculated by spreading the bacterial suspension evenly over it. The sterile paper discs (6 mm) impregnated with fixed dose viz., 800 μg/mL of compound were placed on the pre-inocculated surface. The disc bearing plates were incubated at 37°C and examined at 48 h for zone of inhibition around the disc. An additional negative control disc impregnated with plane solvent (DMF) and a positive control disc with standard drug Chloramphenicol (for bacterial strains) & fluconazole (for fungal strains) were also performed. The diameter of inhibition zone is directly proportional to the degree of sensitivity of bacterial pathogens and the concentration of the compound under test.

Results and discussion

The synthetic strategy (scheme-1) includes diazotization of aromatic amines and its coupling with salicylaldehyde to obtained 2-hydroxy-5(2-methylphenyl-azo)-benzaldehyde (**1a**) and 2-hydroxy-5(2-chlorophenyl-azo)-benzaldehyde (**1b**). Thiosemicarbazides (**2a-e**) were prepared by the reported methodology. The active thiosemicarbazones (**3a-e** and **4a-e**) were obtained by typical refluxing of reactants in equimolar quantity. Further terephthaloyl bis-4(4'-substituted-phenyl)thiosemicarbazides (**5a-e**) have been synthesized by three step reaction. Structure of all the synthesized compounds have been ascertained on the basis of IR, ^{1}HNMR, Mass spectral data and elemental analysis. Physical data of all the synthesized compounds have been highlighted in table 1.



Reagents & reaction conditions:

(i) $NaNO_2$, HCl; 0-5°C

(ii) NaOH,$C_6H_4(OH)CHO$; 0-5°C

(iii) CS_2, $NH_3.H_2O$; 0-12°C (iv) $Pb(NO_3)$; RT,

(v) NH_2NH_2/C_2H_5OH; Δ

(vi) $C_6H_4(COOH)_2$, PCl_5; C_6H_6/Δ (vii) C_2H_5OH, $NaHCO_3$; Δ

(viii) DMF; Δ8,hrs

Scheme 1: General synthetic strategy

The synthesized title compounds (**3a-e, 4ae & 5a-e**) were evaluated for antimicrobial activity through Kirby-Boar disc-diffusion method against fungal pathogens, *C. albicanes, A. fumigatus, C. neoformans, A. niger, P. ittalecum* and bacterial pathogens, *S. aurous, E. coli, B. anthrasis, S. flaxinerri* and *K. pneumonie* and results were compared with reference drugs. The experimental results of antimicrobial activity indicated variable degree of efficacy of compounds against tested fungal and bacterial strains. The results obtained from microbial sensitivity studies

reveals that screened compounds **3, 4** and **5** exhibits moderate to potent activity against the tested pathogens.

In table 2, the result of antibacterial sensitivity reveals that the compounds **3b, 4b, 4c, 4d, 5c** and **5d** shows the highest sensitivity against a panel of bacterial strains, out of these most potent compounds only **3c, 4c** and **5c** demonstrates the best growth inhibitory activity. Compound **3c** exhibits highest sensitivity against *S. typhimurium* (35mm, 87.5%) and lowest activity against *S. areus* (25mm, 62.5%), compound **4c** exhibits highest sensitivity against *S. typhimurium* (38mm, 95%) and lowest activity against *S. aureous* (26mm, 65%), compound **5c** exhibits highest sensitivity against *S. typhimurium* (35mm, 87.5%) and lowest activity against *S. flaxinerri* (28mm, 62.2%). Compound **3a** shows minimum activity for all bacterial strains. Compound **3b, 3d, 4a, 4b, 4d** and **4e** shows maximum sensitivity for *S. typhimurium* and followed by *K. pneumoniae > S. flaxinerri > E. coli > S. aureus.* Compound **5a, 5b, 5d** and **5e** shows highest activity for *S. typhimurium* and minimum activity is exhibited by compound **5a** & **5e** for *S. flexinerri* (33.3%).

Table 2 In-vitro antimicrobial activity of title compounds 3, 4 & 5(a-e).

Comp. No.	Bacterial pathogens					Fungal pathogens				
	S. aureus	E. coli	S. typhimuriun	S. flaxinerri	K. pneumoniae	C. albicanes	A. fumigatus	C. neoformans	A. niger	P. ittalecum
3a	15	16	20	22	22	- -	09	12	- -	08
3b	20	20	28	29	30	10	15	18	12	19
3c	25	22	35	31	33	20	20	20	18	21
3d	18	18	30	28	28	13	17	17	14	15
3e	15	18	25	23	24	08	13	12	10	10
4a	22	20	24	25	26	10	11	16	08	10
4b	23	24	31	32	34	12	18	20	15	21
4c	26	27	38	33	36	23	25	24	20	25
4d	20	22	33	30	32	18	20	21	18	20
4e	19	21	30	28	30	10	16	15	10	13
5a	15	15	22	15	22	10	10	11	12	10
5b	18	22	28	23	28	16	18	15	17	14
5c	28	30	38	28	30	20	26	20	28	18
5d	20	18	32	20	24	14	20	12	20	16
5e	15	16	25	15	20	10	12	09	10	12
Chl	*40*	*38*	*40*	*45*	*48*	- -	- -	- -	- -	- -
Flu	- -	- -	- -	- -	- -	*25*	*30*	*26*	*26*	*28*
DMFFF	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -

- *Diameter of zone of Inhibition in millimeters at 1000µg/mL concentration of compounds.*

- *Antimicrobial susceptibilities of compounds were measured in the term of zone of growth inhibition.*

- *Reference drug Chl = Chloramphenicol, Flu = Fluconazole and DMF = Dimethyl formamide.*

For fungal pathogens, the best growth inhibitory activity exhibited by compound **3c, 4c, 4d** and **5c**. Compound **4c** shows maximum activity for *C. neoformans* (24mm, 92.3%) and lowest one for *A. fumigatus*(20mm, 66.6%), compound **5c** shows 86% sensitivity for *A. fumigatus,* compound **3c** shows 80% for *C. albicanes,* compound **3b, 3d, 4b** and **4d** shows maximum activity for *C. neoformans* 69%, 65%, 76% and 80% respectively. Compound **5d** shows 76.9% sensitivity for *A. niger.* Compound **3a** is inactive for *C. albicanes* and *A. niger.* Percentage of sensitivity has calculated with respect to control drugs.

CONCLUSION

Microbial sensitivity tests clearly indicated that the nature of substitution and position on thiosemicarbazone and thiosemicarbazide molecule affect the activity. The chloro substituent frequently appears in many drugs and it follow the trend here also as chloro substituted compound seem to be more potent than other compounds, suggested that some steric hindrance might be present around the ortho position of chloro, thus *o*-Cl phenyl on thisemicarbazone and thiosemicarbazide is an essential part of the pharmacophore. The major findings gathered from the antimicrobial results in table-2 are highlighted as:-

- Chloro moiety in the thiosemicarbazone and thiosemicarbazide enhance the antimicrobial profile.

- Methyl substituent shows poor activity.

- Introduction of electron withdrawing moiety in ring increases the activity gradually.

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