Indian Journal of Chemistry
Vol. 47B, July 2008, pp. 1135-1144

Synthesis and QSAR studies of 4-oxo-thiazolidines and 2-oxo-azetidines as potential antibacterial agents

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Accepted 15 March 2008

Several 2-(4-chlorophenyl)-*N*-(4-oxo-2-aryl(l,3,thiazolidin-3-yl))acetamides **2**, *N*-[3-chloro-4-(2-aryl)-2-oxo-azetidinyl]-2-(4-chlorophenyl)acetamides **3**, *N*-(4-oxo-2-aryl(1,3,-thiadiazolidin-3-yl){4-[5-oxo-2-phenyl-4-(phenylmethylene) (2-imidazolinyl)phenyl}carboxamides **7** and *N*-(3-chloro-2-oxo-4-arylazetidinyl){4-[5-oxo-2-phenyl-4-(phenylmethylene)(2-imidazolinyl)] phenyl}carboxamides **8** have been synthesized and evaluated for their antibacterial activity against gram +ve and gram -ve bacteria i.e. *S. aureus* and *E. coli*. Most of the compounds are showed moderate to good activity against gram +ve and gram -ve bacteria. The QSAR studies of these compounds have been carried out in terms of structural and physicochemical parameters where positive contribution of substituents present at position-3 of *N*-[3-chloro-4-(2-aryl)-2-oxo-azetidinyl]-2-(4-chlorophenyl)acetamides with bulkier group indicating increase in hydrophobicity or steric bulk character.

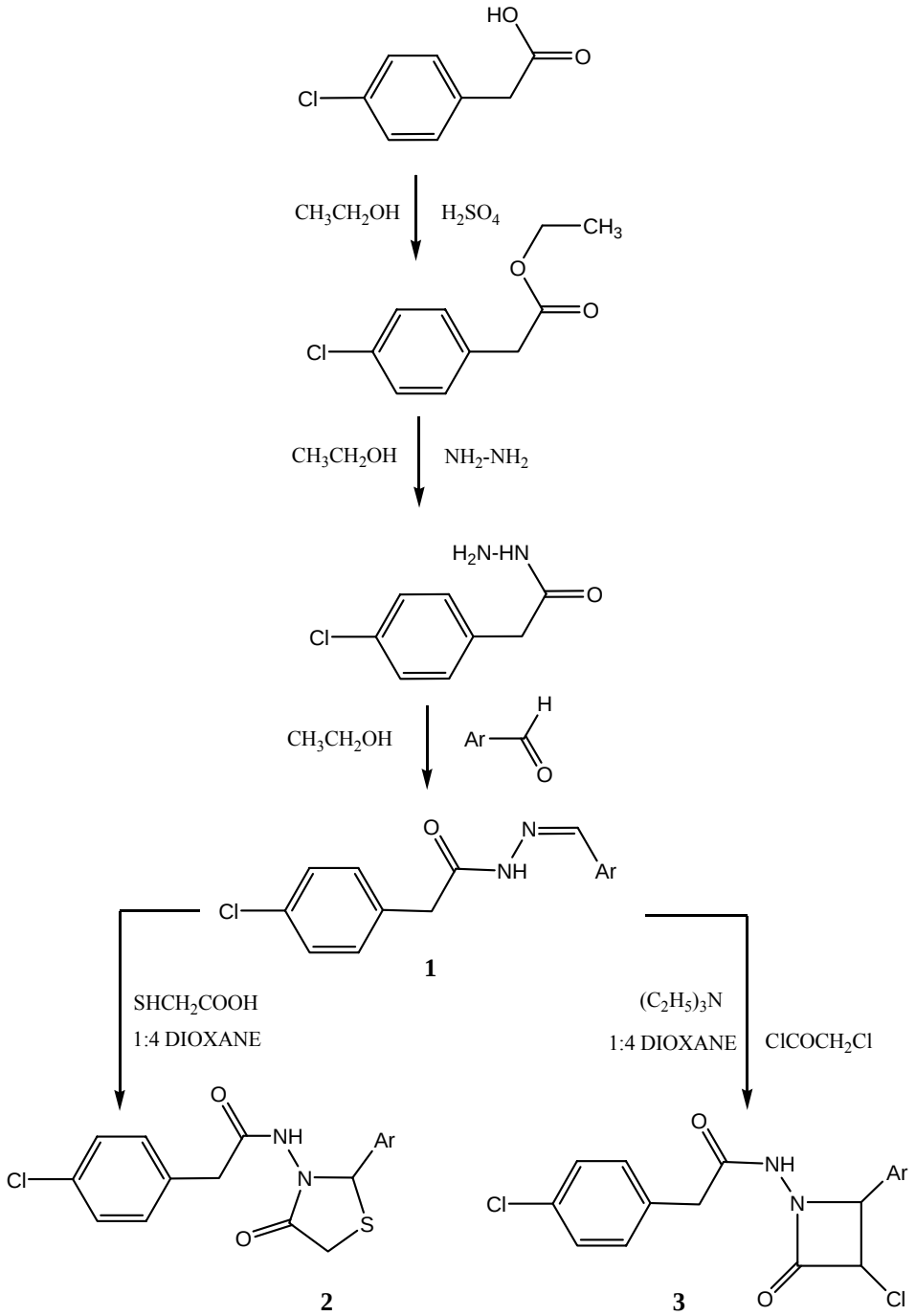
Keywords: 4-Oxo-thiazolidines, 2-oxo-azetidines, antibacterial activity, linear free energy relationship (LFER), QSAR study

Antibacterial and antifungal diseases are very common all over the world. Currently used antimicrobial agents are not very useful due to the resistance developed by the microbes. Over and above there is no permanent structure and activity relationship between the pharmacophore groups and heterocyclic frame work. In continuation to this, it is an ongoing effort to synthesize new antimicrobial agents. During last two decades there has been tremendous progress in computational chemistry and Computer Aided Drug Design (CAD) which has played a major role for the search of new chemical entities. This technique is much popularized among the medicinal chemists. QSAR studies of the bioactive molecules are useful for the optimization of the lead molecules. Therefore the present paper reports the QSAR studies of the two different heterocyclic moieties i.e. 4-oxo-thiazolidines and 2-oxo-azetidines.

4-Oxo-thiazolidines and 2-oxo-azetidines have been found to be structurally as well as pharmacologically important. 4-Oxo-thiazolidines and 2-oxo-azetidines have shown diverse biological activities such as anesthetic, analgesic, hypnotic, sedative, anticonvulsant, antitubercular, spasmopreventive, bactericidal, pesticidal, fungicidal, insecticidal, antithyrodial, antibacterial, antifungal, anticonvulsant, anti-inflammatory and antithrombin[1–11]. In view of these findings new 4-oxo-thiazolidines and 2-oxo-azetidines derivatives have been synthesized and tested against *S. aureus* and *E. coli* respectively. The synthesis, biological activity and their QSAR studies are reported in this paper.

Chemistry

Various 2-(4-chlorophenyl)-*N*-(4-oxo-2-arylthiazolidin-3-yl)acetamides **2 (Scheme I)** and *N*-(4-oxo-2-aryl(l,3,thiazolidin-3-yl)){4-[5-oxo-2-phenyl-4(phenylmethylene) (2-imidazolinyl)phenyl} carboxamides (ref. 12-16, **Sheme II**)[12-16] **7** were prepared by the cyclization of (Z)-*N*'-arylidene-2-(4-chlorophenyl)-acetohydrazides **1** and *N*-(l-aza-2-arylvinyl){4-[5-oxo-2-phenyl-4-(phenyl methelene) (2-imidazolinyl)-phenyl}carboxamides **6** in presence of thioglycolic acid and 1:4 dioxane. *N*-(3-chloro-2-oxo-4-aryl-azetidin-1-yl)-2-(4-chlorophenyl)acetamides **3** and



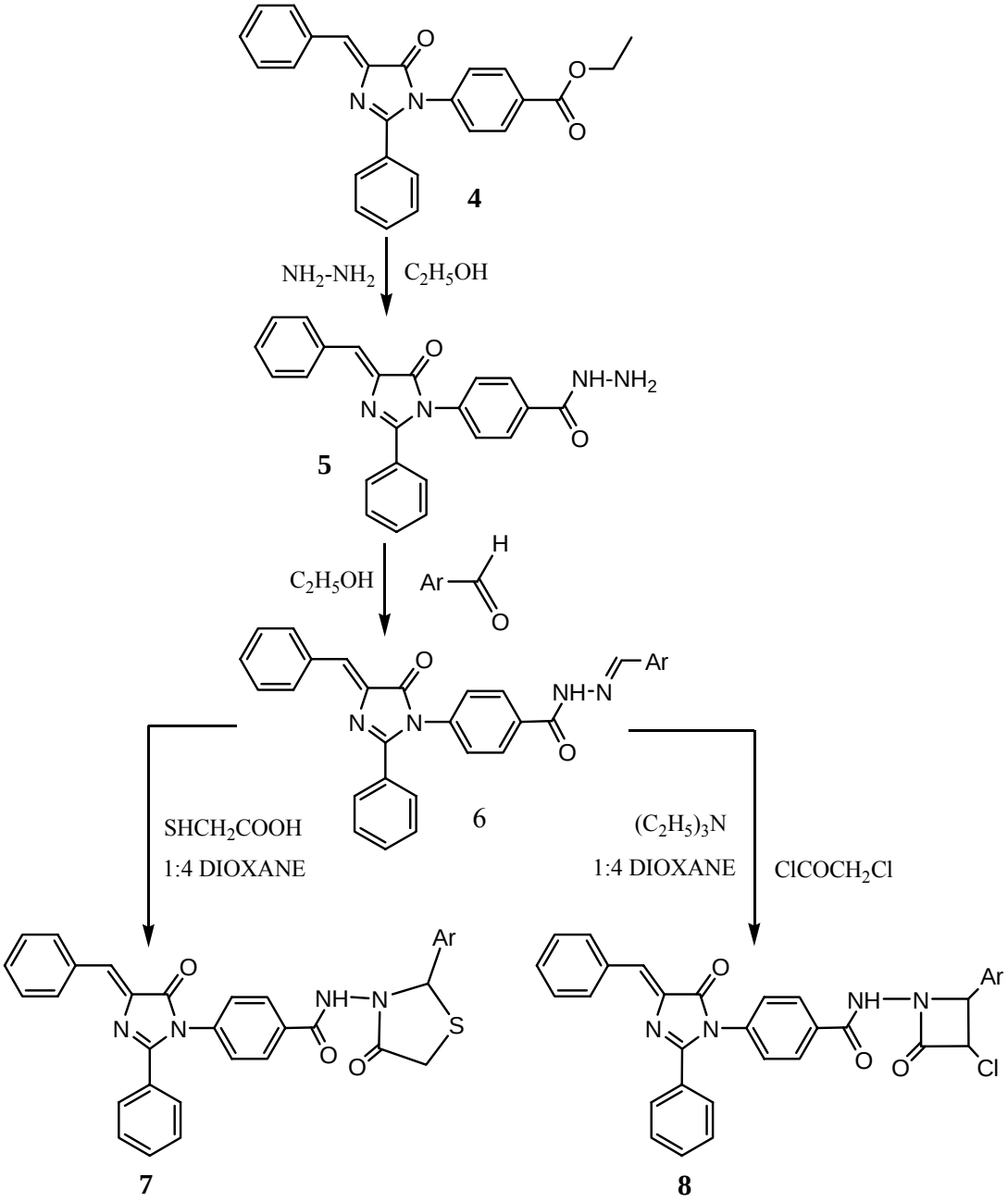
Where, Ar = Different aryl groups

Scheme I

N-(3-chloro-2-oxo-4-arylazetidinyl){4-[5-oxo-2-phenyl-4-(phenylmethylene)(2-imidazolinyl)] phenyl}-carboxamides **8** (ref 17-19) were prepared by the reaction of compound **1** and compound **6**, in presence of 2-chloroacetylchloride, triethylamine and 1:4 dioxane. Compounds **1** and **6** (**Tables I** and **II**) were prepared by the condensation reaction of 4-chlorophenyl acetyl hydrazine and *N*-amino{4-[5-oxo-2-aryl-4-(phenylmethylene)(2-imidazolinyl)] phenyl carboxamides with different aryl aldehydes in ethanol (95%).

QSAR studies

In order to establish the quantitative structural activity relationship (QSAR)[20-25], the antibacterial activity measured in the form of Minimum Inhibitory



Where, Ar = Different aryl groups

Scheme II

Concentration (MIC) [*E. coli* (MIC_E) and *S. aureus* (MICs)] and transformed into percent zone of inhibition in mm at fixed concentration for the *E. coli* and *S. aureus* was correlated to check the complimentary nature of the two 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 logPs) of both the activity and Minimum Inhibitory Concentration log(l/MIC) [log (l/MIC_E or log (1/MICs)] for *E. coli* and *S. aureus* respectively. The correlation analyses between the two models $logP_{E/S}$ for each type of molecules **(2a-h**, **3a-i**, **7a-j** and **8a-c)** were carried out separately and are described in **Table III**. The examination of correlation data for antibacterial activity against *E. coli*, each type of compounds **(2**, **3**, **7** and **8)** in eqs. nos. 1-4 respectively suggest the same dependence on each

other with different slope and intercept values. Hence, all the data were analyzed together and the derived eqs. no. 5 which describes statistically significant correlation between two models of antibacterial activity against *E. coli* with moderate correlation coefficient value (R=0.753) of high statistical significance ($F_{1, 27}$ $\alpha_{0.001}$ = 7.56; $F_{1, 27}$ = 32.733) and for *S. aureus* showed correlation coefficient value (R=0.639) of statistical significance ($F_{1, 28}$ $\alpha_{0.001}$ = 7.56; $F_{1, 28}$ = 17.918). However, similar correlation analysis with antibacterial activity data for *S. aureus* show good correlation either in individual sets for each type of compounds **(2**, **3**, **7** and **8)** in (eq. nos. 6-9) respectively or in combined set of all compounds (eq. no. 10).

In view of above and MIC being a better indicator of antibacterial activity log ($l/MIC_{E/S}$) was used as a dependent variable against different physicochemical parameters, hydrophobic (π), electronic (σ, Polar, Res) and steric (MR) as independent variable for deriving quantitative structure activity relationships in all the four type of molecules. It appears from the explanation of eqs. nos. 16 to 19 that substitution are at position 1 of thiazolidine with bulkier group indicating that log ($1/MIC_E$) increase in hydrophobic or steric bulk in the aryl part at 1 position of thiazolidine **7** and decrease in electropositive character. However with the limitation of the data set of nine compounds for two parameter equation, it needs more exploration for establishing the reliability of this model. Over all QSAR analyses 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 parameters. It also indicated that among the four variations at 1-position of thiazolidines and 2-oxo-azetidines **(2**, **3**, **7** and **8)** the substitution *N*-{4-[5-oxo-2-phenyl-4-(arylmethylene) (2-imidazolinyl)] phenyl carboxamides have highest contribution for log(I/MIC_E) activity.

The correlation analyses between the two models $logP_{E/S}$ and log($l/ MlC_{E/S}$) for each type of molecules **(2a-h**, **3a-i**, **7a-j** and **8a-c)** were carried out separately and are described in **Table IV**. Preliminary structure activity analysis in terms of the correlation between log($l/MIC_{E/S}$) as dependent parameter and hydrophobic (π), electronic (σ, Polar, Res) and steric (MR) as independent parameters in each group of compounds **(2a-h**, **3a-i**, **6a-j** and **7a-c)** showed poor correlation (R < 0.412) of less than 85 % significance. However, in case of 2-(4-chlorophenyl)-*N*-(4-oxo-2-*p*-tolylthiazolidin-3-yl)acetamide **2a** there were some correlation of log($1/MIC_E$) with π(0.581), Res(0.244), σ(R=0.237). In this set there were some correlation between log($1/MIC_S$) with π (R=0.490), MR (R = 0.617) **Table V**. In this set of molecules **2a-k** the 3-nitro compound **2h** always behaved as an out liner and its exclusion from the analysis improved the correlation significantly (**Table V**, eqs. nos 11-15). There were some correlation of log($1/MIC_E$) with MR (R = 0.756), Poalr (R= 0.344), Res (R = 0.432) and σ (R=0.455) and also showed correlation with log(1/MICs) with MR (R=0.128), Polar (R=0.608), σ (R=0.533). All the data shown in **Table V** (eqs. nos. 16 - 22). *N*-(4-oxo-2-aryl(l,3-thiazolidin-3-yl)){4-[5-oxo-2-phenyl-4-(phenylmethylene)(2-imidazolinyl)] - phenyl}carboxamides showed good correlation of log($1/MIC_E$) with π (R=0.117), MR (R=0.190), Polar (R=0.683), Res (R=0.452) and σ (R=0.730) and log(1/MICs) with π (R=0.657), MR (R= 0.228), Polar (R =0.344), Res (R=0.302) and σ (R=0.399). The derived equations are reported in **Table VI** (eqs. nos. 23 - 31). It was observed that log($1/MIC_E$) showed best correlation with σ (R=0.730) of >90% statistical significance ($F_{1, 9\ \alpha\ 0.001}$ = 5.12; $F_{1, 9}$ = 7.969) followed by the correlations with electronic polar (R=0.683), Res (R= 0.452) parameters. In view of some inter correlation between MR and Polar (R=0.724) in **Table VII**, 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 hydrophobic or steric bulk. These correlation indicated that variation of the log($1/MIC_E$) was more influenced by hydrophobic (π) than steric (MR) parameter along with decreasing order of influence of the electronic parameters (σ, Res or Polar). Among the different equations generated the best correlation of log($1/MIC_E$) was obtained with molar steric parameter in this data set, MR + Polar with high correlation coefficient value (R=0.724) of >90% statistical significance ($F_{1, 10}$ $\alpha_{0.001}$ = 4.96; $F_{1,10}$ = 3.864) eqs. no. 32, MR + σ (R = 0.631) eq. no. 33, MR + Res (R = 0.397) eqs. no. 34 (**Table VII)**.

It appears from the examination of eqs. nos. 32-34 that substitution in the aryl part at position 1 of 2-oxo-azetidines **3** with groups having increased hydrophobicity or steric bulk and electropositive character should result in the increase of antibacterial activity i.e. the log($1/MIC_E$) and log(1/MICs) values. However, with the limitation of the data set of

Table I — Physical constants of *N*-(l-aza-2-arylvinyl)-2-(4-chlorophenyl)acetamides **1a-n** and *N*-(l-aza-2-arylvinyl){4-(5-oxo-2-phenyl-4-(phenylmethylene)(2-imidazolinyl)phenyl} carboxamides **6a-k**

Compd	Ar-	Mol. formula	m.p. ºC	% of Nitrogen	
				Found	Required
1a	4-CH_3-C_6H_4	$C_{16}H_{15}N_2OCl$	175	9.75	9.77
1b	4-OCH_3-C_6H_4	$C_{16}H_{15}N_2O_2Cl$	142	9.24	9.26
1c	-CH=CH-C_6H_5	$C_{17}H_{15}N_2OCl$	181	9.78	9.37
1d	2-OH-C_6H_4	$C_{15}H_{13}N_2O_2Cl$	218	9.71	9.70
1e	2-OH-5-Br-C_6H_3	$C_{15}H_{12}N_2O_2ClBr$	222	7.60	7.62
1f	2-Cl-C_6H_4	$C_{15}H_{12}N_2OCl_2$	146	9.05	9.12
1g	4$(CH_3)_2$-N-C_6H_4	$C_{17}H_{18}N_3OCl$	234	13.30	13.31
1h	3-OCH_3-4-OH-C_6H_3	$C_{16}H_{15}N_2O_3Cl$	182	8.94	8.79
1i	4-Cl-C_6H_4	$C_{15}H_{12}N_2OCl_2$	170	9.06	9.12
1j	4-OH-C_6H_4	$C_{15}H_{13}N_2O_2Cl$	89	9.67	9.70
1k	3-OH-C_6H_4	$C_{15}H_{13}N_2O_2Cl$	105	9.69	9.71
1l	3-NO_2-C_6H_4	$C_{15}H_{12}N_3O_3Cl$	155	13.20	13.23
1m	2,4-$(Cl)_2$- C_6H_3	$C_{15}H_{11}N_2OCl_3$	200	8.14	8.20
1n	3-OCH_3-4-OH-5-Br-C_6H_2	$C_{16}H_{14}N_2O_3ClBr$	230	7.00	7.04
6a	4-CH_3-C_6H_4	$C_{31}H_{24}N_4O_2$	158	11.55	11.56
6b	4-OCH_3-C_6H_4	$C_{31}H_{24}N_4O_3$	169	11.18	11.20
6c	2-OH-C_6H_4	$C_{30}H_{22}N_4O_3$	158	11.27	11.29
6d	2-OH-5-Br-C_6H_3	$C_{30}H_{21}N_4O_3Br$	111	9.89	9.91
6e	2-Cl-C_6H_4	$C_{30}H_{21}N_4O_2Cl$	135	10.95	10.97
6f	4$(CH_3)_2$-N-C_6H_4	$C_{32}H_{27}N_5O_2$	105	13.63	13.64
6g	3-OCH_3-4-OH-C_6H_3	$C_{31}H_{24}N_4O_4$	132	11.44	11.48
6h	4-Cl-C_6H_4	$C_{30}H_{21}N_4O_2Cl$	120	10.93	10.97
6i	4-OH-C_6H_4	$C_{30}H_{22}N_4O_3$	116	11.27	11.29
6j	3-OH-C_6H_4	$C_{30}H_{22}N_4O_3$	128	11.24	11.29
6k	4-NO_2-C_6H_4	$C_{30}H_{21}N_5O_4$	110	13.56	13.59

9 compounds for two parameters equation it needs more exploration for establishing the reliability of this model. Over all QSAR analysis in the total set of molecules with or without indicator variables for each set of compounds were also carried out however it yielded statistically insignificant equations describing > 50% variation of activity with physicochemical parameters. It also indicated that among the four variations at 1-position of 2-oxo-azetidines **3** the substitution by 4-chlorophenyl acetamides has highest contribution for log(1/MIC_E) and log(1/MICs) activity.

Biological evaluation

The compounds **(2a-h, 3a-i, 7a-j** and **8a-c)** were screened against gram +ve and gram -ve bacteria i.e. *S. aureus* and *E. coli* by cup plate method[26]. As compared to the standard drug ciprofloxacin, these compounds showed moderate to good antibacterial activity.

Experimental Section

Melting points were taken in open capillaries using paraffin-bath and are uncorrected. IR spectra were record on Bachman spectrophotometer (mul-nujol method, cm^{-1}), PMR spectra on Brucker Avance DPX 200 MHZ instrument (chemical shift in δ ppm) using TMS as internal reference. Purity of all the compounds was checked by TLC on silica gel G plates. The spots were located by keeping the plates in iodine vapour. All the compounds were analyzed for carbon, hydrogen and nitrogen and the result were within ± 0.4 % of calculated values.

Preparation of *N*-(l-aza-2-(4-methylphenylvinyl)-2-(4-chlorophenyl)acetamide la

A mixture of 4-chlorophenyl acetyl hydrazine (0.01 moles), 4-methylbenzaldehyde (0.01 moles) and ethanol (95%, 35-40 mL) was refluxed for 3 hr. The excess of solvent was removed by distillation and the

Table II — Physical constants and antibacterial activity of 4-oxo-thiazolidines **2a-h** and **7a-j** and 2-oxo-azetidines **3a-i** and **8a-c**

Compd	Ar-	Mol. formula	m.p. ºC	MIC mg/liter		Zone of inhibition in mm at conc. of 10 µg/mL	
				E. coli	*S. aureus*	*E. coli*	*S. aureus*
2a	4-CH_3-C_6H_4	$C_{18}H_{17}N_2O_2ClS$	140	18	24	++	+
2b	2-OH-C_6H_4	$C_{17}H_{15}N_2O_3ClS$	300(d)	-	8	-	+
2c	2-OH-5-Br-C_6H_3	$C_{17}H_{14}N_2O_3ClBrS$	198	24	24	+	+
2d	2-Cl-C_6H_4	$C_{17}H_{14}N_2O_2Cl_2S$	168	8	18	+++	++
2e	4$(CH_3)_2$-N-C_6H_4	$C_{19}H_{20}N_3O_2ClS$	300(d)	12	24	+++	+
2f	3-OCH_3-4-OH-C_6H_3	$C_{18}H_{17}N_2O_4ClS$	300(d)	6	24	+++	+
2g	4-Cl-C_6H_4	$C_{17}H_{14}N_2O_2Cl_2S$	300(d)	24	24	+	+
2h	3-NO_2-C_6H_4	$C_{17}H_{14}N_3O_4ClS$	197	18	24	++	+
3a	4-CH_3-C_6H_4	$C_{18}H_{16}N_2O_2Cl_2$	300(d)	18	24	++	++
3b	4-OCH_3-C_6H_4	$C_{18}H_{16}N_2O_3Cl_2$	300(d)	24	8	+	+++
3c	2-OH-5-Br-C_6H_3	$C_{17}H_{13}N_2O_3Cl_2Br$	228	14	16	++	++
3d	4$(CH_3)_2$-N-C_6H_4	$C_{19}H_{19}N_3O_2Cl_2$	165	6	12	+++	++
3e	3-OCH_3-4-OH-C_6H_3	$C_{18}H_{16}N_2O_4Cl_2$	295	8	24	+++	+
3f	4-Cl-C_6H_4	$C_{17}H_{13}N_2O_2Cl_3$	160	18	24	++	+
3g	3-OH-C_6H_4	$C_{17}H_{14}N_2O_3Cl_2$	320(d)	24	-	+	-
3h	2,4-$(Cl)_2$- C_6H_3	$C_{17}H_{12}N_2O_2Cl_4$	240	10	24	+++	+
3i	3-OCH_3-4-OH-5-Br-C_6H_2	$C_{18}H_{15}N_2O_4Cl_2Br$	300(d)	-	24	-	+
7a	2-OH-C_6H_4	$C_{32}H_{24}N_4O_4S$	145	12	24	++	+
7b	4-OCH_3-C_6H_4	$C_{33}H_{26}N_4O_4S$	230	12	18	++	++
7c	4-CH_3-C_6H_4	$C_{33}H_{26}N_4O_3S$	92	8	18	+++	++
7d	2-OH-5-Br-C_6H_3	$C_{32}H_{23}N_4O_4BrS$	230	12	12	++	++
7e	2-Cl-C_6H_4	$C_{32}H_{23}N_4O_3ClS$	215	18	12	++	++
7f	4$(CH_3)_2$-N-C_6H_4	$C_{34}H_{29}N_5O_3S$	300(d)	10	18	+++	++
7g	4-Cl-C_6H_4	$C_{32}H_{23}N_4O_3ClS$	300(d)	12	18	++	++
7h	3-OH-C_6H_4	$C_{32}H_{24}N_4O_4S$	297	-	20	-	+
7i	4-NO_2-C_6H_4	$C_{32}H_{23}N_5O_6S$	300(d)	20	16	-	+
7j	3-OCH_3-4-OH-C_6H_3	$C_{33}H_{26}N_4O_5S$	300(d)	12	24	+++	+
8a	4-CH_3-C_6H_4	$C_{33}H_{25}N_4O_3Cl$	118	24	-	+	-
8b	2-Cl-C_6H_4	$C_{32}H_{22}N_4O_3Cl_2$	132	24	24	+	+
8c	4-Cl-C_6H_4	$C_{32}H_{22}N_4O_3Cl_2$	115	12	18	+++	++

Table III — Structural parameters of 4-oxo-thiazolidines **2a-h** and **7a-j** and 2-oxo-azetidines **3a-i** and **8a-c**

Compd	Functional Group	π	MR	Polar	σ	log(1/MIC_E)	log(1/MIC_S)	Log P_E	Log P_S
2a	4-CH_3-	0.56	5.65	-0.04	-0.17	-1.255	-1.380	-0.025	-0.501
2b	2-OH-	-0.67	2.85	0.29	-0.37	-	-0.903	-	-0.501
2c	2-OH-5-Br-	0.19	11.73	0.73	0.02	-1.380	-1.380	-0.501	-0.501
2d	2-Cl-	0.71	6.03	0.41	0.23	-0.903	-1.255	0.410	-0.035
2e	4$(CH_3)_2$-N-	0.18	15.55	0.10	-0.83	-1.079	-1.380	0.410	-0.035
2f	3-OCH_3-4-OH-	-0.69	10.72	0.55	-0.25	-0.778	-1.380	0.410	-0.501
2g	4-Cl-	0.71	6.03	0.41	0.23	-1.380	-1.380	-0.501	-0.501
2h	3-NO_2-	-0.28	7.36	0.67	0.71	-1.255	-1.380	0.410	-0.501
3a	4-CH_3-	0.56	5.65	-0.04	-0.24	-1.255	-1.079	-0.501	-0.035
3b	4-OCH_3-	-0.02	7.87	0.26	-0.27	-1.380	-0.903	-0.501	0.410
3c	2-OH-5-Br-	0.19	11.73	0.73	0.02	-1.146	-1.204	-0.035	-0.035
3d	4$(CH_3)_2$-N-	0.18	15.55	0.10	-0.83	-0.778	-1.079	0.410	-0.035
3e	3-OCH_3-4-OH	-0.69	10.72	0.55	-0.25	-0.903	-1.380	0.410	-0.501
3f	4-Cl-	0.71	6.03	0.41	0.23	-1.255	-1.380	-0.035	-0.501
3g	3-OH-	-0.67	2.85	-0.29	0.12	-1.380	-	-0.501	-
3h	2,4-$(Cl)_2$-	1.42	12.06	0.82	0.74	-1.000	-1.380	0.410	-0.501
3i	3-OCH_3-4-OH-5-Br-	0.17	19.60	0.99	-0.25	-	-1.380	-	-0.501
7a	2-OH-	0.56	5.65	-0.04	0.17	-0.903	-1.255	0.410	-0.501
7b	4-OCH_3-	-0.02	7.87	0.26	0.27	-1.079	-1.255	-0.035	-0.501
7c	4-CH_3-	-0.67	2.85	0.29	-0.37	-1.079	-1.380	-0.035	-0.501
7d	2-OH-5-Br-	0.19	11.73	0.73	-0.14	-1.079	-1.079	0.501	-0.035
7e	2-Cl-	0.71	6.03	0.41	0.23	-1.255	-1.079	-0.035	-0.035
7f	4$(CH_3)_2$-N-	0.18	15.55	0.10	-0.83	-1.000	-1.255	0.410	-0.035
7g	4-Cl-	-0.69	10.72	0.55	-0.25	-1.079	-1.255	-0.035	-0.501
7h	3-OH-	0.71	6.03	0.41	0.23	-	-1.301	-	-0.501
7i	4-NO_2-	-0.67	2.85	0.29	0.12	-1.301	-1.204	-0.035	-0.035
7j	3-OCH_3-4-OH-	-0.28	7.36	0.67	0.78	-1.079	-1.380	0.410	-0.501
8a	4-CH_3-	0.56	5.65	-0.04	-0.17	-1.380	-	-0.501	-
8b	2-Cl-	0.71	6.03	0.41	0.23	-1.380	-1.380	-0.501	-0.501
8c	4-Cl-	0.71	6.03	0.41	0.23	-1.079	-1.255	0.410	-0.035

solid product was filtered, washed with ice-cold water, dried and recrystallised from ethanol (99%), m.p. 175°C; yield: 85%. Other compounds **1b-n** of the series were prepared by a similar method. Found: C, 65.95; N, 10.14. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.06; N, 10.27%.

Preparation of 2-(4-chlorophenyl)-*N*- (4-oxo-2-*p*-tolylthiazolidin-3-yl)acetamide 2a.

A mixture of *N*-(l-aza-2-(4-methylphenylvinyl)-2-(4-chlorophenyl)acetamide **la** (0.01 mole) in an anhydrous 1:4 dioxane (25 mL) was added to thioglycolic acid (0.01 mole). The mixture was refluxed for 12 hr, cooled and poured into aqueous saturated solution of sodium bicarbonate to remove unreacted thioglycolic acid. The solid product was filtered, dried and recrystallized from ethanol (99%), m.p. 140°C; yield 72%. Found: C, 58.75; N, 7.99; Calcd. for $C_{17}H_{15}ClN_2O_2S$: C, 58.87; N, 8.08%. IR (cm^{-1}): 3100 (-N-H str., secondary amide), 3010 (-C-H str., aromatic), 2995 (-C-H str., -CH_2-), 1730 (>C=O str., thiazolidine ring), 1480 (-C=C- str., aromatic ring), 810 (-C-S-C str.).

^{1}H NMR: δ 8.641 (1H, -N-H), 7.694-6.975 (8H, Ar-H), 3.89 (2H, -CH_2-), 2.37 (3H, Ar-CH_3).

Other compounds **2b-h** of the series were prepared by same procedure and their physical constants are presented in **Table II**.

Table IV — Equations for correlations between antibacterial activity in two models

Eq. No.	Equations	Statistics			
		N	R	S	F
1	Log ($1/MIC_E$) = 0.477 (±0.204)logP_E-1.220 (±0.074)	7	0.723	0.178	5.426
2	Log ($1/MIC_E$) = 0.175 (±0.135)logP_E - 1.106 (±0.039)	9	0.440	0.115	1.680
3	Log ($1/MIC_E$) = 0.487 (±0.084)logP_E-1.116 (±0.033)	8	0.921	0.094	33.346
4	Log ($1/MIC_E$) = 0.330 (±0.000)logP_E -1 .215 (±0.000)	3	1.000	0.000	-
5	Log ($1/MIC_E$) = 0.384 (±0.063)logP_E - 1.161 (±0.025)	27	0.753	0.127	32.733
6	Log (1/MICs) = -0.037 (±0.318)logP_S -1 ,319(± 0.138)	8	0.047	0.181	0.013
7	Log (1/MICs) = 0.193 (±0. 1 33)logP_S- 1 .193 (±0.047)	10	0.456	0.098	2.106
8	Log (1/MICs) = 0.534 (±0.047)logP_S -1.110 (±0.018)	8	0.978	0.042	129.396
9	Log (1/MCs) = 0.268 (±0.000)logP_S - 1 .246 (±0,00)	2	1.000	-	-
10	Log (1/MICs) = 0.354 (±0.084)logP_S- 1 .154 (±0.033)	28	0.639	0.115	17.918

Where, N = No. of compounds, R = Correlation coefficient, S = Standard error of tolerance, F = Fraction ratio

Table V — Equations for regression analysis

Eq. No.	Equations	Statistics			
		N	R	S	F
11	Log ($1/MIC_E$) = -0.262 (± 0.199)π -1.057(±0.111)	6	0.551	0.236	1.743
12	Log ($1/MIC_E$) = -0.156 (±0.31 l)Res -1.208 (±0.192)	6	0.244	0.274	0.253
13	Log ($1/MIC_E$) = -0.151 (±0.309)σ -1.149 (±0.119)	6	0.237	0.274	0.238
14	Log (1/MICs) = -0.145 (±0.1 16) π - 1.274 (±0.067)	7	0.490	0.171	1.578
15	Log ($1/MIC_S$) = -0.025 (±0.014)MR - 1.085 (±0.132)	7	0.617	0.154	3.076
16	Log ($1/MIC_E$) = 0.041 (±0.0 15)MR- 1.479 (±0.133)	8	0.756	0.158	8.011
17	Log ($1/MIC_E$) = 0.232 (±0.258)Polar - 1.199(±0.105)	8	0.344	0.226	0.808
18	Log ($1/MIC_E$) = -0.306 (±0.261)Res- 1.302 (±0.160)	8	0.432	0.217	1.377
19	Log ($1/MIC_E$) = -0.269 (±0.215)σ- 1.166 (±0.079)	8	0.455	0.215	1.570
20	Log ($1/MIC_S$) = -0.005 (±0.015)MR- 1.174 (±0.170)	8	0.128	0.200	0.101
21	Log ($1/MIC_S$) = -0.340 (±0.181)Polar-l .078 (±0.096)	8	0.608	0.160	3.526
22	Log (1/MICs) = -0.270 (±0.175)σ- 1.264 (±0.066)	8	0.533	0.170	2.384

Where, N = No. of compounds, R = Correlation coefficient, S = Standard error of tolerance, F = Fraction ratio

Table VI — Equations for regression analysis

Eq. No.	Equations	Statistics			
		N	R	S	F
23	Log ($1/MIC_E$) = 0.026 (± 0.083)π - 1 .097 (± 0.043)	9	0.117	0.127	0.098
24	Log ($1/MC_E$) = 0.006 (± 0.012)MR- 1.144 (± 0.164)	9	0.190	0.126	0.262
25	Log ($1/MIC_E$) = -0.323 (± 0.131)Polar - 0.974 (± 0.058)	9	0.683	0.094	6.132
26	Log (MIC_E) = -0.140 (± 0.104)Res - 1 .157 (± 0.060)	9	0.452	0.114	1.793
27	Log ($1/MIC_E$)= -0.192 (± 0.068) σ - 1 .108 (± 0.030)	9	0.730	0.088	7.969
28	Log (1/MICs) = 0.121 (± 0.049) π - 1.245 (± 0.026)	10	0.657	0.083	6.069
29	Log (1/MICs) = 0.006 (± 0.009)MR - 1.290 (± 0.076)	10	0.228	0.107	0.440
30	Log (1/MICs) = 0.148 (± 0,143)Polar - 1.299 (± 0.062)	10	0.344	0.103	1.075
31	Log ($1/MIC_S$) = 0.084 (± 0.094)Res - 1.205 (± 0.055)	10	0.399	0.101	1.512

Where, N = No. of compounds, R = Correlation coefficient, S = Standard error of tolerance, F = Fraction ratio

Table VII — Equations for regression analysis

Eq. No.	Equations	Statistics			
		N	R	S	F
32	Log (l/MIC_E) = 0.011 (± 0.008)MR - 0.330 (±0.129)Polar-1.072 (±0.077)	10	0.724	0.092	3.864
33	Log (l/MIC_E) = 0.004 (± 0.009)MR - 0.157 (±0.082)σ -1.150 (±0.075)	10	0.631	0.104	2.310
34	Log (l/MIC_E) = 0.004 (± 0.012)MR - 0.099 (±0.126)Res-1.184 (±0.089)	10	0.387	0.123	0.654

Where, N = No. of compounds, R = Correlation coefficient, S = Standard error of tolerance, F = Fraction ratio

Preparation of *N*-(3-chloro-2-oxo-4-(4-methyl phenyl)azetidine)-2-(4-chlorophenyl) acetamide 3a

N-(l-aza-2-(4-methylphenylvinyl)-2-(4-chlorophenyl)acetamide **la** (0.01 mole) was dissolved in 1:4 dioxane (25 mL) with constant stirring at room temperature. Triethylamine (0.02 mole) was added slowly followed by drop wise addition of 2-chloroacetylchloride (0.02 mole). Stirring was continued for 30 minutes. The contents were transferred to round bottom flask and heated under reflux for 5 hr. The mixture was allowed to cool at room temperature, filtered to remove insoluble salt. Excess of the solvent was distilled; semi solid residue was poured over crushed ice with constant stirring. The product separated was filtered, washed with cold water, dried and recrystallized from ethanol (99%) m.p. 300°C(d); yield: 65%. Found: C, 59.35; N, 7.51. Calcd. for $C_{18}H_{16}C_{l2}N_2O_2$: C, 59.52; N, 7.71%. IR (cm^{-1}): 3370 -N-H str., secondary amide), 3000 (-C-H str., aromatic), 1680 (>C=O str., strong band cyclic, β-lactam), 1615 (>C=O str., strong band, acyclic), 1400 (-C-H bending, $-CH_2-$). ^{1}H NMR: δ 8.27 (1H, -N-H), 7.8-7.2 (8H, Ar-H), 4.32-4.10 (1H, CH-Cl of β-lactam), 2.50 (1H, -CH-Ar).

Other compounds **3b-i** of the series were prepared by the same procedure and their physical constants are presented in **Table II.**

Preparation of ethyl-4- [5-oxo-2-phenyl -4-(phenyl methylene) -2-imidazolinyl] benzoate 4

Ethyl 4-aminobenzoate (0.01 mole) was added to a solution of 2-phenyl-4-(phenylmethylene)-l,3-oxazolin-5-one (0.01 mole) in ethanol (95%, 35 mL). The reaction-mixture was refluxed for 5 hr. Excess solvent was removed by distillation and the solid residue was washed with ice-cold water, filtered, dried and recrystallized from ethanol (99%). m.p. 126°C. Found: C, 75.66; N, 7.01. Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; N, 7.07%.

Preparation of *N*-amino{4-[5-oxo-2-phenyl-4-(phenylmethylene) (2-imdazolinyl)] phenyl} carboxamide 5

4-[5-oxo-2-phenyl-4-(phenylmethenylene)2-imidazolinyl]phenyl propanoate (0.01 mole), hydrazine hydrate (99 %, 0.01 mole) and ethanol (99 %, 35 mL) were refluxed for 2.5 hr. The excess solvent was distilled and the remaining solid washed with ice-cold water, filtered, dried and recrystallized from ethanol (95 %), m.p. 140°C. Found: C, 76.66; N, 11.51; Calcd. for $C_{31}H_{24}N_4O_2$: C, 76.84; N, 11.56%.

Preparation of *N*-(l-aza-2-(4-methylphenylvinyl) {4-[5-oxo-2-phenyl-4-(phenylmethylene) (2-imidazolinyl) phenyl}carboxamide 6a

N-amino{4-[5-oxo-2-phenyl-4-(phenylmethylene) (2-imidazolinyl)phenyl}carboxamide 5 (0.005 mole), 4-methylbenzaldehyde (0.005 mole) and ethanol (95%, 30 mL) were refluxed together for 3 hr. The reaction-mixture was poured into ice-cold water and the solid formed was filtered, dried and recrystallized from ethanol (99%) m.p. 158°C; yield; 85%. Other compounds **6b-k** of the series were prepared by the same procedure.

Preparation of *N*-(4-oxo-2-(4-methylphenyl)(l,3-thiazolidin-3-yl){4-[5-oxo-2-phenyl-4-(phenyl methylene)(2-imidazolinyl)]phenyl}carboxamide 7a

Compound **6a** (0.001 mole) in anhydrous 1:4 dioxane (20 mL) was added to thioglycolic acid (0.001 mole). The mixture was refluxed for 12 hr, cooled and then poured into aqueous saturated solution of sodium bicarbonate to remove unreacted thioglycolic acid. The residue was filtered, dried and recrystallised from ethanol (99%) m.p. 92°C; yield: 73%. Found: C, 70.76; N, 9.91. Calcd. for $C_{33}H_{26}N_4O_3S$: C, 70.95; N, 10.03%. IR (cm^{-1}): 3200 (-N-H str., secondary amide), 3040 (-C-H str,, aromatic), 2840 (-C-H str.. alkyl gr.), 1745 (>C=O str., strong band cyclic), 1690 (>C=O str., cyclic imidazole), 1400 (-C-H bending, -CHz-), 1242 (-C=N str.. imidazole); ^{1}H NMR: δ 8.24 (2H, -NH), 7.21-7.1186 (18H, Ar-H), 5.5 (1H, -C=CH-), 3.82 (2H, $-CH_2-$, thiazolidine ring), 3.2 (methine proton).

Other compounds **7b-j** of the series were prepared by the same procedure and their physical constants are presented in **Table II**.

***N*-(3-chloro-2-oxo-4-methy]phenylazetidtnyl){4-[5-oxo-2-phenyl-4-(phenyl methylene)(2-imidazo-linyl)]phenyl}carboxamide 8a**

Compounds **6a** (0.005 mole) was dissolved in anhydrous 1:4 dioxane (20 mL) with constant stirring at room temperature. Triethylamine (0.01 mole) was added slowly followed by drop wise addition of 2-chloroacetylchloride (0.01 mole). Stirring was continued for 30 minutes. The contents were transferred to a round bottom flask and heated under reflux for 5 hr. The mixture was allowed to cool at room temperature and filtered to remove insoluble salt. Excess of solvent was distilled; semisolid residue was poured over crushed ice with constant stirring. The product separated was filtered, washed with saturated sodium bicarbonate solution, dried and recrystallized from ethanol (99%) m.p. 118°C; yield: 65%. Found: C, 70.46; N, 9.91. Calcd. for $C_{33}H_{25}ClN_4O_3$: C, 70.65; N, 9.99%. IR(cm^{-1}): 3240 (-N-H str., secondary amide), 3080 (-C-H str., aromatic), 2950 (-N-H str., R-CO-NH-N), 1830 (>C=O str., strong band cyclic, β-lactam), 1690 (>C=O str., strong band, cyclic), 1640 (>C=O str., strong band acyclic), 1400 (-C-N str., heterocyclic ring). ^{1}H NMR: δ 8.24 (1H, NH), 7.63-7.23 (18H, Ar-H), 5.2 1H, -C=CH-), 4.39-4.12 (1H, -CH-C1, β-lactam), 2.3 (3H, Ar-CH_3).

Other compounds **8b-c** of the series were prepared by the same procedure and their physical constants are presented in **Table II**.

Acknowledgement

The authors are thankful to the Director, CDRI, Lucknow for providing training and computer facilities and Mr. A. S. Khushwaha for excellent technical assistance in QSAR work. One of the author AMB is thankful to Dr. M T Chhabaria for his critical suggestions and MDS is thankful to Gujarat Government for providing fellowship. NCD and MDS are thankful to the authority of Bhavnagar University for providing research facilities. This work is carried out by N. C. Desai under " Career Award Scheme" and for this, he is thankful to University Grants Commission, New Delhi.

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