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SYNTHESIS, ANTIMICROBIAL AND ANTIOXIDANT ACTIVITIES OF 1,3,5-THIADIAZINE DERIVATIVES

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Abstract:

*A series of N-(4-(benzyloxy)benzylidene)-2-(arylimino)-6-(phenylimino)-3,6-dihydro-2H-1,3,5-thiadiazin-4-amine derivatives **(4a-d)** have been synthesized by condensation of 1-(N-4-(benzyloxy) benzylidenecarbamimidoyl)-3-arylthiourea **(3a-d)** with phenyl isocyanodichloride. Interaction of 1-carbamimidoyl-3-arylthiourea **(2a-d)** and p-benzyloxy benzaldehyde yielded **(3a-d)**. Monoacetyl **(5b)** and mononitroso **(6b)** derivatives were also synthesised by substitution of hydrogen atom of cyclic –NH- of **4b** on treatment with acetic anhydride and sodium nitrite respectively. Further, **4b** upon boiling with 5% aqueous ethanolic (1:1) sodium hydroxide solution underwent isomerisation into corresponding 4-(4-(benzyloxy)benzylideneamino)-6-(4-chlorophenylimino)-1-phenyl-5,6-dihydro-1,3,5-triazine-2(1H)-thione **(7b)**. The structures of the newly synthesized 1,3,5-thiadiazine derivatives have been established on the basis of chemical transformations, elemental analysis and IR, ^{1}H NMR, and Mass spectral studies. The zone of inhibition for some of the title compounds synthesized were determined against E. coli, S. aureus, B. thurengienesis and E. aerogenes and compared with Chloramphenicol as a reference drug. Some of the newly synthesized compounds showed moderate to high antimicrobial activity. Antioxidant activities of all the compounds were also determined. **4a, 4c** and **4d** were found to possess significant antioxidant activity.*

Keywords: *Carbamimidoyl-3-arylthiourea, 1,3,5-thiadiazine, 1,3,5-triazine, antibacterial activity, anti-oxidant activity.*

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INTRODUCTION:

A large number of organic compounds containing nitrogen or sulphur or both are known to possess antimicrobial activity. Thiadiazine is a six membered heterocyclic compound containing two nitrogen atoms and one sulphur atom in alternate position. Different synthetic routes are available in the literature (1-7) which focuses on its synthesis. Novel heterocycles like 1,3,5-thiadiazines possessing wide spectrum biological activities that have stimulated considerable research work in last few decades leading to the synthetic utility of the derivatives of this ring system. 1,3,5-thiadiazines have been shown to possess various pharmacological activities such as antimicrobial (8-11), antifungal (12-13), herbicidal, nematocidal (14), antiprotozoal (15), tuberculostatic (16-17) and anticancer (18). The tetrahydro-2*H*-1,3,5-thiadiazine-2-thione (THTT) scaffold has been used for arteriosclerosis treatment (19) while its application in antiepileptic pro-drugs has been reported recently (20). In our search for new potential antimicrobial compounds, the reaction of N-phenyl isocyanodichloride and 1-(N-4-(benzyloxy) benzylidenecarbamimidoyl)-3-aryl thiourea to yield a series of 1,3,5-thiadiazin-4-amines was found to be interesting. This stimulated us to synthesize some novel 1,3,5-thiadiazine derivatives and considering the structural features, it was thought to carry out the biological screening and the compounds reported in this communication have been also tested for their antioxidant activity.

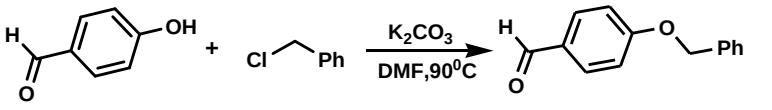
MATERIAL AND METHODS:

Chemicals used for the synthesis were of AR grade of Merck, S.D.Fine and Aldrich. The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, v max in cm^{-1}). Positive-ion Electro Spray Ionization (ESI) mass spectra were obtained with a Waters Micromass Q–TOF Micro, Mass Spectrophotometer. ^1H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d6 as solvent. Chemical Shifts are given in parts per million (ppm). Elemental (CHN) analysis was done using Thermo Scientific (Flash-2000), the compounds were analyzed for carbon, hydrogen and nitrogen and the results obtained are in good agreement with the calculated values. The reactions were monitored by E. Merck TLC aluminum sheet silica gel 60 F254 and visualizing the spot in UV Cabinet and iodine chamber.

Experimental

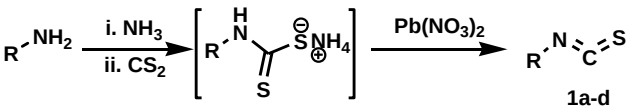
The preparation of starting material such as p-benzyloxy benzaldehyde**,** aryl isothiocyanate (RNCS) and aryl isocynodichloride were carried out according to the schemes **(1-3)** following the procedure as per the literature (21).

Reaction Scheme 1



4-Benzyloxy benzaldehyde

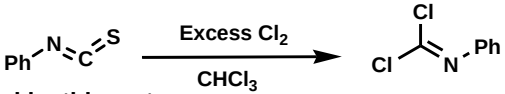
Reaction Scheme 2



1a-d

Code	R
a	$-C_6H_5$
b	$-C_6H_4$-4Cl
c	$-C_6H_4$-4CH_3
d	$-C_6H_4$-2CH_3

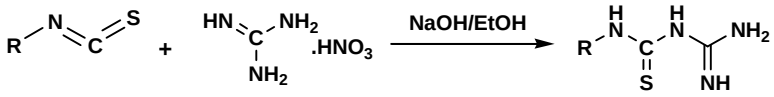
Reaction Scheme 3



Phenyl isothicynate Phenylisocynodichloride

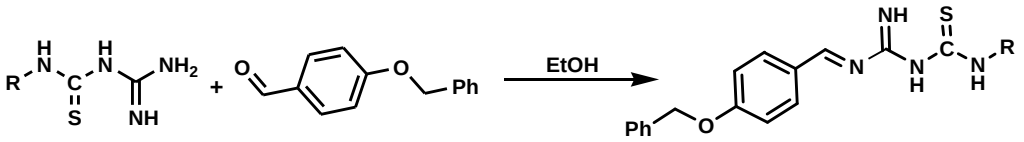
Procedure for synthesis of 1-carbamimidoyl-3-phenylthiourea (2a): In a clean dry round-bottomed flask containing mixture of guanidine nitrate (10 mmol) and phenyl isothiocyanate **(1a,** 10 mmol) in alcohol (25 mL) sodium hydroxide (10 mmol) was added. The reaction mixture was refluxed for 2h and poured into crushed ice, filtered, dried and recrystallized from ethanol to give **2a (**Scheme **4).** Similarly, **2b-d** were synthesised from **1b-d** by extending the same procedure followed for **2a**.

Reaction Scheme : 4



(1a-d) (2a-d)

Reaction Scheme : 5



(2a-d) (3a-d)

1-carbamimidoyl-3-phenylthiourea (2a): White crystalline solid, mp: 170-172°C yield: 78.0%, M. F. $C_8H_{10}SN_4$, Recrystallizing solvent: Ethanol, **1-carbamimidoyl-3-(4-chlorophenyl)thiourea (2b):** White crystalline solid, mp: 178-180°C yield: 84.0%, M. F. $C_8H_9N_4SCl$, Recrystallizing solvent: Ethanol, **1-carbamimidoyl-3-(4-methylphenyl) thiourea (2c):** White crystalline solid, mp: 190-192°C yield: 82.0%, M. F. $C_9H_{12}N_4S$, Recrystallizing solvent: acetic acid, **1-carbami midoyl-3-(2-methylphenyl)thiourea (2d):** White crystalline solid, mp: 164-166°C yield: 81.0%, M. F. $C_8H_{10}N_4S$, Recrystallizing solvent: Ethanol.

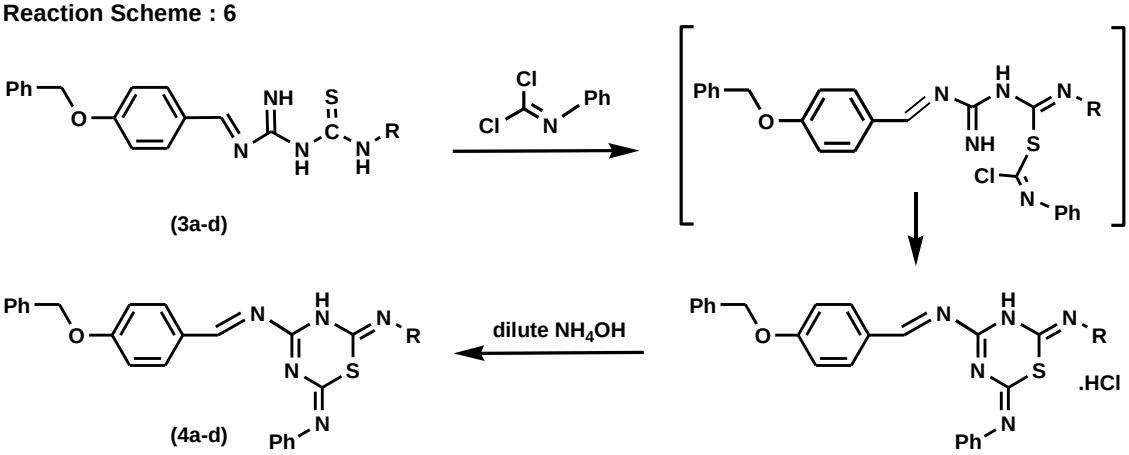
Procedure for synthesis of 1-(N-4-(benzyloxy) benzylidenecarbamimidoyl)-3-phenyl thiourea (3a): To a mixture of 1-carbamimidoyl-3-phenylthiourea (10 mmol), p-benzyloxy benzaldehyde (10 mmol) in ethanol (30 mL), few drops of glacial acetic acid were added and was refluxed for 2h. It was then cooled poured into crushed ice, filtered, dried and recrystallized from ethanol to afford **3a (**Scheme **5).** Similarly, 3**b-d** were synthesised from **2b-d** by adopting the same procedure followed for **3a**.

1-(N-4-(benzyloxy)benzylidenecarbamimidoyl)-3-phenylthiourea (3a): Pale yellow crystals, mp: 90-92°C yield: 76.0%, M. F. $C_{22}H_{18}N_3S$, *Rf*: 0.88, Recrystallizing solvent: Ethanol, **1-(N-4-(benzyloxy)benzylidenecarbamimidoyl)-3-(4-chlorophenyl)thiourea (3b):** Pale yellow crystals, mp: 107-109°C yield: 82.0%, M. F. $C_{22}H_{18}N_3S$, *Rf*: 0.94, Recrystallizing solvent: Ethanol, **1-(N-4-(benzyloxy)benzylidenecarbamimidoyl)-3-p-tolylthiourea (3c):** Pale yellow crystals, mp: 160-162°C yield: 84.0%, M. F. $C_{23}H_{20}N_3S$, *Rf* : 0.91, Recrystallizing solvent: Methanol. **1-(N-4-(benzyloxy)benzylidenecarbamimidoyl)-3-o-tolyl thiourea (3d):** Pale yellow crystals, mp: 120-122°C yield: 82.0%, M. F. $C_{23}H_{20}N_3S$, *Rf* : 0.85, Recrystallizing solvent: Ethanol.

Procedure for preparation of N-(4-(benzyloxy) benzylidene)-2,6-bis(phenylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (4a): 3a (10 mmol) and phenyl isocyanodichloride (10 mmol) were refluxed in chloroform (25 mL) for 2h over a water bath. The reaction mixture was allowed to evaporate the solvent and kept overnight; the sticky mass so obtained was washed with petroleum ether followed by alcohol. The reaction mixture was neutralized by adding ammonium hydroxide. The precipitate so obtained was washed, dried and recrystallized from ethanol to afford **4a**. Similarly, **4b-d** were synthesised from **3b-d** following the same procedure as for **4a (**Scheme **6).**

N-(4-(benzyloxy)benzylidene)-2,6-bis(phenyl imino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (4a): Pale yellow crystals, mp: 96-99°C yield: 84.0%, M. F. $C_{29}H_{23}N_5OS$, *Rf* : 0.94, **IR:** 3411 (NH str.),3033 (ArH str.), 2906, 2864 (-CH_2- str.), 1624, 1605, 1590, 1573 (C=N str.), 1251, 1011 (C-O-C asym.), 1573, 1508, 1484 (C=C), 1106, 1164 (C-N), 694 (C-S-C), 908, 880, 821 (C-S str.) **^{1}H NMR:** 5.19 (s, 2H, Ph-C$\underline{H_2}$O-), 4.8-5.0 (br., 1H, C-NH-C), 8.50 (s, 1H, N=C$\overline{H}$), 6.54-7.89 (m, 19H, ArH) **MS:** *m/z* 489 M^+, 512 [$(M+Na)^+$], 490 [$(M+H)^+$], **Calculated:** C, 71.16, H, 4.70, N, 14.31 **Found:** C, 78.12, H, 5.63, N, 5.50

Reaction Scheme : 6

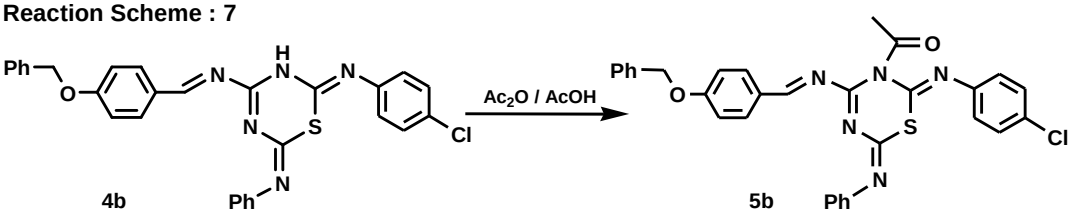


N-(4-(benzyloxy)benzylidene)-2-(4-chlorophenyl imino)-6-(phenylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (4b): Pale yellow crystals, mp: 66-68°C yield: 82.0%, M. F. $C_{29}H_{22}N_5OSCl$, *Rf* : 0.87, Recrystallizing solvent: Ethanol. **N-(4-(benzyloxy)benzylidene)-6-(phenylimino)-2-(p-tolylimino)-3,6-dihydro-2H-1,3,5-thiadiazin-4-amine (4c):** Pale yellow crystals, mp: 164-166°C yield: 85.0%, M. F. $C_{30}H_{25}N_5OS$, *Rf* : 0.90, Recrystallizing solvent: Ethanol. **N-(4-(benzyloxy)benzylidene)-6-(phenylimino)-2-(o-tolylimino)-3,6-dihydro-2H-1,3,5-thiadiazin-4-amine (4d):** Pale yellow crystals, mp: 168-170°C yield: 87.0%, M. F. $C_{30}H_{25}N_5OS$, *Rf* : 0.87, Recrystallizing solvent: Ethanol.

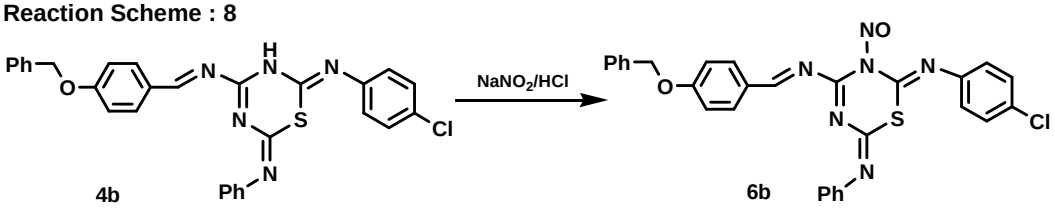
Procedure for the synthesis of 1-(4-(4-(benzyloxy)benzylideneamino)-2-(4-chloro phenylimino)-6-(phenylimino)-2*H*-1,3,5-thiadiazin-3(6*H*)-yl)ethanone (5b): A mixture of acetic anhydride (10 mmol), glacial acetic acid (10 mL) and **4b** (10 mmol) were refluxed for 2h. Then the reaction mixture was poured in crushed ice and separated product was filtered and recrystallized from ethanol to yield **5b (**Scheme **7).**
Physical data: Colour: Pale yellow crystals, mp: 75-77°C yield: 73.0%, M. F. $C_{31}H_{24}N_5OSCl$, *Rf* : 0.74.

Procedure for the synthesis of N-(4-(benzyloxy) benzylidene)-2-(4-chlorophenylimino)-3-nitroso-6-(phenylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin -4-amine (6b): A mixture of ethanol (10 mL) and **4b** (10 mmol) was cooled below 5°C. Sodium nitrite solution (10 mmol) in water (2mL) was added to this cold solution drop wise with stirring, yellowish solid so obtained was filtered and recrystallized from ethanol **(**Scheme **8). Physical data:** Colour: Pale yellow crystals, mp: 76-79°C yield: 68.0%, M. F. $C_{29}H_{21}ClN_6O_2S$, *Rf*: 0.76.

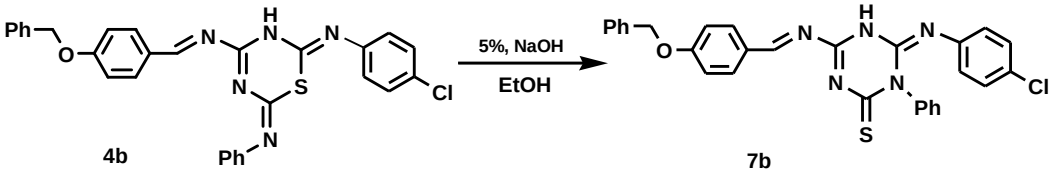
Reaction Scheme : 7



Reaction Scheme : 8



Reaction Scheme : 9



Procedure for the synthesis of 4-(4-(benzyloxy) benzylideneamino)-6-(4-chlorophenylimino)-1-phenyl-5,6-dihydro-1,3,5-triazine-2(1*H*)-thione (7b): A mixture of 5% ethanolic sodium hydroxide solution (1:1) and **4b** (10mmol) was boiled in a round bottom flask for 1.5h. The reaction mixture was cooled and the product obtained was filtered and recrystallized from ethanol to get **7b** (Scheme **9)**. **Physical data:** Colour: Brown solid, mp: 78-82°C yield: 65.0%, M. F. $C_{23}H_{17}ClN_5OS$, *Rf*: 0.84.

Antibacterial Activity:

The novel synthesized heterocyclic compounds were screened for their *in vitro* antimicrobial activity using cup plate agar disc-diffusion method against two Gram positive bacterial strains, *B. thurengienesis* and *S. aureus* and two Gram negative strains, *E. coli* and *E. aerogenes*. Chloramphenicol was used as standard drugs for bacteria.

Procedure for the determination of Zone of Inhibition by Agar disc-diffusion method:

Test solutions were prepared with known weight of compound in dimethyl sulphoxide (DMSO) and diluted suitably to give the resultant concentration of 31, 62, 125, 250, 500 and 1000µg/mL. Whatmann no. 1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. *In vitro* antibacterial activity was determined by using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai. Twenty-four hours old culture of selected bacterial strain was mixed with physiological saline and the turbidity was corrected by adding sterile physiological saline and sub cultured on Sabouraud Dextrose and suspended in sterile distilled water to an absorbance of 0.6 at 450 nm. Petri plates were prepared by pouring 10 ml of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. The discs were then applied and the plates were incubated at 37°C for 24h (bacteria) and the inhibition zone was measured as diameter in four directions and expressed as mean. The results were compared using Chloramphenicol as a standard antibacterial agent. The results of antibacterial activity (i.e. Zone of inhibition in mm) of the synthesized compounds are given in the Table **1-8**.

Antioxidant Activity: The reducing power in-vitro model was used to evaluate antioxidant activity according to the method of Oyaizu (22). This method is based on the principle of increase in the absorbance of the reaction mixture, indicates increase in the antioxidant activity hence increasing reducing power of the samples. In this method antioxidant compound gives a colored complex with potassium ferricyanide, trichloroacetic acid and ferric chloride, which is measured at 700 nm.

Procedure: The standard drug and test compounds were dissolved in dimethyl formamide so as to get different concentrations (20µg/mL to 100µg/mL). This was mixed with 2.5mL of (pH 6.6) 0.2 mol phosphate buffer and 2.5mL of 1 % potassium ferricyanide. The mixture was incubated at 50°C for 20 minutes. 2.5mL of 10 % trichloroacetic acid was added to the mixture, which was then centrifuged for 10 minutes at 1000 rpm. 2.5mL upper layer of solution was mixed with 2.5mL of distilled water and 0.5mL of 0.1% ferric chloride. The absorbance was measured at 700nm. The absorbance of the blank was also measured in similar manner. The results were compared with ascorbic acid, which was used as a reference standard antioxidant. Antioxidant activities of some representative compounds are given in Table **9**.

RESULT AND DISCUSSIONS:

The targeted products **2-7** have been synthesized by common pathway as summarized in reaction scheme **1-7.** The reactions were monitored by TLC. The identities of the newly synthesized compounds have been established on the basis of their general chemical investigation, elemental analysis and spectral data such as IR, ^{1}H NMR and Mass spectral studies (23).

Reaction of RNCS (aryl isothiocyanate, **1a-d**) with 1-carbamimidoyl-3-arylthiourea (**2a-d**) afforded 1-(N-4-(benzyloxy) benzylidenecarbamimidoyl)-3-arylthiourea (**3a-d).** Reaction of **3a-d** with one equivalent of phenyl isocyanodichloride in refluxing chloroform yielded respective 1,3,5-thiadiazines **4a-d.** The IR spectra of **4a** exhibited characteristic band at 3411 cm^{-1} (broad) for free and bonded N-H. The peak at 1251 cm^{-1} was assigned to C-O-C, the peak at 1624 cm^{-1} was assigned to C=N, a peak at 694 and 908, 880, 821 cm^{-1} is due to C-S-C and C-S stretch, in association of these peaks other bands due C-H and C=C stretch in aromatic region appeared in accordance with the literature. Further support for **4a** came from the ^{1}H NMR spectrum which exhibited singlet and a broad peak at 5.19 ppm and 4.8-5.0 ppm which integrated for two proton and one proton were designated to the -CH_2- of Ph-CH_2-O- group

and –NH protons respectively, other signals associated with aromatic protons were obtained as multiplet in the range of δ 6.54 to 7.89 ppm due to nineteen protons confirms the formation of **4a** which was also confirmed by mass spectrum with a molecular ion peak at *m/z* 489 [(M +Na)$^+$, 512] is in agreement with the molecular formula $C_{29}H_{23}N_5OS$ (Scheme **6**). Elemental analysis revealed that the expected percentage of elements such as carbon, hydrogen and nitrogen in **4a.**

Extending the reactions of **(4b),** on acylation it yielded monoacetyl derivative **(5b),** while its reaction with sodium nitrite in acidic medium yielded mononitroso derivative **(6b),** and on boiling with 5% aqueous ethanolic (1:1) sodium hydroxide solution isomerizes into corresponding 1-phenyl-2-phenylimino-4-(substituted)-benzylidene amino-6-thio-1,3,5-triazine **(7b)**.

Antimicrobial activity:

All the synthesized substituted 1, 3, 5-thiadiazines (**4a-d)** and derivatives **5b, 6b** and **7b** were screened for antimicrobial activity. Table no. **2-8** shows the inhibition zone determined in mm for title compounds at different concentrations from 31-1000 µg/mL using Chloramphenicol as the standard drug (Table **1**). Data obtained revealed that the test compound (**4a-d)** showed to possess moderate to high activity and derivatives **5b, 6b, 7b** possess least antimicrobial activity when compared with standard drug; however in some cases it was better than Chloramphenicol**. 4a-d** are highly active against *E. areogenes* and *S. aureus* at the almost all concentration and moderately active against *E. coli* whereas inactive against *B. thurengienesis.* The results were found to be excellent at 31 µg/mL concentrations.

Antibacterial activity: Zone of Inhibition in mm

Table 1: For Chloramphenicol (Standard)

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	29	19	27	30
2	500	20	16	30	20
3	250	18	17	27	21
4	125	17	16	21	16
5	62.2	11	15	20	16
6	31.125	12	11	11	15

Table 2: For N-(4-(benzyloxy)benzylidene)-2,6-bis(phenylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (4a)

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	19	18	35	17
2	500	13	20	32	26
3	250	15	18	30	20
4	125	11	-	28	22
5	62.2	14	-	26	11
6	31.125	14	19	24	16

Table 3: For N-(4-(benzyloxy)benzylidene)-2-(4-chlorophenylimino)-6-(phenylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (4b)

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	19	18	34	17
2	500	13	20	30	26
3	250	15	18	-	20
4	125	11	-	-	22
5	62.2	14	-	-	11
6	31.125	14	19	20	16

Table 4: For N-(4-(benzyloxy)benzylidene)-6-(phenylimino)-2-(p-tolylimino)-3,6-dihydro-2H-1,3,5-thiadiazin-4-amine (4c)

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	19	18	37	17
2	500	13	20	32	26
3	250	15	18	-	20
4	125	11	-	-	22
5	62.2	14	-	-	11
6	31.125	14	12	18	16

Table 5: For N-(4-(benzyloxy)benzylidene)-6-(phenylimino)-2-(o-tolylimino)-3,6-dihydro-2H-1,3,5-thiadiazin-4-amine (4d)

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	19	18	37	17
2	500	13	20	34	26
3	250	15	18	-	20
4	125	11	-	-	22
5	62.2	14	-	-	11
6	31.125	14	13	18	16

Table 6: For 1-(4-(4-(benzyloxy)benzylideneamino)-2-(4-chlorophenylimino)-6-(phenylimino)-2*H*-1,3,5-thiadiazin-3(6*H*)-yl)ethanone (5b):

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	-	11	10	8
2	500	8	10	8	11
3	250	-	15	7	10
4	125	-	-	7	7
5	62.2	7	7	-	7
6	31.125	6	6	-	9

Table 7: For *N*-(4-(benzyloxy)benzylidene)-2-(4-chlorophenylimino)-3-nitroso-6-(phenylimino)-3,6-dihydro-2*H*-1,3,5-thiadiazin-4-amine (6b)

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	-	12	20	8
2	500	8	11	8	9
3	250	-	15	6	10
4	125	7	-	12	9
5	62.2	-	-	11	14
6	31.125	5	14	10	12

Table 8: For 4-(4-(benzyloxy)benzylideneamino)-6-(4-chlorophenylimino)-1-phenyl-5,6-dihydro-1,3,5-triazine-2(1*H*)-thione (7b)

Sr. No.	Concentration of Solution In µg/ml	*E. coli* (Gm-ve)	*E. aerogenes* (Gm-ve)	*S. aureus* (Gm+ve)	*B. thurengienesis* (Gm+ve)
1	1000	-	13	22	6
2	500	7	12	6	10
3	250	-	16	8	10
4	125	8	-	10	11
5	62.2	-	-	9	12
6	31.125	6	13	7	10

Table 9 : Antioxidant Activity of 4a-d and 5b-7b

	Absorbance					%Increase in Absorbance				
Compound Code	**20** µg/mL	**40** µg/mL	**60** µg/mL	**80** µg/mL	**100** µg/mL	**20** µg/mL	**40** µg/mL	**60** µg/mL	**80** µg/mL	**100** µg/mL
Control			0.100					--		
Standard (Ascorbic acid)	0.148	0.157	0.162	0.176	0.183	48	57	62	76	83
4a	0.106	0.110	0.150	0.167	0.178	6	10	50	67	94
4b	0.115	0.124	0.133	0.148	0.159	15	24	33	48	59
4c	0.142	0.160	0.173	0.181	0.183	42	60	73	81	83
4d	0.143	0.158	0.164	0.179	0.182	43	58	64	79	82
5b	0.153	0.157	0.170	0.175	0.179	53	57	70	75	79
6b	0.152	0.155	0.160	0.170	0.189	52	55	60	70	89
7b	0.135	0.147	0.168	0.179	0.181	35	47	68	79	81

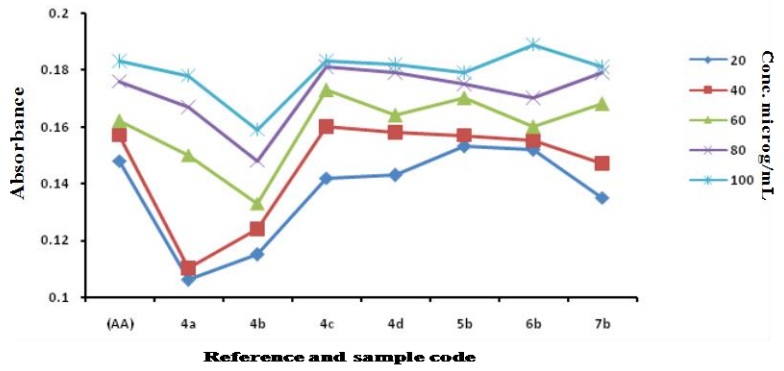


Fig 1: Reducing power of the synthesized compounds as compared with the standard Ascorbic Acid (AA) at concentrations from 20-100µg/ mL

Antioxidant activity:

All the synthesized compounds **(4a-d)** and its derivatives **5b, 6b** and**7b** were assessed for their in vitro antioxidant activities using free radical reducing power at various concentrations. The results revealed that the tested compounds **4a, 4c** and **4d** possesses significant antioxidant activity while **4b, 5b, 6b, 7b** gives mild antioxidant activity when compared to control (Figure **1**).

CONCLUSION: In conclusion, we have reported here the title compounds **(4a-d)** synthesized by condensation of 1-(N-4-(benzyloxy) benzylidene carbamimidoyl)-3-arylthiourea and phenyl isocyanodichloride were confirmed to be 1,3,5-thiadiazine derivatives by spectral analysis. Antibacterial screening of all the synthesized compounds was done and found to possess moderate to good activity against selected strains of bacteria. The results were found to be excellent with solution having minimum concentration; moreover the prepared derivatives **5b** and **6b** and the isomer **7b** were found to be inactive against all four bacterial strains. Antioxidant activity of the synthesized compounds also showed moderate to good activity.

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