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Synthesis and QSAR studies of thiosemicarbazides, 1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles derivatives as potential antibacterial agents

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Several new 2-(2-(4-chlorophenyl)acetyl)-*N*-arylhydrazinecarbothioamides **1,** 5-(4-chlorobenzyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols **2**, 5-(4-chlorobenzyl)-*N*-aryl-1,3,4-thiadiazol-2-amines **3** and 5-(4-chlorobenzyl)-*N*-aryl-1,3,4-oxadiazol-2-amines **4** have been synthesized and screened for their antibacterial activity against gram +ve and gram –ve bacteria *i.e S.aureus* and *E. coli*. The QSAR studies of these compounds have been carried out in terms of structural and physico-chemical parameters. Positive contribution of substituents present at position-2 of 2-[2-(4-chlorophenyl)acetyl]-*N*-arylhydrazine carbothioamides **1** with bulkier group indicate increase in hydrophobicity or steric bulk character.

Keywords: Antibacterial activity, triazole, thiadiazole, oxadiazole, linear free energy relationship (LFER), QSAR.

Thiosemicarbazides, 1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles exhibit some interesting pharmacological properties like antipanosomal, antibacterial, anticoccodial, fungicidal, herbicidal, insecticidal, antitumor, hypoglycemic, diuretic, anti-inflammatory, antiviral, antiacetylcholine, stearase, antitubercular, tranquillizer and sedative[1-11].

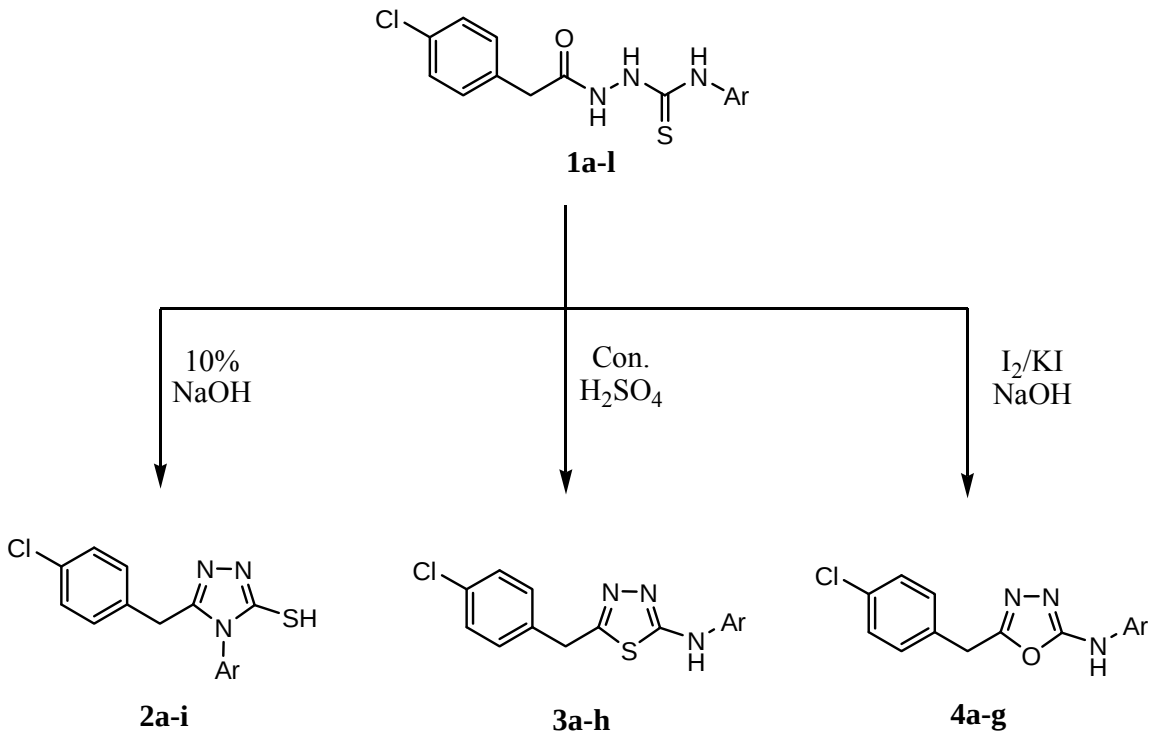
In this paper, we have focused on the incorporation of thiosemicarbazides, triazoles, thiadiazoles and oxadiazoles in one framework, and have tried to observe the antibacterial activity. In some cases, antibacterial activity is found to be enhanced as compared to standard drug ciprofloxacin. Earlier we have synthesized some bioactive heterocyclic molecules and screened for antimicrobial, anticancer and anti-HIV activities[12-17]. Medicinal utilities of these compounds prompted us to synthesize some new thiosemicarbazides, 1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles. In order to established structure activity relationship, we have carried out QSAR studies of title compounds.

Chemistry

2-[2-(4-Chlorophenyl)acetyl]-*N*-arylhydrazinecarbothioamides **1** were prepared by reacting 4-chlorophenyl acetylhydrazide and aryl isothiocyanates in the presence of ethanol. Various 5-(4-chlorobenzyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols **2**, 5-(4-chlorobenzyl)-*N*-aryl-1,3,4-thiadiazol-2-amines **3** and 5-(4-chlorobenzyl)-*N*-aryl-1,3,4-oxadiazol-2-amines **4** have been prepared[18-20] by the cyclization with sodium hydroxide, sulfuric acid and iodine in potassium iodide in presence of sodium hydroxide respectively (**Scheme I** and **Table I**).

Biological evaluation

The study has been conducted according to the method adopted by Kirby W M M *et al*.[21] The discs have been prepared from Whatman filter paper no. 1 with 4 mm diameter and sterilized at 160°C for 30 min. The concentration of compounds has been 20 mm disc in each case using appropriate solvents (DMF/1, 4-Dioxane). The suspension of the organism was spread on a nutrient agar plate by sterilized cotton swab and the disc containing compound was placed by sterilized forceps. Incubation carried out at 37°C for 24 hr and the width of growth inhibition zone noted. The compounds **(1a-l, 2a-i, 3a-h** and **4a-g)** were screened against gram +ve and gram –ve bacteria *i.e S. aureus* and *E. coli* (**Table I**). The drug ciprofloxacin was used as a standard drug and screened under the similar conditions for the comparison, which showed 20 mm zone of inhibition.



Where, Ar = Different aryl groups.

Scheme I

QSAR studies

In order to establish the quantitative structure activity relationship (QSAR)[22-27], the antibacterial activity measured in the form of Minimum Inhibitory Concentration (MIC) [*E. coli* (MIC_E) and *S. aureus* (MIC_S)] and transformed percent zone of inhibition in mm at fixed concentration for the *E. coli* and *S. aureus* were correlated to check the complimentary between the two antibacterial screening models. The transformation of zone of inhibition to percentage inhibition was based on weightage value of 24 for one +ve and thus marking the active compounds between 24 and 96%. The percent inhibition (P) was considered in its logit transformation [log (P/100-P)] ($logP_E$ or $logP_S$) of both the activity and Minimum Inhibitory Concentration (log1/MIC) ($log1/MIC_E$ or $log1/MIC_S$) for *E. coli* and *S. aureus* respectively. The correlation analysis between the two models $logP_{E/S}$ for each type of molecules **(1a-l, 2a-i, 3a-h** and **4a-g)** were carried out separately and are described in **Table II**. The correlation data (Eqns.1-3) for antibacterial activity against *E. coli* each type of compounds **1-4** respectively showed reasonable inter co-relation between the two models with almost similar slope and the intercept values. Hence, all the data were analyzed together and the derived Eqns. 4 describes statistically significant correlation between two models of antibacterial activity against *E. coli* with moderate correlation coefficient value (R=0.845) of > 99.9% statistical significance ($F_{1,\ 31\alpha\ 0.001}$= 7.56; $F_{1,\ 31}$ = 72.469) (**Table III**). However, similar correlation analysis with antibacterial activity data for *S. aureus* shows good correlation either in individual sets for each type of compounds **1-5** in (Eqns. 5-8) respectively or in combined set of all compounds (Eqns. 9) (**Table III**).

Preliminary structure activity analysis in the terms of correlation between log $1/MIC_E$ or log $1/MIC_S$ as dependent parameter and hydrophobic (π), electronic (σ, Polar, Res) and steric (MR) as independent parameters in each group of compounds **(1a-l, 2a-i, 3a-h** and **4a-g)** showed average correlation (R<0.720) which is less than 95% significance. However, in case of 2-(2-(4-chlorophenyl)acetyl)-*N*-arylhydrazinecarbothioamides (**1a-l**), there were some correlations existed between log $1/MIC_E$ and with π (R= 0.477), MR (R= 0.676), Polar (R= 0.497), Res (R= 0.629) or σ (R= 0.490) (**Table III**) (eq. 10-14). It was observed that log $1/MIC_E$ showed best correlation with MR (R= 0.676) of >90% statistical significance ($F_{1,\ 6\ \alpha\ 0.001}$= 5.99; $F_{1,\ 6}$ = 5.884) followed by correlation with polar (R=0.497) and Res (R=0.629) parameters. In the view

Table I — Physical constant and antibacterial activity of thiosemicarbazides (**1a-l**), 1,3,4-triazoles (**2a-i**), 1,3,4-thiadiazoles (**3a-h**) and 1,3,4-oxadiazoles (**4a-g**)

Compd.	Ar-	Mol. formula	m.p. °C	MIC µg/mL		Zone of inhibition	
				E.coli	*S.aureus*	*E.coli*	*S.aureus*
1a	2-CH_3-C_6H_4-	$C_{16}H_{16}N_3OSCl$	144	6	24	++++	+
1b	2,4-$(Cl)_2$-C_6H_3-	$C_{15}H_{12}N_3OSCl_3$	110	12	-	++	-
1c	2,4-$(OCH_3)_2$-C_6H_3-	$C_{17}H_{18}N_3O_3SCl$	146	12	6	++	++
1d	2,6-$(OCH_3)_2$-C_6H_3-	$C_{17}H_{18}N_3O_3SCl$	194	24	8	+	+++
1e	2,5-$(Cl)_2$-C_6H_3-	$C_{15}H_{12}N_3OSCl_3$	222	24	-	+	-
1f	-CH_2-C_6H_5	$C_{16}H_{16}N_3OSCl$	152	24	18	+	++
1g	2-OCH_3-C_6H_4-	$C_{16}H_{16}N_3O_2SCl$	128	24	6	+	+
1h	3-OCH_3-C_6H_4-	$C_{16}H_{16}N_3O_2SCl$	140	24	24	+	-
1i	2-OC_2H_5-C_6H_4-	$C_{17}H_{18}N_3O_2SCl$	120	12	-	+	+
1j	4-Cl-C_6H_4-	$C_{15}H_{13}N_3OSCl_2$	125	12	18	+++	+
1k	4-OCH_3-C_6H_4-	$C_{16}H_{16}N_3O_2SCl$	151	12	12	++	++
1l	3-CH_3-C_6H_4-	$C_{16}H_{16}N_3OSCl$	117	24	12	+	++
2a	2-CH_3-C_6H_4-	$C_{16}H_{14}N_3SCl$	176	12	8	++	+++
2b	2,4-$(CH_3)_2$-C_6H_3-	$C_{17}H_{16}N_3SCl$	126	12	18	+++	++
2c	2,5-$(OCH_3)_2$-C_6H_3-	$C_{17}H_{16}N_3O_2SCl$	186	12	-	+++	-
2d	3-OCH_3-C_6H_4-	$C_{16}H_{14}N_3OSCl$	150	-	6	-	++++
2e	4-OC_2H_5-C_6H_4-	$C_{17}H_{16}N_3OSCl$	162	12	6	++	++++
2f	4-Cl-C_6H_4-	$C_{15}H_{11}N_3SCl_2$	89	-	12	-	++
2g	4-OCH_3-C_6H_4-	$C_{16}H_{14}N_3OSCl$	135	-	6	-	++++
2h	4-CH_3-C_6H_4-	$C_{16}H_{14}N_3SCl$	108	-	8	-	+++
2i	C_6H_5-	$C_{15}H_{12}N_3SCl$	216	12	-	+++	-
3a	2-CH_3-C_6H_4-	$C_{16}H_{14}N_3SCl$	190	12	-	+++	-
3b	-CH_2-C_6H_5	$C_{16}H_{14}N_3SCl$	325(d)	12	24	+++	-
3c	3-OCH_3-C_6H_4-	$C_{16}H_{14}N_3OSCl$	330(d)	24	-	++	-
3d	2-OC_2H_5-C_6H_4-	$C_{17}H_{16}N_3OSCl$	270	12	18	+++	++
3e	4-OC_2H_5-C_6H_4-	$C_{17}H_{16}N_3OSCl$	217	12	12	++	++
3f	2-OCH_3-C_6H_4-	$C_{16}H_{14}N_3OSCl$	168	18	6	+	+++
3g	3-CH_3-C_6H_4-	$C_{16}H_{14}N_3SCl$	200	8	-	+++	-
3h	C_6H_5-	$C_{15}H_{12}N_3SCl$	120	-	12	-	++
4a	2-CH_3-C_6H_4-	$C_{16}H_{14}N_3OCl$	178	12	-	++	-
4b	-CH_2-C_6H_5	$C_{16}H_{14}N_3OCl$	150	12	-	++	-
4c	2-OC_2H_5-C_6H_4-	$C_{17}H_{16}N_3O_2Cl$	160	24	12	+	+++
4d	4-Cl-C_6H_4-	$C_{15}H_{11}N_3OCl_2$	172	12	-	++	-
4e	2,5-$(OCH_3)_2$-C_6H_3-	$C_{17}H_{16}N_3O_3Cl$	194	6	18	++++	+
4f	3-CH_3-C_6H_4-	$C_{16}H_{14}N_3OCl$	168	6	-	+++	-
4g	4-CH_3-C_6H_4-	$C_{16}H_{14}N_3OCl$	160	6	6	+++	+++

of some inter correlation between polar and Res (R=0.659) (**Table III**), each of them was considered separately in combination with each one of the electronic parameters (σ, Polar, Res) to have some idea about the combined effect of electronic influence and hydrophobicity or steric bulk. These correlations indicated that variation of the log $1/MIC_E$ was more influenced by hydrophobic (π) than steric (MR) parameters along with decreasing order of influence of the electronic parameters (σ, Polar or Res). Among the different equations generated, the best correlation of log 1/MICE was obtained with Polar + π (R = 0.561, $F_{1, 9\ \alpha\ 0.001}$= 5.12; $F_{1, 9}$ =1.376) Eqn. 15, σ + π (R= 0.598; $F_{1, 9\ \alpha\ 0.001}$= 5.12; $F_{1, 9}$ =1.671) Eqn. 16, π +

Table II — Structural parameters of thiosemicarbazides, 1,2,4-triazole, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles

Compd	Functional group	π	MR	Polar	σ	log(1/MIC_E)	Log(1/MIC_S)	$logP_E$	$logP_S$
1a	2-CH_3	0.56	5.65	-0.04	-0.17	-0.778	-1.380	1.380	-0.501
1b	2,4-$(Cl)_2$	1.42	12.06	0.82	0.37	-1.079	-	-0.035	-
1c	2,4-$(OCH_3)_2$	-0.04	15.74	0.52	-0.15	-1.079	-0.778	-0.035	1.380
1d	2,6-$(OCH_3)_2$	-0.04	15.74	0.52	-0.54	-1.380	-0.903	-0.501	0.410
1e	2,5-$(Cl)_2$	1.42	12.06	0.82	0.60	-1.380	-	-0.501	-
1f	-CH_2-C_6H_5	0.05	4.65	-	-	-1.380	-1.255	-0.501	-0.035
1g	2-OCH_3	-0.02	7.87	0.26	-0.27	-1.380	-0.778	-0.501	-
1h	3-OCH_3	-0.02	7.87	0.26	0.12	-1.380	-1.380	-0.501	-0.501
1i	2-OC_2H_5	0.38	12.47	0.22	-0.24	-1.079	-	0.410	-
1j	4-Cl	0.71	6.03	0.41	0.23	-1.079	-1.255	0.410	-0.501
1k	4-OCH_3	-0.02	7.87	0.26	-0.27	-1.079	-1.079	-0.035	-0.035
1l	3-CH_3	0.56	5.65	-0.04	-0.07	-1.380	-1.079	-0.501	-0.035
2a	2-CH_3	0.56	5.65	-0.04	-0.17	-1.079	-0.903	-0.035	0.410
2b	2,4-$(CH_3)_2$	1.12	11.30	-0.08	-0.34	-1.079	-1.255	0.410	1.380
2c	2,5-$(OCH_3)_2$	-0.04	15.74	0.52	-0.15	-1.079	-	0.410	-
2d	3-OCH_3	-0.02	7.87	0.26	0.12	-	-0.778	-	1.380
2e	4-OC_2H_5	0.38	12.47	0.22	-0.24	-1.079	-0.778	-0.035	1.380
2f	4-Cl	0.71	6.03	0.41	0.23	-	-1.079	-	-0.035
2g	4-OCH_3	-0.02	7.87	0.26	-0.27	-	-0.778	-	-
2h	4-CH_3	0.56	5.65	-0.04	-0.17	-	-0.903	-	0.410
2i	H-	-	1.03	-	-	-1.079	-	0.410	-
3a	2-CH_3	0.56	5.65	-0.04	-0.17	-1.079	-	-0.035	-
3b	-CH_2-C_6H_5	0.05	4.65	-	-	-1.079	-1.380	0.410	-0.501
3c	3-OCH_3	-0.02	7.87	0.26	0.12	-1.380	-	-0.035	-
3d	2-OC_2H_5	0.38	12.47	0.22	-0.24	-1.079	-1.255	0.410	-0.035
3e	4-OC_2H_5	0.38	12.47	0.22	-0.22	-1.079	-1.079	-0.035	-0.035
3f	2-OCH_3	-0.02	7.87	0.26	-0.27	-1.255	-0.778	-0.501	0.410
3g	3-CH_3	0.56	5.56	-0.04	-0.07	-0.903	-	0.410	-
3h	H-	-	1.03	-	-	-	-1.079	-	-0.035
4a	2-CH_3	0.56	5.65	-0.04	-0.17	-1.079	-	0.410	-
4b	-CH_2-C_6H_5	0.05	4.65	-	-	-1.079	-	-0.035	-
4c	2-OC_2H_5	0.38	12.47	0.22	-0.24	-1.380	-1.079	-0.501	0.410
4d	4-Cl	0.71	6.03	0.41	0.23	-1.079	-	-0.035	-
4e	2,5-$(OCH_3)_2$	-0.04	15.74	0.52	-0.15	-0.778	-1.255	1.380	-0.501
4f	3-CH_3	0.56	5.56	-0.04	-0.07	-0.778	-	0.410	-
4g	4-CH_3	0.56	5.56	-0.04	-0.17	-0.778	-0.778	0.410	0.410

Res (R= 0.664; $F_{1,9\ \alpha\ 0.001}$= 5.12; $F_{1,9}$ =2.372) eqn. 17 and with Polar + Res (R= 0.659; $F_{1,9\ \alpha\ 0.001}$= $F_{1,9}$ =2.297) Eqn. 18, (**Table III**).

However, with the limitation of the data set of seven compounds for two parameter equation, it needs more exploration for establishing the reliability of this model. Overall QSAR analysis in the total set of molecules with or without indicator variables for each set of compounds were also carried out, but it also did not yield statistically significant equations describing >50% variation of activity with physico-chemical parameter (**Table IV**). It also indicated that the 2-(2-(4-chlorophenyl)acetyl)-*N*-arylhydrazine-carbothioamides **1** has highest contribution for log 1/MIC_E activity.

Experimental Section

Melting points were taken in open capillaries using paraffin bath and are uncorrected. IR spectra were recorded on a FTIR-Shimadzu-8201pc (ν_{max} in cm^{-1});

Table III — Equations derived for regression analysis

Eq. No.	Equations	Statistics N	r	s	F
1	$\log 1/MIC_E = 0.328(\pm0.037)\log P_E - 1.18(\pm0.021)$	12	0.942	0.071	78.396
2	$\log 1/MIC_E = 0.281(\pm0.155)\log P_E - 1.147(0.051)$	07	0.631	0.130	3.308
3	$\log 1/MIC_E = 0.317(\pm0.095)\log P_E - 1.065(\pm0.057)$	07	0.831	0.139	11.116
4	$\log 1/MIC_E = 0.328(\pm0.039)\log P_E - 1.144(\pm0.019)$	31	0.845	0.104	72.469
5	$\log 1/MIC_S = 0.317(\pm0.056)\log P_S - 1.146(\pm0.033)$	08	0.918	0.094	31.940
6	$\log 1/MIC_S = 0.244(\pm0.056)\log P_S - 1.095(\pm0.052)$	07	0.889	0.091	18.813
7	$\log 1/MIC_S = 0.659(\pm0.144)\log P_S - 1.089(\pm0.042)$	05	0.935	0.093	20.921
8	$\log 1/MIC_S = 0.359(\pm0.286)\log P_S - 1.076(\pm0.127)$	03	0.782	0.213	1.570
9	$\log 1/MIC_S = 0.304(\pm0.037)\log P_S - 1.124(\pm0.033)$	23	0.875	0.108	68.611
10	$\log 1/MIC_S = -0.359(\pm0.249)\pi - 1.029(\pm0.089)$	9	0.477	0.223	2.067
11	$\log 1/MIC_S = 0.038(\pm0.016)MR - 1.424(\pm0.148)$	9	0.676	0.187	5.884
12	$\log 1/MIC_S = 0.558(\pm0.398)Polar - 1.229(\pm0.134)$	8	0.497	0.231	1.967
13	$\log 1/MIC_S = -0.398(\pm0.201)Res - 1.247(\pm0.112)$	8	0.629	0.207	3.919
14	$\log 1/MIC_S = -0.494(\pm0.359)\sigma - 1.140(\pm0.093)$	8	0.490	0.232	1.897
15	$\log 1/MIC_S = 0.418(\pm0.446)Polar - 0.068(\pm0.156)\pi - 1.167(\pm0.170)$	9	0.561	0.227	1.376
16	$\log 1/MIC_S = -0.408(\pm0.352)\sigma - 0.127(\pm0.119)\pi - 1.095(\pm0.103)$	9	0.598	0.220	1.671
17	$\log 1/MIC_S = -0.043(\pm0.132)\pi - 0.359(\pm0.229)Res - 1.216(\pm0.143)$	9	0.664	0.205	2.372
18	$\log 1/MIC_S = 0.070(\pm0.496)Polar - 0.369(\pm0.301)\ Res - 1.204(\pm0.102)$	9	0.659	0.207	2.297

Where, N = No. of compounds, r = Correlation coefficient,
s = Standard error of tolerance, F = Fraction ration.

Table IV — Correlation matrix

	$\log 1/MIC_E$	π	σ	MR	Polar	Res
$\log 1/MIC_E$	1.000					
π	-0.426	1.000				
σ	0.290	-0.324	1.000			
MR	0.045	-0.869	0.257	1.000		
Polar	-0.509	0.323	-0.532	-0.133	1.000	
Res	0.049	0.466	-0.362	0.539	0.563	1.000

^{1}H NMR spectra were recorded on a Bruker Advance 200 FT-NMR spectrometer using $CDCl_3$ as a solvent and Mass spectra carried out on Applied Bio system Qtrap LC-Mass spectrometer respectively. Elemental analysis of all the compounds was performed on Heracus CHN-Rapid analyzer and the results were within ±0.4% of theoretical values. Purity was checked by TLC using TLC aluminum sheet coated with silica gel 60, supplied by E. Merck. The spots were located by keeping the plates in iodine vapor. Aryl isothiocyanates, 4-chlorophenyl acetyl hydrazine and 2-(2-(4-chlorophenyl)acetyl)-*N*-arylhydrazine-carbothioamides **1** were prepared by the literature method[28].

Preparation of 2-(2-(4-chlorophenyl)acetyl)-*N*-*o*-tolylhydrazinecarbothioamide 1a

An ethanolic solution of 4-chlorophenyl acetyl hydrazine (0.01 mole) and *o*-tolyl isothiocyanate (0.01 mole) was refluxed for 4 hr. The resulting solution was cooled and solid obtained was re-crystallized from DMF, m.p. 161°C; yield: 78%.

IR (KBr): 3270 (-N-H str., secondary amide), 3110 (-C-H str., aromatic), 2740 (-C-H str., methyl), 1690 (>C=O str., acetamido), 1610 (-C=C-, aromatic), 1420 (-C-H bending, methylene), 1280 and 1150 (>C=S str., thioamide), 1090 and 1010 (>C=S str., thioketone), 769.40 (-N-H bending, -NH-CS-NH-). ^{1}H NMR ($CDCl_3$): δ 3.65 (s, 3H, $-CH_3$), 3.89 (s, 2H, -

CH_2-), 7.125-7.32 (m. 8H, Ar-H), 9.6 (s, 2H, -NH-NH-), 9.8 (s, 1H, -CS-NH-). LC-MS: *m/z* 334.07 with 39% relative intensity [M^+].

Other compounds **1b-l** of the series was prepared by same procedure. Physical constants and their antibacterial activity data are reported in **Table I**.

Preparation of 5-(4-chlorobenzyl)-4-*o*-tolyl-4*H*-1,2,4-triazole-3-thiol 2a

To the aqueous solution of sodium hydroxide (10% 40 mL) was added in 2-(2-(4-chlorophenyl)acetyl)-*N*-*o*-tolylhydrazinecarbothioamide **1a** (0.01 mole) and the reaction mixture refluxed gently for 2 hr. The resulting solution was treated with charcoal, cooled and filtered. The filtrate was acidified with 10% HCl and adjusted *p*H 5 to 6. The solid mass was precipitated, filtered, washed with ice-cold water, and re-crystallized from ethanol (99.9%), m.p. 216°C; Yield: 70%. IR (KBr): 2780 (-C-H str., methyl), 2485 (-S-H str., thiol),1680 (>C=N str., thiazole ring), 1575 (-C=C-, aromatic), 1480-1450 (-C-H bending, -CH_2-), 1400 (-C-H, methylene), 1150 (>C=N bending, heterocyclic), 820 (-C-S str., thiol), 800 (-C-H bending, disubstituted benzene). ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 1H, -SH), 2.65 (s, 3H, -CH_3), 3.84 (s, 2H, -CH_2-), 6.85-7.30 (m. 8H, Ar-H). LC-MS: *m/z* 316.06 with 19% relative intensity [M^+].

Other compounds **2b-i** of the series were prepared by same procedure. Physical constants and their antibacterial activity data are reported in **Table I**.

Preparation of 5-(4-chlorobenzyl)-*N*-*o*-tolyl-1,3,4-thiadiazol-2-amine 3a

2-(2-(4-chlorophenyl)acetyl)-*N*-*o*-tolylhydrazine-carbothioamide **1a** (0.01 mole) was dissolved with cooling in con. H_2SO_4 and the contents were kept at room temperature for 3 hr, stirred it occasionally and than poured onto crushed ice. The resulting solid was re-crystallized from ethanol (99.9%), m.p. 120°C, yield: 80%. IR (KBr): 3300 (-N-H str., secondary amide), 3080 (-C-H str., aromatic), 2740 (-C-H str., methyl), 1625 (>C=N str., acetamido), 1520 (-C=C-, aromatic), 1450 (-C-H bending, methylene), 1030 (-C-N str., aliphatic amine), 840 (-C-S str.). ^{1}H NMR ($CDCl_3$): δ 2.62 (s, 3H, -CH_3), 3.82 (s, 2H, -CH_2-), 7.10-7.40 (m. 8H, Ar-H), 9.6 (s, 1H, -N-H-). LC-MS: *m/z* 315.07 with 65% relative intensity [M^+].

Other compounds **3b-h** of the series were prepared by same procedure. Physical constants and their antibacterial activity data are reported in **Table I**.

Preparation of 5-(4-chlorobenzyl)-*N*-*o*-tolyl-1,3,4-oxadiazol-2-amine 4a

To the alcoholic solution of 2-(2-(4-chlorophenyl)-acetyl)-*N*-*o*-tolylhydrazinecarbothioamide **1a** (0.01 mole) was added into 10 mL 10% NaOH with cooling and shaking iodine solution in KI (10%) was added gradually and shaking until the iodine color persisted. Heating was continued for 5 hr and it was concentrated. The residue was cooled and poured onto ice-cold water. The solution was filtered and acidified with 10% HCl to isolate the product. It was filtered, washed with cold water, and little amount of carbon disulphide was added. The product was re-crystallized from ethanol (99.9%), m.p. 168 °C, yield: 75%. IR (KBr): 3288 (-N-H str., secondary amide), 3020 (-C-H str., aromatic ring), 2740 (-C-H str., methyl), 1550 (-N-H bending, secondary amine), 1460 (-C-H bending, methylene), 1220 (>C=N str., heterocyclic ring), 1140 (-C-O-C- str., heterocyclic ether, oxadiazole ring), 860 (-N-Cl str., mono chloro). ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 3H, -CH_3), 3.9 (s, 2H, -CH_2-), 7.09-7.35 (m. 8H, Ar-H), 9.2 (s, 1H, -N-H-). LC-MS: *m/z* 301.08 with 32% relative intensity [M^+].

Other compounds **4b-g** of the series were prepared by same procedure. Physical constants and their antibacterial activity data are reported in **Table I**.

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