Digest Journal of Nanomaterials and Biostructures Vol. 4, No.1, March 2009, p. 223 - 232

QSAR, SYNTHESIS AND BIOLOGICAL ACTIVITY STUDIES OF SOME THIAZOLIDINONES DERIVATIVES

M. C. SHARMA[*a], N. K. SAHU[a], D. V. KOHALI[a], S. C. CHATURVEDI[b], SMITA .SHARMA[c]
[a]*Department Of Pharmaceutical Sciences Dr.H.S.Gour.University Sagar (M.P) 470003 India* [b]*College Of Pharmacy Ips Academy Indore (M.P) 452 001 India*
[c]*Department Of Chemistry Yadhunath Mahavidyalya Bhind (M.P) 477001 India*

Some new N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide have been synthesized by condensation of nicotinic acid hydrazide with various aromtatic or heterocyclic aldehydes to yield the Schiff bases. Cyclocondensation of schiffs bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives. The structures of the newly synthesized compounds were confirmed by analytical IR, NMR and mass spectral data. All the synthesized compounds of the series elicit remarkable activity in comparison to standard drug (ampicillin). A number of descriptors were tested to adjudge a quantitative correlation between activity and structural features. However, significant correlation has emerged between activity and physicochemical parameters viz. hydrophobic parameter (log P). Moreover, results are interpreted on the basis of multiple regression analysis and cross-validation methodology.

(Received March 5, 2009; acvcepted March 31, 2009)

Keywords: QSAR, Thiazolidinones, Antibacterial activity, Antifungal activity

1. Introduction

Nicotinic acid and its amides proved to be powerful antimicrobial agent. 4-thiazolidinones are associated with antibacterial, antifungal [1-7], and antitubercular [8-11] activities and have diverse biological activities. β-lactam compounds are of interest due to the therapeutic significance of penicillin and cephalosporin antibiotics and possess significant antibacterial ,antifungal and antitubercular activities [12-18]. 4-thiazolidinone derivatives occupy an important place in medicinal chemistry as they show a variety of microbiological activity. Therefore, an attempt was made to study the antibacterial, antifungal and antitubercular activities of 4-thiazolidinone in present investigation. Quantitative structure-activity relationship (QSAR) studies have also been performed on the basis of the fact that the biological activity of a compound is a function of its physicochemical properties[19]. For the sake of present study QSAR analysis of N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives 5a-j was performed based on the assumption of linear additive contributions of the different physicochemical properties viz., vander waals volume (VDW), connolly accessible area (CAA), connolly molecular area (CMA), Connolly solvent excluded area (CSEV), dipole-dipole energy (DDENE), partition coefficient (log P). The best-derived QSAR model was used to predict activity of the tested compounds and to suggest

* Corresponding author: mukesh2206@rediffmail.com

structural features, which should be incorporated to improve the pharmacological activity of the synthesized compounds.

2. Expermintal

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu 8201 IR spectrophotometer. NMR spectra were recorded on Bruker DPX 300 using TMS as internal standard. Mass spectra were recorded on JEOL SX 102 (FAB) mass spectrometer. All the chemicals used were of analytical grade.

Table 1. Physical constants of the synthesized compounds 4a-j and 5a-j

Compound	R	M.F.	Yield (%)	M.P.(°)
4a	2-hydroxy-4-methoxy	$C_{17}H_{17}N_3O_3$	71	185-188
4b	4-chlorophenyl	$C_{13}H_{13}ON_3Cl$	74	200-203
4c	2-nitrophenyl	$C_{16}H_{14}N_4O_4$	82	172-174
4d	4-dimethylamino phenyl	$C_{18}H20N_4O_2$	72	165-166
4e	2-chlorophenyl	$C_{16}H_{10}N_3OCl$	75	170-172
4f	Phenyl	$C_{13}H_{11}N_3O$	77	135-136
4g	Furfural	$C_{14}H_{13}N_3O_4$	69	155-156
4h	2-hydroxyphenyl	$C_{16}H_{15}N_3O_3$	72	207-209
4i	4-methoxyphenyl	$C_{17}H_{17}N_3O_4$	67	130-132
4j	3,4,5-trimethoxyphenyl	$C_{17}H_{21}N_3O_5$	65	145-146
5a	2-hydroxy-4-methoxy	$C_{17}H_{17}N_3O_3S$	66	210-212
5b	4-chlorophenyl	$C_{13}H_{13}O_2N_3SCl$	69	219-221
5c	2-nitrophenyl	$C_{16}H_{13}N_4O_4S$	72	211-214
5d	4-dimethylaminophenyl	$C_{18}H20N_4O_2S$	66	240-242
5e	2-chlorophenyl	$C_{16}H_{14}N_3O_2ClS$	75	228-229
5f	Phenyl	$C_{13}H_{11}N_3OS$	67	180-182
5g	Furfural	$C_{14}H_{13}N_3O_4S$	76	191-193
5h	2-hydroxyphenyl	$C_{16}H_{15}N_3O_3S$	82	226-231
5i	4-methoxyphenyl	$C_{17}H_{17}N_3O_4S$	86	234-236
5j	3,4,5 – trimethoxyphenyl	$C_{17}H_{21}N_3O_5S$	80	185-189

Nicotinic acid (0.01 mol) was refluxed with sulphruric acid (50 ml) and absolute alcohol (115 ml) for 10 h. and the mixture was cooled to the room temperature and poured on to the crushed ice. The mixture was then made strongly alkaline by the addition of ammonia solution.

The resulting mixture was extracted with ether solvent. The ether was then distilled off and the resultant liquid was recovered. (2) Ethyl nicotinate (0.01 mol) was condensed with hydrazine hydrate by maintaining the reaction temperature of 0^{o}. This resulted in solid nicotinic acid hydrazide. The resultant nicotinic acid hydrazide was recrystillised from warm ethanol. (3)Nicotinic acid hydrazide (0.01 mol) was refluxed were various aromatic / heterocyclic aldehydes (0.02 mol) in the presence of sulphuric acid for 6 h. The reaction mixture was then poured into the crushed ice. The resultant solid was washed with distilled water, dried in vacuum and recrystallised from warm ethanol. (4a-j) To a mixture of compound 4a (4.52 g, 0.01 mol) in dry dioxane (10 ml), a solution of 2-mercaptopropionic acid(2.17 ml, 0.025 mol) in dry dioxane (10 ml) was added and the reaction mixture was refluxed for 24 h. The reaction mixture was then poured into crushed ice. The separated solid was neutralized by sodium bicarbonate to remove excess of 2-mercaptopropionic acid. solid compound obtained was crystallized from ethanol to give thiazolidin derivatives (5a-j)

Table 2. Antimocrobial,antifungal activity of the compounds 5a-j.

Compounds	**Zone of Inhibition in (mm)**					
	S. Aureus	**B. Subtillis**	**E. Coli**	**P. aeroginosa**	**A. niger**	**C. albicana**
	-logMIC	**-logMIC**	**-logMIC**	**-logMIC**	**-logMIC**	**-logMIC**
5a	3.012	5.562	4.073	5.622	5.533	4.424
5b	3.841	4.815	5.990	3.868	4.176	5.396
5c	2.791	3.768	3.965	5.828	5.296	5.529
5d	3.918	3.686	5.917	3.751	4.037	4.540
5e	4.690	3.012	3.873	5.729	5.982	4.565
5f	4.269	5.202	5.640	4.394	3.931	4.701
5g	4.172	4.117	4.673	4.269	5.605	4.900
5h	3.661	3.643	3.390	5.701	4.533	5.424
5i	3.629	3.616	3.065	5.671	4.176	5.163
5j	2.910	4.475	5.397	3.776	5.096	4.229
Ampicillin	3.100	4.337	4.873	3.822	-	-
Greiscofulvin	-	-	-	-	4.705	4.950
DMF	-	-	-	-	-	-

Table 3. Values of selected descriptors calculated for n-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide

R	HOMO	LUMO	LOG P	VDW	NVDW	MR	CSEV	CAA	CMA
5a	-8.65548	-0.6871	5.6008	15.81	2.649	14.4	254.9	334.61	361.46
5b	-8.71065	-0.8888	7.2255	14.74	5.607	15.1	65.7	349.92	393.67
5c	-8.66524	-0.701	6.7384	11.83	5.845	14.7	119.3	350.75	394.33
5d	-7.99055	-0.663	7.0306	15.43	2.652	15.4	131.8	356.53	392.42
5e	-8.13336	-0.715	6.5435	13.05	9.606	15.0	150.9	349.66	388.11
5f	-8.07344	-0.987	6.5249	13.19	1.517	16.1	135.5	341.53	382.95
5g	-8.26894	-0.916	6.33	12.92	0.107	15.6	169.3	349.12	377.01
5h	-8.96708	-0.944	6.7263	13.25	3.443	14.9	119.5	339.54	383.01
5i	-8.69043	-0.833	6.2392	12.05	5.316	15.6	125.2	345.32	367.88
5j	-8.29894	-0.592	6.3798	11.63	2.248	14.4	115.5	384.52	421.82

Table 4. Correlation matrix of used molecular descriptors

	HOMO	LUMO	DDENE	VDW	NVDW	LogP	CSEV	CAA	CMA
HOMO	1.000								
LUMO	0.820	1.000							
DDENE	0.303	0.674	1.000						
VDW	0.342	0.455	0.580	1.000					
NVDW	0.156	0.279	0.396	0.518	1.000				
Log P	0.612	0.655	0.423	0.547	0.307	1.000			
CSEV	0.282	0.0149	0.046	0.754	0.478	0.695	1.000		
CAA	0.439	0.319	0.420	0.559	0.158	0.609	0.689	1.000	
CMA	0.117	0.235	0.193	0.753	0.479	0.645	0.935	0.734	1.000

2.1 qsar studies

In order to deduce the correlation of observed activity, in terms of MIC (μg/mL) of reported compounds with different structural parameters, systematic QSAR investigations have been carried out using the model proposed by Hansch and coworkers [20].The biological activity data MIC (minimum relevant pathogens are now resistant[5]. (inhibitory concentration in mg/ml) were converted to negative logarithmic dose in moles (pMIC) for QSAR 3D-QSAR studies using CS Chem-Office 6.0[21]running on a P-III processor. Structures of all the compounds were sketched using builder module of the programme. These structures were then subjected to energy minimization using force field molecular mechanics-2 (MM2) until the root mean square (RMS)

gradient value became smaller than 0.1 kcal/mol. Å. Minimized molecules were subjected to re-optimization via Austin model-1 (AM1)[22] method until the RMS gradient attained a value smaller than 0.0001 kcal/mol. Å using MOPAC. The geometry optimization of the lowest energy structure was carried out using Eigenvector following routine. The descriptor values for all the molecules were calculated using "compute properties" module of programme. Calculated thermodynamic descriptors included critical temperature (T), ideal gas thermal capacity (C), critical pressure (P_c), boiling point (BP), Henry's law constant (H), bend energy (E_b), heat of formation (H_f), total energy (TE), and partition coefficient (PC). Steric descriptors derived were Connolly accessible area (CAA), Connolly molecular area (CMA), Connolly solvent excluded volume (CSEV), exact mass (EM), molecular weight (MW), principal moment of inertia-X component (PMI-X), principal moment of inertia-Y component (PMIY), principal moment of inertia-Z component (PMI-Z), molar refractivity (MR), and Ovality (OVAL). Electronic descriptors such as dipole (DPL), electronic energy (ElcE), highest occupied molecular orbital energy (HOMO), lowest unoccupied molecular orbital energy (LUMO), repulsion energy (NRE), VDW-1,4-energy (E14), Non-1, 4-VDW energy (E), and total energy (E) were calculated. Multiple linear regression (MLR) analysis was used to investigate the correlation between biological activity and physicochemical properties. The MLR was performed by using the VALSTAT [23] by the stepwise method. The highest correlation of independent variables with dependent variable was chosen for deriving the QSAR model. The statistical values, multiple correlation coefficient (r), standard errors (s), cross validation r^2 (q^2) and standard error of prediction (SPRESS) were used to evaluate the obtained QSAR models. Several combinations of independent variables were firstly attempted using three variables (one representative from each property) for individual models, and then, more variables were added in order to optimize the statistical values but not more than five independent variables were used. The best model derived from the MLR analysis was used to predict the inhibitory activity of the synthesized compounds. Calculated parameters and correlation matrix needed are shown in Tables 5 and 6.The resulting mono parametric models are depicted in Eqs. 1-4, along with statistical parameters of the regression. No outliers have been determined the equations were derived using the entire data set (n=10).Furthermore, in order to deduce effective QSAR models, a correlation matrix, which is required to have a better selection for calculated parameters, is shown in Tables 4 and 5.The resulting mono parametric biparametric, models are depicted in Eqs. 1-4, along with statistical parameters of the regression. No outliers have been determined and the equations were derived using the entire data set (n=10).

QSAR model for S. Aureus

-log MIC = [3.3369(± 0.148899)] +MR [0.970949(± 0.1925)]
n=10, r=0.91078, r^2=0.894496, variance=0.0126243, std=0.112358, F=88.69 (1)

Bi parametric QSAR model for S. Aureus

-log MIC =[3.76144(±0.392303)]+log P[0.827092(±0.207958)]+CSEV[-0.000924602(± 0.0008075)]
n=10, r=0.95369, r^2=0.908658, variance=0.00919326, std=0.0958815, F=78.61 (2)

QSAR model for B. Subtilis

-log MIC = [3.34863(± 0.119106)] +HOMO [0.866572(± 0.153983)]
n=10, r=0.89748, r^2=0.813455, variance=0.00807774, std=0.0898762, F=67.76 (3)

QSAR model for E.Coli

-log MIC = [3.36056(± 0.106156)] +MR [0.790665(± 0.13724)]
n=10, r=0.92148, r^2=0.84209, variance=0.00641665, std=0.080104, F=81.85 (4)

The *F*-values obtained in Eqs. 1 and 2, 3, 4 are found statistically significant at 99% level. Similarly, cross validation of obtained equations were checked by employing the leave one out (LOO) method ($r^2_{cv} > 0.83$). Conclusively, a series of N-(2-5-Dimethyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives has been synthesized as potent antimicrobial agents. The synthesized compounds showed a remarkable antimicrobial potency. Furthermore, QSAR studies performed on N-(2-5-Dimethyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives have revealed that the substitution of the bulky group with higher polaraizability probably enhances the potency of these compounds as antibacterial and anti fungal agents. Similarly, QSAR studies performed on N-(2-5-Dimethyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives have revealed that hydrophobic parameter i.e., partition coefficient corroborated towards the enhanced biological activity.

2.2 Spectral and analytical data

N-[5-methyl 2-(2-nitrophenyl)-4-oxo-thiazolidin-3-yl] nictotinamide:
IR (KBr) cm^{-1}. 1196 (SO_2,Symmetrical str.), 1309 (SO_2,Asymmetrical str.), 1702.2 (C=O), 1584.5 (c=c), 2875.2 (C-H), 3430.1 (N-H). ^{1}HNMR δppm : 4.07 (s, 1H, CH-S),1.48 (s,3H-CH_3) 3.58 (s, 1H, NH), 6.51-8.90 (m,8H-Ar). MS m/z : 358 (M^+)

N-[5-methyl 2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl] nictotinamide:
IR (KBr) cm^{-1}. 1190 (SO_2,Symmetrical str.), 1314 (SO_2,Asymmetrical str.), 1692.2 (C=O), 1590.5 (c=c), 2898.2 (C-H), 3436.1 (N-H). ^{1}HNMR δppm : 4.11 (s, 1H, CH-S), 1.51 (s,3H-CH_3)3.62 (s, 1H, NH), 6.90-9.01 (m,8H-Ar). MS m/z : 358 (M^+)

N-(2-(4-dimethylamino) phenyl)-5methyl-4-oxo-thiazolidin-3-yl) nicotinamide:
IR (KBr) cm^{-1} : 1166 (SO_2,Symmetrical str.), 1300 (SO_2,Asymmetrical str.) 1710.5 (C=0), 1600.1 (C=C), 3029.9 (C-H), 3403.6 (N-H). ^{1}HNMR δppm : 3.96 (s, 1H, CH-S), 5.0 – 5.01 (s, 3H, CH_3), 3.53 (s, 1H, NH), 6.95 – 8.89 (m, 9H-Ar) 1.45 – 1.49(s, 6H, Ar-CH_3). MS m/z 356 (M+)

N-(5-methyl -4-oxo-(3, 4, 5-trimethoxylphenyl)-thiazolidin-3-yl) nicotinamide:
IR(KBr)cm^{-1} :1176 (SO_2,Symmetrical str.), 1324 (SO_2,Asymmetrical str.) 1689 (C=0), 1628.1 (C=C),3020.9 (C-H), 3423.6 (N-H).). ^{1}HNMR δppm : 3.75 (s, 1H, CH-S), 6.34-6.45 (s, 1H, CH), 3.46 (s, 1H, NH), 6.98-9.20 (m, 8H-Ar), 3.78 (s, 9H, 0CH_3) MS m/z : 403 (M^+)

N-(2-(2- Furfural -2-yl-5-methyl-4-oxo-thiazolidin-3-yl) nicotinamide:
IR(KBr)cm^{-1} :1156 (SO_2,Symmetrical str.), 1304 (SO_2,Asymmetrical str.) 1680 (C=0), 1625.1 (C=C),3020.9 (C-H), 3453.6 (N-H).). ^{1}HNMR δppm : 3.63 (s, 1H, CH-S), 6.34-6.45 (s, 1H, CH), 3.66 (s, 1H, NH), 6.98-9.02(m, 9H-Ar), 5.78 (s, 1H, OH) MS m/z : 331 (M^+)

N-(2-(2-Chloro-phenyl)-5-methyl-4-oxo-thiazolidin-3-yl) nicotinamide:
IR(KBr)cm^{-1} :1147 (SO_2,Symmetrical str.), 1316 (SO_2,Asymmetrical str.) 1701 (C=0), 1625.1 (C=C),3020.9 (C-H), 3453.6 (N-H).). ^{1}HNMR δppm : 3.70 (s, 1H, CH-S), 6.34-6.45 (s, 1H, CH), 3.76(s, 1H, NH), 6.50-8.85 (m, 8H-Ar), 5.78 (s, 3H, CH_3) MS m/z : 347 (M^+)

N-(2-(4-Chloro-phenyl)-5-methyl-4-oxo-thiazolidin-3-yl) nicotinamide:
IR(KBr)cm^{-1} :1147 (SO_2,Symmetrical str.), 1316 (SO_2,Asymmetrical str.) 1701 (C=0), 1625.1 (C=C),3020.9 (C-H), 3453.6 (N-H).). ^{1}HNMR δppm : 3.73 (s, 1H, CH-S), 6.26 (s, 1H, CH), 3.71(s, 1H, NH), 6.61-9.15 (m, 8H-Ar), 5.59 (s, 3H, CH_3) MS m/z : 347 (M^+)

N-(2-(2-hydroxy-phenyl)-5-methyl-4-oxo-thiazolidin-3-yl) nicotinamide:
IR(KBr)cm^{-1} :1159 (SO_2,Symmetrical str.), 1314 (SO_2,Asymmetrical str.) 1698 (C=0), 1615.1 (C=C),3021.9 (C-H), 3422.6 (N-H).). ^{1}HNMR δppm : 3.62 (s, 1H, CH-S),5.31(s,3H-CH_3), 6.34 (s, 1H, CH), 7.65 (s, 1H, NH), 6.80-8.76 (m, 8H-Ar), 5.12 (s, 1H, OH) MS m/z : 329 (M^+)

2.3 Antimicrobial activity

The *in-vitro* antibacterial activity of the substituted N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives has been investigated against several representative pathogenic bacteria. Nutrient agar media was employed for bacterial growth. Inocula containing approximately 10^7CFUs/mLof bacteria were prepared from broth culture in log phase. Bacterial plate was incubated at 37^0C for 24 h. Four microbial strains i.e., S. Aureus, B. Subtillis ,E. Coli ,P. aeroginosa were used in antimicrobial assay. Ampicillin was also screened under similar conditions as reference antibacterial drug. Antifungal activity two microbial strain i.e., A. Niger, C. albicana were used antimicrobial assay Greiscofulvin was also screened under similar conditions as reference antifungal drug. All the synthesized compounds have been found to delineate profound antimicrobial potency as compared to reference drug within a MIC range of 3.1.-4.88 μg/mL. The screening results depicted in Table-2, Ampicillin (10 μg/disc) and greiscofulvin 10 μg/disc) was used as standard for antibacterial and antifungal activity respectively.

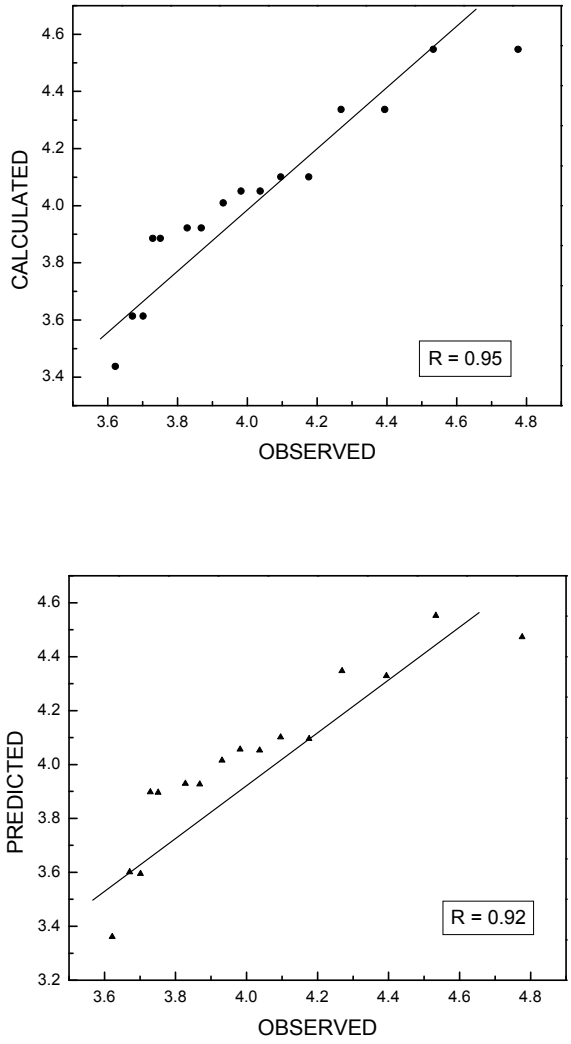
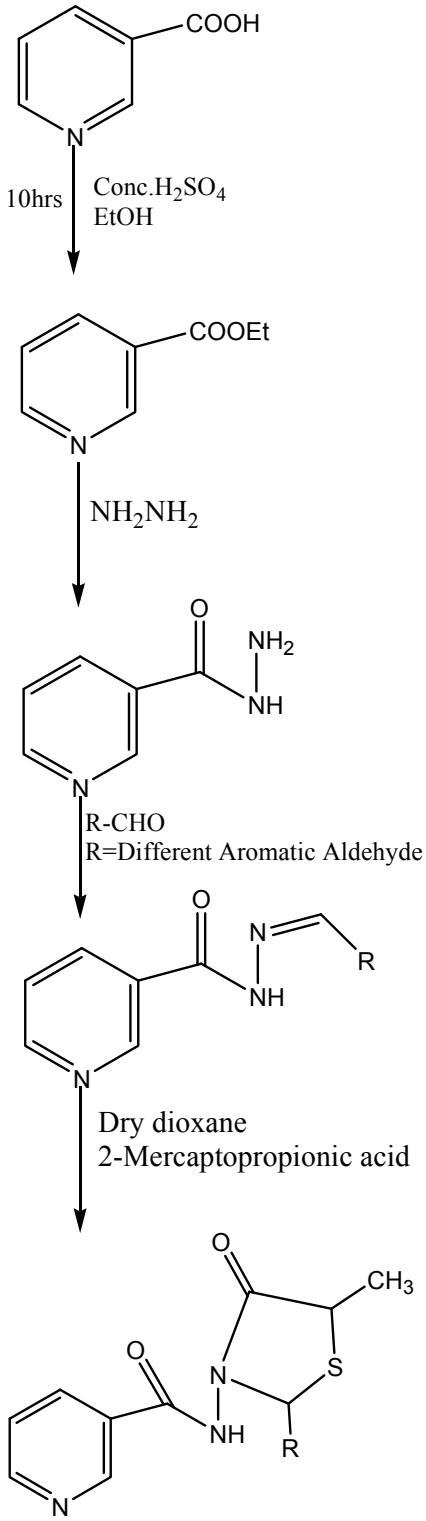


Fig. 1. Plots of observed vs. calculated and observed vs. predicted activity of N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide [5a-j] against B. Subtillis

SCHEME



N-(5-Methyl-4-oxo-thiazolidin-3-yl)-nicotinamide

3. Results and discussion

All the compounds exhibited significant antibacterial and antifungal activities. Good antibacterial activity was observed in 5a, 5b, 5f, 5j against *B. Subtilis* compounds 5b, 5d, 5e,5f,5g showed good activity against *S. aureus* compounds 5a, 5c, 5e, 5h,5i showed significant activity against *P. aeruginosa* and whereas compounds 5b,5d,5f,5j showed noticeable activity against *E. coli.* Compound 5a, 5c, 5e, 5g, 5j and 5b, 5c, 5h.5i showed marked activity against *A-niger* and *C.albicans.* N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives has been synthesized as potent antimicrobial agents. Furthermore, QSAR studies performed on these compounds have revealed that the positive coefficient of the log P descriptor, which relates to the hydrophobicity of the molecule, suggested that an increase in the lipophilicity might increase the activity. This corresponds to the presence of hydrophobic binding site in the N-(5-Dimethyl-4-oxo-thiazolidin-3-yl)-nicotinamide.

4. Conclusion

Conclusively, a variety of Thiazolidinones derivatives have been successfully synthesized in appreciable yields and screened in vitro for their antimicrobial activities against both strains of Gram-positive and Gram-negative bacteria. Moreover, Log P, HOMO, molar refractivity and polarizability parameters were the main governing physicochemical factors for the displayed antimicrobial activities of these synthesized compounds. Such a QSAR evaluation would open future perspectives to use these compounds as new lead compounds in clinical trials.

Acknowledgement

The authors are thankful to Prof.E.V.Submanyam Director N.G.S.M Pharmaceutical Sciences Derlakatte Mangalore (Karnataka) for given valuable suggestions .

References

[1] T. Kamyia, M. Hashimotoo, O. Nakaguchi, Oka, T., Tetrahedron Gilamann, H., Pecter, M. J. Am. Chem. Soc., 65 (1943).
[2] Trivedi, Bhavin and Shah, V.H., Indian J. Chem. Soc., **70**, 601(1993)
[3] Udapi, R.H., Jeeson, M. and Bhatt, A.R., Indian J. Het. Chem., **6**, 99 (1996).
[4] Vashi, B.S. and Shah, V.H., Indian J. Chem. Soc., **73** ,491 (1996).
[5] Desai, N.C., Dipika, Shah, M.D. and Vyas, G.D. Indian J. chem., **39B** 256 (2000).
[6] Mehta, D.S. and Shah, V.H., Indian Het. Chem., **11**, 139 (2001).
[7] Trivedi, P.B., Undavia N.K., Dave, A.M., Indian J. chem., **32B** ,760 (1993).
[8] Desai, Sunil B., Desai, P.B. and Desai K.R., Asia. J. Chem., **14**, 1431 (1990).
[9] Gillespie, S.H. in Medical Microbiology – Illustrated; Butterworth, Heinemann, London, 234 (1994) .
[10] Hawkey, P.M. and Lewis, D.A., in; Medical Bacteriology – A Practical Approach Oxford University, Press, 181 (1994).
[11] Collins, C.H., In; Microbiological Methods, Butterworth's, London. 36 (1974).
[12] Gajare, A.S., Bhawsar, S.B., Shinde, D.B. and Shingare, M.S., Indian J. Chem., **36B**, 449 (1997).
[13] Mogilaiah, K., Reddy, P.R. and Rao, R.B., Indian J. Chem., **38B**, 495 (1999).
[14] Srivastava, S.D. and Gure, N.,Indian. J Chem. Soc., **77**, 400 (2000).
[15] Hogale, M.B., Uthale, A.C. and Nikam, B.P., Indian J. Chem., **30B**, 717 (1991).
[16] Desai, S.B., Desai, P.B. and Desai, K.R., Asian J. Chem., **11**, 1431 (1999).
[17] Mehta, D.S. and Shah, V.H., Indian J. Heterocycl.Chem., **11**, 139 (2001).
[18] Mehta, R.M., Desai, J.M. and Shah, V.H., Indian J. Heterocycl.Chem., **8**, 329 (1999).
[19] Hansch C.; Fujita, T. J Am. Chem. Soc. **86**, 1616 (1964).

[20] Kubinyi, H.; Vol 1 (Edited by Mannhold R, Krogsgaard-Larsen P and Timmerman H),.VCH Publishers, New York pp 21-137 (1993).
[21] Cambridge Soft corp., 100 Cambridge Park, MA 02140-2317, USA
[22] Stewart, J. J. P; J. Comput. Chem. **10** (1989) 209.
[23] Gupta,A.K.,Arockia.Babu M. and Kaskhedikar, S.G.,Indian.J.Pharm. Sci., **66** ,396 (2004).